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The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function.

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Abstract

Introduction: Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. This weakness of limb muscles increases morbidity and delay rehabilitation and recovery of walking ability. Although full recovery has been reported people with severe weakness may take months to improve walking. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance.

However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe the time course of recovery of walking function and other activities of daily living in these patients.

Methods and analysis: We conduct a prospective cohort study of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Based on our sample size calculation, approximately 150 patients will be recruited from the intensive care unit of our hospital in Germany. Amount and content of physical rehabilitation, clinical tests e.g. muscle strength and motor function and neuropsychological assessments will be used as independent variables. The primary outcomes will include recovery of walking function and mobility. Secondary outcomes will include global motor function, activities in daily life and participation.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and conducted with the approval of the local medical Ethics Committee (Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1) and with the understanding and written consent of each patient's guardian.

The results of this study will be published in peer-reviewed journals and disseminated to the medical society and general public.

Article Summary

Article focus:

The aim of the General Weakness Syndrome Therapy (GymNAST) study is to determine the time course of recovery of walking function, to describe the detailed content of physical rehabilitation and also to describe possible risk factors and chances for recovery of walking function in the first year after ICU-acquired muscle weakness.

Key messages:

This study will determine how people with ICU-acquired muscle weakness are related to clinical characteristics and describe the time course of motor and cognitive performance and activities of daily life.

The results will be of interest of clinicians working with critical ill patients and will give insights into the black box of rehabilitation and its impact on recovery of ICU-acquired muscle weakness due to CIM/CIP. The results of this study may therefore inform patients and their caregivers, therapists working in rehabilitation to choose the most appropriate treatment, and to develop adapted rehab programs.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first year of ICU-acquired muscle weakness with daily documentation of physical rehabilitation and walking function. Multiple repeated assessments, with a wide range of clinical measures will be done. Such a measurement design has several advantages compared to other prognostic studies done so far using just two measurements in time. Our longitudinal repeated measure design may provide further insights into dynamics of recovery of walking function and other activities over the first year of people with ICU-acquired muscle weakness.

One limitation could be that most severe affected patients have to be excluded in this study. This may reduce the generalisability of the results to the whole population critical ill patients. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Introduction

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1]. The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [2-4]. This increases morbidity and delays rehabilitation and recovery of walking [5 6]. Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition e.g. people with severe weakness may take months to improve, or even remain severely affected [7]. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects [1]. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature [1 8-11].

However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of

daily live. Furthermore a multivariate model for recovery of walking ability will be developed.

Methods and analysis

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily live

Secondary objectives are to:

- describe the concomitant physical rehabilitation therapies
- describe the clinical course of recovery using standardized outcome measures and their results
- identify a prognostic model for regain walking and sit to stand abilities

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow up will be made in 2015.

Based on our sample size calculation [12 13], approximately 150 patients will be recruited from a intensive care unit of our hospital in Germany [14] over the time course of three years. In a first cross sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month [15]. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within three years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- patient is chronic critical ill
- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP) [16 17]
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [18]
- written informed consent of the patient or his legal guardian

Exclusion criteria

- Patients receiving palliative care
- Co-morbidities of the trunk or the lower limbs interfering with upright posture and walking function (e.g. Amputation or fracture of lower limb)
- Other neuromuscular or neurological disease (e.g. Guillain-Barré Syndrom, Stroke)
- severe physical co-morbidity before becoming critical ill (e.g, frailty due to neurological conditions)

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the demographic and clinical characteristics will be measured (baseline assessment T0). Patients will then be measured every two weeks after baseline up to 20 weeks (week two (T1), week four (T2), week six (T3), week eight (T4) week ten (T5) and so on until week twenty (T10)). Two follow ups are planned: FU1 after six month and FU2 after one year after study entry. For follow-up assessments (FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate.

The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets [15]. All assessments and standardized measures will be administered

by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility.

Measures and Outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the Functional Ambulation Categories (FAC) is used [19]. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height).

Secondary outcomes includes

- Richmond Agitation-Sedation Scale (RASS) [18]
- activities measured with the Barthel Index (BI; 10 items) [20]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC) [1 21]
- grip strength [22 23]
- Functional Status Score for the Intensive Care Unit Scored (FSS-ICU) [24]
- Physical Function –ICU Test (PFIT) [25] and Physical Function –ICU Test- Scored (PFIT-S) [26]
- Pain using a visual analogue scale
- Lateral and frontal sit and stance balance (functional reach) [27 28]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [29] and clock drawing test (CDT) [30]
- walking ability (FAC) [31], walking speed and endurance [5 6]
- quality of life (EQ-5D) [32]
- participation (Reintegration to Normal Living, RNL-Index) [33 34]
- fitness and mobility (PASIPD) [35 36]

All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardized sheets for this purpose.

At baseline assessment (T0) and then every two weeks until twenty weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow ups FU1 after six month and FU2 after one year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Tables 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics (such as diagnosis, duration of illness).

Planned statistical analyses

We will use descriptive analyses, e.g. means and standard deviations of the continuous variables and frequencies and proportions of categorical variables as appropriate [37]. We will explain differences across the time points (T1–T10 and FU1 - FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate e.g. repeated measures analysis of variance [37]. The global alpha level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analyzed for their association with these endpoints:

- demographic variables (such as age and sex),

- clinical variables (such as muscle strength, FSS-ICU, PFIT-S) and
- medical characteristics (such as diagnosis and duration of illness)

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier [38]. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [39]. A stepwise multivariable Cox regression analysis will be applied with a variable selection [39 40].

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance [41-43]. The final model selection will be performed based on clinical decision, together with Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) [40]. Aim of our analysis is to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

To prevent overfitting, only variables with clinically important *and* statistically significant bivariate association with our endpoint will be included in the final model [40].

The effects of prognostic factors in the final model will be expressed as hazard ratios (HR) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards.

We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

Results

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1 - FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

Sample size and power calculation

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the 'rule of ten events per variable (EPV)' [12 13 43]. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the intensive care unit of our long term intensive care hospital in Germany [14]. We anticipate reaching this study size over the time course of three years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our intensive care units [15]. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within three years of recruitment.

Ethics and Dissemination

Ethical considerations

The GymNAST study will be conducted in accordance with the 'Helsinki Declaration'. The study is non-invasive, imposes no risk on patients, seems to have enough power to detect meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

Discussion

The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of one year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups [5 25 26] and only some studies measures continuously over time [44]. However, instead of comparing two or more measurements of the patient's performance it seems to be more informative to analyze the dynamic recovery systematically using equal time intervals over an appropriate time period e.g. with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (e.g. clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every two weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Authors' contributions:

J.M., S.M, FO and M.P. planned the study. F.O. and M.P. contributed to the procurement of funding. J.M., S.M, and M.P. developed the protocol. All authors contributed to and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Summary of outcome measures and time points of assessment in GymNAST

	Baseline	Daily	Biweekly (T1 to T12)	Follow-up (FU 1 and 2)
Amount and content of Physical Rehabilitation				
Physiotherapy		x		x
Occupational Therapy		x		x
Other therapies (e.g. groups)		x		x
Primary Outcome				
FAC and STS	x	x		
Delir measures				
RASS	x		x	
Strength measures				
MRC score	x		x	x
Grip strength	x		x	x
Physical function measures				
PFIT and PFIT-S	x		x	x
FSS-ICU score	x		x	x
10m walking time	x		x	x
6-MWT	x		x	x
Pain (VAS)	x		x	x
functional reach	x		x	x
Cognition measures				
MOCA	x		x	x
CDT	x		x	x
Activities and Mobility				
BI	x		x	x
PASIPD				x
Participation and quality of life				
EQ-5D				x
RNL-Index				x

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However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe the time course of recovery of walking function and other activities of daily living in these patients.

Methods and analysis: We conduct a prospective cohort study of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Based on our sample size calculation, approximately 150 patients will be recruited from the intensive care unit of our hospital in Germany. Amount and content of physical rehabilitation, clinical tests e.g. muscle strength and motor function and neuropsychological assessments will be used as independent variables. The primary outcomes will include recovery of walking function and mobility. Secondary outcomes will include global motor function, activities in daily life and participation.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and conducted with the approval of the local medical Ethics Committee (Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1) and with the understanding and written consent of each patient's guardian.

The results of this study will be published in peer-reviewed journals and disseminated to the medical society and general public.

Article Summary

Article focus:

The aim of the General Weakness Syndrome Therapy (GymNAST) study is to determine the time course of recovery of walking function, to describe the detailed content of physical rehabilitation and also to describe possible risk factors and chances for recovery of walking function in the first year after ICU-acquired muscle weakness.

Key messages:

This study will determine how people with ICU-acquired muscle weakness are related to clinical characteristics and describe the time course of motor and cognitive performance and activities of daily life.

The results will be of interest of clinicians working with critical ill patients and will give insights into the black box of rehabilitation and its impact on recovery of ICU-acquired muscle weakness due to CIM/CIP. The results of this study may therefore inform patients and their caregivers, therapists working in rehabilitation to choose the most appropriate treatment, and to develop adapted rehab programs.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first year of ICU-acquired muscle weakness with daily documentation of physical rehabilitation and walking function. Multiple repeated assessments, with a wide range of clinical measures will be done. Such a measurement design has several advantages compared to other prognostic studies done so far using just two measurements in time. Our longitudinal repeated measure design may provide further insights into dynamics of recovery of walking function and other activities over the first year of people with ICU-acquired muscle weakness.

One limitation could be that most severe affected patients have to be excluded in this study. This may reduce the generalisability of the results to the whole population critical ill patients. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Introduction

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1]. The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [2-4]. This increases morbidity and delays rehabilitation and recovery of walking [5 6]. Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition e.g. people with severe weakness may take months to improve, or even remain severely affected [7 8]. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects [1]. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature [1 8-12].

However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of

daily live. Furthermore a multivariate model for recovery of walking ability will be developed.

Methods and analysis

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily live

Secondary objectives are to:

- describe the concomitant physical rehabilitation therapies
- describe the clinical course of recovery using standardized outcome measures and their results
- identify a prognostic model for regain walking and sit to stand abilities

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow up will be made in 2015.

Based on our sample size calculation [13 14], approximately 150 patients will be recruited from a intensive care unit of our hospital in Germany [15] over the time course of three years. In a first cross sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month [16]. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within three years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- patient is chronic critical ill defined as more than 21 days intensive care unit treatment including mechanical ventilation (we will include patients after 3 weeks of intensive care unit treatment including mechanical ventilation. Many patients will still be treated and monitored at this time point on our ICU).
- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP) [17 18] (we will involve a neurologist consultant for the defined diagnosis of CIM/CIP and we will use neurophysiological techniques and also the clinical criteria for the diagnosis of CIM and/or CIP [17 18] and differential diagnosis. However we will not apply muscle biopsy for differential diagnosis)
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [19]
- written informed consent of the patient or his legal guardian

Exclusion criteria

- Patients receiving palliative care
- Co-morbidities of the trunk or the lower limbs interfering with upright posture and walking function (e.g. Amputation or fracture of lower limb)
- Other neuromuscular or neurological disease and/or syndromes causing weakness in patients in the ICU (we will exclude patients with diseases and syndromes causing weakness in patients in the ICU[8], due to Guillain–Barré syndrome, myasthenia gravis, porphyria, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, vasculitic neuropathy, cervical myelopathy and botulism)
- severe physical co-morbidity before becoming critical ill (e.g, frailty due to neurological conditions)

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the

demographic and clinical characteristics will be measured (baseline assessment T0). Patients will then be measured every two weeks after baseline up to 20 weeks (week two (T1), week four (T2), week six (T3), week eight (T4) week ten (T5) and so on until week twenty (T10)). Two follow ups are planned: FU1 after six month and FU2 after one year after study entry. For follow-up assessments (FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate.

The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets [16]. All assessments and standardized measures will be administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility. Additionally, we will try to get all information about the content and duration of physiotherapy and or physical rehabilitation applied at all stages of illness.

Measures and Outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the Functional Ambulation Categories (FAC) is used [20]. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height).

Secondary outcomes includes

- Richmond Agitation-Sedation Scale (RASS) [19]
- activities measured with the Barthel Index (BI; 10 items) [21]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC) [1 22]
- grip strength (measured bilaterally using a dynamometer) [23 24]
- Functional Status Score for the Intensive Care Unit Scored (FSS-ICU) [25]
- Physical Function –ICU Test (PFIT) [26] and Physical Function –ICU Test- Scored (PFIT-S) [27]

- Pain using a visual analogue scale
- Lateral and frontal sit and stance balance (functional reach) [28 29]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [30] and clock drawing test (CDT) [31]
- walking ability (0- 5; FAC) [32], walking speed (we will use a 10m walking test, adopting a 14-m course and will measure the walking speed over the central 10 m) and walking endurance (we will use a six minute walking test, using 40m course and will measure the distance walked in six minutes; if patients cannot walk the whole six minutes we will measure the maximum walking distance here) [5 6]
- quality of life (EQ-5D) [33]
- participation (Reintegration to Normal Living, RNL-Index) [34 35]
- fitness and mobility (PASIPD) [36 37]

All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardized sheets for this purpose.

At baseline assessment (T0) and then every two weeks until twenty weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow ups FU1 after six month and FU2 after one year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Tables 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics (such as diagnoses, reason for ICU-treatment, duration of mechanical ventilation, duration of illness) and anthropometric measures, such as body weight and body mass index (but not limb circumference).

Planned statistical analyses

We will use descriptive analyses, e.g. means and standard deviations of the continuous variables and frequencies and proportions of categorical variables as appropriate [38]. We will explain differences across the time points (T1–T10 and FU1 - FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate e.g. repeated measures analysis of variance [38]. The global alpha level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analyzed for their association with these endpoints:

- demographic variables (such as age and sex),
- clinical variables (such as muscle strength, FSS-ICU, PFIT-S) and
- medical characteristics (such as diagnosis and duration of illness)

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier [39]. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [40]. A stepwise multivariable Cox regression analysis will be applied with a variable selection [40 41].

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance [42-44]. The final model selection will be performed based on clinical decision, together with Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) [41]. Aim

of our analysis is to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

To prevent overfitting, only variables with clinically important *and* statistically significant bivariate association with our endpoint will be included in the final model [41].

The effects of prognostic factors in the final model will be expressed as hazard ratios (HR) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards.

We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

Results

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1 - FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

Sample size and power calculation

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the 'rule of ten events per variable (EPV)' [13 14 44]. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the intensive care unit of our long term intensive care hospital in Germany [15]. We anticipate reaching this study size over the time course of three years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our intensive care units [16]. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within three years of recruitment.

Ethics and Dissemination

Ethical considerations

The GymNAST study will be conducted in accordance with the 'Helsinki Declaration'. The study is non-invasive, imposes no risk on patients, seems to have enough power to detect meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

Discussion

The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of one year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups [5 26 27] and only some studies measures continuously over time [45]. However, instead of comparing two or more measurements of the patient's performance it seems to be more informative to analyze the dynamic recovery systematically using equal time intervals over an appropriate time period e.g. with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (e.g. clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every two weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Authors' contributions:

J.M., S.M, FO and M.P. planned the study. F.O. and M.P. contributed to the procurement of funding. J.M., S.M, and M.P. developed the protocol. All authors contributed to and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Summary of outcome measures and time points of assessment in GymNAST

	Baseline	Daily	Biweekly (T1 to T12)	Follow-up (FU 1 and 2)
Amount and content of Physical Rehabilitation				
Physiotherapy		x		x
Occupational Therapy		x		x
Other therapies (e.g. groups)		x		x
Primary Outcome				
FAC and STS	x	x		
Delir measures				
RASS	x		x	
Strength measures				
MRC score	x		x	x
Grip strength	x		x	x
Physical function measures				
PFIT and PFIT-S	x		x	x
FSS-ICU score	x		x	x
10m walking time	x		x	x
6-MWT	x		x	x
Pain (VAS)	x		x	x
functional reach	x		x	x
Cognition measures				
MOCA	x		x	x
CDT	x		x	x
Activities and Mobility				
BI	x		x	x
PASIPD				x
Participation and quality of life				
EQ-5D				x
RNL-Index				x

Abbreviations: GymNAST: General Weakness Syndrome Therapy study; FU= Follow Up; T= Time point; FAC: Functional Ambulation; STS: ability to stand up from a chair independently; RASS: Richmond Agitation-Sedation Scale; MRC: Medical Research Council (muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle)); PFIT: Physical Function –Intensive Care Unit- Test; PFIT-S: Physical Function – Intensive Care Unit Test- Scored; FSS-ICU: Functional Status Score for the Intensive Care Unit Scored; 6-MWT: six minute walking test; VAS: visual analogue scale; MOCA= Montreal Cognitive Assessment; CDT: clock drawing test; BI: Barthel Index; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; EQ-5D: EuroQol (5 dimensions); RNL-Index: Reintegration to Normal Living Index

The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function.

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Abstract

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However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood.

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Key messages:

This study will determine how people with ICU-acquired muscle weakness are related to clinical characteristics and describe the time course of motor and cognitive performance and activities of daily life.

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Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first year of ICU-acquired muscle weakness with daily documentation of physical rehabilitation and walking function. Multiple repeated assessments, with a wide range of clinical measures will be done. Such a measurement design has several advantages compared to other prognostic studies done so far using just two measurements in time. Our longitudinal repeated measure design may provide further insights into dynamics of recovery of walking function and other activities over the first year of people with ICU-acquired muscle weakness.

One limitation could be that most severe affected patients have to be excluded in this study. This may reduce the generalisability of the results to the whole population critical ill patients. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Introduction

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1]. The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [2-4]. This increases morbidity and delays rehabilitation and recovery of walking [5 6]. Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition e.g. people with severe weakness may take months to improve, or even remain severely affected [7 8]. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects [1]. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature [1 8-12].

However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of

daily live. Furthermore a multivariate model for recovery of walking ability will be developed.

Methods and analysis

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily live

Secondary objectives are to:

- describe the concomitant physical rehabilitation therapies
- describe the clinical course of recovery using standardized outcome measures and their results
- identify a prognostic model for regain walking and sit to stand abilities

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow up will be made in 2015.

Based on our sample size calculation [13 14], approximately 150 patients will be recruited from a intensive care unit of our hospital in Germany [15] over the time course of three years. In a first cross sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month [16]. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within three years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- patient is chronic critical ill **defined as more than 21 days intensive care unit treatment including mechanical ventilation (we will include patients after 3 weeks of intensive care unit treatment including mechanical ventilation. Many patients will still be treated and monitored at this time point on our ICU).**
- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP) [17 18] **(we will involve a neurologist consultant for the defined diagnosis of CIM/CIP and we will use neurophysiological techniques and also the clinical criteria for the diagnosis of CIM and/or CIP [17 18] and differential diagnosis. However we will not apply muscle biopsy for differential diagnosis)**
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [19]
- written informed consent of the patient or his legal guardian

Exclusion criteria

- Patients receiving palliative care
- Co-morbidities of the trunk or the lower limbs interfering with upright posture and walking function (e.g. Amputation or fracture of lower limb)
- Other neuromuscular or neurological disease **and/or syndromes causing weakness in patients in the ICU (we will exclude patients with diseases and syndromes causing weakness in patients in the ICU[8], due to Guillain–Barré syndrome, myasthenia gravis, porphyria, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, vasculitic neuropathy, cervical myelopathy and botulism)**
- severe physical co-morbidity before becoming critical ill (e.g, frailty due to neurological conditions)

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the

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demographic and clinical characteristics will be measured (baseline assessment T0). Patients will then be measured every two weeks after baseline up to 20 weeks (week two (T1), week four (T2), week six (T3), week eight (T4) week ten (T5) and so on until week twenty (T10)). Two follow ups are planned: FU1 after six month and FU2 after one year after study entry. For follow-up assessments (FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate.

The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets [16]. All assessments and standardized measures will be administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility. **Additionally, we will try to get all information about the content and duration of physiotherapy and or physical rehabilitation applied at all stages of illness.**

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Measures and Outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the Functional Ambulation Categories (FAC) is used [20]. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height).

Secondary outcomes includes

- Richmond Agitation-Sedation Scale (RASS) [19]
- activities measured with the Barthel Index (BI; 10 items) [21]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC) [1 22]
- grip strength **(measured bilaterally using a dynamometer)** [23 24]

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- Functional Status Score for the Intensive Care Unit Scored (FSS-ICU) [25]
- Physical Function –ICU Test (PFIT) [26] and Physical Function –ICU Test- Scored (PFIT-S) [27]

- Pain using a visual analogue scale
- Lateral and frontal sit and stance balance (functional reach) [28 29]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [30] and clock drawing test (CDT) [31]
- walking ability **(0- 5; FAC) [32], walking speed (we will use a 10m walking test, adopting a 14-m course and will measure the walking speed over the central 10 m) and walking endurance (we will use a six minute walking test, using 40m course and will measure the distance walked in six minutes; if patients cannot walk the whole six minutes we will measure the maximum walking distance here) [5 6]**
- quality of life (EQ-5D) [33]
- participation (Reintegration to Normal Living, RNL-Index) [34 35]
- fitness and mobility (PASIPD) [36 37]

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All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardized sheets for this purpose.

At baseline assessment (T0) and then every two weeks until twenty weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow ups FU1 after six month and FU2 after one year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Tables 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics (such as **diagnoses, reason for ICU-treatment, duration of mechanical ventilation, duration of illness) and anthropometric measures, such as body weight and body mass index (but not limb circumference).**

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Planned statistical analyses

We will use descriptive analyses, e.g. means and standard deviations of the continuous variables and frequencies and proportions of categorical variables as appropriate [38]. We will explain differences across the time points (T1–T10 and FU1 - FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate e.g. repeated measures analysis of variance [38]. The global alpha level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analyzed for their association with these endpoints:

- demographic variables (such as age and sex),
- clinical variables (such as muscle strength, FSS-ICU, PFIT-S) and
- medical characteristics (such as diagnosis and duration of illness)

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier [39]. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [40]. A stepwise multivariable Cox regression analysis will be applied with a variable selection [40 41].

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance [42-44]. The final model selection will be performed based on clinical decision, together with Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) [41]. Aim

of our analysis is to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

To prevent overfitting, only variables with clinically important *and* statistically significant bivariate association with our endpoint will be included in the final model [41].

The effects of prognostic factors in the final model will be expressed as hazard ratios (HR) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards.

We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

Results

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1 - FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

Sample size and power calculation

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the 'rule of ten events per variable (EPV)' [13 14 44]. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the intensive care unit of our long term intensive care hospital in Germany [15]. We anticipate reaching this study size over the time course of three years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our intensive care units [16]. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within three years of recruitment.

Ethics and Dissemination

Ethical considerations

The GymNAST study will be conducted in accordance with the 'Helsinki Declaration'. The study is non-invasive, imposes no risk on patients, seems to have enough power to detect meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

Discussion

The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of one year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups [5 26 27] and only some studies measures continuously over time [45]. However, instead of comparing two or more measurements of the patient's performance it seems to be more informative to analyze the dynamic recovery systematically using equal time intervals over an appropriate time period e.g. with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (e.g. clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every two weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Authors' contributions:

J.M., S.M, FO and M.P. planned the study. F.O. and M.P. contributed to the procurement of funding. J.M., S.M, and M.P. developed the protocol. All authors contributed to and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Summary of outcome measures and time points of assessment in GymNAST

	Baseline	Daily	Biweekly (T1 to T12)	Follow-up (FU 1 and 2)
Amount and content of Physical Rehabilitation				
Physiotherapy		x		x
Occupational Therapy		x		x
Other therapies (e.g. groups)		x		x
Primary Outcome				
FAC and STS	x	x		
Delir measures				
RASS	x		x	
Strength measures				
MRC score	x		x	x
Grip strength	x		x	x
Physical function measures				
PFIT and PFIT-S	x		x	x
FSS-ICU score	x		x	x
10m walking time	x		x	x
6-MWT	x		x	x
Pain (VAS)	x		x	x
functional reach	x		x	x
Cognition measures				
MOCA	x		x	x
CDT	x		x	x
Activities and Mobility				
BI	x		x	x
PASIPD				x
Participation and quality of life				
EQ-5D				x
RNL-Index				x

Abbreviations: GymNAST: General Weakness Syndrome Therapy study; FU= Follow Up; T= Time point; FAC: Functional Ambulation; STS: ability to stand up from a chair independently; RASS: Richmond Agitation-Sedation Scale; MRC: Medical Research Council (muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle)); PFIT: Physical Function –Intensive Care Unit- Test; PFIT-S: Physical Function – Intensive Care Unit Test- Scored; FSS-ICU: Functional Status Score for the Intensive Care Unit Scored; 6-MWT: six minute walking test; VAS: visual analogue scale; MOCA= Montreal Cognitive Assessment; CDT: clock drawing test; BI: Barthel Index; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; EQ-5D: EuroQol (5 dimensions); RNL-Index: Reintegration to Normal Living Index

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The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function.

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Primary Subject Heading:	Intensive care
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The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function.

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Abstract

Introduction: Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. This weakness of limb muscles increases morbidity and delay rehabilitation and recovery of walking ability. Although full recovery has been reported people with severe weakness may take months to improve walking. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance.

However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe the time course of recovery of walking function and other activities of daily living in these patients.

Methods and analysis: We conduct a prospective cohort study of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Based on our sample size calculation, approximately 150 patients will be recruited from the intensive care unit of our hospital in Germany. Amount and content of physical rehabilitation, clinical tests e.g. muscle strength and motor function and neuropsychological assessments will be used as independent variables. The primary outcomes will include recovery of walking function and mobility. Secondary outcomes will include global motor function, activities in daily life and participation.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and conducted with the approval of the local medical Ethics Committee (Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1) and with the understanding and written consent of each patient's guardian.

The results of this study will be published in peer-reviewed journals and disseminated to the medical society and general public.

Article Summary

Article focus:

The aim of the General Weakness Syndrome Therapy (GymNAST) study is to determine the time course of recovery of walking function, to describe the detailed content of physical rehabilitation and also to describe possible risk factors and chances for recovery of walking function in the first year after ICU-acquired muscle weakness.

Key messages:

This study will determine how people with ICU-acquired muscle weakness are related to clinical characteristics and describe the time course of motor and cognitive performance and activities of daily life.

The results will be of interest of clinicians working with critical ill patients and will give insights into the black box of rehabilitation and its impact on recovery of ICU-acquired muscle weakness due to CIM/CIP. The results of this study may therefore inform patients and their caregivers, therapists working in rehabilitation to choose the most appropriate treatment, and to develop adapted rehab programs.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first year of ICU-acquired muscle weakness with daily documentation of physical rehabilitation and walking function. Multiple repeated assessments, with a wide range of clinical measures will be done. Such a measurement design has several advantages compared to other prognostic studies done so far using just two measurements in time. Our longitudinal repeated measure design may provide further insights into dynamics of recovery of walking function and other activities over the first year of people with ICU-acquired muscle weakness.

One limitation could be that most severe affected patients have to be excluded in this study. This may reduce the generalisability of the results to the whole population critical ill patients. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Introduction

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1]. The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [2-4]. This increases morbidity and delays rehabilitation and recovery of walking [5 6]. Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition e.g. people with severe weakness may take months to improve, or even remain severely affected [7 8]. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects [1]. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature [1 8-12].

However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of

daily live. Furthermore a multivariate model for recovery of walking ability will be developed.

Methods and analysis

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily live

Secondary objectives are to:

- describe the concomitant physical rehabilitation therapies
- describe the clinical course of recovery using standardized outcome measures and their results
- identify a prognostic model for regain walking and sit to stand abilities

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow up will be made in 2015.

Based on our sample size calculation [13 14], approximately 150 patients will be recruited from a intensive care unit of our hospital in Germany [15] over the time course of three years. In a first cross sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month [16]. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within three years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- patient is chronic critical ill or has a contemporary history of chronic critical ill defined as more than 21 days ICU-treatment including mechanical ventilation and at least 14 days further existing critical situation with the need for ICU-treatment [17]

- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP). The diagnosis of CIM/CIP will be confirmed by a neurologist. Therefore, clinical and neurophysiologic data will be revealed. The procedure of diagnosis of CIP and CIM is described in detail elsewhere [18-20]
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [21]
- written informed consent of the patient or his legal guardian

Exclusion criteria

- Patients receiving palliative care
- Co-morbidities of the trunk or the lower limbs interfering with upright posture and walking function (e.g. Amputation or fracture of lower limb)
- Other neuromuscular or neurological disease and/or syndromes causing weakness in patients in the ICU (we will exclude patients with diseases and syndromes causing weakness in patients in the ICU[8], due to Guillain–Barré syndrome, myasthenia gravis, porphyria, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, vasculitic neuropathy, cervical myelopathy and botulism)
- severe physical co-morbidity before becoming critical ill (e.g, frailty due to neurological conditions)

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the demographic and clinical characteristics will be measured (baseline assessment T0). Patients

will then be measured every two weeks after baseline up to 20 weeks (week two (T1), week four (T2), week six (T3), week eight (T4) week ten (T5) and so on until week twenty (T10)). Two follow ups are planned: FU1 after six month and FU2 after one year after study entry. For follow-up assessments (FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate.

The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets [16]. All assessments and standardized measures will be administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility. Additionally, we will try to get all information about the content and duration of physiotherapy and or physical rehabilitation applied at all stages of illness.

Measures and Outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the Functional Ambulation Categories (FAC) is used [22]. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height).

Secondary outcomes includes

- Richmond Agitation-Sedation Scale (RASS) [21]
- activities measured with the Barthel Index (BI; 10 items) [23]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC) [1 24]
- grip strength (measured bilaterally using a dynamometer) [25 26]
- Functional Status Score for the Intensive Care Unit Scored (FSS-ICU) [27]
- Physical Function –ICU Test (PFIT) [28] and Physical Function –ICU Test- Scored (PFIT-S) [29]
- Pain using a visual analogue scale

- Lateral and frontal sit and stance balance (functional reach) [30 31]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [32] and clock drawing test (CDT) [33]
- walking ability (0- 5; FAC) [34], walking speed (we will use a 10m walking test, adopting a 14-m course and will measure the walking speed over the central 10 m) and walking endurance (we will use a six minute walking test, using 40m course and will measure the distance walked in six minutes; if patients cannot walk the whole six minutes we will measure the maximum walking distance here) [5 6]
- quality of life (EQ-5D) [35]
- participation (Reintegration to Normal Living, RNL-Index) [36 37]
- fitness and mobility (PASIPD) [38 39]

All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardized sheets for this purpose.

At baseline assessment (T0) and then every two weeks until twenty weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow ups FU1 after six month and FU2 after one year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Tables 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics

(such as diagnoses, reason for ICU-treatment, duration of mechanical ventilation, duration of illness) and anthropometric measures, such as body weight and body mass index (but not limb circumference).

Planned statistical analyses

We will use descriptive analyses, e.g. means and standard deviations of the continuous variables and frequencies and proportions of categorical variables as appropriate [40]. We will explain differences across the time points (T1–T10 and FU1 - FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate e.g. repeated measures analysis of variance [40]. The global alpha level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analyzed for their association with these endpoints:

- demographic variables (such as age and sex),
- clinical variables (such as muscle strength, FSS-ICU, PFIT-S) and
- medical characteristics (such as diagnosis and duration of illness)

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier [41]. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [42]. A stepwise multivariable Cox regression analysis will be applied with a variable selection [42 43].

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance [44-46]. The final model selection will be performed based on clinical decision, together with Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) [43]. Aim of our analysis is to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

To prevent overfitting, only variables with clinically important *and* statistically significant bivariate association with our endpoint will be included in the final model [43].

The effects of prognostic factors in the final model will be expressed as hazard ratios (HR) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards.

We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

Results

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1 - FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

Sample size and power calculation

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the 'rule of ten events per variable (EPV)' [13 14 46]. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the intensive care unit of our long term intensive care hospital in Germany [15]. We anticipate reaching this study size over the time course of three years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our intensive care units [16]. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within three years of recruitment.

Ethics and Dissemination

Ethical considerations

The GymNAST study will be conducted in accordance with the 'Helsinki Declaration'. The study is non-invasive, imposes no risk on patients, seems to have enough power to detect

meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

Discussion

The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of one year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups [5 28 29] and only some studies measures continuously over time [47]. However, instead of comparing two or more measurements of the patient's performance it seems to be more informative to analyze the dynamic recovery systematically using equal time intervals over an appropriate time period e.g. with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (e.g. clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every two weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-

acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Authors' contributions:

J.M., S.M, FO and M.P. planned the study. F.O. and M.P. contributed to the procurement of funding. J.M., S.M, and M.P. developed the protocol. All authors contributed to and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Summary of outcome measures and time points of assessment in GymNAST

	Baseline	Daily	Biweekly (T1 to T12)	Follow-up (FU 1 and 2)
Amount and content of Physical Rehabilitation				
Physiotherapy		x		x
Occupational Therapy		x		x
Other therapies (e.g. groups)		x		x
Primary Outcome				
FAC and STS	x	x		
Delir measures				
RASS	x		x	
Strength measures				
MRC score	x		x	x
Grip strength	x		x	x
Physical function measures				
PFIT and PFIT-S	x		x	x
FSS-ICU score	x		x	x
10m walking time	x		x	x
6-MWT	x		x	x
Pain (VAS)	x		x	x
functional reach	x		x	x
Cognition measures				
MOCA	x		x	x
CDT	x		x	x
Activities and Mobility				
BI	x		x	x
PASIPD				x
Participation and quality of life				
EQ-5D				x
RNL-Index				x

Abbreviations: GymNAST: General Weakness Syndrome Therapy study; FU= Follow Up; T= Time point; FAC: Functional Ambulation; STS: ability to stand up from a chair independently; RASS: Richmond Agitation-Sedation Scale; MRC: Medical Research Council (muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle)); PFIT: Physical Function –Intensive Care Unit- Test; PFIT-S: Physical Function – Intensive Care Unit Test- Scored; FSS-ICU: Functional Status Score for the Intensive Care Unit Scored; 6-MWT: six minute walking test; VAS: visual analogue scale; MOCA= Montreal Cognitive Assessment; CDT: clock drawing test; BI: Barthel Index; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; EQ-5D: EuroQol (5 dimensions); RNL-Index: Reintegration to Normal Living Index

The General Weakness Syndrome Therapy (GymNAST) study: protocol for a cohort study on recovery on walking function.

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Abstract

Introduction: Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. This weakness of limb muscles increases morbidity and delay rehabilitation and recovery of walking ability. Although full recovery has been reported people with severe weakness may take months to improve walking. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance.

However, although physical rehabilitation is common, detailed knowledge about the pattern and the time course of recovery of walking function are not well understood.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe the time course of recovery of walking function and other activities of daily living in these patients.

Methods and analysis: We conduct a prospective cohort study of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Based on our sample size calculation, approximately 150 patients will be recruited from the intensive care unit of our hospital in Germany. Amount and content of physical rehabilitation, clinical tests e.g. muscle strength and motor function and neuropsychological assessments will be used as independent variables. The primary outcomes will include recovery of walking function and mobility. Secondary outcomes will include global motor function, activities in daily life and participation.

Ethics and dissemination: The study is being carried out in agreement with the Declaration of Helsinki and conducted with the approval of the local medical Ethics Committee (Landesärztekammer Sachsen, Germany, reference number EK-BR-32/13-1) and with the understanding and written consent of each patient's guardian.

The results of this study will be published in peer-reviewed journals and disseminated to the medical society and general public.

Article Summary

Article focus:

The aim of the General Weakness Syndrome Therapy (GymNAST) study is to determine the time course of recovery of walking function, to describe the detailed content of physical rehabilitation and also to describe possible risk factors and chances for recovery of walking function in the first year after ICU-acquired muscle weakness.

Key messages:

This study will determine how people with ICU-acquired muscle weakness are related to clinical characteristics and describe the time course of motor and cognitive performance and activities of daily life.

The results will be of interest of clinicians working with critical ill patients and will give insights into the black box of rehabilitation and its impact on recovery of ICU-acquired muscle weakness due to CIM/CIP. The results of this study may therefore inform patients and their caregivers, therapists working in rehabilitation to choose the most appropriate treatment, and to develop adapted rehab programs.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first year of ICU-acquired muscle weakness with daily documentation of physical rehabilitation and walking function. Multiple repeated assessments, with a wide range of clinical measures will be done. Such a measurement design has several advantages compared to other prognostic studies done so far using just two measurements in time. Our longitudinal repeated measure design may provide further insights into dynamics of recovery of walking function and other activities over the first year of people with ICU-acquired muscle weakness.

One limitation could be that most severe affected patients have to be excluded in this study. This may reduce the generalisability of the results to the whole population critical ill patients. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Introduction

Critical illness myopathy (CIM) and polyneuropathy (CIP) are common complications of critical illness that frequently occur together. Both cause so called intensive-care-unit-acquired (ICU)-acquired muscle weakness. According to Norton-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1]. The weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [2-4]. This increases morbidity and delays rehabilitation and recovery of walking [5 6]. Although full recovery has been reported in approximately 50% of people with ICU-acquired muscle weakness, improvement is related to the severity of the condition e.g. people with severe weakness may take months to improve, or even remain severely affected [7 8]. Focused physical rehabilitation of people with ICU-acquired muscle weakness is therefore of great importance. There is practical evidence that physical rehabilitation of patients can be implemented with few adverse effects [1]. In recent years appropriate assessments were developed and description of suitable physical intervention strategies were described in the literature [1 8-12].

However, detailed knowledge about the time course of recovery of walking and other activities, their risk factors and chances for good recovery such are not well described or understood. Furthermore it lacks on detailed description of physical rehabilitation and on a repeated measure cohort study in the first year of people with ICU-acquired muscle weakness. Such a design would give better insights in to the time course of recovery of walking function and activities of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study is to describe and to identify time course and the pattern of recovery of walking, motor functions and of activities of daily living in these patients. Other aims are to describe the detailed content of physical rehabilitation and to develop a multivariate model of risk factors for recovery of walking function in the first year of ICU-acquired muscle weakness.

Here we describe the design and protocol of the GymNAST study, which is an appropriate large prospective cohort study of critical ill people with ICU-acquired muscle weakness including a detailed description of physical rehabilitation contents. This study will help to understand the time course and pattern of recovery of walking function and of activities of

daily live. Furthermore a multivariate model for recovery of walking ability will be developed.

Methods and analysis

Study objectives

The primary objective of the GymNAST study is to assess the time course of regaining walking and sit to stand ability as important activities of daily live

Secondary objectives are to:

- describe the concomitant physical rehabilitation therapies
- describe the clinical course of recovery using standardized outcome measures and their results
- identify a prognostic model for regain walking and sit to stand abilities

Design

We conduct a prospective cohort study of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP. We started in 2013 and the final assessments including follow up will be made in 2015.

Based on our sample size calculation [13 14], approximately 150 patients will be recruited from a intensive care unit of our hospital in Germany [15] over the time course of three years. In a first cross sectional pilot study in our hospital we found a point prevalence of 88 patients with defined diagnosis of CIM/CIP and ICU-acquired muscle weakness per month [16]. Therefore, based on this pilot study it seems to be realistically to reach the anticipated sample size in our cohort study within three years of recruitment.

Study population

Patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP will be recruited consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of Klinik Bavaria Kreischa in Germany.

Inclusion criteria

- patient is chronic critical ill **or has a contemporary history of chronic critical ill defined as more than 21 days ICU-treatment including mechanical ventilation and at least 14 days further existing critical situation with the need for ICU-treatment [17]**

- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP)**. The diagnosis of CIM/CIP will be confirmed by a neurologist. Therefore, clinical and neurophysiologic data will be revealed. The procedure of diagnosis of CIP and CIM is described in detail elsewhere [18-20]**
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [21]
- written informed consent of the patient or his legal guardian

Exclusion criteria

- Patients receiving palliative care
- Co-morbidities of the trunk or the lower limbs interfering with upright posture and walking function (e.g. Amputation or fracture of lower limb)
- Other neuromuscular or neurological disease and/or syndromes causing weakness in patients in the ICU (we will exclude patients with diseases and syndromes causing weakness in patients in the ICU[8], due to Guillain–Barré syndrome, myasthenia gravis, porphyria, Eaton–Lambert syndrome, amyotrophic lateral sclerosis, vasculitic neuropathy, cervical myelopathy and botulism)
- severe physical co-morbidity before becoming critical ill (e.g, frailty due to neurological conditions)

Procedure

Eligible patients will be screened and afterwards will get oral and written information about the study from their treating physician or researcher. After written informed consent the

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demographic and clinical characteristics will be measured (baseline assessment T0). Patients will then be measured every two weeks after baseline up to 20 weeks (week two (T1), week four (T2), week six (T3), week eight (T4) week ten (T5) and so on until week twenty (T10)). Two follow ups are planned: FU1 after six month and FU2 after one year after study entry. For follow-up assessments (FU1 and FU2), patients and their guardians will be informed and invited by letter and telephone to participate.

The amount and the content of physical rehabilitation, activities of daily life such as the ability to walk will be documented every day by physiotherapists and occupational therapist using predefined sheets [16]. All assessments and standardized measures will be administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation, at home or residence facility. Additionally, we will try to get all information about the content and duration of physiotherapy and or physical rehabilitation applied at all stages of illness.

Measures and Outcomes

Primary outcomes of the GYMNAST study are walking ability and ability to stand up alone.

To measure walking ability the Functional Ambulation Categories (FAC) is used [22]. The ability to stand up alone will be measured by the ability to stand up from a chair independently, STS (standardised chair height is defined with 120% of knee height).

Secondary outcomes includes

- Richmond Agitation-Sedation Scale (RASS) [21]
- activities measured with the Barthel Index (BI; 10 items) [23]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC) [1 24]
- grip strength (measured bilaterally using a dynamometer) [25 26]
- Functional Status Score for the Intensive Care Unit Scored (FSS-ICU) [27]
- Physical Function –ICU Test (PFIT) [28] and Physical Function –ICU Test- Scored (PFIT-S) [29]

- Pain using a visual analogue scale
- Lateral and frontal sit and stance balance (functional reach) [30 31]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [32] and clock drawing test (CDT) [33]
- walking ability (0- 5; FAC) [34], walking speed (we will use a 10m walking test, adopting a 14-m course and will measure the walking speed over the central 10 m) and walking endurance (we will use a six minute walking test, using 40m course and will measure the distance walked in six minutes; if patients cannot walk the whole six minutes we will measure the maximum walking distance here) [5 6]
- quality of life (EQ-5D) [35]
- participation (Reintegration to Normal Living, RNL-Index) [36 37]
- fitness and mobility (PASIPD) [38 39]

All measures chosen are frequently used in research and/or daily clinical practice dealing with the above described patients.

The primary outcome variables FAC and STS will be measured daily with standardized sheets for this purpose.

At baseline assessment (T0) and then every two weeks until twenty weeks after baseline (T10) we will assess RASS, BI, muscle strength of the upper and lower limb (MRC), grip strength, FSS-ICU, PFIT and PFIT-S, pain, functional reach, cognitive measures, walking speed and endurance.

At follow ups FU1 after six month and FU2 after one year after study entry we will measure the EQ-5D, the RNL-Index and PASIPD. Additionally we will be gathering detailed survival data.

Tables 1 gives a detailed overview of the variables used at each time point of study.

Possible clinical prognostic factors

Depending on the primary outcomes (walking ability and activities), a range of potentially prognostic factors will be taken into account. These factors include: demographic variables (such as age, sex), clinical variables (such as FSS-ICU, PFIT-S) and medical characteristics (such as diagnoses, reason for ICU-treatment, duration of mechanical ventilation, duration of illness) and anthropometric measures, such as body weight and body mass index (but not limb circumference).

Planned statistical analyses

We will use descriptive analyses, e.g. means and standard deviations of the continuous variables and frequencies and proportions of categorical variables as appropriate [40]. We will explain differences across the time points (T1–T10 and FU1 - FU2) descriptively and with appropriate inference statistics use parametric and non-parametric tests as appropriate e.g. repeated measures analysis of variance [40]. The global alpha level will be set at 0.05.

Time to regain walking ability and time to stand up from a chair independently will be the main end point for this analysis. The following factors will be analyzed for their association with these endpoints:

- demographic variables (such as age and sex),
- clinical variables (such as muscle strength, FSS-ICU, PFIT-S) and
- medical characteristics (such as diagnosis and duration of illness)

The probability in regaining walking ability and sit to stand ability will be calculated with the method of Kaplan and Meier [41]. Cox regression analysis will be used to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [42]. A stepwise multivariable Cox regression analysis will be applied with a variable selection [42 43].

Time to event or censoring will be defined as time difference between study entry (T0) and date of reaching a FAC score equal to 3, or the possible censoring dates of discharge or dead, respectively. Possible prognostic factors from demographic, clinical and medical variables will be selected for a multivariable model based on clinical and statistical significance [44-46]. The final model selection will be performed based on clinical decision, together with Akaike's information criterion (AIC) and the Bayesian information criterion (BIC) [43]. Aim

of our analysis is to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables.

To prevent overfitting, only variables with clinically important *and* statistically significant bivariate association with our endpoint will be included in the final model [43].

The effects of prognostic factors in the final model will be expressed as hazard ratios (HR) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards.

We will use SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA). The proportional hazards assumption will be tested with the implemented function (proc phreg).

Results

We will describe the demographic and clinical characteristics at each of the individual time points (T1–T10 and FU1 - FU2) descriptively. We will describe the probability in regaining walking ability and other activities with the method of Kaplan and Meier. We will present the final statistical multivariate model for regaining walking ability.

Sample size and power calculation

The sample size needed in the GymNAST study is calculated using the method for one of the most cited recommendation for prognostic research: the 'rule of ten events per variable (EPV)' [13 14 46]. Based on our sample size calculation using the EPV-approach approximately 150 patients will be recruited from the intensive care unit of our long term intensive care hospital in Germany [15]. We anticipate reaching this study size over the time course of three years. Our confidence results from a cross-sectional study. We found a point prevalence of 88 patients per month of people with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP in our intensive care units [16]. Therefore, based on this pilot study it seems to be a realistically to reach the estimated sample size in our cohort study within three years of recruitment.

Ethics and Dissemination

Ethical considerations

The GymNAST study will be conducted in accordance with the 'Helsinki Declaration'. The study is non-invasive, imposes no risk on patients, seems to have enough power to detect meaningful determinants and our protocol has been approved by the medical ethical committees. Furthermore, written informed consent is obtained from all participants or if necessary from its legal guardian. The study will be registered before publication.

Dissemination

The results obtained will be disseminated to the scientific, medical and general public by publication in national and international peer-reviewed journals, as well as by presentations in conferences and meetings with clinicians dealing with patients with ICU-acquired muscle weakness syndrome.

Discussion

The GymNAST study will be one of the first studies with rigorous repeated measures over the time course of one year with daily documentation of rehabilitation therapies of people with ICU-acquired muscle weakness. Also a wide range of functional variables to describe the pattern of regaining of walking is used.

Until now many prognostic studies including people with ICU-acquired muscle weakness used rather a traditional prognostic design using a baseline test and compared with ICU discharge and follow-ups [5 28 29] and only some studies measures continuously over time [47]. However, instead of comparing two or more measurements of the patient's performance it seems to be more informative to analyze the dynamic recovery systematically using equal time intervals over an appropriate time period e.g. with daily assessments of walking function and with daily description of physical rehabilitation over months. This might provide a more detailed understanding of the pattern and the dynamics of recovery of walking function, and allows a better understanding of changes in clinical characteristics and the applied rehabilitation therapies.

Also, detailed knowledge about the time course of recovery of walking ability, their risks and chances (e.g. clinical and therapeutic determinants) are still not very well understood. The present study documents clinical determinants at equal time intervals (every two weeks) and will document therapeutic determinants daily.

Strong aspects of GymNAST are therefore its prospective design with multiple repeated assessments during the first year after illness using equal time intervals of people with ICU-acquired muscle weakness. The present study might therefore provide new and more detailed information about the pattern of walking recovery and the physical rehabilitation content of people with ICU-acquired muscle weakness.

A potential limitation of the study is that the most seriously affected patients might be unable to participate, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no objective measures for muscle weakness such as electromyography or magnetic resonance tomography will be used.

Authors' contributions:

J.M., S.M, FO and M.P. planned the study. F.O. and M.P. contributed to the procurement of funding. J.M., S.M, and M.P. developed the protocol. All authors contributed to and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Summary of outcome measures and time points of assessment in GymNAST

	Baseline	Daily	Biweekly (T1 to T12)	Follow-up (FU 1 and 2)
Amount and content of Physical Rehabilitation				
Physiotherapy		x		x
Occupational Therapy		x		x
Other therapies (e.g. groups)		x		x
Primary Outcome				
FAC and STS	x	x		
Delir measures				
RASS	x		x	
Strength measures				
MRC score	x		x	x
Grip strength	x		x	x
Physical function measures				
PFIT and PFIT-S	x		x	x
FSS-ICU score	x		x	x
10m walking time	x		x	x
6-MWT	x		x	x
Pain (VAS)	x		x	x
functional reach	x		x	x
Cognition measures				
MOCA	x		x	x
CDT	x		x	x
Activities and Mobility				
BI	x		x	x
PASIPD				x
Participation and quality of life				
EQ-5D				x
RNL-Index				x

Abbreviations: GymNAST: General Weakness Syndrome Therapy study; FU= Follow Up; T= Time point; FAC: Functional Ambulation; STS: ability to stand up from a chair independently; RASS: Richmond Agitation-Sedation Scale; MRC: Medical Research Council (muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle)); PFIT: Physical Function –Intensive Care Unit- Test; PFIT-S: Physical Function – Intensive Care Unit Test- Scored; FSS-ICU: Functional Status Score for the Intensive Care Unit Scored; 6-MWT: six minute walking test; VAS: visual analogue scale; MOCA= Montreal Cognitive Assessment; CDT: clock drawing test; BI: Barthel Index; PASIPD: Physical Activity Scale for Individuals with Physical Disabilities; EQ-5D: EuroQol (5 dimensions); RNL-Index: Reintegration to Normal Living Index