Statistical Analysis Plan

Effects of mobilization dose in surgical intensive care unit patients on adverse discharge disposition

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1. Primary and Secondary Aim Overview

Primary Aim
The primary aim of this study is to assess the effects of mobilization dose in critically ill patients on adverse discharge disposition (ADD) (primary outcome). The primary hypothesis of this study is that the mobilization dose in the surgical intensive care unit measured by Mobilization Quantification Score (MQS) is associated with ADD.

Secondary Aim
The secondary aim is to evaluate the association between rectus femoris cross sectional area (RFCSA) measured by bedside ultrasound within 48 hours of enrollment and mobilization dose received in the surgical intensive care unit (SICU).

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2. Primary Aim

This study aim is driven by the research hypothesis that the MQS - a new method to quantify mobilization dose based on intensity and duration with more granularity than currently used mobilization quantification instruments - reflects the improving effects of early mobilization on discharge disposition.

Exposure variable
The primary exposure variable is the mean daily mobilization dose quantified by the MQS. The MQS is a newly developed score that quantifies mobilization provided by SICU nurses and physical therapists incorporating the mobilization level as well as its duration. The MQS is calculated daily throughout the SICU stay and will be divided by the number of ICU days to arrive at the exposure variable mean daily mobilization dose.

The secondary exposure variable used for comparison is the SICU optimal mobilization score (SOMS).

Primary Outcome
The primary outcome ADD is defined as discharge to facilities providing long-term care assistance for daily activities, including nursing homes and skilled nursing facilities, hospice at the patient's home, hospice in a healthcare facility, or in-hospital mortality.

Hypotheses

Primary Hypothesis
The primary hypothesis is that mobilization dose quantified via MQS predicts adverse discharge disposition.

Secondary Hypothesis
The key secondary hypothesis is that the MQS predicts ADD better than the SICU optimal mobilization score [SOMS] (Schaller et al., 2016).

We also hypothesize that the MQS predicts ICU length of stay, hospital length of stay, functional independence measure (mmFIM) at ICU and hospital discharge, 3-month mortality, change in muscle mass quantified by change in RF-CSA, ICU coma- and delirium-free days, ICU ventilator-free days, ICU vasopressor-free days, ICU neuromuscular blocking agent free days, opioid dosage, corticosteroid days, and physical work capacity 3 months after hospital discharge quantified by the Duke Activity Status Index (DASI).

Covariate Data

Predefined confounders in multivariable adjusted analyses include APACHE2 (Knaus, Draper, Wagner, & Zimmerman, 1985), sex-adjusted rectus femoris cross sectional area (RFCSA) (Janssen, Heymsfield, Wang, & Ross, 2000) measured via bedside ultrasound upon admission, and the Risk Quantification Index for 30-day Postoperative Morbidity (PSS morbidity) (Dalton et al., 2011).

RFCSA measured by bedside ultrasound has been shown to be an independent predictor of adverse patient outcomes (Mueller, Eikermann 2016).
RFCSA will be adjusted for sex using published skeletal muscle mass values of the lower body of healthy adults (Janssen et al., 2000). Thus, RFCSA of female patients are multiplied with the coefficient 1.484, whereas male patients represent the reference group (adjustment coefficient 1). Sex-adjusted RFCSA will be used for further statistical analyses.

Statistical Analysis

All analyses are performed prospectively with prespecified endpoints and statistical methods.

Primary analysis

Unadjusted Analysis: We will conduct univariate logistic regression analysis to investigate the association between mobilization dose quantified by MQS and ADD.

Adjusted analysis: Multivariable logistic regression (mean daily mobilization dose (MQS)/ ADD) analyzing whether mobilization dose predicts adverse discharge independent from the defined covariates (APACHE2, PSS Morbidity score, and sex adjusted admission RFCSA).

Secondary analyses

We will perform Net Reclassification Index and c-statistics to compare the predictive capability for ADD of the MQS to the SOMS. To further confirm the robustness of our results we will conduct Aikaike Information Criterion (AIC) and likelihood ratio test. AIC provides the relative quality of the estimated model. The likelihood ratio test compares the goodness of fit of two statistical models.

Multivariable logistic regression will be performed to evaluate the relationship between mean daily mobilization dose and other binary secondary outcomes controlling for above defined covariates. Zero truncated negative binomial regression will be used to analyze the association between mobilization dose and the secondary outcomes ICU and hospital length of stay. Negative binomial regression will be used to analyze the association between mobilization and the secondary outcomes coma- and delirium-free days, NMBA-free days, ventilator-free days, and functional independence measure (mmFIM) at ICU and Hospital discharge.

We will use linear regression to analyze the association between mobilization and physical work capacity 3 months after hospital discharge quantified by the Duke Activity Status Index (DASI) and opioids dosage (mg), if normality assumption is satisfied. Otherwise, transformation of the variables will be performed, and the transformed variables will be used as the outcome in the linear model.

Planned Sensitivity Analyses

Evaluation of confounder model: AUC-Analysis including the predefined confounders to determine the Area Under the receiver operator curve.

Categorized exposure variable: (2-quantile [high, low mobilization dose], tertiles [low, intermediate, high mobilization dose])

Alternative Exposure Variable: For each patient, mobilization data will be centered, and we will perform simple linear regression with the individual mean mobilization dose being the estimated intercept of each patient. The estimated slope from the linear regression will be considered as the change rate of mobilization dose. Two exposures will be included in our model, the slope of the mobilization dose and the intercept. We will conduct multivariable logistic analysis controlling for the same confounder variables (expected 4DoF: Intercept, Slope, APACHE2, RFCSA (continuous), PSS morbidity) from the primary analysis.

Evaluate the AUC with alternative Exposure Variable (intercept/ slope): We will compare discriminative ability of our primary model to a model with two exposure variables (intercept (mean mobilization dose for each patient) and slope) utilizing Net Reclassification Index, Brier Score and c-statistics.

Generalized propensity score: In an exploratory approach, accounting for the degrees of freedom available, we will include a generalized propensity score to reduce bias induced by discrepancies in patient characteristics. The propensity score will be generated from different covariates identified as influencing the exposure including APACHE, GCS at enrollment, ASA at admission, PSS-Morbidity, duration of ventilation, duration of sedation, duration of delirium, opioid dose, vasopressors. The propensity score will be confined for a binary exposure variable. To derive at a binary variable, we will categorize the mean mobilization dose (MQS) into two categories, high vs. low.

Subgroup analyses: We will perform a subgroup analysis in patients who received surgery upon admission to the ICU.

Planned Exploratory Analyses

We aim to explore the association of other variables that can be used to quantify mobilization intensity and duration (other than the composite exposure MQS) and adverse discharge disposition.

The additional variables used to quantify mobilization intensity and/or dose are:

- Mean highest achieved level of mobilization therapy (Daily highest achieved ICU mobilization scale level/ICU days)
- Highest achieved mobilization level using ICU mobilization score
- Mean number of daily mobilization sessions (Total number of mobilization units/ICU days)
- Mean duration of mobilization units according to MQS (Total duration of mobilization treatment based on MQS/number of sessions throughout the ICU stay)
- Fraction of days mobilized (Number of mobilization days/ ICU days)
- Early mobilization frequency (Total number of mobilization units from day 1 through 3 on the ICU)

We will use multivariable logistic regression for exploratory analyses analyzing the association between the above-mentioned variables used to quantify mobilization intensity and/or dose.

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3. Secondary Aim

Exposure variable
The RFCSA assessed through bedside ultrasound measurements within 48h is used as a continuous exposure variable.

Outcomes
The outcome for the secondary aim of the study is the repeatedly measured daily mobilization dose as quantified by the MQS.

Hypothesis

Primary hypothesis
The primary hypothesis is that RFCSA is an independent predictor of mobilization dose in the SICU.

Statistical Analysis

All analyses are performed prospectively with prespecified endpoints and statistical methods.

We will conduct a generalized linear mixed effect model to analyze whether the RFCSA quantified via bedside ultrasound is an independent predictor of daily mobilization dose in the ICU.

Predefined confounders include the Barthel Index at hospital admission, APACHE2 and Charlson Comorbidity Index (CCI).

Secondary analysis

We will conduct a generalized linear mixed effect model to analyze whether the RFCSA quantified via bedside ultrasound is an independent predictor of daily mobilization dose in the ICU utilizing an alternative exposure variable. The exposure variable will be the binary variable “Sarcopenia

yes/no". Sarcopenia is quantified by RFCSA assessed through bedside ultrasound measurements within 48h. We will apply Youden's Index to define the optimal cutoff point of RFCSA for Sarcopenia. (Mueller, Eikermann 2016).
Sarcopenia is a clinical syndrome that describes progressive and generalized loss of skeletal muscle mass and strength and is associated with patient outcomes. (Delmonico, Harris, Lee, J Am Geriatr Soc, 2007)

Sample Size and Power

Based on data obtained by the same centers in the SOMS trial (Schaller et al., 2016) there is a correlation between mobilization dose and discharge disposition of 0.25. We therefore calculate that a sample size of 150 patients provides a power of >0.8 to identify a significant effect (alpha-error: 0.05) for our primary outcome.

Data collection

Data collection

On ICU admission, patients' baseline characteristics [age, sex, race, ethnicity, height, weight, admission diagnoses, Charlson comorbidity index (CCI), ASA PS, Frailty Score, Short Nutritional Assessment Score Questionnaire (SNAQ) Score reason for ICU admission] will be noted. Admission laboratory data and vital signs to calculate the APACHE II score, will be recorded as well as the severity of organ dysfunction [Sequential Organ Failure Assessment (SOFA) score]. SOFA scores will be obtained within 48 hours of SICU admission and on days when follow up ultrasound measurements are conducted (every 8 days/ at ICU discharge). Daily laboratory data, vital signs, medication and ventilation/ABG will be noted. We will further collect data at ICU discharge, Hospital discharge and 3 months after discharge. A summary of the data that we will collect is listed below.

Baseline
Medical Record Number, First name, Last name , Date of Birth, Age, Sex, Race, Ethnicity, Height, Weight at ICU admission, ICU admission [date] , Hospital admission [date], Admission category, Patient had surgery prior to inclusion (y/n) Date of surgery, Surgery CPT Code, Charlson Comorbidity Index, ASA, Frailty Phenotype Modified, Short Nutritional Assessment Questionnaire, APACHE II, Barthel Index 2 weeks prior to admission, Glasgow Coma Scale motor component at enrollment, Absence of lower extremity (y/n), Pregnancy (y/n), Procedural Severity Score.

Follow-up
Richmond Agitation and Sedation Score (RASS), SOFA score, Medical Research Council Muscle scale (MRC scale), Confusion Assessment Method for the ICU (CAM-ICU), Nutrition, Renal replacement therapy (y/n)

Mobility
MQS score, SOMS score, Physical Therapy (PT) time [mins], nonPTMobilization [mins], walking distance [feet], Rectus femoris diameter left [cm^2], Rectus femoris diameter right [cm^2]

Vital Signs
Systolic blood pressure, diastolic blood pressure, mean arterial blood pressure (MAP), Respiratory rate, Body temperature, Heart rate.

Laboratory
Hb [g/dL], Hk, Creatinine [mg/dL], Urine output [µmol/L], Alb (g/dL), INR, blood Glucose [mg/dL], serum sodium (Na) [mEq], K [mEq/L], glomerular filtration rate (GFR), Bilirubin [µmol/L], CRP, WBC count, CKD, Platelets [×10^9/L].

Medication
Sedation needed (y/n), Steroids (y/n), Opioids total dose per day [morphine equivalent dose, mg], Vasopressors (y/n), NMBAs (y/n + drug), Propofol (y/n), Total propofol dose per day.

Ventilation/ABG
Date intubated, Date extubated, Reintubation (y/n)

ICU Discharge
mmFIM score in domains transfer and locomotion, ICU Discharge [date], ICU LOS, number of PT visits, ICU Readmission, weight at ICU discharge, medical interventions during ICU stay

Hospital Discharge
Hospital Discharge [date], Hospital Readmission, Hospital LOS, In-Hospital Mortality, Discharge destination, Total costs of care

Phone Call
DASI, Readmission to any Hospital, One-month mortality, Three-month mortality.