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Recovery of walking function in patients with intensive-care-unit-acquired muscle weakness due to critical illness myopathy and polyneuropathy. First results from the General Weakness Syndrome Therapy (GymNAST) study.

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Abstract

Objectives:

To describe the time course of recovery of walking function and other activities of daily living in patients with intensive-care-unit (ICU)-acquired muscle weakness due to critical illness myopathy (CIM) and polyneuropathy (CIP).

Design:

This is a cohort study.

Participants:

We included critical ill patients with ICU-acquired muscle weakness and a defined diagnosis of CIM or CIP.

Setting:

Post-acute ICU and rehabilitation units in Germany.

Measures:

We measured walking function, muscle strength, activities in daily living, motor and cognitive function.

Results:

We recruited 150 patients (30% female) who fulfilled our inclusion and exclusion criteria. The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. Our final multivariate model for recovery of walking function included two clinical variables from baseline: the Functional Status Score ICU (adjusted Hazard Ratio (HR)= 1.07 (95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02 (95% CI 1.00 to 1.04). All secondary outcomes but not pain improved in the first eight weeks after study onset significantly.

Conclusion:

We found good recovery of walking function for most patients and described the recovery of walking function of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Registrations: EK-BR-32/13-1; DRKS00007181, German Register of Clinical Trials

Article Summary

Article focus:

In the General Weakness Syndrome Therapy (GymNAST) study we describe the time course of recovery of walking ability, and risk factors and chances for walking function after ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Key messages:

This study described clinical characteristics and the time course of motor performance and of walking ability of people with ICU-acquired muscle weakness.

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.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first months of ICU-acquired muscle weakness with daily documentation of recovery of walking function. Multiple repeated assessments, with a wide range of clinical measures were used. Our results may provide further insights into dynamics of recovery of walking function over time of critical ill patients with ICU-acquired muscle weakness.

One limitation might be that most severe affected ICU patients (e.g. patients who were enormously sedated) were excluded in this study. This could reduce the generalisability of our results to the whole population of critical ill patients. Another limitation might be that neither electromyography nor magnetic resonance tomography were used for differential diagnostics of muscle weakness.

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 (ICU)-acquired muscle weakness. According to Nordon-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 suitable physical intervention strategies were described in the literature [1 8-11].

However, detailed knowledge about the time course of recovery of walking, their risk factors and chances for good recovery (e.g. for walking) are not well described. 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 [12]. Such a depiction could give insights in to the time course of recovery of walking function of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study was to describe and to identify the time course and the pattern of recovery of walking function in these patients [13]. Another aim of GymNAST is to develop a multivariate risk factor model for recovery of walking function of people with ICU-acquired muscle weakness.

Here we describe the first short-term results of the GymNAST study for walking recovery.

Methods and analysis

Between January 2013 to March 2015 we screened all patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP consecutively from the intensive care units of our acute care, weaning and early rehabilitation centers of the Klinik Bavaria Kreischa in Germany and recruited patients who met our following inclusion and exclusion criteria (as previously reported [13]):

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 [14]
- 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 [15-17]
- 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 and/or syndromes causing weakness in patients in the ICU (e.g. Guillain–Barré syndrome, myasthenia gravis, porphyria, Lambert- Eaton 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)

Measures and Outcomes

We defined walking ability as the primary outcomes of the GYMNAST study with more or equal than 3 of the Functional Ambulation Categories (0 -5; FAC) [19]. We assessed walking ability daily.

Secondary outcomes included

- Richmond Agitation-Sedation Scale (RASS) [18]
- activities measured with the Barthel Index (BI; 10 items) [20]
- clinical severity (e.g. mechanical ventilation, dysphagia, tracheostoma) measured with the Frühreha-Index [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 26]
- Physical Function ICU Test (scored) (PFIT-s) [27 28]
- pain using a numeric pain rating scale [29]
- Sit and stance balance (functional reach)[30 31]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [32] and clock drawing test (CDT) [33 34]
- walking ability (0- 5; FAC) [35], walking speed and walking endurance [5 6]

All assessments and standardized measures were administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation. We measured patients from baseline (T0) every two weeks up to 8 weeks (T4). We describe the results of the first eight weeks of GYMNAST as first or short-term results. We will further describe the results of additional time points and follow-up as long-term results in a separate publication.

Ethical considerations

We conducted this study in accordance with the 'Helsinki Declaration' and received ethical approval by the local ethic commission (EK-BR-32/13-1 / 106755) and registered the study before publication (DRKS00006528).

Statistical analyses

We used descriptive analyses, e.g. median and interquartile ranges and means and standard deviations of continuous variables and frequencies and proportions of categorical variables as appropriate [36]. We applied inference statistics and parametric and non-parametric tests as appropriate [36]. The global alpha level was be set at 0.05.

We calculated the probability in regaining walking ability with the method of Kaplan and Meier [37]. The time to event or censoring was defined as the time between study entry (T0) and the date of reaching a FAC score equal or more than 3, or the possible censoring dates of discharge or dead, respectively. We used Cox regression analysis to estimate relative hazard rates and to test for differences in variables or trends in subgroups of each factor [38]. We used a stepwise multivariable Cox regression analysis with a variable selection of possible prognostic factors [38 39]. Possible prognostic factors included demographic variables (age, BMI and sex), clinical variables (muscle strength of the upper and lower limbs, grip strength, pain, FSS-ICU score and PFIT-S score) and medical characteristics (diagnosis and duration of illness and duration of respirator use).

After a univariate description and analysis of above mentioned demographic, clinical and medical variables we selected all clinical meaningful and statistical significant variables into a multivariable model [40-42]. We performed a final multivariable model selection based on clinical decision, together with Akaike's information criterion (AIC) [39]. The aim of our analysis was to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables. To prevent overfitting, we included only variables with clinically important *and* statistically significant bivariate association with our endpoint in our final multivariate model [39]. We expressed the effects of our final multivariate model as hazard ratios (HRs) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards. We used SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA) and proportional hazards assumptions were tested with the implemented function (proc phreg).

Results

After screening of 1387 patients between January 2013 to March 2015 we included 150 patients with ICU-acquired muscle weakness and defined diagnosis of CIM/CIP (30% female) in our study and analyses (see figure 1 flow chart and table 1). The demographic and clinical characteristics at each of the individual time points (T0 to T4) can be found in table 1 and 3.

The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. The time course of the probability in regaining walking ability is shown in two modes: first dependent on time from study onset (figure 2a) and second based on duration of illness (figure 2b).

Our final multivariate model for recovery of walking function included two main variables: first the score in the FSS-ICU (adjusted HR= 1.07 (95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02 (95% CI 1.00 to 1.04; see table 2).

All secondary outcomes except pain improved from T0 to T4 significantly (see table 3 for details).

Discussion

The present study is one of the first studies with rigorous repeated measures design over the time course of one year of people with ICU-acquired muscle weakness due to CIP or CIM.

As a main result we found that 50% of all included patients were able to walk at a median of 28.5 days after rehabilitation and after a median duration of illness of 81.5 days.

We used a wide range of functional variables to describe the pattern of regaining of walking. The main variables in our final multivariate model to explain ability to walk, however, were clinical scales the FSS-ICU score and the ability to reach forward in sitting and standing at baseline. Both assessments can be used very early and very easy in patients on ICU and may predict the recovery of walking ability of people with ICU-acquired muscle weakness.

From our knowledge, many prognostic studies including people with ICU-acquired muscle weakness used rather a conventional prognostic design using a baseline test and compared with ICU discharge and follow-up data [5 27 28] and just some studies measured functional recovery continuously over time [43]. Instead of comparing two or more measurements of the patient's performance, however, 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 ability. Our study therefore might provide a more detailed understanding of a pattern and the dynamics of recovery of walking ability of chronic ill people with ICU-acquired muscle weakness.

As recently shown there are no randomized trials so far including people with ICU-acquired muscle weakness with a defined diagnosis of CIP or CIM [12]. To our knowledge cohort studies describing the recovery of walking ability in people with ICU-acquired muscle weakness with a defined diagnosis of CIP or CIM are also quite rare.

One recent study of Denehy and coworkers included one hundred and fifty people after 5 or more days on ICU admission but did not used a defined diagnosis of CIP or CIM as inclusion criteria [10]. Compared to the population of Denehy et al. our patients had a longer length of hospital stay in acute hospital (median 41 days vs. 20 to 23.5 days) and a longer duration of mechanical ventilation (median 53 days vs. 98 hours) and only 17 to 21 % of included patients in the Denehys trial had ICU-acquired muscle weakness.

A recent multi-center cohort study investigated functional recovery at six months among 192 mechanically ventilated ICU patients (about 50% of these patients had ICU-acquired

weakness) [44]. The authors, however, did not describe the functional recovery of walking in this population.

Cuthbertson and colleagues investigated 286 patients after discharge from intensive care and 192 patients completed the one year follow-up [45], but a defined diagnosis to CIP or CIM as cause for muscle weakness was not used as an inclusion criteria. The authors conclude, however, that further work should focus on the recovery from critical illness [45].

In our study we chose the PFIT-s and FSS-ICU as main clinical assessments. Both measures are common and recommended for patients in ICU and were well described in this population [25-28]. Other studies used the Rivermead Mobility Index, a scale well known in stroke rehabilitation [46]. Nordon-Craft et al. described on the basis of 51 patients from ICU that the PFIT-s was highly correlated to MRC sum score and grip strength [27]. Additionally at ICU discharge, an MRC sum score cut point of 41.5 predicted subject's ability to perform the standing components of the PFIT-s [27]. In our study, however, we did found a predictive value neither for the MRC sum score nor for the PFIT-s predicting walking recovery. We found the best prediction for walking recovery from a model containing the FSS-ICU score and the functional reach in the first week of rehabilitation.

Eventually, the patients included in our study were relatively chronically and severe ill, had all ICU-acquired muscle weakness due to a defined diagnosis of CIP or CIM and were therefore not directly comparable to other published clinical trials in the field of ICU research.

Strong aspects of GymNAST are the prospective design with multiple repeated assessments during the first months of 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 short-term 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 very seriously affected patients in terms of very sedated or very agitated, who were not able to perform the assessments, were not included, thereby reducing the possibility to generalize the results to the whole critical ill population. Another limitation might be that no electromyography or magnetic resonance tomographies were used as diagnostic tools for differential diagnosis of muscle weakness.

Further studies should use a randomized controlled design, should include people with ICU-acquired muscle weakness and investigate specific rehabilitation therapies to improve or to speed up walking recovery in this population of severe ill people.

Authors' contributions:

JM, SM, FO and MP planned the study. FO, JM and MP contributed to the procurement of funding. JM., SM, and MP developed the protocol, SM, MP and JM evaluated and interpreted the data, JM, SM and MP did the statistical analysis. All authors contributed to writing and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Patient characteristics

Variable (n=150)	median, IQR	mean±SD
Age [years]	71, 12	69.16±9.02
Height [cm]	173, 18	171.89±10.69
Weight [kg]	82, 21	86.07±25.58
BMI [points]	27.4, 6.7	29.11±8.25
Duration of illness [days]	41, 30	49.13±29.13
Duration of mechanical ventilation [days]	53, 42	65.22±45.14
Primary ICU diagnosis, frequency (%)		
sepsis		82 (55)
pneumonia		29 (19)
cardiac		21 (14)
other		18 (12)
female, frequency (%)		50 (30)
mechanically ventilated at baseline, frequency (%)		103 (69)
tracheostoma at baseline, frequency (%)		120 (81)
dysphagia, frequency (%)		81 (54%)
dialysis, frequency (%)		45 (30%)
patients recruited at ICU or acute stage, frequency (%)		121 (81)
patients recruited at post-ICU stage or inpatient rehab centre, frequency (%)		29 (19)

Barthel-Index [points]	5, 25	14.68 ± 19.20
MRC sum score at baseline, upper limb	9.5, 3.25	0.5 ± 0.8
MRC sum score at baseline, lower limb	9, 3.25	0.5 ± 0.8
MOCA score at baseline [points]	16, 10	14.3 ± 7.0

Table 2 Summary of the final multivariate Cox proportional hazard model for regaining walking ability

variable	Chi^2	p value	HR	95% CI
FSS-ICU score in points	13.36	0.0003	1.074	1.033 to 1.115
ability to reach forward in cm	5.25	0.0219	1.019	1.003 to 1.036

FSS-ICU score= functional status score ICU

Table 3 Summary of secondary outcome measures at time points

	T0	T1	T2	T3	T4	p value
Primary Outcome						
FAC=0 (in %)	105(70)	52(40)	40(35)	26(26)	16(24)	<.001
FAC=1 (in %)	7(5)	8(6)	3(3)	6(6)	3(4)	
FAC=2 (in %)	38(25)	3(2)	5(4)	12(12)	3(4)	
FAC=3 (in %)	0(0)	30(23)	22(19)	13(13)	15(22)	
FAC=4 (in %)	0(0)	30(23)	29(25)	28(28)	21(31)	
FAC=5 (in %)	0(0)	7(5)	16(14)	16(16)	9(13)	
muscle strength measures						
MRC sum score upper limbs	9.45±2.55	11.20±2.46	11.46±2.49	11.65±2.27	12.22±2.15	<.001
MRC sum score lower limbs	8.45±2.50	10.07±2.84	10.24±2.56	10.51±2.54	11.11±2.08	<.001
grip strength (in kg)	9.33±5.35	11.92±6.22	13.32±6.99	13.54±6.18	14.19±7.66	<.001
Physical function measures						
PFIT-S score (points)	3.89±3.22	6.52±3.54	7.39±3.24	7.34±3.38	7.61±3.43	<.001
FSS-ICU score (points)	15.77±9.80	23.64±9.95	25.53±9.80	26.39±9.09	26.61±9.47	<.001
10m walking speed (km/h)	0.86±0.91	1.80±1.79	1.84±1.92	1.59±1.68	1.26±1.53	<.001
6-MWT (m)	25.8±60.0	87.1±109.7	114.2±126.3	112.8±121.0	126.3±125.1	<.001
pain (mm VAS)	4.0±8.3	7.6±12.3	6.2±10.7	6.2±9.8	4.6±8.3	.751
functional reach (cm)	31.9±23.4	46.9±23.5	50.6±25.9	49.7±24.8	54.4±22.2	<.001
Cognition measures						
MOCA (points)	14.3±7.0	17.1±7.4	18.9±6.6	19.8±6.3	20.4±6.3	<.001
CDT (points)	3.9±1.8	3.2±1.6	2.9±1.4	2.6±1.6	2.6±1.7	<.001
Activities and Mobility						
BI (points)	14.7±19.2	36.0±31.1	46.6±34.0	50.5±33.2	55.0±32.4	<.001

Abbreviations: T= Time point; FAC: Functional Ambulation; MRC: Medical Research Council (muscle strength of the upper (sum of shoulder, elbow and wrist) and lower limb (sum of hip, knee and ankle)); 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

Figure 1

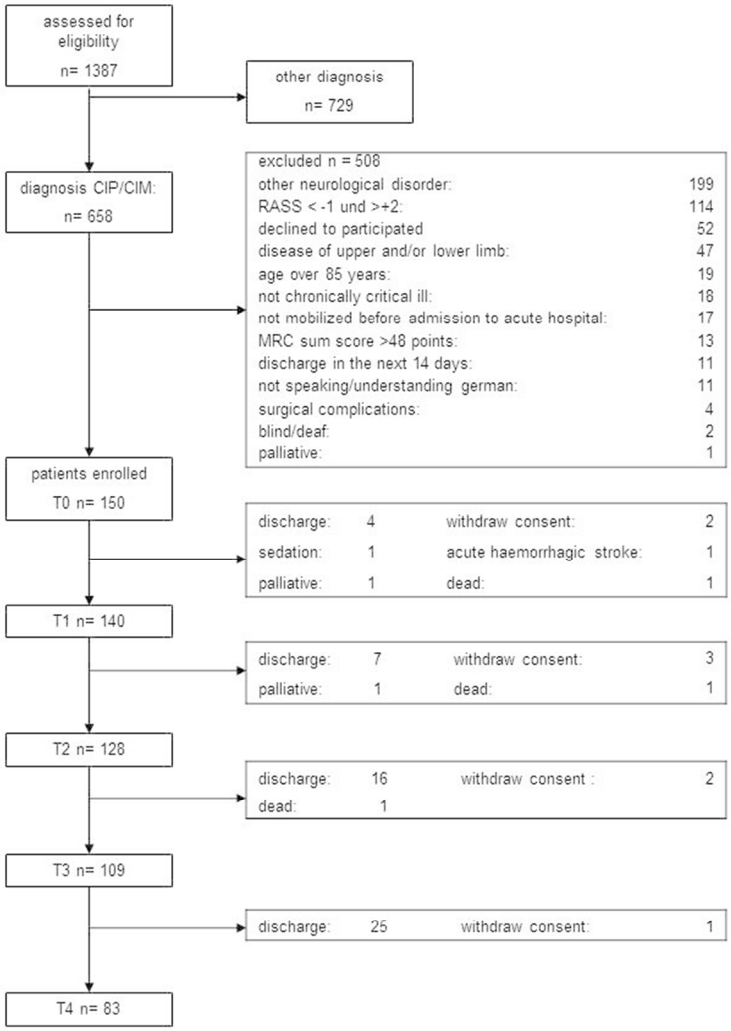
Flow chart

Figure 2a

Time course of recovery of walking function during inpatient rehabilitation and early intensive rehabilitation stage

Figure 2b

Time course of recovery of walking function during duration of illness



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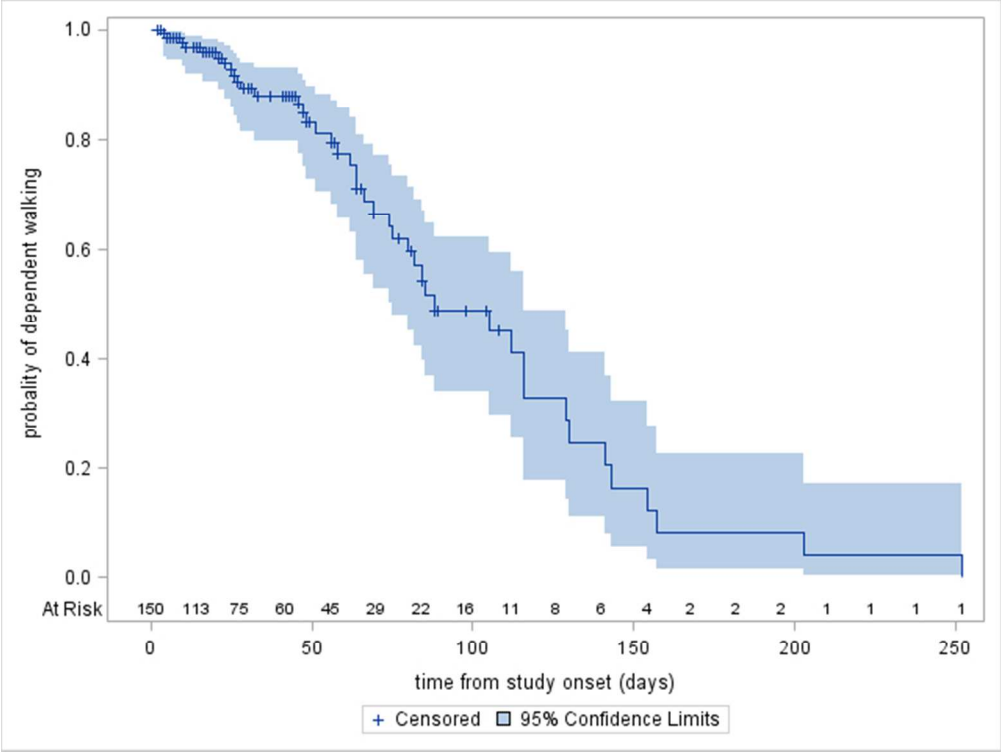

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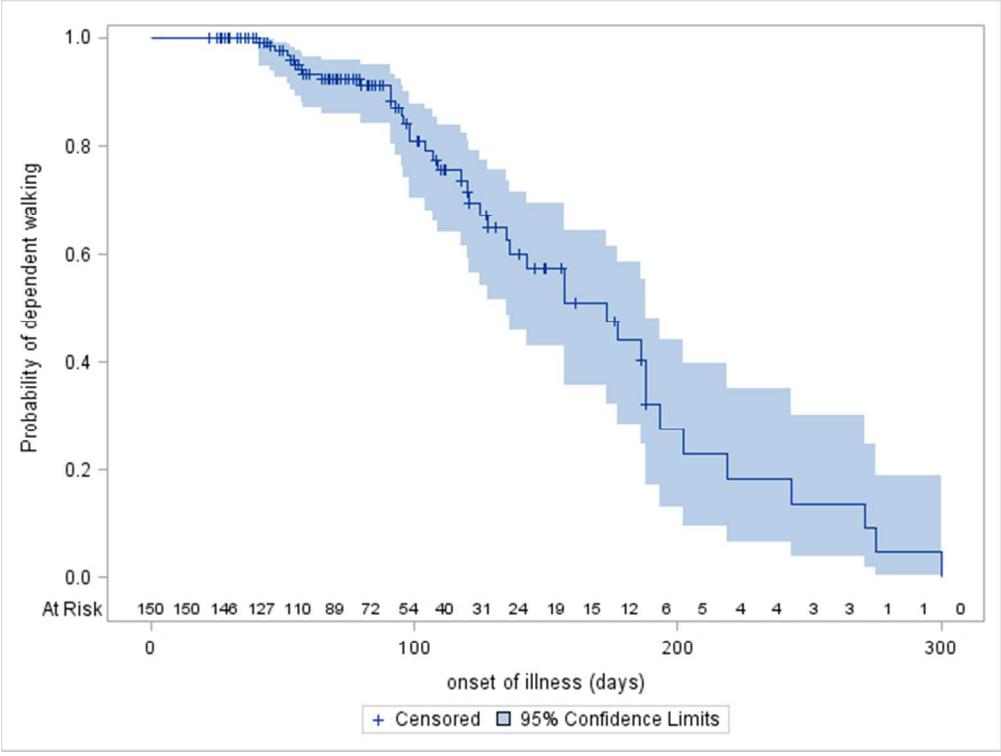

225x169mm (72 x 72 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Recovery of walking function in patients with intensive-care-unit-acquired muscle weakness due to critical illness myopathy and polyneuropathy. First results from the General Weakness Syndrome Therapy (GymNAST) study.

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Recovery of walking function in patients with intensive-care-unit-acquired muscle weakness due to critical illness myopathy and polyneuropathy. First results from the General Weakness Syndrome Therapy (GymNAST) study.

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Short title: recovery of walking and intensive-care-unit-acquired weakness

Keywords: intensive care - rehabilitation - walking - muscle weakness

Word count: 4 593

Abstract

Objectives:

To describe the time course of recovery of walking function and other activities of daily living in patients with intensive-care-unit (ICU)-acquired muscle weakness due to critical illness myopathy (CIM) and polyneuropathy (CIP).

Design:

This is a cohort study.

Participants:

We included critical ill patients with ICU-acquired muscle weakness and a defined diagnosis of CIM or CIP.

Setting:

Post-acute ICU and rehabilitation units in Germany.

Measures:

We measured walking function, muscle strength, activities in daily living, motor and cognitive function.

Results:

We recruited 150 patients (30% female) who fulfilled our inclusion and exclusion criteria. The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. Our final multivariate model for recovery of walking function included two clinical variables from baseline: the Functional Status Score ICU (adjusted Hazard Ratio (HR)= 1.07 (95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02 (95% CI 1.00 to 1.04). All secondary outcomes but not pain improved in the first eight weeks after study onset significantly.

Conclusion:

We found good recovery of walking function for most patients and described the recovery of walking function of people with ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Registrations: EK-BR-32/13-1; DRKS00007181, German Register of Clinical Trials

Article Summary

Article focus:

In the General Weakness Syndrome Therapy (GymNAST) study we describe the time course of recovery of walking ability, and risk factors and chances for walking function after ICU-acquired muscle weakness with defined diagnosis of CIM or CIP.

Key messages:

This study described clinical characteristics and the time course of motor performance and of walking ability of people with ICU-acquired muscle weakness.

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.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first months of ICU-acquired muscle weakness with daily documentation of recovery of walking function. Multiple repeated assessments, with a wide range of clinical measures were used. Our results may provide further insights into dynamics of recovery of walking function over time of critical ill patients with ICU-acquired muscle weakness.

One limitation might be that some of the severe affected ICU patients (e.g. patients who were moderate or deep sedated) were excluded in this study. This could reduce the generalisability of our results to the whole population of critical ill patients. Further limitations include that electromyography was not used for differential diagnostics of muscle weakness between CIM and CIP, that magnetic resonance tomography was not used as prognostic tool and that creatine kinase was not measured.

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 (ICU)-acquired muscle weakness. According to Nordon-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1] and therefore designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. A more precise definition ICU-acquired muscle weakness includes: 1) weakness must follow the onset of the critical illness; 2) physical examination shows diffuse, symmetric weakness involving all extremities and respiratory muscles; 3) Medical Research Council (MRC) sum score is less than 48 out of 60, or mean MRC score is equal to four in all testable muscle groups noted on two occasions separated by 24 hours, 4) dependence on mechanical ventilation, 5) causes of weakness not related to the underlying critical illness have been excluded [2]. The acquired weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [3-5]. This increases morbidity and delays rehabilitation and recovery of walking [6 7]. 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 [8 9]. 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 10] . In recent years appropriate assessments were developed and suitable physical intervention strategies were described in the literature [1 9 11-13]. There are recent longitudinal studies in this field. For instance Fan et al. investigated 222 survivors of severe critical illness and determined the longitudinal epidemiology of muscle weakness, physical function, and health-related quality of life, and their associations with critical illness and intensive care unit exposures [14]. Needham et al. evaluated muscle strength, 6-minute-walk distance, and the Short Form-36 Physical Function score of 203 survivors after 6- and 12-month of acute lung injury [15]. Semmler and colleagues analyzed the long-term neuromuscular deficits of survivors of 51 patients with critical illness six to 24 months after discharge from the ICU, measured the MRC sum score, the Overall Disability Sum score (ODSS), and performed nerve conduction studies and electromyography [16]. MRC sum score and the ODSS score were correlated with the days of ICU treatment and with the days of ventilator support, but the neuromuscular long-term consequences of critical illness were not severe.

Wieske et al. investigated post-ICU mortality and physical functioning in 80 patients with acquired weakness at 6 months after ICU discharge. They found that ICU-acquired weakness is independently associated with post-ICU mortality and with clinically physical at six months after ICU discharge [17].

Taken all these essential studies together one could argue that a detailed knowledge about the exact time course of recovery of walking assessed on a daily basis, their risk factors and chances for good recovery, however, are still not entirely known. It lacks, from a rehabilitation point of view on a detailed description of the exact pattern of walking recovery and of physical rehabilitation treatment in the first year of people with ICU-acquired muscle weakness [18]. Such a depiction could give insights in to the particular time course of recovery of walking function of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study was to describe and to identify the time course and the pattern of recovery of walking function in these patients [19]. Another aim of GymNAST was to develop a multivariate risk factor model for recovery of walking function of people with ICU-acquired muscle weakness.

Here we describe the first short-term results of the GymNAST study for walking recovery.

Methods and analysis

Between January 2013 to March 2015 we screened all patients consecutively from the intensive care units of our post-acute ICU and rehabilitation units of the Klinik Bavaria Kreischa in Germany and recruited patients who met our following inclusion and exclusion criteria (as previously reported [19]):

Inclusion criteria

- patient is chronic critical ill or has a contemporary history of chronic critical ill. Chronic critical ill was 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 [20 21])
- defined diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP). The diagnosis of CIM/CIP was performed by a physician in acute or post-acute hospital and always confirmed by a neurologist. Therefore, clinical and (if needed) neurophysiologic information were used for diagnosis of CIM/CIP. The procedure of diagnosis of CIP and CIM is described in detail elsewhere [22] and will be only briefly described here. All patients underwent clinical examination by a physician and a specialist in neurology and electrophysiological workup was performed only by another specialist if the neurologist were in any uncertainty of the clinical diagnosis [22]. We used this approach because we could recently shown, that in a total of 280 patients with complicated weaning in our post-acute hospital the positive predictive value of our diagnostic procedure for CIP/CIM was 97.9% with a 95% confidence interval (CI) 69.4 to 99.9 and the negative predictive value was 88.9% (95% CI 82.7 to93.0) [22].
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- more than or equal to 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [23]
- 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 (e.g. Guillain–Barré syndrome, myasthenia gravis, porphyria, Lambert- Eaton 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)

All patients received from the first day of admission to our intensive care units of our post-acute ICU and rehabilitation units their individual treatment including physiotherapy, occupational therapy. Physical rehabilitation treatments started, even if patients were mechanically ventilated, on the first day of admission, but differed in amount and methods individually due to the severity of critical illness and indication. We did not, however measured the start, content and amount of treatments in the earlier acute stage.

Measures and Outcomes

We defined walking ability as the primary outcomes of the GYMNAST study with more or equal than 3 of the Functional Ambulation Categories (FAC; and ranging from 0 -5) first described by Holden and colleagues in 1984 [24]. The FAC is a quick visual measurement of walking, is simple to use and easy to interpret and distinguishes six levels of walking ability on the basis of the amount of physical support required [24 25]. For instance a FAC of '0' indicates a patient who is not able to walk at all or needs the help of two therapists (nonfunctional ambulator) and a FAC of '5' indicates a patient who can walk everywhere independently, including stairs (independent ambulator) [24 25]. Research showed that the FAC has very good reliability, good concurrent and predictive validity, and good responsiveness in neurological rehabilitation [24-26]. In the present study we used previously described key questions for every FAC level, used experienced rater and assessed walking ability with FACs daily [25]. The definition of a good outcome we used was a minimum of FAC of '3' and better (ambulator, dependent on supervision) which indicates a patient who

can at least ambulate on level surface without manual contact of another person but requires standby guarding of one person either for safety or for verbal cueing.

Secondary outcomes included

- activities of daily living measured with the Barthel Index (BI; 10 items) [27]. The Barthel Index (score range, 0 to 100) is a valid and reliable index measuring activities of daily life [28]. Included are ten items relating to the degree of independence from any help [27 28].
- clinical severity (e.g. mechanical ventilation, dysphagia, tracheostomy) measured with the Early Rehabilitation Barthel Index (ERBI) (in the original form described as Frühreha-Index (FRI) [29 30]. The ERBI was designed to allow for a simple determination of clinical severity and contains seven items. Every item will be dichotomous scored as present or absent. These seven items are as translated by Rollnik 2010 [30]:
    - intensive care supervision (-50 or 0 points)
    - tracheostomy tube management and supervision (-50 or 0 points)
    - Intermittent (or continuous) mechanical ventilation (-50 or 0 points)
    - confused patient (in need of supervision) (-50 or 0)
    - behavioural disturbances (patient being a danger to himself or others) (-50 or 0 points)
    - severe impairment of communication (-25 or 0 points)
    - dysphagia patient in need of supervision (-50 or 0 points)

  The sum ERBI score is between 0 and -325 points. Rollnik described 2010 high inter-rater-reliability for the ERBI (r= 0.849) [30]
- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC). We used MRC sum scores for upper and lower limbs. [1 31]

- grip strength (measured bilaterally using a dynamometer) [32 33]. We summed up the means of both hands. We did not define ICU acquired weakness on the base of cut off values from hand grip dynamometry.
- Functional Status Score for the Intensive Care Unit (FSS-ICU) [34 35]. The FSS-ICU rates two functional and three additional tasks that are relevant and feasible to perform in the ICU setting [34 35]. All five tasks are evaluated using a 7-point scoring system, with higher scores indicating higher function [34]. A score of 0 will be assigned if a patient is unable to perform a task, due to either physical limitation or medical status [34,35].
- Physical Function ICU Test (scored) (PFIT-s) [36 37]. The PFIT-s is a modified versions of the Physical Function ICU Test and contains four items: a) assistance in sit to stand manoeuvres (0, 1, or 2 people needed), b) cadence (steps per minute), c) shoulder flexion strength (muscle strength graded as: 0=no contraction, 1=visible/palpable muscle contraction, 2=movement across gravity, 3=movement against gravity, 4=movement against gravity with some resistance, or 5=movement against gravity with full resistance), and d) knee extension strength (same muscle strength grading as for shoulder flexion strength) [37]
- pain using a numeric pain rating scale [38]
- the ability to reach forward as a measure for sit and stance balance. We measured the ability to reach forward while sitting and standing (also called 'functional reach') and summed up the results in cm [39 40]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [41] and clock drawing test (CDT) [42 43]
- walking speed (m/s) and walking endurance (6-MWT; metres walked in six minutes) [6 7]

All assessments and standardized measures were administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation. We measured patients from baseline (T0) every two weeks up to 8 weeks (T4). We defined baseline as the first admission to our post-acute hospital or to our inpatient rehabilitation centre respectively (T0). Based on this definition the duration of illness was defined as the time between the very first day on ICU (first admission to the acute hospital due to the onset of primary illness) until the study onset (T0, baseline, admission to the post-acute hospital or inpatient rehabilitation) or

until the observation of the primary outcome or until T1, T2 and so on respectively. The duration of study was therefore the time between study onset (T0, admission to the post-acute hospital or inpatient rehabilitation) until the observation of the primary outcome or T1, T2 and so on, respectively.

We describe here the results of the first eight weeks of GYMNAST as primary or short-term results. We will further describe the results of additional time points and follow-up as long-term results in a separate publication.

Ethical considerations

We conducted this study in accordance with the 'Helsinki Declaration' and received ethical approval by the local ethic commission (EK-BR-32/13-1 / 106755) and registered the study before publication (DRKS00006528).

Statistical analyses

We used descriptive analyses, e.g. median and interquartile ranges and means and standard deviations of continuous variables and frequencies and proportions of categorical variables as appropriate [44]. We applied inference statistics and parametric and non-parametric tests as appropriate [44]. The global alpha level was be set at 0.05.

We calculated the probability in regaining walking ability with the method of Kaplan and Meier [45]. The time to event or censoring was defined as the time between study entry (T0) and the date of reaching a FAC (score 0 to 5) equal or more than 3, or the possible censoring dates of discharge or dead, respectively. We used Cox regression analysis to estimate relative hazard rates and to test for differences in variables [46]. We used univariate and multivariate Cox regression analysis with a selection of possible predictor variables for the primary outcome [46 47] as follows.

univariate analysis

These possible predictor variables included: age at study onset, body mass index (BMI), sex, duration of illness, number of medical tubes (catheters and vascular access), duration of mechanical ventilation, number secondary diagnosis, ERBI item 1, ERBI item 2, ERBI item 3, ERBI item 4, ERBI item 5, ERBI item 6, ERBI item 7, ability to reach forward, FSS-ICU score, PFIT-s score, grip strength, MRCsum score upper limb, MRCsum score lower limb,

VAS, MoCA, and CDT. We did univariate Cox regression analysis of these possible predictor variables and listed the results.

multivariate analysis and model building

After the univariate analysis and description of above mentioned variables we selected all clinical meaningful and statistical significant variables (alpha level of 0.2 for selection) as so called candidate predictor variables. Afterwards we used a stepwise regression analysis with all candidate predictor variables. We used for this purpose the procedure proc phreg implemented in SAS/STAT 9.3; SAS Institute Inc., Cary, NC, USA). In the process of stepwise regression a predictor variable had to be significant at the 0.2 level to be entered into the multivariate model and a variable in the model had to be significant at the 0.1 level to remain in the multivariate model. Variables with the highest global score chi-square scores were selected first into a multivariable model [48-50]. As the aim of our analysis was to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables (to prevent overfitting) we limited this process to two, three, four and to a maximum of five remaining variables in the multivariate model. After that we compared the multivariate models (with two, three, four and five remaining variables respectively) on the global score chi-square statistic (so called best subset selection) and on the Akaike's information criterion (AIC) to decide for our final multivariate model [47]. We expressed the effects of our final multivariate model as hazard ratios (HRs) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards. We used SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA) and proportional hazards assumptions were tested with the implemented function (proc phreg).

Results

After screening of 1387 patients between January 2013 to March 2015 we included 150 patients with ICU-acquired muscle weakness and diagnosis of CIM/CIP (30% female) in our study and analyses (see figure 1 flow chart and table 1).

The demographic and clinical characteristics at each of the individual time points (T0 to T4) can be found in table 1 and 3.

The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days

(interquartile range= 64) after onset of illness. The time course of the probability in regaining walking ability is shown in two modes: first dependent on time from study onset (figure 2a) and second based on duration of illness (figure 2b). The ability to walk improved over time significantly (as shown graphically in figure 2a and 2b). The percentage of patients who could walk progressed from T0 (0%) to T1 (37%) to T2 (68%) to T3 (71%) to T4 (85%; see table 3 for details).

To explain the dependent variable recovery of walking a Cox regression analysis was done. The results for every possible predictor variable in our first univariate regression analysis to explain recovery of walking are shown in table 2a. After univariate regression analysis we selected the following candidate predictor variables; age at study onset, body mass index (BMI), number of medical tubes (catheters and vascular access), duration of mechanical ventilation, ERBI item 4 to 7, ability to reach forward, FSS-ICU score, grip strength, and MRCsum score upper limb. Based on these candidate predictor variables we did multivariate regression analysis to explain the primary outcome recovery of walking. After comparing different multivariate models using we selected on statistical and clinical decision our final multivariate model for recovery of walking. This final model included two variables (model fit statistics AIC= 656.4 with covariates): the FSS-ICU score in points (adjusted HR= 1.07; 95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02; 95% CI 1.00 to 1.04; see table 2b).

All secondary outcomes except pain improved from T0 to T4 significantly (see table 3). The greatest effects for muscle strength measures (T0 to T4) were found for the MRC sum score upper limbs with a large effect size of 1.28. MRC sum score lower limbs and grip strength, however, improved with an effect size of 0.59 and 0.75, respectively. The effect sizes for the physical function measures PFIT-S score, FSS-ICU, 10m walking speed, 6-MWT, and functional reach were 0.73, 1.19, 0.33, 1.09, and 0.99 respectively. The effect sizes for the cognition measures MOCA, and CDT were 0.92 and 0.74 respectively. The effect size for the BI was 1.29.

Physiotherapy was provided between T0 and T1 every week day in average for 45 minutes. The following main methods of physiotherapy/ physical rehabilitation in these 45 minutes daily contact time in the first two weeks after study onset included: training of sitting balance (in and outside of bed), sit to stand training (in and outside of bed), transfer training to get out

of bed or to get from bed to wheelchair and vice versa, gait training (including stepping in front of bed), strengthening exercise (in and outside of bed), stepping stairs (including stepping in front of bed), and assistive standing exercises.

Discussion

The present study is one of the first studies with rigorous repeated measures design over the time course of one year of people with ICU-acquired muscle weakness due to CIP or CIM.

As a main result we found that 50% of all included patients were able to walk at a median of 28.5 days after rehabilitation and after a median duration of illness of 81.5 days.

We used a wide range of functional variables to describe the pattern of regaining of walking. The main variables in our final multivariate model to explain ability to walk, however, were clinical scales the FSS-ICU score and the ability to reach forward in sitting and standing at baseline. Both assessments can be used very early and very easy in patients on ICU and may predict the recovery of walking ability of people with ICU-acquired muscle weakness.

From our knowledge, many prognostic studies including people with ICU-acquired muscle weakness used rather a conventional prognostic design using a baseline test and compared with ICU discharge and follow-up data [6 36 37] and just some studies measured functional recovery continuously over time [51]. Instead of comparing two or more measurements of the patient's performance, however, 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 ability. Our study therefore might provide a more detailed understanding of a pattern and the dynamics of recovery of walking ability of chronic ill people with ICU-acquired muscle weakness.

As recently shown there are no randomized trials so far including people with ICU-acquired muscle weakness with a defined diagnosis of CIP or CIM [18]. To our knowledge cohort studies describing the recovery of walking ability in people with ICU-acquired muscle weakness with a defined diagnosis of CIP or CIM are also quite rare.

One recent study of Denehy and coworkers included one hundred and fifty people after 5 or more days on ICU admission but did not used a defined diagnosis of CIP or CIM as inclusion criteria [12]. Compared to the population of Denehy et al. our patients had a longer length of

hospital stay in acute hospital (median 41 days vs. 20 to 23.5 days) and a longer duration of mechanical ventilation (median 53 days vs. 98 hours) and only 17 to 21 % of included patients in the Denehys trial had ICU-acquired muscle weakness.

Compared to Fan et al. who described a mean Apache II of 26 points [14] our study population, however, had a mean of 16 points and could therefore seen as somewhat less severe affected. Given the long duration of illness, however, our patients were more chronically affected.

A recent multi-center cohort study investigated functional recovery at six months among 192 mechanically ventilated ICU patients (about 50% of these patients had ICU-acquired weakness) [52]. The authors, however, did not describe the functional recovery of walking in this population.

Cuthbertson and colleagues investigated 286 patients after discharge from intensive care and 192 patients completed the one year follow-up [53], but a defined diagnosis to CIP or CIM as cause for muscle weakness was not used as an inclusion criteria. The authors conclude, however, that further work should focus on the recovery from critical illness [53].

In our study we chose the PFIT-s and FSS-ICU as main clinical assessments. Both measures are common and recommended for patients in ICU and were well described in this population [34-37]. Other studies used the Rivermead Mobility Index, a scale well known in stroke rehabilitation [54]. Nordon-Craft et al. described on the basis of 51 patients from ICU that the PFIT-s was highly correlated to MRC sum score and grip strength [36]. Additionally at ICU discharge, an MRC sum score cut point of 41.5 predicted subject's ability to perform the standing components of the PFIT-s [36]. In our study, however, we did find a predictive value neither for the MRC sum score nor for the PFIT-s predicting walking recovery. We found the best prediction for walking recovery from a model containing the FSS-ICU score and the functional reach in the first week of rehabilitation.

At the one hand this study shows on the first glance good recovery of walking function measured with the FAC. On the other hand comparing with reference values of healthy persons from six countries for the 6-MWTs and the walking speed we found many of our patients still reasonably below the 10th percentile of age adjusted walking distance and speed [55]. This shows obviously that the recovery of walking even after eight weeks of physical rehabilitation is still not at a normal level. Further studies should therefore provide insights into specific treatment approaches to improve the walking distance in chronically ill

population [18 56]. In practice a long term treatment approach seems warranted for this chronically ill population.

At a first look it seems a bit strange that the average walking speed improved from T0 to T3 and declined then to T4. This is, however, due to the fact, that patients with good recovery including good recovered walking function were discharged earlier (and therefore excluded from analysis) than patients with not so good recovery.

Eventually, the patients included in our study were relatively chronically and severely ill, had all ICU-acquired muscle weakness due to a defined diagnosis of CIP or CIM and were therefore not directly comparable to other published clinical trials in the field of ICU research.

Strong aspects of GymNAST are the prospective design with multiple repeated assessments during the first months of illness using equal time intervals of people with ICU-acquired muscle weakness with an daily assessment of walking ability. The present study might therefore provide new and more detailed information about the short-term 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 very seriously affected patients in terms of very sedated or very agitated, who were not able to perform the assessments, were not included, thereby reducing the possibility to generalize the results to the whole critical ill population. Further limitations include that electromyography was not used for differential diagnostics of muscle weakness between CIM and CIP, that magnetic resonance tomography was not used as prognostic tool and that creatine kinase was not measured.

Further studies should use a randomized controlled design, should include people with ICU-acquired muscle weakness and investigate specific rehabilitation therapies to improve or to speed up walking recovery in this population of severe ill people.

Authors' contributions:

JM, SM, FO and MP planned the study. FO, JM and MP contributed to the procurement of funding. JM., SM, and MP developed the protocol, SM, MP and JM evaluated and interpreted the data, JM, SM and MP did the statistical analysis. All authors contributed to writing and checked the final draft of the manuscript**.**

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Competing interests statement:

None declared

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Table 1 Patient characteristics

Variable (n=150)	Median (IQR)	Mean (SD)
Age [years]	71(12)	69.16 (9.02)
BMI [points]	27.4 (6.7)	29.11 (8.25)
Duration of illness [days]	41 (30)	49.13 (29.13)
Duration of mechanical ventilation [days]	53 (42)	65.22 (45.14)
Apache II [points]	16 (5)	16.45 (4.08)
Barthel-Index [points]	5 (25)	14.68 (19.20)
MRC sum score at baseline, upper limb	9.5 (3.25)	0.5 (0.8)
MRC sum score at baseline, lower limb	9 (3.25)	0.5 (0.8)
MOCA score at baseline [points]	16 (10)	14.3 (7.0)
Primary ICU diagnosis	**frequency (%)**	
sepsis	82 (55)	
pneumonia	29 (19)	
cardiac	21 (14)	
other	18 (12)	
female	50 (30)	
dialysis	45 (30%)	
patients recruited at post-ICU	121 (81)	
patients recruited at inpatient rehab centre	29 (19)	
ERBI item 1: intensive care supervision	121 (81)	
ERBI item 2: tracheostomy tube management and supervision	120 (80)	
ERBI item 3: intermittent (or continuous)	103 (69)	

mechanical ventilation	
ERBI item 4: confused patient (in need of supervision)	3 (2)
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	8 (5)
ERBI item 6: severe impairment of communication	41 (21)
ERBI item 7: dysphagia patient in need of supervision	81 (54)

Table 2a Summary of the univariate Cox proportional hazards for regaining walking ability of all potential predictor variables

variable (at T0)	Chi^2	p value	HR	95% CI
Age (years)	7.37	0.007	0.970	0.949 to 0.992
BMI	3.92	0.048	0.972	0.944 to 1.000
Sex (male)	0.00	0.996	1.001	0.637 to 1.573
duration of illness (days)	1.33	0.249	0.995	0.986 to 1.004
number of medical tubes (catheters and vascular access)	1.83	0.176	0.901	0.774 to 1.048
duration of mechanical ventilation (days)	8.05	0.005	0.992	0.986 to 0.997
number secondary diagnosis	0.07	0.790	0.996	0.965 to 1.03
ERBI item 1: intensive care supervision	1.37	0.242	1.009	0.994 to 1.023
ERBI item 2: tracheostomy tube management and supervision	0.41	0.524	1.005	0.990 to 1.019
ERBI item 3: intermittent or continuous mechanical ventilation	0.00	0.986	1.000	0.987 to 1.014
ERBI item 4: confused patient (in need of supervision)	2.14	0.144	1.023	0.992 to 1.055
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	2.37	0.124	0.984	0.965 to 1.004
ERBI item 6: severe impairment of communication	11.24	0.001	1.037	1.015 to 1.060
ERBI item 7: dysphagia patient in need of supervision	2.43	0.119	0.993	0.983 to 1.002
ability to reach forward (cm)	4.06	0.044	1.028	1.001 to 1.056
FSS-ICU score (points)	1.99	0.159	1.062	0.977 to 1.115
PFIT-s score (points)	0.51	0.475	1.095	0.854 to 1.403
grip strength (kg)	3.03	0.082	1.075	0.991 to 1.167
MRCsum score upper limb (points)	8.44	0.004	0.715	0.571 to 0.897
MRCsum score lower limb (points)	0.00	0.970	1.004	0.808 to 1.248

VAS (mm)	0.43	0.514	1.012	0.977 to 1.047
MoCA (points)	1.34	0.247	0.960	0.896 to 1.029
CDT (points)	1.23	0.267	0.847	0.632 to 1.136

HR= Hazard Ratio; CI= confidence interval; ERBI= Early Rehabilitation Barthel Index; FSS-ICU= Functional Status Score for the Intensive Care Unit; PFIT-s= Physical Function ICU Test (scored); MRC= Medical Research Council; VAS= visual analogue scale; MoCA= Montreal - Cognitive Assessment; CDT= Clock drawing test

Table 2b Summary of the final multivariate Cox proportional hazard model for regaining walking ability

variable	Chi^2	p value	HR	95% CI
FSS-ICU score in points	13.36	0.0003	1.074	1.033 to 1.115
ability to reach forward in cm	5.25	0.0219	1.019	1.003 to 1.036

FSS-ICU score= functional status score ICU; HR= Hazard Ratio; CI= confidence interval

Description: higher scores of the FSS-ICU and the greater ability to reach forward at T0 are indicating significantly higher chances to regain walking ability

Table 3 Summary of secondary outcome measures at time points

	T0	T1	T2	T3	T4	p value
Primary Outcome, frequencies						
FAC=0 (in %)	105 (70)	52 (40)	40 (35)	26 (26)	16 (24)	<.001
FAC=1 (in %)	7 (5)	8 (6)	3 (3)	6 (6)	3 (4)	
FAC=2 (in %)	38 (25)	3 (2)	5 (4)	12 (12)	3 (4)	
FAC=3 (in %)	0 (0)	30 (23)	22 (19)	13 (13)	15 (22)	
FAC=4 (in %)	0 (0)	30 (23)	29 (25)	28 (28)	21 (31)	
FAC=5 (in %)	0 (0)	7 (5)	16 (14)	16 (16)	9 (13)	
muscle strength measures						
MRC sum score upper limbs*	9.50 (2.55)	11.50 (2.46)	12.00 (2.49)	12.00 (2.27)	12.50 (2.15)	<.001
MRC sum score lower limbs*	9.00 (3.25)	10.50 (3.00)	10.50 (3.00)	11.00 (3.50)	11.00 (3.50)	<.001
grip strength (in kg)#	9.33 (5.35)	11.92 (6.22)	13.32 (6.99)	13.54 (6.18)	14.19 (7.66)	<.001
Physical function measures						
PFIT-S score (points)*	4.00 (6.00)	8.00 (5.50)	8.00 (5.00)	8.00 (6.00)	8.00 (5.00)	<.001
FSS-ICU score (points)*	16.0 (15.0)	25.0 (16.0)	30.0 (14.0)	29.0 (13.0)	31.5 (11.0)	<.001
10m walking speed (m/s)#	0.24 (0.25)	0.50 (0.50)	0.51 (0.53)	0.45 (0.48)	0.35 (0.42)	<.001
6-MWT (m)#	25.8±60.0	87.1±109.7	114.2±126.3	112.8±121.0	126.3±125.1	<.001
pain (mm VAS)#	4.0±8.3	7.6±12.3	6.2±10.7	6.2±9.8	4.6±8.3	.751
functional reach (cm)#	31.9±23.4	46.9±23.5	50.6±25.9	49.7±24.8	54.4±22.2	<.001
Cognition measures						
MOCA (points)#	14.3±7.0	17.1±7.4	18.9±6.6	19.8±6.3	20.4±6.3	<.001
CDT (points)#	3.9±1.8	3.2±1.6	2.9±1.4	2.6±1.6	2.6±1.7	<.001
Activities and Mobility						
BI (points)*	5.0 (25.0)	35.0 (55.0)	45.0 (65.0)	50.0 (60.0)	60.0 (60.0)	<.001

*presented as median and interquartile ranges; # presented as means and standard deviations

Abbreviations: T= Time point; FAC: Functional Ambulation; MRC: Medical Research Council (muscle strength of the upper (sum of shoulder, elbow and wrist) and lower limb (sum of hip, knee and ankle)); 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

Figure 1

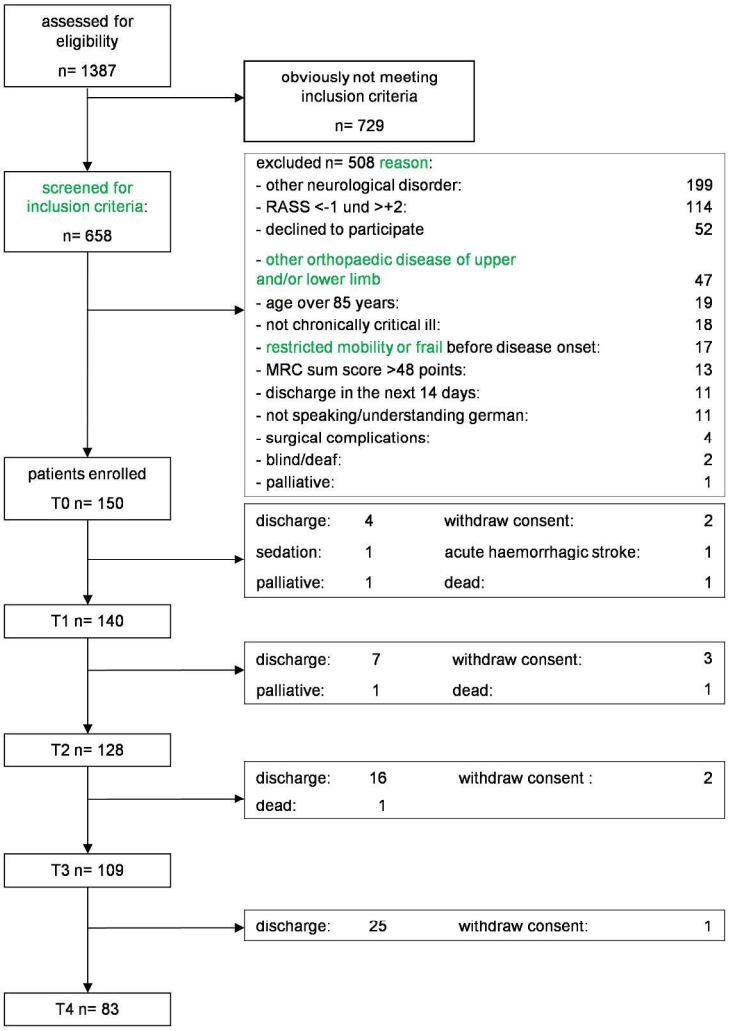
Flow chart

Figure 2a

Time course of recovery of walking function from study onset (T0)

Figure 2b

Time course of recovery of walking function from onset of the primary illness



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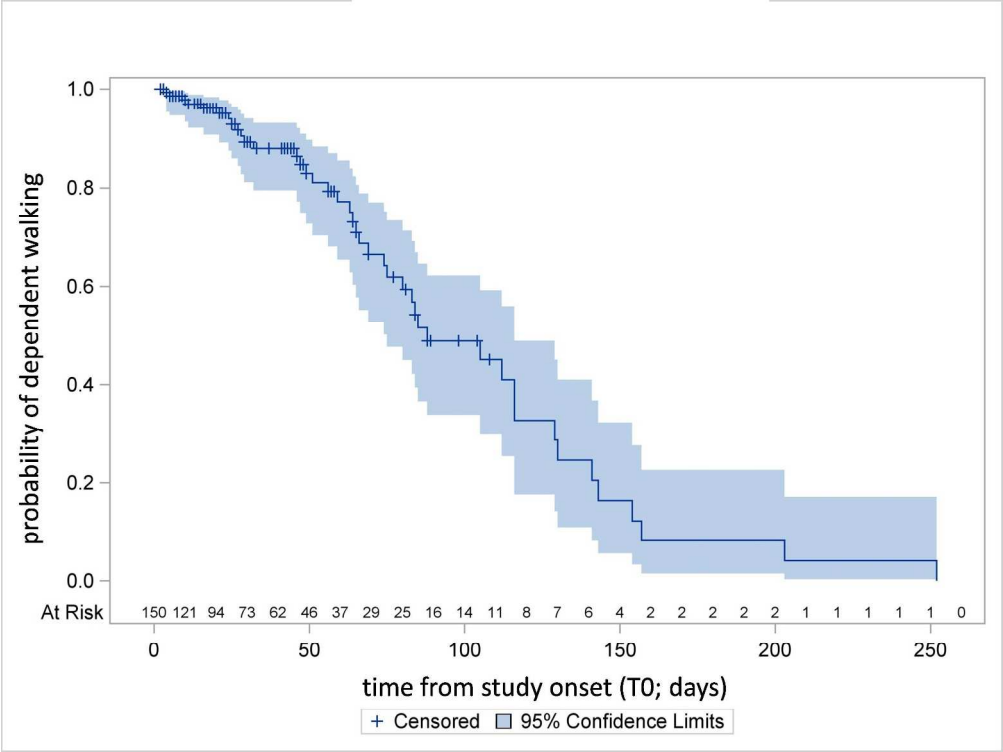

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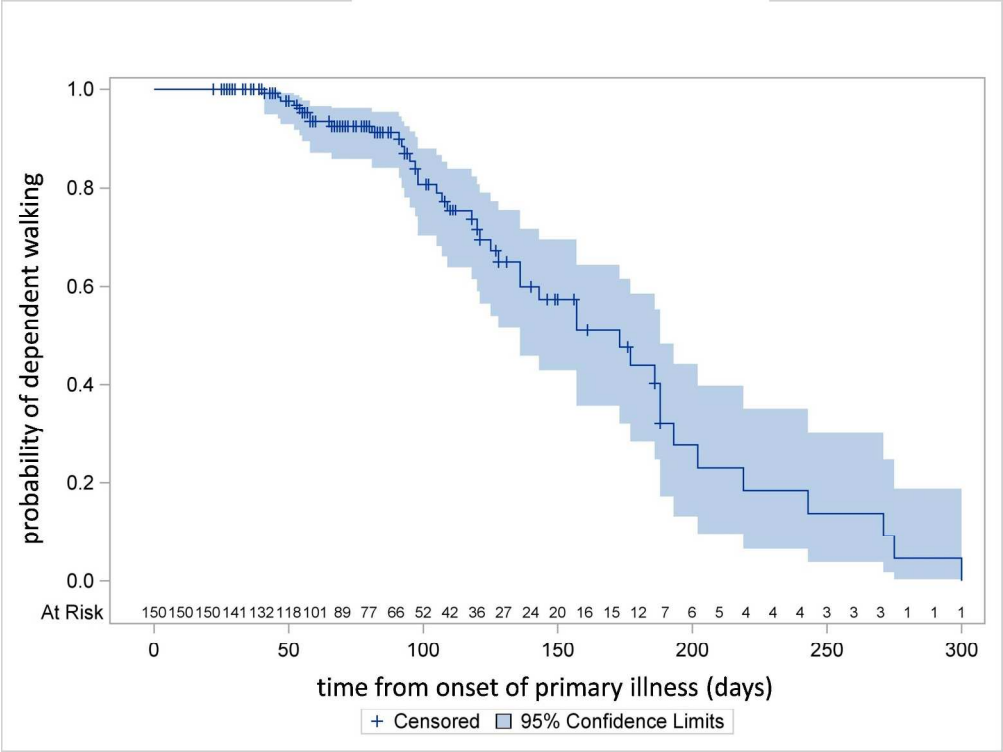

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) Summarise follow-up time (eg, average and total amount)
Outcome data	15*	Report numbers of outcome events or summary measures over time
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Recovery of walking function in patients with intensive-care-unit-acquired muscle weakness. First results from the General Weakness Syndrome Therapy (GymNAST) study.

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Recovery of walking function in patients with intensive-care-unit-acquired muscle weakness. First results from the General Weakness Syndrome Therapy (GymNAST) study.

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Keywords: intensive care - rehabilitation - walking - muscle weakness

Word count: 4 593

Abstract

Objectives:

To describe the time course of recovery of walking function and other activities of daily living in patients with intensive-care-unit (ICU)-acquired muscle weakness.

Design:

This is a cohort study.

Participants:

We included critical ill patients with ICU-acquired muscle weakness.

Setting:

Post-acute ICU and rehabilitation units in Germany.

Measures:

We measured walking function, muscle strength, activities in daily living, motor and cognitive function.

Results:

We recruited 150 patients (30% female) who fulfilled our inclusion and exclusion criteria. The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. Our final multivariate model for recovery of walking function included two clinical variables from baseline: the Functional Status Score ICU (adjusted Hazard Ratio (HR)= 1.07 (95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02 (95% CI 1.00 to 1.04). All secondary outcomes but not pain improved in the first eight weeks after study onset significantly.

Conclusion:

We found good recovery of walking function for most patients and described the recovery of walking function of people with ICU-acquired muscle weakness.

Registrations: EK-BR-32/13-1; DRKS00007181, German Register of Clinical Trials

Article Summary

Article focus:

In the General Weakness Syndrome Therapy (GymNAST) study we describe the time course of recovery of walking ability, and risk factors and chances for walking function after ICU-acquired muscle weakness.

Key messages:

This study described clinical characteristics and the time course of motor performance and of walking ability of people with ICU-acquired muscle weakness.

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.

Strengths and limitations:

The strength of this study is that it is one of the first prospective cohort studies in the first months of ICU-acquired muscle weakness with daily documentation of recovery of walking function. Multiple repeated assessments, with a wide range of clinical measures were used. Our results may provide further insights into dynamics of recovery of walking function over time of critical ill patients with ICU-acquired muscle weakness.

One limitation might be that some of the severe affected ICU patients (e.g. patients who were moderate or deep sedated) were excluded in this study. This could reduce the generalisability of our results to the whole population of critical ill patients. Further limitations include that electromyography was not used in all of the included patients for diagnostics of muscle weakness (e.g. to differentiate CIM and CIP), and that magnetic resonance tomography was not used as prognostic tool and that creatine kinase was not measured.

Introduction

In clinical practice it is often seen that critically ill patients on intensive-care-unit (ICU) get weak muscles. According to Nordon-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1] and therefore designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. A more precise definition ICU-acquired muscle weakness includes: 1) weakness must follow the onset of the critical illness; 2) physical examination shows diffuse, symmetric weakness involving all extremities and respiratory muscles; 3) Medical Research Council (MRC) sum score is less than 48 out of 60, or mean MRC score is equal to four in all testable muscle groups noted on two occasions separated by 24 hours, 4) dependence on mechanical ventilation, 5) causes of weakness not related to the underlying critical illness have been excluded [2]. The acquired weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required [3-5]. This increases morbidity and delays rehabilitation and recovery of walking [6 7]. 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 [8 9]. 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 10] . In recent years appropriate assessments were developed and suitable physical intervention strategies were described in the literature [1 9 11-13]. There are recent longitudinal studies in this field. For instance Fan et al. investigated 222 survivors of severe critical illness and determined the longitudinal epidemiology of muscle weakness, physical function, and health-related quality of life, and their associations with critical illness and intensive care unit exposures [14]. Needham et al. evaluated muscle strength, 6-minute-walk distance, and the Short Form-36 Physical Function score of 203 survivors after 6- and 12-month of acute lung injury [15]. Semmler and colleagues analyzed the long-term neuromuscular deficits of survivors of 51 patients with critical illness six to 24 months after discharge from the ICU, measured the MRC sum score, the Overall Disability Sum score (ODSS), and performed nerve conduction studies and electromyography [16]. MRC sum score and the ODSS score were correlated with the days of ICU treatment and with the days of ventilator support, but the neuromuscular long-term consequences of critical illness were not severe.

Wieske et al. investigated post-ICU mortality and physical functioning in 80 patients with acquired weakness at 6 months after ICU discharge. They found that ICU-acquired weakness is independently associated with post-ICU mortality and with clinically physical at six months after ICU discharge [17].

Taken all these essential studies together one could argue that a detailed knowledge about the exact time course of recovery of walking assessed on a daily basis, their risk factors and chances for good recovery, however, are still not entirely known. It lacks, from a rehabilitation point of view on a detailed description of the exact pattern of walking recovery and of physical rehabilitation treatment in the first year of people with ICU-acquired muscle weakness [18]. Such a depiction could give insights in to the particular time course of recovery of walking function of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study was to describe and to identify the time course and the pattern of recovery of walking function in these patients [19]. Another aim of GymNAST was to develop a multivariate risk factor model for recovery of walking function of people with ICU-acquired muscle weakness.

Here we describe the first short-term results of the GymNAST study for walking recovery.

Methods and analysis

Between January 2013 to March 2015 we screened all patients consecutively from the intensive care units of our post-acute ICU and rehabilitation units of the Klinik Bavaria Kreischa in Germany and recruited patients who met our following inclusion and exclusion criteria (as previously reported [19]):

Inclusion criteria

- patient is chronic critical ill or has a contemporary history of chronic critical ill. Chronic critical ill was 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 [20 21])
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- a defined reason for muscle weakness such as a clinical diagnosis of Critical illness myopathy (CIM) and polyneuropathy (CIP). The diagnosis of CIM/CIP was performed by a physician in acute or post-acute hospital and always confirmed by a neurologist. Therefore, clinical and (if needed) neurophysiologic information were used for diagnosis of CIM/CIP. The procedure of diagnosis of CIP and CIM is described in detail elsewhere [22] and will be only briefly described here. All patients underwent clinical examination by a physician and a specialist in neurology and electrophysiological workup was performed only by another specialist if the neurologist were in any uncertainty of the clinical diagnosis [22]. We used this approach because we could recently shown, that in a total of 280 patients with complicated weaning in our post-acute hospital the positive predictive value of our diagnostic procedure for CIP/CIM was 97.9% with a 95% confidence interval (CI) 69.4 to 99.9 and the negative predictive value was 88.9% (95% CI 82.7 to 93.0) [22].
- more than or equal to 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [23]
- 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 (e.g. Guillain–Barré syndrome, myasthenia gravis, porphyria, Lambert- Eaton 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)

All patients received from the first day of admission to our intensive care units of our post-acute ICU and rehabilitation units their individual treatment including physiotherapy, occupational therapy. Physical rehabilitation treatments started, even if patients were mechanically ventilated, on the first day of admission, but differed in amount and methods individually due to the severity of critical illness and indication. We did not, however measured the start, content and amount of treatments in the earlier acute stage.

Measures and Outcomes

We defined walking ability as the primary outcomes of the GYMNAST study with more or equal than 3 of the Functional Ambulation Categories (FAC; and ranging from 0 -5) first described by Holden and colleagues in 1984 [24]. The FAC is a quick visual measurement of walking, is simple to use and easy to interpret and distinguishes six levels of walking ability on the basis of the amount of physical support required [24 25]. For instance a FAC of '0' indicates a patient who is not able to walk at all or needs the help of two therapists (nonfunctional ambulator) and a FAC of '5' indicates a patient who can walk everywhere independently, including stairs (independent ambulator) [24 25]. Research showed that the FAC has very good reliability, good concurrent and predictive validity, and good responsiveness in neurological rehabilitation [24-26]. In the present study we used previously described key questions for every FAC level, used experienced rater and assessed walking ability with FACs [25]. FACs were measured on a daily basis because we were primarily interested to determine precisely when the good outcome, the ability to walk, occurred in the time course. The definition of a good outcome we used was a minimum of FAC of '3' and

better (ambulator, dependent on supervision) which indicates a patient who can at least ambulate on level surface without manual contact of another person but requires standby guarding of one person either for safety or for verbal cueing. Our primary outcome was therefore analysed as time to event ('event' defined as the time point when ability to walk occurred measured by FAC of '3').

Secondary outcomes included

- activities of daily living measured with the Barthel Index (BI; 10 items) [27]. The Barthel Index (score range, 0 to 100) is a valid and reliable index measuring activities of daily life [28]. Included are ten items relating to the degree of independence from any help [27 28].
- clinical severity (e.g. mechanical ventilation, dysphagia, tracheostomy) measured with the Early Rehabilitation Barthel Index (ERBI) (in the original form described as Frühreha-Index (FRI) [29 30]. The ERBI was designed to allow for a simple determination of clinical severity and contains seven items. Every item will be dichotomous scored as present or absent. These seven items are as translated by Rollnik 2010 [30]:
    - intensive care supervision (-50 or 0 points)
    - tracheostomy tube management and supervision (-50 or 0 points)
    - Intermittent (or continuous) mechanical ventilation (-50 or 0 points)
    - confused patient (in need of supervision) (-50 or 0)
    - behavioural disturbances (patient being a danger to himself or others) (-50 or 0 points)
    - severe impairment of communication (-25 or 0 points)
    - dysphagia patient in need of supervision (-50 or 0 points)

  The sum ERBI score is between 0 and -325 points. Rollnik described 2010 high inter-rater-reliability for the ERBI (r= 0.849) [30]

- muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC). We used MRC sum scores for upper and lower limbs. [1 31]
- grip strength (measured bilaterally using a dynamometer) [32 33]. We summed up the means of both hands. We did not define ICU acquired weakness on the base of cut off values from hand grip dynamometry.
- Functional Status Score for the Intensive Care Unit (FSS-ICU) [34 35]. The FSS-ICU rates two functional and three additional tasks that are relevant and feasible to perform in the ICU setting [34 35]. All five tasks are evaluated using a 7-point scoring system, with higher scores indicating higher function [34]. A score of 0 will be assigned if a patient is unable to perform a task, due to either physical limitation or medical status [34,35].
- Physical Function ICU Test (scored) (PFIT-s) [36 37]. The PFIT-s is a modified versions of the Physical Function ICU Test and contains four items: a) assistance in sit to stand manoeuvres (0, 1, or 2 people needed), b) cadence (steps per minute), c) shoulder flexion strength (muscle strength graded as: 0=no contraction, 1=visible/palpable muscle contraction, 2=movement across gravity, 3=movement against gravity, 4=movement against gravity with some resistance, or 5=movement against gravity with full resistance), and d) knee extension strength (same muscle strength grading as for shoulder flexion strength) [37]
- pain using a numeric pain rating scale [38]
- the ability to reach forward as a measure for sit and stance balance. We measured the ability to reach forward while sitting and standing (also called 'functional reach') and summed up the results in cm [39 40]
- cognitive measures (Montreal Cognitive Assessment (MoCA) [41] and clock drawing test (CDT) [42 43]
- walking speed (m/s) and walking endurance (6-MWT; metres walked in six minutes) [6 7]

All assessments and standardized measures were administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation. We measured patients from baseline (T0) every two weeks up to 8 weeks (T4). We defined baseline as the first

admission to our post-acute hospital or to our inpatient rehabilitation centre respectively (T0). Based on this definition the duration of illness was defined as the time between the very first day on ICU (first admission to the acute hospital due to the onset of primary illness) until the study onset (T0, baseline, admission to the post-acute hospital or inpatient rehabilitation) or until the observation of the primary outcome or until T1, T2 and so on respectively. The duration of study was therefore the time between study onset (T0, admission to the post-acute hospital or inpatient rehabilitation) until the observation of the primary outcome or T1, T2 and so on, respectively.

We describe here the results of the first eight weeks of GYMNAST as primary or short-term results. We will further describe the results of additional time points and follow-up as long-term results in a separate publication.

Ethical considerations

We conducted this study in accordance with the 'Helsinki Declaration' and received ethical approval by the local ethic commission (EK-BR-32/13-1 / 106755) and registered the study before publication (DRKS00006528).

Statistical analyses

We used descriptive analyses, e.g. median and interquartile ranges and means and standard deviations of continuous variables and frequencies and proportions of categorical variables as appropriate [44]. We applied inference statistics and parametric and non-parametric tests as appropriate [44]. The global alpha level was be set at 0.05.

We calculated the probability in regaining walking ability with the method of Kaplan and Meier [45]. The time to event or censoring was defined as the time between study entry (T0) and the date of reaching a FAC (score 0 to 5) equal or more than 3, or the possible censoring dates of discharge or dead, respectively. We used Cox regression analysis to estimate relative hazard rates and to test for differences in variables [46]. We used univariate and multivariate Cox regression analysis with a selection of possible predictor variables for the primary outcome [46 47] as follows.

univariate analysis

These possible predictor variables included: age at study onset, body mass index (BMI), sex, duration of illness, number of medical tubes (catheters and vascular access), duration of

mechanical ventilation, number secondary diagnosis, ERBI item 1, ERBI item 2, ERBI item 3, ERBI item 4, ERBI item 5, ERBI item 6, ERBI item 7, ability to reach forward, FSS-ICU score, PFIT-s score, grip strength, MRCsum score upper limb, MRCsum score lower limb, VAS, MoCA, and CDT. We did univariate Cox regression analysis of these possible predictor variables and listed the results.

multivariate analysis and model building

After the univariate analysis and description of above mentioned variables we selected all clinical meaningful and statistical significant variables (alpha level of 0.2 for selection) as so called candidate predictor variables. Afterwards we used a stepwise regression analysis with all candidate predictor variables. We used for this purpose the procedure proc phreg implemented in SAS/STAT 9.3; SAS Institute Inc., Cary, NC, USA). In the process of stepwise regression a predictor variable had to be significant at the 0.2 level to be entered into the multivariate model and a variable in the model had to be significant at the 0.1 level to remain in the multivariate model. Variables with the highest global score chi-square scores were selected first into a multivariable model [48-50]. As the aim of our analysis was to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables (to prevent overfitting) we limited this process to two, three, four and to a maximum of five remaining variables in the multivariate model. After that we compared the multivariate models (with two, three, four and five remaining variables respectively) on the global score chi-square statistic (so called best subset selection) and on the Akaike's information criterion (AIC) to decide for our final multivariate model [47]. We expressed the effects of our final multivariate model as hazard ratios (HRs) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards. We used SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA) and proportional hazards assumptions were tested with the implemented function (proc phreg).

Results

After screening of 1387 patients between January 2013 to March 2015 we included 150 patients with ICU-acquired muscle weakness (30% female) in our study and analyses (see figure 1 flow chart and table 1).

The demographic and clinical characteristics at each of the individual time points (T0 to T4) can be found in table 1 and 3.

The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. The time course of the probability in regaining walking ability is shown in two modes: first dependent on time from study onset (figure 2a) and second based on duration of illness (figure 2b). The ability to walk improved over time significantly (as shown graphically in figure 2a and 2b). The percentage of patients who could walk progressed from T0 (0%) to T1 (37%) to T2 (68%) to T3 (71%) to T4 (85%; see table 3 for details).

To explain the dependent variable recovery of walking a Cox regression analysis was done. The results for every possible predictor variable in our first univariate regression analysis to explain recovery of walking are shown in table 2a. After univariate regression analysis we selected the following candidate predictor variables; age at study onset, body mass index (BMI), number of medical tubes (catheters and vascular access), duration of mechanical ventilation, ERBI item 4 to 7, ability to reach forward, FSS-ICU score, grip strength, and MRCsum score upper limb. Based on these candidate predictor variables we did multivariate regression analysis to explain the primary outcome recovery of walking. After comparing different multivariate models using we selected on statistical and clinical decision our final multivariate model for recovery of walking. This final model included two variables (model fit statistics AIC= 656.4 with covariates): the FSS-ICU score in points (adjusted HR= 1.07; 95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02; 95% CI 1.00 to 1.04; see table 2b).

All secondary outcomes except pain improved from T0 to T4 significantly (see table 3). The greatest effects for muscle strength measures (T0 to T4) were found for the MRC sum score upper limbs with a large effect size of 1.28. MRC sum score lower limbs and grip strength, however, improved with an effect size of 0.59 and 0.75, respectively. The effect sizes for the physical function measures PFIT-S score, FSS-ICU, 10m walking speed, 6-MWT, and functional reach were 0.73, 1.19, 0.33, 1.09, and 0.99 respectively. The effect sizes for the cognition measures MOCA, and CDT were 0.92 and 0.74 respectively. The effect size for the BI was 1.29.

Physiotherapy was provided between T0 and T1 every week day in average for 45 minutes. The following main methods of physiotherapy/ physical rehabilitation in these 45 minutes daily contact time in the first two weeks after study onset included: training of sitting balance (in and outside of bed), sit to stand training (in and outside of bed), transfer training to get out of bed or to get from bed to wheelchair and vice versa, gait training (including stepping in front of bed), strengthening exercise (in and outside of bed), stepping stairs (including stepping in front of bed), and assistive standing exercises.

Discussion

The present study is one of the first studies with rigorous repeated measures design over the time course of one year of people with ICU-acquired muscle weakness.

As a main result we found that 50% of all included patients were able to walk at a median of 28.5 days after rehabilitation and after a median duration of illness of 81.5 days.

We used a wide range of functional variables to describe the pattern of regaining of walking. The main variables in our final multivariate model to explain ability to walk, however, were clinical scales the FSS-ICU score and the ability to reach forward in sitting and standing at baseline. Both assessments can be used very early and very easy in patients on ICU and may predict the recovery of walking ability of people with ICU-acquired muscle weakness.

From our knowledge, many prognostic studies including people with ICU-acquired muscle weakness used rather a conventional prognostic design using a baseline test and compared with ICU discharge and follow-up data [6 36 37] and just some studies measured functional recovery continuously over time [51]. Instead of comparing two or more measurements of the patient's performance, however, 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 ability. Our study therefore might provide a more detailed understanding of a pattern and the dynamics of recovery of walking ability of chronic ill people with ICU-acquired muscle weakness.

As recently shown there are no randomized trials so far including people with ICU-acquired muscle weakness with a diagnosis of CIP or CIM [18]. To our knowledge cohort studies describing the detailed recovery pattern of walking ability in people with ICU-acquired muscle weakness are also quite rare.

One recent study of Denehy and coworkers included one hundred and fifty people after 5 or more days on ICU admission but did not used a defined diagnosis of CIP or CIM as inclusion criteria [12]. Compared to the population of Denehy et al. our patients had a longer length of hospital stay in acute hospital (median 41 days vs. 20 to 23.5 days) and a longer duration of mechanical ventilation (median 53 days vs. 98 hours) and only 17 to 21 % of included patients in the Denehys trial had ICU-acquired muscle weakness.

Compared to Fan et al. who described a mean Apache II of 26 points [14] our study population, however, had a mean of 16 points and could therefore seen as somewhat less severe affected. Given the long duration of illness, however, our patients were more chronically affected.

A recent multi-center cohort study investigated functional recovery at six months among 192 mechanically ventilated ICU patients (about 50% of these patients had ICU-acquired weakness) [52]. The authors, however, did not describe the functional recovery of walking in this population.

Cuthbertson and colleagues investigated 286 patients after discharge from intensive care and 192 patients completed the one year follow-up [53], but a defined diagnosis to CIP or CIM as cause for muscle weakness was not used as an inclusion criteria. The authors conclude, however, that further work should focus on the recovery from critical illness [53].

In our study we chose the PFIT-s and FSS-ICU as main clinical assessments. Both measures are common and recommended for patients in ICU and were well described in this population [34-37]. Other studies used the Rivermead Mobility Index, a scale well known in stroke rehabilitation [54]. Nordon-Craft et al. described on the basis of 51 patients from ICU that the PFIT-s was highly correlated to MRC sum score and grip strength [36]. Additionally at ICU discharge, an MRC sum score cut point of 41.5 predicted subject's ability to perform the standing components of the PFIT-s [36]. In our study, however, we did find a predictive value neither for the MRC sum score nor for the PFIT-s predicting walking recovery. We found the best prediction for walking recovery from a model containing the FSS-ICU score and the functional reach in the first week of rehabilitation.

At the one hand this study shows on the first glance good recovery of walking function measured with the FAC. On the other hand comparing with reference values of healthy persons from six countries for the 6-MWTs and the walking speed we found many of our patients still reasonably below the 10th percentile of age adjusted walking distance and speed

[55]. This shows obviously that the recovery of walking even after eight weeks of physical rehabilitation is still not at a normal level. Further studies should therefore provide insights into specific treatment approaches to improve the walking distance in chronically ill population [18 56]. In practice a long term treatment approach seems warranted for this chronically ill population.

At a first look it seems a bit strange that the average walking speed improved from T0 to T3 and declined then to T4. This is, however, due to the fact, that patients with good recovery including good recovered walking function were discharged earlier (and therefore excluded from analysis) than patients with not so good recovery.

Eventually, the patients included in our study were relatively chronically and severely ill, had all ICU-acquired muscle weakness and were therefore not directly comparable to other published clinical trials in the field of ICU research.

Strong aspects of GymNAST are the prospective design with multiple repeated assessments during the first months of illness using equal time intervals of people with ICU-acquired muscle weakness with an daily assessment of walking ability. The present study might therefore provide new and more detailed information about the short-term 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 very seriously affected patients in terms of very sedated or very agitated, who were not able to perform the assessments, were not included, thereby reducing the possibility to generalize the results to the whole critical ill population. Further limitations include that electromyography was not used for differential diagnostics of muscle weakness between CIM and CIP and other reasons for acquired muscle weakness, and that creatine kinase was not measured.

Diagnosis of CIP and CIM requires both clinical evaluation and electrophysiological investigations [57]. Another limitation is therefore that just a clinical but not always both a clinical and an electrophysiological evaluation were given.

Further studies should use a randomized controlled design, should include people with ICU-acquired muscle weakness with a defined reason for muscle weakness such as diagnosis of CIP/CIM and should investigate specific rehabilitation therapies to improve or to speed up walking recovery in this population of severe ill people.

Authors' contributions:

JM, SM, FO and MP planned the study. FO, JM and MP contributed to the procurement of funding. JM., SM, and MP developed the protocol, SM, MP and JM evaluated and interpreted the data, JM, SM and MP did the statistical analysis. All authors contributed to writing and checked the final draft of the manuscript**.**

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Competing interests statement:

No, there are no competing interests.

Data sharing

No additional data available.

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Table 1 Patient characteristics

Variable (n=150)	Median (IQR)	Mean (SD)
Age [years]	71(12)	69.16 (9.02)
BMI [points]	27.4 (6.7)	29.11 (8.25)
Duration of illness [days]	41 (30)	49.13 (29.13)
Duration of mechanical ventilation [days]	53 (42)	65.22 (45.14)
Apache II [points]	16 (5)	16.45 (4.08)
Barthel-Index [points]	5 (25)	14.68 (19.20)
MRC sum score at baseline, upper limb	9.5 (3.25)	0.5 (0.8)
MRC sum score at baseline, lower limb	9 (3.25)	0.5 (0.8)
MOCA score at baseline [points]	16 (10)	14.3 (7.0)
Primary ICU diagnosis	**frequency (%)**	
sepsis	82 (55)	
pneumonia	29 (19)	
cardiac	21 (14)	
other	18 (12)	
female	50 (30)	
dialysis	45 (30%)	
patients recruited at post-ICU	121 (81)	
patients recruited at inpatient rehab centre	29 (19)	
ERBI item 1: intensive care supervision	121 (81)	
ERBI item 2: tracheostomy tube management and supervision	120 (80)	
ERBI item 3: intermittent (or continuous)	103 (69)	

mechanical ventilation	
ERBI item 4: confused patient (in need of supervision)	3 (2)
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	8 (5)
ERBI item 6: severe impairment of communication	41 (21)
ERBI item 7: dysphagia patient in need of supervision	81 (54)

Table 2a Summary of the univariate Cox proportional hazards for regaining walking ability of all potential predictor variables

variable (at T0)	Chi^2	p value	HR	95% CI
Age (years)	7.37	0.007	0.970	0.949 to 0.992
BMI	3.92	0.048	0.972	0.944 to 1.000
Sex (male)	0.00	0.996	1.001	0.637 to 1.573
duration of illness (days)	1.33	0.249	0.995	0.986 to 1.004
number of medical tubes (catheters and vascular access)	1.83	0.176	0.901	0.774 to 1.048
duration of mechanical ventilation (days)	8.05	0.005	0.992	0.986 to 0.997
number secondary diagnosis	0.07	0.790	0.996	0.965 to 1.03
ERBI item 1: intensive care supervision	1.37	0.242	1.009	0.994 to 1.023
ERBI item 2: tracheostomy tube management and supervision	0.41	0.524	1.005	0.990 to 1.019
ERBI item 3: intermittent or continuous mechanical ventilation	0.00	0.986	1.000	0.987 to 1.014
ERBI item 4: confused patient (in need of supervision)	2.14	0.144	1.023	0.992 to 1.055
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	2.37	0.124	0.984	0.965 to 1.004
ERBI item 6: severe impairment of communication	11.24	0.001	1.037	1.015 to 1.060
ERBI item 7: dysphagia patient in need of supervision	2.43	0.119	0.993	0.983 to 1.002
ability to reach forward (cm)	4.06	0.044	1.028	1.001 to 1.056
FSS-ICU score (points)	1.99	0.159	1.062	0.977 to 1.115
PFIT-s score (points)	0.51	0.475	1.095	0.854 to 1.403
grip strength (kg)	3.03	0.082	1.075	0.991 to 1.167
MRCsum score upper limb (points)	8.44	0.004	0.715	0.571 to 0.897
MRCsum score lower limb (points)	0.00	0.970	1.004	0.808 to 1.248

VAS (mm)	0.43	0.514	1.012	0.977 to 1.047
MoCA (points)	1.34	0.247	0.960	0.896 to 1.029
CDT (points)	1.23	0.267	0.847	0.632 to 1.136

HR= Hazard Ratio; CI= confidence interval; ERBI= Early Rehabilitation Barthel Index; FSS-ICU= Functional Status Score for the Intensive Care Unit; PFIT-s= Physical Function ICU Test (scored); MRC= Medical Research Council; VAS= visual analogue scale; MoCA= Montreal - Cognitive Assessment; CDT= Clock drawing test

Table 2b Summary of the final multivariate Cox proportional hazard model for regaining walking ability

variable	Chi^2	p value	HR	95% CI
FSS-ICU score in points	13.36	0.0003	1.074	1.033 to 1.115
ability to reach forward in cm	5.25	0.0219	1.019	1.003 to 1.036

FSS-ICU score= functional status score ICU; HR= Hazard Ratio; CI= confidence interval

Description: higher scores of the FSS-ICU and the greater ability to reach forward at T0 are indicating significantly higher chances to regain walking ability

Table 3 Summary of secondary outcome measures at time points

	T0	T1	T2	T3	T4	p value
Primary Outcome, frequencies						
FAC=0 (in %)	105 (70)	52 (40)	40 (35)	26 (26)	16 (24)	<.001
FAC=1 (in %)	7 (5)	8 (6)	3 (3)	6 (6)	3 (4)	
FAC=2 (in %)	38 (25)	3 (2)	5 (4)	12 (12)	3 (4)	
FAC=3 (in %)	0 (0)	30 (23)	22 (19)	13 (13)	15 (22)	
FAC=4 (in %)	0 (0)	30 (23)	29 (25)	28 (28)	21 (31)	
FAC=5 (in %)	0 (0)	7 (5)	16 (14)	16 (16)	9 (13)	
muscle strength measures						
MRC sum score upper limbs*	9.50 (2.55)	11.50 (2.46)	12.00 (2.49)	12.00 (2.27)	12.50 (2.15)	<.001
MRC sum score lower limbs*	9.00 (3.25)	10.50 (3.00)	10.50 (3.00)	11.00 (3.50)	11.00 (3.50)	<.001
grip strength (in kg)#	9.33 (5.35)	11.92 (6.22)	13.32 (6.99)	13.54 (6.18)	14.19 (7.66)	<.001
Physical function measures						
PFIT-S score (points)*	4.00 (6.00)	8.00 (5.50)	8.00 (5.00)	8.00 (6.00)	8.00 (5.00)	<.001
FSS-ICU score (points)*	16.0 (15.0)	25.0 (16.0)	30.0 (14.0)	29.0 (13.0)	31.5 (11.0)	<.001
10m walking speed (m/s)#	0.24 (0.25)	0.50 (0.50)	0.51 (0.53)	0.45 (0.48)	0.35 (0.42)	<.001
6-MWT (m)#	25.8±60.0	87.1±109.7	114.2±126.3	112.8±121.0	126.3±125.1	<.001
pain (mm VAS)#	4.0±8.3	7.6±12.3	6.2±10.7	6.2±9.8	4.6±8.3	.751
functional reach (cm)#	31.9±23.4	46.9±23.5	50.6±25.9	49.7±24.8	54.4±22.2	<.001
Cognition measures						
MOCA (points)#	14.3±7.0	17.1±7.4	18.9±6.6	19.8±6.3	20.4±6.3	<.001
CDT (points)#	3.9±1.8	3.2±1.6	2.9±1.4	2.6±1.6	2.6±1.7	<.001
Activities and Mobility						
BI (points)*	5.0 (25.0)	35.0 (55.0)	45.0 (65.0)	50.0 (60.0)	60.0 (60.0)	<.001

*presented as median and interquartile ranges; # presented as means and standard deviations

Abbreviations: T= Time point; FAC: Functional Ambulation; MRC: Medical Research Council (muscle strength of the upper (sum of shoulder, elbow and wrist) and lower limb (sum of hip, knee and ankle)); 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

Figure 1

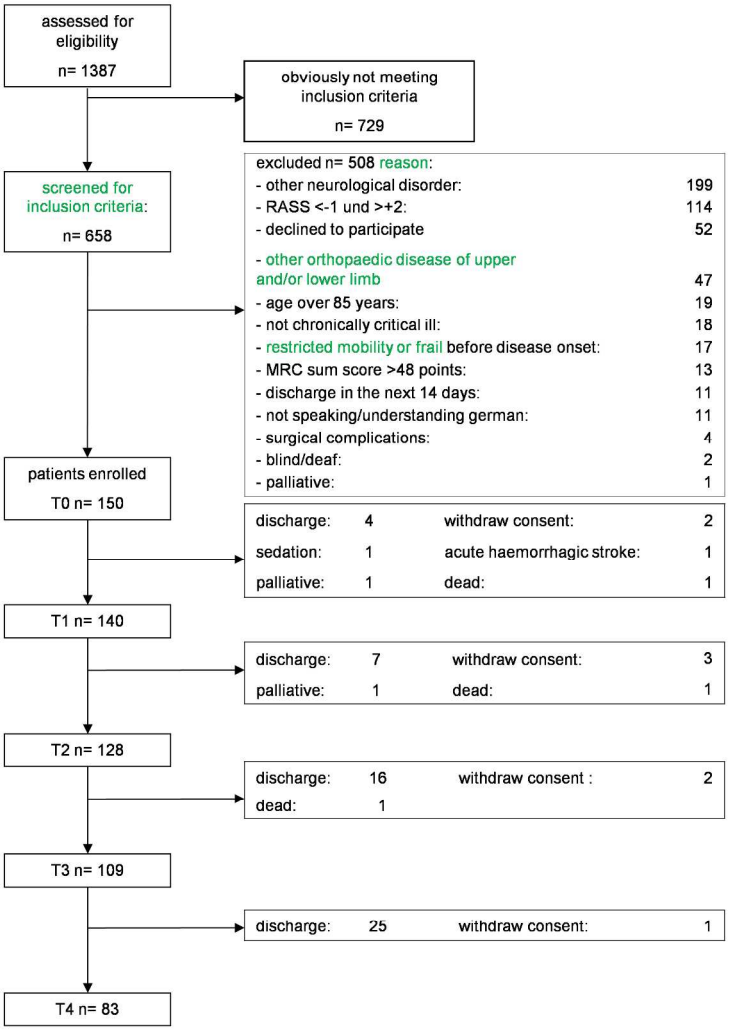
Flow chart

Figure 2a

Time course of recovery of walking function from study onset (T0)

Figure 2b

Time course of recovery of walking function from onset of the primary illness



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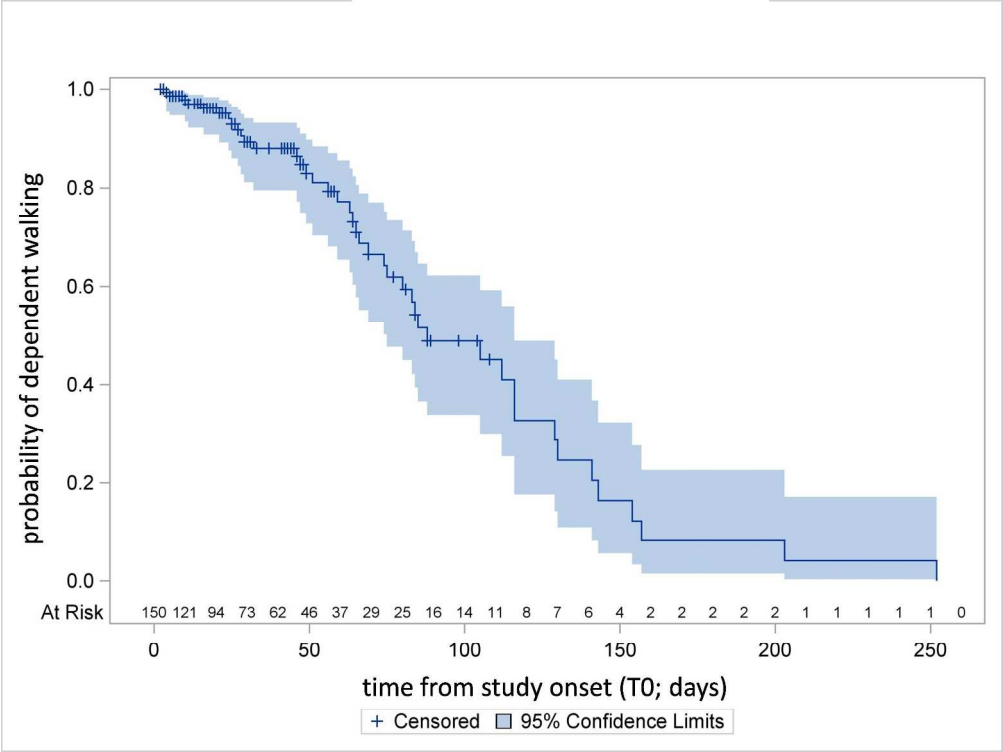

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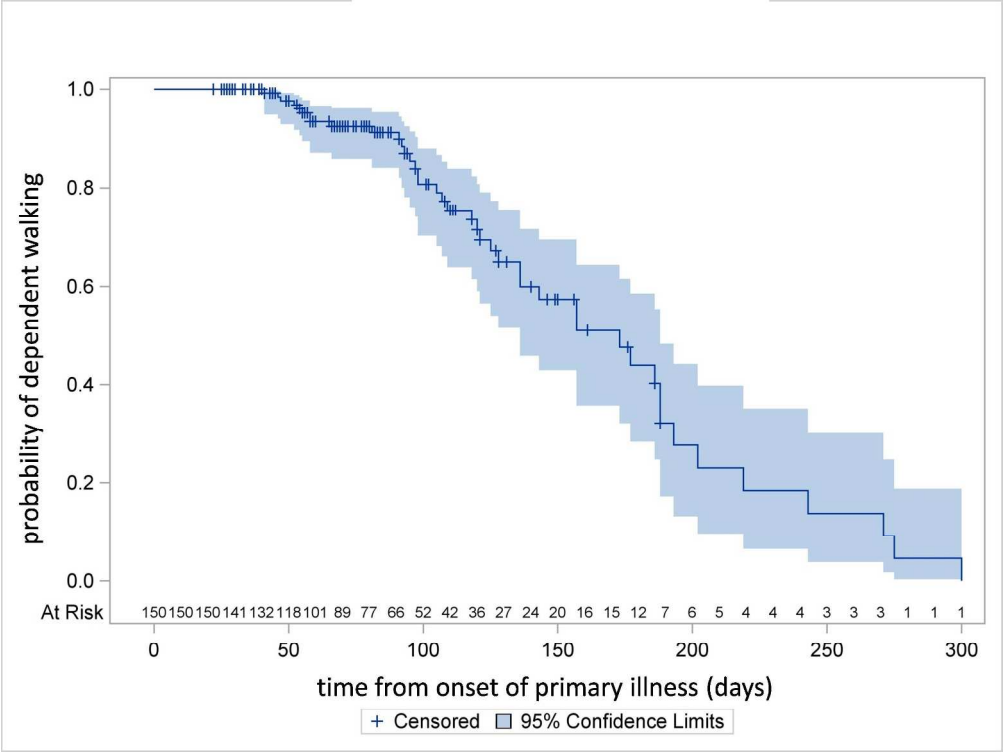

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First results about recovery of walking function in patients with intensive-care-unit-acquired muscle weakness from the General Weakness Syndrome Therapy (GymNAST) cohort study.

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First results about recovery of walking function in patients with intensive-care-unit-acquired muscle weakness from the General Weakness Syndrome Therapy (GymNAST) cohort study.

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Abstract

Objectives:

To describe the time course of recovery of walking function and other activities of daily living in patients with intensive-care-unit (ICU)-acquired muscle weakness.

Design:

This is a cohort study.

Participants:

We included critical ill patients with ICU-acquired muscle weakness.

Setting:

Post-acute ICU and rehabilitation units in Germany.

Measures:

We measured walking function, muscle strength, activities in daily living, motor and cognitive function.

Results:

We recruited 150 patients (30% female) who fulfilled our inclusion and exclusion criteria. The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. Our final multivariate model for recovery of walking function included two clinical variables from baseline: the Functional Status Score ICU (adjusted Hazard Ratio (HR) = 1.07 (95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02 (95% CI 1.00 to 1.04). All secondary outcomes but not pain improved in the first eight weeks after study onset significantly.

Conclusion:

We found good recovery of walking function for most patients and described the recovery of walking function of people with ICU-acquired muscle weakness.

Registrations: Sächsische Landesärztekammer EK-BR-32/13-1; DRKS00007181, German Register of Clinical Trials

Article Summary

Article focus:

In the General Weakness Syndrome Therapy (GymNAST) study we describe the time course of recovery of walking ability, and risk factors and chances for walking function after ICU-acquired muscle weakness.

Key messages:

This study describes clinical characteristics and the time course of motor performance and of walking ability of people with ICU-acquired muscle weakness.

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.

Strengths and limitations:

- strengths include that a precise daily documentation of the recovery of walking function in the first months of ICU-acquired muscle weakness was provided
- functional clinical scores may give a prognosis for recovery of walking function of patients with ICU-acquired muscle weakness
- limitations are that some of the severe affected ICU patients e.g. patients who were sedated were excluded in this study
- electromyography was not used in all of the included patients for diagnostics of muscle weakness

Introduction

In clinical practice it is often seen that critically ill patients on intensive-care-unit (ICU) get weak muscles. According to Nordon-Craft this weakness is characterized by a profound weakness that is greater than might be expected to result from prolonged bed rest [1] and therefore designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. A more precise definition ICU-acquired muscle weakness includes: 1) weakness must follow the onset of the critical illness; 2) physical examination shows diffuse, symmetric weakness involving all extremities and respiratory muscles; 3) Medical Research Council (MRC) sum score is less than 48 out of 60, or mean MRC score is equal to four in all testable muscle groups noted on two occasions separated by 24 hours, 4) dependence on mechanical ventilation, 5) causes of weakness not related to the underlying critical illness have been excluded. [2] The acquired weakness of limb muscles limits significantly activities and assistance for basic activities such as sit-to stand or sitting and standing is oftentimes required.[3-5] This increases morbidity and delays rehabilitation and recovery of walking.[6 7] 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.[8 9] 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 10] In recent years appropriate assessments were developed and suitable physical intervention strategies were described in the literature.[1 9 11-13] There are recent longitudinal studies in this field. For instance Fan et al. investigated 222 survivors of severe critical illness and determined the longitudinal epidemiology of muscle weakness, physical function, and health-related quality of life, and their associations with critical illness and intensive care unit exposures.[14] Needham et al. evaluated muscle strength, 6-minute-walk distance, and the Short Form-36 Physical Function score of 203 survivors after 6- and 12-month of acute lung injury.[15] Semmler and colleagues analyzed the long-term neuromuscular deficits of survivors of 51 patients with critical illness six to 24 months after discharge from the ICU, measured the MRC sum score, the Overall Disability Sum score (ODSS), and performed nerve conduction studies and electromyography.[16] MRC sum score and the ODSS score were correlated with the days of ICU treatment and with the days of ventilator support, but the neuromuscular long-term consequences of critical illness were not severe.

Wieske et al. investigated post-ICU mortality and physical functioning in 80 patients with acquired weakness at 6 months after ICU discharge. They found that ICU-acquired weakness is independently associated with post-ICU mortality and with clinically physical at six months after ICU discharge.[17]

Taken all these essential studies together one could argue that a detailed knowledge about the exact time course of recovery of walking assessed on a daily basis, their risk factors and chances for good recovery, however, are still not entirely known. It lacks, from a rehabilitation point of view on a detailed description of the exact pattern of walking recovery and of physical rehabilitation treatment in the first year of people with ICU-acquired muscle weakness.[18] Such a depiction could give insights in to the particular time course of recovery of walking function of these patients.

Therefore the aim of the General Weakness Syndrome Therapy (GymNAST) study was to describe and to identify the time course and the pattern of recovery of walking function in these patients.[19] Another aim of GymNAST was to develop a multivariate risk factor model for recovery of walking function of people with ICU-acquired muscle weakness.

Here we describe the first short-term results of the GymNAST study for walking recovery.

Methods and analysis

Between January 2013 to March 2015 we screened all patients consecutively from the intensive care units of our post-acute ICU and rehabilitation units of the Klinik Bavaria Kreischa in Germany and recruited patients who met our following inclusion and exclusion criteria (as previously reported [19]) for our cohort study:

Inclusion criteria

- patient is chronic critical ill or has a contemporary history of chronic critical ill. Chronic critical ill was 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)[20 21]
- muscle weakness defined as a Medical Research Council (MRC) sum score of less than 48 points [1]
- a defined reason for muscle weakness such as a clinical diagnosis of critical illness myopathy (CIM) and polyneuropathy (CIP). The diagnosis of CIM/CIP was performed by a physician in acute or post-acute hospital and always confirmed by a neurologist. Therefore, clinical and (if needed) neurophysiologic information were used for diagnosis of CIM/CIP. The procedure of diagnosis of CIP and CIM is described in detail elsewhere [22] and will be only briefly described here. All patients underwent clinical examination by a physician and a specialist in neurology and electrophysiological workup was performed only by another specialist if the neurologist were in any uncertainty of the clinical diagnosis.[22] We used this approach because we have recently shown, that in a total of 280 patients with complicated weaning in our post-acute hospital the positive predictive value of our diagnostic procedure for CIP/CIM was 97.9% with a 95% confidence interval (CI) 69.4 to 99.9 and the negative predictive value was 88.9% (95% CI 82.7 to 93.0).[22]
- more than or equal to 18 years old
- Richmond Agitation Sedation Scale (RASS) score from -1 to 2 [23]
- 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 (e.g. Guillain–Barré syndrome, myasthenia gravis, porphyria, Lambert- Eaton 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)

All patients received from the first day of admission to our intensive care units of our post-acute ICU and rehabilitation units their individual treatment including physiotherapy and occupational therapy. Physical rehabilitation treatments started, even if patients were mechanically ventilated, on the first day of admission, but differed in amount and methods individually due to the severity of critical illness and indication. We did not, however measured the start, content and amount of treatments in the earlier acute stage.

Measures and Outcomes

We defined walking ability as the primary outcomes of the GYMNAST study with more or equal than 3 of the Functional Ambulation Categories (FAC; ranging from 0 - 5) first described by Holden and colleagues in 1984.[24] The FAC is a quick visual measurement of walking, is simple to use and easy to interpret and distinguishes six levels of walking ability on the basis of the amount of physical support required.[24 25] For instance a FAC of '0' indicates a patient who is not able to walk at all or needs the help of two therapists (nonfunctional ambulator) and a FAC of '5' indicates a patient who can walk everywhere independently, including stairs (independent ambulator).[24 25] Research showed that the FAC has very good reliability, good concurrent and predictive validity, and good responsiveness in neurological rehabilitation.[24-26] In the present study we used previously described key questions for every FAC level, used experienced rater and assessed walking ability with FACs.[25] FACs were measured on a daily basis because we were primarily interested to determine precisely when the good outcome, the ability to walk, occurred in the time course. The definition of a good outcome we used was a minimum of FAC of '3' and

better (ambulator, dependent on supervision) which indicates a patient who can at least ambulate on level surface without manual contact of another person but requires standby guarding of one person either for safety or for verbal cueing. Our primary outcome was therefore analysed as time to event ('event' defined as the time point when ability to walk occurred measured by FAC of '3').

Secondary outcomes included

- activities of daily living measured with the Barthel Index (BI; 10 items).[27] The Barthel Index (score range, 0 to 100) is a valid and reliable index measuring activities of daily life.[28] Included are ten items relating to the degree of independence from any help.[27 28]

- clinical severity (e.g. mechanical ventilation, dysphagia, tracheostomy) measured with the Early Rehabilitation Barthel Index (ERBI) (in the original form described as Frühreha-Index (FRI) [29 30]. The ERBI was designed to allow for a simple determination of clinical severity and contains seven items. Every item will be dichotomous scored as present or absent. These seven items are as translated by Rollnik 2010:[30]

    - intensive care supervision (-50 or 0 points)
    - tracheostomy tube management and supervision (-50 or 0 points)
    - Intermittent (or continuous) mechanical ventilation (-50 or 0 points)
    - confused patient (in need of supervision) (-50 or 0)
    - behavioural disturbances (patient being a danger to himself or others) (-50 or 0 points)
    - severe impairment of communication (-25 or 0 points)
    - dysphagia patient in need of supervision (-50 or 0 points)

  The sum ERBI score is between 0 and -325 points. Rollnik described 2010 high inter-rater-reliability for the ERBI (r= 0.849).[30]

- Muscle strength of the upper (shoulder, elbow and wrist) and lower limb (hip, knee and ankle) using the Medical Research Council (MRC). We used MRC sum scores for upper and lower limbs. [1 31]
- Grip strength (measured bilaterally using a dynamometer).[32 33] We summed up the means of both hands. We did not define ICU acquired weakness on the base of cut off values from hand grip dynamometry.
- Functional Status Score for the Intensive Care Unit (FSS-ICU).[34 35] The FSS-ICU rates two functional and three additional tasks that are relevant and feasible to perform in the ICU setting.[34 35] All five tasks are evaluated using a 7-point scoring system, with higher scores indicating higher function.[34] A score of 0 will be assigned if a patient is unable to perform a task, due to either physical limitation or medical status.[34,35]
- Physical Function ICU Test (scored) (PFIT-s).[36 37] The PFIT-s is a modified versions of the Physical Function ICU Test and contains four items: a) assistance in sit to stand manoeuvres (0, 1, or 2 people needed), b) cadence (steps per minute), c) shoulder flexion strength (muscle strength graded as: 0=no contraction, 1=visible/palpable muscle contraction, 2=movement across gravity, 3=movement against gravity, 4=movement against gravity with some resistance, or 5=movement against gravity with full resistance), and d) knee extension strength (same muscle strength grading as for shoulder flexion strength).[37]
- Pain using a numeric pain rating scale.[38]
- The ability to reach forward as a measure for sit and stance balance. We measured the ability to reach forward while sitting and standing (also called 'functional reach') and summed up the results in cm.[39 40]
- Cognitive measures (Montreal Cognitive Assessment (MoCA) [41] and clock drawing test (CDT).[42 43]
- Walking speed (m/s) and walking endurance (6-MWT; metres walked in six minutes).[6 7]

All assessments and standardized measures were administered by trained and experienced assessors or therapists in the hospital and/or inpatient rehabilitation. We measured patients from baseline (T0) every two weeks up to 8 weeks (T4). We defined baseline as the first

admission to our post-acute hospital or to our inpatient rehabilitation centre respectively (T0). Based on this definition the duration of illness was defined as the time between the very first day on ICU (first admission to the acute hospital due to the onset of primary illness) until the study onset (T0, baseline, admission to the post-acute hospital or inpatient rehabilitation) or until the observation of the primary outcome or until T1, T2 and so on respectively. The duration of study was therefore the time between study onset (T0, admission to the post-acute hospital or inpatient rehabilitation) until the observation of the primary outcome or T1, T2 and so on, respectively.

We describe here the results of the first eight weeks of GYMNAST as primary or short-term results. We will further describe the results of additional time points and follow-up as long-term results in a separate publication.

Ethical considerations

We conducted this study in accordance with the 'Helsinki Declaration' and received ethical approval by the local ethic commission (Sächsische Landesärztekammer, EK-BR-32/13-1 / 106755) and registered the study before publication (German Register of Clinical Trials, DRKS00006528).

Statistical analyses

We used descriptive analyses, e.g. median and interquartile ranges and means and standard deviations of continuous variables and frequencies and proportions of categorical variables as appropriate.[44] We applied inference statistics and parametric and non-parametric tests as appropriate.[44] The global alpha level was set at 0.05.

We calculated the probability in regaining walking ability with the method of Kaplan and Meier.[45] The time to event or censoring was defined as the time between study entry (T0) and the date of reaching a FAC (score 0 to 5) equal or more than 3, or the possible censoring dates of discharge or dead, respectively. We used Cox regression analysis to estimate relative hazard rates and to test for differences in variables.[46] We used univariate and multivariate Cox regression analysis with a selection of possible predictor variables for the primary outcome as follows.[46 47]

univariate analysis

These possible predictor variables included: age at study onset, body mass index (BMI), sex, duration of illness, number of medical tubes (catheters and vascular access), duration of mechanical ventilation, number secondary diagnosis, ERBI item 1, ERBI item 2, ERBI item 3, ERBI item 4, ERBI item 5, ERBI item 6, ERBI item 7, ability to reach forward, FSS-ICU score, PFIT-s score, grip strength, MRCsum score upper limb, MRCsum score lower limb, VAS, MoCA, and CDT. We did univariate Cox regression analysis of these possible predictor variables and listed the results.

multivariate analysis and model building

After the univariate analysis and description of above mentioned variables we selected all clinical meaningful and statistical significant variables (alpha level of 0.2 for selection) as so called candidate predictor variables. Afterwards we used a stepwise regression analysis with all candidate predictor variables. We used for this purpose the procedure proc phreg implemented in SAS/STAT 9.3; SAS Institute Inc., Cary, NC, USA). In the process of stepwise regression a predictor variable had to be significant at the 0.2 level to be entered into the multivariate model and a variable in the model had to be significant at the 0.1 level to remain in the multivariate model. Variables with the highest global score chi-square scores were selected first into a multivariable model.[48-50] As the aim of our analysis was to *explain* the dependent variable (regaining walking function) by a multivariate Cox proportional hazard model with not too many variables (to prevent overfitting) we limited this process to two, three, four and to a maximum of five remaining variables in the multivariate model. After that we compared the multivariate models (with two, three, four and five remaining variables respectively) on the global score chi-square statistic (so called best subset selection) and on the Akaike's information criterion (AIC) to decide for our final multivariate model.[47] We expressed the effects of our final multivariate model as hazard ratios (HRs) with 95% confidence intervals (CI) after a graphical assessment of proportionality of hazards. We used SAS/STAT 9.3 for all statistical procedures (SAS Institute Inc., Cary, NC, USA) and proportional hazards assumptions were tested with the implemented function (proc phreg).

Results

After screening of 1387 patients between January 2013 to March 2015 we included 150 patients with ICU-acquired muscle weakness (30% female) in our study and analyses (see figure 1 flow chart and table 1).

The demographic and clinical characteristics at each of the individual time points (T0 to T4) can be found in table 1 and 2.

The primary outcome recovery of walking function was achieved after a median of 28.5 days (interquartile range= 45) after rehabilitation onset and after a median of 81.5 days (interquartile range= 64) after onset of illness. The time course of the probability in regaining walking ability is shown in two modes: first dependent on time from study onset (figure 2a) and second based on duration of illness (figure 2b). The ability to walk improved over time significantly (as shown graphically in figure 2a and 2b). The percentage of patients who could walk progressed from T0 (0%) to T1 (37%) to T2 (68%) to T3 (71%) to T4 (85%; see table 2 for details).

All secondary outcomes except pain improved from T0 to T4 significantly (see table 2). The greatest effects for muscle strength measures (T0 to T4) were found for the MRC sum score upper limbs with a large effect size of 1.28. MRC sum score lower limbs and grip strength, however, improved with an effect size of 0.59 and 0.75, respectively. The effect sizes for the physical function measures PFIT-S score, FSS-ICU, 10m walking speed, 6-MWT, and functional reach were 0.73, 1.19, 0.33, 1.09, and 0.99 respectively. The effect sizes for the cognition measures MOCA, and CDT were 0.92 and 0.74 respectively. The effect size for the BI was 1.29.

To explain the dependent variable recovery of walking a Cox regression analysis was done. The results for every possible predictor variable in our first univariate regression analysis to explain recovery of walking are shown in table 3a. After univariate regression analysis we selected the following candidate predictor variables; age at study onset, body mass index (BMI), number of medical tubes (catheters and vascular access), duration of mechanical ventilation, ERBI item 4 to 7, ability to reach forward, FSS-ICU score, grip strength, and MRC sum score upper limb. Based on these candidate predictor variables we did multivariate regression analysis to explain the primary outcome recovery of walking. After comparing different multivariate models using we selected on statistical and clinical decision our final multivariate model for recovery of walking. This final model included two variables (model fit statistics AIC= 656.4 with covariates): the FSS-ICU score in points (adjusted HR= 1.07; 95% CI 1.03 to 1.12) and the ability to reach forward in cm (adjusted HR= 1.02; 95% CI 1.00 to 1.04; see table 3b).

Physiotherapy was provided between T0 and T1 every week day in average for 45 minutes. The following main methods of physiotherapy/ physical rehabilitation in these 45 minutes daily contact time in the first two weeks after study onset included: training of sitting balance (in and outside of bed), sit to stand training (in and outside of bed), transfer training to get out of bed or to get from bed to wheelchair and vice versa, gait training (including stepping in front of bed), strengthening exercise (in and outside of bed), stepping stairs (including stepping in front of bed), and assistive standing exercises.

Discussion

The present study is one of the first studies with rigorous repeated measures design over the time course of one year of people with ICU-acquired muscle weakness.

As a main result we found that 50% of all included patients were able to walk at a median of 28.5 days after rehabilitation and after a median duration of illness of 81.5 days.

We used a wide range of functional variables to describe the pattern of regaining of walking. The main variables in our final multivariate model to explain ability to walk, however, were clinical scales the FSS-ICU score and the ability to reach forward in sitting and standing at baseline. Both assessments can be used very early and very easy in patients on ICU and may predict the recovery of walking ability of people with ICU-acquired muscle weakness.

From our knowledge, many prognostic studies including people with ICU-acquired muscle weakness used rather a conventional prognostic design using a baseline test and compared with ICU discharge and follow-up data [6 36 37] and just some studies measured functional recovery continuously over time.[51] Instead of comparing two or more measurements of the patient's performance, however, 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 ability. Our study therefore might provide a more detailed understanding of a pattern and the dynamics of recovery of walking ability of chronic ill people with ICU-acquired muscle weakness.

As recently shown there are no randomized trials so far including people with ICU-acquired muscle weakness with a diagnosis of CIP or CIM.[18] To our knowledge cohort studies

describing the detailed recovery pattern of walking ability in people with ICU-acquired muscle weakness are also quite rare.

One recent study of Denehy and coworkers included one hundred and fifty people after 5 or more days on ICU admission but did not used a defined diagnosis of CIP or CIM as inclusion criteria.[12] Compared to the population of Denehy et al.[12] our patients had a longer length of hospital stay in acute hospital (median 41 days vs. 20 to 23.5 days) and a longer duration of mechanical ventilation (median 53 days vs. 98 hours) and only 17 to 21 % of included patients in the Denehys trial had ICU-acquired muscle weakness.

Compared to Fan et al. who described a mean Apache II of 26 points [14] our study population, however, had a mean of 16 points and could therefore seen as somewhat less severe affected. Given the long duration of illness, however, our patients were more chronically affected.

A recent multi-center cohort study investigated functional recovery at six months among 192 mechanically ventilated ICU patients (about 50% of these patients had ICU-acquired weakness).[52] The authors, however, did not describe the detailed functional recovery of walking in this population.

Cuthbertson and colleagues investigated 286 patients after discharge from intensive care and 192 patients completed the one year follow-up,[53] but a defined diagnosis to CIP or CIM as cause for muscle weakness was not used as an inclusion criteria. The authors conclude, however, that further work should focus on the recovery from critical illness.[53]

In our study we chose the PFIT-s and FSS-ICU as main clinical assessments. Both measures are common and recommended for patients in ICU and were well described in this population.[34-37] Other studies used the Rivermead Mobility Index, a scale well known in stroke rehabilitation.[54] Nordon-Craft et al. described on the basis of 51 patients from ICU that the PFIT-s was highly correlated to MRC sum score and grip strength.[36] Additionally at ICU discharge, an MRC sum score cut point of 41.5 predicted subject's ability to perform the standing components of the PFIT-s.[36] In our study, however, we did find a predictive value neither for the MRC sum score nor for the PFIT-s predicting walking recovery. We found the best prediction for walking recovery from a model containing the FSS-ICU score and the functional reach in the first week of rehabilitation.

At the one hand this study shows on the first glance good recovery of walking function measured with the FAC. On the other hand comparing with reference values of healthy persons from six countries for the 6-MWTs and the walking speed we found many of our patients still reasonably below the 10th percentile of age adjusted walking distance and speed.[55] This shows clearly that the recovery of walking even after eight weeks of physical rehabilitation is still not at a normal level. Further studies should therefore provide insights into specific treatment approaches to improve the walking speed and distance in patients with ICU-acquired muscle weakness.[18 56] In practice a long term treatment approach seems warranted for this chronically ill population.

At a first look it seems a bit strange that the average walking speed improved from T0 to T3 and then declined to T4. This is, however, due to the fact, that patients with good recovered walking function were discharged earlier (and therefore excluded from analysis) compared to patients with not well recovered walking function.

Eventually, the patients included in our study were relatively chronically and severely ill, had all ICU-acquired muscle weakness and were therefore not directly comparable to other published clinical trials in the field of ICU research.

Strong aspects of GymNAST are the prospective design and multiple repeated assessments during the first months of illness using equal time intervals of people with ICU-acquired muscle weakness with daily assessment of walking ability. The present study might therefore provide new and more detailed information about the short-term 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 very seriously affected patients in terms of very sedated or very agitated, who were not able to perform the assessments, were not included, thereby reducing the possibility to generalize the results to the whole critical ill population. Diagnosis of CIP and CIM requires clinical evaluation and electrophysiological investigations [57]. Another limitation is therefore that a clinical but not always both a clinical and an electrophysiological evaluation were provided. Limitations of this study are that electromyography was not used for differential diagnostics of muscle weakness e.g. between CIM and CIP and for other reasons of acquired muscle weakness, and that creatine kinase was not measured.

.Further studies should use a randomized controlled design, should include people with ICU-acquired muscle weakness with a defined reason for muscle weakness such as a defined

diagnosis of CIP and/or CIM and should investigate specific rehabilitation therapies to improve or to speed up walking recovery in this population with ICU-acquired muscle weakness.

Authors' contributions:

JM, SM, FO and MP planned the study. FO, JM and MP contributed to the procurement of funding. JM., SM, and MP developed the protocol, SM, MP and JM evaluated and interpreted the data, JM, SM and MP did the statistical analysis. All authors contributed to writing and checked the final draft of the manuscript**.**

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Competing interests statement:

No, there are no competing interests.

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Table 1 Patient characteristics

Variable (n=150)	Median (IQR)	Mean (SD)
Age [years]	71(12)	69.16 (9.02)
BMI [points]	27.4 (6.7)	29.11 (8.25)
Duration of illness [days]	41 (30)	49.13 (29.13)
Duration of mechanical ventilation [days]	53 (42)	65.22 (45.14)
Apache II [points]	16 (5)	16.45 (4.08)
Barthel-Index [points]	5 (25)	14.68 (19.20)
MRC sum score at baseline, upper limb	9.5 (3.25)	0.5 (0.8)
MRC sum score at baseline, lower limb	9 (3.25)	0.5 (0.8)
MOCA score at baseline [points]	16 (10)	14.3 (7.0)
Primary ICU diagnosis	**Frequency (%)**	
sepsis	82 (55)	
pneumonia	29 (19)	
cardiac	21 (14)	
other	18 (12)	
female	50 (30)	
dialysis	45 (30)	
patients recruited at post-ICU	121 (81)	
patients recruited at inpatient rehab centre	29 (19)	
ERBI item 1: intensive care supervision	121 (81)	
ERBI item 2: tracheostomy tube management and supervision	120 (80)	
ERBI item 3: intermittent (or continuous)	103 (69)	

mechanical ventilation	
ERBI item 4: confused patient (in need of supervision)	3 (2)
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	8 (5)
ERBI item 6: severe impairment of communication	41 (21)
ERBI item 7: dysphagia patient in need of supervision	81 (54)

Table 2 Summary of secondary outcome measures at time points

	T0	T1	T2	T3	T4	p-value
Primary Outcome, frequencies						
FAC=0 (in %)	105 (70)	52 (40)	40 (35)	26 (26)	16 (24)	<.0001
FAC=1 (in %)	7 (5)	8 (6)	3 (3)	6 (6)	3 (4)	
FAC=2 (in %)	38 (25)	3 (2)	5 (4)	12 (12)	3 (4)	
FAC=3 (in %)	0 (0)	30 (23)	22 (19)	13 (13)	15 (22)	
FAC=4 (in %)	0 (0)	30 (23)	29 (25)	28 (28)	21 (31)	
FAC=5 (in %)	0 (0)	7 (5)	16 (14)	16 (16)	9 (13)	
muscle strength measures						
MRC sum score upper limbs*	9.50 (2.55)	11.50 (2.46)	12.00 (2.49)	12.00 (2.27)	12.50 (2.15)	<.0001
MRC sum score lower limbs*	9.00 (3.25)	10.50 (3.00)	10.50 (3.00)	11.00 (3.50)	11.00 (3.50)	<.0001
grip strength (in kg)#	9.33 (5.35)	11.92 (6.22)	13.32 (6.99)	13.54 (6.18)	14.19 (7.66)	<.0001
Physical function measures						
PFIT-S score (points)*	4.00 (6.00)	8.00 (5.50)	8.00 (5.00)	8.00 (6.00)	8.00 (5.00)	<.0001
FSS-ICU score (points)*	16.0 (15.0)	25.0 (16.0)	30.0 (14.0)	29.0 (13.0)	31.5 (11.0)	<.0001
10m walking speed (m/s)#	0.24 (0.25)	0.50 (0.50)	0.51 (0.53)	0.45 (0.48)	0.35 (0.42)	<.0001
6-MWT (m)#	25.8±60.0	87.1±109.7	114.2±126.3	112.8±121.0	126.3±125.1	<.0001
pain (mm VAS)#	4.0±8.3	7.6±12.3	6.2±10.7	6.2±9.8	4.6±8.3	.755
functional reach (cm)#	31.9±23.4	46.9±23.5	50.6±25.9	49.7±24.8	54.4±22.2	<.0001
Cognition measures						
MOCA (points)#	14.3±7.0	17.1±7.4	18.9±6.6	19.8±6.3	20.4±6.3	<.0001
CDT (points)#	3.9±1.8	3.2±1.6	2.9±1.4	2.6±1.6	2.6±1.7	<.0001
Activities and Mobility						
BI (points)*	5.0 (25.0)	35.0 (55.0)	45.0 (65.0)	50.0 (60.0)	60.0 (60.0)	<.0001

*presented as median and interquartile ranges; # presented as means and standard deviations

Abbreviations: T= Time point; FAC: Functional Ambulation; MRC: Medical Research Council (muscle strength of the upper (sum of shoulder, elbow and wrist) and lower limb (sum of hip, knee and ankle)); 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

Table 3a Summary of the univariate Cox proportional hazards for regaining walking ability of all potential predictor variables

variable (at T0)	Chi^2	p-value	HR	95% CI
Age (years)	7.37	0.007	0.970	0.949 to 0.992
BMI	3.92	0.048	0.972	0.944 to 1.000
Sex (male)	0.00	0.996	1.001	0.637 to 1.573
duration of illness (days)	1.33	0.249	0.995	0.986 to 1.004
number of medical tubes (catheters and vascular access)	1.83	0.176	0.901	0.774 to 1.048
duration of mechanical ventilation (days)	8.05	0.005	0.992	0.986 to 0.997
number secondary diagnosis	0.07	0.790	0.996	0.965 to 1.03
ERBI item 1: intensive care supervision	1.37	0.242	1.009	0.994 to 1.023
ERBI item 2: tracheostomy tube management and supervision	0.41	0.524	1.005	0.990 to 1.019
ERBI item 3: intermittent or continuous mechanical ventilation	0.00	0.986	1.000	0.987 to 1.014
ERBI item 4: confused patient (in need of supervision)	2.14	0.144	1.023	0.992 to 1.055
ERBI item 5: behavioural disturbances (patient being a danger to himself or others)	2.37	0.124	0.984	0.965 to 1.004
ERBI item 6: severe impairment of communication	11.24	0.001	1.037	1.015 to 1.060
ERBI item 7: dysphagia patient in need of supervision	2.43	0.119	0.993	0.983 to 1.002
ability to reach forward (cm)	4.06	0.044	1.028	1.001 to 1.056
FSS-ICU score (points)	1.99	0.159	1.062	0.977 to 1.115
PFIT-s score (points)	0.51	0.475	1.095	0.854 to 1.403
grip strength (kg)	3.03	0.082	1.075	0.991 to 1.167
MRCsum score upper limb (points)	8.44	0.004	0.715	0.571 to 0.897
MRCsum score lower limb (points)	0.00	0.970	1.004	0.808 to 1.248

VAS (mm)	0.43	0.514	1.012	0.977 to 1.047
MoCA (points)	1.34	0.247	0.960	0.896 to 1.029
CDT (points)	1.23	0.267	0.847	0.632 to 1.136

HR= Hazard Ratio; CI= confidence interval; ERBI= Early Rehabilitation Barthel Index; FSS-ICU= Functional Status Score for the Intensive Care Unit; PFIT-s= Physical Function ICU Test (scored); MRC= Medical Research Council; VAS= visual analogue scale; MoCA= Montreal - Cognitive Assessment; CDT= Clock drawing test

Table 3b Summary of the final multivariate Cox proportional hazard model for regaining walking ability

variable	Chi^2	p-value	HR	95% CI
FSS-ICU score in points	13.36	0.0003	1.074	1.033 to 1.115
ability to reach forward in cm	5.25	0.0219	1.019	1.003 to 1.036

FSS-ICU score= functional status score ICU; HR= Hazard Ratio; CI= confidence interval

Description: higher scores of the FSS-ICU and the greater ability to reach forward at T0 are indicating significantly higher chances to regain walking ability

Figure 1

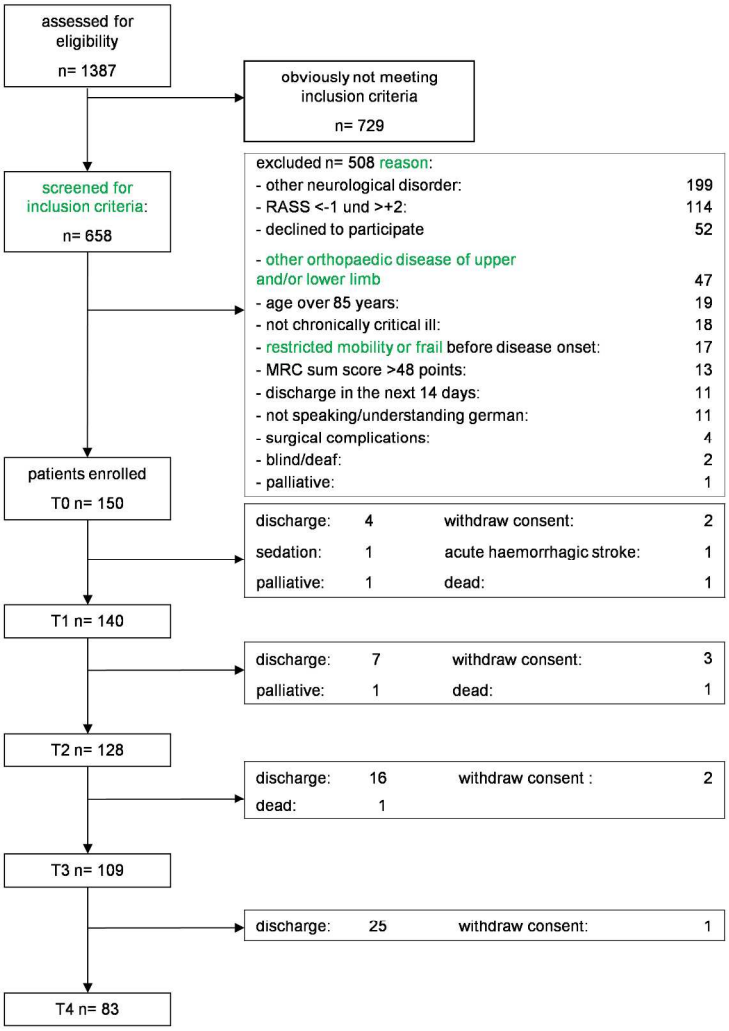
Flow chart

Figure 2a

Time course of recovery of walking function from study onset (T0)

Figure 2b

Time course of recovery of walking function from onset of the primary illness



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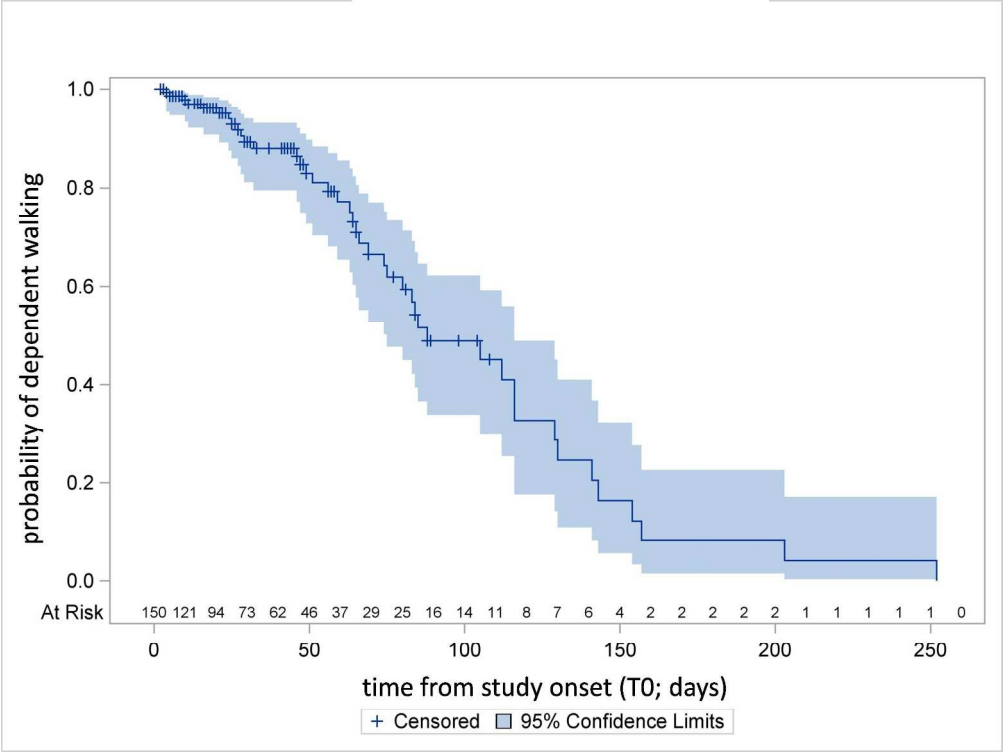

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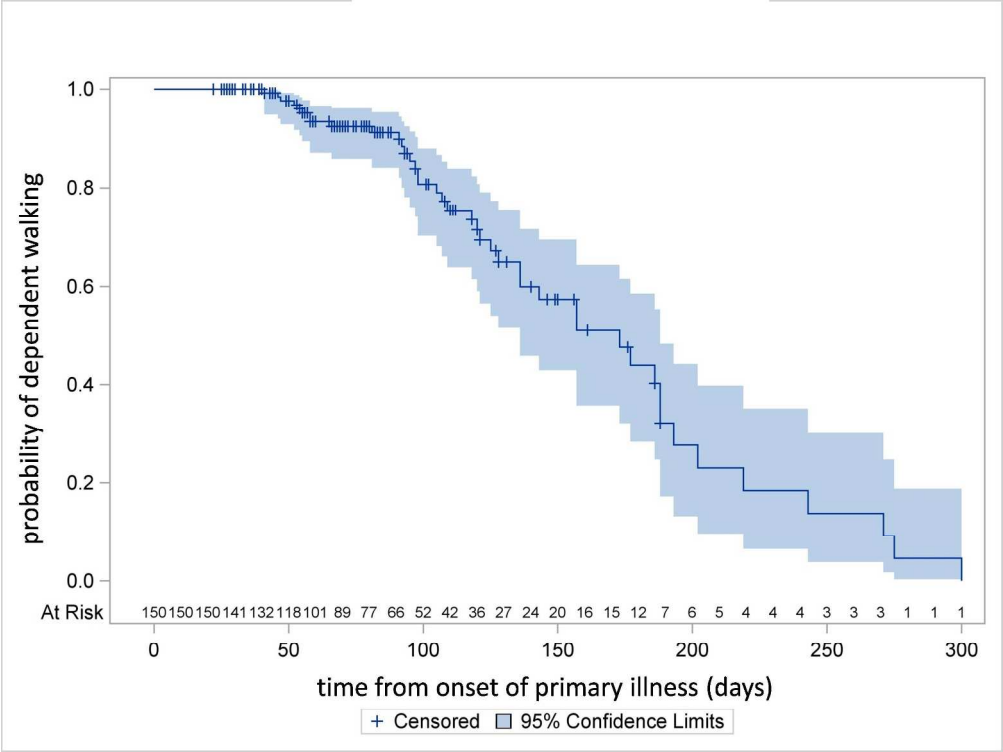

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	page
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5, 9-10
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7 -10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n.a.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-10
Bias	9	Describe any efforts to address potential sources of bias	9 -11
Study size	10	Explain how the study size was arrived at	6 (and in our published protocol for this study)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10-11
		(*b*) Describe any methods used to examine subgroups and interactions	10-11
		(*c*) Explain how missing data were addressed	10-11
		(*d*) If applicable, explain how loss to follow-up was addressed	10-11
		(*e*) Describe any sensitivity analyses	n.a.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11-13 Table 1, 2a, 3 Figure 2a, 2b
		(b) Give reasons for non-participation at each stage	n.a.
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1, 3

		(b) Indicate number of participants with missing data for each variable of interest	Table 1, 3 Figure 2a, 2b
		(c) Summarise follow-up time (eg, average and total amount)	Figure 2a, 2b
Outcome data	15*	Report numbers of outcome events or summary measures over time	Figure 2a, 2b
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	12 Table2a and 2b
		(*b*) Report category boundaries when continuous variables were categorized	n.a.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n.a.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n.a.
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	3, 14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	3, 14-15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.