Intensive Care Med (2019) 45:201–210
https://doi.org/10.1007/s00134-019-05528-x

ORIGINAL

Influence of the initial level of consciousness on early, goal-directed mobilization: a post hoc analysis

Stefan J. Schaller[1], Flora T. Scheffenbichler[2], Somnath Bose[3], Nicole Mazwi[4], Hao Deng[2], Franziska Krebs[1], Christian L. Seifert[5], George Kasotakis[6], Stephanie D. Grabitz[2], Nicola Latronico[7], Timothy Houle[2], Manfred Blobner[1] and Matthias Eikermann[3,8*]

Abstract

Purpose: Early mobilization within 72 h of intensive care unit (ICU) admission improves functional status at hospital discharge. We aimed to assess the effectiveness of early, goal-directed mobilization in critically ill patients across a broad spectrum of initial consciousness levels.

Methods: Post hoc analysis of the international, randomized, controlled, outcome-assessor blinded SOMS trial conducted 2011–2015. Randomization was stratified according to the immediate post-injury Glasgow Coma Scale (GCS) (≤ 8 or >8). Patients received either SOMS-guided mobility treatment with a facilitator or standard care. We used general linear models to test the hypothesis that immediate post-randomization GCS modulates the intervention effects on functional independence at hospital discharge.

Results: Two hundred patients were included in the intention-to-treat analysis. The significant effect of early, goal-directed mobilization was consistent across levels of GCS without evidence of effect modification, for the primary outcome functional independence at hospital discharge ($p = 0.53$ for interaction), as well as average achieved mobility level during ICU stay (mean achieved SOMS level) and functional status at hospital discharge measured with the functional independence measure. In patients with low GCS, delay to first mobilization therapy was longer (0.7 ± 0.2 days vs. 0.2 ± 0.1 days, $p = 0.008$), but early, goal-directed mobilization compared with standard care significantly increased functional independence at hospital discharge in this subgroup of patients with immediate post-randomization GCS ≤ 8 (OR 3.67; 95% CI 1.02–13.14; $p = 0.046$).

Conclusion: This post hoc analysis of a randomized controlled trial suggests that early, goal-directed mobilization in patients with an impaired initial conscious state (GCS ≤ 8) is not harmful but effective.

Keywords: Early mobilization, Early rehabilitation, Critical care, Functional status, Consciousness, Neurocritical care, Delirium

*Correspondence: meikerma@bidmc.harvard.edu
[3] Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA
Full author information is available at the end of the article

Stefan J. Schaller and Flora T. Scheffenbichler made equal contributions to the study.

Springer

Introduction

Early, goal-directed mobilization can improve outcomes of critically ill patients admitted to medical [1] and surgical intensive care units (SICU) [2]. However, after ischemic stroke early neuronal activity from somatosensory stimulation can increase stroke size and adversely affect functional outcomes [3]. Early mobilization of patients with acute stroke might affect long-term neurologic outcomes [4, 5]. In our recently published international randomized controlled study [2] conducted in surgical ICUs, the intervention was based on the Surgical Optimal Mobilization Score (SOMS), a simple score ranging from 0 to 4 describing mobilization levels. This score, already validated in several languages (English [6], German [7] and Italian [8]) was used to create a basic mobilization algorithm. Although we had stratified our randomization [2] based on immediate post-injury GCS, we did not test whether the treatment effect of our intervention was influenced by the level of consciousness. In this post hoc analysis of our randomized controlled study [2], we tested the hypothesis that initial impairment of the level of consciousness modifies the effects of early, goal-directed mobilization therapy. We speculated that—similarly to patients with acute stroke—early mobilization in the ICU may not be effective but potentially harmful in patients presenting with an impaired level of consciousness.

Take-home message

Early, goal-directed mobilization is both feasible and effective in patients presenting with impairment of consciousness.

Methods

Study design

Data were obtained from the SOMS trial, with a previously described study design [2, 9]. Patients were enrolled at surgical ICUs in five university hospitals in Austria (Landeskrankenhaus Salzburg, Salzburg), Germany (Klinikum Rechts der Isar der Technischen Universität München, Munich) and the USA (Beth Israel Deaconess Medical Center, Boston; Massachusetts General Hospital, Boston; and University of Massachusetts Medical Center, Worcester) [2]. Data were collected between 1 July 2011 and 4 November 2015. Briefly, the study population consisted of 200 patients who were mechanically ventilated (for < 48 h at time of randomization and expected to be ventilated for at least another 24 h) and functionally independent (Barthel score [10] ≥ 70) prior to hospital admission. Patients were excluded if they were admitted to the hospital > 5 days before screening, had a motor component of the immediate post-injury GCS < 5, an irreversible disorder with expected 6-month mortality of > 50%, evidence of increased intracranial pressure, cardiopulmonary arrest, unstable fractures contributing to probable immobility, recent acute myocardial infarction, had undergone lower extremity amputation, had rapidly developing neuromuscular disease, were pregnant, or had a ruptured or leaking aortic aneurysm. The initial level of consciousness was defined as the baseline, immediate post-randomization GCS after study enrollment, measured in a spontaneous awakening trial, no later than the morning following study enrollment. Since the immediate post-randomization GCS was assessed in intubated patients, the verbal subcomponent was estimated by using a combination of the Richmond Agitation Sedation Scale [11] (RASS), which was used to examine a participant's arousal, and the Confusion Assessment Method for the ICU [12] (CAM-ICU). If the participant was sufficiently alert (RASS ≥ 1), attention and the capacity to follow instructions were screened by asking the participant to follow a series of one- and two-step instructions. CAM-ICU negative patients had a verbal sub-score of 5 (oriented), while CAM-ICU positive led to a sub-score of 4 (confused). If subjects did not respond appropriately to commands, 1, 2 or 3 points were given as appropriate based on a combination of RASS and CAM-ICU results.

Ethical approval for this analysis was obtained by the institutional review board of Massachusetts General Hospital (protocol no. 2016P002199) and registered at Clinical Trials (NCT03666338). A Strenghtening the Reporting of Observational Studies in Epidemiology (STROBE) checklist is provided as a supplemental file.

Intervention

Patients were randomized to receive either standard of care or early, goal-directed mobilization (intervention). Randomization was completed through an internet-based access-restricted platform stratified by GCS (≤ 8 or > 8), based on chart review, using the last known immediate post-injury GCS without sedation at the time of screening. Both groups were managed by goal-directed sedation with daily awakening trials, daily synchronized spontaneous awakening and breathing trials, screening for pain intensity, arousal and delirium and were regularly evaluated for early enteral feeding. The decision to wean from mechanical ventilation and to extubate was based on defined, local protocols. The intervention group received the same level of clinical care as the control group (institutional standard of care) except for early, goal-directed mobilization [2].

The intervention consisted of two parts: (1) a mobilization goal was defined during daily morning ward rounds according to the Surgical Optimal Mobilization (SOMS)

algorithm and (2) a facilitator ensured goal implementation across shifts and addressed barriers to mobilization [2]. The intervention began no later than 1 day following enrollment. The goal of a specific day was set to SOMS 0 (no mobilization), SOMS 1 [passive range of motion (PROM) exercises in bed], SOMS 2 (sitting), SOMS 3 (standing) or SOMS 4 (ambulation) [2, 6]. During daily rounds, the facilitator guided the clinical team to implement specific procedures to achieve this goal and to identify and address barriers. Following this, a sign with the target mobility goal was posted at the participant's bedside. To ensure achievement of the goal, patient's progress and barriers were identified by the facilitator and communicated back to the team. On the basis of the input received, treatment plans were adapted to achieve set mobilization goals.

Outcome measures

In this post hoc analysis, we selected the most clinically-relevant end point of the original study [2] as the primary outcome ie.: functional independence at hospital discharge, defined as a minimal modified Functional Independence Measure score (mmFIM: range 0–8) of 8. The mmFIM assesses functional capacity for the domains locomotion and transfer (i.e., moving oneself between bed and chair) [13, 14]. In each subdomain the score ranges from 0 to 4 with level 4 defined as an activity executed independently, level 3 if help was only needed with the set-up but otherwise executed independently, level 2 if the patient was partially dependent on help, level 1 as near complete dependence or complete dependence, and level 0 if the activity was not executed at all.

Secondary outcomes were (1) the average achieved mobility level during the ICU stay (mean achieved SOMS level) and (2) the functional status at hospital discharge measured with the mmFIM (range 0–8).

Statistical analysis

Analyses were conducted in the intention-to-treat population without imputation for missing data. Descriptive statistics were assessed and reported as mean ± standard deviation, median (interquartile range [IQR]) or *n* (%) depending on the type and distribution of data. Effect modification of GCS was analyzed using two methods: (1) a likelihood ratio test to compare the model with and without the interaction term and (2) the original multivariable regression model with the interaction term [intervention (binary; yes/no) × immediate post-randomization GCS (binary; high > 8/low ≤ 8)] included. Multivariable logistic regression was used for the primary end point of functional independence. We also conducted subgroup analyses of our primary outcomes stratified by GCS group (binary; high > 8/low ≤ 8). The linear regression model was used for the end points mean achieved SOMS and mmFIM.

Sensitivity analysis

Differences in delay to mobilization were compared using Student's *t* test. To evaluate whether missing data in patients who died in the hospital resulted in an appreciable bias, we applied additional sensitivity analyses. We re-assessed whether immediate post-randomization GCS as a continuous instead of a binary variable (high/low) would change our findings by including this interaction term [intervention (binary; yes/no) × immediate post-randomization GCS (continuous)] to our main model. To explore the relative importance of confounding factors influencing functional independence at hospital discharge, we developed our final model using a theory-based approach (see Online Appendix).

All analyses were performed prospectively with a priori defined end points and statistical methods using the R statistical analysis program (version 3.2.2). We considered a two-tailed p value < 0.05 to be statistically significant.

Results

From 1 July 2011 to 4 November 2015, we randomly assigned 200 eligible adult patients to receive either standard care (96 patients; control group) or early, goal-directed mobilization therapy (104 patients; intervention group). Data of the patients enrolled in this RCT were analyzed in the present study. In the intervention group, 44 subjects (51%) achieved functional independence at hospital discharge, whereas 25 (28%) did in the control group. At enrollment, 60 patients (Table 1) had an impaired level of consciousness (GCS ≤ 8), and 140 patients had a GCS > 8, which were equally distributed between the intervention and control group with a median post-randomization GCS [IQR] of 9 [8–10.5] and 9 [8–11], respectively. Baseline patient characteristics are shown in Table 2, and distribution of the immediate post-randomization GCS can be found in Online Appendix.

Primary outcome—functional independence at hospital discharge

There was no evidence of modification of the effects of early, goal-directed mobilization by immediate post-randomization GCS on the primary outcome of functional independence at hospital discharge (likelihood ratio test: $p = 0.40$, general linear model: $p = 0.53$ for the interaction GCS × intervention; Fig. 1a). In GCS-based subgroup analyses, our intervention significantly increased the functional independence at hospital discharge in patients with both low and high GCS [odds ratio (OR) 3.67,

Table 1 Neurologic diagnosis of patients with impaired consciousness (immediate post-randomization GCS ≤ 8)

Diagnosis	Total $n=60$	Intervention $n=31$	Control $n=29$	ICD-9 code
Toxic metabolic encephalopathy				
Inadequate mental status during spontaneous awakening trial, no anatomical lesion identified	13	10	3	348.39
Sedative drug-induced intoxication	3	2	1	349.82
Hepatic encephalopathy	2	2	0	572.2
Septic encephalopathy	12	7	5	348.31
Other acute non-traumatic brain damage				
Non-traumatic intracranial hemorrhage	3	1	2	431
Acute encephalopathy in leukemia	1	0	1	348.3
Trauma				
Polytrauma with head injury	7	2	5	959.8
Isolated head trauma	7	1	6	959.0; 850.5; 801.0; 803.0
Trauma without head injury	3	2	1	959.1–959.7
Shock				
Neurogenic shock	1	0	1	785.59
Other				
Delirium	3	2	1	293.0; 780.09
Severe agitation requiring prolonged sedation	5	2	3	293.0; 307.9

Table 2 Baseline characteristics of all patients divided by intervention and initial level of consciousness (immediate post-randomization GCS)

Baseline characteristics	Intervention group ($n=104$)		Control group ($n=96$)	
	GCS ≤ 8 ($n=31$)	GCS > 8 ($n=73$)	GCS ≤ 8 ($n=29$)	GCS > 8 ($n=67$)
Age—median [IQR]	65 [50–78]	66 [47–71]	53 [34–77]	66 [50–75]
Male—*n* (%)	21 (68)	44 (60)	21 (72)	40 (60)
APACHE II—median [IQR]	21 [15–26]	14 [11–19]	20 [14–25]	16 [10–21]
GCS—median [IQR]	7 [5–8]	10 [9–12]	7 [5–8]	10 [9–12]
Total physical therapy time during ICU stay—mean ± SD	152 ± 260	102 ± 172	124 ± 203	124 ± 199
Charlson Comorbidity Index—mean ± SD	2.1 ± 1.9	3.2 ± 3.9	1.5 ± 1.5	3.1 ± 3.3
Comorbidities				
Myocardial infarction—*n* (%)	2 (6)	4 (5)	2 (7)	7 (10)
Cerebrovascular disease—*n* (%)	2 (6)	7 (10)	5 (17)	12 (18)
Diabetes mellitus—*n* (%)	4 (13)	12 (16)	4 (14)	17 (25)
Hemiplegia or paraplegia—*n* (%)	2 (6)	3 (4)	1 (3)	2 (3)

95% confidence interval (95% CI) 1.02–13.14, $p=0.046$ for GCS ≤ 8; OR 2.29, 95% CI 1.11–4.71, $p=0.025$ for GCS > 8; Fig. 2].

Secondary outcomes

There was no evidence of modification of the effects of early, goal-directed mobilization by immediate post-randomization GCS on the secondary outcomes: For mean achieved mobilization level, results of the likelihood ratio test ($p=0.33$) as well as interaction term analyses in the regression model ($p=0.17$ for the interaction GCS × intervention) were insignificant (Fig. 1b). Additionally, immediate post-randomization GCS did not modify the effect of early, goal-directed mobilization on functional status (mmFIM range 0–8) at hospital

(See figure on next page.)

Fig. 1 Interaction effect of initial conscious state measured by Glasgow Coma Scale (GCS) and intervention on outcomes. For each plot, the *x*-axis represents the immediate post-randomization GCS after enrollment. The *y*-axis for each plot represents the clinical outcome for which effect modification is being evaluated. Differences between the randomized treatment groups can be evaluated by each level of GCS. The shaded error represents 95% confidence intervals. Consistent differences across groups (i.e., parallel lines) reflect the lack of an interaction as the treatment effect remains constant regardless of the GCS (i.e., interaction $p > 0.05$). **a** Probability of functional independence at different GCS levels. Functional independence at hospital discharge was not modified by initial conscious state ($p = 0.53$ for the interaction GCS high/low × intervention). **b** Mean achieved mobility level during the ICU stay across GCS levels. The association between early, goal-directed mobilization and average achieved mobility level during ICU treatment was not modified by initial conscious state ($p = 0.17$ for the interaction GCS high/low × intervention). **c** Functional status at hospital discharge across GCS levels. Functional status, quantified by the sum of mmFIM subdomains locomotion and transfer, was not modified by the initial conscious state ($p = 0.96$ for the interaction GCS high/low × intervention)

discharge (likelihood ratio test $p = 0.97$, $p = 0.96$ for the interaction GCS × intervention; Fig. 1c).

Sensitivity analyses

In the intervention group mobilization was started on average on the 1st day, while in the control group start of mobilization was delayed for > 2 days ($p < 0.001$). This was also true for the subgroup of patients with impaired consciousness ($p = 0.014$); however, compared with patients with a high GCS, the time without mobilization was significantly longer in the intervention group (0.7 ± 0.2 days vs. 0.2 ± 0.1 days, $p = 0.008$). The predicted probabilities of achieving a specific mobilization level over the ICU stay in the subgroups of high and low GCS are shown in Fig. 3. Using the immediate post-randomization GCS as continuous instead of a binary variable (≤ 8 vs. > 8) did not change the results of our analysis (see Online Appendix). When functional outcome data in patients who had died during the hospital stay were defined as zero, the results of our analysis did not change: There was no effect modification for functional independence ($p = 0.67$ for the interaction GCS × intervention) as well as functional status at hospital discharge ($p = 0.75$ for the interaction GCS × intervention). The AUC of possible confounders for the outcome functional independence at hospital discharge are shown in Online Appendix. In a theory-based approach, early goal-directed mobilization was significantly associated with mean achieved SOMS ($p < 0.001$) and functional status at hospital discharge ($p < 0.001$), while GCS did not influence our model ($p = 0.12$ and $p = 0.54$, respectively; Online Appendix). Further exploratory analyses additionally accounting for traumatic brain injury and trauma are provided in Online Appendix.

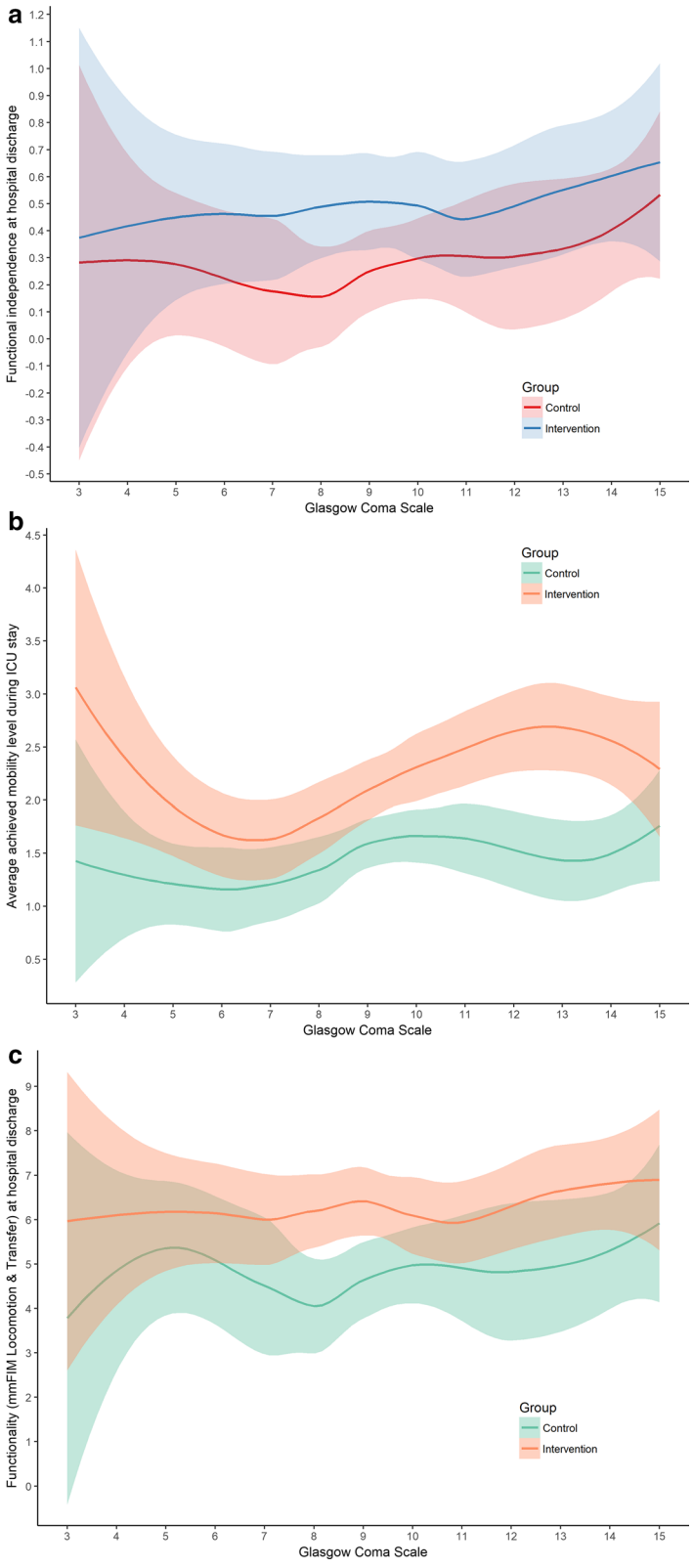
To analyze the power of this post hoc analysis of a previously published study [2], we conducted an a priori power analysis prior to making statistical comparisons between groups. The power analysis was based on the number of patients enrolled in the SOMS trial with GCS ≤ 8 and > 8 (60 and 140 patients, respectively) and the effect size of early, goal-directed mobilization observed in the SOMS cohort on functional independence at hospital discharge: the estimated proportions of patients with functional independence at hospital discharge were 0.15 and 0.25 in patients without and with early, goal-directed mobilization therapy. We calculated a priori, based on the patients enrolled in the SOMS trial with GCS ≤ 8 and > 8, that our study would have a power=0.8 to find an interaction effect of Cohen's $W = 0.23$ for the interaction intervention × GCS. Our observed data indicate that the effect size of early, goal-directed mobilization is even greater than we had anticipated a priori (details in Online Appendix).

Discussion

In this post hoc analysis of a trial on early, goal-directed mobilization [2], we did not find any difference in the effectiveness of early, goal-directed mobilization based on the immediate post-randomization level of consciousness as assessed by GCS. There is no randomized controlled trial investigating the effects of early mobilization in a neurocritical intensive care population [15]. Data obtained in a randomized controlled study conducted in stroke units suggest that very early mobilization is harmful, but these data may not apply to patients admitted to the ICUs [5, 16]. Infact, observational studies from neuro-intensive care unit patients noted that early mobilisation was associated with lower ICU morbidity [17, 18].

Our observation that early, goal-directed mobilization is effective in increasing the likelihood of patients with initial impairment of consciousness to leave the hospital functionally independent is clinically meaningful. In fact, in our institution neurologic impairment represents a significant barrier to physical therapists and nurses in the implementation of early mobilization therapy [19].

The GCS is the most common bedside tool to assess impairment of consciousness [20–25]. Translated to the local clinical language in more than 74% of over 80 countries, this scale is a useful tool for clinicians across the globe [25]. It is also part of commonly used critically ill scoring systems representing the central nervous system—e.g., in the APACHE II and the SOFA score [26, 27]. These factors make GCS an effective, easy-to-use


a
Functional independence at hospital discharge
Glasgow Coma Scale
Group
Control
Intervention
b
Average achieved mobility level during ICU stay
Glasgow Coma Scale
Group
Control
Intervention
c
Functionality (mmFIM Locomotion & Transfer) at hospital discharge
Glasgow Coma Scale
Group
Control
Intervention

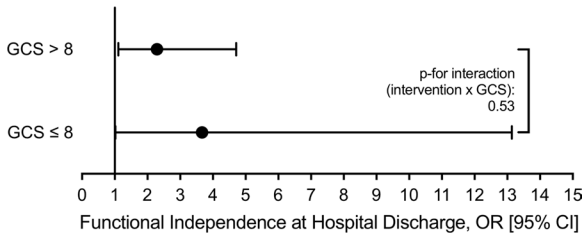


Fig. 2 Effects of early, goal-directed mobilization in patients with different initial conscious states measured by the immediate post-randomization Glasgow Coma Scale (GCS) on functional independence at hospital discharge. Using logistic regression analysis, we calculated the odds ratio for functional independence in the subgroup with impaired consciousness (GCS ≤ 8) and without impaired consciousness (GCS > 8). Early, goal-directed mobilization significantly increased the odds for functional independence in patients with low and high GCS (OR 3.67; 95% CI 1.02–13.14; $p = 0.046$ and OR 2.29; 95% CI 1.11–4.71; $p = 0.025$, respectively). In the entire cohort, there was no evidence of modification of the effects of early, goal-directed mobilization by GCS on functional independence ($p = 0.53$ for the interaction GCS × intervention). *GCS* Glasgow Coma Scale, intervention = early, goal-directed mobilization

and pragmatic tool to stratify the level of consciousness in patients.

Our study suggests that ICU patients with an impaired conscious state can be mobilized safely and effectively early on. Of note, the sub-cohorts of patients with GCS ≤ 8 and GCS > 8 showed similar mobilization patterns, but PROM was initiated later in patients with low GCS. The reasons for the delayed start of mobilization are unclear. Possibly, the existing equipoise on the effectiveness of very early mobilization therapy (i.e., within 24 h) in stroke patients outside intensive care [5] may have been contributing.

The feasibility of applying early mobilization and the observed benefit may in part be related to the initial step of our algorithm, PROM and upright position in bed, which was applied in almost all patients in the early, goal-directed mobilization group, on average > 2 days earlier than in the control group. PROM has very few contraindications and can therefore be applied independent of the level of consciousness of a patient [28–31]. Data suggest that an early start of mobilization therapy in the ICU is key to success, since studies starting their (even rigorous) interventions later than 72 h after ICU admission were not able to show a positive effect on functional outcomes [32–34] compared with early interventions [1, 2, 35]. Consistent with this speculation on the effectiveness of early passive range of motion therapy, PROM after acute stroke, delivered as part of a structured program, reduced edema, increased range of motion, and improved upper extremity function and activities of daily living [36]. PROM may promote muscle regeneration by activating satellite cells [37]. Additionally, PROM with repeated proprioceptive stimulation may induce a reorganization of sensorimotor representation [38] and may influence the excitability of the corticomotor pathway [39]. Although PROM can be safely administered in patients with and without impaired conscious state, there was a significant delay in the start of mobilization even in the intervention group in patients with impaired consciousness compared with patients without.

During randomization patients with elevated intracranial pressure and those with an immediate post-injury GCS motor score < 5 were excluded. This approach is consistent with other studies [1, 32–35, 40]. However, after the initial resuscitation and completion of hemodynamic stabilization and after a spontaneous awakening trial, five patients had an immediate post-randomization GCS of 3 and 4, and 39 patients had a GCS ≤ 7. The observed effect size of early mobilization was higher than anticipated in our a priori power calculation. Our data show that in the subgroup of patients with GCS ≤ 8, early, goal-directed mobilization improved the odds of functional independence at hospital discharge (OR 3.67, 95% CI 1.02–13.14; $p = 0.046$). Interestingly, this OR was even numerically higher than in the group of patients with GCS > 8 (OR 2.29; 95% CI 1.11–4.71; $p = 0.025$), which supports the view that meaningful conclusions can be drawn in this post hoc analysis.

We used GCS as a proxy for primary neurologic insult. Head trauma was the most common mechanism and was observed in 23% of our patients with impaired conscious state. One out of six patients carried a diagnosis of documented cerebrovascular disease, whereas in 21% of our patients with impaired consciousness there was no structural mechanism of impaired consciousness identified, and we speculate that a toxic metabolic encephalopathy or medication effects may have been contributing.

This study has several limitations. This is a post hoc analysis of data obtained in the SOMS trial, and we did not control the alpha error for multiple testing. Despite adequate power of this post hoc analysis, we would like to inform the readers that the parent SOMS trial was not originally planned for interaction and subgroup analyses. Confirmatory studies will be needed to create personalized mobilization interventions for patients with an impaired level of consciousness. Furthermore, this trial was conducted in the surgical ICU so that the results might not be generalizable to all critically ill patients. Lastly, the assessment of immediate post-randomization GCS was carried out in intubated patients. The estimated GCS may provide a lower resolution of the verbal response compared with GCS assessment in patients without an endotracheal tube.

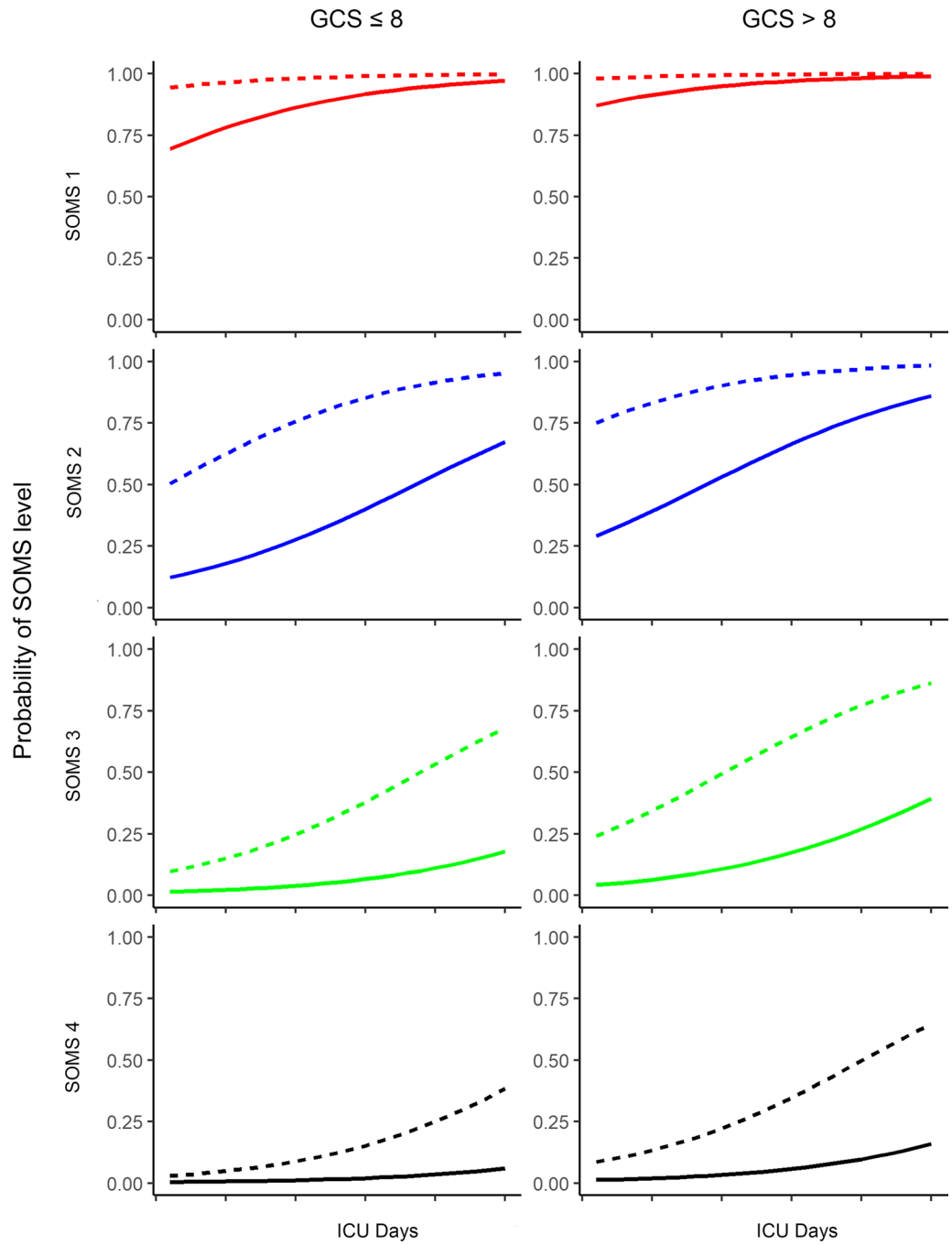


Fig. 3 Predicted probability from longitudinal ordinal regression model of patients reaching a specific mobilization level (1–4) during their stay in the surgical intensive care unit in the subgroups GCS ≤ 8 and > 8. Solid lines represent the control group; dotted lines represent the intervention group. Red representing passive range of motion (level 1), blue sitting (level 2), green standing (level 3) and black ambulating (level 4). The left column represents patients with an immediate post-randomization GCS ≤ 8 compared with the right column with GCS ≥ 8. *GCS* Glasgow Coma Scale; *SOMS* surgical intensive care unit optimal mobilization score

In summary, this post hoc analysis of a randomized controlled trial suggests that early, goal-directed mobilization initiated within 72 h after ICU admission in patients with an impaired initial conscious state (GCS ≤ 8) is not harmful but effective.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05528-x) contains supplementary material, which is available to authorized users.

Author details
[1] Department of Anesthesiology and Intensive Care, Klinikum Rechts der Isar, School of Medicine, Technical University of Munich, Munich, Germany. [2] Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [3] Department of Anesthesia, Critical Care and Pain Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, 330 Brookline Ave, Boston, MA 02215, USA. [4] Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA. [5] Department of Neurology, Klinikum Rechts Der Isar, School of Medicine, Technical University of Munich, Munich, Germany. [6] Department of Surgery, Boston University, Boston, MA, USA. [7] Department of Anesthesia, Critical Care and Emergency Medicine, Spedali Civili University Hospital, University of Brescia, Brescia, Italy. [8] Essen-Duisburg University, Medical Faculty, Essen, Germany.

Author contributions
Study concept and design: MB, ME, SJS. Acquisition, analysis or interpretation of data: All authors. Drafting of the manuscript: SJS and ME. Revising the manuscript critically for important intellectual content: All authors. Statistical analysis: MB, HD, TH, SJS, FTS. Final approval of the version to be published: All authors. ME had full access to all the data in the study and is the guarantor for the integrity of the data and the accuracy of the data analysis.

Funding
This study was funded by an unrestricted grant from Jeff and Judy Buzen to Matthias Eikermann. The funders had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; and the decision to submit the manuscript for publication.

Compliance with ethical standards

Conflicts of interest
Stefan J. Schaller received research support from MSD (Haar, Germany) not related to this manuscript. He holds stocks from Rhoen-Klinikum, Bayer AG and Siemens AG and held stocks in the recent past from GE Healthcare, Merck and Co., Inc., and Fresenius SE. These holdings have not affected any decisions regarding his research or this study. Flora T. Scheffenbichler reports no disclosures. Nicole Mazwi reports no disclosures. Hao Deng reports no disclosures. Franziska Krebs reports no disclosures. Christian L. Seifert reports no disclosures. George Kasotakis reports no disclosures. Stephanie D Grabitz reports no disclosures. Nicola Latronico reports no disclosures. Somnath Bose reports no disclosures. Timothy Houle reports no disclosures. Manfred Blobner received research support from MSD (Haar, Germany) not related to this manuscript; he received honoraria for lectures from GE Healthcare (Helsinki, Finland) and Grünenthal (Aachen, Germany). Matthias Eikermann received research support from Merck not related to this manuscript; he also received research support for this study from Jeff and Judy Buzen.

Ethical approval
For this analysis was obtained by the institutional review board of Massachusetts General Hospital (protocol number 2016P002199) and registered at Clinical Trials (NCT03666338).

Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 23 November 2018 Accepted: 9 January 2019
Published online: 21 January 2019

References

1. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, Schmidt GA, Bowman A, Barr R, McCallister KE, Hall JB, Kress JP (2009) Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 373:1874–1882
2. Schaller SJ, Anstey M, Blobner M, Edrich T, Grabitz SD, Gradwohl-Matis I, Heim M, Houle T, Kurth T, Latronico N, Lee J, Meyer MJ, Peponis T, Talmor D, Velmahos GC, Waak K, Walz JM, Zafonte R, Eikermann M, International Early S-gMRI (2016) Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. Lancet 388:1377–1388
3. von Bornstadt D, Houben T, Seidel JL, Zheng Y, Dilekoz E, Qin T, Sandow N, Kura S, Eikermann-Haerter K, Endres M, Boas DA, Moskowitz MA, Lo EH, Dreier JP, Woitzik J, Sakadzic S, Ayata C (2015) Supply-demand mismatch transients in susceptible peri-infarct hot zones explain the origins of spreading injury depolarizations. Neuron 85:1117–1131
4. Group ATC, Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, Churilov L, Moodie M, Dewey H, Donnan G (2015) Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 386:46–55
5. Langhorne P, Collier JM, Bate PJ, Thuy MN, Bernhardt J (2018) Very early versus delayed mobilisation after stroke. Cochrane Database Syst Rev 10:CD006187
6. Kasotakis G, Schmidt U, Perry D, Grosse-Sundrup M, Benjamin J, Ryan C, Tully S, Hirschberg R, Waak K, Velmahos G, Bittner EA, Zafonte R, Cobb JP, Eikermann M (2012) The surgical intensive care unit optimal mobility score predicts mortality and length of stay. Crit Care Med 40:1122–1128
7. Schaller SJ, Stauble CG, Suemasa M, Heim M, Duarte IM, Mensch O, Bogdanski R, Lewald H, Eikermann M, Blobner M (2016) The German validation study of the surgical intensive care unit optimal mobility score. J Crit Care 32:201–206
8. Piva S, Dora G, Minelli C, Michelini M, Turla F, Mazza S, D'Ottavi P, Moreno-Duarte I, Sottini C, Eikermann M, Latronico N (2015) The surgical optimal mobility score predicts mortality and length of stay in an Italian population of medical, surgical, and neurologic intensive care unit patients. J Crit Care 30:1251–1257
9. Meyer MJ, Stanislaus AB, Lee J, Waak K, Ryan C, Saxena R, Ball S, Schmidt U, Poon T, Piva S, Walz M, Talmor DS, Blobner M, Latronico N, Eikermann M (2013) Surgical intensive care unit optimal mobilisation score (SOMS) trial: a protocol for an international, multicentre, randomised controlled trial focused on goal-directed early mobilisation of surgical ICU patients. BMJ Open 3:e003262
10. Mahoney FI, Barthel DW (1965) Functional evaluation: the Barthel index. Md State Med J 14:61–65
11. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK (2002) The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 166:1338–1344
12. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, Truman B, Speroff T, Gautam S, Margolin R, Hart RP, Dittus R (2001) Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 286:2703–2710
13. Gennarelli TA, Champion HR, Copes WS, Sacco WJ (1994) Comparison of mortality, morbidity, and severity of 59,713 head injured patients with 114,447 patients with extracranial injuries. J Trauma 37:962–968
14. Wagner AK, Fabio T, Zafonte RD, Goldberg G, Marion DW, Peitzman AB (2003) Physical medicine and rehabilitation consultation: relationships with acute functional outcome, length of stay, and discharge planning after traumatic brain injury. Am J Phys Med Rehabil 82:526–536
15. Fuest K, Schaller SJ (2018) Recent evidence on early mobilization in critical-Ill patients. Curr Opin Anaesthesiol 31:144–150
16. Li Z, Zhang X, Wang K, Wen J (2018) Effects of early mobilization after acute stroke: a meta-analysis of randomized control trials. J Stroke Cerebrovasc Dis 27:1326–1337
17. Titsworth WL, Hester J, Correia T, Reed R, Guin P, Archibald L, Layon AJ, Mocco J (2012) The effect of increased mobility on morbidity in the neurointensive care unit. J Neurosurg 116:1379–1388
18. Lee JJ, Waak K, Grosse-Sundrup M, Xue F, Lee J, Chipman D, Ryan C, Bittner EA, Schmidt U, Eikermann M (2012) Global muscle strength but

not grip strength predicts mortality and length of stay in a general population in a surgical intensive care unit. Phys Ther 92:1546–1555
19. Garzon-Serrano J, Ryan C, Waak K, Hirschberg R, Tully S, Bittner EA, Chipman DW, Schmidt U, Kasotakis G, Benjamin J, Zafonte R, Eikermann M (2011) Early mobilization in critically ill patients: patients' mobilization level depends on health care provider's profession. PM&R 3:307–313
20. Waxman K, Sundine MJ, Young RF (1991) Is early prediction of outcome in severe head injury possible? Arch Surg 126:1237–1241 **(discussion 1242)**
21. Singh B, Murad MH, Prokop LJ, Erwin PJ, Wang Z, Mommer SK, Mascarenhas SS, Parsaik AK (2013) Meta-analysis of Glasgow Coma Scale and simplified motor score in predicting traumatic brain injury outcomes. Brain Inj 27:293–300
22. Jiang JY, Gao GY, Li WP, Yu MK, Zhu C (2002) Early indicators of prognosis in 846 cases of severe traumatic brain injury. J Neurotrauma 19:869–874
23. Koulouloas EJ, Papadeas AG, Michail X, Sakas DE, Boviatsis EJ (2013) Prognostic value of time-related Glasgow Coma Scale components in severe traumatic brain injury: a prospective evaluation with respect to 1-year survival and functional outcome. Int J Rehabil Res 36:260–267
24. Kevric J, Jelinek GA, Knott J, Weiland TJ (2011) Validation of the full outline of unresponsiveness (FOUR) scale for conscious state in the emergency department: comparison against the Glasgow Coma Scale. Emerg Med J 28:486–490
25. Teasdale G, Maas A, Lecky F, Manley G, Stocchetti N, Murray G (2014) The Glasgow Coma Scale at 40 years: standing the test of time. Lancet Neurol 13:844–854
26. Knaus WA, Draper EA, Wagner DP, Zimmerman JE (1985) APACHE II: a severity of disease classification system. Crit Care Med 13:818–829
27. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG (1996) The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 22:707–710
28. Zanni JM, Korupolu R, Fan E, Pradhan P, Janjua K, Palmer JB, Brower RG, Needham DM (2010) Rehabilitation therapy and outcomes in acute respiratory failure: an observational pilot project. J Crit Care 25:254–262
29. Clavet H, Doucette S, Trudel G (2015) Joint contractures in the intensive care unit: quality of life and function 3.3 years after hospital discharge. Disabil Rehabil 37:207–213
30. Clavet H, Hebert PC, Fergusson DA, Doucette S, Trudel G (2011) Joint contractures in the intensive care unit: association with resource utilization and ambulatory status at discharge. Disabil Rehabil 33:105–112
31. Koch SM, Fogarty S, Signorino C, Parmley L, Mehlhorn U (1996) Effect of passive range of motion on intracranial pressure in neurosurgical patients. J Crit Care 11:176–179
32. Moss M, Nordon-Craft A, Malone D, Van Pelt D, Frankel SK, Warner ML, Kriekels W, McNulty M, Fairclough DL, Schenkman M (2016) A randomized trial of an intensive physical therapy program for patients with acute respiratory failure. Am J Respir Crit Care Med 193:1101–1110
33. Wright SE, Thomas K, Watson G, Baker C, Bryant A, Chadwick TJ, Shen J, Wood R, Wilkinson J, Mansfield L, Stafford V, Wade C, Furneval J, Henderson A, Hugill K, Howard P, Roy A, Bonner S, Baudouin S (2018) Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. Thorax 73:213–221
34. McWilliams D, Jones C, Atkins G, Hodson J, Whitehouse T, Veenith T, Reeves E, Cooper L, Snelson C (2018) Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: a feasibility randomised controlled trial. J Crit Care 44:407–412
35. Morris PE, Berry MJ, Files DC, Thompson JC, Hauser J, Flores L, Dhar S, Chmelo E, Lovato J, Case LD, Bakhru RN, Sarwal A, Parry SM, Campbell P, Mote A, Winkelman C, Hite RD, Nicklas B, Chatterjee A, Young MP (2016) Standardized rehabilitation and hospital length of stay among patients with acute respiratory failure: a randomized clinical trial. JAMA 315:2694–2702
36. Kim HJ, Lee Y, Sohng KY (2014) Effects of bilateral passive range of motion exercise on the function of upper extremities and activities of daily living in patients with acute stroke. J Phys Ther Sci 26:149–156
37. Relaix F, Zammit PS (2012) Satellite cells are essential for skeletal muscle regeneration: the cell on the edge returns centre stage. Development 139:2845–2856
38. Carel C, Loubinoux I, Boulanouar K, Manelfe C, Rascol O, Celsis P, Chollet F (2000) Neural substrate for the effects of passive training on sensorimotor cortical representation: a study with functional magnetic resonance imaging in healthy subjects. J Cereb Blood Flow Metab 20:478–484
39. Edwards DJ, Thickbroom GW, Byrnes ML, Ghosh S, Mastaglia FL (2002) Reduced corticomotor excitability with cyclic passive movement: a study using transcranial magnetic stimulation. Hum Mov Sci 21:533–540
40. Investigators TS, Hodgson C, Bellomo R, Berney S, Bailey M, Buhr H, Denehy L, Harrold M, Higgins A, Presneill J, Saxena M, Skinner E, Young P, Webb S (2015) Early mobilization and recovery in mechanically ventilated patients in the ICU: a bi-national, multi-centre, prospective cohort study. Crit Care 19:81