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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.

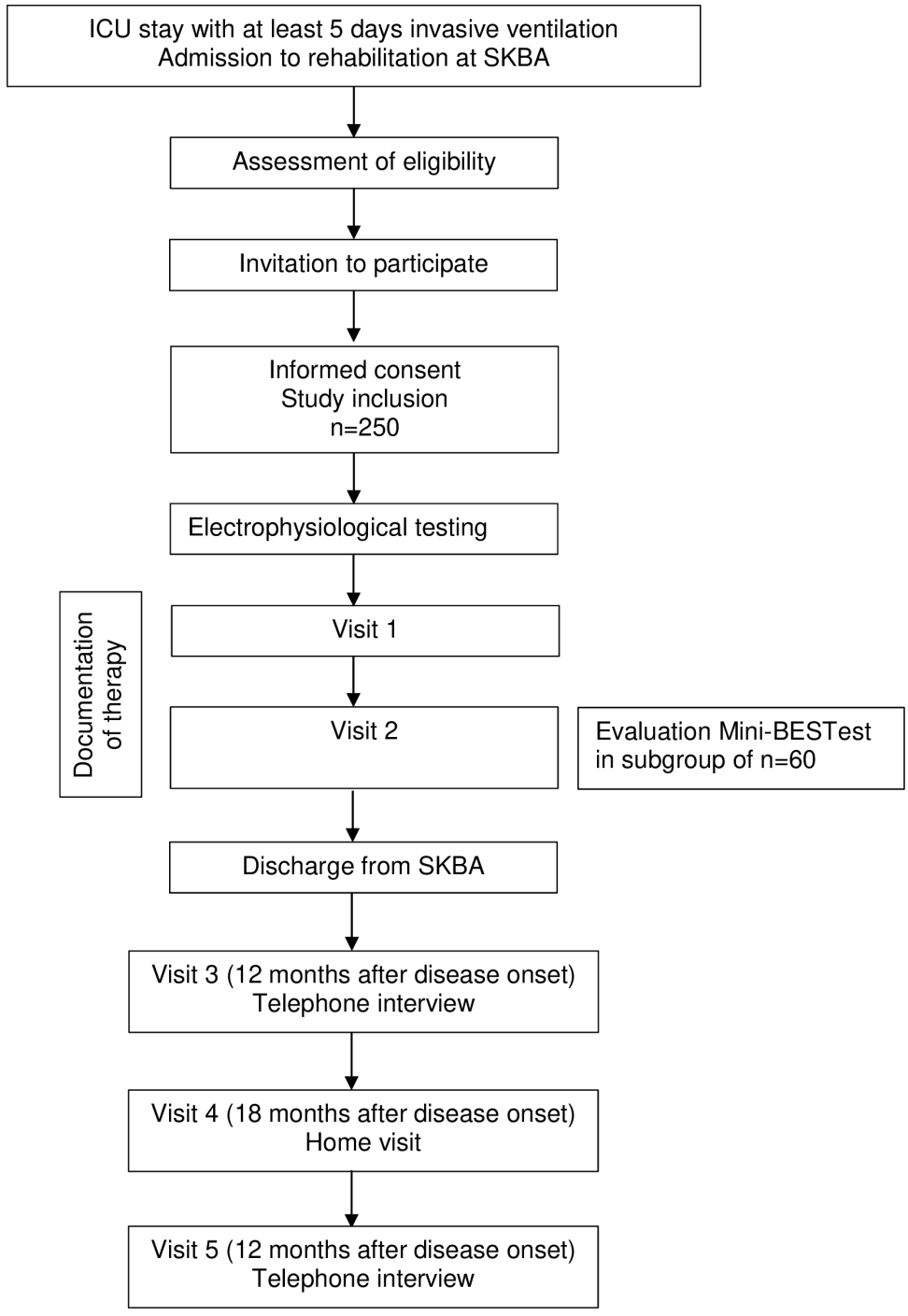

Figure 1 Flow chart of the study. ICU, intensive care unit; SKBA, Schoen Clinic Bad Aibling.

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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Contributors JB is grant holder and supervises the project. ME and JB conceived the study, and JB, ME, FM and KJ initiated the study design. ME coordinates the study, is responsible for the data collection and is conducting the primary statistical analysis. ME is responsible for the study's quality assessment and is, together with JB, in charge of the overall study management. JB drafted the manuscript. All authors approved and critically revised the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethical approval The study protocol and the template informed consent forms are reviewed and approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (project number 20-166).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The data set will be available on reasonable request

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

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