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REhabilitation Practice and Association with Outcomes in Critically Ill Invasively Ventilated Patients (REPOrt)—an international multicenter observational study

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Table of contents

1. Study Summary

Study Title	Practice of REhabilitation Practice and associations with Outcomes in critically ill invasively ventilated patients (REPOrt)–an international multicenter observational multimodule study.
Background	Critically ill patients on invasive ventilation often develop ICU-acquired weakness (ICU–AW), linked to higher mortality and long-term morbidity. Rehabilitation interventions, including mobilization, physical activity, respiratory physiotherapy, dysphagia training, occupational therapy, and cognitive/ pshycological support, has been reported beneficial but remain underused, which may be due to limitations in resources. Moreover, its impact on clinical outcomes remains uncertain.
Aim	The primary objective of this worldwide multicenter observational multimodule study is to describe rehabilitation practices in ICUs at a global level. The secondary objective is to determine the association between rehabilitation and key ICU outcomes such as ICU and hospital mortality, lengths of stay, duration of invasive ventilation, extubation failures, and ICU and hospital mortality. We will additionally explore the association between rehabilitation and quality of life and functional performance 28 days after ICU discharge. We will also compare rehabilitation practices and association with outcomes across different geo–economic regions. The study consists of three modules, with participation contingent on local capabilities and feasibility: (A) a BASIC module [madatory for all participating centers], that collects basic information on rehabilitation practices and association with outcomes. (B) an EXTENDED module [optional for all participating centers], that in addition to the BASIC module collects more granular data on rehabilitation interventions, including type, timing, duration, safety, and professionals who deliver rehabilitation interventions. This module details the following rehabilitation interventions: (1) passive interventions, such as passive exercises, stretching, cycling, neuromuscular electical stimulation, continuous and passive range of motion; (2) active interventions, such as exercise therapy, activities of daily living training, mobilization, and cycling; (3) respiratory interventions such as positioning, airways clearance techniques, lung expansion exercises, positive airway pressure devices, active cycle of breathing techniques, forced expiratory techniques, assisted or stimulated cough maneuvers, insufflation–exsufflation, and inhalation therapy; (4) dysphagia training, and swallow screening test; (5) occupational therapy, and (6) cognitive/phsycological therapy.

	(C) an EXTENDED FOLLOW–UP module [optional for all participating centers], that in addition to the BASIC outcomes collects quality of life and functional performance 28 days after ICU discharge.
Study Design	International multicenter observational multimodule study.
Participants	Patients are eligible if: (1) admitted to a participating ICU; (2) adult patients (aged 16 years or older, depending on local regulations for definition of “adults”) (3) having received invasive ventilation for at least 48 hours, and (4) obtained written informed consent from the patient or next of kin (if local legislation demand so, see below). Patients admitted for withdrawn of life sustain therapy are excluded. We foresee that no informed consent is needed for the BASIC and the FOLLOW-UP module in most countries, as data are collected as part of routine care. The EXTENDED FOLLOW–UP module, however, collects data that is not collected as part of routine care, and requires informed consent in all countries. Written informed consent will be combined for participation in the BASIC and EXTENDED module, and separately for the EXTENDED FOLLOW–UP module.
Target number of cases	Invasively ventilated patients will be screened for eligibility during a locally decided and predefined period of 120 days, depending on the preferences of the national coordinator, but always within a year after the start of the study. No formal sample size calculation is performed. We expect each center to enroll 20 to 40 patients, yielding a total of 1,200–2,400 patients if 60 centers will participate. This number seems sufficient to achieve a global picture of current practice of rehabilitation and associated clinical outcomes.
Study Period	Start of enrollment is planned for 2025; total duration of enrollment is 120 days in each center.
Data Collection Method	All data will be captured and stored in an electronic database. The study consists of 3 separate modules, with participation contingent on local capabilities. Each center must at least participate in the BASIC module.
Research Organization	**Principal Investigators & Study coordination** Denise Battaglini (Italy), MD, PhD denise.battaglini@unige.it

	Core steering committee members Denise Battaglini (Italy), MD, PhD Marcus J. Schultz (Switzerland), MD, PhD Sabrine Hemmes (Netherlands), MD, PhD Ary Serpa Neto (Australia), MD, PhD Carol L. Hodgson, PhD FACP FAHMS BAppSc (PT) Mphil PGDip (Cardio) Ricardo Kenji Nawa (Brazil), PT, PhD Rik Gosselink (Belgium), PT, PhD Gentle S. Shrestha (Nepal), MD Irene Schiavetti (Italy), PhD **Data management office** IRCCS Ospedale Policlinico San Martino, Genova, Italy University of Genoa, Genova, Italy **Research Office** Largo Rosanna Benzi, 10, Ospedale Policlinico San Martino, Genova, Italy Phone number: ┼39010 5554970 **Support by:** PRotective Ventilation Network (PROVE Network, www.provenetwork.org).
Research Consultation Service	N.A.

2. Background and significance of the study

2.1. Background

Critically ill patients often develop intensive care unit (ICU)–acquired weakness (AW), defined as clinically detectable weakness with no plausible explanation except for critical illness. Indeed, around 40% of critically ill patients developed ICU–AW [1], which is linked to increased risk of mortality and long–term morbidity [1–6]. Particularly patients under invasive ventilation rapidly waste skeletal muscle mass, contributing to ICU–AW [7–9].

Early mobilization within rehabilitation interventions is an effective measure for improving both the short– and long–term outcome of critically ill patients [10], reducing hospital stay and improving functional outcome [11–13]. Rehabilitation interventions, such as mobilization, exercise and muscle training, physical activity, respiratory physiotherapy, dysphagia training, occupational therapy, and cognitive/ pshycological support, are reported beneficial but remain underused, which may be due to limitations in resources [14,15]. Rehabilitative interventions specifically include passive interventions, such as exercise, stretching, electro muscular stimulation, continuous passive motion, and splinting, active interventions, such as training, muscle training, activities of daily living (ADL) training, out of bed mobilization with verticalization and ambulation, and cycling, and respiratory physiotherapy including patient positioning, airway clearance techniques, lung expansion exercises and devices, active cycle of breathing technique, forced expiratory technique, assisted or stimulated cough maneuvers, and insufflation–exsufflation, have a strong potential to benefit critically ill patients [16–18]. These interventions are performed by various healthcare professionals, including intensivist doctors, nurses, occupational therapists, physiotherapists, physiatrists, and others. Indeed, studies have shown improved outcome in patients undergoing these measures, highlighting the importance of rehabilitation professionals in ICUs [19–24]. Indeed, timely initiation of rehabilitation reduces time on the ventilator and prevents hospital–acquired respiratory infections and other ICU complications [25]. Last but not least, rehabilitation impacts on quality of life (QoL) and cognitive function after ICU discharge [26,27].

Benefits of these interventions have not been confirmed in some studies [28–30], questioning if we need these time–consuming and labor–intensive measures. Therefore, there is an urgent need for further investigation of rehabilitation and physiotherapy interventions that is supported by discrepancies and a dearth of evidence on real effectiveness in clinical trials [18,29,31,32]. Specifically, it is necessary to identify patient features and detailed information on the interventions (modality, duration, intensity, frequency) that allow for the specific prescription and continuation of therapies [33–35]. Standardizing clinical decision–making and educational routes, defining the physiotherapists' professional profile, and raising awareness of the advantages of treating and preventing immobility and deconditioning in critically ill adult patients are all

necessary [36,37]. No clear and univocal recommendations are available regarding timing, dose, type of interventions, safety assessment and criteria for initiation and discontinuation [36]. Insights in adverse events as was highlighted from the TEAM trial [28], is an important aspect of rehabilitation practice [38].

In this prospective, international, multicenter, observational study, named 'REhabilitation Practice and association with Outcomes in critically ill invasively ventilated patients' (REPOrt) we will capture the worldwide practice of rehabilitation, in particular modality, timing, intensity, frequency, who perform the interventions, and typical ICU outcomes to determine their clinical impact, in a worldwide, large sample of ICUs.

2.2. Importance of this study

The findings of REPOrt have the potential to improve the care for invasively ventilated patients, as it may help to identify those interventions with the largest impact, and which patients may benefit most from each measure. This study will provide a comprehensive overview of practice worldwide, also allowing geo–economic comparisons. Last but not the least, the findings of this study can be used for planning future studies.

2.3. Methods

2.3.1 Design

REPOrt is a prospective, international, multicenter, observational cohort study in critically ill invasively ventilated patients, that uses three modules in which centers can participate, contingent on local capabilities.

2.3.2 Reason for the design

Practice of rehabilitation can only be studied reliably by means of a prospective observational study. We specifically do not choose for a survey, as there is the risk of reporting bias.

2.3.3 Study period

The study is planned to start in 2025; total enrollment period will be 120 days per each center.

2.3.4 Participating sites

This study will be conducted with support of the Protective Ventilation Network (PROVE Network) (www.provenetwork.org), and in partnership with national and international ICU societies and research institutions. Potentially interested ICUs will be identified. All ICUs that take care of adult critically ill invasively ventilated patients can participate in REPOrt. If a hospital has more than one ICU, each ICU can participate for as long patients that are cared for are > 16 years of age. The Research Office will handle the list of participating locations as well as the list of primary investigators from each participating institution.

2.3.5 Inclusion and exclusion criteria

Patients are eligible for participation if:

- Admitted to a participating ICU;
- Adult patient according to local Regulations (e.g., aged >16 or >18 depending on local rules)
    - Of note, we will consistently adhere to local legislation concerning informed consent, including protocols for determining who may provide informed consent in cases where a patient is deemed incapable of doing so themselves;
- Having received invasive ventilation for at least 48 hours; and
- After written informed consent from the patient or next of kin has been obtained (depending on legislation, and only if rules demand so).
    - Of note, we foresee that no informed consent for the BASIC and EXTENDED modules is needed in many countries, as data are collected as part of routine care, with the exception of what will be collected in the EXTENDED FOLLOW–UP module [see below].

Exclusion criteria

- Withdrawing of life sustaining treatment.

2.3.6 Co–enrollment with other studies

Since this is an observational study, concomitant participation and institutional enrollment in other observation and intervention studies are acceptable.

3. Aims of the study and evaluation items

3.1. Aims

The primary aim is to describe and compare practice of rehabilitation in ICU worldwide.

Secondary aims include:

To determine the association of rehabilitation and physiotherapy with typical ICU outcomes, including:

- ICU and hospital length of stay; and
- Duration of mechanical ventilation, expressed as ventilator free days and alive at day 28 after ICU admission; and in the number of days of mechanical ventilation from intubation to extubation in survivors; and
- Functional outcome; and
- ICU and hospital mortality

To determine the association of rehabilitation and physiotherapy with quality of life and functional performance at 28-days after ICU discharge.

This study is divided into three modules, according to the different aims described above:
BASIC module – to capture basic information on rehabilitation practice worldwide, and simple ICU and hospital outcomes, including:

- Length of stay in ICU and hospital;
- Duration of ventilation and weaning;
- Airway management;
- ICU complications, and
- Death.

EXTENDED module – to capture granular data on type, timing, and duration of rehabilitative interventions, who delivers them, and safety assessment. In this module, we focus on the following rehabilitation interventions:

- Passive interventions (passive exercises, stretching, cycling, electro muscular stimulation, continuous passive motion);
- Active interventions (exercise therapy, activities of daily living training, mobilization, cycling);
- Respiratory physiotherapy (positioning, airways clearance techniques, lung expansion exercises, end-positive airway pressure devices, active cycle of breathing techniques, forced expiratory techniques, assisted or stimulated cough maneuvers, insufflation/ exsufflation, inhaled therapy); and
- Adjunctive techniques (dysphagia training, swallow screening test, cognitive/ phycological therapy).

EXTENDED FOLLOW–UP module – to capture quality of life and functional performance at 28 days after ICU discharge.

3.2. Evaluation items

The following evaluation items will be considered:

- Epidemiology, i.e., use and techniques of rehabilitation, who delivers rehabilitation interventions, practice of mechanical ventilation, mortality, length of ICU /hospital stay, complications/adverse events, general ICU care, mortality;
- Rehabilitation practices, i.e., detailed description of ventilatory support, physiotherapy, nursing practice, occupational therapy, psychological treatment, and respiratory physiotherapy; and
- Outcomes, i.e., mortality, length of stay, duration of ventilation, and quality of life and physical activity after discharge.

3.3 Definitions

Definitions can be find in the Appendix I.

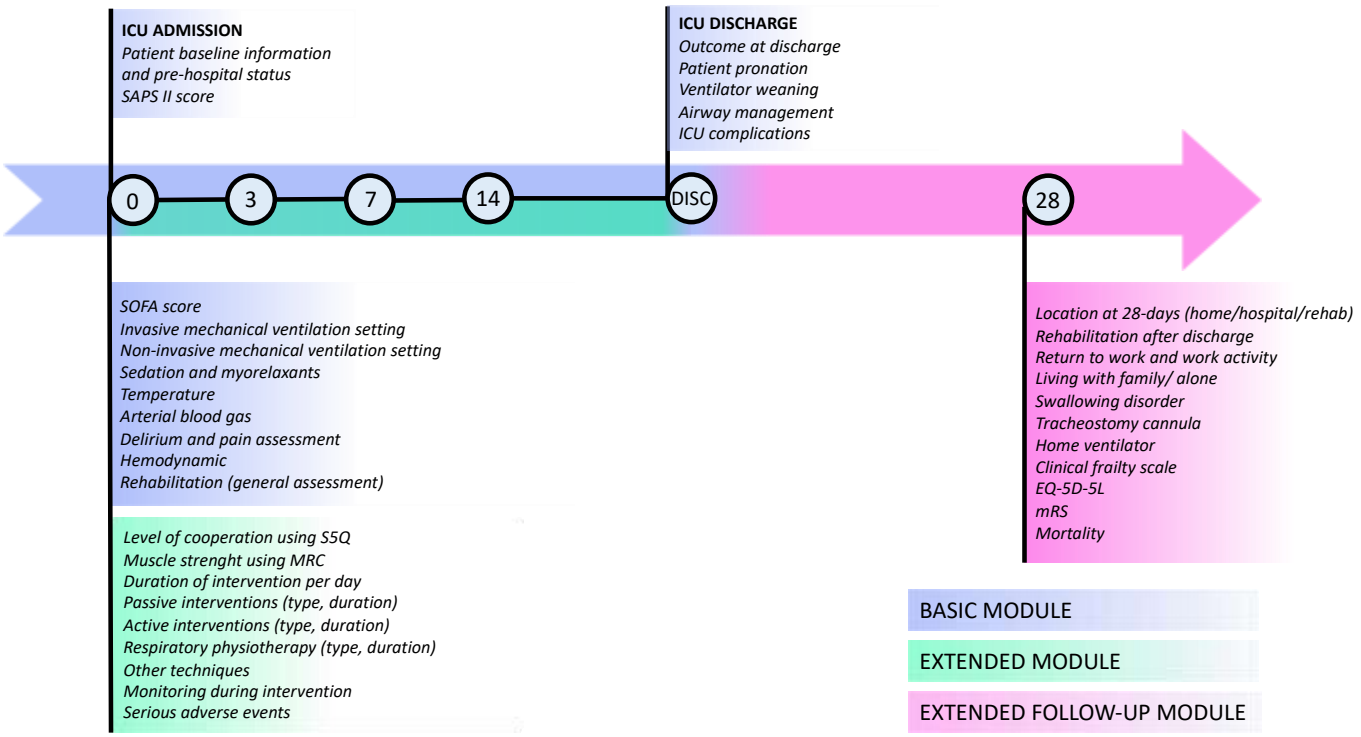
4. Data protection

Data collected in the study will be captured on electronic case report form (eCRF) developed in REDCAP Platform, using an identity code (pseudonym) of the patient from countries governed by the General Data Protection Regulation (GDPR) (i.e., European countries). After a patient's eCRF is finalized and approved by the local investigator, anonymization occurs: the identification number is removed, making it impossible to trace back to the patient.

Data obtained in the research will be placed immediately into a separate online database for people from countries not subjected to the laws.

5. Data Collection

Data collection Flow-chart (Figure 1).



5.1 BASIC MODULE [Mandatory]

General (department level) information*

*Collected during site enrollment.

Country
Number of hospital beds (number)
Number of ICU beds (number)
Hospital type
- University
- Non-university
- Private Institution
- Tertiary Hospital/ Non-Tertiary Hospital

ICU type
- General
- Post-Surgical
- Neurological
- Cardiovascular
- Other

Rehabilitation practitioners:
- Physical therapists (PT) (yes/no)

- Occupational therapists (OT) (yes/no)
- Speech and language therapists (SLT) (yes/no)
- Respiratory therapists (RT) (yes/no)
- Psychologists (yes/no)
- Physiatric doctors (yes/no)
- Dedicated nurses (yes/no)
- Other (type _____)
- None

N. of Rehabilitation practitioners:

- Physical therapists (PT) (number)
- Occupational therapists (OT) (number)
- Speech and language therapists (SLT) (number)
- Respiratory therapists (RT) (number)
- Psychologists (number)
- Physiatric doctors (number)
- Dedicated nurses (number)
- Other (type _____) (number)
- None

Weekly Frequency of Interventions:

- Every day including weekend
- Every day excluding weekend
- More than twice a week
- Twice a week
- Less than twice a week
- Never

Daily Frequency of Interventions:

- One Intervention per Day
- More than One Intervention per Day

Are there local protocols for rehabilitation in your ICU? (yes/ no)

General (patient level) information – Day 0 ICU Admission

General

- Age (years)
- Sex (male / female)
- Presumed body weight (kg)
- Body height (cm)
- Race*
- Caucasoid White (European, Euro Africa-Asian)
- Negroid (Africa, Asia, Pacific Islands)
- Mongoloid (Asia, Pacific Islands North and South)

**UNESCO Classification*

Comorbidities

- Cardiac failure (yes/ no)

- Chronic obstructive pulmonary disease (yes/ no)
- Smoking status (yes/ no)
- Liver failure (yes/ no)
- Diabetes mellitus (yes/ no)
- Immunocompromised state (yes/ no)
- Chronic kidney disease (yes/ no)
- Active cancer (yes/ no)
- Hematologic malignancy (yes/ no)
- AIDS (yes/ no)
- Chronic neurologic diseases (yes/ no)

Type of ICU admission

- Medical condition
- Emergency surgery/trauma
- Planned surgery

Main reason for ICU admission

- Infectious
- Gastrointestinal
- Neurological
- Cardiovascular
- Respiratory
- Renal
- Metabolic
- Hematological
- Psychiatric
- Polytrauma (non-neurological)
- Other, specify _____

Did the patient receive Surgery?

- Yes/ No
- Type: Neurosurgery, Cardiac Surgery, Vascular Surgery, Abdominal Surgery, Thoracic Surgery, Orthopedic Surgery, Other Surgery (Multiple Selection)

Days between hospital admission to ICU admission (number)

Clinical Frailty Scale pre-admission

- Very Fit (regular exercise)
- Fit (occasionally active)
- Managing well (often are active, like walking)
- Very mild frailty (slowed up or tired during the day, no need assistance)
- Mild frailty (evident slowing and need help with high order instrumental activities of daily living, like finances, transportation, housework)
- Moderate frailty (needing help with all outside activities, and with keeping house, frequently need help with stairs or with bathing)

- Severe frailty (completely dependent for personal care)
- Very severe frailty (completely dependent for personal care and approaching end of life)
- Terminally ill (life expectancy < 6 months)

Living Status:

- Other People
- Nursing Home
- Alone

Employment status pre-admission

- Working full time
- Working partial time
- Unoccupied
- Retired

General status and biochemistry (for SOFA and APACHE II calculation):

- Blood Urea Nitrogen (BUN) (mg/dL or mmol/L)
- Estimated Urine Output (mL/24 h) - E.g. if 1000 mL in 8 hours, then mark 3000 mL in 24 hours
- Sodium (mEq/L or mmol/L)
- Potassium (mEq/L or mmol/L)
- Glasgow Coma Scale (GCS) (from 3 to 15) – use the lowest value in the past 24 h, if the patient is currently sedated, use an estimated GCS prior to sedation.

Intended Frequency of Interventions in the patient:

- Every day included weekend
- Every day excluded weekend
- Twice daily
- More than twice a week
- Twice a week
- Less than twice a week

Compile at Day 0 (ICU Admission) – Day 3 – Day 7 – Day 14 – ICU discharge

Day (select the day)

- Day 0 (ICU Admission)
- Day 3
- Day 7
- Day 14
- ICU discharge

General status and biochemistry (first available setting of the day around 8 AM) (for SOFA and APACHE II calculation):

- Bilirubin, if available (mg/dL or μmol/L)

- Creatinine (mg/dL or μmol/L)
- Estimated Urine Output (mL/24 h) - E.g. if 1 L in 8 hours, then mark 3 L in 24 hours
- WBC (x10^3/mm^3)
- Platelets, if available (x10^3/mm^3)
- Glasgow Coma Scale (GCS) (from 3 to 15) – use the lowest value in the past 24 h, if the patient is currently sedated, use an estimated GCS prior to sedation.

First arterial blood gas of the day (first available setting of the day around 8 AM)

- FiO_2 (%)
- PaO_2 (mmHg or kPa)
- $PaCO_2$ (mmHg or kPa)
- pH
- HCO_3^- (mmol/L)
- Lactate (mg/dL or mmol/L)
- Hemoglobin (g/dL)
- SaO_2 (%)

First setting of the day (first available setting of the day around 8 AM)

- IMV (yes/no)
- Type of IMV
  - Volume Controlled
  - Pressure Controlled
  - Pressure Support
  - Volume Support
  - SIMV Pressure Mode
  - SIMV Volume Mode
  - iNTELLIVENT-ASV
  - Other (specify _____)
- Vt set (mL)
- Vt expiration (mL)
- PEEP (cm H_2O)
- Respiratory Rate set (breaths/min)
- Respiratory Rate total (breaths/min)
- Pressure Support above PEEP (cm H_2O)
- P plateau (cm H_2O)
- P peak or P max (cm H_2O)
- FiO_2 (%)
- P support above PEEP (if NIMV)
- HFOT (Flow, L/min)
- Patient pronation (yes/no)

Sedation and muscle relaxants (first available setting of the day around 8 AM)

- Propofol (yes/ no)

- Midazolam (yes/ no)
- Ketamine (yes/ no)
- Volatile anesthetic agent (yes/ no)
- Other (yes/ no) (type_____)
- NMBAs (yes/ no)

Medications

- Aerosol therapy (yes/no)
- Corticosteroids (yes/no)
- Antibiotics (yes/no)
- Platelets transfusion (yes/no)
- Red Blood Cells transfusion (yes/no)

Other parameters

- Temperature (°C)
- SpO_2 (%)

Delirium and Pain (first available setting of the day around 8 AM)

- Delirium, if scored (yes/ no)
- Pain scale from 0 to 10, if scored
- Scale used for Sedation (e.g., RASS, other, specify _____)
- RASS (if scored)
    - Combative +4
    - Very agitated +3
    - Agitated +2
    - Restless +1
    - Alert and Calm 0
    - Drowsy -1
    - Light sedation -2
    - Moderate sedation -3
    - Deep sedation -4
    - Unrousable sedation -5

Hemodynamic (first available setting of the day around 8 AM)

- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Heart Rate (beats/min)
- Vasoactive agents / Inotropes (yes/ no)

Rehabilitation practice:

- Rehabilitation : yes/ no
    - If no, reason for not starting Rehabilitation
        - Deep sedation/ curarization
        - Lack of rehabilitation assistants
        - Lack of material

- Unstable hemodynamic
- Patient refuse
- Agitation/ not collaborative
- Criteria to start not achieved (hypotension, FiO_2>60%, PaO_2/FiO_2<200, RR>30 bpm)

- Aim of Intervention:
  - Prophylactic/ Curative
  - Passive interventions (yes/no)
  - Active interventions (yes/ no)
  - Transfer and walking (yes/no)
  - Occupational Therapy (yes/no)
  - SLT (yes/no)
  - Psychological support (yes/no)
  - Respiratory physiotherapy (yes/ no)
- Monitoring during Rehabilitation
  - Oxygen therapy during rahabilitation (yes/no)
  - MAP monitoring during rahabilitation (yes/no)
  - SpO_2 monitoring during rahabilitation (yes/no)
  - ECG monitoring during rahabilitation (yes/no)

Serious adverse events (yes/no)

- Type of event, during rehabilitation:
  - Falls out of the bed
  - Accidental removal of lines and catheters
  - Arrhythmias (tachycardia – bradycardia)
  - Cardiac arrest
  - Noradrenaline/adrenaline infusion rate has increased by more than 25% during the rehabilitation intervention compared to the start
  - Need for increasing FiO_2 more than 20% or any increase of PEEP
  - Major desaturation (SpO_2 < 80% for more than 1 minutes)
  - Unplanned extubation
- Type of event, during respiratory physiotherapy:
  - Falls out of the bed
  - Accidental removal of lines and catheters
  - Arrhythmias (tachycardia – bradycardia)
  - Cardiac arrest
  - Noradrenaline/adrenaline infusion rate has increased by more than 25% during the rehabilitation intervention compared to the start
  - Need for increasing FiO_2 more than 20% or any increase of PEEP
  - Major desaturation (SpO_2 < 80% for more than 1 minutes)
  - Unplanned extubation

ICU Outcomes – ICU Discharge

ICU outcomes
- Days from ICU discharge to hospital discharge (days)
- Days from ICU admission to ICU discharge (days)
- Days from hospital admission to ICU admission
- Death in ICU (yes/no)

If yes, days from ICU admission to ICU death/ death date in ICU (days)
- Death in hospital (yes/no)

If yes, days from ICU discharge to hospital death/ date of death (hospital/ ICU)

Ventilator Weaning
- Day of First Spontaneous Breathing Trial (SBT) (days after start MV)
- Total invasive mechanical ventilation days (days from intubation to discontinuation)
- Type (T piece/ P support/ other)
- Reintubation after extubation (yes/ no)
  - After how many days? (_____)
  - Need re-intubation more than once? (yes/no)

Airway Management
- Tracheal tube (days from in/ out)
- Tracheostomy (days from in/ out)
- Tracheostomy type
  - Surgical
  - Percutaneous
  - Hybrid
- Reason for Tracheostomy
  - Weaning failure/ difficult weaning
  - Preventive
  - Swallowing/ dysphagia disorders
  - Other, specify (_____)
- Decannulation (yes/ no)
- Other professional than physicians managing airway (yes/no)

ICU complications
- Neurological (yes/no)
  - Cerebrovascular complications (yes/no)
  - Hemorrhagic intracranial bleeding (yes/no)
  - Coma unknown origin (yes/no)
- Infective
  - Blood stream infection (yes/no)
  - Suspected ventilator-associated pneumonia (VAP) (yes/no)

- Suspected healthcare associated pneumonia non-VAP (yes/no)
- Suspected VAT (yes/no)

- Respiratory
  - ARDS (yes/no)
  - Acute hypoxemic respiratory failure (non-ARDS) (yes/no)
  - Acute hypercapnic respiratory failure (yes/no)
- Pulmonary embolism (yes/no/NA)
- Deep venous thrombosis (yes/no/NA)
- Cardiovascular complications (yes/no)
- Pressure ulcers (yes/no)

5.2 EXTENDED MODULE [Optional]

Patient Assessment
Level of cooperation using S5Q:

- Open and close your eyes
- Look at me
- Open your mouth and put out your tongue
- Nod your head
- Raise your eyebrows after I have counted to five

Muscle strength using MRC (Grade 0 to 5) - (Appendix II)
Muscle strength using handgrip strength (yes/ no)
Total duration of Rehabilitation per day: _____(minutes)
Use of assistance devices (yes/ no)
If yes, specify:

- Lifter
- Tilt table
- Transfering devices
- Walker
- Other (_____)

Passive interventions (yes/no)
If yes, specify the interventions:

- Passive exercise (yes/no)
- Stretching (yes/no)
- Passive cycling (yes/no)
- Electro muscular stimulation (yes/no)
- Continuous passive motion (yes/no)
- Splinting (yes/no)
- Other, specify (_____)

Duration of Passive interventions per day: _____(minutes)

Active interventions (yes/no)
If yes, specify the interventions:
- Active exercise therapy (yes/no)
- Activities of daily living (ADL) training (yes/no)
- Out of bed mobilization (yes/ no)
  If yes, specify:
  - Active bed exercises such as rolling, bridging, active assisted exercises or cycle ergometry (yes/no)
  - Passively moved to the chair (yes/no)
  - Sitting at the edge of bed/ sitting out of bed with some control of the trunk (yes/no)
  - Verticalization/ maintaining standing position (with and without arm support/assistance) (yes/no)
  - Transferring from the bed to chair (yes/no)
  - Marching on the spot at the bedside by lifting the feet alternately (yes/no)
  - Walking with 2 people assisting for 5 meters (yes/no)
  - Walking with 1 person assisting for 5 meters (yes/no)
  - Walking with a gait aid for 5 meters (yes/no)
  - Walking independently without a gait aid for 5 meters (yes/no)
  - No active movement (yes/no)
- Other, specify (_____)

Duration of Active interventions per day: _____(minutes)
Respiratory Physiotherapy (yes/ no)
If yes, specify the interventions:
- Patient positioning (yes/no)
- Airways clearance techniques (yes/no)
- Lung expansion exercises (yes/no)
- EPAP/ PEP devices (yes/no)
- Active cycle of breathing technique (yes/no)
- Forced expiratory technique (yes/no)
- Assisted or stimulated cough maneuvers (yes/no)
- Insufflation/ exsufflation (yes/no)
- Inspiratory muscle training (yes/no)
- Manual hyperinflation (yes/no)
- Ventilator hyperinflation (yes/no)
- Other, specify (_____)

Duration of Respiratory Physiotherapy interventions per day: _____(minutes)
Other techniques (yes/ no)
If yes, specify the techniques:
- Dysphagia training (yes/no)

- Non-physicians managing Airway:
  - Tracheal tube/ tracheostomy (yes/no)
  - Decannulation (yes/no)
- Swallow screening test (yes/no)
- Psychological/ cognitive therapy (yes/no)
- Other, specify (_____)

5.3 EXTENDED FOLLOW-UP MODULE [Optional]

Long-term Outcomes

Phone interview at 28 days after ICU discharge

Death (yes/no)
If yes, death (days from Hospital discharge to death)
Current location:

- Home
- Rehabilitation center
- Still in Hospital
- Other Hospital

Rehabilitation after discharge (yes/no)
Return to work (yes/no)
Employment status

- Working full time
- Working partial time
- Unoccupied
- Retired

Living with family/ alone (select)
Swallowing problems (yes/no)
Speech problems (yes/no)
Tracheostomy cannula (yes/no)
Home ventilator (yes/no)
Clinical Frailty scale (Appendix III)
EQ-5D-5L (Appendix IV)
Modified Rankin Scale (mRS) – (Appendix V)

6. Statistical analysis

6.1 Sample size

Invasively ventilated patients will be screened for eligibility during a predefined period of 120 days will be enrolled, timing of which depending on the preferences of the national coordinator, but within a year after start of the study. No formal sample size calculation is performed, but we expect centers to enroll 20 to 40 patients, yielding a total of 1200–2400 patients if we include 60 centers for the module A). This number is sufficient to achieve a global picture of current practice around rehabilitation practice and associated clinical outcomes.
All data will be captured and stored in an electronic database.

6.2 Statistical analysis

Continuous variables will be reported as mean ± standard deviation (SD) or median with interquartile range (IQR), while categorical variables will be presented as numbers with percentages.

Standardized mean differences between two groups (presence or absence of physiotherapy) at baseline will be assessed both before and after applying an inverse probability of treatment weighting (IPTW) based on the propensity score. The propensity score will be calculated through a logistic regression model, with the treatment group as the dependent variable and a selected set of baseline variables as the independent explanatory covariates [39,40].

Differences between groups in binary outcomes will be evaluated using weighted logistic regression models, while differences in continuous outcomes will be assessed using a weighted linear regression model (or Poisson regression for counting variables).

Time to events will be analysed through weighted Kaplan-Meier survival analysis, and group comparisons will be made using the log-rank test.
The threshold for statistical significance will be set at < 0.05.
Statistical analysis will be supported in collaboration with the Department of Health Science (DISSAL), University of Genoa, Italy.

7. Ethical considerations and Informed Consent

The REPOrt study will be conducted according to the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subjects Act (WMO) [41]. Data management, monitoring and reporting of the study will be performed in accordance with the ICH-GCP Guidelines.

Approval for conducting REPOrt in each participating center will be obtained by the local medical ethics committees. Since this study will be conducted as a multi-center study, the chief investigator at each participating site must obtain the ethical approval by the local Ethics Committee to conduct this study according to local regulations.

We foresee that no informed consent is needed for the BASIC and the FOLLOW-UP module in most countries, as data are collected as part of routine care. The EXTENDED FOLLOW–UP module, however, collects data that is not collected as part of routine care, and requires informed consent in all countries. Written informed consent will be combined for participation in the BASIC and EXTENDED module, and separately for the EXTENDED FOLLOW–UP module.

Of note, we will consistently adhere to local legislation concerning informed consent, including protocols for determining who may provide informed consent in cases where a patient is deemed incapable of doing so themselves

8. Expected Benefits and Burden of Participation

Because evidence-based ICU treatment delivered within the scope of routine medical care is derived from the medical records of each participating hospital, this study will be done at no burden to patients and their families.

9. Rules for Authorship

For publications we will follow the guidelines as set out by the PROVE Network (https://www.provenetwork.org/information-for-investigators).

10. Secondary analyses

10.1 Preplanned secondary analyses

Preplanned secondary analyses include:

- Impact of rehabilitation on respiratory complications
- Impact of rehabilitation on tracheostomy and weaning outcomes
- Impact of sedation and delirium on rehabilitation practice and outcomes
- Practice of rehabilitation in neurocritically ill patients
- Impact of rehabilitation on invasive and non-invasive mechanical ventilation practice
- Cost-effectiveness analysis

11. Appendix

Appendix I – Definitions

Ventilator-free days is the timing between the first ventilation day and the last ventilation day, considering patients who are not ventilated anymore, either with tracheal tube or tracheostomy.

Extubation success, defined as a need for reintubation within hours or days after planned extubation [42].

Ventilator-associated pneumonia (VAP), defined as lung infection that develops after 48 hours of mechanical ventilation [43].

Ventilator-associated tracheobronchitis (VAT), defined as tracheobronchitis in a patient on a ventilator [43].

Deep venous thrombosis is defined as a blood clot (thrombus) formed in one or more of the deep veins in the body.

Cardiovascular complications are defined as any of the following: coronary artery disease, peripheral arterial disease, aortic disease.

Acute Respiratory Distress Syndrome (ARDS), defined according to the 2024 New Global definition as: (1) presence of acute hypoxemic respiratory failure, (2) onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms; (3) bilateral opacities on chest x-ray or computed tomography (CT) or lung ultrasound not fully explained by effusions, lobar or lung collapse, or nodules; and (4) cardiac failure not the primary cause of acute respiratory failure . The following categories will apply: (1) Non-intubated ARDS: $PaO_2/FiO_2 \leqslant 300$ mmHg or $SpO_2/FiO_2 \leqslant 315$ mmHg (if $SpO_2 \leqslant 97\%$) on high flow nasal oxygen with flow $\geqslant 30$ L/min or non-invasive mechanical ventilation (NIV)/ continuous positive airway pressure (CPAP) with at least 5 cmH_2O PEEP; (2) Intubated ARDS: Mild – $200 < PaO_2/FiO_2 \geqslant 300$ mmHg or $235 < SpO_2/FiO_2$ (if $SpO_2 \leqslant 97\%$); Moderate – $100 < PaO_2/FiO_2 \leqslant 200$ mmHg or $148 < SpO_2/FiO_2 \leqslant 235$ mmHg (if $SpO_2 \leqslant 97\%$); Severe – $PaO_2/FiO_2 \leqslant 100$ mmHg or $\leqslant 200$ mmHg or $SpO_2/FiO_2 \leqslant 148$ mmHg (if $SpO_2 \leqslant 97\%$). Modified definition in Resource-Limited Settings: $SpO_2/FiO_2 \leqslant 315$ (if $SpO_2 \leqslant 97\%$) not requiring PEEP or minimum flow rate of oxygen [44].

Acute hypoxemic respiratory failure (non-ARDS), defined as $PaO_2 < 60$ mmHg [45].

Hypercapnic respiratory failure is defined as $PaCO_2$ >45 mmHg with a pH < 7.35 due to respiratory pump failure and/or increased CO_2 production [45].

Deep venous thrombosis is defined as a blood clot (thrombus) formed in one or more of the deep veins in the body [46].

Cardiovascular complications are defined as any of the following: coronary artery disease, peripheral arterial disease, aortic disease [47].

Number of days that the patients are alive and out of the hospital at 28-days after initiation of physiotherapy and rehabilitative interventions.

Quality of Life (QoL) will be evaluated with EQ-5D-5L score, physical activity, and cognitive outcome at 28-days [48].

Safety assessment, defined as an event immediately related to rehabilitation/ physiotherapy practice:

- Falls out of the bed
- Accidental removal of lines and catheters
- Arrhythmias (tachycardia – bradycardia)
- Cardiac arrest
- Noradrenaline/adrenaline infusion rate has increased by more than 25% during the rehabilitation intervention compared to the start
- Need for increasing FiO_2 more than 20% or any increase of PEEP
- Major desaturation (SpO_2 < 80% for more than 1 minutes)
- Unplanned extubation

Appendix II – Muscle strength using MRC scale

Muscle strength using Muscle Power Scale (MRC) (Grade 0 to 5):

- Grade 5: Normal, movement against gravity and great/large resistance of the examiner
- Grade 4: Movement against gravity and moderate resistance of the examiner
- Grade 3: Movement against gravity over (almost) the full range of motion
- Grade 2: Movement of the limb with elimination of gravity
- Grade 1: Visible or palpable contraction without movement of the limb
- Grade 0: No visible or palpable contraction

- Shoulder abductors Left Right
- Elbow flexors Left Right

- Wrist extensors Left Right
- Hip flexors Left Right
- Knee extensors Left Right
- Foot dorsiflexors Left Right

Appendix III – Clinical Frailty Scale

- Very Fit (regular exercise)
- Fit (occasionally active)
- Managing well (often are active, like walking)
- Very mild frailty (slowed up or tired during the day, no need assistance)
- Mild frailty (evident slowing and need help with high order instrumental activities of daily living, like finances, transportation, housework)
- Moderate frailty (needing help with all outside activities, and with keeping house, frequently need help with stairs or with bathing)
- Severe frailty (completely dependent for personal care)
- Very severe frailty (completely dependent for personal care and approaching end of life)
- Terminally ill (life expectancy < 6 months)

Appendix IV - EQ-5D-5L Quality of Life Questionnaire

We would like to know how bad your health is today. The scale is numbered from 0 to 100, where 100 is the best health you can imagine, and 0 the worst health you can imagine. Mark an X on the scale to indicate how your health is today.
Please write the number (from 0 to 100) you marked on the scale here (_____).

- Mobility
    - I have no problems in walking about
    - I have slight problems in walking about
    - I have moderate problems in walking about
    - I have severe problems in walking about
    - I am unable to walk about
- Self-Care
    - I have no problems washing or dressing myself
    - I have slight problems washing or dressing myself
    - I have moderate problems washing or dressing myself
    - I have severe problems washing or dressing myself
    - I am unable to wash or dress myself
- Usual Activities (e.g. work, study, housework, family or leisure activities)
    - I have no problems doing my usual activities

    - I have slight problems doing my usual activities
    - I have moderate problems doing my usual activities
    - I have severe problems doing my usual activities
    - I am unable to do my usual activities
- Pain/ Discomfort
    - I have no pain or discomfort
    - I have slight pain or discomfort
    - I have moderate pain or discomfort
    - I have severe pain or discomfort
    - I have extreme pain or discomfort
- Anxiety / Depression
    - I am not anxious or depressed
    - I am slightly anxious or depressed
    - I am moderately anxious or depressed
    - I am severely anxious or depressed
    - I am extremely anxious or depressed

Appendix V - Modified Rankin Scale (mRS)

Modified Rankin Scale:

- 0: No symptoms at all
- 1: No significant disability despite symptoms; able to carry out all usual duties and activities
- 2: Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
- 3: Moderate disability; requiring some help, but able to walk without assistance
- 4: Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
- 5: Severe disability; bedridden, incontinent and requiring constant nursing care and attention
- 6: Dead

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