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Klinik für Neurologie
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Neurorehabilitation and Long-Term Outcomes in Critically Ill Patients

Dissertation
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vorgelegt von
Marion Christina Egger

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Ludwig-Maximilians-Universität München

Erstes Gutachten:	Prof. Dr. Klaus Jahn
Zweites Gutachten:	Prof. Dr. Eva Grill
Drittes Gutachten:	Priv. Doz. Dr. Sandra Frank
Viertes Gutachten:	Prof. Dr. Jan Rémi

Dekan: Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 04.11.2024

Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Promotionsbüro
Medizinische Fakultät

MMRS

Affidavit

Egger, Marion Christina

_____

Surname, first name

Kolbermoorer Str. 72

_____

Street

83043 Bad Aibling, Germany

_____

Zip code, town, country

I hereby declare, that the submitted thesis entitled:

Neurorehabilitation and Long-Term Outcomes in Critically Ill Patients

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is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

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Confirmation of congruency between printed and electronic version of the doctoral thesis

Egger, Marion Christina

_____

Surname, first name

Kolbermoorer Str. 72

_____

Street

83943 Bad Aibling, Germany

_____

Zip code, town, country

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_____ _____

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Table of content

List of abbreviations

CIM	Critical Illness Myopathy
CINAMOPS	Critical Illness Polyneuropathy and Myopathy: Outcome, Predictors and Longitudinal Trajectories
CIP	Critical Illness Polyneuropathy
COVID-19	Coronavirus disease 2019
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit-Acquired Weakness
PICS	Post-Intensive Care Syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2

List of publications

- **Paper I:**

Wimmer C, **Egger M**, Bergmann J, Huge V, Müller F, Jahn K. Critical COVID-19 disease: Clinical course and rehabilitation of neurological deficits. Front Neurol. 2022 Oct 28; 13:1012685. doi: 10.3389/fneur.2022.1012685. (1)

- **Paper II:**

Egger M, Wimmer C, Stummer S, Reitelbach J, Bergmann J, Müller F, Jahn K. Reduced health-related quality of life, fatigue, anxiety and depression affect COVID-19 patients in the long-term after chronic critical illness. *Sci Rep*. 2024 Feb 6;14(1):3016. doi: 10.1038/s41598-024-52908-5. (2)

- **Paper III**:

Egger M, Finsterhölzl M, Buetikofer A, Wippenbeck F, Müller F, Jahn K, Bergmann J. Balance function in critical illness survivors and evaluation of psychometric properties of the Mini-BESTest. *Sci Rep*. 2024 May 27; 14(1):12089. doi: 10.1038/s41598-024-61745-5. (3)

- **Paper IV (Appendix A):**

Bergmann J, **Egger M**, Müller F, Jahn K. Outcome, predictors and longitudinal trajectories of subjects with critical illness polyneuropathy and myopathy (CINAMOPS): study protocol of an observational cohort study in a clinical and post-clinical setting. *BMJ Open* 2024;14:e083553. doi:10.1136/ bmjopen-2023-083553. (4)

- **Paper V (Appendix B):**

Egger M, Finsterhölzl M, Farabegoli D, Wippenbeck F, Schlutt M, Müller F, Huge V, Jahn K, Bergmann J. Comprehensive assessment and progression of health status during neurorehabilitation in survivors of critical illness: a prospective cohort study. *Annals of Intensive Care*. 2024 Nov 26; 14 (1):175. doi: https://doi.org/10.1186/s13613-024-01396-x. (5) (Annotation: This paper was still under review at the time the thesis was submitted and has therefore been included in the Appendix.)

- **Paper VI (Appendix C):**

Egger M, Vogelgesang L, Reitelbach J, Bergmann J, Müller F, Jahn K. Severe Post-COVID-19 Condition after Mild Infection: Physical and Mental Health Eight Months Post

Infection: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2024; 21 (1): 21. doi: 10.3390/ijerph21010021. (6)

1. My contribution to the publications

1.1 Contribution to the CINAMOPS project

ME was substantially involved in the conceptualization, methodology, and initiation of the CINAMOPS project. She was majorly responsible for the ethical approval, funding acquisition from the Else Kröner-Fresenius-Stiftung, and the study registration at the German Clinical Trials Register.

ME was substantially involved in the entire CINAMOPS project, overseeing the project and conducting individual studies. Her responsibilities encompassed project management, project administration, and study investigation. Specifically, she was responsible for recruiting 250 patients and conducting five study visits for each participant, which included various outcome measures, performed at the clinic, via telephone, and even at the patients' homes. She was responsible for the data management. She took the lead in planning of the manuscripts, analyzing the data, writing, and publishing the manuscripts. She presented the project at several conferences. Furthermore, she coordinated and supervised several colleagues who contributed to the study.

Furthermore, ME supervised five bachelor students and one master student, who conducted their final thesis within the project and supported them in data collection and statistical analysis.

1.2 Contribution to the COVID-19 project

ME was substantially involved in the conceptualization and methodology of the whole COVID-19 study project. She was responsible for the ethical approval and the study registration at the German Clinical Trials Register. She supported the funding acquisition.

ME was substantially involved in the entire COVID-19 project, overseeing the project and conducting individual studies. ME was mainly involved in project management, project administration and study investigation. Specifically, the recruitment of patients, the organization and the conduction of study visits including several outcome measures. She was responsible for the data management. She took the lead in planning of the manuscripts, analyzing the data, writing, and publishing the manuscripts. She presented the project at several conferences. She coordinated and supervised several colleagues who contributed to the study.

1.3 Contribution to paper I

Paper I is a shared first authorship between Marion Egger and Corinna Wimmer.

Paper I was developed within the framework of the COVID-19 project.

ME and CW primarily performed the statistical analyses, visualized and validated the results. ME was responsible for the writing process, as she prepared the original draft and also reviewed and edited the manuscript. She led the submission process and was responsible for incorporating and implementing the reviewer comments.

CW was introduced and advised by ME. CW supported the study by contributing to the recruitment of participants, investigation, data curation, analysis and writing of the manuscript.

1.4 Contribution to paper II

ME is the first author of paper II.

Paper II was developed within the framework of the COVID-19 project.

ME was substantially involved in the conceptualization and methodology of the paper, and was mainly responsible for the statistical analysis, visualization, validation, and writing process (original draft, review and editing). ME was responsible for the selection of an appropriate journal, the submission process, and the peer-review process.

1.5 Contribution to paper III

ME is the first author of paper III.

Paper III was developed within the framework of the CINAMOPS project.

ME was responsible for the conceptualization and methodology of the paper. ME performed all statistical analyses, visualized and validated the results. She took the lead in the writing process, preparing the original draft, and reviewing and editing the manuscript. She managed the submission process, chose an appropriate journal, and was responsible for incorporating and implementing the reviewers' comments.

1.6 Contribution to paper IV (Appendix A)

ME is the second author of paper IV.

Paper IV was developed within the framework of the CINAMOPS project.

ME was majorly involved in writing the introduction and in critically reviewing, revising, and validating the manuscript.

1.7 Contribution to paper V (Appendix B)

ME is the first author of paper V.

Paper V was developed within the framework of the CINAMOPS project.

ME was responsible for the conceptualization and methodology of the paper. ME performed all statistical analyses, visualized and validated the results. She took the lead in the writing process, preparing the original draft, and reviewing and editing the manuscript. She managed the submission process, chose an appropriate journal, and was responsible for incorporating and implementing the reviewers' comments.

1.8 Contribution to paper VI (Appendix C)

ME is the first author of paper VI.

This paper is based on the COVID-19 study and on another study in which an outpatient neurorehabilitation program was developed to improve post-COVID-19 condition. ME was mainly responsible for all phases of this therapy study, including conceptualization, methodology, study design, writing the ethical approval, recruiting participants, conducting study visits, partially conducting therapies (e.g., breathing therapy, Nordic Walking), data management, data analysis, project management, supervising colleagues who supported the study, and communication and coordination with external partners. The manuscript for the post-COVID-19 therapy study is currently in preparation by ME.

In the context of Paper VI, ME undertook critical responsibilities including conceptualization, methodology design, formal data analysis, validation, visualization, initial draft preparation, and manuscript reviewing and editing. She managed the submission process, selected the journal, and was responsible for incorporating and implementing the reviewers' comments.

2. Introductory summary

2.1 Critical illness and its consequences

2.1.1 Post-Intensive Care Syndrome

Advances in intensive care medicine led to a decrease in mortality and to an improvement in the outcome of patients.(7) Nowadays, intensive care units (ICU) are of major significance within the healthcare system, as it was emphatically shown during the COVID-19 pandemic.(7-9) Together with the improvements in intensive care medicine, the worldwide growing and aging population resulted in a steadily increasing number of critical illness survivors.(10, 11)

Despite these achievements, there are also drawbacks. Especially prolonged treatments in ICU frequently come along with long-term impairments, being summarized as Post-Intensive Care Syndrome (PICS).(12) It was agreed that PICS “describe[s] new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalization” ((12), p. 505). The relatives of critically ill patients can also be affected by the negative experiences in the ICU, which are coined by the term PICS-family.(13)

Incidences of PICS vary depending on the ICU population, the diagnostic tools and the time frame since the ICU treatment. Percentages of up to 80% were reported for physical and cognitive impairments, and up to 57% for mental impairments.(14) Furthermore, symptoms can even persist for years after the onset of critical illness.(14-16) As expected, the presence of these comprehensive symptoms negatively influences activities of daily living, social participation, and independence. Moreover, critical illness survivors may experience delays in return to work, or require part-time employment, or are even unable to work at all, which all lead to financial burdens for the survivors and their relatives.(17, 18) As a consequence of all these impairments, health-related quality of life is often substantially decreased in critical illness survivors, with this observation reported to persist for up to ten years following ICU treatment.(19-22) Several parameters were reported as risk factors for PICS including older age, female sex, longer duration in ICU, high disease severity, and delirium.(23)

PICS also imposes challenges on the healthcare system. Former ICU patients were shown to experience more new diseases, have more interactions with their general practitioners, and require more hospital readmissions compared to age- and comorbidity-matched individuals without ICU treatment.(18, 24)

Despite the high prevalences of PICS, awareness and recognition are still insufficient, also among primary care physicians.(25, 26) Furthermore, the concept PICS is constantly evolving, as for example recently aspects like pain and fatigue were added.(27) Many aspects of PICS were thus not sufficiently investigated, such as the co-occurrence of different impairments, or effective rehabilitation and long-term therapies (as described in 2.1.5). Adding to the complexity is the heterogeneous assessment of PICS, as there are several different recommendations proposing various diagnostic/outcome measures.(28-31) Thus, PICS prevalence and outcomes vary and are often not comparable in different settings and studies.

2.1.2 Intensive Care Unit-Acquired Weakness

The primary symptom within the category of physical impairments in PICS is generalized muscle weakness, typically referred to as Intensive Care Unit-Acquired Weakness (ICUAW). Dysfunctions of nerves (Critical Illness Polyneuropathy; CIP) and muscles (Critical Illness Myopathy; CIM) resulting in a symmetric weakness of limbs and respiratory muscles are the main reasons for ICUAW.(32, 33) CIP can be described as a length-dependent sensory-motor axonal polyneuropathy (34), whereas CIM is a primary myopathy.(35) The diagnosis of CIP, CIM or the common co-occurrence thereof, typically involves electrophysiological investigations, including nerve conduction studies, needle electromyography, and direct muscle stimulation.(32, 34, 35) For the diagnosis of ICUAW, volitional functional muscle testing is a common method in non-sedated and cooperative patients. Shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and foot dorsiflexion are thereby evaluated by means of the Medical Research Council (MRC) scale. A sum score lower than 48/60 points indicates ICUAW.(32, 36) Several risk factors have been reported for the development of ICUAW, including age, female sex, weight, comorbidities, illness severity (e.g. multiple organ failure, sepsis, longer durations of mechanical ventilation), immobility, hyperglycemia, and exposure to specific drugs (e.g. vasoactive medications, corticosteroids, sedatives).(32, 33) Unfortunately, the presence of ICUAW elicits several negative short- and long-term consequences. These include increased mortality, longer durations of mechanical ventilation, hospital and ICU stay, swallowing disorders, poor physical functioning even in the long-term and reduced participation and health-related quality of life.(32, 37) Current strategies to prevent ICUAW encompass avoiding hyperglycemia, avoiding early parenteral nutrition, minimizing sedation, and emphasizing early mobilization.(32, 38-40)

Scientific knowledge about patients with (confirmed) CIP/CIM and in the broader sense ICUAW is still scarce. Studies often did not include electrophysiological measurements

which are required to differentiate the diagnoses of CIP from CIM. Thus, suggested differences in prognosis between CIP and CIM could not be confirmed.(41) Previous studies on CIP/CIM and ICUAW lacked large sample sizes, neglected premorbid health status and frailty, and did not account for the primary ICU diagnosis.(42, 43) Long-term investigations are rare, and when conducted, only telephone or postal follow-ups were performed. Thus, information about performance-based long-term outcomes like muscle strength or walking ability is hardly available. As it has been demonstrated that self-reported outcome measures capture different aspects than performance-based outcomes, self-reported outcome measures can only poorly serve as substitutes.(44) Moreover, many outcomes such as fatigue, depression, balance, pain, and participation have been largely overlooked for many years.(43) Additionally, many studies have not incorporated validated outcome measures.(42, 43) Overall, it is an issue that the psychometric properties of many outcome measures have not yet been evaluated for survivors of critical illness.

2.1.3 Critical illness due to COVID-19

The Coronavirus disease 2019 (COVID-19) caused millions of infections worldwide and caused more than seven million deaths until May 2024.(45) The majority of individuals infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) experienced asymptomatic or mild cases.(46) However, during the first wave, 14% developed severe cases and 5% even experienced critical cases (i.e., respiratory failure, septic shock, and/or multiple organ dysfunction/ failure).(46) Accordingly, hospital admission rates among individuals with confirmed SARS-CoV-2 infection were high and reached from 6% in Austria, over 13% in Germany, to 32% in Italy. ICU admission rates among hospitalized individuals with confirmed infection ranged from 3% in Norway, to 16% in Germany, and as high as 62% in Finland.(47) Characteristics of COVID-19 changed during the waves, and ICU admission rates and mortality were the highest in wave 3 (September 2020-November 2020).(48) Most important risk factors for severe or critical COVID-19 cases included old age, male gender, and underlying comorbidities such as hypertension, diabetes, and obesity.(49)

Symptoms after SARS-CoV-2 infections can persist for months and include impairments in mental health, and the nervous, cardiovascular, gastrointestinal, respiratory, and musculoskeletal systems.(50) According to the World Health Organization, individuals exhibiting symptoms more than three months following the onset of COVID-19, suffer from the so-called post-COVID-19 condition.(51) The most common symptoms include fatigue, dyspnea, sleep disorder, concentration problems, and effort intolerance.(50) Additionally, neurological symptoms like headache, anosmia, ageusia, encephalopathy,

encephalitis, stroke, and CIP/CIM were reported in individuals suffering from COVID-19.(41, 52, 53) Post-COVID-19 conditions can occur in both hospitalized and non-hospitalized COVID-19 patients, albeit higher prevalences were reported for hospitalized individuals.(54)

The outcome after critical COVID-19 is comparable to other diagnoses requiring intensive care. Thus, PICS was frequently observed in individuals after critical COVID-19 (55), with percentages of up to 91% reported at one month post-hospital discharge.(56, 57) Even one year after ICU treatment, 74% reported physical symptoms, 26% suffered from mental symptoms, and 16% described cognitive impairments.(58) Consequently, return to work was often limited and health-related quality of life was persistently reduced.(59, 60)

Although scientific research increased gradually during the COVID-19 pandemic, at the time of the PhD project´s initiation, the pandemic was still in its early stages. Accordingly, knowledge was scant regarding COVID-19, including the clinical and rehabilitative trajectory of severely affected patients, the prevalence of neurological symptoms among them, and their short- and long-term outcomes.

2.1.4 Chronic critical illness

Some individuals with critical illness suffer from a prolonged dependence of mechanical ventilation. Together with persistent organ dysfunction, the condition is referred to as chronic critical illness.(61) However, different definitions for chronic critical illness were used in the scientific literature. One definition involves a minimum of 21 days of mechanical ventilation.(61) Another definition, based on a consensus-derived definition from the U.S., characterizes chronic critical illness as at least eight days in the ICU in conjunction with the presence of at least one of six specified clinical conditions (mechanical ventilation ≥96 hours, tracheotomy, sepsis, severe wounds, stroke, and traumatic brain injury).(62) Compared to critically ill patients, patients with chronic critical illness suffer from significantly higher mortality, longer treatments at hospital, lower physical function, and lower health-related quality of life in the long-term.(63) Mortality rates ranging from 50% to 68% were reported and only 9% of patients with chronic critical illness experienced a favorable health outcome after one year.(64) Chronic critical illness also occurred in patients suffering from critical COVID-19, whereby frequencies of up to 55% were reported.(65, 66) Interestingly, short- and long-term survival in chronically critically ill COVID-19 patients were higher than in patients without chronic critical illness (65) and chronic critical illness was not associated with long-term mortality or hospital readmissions.(66) However, studies on chronic critical illness in general are relatively

rare, and there is correspondingly limited information available on patients with this condition following a COVID-19 disease. Furthermore, research on patient-reported outcomes and PICS assessments in the field of chronic critical illness remains lacking.

2.1.5 Rehabilitation and therapy for critical illness survivors

The high prevalences of PICS underscore the necessity for effective rehabilitation strategies. However, therapy recommendations for optimal treatment of critical illness survivors with PICS are scarce thus far. In Germany, severely affected critical illness survivors are often admitted to inpatient (early) neurologic rehabilitation, as many have been diagnosed with CIP/CIM.(67) As PICS is complex and includes a variety of symptoms, multidisciplinary rehabilitation is required. With regards to critical COVID-19, a comprehensive rehabilitation program along the continuum of care (ICU, recovery unit, inpatient rehabilitation facility) with a multidisciplinary approach was recommended early during the pandemic.(68) Recently, a guideline on multimodal rehabilitation for patients with PICS in general was published, which includes recommendations like early mobilization, motor training, delirium prophylaxis, and ICU diaries.(69) Other evidence also suggests beneficial effects of physical rehabilitation like neuromuscular stimulation, physical exercise, ergometer training, resistance training, and respiratory training.(70-74) However, the majority of interventions focuses on the time during the ICU treatment, and high-quality studies about therapy options in the long-term, especially for physical rehabilitation, are missing.(69, 75-77) With regards to the treatment and prevention of mental health impairments in patients with PICS, the new guideline recommended psychological interventions, psychoeducation, psychotherapy, and access to professional support targeting psychological stabilization. However, quality of the recommendations was low.(69) Furthermore, computer-based learning and therapies to improve cognition were recommended, as there are some indications for improved cognitive outcomes.(78) However, the quality of evidence of this recommendation was again low.(69)

One approach for the management of PICS in the long-term is the establishment of PICS follow-up clinics. Some of these clinics are located in the U.K., Sweden and the U.S., and provide treatment interventions for the time post-hospital discharge, consisting of medication, rehabilitation, and nutrition.(25) However, there is insufficient evidence for the efficacy of PICS follow-up clinics (25, 79), although there are some indications for less depressive symptoms and improved mental health-related quality of life in individuals after visiting a PICS follow-up clinic.(80) In Germany, the Charité in Berlin hosts the only outpatient clinic for PICS, and follow-up clinics for PICS are still not widely established on an international scale. Reasons, besides the lack of scientific evidence,

include insufficient funding (without any financial support from national health insurance systems worldwide), and a lack of recognition and awareness of PICS.(25) Moreover, despite the high prevalence of PICS, there is still no International Classification of Disease Diagnostic billing code for this condition.(81)

In summary, while the necessity for rehabilitation following critical illness is widely recognized, there remains a lack of evidence regarding the most effective therapy approaches for alleviating symptom burden in survivors of critical illness. Fundamentally, the development of effective therapies requires understanding the type and manifestation of impairments, their changes over time, and their associations and interactions with different factors. The research project CINAMOPS was initiated to address these issues and to ultimately create a basis for research on effective therapies.

2.2 The research project CINAMOPS

2.2.1 Rationale and significance of the PhD project

The studies for this doctoral thesis were conducted within the framework of the project CINAMOPS (Critical Illness Polyneuropathy and Myopathy: Outcome, Predictors and Longitudinal Trajectories). Conceptualization and planning of the CINAMOPS project began in October 2019. At that time, approximately 30% of all patients admitted to the Schoen Clinic Bad Aibling had the diagnosis CIP/CIM. Most of these patients had survived prolonged critical illness, with durations of ICU treatment and mechanical ventilation substantially longer than those previously described in the scientific literature. However, as electrophysiological measurements were not available for every patient during clinical routine, it was unclear how many of these patients had a confirmed diagnose of CIP/CIM. Additionally, as outlined in the Section 2.1.2, scientific literature did not provide information on whether patients with confirmed CIP/CIM developed differently and had different outcomes compared to patients without CIP/CIM.

In the expansive field of critical illness and its consequences, encompassing conditions such as ICUAW, CIP/CIM, PICS, and chronic critical illness, several areas exhibited inadequate understanding, as delineated in the Section 2.1. These areas included, for example, appropriate and validated outcome measures, performance-based outcomes, therapy approaches, consideration of the preclinical condition, and medium- to long-term follow-ups. Consequently, the CINAMOPS project was initiated to address these research gaps.

2.2.2 Overview

CINAMOPS is a monocentric, prospective cohort study, being conducted at the Schoen Clinic Bad Aibling in Germany, a center for acute neurology, neurologic intensive care medicine, and inpatient neurorehabilitation.(4) The focus of the clinic is on severely affected patients. Ethical approval was obtained in May 2020. Funding for the project was successfully obtained from the Else Kröner-Fresenius-Stiftung in September 2020.

In CINAMOPS, 250 patients who have experienced critical illness are followed-up for up to two years after the onset of critical illness. Patients were eligible for the study, if they were 18 years or older and had received mechanical ventilation in the ICU for at least five days. Exclusion criteria were 1) patients receiving palliative care, 2) neuromuscular or neurologic diseases/syndromes causing muscular weakness (e.g. Guillain-Barré syndrome, myasthenia gravis, porphyria, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, severe autoimmune neuropathy, cervical myelopathy, botulism), 3) lack of adequate communication skills, including proficiency in the German language or cognitive abilities, which would impede the completion of the questionnaires, 4) full muscle strength according to the Medical Research Council (MRC) scale (i.e. an MRC score of 5/5). In every patient, an electrophysiological measurement was conducted after study admission to identify CIP/CIM.

Five study visits were scheduled for every study participant. The first study visit (V1) was conducted after admission to neurorehabilitation, the second visit (V2) shortly before discharge from rehabilitation. The three follow-up study visits (V3, V4, V5) were conducted at 12, 18, and 24 months after the onset of critical illness. V3 and V5 were conducted as telephone interviews and questionnaires sent by post. V4 involved visiting the participants at their homes. The CINAMOPS study comprised a comprehensive set of patient-reported outcomes, clinician-reported outcomes, and performance outcomes. Examples are health-related quality of life, mental health, fatigue, frailty, independence in activities of daily living, muscle strength, balance, and participation. Furthermore, in the follow-up visits V3-V5, living- and working situations, provision with medical and assistive devices, physician contacts, hospital readmission, and therapy utilization were assessed. During the first two study visits at the rehabilitation clinic, all therapies (e.g. physiotherapy, occupational therapy, neuropsychology, swallowing therapy) were extracted biweekly from the medical records. Figure 1 gives an overview of the study design of the CINAMOPS project. A detailed description of the whole project, encompassing all assessments, can be found in the study protocol (Bergmann et al., 2024; (4)), which is included in the appendix (Study IV, Appendix A).

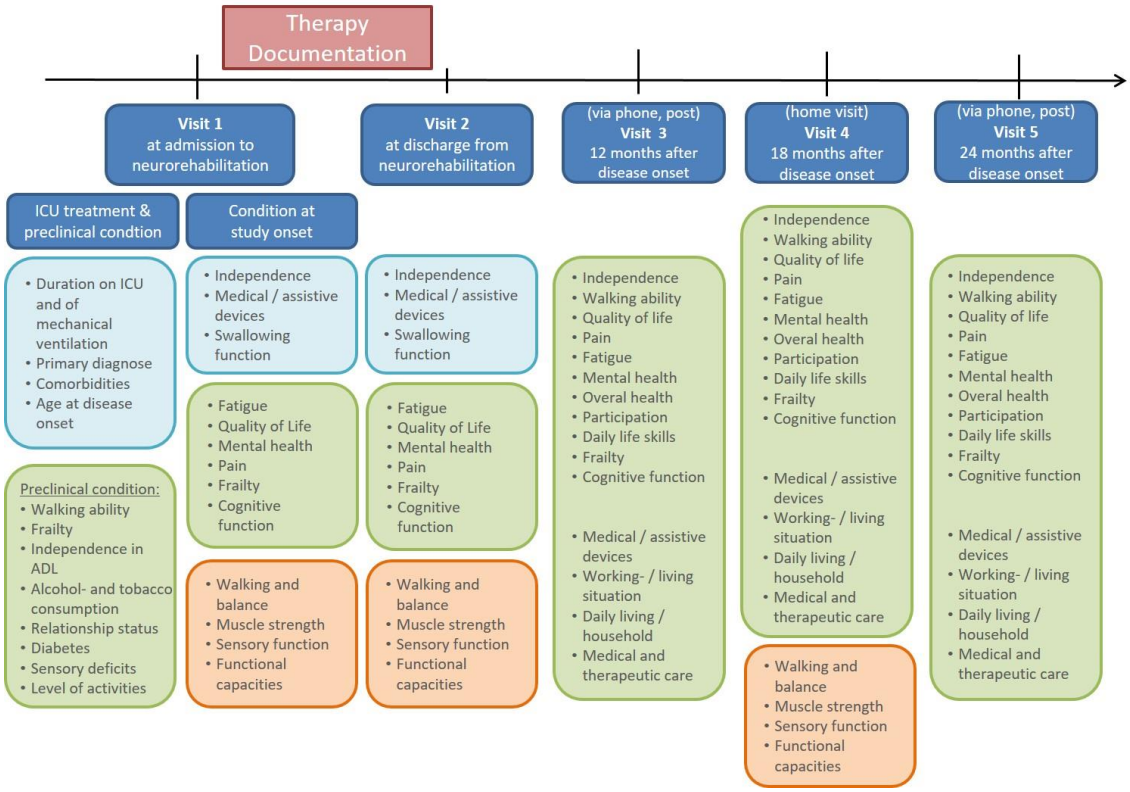

Figure 1 Overview of the CINAMOPS project

ICU: Intensive Care Unit, ADL: Activities of daily living; blue: data from medical records; green: questionnaires, patient- and clinician-reported outcomes; orange: performance outcomes

2.2.3 Research objectives

The project CINAMOPS aims to address the following research objectives:

Primary objectives:

- Description of the clinical and post-clinical course of critical illness survivors; especially survivors with CIP/CIM in comparison to those without CIP/CIM
- Evaluation of predictive parameters for the middle- to long-term outcomes independence, functional abilities and health-related quality of life (12, 18, 24 months after disease onset)
- Evaluation of the impact of the preclinical condition and frailty on the trajectory of rehabilitation

Secondary objectives:

- Evaluation of the clinical and post-clinical course of patients with COVID-19 as primary ICU diagnose
- Evaluation of the psychometric properties of the Mini-BESTest

- Evaluation of the feasibility and practicability of a new electrophysiological approach for diagnosing CIP/CIM
- State-of-the-art description of multi-professional neurologic rehabilitation

2.2.4 Extension of the project: COVID-19 study

By the time writing the CINAMOPS ethics approval request, the first patients with critical SARS-CoV-2 infection were treated at our hospital. Number of patients increased rapidly, thus we decided to implement a project to evaluate the outcome after COVID-19 disease, whereby the design of the CINAMOPS project served as guidance. The project structure of the COVID-19 study was very similar to the one of CINAMOPS, as it included two study visits at admission to and at discharge from rehabilitation (V1, V2), and three follow-up study visits (V3-V5). However, V3-V5 were set to different time points, namely 3, 6, and 12 months after discharge from rehabilitation, as it was not expected that the COVID-19 disease would lead to particularly long-lasting disabilities. Furthermore, the number of outcome assessments was slightly reduced compared to CINAMOPS, and V3-V5 study visits were all conducted via telephone interviews and postal questionnaires. Ethical approval was reached as an amendment to CINAMOPS in May 2020. A supplemental funding grant from the Else Kröner-Fresenius-Stiftung was obtained for the COVID-19 study. Adult patients were enrolled between June 2020 and January 2022 and deemed eligible for the study after the infectious phase of COVID-19, as confirmed by laboratory testing using real-time reverse transcriptase PCR. Exclusion criteria were 1) patients receiving palliative care, and 2) lack of adequate communication skills, including proficiency in the German language or cognitive abilities, which would impede the completion of the questionnaires.

The primary research objectives included investigating patients with COVID-19 throughout the course of neurologic rehabilitation, examining neurological complications such as CIP/CIM, and evaluating associations between ICU and demographic parameters with long-term outcomes.

2.2.5 Current status of the projects

Recruitment of 250 critical illness survivors began in September 2020 and was concluded successfully in July 2023. In December 2023, all clinical study visits (V1 and V2) were finalized. Therapy documentation was completed in April 2024. V3 is anticipated to be completed by the beginning of June 2024. The final study visit (V5) is scheduled for June 7, 2025.

With regard to the COVID-19 extension project, a total of 130 patients were enrolled between June 2020 and January 2022. The last study visit was completed on April 12, 2023.

Besides the studies included in the PhD thesis, the following publications are currently in preparation:

- Weghorn J, **Egger M**, Finsterhölzl M, Wippenbeck F, Müller F, Jahn K, Bergmann J: Long-term Recovery of Sensorimotor Functions and Prediction of Participation in Critical Illness Survivors – A cohort study. *Eur J Phys Rehabil Med.*
- **Egger M**, Reitelbach J, Finsterhölzl M, Wippenbeck F, Müller F, Jahn K, Bergmann J: Swallowing Dysfunction and Tracheostomy in Survivors of Critical Illness: A Prospective Cohort Study.
- Plechinger O, Bergmann J, Schlutt M, Jahn K, **Egger M**: Current State of Multi-Professional Rehabilitation in Survivors of Critical Illness. A Prospective Cohort Study.

Additionally, studies investigating the long-term outcome and PICS prevalence for the study visits V3, V4, and V5 are planned, and the feasibility and practicability of our electrophysiological approach for diagnosing CIP/CIM will be evaluated.

2.3 Contribution of this PhD thesis

This PhD thesis contributes to our understanding of survivors of critical illness who underwent exceptional prolonged treatment in the ICU and required extended mechanical ventilation. Given that the PhD project was conducted during the COVID-19 pandemic, there is a major focus on individuals critically infected by SARS-CoV-2.

Paper I is about the rehabilitative course and neurological symptoms of critically affected COVID-19 patients. We demonstrated that the neurological diagnosis CIP/CIM and delirium/encephalopathy were common among these patients. Furthermore, many patients continued to experience impairments even after being hospitalized up to four months following the SARS-CoV-2 infection. The preclinical health state was largely not regained, and health-related quality of life was diminished. Therefore, continued medical and therapeutic support is warranted.(1)

Paper II adds knowledge about patients suffering from chronic critical illness and their long-term outcomes up to 12 months after SARS-CoV-2 infection. Studies including comprehensive assessments beyond the scope of survival are still scarce in the population of chronic critical illness survivors. We demonstrated increases in the

prevalences of fatigue, anxiety, and depression over time, which is contrary to what would be expected. Accordingly, health-related quality of life was reduced without improvements over time. Even one year after discharge from rehabilitation, the burden of symptoms was high and reached particularly high values for problems with usual activities (77%) and pain / discomfort (84%). These findings underscore the vital need for supportive structures and ongoing (physical and psychological) therapies in this group of patients.(2)

Paper III comprises one of the first and most comprehensive investigations of balance function in critical illness survivors. Although muscle weakness and sensory impairments suggest reduced balance, there have been no significant publications on this topic to date. We found that balance impairments were common in these patients, persisting even after significant improvements achieved during neurological rehabilitation. Furthermore, we identified significant associations between balance and muscle strength, cognitive function, and depression. Moreover, the presence of CIP/CIM and cerebral disease as primary diagnosis significantly negatively impacted balance. These findings suggest that resistance and cognitive training, along with psychological support, may positively influence balance. Additionally, critically ill patients with cerebral damage and/or CIP/CIM require special attention to improve balance function. Furthermore, we assessed the psychometric properties of the Mini-BESTest. Excellent reliability and validity were found, and no floor or ceiling effects occurred, which indicates the suitability of the Mini-BESTest for this kind of patients. As validated outcome measures for critical illness survivors are still scarce, especially regarding performance outcomes, the evaluation of the Mini-BESTest makes an important contribution to a validated assessment pool for this patient group.(3)

Paper IV (Appendix A) contains the study protocol of the CINAMOPS project.(4)

In Paper V (Appendix B) a large cohort of critical illness survivors was prospectively investigated throughout neurological rehabilitation. All patients met the diagnostic criteria for chronic critical illness. A comprehensive set of validated assessments was applied, including outcome measures like fatigue, depression, motor and sensory function, and pain, which were previously often neglected. We demonstrated a high burden of PICS, even after several weeks of intensive rehabilitation. Furthermore, this was the first study that investigated factors associated with ICUAW at rehabilitation discharge and with rehabilitation success in critically ill patients. Significant associations between these two dependent outcomes were found for muscle strength at admission to rehabilitation, duration of mechanical ventilation, and female sex. Interestingly, CIP/CIM was not found to be associated with any of these outcomes. These results aid in planning rehabilitation procedures and in formulating outcome expectations. Overall, this study again

underscores the vital need for long-term supportive structures and multi-disciplinary therapy for (chronic) critical illness survivors. (5)

In Paper VI (Appendix C) we have demonstrated that the post-COVID-19 condition can manifest severely even in individuals who experienced mild infections and did not require hospitalization during the acute phase. According to the findings of this cross-sectional study, conducted on average seven months after SARS-CoV-2 infection, our sample of non-hospitalized patients exhibited a higher prevalence of fatigue, anxiety, and reduced health-related quality of life compared to patients who were previously hospitalized and critically ill. Female gender was significantly associated with disability and health-related quality of life, while hospitalization status was not. These findings suggest that all individuals experiencing post-COVID-19 conditions necessitate long-term medical and therapeutic support, irrespective of their hospitalization status during the acute phase.(6)

In summary, through the ongoing CINAMOPS project, we are gathering a comprehensive and extensive dataset spanning up to two years following the onset of critical illness. The project will enable us to thoroughly describe the health and living circumstances of survivors of (chronic) critical illness, including diagnoses of CIP/CIM, ICUAW, and PICS. Although acute critical illness due to COVID-19 is currently very rare, the findings about this disease contribute to a better understanding of critically ill patients in general. The data collected in the CINAMOPS project can be useful for improved planning and implementation of rehabilitation and post-hospitalization care, research on effective and tailored therapies, enhanced awareness for patients, relatives, and healthcare professionals, improved decision-making, realistic expectations regarding long-term improvements, and fostering policy recommendations, for example, regarding increased funding for long-term care programs. Overall, this work contributes to raising awareness for the consequences after critical illness and to enhancing healthcare services for this vulnerable and burdened group of individuals.

3. Paper I

Wimmer C, **Egger M**, Bergmann J, Huge V, Müller F, Jahn K. Critical COVID-19 disease: Clinical course and rehabilitation of neurological deficits. Front Neurol. 2022 Oct 28;13:1012685. doi: 10.3389/fneur.2022.1012685.

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EDITED BY
Luigi Tesio,
University of Milan, Italy

REVIEWED BY
Alessandro de Sire,
University of Magna Graecia, Italy
Stefano Scarano,
University of Milan, Italy

*CORRESPONDENCE
Klaus Jahn
klaus.jahn@med.uni-muenchen.de

†These authors have contributed equally to this work and share first authorship

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Critical COVID-19 disease: Clinical course and rehabilitation of neurological deficits

Corinna Wimmer[1,2†], Marion Egger[1,3†], Jeannine Bergmann[1], Volker Huge[1], Friedemann Müller[1] and Klaus Jahn[1,2*]

[1]Department of Neurology and Intensive Care Medicine, Schoen Clinic Bad Aibling, Bad Aibling, Germany, [2]German Center for Vertigo and Balance Disorders, Ludwig-Maximilians University (LMU), Munich, Germany, [3]Pettenkofer School of Public Health, Institute for Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians University (LMU), Munich, Germany

Background: The COVID-19 disease frequently causes neurological symptoms. Critically ill patients often require neurorehabilitation for manifestations like intensive care unit (ICU) acquired weakness or encephalopathy. The outcome of these patients, however, is largely unknown. Here we report the clinical course of critical affected COVID-19 patients from hospital admission to discharge from inpatient neurorehabilitation.

Methods: Prospective cohort study. COVID-19 patients admitted to neurorehabilitation were included based on a laboratory-confirmed SARS-CoV-2 infection. Assessments [modified Rankin Scale (mRS), Barthel-Index, Fatigue-Severity-Scale-7 and health-related quality of life (EQ-5D-5L)] were conducted at admission and before discharge from inpatient care. Data were compared to the preclinical health status.

Results: Sixty-one patients (62 ± 13 years, 16 female) were included in the analysis. Most patients had been treated on ICU ($n = 58$; 57 ± 23 days) and had received invasive ventilation ($n = 57$; 46 ± 21 days). After discharge from ICU, patients spent on average 57 ± 26 days in neurorehabilitation. The most frequent neurological diagnoses were ICU-acquired weakness ($n = 56$) and encephalopathy ($n = 23$). During rehabilitation overall disability improved [mRS median (IQR) 4.0 (1.0) at inclusion and 2.0 (1.0) at discharge]. However, the preclinical health state [mRS 0.0 (0.0)] was not regained ($p < 0.001$). This was also reflected by the Barthel-Index [preclinical 100.0 (0.0), at inclusion 42.5 (35.0), at discharge 65.0 (7.5); $p < 0.001$]. Patients had only minor fatigue during inpatient care. Quality of life generally improved but was still low at discharge from hospital.

Conclusion: Patients with neurological sequelae after critical COVID-19 disease showed substantial deficits at discharge from inpatient care up to 4 months after the initial infection. They were restricted in activities of daily living and had reduced health-related quality of life. All patients needed continued medical support and physical treatment.

KEYWORDS

COVID-19, SARS-CoV-2, neurological rehabilitation, critical care outcomes, neurological manifestations

Introduction

The Corona pandemic has resulted in millions of infections with SARS-CoV-2 worldwide and continues to cause numerous new infections. By August 2022, more than 6.4 million people had died in association with SARS-CoV-2 infection (https://covid19.who.int/, as of August 04, 2022). Although many patients recover within days to weeks, a substantial proportion develops long-standing symptoms (long-COVID) ranging from mild fatigue and reduced physical fitness to immobility and long-term disability. The presumed number of patients affected by long-COVID ranges from 2.3 to 53.0% in the current literature (1). Different parameters, such as multiple organ involvement during the acute phase of the disease, persistent reservoirs of the virus in different tissues, as well as manifestation in the central nervous system and immune system dysregulation, are hypothesized to contribute to symptom persistence (2, 3).

Neurological and neuropsychiatric complications of SARS-CoV-2 infections frequently occur, with the utmost prevalence reported for anosmia (43.1%), muscular weakness (40.0%), and fatigue (37.8%). Other common neurologic or neuropsychiatric symptoms include headache, dysgeusia, myalgia, depression as well as sleep disorder (4). Within a study including nearly 5,000 hospitalized patients with COVID-19, a 38% increased hazard of in-hospital death and a decreased likelihood of discharge home among patients diagnosed with a neurological disorder was reported (5). The pooled prevalences of severe complications such as stroke (2%) and encephalopathy (7%) might be lower (6), however, they can cause substantial disability and often trigger neurorehabilitation. Furthermore, patients with critical COVID-19 disease and prolonged invasive ventilation are at high risk of developing neuromuscular weakness. This was shown in an observational study in 110 critically ill patients with COVID-19 treated in the intensive care unit (ICU). All patients showed ICU-acquired weakness (ICUAW) on awakening (7). In another study with patients requiring intubation due to COVID-19, neurologic outcomes were investigated 3 and 6 months after ICU discharge. Cognitive impairment, muscle weakness, and psychologic symptoms were frequent and 74% still required follow-up interventions like physiotherapy or neuropsychological therapy (8). These cases emphasize the necessity of neurorehabilitation in most cases (9, 10). However, studies about rehabilitation after COVID-19 often focused on pulmonary rehabilitation, reported on rehabilitation in less severely affected patients, investigated therapies in patients during the acute phase or with community-dwelling participants or outpatients (11–15).

The rehabilitation of critically ill patients after COVID-19 with neurologic symptoms has not yet been described. Therefore, the objective of this study was to describe the clinical course of critically ill patients with COVID-19 and neurological sequelae during inpatient neurorehabilitation. We hypothesized that patients would show incomplete recovery and that disability and fatigue at discharge can be predicted by the severity of the disease, i.e., the length of stay on ICU.

Methods

Study population

Patients for this prospective cohort study were recruited at one of the largest neurorehabilitation centers in Germany (Schoen Clinic Bad Aibling). Adult patients (≥18 years) with laboratory-confirmed COVID-19 (nasal or pharyngeal swab for SARS-CoV-2, evaluated by real-time reverse transcriptase-polymerase chain reaction (PCR) assay) were included after being tested non-infectious (two negative PCR-tests) and discharged from the ICU. Exclusion criteria were insufficient communication skills (that would interfere with the accomplishment of the questionnaires and assessments) and patients treated with a main diagnosis different than COVID-19 during hospitalization. Data represent the interim analysis of an ongoing larger cohort study with follow-up assessments up to 1 year after hospital discharge. Patients who completed the first two study visits (at study inclusion and at hospital discharge) are entailed in this analysis. All patients received at least 100 min per day of neurorehabilitation therapies including physiotherapy (gait rehabilitation, aerobic, endurance and resistance training, balance training, physical therapy etc.), occupational therapy (training of gross and fine motor skills of the upper extremities, training of activities of daily living like grooming, dressing, using the toilet, resistance training, treatment of sensory deficits etc.) dysphagia therapy, respiratory therapy and neuropsychology (therapy for deficits of attention, concentration, processing speed, memory and executive functions, supportive conversations for coping with the illness and relaxation training). Treatment distribution was tailored to individual patient necessities and therapies were conducted in single or group settings.

Standard protocol approvals, registrations, and patient consents

The study was approved by the medical ethics committee of the Ludwig-Maximilians University of Munich (project no. 20-0478) and the study conforms with the World Medical Association Declaration of Helsinki. Written informed consent was obtained from all participants (or their legal guardians). The study was registered at the German Clinical Trials Register (No. DRKS00025606).

TABLE 1 Overview of questionnaires and functional tests conducted.

Type	Questionnaires / scales	Description
Fatigue	Fatigue Severity Scale−7 (FSS-7)	This scale evaluates fatigue within seven items. The version with seven items has better psychometric properties compared to the version with nine items (17). Score: 1–7. The cut-off ≥ 4 was interpreted as indicative of fatigue (18).
Anxiety and depression	Hospital Anxiety and Depression Scale (HADS)	This tool is widely used, valid and reliable and repeatedly used in critically ill patients (19, 20). Score: 0–21, each for anxiety and depression. The cutoff value of > 7 indicates the presence of symptoms of anxiety or depression for both subscales (21).
Frailty	Clinical Frailty Scale (CFS)	This scale is reliable and widely used in critical care (22, 23). The revised version with nine items was used (24). Score: 1–9.
Health related quality of life	EQ-5D-5L	This widely used test assesses health-related quality of life (25). Due to higher sensitivity and precision, the version with five answers was used (26). Score:−0.205-1.000.
Dyspnea	Descriptive, visual analog scale (VAS)	Using a VAS from 0 to 10, patients were asked to quantify their severity of dyspnea when walking to the toilet and back (approximately 10 meters). 0 indicates no dyspnea.
Disability/dependence in daily activities	Modified Rankin Scale (mRS)	This clinician-reported, valid and reliable measure of global disability has been widely applied in patients after stroke (27), but it is also used in critically ill patients who are being treated on intensive care units (28, 29). Score: 0–6.
	Functional test	**Description**
Functional independence in activities of daily living	Barthel-Index (BI)	This widely used assessment (30) describes the patients' dependence in activities of daily living like washing, grooming, climbing stairs, toilet use etc. It is a reliable and valid tool for patients after critical illness (31). Score 0–100.
Neurological characteristics	Early Rehabilitation Barthel-Index (ERBI)	This reliable and valid extended version of the Barthel-Index containts items like confusion, tracheostomy or dysphagia (32). Score:−325-0.
Olfactory function	Sniffin' sticks	The Sniffin'Sticks screening test with 12 different flavors was used (Burghart Messtechnik, Holm, Germany). The flavors included orange, peppermint, fish, coffee, banana, rose, lemon, pineapple, cinnamon, leather, clove and licorice. Score: 0–12.
Functional mobility (Walking)	Timed-Up-and-Go (TUG)	Functional mobility and balance impairments were assessed with this widely used test which has good psychometric properties (33).
Muscle strength	Grip strength	Grip strength was assessed twice per hand with a digital dynamometer (Kern MAP 130K1, Balingen, Germany). The maximum value was documented.
Walking ability	Functional Ambulation Categories (FAC)	This 6-point scale assesses the ambulation status by determining how much human support the patient requires when walking (34). Score: 0–5.
Basic physical function	Functional Status Score on ICU (FSS-ICU)	This physical function measure was designed for the ICU, comprises five items and has good psychometric properties (35). Score: 0–35.
Cognitive function	Evaluation of attentiveness [Testbatterie zur Aufmerksamkeitsprüfung (TAP)]	This is a computer-based attention test, created by Zimmermann and Fimm (36), which is commonly used in German clinical practice. The TAP consists of the subtests: alertness, Go/NoGo and divided attention.
Cognitive function	Visual and verbal test for retentive-ness [Visueller und Verbaler Merk-fähigkeitstest (VVM)]	Evaluation of retentiveness by using the German test from Schellig and Schächtele (37). Patients have to remember and reproduce visual (a route on a map) and verbal content (information about the building of a museum) within a limited timeframe.

Procedures, scales and scores

Disease severity was categorized by the Seven-Category Ordinal Scale (16). The first two categories describe patients not being hospitalized, categories three to six comprise patients being hospitalized with increasing disease severity (e.g., need for non-invasive mechanical ventilation) and the seventh category includes death.

During rehabilitation, two study visits were conducted. The first visit (visit 1) was scheduled at study inclusion after patients had been transferred from ICU to the early neurorehabilitation unit of our hospital. The second visit was conducted at discharge from inpatient care (visit 2). Study visits included comprehensive questionnaires and tests (Table 1). The study visits were predominantly conducted by a physiotherapist (M.Sc.) with 6 year experience in the conduction of clinical trials (ME) or by a medical student after 5 years of medical school (CW).

In order to comprehensively determine the patient's clinical course, we retrospectively assessed the preclinical status with regard to preclinical health status, walking ability and frailty. Furthermore, level of education, living and working conditions were recorded. This information was collected during the personal interview of visit 1. Data regarding symptom onset, ICU length of stay, duration of invasive mechanical ventilation, neurological diagnoses as well as pre-existing diseases, Barthel-Index (BI), and Early Rehabilitation Barthel-Index (ERBI) were extracted from patient's health records (32).

Cognitive evaluation was conducted by experienced neuropsychologists (see Table 1). Spirometry was performed to evaluate pulmonary function and to identify restrictive lung diseases.

Medical records were screened for complications and neurological diagnoses, symptoms, and syndromes (e.g., ICUAW, peripheral neuropathy, critical illness polyneuropathy (CIP), critical illness myopathy (CIM), delirium, tetraparesis, dysphagia). The diagnosis ICUAW was defined "as the acute development of generalized weakness in a critically ill patient that cannot be explained by other causes" (38, 39). It encompasses pathologies including critical illness polyneuropathy (CIP), critical illness myopathy (CIM), the combination critical illness neuromyopathy (CINM) and / or muscle atrophy. The diagnose ICUAW based on the medical reports of our or the referring hospital, where the diagnose was set either by the clinical manifestation (weakness, atrophy) or by an electrophysiological investigation. If the patient was transferred from another hospital to ours, we validated the ICUAW diagnose by a clinical investigation of muscle strength (mean strength $\leq$ 4/5 according to the MRC scale). In inconclusive cases, electrophysiological investigations were conducted (including nerve conduction studies and electromyography were appropriate).

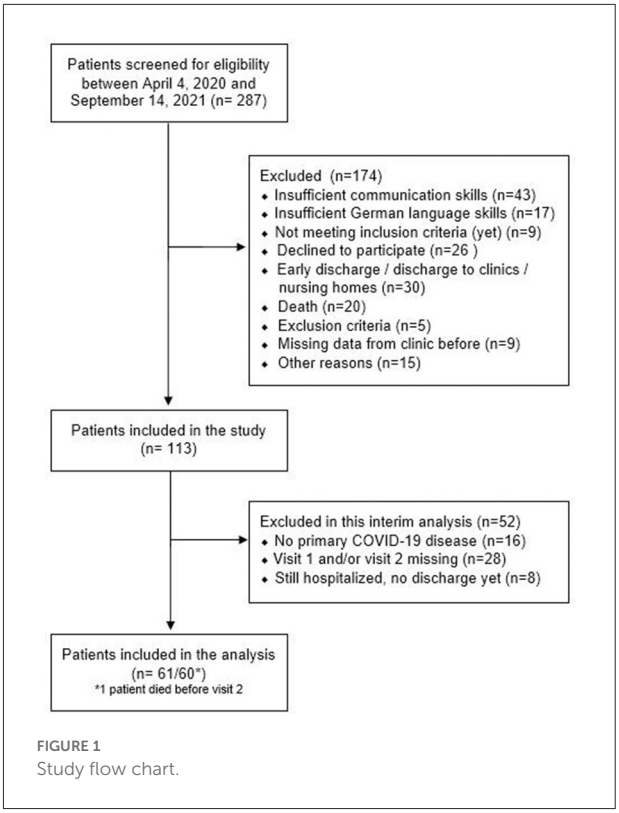

FIGURE 1
Study flow chart.

Statistical analysis

Clinical characteristics are presented as absolute values and percentages, as mean values and standard deviations or as median and interquartile range, as appropriate.

Cognitive impairment was evaluated in percentages according to normative age-dependent values. If the subtest results in the test for attentiveness (TAP) were below 16%, the patient was classified as having limitations concerning attentiveness. If the result of the test for retentiveness (VVM) was below 16%, the patient was classified as having memory and retentiveness limitations. If one result of both test parts was noticeably low, a patient was classified as having general cognitive limitations.

The pulmonary function tests were evaluated to classify the grade of restrictive lung disease. Forced vital capacity (FVC) was set in relation to normative age-dependent values. Percentages $\leq$ 40% were classified as severe, 41–60% as moderate, 61–80% as light and >80% as no restrictive lung disease. Additionally, FEV1 (forced expiratory volume in 1 s) divided by FVC was used to exclude obstructive lung diseases (with formula values >70%).

For the comparison of symptoms between visit 1 and visit 2 paired *t*-tests were used for interval scaled values, Wilcoxon tests were applied for ordinal scaled values. Friedman-tests with *post-hoc* analysis *via* Dunn-Bonferroni test (including corrected

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TABLE 2 Characteristics of included patients.

	Total $n = 61$
Age, years	61.9 ± 12.9, min/max: 38/90
Sex	
Women	16 (26.2%)
Men	45 (73.8 %)
Duration of total hospitalization, days	117.8 ± 38.9
Duration of ICU stay, days ($n = 58$)	57.0 ± 22.9
Duration of invasive mechanical ventilation, days ($n = 57$)	45.7 ± 20.7
Duration of inpatient rehabilitation, days	57.3 ± 26.6
Time from first positive PCR-test to study inclusion, days	84.6 ± 28.2
Time from first positive PCR-test to visit 2, days	120.4 ± 36.9
Time from study inclusion to visit 2, days	36.3 ± 23.3, min/max: 8/111
Highest seven-category scale during hospital stay	
3: Admitted to hospital, not requiring supplemental oxygen	2 (3.3%)
4: Admitted to hospital, requiring supplemental oxygen	1 (1.6%)
5: Admitted to hospital, requiring HFNC or NIV or both	1 (1.6%)
6: Admitted to hospital, requiring ECMO or IMV, or both	57 (93.4%)
Complications	
ARDS	35 (57.4%)
ECMO	10 (16.4%)
Acute kidney failure	20 (32.8%)
Bacterial superinfection	38 (62.3%)
Cigarette smoking	
Current smoker	3 (4.9%)
Former smoker	6 (9.8%)
Comorbidities	
Diabetes	15 (24.6%)
Obesity	11 (18.0%)
Hypertension	26 (42.6%)
Elixhauser comorbidity index	4.1 ± 7.4, min/max: −7/27
Education ($n = 51$)	
Primary school	2 (3.9%)
Comprehensive school	31 (60.8%)
Grammar school	15 (29.4%)
University	3 (5.9%)
Occupation before COVID-19	
Employed	34 (55.7%)
Retired	22 (36.1%)
Volunteer work	3 (4.9%)
Unemployed	2 (3.3%)
Living conditions	
At home alone	11 (18.0%)
At home not alone (e.g., with family)	49 (80.3%)
Nursing home	1 (1.6%)
Preclinical status	
Frailty (CFS)	2 (1)
Overalls disability (mRS)	0 (0)
Functional independence (Barthel-Index)	100 (0)
Walking ability (FAC)	5 (0)

Data are n (%), mean ± SD or median (interquartilerange).
HFNC, high-flow nasal cannula for oxygen therapy; NIV, non-invasive ventilation; IMV, invasive mechanical ventilation; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; BMI, Body Mass Index: normal weight = BMI < 25 and obesity = BMI ≥ 25; Never smoker, never smoked at all or quit smoking more than 10 years ago. CFS, Clinical Frailty Scale; mRS, modified Rankin Scale; FAC, Functional Ambulation Categories.

p-values) were used for categorical values and comparisons of more than two time points.

A binary logistic regression was calculated to analyze predictors for a high degree of disability and dependence in daily activities (mRS ≥3) at discharge. The independent variables were entered hierarchically: Model 1: age, gender; Model 2: Elixhauser Comorbidity Index, diabetes; Model 3: length of invasive mechanical ventilation. Another hierarchical binary logistic regression model was applied to investigate coefficient predicting whether a subject developed severe fatigue (FSS-7 ≥4 (18)): Model 1: age, gender; Model 2: Elixhauser Comorbidity Index, diabetes; Model 3: length of total hospitalization. A linear multiple regression analysis was used to investigate predictors for hospitalization length. The independent variables were entered hierarchically: Model 1: age, gender; Model 2: Elixhauser Comorbidity Index, diabetes, smoking (within the last 10 years); Model 3: preclinical frailty (CFS).

Statistical analyses were performed using IBM SPSS Statistics 19. A $p < 0.05$ was considered significant. Missing data were not replaced.

Results

Study population and disease severity

Of the 287 patients with COVID-19 admitted to our hospital between April 2020 and September 2021, 113 were enrolled in the study and 61 were included in the current interim analysis. Reasons for exclusion are shown in Figure 1. Patients were included in the study on average 84.6 ± 28.2 days and performed visit 2 on average 120.4 ± 36.9 days after their first positive PCR test.

Patients in our study were profoundly affected by the disease: They overwhelmingly needed long-term critical care therapy (mean ICU length of stay 57.0 ± 22.9 days) with prolonged invasive mechanical ventilation (duration of mechanical ventilation: 45.7 ± 20.7 days) or even extracorporeal

membrane oxygenation (ECMO) therapy (16.4%). The length of neurologic rehabilitation after ICU discharge added up to an average of 57.3 ± 26.6 days. Table 2 displays the detailed clinical characteristics of the study population.

Pulmonary dysfunction

Forty-seven patients underwent a lung function test at study inclusion (87.5 ± 31.4 days after the first positive PCR test), of which four had to be excluded due to a lack of cooperation. Of the remaining 43, only two showed signs of obstructive lung disease, whereas most patients ($n = 31$; 72.1%) were diagnosed with restrictive lung disease of varying severity [light: $n = 16$ (37.0%); moderate: $n = 12$ (27.9%); severe: $n = 3$ (7%)]. Only 10 patients (23.2%) displayed a normal lung function test.

Neurological disorders and cognitive impairment after severe COVID infection

All patients had severe neurological deficits requiring intense neurological rehabilitation. ICUAW (CIP/CIM) was the hallmark diagnosis ($n = 56$; 91.8%), followed by delirium in 19 (31.1%), and encephalopathy in 11 patients (18.0%). Other neurological diagnoses were cerebral ischemia ($n = 5$; 8.2%), epileptic seizures ($n = 4$; 6.6%), and Guillain-Barré-Syndrome ($n = 2$; 3.3%).

In accordance with the high prevalence of CIP/CIM, most patients suffered from incomplete tetraparesis. Other common symptoms were dysphagia ($n = 28$; 45.9%), hypoesthesia/paresthesia/neuropathic pain ($n = 9$; 14.8%), paresis ($n = 7$; 11.5%; hemiparesis, facial palsy or monoparesis due to peripheral nerve lesions), and tremor ($n = 2$; 3.3%).

At study inclusion, 47 participants underwent cognitive testing, with $n = 36$ (76.6%) showing cognitive impairments. Deficits in the memory and retentiveness component were apparent in $n = 26$ of 44 participants (59.0%). Regarding the attentiveness component (conducted in 46), $n = 26$ (56.6%) showed deficits. Problems in both components were apparent in $n = 16$ (37.2%, $n = 43$ completed both tests). The 14 remaining patients were either not able to perform the tasks of cognitive testing due to language barriers or due to an insufficient functional ability to use the computer or to hold a pencil.

Clinical course and health status at discharge

Results of assessments and questionnaires are shown in Table 3. From study inclusion to discharge, patient's health status significantly improved in all measured categories except for fatigue and anxiety. Figure 2 illustrates this for the mRS, where most of the patients improved their status [at admission most patients were classified into category 3 (38%) or 4 (36%), whereas at discharge most patients improved to category 2 (51%) and 3 (36%)]. However, health status and body function remained substantially reduced at discharge, represented by reduced mobility, restricted independence in activities of daily living, muscle strength, and breathing. Furthermore, impairments were observed for the olfactory sense with 37/56 (66.1%) being impaired, and pain/ discomfort with 45/60 (75%) being affected. Altogether, patients' health-related quality of life improved significantly during neurorehabilitation, but was still impaired at discharge.

Figure 3 shows a significant improvement of the BI from initial admission (median 17.5; IQR 30.0) *via* visit 1 (median 42.5; IQR 35.0) to visit 2 (median 65.0; IQR 7.5) [$\chi 2(3) = 167.7$; $p < 0.001$]. Notably, there was still a significant gap regarding the BI between the patients' condition at hospital discharge and their preclinical condition (median 100.0; IQR 0.0, $p < 0.001$). *Post-hoc* analysis revealed significant differences between all measurements of the BI.

As shown in Figure 4, the condition of the patients was still limited at hospital discharge in comparison to the preclinical state. The FAC showed complete independence in preclinical walking but a significantly restricted ability at discharge ($Z = -3.862$, $p < 0.001$). As presented with the CFS, patients did not achieve their preclinical state of frailty ($Z = -6.570$, $p < 0.001$). The mRS underlines the overall significantly impaired health state at discharge ($Z = -6.885$, $p < 0.001$).

Forty-four patients (73.3%) were discharged to their homes, 14 (23.3%) were discharged to another rehabilitation facility (not to hospitals), and 2 (3.3%) returned to their nursing home and assisted living facility. Among those participants employed before disease onset, all were discharged as incapable of working.

Predictors for disability, fatigue and hospitalization length

Regression analyses did not result in significant models ($p > 0.18$); none of the coefficients was found to be predictive for the disability at discharge, fatigue at discharge, or the length of hospitalization ($p > 0.10$).

Medical and assistive devices

At study inclusion, 15 patients (25.0%) needed oxygen, 15 (25%) had a permanent bladder catheter, 13 (21.7%) required a tracheal tube, 4 (6.7%) had a percutaneous endoscopic gastrostomy, 3 (5.0%) needed an ileostomy, 2 (3.3%) had a nasogastric tube, and 1 (1.7%) required negative pressure wound therapy.

TABLE 3 Results of the questionnaires and functional tests.

	At study inclusion	At discharge	*p*-values	Z / T / χ2	Effect size r / Cramer's V
mRS	4.0 (1.0)	2.0 (1.0)	$p < 0.001$	$Z = -5.675$	$r = -0.514$
FAC	3.0 (2.75)	5.0 (1.0)	$p < 0.001$	$Z = -6.491$	$r = -0.593$
CFS	6.0 (1.75)	5.0 (2.0)	$p < 0.001$	$Z = -5.656$	$r = -0.516$
FSS-7	2.8 (2.8)	2.9 (2.6)	$p = 0.970$	$Z = -0.038$	$r = -0.003$
Fatigue ≥ 4	17 (28.3%)	13 (22.1%)	$p = 0.429$	$\chi 2 = 0.626$	$\varphi. = 0.73$
Grip Strength max. [kg]	17.1 ± 6.7	20.3 ± 7.9	$p < 0.001$	$T = -5.645$	$r = 0.720$
Barthel-Index	42.5 (35.0)	65.0 (7.5)	$p < 0.001$	$Z = -6.477$	$r = -0.591$
Early rehabilitation Barthel-Index	0.0 (−100.0)	0.0 (0.0)	$p < 0.001$	$Z = -4.163$	$r = -0.380$
FSS-ICU	30.0 (7.75)	34.0 (2.0)	$p < 0.001$	$Z = -6.381$	$r = -0.583$
HADS					
Anxiety	5.0 (5.8)	4.0 (4.0)	$p = 0.142$	$Z = -3.385$	$r = -0.312$
Anxiety > 7	21/61 (34.4%)	11/59 (18.6%)	$p = 0.062$	$\chi 2 = 4.048$	$\varphi. = 0.184$
Depression	4.0 (5.0)	3.0 (5.0)	$p = 0.026$	$Z = -2.810$	$r = -0.259$
Depression > 7	15/61 (24.6%)	8/59 (13.6%)	$p = 0.170$	$\chi 2 = 1.886$	$\varphi. = 0.126$
Sniffin' Sticks	8.6 ± 2.3	9.2 ± 2.4	$p = 0.003$	$T = -3.057$	$r = 0.384$
Normal (11–12)	14/59 (23.7%)	19/56 (33.9%)	$p = 0.473$	$\chi 2 = 1.495$	$\varphi. = 0.114$
Hyposmia (7–10)	37/59 (62.7%)	31/56 (55.4%)			
Anosmia (1–6)	8/59 (13.6%)	6/56 (10.7%)			
TUG [s]	22.6 ± 17.2	16.4 ± 16.3	$p = 0.001$	$T = 3.498$	$r = 0.489$
Unable to walk	14/58 (24.1%)	1/56 (1.8%)	$p < 0.001$	$\chi 2 = 12.458$	$\varphi. = 0.331$
Walking aid required (of those who were able to walk)	23/44 (52.3%)	13/55 (23.6%)	$p = 0.003$	$\chi 2 = 8.663$	$\varphi. = 0.296$
EQ-5D-5L					
Health Scale	52.3 ± 18.0	67.4 ± 16.6	$p < 0.001$	$T = -5.730$	$r = 0.601$
Index value	0.554 ± 0.287	0.749 ± 0.176	$p < 0.001$	$T = -5.877$	$r = 0.608$
Problems with walking around	58/60 (96.7%)	45/59 (76.3%)	$p = 0.001$	$\chi 2 = 10.633$	$\varphi. = 0.299$
Problems with washing or dressing	49/60 (81.7%)	32/59 (54.2%)	$p = 0.001$	$\chi 2 = 10.297$	$\varphi. = 0.294$
Problems with usual activity	49/60 (81.7%)	32/59 (54.2%)	$p = 0.001$	$\chi 2 = 10.297$	$\varphi. = 0.294$
Pain or discomfort	48/60 (80.0%)	45/59 (76.3%)	$p = 0.623$	$\chi 2 = 0.242$	$\varphi. = 0.045$
Anxiety or depression	32/60 (53.3%)	15/59 (25.4%)	$p = 0.002$	$\chi 2 = 9.697$	$\varphi. = 0.285$
Dyspnea	4.3 ± 2.6	3.3 ± 2.6	$p = 0.035$	$T = 2.156$	$r = 0.277$

Data are n/N (%), mean ± SD or median (Interquartilerange).
mRS, modified Rankin Scale; FAC, Functional Ambulation Categories; CFS, Clinical Frailty Scale; FSS-7, Fatigue-Severity-Scale-7; FSS-ICU, Functional Status Score on ICU; HADS, Hospital Anxiety and Depression Scale; TUG, Timed-Up-and-Go. The effect size r was calculated with $r = z/\sqrt{N}$ for ordinal scaled values and with $r = \sqrt{\frac{t^2}{t^2+df}}$ for metric scaled values and with Cramer's V (calculation by SPSS) for categorical values.

At discharge, 7 participants (11.7%) still needed oxygen, 6 (10%) had a permanent bladder catheter, and 2 (3.3%) needed an ileostomy.

At discharge, the majority of participants still needed assistive devices for their activities of daily living. Only 14 participants (23.3%) did not require any aids and appliances. Most frequently used were walker-rollators [33 (55.0%)], wheelchairs [16 (26.7%)], toilet and shower chairs [14 (23.3%)], ankle-foot orthosis [7 (11.7%)], nursing beds [6 (10.0%)], bathroom handles [6 (10.0%)] and oxygen concentrators [5 (8.3%)].

Discussion

We here report on the clinical course in a cohort of the most severely affected patients with COVID-19 disease who required long-term inpatient care and rehabilitation because of neurological deficits. After the ICU-treatment, patients showed mainly muscular weakness (ICUAW, CIP/CIM) and cognitive deficits (delirium, encephalopathy). Our main findings are: (1) Patients with critical COVID-19 spent on average 4 months in hospital; most of them showed relevant muscular weakness due to ICUAW. (2) Patients improved over time, but still suffered

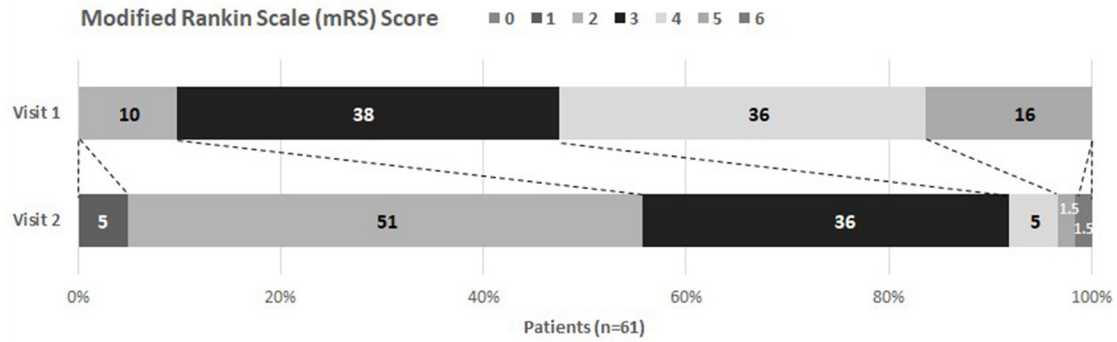

FIGURE 2
Modified Rankin Scale at visit 1 and 2. Visit 1 took place at study inclusion, visit 2 at discharge from inpatient care. Percentages of each category are given. A shift of mRS values can be noticed (depicted with dotted lines) showing improvement between visits.

from substantial deficits at discharge. Patients in general did not reach the preclinical health status, as indicated by the overall disability (mRS) and frailty (CFS). (3) We could not identify any predictors for the degree of disability and fatigue at discharge or for the length of hospitalization.

Previous studies reported on benefits and effectiveness of rehabilitation in patients after COVID-19. However, these studies focused on less severely affected patients, shorter rehabilitation periods, earlier rehabilitation phases, less intensive rehabilitation, or other organ systems (e.g., pulmonary rehabilitation) (11, 12, 40, 41).

Despite the long duration of rehabilitation and total hospitalization in our cohort, the functional and health status at discharge was worse compared to other studies (12, 40, 41). This most likely reflects the prolonged treatment on ICU with mechanical ventilation in our sample. The maximum number of days on ICU reported before were 18–22 days (40, 42, 43).

The impaired health status at discharge is clearly represented by the gap in mRS and the CFS between the preclinical state and the state at discharge. Both assessments, as well as the BI, indicate the patients' need for help in nearly all their activities of daily living (ADL). This clearly affects their level of independence. Limitations in ADLs after the acute phase of COVID-19 were previously reported (44). Our results show that ADL limitations after critical COVID-19 disease last for a prolonged period of time. Furthermore, health-related quality of life was still substantially impaired compared to a sample of healthy German seniors, although we found a significant improvement over time (45). Our values in this domain were also lower than those reported in a study on 47 patients after COVID-19 who required mechanical ventilation for a median of 12 days. In that study, the VAS in the EQ-5D-5L was 80 (70–90) 3 months after hospital admission and only 40% reported problems in the dimension of mobility (compared to 75% in our cohort) (46). This difference again can be explained by the critical course of disease with a prolonged

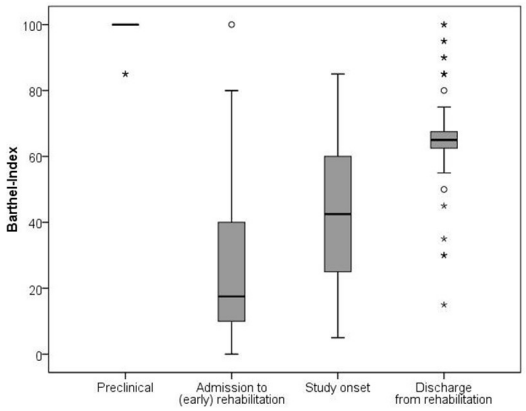

FIGURE 3
Development of the Barthel Index from preclinical state throughout rehabilitation. The comparison between the four time points showed significant differences and large effect sizes (Friedman-test and effect size with $r = z/\sqrt{N}$): preclinical-hospital admission ($p < 0.001$, $r = -0.612$); preclinical-study onset ($p < 0.001$, $r = -0.616$); preclinical-hospital discharge ($p < 0.001$, $r = -0.615$); hospital admission-study onset ($p = 0.035$; $r = -0.487$); hospital admission-hospital discharge ($p < 0.001$, $r = -0.600$); study onset-hospital discharge ($p < 0.001$, $r = -0.591$).

length of hospitalization in our cohort. Our EQ-5D-5L results are in a similar range as reported for (1) patients with chronic conditions like cardiovascular disease or depression (VAS: 64±23) (47) and (2) general critical illness survivors with a median length of 10 days for mechanical ventilation [e.g., VAS: 64 ± 23; index: 0.73 (IQR = 0.3)] (48). However, those patients reported higher values of anxiety (as measured by the HADS; median = 7.0) compared to our patients (median = 4.0). This might be explained by feelings of relief and gratefulness for surviving COVID-19, which were frequently mentioned by our

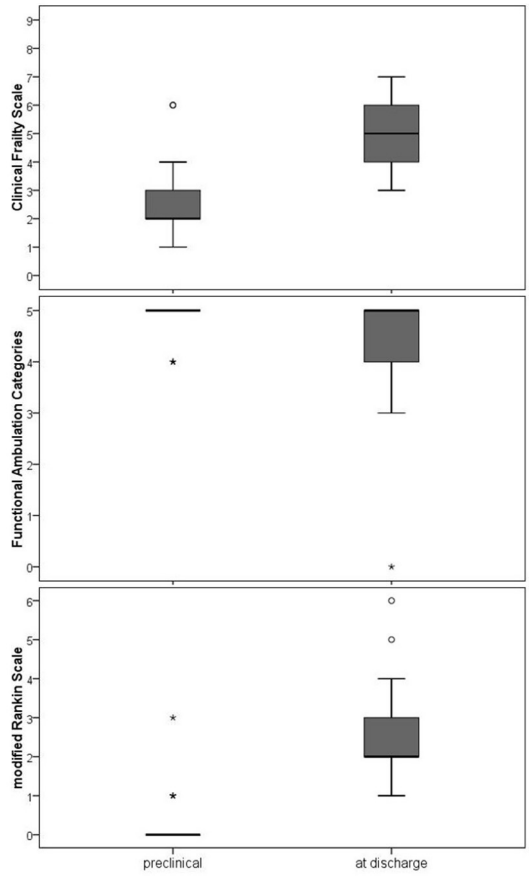

FIGURE 4
Walking ability, frailty and overall disability at clinical discharge compared to the preclinical condition. FAC (Functional Ambulation Categories), Frailty (Clinical Frailty Scale), mRS (modified Rankin Scale). The Wilcoxon test was used to compare the preclinical state and the state at discharge. All three comparisons differed statistically significant ($p < 0.001$).

participants. In contrast, reported depression values were quite similar to the results of our study (48). Our values for anxiety and depression are in accordance with HADS values reported in a cohort ∼4 months after hospital admission due to COVID-19 (median duration of mechanical ventilation: 19 days) (42).

Regarding fatigue, we expected higher values in our group of critically ill patients, similar to reported values in several studies on patients post-COVID (4). In a meta-analysis on hospitalized patients, 38.4% suffered from fatigue (95% CI 30.4–47.4) over 90 days after symptom onset (49). The mild fatigue score in our group (noticeable in only ∼25%) might be explained by the fact that our patients were still in a hospital setup without the challenging responsibilities, duties or long-lasting physical activities required for ADL.

Our results show that even after an average of >100 days of hospitalization including >50 days of intensive neurorehabilitation, the health state and functional capacity after severe COVID-19 disease is limited. Therefore, a long-term disability can be anticipated, especially when considering the sequelae reported in less severely affected patients. Huang et al. (50) reported in a trial on 1,733 hospitalized patients post COVID-19 that 76% experienced at least one symptom like fatigue or muscle weakness, sleep difficulties, anxiety and depression 6 months after infection. This percentage increased to 86% in a subgroup of patients who needed (non-)invasive ventilation (50). Within a cohort of 246 ICU survivors after critical COVID-19, Heesakkers et al. (43) reported than 74.3% experienced physical symptoms, 26.2% experienced mental symptoms and 16.2% experienced cognitive symptoms even 1 year after ICU treatment (43). Therefore, further evaluations of symptoms and their impact on activity and participation in daily life are urgently needed.

Our study has some limitations. First, a non-COVID-19 control group with similar motor and cognitive deficits would have been of value to compare outcomes. It is not clear how specific our findings are for COVID-19. Furthermore, evaluation of lung function, cognitive impairment and nerve conduction studies were only conducted once. Thus, no assertions can be made about their potential improvement during rehabilitation. Additionally, a high number of screened patients were not included in the study (226 of 287) mainly due to insufficient communication skills. Furthermore, 19 patients were excluded, because we were only able to conduct one study visit due to a rapid discharge (∼ 1–5 days) after the first study visit. We did an analysis to investigate the characteristics of those 19 excluded patients compared to the 61 included patients. Patients who were excluded were significantly younger (mean age 54.3 vs. 61.9 years), had significantly less comorbidities, were significantly shorter on ICU (44.1 vs. 57.0 days), had significantly less days of mechanical ventilation (26.9 vs. 45.7 days) and had a significantly shorter duration of complete hospitalization (78.6 cs. 119.4 days). However, both patient groups did not significantly differ in their health status at discharge regarding any assessment (e.g., Barthel Index, HADS, EQ-5D-5L, mRS, CFS, FSS-ICU, FAC, FSS-7). It can be concluded, that younger patients with a better preclinical health status required less intensive care and recovered faster. However, their health status at discharge was as limited as the health status of patients with a longer hospitalization period and a worse preclinical health status. Finally, single-center studies bear the risk of bias, which for example becomes apparent as our center included only critically affected patients.

In summary, our findings stress the need for intensive neurorehabilitation in patients with severe neurological symptoms after critical COVID-19 disease. We cannot determine the specific effect of rehabilitation. However, deficits are pronounced and do not resolve on a short time scale. We report substantial and long-lasting limitations regarding the general health status, dependence in ADL and health related

quality of life even at discharge. As persistent limitations after critical COVID-19 disease are a socioeconomic and medical challenge, further research characterizing the neurological aspects of the pandemic disease and developing tailored rehabilitation and home care programs is of paramount interest.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Committee of the Medical Faculty of the Ludwig-Maximilians University of Munich. The patients/participants provided their written informed consent to participate in this study.

Author contributions

CW: data curation (equal), formal analysis (equal), investigation (equal), resources (support), visualization (equal), writing—original draft preparation (equal), and writing—review and editing (equal). ME: conceptualization (equal), data curation (equal), formal analysis (equal), funding acquisition (support), investigation (lead), methodology (lead), project administration (support), resources (lead), validation (equal), visualization (equal), writing—original draft preparation (equal), and writing—review and editing (equal). JB: formal analysis (equal), funding acquisition (lead), methodology (support), project administration (lead), validation (equal), and writing—review and editing (equal). VH: validation (equal), resources (support), writing—original draft (support), and writing—review and editing (equal). FM: conceptualization (equal), methodology (support), supervision (support), validation (equal), and writing—review and editing (equal). KJ: conceptualization (equal), funding acquisition (support), methodology (support), project administration (lead), supervision (lead), validation (equal), visualization (support), writing—original draft preparation (equal), and writing—review and editing (equal). All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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4. Paper II

Egger M, Wimmer C, Stummer S, Reitelbach J, Bergmann J, Müller F, Jahn K. Reduced health-related quality of life, fatigue, anxiety and depression affect COVID-19 patients in the long-term after chronic critical illness. *Sci Rep*. 2024 Feb 6;14(1):3016. doi: 10.1038/s41598-024-52908-5.

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Reduced health-related quality of life, fatigue, anxiety and depression affect COVID-19 patients in the long-term after chronic critical illness

Marion Egger[1,2]✉, Corinna Wimmer[1,3], Sunita Stummer[1], Judith Reitelbach[1], Jeannine Bergmann[1], Friedemann Müller[1] & Klaus Jahn[1,3]

The term chronic critical illness describes patients suffering from persistent organ dysfunction and prolonged mechanical ventilation. In severe cases, COVID-19 led to chronic critical illness. As this population was hardly investigated, we evaluated the health-related quality of life, physical, and mental health of chronically critically ill COVID-19 patients. In this prospective cohort study, measurements were conducted on admission to and at discharge from inpatient neurorehabilitation and 3, 6, and 12 months after discharge. We included 97 patients (61 ± 12 years, 31% women) with chronic critical illness; all patients required mechanical ventilation. The median duration of ICU-treatment was 52 (interquartile range 36–71) days, the median duration of mechanical ventilation was 39 (22–55) days. Prevalences of fatigue, anxiety, and depression increased over time, especially between discharge and 3 months post-discharge and remained high until 12 months post-discharge. Accordingly, health-related quality of life was limited without noteworthy improvement (EQ-5D–5L: 0.63 ± 0.33). Overall, the burden of symptoms was high, even one year after discharge (fatigue 55%, anxiety 42%, depression 40%, problems with usual activities 77%, pain/discomfort 84%). Therefore, patients with chronic critical illness should receive attention regarding treatment after discharge with a special focus on mental well-being.

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Abbreviations

CCI	Chronic critical illness
ICU	Intensive care unit
PICS	Post-intensive care syndrome

Advances in intensive care have substantially improved survival rates of critically ill patients[1]. However, these advances have also led to a growing population of patients suffering from persistent organ dysfunction and prolonged dependence on mechanical ventilation, a condition termed chronic critical illness (CCI)[2]. The underlying pathophysiology of CCI was suggested to be based on persistent inflammation, immunosuppression, and protein catabolism[3,4]. CCI can develop in all patients requiring treatment for acute medical, surgical, neurologic, or cardiac critical illness. It occurs especially often in older patients with sepsis, mechanical ventilation and underlying comorbid conditions[2]. As a consequence, CCI contributes to long-term mortality, extraordinary health-care costs, reduced long-term physical, psychological and cognitive functions, and diminished health-related quality

[1]Research Group, Department of Neurology, Schoen Clinic Bad Aibling, Kolbermoorer Strasse 72, 83043 Bad Aibling, Germany. [2]Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany. [3]German Center for Vertigo and Balance Disorders, University Hospital Grosshadern, Ludwig-Maximilians-Universität München, Munich, Germany. ✉email: megger@schoen-klinik.de

of life[5–10]. The encompassing long-term disability of ICU survivors with impairments in physical function, psychological health, and cognition was previously described as post-intensive care syndrome (PICS)[11].

The COVID-19 pandemic caused millions of infections worldwide. The disease caused by the severe acute respiratory syndrome coronavirus -2 (SARS-CoV-2) typically manifests as pneumonia and can lead to critical symptoms requiring treatment on ICU and mechanical ventilation[12–15]. Reconvalescence of ICU survivors after COVID-19 disease was shown to be protracted and large numbers suffered from health limitations even months after the infection. Within the first three months after discharge from ICU, around 90% still suffered from health state limitations[16–18]. Symptoms may even be prominent 1 year after ICU treatment, with physical, mental and cognitive impairments reported in 74%, 26% and 16% of the patients respectively[19]. In accordance with the reduced health state, health-related quality of life was also shown to be reduced in COVID-19 ICU survivors[14,20,21]. Additionally, ICU admission and (duration of) mechanical ventilation were found to be predictors for a low health-related quality of life[21–23].

Until now, only few studies investigated CCI in COVID-19 populations. Interestingly, reported mortality rates in COVID-19 CCI populations (90-day mortality = 28%[24]; 1-year mortality = 6.6%[25]) were substantially lower than previously described mortality rates in general CCI populations (1-year mortality = 44%[6]–54%[5]). Although mortality and survival are highly relevant, long-term outcome, prospect of life and quality of life became more and more important in intensive care medicine[26]. As treatment of CCI patients is highly resource-intensive, specific data on long-term trajectories are required for decision-making processes regarding resource allocation, critical care capacity and therapeutic options. Therefore, the outcome of COVID-19 patients with CCI is of high relevance, especially, as up to 50% of the investigated COVID-19 patients (being treated on ICU) were chronically critically ill[24,25]. Additionally, as health limitations are common in COVID-19 ICU survivors even after short durations of ICU therapy[14,16], substantial and enduring health deficits can be expected in COVID-19 CCI patients[6,24]. However, up to now, there are no studies about the long-term outcome beyond the scope of pure survival.

Therefore, the objective of this study was to determine the physical and mental health and the health-related quality of life of chronically critically ill COVID-19 patients 3, 6 and 12 months after discharge from hospital.

Methods

Study population and setting

For this observational prospective cohort study, patients were recruited at the Schoen Clinic Bad Aibling, a center for inpatient neurorehabilitation in Germany with a focus on critically affected patients (ICU, early neurorehabilitation). Adult patients (≥ 18 years) with laboratory-confirmed COVID-19 (evaluated by real-time reverse transcriptase PCR) were eligible after the infectious stage and after being admitted to neurorehabilitation. Exclusion criteria were (1) insufficient (German) communication skills to complete the questionnaires and (2) patients receiving palliative care. For the analysis presented in this manuscript, only chronically critically ill COVID-19 patients were included. An American consensus-derived definition was applied to determine CCI[27], whereby a minor adaption according to[9] was used. This definition consists of at least 8 days in an ICU and one of six eligible clinical conditions (prolonged acute mechanical ventilation (≥ 96 h), tracheotomy, sepsis, severe wounds, stroke (including ischemic stroke and intracerebral hemorrhage), and traumatic brain injury). For the diagnosis of these conditions, the criteria of[9] were applied.

Patients received approximately 100 min of multi-disciplinary neurorehabilitation therapies per day, including physio-, occupational-, dysphagia-, and breathing therapies, as well as neuropsychology. Duration of neurologic rehabilitation was distinct for every patient.

Part of this study population were described previously in a study on the clinical course during neurorehabilitation[20] and a study about severe post-COVID-19 condition[28].

The study was approved by the medical ethics committee of the Ludwig Maximilian University Munich according to the Declaration of Helsinki (project No. 20-0478). Written informed consent was obtained from all participants (or their legal guardians). The study was registered at the German Clinical Trials Register (DRKS00025606).

Study visits and outcomes

Patients were included after admission to neurological rehabilitation (after discharge from ICU and after weaning from mechanical ventilation). Each of the 5 study visits (at study inclusion, at discharge from neurorehabilitation, and 3, 6, and 12 months after discharge) comprised a comprehensive set of questionnaires, functional tests, and questions about personal living conditions. The visits at study onset (visit 1 = V1) and at discharge (visit 2 = V2) from inpatient rehabilitation took place in person, visits 3, 4, and 5 (V3–V5) after discharge were conducted via structured telephone interviews and questionnaires sent by post. The study visits were conducted by trained and experienced study staff.

ICU treatment characteristics, complications, and pre-existing diseases were extracted from the medical records. To describe pre-existing diseases, a comorbidity index based on the Elixhauser classification system was used[29]. In order to investigate critical illness polyneuropathy and –myopathy, sensory and motor nerve conduction studies and needle electromyography (if applicable) were conducted after study inclusion.

This analysis focuses on the following assessments:

- The Fatigue Severity Scale-7 (FSS-7) is used to evaluate fatigue. The seven-item version has better psychometric properties than the nine–item version[30]. Score: 1–7. The cut-off ≥ 4 was interpreted as indicative of fatigue[31].

- The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable tool to measure anxiety and depression and was repeatedly used in critically ill patients[32]. Score: 0–21 each for anxiety and depression. A score of > 7 in each category was interpreted as clinically significant[33].
- The EuroQol-5 dimensions-5 level (EQ-5D-5L) was used to measure health-related quality of life[34]. The index value for the German population ranges from − 0.205 (0 = health state equivalent to death; negative values = health state worse than death) to 1.000 (best health state)[35]. Patients who died after V1 were assigned a score of 0 in all further study visits. Additionally, the visual analogue scale (included in the EQ-5D-5L; 0–100) was used. 100 indicates the best imaginable state of health.
- The generic World Health Organization Disability Assessment Schedule 2.0 (WHODAS-12) measures health and disability and comprises the categories cognition, mobility, self-care, getting along, life activities, and participation. It is reliable, widely used and has good internal consistency[36]. The total score was converted into a percentage ((sum/48)*100): no (0–4%); mild (5–24%); moderate (25–49%); severe (50–95%); and complete (96–100%) disability.
- Frailty (Clinical Frailty Scale, score 1–9; 9 = deathly ill[37]), overall disability (modified Rankin Scale, score 0–6; 6 = death[38]) and dyspnea (modified Medical Research Council dyspnea scale, score 0–4; 4 = severest dyspnea[39]. For frailty and overall disability, a preclinical value was recorded retrospectively at visit 1.

Statistical analysis

Categorical variables are presented as absolute values and percentages, continuous variables as mean ± standard deviation or median (quartile 1–quartile 3).

For the comparison of symptoms between different study visits, Friedman-Test was used as data were either non-parametric or did not follow normal distribution (as checked visually by means of QQ-plots). Effect sizes were calculated based on the Wilcoxon signed-rank test as Z statistic divided by square root of the sample size ($r = Z/\sqrt{N}$) for the comparisons of different study visits (in all patients with available data pairs).

Correlation between fatigue, depression, anxiety and health-related quality of life (index value) was calculated by spearman´s rank correlation coefficient and interpreted according to[40].

Linear mixed-effect models for repeated measures were used to investigate the impact of preclinical health states and ICU treatment characteristics over time. Models were calculated separately for each of the outcomes, i.e. health related quality of life, fatigue, anxiety and depression. Variable selection was done based on literature research and expert knowledge. Multicollinearity was assessed for the independent variables using generalized variance inflation factors. The final model included age (included either annually or in decades for enhanced interpretability), sex, duration of mechanical ventilation (included either in days or with z-standardized values for enhanced interpretability), preclinical frailty, comorbidities (Elixhauser Comorbidity Index), obesity, diabetes, and ECMO treatment as fixed effects and a random intercept. A random intercept can be interpreted as individual variations of the referring outcome at baseline. Assumptions (normality of residuals, linearity and homogeneity of residual variance) were inspected visually for systematic violations. The adjusted intraclass-correlation coefficient (ICC) (the proportion of explained variance that can be attributed to the random effects) and the conditional R^2 (the proportion of the explained variance of the full model, taking the fixed and random effects into account) were reported for each model. As a sensitivity analysis, models with additional random slopes were investigated. A random slope can be interpreted as individual variation in change of the outcome over time. Likelihood-ratio tests were used to compare models with random intercepts alone and models with additional random slopes. Although including a random slope significantly improved the model over a random intercept model, the conditional R^2 and ICC were > 0.9 and therefore indicated a risk for overfitting. The results of the models with random slopes were included in Supplementary Table 2.

Statistical analyses were performed using R version 4.1.1 and IBM SPSS Statistics 19. The linear mixed-effect models was fitted using the 'lme' function of the 'nlme' package. The ICC and the R^2 were calculated using the 'icc' and the 'r2_nakagawa' function of the 'performance' package. A p-value ≤ 0.05 was considered significant. Missing data was not replaced.

Ethics approval and consent to participate

The study was approved by the medical ethics committee of the Ludwig Maximilian University Munich according to the Declaration of Helsinki (project No. 20-0478). Written informed consent was obtained from all participants (or their legal guardians).

Results

A total of 349 patients were screened between April 2020 and January 2022. 130 were enrolled in the study from June 2020 until January 2022 and 97 were included in this analysis (Fig. 1). The median length of stay on ICU was 52 days (Table 1). Patients were admitted from 33 different ICUs and 52% patients were treated on two or three different ICUs. All patients required prolonged mechanical ventilation (median = 39 days), which led to the definition of CCI. The last telephone interview was conducted on February 1, 2023. Seven patients (7.2%) died over the course of the study. Patients frequently had suffered from sepsis (87.6%), acute respiratory distress syndrome (81.4%) and critical illness polyneuropathy and –myopathy (84.2%).

Table 2 shows the results of the outcomes from visit 1–5 (see Supplementary Table 1 for numbers of available data for every assessment and every time point). The general health state improved over time regarding the overall disability, frailty and dyspnea, as illustrated by the large effect sizes from visit 1–2 (which indicates the positive effect of the neurological rehabilitation) and visit 1–5. However, values for fatigue, anxiety and depression at visits 3–5 were higher than at visit 1 (shortly after discharge from ICU) and their prevalence increased since that

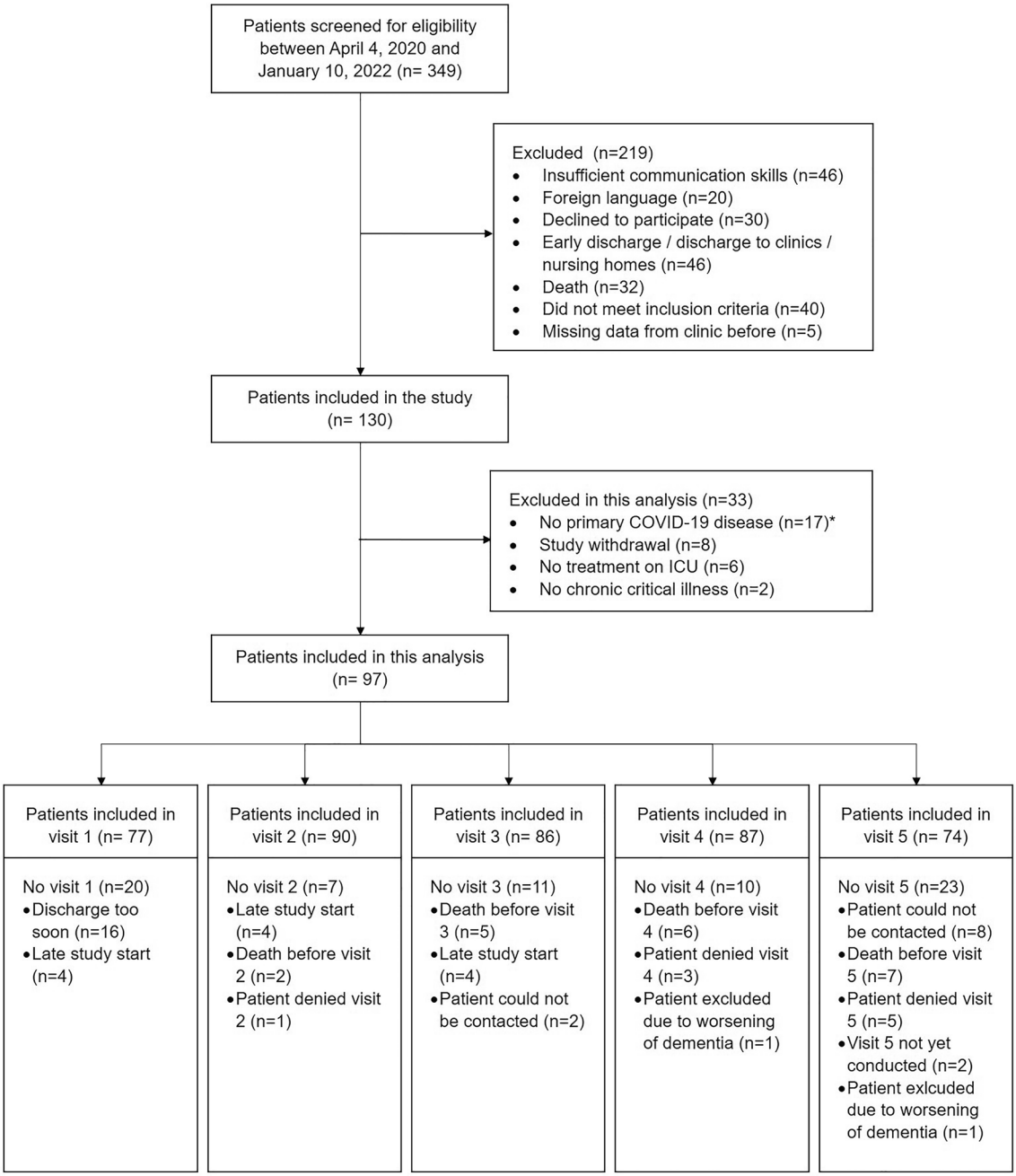

Figure 1. Flow chart. *no primary COVID-19 disease: patients hospitalized due to another neurologic disease who became infected with COVID-19 as a complication during the hospital stay.

time. Health-related quality of life improved since study onset, although the maximum value was found to be at discharge from rehabilitation (index value 0.73 ± 0.20).

The largest changes were found to be between visit 2 (at discharge) and visit 3 (3 months after discharge), especially regarding the prevalence of fatigue, anxiety, and depression. This is also illustrated in Fig. 2, in which the shape of the violin plots clearly changes from visit 2 to visit 3. Corresponding to this symptom deterioration, health-related quality of life decreased significantly from visit 2 to visit 3. Especially the frequency of problems regarding usual activities, anxiety and depression increased within this timeframe (Fig. 3). Overall, this symptom deterioration is also displayed by moderate to large effect sizes (r = 0.32–0.53).

Between visit 3–5, the burden of symptoms stayed mostly unchanged (small effect sizes for most outcomes, except for the Clinical Frailty Scale and modified Rankin Scale). Three months after discharge, the majority of patients suffered from pain or discomfort (83.1%) and faced most problems regarding usual activities (80.5%) and walking around (75.3%). The frequency of problems remained high until visit 5 (Fig. 3). Approximately one third suffered from severe disability, whereas approximately 50% had no or only mild disability according to WHODAS-12 (Fig. 3). Although severity of dyspnea decreased over time, nearly two thirds still had problems with breathing (62.9%, data not shown) at visit 5.

	Total n = 97
Age, years	61.1 ± 12.1, min/max: 29/90
Sex, women	30 (30.9%)
Length of hospitalization, days	110 (77.5–142.5); 117.0 ± 50.2
Length of ICU stay, days	52 (36–71); 55.7 ± 26.5
Length of mechanical ventilation, days	39 (22–54.5); 42.5 ± 24.3
Length of neurological rehabilitation, days	46 (28–68); 52.1 ± 32.9
Chronic critical illness—conditions	
Prolonged acute mechanical ventilation (≥ 96 h)	97 (100.0%)
Tracheotomy	73 (75.3%)
Sepsis	85 (87.6%)
Severe wounds	28 (28.8%)
Stroke	9 (9.3%)
Traumatic brain injury	0 (0.0%)
Complications	
Acute Respiratory Distress Syndrome (ARDS)	79 (81.4%)
Bacterial superinfection	62 (63.9%)
Dysphagia	50 (51.5%)
Acute kidney injury	30 (36.6%)
Delirium	31 (32.0%)
ECMO treatment	23 (23.7%)
Severe encephalopathy	15 (15.5%)
Guillain-Barré-Syndrome	2 (2.1%)
Critical illness polyneuropathy/myopathy	
Electrophysiological measurement conducted	76 (78.4%) (missing n = 21)
Time between infection and measurement, days	89.9 ± 36.4
Critical illness polyneuropathy/myopathy diagnosed	64 (84.2%)
Comorbidities	
Diabetes (all type II)	22 (22.7%)
Obesity	24 (24.7%)
Hypertension	47 (48.5%)
Elixhauser Comorbidity Index	3.1 ± 6.5, min/max: − 7/27
Preclinical status	
Frailty (Clinical Frailty Scale)	2 (1–3)
Disability (modified Rankin Scale)	0 (0–0)
Vaccination status at first SARS-CoV-2 infection	
No COVID-19 vaccination	83 (85.6%)
First COVID-19 vaccination	1 (1.0%)
Two/three COVID-19 vaccinations	6 (6.2%)
Missing	7 (7.2%)
Occupation	
Employed	40 (41.3%)
Self-employed	15 (15.5%)
Retired	34 (35.1%)
Volunteer work	4 (4.1%)
Housewife	2 (2.1%)
Unemployed	2 (2.1%)
Living conditions	
At home alone	20 (20.6%)
At home not alone (e.g., with family)	76 (78.4%)
Sheltered housing	1 (1.0%)
Relationship	
Married/in a relationship	72 (74.2%)
Single/divorced	16 (16.5%)
Widowed	9 (9.3%)
Cigarette smoking (missing n = 3)	
Current smoker	7 (7.5%)
Continued	

	Total n = 97
Former smoker (quit a maximum of 10 years ago)	14 (14.9%)
Alcohol consumption (missing n = 2)	
Never	30 (30.9%)
Once per month	10 (10.3%)
2–4 times per month	20 (20.6%)
2–3 times per week	14 (14.4%)
4 times per week or more	21 (21.6%)
Discharge destination (n = 95; 2 deaths during rehabilitation)	
Further rehabilitation	21 (22.1%)
Home	64 (67.4%)
Home with (mobile) nursing service	5 (5.3%)
Other hospital	3 (3.2%)
Sheltered housing	1 (1.0%)
Nursing home	1 (1.0%)
Days from first positive PCR until…	
V1	86.2 ± 29.9
V2	119.2 ± 47.2
V3	226.2 ± 50.7
V4	309.6 ± 46.8
V5	504.5 ± 57.1
Days between ICU discharge and V1	15 (9–30); 22.8 ± 21.6
Living conditions at V3-V5 (n = 92; 5 deaths before V3)	
At home alone	18 (19.6%)
At home not alone (e.g., with family)	72 (78.2%)
Sheltered housing	1 (1.1%)
Nursing home	1 (1.1%)

Table 1. Characteristics of included patients. Data are n (%), mean ± SD or median (quartile 1–quartile 3). *ICU* intensive care unit, *ECMO* extracorporeal membrane oxygenation, *V1* Study onset after admission to neurorehabilitation, *V2* discharge from neurorehabilitation, *V3* / *V4* / *V5* 3 / 6 / 12 months after discharge from neurorehabilitation.

Correlations of fatigue with depression ($r_s = 0.55$, $p < 0.001$), anxiety ($r_s = 0.60$, $p < 0.001$) and health-related quality of life ($r_s = -0.33$, $p < 0.001$) were fair to moderate.

Results of the linear mixed-effect models are displayed in Table 3. In the final model, time since disease onset (β = 0.09–0.18, $p < 0.01$), mechanical ventilation (β = − 0.06, $p = 0.01$ (z-standardized)) and preclinical frailty (β = − 0.07, $p = 0.02$) were significant predictors for health-related quality of life. Time was also a significant predictor for the outcomes fatigue (β = 1.02–1.18, $p < 0.0001$), anxiety (β = − 1.12–1.20, $p < 0.04$) and depression (β = 1.09–1.50, $p < 0.04$). All model confirmed the significant increase of fatigue, anxiety and depression over time compared to the levels at visit 1. Additionally, a significant association of obesity with anxiety was found (β = − 2.18, $p = 0.02$).

Discussion

We investigated the physical and mental health, and the health-related quality of life of chronically critically ill COVID-19 patients 3, 6 and 12 months after discharge from neurorehabilitation. We showed that the overall disability, frailty and dyspnea improved after admission to neurologic rehabilitation. However, the prevalence of fatigue, anxiety, and depression increased over time, especially between discharge and the first study visit three months later, and remained on a high level until the last study visit one year after discharge. Accordingly, health-related quality of life was shown to be limited without noteworthy improvement until the last study visit. Time (since disease onset) had a significant influence on the outcomes anxiety, depression, fatigue and health-related quality of life.

Post-intensive care syndrome (PICS) and symptom prevalences

Patients after critical illness in general frequently suffer from physical, mental and cognitive symptoms in the long-term, which is described as PICS[7]. As an example, PICS problems were reported to be present in 56% of patients with respiratory failure or shock 12 months after hospital discharge[41]. PICS was also frequently described in patients after severe COVID-19 disease[42] and percentages were similar, as PICS was reported in 61% of patients 13.5 months after ICU discharge[43]. As we did not plan to investigate PICS in our study, no cognitive evaluation was included in the outcome parameters. However, physical function and mental health were investigated by the

	Visit 1 at study onset	Visit 2 at discharge	Visit 3: 3 months after discharge	Visit 4: 6 months after discharge	Visit 5: 12 months after discharge	Friedman-Test V1–V5	Effect size			
							V1–V2	V2–V3	V1–V5	V3–V5
Modified Rankin Scale	4 (3–4)	2 (2–3)	3 (2–3)	2 (1–3)	2 (1–3)	χ^2 (4) = 64.06, p < .001	0.76 ▲	0.07 ▼	0.63 ▲	0.39 ▲
Clinical Frailty Scale	6 (6–7)	5 (4–6)	5 (3–6)	4 (3–5)	4 (3–5)	χ^2 (4) = 115.8, p = < .001	0.85 ▲	0.26 ➤	0.85 ▲	0.57 ▲
Modified Medical Research Council Dyspnea Scale	3 (2–4)	2 (1–2)	1 (0–2)	1 (0–2)	1 (0–2)	χ^2 (4) = 32.39, p < .001	0.84 ▲	0.44 ▲	0.80 ▲	0.12 ➤
FSS-7	2.7 ± 1.5	2.8 ± 1.7	3.8 ± 2.0	3.9 ± 2.0	4.0 ± 1.9	χ^2 (4) = 29.38, p < .001	0.07 ▼	0.47 ▼	0.52 ▼	0.01 ▼
Fatigue ≥ 4	18 (23.7%)	20 (22.5%)	34 (44.7%)	38 (53.5%)	35 (54.7%)					
HADS										
Anxiety	5 (2–8)	4 (1–6)	7 (3–10)	6 (3–9)	7 (3–11)	χ^2 (4) = 10.95, p = .027	0.33 ▲	0.54 ▼	0.14 ▼	0.02 ➤
Anxiety > 7	23 (29.9%)	19 (21.6%)	32 (42.7%)	26 (37.1%)	27 (42.2%)					
Depression	4 (2–8)	3 (1–7)	6 (3–10)	5 (2–9)	6 (3–9)	χ^2 (4) = 12.32, p = .015	0.29 ▲	0.53 ▼	0.26 ▼	0.03 ➤
Depression > 7	20 (26.0%)	14 (15.9%)	32 (42.7%)	20 (28.6%)	25 (39.1%)					
EQ-5D-5L										
Visual analogue scale	51.2 ± 20.2	64.1 ± 18.8	56.0 ± 21.2	60.9 ± 22.1	59.0 ± 23.9	χ^2 (4) = 13.70, p = .008	0. 55 ▲	0. 37 ▼	0. 26 ▲	0. 24 ▲
Index value	0.53 ± 0.29	0.73 ± 0.20	0.63 ± 0.29	0.64 ± 0.30	0.63 ± 0.33	χ^2 (4) = 10.76, p = .029	0.63 ▲	0.32 ▼	0.26 ▲	0.06 ➤
Problems with walking around	74 (96.1%)	65 (74.7%)	58 (75.3%)	46 (63.9%)	42 (67.7%)					
Problems with washing/ dressing	65 (84.4%)	43 (49.4%)	38 (49.4%)	37 (51.4%)	25 (40.3%)					
Problems with usual activity	64 (83.1%)	45 (51.7%)	62 (80.5%)	49 (68.1%)	48 (77.4%)					
Pain or discomfort	62 (80.5%)	71 (81.6%)	64 (83.1%)	64 (88.9%)	52 (83.9%)					
Anxiety or depression	43 (55.8%)	23 (26.4%)	41 (53.2%)	38 (52.8%)	34 (54.8%)					
WHODAS-12 score, %	N/A	N/A	38.1 ± 24.3	33.7 ± 25.0	34.6 ± 23.7	χ^2 (2) = 4.41, p = .110	N/A	N/A	N/A	0.20 ▲

Table 2. Results of the questionnaires over the course of the study. Data are n (%), mean ± SD or median (quartile 1–quartile 3); FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5 l = EuroQol-5 dimensions-5 level; WHODAS-12 = World Health Organization Disability Assessment Schedule 2.0–12 items; The effect size was calculated with $r = z/\sqrt{N}$. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), pp. 79–81. ➤ unchanged ▲ Improvement View Deterioration; Due to missing values, sample size included in the Friedman-test for V1–V5 differs per assessment: modified Rankin Scale n = 56; Clinical Frailty Scale n = 50; Modified Medical Research Council Dyspnea Scale n = 18; FSS-7 n = 38; HADS n = 38; EQ-5D-5L Index n = 43; EQ-5D-5L Visual Analogue Scale n = 37; WHODAS-12 n = 49.

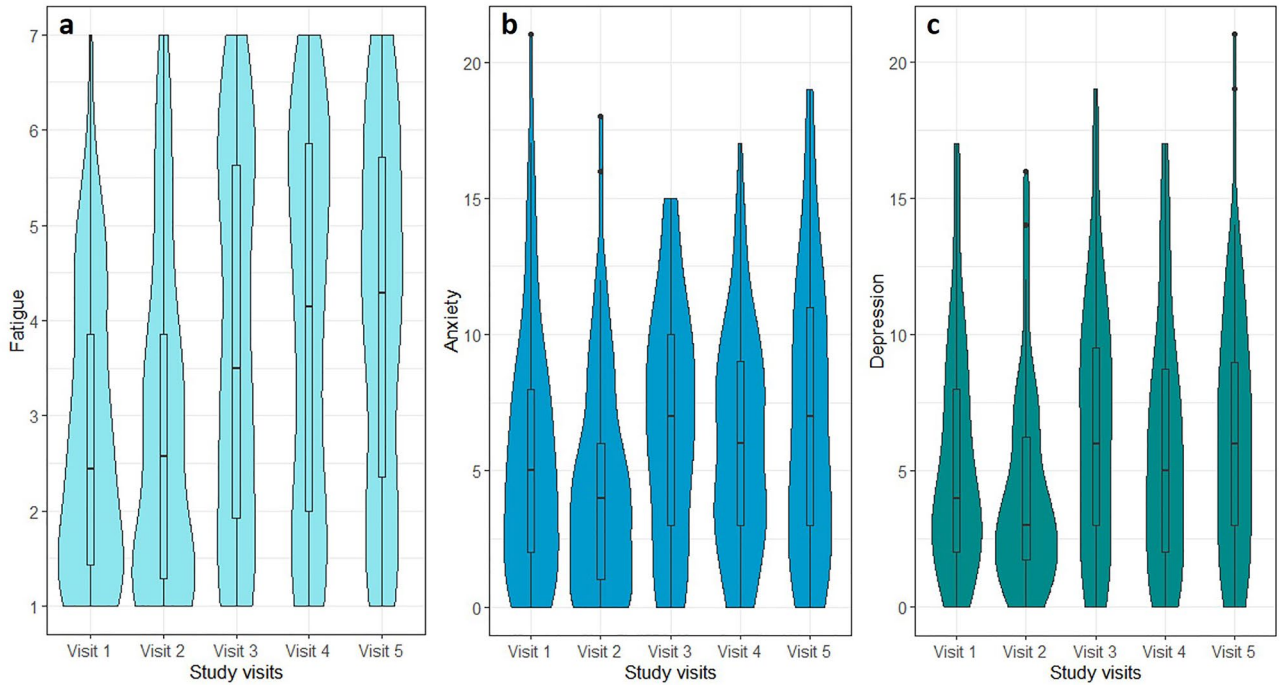

Figure 2. Violin plots including boxplots for comparing probability distributions of fatigue (**a**), anxiety (**b**) and depression (**c**) over the time course of visits 1–5. The remarkable change of data between visits 2 and 3 (i.e. the distribution) is clearly visualized by the plots' change of shape and the increased medians and interquartile ranges within the boxplots.

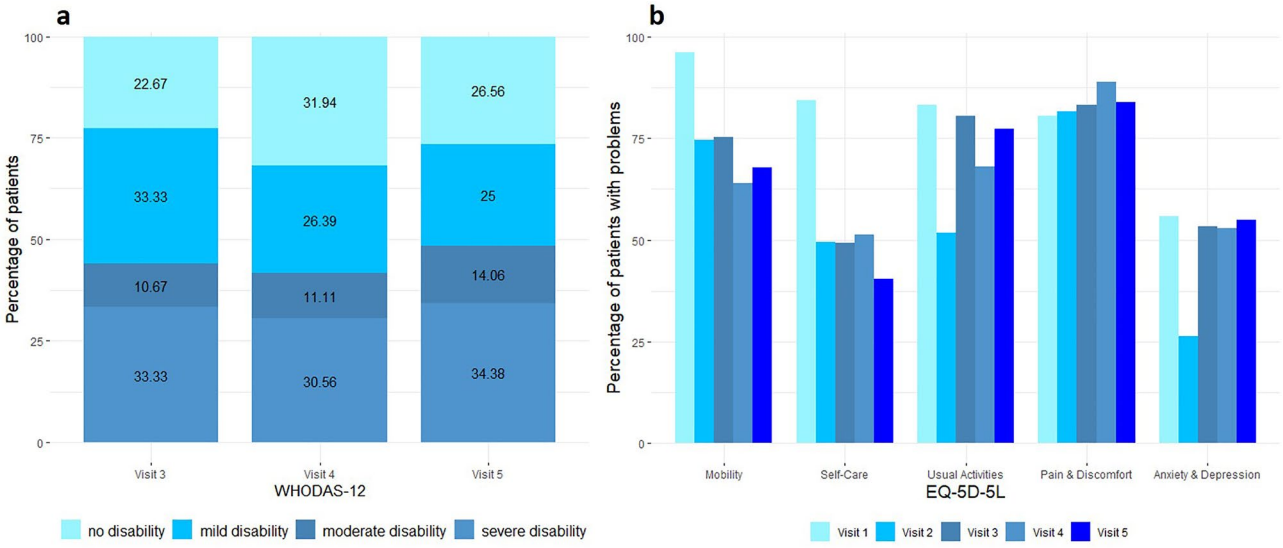

Figure 3. Percentage of patients with different degrees of disability according to WHODAS-12 (**a**) and with problems according to the five domains of the EQ-5D–5L (**b**) over the time course of visits 1–5.

EQ-5D-5L and the HADS, which are both recommended assessments to detect PICS[44]. 12 months after discharge from rehabilitation, anxiety and depression were present in 42% and 39% of patients, respectively. 68% reported problems with walking and even 84% reported pain or discomfort, wherefore we can conclude that the majority of our participants suffered from PICS, even more than one year after the infection.

Previously described long-term outcomes of COVID-19 ICU survivors included a variety of symptoms, which are summarized by the terms post COVID-19 condition (according to the WHO's case definition) or post-COVID-19 syndrome (according to the NICE guideline on long COVID) and often meet the diagnostic criteria for PICS. However, the symptom load of the post COVID-19 condition is substantially higher in our CCI cohort (Supplementary Table 3). Heesakkers et al.[19] reported anxiety and depression in 18% of patients one year after ICU (median 18.5 days on ICU), compared to ~ 40% in our cohort. These authors also reported a median frailty of 2 (vs. 4 in our cohort). Hodgson et al.[14] investigated the outcome of a cohort at 6 months (median 8.3 days

	Health Index		Fatigue		Anxiety		Depression	
	Fix Eff	95% CI	Fix Eff	95% CI	Fix Eff	95% CI	Fix Eff	95% CI
Intercept	**0.83****	0.55–1.11	**3.45*****	1.49–5.42	**8.30*****	3.53–13.08	4.44	− 0.38–9.27
Age								
Age [years]	− 0.00	− 0.00–0.00	− 0.01	− 0.04–0.02	− 0.06	− 0.13–0.01	− 0.01	− 0.09–0.06
Age [decades]	− 0.01	− 0.05–0.03	− 0.12	− 0.40–0.17	− 0.56	− 1.25–0.14	− 0.15	− 0.85–0.55
Sex = male	0.02	− 0.09–0.12	− 0.49	− 1.19–0.21	− 0.70	− 2.41–1.01	0.02	− 1.88–1.57
Mechanical ventilation								
Duration MV [days]	− **0.00***	− 0.00– (− 0.00)	− 0.00	− 0.01–0.01	0.01	− 0.02–0.04	0.01	− 0.02–0.04
Duration MV [z-standardized]	− **0.06***	− 0.10– (− 0.01)	− 0.02	− 0.35–0.31	0.24	− 0.55–1.04	0.25	− 0.55–1.05
Time visit 2 (vs. time visit 1)	**0.18******	0.12–0.25	0.08	− 0.33–0.49	− **1.12***	− 2.01–(− 0.22)	− 0.90	− 1.81–0.02
Time visit 3 (vs. time visit 1)	**0.09****	0.03–0.16	**1.02******	0.59–1.45	**1.20***	0.26–2.13	**1.50****	0.54–2.46
Time visit 4 (vs. time visit 1)	**0.09****	0.02–0.15	**1.15******	0.70–1.59	0.54	− 0.43–1.51	0.72	− 0.28–1.71
Time visit 5 (vs. time visit 1)	**0.10****	0.03–0.16	**1.18******	0.73–1.63	**1.05***	0.06–2.04	**1.09***	0.07–2.10
Comorbidities	0.00	− 0.00–0.01	0.01	− 0.04–0.06	− 0.04	− 0.16–0.07	0.01	− 0.11–0.13
Obesity = yes	0.05	− 0.06–0.16	− 0.28	− 1.03–0.47	− **2.18***	− 4.02–(− 0.33)	− 1.43	− 3.30–0.43
Diabetes = yes	− 0.06	− 0.17–0.05	0.10	− 0.66–0.86	0.25	− 1.60–2.11	0.25	− 1.62–2.13
Preclinical frailty	− **0.07***	− 0.12–(− 0.01)	0.13	− 0.23–0.49	0.50	− 0.39–1.38	0.64	− 0.25–1.53
ECMO = yes	− 0.10	− 0.21–0.01	0.64	− 0.16–1.44	1.04	− 0.91–2.99	1.25	− 0.73–3.22
Adjusted ICC	0.445		0.479		0.551		0.542	
Conditional R^2	0.541		0.544		0.600		0.582	

Table 3. Predictors for health-related quality of life, fatigue and mental health (linear mixed model). Fix Eff = fixed effects; 95% CI = 95% Confidence interval; Duration MV = Duration of mechanical ventilation in days; Comorbidities were measured by the Elixhauser Comorbidity Index; *ECMO* extracorporeal membrane oxygenation; *ICC* intraclass-correlation coefficient; *$p < .05$. **$p < .01$. ***$p < .001$. ****$p < .0001$. For enhanced interpretability, fixed effects were additionally calculated for models with age per decade and z-standardized values for mechanical ventilation instead of age (annually) and mechanical ventilation in days. Significant values are in bold.

on ICU). In this cohort, only 5% suffered from a severe disability according to the WHODAS-12, compared to 31% in our cohort. Accordingly, health-related quality of life was substantially lower in our cohort (visual analogue scale, 61 ± 22), compared to the Hodgson-cohort (median = 70 (IQR 60–85)). These examples illustrate the diverging convalescence of patients, which is most likely due to differences in the length of ICU treatment and mechanical ventilation (median 13–14 days[14,19] compared to 39 days in our cohort).

PICS and an impaired health status were also frequently described in patients after critical illness in general (non-COVID-19 diseases)[7]. Just like in COVID-19 patients, symptom load seems to be associated with the length of stay on ICU or the duration of mechanical ventilation in patients with general critical illness (Supplementary Table 3). In patients after sepsis (median duration on ICU 10 days), 6 months after ICU admission, anxiety and depression were only reported in 26% and 21% (compared to our reports of 37% and 29%).[45] Accordingly, 12 months after ICU, health-related quality of life (expressed by the visual analogue scale of the EQ-5D-5L) was 66 (44–80) in patients with a median of 8 days on ICU[46] and 75 (60–89) in patients with a median of 2 days on ICU[47]. Both values were substantially higher compared to our cohort (59 ± 24). In patients with CCI, the quality of life is more similar to ours (Supplementary Table 3). Thomas et al. reported a value of 60 (IQR 29) in patients after 41 days on ICU[48], Gardner et al. reported a value of 49 ± 7 in patients after 21 days on ICU[5]. According to our results in comparison with the literature it might be assumed that ICU parameters have a greater influence on CCI outcome than the disease leading to ICU admission. However, up to now, studies in patients with CCI examining patient-reported outcomes / PICS and their predictors are scarce.

Health-related quality of life

Health-related quality of life improved after ICU discharge, but then remained rather unchanged at a low level. This level is substantially lower compared to an equally aged general population in Germany (index value 0.87 ± 0.20; our cohort at visit 5 0.63 ± 0.33). This lack of improvement is contrary to published studies, in which improvements in health-related quality of life from 3 to 12 months in critically ill COVID-19 patients were reported[23,49,50]. As the duration of mechanical ventilation was shown to negatively influence health-related quality of life[50], this might be one explanation for the low level reported in our cohort with particularly long durations of mechanical ventilation.

The peak quality of life at discharge from inpatient care in our study might be explained by the patients' improvements of independence in activities of daily living and happiness at finally going home. Additionally, at visit 2, the patients were still in the sheltered environment of the neurorehabilitation center with offers of help, prepared meals and accessible surroundings. The return to home with its responsibilities and being on one's own might have been challenging and therefore might cause a reduction of health-related quality of life. The same might apply for fatigue. Inability to manage activities of daily living without help and being confronted with the prior healthy living conditions might further lead to anxiety and depression.

Fatigue, anxiety and depression

Although COVID-19 ICU survivors usually improve their physical functions over time[49,51], fatigue prevalence may rise, as observed in our cohort. Mazza et al. made the same observation in a cohort of hospitalized COVID-19 patients (~ 8% of ICU admissions), where fatigue increased from 22 to 34% from 1 to 12 months after COVID-19[52]. Likewise, the results of a meta-analysis (68 studies, hospitalized and non-hospitalized patients) indicated no significant improvement of fatigue frequency ≥ 6 months compared to < 6 months after COVID-19 infection[53]. Two studies with non-COVID-19 CCI patients also concluded that time after discharge had no influence on fatigue severity[54,55]. Regarding anxiety and depression after COVID-19, different trajectories were described[56]. Rosa et al. showed a slight increase of symptoms of anxiety (16–25%) and depression (15–20%) from 3 to 12 months[23]. Vlake et al. and Lorent et al. (median ICU stay 13/18 days) reported unimproved severities of anxiety and depression over the course from 1.5 to 6 months and 3–12 months after hospital discharge, respectively[51,57]. In contrast, Gramaglia et al. described a significant reduction of anxiety and depression symptoms from 4 to 12 months after discharge in their less affected cohort (~ 12% ICU admissions)[58]. In a review, several studies were mentioned in which disease severity was a risk factor for anxiety and depression[56], which speaks for the high percentages in our CCI cohort.

Inflammatory processes

Inflammatory parameters are subject of several COVID-19 investigations. One review reported elevations in at least one measure of inflammation in 13 of 14 studies. Additionally, in 9 of 14 studies, proinflammatory markers and persistent fatigue and/or cognitive dysfunction were present[53]. Furthermore, it was reported that chronic fatigue, anxiety and depression of COVID-19 patients share the same pathophysiological mechanisms, which have a strong association with increased oxidative toxicity, lowered antioxidant defenses and inflammatory signs[59]. In addition to COVID-19, persistent inflammation is also one underlying pathophysiology of CCI and PICS[3,4,7]. Furthermore, systemic inflammation is the primary cause of critical illness polyneuropathy and myopathy[60], which was diagnosed in 84% of our CCI patients. Therefore, inflammatory processes might be one explanation for the extraordinarily high percentages of fatigue, anxiety and depression in our cohort of CCI patients after COVID-19.

Limitations

We are aware that our study may have several limitations. First, our study was monocentric and the sample size was rather small; additionally, some patients did not participate in every study visit, so the sample size per assessment and per study visit differs and is reduced. Thus, larger multicenter cohorts with CCI patients are needed to confirm our findings. Second, our patients were largely unvaccinated (as most got infected before vaccination got available). As vaccinations was shown to have protective effect on post-COVID-19 condition[61], symptoms might differ in CCI COVID-19 populations with vaccination. Furthermore, symptoms of anxiety and depression were shown to be more frequent in patients with previous psychiatric history[56], which was not assessed in our study. Additionally, we were not able to include CCI patients with non-COVID-19 diagnoses as a control group, thus we cannot conclude that the reported symptoms are specific for COVID-19.

Conclusions

Persons with CCI associated with COVID-19 suffer greatly from fatigue, anxiety, depression and low health-related quality of life, even one year after discharge from hospital. Improvements were found regarding basic functional capacities and dyspnea. In contrast, fatigue, mental health and health-related quality of life deteriorated over time or remained unchanged at an undesirable level. This analysis showed a higher burden of symptoms compared to other studies with shorter durations of ICU treatment and mechanical ventilation. Therefore, patients with CCI in COVID-19 require adapted therapies and supportive structures even several months after discharge. Special attention should be paid to this group in research and medical treatment.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

ME: Conceptualization, Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. CW: Conceptualization; Investigation; Writing—review & editing. SS: Investigation; Writing—review & editing. JR: Investigation; Writing—review & editing. JB: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Writing—review & editing. FM: Conceptualization; Methodology; Resources; Writing—review & editing. KJ: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing—review & editing. All authors read and approved the submitted version and have agreed to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to M.E.

Supplementary Information

Reduced Health-Related Quality of Life, Fatigue, Anxiety and Depression affect COVID-19 Patients in the Long-Term after Chronic Critical Illness

Marion Egger*, Corinna Wimmer, Sunita Stummer, Judith Reitelbach, Jeannine Bergmann, Friedemann Müller, Klaus Jahn

*Corresponding author:

Marion Egger, M.Sc.
Schoen Clinic Bad Aibling, Department of Neurology, Research Group
Kolbermoorer Strasse 72, 83043 Bad Aibling, Germany
Phone +49 8061 / 903-1954
E-Mail: megger@schoen-klinik.de

Supplementary Table 1 Available number of data for every assessment at every time point

	Visit 1 at study onset	**Visit 2 at discharge**	**Visit 3 3 months after discharge**	**Visit 4 6 months after discharge**	**Visit 5 12 months after discharge**	**Friedman-test V1-V5**
Modified Rankin Scale	77	92	88	91	74	56
Clinical Frailty Scale	77	90	83	84	67	50
Modified Medical Research Council Dyspnea Scale	33	54	61	63	64	18
FSS-7	76	89	76	71	64	38
HADS						
Anxiety	77	88	75	70	65	38
Depression	77	88	75	70	65	38
EQ-5D-5L						
Visual Analogue Scale	77	91	82	72	63	37
Index value	77	91	76	78	69	43
WHODAS-12 Score	N/A	N/A	76	72	66	49

Data are absolute numbers; FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5l = EuroQol – 5 dimensions – 5 level; WHODAS-12 = World Health Organization Disability Assessment Schedule 2.0 – 12 items;

Supplementary Table 2 Predictors for health-related quality of life, fatigue and mental health (linear mixed model including random slopes)

	Health Index		**Fatigue**		**Anxiety**		**Depression**	
	Fix Eff	95% CI	Fix Eff	95% CI	Fix Eff	95% CI	Fix Eff	95% CI
Intercept	**0.77****	0.52-1.02	**3.05****	1.22-4.88	**8.77*****	4.22-13.32	4.11	-0.53-8.75
Age								
Age [years]	0.00	-0.00-0.00	-0.01	-0.04-0.01	-0.06	-0.13-0.00	-0.01	-0.08-0.06
Age [decades]	-0.00	-0.04-0.03	-0.14	-0.40-0.13	-0.65	-1.31-0.01	-0.11	-0.79-0.56
Sex = male	-0.01	-0.10-0.08	-0.19	-0.84-0.47	-0.37	-1.98-1.25	0.02	-1.63-1.68
Mechanical ventilation								
Duration MV [days]	**-0.00****	-0.00-0.00	-0.00	-0.02-0.01	0.02	-0.02-0.05	0.01	-0.02-0.04
Duration MV [z-standardized]	**-0.05****	-0.09-(-0.01)	-0.06	-0.36-0.25	0.39	-0.37-1.15	0.30	-0.47-1.06
Time visit 2	**0.19*****	0.13-0.24	0.11	-0.22-0.44	**-1.11****	-1.88-(-0.33)	**-0.97****	-1.7-(-0.24)
Time visit 3	**0.09***	0.02-0.17	**0.96*****	0.47-1.45	**1.13***	0.09-2.16	**1.36***	0.26-2.47
Time visit 4	**0.09***	0.01-0.16	**1.14*****	0.69-1.60	0.68	-0.37-1.72	0.73	-0.35-1.81
Time visit 5	**0.10***	0.01-0.19	**1.21*****	0.74-1.67	1.08	-0.16-2.33	1.02	-0.19-2.24
Comorbidities	0.00	-0.00-0.01	0.01	-0.03-0.05	0.02	-0.09-0.13	0.00	-0.12-0.11
Obesity = yes	0.05	-0.04-0.15	-0.18	-0.89-0.52	**-2.47****	-4.21-(-0.72)	-1.72	-3.50-0.06
Diabetes = yes	-0.05	-0.15-0.04	0.32	-0.38-1.02	-0.11	-1.87-1.64	0.11	-1.68-1.91
Preclinical frailty	**-0.05***	-0.10-(-0.00)	0.26	-0.08-0.61	0.31	-0.53-1.14	0.68	-0.18-1.54
ECMO = yes	-0.06	-0.16-0.04	0.60	-0.14-1.34	0.65	-1.20-2.51	1.26	-0.62-3.15
Adjusted ICC	0.911		0.907		0.918		0.907	
Conditional R^2	0.923		0.919		0.927		0.916	

Fix Eff = fixed effects;95% CI = 95% Confidence interval; Duration MV = Duration of mechanical ventilation in days; ECMO = extracorporeal membrane oxygenation; ICC= Intraclass-correlation coefficient; *p < .05. **p < .01. ***p < .001. ****p < .0001. For enhanced interpretability, fixed effects were additionally calculated for models with age per decade and z-standardized values for mechanical ventilation instead of age (annually) and mechanical ventilation in days.

Supplementary Table 3 Symptoms after critical illness due to COVID-19 and non-COVID-19

Publication	Evaluation time	Disease	ICU length [days]	MC length [days]	EQ-5D-5L VAS	Anxiety [HADS]	Depression [HADS]	Problems with walking, activities of daily living, pain & discomfort	WHODAS-12 Score %
Egger et al. (current study as comparison)	3,6,12 months after discharge	COVID-19	52 (36-71)	39 (22-55)	3 months: 56.0 ± 21.2 6 months: 61±22 12 months: 59.0±23.9	6 months: 37% 12 months: 42%	6 months: 29% 12 month: 39%	6 months: Problems with walking 64% Problems with ADL 68% Pain / discomfort 89% 12 months: Problems with walking 68% Problems with ADL 78% Pain / discomfort 84%	6 months: 33.7±25.0
COVID-19									
Hodgson et al. 2021[1]	6 months after ICU admission	COVID-19	8.3 (3.6-19)	13 (5-19)	70 (60-85)	20%	20%	Problems with walking 42% Problems with ADL 44% Pain / discomfort 50%	10.4 (2.1–22.9)
Cavalleri et al. 2022[2]	12 months after ICU discharge	COVID-19	8.5 (4.5-20)	13 (8-23)	73 (60-80)				
Heesakkers et al. 2022[3]	12 months after ICU treatment	COVID-19	18.5 (11-32)	14 (8-22)		18%	18%		
Non-COVID-19									
Hodgson et al. 2022[4]	6 months after ICU admission	Sepsis	9.8 (5.7-14.9)	5.5 (2.7-9.6)	66.1±20.7	26%	21%	Problems with walking 47% Problems with ADL 69% Pain / discomfort 53%	26.1±22.1
Gardner et al. 2019[5]	3,6,12 months after sepsis onset	Sepsis	21 (15-39)	Not given	3 months; 52±4.5 6 months: 50±3.9 12 months: 49±6.8				

Griffiths et al. 2013[6]	6 and 12 months after ICU admission	Mainly Pneumonic, septic shock	8 (5-16)	4 (2-11)	6 months: 64 (46-80) 12 months: 66 (44-80)			6 months: Problems with walking 59% Problems with ADL 69% Pain / discomfort 73% 12 months: Problems with walking 55% Problems with ADL 65% Pain / discomfort 69%	
Cavalleri et al. 2022[2]	12 months after ICU discharge	Medical + surgical critical illlness	2 (2-4)	1 (1-2)	75 (60-89)				
Thomas et al. 2018[7]	6 and 12 months after start of neurologic rehabilitation	ICUAW defined by CIP/CIM	41 (IQR 30)	53 (IQR 42)	6 months: 60 (IQR 30) 12 months: 60 (29)				
Myhren et al. 2010[8]	12 months after ICU discharge	Medical, surgical, trauma	12.0 (95% CI 10.3-13.8)	11.0 (95% CI 9.3-12.7)		33%	27%		
Rattray et al. 2005[9]	6 and 12 months after hospital discharge	Gastro-intestinal, respiratory, trauma, vascular & others	5.9 (2.2-13.0)	Not given		6 months: 41% 12 months: 45%	6 months: 26% 12 months: 27%		
Hatch et al. 2018[10]	3 and 12 months after discharge from ICU	Level 3 care on ICU > 24h	3 (2-6)	Not given		46%	40%		

ICU= Intensive care unit; MC=mechanical ventilation; EQ-5D-5l = EuroQol – 5 dimensions – 5 level; IQR = Interquartilerange; CI= Confidence Interval

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5. Paper III

Egger M, Finsterhölzl M, Buetikofer A, Wippenbeck F, Müller F, Jahn K, Bergmann J. Balance function in critical illness survivors and evaluation of psychometric properties of the Mini-BESTest. *Sci Rep*. 2024 May 27; 14(1):12089. doi: 10.1038/s41598-024-61745-5.

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Balance function in critical illness survivors and evaluation of psychometric properties of the Mini-BESTest

Marion Egger[1,2]✉, Melanie Finsterhölzl[1], Alisa Buetikofer[1], Franziska Wippenbeck[1], Friedemann Müller[1], Klaus Jahn[1,3] & Jeannine Bergmann[1,3]

Critical illness survivors commonly face impairments, such as intensive care unit-acquired weakness (ICUAW) which is characterized by muscle weakness and sensory deficits. Despite these symptoms indicating potential balance deficits, systematic investigations and validated assessments are lacking. Therefore, we aimed to assess balance function using the Mini-BESTest, evaluate its psychometric properties, and identify associated variables. Balance was assessed post-ICU discharge (V1) and at discharge from inpatient neurorehabilitation (V2) in patients with ≥ 5 days of invasive ventilation. Mini-BESTest measurement characteristics were evaluated in an ambulatory subgroup. A multiple linear regression was conducted. The prospective cohort study comprised 250 patients (34% female, 62 ± 14 years, median ICU stay 55 days). Median Mini-BESTest scores improved significantly from V1 (5 (IQR 0–15)) to V2 (18.5 (10–23)) with a large effect size. Excellent inter-rater and test–retest reliabilities of the Mini-BESTest were observed (ICC = 0.981/0.950). Validity was demonstrated by a very high correlation with the Berg Balance Scale (ρ = 0.90). No floor or ceiling effects were detected. Muscle strength, cognitive function, cerebral disease, critical illness polyneuropathy/myopathy, and depression were significantly associated with balance. Despite significant improvements during the rehabilitation period, balance disorders were prevalent in critical illness survivors. Ongoing therapy is recommended. Due to its excellent psychometric properties, the Mini-BESTest is suitable for use in critical illness survivors.

Registration: The study was registered at the German Clinical Trials Register (DRKS00021753, date of registration: 2020-09-03).

Keywords Neurological rehabilitation, Postural balance, Psychometric properties, Critical illness, ICUAW, Polyneuropathies

A prolonged stay on intensive care unit (ICU) can lead to various complications, including impairments in physical health, cognitive function, mental health or a combination thereof[1]. These symptoms are referred to as post-intensive care syndrome (PICS) and occur in up to 80% of ICU survivors[2]. Even 1 year after ICU discharge, many patients continue to suffer from multiple symptoms[3]. A common example of physical health impairment after ICU treatment is the occurrence of a general muscle weakness which is termed ICU-acquired weakness (ICUAW). This weakness is mainly caused by dysfunction of muscles and nerves, namely critical illness polyneuropathy (CIP) and/or critical illness myopathy (CIM)[4]. The incidence of ICUAW can reach up to 80% of critically ill patients, whereby risk factors include prolonged duration of intensive care and mechanical ventilation, sepsis, multi-organ failure and immobility[4–6]. Negative outcomes accompany ICUAW, as associations with mortality, prolonged hospitalization, impaired and delayed functional recovery, and decreased health-related quality of life were shown[4,7].

[1]Research Group, Department of Neurology, Schoen Clinic Bad Aibling, Kolbermoorer Str. 72, 83043 Bad Aibling, Germany. [2]Institute for Medical Information Processing, Biometry and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany. [3]German Center for Vertigo and Balance Disorders, University Hospital Grosshadern, Ludwig-Maximilians-Universität München, Munich, Germany. ✉email: megger@schoen-klinik.de

PICS can improve with time and it was recently reported that 70% of critical illness survivors with ICUAW could achieve a successful recovery[2,8]. However, intensive (neurological) rehabilitation is highly recommended to regain a good health status, but high-quality evidence about the effectiveness of rehabilitation programs (especially after ICU discharge) in patients with PICS and ICUAW is lacking[8–10]. However, physical therapy interventions were shown to be feasible, safe, and most often applied in rehabilitation[11,12]. To regain walking ability, patients with ICUAW benefited from physiotherapy interventions such as practicing walking, sit-to-stand training, and balance training[13].

Muscular weakness is associated with decreased balance performance in older adults[14,15]. Furthermore, sensory impairment influences functional balance[16,17]. Since both motor and sensory deficits are frequent in ICUAW, balance impairments are likely present in these patients. As balance training was among the most frequently described interventions in the first two weeks of rehabilitation[13], it is also likely that patients with ICUAW suffer from some kind of balance disorder. However, although there are some indications for impaired balance[11,18,19], up to now there is no investigation of balance functions of critical illness survivors.

Good balance performance is crucial for independence in activities of daily living. Accordingly, leisure and social activities may be restricted by balance impairments. It was shown that community participation was affected in individuals post stroke and multiple sclerosis who displayed balance impairments[20–22]. Furthermore, balance impairments can lead to falls, which in turn increase fear of falling, which all consequently limit independence, participation and even health-related quality of life[23–25]. Hence, it is essential to tackle balance impairments. Alongside balance training, targeting factors linked to balance (such as muscle strength, cognitive function, and mental health[26–28]) may provide an opportunity for enhancing balance. However, neither balance nor associated factors were so far evaluated in ICU survivors.

The Mini-Balance Evaluation System Test (Mini-BESTest) is a balance assessment which was developed in 2010 as a short form of the BESTest[29]. To date, the assessment was mostly evaluated in patients affected by neurological diseases such as Parkinson's disease, stroke, and multiple sclerosis, whereby good reliability, validity, and responsiveness were demonstrated[30,31]. In comparison with the widespread Berg Balance Scale, the superiority of the Mini-BESTest was shown in patients with balance disorders, Parkinson's disease and stroke regarding reliability, ceiling effects and discriminative ability[32–34]. However, up to now, the psychometric properties of the Mini-BESTest have not been evaluated in patients after critical illness.

Although balance impairments seem to be a major aspect in the recovery of patients after critical illness, no investigations about manifestations, the development over time, or associated factors were done in this population. For careful systematic evaluation of balance function, well established and validated clinical assessment tools are needed. However, these are missing so far for individuals after critical illness. Therefore, the aims of this study were: (1) to describe balance function in critical illness survivors during neurorehabilitation, (2) to investigate independent variables associated with balance, and (3) to evaluate the psychometric properties of the Mini-BESTest in critical illness survivors.

Methods

Study population and setting

This analysis is a subanalysis of the single-center, prospective cohort study CINAMOPS (Critical Illness Polyneuropathy and Myopathy: Outcomes, Predictors and Longitudinal Trajectories), which is currently being conducted at the Schoen Clinic Bad Aibling, Germany[35]. The CINAMOPS study aims to gain more knowledge about critical illness survivors in terms of their progress during neurorehabilitation, their long-term outcome (physical, mental and cognitive health), the occurrence of ICUAW or CIP/CIM, predictors for the long-term outcomes, and the current therapy spectrum in neurological rehabilitation. The Schoen Clinic Bad Aibling is a centre for inpatient neurorehabilitation with a focus on critically affected patients (ICU, early neurorehabilitation); all patients with neurological deficits that need rehabilitation can be admitted. Five study visits were planned for every individual participating in the CINAMOPS study: V1 after discharge from ICU, V2 before discharge from neurorehabilitation, V3, V4, and V5 12, 18, and 24 months after disease onset.

All adult patients (≥ 18 years) with neurological deficits who were invasively ventilated on the ICU for at least 5 days were eligible for the CINAMOPS study. Patients were recruited at admission to neurorehabilitation, after discharge from the ICU. Exclusion criteria were (1) palliative care, (2) neuromuscular or neurologic diseases/syndromes causing a high-level of muscular weakness (Guillain-Barré syndrome, mysasthenia gravis, porphyria, Lambert–Eaton syndrome, amyotrophic lateral sclerosis, severe vasculitic neuropathy, cervical myelopathy, botulism; in accordance with[36]), (3) insufficient communicative abilities (German language skills or cognition) interfering with answering the questionnaires, (4) no muscular weakness (i.e. muscle strength according to the Medical Research Council (MRC) scale 5/5). A subgroup of consecutive participants (for whom the date of discharge was scheduled) was included in the evaluation of the psychometric properties of the Mini-BESTest. Exclusion criteria were (1) non-ambulatory patients (as a balance evaluation is not meaningful without any walking capacity) and (2) hemiplegia (as this is not a characteristic symptom in critical illness survivors).

During the study, patients received inpatient neurological rehabilitation (of individual length) with approximately 100 minutes of multi-disciplinary functional therapies per day, including physiotherapy, occupational, dysphagia, physical, neuropsychological and breathing therapies.

Study visits and outcomes

The analysis includes two study visits: study visit 1 (V1) took place after discharge from ICU and therefore after admission to neurorehabilitation, study visit 2 (V2) was conducted shortly before discharge from neurorehabilitation. Generally, patients were discharged from ICU after weaning from mechanical ventilation and if their general condition was stable. Patients were discharged from neurorehabilitation after reaching sufficient

functional improvement or if the patients had not improved over several weeks of rehabilitation. As the study visits were part of the CINAMOPS study, they included a variety of questionnaires and functional assessments.

The Mini-BESTest was the main outcome parameter to evaluate balance function[29]. This test evaluates dynamic balance and includes 14 items in the categories of anticipatory postural adjustments, postural responses, sensory orientation and balance during gait. The score ranges from 0 to 28 points, with higher scores indicating better balance. We used a validated German version of the Mini-BESTest[37].

For a further evaluation of body function and walking ability, additional assessments were conducted. The functional ambulation categories (FAC; score 0–5) were used to classify walking ability[38]. Their good psychometric properties in neurological rehabilitation were shown[39] and the assessment was also used in patients with ICUAW[36]. The Functional Reach test provides information about balance control[40]. The ability to reach forward in a standing position (or sitting if otherwise not possible) was measured in centimetres. Both arms and hands had to be extended. Assistive devices were not allowed. The score has been used before in neurological patients such as stroke[41] and CIP/CIM patients[36]. The Timed Up and Go (TUG) is a well-established outcome measure to assess functional mobility in various populations[42]. The patient is asked to rise from a chair, walk 3 m, turn, walk back, and sit down again. The tester measures the time the patient needs to complete the task. A shorter time indicates better mobility. Good to excellent psychometric properties were shown in different neurological patient groups[43]. Muscle strength was evaluated by manual muscle testing using the scoring system of the Medical Research Council (MRC). The scale ranges from 0 to 5, with 5 indicating normal muscle strength. The following functional muscle groups were evaluated: shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsal flexion[11,44]. Aggregating the MRC from all extremities yields a maximum cumulative score of 60. A sum score of < 48 was used as indicative for ICUAW[6,45,46]. Furthermore, the handgrip strength was measured twice per hand using a digital handheld dynamometer. We reported the maximum value and the normalized value, which was calculated as a percentage of the reference grip strength determined by the patient's sex, age, and height[47].

Patient characteristics and data about the ICU stay were collected retrospectively using the electronic medical record. Comorbidities were described by the Elixhauser Comorbidity Index[48].

To evaluate the psychometric properties of the Mini-BESTest, an additional study visit was scheduled in a subgroup of patients shortly before or after V2 (± 2 days; patients' conditions were assumed to be stable within this time period, as it was at the end of the rehabilitation phase). At this study visit, the Mini-BESTest was repeated by the same rater as at V2 (test–retest-reliability); a second rater observed the performance of the Mini-BESTest and scored the items independently (inter-rater-reliability). To evaluate validity, the FAC, the Functional Reach test, the MRC, and the TUG were used. Furthermore, the Berg Balance Scale was additionally carried out to evaluate validity. The Berg Balance Scale is one of the most widely used assessments to evaluate balance[49]. Its sound psychometric properties and good clinical utility were repeatedly demonstrated in various patient populations[50,51]. Out of 14 items, a score of 0–56 can be reached, with higher values indicating a better balance function. We used a validated German version of the Berg Balance Scale[52]. Floor- and ceiling effects were investigated at V2.

All tests were conducted by experienced physiotherapists trained to use the assessments.

Statistical analysis

Categorical variables are presented as absolute values and percentages, continuous variables as mean ± standard deviation or median (quartile 1–quartile 3).

Description of balance function

Balance function was compared between the two study visits by the Wilcoxon signed rank test on paired samples as data were either non-parametric or did not follow normal distribution (as checked by the Shapiro–Wilk test and visually by means of QQ-plots). Effect sizes were calculated with $r = z/\sqrt{N}$. Chi-squared test and McNemar's test were used for categorical values. Fisher's exact test was applied in cases where more than 20% of cells had expected cell counts less than 5.

Multiple linear regression

We conducted a multiple linear regression analysis in order to capture factors being associated with balance function (dependent variable = Mini-BESTest at V2). Variable selection of the full model was based on previous literature and expert knowledge. Independent variables of the full model included age, MRC muscle sum score at V2, MoCA at V2, obesity, anxiety at V2, depression at V2, handgrip strength at V2 in % of reference, Elixhauser comorbidity scale, somatosensory deficits of the lower extremities at V2, duration of mechanical ventilation, diabetes, and CIP/CIM (yes = CIP, CIM or CIP/CIM; no = no CIP/CIM). Furthermore, the primary diagnoses cerebral disease (ischemic/hemorrhagic stroke; traumatic brain injury; hypoxia) and COVID-19 were included. Somatosensory function was investigated as sensation of light touch (thighs, plantar surfaces), of position sensation of the joints (ankle, knee, hip), and as vibration sensation (dorsum of the caput of os metatarsale I, internal malleolus and the tuberosity of the tibia; deficit if < 4/8 with tuning fork). A sensory deficit was apparent if any of the three categories was pathological. Anxiety and depression were measured by the Hospital Anxiety and Depression Scale[53], cognitive function was measured by the Montreal Cognitive Assessment (MoCA)[54]. Walking ability (FAC) was not chosen as an independent variable as walking is included in several items of the Mini-BESTest and walking and balance are mutually dependent (high correlation of the FAC and the Mini-BESTest ($\rho = 0.82$)).

Variable selection was done according to the recommendations given by Heinze et al.[55]. We conducted a backward elimination with the Akaike information criterion (AIC, significance level 0.157) as the stopping criterion. Stability investigations of the selected model were performed according to Heinze et al.[55]. Bootstrap resampling

with replacement (1000 replicates) was done for the calculation of inclusion frequencies, sampling distributions of regression coefficients, and model selection frequencies. Furthermore, the relative conditional bias (which measures the anticipated level of bias introduced by variable selection when a particular independent variable is chosen) was calculated as suggested in Heinze et al.[55]. Postestimation shrinkage factors were calculated using the R package "shrink"[56]. The goodness of fit of the model was assessed using the adjusted R^2 statistic. The AIC was reported for model comparison. Assumptions for the multiple linear regression (linearity, homoscedasticity, multivariate normality and autocorrelation) were tested graphically for systematic violations in the selected model. For homoscedasticity, the Score Test for Non-Constant Error Variance was additionally computed. Multicollinearity was assessed by calculating variance inflation factors (VIF). The assumption of linear relationship was improved by excluding patients with a Mini-BESTest score of 0. After exclusion of the zero values and cases with missing data, the final dataset for the regression analysis included 169 cases. Accordingly, the events-per-variable (EPV_{global}) was of 169/12 = 14.1.

Psychometric properties of the Mini-BESTest

The evaluation of the psychometric properties was done in accordance with the GRRAS[57] and COSMIN guidelines[58,59]. We aimed to include at least 60 patients in the Mini-BEST evaluation, according to COSMIN's rating of a good sample size[58].

For the inter-rater and the test–retest reliability, the intraclass-correlation-coefficients (ICC) and the corresponding 95% confidence intervals were calculated. For the calculation of the ICC of the inter-rater reliability, the two-way random-effects model with type single and absolute agreement was applied[60]. For the ICC calculation of the test–retest reliability, the two-way mixed-effects model with type single and absolute agreement was applied[60]. The ICC was interpreted according to the recommendation of Koo and Li[60].

To examine the inter-rater and test–retest reliabilities of each individual Mini-BESTest item, the quadratic (according to Fleiss–Cohen[61]) weighted kappa and the corresponding 95% confidence intervals were calculated. We used the more stringent interpretation as suggested by McHugh[62] (0–0.20 no agreement, 0.21–0.39 minimal, 0.40–0.59 weak, 0.60–0.79 moderate, 0.80–0.90 strong and > 0.90 almost perfect agreement).

The minimal detectable change at the 95% confidence interval (MDC_{95}) was computed using the formula $MDC_{95} = 1.96 \times SEM \times \sqrt{2}$[63], whereby the standard error of measurement (SEM) value of the Mini-BESTest total score was calculated according to[64]: $SEM = SD_t \times \sqrt{(1 - ICC_{intrarater})}$.

Concurrent criterion validity was assessed by exploring the correlation between the Mini-BESTest and the Berg Balance Scale. Furthermore, construct validity (i.e. convergent validity) was assessed by exploring the correlation between the Mini-BESTest and the TUG, the Functional Reach test (standing position) and the FAC[65]. We expected high correlations as the assessments measure the same construct (except for the FAC) and as high correlations were shown before[32,64,66]. The Mini-BESTest score was correlated with the named assessments using the Spearman's rank correlation coefficient (ρ), as data were ordinal scaled or did not follow normal distribution (controlled by Shapiro–Wilk test). Munro's recommendations were used to interpret the correlation (no or very low: ρ = 0–0.25; low: ρ = 0.26–0.40; moderate: ρ = 0.41–0.69; high: ρ = 0.70–0.89; very high: ρ = 0.90–1.0)[67].

Floor and ceiling effects were quantified at V2 for the Mini-BESTest (total cohort and balance evaluation group) and the Berg Balance Scale by calculating the percentage of patients with the minimum and maximum total score. A floor or ceiling effect was deemed present when more than 15% of the scores were at the minimum or maximum of the score range[63]. The skewness was calculated for a further investigation of the score distribution of the Mini-BESTest and the Berg Balance Scale.

Statistical analyses were performed using R version 4.3.2. A p-value ≤ 0.05 was considered significant. Missing data was not replaced.

Ethics approval and consent to participate

The study was approved by the medical ethics committee of the Ludwig-Maximilians-Universität in Munich according to the Declaration of Helsinki (Project No. 20-166). Written informed consent was obtained from all participants (or their legal guardians).

Results

Study population

A total of 1064 patients were screened between August 2020 and July 2023. 250 patients were enrolled in the study and study visits (V1 and V2) were conducted between September 2020 and December 2023 (Fig. 1). V1 was completed in 250 patients, V2 in 217 patients. 11 patients (4.4%) deceased before V2. Balance evaluations for the evaluation of the Mini-BESTest were conducted in 68 patients between September 2021 and September 2023. Patients' characteristics are displayed in Table 1. Patients suffered frequently from acute renal failure (53.6%), sepsis (55.2%), delirium (42.4%), and acute respiratory distress syndrome (ARDS; 36.4%). According to the nerve conduction studies (performed in 216 patients), CIP, CIM or their coexistence was observed in 173 (80.1%) patients. ICUAW, as indicated by a MRC sum score < 48, was present in 216 patients (86.7%).

Balance function

Patients' walking and balance capabilities at V1 and V2 are displayed in Table 2. Approximately two weeks after discharge from ICU, about one third of patients was not able to walk (FAC = 0) and 44% required help for walking (FAC 1–3). Accordingly, balance function assessed using the Mini-BESTest was low at V1 (total group: 7.9 ± 8.7; subgroup with FAC > 0: 12.1 ± 8.1). Only about half of the patients were able to conduct the Functional Reach test in a standing position and the TUG. In accordance with the Mini-BESTest, the means of the Functional Reach test, and the TUG were rather low and correlated highly with the Mini-BESTest (see paragraph "Validity").

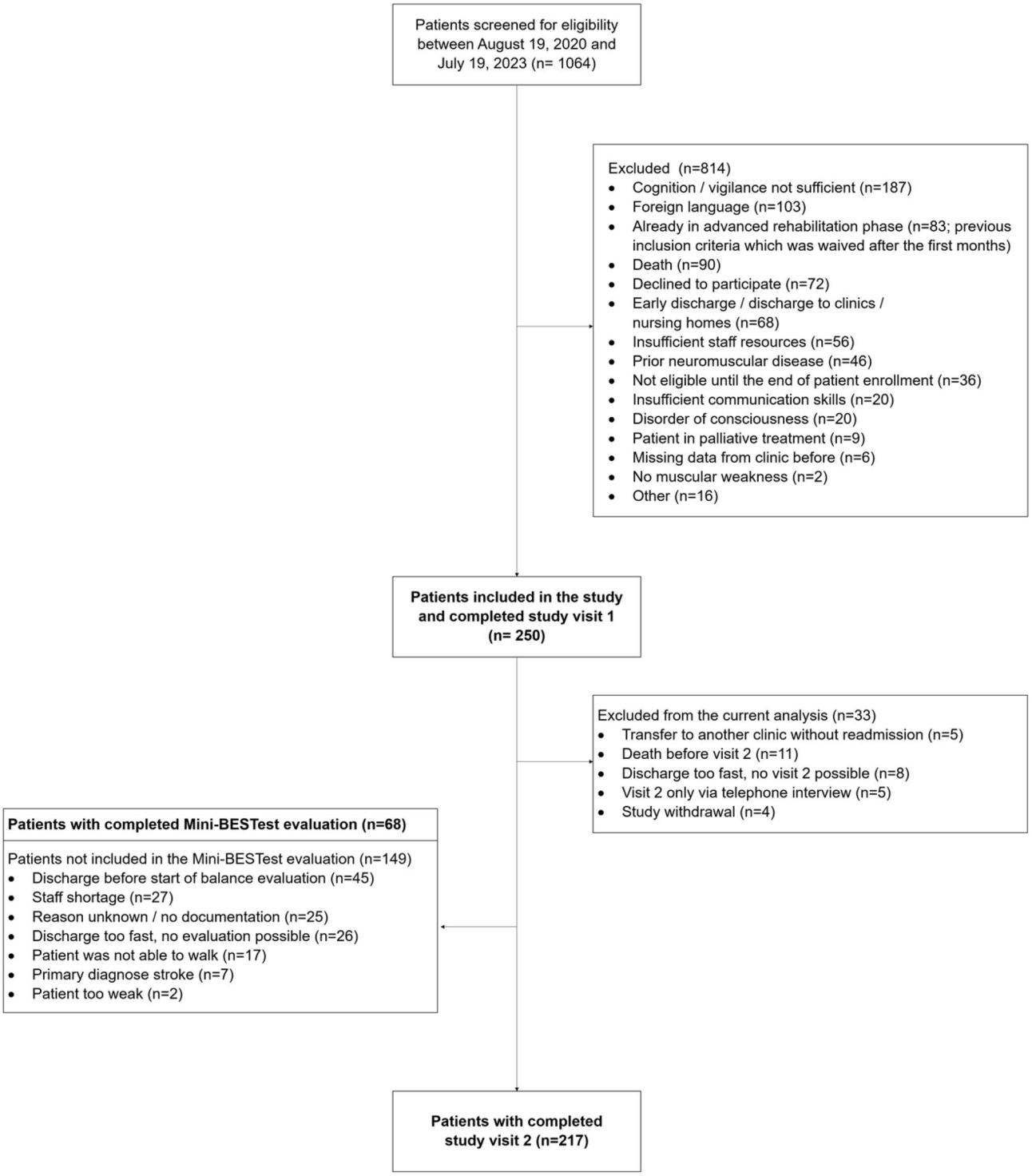

Figure 1. Flow chart.

Balance and walking improved significantly during neurorehabilitation, as shown by large effect sizes in all assessments ($r = 0.547–0.831$). The average Mini-BESTest score doubled to 16.3 ± 8.2 points at V2, which is reflected by a large effect size of 0.819. Nearly 75% of patients were able to walk without any help (FAC 4 and 5) at discharge from rehabilitation. Accordingly, overall muscle strength improved significantly ($p < 0.001$) and the majority of patients was able to do the Functional Reach test in standing position and the TUG and Dual Task TUG.

Multiple linear regression

The diagnostic plots for the model assumptions (Supplementary Fig. 1) revealed slight deviations from the regression assumptions, especially regarding the normality of residuals and homoscedasticity (although the

	Total group (n = 250)	Subgroup for the evaluation of psychometric properties (n = 68)
Age, years	62.4 ± 13.6, min/max: 18/92	64.9 ± 11.6, min/max: 38/88
Sex, women	86 (34.4)	20 (29.4)
Length of hospitalization, days	141 (98–193); 156.4 ± 81.8	145 (106–180); 153.2 ± 70.5
Length of ICU stay, days	55 (39–78); 64.7 ± 40.3	54 (42–73); 62.0 ± 33.3
Length of mechanical ventilation, days	39 (27–58); 45.8 ± 31.1	39 (24–57); 44.8 ± 31.8
Length of neurological rehabilitation at Schoen Clinic Bad Aibling, days	67 (44–100); 82.2 ± 60.2	63 (46–104); 80.8 ± 60.6
Time between		
First hospital admission and V1, days	81 (57–113); 90.8 ± 47.0	84 (57–111); 87.2 ± 35.9
ICU discharge and V1, days	14 (8–23); 20.3 ± 18.4	14 (7–26); 20.0 ± 18.3
V1 and V2, days	52 (29–82); 64.8 ± 50.8	48 (29–76); 59.3 ± 43.2
Primary diagnosis		
COVID-19	67 (26.8)	15 (22.0)
Cardiac disease	46 (18.4)	15 (22.0)
Pulmonary disease	45 (18.0)	15 (22.0)
Gastrointestinal/urological disease	25 (10.0)	8 (11.8)
Bacterial infection	21 (8.4)	5 (7.4)
Cerebral infarction/haemorrhage	20 (8.0)	1 (1.5)
Polytrauma	8 (3.2)	3 (4.4)
Oncological surgery	7 (2.8)	3 (4.4)
Hypoxia	5 (2.0)	2 (2.9)
Other	6 (2.4)	1 (1.5)
Nerve conduction studies[#]		
CIP	42 (19.4)	13 (21.7)
CIM	25 (11.6)	11 (18.3)
CIP/CIM	73 (33.8)	21 (35.0)
CIP but unclear CIM	22 (10.2)	3 (5.0)
No CIP but unclear CIM	11 (5.1)	2 (3.3)
No CIP/CIM	43 (19.9)	10 (16.7)
Comorbidities		
Diabetes (all type II)	47 (18.8)	15 (22.1)
Obesity	60 (24.0)	19 (27.9)
Hypertension	113 (45.2)	35 (51.5)
Elixhauser comorbidity index	4.7 ± 7.0, min/max: − 7/28	4.5 ± 6.8, min/max: − 4/27
Discharge destination*		
Home	171 (71.6)	54 (79.4)
Further rehabilitation	29 (12.1)	6 (8.8)
Home with (mobile) nursing service	18 (7.5)	5 (7.4)
Nursing home	7 (2.9)	2 (2.9)
Outpatient intensive care unit	6 (2.5)	0
Sheltered housing	4 (1.7)	1 (1.5)
Other hospital	4 (1.7)	0

Table 1. Characteristics of included patients. Data are n (%), mean ± SD or median (quartile 1–quartile 3). *ICU* intensive care unit, *CIP* critical illness polyneuropathy, *CIM* critical illness myopathy. *11 patients (4.4%) died before visit 2. [#]Electrophysiological measurement was conducted in 216 persons (86.4%). In the subgroup for the evaluation of psychometric properties, in 60 patients (88.2%) the measurement was conducted. Median time between disease onset and measurement was 91 days (67–127), the average time was 103.0 ± 50.5 days.

statistical test did not confirm heteroscedasticity, p = 0.116). After the backward elimination with AIC as the stopping criterion, a significant model with the independent variables MRC sum score (i.e., muscle strength), CIP/CIM, MoCA (i.e., cognitive function), cerebral disease, depression, duration of mechanical ventilation, anxiety, diabetes, and handgrip strength in % of reference was identified (Table 3). However, only muscle strength, CIP/CIM, cognitive function, cerebral disease and depression were significantly associated with balance ($p < 0.032$). The adjusted R^2 for the full model was 29.5%, for the selected model 31.1%. Regarding the bootstrapping results, MRC sum score, CIP/CIM, MoCA, cerebral disease, and depression were most often selected as displayed by bootstrap inclusion frequencies > 70%. In contrast, inclusion frequencies were rather low for diabetes (50%) and even lower for grip strength (45%). Accordingly, the bootstrap median for diabetes and grip strength were 0 and therefore the model suggested by bootstrap medians differed from the selected model. Bootstrap resampling

	Admission (V1)	Discharge (V2)	Test statistic	Effect size
Mini-BESTest				
Anticipatory				
1. Sit to stand	1 (0–1)	2 (1–2)		
2. Rise to toes	0 (0–1)	1 (1–2)		
3. Stand on one leg	0 (0–1)	1 (1–1)		
Reactive postural control				
4. Compensatory stepping correction—forward	0 (0–2)	2 (0–2)		
5. Compensatory stepping correction—backward	0 (0–1)	1 (0–2)		
6. Compensatory stepping correction—lateral	0 (0–1)	1 (0–1)		
Sensory orientation				
7. Stance (feet together), eyes open, firm surface	1 (0–2)	2 (2–2)		
8. Stance (feet together), eyes closed, foam surface	0 (0–1)	1 (1–2)		
9. Incline—eyes closed	0 (0–2)	2 (1–2)		
Dynamic gait				
10. Change in gait speed	0 (0–1)	2 (1–2)		
11. Walk with head turns—horizontal	0 (0–1)	1 (1–2)		
12. Walk with pivot turns	0 (0–1)	1 (0–2)		
13. Step over obstacles	0 (0–0)	1 (0–2)		
14. Timed up and go with dual task	0 (0–1)	1 (0–1)		
Mini-BESTest total score	5 (0–15); 7.9 ± 8.7	18.5 (10–23); 16.3 ± 8.3	$Z = -11.52$, $p < 0.001$	0.819
Functional ambulation categories (FAC)				
FAC total	2 (0–3)	4 (3–5)	$Z = -11.64$, $p < 0.001$	0.831
FAC 0: patient cannot walk	87 (34.8)	19 (8.6)		
FAC 1: patient requires physical assistance with continuous contacts	18 (7.2)	1 (0.5)		
FAC 2: patient requires physical assistance with intermittent light contact	24 (9.6)	5 (2.2)		
FAC 3: patient requires verbal supervision or stand-by help without physical contact	68 (27.2)	34 (15.3)		
FAC 4: patient can walk independently on level ground but requires help on stairs, slopes, or uneven surfaces	46 (18.4)	83 (37.4)		
FAC 5: patient can walk independently anywhere	7 (2.8)	80 (36.0)		
Functional Reach test [cm]				
Sitting position (V1 n = 115; V2 n = 29)	14.2 ± 14.0	23.2 ± 17.0	$Z = -3.15$, $p = 0.002$	0.626
Standing position (V1 n = 232; V2 n = 211)*	10.6 ± 12.5	20.6 ± 11.4	$Z = -10.39$, $p < 0.001$	0.751
Timed up and go (TUG) [s]				
Normal TUG (V1: n = 130, V2: 184)	15.3 (11.2–28.8) 20.3 ± 12.2	11.9 (9.0–20.2) 16.2 ± 11.4	$Z = -8.25$, $p < 0.001$	0.796
Dual task TUG (V1: n = 114, V2: 178)	18.6 (13.4–28.5) 21.7 ± 11.5	13.9 (10.9–24.3) 19.1 ± 16.4	$Z = -7.12$, $p < 0.001$	0.725
Muscle strength				
Muscle strength sum score (MRC)	39.1 ± 7.9	44.6 ± 7.2	$Z = -10.96$, $p < 0.001$	0.760
Intensive care unit-acquired weakness (MRC sum score < 48)	216 (86.7)	141 (65.6)	McNemar's $\chi^2(1) = 68.55$, $p < 0.001$	0.245#
Maximum handgrip strength in kg	15.5 ± 7.5	20.5 ± 7.6	$Z = -11.20$, $p < 0.001$	0.766
Maximum handgrip strength in % of reference	0.39 ± 0.18	0.52 ± 0.16	$Z = -11.22$, $p < 0.001$	0.767

Table 2. Balance function and further assessments at admission to and at discharge from neurorehabilitation. Data are n (%), mean ± SD or median (quartile 1-quartile 3). *n = 115 (V1)/n = 29 (V2) were only able to perform the Functional Reach test in sitting position, they were therefore assigned 0 cm in the standing position. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), p.79–81. # Effect size for McNemar's test was calculated with the non-directional Cohen's g and is interpreted as small (0.05 to < 0.15), medium (0.15 to <0.25), and large (≥0.25) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), p.147-149.

revealed the model's instability, as it was chosen in merely 1.3% of the resamples (see Supplementary Table 1 for model frequencies). Model selection frequencies support the inclusion of the MRC sum score, CIP/CIM, MoCA, and cerebral disease, as they were always included in the ten most often selected models. In contrast, duration of mechanical ventilation, anxiety, and grip strength were only chosen in five of the ten most often selected models, which adds to the uncertainty of these variables. Accordingly, the relative conditional bias was rather high for

	Global model			Selected model			Bootstrap inclusion frequency (%)	Relative conditional bias (%)	Bootstrap median	Bootstrap 95% CI
	Beta coefficient	95% CI	p-value	Beta coefficient	95% CI	p-value				
(Intercept)	−5.69	−18.67; 7.28	0.386	−7.13	−17.34; 3.09	0.170	100	1.05	−6.03	−18.58; 8.47
MRC Sum Score at V2	**0.51**	**0.32; 0.69**	**<0.001**	**0.55**	**0.38; 0.71**	**<0.001**	100	0.39	0.51	0.31; 0.71
Nerve/muscle function										
No dysfunction										
CIP/CIM	**−2.74**	**−5.13; −0.35**	**0.025**	**−3.05**	**−5.31; −0.79**	**0.008**	83.5	10.37	−2.68	−4.92; 0
MoCA at V2	**0.31**	**0.05; 0.58**	**0.020**	**0.30**	**0.06; 0.54**	**0.015**	82.6	7.25	0.29	0; 0.56
Cerebral disease	**−3.63**	**−6.75; −0.52**	**0.022**	**−3.48**	**−6.36; −0.61**	**0.018**	82.5	13.46	−3.57	−6.92; 0
Depression at V2	−0.35	−0.71; 0.01	0.056	**−0.38**	**−0.72; −0.03**	**0.032**	74.8	25.55	−0.35	−0.75; 0
Duration of mechanical ventilation [days]	−0.02	−0.05; 0.01	0.167	−0.02	−0.05; 0.01	0.131	54.1	49.13	−0.02	−0.05; 0
Anxiety at V2	0.21	−0.12; 0.54	0.209	0.24	−0.08; 0.55	0.136	53.1	70.40	0.21	0; 0.61
Diabetes										
No diabetes	*Reference*									
Diabetes	−1.44	−3.99; 1.10	0.264	−1.74	−4.14; 0.66	0.153	50.1	82.96	0	−4.42; 0
Handgrip strength % of reference	−0.04	−0.12; 0.03	0.233	−0.06	−0.12; 0.01	0.091	44.8	68.92	0	−0.12; 0
Somatosensory function										
No impairment	*Reference*									
Somatosensory deficits	−0.96	−3.04; 1.13	0.365				39.1	118.17	0	−3.39; 0
Body weight status										
No obesity	*Reference*									
Obesity	−0.81	−3.26; 1.64	0.514				32.3	131.60	0	−3.24; 1.58
Age [years]	0.00	−0.08; 0.08	0.997				26.8	14,814.57	0	−0.10; 0.08
Elixhauser comorbidity index	−0.04	−0.20; 0.11	0.582				26.5	143.13	0	−0.18; 0.10
COVID-19 disease	−0.33	−2.62; 1.96	0.775				21.4	148.03	0	−2.5; 1.98
R^2	0.334			0.347						
Adjusted R^2	0.295			0.311						
Residual std. error	5.96 (df = 154)			5.90 (df = 159)						
F-statistic	6.02 (df = 14; 154); p < 0.001			9.41 (df = 9; 159); p < 0.001						
AIC	1099.3			1091.0						

Table 3. Multiple linear regression analysis for the global and selected model and chosen bootstrap results. *AIC* Akaike information criterion, *95% CI* 95% confidence interval, *MRC* Medical Research Council, *MoCA* Montreal Cognitive Assessment, *V2* Visit 2 at discharge from rehabilitation, *CIP/CIM* Critical Illness Polyneuropathy/Myopathy. The bootstrap median is zero in case a variable was chosen in < 50% of the resamples. Significant values are in bold.

these variables (49–70%), just like for duration of mechanical ventilation (83%). The global shrinkage factor for the selected model was 0.861. The parameterwise shrinkage factors are displayed in Supplementary Table 2.

In summary, according to the model stability investigations, the associations between balance and muscle strength ($\beta = 0.55$, shrunken $\beta = 0.52$, $p < 0.001$), CIP/CIM ($\beta = -3.05$, shrunken $\beta = -2.07$, $p = 0.008$), cognitive function ($\beta = 0.30$, shrunken $\beta = 0.29$, $p = 0.015$), cerebral disease ($\beta = -3.48$, shrunken $\beta = -2.29$, $p = 0.018$), and depression ($\beta = -0.38$, shrunken $\beta = -0.13$, $p = 0.032$) in patients after critical illness can be considered as confirmed. The associations between balance and duration of mechanical ventilation, anxiety, diabetes, and handgrip strength are less certain as indicated by low bootstrap inclusion frequencies, conflicting model selection frequencies, and low parameterwise shrinkage factors.

Evaluation of the psychometric properties of the Mini-BESTest

The subgroup of patients for the Mini-BESTest evaluation was similar to the total population in all parameters ($p > 0.134$; Table 1, Supplementary Table 3). 39 patients (57.4%) had an MRC sum score < 48 and therefore exhibited an ICUAW. As three patients refused to repeat the Mini-BESTest on the second day, test–retest reliability could only be calculated for 65 patients. The average time between the two Mini-BESTest measurements was 1.8 ± 1.4 days. The mean Mini-BESTest score of the investigator was 18.2 ± 6.0, of the observer 18.3 ± 5.9 and of the retest was 18.1 ± 6.0. The mean score of the Berg Balance Scale was 46.1 ± 11.2.

Reliability
Inter-rater reliability of the Mini-BESTest total score was found to be excellent with ICC = 0.981 (95% CI 0.969–0.988), yielding an MDC_{95} value of 2.3 points with SEM = 0.87. Likewise, an excellent ICC for the test–retest reliability was found (ICC = 0.950 (95% CI 0.920–0.970), yielding an MDC_{95} value of 3.7 points with SEM = 1.34. The inter-rater reliability for the single items (Table 4) was strong or almost perfect for all items except item 11 (walk with head turns; 0.74 (95% CI 0.56–0.91)). The test–retest reliability for the single items was slightly inferior, as there were some items with only moderate agreement (items 4, 5, 6, 8; kappa 0.70–0.72); items 11 (walk with head turns) and 14 (dual task) showed only weak agreement (kappa 0.59 and 0.52).

Validity
Convergent validity was demonstrated, as the correlations between the Mini-BESTest and the Berg-Balance-Scale ($\rho = 0.90$), the TUG ($\rho = -0.86$), the FAC ($\rho = 0.82$), and the Functional Reach test ($\rho = 0.73$) were high to very high and significant ($p < 0.001$).

Floor and ceiling effects
At V2, 212 Mini-BESTest measurements were conducted. 17 patients (8.0%) had a total Mini-BESTest score of 0, 3 patients (1.4%) scored the maximum of 28. The skewness was − 0.61. Therefore, no floor- and ceiling effects were apparent for the Mini-BESTest at discharge from rehabilitation.

Regarding the subgroup of patients for the evaluation of psychometric properties of the Mini-BESTest, no patient scored 0 on the Mini-BESTest or the Berg Balance Scale, therefore no floor effects were apparent. No patient had the maximum Mini-BESTest score (i.e., 28 points), but 10 patients had the Berg Balance Scale maximum value of 56 points (14.7%). Therefore, a trend for a ceiling effect for the Berg Balance Scale was apparent. Accordingly, the skewness of the Mini-BESTest in the subgroup was substantially lower than for the Berg Balance Scale (− 0.55 vs. − 1.71). Score distributions of the Mini-BESTest and the Berg-Balance-Scale are shown in Fig. 2.

Discussion

Summary of results

In this study, we aimed to describe balance function in patients after critical illness, investigate variables associated with balance and evaluate the psychometric properties of the Mini-BESTest in this group of patients. The analysis showed that the majority of the ICU survivors exhibited CIP/CIM and/or ICUAW and balance function and walking ability were highly impacted. After admission to neurorehabilitation, 35% of patients were not able to walk at all (FAC = 0) and the median Mini-BESTest score was only 5 of the maximum 28 points. Accordingly, muscle strength was substantially reduced. During neurorehabilitation, patients considerably improved balance function and walking ability. However, balance was still impaired at discharge in many participants and the median Mini-BESTest was only 18.5 of 28 points. According to the multiple linear regression, muscle strength, cognitive function, the presence of CIP/CIM, cerebral disease, and depression were associated with balance function. According to the evaluation of the psychometric properties, the Mini-BESTest was shown to be a reliable and valid tool in patients after critical illness and no floor or ceiling effects were detected.

Mini-BESTest scores and cutoff values in other populations

Balance was rarely measured in patients after critical illness or with ICUAW before. In a population with chronic stroke patients (median stroke duration 2.9 years; mean age 57 ± 11 years), a Mini-BESTest score of 19.0 (IQR 14.0–22.0) was recorded[64]. In a sub-acute stroke population (mean stroke duration 124.4 ± 106.5 days; mean age

	Inter-rater reliability	Test–retest reliability
Item 01—Sit to stand	0.97 (0.91–1)	0.90 (0.80–1)
Item 02—Rise to toes	0.90 (0.83–0.98)	0.82 (0.72–0.92)
Item 03—Stand on one leg	0.93 (0.84–1)	0.89 (0.77–1)
Item 04—Compensatory stepping correction—forward	0.91 (0.83–0.99)	0.72 (0.55–0.90)
Item 05—Compensatory stepping correction—backward	0.94 (0.88–0.99)	0.70 (0.56–0.85)
Item 06—Compensatory stepping correction—lateral	0.92 (0.84–0.99)	0.72 (0.59–0.85)
Item 07—Stance (feet together), eyes open, firm surface	1 (1–1)	1 (1–1)
Item 08—Stance (feet together), eyes closed, foam surface	0.87 (0.75–0.98)	0.71 (0.54–0.88)
Item 09—Incline, eyes closed	0.91 (0.83–1)	0.73 (0.58–0.88)
Item 10—Change in gait speed	0.90 (0.81–0.99)	0.88 (0.79–0.98)
Item 11—Walk with head turns—horizontal	0.74 (0.56–0.91)	0.59 (0.43–0.76)
Item 12—Walk with pivot turns	0.82 (0.72–0.92)	0.84 (0.75–0.93)
Item 13—Step over obstacles	0.90 (0.84–0.96)	0.81 (0.71–0.92)
Item 14—Timed up and go with dual task	0.93 (0.87–0.99)	0.52 (0.32–0.72)

Table 4. Inter-rater and test–retest reliability for the individual items of the Mini-BESTest. Reliability values are measured with quadratic weighted kappa and are displayed with their 95% confidence intervals.

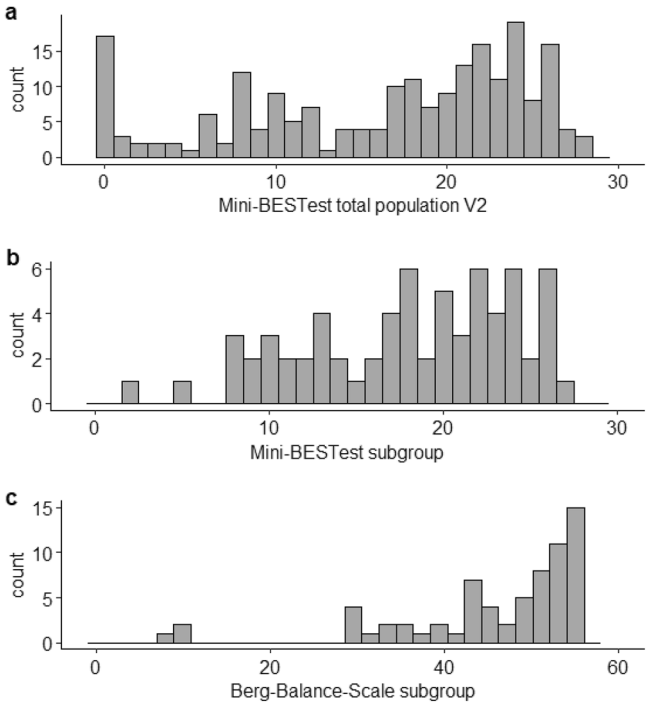

Figure 2. Count of total scores of the Mini-BESTest for the total population being investigated at discharge from neurorehabilitation (V2; n = 212; Figure **a**) and for the Mini-BESTest (**b**) and the Berg Balance Scale (**c**) in the subgroup of patients for the Mini-BESTest evaluation (n = 68).

61 ± 9 years) admitted to an outpatient stroke rehabilitation, a mean score of 18.2 ± 6.5 points was reached[68]. In a study including individuals with Parkinson's disease (66 ± 11 years, mostly Hoehn and Yahr stages II and III), a mean score of 18.8 ± 6.7 was reported[69]. In comparison, healthy subjects (70 ± 6 years; 60 ± 9 years) reached on average 25.3 ± 2.2 points and a median of 27 (IQR 27–28) points in the Mini-BESTest[64,70]. Based on these literature findings, balance function of ICU survivors upon discharge from rehabilitation (~ 150 days after disease onset) is comparable to that of individuals with chronic and sub-acute stroke and with Parkinson's Disease at stages II and III, but noticeably differs from the balance function of healthy subjects of the same age group.

Cut-off values of the Mini-BESTest score were previously established to describe manifestation of balance deficits and to distinguish fallers and non-fallers in patients with Parkinson's disease, stroke and peripheral neuropathy as well as in community-dwelling adults[33,69,71–74]. Having a cut-off for the detection of limited balance function or for fall prediction would also be of high relevance for patients after critical illness; however, this was not the subject of the current study and requires future investigation.

Factors associated with balance

We found that muscle strength, cognitive function, the presence of CIP/CIM, the primary diagnosis cerebral disease, and depression were the key factors associated with balance. This is partly in line with previous study results, as higher muscle strength was also reported as an independent predictor for enhanced balance function in patients with chronic stroke[26] and in older hip fracture patients after motor rehabilitation[75]. However, no such association was found in healthy individuals[76]. Cognitive function was also reported as an independent predictor for balance in patients with Parkinson's disease[27] and older hip fracture patients[75]. The influence of CIP/CIM on balance has not been assessed before. Patients with stroke and other cerebral diseases frequently suffer from impaired postural control and balance disorders[77–80]. Furthermore, depression was included in the selected model and the results of a review strengthen the association between depression and impaired balance[81].

Handgrip strength was also included in the selected model with a p-value very near to the significance level. However, stability investigations indicated uncertainty about its true influence. In the literature, weaker handgrip strength was repeatedly shown to correlate with worse dynamic postural balance, e.g. in older adults and people under long-term care facilities[82–84]. Duration of mechanical ventilation was also included in the selected model; however, there was no significant p-value and stability investigations led to uncertainty regarding its association with balance. The influence of the duration of ventilation on balance had not been evaluated before. However, a longer duration of mechanical ventilation was frequently reported as risk factor for muscle weakness and CIP/CIM[46,85,86], therefore an association is comprehensible. Diabetes was also included in the selected model, however stability investigations led to uncertainty regarding its association with balance. In contrast, previous studies supported the association between diabetes and balance impairments[87,88]. Anxiety was also included in the selected model, albeit without statistical significance and with indications of uncertainty resulting from the stability investigations. However, the influence of anxiety on postural control was frequently demonstrated, even

on a neurobiological basis[89–91]. In light of the minor deviations from the regression assumptions, they might have also introduced some uncertainty into the interpretation of our results.

Reliability and validity in comparison with previous literature

As this is the first investigation of the psychometric properties of the Mini-BESTest in patients after critical illness, no direct comparison within the same patient group is possible. However, our results align with previous investigations involving other patient groups. We found excellent values for inter-rater reliability (ICC = 0.98), which was also found in patients with balance disorders due to stroke, Parkinson's disease and other neurological diseases (ICC = 0.86–0.99)[30]. The same applies for the test–retest reliability, where our results (ICC = 0.95) are in line with those previously reported (ICC = 0.92–0.98)[30]. For the inter-rater reliability of the single items, we received better kappa values than reported in a group of persons with chronic stroke[64]. Furthermore, in this study, values for intra-rater reliability of the single items were calculated, which can be compared to our test–retest values. They explored only fair reliability for items 5, 8, and 13, whereas we found limited reliability for items 11 and 14. The learning effect might not be causal, as the same number of participants had worse and improved values respectively on the second day of evaluation. As scheduling of the two evaluations varied (morning/afternoon after full day of therapies), this might have potentially influenced the patients' performance and therefore also the reliability values. An MDC of 3.0[64] and 3.5[32] was found in patients with chronic stroke and mixed neurological diseases, which is comparable to our reported MDC of 3.7. Furthermore, validity of the Mini-BEST was confirmed and previously reported correlations with the Berg Balance Scale ($r/\rho = 0.79–0.94$)[30], the TUG ($r/\rho = 0.66–0.89$)[30] and the Functional Reach test ($\rho = 0.55$)[64] were similar to those in our study. Neither floor nor ceiling effects were apparent in any of the previously investigated patient groups, which is in line with our results[30]. In conclusion, the Mini-BESTest appears well-suited to measuring balance in patients after critical illness.

Clinical and scientific implications

This analysis provides evidence for the existence of balance impairments in individuals after critical illness. It was shown that a majority of patients exhibited a lack of balance control after discharge from the ICU. Accordingly, walking ability and muscle strength were substantially impaired. During neurorehabilitation, balance function (as well as walking and muscle strength) improved significantly with large effect sizes. However, due to the study design, it is uncertain to which extent the observed effects can be attributed to the rehabilitation interventions. Average balance function was still reduced at discharge from rehabilitation and the Mini-BESTest scores were comparable to individuals after stroke or with Parkinson's disease[64,68,69]. Consequently, intensive neurorehabilitation is highly indicated for patients after discharge from ICU, especially for patients with proven CIP/CIM and cerebral diseases, and ongoing (physio-) therapy even beyond discharge from rehabilitation is recommended. As muscle strength, cognitive function, and depression were found to be significantly associated with balance, these factors should be addressed in rehabilitation therapies.

No valid clinical tool was so far available for measuring balance in patients after critical illness. According to its excellent psychometric properties, the Mini-BESTest is suitable for clinical practice and research. Regarding the almost present ceiling effect of the Berg Balance Scale at V2, the Mini-BESTest seems superior for measuring balance in patients after critical illness. Follow-up studies are required to further investigate the long-term development of balance function.

Limitations

Conditions for the evaluation of test–retest reliability varied in some patients. Due to the full therapy schedule, balance tests were sometimes conducted at different points in the day, e.g., in extreme cases, one test was conducted in the morning whereas the retest was conducted on another day in the evening, when the patient was possibly exhausted after the rehabilitation therapies. However, this was only the case in the minority of balance evaluations and the test–retest reliability was still found to be excellent. Nevertheless, it should be acknowledged that exhaustion could influence balance function which should be considered in future studies examining ICU survivors.

Responsiveness and the minimal clinically import difference are important psychometric properties which we did not investigate in this study. Although the change in the Mini-BESTest score over the rehabilitation period was comparable to the improvements in the FAC, Functional Reach test and TUG according to the effect sizes, a comparison with the Berg Balance Scale for the responsiveness would have been more accurate and needs to be done in future studies. This also applies for the cutoff values as mentioned before.

The generalizability of our results might be limited, as our participants had extremely long durations of ICU treatment and mechanical ventilation compared to the previous studies describing the outcome of ICU survivors and patients with ICUAW[92–95]. Additionally, 26% of our cohort were participants suffering from COVID-19.

Conclusions

Balance disorders were frequent in individuals after discharge from the ICU as well as after several weeks of neurorehabilitation. However, large effect sizes were found for the improvement of balance function over the period of rehabilitation, which suggests a potential positive effect of the therapies. Muscle strength, cognitive function, CIP/CIM, cerebral disease, and depression were significantly associated with balance function. The Mini-BESTest was shown to be a reliable and valid tool for assessing balance in individuals after critical illness and therefore seems well-suited for clinical practice and research. As balance disorders were still substantial at discharge from rehabilitation and comparable to patients with stroke and Parkinson's disease, further follow-up investigations and therapies are required in this patient group.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

ME: Conceptualization, Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. MF: Investigation; Validation; Writing—review & editing AB: Investigation; Writing—review & editing. FW: Investigation; Validation; Writing—review & editing. FM: Conceptualization; Methodology; Resources; Validation; Writing—review & editing. KJ: Conceptualization; Funding acquisition; Methodology; Project administration; Resources; Supervision; Validation; Writing—review & editing. JB: Conceptualization; Funding acquisition; Methodology; Project administration; Supervision; Validation; Writing—review & editing. All authors read and approved the final manuscript.

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Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to M.E.

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Supplementary material

Balance Function in Critical Illness Survivors and Evaluation of Psychometric Properties of the Mini-BESTest

Authors: Marion Egger, Melanie Finsterhölzl, Alisa Buetikofer, Franziska Wippenbeck, Friedemann Müller, Klaus Jahn, Jeannine Bergmann

Corresponding author:

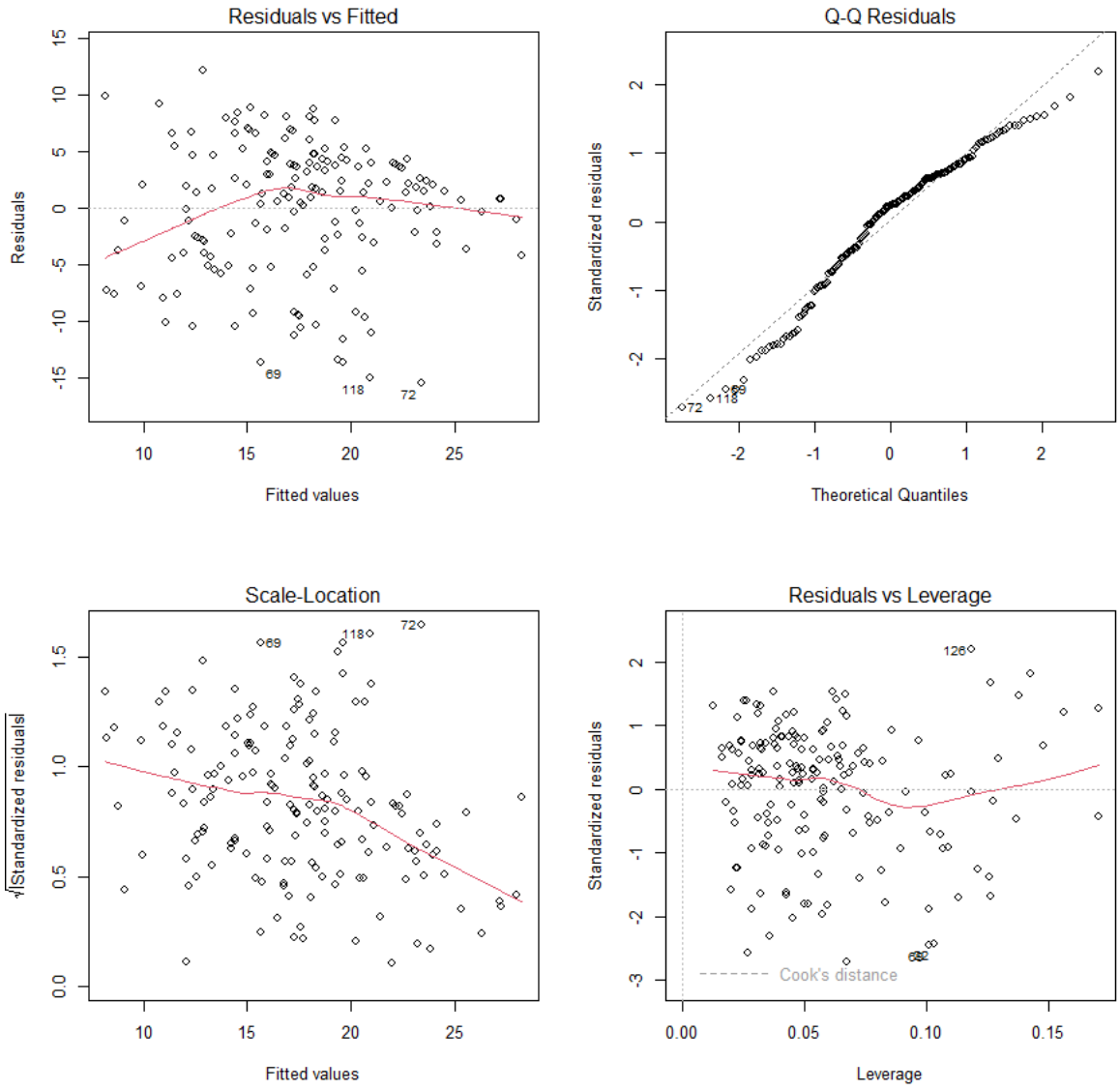
Marion Egger, MSc

Mail: megger@schoen-klinik.de

Affiliations:

- Research Group, Department of Neurology, Schoen Clinic Bad Aibling, Bad Aibling, Germany
- Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany

Supplementary Fig. 1 Diagnostic plot for model assumptions of the selected model



Supplementary Table 1 Model selection frequencies

Model	Included predictors	Count	Percent	Cumulative Percent
1	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 gripstrength	14	1.4	1.4
2	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 diabetes gripstrength	13	1.3	2.7
3	mrcv2 cipcim mocav2 brain depressionv2 anxietyv2 diabetes	12	1.2	3.9
4	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 diabetes	10	1	4.9
5	mrcv2 cipcim mocav2 brain depressionv2 diabetes	8	0.8	5.7
6	mrcv2 cipcim mocav2 brain depressionv2 anxietyv2	7	0.7	6.4
7	mrcv2 cipcim mocav2 brain diabetes	6	0.6	7
8	mrcv2 cipcim mocav2 brain ventilation gripstrength	6	0.6	7.6
9	mrcv2 cipcim mocav2 brain depressionv2 diabetes gripstrength	6	0.6	8.2
10	mrcv2 cipcim mocav2 brain ventilation diabetes gripstrength	6	0.6	8.8
11	mrcv2 cipcim mocav2 brain depressionv2 ventilation diabetes gripstrength	6	0.6	9.4
12	mrcv2 cipcim brain depressionv2 anxietyv2 diabetes gripstrength	6	0.6	10
13	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 gripstrength sensorydeficit	6	0.6	10.6
14	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 diabetes gripstrength	6	0.6	11.2
15	mrcv2 cipcim mocav2 brain depressionv2 ventilation gripstrength	5	0.5	11.7
16	mrcv2 cipcim mocav2 depressionv2 anxietyv2 diabetes gripstrength	5	0.5	12.2
17	mrcv2 cipcim mocav2 brain depressionv2 anxietyv2 diabetes gripstrength	5	0.5	12.7
18	mrcv2 cipcim mocav2 brain depressionv2 anxietyv2 sensorydeficit	5	0.5	13.2
19	mrcv2 cipcim mocav2 brain depressionv2 anxietyv2 diabetes sensorydeficit	5	0.5	13.7
20	mrcv2 cipcim mocav2 brain depressionv2 ventilation anxietyv2 diabetes sensorydeficit	5	0.5	14.2

Supplementary Table 2 Parameterwise shrinkage factors

	Parameterwise shrinkage factors	Selected model β-coefficients	Shrunken β-coefficients
MRC sum score	0.95	0.55	0.52
CIP/CIM	0.89	-3.05	-2.07
MoCA	0.96	0.30	0.29
Cerebral disease	0.66	-3.48	-2.29
Depression*	0.34	-0.38	-0.13
Duration of mechanical ventilation	0.59	-0.02	-0.01
Anxiety*	0.34	0.24	0.08
Diabetes	0.58	-1.74	-1.02
Handgrip strength	0.48	-0.06	-0.03

*As the parameterwise shrinkage factor for anxiety was -0.05 and correlated moderately (0.57) with the parameterwise shrinkage factor of depression (0.42), a joint shrinkage factor for anxiety and depression was calculated and numbered 0.34.

Supplementary Table 3 Characteristics of included patients and comparison of the subgroup

	Group without participants of balance evaluation (n=182)	Psychometric properties n=68	p-value
Age, years	61.4±14.1, min/max: 18/92	64.9±11.6, min/max: 38/88	0.134
Sex, women	66 (36.3)	20 (29.4)	0.387
Length of hospitalization, days	138 (97-197); 157.6±85.7	145 (106-180); 153.2±70.5	0.834
Length of ICU stay, days	55 (38-66); 65.6±42.7	54 (42-73); 62.0±33.3	0.853
Length of mechanical ventilation, days	39 (28-57); 45.9±30.9	39 (24-57); 44.8±31.8	0.722
Length of neurological rehabilitation at Schoen Clinic Bad Aibling, days	67 (42-100); 82.1±60.5	63 (46-104); 80.8±60.6	0.936
Time between…			
first hospital admission and V1	78 (58-113); 92.3±50.4	84 (57-111); 87.2±35.9	0.806
ICU discharge and V1	15 (8-23); 20.6±18.5	14 (7-26); 20.0±18.3	0.342
V1 and V2	54 (30-86); 67.4±53.8	48 (29-76); 59.3±43.2	0.297
Primary diagnosis			0.371
COVID-19	52 (20.8)	15 (22.0)	
Cardiac disease	31 (12.4)	15 (22.0)	
Pulmonary disease	30 (12.0)	15 (22.0)	
Gastrointestinal / urological disease	17 (6.8)	8 (11.8)	
Bacterial infection	16 (6.4)	5 (7.4)	
Cerebral infarction / haemorrhage	19 (7.6)	1 (1.5)	
Polytrauma	5 (2.0)	3 (4.4)	
Oncological surgery	4 (1.6)	3 (4.4)	
Hypoxia	3 (1.2)	2 (2.9)	
Other	5 (2.0)	1 (1.5)	
Nerve conduction studies[#]			0.247
CIP	29 (18.6)	13 (21.7)	
CIM	14 (9.0)	11 (18.3)	
CIP/CIM	52 (33.3)	21 (35.0)	
CIP but unclear CIM	19 (12.2)	3 (5.0)	
No CIP but unclear CIM	9 (5.8)	2 (3.3)	
No CIP/CIM	33 (18.1)	10 (16.7)	
Comorbidities			
Diabetes (all type II)	32 (17.6)	15 (22.1)	0.533
Obesity	41 (22.5)	19 (27.9)	0.468
Hypertension	78 (42.9)	35 (51.5)	0.282
Elixhauser Comorbidity Index	4.8±7.1, min/max: -7/28	4.5±6.8, min/max: -4/27	0.778

Data are n (%), mean ± SD or median (quartile 1-quartile 3)

ICU=intensive care unit, CIP=Critical Illness Polyneuropathy, CIM=Critical Illness Myopathy; [#] Electrophysiological measurement was conducted in 156 of 182 persons (85.7%). In the subgroup for the evaluation of psychometric properties, in 60 patients (88.2%) the measurement was conducted. 11 patients (4.4%) of the whole 250 patients died before visit 2. P-values were calculated with the Mann-Whitney-U test except for sex, comorbidities, and nerve conduction studies which were calculated with the Chi-squared test and the primary diagnosis, which was calculated with the Fisher´s Exact test.

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Appendix A: Paper IV

Bergmann J, **Egger M**, Müller F, Jahn K. Outcome, predictors and longitudinal trajectories of subjects with critical illness polyneuropathy and myopathy (CINAMOPS): study protocol of an observational cohort study in a clinical and post-clinical setting. *BMJ Open* 2024;14:e083553. doi:10.1136/ bmjopen-2023-083553.

BMJ Open

Outcome, predictors and longitudinal trajectories of subjects with critical illness polyneuropathy and myopathy (CINAMOPS): study protocol of an observational cohort study in a clinical and post-clinical setting

Jeannine Bergmann ,[1,2] Marion Egger,[1,3] Friedemann Müller,[1,2] Klaus Jahn[1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Jeannine Bergmann; jbergmann@schoen-klinik.de

ABSTRACT

Introduction Critical illness polyneuropathy and myopathy (CIP/CIM) are frequent complications in the intensive care unit (ICU) with major consequences for the progress and outcome of subjects. CIP/CIM delays the weaning process, prolongs the hospital stay and increases the mortality rate. Additionally, it may have long-term consequences beyond the hospitalisation phase with prolonged disability. Even though there is growing interest in CIP/CIM, research about the clinical and post-clinical course as well as the middle-term and long-term outcomes of subjects with CIP/CIM is scarce. A large prospective study of critically ill subjects is needed with accurate diagnosis during the acute stage and comprehensive assessment during long-term follow-up.

Methods and analysis This prospective observational cohort study aims to compare the clinical and post-clinical course of chronically critically ill subjects with and without the diagnosis of CIP/CIM and to determine predictors for the middle-term and long-term outcomes of subjects with CIP/CIM. In addition, the influence of the preclinical health status and the preclinical frailty on the long-term outcome of subjects with CIP/CIM will be investigated.

This single-centre study will include 250 critically ill patients who were invasively ventilated for at least 5 days at the ICU and show reduced motor strength. At five study visits at admission and discharge to neurological rehabilitation, and 12, 18 and 24 months after disease onset, a comprehensive test battery will be applied including assessments of functioning and impairment, independence, health-related quality of life, activity and participation, cognition, gait and balance, fatigue, mental health and frailty.

Secondary objectives are the documentation of therapy goals, therapy content and achieved milestones during the rehabilitation, to evaluate the clinimetric properties of the Mini-BESTest in critically ill patients, and to evaluate the time course and outcome of subjects with CIP/CIM after SARS-CoV-2 infection.

Ethics and dissemination The study was approved by the ethical committee of the Ludwig-Maximilians University Munich. Participants will be included in the study after having signed informed consent.

Results will be published in scientific, peer-reviewed journals and at national and international conferences.

Trial registration number German Clinical Trial Register (DRKS00021753).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The CINAMOPS Study is a prospective observational cohort study to investigate the clinical and post-clinical course in subjects with critical illness polyneuropathy and myopathy (CIP/CIM) compared with critically ill patients without CIP/CIM.
⇒ Various parameters such as physical function, impairment, independence, quality of life, activity and participation will be longitudinally assessed.
⇒ Factors associated with the middle-term and long-term outcomes of patients with CIP/CIM will be determined, and the influence of preclinical health status and preclinical frailty will be assessed.
⇒ Major strengths of the study are the large number of patient-reported, validated outcome parameters and the in-person study visit in the long follow-up period.
⇒ There is a risk of limited participant recruitment and retention during the long follow-up period.

INTRODUCTION

Background and rationale

Advances in treatment approaches have led to an increase in survival rates for critically ill patients who need intensive care. However, long-term disability after critical illness is common and is described as post-intensive care syndrome (PICS). Therefore, patients suffer from new or worsening of impairments in physical, cognitive or mental health status arising after critical illness and persisting beyond acute care hospitalisation.[1]

Intensive care unit (ICU)-acquired muscle weakness (ICUAW) is a major complication

in the ICU among critically ill patients and is characterised by diffuse, symmetric weakness involving the limbs and respiratory muscles.[2] The most common causes of ICUAW are critical illness polyneuropathy (CIP) and myopathy (CIM) or the frequent combination of both.[3] CIP is primarily an axonal sensorimotor polyneuropathy that affects the innervation of respiratory muscles and of muscles at the extremities. In less severe cases, muscle weakness is pronounced distally.[4] CIM is a primary myopathy that manifests mainly in proximal respiratory and extremity muscles.[4 5] The underlying pathophysiological process of CIP/CIM is not yet fully understood. A systemic inflammation that results in a dysfunction of the microcirculation seems to be a main cause.[3]

The incidence rate of CIP and/or CIM varies between 25% and 83% depending on the subpopulation, the risk factors and the diagnostic criteria.[6 7] Very high incidences are observed in subjects with sepsis, systemic inflammatory response syndrome and multiple organ failure. These disorders are also the main risk factors for developing CIP/CIM.

For the diagnosis, the Medical Research Council sum score (MRC-SS) or handgrip dynamometry is typically used in combination with electrophysiological tests of peripheral nerves and muscles.[8] So far, different neurophysiological approaches have been proposed.[4 9 10] However, they are often difficult to implement in the clinical setting and a standardised diagnostic gold standard is missing.

CIP/CIM has important consequences on the progress and outcome of critically ill subjects. It prolongs the need for ventilator dependency and delays the weaning process in patients during ICU stay. It is further associated with prolonged hospital and ICU stays and increased mortality rates.[2 6 11] Recent studies revealed that CIP/CIM may also have long-term consequences beyond the hospitalisation phase with prolonged severe disability. As such, limb and diaphragm weakness caused by CIP/CIM can persist for month or years after resolution of critical illness.[4 12] Recovery after CIP/CIM is characterised by progressive reinnervation of muscle and, in CIP, restoration of sensory function. This can occur within weeks in mild cases but may take months in more severe cases. In the latter, recovery may be incomplete or not even occur at all.[6] Therefore, physical function seems not only restricted by persisting muscle weakness, but other factors such as proprioception, gait and balance, spatial attention, cognitive function, mental health and pain seem to play a role.[2] It was further shown that survivors of critical illness often experience decreased health-related quality of life, pain, fatigue and financial burden due to delayed return to work.[13] Furthermore, family members of critical illness survivors might be affected by secondary disabilities like mental impairments.[14]

Treatment of CIP/CIM so far mainly focuses on prevention of risk factors during the ICU stay and supportive treatment. ICU treatment includes the management of sepsis and multiple organ failure, the control of hyperglycaemia, the minimisation of sedation and early rehabilitation.[4] Few small studies showed that physiotherapeutic interventions are feasible and safe and that an additional multimodal therapy programme results in more successful weaning and more frequent discharge at home.[15 16] There is preliminary evidence that intensive neurorehabilitation after ICU discharge could improve functional recovery and independence. Further, early rehabilitation at the ICU appears to decrease the likelihood of developing ICUAW, improves the functional capacity and increases the number of ventilator-free days.[17 18]

Even though there is growing interest in CIP/CIM, current insight into the clinical and post-clinical course as well as the middle-term and long-term outcomes of subjects with CIP/CIM is very limited. In addition, knowledge about the influence of the preclinical health status would be of great value to improve the prognosis and planning of the rehabilitation process.[19] Moreover, clearly defined outcome measures with validated assessments are scarce in CIP/CIM thus far.[20] Therefore, a large prospective study of critically ill subjects is needed with accurate diagnosis during the acute stage and comprehensive assessment during long-term follow-up.[4 19 21 22] This prospective observational cohort study aims to compare the clinical and post-clinical course of critically ill subjects with and without the diagnosis of CIP/CIM and to determine predictors for the middle-term and long-term outcomes of subjects with CIP/CIM.

Objectives

The primary objectives of this study are:

1. To describe the clinical and post-clinical time course of subjects with CIP/CIM compared with subjects after critical illness but without diagnosed CIP/CIM.
2. To evaluate potential predictors for the middle-term and long-term outcomes in the field of functioning and impairment and health-related quality of life of critically ill subjects with and without CIP/CIM.
3. To determine the influence of the preclinical health status and the preclinical frailty on the rehabilitation of critically ill subjects with and without CIP/CIM.

Secondary objectives are:

4. To investigate therapy goals, therapy content and achieved milestones during rehabilitation.
5. To determine the clinimetric properties of the Mini-BESTest in subjects with critical illness survivors.
6. To evaluate the clinical time course and outcome of subjects with ICUAW after SARS-CoV-2 infection.

METHODS AND ANALYSIS

Study setting and design

The CINAMOPS Study is designed as a prospective observational cohort single-centre trial to assess different parameters about functional independence, quality of life, activity and participation, cognition, and walking and balance abilities up to 2 years after the onset of critical

illness. In addition, status of health services, living and employment situation in the post-clinical setting will be determined.

The study is performed at the Schoen Clinic Bad Aibling. The Schoen Clinic Bad Aibling is one of the largest neurorehabilitation centres in Germany. The patients' recruitment started in January 2021. Data collection will end in June 2025 with the last patient completing the 24-month follow-up. All participants receive inpatient neurological rehabilitation (as needed) with approximately 100 min of multidisciplinary functional therapies per day, including physiotherapy, occupational, dysphagia and breathing therapies, as well as neuropsychology.

Participants and recruitment

All subjects who have survived to ICU discharge will be assessed for inclusion in the CINAMOPS Study. Subjects are eligible for the study if they were invasively ventilated in the ICU for at least 5 days and are ≥18 years old. Exclusion criteria are palliative treatment, neuromuscular or neurological diseases and/or syndromes leading to a high grade of muscular weakness (eg, Guillain-Barré syndrome, myasthenia gravis, amyotrophic lateral sclerosis, cervical myelopathy, porphyria, Lambert-Eaton syndrome, severe vasculitic neuropathy, botulism); insufficient communicative ability (knowledge of the German language, cognition), which makes the execution of the assessments impossible (additionally no relative or legal guardian available as compensation); and full motor strength (MRC 5/5, no paresis). As patients with acquired brain injury can also exhibit CIP/CIM,[23] these patients will also be included in the study.

Trained study members will coordinate identification of subjects eligible for the study and introduce the study to subjects. Subjects will also receive an information sheet and are then able to have an informed discussion with the principal investigator. Subjects willing to participate will be asked to sign the informed consent form. All subjects or a representative must provide written informed consent before the start of the study procedures.

Patient and public involvement

The final assessment battery was pretested in subjects with CIP/CIM at the Schoen Clinic Bad Aibling before starting the actual data collection. Time to complete the assessments and any problems in filling out the questionnaires and performing the assessments were documented. Patients were asked about the burden of the assessments. Individual reports are created at the end of the individual study period if desired by the participant. In addition, a newsletter will be created in plain language to inform the participants about the study results. Study results will also be disseminated in the news section of the homepage of the Schoen Clinic and in the intranet of the clinic.

Outcomes

Primary outcome measures

Table 1 gives an overview of the outcome parameters and the schedule of collection. The repeated collection of validated assessments and questionnaires over a period of 24 months after disease onset will allow investigation of longitudinal changes in independence and participation, functioning and impairment, and health-related quality of life. Disease onset refers to the time when the primary pathology led to ICU or hospital admission. Data collection will be done by trained personnel via interviews with the participants, physiological testing and data extraction from the medical records. Study visits are expected to take between 30 and 120 min.

Data about the stay in the ICU will be collected retrospectively using the electronic medical record and include the following parameters: length of stay in the ICU, duration of invasive ventilation, sepsis, primary disease (type and duration), secondary diagnoses, age at disease onset, therapies, duration of rehabilitation and the Elixhauser Comorbidity Index.[24] Data about the preclinical status are collected through an interview with the participant and involve the following outcomes: Functional Ambulation Categories (FAC), Clinical Frailty Scale, Barthel Index, consumption of alcohol and tobacco, Lawton Instrumental Activities of Daily Living, International Physical Activity Questionnaire-short version (IPAQ), living conditions, relationship status, employment, diabetes, and preclinical physical or cognitive disabilities.

Secondary outcome measures

For the evaluation of the therapeutic applications, therapy goals, therapy contents, therapy methods as well as achieved milestones will be documented every 2 weeks for all medical and therapeutic disciplines (physiotherapy, occupational therapy, neuropsychology, swallowing and speech therapy, physical therapy, respiratory therapy). The information is mainly extracted from the medical records or in case of incomplete documentation or questions, the therapists are addressed. In addition, medical complications or special medical interventions will be documented. As there is a lack of rehabilitation approaches for patients with CIP/CIM, we will examine potential differences in rehabilitation in patients with and without CIP/CIM.

For the evaluation of the clinimetric properties of the Mini-BESTest, the schedule at visit 2 is slightly adapted in a subgroup of 60 participants after critical illness. In these subjects, the Mini-BESTest will be assessed a second time shortly before or after visit 2 (test–retest reliability). This assessment will be observed and rated by a second, independent examiner in order to determine the inter-rater reliability. In addition, the Berg Balance Scale will be assessed for validity testing.

Several patients critically affected after SARS-CoV-2 infection suffer from ICUAW. These patients are also included in the study and will be analysed in a subanalysis. The clinical course and the middle-term and

Table 1 Protocol schedule of forms and procedures

		0	T1	T2	T3	T4	T5
Activity/assessment	**Prestudy screening**	**Enrolment**	**Study visit 1 (admission)**	**Study visit 2 (discharge)**	**Study visit 3 (12 months after disease onset*)**	**Study visit 4 (18 months after disease onset*)**	**Study visit 5 (24 months after disease onset*)**
Screening log	x						
Consent form		x					
Electrophysiological testing		x					
Data about stay in ICU			x				
Preclinical status			x				
Barthel Index[35]			x	x	x	x	x
Modified Rankin Scale[36 37]			x	x	x	x	x
Medical devices			x	x	x	x	x
Living and working situation					x	x	x
Household					x	x	x
Medical and therapeutic care					x	x	x
Swallowing impairments			x	x			
Modified Medical Research Council Dyspnoea Scale[38 39]			x	x	x	x	x
Fatigue Severity Scale (7-item version)[40 41]			x	x	x	x	x
EuroQol 5-dimensions-5 levels questionnaire[42 43]			x	x	x	x	x
Hospital Anxiety and Depression Scale[44]			x	x	x	x	x
Pain (Visual Analogue Scale)[45]			x	x	x	x	x
Clinical Frailty Scale[46–48]			x	x	x	x	x
Montreal Cognitive Assessment[49]			x	x		x	
Questionnaire for Experiences of Attention Deficit					x	x	x
WHO Disability Assessment Schedule-short version[50 51]					x	x	x
Impact of Event Scale-6[52 53]					x	x	x
Reintegration to Normal Living Index[54 55]					x	x	x
Lawton Instrumental Activities of Daily Living[56]					x	x	x
International Physical Activity Questionnaire-short version[57]					x	x	x
Mini-BESTest[58]			x	x		x	
Functional Status Score for ICU[59 60]			x	x		x	
Five-times Sit-to-Stand Test[61 62]			x	x		x	
Functional Reach[63]			x	x		x	
Box and Block Test[64]			x	x		x	
Grip strength (digital dynamometer)[65 66]			x	x		x	
Medical Research Council Scale[67 68] sum score			x	x		x	
Functional Ambulation Categories[69 70]			x	x	x	x	x
2-Minute Walk Test[71]						x	
Sensibility (type, intensity, location; sensory subtest Fugl-Meyer Assessment,[72] vibratory sensation[73 74])			x	x		x	
Documentation of therapy			X———	———X			

*Disease onset refers to the time when the primary pathology led to ICU or hospital admission.
ICU, intensive care unit.

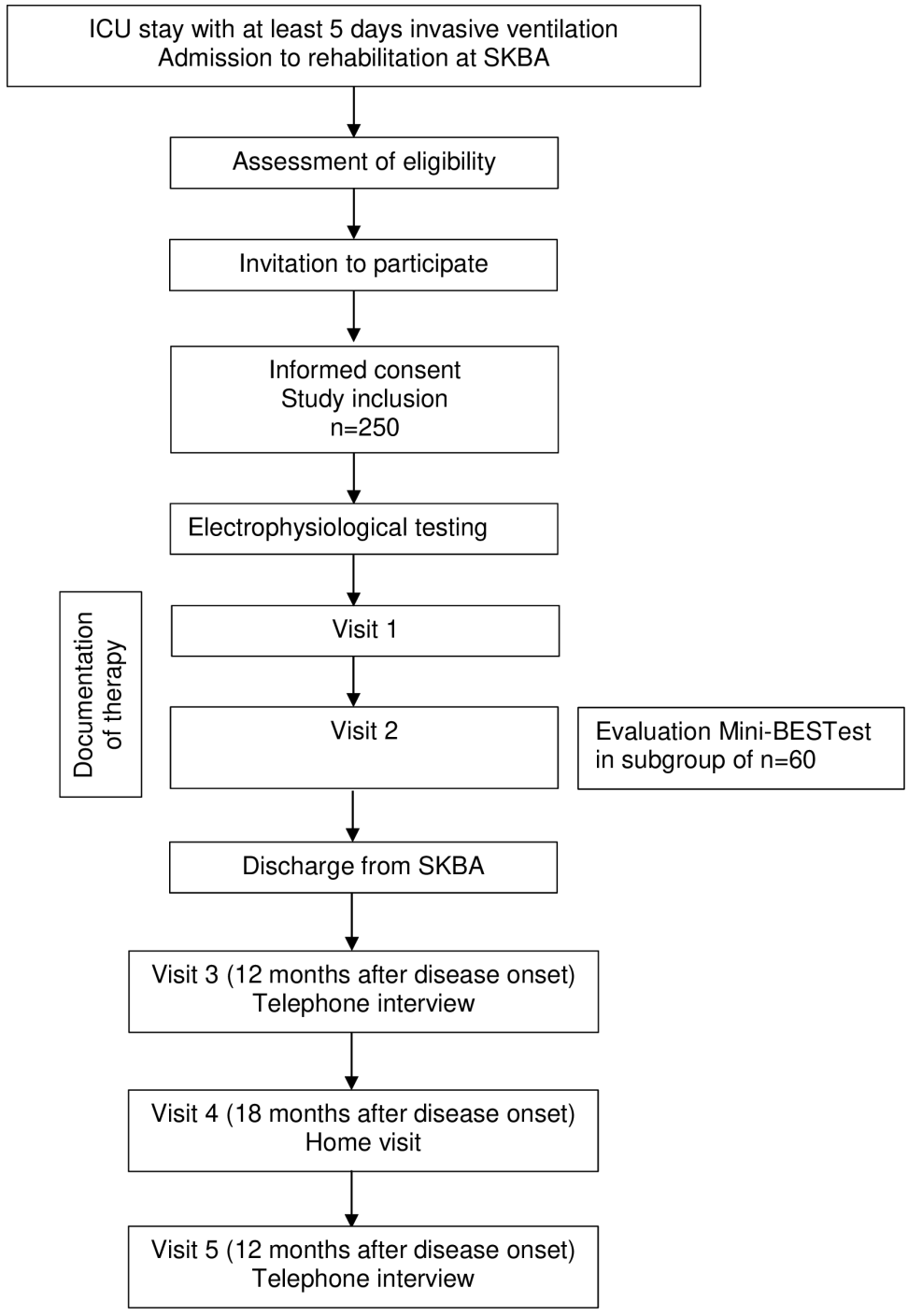

Figure 1 Flow chart of the study. ICU, intensive care unit; SKBA, Schoen Clinic Bad Aibling.

long-term outcomes of these subjects will be compared with subjects with ICUAW due to a primary disease other than COVID-19.

Participant timeline

Figure 1 gives an overview of the flow of subjects through the study. Subjects included in this study will be examined five times (visits 1–5) during the first 2 years after disease onset. The first study visit takes place at admission to neurological rehabilitation at the Schoen Clinic Bad Aibling and the second study visit at discharge from rehabilitation at the Schoen Clinic Bad Aibling. The follow-up phase includes visits 3, 4 and 5 which will be conducted 12, 18 and 24 months after disease onset. Visits 3 and 5 are done via telephone interviews, and visit 4 is done at the patients' home, nursing home or hospital.

Electrophysiological testing is performed at the beginning of the study to confirm a potential diagnosis of CIP/CIM. In some subjects, the testing will have been done as part of the clinical routine before entering the study. A study member will check after study inclusion whether the electrophysiological testing was done before and whether the results are complete. The testing is performed by a

Table 2 Neurological criteria to diagnose CIP, CIM or CIP/CIM

Diagnosis	Criteria
CIP	Reduced SNAP amplitudes (Or reduced SNAP and/or neCMAP/dmCMAP ratio <0.5 and unspecific findings (pathological spontaneous muscle activity and reduced neCMAP))
CIM	Reduced dmCMAP (<3 mV) or reduced MUAP duration (Or reduced dmCMAP of at least one muscle and unspecific findings (pathological spontaneous muscle activity and reduced neCMAP) and normal sensory and motor nerve conduction velocity)
CIP/CIM	Reduced neCMAP and abnormal spontaneous muscle activity (Or reduced dmCMAP and reduced SNAP and/or neCMAP/dmCMAP ratio <0.5)
Unspecific	Pathological spontaneous muscle activity and reduced neCMAP

CIM, critical illness myopathy; CIP, critical illness polyneuropathy; dmCMAP, compound muscle action potential after direct muscle stimulation; MUAP, motor unit action potential; neCMAP, compound muscle action potential after nerve stimulation; SNAP, sensory nerve action potential.

trained neurologist and includes measurements of motor nerve conduction velocity and compound muscle action potential after nerve stimulation of the peroneal, tibial, ulnar and radial nerves, sensory nerve conduction velocity and sensory nerve action potential of the sural and radial nerves, and electromyogram, motor unit action potential (duration) and compound muscle action potential after direct muscle stimulation of the tibialis anterior and the extensor digitorum communis. Criteria to diagnose CIP, CIM or a combination of both are based on previous literature and shown in table 2.[7 8 10 25 26]

Documentation of therapeutic applications of all disciplines starts with visit 1 and ends with discharge from the Schoen Clinic Bad Aibling.

Sample size

Two prior sample size calculations were done for this study based on the primary study objectives. As there are so far no data available on the clinical time course and outcome of subjects with CIP/CIM compared with critically ill patients without CIP/CIM, an effect size of 0.5 was assumed to answer objective 1. With a power of 0.9 and an alpha of 0.05, a total of 176 is required. As the outcome of the subjects should not only be evaluated in the short term, but also in the middle and long term (up to 24 months after disease onset), we expect a dropout rate of 40% for the long follow-up period. Previous studies with critically ill patients show a high variability in their dropout rates ranging from 5% to 67%.[12 27] Since we will make several arrangements to minimise loss to follow-up (see below), a dropout rate of 40% seems reasonable. If we assume the loss to the 24-month follow-up to be 40%, the sample size required is 246.

The secondary sample size calculation is based on the regression analyses to prove objective 2. The rule of 10 events per variable is applied.[28 29] For the dependent variables 'functioning and impairment' and 'quality of life and independence', nine independent variables will be included. This results in 90 subjects. If we assume the above-discussed dropout rate of 40%, the sample size required is 126. Based on the hypothesis that the clinical course and outcome differ between subjects with CIP/CIM and critically ill subjects without CIP/CIM, only subjects with diagnosed CIP/CIM will be included in the regression analyses. Based on our clinical experience, we expect about 50% of the included critically ill subjects to have CIP/CIM. This results in a sample size of 250 subjects to prove the primary objectives. The Schoen Clinic Bad Aibling sees an average of 15 subjects with critical illness per month. If we assume a study enrolment rate of about 10 subjects per month, a recruitment period of 2 years is required.

Participant retention and withdrawal

Once a subject is enrolled, the study site will make every reasonable effort to follow the subject for the entire study period. However, due to the long follow-up period, missing data points may challenge the internal validity of results. Efforts to minimise loss to follow-up will include respecting the time commitment of patients, formal tracking procedures such as multiple ways to be contacted, strong interpersonal skills of the study personnel and flexible hours for testing.

Participants may choose to withdraw from the study at any time. Participants who withdraw from the study can permit data and samples obtained up until the point of withdrawal to be retained for analysis. The investigator may also discontinue a participant from the study at any time in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the principal investigator.

Subjects who withdraw during the study will not be replaced and are not likely to jeopardise study power as sample size calculation accounted for a loss to 2-year follow-up of 40%. Lost to follow-up will be assessed for bias.

Data management

Data will be handled in compliance with the European General Data Protection Regulation and will be pseudonymised. All data will be entered electronically at the

Schoen Clinic Bad Aibling in a Microsoft Access database stored on a password-protected hospital network drive with firewalls and security measures. The database will be secured with password-protected access systems. Backup of the database will be performed daily. All records that contain names or other personal identifiers, such as the informed consent form, will be stored separately from study records identified by code numbers. Access to records and data will be limited to study personnel. Original study forms will be kept on file at the study site and stored in a secure place and manner for a period of 10 years after completion of the study. Members of the study team will monitor the data. Monitoring will ensure data validity, protocol compliance, proper study management and timely completion of study procedures.

Statistical methods

Analysis will be performed with the support of the Institute for Medical Information Processing, Biometry, and Epidemiology of the Ludwig-Maximilians-Universität München.

Categorical or dichotomous outcomes will be presented as absolute numbers and percentages. Descriptive outcomes will be reported as median with IQR or mean with SD. To analyse objective 1, outcomes of the clinical course (duration of ventilation, duration on ICU, duration rehabilitation) and the clinical outcome (functioning and impairment, health-related quality of life) will be compared between subjects with CIP/CIM and subjects without CIP/CIM by using tests for independent samples (Student's t-test, Mann-Whitney U test) or linear mixed models with random slopes if applicable. In addition, Cox and multiple linear regressions will be calculated to investigate the effects of the primary disease on survival time and 'functionality and disability' measured with the WHO Disability Assessment Schedule-short version (WHODAS 2.0).

Objectives 2 and 3 will be analysed by linear regression models. Analysis of the long-term outcomes includes the independent parameters functioning and impairment (based on WHODAS 2.0) and quality of life (based on the EuroQol 5-dimensions-5 levels questionnaire). To determine predictors for functioning and impairment, the following independent variables are used: primary disease, Comorbidity Index, sepsis or multiple organ failure, time of invasive ventilation, FAC at study inclusion, grip strength at study inclusion, Montreal Cognitive Assessment (MoCA) at study inclusion, Functional Status Score for ICU (FSS-ICU) at study inclusion and age. To analyse predictors for quality of life, the following independent variables are used: primary disease, Comorbidity Index, duration of invasive ventilation, FAC at study inclusion, grip strength at study inclusion, MoCA at study inclusion, Hospital Anxiety and Depression Scale (HADS) at study inclusion, FSS-ICU at study inclusion and Clinical Frailty Scale at study inclusion. In addition, predictors for the clinical course will be analysed. The analyses include the following dependent variables: duration of invasive ventilation, length of stay in the ICU and time of rehabilitation; and the following independent variables: primary disease, Comorbidity Index, sepsis or multiple organ failure, Clinical Frailty Scale at study inclusion, age, body mass index, IPAQ, sex, and consumption of alcohol and tobacco. For all regression models, the relevant variables are selected by backward elimination and the Bayesian Information Criterion, and multicollinearity of the variables is tested before adapting the models by Spearman's correlation. The final models are analysed by backward elimination with the Akaike Information Criterion as stopping criterion. Stability investigations including bootstrap resampling will be done according to Heinze *et al*.[30]

The therapeutic documentation (objective 4) will be analysed by applying descriptive statistics. For the evaluation of the Mini-BESTest (objective 5), the weighted kappa, the intraclass correlation coefficient, the SE of measurement and the minimal detectable change will be calculated to investigate the test–retest and inter-rater reliability. For evaluation of the validity, Spearman's rank correlation coefficients will be calculated for correlations of the Mini-BESTest with the Berg Balance Scale, the Timed-up-and-Go, the Functional Reach and the FAC.

The clinical time course and outcome of subjects with CIP/CIM after SARS-CoV-2 infection will be compared with subjects with CIP/CIM after another primary disease by using tests for independent samples, analyses of variance and linear mixed models.

Additional analysis: The prevalence of PICS will be evaluated at all five study visits in all study participants. Physical impairment will be evaluated using grip strength and the MRC-SS. Mental health will be evaluated using the HADS and the Impact of Event Scale-Revised, and cognitive function will be assessed by the MoCA. These assessments were recently recommended to identify PICS.[31] Logistic regression analyses will be conducted to identify predictors for mental and cognitive impairments in the long term, whereby the independent variables are the HADS (cut-off >7 points) and the MoCA (cut-off <26 points for mild cognitive impairment). Dependent variables for mental and cognitive health include age, sex, delirium during ICU stay, previous mental health problems, duration of mechanical ventilation, multiple organ failure, primary disease and Comorbidity Index.[32 33]

As CIP and CIM differ in pathophysiology, clinical features and outcome,[26 34] we will run analyses to investigate differences in clinical outcomes and patient-reported outcomes.

ETHICS AND DISSEMINATION

The study protocol and the template informed consent forms contained are reviewed and approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (project number 20-166) with respect to scientific content and compliance with applicable research and human subject regulations. Any modifications to the protocol which may impact on the conduct of the study,

potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such an amendment will be approved by the Ethics Committee prior to implementation.

Participants are not at any increased risk as all study interventions such as assessments and questionnaires are standard practice.

Findings of the CINAMOPS Study will be disseminated through articles in scientific, peer-reviewed journals, and at national and international neurological or intensive care conferences. The dataset will be available on reasonable request.

Author affiliations
[1]Department of Neurology, Schoen Clinic Bad Aibling Harthausen, Bad Aibling, Germany
[2]German Center for Vertigo and Balance Disorders (DSGZ), Ludwig-Maximilians-Universität München, Munich, Germany
[3]Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Ludwig-Maximilians-Universität München, Munich, Germany

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ORCID iD
Jeannine Bergmann http://orcid.org/0000-0003-0414-6106

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Appendix B: Paper V

Egger M, Finsterhölzl M, Farabegoli D, Wippenbeck F, Schlutt M, Müller F, Huge V, Jahn K, Bergmann J. Comprehensive assessment and progression of health status during neurorehabilitation in survivors of critical illness: a prospective cohort study. *Annals of Intensive Care*. 2024 Nov 26; 14 (1):175. doi: https://doi.org/10.1186/s13613-024-01396-x (Annotation: This paper was still under review at the time the thesis was submitted and has therefore been included in the Appendix).

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RESEARCH

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Comprehensive assessment and progression of health status during neurorehabilitation in survivors of critical illness: a prospective cohort study

Marion Egger[1,2*], Melanie Finsterhölzl[1], Daria Farabegoli[1], Franziska Wippenbeck[1], Maria Schlutt[1], Friedemann Müller[1], Volker Huge[3,4], Klaus Jahn[1,5] and Jeannine Bergmann[1,5]

Abstract

Background Critical illness survivors frequently suffer from long-term impairments, often described as post-intensive care syndrome (PICS). PICS encompasses physical, cognitive, and mental impairments. Additionally, the term intensive care unit (ICU)-acquired weakness (ICUAW) was coined for muscle weakness after critical illness. Research on the progression and outcome of individuals affected by PICS and ICUAW is scant. Thus we aimed to assess the health status and its progression during neurorehabilitation in critically ill patients using comprehensive outcome measures, describe the prevalence of PICS, and evaluate factors associated with rehabilitation outcomes.

Methods Patients with mixed reasons for critical illness who received ≥ 5 days of mechanical ventilation on the ICU and who were admitted to neurorehabilitation, were eligible to be included in this prospective cohort study. A number of outcomes (patient-reported, clinician-reported, and performance) were assessed after discharge from the ICU (V1) and shortly before discharge from inpatient neurorehabilitation (V2). The prevalence of PICS, defined as having at least one impairment in any PICS dimension), was calculated at V1 and V2. Multiple logistic regressions were conducted to identify factors associated with rehabilitation outcome (poor outcome = modified Rankin Scale > 2) and ICUAW at V2 (MRC sum score < 48).

Results In total, 250 critical illness survivors (62 ± 14 years, 34% female, median stay on ICU 55 days, median inpatient rehabilitation 65 days) were included. 11 participants (4.4%) died before V2. All outcomes improved significantly during rehabilitation except sensory impairment and pain. PICS was present in 96% at V1 and in 85% at V2, whereby mainly the physical domain (V1: 87%, V2: 66%; ICUAW with MRC sum score < 48) and the cognitive domain (V1:65%, V2:55%; Montreal Cognitive Assessment < 26) were affected. Mental impairment was lower (V1:48%, V2:29%; Hospital Anxiety and Depression Scale > 7), but still affected a considerable number of participants. Accordingly, health-related quality of life was rather low at discharge (0.64 ± 0.28, index value of EQ-5D-5L). MRC sum score at V1, duration of mechanical ventilation, and female gender were significantly associated with a poor rehabilitation outcome. Grip strength in % of reference at V1, age, female gender, and comorbidities were significantly associated with persistent ICUAW at discharge.

*Correspondence:
Marion Egger
megger@schoen-klinik.de
Full list of author information is available at the end of the article

Conclusions Despite significant improvements during rehabilitation, survivors after critical illness experience a substantial burden of PICS and ICUAW at discharge from rehabilitation care. Survivors of critical illness require long-term follow-up, supportive structures, and tailored long-term multi-disciplinary therapies even after intensive rehabilitation.

Trial registration: German Clinical Trials Register, DRKS00021753. Registered 03 September, 2020. https://drks.de/search/en/trial/DRKS00021753.

Keywords Critical care, Critical illness, Intensive Care Units, ICU-acquired weakness, Neurological rehabilitation, Outcome, Patient-reported outcomes, Post-intensive care syndrome

Background

Progress in critical care medicine has substantially increased the probability of surviving life-threatening illnesses [1]. However, the short- and long-term outcomes of intensive care unit (ICU) survivors are often characterized by impairments, which restrict their independence, diminish their health-related quality of life, and hinder their return to their living and working situations [2, 3]. A frequent consequence of critical illness is the post-intensive care syndrome (PICS) [4, 5]. PICS affects up to 80% of ICU survivors and describes the combination of physical, mental, and cognitive impairments [2, 6]. Known risk factors for PICS are, among others, older age, female sex, delirium, and high disease severity [5]. PICS decreases long-term survival and has been reported to persist 1 year after discharge from the ICU in 50% of affected persons, often enduring for even longer periods [6–9]. ICU-acquired weakness (ICUAW) is the major complication arising in the physical domain of PICS, and in turn affects up to 80% of ICU survivors [10]. The term ICUAW was coined to describe a profound muscle weakness in critically ill patients, which is primarily caused by critical illness polyneuropathy (CIP), -myopathy (CIM) or their co-occurrence [11]. Prolonged duration of mechanical ventilation, sepsis, and multiple organ system failure are risk factors for the development of an ICUAW [12, 13]. ICUAW is associated with increased mortality [14], persisting disability, and limited health-related quality of life [15, 16].

Although negative consequences after ICU treatment are commonly observed, many areas of uncertainty exist, as previous studies often neglected important aspects [17]. These include the impact of the patient's pre-admission status, the need for long-term follow-up, and a lack of well-defined, validated outcome measures [18]. Furthermore, effective multi-disciplinary rehabilitation strategies are urgently needed, but knowledge of treatment beyond the ICU is currently limited [19–22]. Consequently, the effect of post-ICU therapies on long-term outcomes are uncertain [17, 18, 23, 24].

Knowledge of factors associated with ICU outcomes is crucial for developing optimal strategies for prevention and treatment [5]. However, risk factors related to the occurrence of ICUAW, have been evaluated only during the ICU stay [25]. Similarly, factors associated with poor rehabilitation outcomes are currently missing. Identifying variables associated with persistent ICUAW and poor rehabilitation outcomes could aid in tailoring rehabilitation approaches, improving prognosis, and planning post-hospital care.

The prospective cohort study CINAMOPS (Critical Illness Polyneuropathy and Myopathy: Outcomes, Predictors and Longitudinal Trajectories) was designed to address the research gaps described and enhance the understanding of the long-term sequelae after ICU treatments, such as PICS and ICUAW [26]. Within this project, survivors of critical illness are evaluated comprehensively during neurological rehabilitation and up to 2 years after disease onset [26].

Using a large set of patient- and clinician-reported outcomes as well as performance outcomes, the primary aim of this analysis was to comprehensively assess the health status and its progression during neurorehabilitation of critical illness survivors. Furthermore, we aimed to assess the PICS prevalence, and to explore factors associated with rehabilitation outcome and persistent ICUAW. Improved knowledge on the clinical course of ICU survivors is the prerequisite for the development and evaluation of interventions in the future.

Methods

Study population and setting

This analysis is part of the single-center, prospective cohort study CINAMOPS, which is currently being conducted at the Schoen Clinic Bad Aibling, Germany. The hospital is a centre for inpatient neurorehabilitation with a focus on critically affected patients (ICU, early neurorehabilitation). Details of the study were previously described [26].

Adult patients (≥18 years) who were mechanically ventilated in the ICU for at least 5 days were eligible for the CINAMOPS study. Patients were recruited on admission to neurorehabilitation, after discharge from ICU. Exclusion criteria were (1) palliative care, (2) neuromuscular or neurologic diseases/syndromes causing muscular weakness

(e.g. Guillain-Barré syndrome, mysasthenia gravis, porphyria, Lambert-Eaton syndrome, amyotrophic lateral sclerosis, severe autoimmune neuropathy, cervical myelopathy, botulism; in accordance with [27]), (3) insufficient communication abilities (German language skills or cognition) interfering with answering the questionnaires, (4) no muscular weakness (i.e. muscle strength according to the Medical Research Council (MRC) scale 5/5).

During the study, patients received inpatient neurological rehabilitation of individual length with approximately 100 minutes of multi-disciplinary functional therapies per day, including physiotherapy, occupational, dysphagia, and breathing therapies, as well as neuropsychology.

The study was approved by the medical ethics committee of the Ludwig-Maximilians-Universität in Munich according to the Declaration of Helsinki (project no. 20-166). Written informed consent was obtained from all participants (or their legal guardians). The project CINAMOPS was prospectively registered at the German Clinical Trials Register (DRKS00021753). The reporting of this study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Study visits and outcomes

The first study visit (V1) took place after admission to neurorehabilitation (a median of 14 days after discharge from ICU), the second study visit (V2) was conducted shortly before discharge from inpatient neurorehabilitation. In order to comprehensively assess the health status, the study visits included a variety of established patient-reported outcomes, performance outcomes, and clinician-reported outcomes, which are displayed in Table 1.

All assessments were conducted by experienced physiotherapists who were extensively trained in using the different outcome measures to minimize the risk of bias. Balance function and walking ability in this group of patients were analysed and described in [58].

Patients' characteristics and ICU data

Patients´ characteristics and data about the ICU stay were collected retrospectively using the electronic medical records and included the following parameters: age at disease onset, length of ICU stay, duration of mechanical ventilation, complications (e.g. sepsis, delirium), primary disease (type and duration), secondary diagnoses, duration of rehabilitation, and the Elixhauser Comorbidity Index [59]. Data about the preclinical status was collected during the first study visit and included the Functional Ambulation Categories, Clinical Frailty Scale, modified Rankin Scale, Barthel Index, consumption of alcohol and tobacco, physical activities, living conditions, relationship status, employment, and preclinical physical and cognitive disabilities.

Electrophysiological testing was used to confirm a potential diagnosis of CIP/CIM and was carried out shortly after study enrolment. The testing included motor and sensory nerve conduction velocities, compound muscle action potential after nerve stimulation (neCMAP) and after direct muscle stimulation (dmCMAP), and electromyography. More details and criteria used to diagnose CIP/CIM can be found in [26].

Evaluation of PICS

In order to assess the percentage of patients with PICS at V1 and V2, we used assessments in accordance with a current Delphi study about instruments in PICS [57]. For physical function we used the MRC score, for cognitive function the MoCA, and for mental health the HADS. The following cut-offs were set to be indicative for impairments: Physical function impaired if MRC sum socre < 48 [13], mental health deficits if HADS > 7 separate for the two categories anxiety and depression [31], cognitive deficits if MoCA < 26 [54]. PICS was deemed to be present, if at least one of the three domains was impaired. Further aspects relevant to PICS, such as health-related quality of life (EQ-5D-5L), independence in activities of daily living (Barthel-Index), and pain, are not included in our PICS definition but were measured as part of the comprehensive assessment of health status (Table 1).

Statistical analysis

Categorical variables are presented as absolute values and percentages, continuous variables as mean ± standard deviation or median (quartile 1-quartile 3).

Change in clinical outcome assessments

The Wilcoxon test was used to compare the two time points (V1 and V2) as data were either non-parametric or did not follow normal distribution (as checked by Shapiro–Wilk test and visually by means of QQ-plots). Effect sizes were calculated with $r = z/\sqrt{N}$. McNemar's test was used for categorical values. Continuity Correction was used in case of < 30 discordant pairs. Cohen's g (non-directional) was used to calculate the respective effect sizes [60].

Multiple logistic regression

Multiple logistic regressions were conducted to explore associated factors with (1) the rehabilitation outcome and (2) ICUAW at V2 (i.e., < 48 points according to the MRC sum score). The rehabilitation outcome was defined according to the modified Rankin Scale at V2, whereby the scores 0 to 2 indicated a desirable rehabilitation

Table 1 Overview of clinical outcome assessments

Patient-reported outcomes	
Fatigue Severity Scale-7 (FSS-7)	This assessment is used to evaluate fatigue. The seven-item version was used, as it was demonstrated to have better psychometric properties than the nine–item version [28]. Score: 1–7. The cut-off ≥ 4 was interpreted as indicative of fatigue [29]
Hospital Anxiety and Depression Scale (HADS)	This valid and reliable tool measures anxiety and depression and was repeatedly used in critically ill patients [30]. Score: 0–21 each for anxiety and depression. A score of > 7 in each category was interpreted as clinically significant [31]
EuroQol-5 dimensions-5 level (EQ-5D-5L)	The internationally wide-spread scale is used to measure health-related quality of life [32]. The index value for the German population ranges from -0.205 (0 = health state equivalent to death; negative values = health state worse than death) to 1.000 (best health state) [33]. Patients who died after V1 were assigned a score of 0 in all further study visits. Additionally, the visual analogue scale (included in the EQ-5D-5L; 0–100) was used. 100 indicates the best imaginable state of health
Pain / sensory disturbances	Presence of pain and sensory disturbances: patients were asked to report any experiences of pain and sensory disturbances
Clinician-reported outcomes	
Clinical Frailty Scale	Frailty was assessed by this scale [34], whereby the score ranges from 1 to 9 and 9 indicates deathly ill. A preclinical value was recorded retrospectively at V1
Modified Rankin Scale	This scale describes the overall disability [35]. The score ranges from 0 to 6, whereby 6 indicates death. A preclinical value was recorded retrospectively at V1
Barthel-Index	The Barthel Index [36] is widely used and describes the patients´ independence in activities of daily living like washing, grooming, climbing stairs, toilet use etc. It is a reliable and valid tool for patients after critical illness [37]. A preclinical value was recorded retrospectively at visit 1. The score extends from 0 to 100. The Barthel-Index was first collected from the medical records, but due to invalid data, the Barthel-Index was later gathered by the research team. This led to a lower number of available Barthel-Index data (Table 3)
Early Rehabilitation Barthel Index	This extension of the Barthel-Index contains items like confusion, tracheostomy or dysphagia and is a valid and reliable tool for patients in neurological rehabilitation [38]. Score: – 325–0
Modified Medical Research Council dyspnea scale	This scale was used to evaluate dyspnea. The score ranges from 0 to 4, whereby 4 indicates the severest dyspnea [39]
Functional Ambulation Categories	The assessment extends from 0 to 5 and was used to classify walking ability [40]. Their good psychometric properties in neurological rehabilitation were shown [41] and the assessment was also used in patients with ICUAW [27]
Performance outcomes	
Grip strength	Grip strength was assessed twice on both hands with a digital dynamometer (Kern MAP 130K1, Balingen, Germany) and was measured in kilogram (kg). The maximum grip strength was standardized as a percentage of the reference grip strength, which was determined based on the patient's sex, age, and body height according to [42]
MRC sum score	Muscle strength was evaluated by manual muscle testing using the scoring system of the Medical Research Council (MRC). The scale ranges from 0 to 5, whereby 5 indicates normal muscle strength. The following functional muscle groups were evaluated: Shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, ankle dorsal flexion [43, 44]. Consequentially, a maximum sum score of 60 is possible. A sum score of < 48 was repeatedly used as indicative for ICUAW [11, 13, 15]
Functional Status Score for the ICU	This scale measures basic physical functions on the ICU, comprises five items (e.g. rolling, transfer from supine to sitting) and has good psychometric properties [45]. Score: 0–35
Five Times Sit to Stand Test	This test was applied as it can be used to evaluate muscle strength of the lower extremities, risk of falling, dynamic balance and functional mobility [46–48] The test has good psychometric properties in patients after critical illness [49]
Box and Block Test	The Box and Block test [50] is a test for manual dexterity, where the patient is asked to transport as many blocks as possible from one compartment of a box to another within one minute. It shows a very high interrater- and test–retest-reliability and very good construct validity in neurologic patients [51]. Reference values were determined based on the patient's sex and age [50]

Table 1 (continued)

Sensory examination	On the basis of the Fugl-Meyer-Assessment [52], the sensation of light touch (upper arm, the palmar surface of the hand, the thighs and plantar surfaces of the feet) and position of the joints (thumb (interphalangeal joint), wrist, elbow, gleno-humeral joint, ankle, knee, hip) was examined. Score 0–2, whereby 0 indicates anesthesia or absence of joint positions sense. Furthermore, vibration perception was evaluated with a vibrating tuning fork on the bony prominences ulnar styloid process, lateral epicondyle of the humerus, dorsum of the caput of os metatarsale I, the internal malleolus, and the tuberosity of the tibia. Values below 6/8 for the upper extremity and below 4/8 for the lower extremity indicated abnormal vibration perception [53]. Joint position sense and vibration examination were always started at the most distal body part and only continued to more proximal parts in case of pathological findings
Montreal Cognitive Assessment (MoCA)	The MoCA was used evaluate to cognitive function [54]. Good psychometric properties were so far only reported in patients with cerebrovascular diseases [55], but the MoCA was also already used in patients with critical illness and is recommended to evaluate cognitive function in post-intensive care syndrome [16, 56, 57]. Score 0–30, whereby a score < 26 indicated cognitive impairment

outcome and the scores 3 to 6 indicated a poor rehabilitation outcome.

Variables for the full model were included based on previous literature and expert knowledge. Independent variables for the rehabilitation outcome model included age, sex, obesity, MRC muscle sum score at V1, MoCA at V1, Elixhauser comorbidity index, duration of mechanical ventilation, diabetes, delirium, pre-existing mental health impairment, preclinical frailty (binary: 1–4 and 5–9), sepsis, ECMO, social support (approximated by the variable living alone vs. not alone), the primary diagnose acquired brain injury (stroke, hypoxia and traumatic brain injury), the primary diagnose COVID-19, and CIP/CIM (yes = CIP, CIM or CIP/CIM; no = no CIP/CIM). Independent variables for the ICUAW model included age, sex, obesity, grip strength (in % of reference), Elixhauser comorbidity index, duration of mechanical ventilation, diabetes, delirium, preclinical frailty, sepsis, ECMO, and CIP/CIM.

Variable selection was done according to the recommendations given by Heinze et al. [61]. The events-per-variable (EPV_{global}) for the rehabilitation outcome model was 197/17 = 11.6 and for the ICUAW model 191/14 = 13.6. We conducted a backward elimination with the Akaike information criterion (AIC, significance level 0.157) as stopping criterion. Stability investigations of the selected model were performed according to Heinze et al. [61]. Bootstrap resampling with replacement (1,000 replicates) was done for the calculation of inclusion frequencies, sampling distributions of regression coefficients, and model selection frequencies. Furthermore, the relative conditional bias (which measures the anticipated level of bias introduced by variable selection when a particular independent variable is chosen) was calculated as suggested in Heinze et al. [61]. Postestimation shrinkage factors were calculated using the R package "shrink" [62]. The logistic regression model's goodness-of-fit was assessed using a likelihood ratio test. We present the exponential of the coefficients as the odds ratio (OR) and their corresponding 95% confidence intervals. The Akaike Information Criterion (AIC) was reported for model comparison of the full and the selected model. Assumptions for the multiple logistic regression (linearity and influential values) were tested graphically for systematic violations in the selected model (Supplementary Figs. 1 and 2), whereby slight deviations were found. Multicollinearity was controlled by calculating variance inflation factors (VIF).

Statistical analyses were performed using R version 4.3.2. A $p \leq 0.05$ (two-tailed) was considered significant. Missing data was not replaced.

Results

We screened a total of 1064 patients and enrolled 250 patients between September 2020 and July 2023. The study visits (V1 and V2) were conducted between September 2020 and December 2023 (Fig. 1), whereby V1 was performed in 250 patients, V2 in 222 patients. Median time between the two study visits was 53 days. Eleven patients (4.4%) died after the first study visit. In five participants, the V2 was only conducted as a telephone interview. The characteristics of the study participants are presented in Table 2. In accordance with the extraordinary long median length of stay on ICU and duration of invasive ventilation, the diagnosis of chronic critical illness could be assigned to all patients (Table 2) [63]. The most frequent primary diagnoses among the included patients were COVID-19, cardiac diseases, and pulmonary diseases. Nerve conduction studies conducted in 216 patients revealed that 80.1% exhibited signs of CIP, CIM, or a combination of both.

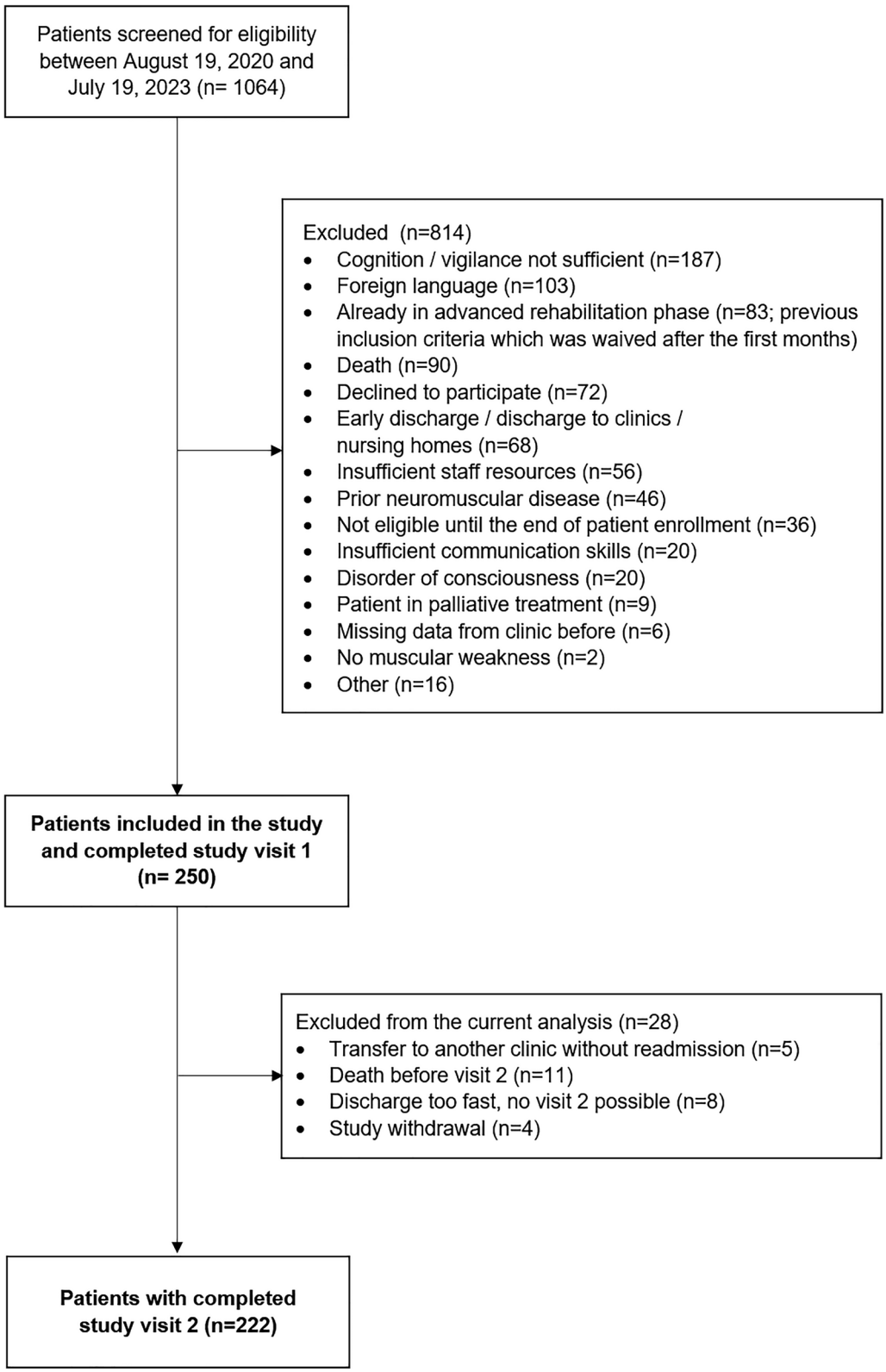

Fig. 1 Flow Chart of the CINAMOPS study

Table 2 Demographic and clinical characteristics of critical illness survivors

Characteristics	Total population (n = 250)
Age, years	62.4 ± 13.6, min/max: 18/92
Sex, women	86 (34.4)
Length of hospitalization, days*	141 (98–192); 156.4 ± 81.8
Length of ICU stay, days	55 (39–78); 64.7 ± 40.3
Length of mechanical ventilation, days	39 (27–58); 45.8 ± 31.1
Length of neurological rehabilitation at Schoen Clinic Bad Aibling, days	67 (44–100); 82.2 ± 60.2
Time between	
First hospital admission and V1	81 (57–113); 90.8 ± 47.0
ICU discharge and V1	14 (8–23); 20.3 ± 18.4
V1 and V2	52 (29–82); 64.8 ± 50.8
Duration of ECMO (n = 51, 20.4%), days	10 (5–22.5); 17.6 ± 21.1
Primary diagnosis	
COVID-19	67 (26.8)
Cardiac disease	46 (18.4)
Pulmonary disease	45 (18.0)
Gastrointestinal/urological disease	25 (10.0)
Bacterial infection	21 (8.4)
Cerebral infarction / haemorrhage	20 (8.0)
Polytrauma	8 (3.2)
Oncological surgery	7 (2.8)
Hypoxia	5 (2.0)
Other	6 (2.4)
Chronic critical illness—conditions	
Prolonged acute mechanical ventilation (≥ 96 h)	250 (100.0)
Tracheotomy	209 (83.6)
Sepsis	149 (59.6)
Severe wounds	49 (19.6)
Stroke	33 (13.2)
Traumatic brain injury	6 (2.4)
Medical conditions	
Acute Respiratory Distress Syndrome (ARDS)	91 (36.3)
Sepsis	149 (59.6)
Acute kidney injury	134 (53.6)
Renal replacement therapy	88 (35.2)
Delirium	106 (42.4)
Severe encephalopathy	25 (10.0)
Multiple organ failure	23 (9.2)
Resuscitation	48 (19.2)
Cerebral ischemia	13 (5.2)
Nerve conduction studies[#]	
CIP	42 (19.4)
CIM	25 (11.6)
CIP/CIM	73 (33.8)
CIP but unclear CIM	22 (10.2)
No CIP but unclear CIM	11 (5.1)
No CIP/CIM	43 (19.9)
Comorbidities	
Diabetes (all type II)	47 (18.8)
Obesity	60 (24.0)

Table 2 (continued)

Characteristics	Total population (n = 250)
Hypertension	113 (45.2)
Psychiatric diagnose	42 (16.8)
Elixhauser Comorbidity Index	4.7 ± 7.0, min/max: -7/28
Preclinical status	
Frailty (Clinical Frailty Scale)	3 (2–3)
Disability (Modified Rankin Scale)	0 (0–1)
Barthel-Index	100 (100–100)
Occupation	
Employed	109 (43.6)
Retired	124 (49.6)
Student	3 (1.6)
Unemployed	14 (5.6)
Living conditions	
At home alone	52 (20.8)
At home not alone (e.g., with family)	194 (77.6)
Sheltered housing	2 (0.8)
Relationship	
Married/in a relationship	180 (72.0)
Single	41 (16.4)
Divorced	12 (4.8)
Widowed	17 (6.8)
Cigarette smoking	
Current smoker	43 (17.2)
Former smoker[##]	25 (10.0)
Non-smoker	182 (72.8)
Alcohol consumption	
Never	78 (31.2)
Once per month	35 (14.0)
2–4 times per month	37 (14.8)
2–3 times per week	29 (11.6)
4 times per week or more	73 (29.2)
Discharge destination	
Home	171 (71.6)
Further rehabilitation	29 (12.1)
Home with (mobile) nursing service	18 (7.5)
Nursing home	7 (2.9)
Outpatient intensive care unit	6 (2.5)
Sheltered housing	4 (1.7)
Other hospital	4 (1.7)
Death	11 (4.4)

Data are n (%), median (quartile 1-quartile 3) or mean ± SD

ICU intensive care unit, *ECMO* extracorporeal membrane oxygenation

[*] Hospitalization is defined as the period from the first day in hospital until discharge from rehabilitation

[#] Electrophysiological measurement was conducted in 216 persons (86.4%). Median time between disease onset and measurement was 91 days (67–127), the average time was 103.0 ± 50.5 days

[##] Patients who quit smoking within the last 10 years

Patient-reported outcomes

Patient-reported outcomes are displayed in Table 3. Health-related quality of life improved significantly during neurorehabilitation, as shown by large effect sizes.

Table 3 Patient reported outcomes at admission to and at discharge from neurorehabilitation

	Visit 1 at study onset	Visit 2 at discharge	Test statistic	Effect size V1-V2
FSS-7	3.0 ± 1.6	2.7 ± 1.6	z = −2.79, p = 0.005	0.18
Fatigue ≥ 4	69 (28.4) n = 243	47 (21.7) n = 216	McNemar's χ^2 (1) = 2.04, p = 0.153	0.11
HADS				
Anxiety	5 (2–8)	3 (1–6.5)	z = −5.22, p < 0.001	0.35
Anxiety > 7	76 (30.9) n = 246	46 (21.2) n = 215	McNemar's χ^2 (1) = 7.52, p = 0.006	0.21
Depression	5 (3–9)	3 (2–6)	z = −6.55, p < 0.001	0.46
Depression > 7	89 (36.3) n = 245	39 (18.2) n = 214	McNemar's χ^2 (1) = 20.28, p < 0.001	0.31
EQ-5D-5L				
Visual Analogue Scale	48.9 ± 19.3 n = 248	61.2 ± 19.4 n = 217	z = −7.78, p < 0.001	0.54
Index value	0.39 ± 0.31 n = 248	0.64 ± 0.28 n = 228	z = −10.46, p < 0.001	0.70
Walking around	4 (3–5)	3 (2–3)	z = −9.60, p < 0.001	0.70
Problems with walking around	242 (98.0)	181 (83.4)	McNemar's χ^2 (1) = 29.12, p < .001	0.47
Washing/dressing	3 (2–4)	2 (1–2)	z = −9.92, p < 0.001	0.70
Problems with washing/dressing	218 (87.9)	128 (59.0)	McNemar's χ^2 (1) = 51.55, p < .001	0.41
Usual activity	4 (3–5)	2 (2–3)	z = −10.36, p < 0.001	0.73
Problems with usual activity	236 (95.1)	166 (76.5)	McNemar's χ^2 (1) = 35.28, p < 0.001	0.42
Pain or discomfort	3 (2–4)	2 (2–3)	z = −2.88, p = 0.004	0.20
Pain or discomfort is present	210 (84.7)	179 (82.5)	McNemar's χ^2 (1) = 0.28, p = 0.599	0.03
Anxiety or depression	2 (1–2)	1 (1–2)	z = −5.24, p < 0.001	0.35
Anxiety or depression is present	138 (55.6)	70 (32.3)	McNemar's χ^2 (1) = 37.7, p < 0.001	0.37
Presence of pain	142 (56.8) n = 250	126 (57.3) n = 220	McNemar's χ^2 (1) = 0.01, p = 0.906	0.01
Presence of sensory disturbances	141 (56.4) n = 250	135 (61.1) n = 220	McNemar's χ^2 (1) = 0.26, p = 0.612	0.03

Data are n (%), mean ± SD or median (quartile 1- quartile 3); FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5 l = EuroQol—5 dimensions—5 level; The effect sizes (of the Wilcoxon tests) were calculated with $r = z/\sqrt{N}$. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Cohen (1988), p.79–81 [60]. Effect sizes for McNemar´s tests were calculated with the non-directional Cohen`s g are interpreted as small (0.05 to < 0.15), medium (0.15 to < 0.25), and large (≥ 0.25) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), p.147–149 [60]

However, at discharge, the majority of patients faced problems with ambulation as well as activities of daily life and suffered from pain or discomfort. Fatigue, anxiety, and depression were observed to a lesser extent, with only about 20% of individuals exhibiting values above the respective cut-offs. Pain and sensory disturbances were reported by more than half of all participants and did not improve over the period of neurorehabilitation.

Clinician-reported outcomes

Clinician-reported outcomes are reported in Table 4. All parameters improved significantly during neurologic rehabilitation, and patients improved substantially as displayed by the large effect sizes. However, the preclinical status as indicated by the preclinical medians (Table 2) of the Barthel Index, the modified Rankin Scale, and the Clinical Frailty Scale could not be regained. According to the outcome categories, the median patients at discharge exhibited mild frailty, moderate disability, and experienced shortness of breath when hurrying or walking up a slight incline.

Performance outcomes

Performance outcomes are displayed in Table 5. All motor performance outcomes improved significantly with large effect sizes. However, muscle strength was still substantially reduced at discharge, as the maximum handgrip strength was on average only 52% of the respective reference values. The cognitive function also showed significant improvement, albeit with a small effect size. The somatosensory investigation revealed more severe deficits in the lower extremity. Around 25% of individuals

Table 4 Clinician-reported outcomes at admission to and at discharge from neurorehabilitation

	Visit 1 at study onset	Visit 2 at discharge	Wilcoxon test statistic	Effect size V1-V2
Modified Rankin Scale	4 (4–5) n = 248	3 (2–4) n = 233	z = −11.06, p < 0.001	0.75
Clinical Frailty Scale	7 (6–7) n = 248	5 (4–6) n = 222	z = −11.29, p < 0.001	0.80
Barthel-Index	45 (20–75) n = 136	85 (70–100) n = 132	z = −9.02, p < 0.001	0.85
Early Rehabilitation Barthel Index	−50 (−100; 0) n = 250	0 (0–0) n = 236	z = −9.56, p < 0.001	0.69
Functional Ambulation Categories	2 (0–3) n = 250	4 (3–5) n = 222	z = −11.64, p < 0.001	0.83
Modified Medical Research Council Dyspnea Scale	3 (1–4) n = 208	1 (0–2) n = 197	z = −7.28, p < 0.001	0.55

Data are displayed as median (quartile 1- quartile 3); The effect size was calculated with $r = z/\sqrt{N}$. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Cohen (1988), p.79–81 [60]

experienced deficits in the superficial sensation of the lower extremity, which did not improve over time. Vibration perception of the lower extremity was impaired in 50% at V1 and improved significantly over time; however, 41% still had deficits at V2. Impairments in proprioception occurred only in the minority of patients.

PICS evaluation

Figure 2 shows impairments according to PICS at V1 and V2 in each domain (physical, mental and cognitive impairments) and the overlap of the domains. At V1, 239 patients (95.6%) and at V2 still 185 (84.5%) suffered from PICS. At both time points, participants were mainly affected by physical symptoms (216 (86.8%) at V1 and 141 (65.6%) at V2). Cognitive symptoms were more frequent than mental symptoms at both study visits. PICS burden decreased in all domains over the period of neurorehabilitation. However, physical and cognitive impairments were still substantial at discharge from rehabilitation.

Logistic regression for poor rehabilitation outcome

The distribution of the modified Rankin Scale for measuring the rehabilitation success is shown in Fig. 3. A poor rehabilitation outcome as reflected by the modified Rankin Scale scores 3 to 6 was seen in 63% of the individuals.

The multiple logistic regression model for the rehabilitation outcome included the variables muscle strength, duration of mechanical ventilation, acquired brain injury, sex, age, diabetes and the Elixhauser comorbidity index after backward elimination (Table 6). Only muscle strength, duration of mechanical ventilation, and sex were significantly associated with the rehabilitation outcome ($p < 0.035$). Acquired brain injury was on the border to significance ($p = 0.059$). Each additional point in the MRC sum score at V1 decreased the chance of a poor rehabilitation outcome by 15%. Each additional day of mechanical ventilation increased the chance of a poor rehabilitation outcome by 2%. The chance of a poor rehabilitation outcome in females is (1/0.45 =)2.22-times higher than in males. The bootstrapping results, model selection frequencies, and parameterwise shrinkage factors are presented in Supplementary Tables 1, 2, and 5, along with an interpretation of the results. In short, according to the model stability investigations, the associations between the rehabilitation outcome and muscle strength, duration of mechanical ventilation, sex, and potentially acquired brain injury seem plausible. In contrast, diabetes, the Elixhauser comorbidity index, and age are less certain as indicated by lower bootstrap inclusion frequencies, contradictory model selection frequencies, and low shrinkage factors.

Logistic regression for ICUAW at discharge

The selected model of the multiple logistic regression for ICUAW at discharge contained the variables handgrip strength, age, sex, Elixhauser comorbidity index, obesity, ECMO, and acquired brain injury after backward elimination. Only handgrip strength, age, and Elixhauser reached statistical significance ($p < 0.036$). Each additional percentage point in the handgrip strength decreased the chance of ICUAW by 7%. Every additional year of age increased the chance of ICUAW by 4%. The odds of ICUAW among male patients was 0.42-times the odds for female patients. This means that the chance of ICUAW among females was (1/0.42 =)2.38-times higher than for males. Each additional point in the Elixhauser comorbidity index increased the chance of ICUAW by 6%. Bootstrapping results, model frequencies, and

Table 5 Performance outcomes at admission to and at discharge from neurorehabilitation

	Visit 1 at study onset	Visit 2 at discharge	Test statistic	Effect size V1-V2
Maximum grip strength in kg	15.5 ± 7.5	20.5 ± 7.6	z = −11.20, p < 0.001	0.77
Maximum grip strength in % of reference	39.3 ± 17.6 n = 247	51.8 ± 16.2 n = 216	z = −11.22, p < 0.001	0.77
MRC Sum Score	40 (35–44)	45 (41–48.5)	z = −10.96, p < 0.001	0.76
MRC Sum Score < 48	216 (86.8) n = 249	141 (65.6) n = 215	McNemar's χ^2 (1) = 40.69, p < 0.001	0.44
Functional Status Score for the ICU	27 (17–32) n = 249	34 (32–35) n = 221	z = −11.56, p < 0.001	0.81
Five Times Sit to Stand Test	20.0 ± 10.0	16.9 ± 7.4	z = −7.19, p < 0.001	0.67
Help required	91 (70.5)	122 (63.9)		
Not possible	114 (46.9) n = 129	19 (9.0) n = 191		
Box and Block Test				
Right	45.4 ± 17.6	55.8 ± 17.1	z = −9.34, p < 0.001	0.69
Right in % of reference	66.1 ± 20.2	79.4 ± 20.2	z = −9.64, p < 0.001	0.73
Left	42.3 ± 18.5	51.8 ± 18.5	z = −9.26, p < 0.001	0.69
Left in % of reference	64.4 ± 20.7 n = 223	78.2 ± 18.6 n = 203	z = −9.49, p < 0.001	0.73
MoCA	23.7 ± 4.3	24.4 ± 4.1	z = −2.08, p = 0.038	0.15
MoCA < 26	154 (64.7) n = 238	116 (55.2) n = 210	McNemar's χ^2 (1) = 4.19, p = 0.041	0.12
Deficits in superficial sensation (light touch)				
- Upper extremity	44 (17.7)	28 (13.2)	McNemar's χ^2 (1) = 2.94, p = 0.086	0.15
- Lower extremity	68 (27.4) n = 247	55 (25.9) n = 212	McNemar's χ^2 (1) = 0.22, p = 0.639	0.04
Deficits in proprioception awareness				
- Upper extremity	18 (7.3)	10 (4.7)	McNemar's χ^2 (1) = 4.08, p = 0.043	0.33
- Lower extremity	19 (7.7) n = 247	12 (5.7) n = 212	McNemar's χ^2 (1) = 0.64, p = 0.423	0.14
Deficits in vibration perception				
- Upper extremity	26 (10.5)	21 (10.2)	McNemar's χ^2 (1) = 0.19, p = 0.663	0.07
- Lower extremity	124 (50.2) n = 247	85 (41.3) n = 212	McNemar's χ^2 (1) = 4.41, p = 0.035	0.15

Data are n (%), mean ± SD or median (quartile 1- quartile 3); MoCA = Montreal Cognitive Assessment; The effect sizes (of the Wilcoxon tests) were calculated with $r = z/\sqrt{N}$. Effect sizes are small (≥ 0.1), moderate (≥ 0.3) or large (≥ 0.5) according to Cohen (1988), p.79–81 [60]. Effect sizes for McNemar´s tests were calculated with the non-directional Cohen`s g are interpreted as small (0.05 to < 0.15), medium (0.15 to < 0.25), and large (≥ 0.25) according to Jacob Cohen: Statistical Power Analysis for the Behavioral Sciences (1988), p.147–149 [60]

parameterwise shrinkage factors are presented in Supplementary Tables 3, 4, and 5, along with an interpretation. In brief, the model stability investigation supports the final selected model, although some uncertainty exist for the non-significant values as displayed by the higher bias percentages and lower shrinkage factors.

Discussion

Here we describe the health status of critical illness survivors at the beginning and the end of neurological rehabilitation. Outcomes show the overall good improvement during rehabilitation. Nonetheless, a majority of individuals exhibited ongoing impairments upon discharge, with PICS prevalent in 84.5% of individuals, alongside high rates of physical and cognitive impairments. The preclinical health status was mostly not yet regained. We found that muscle strength, duration of mechanical ventilation, and female sex were associated with a poor rehabilitation outcome. Furthermore, we found higher age, lower handgrip strength, female sex, and more comorbidities to be associated with higher odds of ICUAW at discharge.

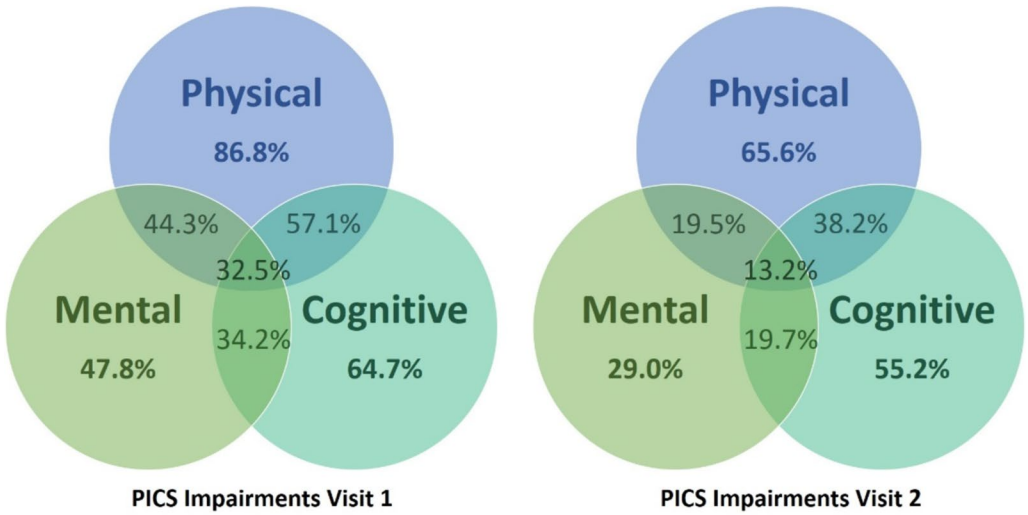

Fig. 2 PICS impairments in each domain and their overlap at study visits 1 and 2

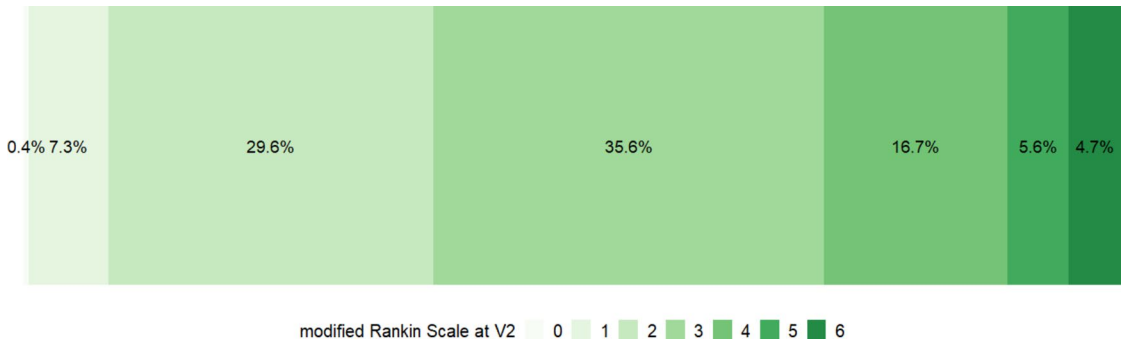

Fig. 3 Distribution of the modified Rankin Scale at V2

Outcome after rehabilitation in survivors of critical illness

Studies in survivors of critical illness describing the course of rehabilitation or including comprehensive outcomes are sparse. There are some studies which reported significant improvements after inpatient rehabilitation, but the description of outcomes is often narrowed down to the Barthel-Index, modified Rankin Scale or Functional Independence Measure (FIM) [64–66]. One study with a set of comprehensive assessments described an 8 week course at a post-ICU hospital and inpatient rehabilitation of patients with ICUAW [27]. All outcome parameters of physical and cognitive function, except pain, improved significantly until discharge, but, the health status at discharge was substantially more impaired compared to our cohort. A shorter time since disease onset and a longer duration of mechanical ventilation in this study may have contributed to these differing findings. Another study reported the outcome of CIP/CIM patients after an average of 11 weeks of rehabilitation [67]. The MRC sum score, the modified Rankin Scale, and the Barthel-Index improved over time and the scores were similar to those we reported. In consequence of our results and the results of prior studies, inpatient rehabilitation seems beneficial for improving the physical functioning of survivors of critical illness. Our study also suggests a slight positive influence on cognitive and mental health, which requires further evaluation. However, randomized controlled trials are needed to evaluate the true effect of rehabilitation and to investigate therapies with the greatest positive influence.

We reported a comprehensive set of outcome assessments. As hardly any psychometric properties have been evaluated for critical illness survivors thus far, we demonstrated their suitability for this patient group and provided reference values. We successfully conducted all performance outcomes except the Five Times Sit to Stand test, which only 129 patients could complete at V1 shortly after ICU discharge. Future studies should investigate psychometric properties of assessment tools for their use in patients after critical illness, as our group

Table 6 Results of the multiple logistic regression analyses

Model poor rehabilitation outcome			**Model ICUAW**		
	Odds Ratio	95% CI		Odds Ratio	95% CI
Intercept	173.98	9.06; 4246.63	Intercept	2.95	0.39; 23.67
MRC Sum V1	**0.85**	**0.79; 0.90**	**Grip strength % V1**	**0.93**	**0.91; 0.96**
Duration MV	**1.02**	**1.005; 1.03**	**Age**	**1.04**	**1.02; 1.08**
Sex			**Sex**		
Women	**Reference**		**Women**	**Reference**	
Men	**0.45**	**0.21; 0.93**	**Men**	**0.42**	**0.19; 0.89**
Brain injury			**Elixhauser**	**1.06**	**1.01; 1.13**
No	Reference				
Yes	3.22	1.00; 11.61			
Diabetes			Obesity		
No	Reference		No	Reference	
Yes	2.23	0.91; 5.85	Yes	2.38	1.01; 5.88
Elixhauser	1.04	0.99; 1.10	ECMO		
			No	Reference	
			Yes	0.42	0.17; 1.06
Age	1.02	0.99; 1.05	Brain injury		
			No	Reference	
			Yes	2.90	0.90; 10.35
R^2 (Nagelkerke)	0.360			0.331	
Somer's D	0.601			0.585	
Chi^2-Statistic	60.60 (df = 7); p < .001			52.01 (df = 7); p < .001	

Significant values are in bold. *ICUAW* Intensive care unit-acquired weakness, *MV* mechanical ventilation, *ECMO* Extracorporeal membrane oxygenation

recently did by evaluating the Mini-BESTest for assessing balance [58].

Investigations of chronically critically ill patients are rare. It was reported that 65% had a devastating outcome at 1 year with complete functional dependency and death [68] and that only around 20% will return home [63]. Our cohort showed superior health statuses, as only 10.3% had a very poor outcome (modified Rankin Scale 5 and 6) and 72% were discharged home. Further studies with chronically critically patients are needed to contextualize our results.

Frequencies of PICS and related aspects

In critically ill patients after COVID-19, 90–94% met the criteria for PICS at 1.5–3 months after ICU discharge [69–71]. Our PICS frequencies are therefore in line with previous results. Reported frequencies in the domains varied, which is also due to differences in diagnosing. Physical impairment was reported in 81–87% [69, 71], which is slightly higher than our results. However, they measured physical impairment with the EQ-5D-5L, in which we found similar percentages of problems in the domains walking, and pain and discomfort. Cognitive impairment varied from 25 to 67% [69, 71, 72] and mental impairment was reported in 49% [69, 71], which was substantially more frequent compared to our cohort. However, PICS is more than just ICUAW and concerning values in HADS or MoCA. Thus, our definition is a simplification of PICS and there might be patients with impairments in activities of daily living, sleep, health-related quality of life or with post-traumatic stress disorder, which we have not considered. Furthermore, it was recently suggested that chronic pain be included in PICS as it was frequently (up to 77%) reported in patients following ICU discharge [73]. In our cohort, 57% of individuals reported pain, which did not improve during neurorehabilitation. This topic requires further attention, as pain can become chronic, greatly affects daily life and often correlates with both anxiety and depression [74].

Fatigue was reported in 47% of chronically critically ill patients at 3 months [75] and in 70% of ARDS survivors at 6 months [76]. Frequency was also high in critical illness survivors due to COVID-19, especially 3–12 months after discharge from rehabilitation (45–55%) [77]. Consequently, while not desirable, we anticipate an increase in the relatively low fatigue frequency for this cohort over the long-term, consistent with an increase in anxiety and depression as recently reported [77].

Health-related quality of life [78] improved during neurorehabilitation but was still substantially reduced at discharge compared to a German general population of equal age [79] and compared to critical COVID-19 survivors [3, 80].

In short, the high frequency of PICS impairments and associated symptoms underscores their clinical and scientific importance. However, our definition of PICS likely simplifies the true and more comprehensive impairments experienced by affected individuals, which needs to be considered in future studies.

Associated factors with rehabilitation outcome and persistent ICUAW

Factors associated with the rehabilitation outcome after critical illness have scarcely been investigated thus far. Miyamoto et al. [81] reported older age, more than one preclinical comorbidity and longer duration of mechanical ventilation as being associated with a worsened status in activities of daily living 3 months after ICU discharge [81]. Kang and Lee 2024 investigated physical impairment in activities of daily living 3 months after ICU discharge and reported female gender, preclinical comorbidities, and a longer ICU stay as associated with physical impairments [82]. According to a meta-analysis, high disease severity, older age and female sex were significant risk factors for physical impairment irrespective of their occurrence date [5]. These results are in line with our results, where longer duration of mechanical ventilation, female sex, and more comorbidities were also associated with a poor rehabilitation outcome.

Factors associated with the occurrence of ICUAW beyond the ICU have scarcely been investigated. Benedini et al. [83] found a strong correlation between handgrip strength and long-term muscle weakness of the lower extremities, which corresponds to our results. Higher age and female sex were previously associated with ICUAW at ICU, which is in line with our results for persistent ICUAW [84]. Contrary to previous findings, the duration of mechanical ventilation was not associated with persistent ICUAW, a factor often deemed significant in previous reports on ICUAW risk within the ICU [13, 84]. ECMO was included in the model despite lacking statistical significance, and the OR indicated a lower risk of ICUAW in ECMO-treated patients, contrary to expectations [85]. Notably, ECMO patients in our cohort were significantly younger than non-ECMO patients, which may explain this unexpected finding.

Although we expected CIP/CIM and preclinical frailty to be associated with the rehabilitation outcome [86, 87], this was not supported by our analyses. Acquired brain injury was included in both models, reinforcing prior findings that critically ill stroke patients, especially those requiring mechanical ventilation or with CIP/CIM, have poor outcomes [88–90].

Practical implications

Although significant improvements were found after neurorehabilitation, most patients did not regain their preclinical health status. PICS was still highly prevalent at discharge from rehabilitation. Therefore, follow-up investigations and ongoing intensive and tailored therapies, implemented for example within a PICS follow-up system [91], are highly recommended. The results of the regression analyses provide insights into the relationships between variables and the likelihood of poor rehabilitation outcomes and persistent ICUAW. As female gender, age, and the Elixhauser comorbidity index were included in the final regression models, women and older individuals with more comorbidities should receive special attention in the long term. Duration of mechanical ventilation was associated with a poor rehabilitation outcome, suggesting prolonged ventilation might impact recovery, though causality remains unclear. The strong association between muscle strength post-ICU discharge and rehabilitation outcomes indicates that interventions aiming to enhance muscle strength could be beneficial, but further research is needed to determine their effectiveness.

Strengths and limitations

Strengths of this study are the comprehensive set of outcome measures, the large number of enrolled patients, and the electrophysiological testing of CIP/CIM. A limitation for generalization of our results might be the high severity of critical illness in our participants, who had extraordinarily long durations of ICU treatment and mechanical ventilation, with all patients fulfilling the criteria for chronic critical illness. Although the results might therefore not be generalizable for all critical illness survivors, it is important to report these patients. Furthermore, as patients were only included in the study when communication abilities were sufficient to perform the assessments, patients with disorders of consciousness, severe dementia, and severe aphasia were not included. Therefore, future studies should consider the inclusion of non-communicative individuals with an adapted study design.

Another limitation is the lack of established psychometric properties for most of the outcome measures. While these measures are frequently used in critical care research and recommended for assessing PICS, the psychometric properties have been insufficiently evaluated. Future studies are required to assess parameters such as reliability and validity, to ensure the robustness and accuracy of the measurements.

As we did not include a control group receiving another type of intervention, no conclusions can be made about the causal effect of neurorehabilitation approaches in critical care survivors. Thus, randomized controlled trials are needed to identify the most effective treatments for improving the outcome of critical illness survivors and patients with PICS/ICUAW [19, 20].

The results of the logistic regressions should be interpreted with caution. Variable selection is widely debated, as it often introduces uncertainty and can impair the validity of results [92]. To address this issue, we followed the recommendations by Heinze et al. [61], conducted the preferred variable selection procedure backward elimination with AIC as stopping criterion (instead of using pre-specified significance levels), and applied post-estimation shrinkage methods and model stability investigations. However, we did not perform external validation, which could have provided further insights into the model's robustness and generalizability. The potential for overfitting should also be considered.

The exclusion criterion of no muscular weakness (i.e., MRC 5/5) could be discussed. It was chosen to ensure the inclusion of only patients showing signs of functional impairment; however, it does not align with typical characterizations like ICUAW. Since only 2 out of 814 patients were excluded due to this criterion, it did not result in a different subset of critical illness survivors than those usually treated at our hospital.

Conclusions

In this prospective cohort study with survivors of critical illness, we demonstrated significant improvements during rehabilitation across a comprehensive set of patient-reported, clinician-reported and performance outcomes. Despite the positive progress, PICS was still present in 85% of individuals at discharge from rehabilitation, whereby mostly physical and cognitive impairments persisted. Accordingly, health-related quality of life was substantially reduced. We found that lower muscle strength after ICU discharge, female gender, longer duration of mechanical ventilation, higher age, and more comorbidities were associated with poor rehabilitation outcomes. Therefore, follow-up investigations and ongoing intensive, tailored, and multidisciplinary therapies are indicated in survivors of critical illness. Accordingly, randomized controlled trials are required to identify the most effective treatments.

Supplementary Information

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Supplementary material 1

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Author contributions
ME: conceptualization, data curation; formal analysis; funding acquisition; investigation; methodology; project administration; software; supervision; validation; visualization; writing—original draft; writing—review & editing. MF: investigation; validation; writing—review & editing DF: investigation; writing—review & editing. FW: investigation; validation; writing—review & editing. MS: investigation; writing—review & editing. FM: conceptualization; methodology; resources; validation; writing—review & editing. VH: writing—review & editing. KJ: conceptualization; funding acquisition; methodology; project administration; resources; supervision; validation; writing—review & editing. JB: conceptualization; funding acquisition; methodology; project administration; supervision; validation; writing—review & editing. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the medical ethics committee of the Ludwig-Maximilians-Universität in Munich according to the Declaration of Helsinki (project no. 20-166). Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Department of Neurology, Schoen Clinic Bad Aibling, Research Group, Kolbermoorer Strasse 72, 83043 Bad Aibling, Germany. [2]Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, Munich, Germany. [3]Department of Critical Care Medicine and Anesthesiology, Schoen Clinic Bad Aibling, Bad Aibling, Germany. [4]Department of Anesthesiology, LMU University Hospital, LMU Munich, Munich, Germany. [5]German Center for Vertigo and Balance Disorders, LMU, University Hospital, Munich, Germany.

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Publisher's Note

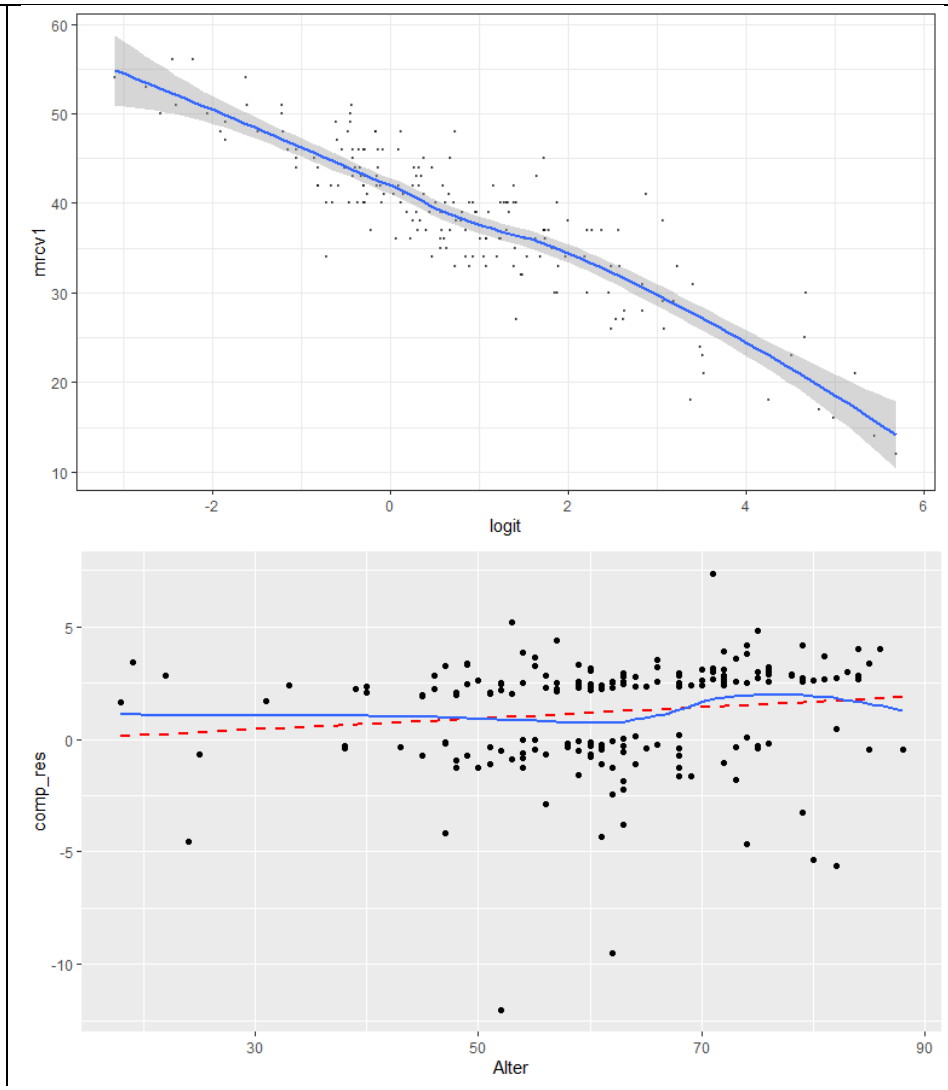
Supplementary Material

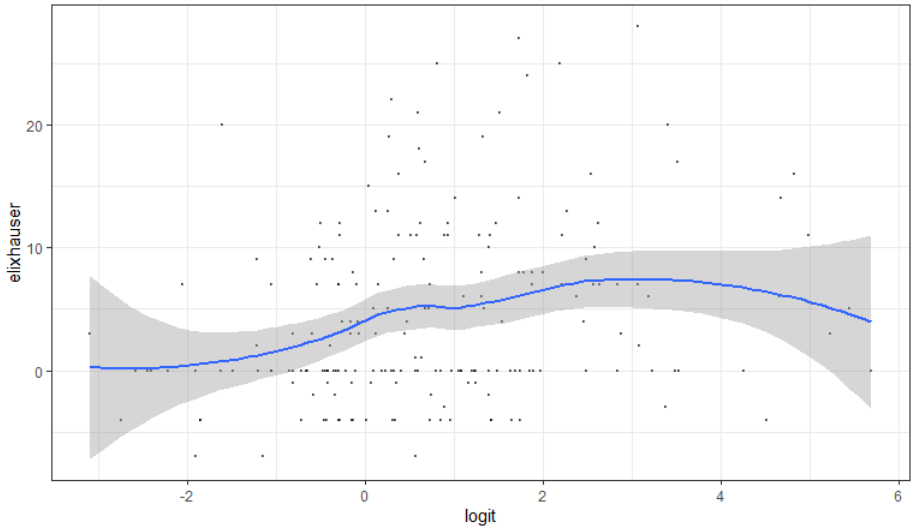
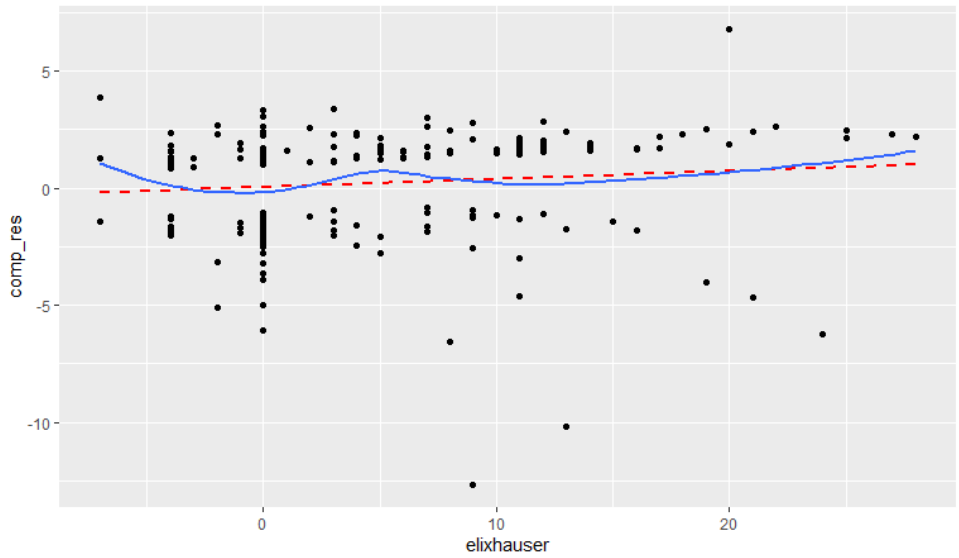
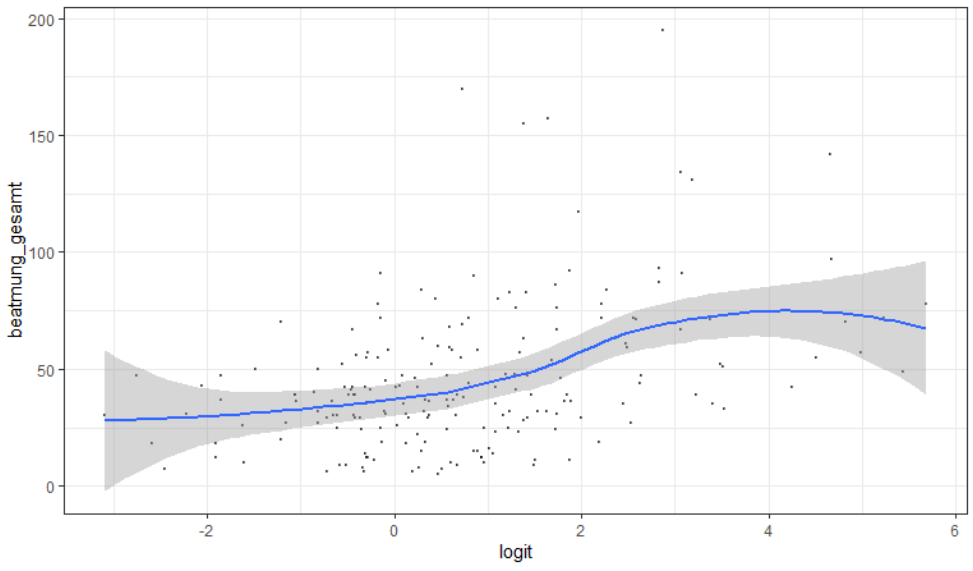
Comprehensive assessment and progression of health status during neurorehabilitation in survivors of critical illness: a prospective cohort study

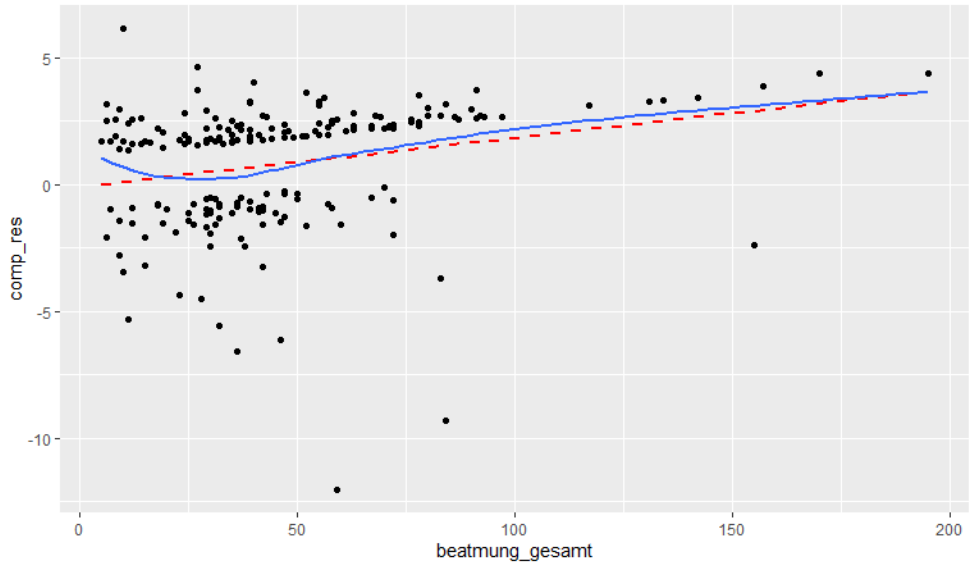
Marion Egger, Melanie Finsterhölzl, Daria Farabegoli, Franziska Wippenbeck, Maria Schlutt, Friedemann Müller, Volker Huge, Klaus Jahn, Jeannine Bergmann

Corresponding author: Marion Egger (megger@schoen-klinik.de)

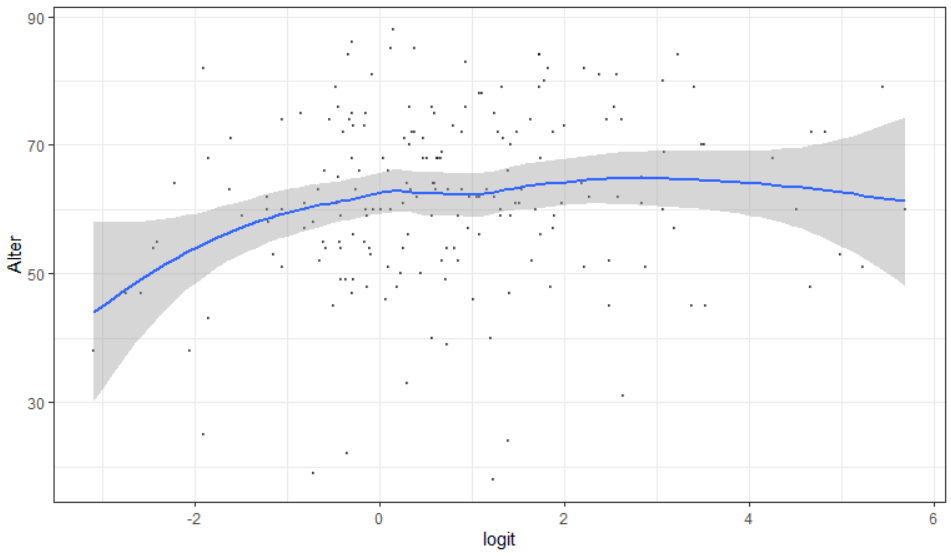
Supplementary Figure 1 Linearity assumption of continuous predictors and the logit of the outcome for model of rehabilitation outcome (modified Rankin Scale)

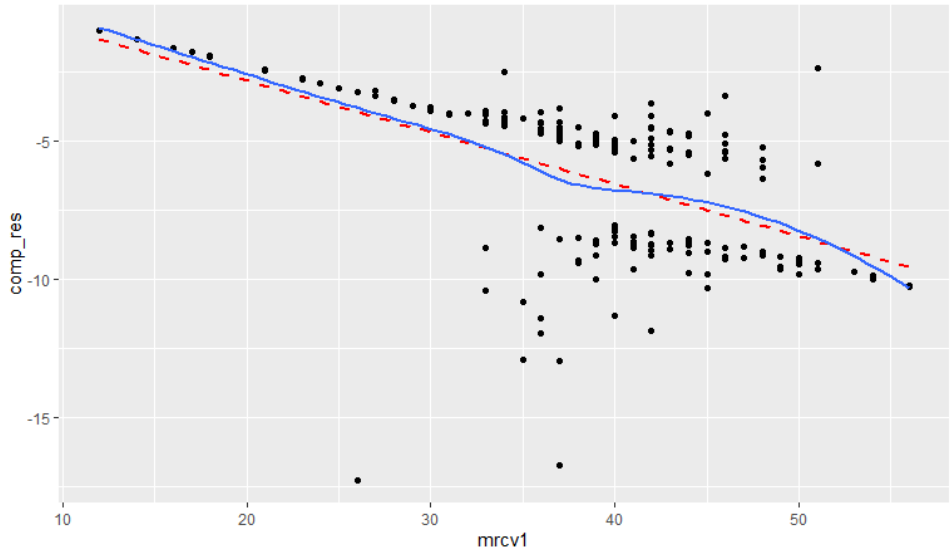
MRC Sum Score V1	

Elixhauser Comorbidity Scale	 
Duration of mechanical ventilation	

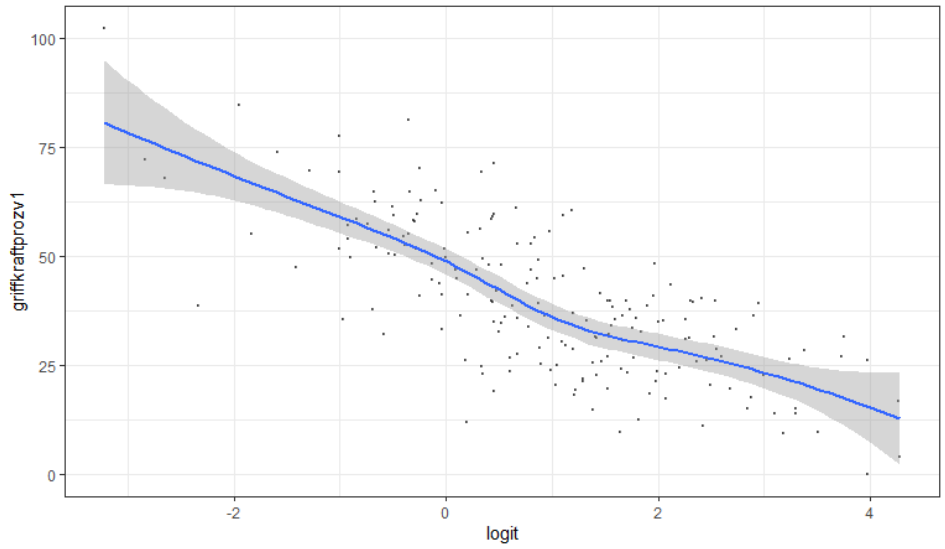
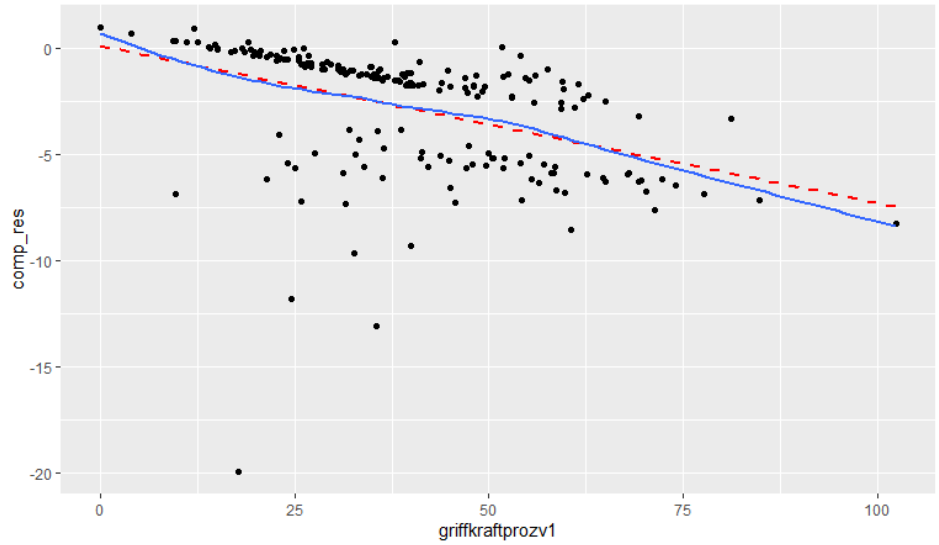
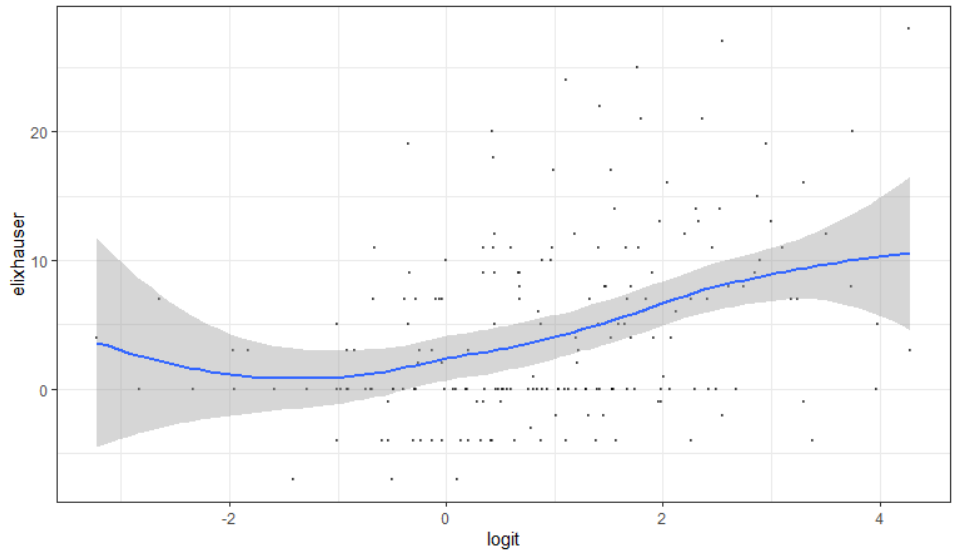


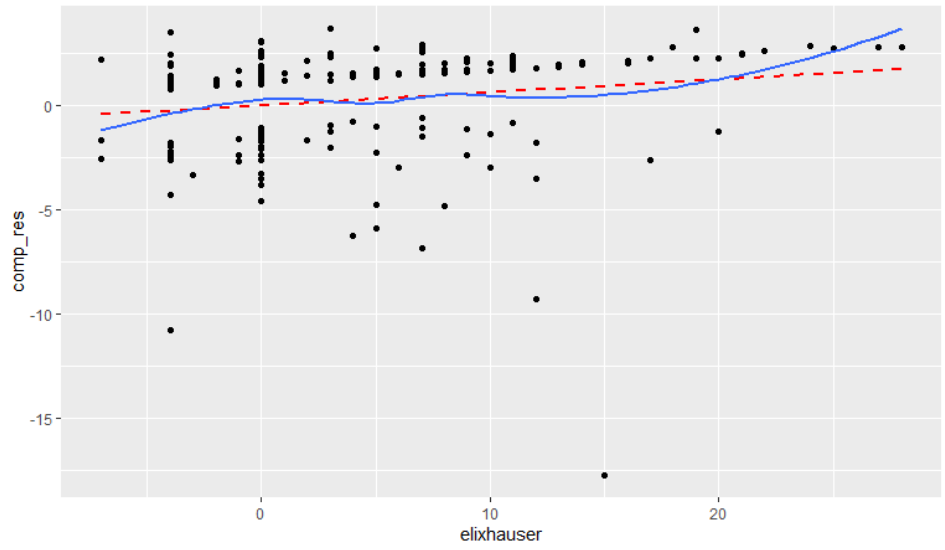
Age





Supplementary Figure 2 Linearity assumption of continuous predictors and the logit of the outcome for model of muscle weakness outcome (MRC sum score)

Handgrip strength at V1	 
Elixhauser Comorbidity Scale	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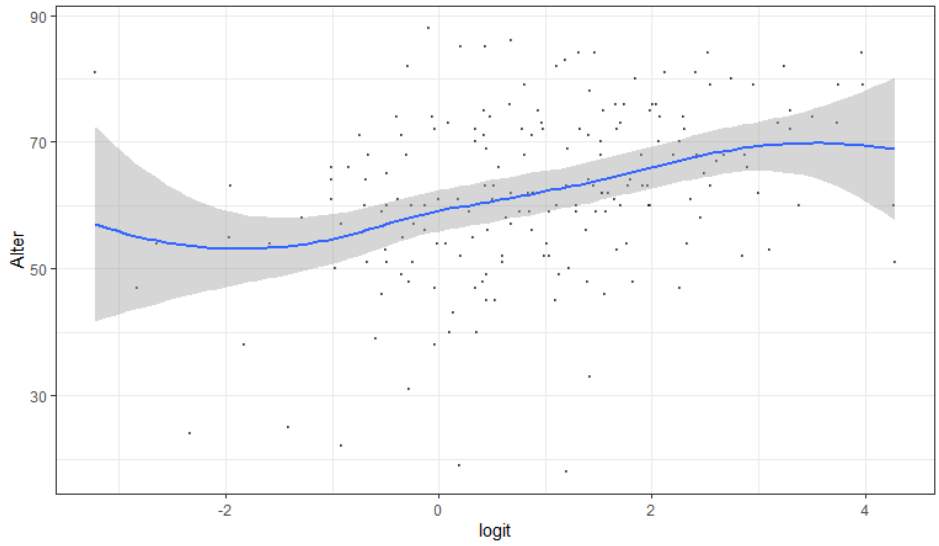
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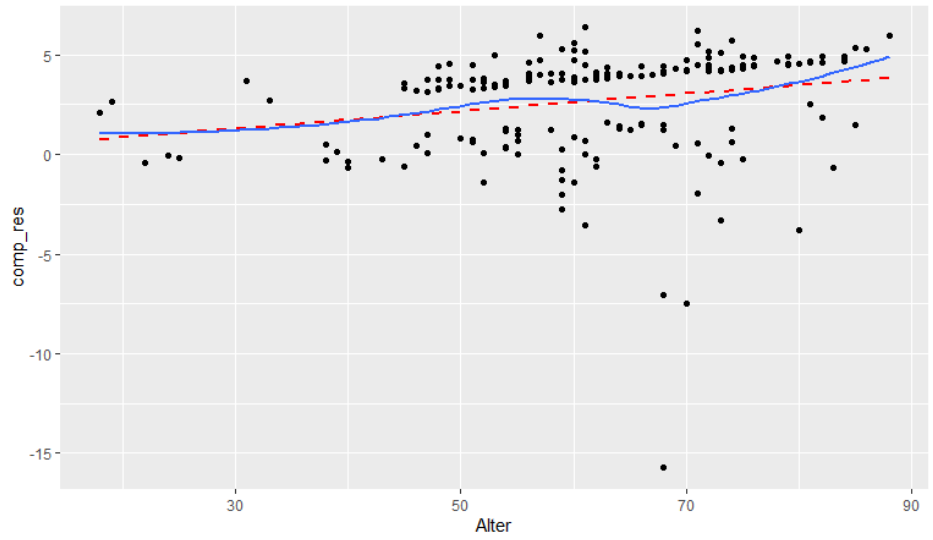
comp_res
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Supplementary Table 1 Multiple logistic regression analysis and bootstrapping results for the rehabilitation outcome

	Global model			Selected model						
	Beta Coefficient	**95% CI**	**p-value**	**Beta Coefficient**	**95% CI**	**p-value**	**Bootstrap inclusion frequency (%)**	**Relative conditional bias (%)**	**Bootstrap median**	**Bootstrap 95% CI**
(Intercept)	3.56	-1.05; 8.39	0.137	5.16	2.2; 8.35	<.001	100	41.34	4.97	-0.81; 11.39
MRC Sum Score at V1	-0.16	**-0.23; -0.10**	**<.001**	-0.16	**-0.23; -0.10**	**<.001**	100	15.19	-0.18	-0.28; -0.12
Duration of mechanical ventilation [days]	0.02	**0.00; 0.03**	**0.019**	0.02	**0.00; 0.03**	**0.011**	88.4	27.3	0.02	0; 0.04
Acquired brain injury										
No	*Reference*									
Yes	**1.55**	**0.22; 3.01**	**0.028**	1.17	0.00; 2.45	0.059	73.5	21.64	1.44	0; 3.43
Sex										
Women	*Reference*									
Men	-0.76	-1.59; 0.02	0.062	-0.80	**-1.57; -0.07**	**0.035**	68.9	37.56	-0.81	-1.77; 0
Age [years]	0.03	0.00; 0.08	0.082	0.02	-0.01; 0.05	0.158	61.2	45.69	0.03	0; 0.08
Diabetes										
No diabetes	*Reference*									
Diabetes	0.69	-0.28; 1.72	0.174	0.80	-0.09; 1.77	0.088	58.8	90.65	0.89	0; 2.27
Elixhauser comorbidity index	0.05	-0.01; 0.11	0.119	0.04	-0.01; 0.09	0.110	56.8	63.46	0.05	0; 0.13
Sepsis										
No	*Reference*									
Yes	0.50	-0.26; 1.28	0.197				41.4	68.84	0	0; 1.36
Preclinical mental health impairment										
None	*Reference*									
Yes	0.52	-0.47; 1.57	0.314				39.8	130.55	0	0; 1.98
Preclinical Frailty										
None-frail	*Reference*									
Frail	0.63	-0.71; 2.15	0.378				37	272.68	0	-0.83; 3.57
Body weight status										
No obesity	*Reference*									
Obesity	0.35	-0.53; 1.25	0.439				34.2	148.52	0	-0.71; 1.60
MoCA at V1	0.02	-0.10; 0.12	0.775				28.8	56.69	0	-0.14; 0.16

Supplementary Table 1 Multiple logistic regression analysis and bootstrapping results for the rehabilitation outcome

	Global model			Selected model						
	Beta Coefficient	**95% CI**	**p-value**	**Beta Coefficient**	**95% CI**	**p-value**	**Bootstrap inclusion frequency (%)**	**Relative conditional bias (%)**	**Bootstrap median**	**Bootstrap 95% CI**
Delirium										
No	*Reference*									
Yes	-0.18	-0.93; 0.58	0.645				23.5	148.67	0	-1.09; 0.76
Living alone										
No	*Reference*									
Yes	-0.15	-1.05; 0.75	0.751				22.8	226.48	0	-1.31; 0.92
ECMO										
No	*Reference*									
Yes	0.22	-0.73; 1.20	0.649				21.5	163.41	0	-0.99; 1.44
Primary diagnose:										
COVID-19	*Reference*									
No	0.07	-0.79; 0.94	0.871				18.1	-125.11	0	-1.06; 0.98
Yes										
CIP/CIM										
No	*Reference*									
Yes	0.01	-0.94; 0.94	0.991				16.9	-542.26	0	-1.12; 1.05
AIC		232.62			217.17					

AIC = Akaike information criterion; 95% CI= 95% Confidence Interval; MRC= Medical Research Council; MoCA=Montreal Cognitive Assessment; V1= Visit 1 at admission to rehabilitation; ECMO= Extracorporeal membrane oxygenation; CIP/CIM=Critical Illness Polyneuropathy / Myopathy. The bootstrap median is zero in case a variable was chosen in <50% of the resamples. Significant values are in bold.

Supplementary Table 2 Model selection frequencies for the model rehabilitation outcome

Model	Included predictors	Count	Percent	Cumulative Percent
1	mrcv1 duration.ventilation brain men age diabetes sepsis Frailty.pre.binary	6	0.6	0.6
2	mrcv1 duration.ventilation brain men age diabetes	5	0.5	1.1
3	mrcv1 duration.ventilation brain men age diabetes elixhauser	5	0.5	1.6
4	mrcv1 duration.ventilation brain men age sepsis Frailty.pre.binary	5	0.5	2.1
5	mrcv1 duration.ventilation men elixhauser	4	0.4	2.5
6	mrcv1 duration.ventilation brain men diabetes elixhauser	4	0.4	2.9
7	mrcv1 duration.ventilation brain men diabetes elixhauser sepsis	4	0.4	3.3
8	mrcv1 duration.ventilation brain men age diabetes elixhauser sepsis	4	0.4	3.7
9	mrcv1 duration.ventilation men age diabetes pre.mental.disease	4	0.4	4.1
10	mrcv1 duration.ventilation brain men diabetes elixhauser sepsis Frailty.pre.binary	4	0.4	4.5
11	mrcv1 duration.ventilation brain men age elixhauser Adipositas moca_v1	4	0.4	4.9
12	mrcv1 duration.ventilation brain men age diabetes elixhauser sepsis	4	0.4	5.3
13	mrcv1 duration.ventilation men diabetes	3	0.3	5.6
14	mrcv1 duration.ventilation brain age diabetes	3	0.3	5.9
15	mrcv1 duration.ventilation brain men age diabetes sepsis	3	0.3	6.2
16	mrcv1 duration.ventilation brain men age elixhauser sepsis	3	0.3	6.5
17	mrcv1 duration.ventilation brain men age elixhauser pre.mental.disease	3	0.3	6.8
18	mrcv1 duration.ventilation brain men diabetes elixhauser pre.mental.disease	3	0.3	7.1
19	mrcv1 duration.ventilation brain men age diabetes elixhauser pre.mental.disease	3	0.3	7.4
20	mrcv1 duration.ventilation brain men age diabetes Frailty.pre.binary	3	0.3	7.7

The model marked in grey is the selected model.

Interpretation of the model stability investigations for the logistic regression for poor rehabilitation outcome:

The model suggested by the bootstrap medians is the same as the selected model, which supports the stability of the model. Bootstrap inclusion frequencies were rather low for age, diabetes and Elixhauser comorbidity scale (57-61%), which is in accordance with rather high relative conditional bias for diabetes (91%) and the Elixhauser scale (63%). Model selection frequencies further added uncertainty for the variables age and the Elixhauser scale, as they were only selected in six of the ten most frequent models. The global shrinkage factor for the selected model was rather low at 0.801 (see Supplementary Table 6 for parameterwise shrinkage factors).

Table 3 Multiple logistic regression analysis for ICUAW at discharge

	Global model			Selected model						
	Beta Coefficient	**95% CI**	**p-value**	**Beta Coefficient**	**95% CI**	**p-value**	**Bootstrap inclusion frequency (%)**	**Relative conditional bias (%)**	**Bootstrap median**	**Bootstrap 95% CI**
(Intercept)	0.97	-1.46; 3.42	0.430	1.08	-0.95; 3.16	0.298	100	25.37	1.2	-1.61; 4.38
Handgrip strength at V1	-0.07	**-0.10; -0.04**	**<.001**	**-0.07**	**-0.10; -0.05**	**<.001**	100	6.91	-0.08	-0.11; -0.05
Age [years]	0.04	**0.01; 0.08**	**0.006**	**0.04**	**0.02; 0.07**	**.004**	92.1	13.05	0.05	0; 0.08
Body weight status										
No obesity	*Reference*									
Obesity	0.90	0.00; 1.85	0.057	0.87	0.01; 1.77	0.052	73.4	33.95	0.98	0; 1.99
Sex										
Women	*Reference*									
Men	-0.80	-1.65; -0.01	0.090	**-0.87**	**-1.68; -0.12**	**0.028**	73	33.63	-0.87	-1.81; 0
ECMO										
No	*Reference*									
Yes	**-1.04**	**-2.05; -0.06**	**0.039**	-0.86	-1.79; 0.06	0.066	73	31.61	-1.08	-2.42; 0
Elixhauser comorbidity index	0.06	-0.01; 0.12	0.089	**0.06**	**0.01; 0.12**	**0.036**	66.2	44.13	0.06	0; 0.14
Acquired brain injury										
No	*Reference*									
Yes	1.08	-0.24; 2.50	0.120	1.06	-0.11; 2.34	0.086	62.2	45.9	1.16	0; 2.56
Preclinical Frailty										
None-frail	*Reference*									
Frail	0.81	-0.75; 2.66	0.341				40	184.4	0	-0.02; 3.91
CIP/CIM										
No	*Reference*									
Yes	0.43	-0.46; 1.33	0.339				32	121.13	0	0; 1.40
Delirium										
No	*Reference*									
Yes	-0.25	-1.02; 0.52	0.525				26	163.42	0	-1.21; 0.65
Sepsis										
No	*Reference*									
Yes	-0.21	-1.02; 0.59	0.616				23.8	232.76	0	-1.34; 0.67

Table 3 Multiple logistic regression analysis for ICUAW at discharge

	Global model			Selected model						
	Beta Coefficient	**95% CI**	**p-value**	**Beta Coefficient**	**95% CI**	**p-value**	**Bootstrap inclusion frequency (%)**	**Relative conditional bias (%)**	**Bootstrap median**	**Bootstrap 95% CI**
Duration of mechanical ventilation [days]	0.00	-0.01; 0.01	0.936				23	-358.62	0	-0.02; 0.02
Primary diagnose:										
COVID-19	*Reference*									
No	0.04	-0.84; 0.93	0.937				22	-523.2	0	-1.14; 1.11
Yes										
Diabetes										
No	*Reference*									
Yes	-0.26	-1.24; 0.74	0.604				20.3	196.6	0	-1.28; 0.68
AIC		218.58			207.59					

AIC = Akaike information criterion; 95% CI= 95% Confidence Interval; MRC= Medical Research Council; MoCA=Montreal Cognitive Assessment; V1= Visit 1 at admission to rehabilitation; ECMO= Extracorporeal membrane oxygenation; CIP/CIM=Critical Illness Polyneuropathy / Myopathy. The bootstrap median is zero in case a variable was chosen in <50% of the resamples. Significant values are in bold.

Supplementary Table 4 Model selection frequencies for model ICUAW at discharge

Model	Included predictors	Count	Percent	Cumulative Percent
1	gripstrength.% age obesity men ecmo elixhauser brain	24	2.4	2.4
2	gripstrength.% age obesity men elixhauser brain	15	1.5	3.9
3	gripstrength.% age obesity men ecmo elixhauser	13	1.3	5.2
4	gripstrength.% age obesity men ecmo elixhauser brain Frailty.pre.binary	12	1.2	6.4
5	gripstrength.% age obesity men ecmo elixhauser brain Frailty.pre.binary delirium	11	1.1	7.5
6	gripstrength.% age obesity ecmo Frailty.pre.binary	9	0.9	8.4
7	gripstrength.% age obesity men ecmo elixhauser brain sepsis	9	0.9	9.3
8	gripstrength.% age obesity men elixhauser brain cipcim	8	0.8	10.1
9	gripstrength.% age obesity men ecmo elixhauser sepsis	8	0.8	10.9
10	gripstrength.% age obesity men elixhauser brain duration.ventilation	8	0.8	11.7

Supplementary Table 4 Model selection frequencies for model ICUAW at discharge

Model	Included predictors	Count	Percent	Cumulative Percent
11	gripstrength.% age obesity men ecmo elixhauser brain duration.ventilation	8	0.8	12.5
12	gripstrength.% age men ecmo elixhauser brain	7	0.7	13.2
13	gripstrength.% age obesity men ecmo elixhauser brain delirium	7	0.7	13.9
14	gripstrength.% age obesity men elixhauser brain	7	0.7	14.6
15	gripstrength.% age obesity men ecmo elixhauser brain Frailty.pre.binary cipcim delirium	6	0.6	15.2
16	gripstrength.% age obesity men ecmo elixhauser cipcim sepsis	6	0.6	15.8
17	gripstrength.% age obesity men ecmo elixhauser brain covid	6	0.6	16.4
18	gripstrength.% age obesity men ecmo elixhauser brain	6	0.6	17
19	gripstrength.% age obesity men ecmo brain	5	0.5	17.5
20	gripstrength.% age obesity men elixhauser brain Frailty.pre.binary	5	0.5	18

The model marked in grey is the selected model.

Supplementary Table 5 Parameterwise shrinkage factors

Model poor rehabilitation outcome		**Model ICUAW**	
Variable	**Parameterwise shrinkage factor**	**Variable**	**Parameterwise shrinkage factor**
MRC sum score	0.916	Handgrip strength	0.846
Duration of mechanical ventilation	0.712	Age	0.753
Sex	0.569	Sex	0.646
Brain injury	0.492	Elixhauser comorbidity scale	0.655
Diabetes	0.572	Obesity	0.583
Elixhauser comorbidity scale	0.513	ECMO	0.689
Age	0.433	Brain injury	0.541

Interpretation of the model stability investigations for the logistic regression for ICUAW at discharge:

Bootstrap inclusion frequencies were ≥ 60% for all variables of the selected model, thus the model suggested by the bootstrap medians was the same as the selected model, which supports the final model. Only the slightly increased relative conditional biases of the Elixhauser scale and brain injury (44-46%) indicate some uncertainty. Model selection frequencies (Supplementary Table 5) supported the stability of the final model, as it was the most frequently chosen model by the bootstrapping procedure. The global shrinkage factor for the selected model was rather low at 0.797 (Supplementary Table 6).

Appendix C: Paper VI

Egger M, Vogelgesang L, Reitelbach J, Bergmann J, Müller F, Jahn K. Severe Post-COVID-19 Condition after Mild Infection: Physical and Mental Health Eight Months Post Infection: A Cross-Sectional Study. *Int J Environ Res Public Health*. 2024; 21 (1): 21. doi: 10.3390/ijerph21010021.

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Article

Severe Post-COVID-19 Condition after Mild Infection: Physical and Mental Health Eight Months Post Infection: A Cross-Sectional Study

Marion Egger [1,2,*], Lena Vogelgesang [1], Judith Reitelbach [1], Jeannine Bergmann [1], Friedemann Müller [1] and Klaus Jahn [1,3]

[1] Research Group, Department of Neurology, Schoen Clinic Bad Aibling, 83043 Bad Aibling, Germany
[2] Institute for Medical Information Processing, Biometry, and Epidemiology (IBE), Faculty of Medicine, LMU Munich, Pettenkofer School of Public Health, 81377 Munich, Germany
[3] German Center for Vertigo and Balance Disorders, University Hospital Grosshadern, Ludwig-Maximilians-Universität (LMU), 81377 Munich, Germany
* Correspondence: megger@schoen-klinik.de

Abstract: Severe acute COVID-19 infections requiring intensive care treatment are reported risk factors for the development of post-COVID-19 conditions. However, there are also individuals suffering from post-COVID-19 symptoms after mild infections. Therefore, we aimed to describe and compare the health status of patients who were initially not hospitalized and patients after critical illness due to COVID-19. The outcome measures included health-related quality of life (EQ-5D-5L, visual analogue scale (VAS)); mental health (hospital anxiety and depression scale (HADS)); general disability (WHODAS-12); and fatigue (Fatigue-Severity-Scale-7). Individuals were recruited at Schoen Clinic Bad Aibling, Germany. A total of 52 non-hospitalized individuals (47 ± 15 years, 64% female, median 214 days post-infection) and 75 hospitalized individuals (61 ± 12 years, 29% female, 235 days post-infection) were analyzed. The non-hospitalized individuals had more fatigue (87%) and anxiety (69%) and a decreased health-related quality of life (VAS 47 ± 20) compared to the hospitalized persons (fatigue 45%, anxiety 43%, VAS 57 ± 21; $p < 0.010$). Severe disability was observed in one third of each group. A decreased quality of life and disability were more pronounced in the females of both groups. After adjusting for confounding, hospitalization did not predict the burden of symptoms. This indicates that persons with post-COVID-19 conditions require follow-up services and treatments, independent of the severity of the acute infection.

Keywords: COVID-19; post-acute COVID-19 syndrome; critical illness; neurological rehabilitation; quality of life; fatigue; mental health; patient reported outcome measures; hospitalization; intensive care units

Citation: Egger, M.; Vogelgesang, L.; Reitelbach, J.; Bergmann, J.; Müller, F.; Jahn, K. Severe Post-COVID-19 Condition after Mild Infection: Physical and Mental Health Eight Months Post Infection: A Cross-Sectional Study. *Int. J. Environ. Res. Public Health* **2024**, *21*, 21. https://doi.org/10.3390/ijerph21010021

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1. Introduction

The SARS-CoV-2 pandemic caused millions of infections all over the globe. Not only did the COVID-19 disease lead to millions of deaths, it has also led to a substantial group of individuals suffering in the long-term from a variety of heterogeneous symptoms after the infection. The so-called post-COVID-19 condition (according to the WHO's case definition) or post-COVID-19 syndrome (according to the NICE guideline on long COVID) occurs in individuals exhibiting symptoms more than three months after the infection. The symptoms can be persistent, fluctuating or relapsing and most commonly include fatigue, dyspnea and sleep disorders. Furthermore, symptoms such as difficulties concentrating, anxiety, depression, effort intolerance, joint pain and myalgia were frequently reported up to more than twelve months after infection [1]. To date, long-term symptoms were even reported up to two years after infection [2,3]. In a recent meta-analysis, considerable (pooled) prevalences were reported for the post-COVID-19 condition, with the prevalence

in hospitalized patients being higher (54% (95% CI 44–63%)) than in non-hospitalized patients (34% (95% CI 29–37%)) [4]. There are several risk factors for a post-COVID-19 condition. Women were especially shown to have a significantly greater likelihood of having post-COVID-19 symptoms than men [5]. Other risk factors include (but are not limited to) pre-existing asthma, more severe COVID-19 during the acute phase and older age [4].

Hospitalization seems to be one crucial factor for the presence and the severity of a post-COVID-19 condition. In several systematic reviews, meta-analyses and studies, the condition was compared between hospitalized and non-hospitalized individuals. It was reported that hospitalization led to greater limitations on activities of daily living, had a greater impact on returning to work [6] and increased the risk of dyspnea, anxiety, myalgia and hair loss [7].

However, although symptom prevalence and risk seem to be lower in non-hospitalized individuals in general, the burden of symptoms can be extraordinarily high in individual cases. Severe fatigue, breathlessness and neurocognitive impairment particularly impede the management of day-to-day work and participation in social activities and thus can jeopardize one's health-related quality of life [8]. According to Tedros Adhanom Ghebreyesus, the director general of the World Health Organization, "long COVID is devastating people's life and livelihoods" [9]. Patients affected by post-COVID-19 symptoms described disruptions in their work life, social life and home life [10]. According to the results of a qualitative study, individuals with post-COVID-19 conditions mainly experienced a loss of abilities and a loss of control, which led them to re-evaluate their life [11].

Correspondingly, multidisciplinary rehabilitation approaches are recommended for all individuals suffering from post-COVID-19 symptoms [12]. However, waiting lists for COVID-19 specialists and rehabilitation were long [13,14], as the number of people affected by post-COVID-19 symptoms was high, but the number of rehabilitation places and knowledge about effective rehabilitation methods were both scarce.

At the end of 2021 when the burden caused by post-COVID-19 became explicit, a study was initiated by the authors at the Schoen Clinic Bad Aibling. The aim was to develop an interdisciplinary rehabilitation approach for patients with post-COVID-19 conditions [15]. During the recruitment and performance of the study, the extensive severity of symptoms of the study participants became apparent. However, hardly any one of the individuals interested in participating in the study had been hospitalized during the acute COVID-19 disease. The severity of the symptoms was substantial and appeared comparable to the severity experienced by critically ill individuals due to COVID-19 who required intensive care therapy and mechanical ventilation (as we reported previously [16]). However, up to now, scientific investigations about severe post-COVID-19 conditions in non-hospitalized individuals are rare. In many studies it is pronounced that the post-COVID-19 condition is particularly severe and long-lasting in hospitalized individuals [6,7,17]. Additionally, the focus of previous studies was mainly on prevalences of the post-COVID-19 condition, the different manifestations of symptoms and their change over time [4,17]. However, the impact of the post-COVID-19 condition on specific activities of daily living was hardly described. Accordingly, societal knowledge about the possible vast extent of the post-COVID-19 condition is poor, leading to a lack of recognition and understanding of those who are severely affected.

Therefore, the aim of this study was to describe and emphasize the extraordinary severity of post-COVID-19 symptoms in persons with asymptomatic to mild acute COVID-19 infections who were not hospitalized. Furthermore, we aimed to evaluate their physical and mental health and health-related quality of life and to compare them with individuals who suffered from critical illness due to COVID-19. As the post-COVID-19 condition is mainly influenced by gender, we aimed to analyze the symptoms according to gender.

2. Materials and Methods

2.1. Study Design, Population and Setting

This cross-sectional study is a secondary analysis of two separate studies. All patients were recruited at the Schoen Clinic Bad Aibling, a center for neurological intensive care and inpatient neurorehabilitation in Germany.

The *post-COVID-19 therapy trial* was a quasi-experimental study in which a new rehabilitation intervention for the post-COVID-19 condition was developed and evaluated [15]. The intervention comprised a two-week outpatient therapy (including Nordic Walking, relaxation techniques, breathing training and balance training) at the Schoen Clinic Bad Aibling and an eight-week digital therapy. Adults (≥18 years) with laboratory-confirmed COVID-19 from at least 3 months ago (evaluated by real-time reverse transcriptase PCR) and post-COVID-19 symptoms limiting their general health were eligible for this study. Exclusion criteria were (1) a potentially life-threatening disease preventing participation in an outpatient rehabilitation program, (2) the requirement for inpatient care with supervision by nursing staff and (3) insufficient (German) communication skills to complete the questionnaires and take part in the therapies. This study comprised six study visits in total; for this analysis, only the first study visit (two weeks before the intervention started) was taken into account. By coincidence, nearly all participants had mild acute COVID-19 infections without hospitalization.

The *COVID-19 rehabilitation trial* was an observational prospective cohort study with hospitalized individuals. Adult patients (≥18 years) with laboratory-confirmed COVID-19 (evaluated by real-time reverse transcriptase PCR) were eligible after the infectious stage and after being admitted to neurorehabilitation. Exclusion criteria were (1) insufficient (German) communication skills to complete the questionnaires and (2) patients receiving palliative care. For this analysis, only critically ill COVID-19 patients who received intensive care treatment and invasive mechanical ventilation for >96 h were included. Patients were included at admission to neurological rehabilitation. The five study visits took place at study inclusion; at discharge from neurorehabilitation (both as in-person interviews at the clinic); and 3, 6, and 12 months after discharge (telephone interviews and questionnaires sent by post). In all study visits, a comprehensive set of functional tests, questionnaires and questions about living and working circumstances were performed. For this analysis, only the study visit at 3 months after discharge was taken into account, as this visit took place at approximately the same length of time since the first COVID-19 infection as for the participants in the *post-COVID-19 therapy trial*. Only patients with complete data at this study visit were considered. Part of this study population was described previously in a study on the clinical course during neurorehabilitation and long-term outcomes [16,18].

Both studies were approved by the medical ethics committee of the Ludwig-Maximilians-Universität in Munich according to the Declaration of Helsinki (project no. 22-0310 and 20-0478). Written informed consent was obtained from all participants. The studies were registered at the German Clinical Trials Register (DRKS00029415 and DRKS00025606).

2.2. Outcome Measures

The study visits of *the post-COVID-19 therapy trial* were conducted in person; the visits of the *COVID-19 rehabilitation trial* were conducted via telephone interviews and questionnaires sent by post. All study visits were conducted by trained and experienced study staff.

The following patient-centered outcomes and assessments were used:

- The Fatigue Severity Scale-7 (FSS-7) was used to evaluate fatigue. The seven-item version was utilized, as it has better psychometric properties than the nine-item version [19]. Score: 1–7. The cut-off of ≥4 was interpreted as indicative of fatigue [20].
- The Hospital Anxiety and Depression Scale (HADS) is a valid and reliable tool to measure anxiety and depression and was also previously used in COVID-19 patients [21]. Score: 0–21, each for anxiety and depression. A score of >7 in each category was interpreted as clinically significant [22].

- The EuroQol-5 dimensions-5 level (EQ-5D-5L) was used to measure the health-related quality of life [23]. The index value for the German population ranges from −0.205 (0 = health state equivalent to death; negative values = health state worse than death) to 1.000 (best health state) [24]. Additionally, the visual analogue scale (VAS; included in the EQ-5D-5L; 0–100) was used. A value of 100 indicates the best imaginable state of health.
- The generic World Health Organization Disability Assessment Schedule 2.0 (WHODAS-12) is a measure of disability and functional impairment and comprises the categories cognition, mobility, self-care, getting along, life activities and participation. It is reliable, widely used and has good internal consistency [25]. Each of the twelve scores was scored from 0 (no difficulties) to 4 (extreme difficulties or cannot do). The total score was converted into a percentage ((sum/48) × 100) and allocated to the following groups: no (0–4%); mild (5–24%); moderate (25–49%); severe (50–95%); and complete (96–100%) disability [26].
- To assess dyspnea, the modified medical research council dyspnea scale (mMRC) was used (score 0–4; 4 = severest dyspnea). This scale was repeatedly used in patients with COPD and COVID-19 disease [27,28].

2.3. Statistical Analysis

Study participants were selected based on convenience sampling by choosing patients being treated at our clinic (*COVID-19 rehabilitation trial*) or patients who expressed an interest in participating in the *post-COVID-19 therapy trial*. Sample sizes were derived from the number of ICU COVID-19 patients who were treated in our hospital (*COVID-19 rehabilitation trial*) and from pragmatic reasons in terms of limited resources of time, staff and funding (*post-COVID-19 therapy trial)*.

Categorical variables are presented as absolute values and percentages and continuous variables as mean ± standard deviation or median (quartile 1–quartile 3).

Symptoms were compared between the two study groups and between male and female participants. The Mann–Whitney U test was used when data were either non-parametric or did not follow normal distribution (as checked by the Shapiro–Wilk test and visually by means of Q–Q plots). Independent *t*-tests were applied in cases of parametric data which followed normal distribution. The Chi-squared test was used for categorical values. Fisher's exact test was applied in cases in which more than 20% of the cells had expected cell counts of less than 5.

Multiple linear regression was performed to show that the health-related quality of life and the degree of disability (WHODAS-12 percentage score) are not predicted by the status of hospitalization (yes/no). To control for confounding, a directed acyclic graph (DAG) was created for the two investigations using DAGitty (https://dagitty.net/, accessed on 04 August 2023). According to the DAG, confounder controlling was conducted for gender, age, vaccination (no, first vaccination and full vaccination) and preclinical comorbidities (Elixhauser comorbidity index). The DAGs with the associated study references can be found in the Supplementary File S1. Effect modification by gender was evaluated by adding a hospitalization-by-gender interaction variable to the regression term and by examining its significance. Assumptions for the multiple linear regression (linearity, multicollinearity, homoscedasticity, multivariate normality and autocorrelation) were tested for systematic violations.

Statistical analyses were performed using R version 4.1.1 and IBM SPSS Statistics 19. A p-value of ≤ 0.05 was considered significant. Missing data were not replaced.

3. Results

In the post-COVID-19 therapy trial (non-hospitalized individuals), 114 individuals were screened between June 2022 and March 2023. A total of 55 were included in the trial, and 52 were enrolled in this analysis. In the COVID-19 rehabilitation trial (hospitalized individuals), 349 patients were screened between April 2020 and January 2022. A total of

130 were enrolled in the study from June 2020 until January 2022, and 75 were included in this analysis (Figure 1).

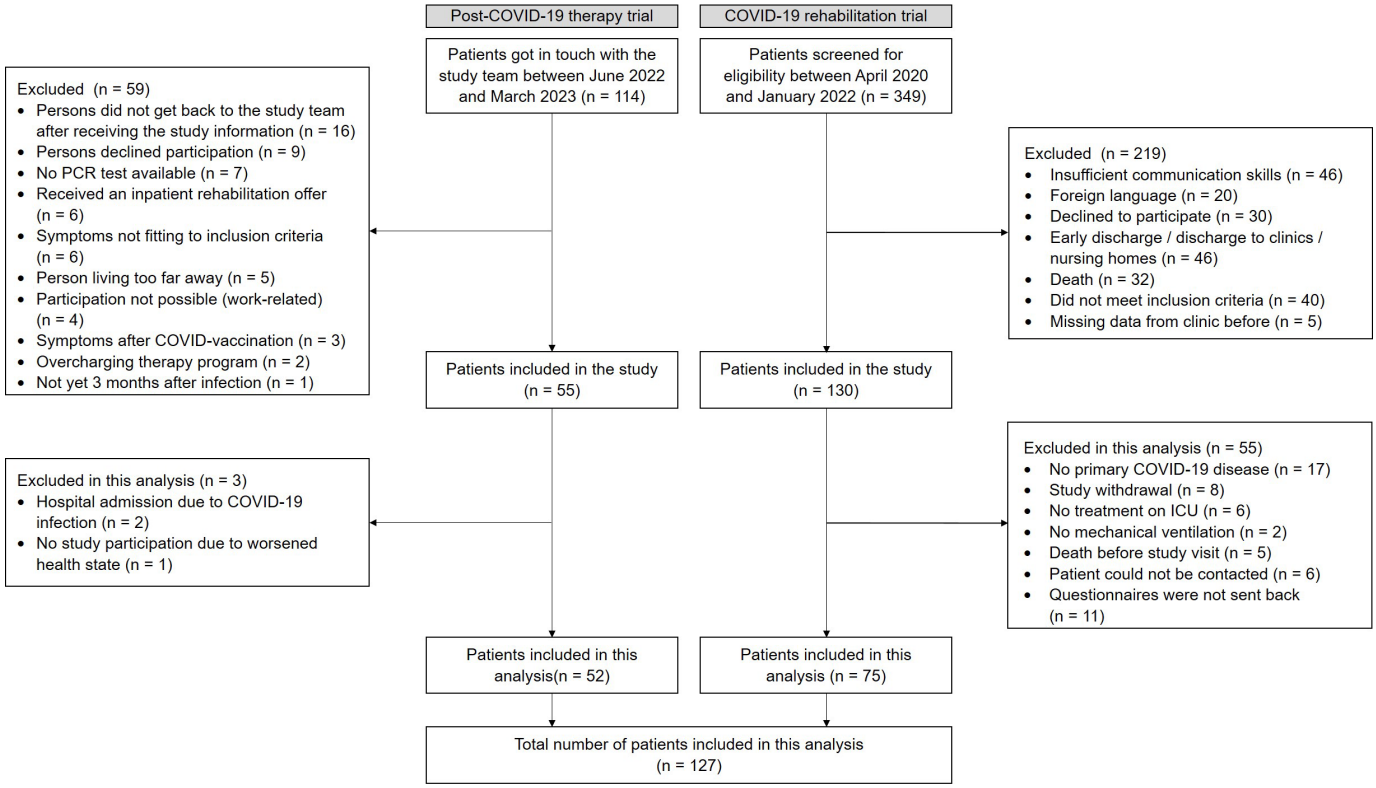

Figure 1. Flow chart for the non-hospitalized individuals (post-COVID-19 therapy trial) and the hospitalized individuals (COVID-19 rehabilitation trial).

The hospitalized patients all had a prolonged stay on the intensive care unit (ICU) (Table 1) and had frequently suffered from sepsis (89.3%), acute respiratory distress syndrome (85.3%) and critical illness polyneuropathy and myopathy (81.4%, as measured by nerve conduction studies). Non-hospitalized individuals were significantly younger, included more females and had significantly fewer prior comorbidities compared to the hospitalized individuals. The duration since the first COVID-19 infection was comparable between the groups and was approximately 7.5 months.

Most of the hospitalized patients were not vaccinated at the time of the SARS-CoV-2 infection, because a high number of patients (n = 36, 48%) were infected during the first two waves in 2020, when a vaccination was not yet available. Another 30 patients were infected during the third wave (until June 2021), when a vaccination was also not yet completely disseminated.

Substantially more individuals in the hospitalized group retired before the infection. The majority of previously employed individuals was on sick leave at the time of the study visits (non-hospitalized: 45%; hospitalized: 59%) or required changes in working hours or working arrangements (non-hospitalized: 27%; hospitalized: 16%). Thus, only a minor group of patients (16–22%) was able to work as before the COVID-19 infection (Table 1).

Fatigue was more frequently reported by non-hospitalized individuals, and nearly everyone in this group had a fatigue score of >4. The prevalence of anxiety was significantly higher, and there was a tendency for a more pronounced depression among non-hospitalized individuals (Table 2), as displayed by the HADS and the EQ-5D-5L. Accordingly, the emotional affection (as measured by item 5 of the WHODAS-12) was also significantly higher in the non-hospitalized group. The health-related quality of life was reduced in both groups; however, it was more affected in the non-hospitalized individuals.

Table 1. Characteristics of the participants.

	Non-Hospitalized Individuals (n = 52)	Hospitalized Individuals (n = 75)
Age at first COVID-19 infection, years	46.9 ± 15.6	61.4 ± 12.1 *
Sex, women	33 (63.5%)	22 (29.3%) †
Duration since first SARS-CoV-2 infection, days	235 (161–412)	214 (178–242) ‡
Length of ICU stay, days	NA	49 (36–66)
Length of mechanical ventilation, days	NA	37 (22–52)
Length of hospitalization, days	NA	107 (78–133)
Extracorporeal membrane oxygenation	NA	16 (21.3%)
Elixhauser Comorbidity Index	0.3 ± 1.8	3.6 ± 6.6 *
Comorbidities		
Diabetes (all type II)	2 (3.8%)	16 (21.3%) †
Obesity	3 (5.8%)	18 (24.0%) †
Hypertension	6 (11.5%)	35 (46.7%) †
Vaccination status at first SARS-CoV-2 infection		
No COVID-19 vaccination	18 (34.6%)	67 (90.5%) §
First COVID-19 vaccination	3 (5.8%)	6 (8.0%)
Full COVID-19 vaccination	28 (53.8%)	1 (1.3%)
Missing	3 (5.8%)	1 (1.3%)
Occupation affected by COVID-19		
Retired before COVID-19	3 (5.8%)	29 (38.7%)
Missing data	-	2 (2.7%)
Subgroup of persons being employed before	49 (100%)	44 (100%) ¶
Employed—no change	11 (22.4%)	7 (15.9%)
Employed—on reduced working hours or changes in working arrangements	13 (26.5%)	7 (15.9%)
Employed—on sickness leave	22 (44.9%)	26 (59.1%)
Employed—had to retire/change job	0 (0.0%)	4 (9.1%)
Employed—lost job	3 (5.8%)	0 (0.0%)

* $p < 0.001$, as tested with independent *t*-tests; † $p < 0.008$, as tested with Chi-squared test; ‡ $p = 0.165$, as tested with Mann—Whitney U test (as data did not follow normal distribution); § $p < 0.001$, as tested with Fisher's exact test; ¶ $p = 0.042$, as tested with Fisher's exact test.

Difficulties in basic physical tasks such as washing and getting dressed were more frequently reported by hospitalized persons. However, more exhausting physical tasks such as walking for one kilometer, household responsibilities or standing for longer periods led to similar difficulties in both groups. Dyspnea was comparable in both groups. Concentration was more impaired in the non-hospitalized individuals. Social activities and participation were also more affected in the non-hospitalized group, and work activities and joining in community activities especially led to severe difficulties in this group (Table 3, Figure 2). However, although the burden of symptoms seemed higher in the non-hospitalized group, most of the hospitalized individuals were also substantially impaired, as two thirds had either a moderate or a severe disability (as measured by the WHODAS-12).

Substantial differences in symptoms were found between males and females. The health-related quality of life and overall disability and functional impairment (as measured by WHODAS-12) were significantly lower in both hospitalized and non-hospitalized women. In contrast, no differences were found for fatigue, anxiety, depression and dyspnea (Table 4).

According to the results of the multiple regression analysis, no significant effect of hospitalization on the health-related quality of life and general disability could be shown after accounting for gender, age, vaccination and comorbidities. It was shown that the

male gender is significantly associated with a higher health-related quality of life and less general disability (Table 5). No effect modification by gender was found.

Table 2. Fatigue, mental health and health related-quality of life of non-hospitalized vs. hospitalized individuals.

	Non-Hospitalized Individuals (n = 52)	Hospitalized Individuals (n = 75)	*p*-Value
FSS-7	5.6 ± 1.3	3.8 ± 2.0	<0.001 ‡
Fatigue ≥4	45 (86.5%)	34 (45.3%)	<0.001 *
HADS			
Anxiety	10 (6–12)	7 (3–10)	0.001 †
Anxiety >7	36 (69.2%)	32 (42.7%)	0.004 *
Depression	8 (5–10)	6 (3–10)	0.064 †
Depression >7	29 (55.8%)	32 (42.7%)	0.154 *
EQ-5D-5L			
Visual Analogue Scale	46.7 ± 20.2	56.5 ± 21.3	0.010 ‡
Index value	0.62 ± 0.23	0.68 ± 0.25	0.130 ‡
Problems with walking around	2 (1–3); 29 (53.8%)	2 (1–4); 56 (74.7%)	0.055 †
Problems with washing/dressing	1 (1–1); 12 (23.1%)	1 (1–3); 36 (48.0%)	0.004 †
Problems with usual activity	3 (2–4); 43 (82.7%)	2 (2–4); 60 (80.0%)	0.114 †
Pain or discomfort	4 (3–4); 49 (94.2%)	3 (2–3); 62 (82.7%)	<0.001 †
Anxiety or depression	2 (2–4); 40 (76.9%)	2 (1–3); 39 (52.0%)	0.002 †
Dyspnea	1 (0–2)	1 (0–2)	0.623 †
No dyspnea (MMRC Score 0)	14 (26.9%)	17 (34.0%) ¶	0.437 *

Data are n (%), mean ± SD or median (quartile 1–quartile 3); FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5l = EuroQol–5 dimensions–5 level; WHODAS-12 = World Health Organization Disability Assessment Schedule 2.0–12 items; † Mann–Whitney U test; ‡ independent *t*-test; * Chi-squared test; ¶ only n = 50 scores available.

Table 3. WHODAS-12 in non-hospitalized vs. hospitalized individuals.

	Non-Hospitalized Individuals (n = 52)	Hospitalized Individuals (n = 75)	*p*-Value
WHODAS-12 percentage score	0.43 ± 0.17	0.38 ± 0.24	0.153 ‡
WHODAS-12 percentage group			
No disability	-	8 (10.7%)	0.053 *
Mild disability	9 (17.3%)	17 (22.7%)	
Moderate disability	25 (48.1%)	25 (33.3%)	
Severe disability	18 (34.6%)	25 (33.3%)	
Complete disability	-	-	
1. Standing for long periods	2 (0–3)	2 (1–3)	0.153 †
2. Household responsibilities	2 (1–3)	2 (1–3)	0.894 †
3. Learning new tasks	2 (1–3)	2 (0–2)	0.090 †
4. Joining in community activities	3 (2–4)	2 (0–3)	0.005 †
5. Emotionally affected	3 (2–4)	2 (1–3)	0.001 †
6. Concentrating for 10 min	2 (1–3)	1 (0–2)	<0.001 †
7. Walking a long distance (1 km)	2 (1–3)	2 (1–4)	0.122 †
8. Washing one's whole body	0 (0–1)	1 (0–2)	<0.001 †
9. Getting dressed	0 (0–0)	1 (0–2)	<0.001 †
10. Dealing with strangers	1 (0–2)	0 (0–1)	0.009 †
11. Maintaining friendships	1 (0–2)	0 (0–1)	0.001 †
12. Work/school activities	3 (2–4)	2 (0–3)	0.001 †

Data are n (%), mean ± SD or median (quartile 1–quartile 3); WHODAS-12 = World Health Organization Disability Assessment Schedule 2.0–12 items; † Mann–Whitney U test; ‡ independent *t*-test; * Chi-squared test.

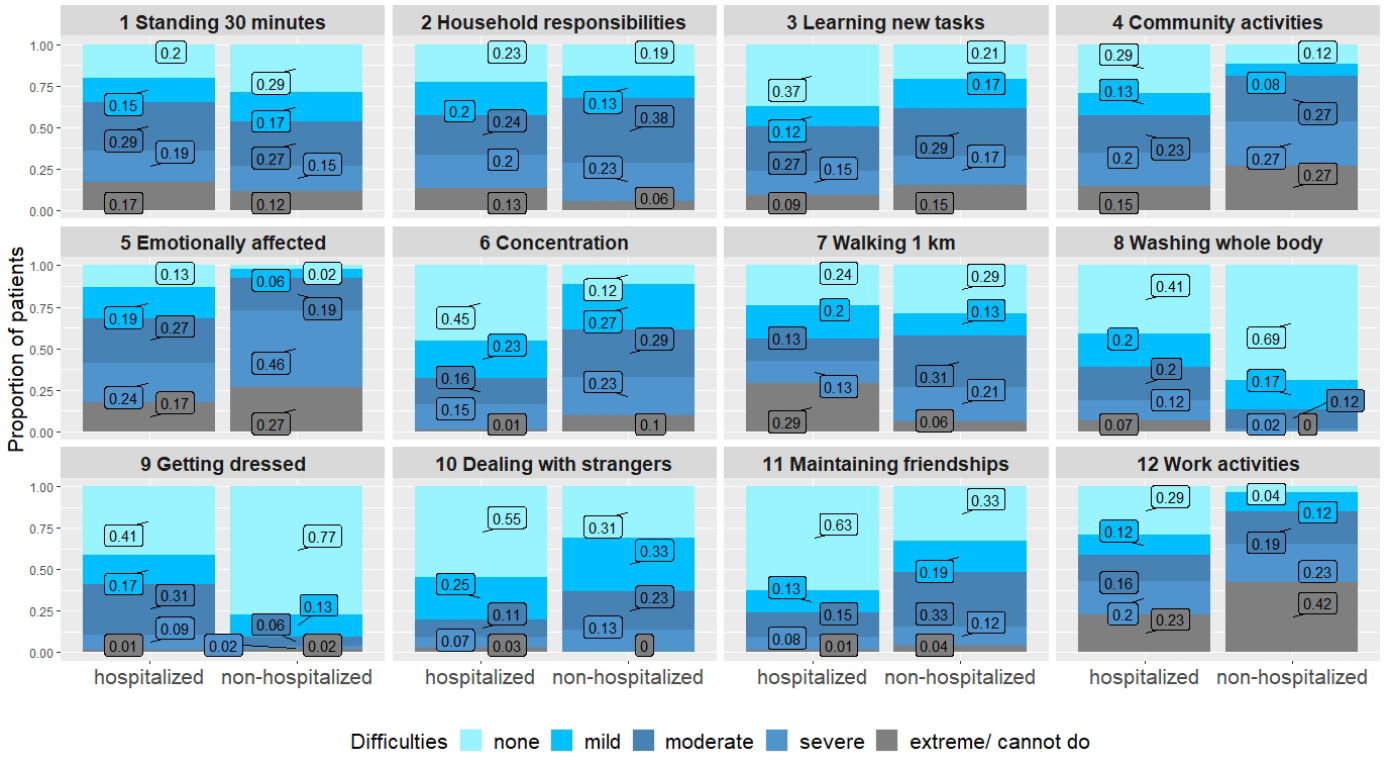

Figure 2. WHODAS-12 comparing hospitalized and non-hospitalized individuals.

Table 4. Post-COVID-19 symptoms by gender and hospitalization status.

	Non-Hospitalized Individuals (n = 52)			Hospitalized Individuals (n = 75)		
	Female (n = 33)	**Male (n = 19)**	***p*-Value**	**Female (n = 22)**	**Male (n = 53)**	***p*-Value**
FSS-7	5.9 ± 1.2	5.1 ± 1.4	0.030 ‡	4.2 ± 2.0	3.6 ± 2.0	0.237 ‡
Fatigue ≥4	30 (90.9%)	15 (78.9%)	0.400 *	12 (54.5%)	22 (41.5%)	0.302 *
HADS						
Anxiety	10 (6–14)	10 (6–12)	0.561 †	7 (4–12)	6 (3–10)	0.327 †
Anxiety >7	23 (69.7%)	13 (68.4%)	0.924 *	10 (45.5%)	22 (41.5%)	0.753 *
Depression	8 (7–10)	7 (5–10)	0.184 †	9 (3–11)	6 (3–9)	0.353 †
Depression >7	21 (63.6%)	8 (42.1%)	0.132 *	12 (54.5%)	20 (37.7%)	0.180 *
EQ-5D-5L						
VAS	41.6 ± 19.0	55.5 ± 19.5	0.015 ‡	47.7 ± 25.0	60.2 ± 18.5	0.020 ‡
Index value	0.55 ± 0.23	0.73 ± 0.17	0.003 ‡	0.60 ± 0.31	0.72 ± 0.22	0.105 ‡
Dyspnea	1 (0–2)	1 (0–2)	0.646 †	1 (0–2)	1 (0–2)	0.831 †
WHODAS-12 percentage score	0.48 ± 0.14	0.34 ± 0.18	0.002 ‡	0.47 ± 0.27	0.34 ± 0.23	0.037 ‡

Data are n (%), mean ± SD or median (quartile 1–quartile 3); FSS-7 = Fatigue-Severity-Scale-7; HADS = Hospital Anxiety and Depression Scale; EQ-5D-5l = EuroQol–5 dimensions–5 level; VAS = Visual Analogue Scale (0–100); WHODAS-12 = World Health Organization Disability Assessment Schedule 2.0–12 items; † Mann–Whitney U test; ‡ independent *t*-test; * Chi-squared test or Fisher's exact test.

Table 5. Results of the multiple linear regression.

	Health Related Quality of Life—Visual Analogue Scale		WHODAS-12 Percentage Score—General Disability	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Intercept	41.33 ***	23.39–59.27	0.42 ***	0.23–0.60
Hospitalization = none	−5.06	−16.54–6.42	−0.00	−0.12–0.12
Gender = male	11.79 **	3.70–19.88	−0.16 ***	−0.24–−0.07

Table 5. *Cont.*

	Health Related Quality of Life—Visual Analogue Scale		WHODAS-12 Percentage Score—General Disability	
	Estimate	**95% CI**	**Estimate**	**95% CI**
Age	0.12	−0.16–0.40	0.00	−0.00–0.00
First Vaccination	5.18	−10.01–20.37	0.09	−0.06–0.24
Full Vaccination	0.98	−10.53–12.49	0.05	−0.07–0.17
Comorbidities	−0.15	−0.88–0.58	0.00	−0.01–0.01

*** < 0.001; ** < 0.01; df = degrees of freedom; Statistical values: Health-related quality of life—R^2 = 0.14, adjusted R^2 = 0.10; F-statistic (degrees of freedom)—(6,115) = 3.23 **; WHODAS-12—R^2 = 0.13, adjusted R^2 = 0.08, F(6,116) = 2.79 *.

4. Discussion

The aim of this analysis was to describe the symptoms of persons with severe post-COVID-19 conditions. Additionally, we evaluated physical and mental health as well as the health-related quality of life and compared them between non-hospitalized individuals with severe post-COVID-19 conditions and individuals after critical illness due to COVID-19. Overall, we demonstrated a high burden of mental and physical symptoms in individuals with severe post-COVID-19 conditions. Persons of both groups mostly suffered from a moderate to severe disability and had a substantially reduced health-related quality of life. However, symptoms such as fatigue, anxiety and difficulties in joining in community activities and work activities were significantly more pronounced in the non-hospitalized individuals. Only gender was found to be significantly associated with health-related quality of life and degree of disability.

4.1. Post-COVID-19 Conditions in Non-Hospitalized vs. Hospitalized Individuals

This investigation differs from previous reports. In former studies comparing non-hospitalized and hospitalized COVID-19 patients, patients were distinguished according to the disease severity of the acute infection. In such studies, it was shown that previously hospitalized patients have a higher risk of the post-COVID-19 condition and suffer more frequently from more severe symptoms than non-hospitalized persons [4,6,7,17,29,30].

However, in some investigations no difference in symptoms according to the hospitalization status [3] or even a worse health state in non-hospitalized individuals were reported. The common factor in most of these investigations was that patients who sought support were recruited, e.g., in outpatient or rehabilitation clinics or in COVID-19 support groups. Houben-Wilke et al. (2022) [31] conducted an online survey among Facebook group members (groups for COVID patients with persistent complaints). Six months after the infection, depression and anxiety were reported in 42% and 29% of hospitalized individuals and in 40% and 37% of non-hospitalized individuals. Johnsen et al. (2021) [32] investigated COVID-19 patients three months after discharge from hospital and patients who were referred to a respiratory outpatient clinic by their general practitioner because of persistent post-COVID-19 symptoms. The health related-quality of life was comparable in both groups, although there was a tendency for lower values in the non-hospitalized individuals (median index value of 0.74 (quartile 1 = 0.66-quartile 3 = 0.80) vs. 0.79 (0.65–0.86); VAS 65 (55–79) vs. 75 (59–90)). Perrot et al. (2022) [33] compared post-COVID-19 symptoms in three groups of patients who were admitted to their post-COVID rehabilitation unit (mean duration of 110 days since discharge from the hospital): patients who were not hospitalized, patients admitted to a general ward and patients admitted to the ICU. Anxiety was found to be significantly less frequent in ICU patients (18.7% vs. 40.7–46.7%), and depression was significantly more common in patients who were not admitted to a hospital (37.0% vs. 17.6–26.7%). Accordingly, the mental component of the health-related quality of life questionnaire SF-36 was more reduced in patients who were not treated in the ICU. However, the physical component of the questionnaire did not differ between the three

groups, and dyspnea was similarly frequent. Accordingly, the health-related quality of life was significantly deteriorated in all patients.

The higher burden of self-reported symptoms in the non-hospitalized individuals might be due to their different points of view. The non-hospitalized individuals perceived themselves as healthy before and during the infection and now suffer from symptoms. In contrast, the hospitalized patients potentially experienced symptom relief at the time of the study visit, e.g., they were able to breathe independently and live back home again with their families. Additionally, they received close supervision, intensive monitoring and rehabilitation during their hospitalization period. Therefore, the point of view of hospitalized patients might be more positive, while the point of view of non-hospitalized patients might be more negative. This assumption is in line with previous reports [33].

4.2. Individuals with Eminently Severe Post-COVID-19 Conditions

Severely affected non-hospitalized participants with symptoms equally severe to those in our particular group of patients have rarely been described so far. Usually, reported symptom prevalences are substantially lower, like in a German population-based study (fatigue, 37%; neurocognitive impairment, 31%; anxiety/depression, 21%) [34]. However, a few studies also reported higher symptom prevalences, similar to our results. For example, Sivan et al. (2021) [35] reported the severity of symptoms of 370 mainly non-hospitalized patients recruited in a dedicated community COVID-19 rehabilitation service. The burden of symptoms (at a median duration of 211 days after infection) was extraordinarily high, as 95% of the patients reported fatigue, 90% reported anxiety, 89% reported pain or discomfort, 85% reported breathlessness and 85% reported cognitive deficits. Tabacof et al. (2022) described the health state of 156 patients (89% initially not hospitalized) who were recruited at an interdisciplinary clinic for post-acute COVID-19 syndrome with a median of 351 days after the infection. A median fatigue score of 5.6 and problematic fatigue (score > 4) were observed in 78% of the patients (as indicated by the Fatigue Severity Scale as in our study). Although fatigue was comparable to our results, and other symptoms such as brain fog (67%), headache (60%) and sleep disturbances (59%) were frequently reported, the frequency of anxiety (19%) and depression (28%) were much lower, and the health-related quality of life was higher (median VAS 64) compared to our two groups of patients.

A reason for the extraordinarily high frequency of symptoms in our group of non-hospitalized patients might be that patients actively got in touch with the study team to participate in the therapy trial due to their high burden of symptoms. This special selection of participants allows for a detailed consideration of patients requiring intensive support and therapies, a group that can easily be overlooked in population studies.

4.3. Gender Inequality of the Post-COVID-19 Condition

In previous studies, it was repeatedly shown that women have a higher risk of developing post-COVID symptoms [5,36]. Fatigue, dyspnea, mental health issues and sleep disturbances were especially more frequently reported in women [5,36–38]. Accordingly, the health-related quality of life was found to be more reduced in women [37]. Our findings are partially in line with these reports. The burden of symptoms seems to be higher in our participating women, as their WHODAS-12 and health-related quality of life scores were significantly more reduced compared to those of the men. Additionally, fatigue and depression were more frequent in women. In contrast, anxiety and dyspnea were equally reported by the male and female participants. This could be either a result of an insufficient sample size or a result of a selection bias in the participants of the post-COVID therapy trial (as outlined in the limitation section). However, the high number of men affected by anxiety (68% of non-hospitalized persons, 42% of hospitalized persons) should be noted, as this indicates a great need for assistance and therapy—not only for women.

4.4. Rehabilitation Recommendations

The reported severity of symptoms, the high percentages of sick leave and reduced working capacities and the negative impact on social life highlight the importance of tailored rehabilitation services. As we confirmed that the manifestation and severity of symptoms can occur irrespective of the severity of the acute illness, the "prescription and provision of rehabilitation programs should be guided by persistent symptoms and functional limitations", as it was stated by the WHO [39]. Individuals suffering mainly from fatigue and mental health issues (like our group of non-hospitalized patients) require approaches like education and skills training on energy conservation techniques and psychological support [39]. In contrast, patients suffering mainly from functional impairments (like our hospitalized patients) and breathing impairments may more likely benefit from education and skills training on self-management strategies for breathing techniques and physical exercise training [39]. However, these recommendations are based on a low certainty of evidence, and high-quality studies are urgently needed to provide beneficial therapy approaches for individuals suffering from long-term persisting symptoms after COVID-19 [40].

4.5. Limitations

There are a number of limitations to our approach. For the non-hospitalized group, only those persons were included who actively applied to take part in our outpatient rehabilitation study. This certainly causes a selection bias. For example, only those individuals with severe symptoms but enough mental confidence, those that were able to come to the clinic, had a sick note or had enough freedom regarding family commitments would apply to participate. Additionally, fatigue might be one of the severest symptoms with the highest impact on normal living. Therefore, it is not surprising that fatigue occurred so frequently in our group of non-hospitalized individuals who sought support. However, we did not intend to give a representative sample but rather aimed to compare two highly affected groups.

Furthermore, our group of hospitalized COVID-19 patients is also very special. In this group, very severely affected patients with extraordinary long durations of ICU treatment and mechanical ventilation are represented [41,42]. As health limitations are common in COVID-19 ICU survivors even after short durations of ICU therapy [43,44], severe and enduring health deficits seem likely in critically ill COVID-19 patients requiring substantially longer times of intensive care treatment [45,46].

Additionally, a larger sample size would have been of advantage to emphasize the concomitant societal burdens and challenges. Therefore, our results are not generalizable regarding hospitalized or non-hospitalized COVID-19 patients in general.

Another limitation is the cross-sectional design of this study, which does not allow for the presence of symptoms to be attributed solely to the infection of SARS-CoV-2. In addition, we did not evaluate the different SARS-CoV-2 variants which might be of relevance, as there were differences in the occurrence, length and severity of the different variants [47].

5. Conclusions

We reported two cohorts with a high burden of post-COVID-19 conditions including mental and physical symptoms as well as a limited health-related quality of life. We observed a moderate to severe disability in both groups. However, symptoms such as fatigue, anxiety and difficulties in joining in community activities and work activities were significantly more pronounced in the non-hospitalized individuals. The female gender, but not hospitalization, was found to be significantly associated with the health-related quality of life and degree of disability. This study emphasizes the severity of post-COVID-19 conditions (even after mild acute infections), its high impact on the daily living of those affected and the need for individualized follow-up services and treatments.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijerph21010021/s1, Supplement S1: DAGs and supporting literature.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki and was approved by the medical Ethics Committee of the Ludwig-Maximilians-Universität in Munich project no. 22-0310 (15 June 2022) and 20-0478 (27 May 2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Supplement S1 – DAGs and supporting literature

Severe Post COVID-19 Condition after Mild Infection: Physical and Mental Health Eight Months Post Infection: A Cross-Sectional Study

Authors: Marion Egger, Lena Vogelgesang, Judith Reitelbach, Jeannine Bergmann, Friedemann Müller, Klaus Jahn

Corresponding author: Marion Egger, megger@schoen-klinik.de

Literature for the DAGs:

- [1] Negative influence of fatigue on health-related quality of life (in ICU survivors) Self-reported fatigue following intensive care of chronically critically ill patients: a prospective cohort study | Journal of Intensive Care | Full Text (biomedcentral.com)
- [2] Fatigue is more frequent in persons with more preexisting medical comorbidities (Post–COVID-19 Symptoms 2 Years After SARS-CoV-2 Infection Among Hospitalized vs Nonhospitalized Patients | Infectious Diseases | JAMA Network Open | JAMA Network)
- [3] Fatigue is more frequent in women (Biomedicines | Free Full-Text | Trajectory of Post-COVID Self-Reported Fatigue and Dyspnoea in Individuals Who Had Been Hospitalized by COVID-19: The LONG-COVID-EXP Multicenter Study (mdpi.com)); Fatigue after COVID-19 in non-hospitalized patients according to sex - PubMed (nih.gov)
- [4] Fatigue is more frequent in hospitalized patients (Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study | Scientific Reports (nature.com))
- [5] Depression has a negative influence on HRQL in ICU survivors Quality of Life, Depression, and Anxiety in Survivors of Critical Illness from a Greek ICU. A Prospective Observational Study - PMC (nih.gov)
- [6] Anxiety has a negative influence on HRQL in ICU survivors (Frontiers | The effect of anxiety and depression on the health-related quality of life of severe acute pancreatitis survivors: structural equation modeling approach (frontiersin.org))
- [7] Women have a lower HRQL than men (Gender differences in health-related quality of life in patients undergoing coronary angiography | Open Heart (bmj.com); Health-related quality of life of COVID-19 patients after discharge: A multicenter follow-up study - PubMed (nih.gov))
- [8] Anxiety is more frequent in women (Gender Effects on Depression, Anxiety, and Stress Regarding the Fear of COVID-19 - PMC (nih.gov))
- [9] Comorbidities influence HRQL (Health-related quality of life in intensive care survivors: Associations with social support, comorbidity, and pain interference | PLOS ONE)
- [10] Comorbidities are a risk factor for anxiety (Prevalence and risk factors of COVID-19-related generalized anxiety disorder among the general public in China: a cross-sectional study - PMC (nih.gov))

- [11] Age negatively influences anxiety and depression (Psych | Free Full-Text | Risk Factors and Changes in Depression and Anxiety over Time in New Zealand during COVID-19: A Longitudinal Cohort Study (mdpi.com))
- [12] Fatigue risk factors are old age, female gender, preclinical comorbidities, severe acute infection (Frontiers | Post-COVID-19 fatigue: A systematic review (frontiersin.org))
- [13] Risk factors for a decline in HRQL are gender, age, severe acute infection, preclinical comorbidity Trajectories of health-related quality of life and their predictors in adult COVID-19 survivors: A longitudinal analysis of the Biobanque Québécoise de la COVID-19 (BQC-19) - PMC (nih.gov)
- [14] Gender is a risk factor for depression (COVID-19 depression and its risk factors in Asia Pacific – A systematic review and meta-analysis - ScienceDirect)
- [15] Risk factors for functional impairment: gender, oxygen therapy during acute disease Risk factors and severity of functional impairment in long COVID: a single-center experience in Croatia - PMC (nih.gov)
- [16] Severity of acute disease influences the degree of function impairments / post-COVID-19 condition Impairments following COVID-19 infection: manifestations and investigations of related factors | Scientific Reports (nature.com); Risk factors for impaired respiratory function post COVID-19: A prospective cohort study of nonhospitalized and hospitalized patients - PubMed (nih.gov)
- [17] Fatigue increases depression Prevalence, trajectory over time, and risk factor of post-COVID-19 fatigue - PMC (nih.gov); Mental health outcomes following COVID-19 infection: impacts of post-COVID impairments and fatigue on depression, anxiety, and insomnia — a web survey in Sweden | BMC Psychiatry | Full Text (biomedcentral.com)
- [18] Fatigue increases anxiety Mental health outcomes following COVID-19 infection: impacts of post-COVID impairments and fatigue on depression, anxiety, and insomnia — a web survey in Sweden | BMC Psychiatry | Full Text (biomedcentral.com)
- [19] Body impairments increase anxiety and depression Mental health outcomes following COVID-19 infection: impacts of post-COVID impairments and fatigue on depression, anxiety, and insomnia — a web survey in Sweden | BMC Psychiatry | Full Text (biomedcentral.com)
- [20] Less post-COVID 19 symptoms after vaccination (Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study - PubMed (nih.gov)), Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review - PubMed (nih.gov), Effect of covid-19 vaccination on long covid: systematic review - PubMed (nih.gov)
- [21] Vaccination leads to less anxiety and depression Mental health outcomes after SARS-CoV-2 vaccination in the United States: A national cross-sectional study - PubMed (nih.gov)
- [22] Vaccines reduce severe or critical disease courses Efficacy and safety of COVID-19 vaccines - PubMed (nih.gov)
- [23] Anxiety and Depression decrease over time Trajectory curves of post-COVID anxiety/depressive symptoms and sleep quality in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study | Psychological Medicine | Cambridge Core
- [24] Fatigue decreases over time Biomedicines | Free Full-Text | Trajectory of Post-COVID Self-Reported Fatigue and Dyspnoea in Individuals Who Had Been Hospitalized by COVID-19: The LONG-COVID-EXP Multicenter Study (mdpi.com)
- [25] Post-COVID symptoms improve over time Trajectories of the evolution of post-COVID-19 condition, up to two years after symptoms onset - ScienceDirect

- [26] Old age, comorbidities and male gender are risk factors for more severe COVID-19 diseases Frontiers | Gender Differences in Patients With COVID-19: Focus on Severity and Mortality (frontiersin.org)
- [27] Multimorbidity is associated with functional decline Functional decline and associated factors in patients with multimorbidity at 8 months of follow-up in primary care: the functionality in pluripathological patients (FUNCIPLUR) longitudinal descriptive study - PMC (nih.gov)
- [28] Differing patterns of multimorbidity by gender, with greater functional impairment in women and more comorbidity in men Multimorbidity gender patterns in hospitalized elderly patients - PMC (nih.gov)
- [29] Depression is more likely in persons with multimorbidity Multimorbidity and depression: A systematic review and meta-analysis - ScienceDirect
- [30] More anxiety in hospitalized COVID-19 patients Frontiers | Post-acute COVID-19 symptom risk in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis (frontiersin.org)
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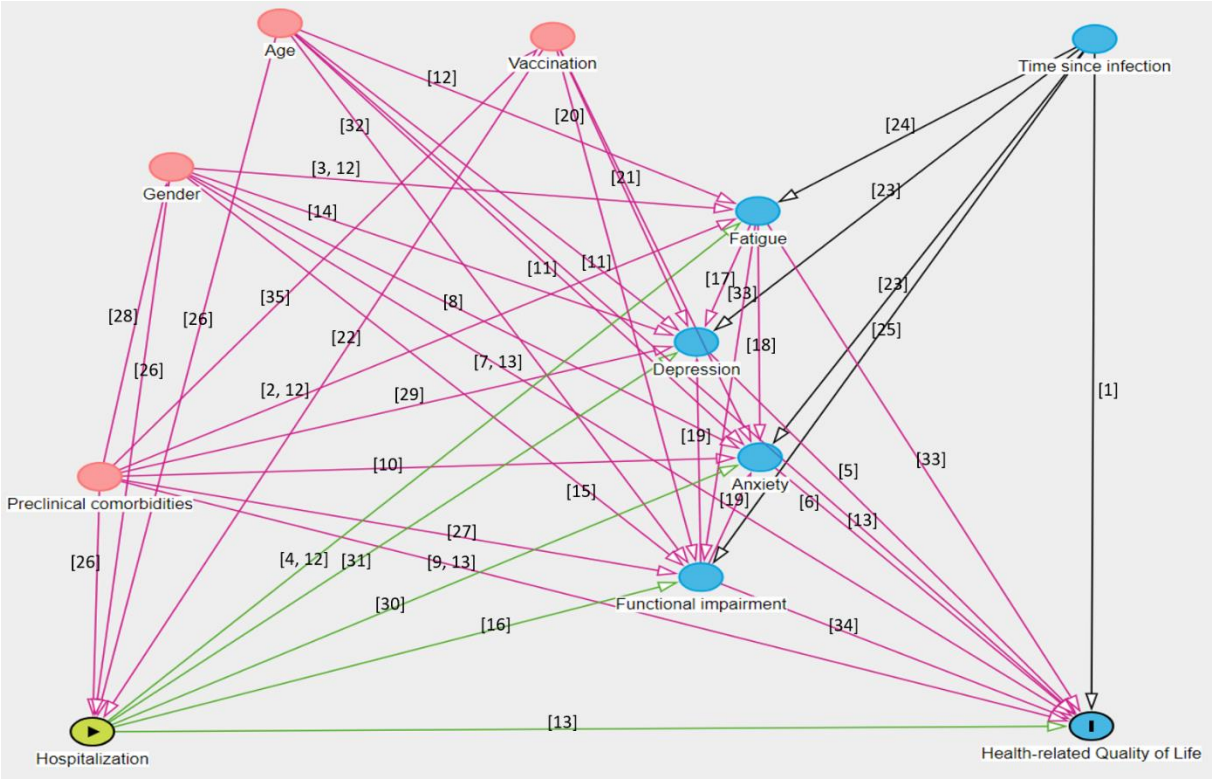
DAG for health-related quality of life:



dag {

"Functional impairment" [pos="-0.647,0.484"]

"Health-related Quality of Life" [outcome,pos="0.040,1.011"]

"Preclinical comorbidities" [pos="-1.705,0.129"]

"Time since infection" [pos="0.046,-1.420"]

Age [pos="-1.305,-1.479"]

Anxiety [pos="-0.543,0.060"]

Depression [pos="-0.655,-0.348"]

Fatigue [pos="-0.547,-0.811"]

Gender [pos="-1.579,-0.967"]

Hospitalization [exposure,pos="-1.718,1.031"]

Vaccination [pos="-0.908,-1.428"]

"Functional impairment" -> "Health-related Quality of Life"

"Functional impairment" -> Anxiety

"Functional impairment" -> Depression

"Preclinical comorbidities" -> "Functional impairment"

"Preclinical comorbidities" -> "Health-related Quality of Life"

"Preclinical comorbidities" -> Anxiety

"Preclinical comorbidities" -> Depression

"Preclinical comorbidities" -> Fatigue

"Preclinical comorbidities" -> Gender

"Preclinical comorbidities" -> Hospitalization

"Preclinical comorbidities" -> Vaccination

"Time since infection" -> "Functional impairment"

"Time since infection" -> "Health-related Quality of Life"

"Time since infection" -> Anxiety

"Time since infection" -> Depression

"Time since infection" -> Fatigue

Age -> "Functional impairment"

Age -> Anxiety

Age -> Depression

Age -> Fatigue

Age -> Hospitalization

Anxiety -> "Health-related Quality of Life"

Depression -> "Health-related Quality of Life"

Fatigue -> "Functional impairment"

Fatigue -> "Health-related Quality of Life"

Fatigue -> Anxiety

Fatigue -> Depression

Gender -> "Functional impairment"

Gender -> "Health-related Quality of Life"

Gender -> Anxiety

Gender -> Depression

Gender -> Fatigue

Gender -> Hospitalization

Hospitalization -> "Functional impairment"

Hospitalization -> "Health-related Quality of Life"

Hospitalization -> Anxiety

Hospitalization -> Depression

Hospitalization -> Fatigue

Vaccination -> "Functional impairment"

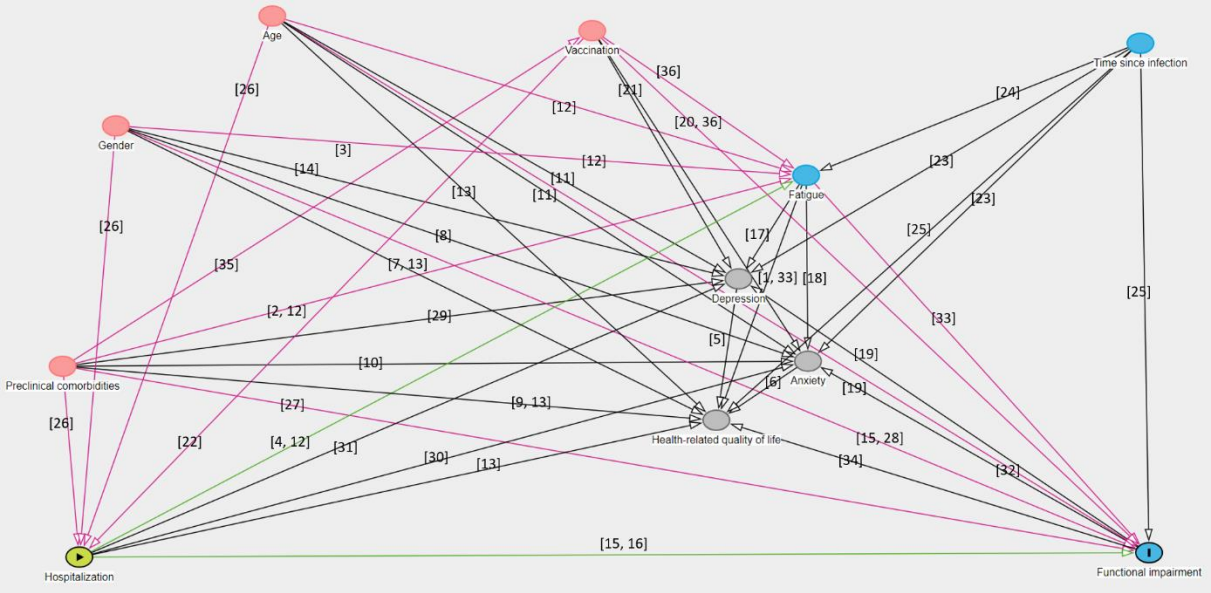
Vaccination -> Anxiety

Vaccination -> Depression

Vaccination -> Hospitalization

}

DAG für WHODAS / Functional impairment:



dag {

"Functional impairment" [outcome,pos="0.007,1.009"]

"Health-related quality of life" [pos="-0.691,0.352"]

"Preclinical comorbidities" [pos="-1.745,0.085"]

"Time since infection" [pos="-0.007,-1.516"]

Age [pos="-1.407,-1.651"]

Anxiety [pos="-0.543,0.060"]

Depression [pos="-0.655,-0.348"]

Fatigue [pos="-0.546,-0.861"]

Gender [pos="-1.659,-1.106"]

Hospitalization [exposure,pos="-1.718,1.031"]

Vaccination [pos="-0.891,-1.578"]

"Functional impairment" -> "Health-related quality of life"

"Functional impairment" -> Anxiety

"Functional impairment" -> Depression

"Preclinical comorbidities" -> "Functional impairment"

"Preclinical comorbidities" -> "Health-related quality of life"

"Preclinical comorbidities" -> Anxiety

"Preclinical comorbidities" -> Depression

"Preclinical comorbidities" -> Fatigue

"Preclinical comorbidities" -> Hospitalization

"Preclinical comorbidities" -> Vaccination

"Time since infection" -> "Functional impairment"

"Time since infection" -> "Health-related quality of life"

"Time since infection" -> Anxiety

"Time since infection" -> Depression

"Time since infection" -> Fatigue

Age -> "Functional impairment"

Age -> "Health-related quality of life"

Age -> Anxiety

Age -> Depression

Age -> Fatigue

Age -> Hospitalization

Anxiety -> "Health-related quality of life"

Depression -> "Health-related quality of life"

Fatigue -> "Functional impairment"

Fatigue -> "Health-related quality of life"

Fatigue -> Anxiety

Fatigue -> Depression

Gender -> "Functional impairment"

Gender -> "Health-related quality of life"

Gender -> Anxiety

Gender -> Depression

Gender -> Fatigue

Gender -> Hospitalization

Hospitalization -> "Functional impairment"

Hospitalization -> "Health-related quality of life"

Hospitalization -> Anxiety

Hospitalization -> Depression

Hospitalization -> Fatigue

Vaccination -> "Functional impairment"

Vaccination -> Anxiety

Vaccination -> Depression

Vaccination -> Fatigue

Vaccination -> Hospitalization

}

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