Study Protocol and Statistical Analysis Plan

Development and validation of a prediction algorithms to estimate the clinical effect of early rehabilitation on ICU survivors received mechanical ventilation in the ICU

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1. Background

Approximately 13 to 20 million people worldwide receive treatment in intensive care units (ICU) each year. Mechanical ventilation is one of the critical treatment measures to maintain vital signs in ICU patients, with 50-70% of ICU patients in China undergoing mechanical ventilation. Critically ill patients receiving mechanical ventilation are often subjected to deep sedation and bed rest, especially during the early stages of their ICU stay. Extensive research has demonstrated that prolonged bed rest can lead to a series of complications such as ICU-acquired weakness, increased infection risk, and decreased cardiopulmonary function, which in turn increases the difficulty of patient recovery, extends hospital stays, and elevates the risk of in-hospital mortality. To prevent various complications during ICU hospitalization and improve patient outcomes, early rehabilitation intervention is crucial. In recent years, an increasing amount of evidence-based medical research has proven that early rehabilitation intervention for mechanically ventilated patients (including early passive and active activities, postural management, and pulmonary rehabilitation) is safe and feasible, and can to some extent promote functional recovery and reduce ICU length of stay.

In recent years, clinical prediction models for the prognosis of ICU survivors have become increasingly prevalent, with related outcome indicators including the incidence of sepsis, survival rates of elderly

patients, mortality risk from acute gastrointestinal bleeding, survival rates of patients with acute respiratory distress syndrome (ARDS), and ICU length of stay. A comprehensive review of existing literature reveals that due to the unique nature of ICU hospitalized patients, clinicians tend to focus more on indicators such as vital signs, mortality rates, and the incidence of severe complications in ICU patients, rather than the functional status of ICU survivors. As medical technology has advanced in recent years, ICU mortality rates have steadily declined, bringing increased attention to the quality of life of ICU survivors. The key issue that early rehabilitation intervention must address is how to facilitate the reintegration of ICU survivors into society and preserve their daily living abilities as much as possible. Currently, no prediction models specifically address the post-discharge physical function of ICU survivors. Upon ICU admission, patients undergo comprehensive clinical examinations or assessments, including evaluations of consciousness, liver and kidney function, cardiopulmonary function, gastrointestinal function, nutritional status, and imaging studies of critical organs. Before receiving rehabilitation interventions, they must also undergo various types of rehabilitation assessments. These clinical data significantly impact patient prognosis.

Although early rehabilitation intervention in the ICU has begun to be implemented in some hospitals in China in recent years, it is still in its early

stages of development. There are significant differences in the severity of ICU patients among different hospitals, and the level of professional knowledge in critical care medicine among rehabilitation physicians and therapists varies widely. Additionally, ICU inpatients within the same hospital come from various departments, with primary diseases exhibiting significant heterogeneity, and their physical conditions when starting early rehabilitation intervention are not entirely consistent. While there are currently guidelines or expert consensus recommending certain indicators for initiating early rehabilitation intervention and suggesting early intervention methods, the early intervention programs that patients with different physical conditions can undergo also vary. These factors result in considerable differences in indicators such as consciousness, muscle strength, respiratory function, and activity of daily living (ADL) when patients who have received early rehabilitation intervention are transferred out of the ICU once their condition stabilizes. Some patients may not experience significant benefits. Therefore, identifying which patients might have a higher potential for benefiting from early rehabilitation intervention is a crucial issue that needs to be addressed in early ICU rehabilitation.

Clinical prediction models estimate the probability of having a certain disease or the likelihood of a specific outcome occurring in the future by using multifactorial models. Prognostic models focus on estimating the

probability of disease recurrence, mortality, disability, and complications over a future period based on the current disease state. This study aims to collect relevant clinical data (including basic patient information, physiological indicators, medical history, etc.) and rehabilitation assessment results (including muscle strength, consciousness status, ADL, etc.) from ICU inpatients undergoing early rehabilitation intervention. By screening and transforming these data, we will use regression equations to construct a prognostic model that can predict the outcomes of ICU patients receiving early rehabilitation intervention. This will help determine whether a patient can benefit from early rehabilitation intervention. The clinical application of this model will enable a more precise determination of whether ICU inpatients need early rehabilitation intervention, thereby reducing the incidence of complications among mechanically ventilated ICU patients and improving their quality of life.

2. Objectives

2.1 Primary Objective: To establish a clinical prediction model that can predict the timeframe in which mechanically ventilated ICU survivors will begin to benefit from early rehabilitation intervention, thus providing guidance for the early initiation of rehabilitation in critical care settings.

2.2 Secondary Objectives: Understanding the Role of Individual Differences in Rehabilitation Benefits. Analyze the impact of individual

differences on the timing of rehabilitation benefits, including factors such as age, gender, and baseline health status. Identify potential disparities in rehabilitation benefits among different patient populations to provide reference for developing personalized rehabilitation strategies. This will help make early rehabilitation interventions more individualized and precise, maximizing patient recovery benefits.

3. Study Design Type, Principles, and Experimental Steps

3.1 Study Design

This study is a multicenter, prospective cohort study, planning to recruit 250 ICU patients undergoing mechanical ventilation. Three additional hospitals in Wuhan (Wuhan No.1 Hospital, Wuhan Brain Hospital, and Wuhan No.6 Hospital) will serve as sub-centers, enrolling ICU patients who receive early rehabilitation intervention for the validation cohort of the model.

Sample Size Calculation: This study plans to include approximately 10 predictive factors to develop the model. According to the one-tenth rule of EPV (Events per Variable), and assuming that 50% of ICU patients will benefit from early rehabilitation intervention during hospitalization, the sample size for the model development cohort is calculated to be at least $(10\times10)/0.5 = 200$ patients. The study aims to collect data on all patients undergoing early rehabilitation intervention within one year from the

enrollment of the first patient. Based on the current number of patients receiving early rehabilitation intervention in our ICU, it is estimated that subject recruitment can be completed within one year. The external validation dataset will consist of a quarter of the model development cohort, amounting to 50 cases. A multicenter prospective cohort study will also be conducted simultaneously, incorporating relevant data from ICU survivors in other hospitals for external validation.

Indications: Based on the detailed assessment and classification of different patient states outlined in the "Chinese Expert Consensus on Neurological Critical Care Rehabilitation," assessment indicators include consciousness level, degree of cooperation, sedation status, and other aspects to ensure the personalization and specificity of rehabilitation interventions. The determination of indications is guided by the " Expert consensus and recommendations on safety criteria for active mobilization of mechanically ventilated critically ill adults", as well as specific assessment tools and standards used in this study design.

3.2 Research procedure

(1) Identify Clinical Issues and Outcome Indicators.

(2) Collection of Predictive Factors: Gather clinical data from ICU patients receiving early rehabilitation intervention, including demographic data, disease diagnosis, and intervention data.

(3) Data Processing: Check for missing values, outliers, or anomalies

in the data, and conduct necessary data processing.

(4) Variable Selection: Perform predictive factor selection using methods such as collinearity analysis, LASSO regression, and expert opinion.

(5) Variable Transformation: Choose appropriate variable transformation methods based on the distribution characteristics of the predictive factors.

(6) Model developing: This study plans to use two main types of modeling approaches. The first approach is the Cox proportional hazards regression model. The second approach involves machine learning algorithms.

(7) Model Diagnosis and Evaluation: Diagnose the efficiency of the model by calculating linear relationships between models, influential points, multicollinearity, and the proportional hazards assumption.

(8) Internal Validation of the Model: Perform internal validation using the bootstrap method.

(9) External Validation of the Model: Utilize data from external sub-centers for external validation.

(10) Assessing Clinical Value of the Model: Apply Decision Curve Analysis (DCA) to evaluate the clinical value of the model.

(11) Model Presentation: Present the predictive model using nomograms and a web-based application.

4. Participants recruitment

4.1 Inclusion Criteria:

(1) Age greater than 18 years;

(2) Received mechanical ventilation during ICU hospitalization, including both endotracheal intubation and tracheostomy;

(3) Met the indications for rehabilitation intervention according to the "Chinese Expert Consensus on Neurological Critical Care Rehabilitation" during ICU hospitalization and underwent corresponding early rehabilitation interventions, including but not limited to awakening from altered consciousness, early active/passive mobilization, and comprehensive pulmonary rehabilitation;

(4) No mortality events occurred during ICU hospitalization;

(5) Informed consent signed by family members or the patient.

4.2 Exclusion Criteria:

(1) Minors under the age of 18;

(2) Inpatients who did not receive mechanical ventilation during ICU hospitalization;

(3) Patients who did not undergo early rehabilitation intervention in the ICU;

(4) Occurrence of mortality events during ICU hospitalization;

(5) Patients transferred out of the ICU due to family decision to withdraw treatment;

(6) Family members who refuse to sign the informed consent or patients who refuse to sign the informed consent while having autonomous consciousness.

5. Methods and flow chart

5.1 Name and Specifications of Study Medication

None

5.2 Early rehabilitation intervention procedure

Based on the indications for early rehabilitation intervention outlined in the "Chinese Expert Consensus on Neurological Critical Care Rehabilitation," early rehabilitation interventions are categorized into three stages according to the patient's consciousness level (GCS score), degree of cooperation (S5Q score), and sedation status (RASS score):

(1) Stage 1:

Patients with altered consciousness or sedation status who are unable to cooperate or only minimally cooperate with rehabilitation treatment, with assessment results indicating the following conditions: altered consciousness (GCS score < 8); S5Q < 3; manual muscle strength testing scoring 0-1; mechanical ventilation (P-SIMV mode); CRRT (CVVHDF mode). The rehabilitation protocol includes: early passive mobilization of limbs, neuromuscular electrical stimulation, chest wall mobilization, postural drainage for secretions, external diaphragm pacing therapy, and

comprehensive awakening treatments (sensory input, ice stimulation, median nerve electrical stimulation, acupuncture, etc.).

(2) Stage 2:

Patients with partial consciousness who can somewhat cooperate with rehabilitation treatment but are unable to get out of bed, with assessment results indicating the following conditions: GCS (8-12); S5Q = 3; MMT muscle strength 2-3; mechanical ventilation (P-CPAP mode with no assisted ventilation) or extubated; CRRT on CVVHDF/CVVH mode or removed; able to complete swallowing assessment. The rehabilitation protocol includes: active/passive mobilization of limbs, sensory stimulation, neuromuscular electrical stimulation, respiratory muscle training, airway clearance techniques (ACBT), external diaphragm pacing therapy, and swallowing function training.

(3) Stage 3:

Patients with full consciousness who can largely cooperate with rehabilitation training and begin sitting, standing, and other out-of-bed training, approaching transfer out of the ICU, with assessment results indicating the following conditions: GCS (13-15); S5Q = 5; RASS (0); muscle strength MMT (most muscle strength ≥ 3); intermittent extubation or extubated; CRRT has been removed, no pressure on catheter sites, and no positional restrictions; able to complete activities of daily living (ADL) assessment; able to complete swallowing function assessment (Wakatani

water test, dye test). The rehabilitation protocol includes: active muscle strength training (dumbbells, resistance bands, sandbags), endurance training, out-of-bed training, standing training, assisted walking training, neuromuscular electrical stimulation, respiratory muscle training, airway clearance techniques (ACBT), external diaphragm pacing therapy, swallowing function training, and occupational therapy (training for activities of daily living).

5.3 Concomitant Medications:

None.

6. Parameters and Time Points

The primary observation items in this study involve collecting predictive factors that serve as variables for the predictive model, which are categorized into the following three major groups. All predictive factors will be collected prior to the initiation of early rehabilitation intervention.

5.1 Demographic Data: This includes gender, age, weight, height, and FIM score. All data are collected prior to the initiation of early rehabilitation intervention.

5.2 Clinical Diagnosis Data: This includes current diagnoses determined based on the patient's recent imaging or blood tests, as well as medical history, detailed as follows:

(1) Acute Myocardial Infarction: Acute myocardial infarction occurring after admission, clearly diagnosed by ICU physicians.

(2) Acute Arrhythmia: Acute arrhythmias occurring after admission, including rapid atrial fibrillation, atrial flutter, paroxysmal tachycardia, premature contractions, and pathological conduction block, with appropriate clinical interventions.

(3) Acute Heart Failure: Acute heart failure due to various causes after admission, with serum BNP or NT-BNP levels above normal, and receiving appropriate clinical interventions.

(4) Acute Cerebral Infarction: Cerebral infarction occurring within one week prior to admission until ICU discharge, clearly diagnosed by CT, MRI, or angiography.

(5) Acute Intracerebral Hemorrhage: Non-traumatic intracerebral hemorrhage due to various causes occurring within three weeks prior to admission until ICU discharge, clearly diagnosed by CT or MRI.

(6) Traumatic Brain Injury: Primary reason for admission being trauma-related skull fractures, intracerebral hemorrhage, brain contusions, or subarachnoid hemorrhage, confirmed by imaging studies.

(7) History of Stroke: History of stroke within the past five years, resulting in unilateral limb muscle strength decline or hemiplegia.

(8) Postoperative Brain Tumor: Diagnosed with a brain tumor prior to ICU admission and having undergone surgical treatment, with tumor

types including but not limited to malignant brain tumors, hemangiomas, etc.

(9) Level of Consciousness: Assessed using the Glasgow Coma Scale (GCS) to evaluate the level of consciousness, treated as a continuous variable.

(10) Respiratory Failure: Respiratory failure due to various causes requiring mechanical ventilation.

(11) Pulmonary Infection: Clinically diagnosed pulmonary infection with unilateral pulmonary consolidation greater than 1/2.

(12) Pleural Effusion: Moderate or greater (500 ml-1000 ml) pleural effusion confirmed by imaging before starting rehabilitation treatment.

(13) Acute Gastrointestinal Bleeding: Diagnosed gastrointestinal bleeding occurring during this hospitalization, accompanied by hemoglobin levels dropping to moderate anemia (below 90 g/L).

(14) Acute Kidney Injury: Sudden decline in renal function within 48 hours, with serum creatinine increasing by ≥0.3 mg/dl, or within 7 days, serum creatinine increasing to 1.5 times the baseline value, confirmed by clinicians as acute kidney injury.

(15) Chronic Kidney Disease: History of chronic kidney disease with serum creatinine exceeding 1.5 times the upper limit during this admission.

(16) Malignant Tumor: Various diagnosed malignant tumors, including those of the digestive tract, urinary system, endocrine glands,

hematologic system, spine, and skeletal system, excluding malignant tumors of the cranial region.

(17) Sepsis: Diagnosed with sepsis by ICU physicians through serological indicators, bacterial cultures, imaging studies, etc.

(18) Multidrug-Resistant Infection: Development of pulmonary, gastrointestinal, urinary infections, or sepsis during hospitalization, confirmed as multidrug-resistant bacteria through sputum, urine, or blood cultures.

(19) Spinal Cord Injury: Severe functional impairment of the lower limbs due to trauma, spinal tumors, or spinal ischemia.

(20) Multiple Trauma: Various causes leading to multiple traumas, excluding traumatic brain injury, and requiring surgical treatment, including but not limited to pulmonary contusion, hemothorax, abdominal injuries, renal contusion, and multiple fractures.

(21) Fractures Without Surgery: Patients with fractures due to trauma who have not yet undergone surgical treatment due to the presence of other severe conditions.

5.3 Disease Intervention Data: This includes important life support and rehabilitation interventions received by ICU patients undergoing mechanical ventilation, specifically as follows:

(1) History of ECMO Application: Whether the patient received ECMO (Extracorporeal Membrane Oxygenation) for life support before

starting rehabilitation interventions.

(2) Continuous Renal Replacement Therapy (CRRT): Whether the patient received CRRT before starting rehabilitation interventions, or if they were undergoing CRRT near the time of intervention.

(3) Duration of CRRT: The total number of days the patient received CRRT during their entire ICU stay, as a continuous variable.

(4) Mode of Mechanical Ventilation: Whether the patient received mechanical ventilation through endotracheal intubation or tracheostomy, as a categorical variable.

(5) Duration of Mechanical Ventilation: The number of days the patient received mechanical ventilation in the ICU before starting rehabilitation interventions, as a continuous variable.

(6) Mode of Ventilatory Support: Whether the patient received ventilatory support in the form of SIMV (Synchronized Intermittent Mandatory Ventilation), including P-SIMV (Pressure-SIMV) and V-SIMV (Volume-SIMV), or CPAP (Continuous Positive Airway Pressure), as a categorical variable.

(7) Analgesic Treatment: Whether the patient received analgesic treatment before and during rehabilitation interventions, including but not limited to NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), opioids, and opioid-like analgesics.

(8) Nutritional Support: The type of nutritional support the patient

received before starting rehabilitation interventions, either enteral nutrition or parenteral nutrition, as a categorical variable.

(9) Comprehensive Pulmonary Rehabilitation: Whether the patient's rehabilitation plan in the ICU included comprehensive pulmonary rehabilitation, including airway clearance, active breathing cycle techniques, and diaphragm pacing.

(10) Early Active/Passive Limb Activity: Whether the patient's rehabilitation plan included early active/passive limb activity and neuromuscular electrical stimulation.

(11) Arousal Therapy for Patients with Consciousness Disorders: Whether patients with consciousness disorders received arousal therapy, including sensory stimulation and median nerve electrical stimulation.

(12) Swallowing Assessment and Therapy: Whether ICU patients underwent swallowing assessments (e.g., water swallow test, VVST) and swallowing therapy (including the Mendelsohn maneuver and swallowing electrical stimulation).

7. Outcome Measurements:

The purpose of this study is to investigate how soon ICU survivors can benefit from early rehabilitation interventions. By observing the changes in ADL (Activities of Daily Living) scores of ICU survivors during their ICU stay, we can determine whether they have benefited.

Thus, the outcome measure is a time-to-event outcome, specifically whether the patient has achieved improvement in ADL function at different time points after receiving early rehabilitation interventions in the ICU. All enrolled participants will undergo FIM (Functional Independence Measure) scoring before the early rehabilitation intervention and every other day after the intervention. An increase of ≥5 points in the FIM score compared to the pre-intervention score will be considered as the patient benefiting from the early rehabilitation intervention.

8. Statistical Analysis

8.1 Data Preprocessing

(1) Processing of Missing Data: This project is a prospective cohort study, and theoretically, the predictor data for each patient can be collected. However, small amounts of data loss due to various reasons cannot be excluded. First, the “ggplot” package in R will be used to visualize and determine if the missing data is random or related. Then, the MICE package will be utilized for multiple imputations, with the number of imputations equal to the percentage of missing data (if n% of the data is missing, n imputations will be performed).

(2) Transformation of Predictors (Variables): Based on the distribution characteristics of the predictor variables, appropriate

transformation methods will be selected. For continuous variables, transformations such as logarithmic, square, or square root transformations will be applied to approximate a normal distribution as closely as possible. For binary or categorical variables, the factor() function in R will be used for conversion. If machine learning algorithms such as SVM or GBM are used for model development, binary or categorical variables do not need to be transformed.

8.2 Model Development Methods

This study plans to use two main model development methods. The first method is the COX proportional hazards regression model. The second method involves machine learning algorithms, such as Support Vector Machines (SVM) and Gradient Boosting Machine (GBM) algorithms.

8.3 Model Diagnostics and Evaluation

The efficiency of the models will be diagnosed by calculating the linear relationships between models, identifying influential points, detecting multicollinearity, and testing the proportional hazards assumption. For the SVM model, evaluation metrics will include accuracy, precision, recall, and F1 score.

8.4 Internal Validation of the Model-Bootstrap Validation

Given that this study is a prospective cohort with a relatively small development sample size, the bootstrap method will be used for internal

validation. The `validate()` function in the RMS package will be applied to calculate model performance metrics such as discrimination and calibration. The C-statistic and calibration will be evaluated by calculating the difference (optimism) between the model's performance in the training set and its bootstrap samples.

8.5 External Validation of the Model

Once the external validation data is collected, the same variable transformation methods used in the development cohort will be applied to the corresponding variables. Linear predictor values and predicted probabilities will be calculated. The model's performance in the external validation cohort will be comprehensively evaluated using metrics such as the C-statistic, Brier score, calibration intercept, and calibration slope.

8.6 Evaluation of the Model's Clinical Value

The clinical value of the model will be assessed using Decision Curve Analysis (DCA). This will be performed using the `mda` and `ggDCA` packages in R.

8.7 Model Presentation

(1) Nomogram: The RMS package will be used to create a nomogram for the fitted COX model, providing a visual representation of the model.

(2) Web Application: The DynNom package will be used to develop a web-based application for the fitted COX model, facilitating easier access and interaction with the model.

9. Research Schedule

July 2024-December 2024: After completing the ethics approval, the clinical trial registration will be finalized. Enroll 100 subjects into the model development cohort while continuously optimizing the machine learning algorithms using the collected data. The writing of the Chinese literature review will also be completed.

January 2025-February 2025: Based on the data from the model development cohort, attempts will be made to construct predictive models using different modeling approaches and to complete the internal validation of the models. The writing of related papers on clinical prediction models will also commence.

January 2025-June 2025: Complete the inclusion of 50 subjects in the external validation cohort. Once inclusion is complete, proceed with the external validation of the models.

July 2025-December 2025: Organize clinical data, write, and publish relevant papers. Plan to establish a database for critical care rehabilitation based on the clinical data framework developed in this study, continue collecting relevant clinical data, and conduct retrospective studies to further train the model.