Early Mobilization of ICU-Admitted Adult Patients: Overview of Systematic Reviews Protocol

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# Introduction

One of the objectives of, among others, of treating critically ill patients is to prevent and considerably reduce complications related to intensive care unit (ICU) hospitalization.

Prolonged immobility is related to musculoskeletal, pulmonary, cardiovascular and endocrine complications (1). Moreover, immobility is one of the risk factors of Post – Intensive Care Syndrome (PICS) that has serious physical, social and financial consequences (2). A part of this syndrome and, also, an important complication of immobility is the Intensive Care Unit – Acquired Weakness (ICU-AW), which is serious neuromuscular dysfunction associated with considerable short- and long-term sequelae. (3)

Early mobilization (EM) of mechanically ventilated critically ill patients is described as early (within the first 3-5 days) application of physical therapy techniques including transcutaneous electrical muscle stimulation and cycle ergometry along with active mobilization (4) whenever the patient’s clinical condition safety permits it. Early mobilization is considered as one of the parameters that can reduce the incidence of ICU-AW, while several guidelines support its implementation in the ICU setting. (5–7)

The term early mobilization covers a wide range of interventions that vary from passive to walking activities. In addition, EM studies related to early mobilization analyze different mobilization protocols, and each ICU implements each own routine mobilization protocol according to the ICU characteristics and settings (8). Additionally, EM is part of a bundle of measures aimed to manage pain, delirium, sedation, sleep disruption and family engagement and, finally, to improve the ICU outcomes. (9,10)

In several studies published on EM, it is generally concluded that early mobilization can reduce the ICU length of stay (LOS), the duration of mechanical ventilation (MV), the incidence of ICU-AW, as well as the cognitive impairment on ICU discharge. (11–13)

However, there are still questions to be answered, before firm conclusions are reached. Recently, a large, randomized control trial, published in New England Journal of Medicine, analyzed 750 patients in invasive mechanical ventilation compared patients in increased early mobilization [ICU mobility scale 3 (sitting at the edge of the bed) or higher] to those under usual care (mobilization protocol provided in each ICU) (14). No statistically significant difference was found between the two groups in the primary outcomes (the median number of days that patients were alive and out of the hospital), as well as, in secondary outcomes (ventilation free days, ICU free days and death at day 180). In addition, they reported that 9,2% in the mobilization group presented adverse events compared to the usual care group 4,1% (p=0.005). The results of this large, randomized trial question the beneficial effect of early mobilization in the ICU patients, at least on certain outcomes. It also highlights that trial results depend on the definitions of the comparators, in our case the definition of early mobility and usual care, as well as on the patient characteristics and treatment. (15)

To address these issues, we will conduct an overview of meta-analyses of randomized control and observational studies that treat early mobilization in ICU patients. We will evaluate the existing evidence on the impact of early mobilization on ICU-AW incidence, on ICU and hospital length of stay, and on mortality and quality of life. We will also estimate the quality of evidence and the potential influence of various early mobilization and usual care protocols on treatment effects. Finally, we will assess the potential biases and will record the adverse events that were reported in the included studies.

# Methods

## Study Design

This protocol showcases the early mobilization practices we will examine for adult patients admitted to the ICU. We will use the PICO formation for our study design and the result will be given based on each systematic review (SR) and their specific treatment methods for the ICU-admitted patients. There will be no exceptions for the study designs of the studies we will acquire for our research, meaning that both RCTs and non-RCTs will be considered eligible for our work.

We will compare adult critically ill patients hospitalized in ICU, for more than 48 hours, that will receive either an early mobilization protocol (in its various forms that may include passive or active exercises or both) or usual care that corresponds to the standard practice of each ICU.

There will be a specific search strategy for the concentration of the systematic reviews with meta-analyses and the appropriate evaluation of their designs to clarify their compatibility with our initial plans. The medical databases we will use for our research will be MEDLINE via PubMed, Epistemonikos, Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Library and CINAHL. This reporting of this study will be guided by the standards of the Preferred Reporting Items for Overviews of Reviews of Healthcare Interventions (PRIOR).

The objective of this overview is to summarize systematic reviews with meta-analyses that assess the efficacy and safety of early mobilization in ICU patients, which will meet the following criteria, and the early mobilization must be the primary intervention for the patients. The control group shouldn’t be receiving early mobilization treatment, as it would disrupt the pattern of the protocol.

## Population

**Inclusion criteria**: We will include systematic reviews with meta-analyses of studies that refer to the early mobilization (early rehabilitation or physical activity) of adult patients (≥18 years old) hospitalized in an Intensive Care Unit, either in Medical ICU (MICU), or Surgical ICU (SICU), or Trauma and Burn ICU (TBICU), and were in mechanical ventilation for more than 48 hours.

**Exclusion criteria**: Systematic reviews that examine the neurosurgical patients, stroke patients, brain and spinal injury patients, as well as cardiac surgery patients will be excluded. Additionally, we will exclude meta-analyses that focus on Post ICU discharge mobilization and papers whose control groups do not align with the list of outcomes we are planning to examine in this study. We will also exclude studies of chest physiotherapy only, narrative reviews, conference abstracts, expert opinions and guidelines.

## Interventions

## 

**Early Mobilization (Early Physical Activity)**

There is no consensus on EM definition. Early mobilization of critically ill patients was described in 2013 as “the intensification and early application (within the first 2 to 5 days of critical illness) of physical therapy, active mobilization of patients requiring mechanical ventilation and the use of novel techniques such as cycle ergometry and transcutaneous electrical muscle stimulation (TEMS)” (4). Many mobilization protocols include passive and active activities with differences regarding the intensive mobilization and the patients target group (5). EM is also a part of ABCDEF bundle that can be implemented in Intensive Care Unit patients and aims to improve clinical outcome of critically ill patients. (16,17)

The first step of EM usually revolves around passive movement and exercises while the patient is lying in his bed, and the rehabilitation process continues with active mobilization (physical activity), with the following being a part of it:

* Passive mobilization: Neuromuscular Electrical Stimulation (NMES), Tilt Table Therapy, Manual passive joints movement of upper and lower limbs, passive cycling
* Active mobilization: Sitting at the edge of the bed, active cycling, transferring from the bed to the chair (and vice versa), active side-to-side turning, walking
* ABCDEF Bundle

There are also several tests to evaluate the progress and the physical function of patients during his stay at the ICU, or the hospital, including the

* 6-Minute Walking Test
* Barthel Index Score
* Medical Research Council Score (MRC)
* Physical Function in ICU Score (PFIT)
* SF-36 Score
* SF-36 Mental Health Score
* ICU Mobility Scale (IMS)
* Functional Independence Measure Score (FIM)
* Surgical Optimization Mobilization Score (SOMS)
* Dominant-Hand Handgrip Dynamometry Score (if mentioned)

Overall, EM usually requires the combination of both passive and active mobilization, and we will consider every one of these methods for our study, as well as bundles that include one or more of the early mobilization treatments we mentioned above.

## Comparator

The standard care (not early mobilization techniques) provided to critically ill adults admitted to the ICU. There are multiple variations for the usual care these patients receive, and this could be influenced by the experience of the doctors and the nursing staff of the hospital/clinic. Although the usual or standard care could be different for each study, we will consider the description for each case (if there is one) and group them according to their features. Our goal is a meticulous inquisition, and the comparator is crucial as a measurement method for the overall efficacy of early mobilization as a (possibly) better treatment for the mechanically ventilated patients in the ICU sector.

## Primary Outcomes

**1. ICU-Acquired Weakness**

The muscle weakness that occurs from the continuous immobilization in the ICU sector after a patient’s hospital discharge that may attribute to their future quality of life. The gold standard for diagnosis is the Medical Research Council (MRC) (sum score of less than 48/60 or mean MRC score of 4 in all testable muscle groups) and the dominant-hand handgrip dynamometry scores (less than 11 kg (interquartile range (IQR) 10-40) in males and less than 7 kg (IQR 0-7.3) in females. (18)

**2. ICU Length of Stay**

The average number of days a patient stays at the ICU.

**3. Hospital Length of Stay**

The average number of days a patient stays at the hospital prior to his discharge.

## Secondary Outcome

**1. ICU Mortality**

The number of ICU patients that passed away during the study.

**2. ICU Morbidity**

The health status of ICU patients.

**3. Mechanical Ventilation**

The duration (days) of mechanical ventilation for the patients admitted in the ICU.

**4. Quality of Life**

The quality of life after the patient’s hospital discharge, described by the patients.

**5. Delirium**

The delirium events from the lengthy stay at the ICU.

**6. Adverse Events**

Adverse events will be recorded as described by the authors.

Table 1: Inclusion and Exclusion Criteria

|  |  |  |
| --- | --- | --- |
|  | **Inclusion Criteria** | **Exclusion Criteria** |
| **Participants** | Adults admitted in the ICU | Neurosurgery  Stroke Events  Brain Injury  Spinal Cord Injury  Cardiac Surgery  Patients <18 years old |
| **Interventions** | (Very) Early Mobilization (Passive & Active)  Early Physical Activity  Out-of-bed Mobilization  Neuromuscular Electrical Stimulation  ABCDEF Bundle  Cycling  Tilt Table Therapy  Manual passive joints movement of upper and lower limbs  Passive Cycling  Active Cycling  Sitting at the edge of the bed  Transferring from the bed to the chair (and vice versa)  Active side-to-side turning  Walking | Rehabilitation outside the ICU  Ambulation |
| **Comparators** | Usual (ICU) Care  Standard Care  Conventional Physical Therapy  Standard/Late Mobilization | Rehabilitation outside the ICU |
| **Outcomes** | | |
| **Primary** | ICU-Acquired Weakness  Hospital Length of Stay  ICU Length of Stay |  |
| **Secondary** | ICU Mortality  ICU Morbidity  Duration of MV  Weaning from MV  Quality of Life  Delirium |  |
| **Study Design** | Systematic Review & Meta Analysis (with potential network meta-analyses) | Non-Systematic Reviews  Systematic Reviews with 0 Studies |

# Search Strategy/Algorithm

The search strategy will include the criteria from Table 1 regarding the systematic reviews and meta-analysis papers we will need for the early mobilization of ICU-admitted adult patients and the overall rehabilitation process leading to their discharge.

Medical subject heading (MeSH) terms and the appropriate free-text keywords for the MEDLINE via PUBMED database searching will include the following:

("meta-analysis as topic"[MESH:NOEXP] OR Meta-Analysis[PT] OR "network meta-analysis"[mesh:noexp] OR "indirect comparison"[TIAB:~1] OR meta analyses[TIAB] OR meta analysis[TIAB] OR meta analytic[TIAB] OR meta analytical[TIAB] OR meta analytics[TIAB] OR meta analyze[TIAB] OR meta analyzed[TIAB] OR metaanalyses[TIAB] OR metaanalysis[TIAB] OR metaanalytic[TIAB] OR metaanalyze[TIAB] OR metaanalyzed[TIAB] OR "network comparison"[TIAB:~1] OR "network meta analyses"[TIAB] OR "network meta analysis"[TIAB] OR "network metaanalyses"[TIAB] OR "network metaanalysis"[TIAB] OR (systematic[tiab] AND (meta regression[TIAB] OR metaregression[TIAB])))

We will work accordingly for the Epistemonikos database for studies that meet our criteria from Table 1 with the following query:

(title:((title:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness) OR abstract:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness)) AND (title:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy) OR abstract:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy)) AND (title:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic) OR abstract:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic))) OR abstract:((title:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness) OR abstract:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness)) AND (title:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy) OR abstract:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy)) AND (title:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic) OR abstract:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic)))) 1) (title:((title:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness) OR abstract:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness)) AND (title:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy) OR abstract:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy)) AND (title:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic) OR abstract:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic))) OR abstract:((title:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness) OR abstract:(critical care OR intensive care OR critical\* ill\* OR mechanical ventilation OR delirium OR acquired weakness)) AND (title:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy) OR abstract:(mobilisation OR mobilization OR mobility OR rehabilitation OR physiotherapy OR physical therapy)) AND (title:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic) OR abstract:(meta-analysis OR metaanalysis OR systematic OR network meta-analysis OR comparison OR systematic))))

We will also search at the CINAHL (Cumulative Index of Nursing and Allied Health Literature) database for studies that meet our criteria from Table 1 with the following query:

(TI/AB (mobilisation OR mobilization OR mobility OR functional mobility OR physiotherapy OR rehabilitation) ) AND TI/AB (critical care OR intensive care OR critical\* ill\* OR invasive mechanical ventilation OR non invasive mechanical ventilation OR intensive care unit acquired weakness OR ICUAW OR delirium ))

and

MW meta-analysis OR PT Meta-Analysis OR MW network meta-analysis OR ( TI/AB (indirect comparison OR meta analyses OR meta analysis OR meta analytic OR meta analytical OR meta analytics OR meta analyze OR meta analyzed OR metaanalyses OR metaanalysis OR metaanalytic OR metaanalyze OR metaanalyzed OR network comparison OR network meta analyses OR network meta analysis OR network metaanalyses OR network metaanalysis ) OR ( TI/AB (systematic AND (meta regression OR metaregression))) )

Finally, we will search at the Cochrane Central Register of Controlled Trials (CENTRAL) database for studies that meet our criteria from Tabe 1 with the following query:

#1 (Intensive care:ab or critical care:ab) or critical\* ill\*:ab or mechanical ventilat\*:ab or acquired weakness or delirium

#2 mobilisation:ab or mobilization:ab or mobility:ab or rehabilitation:ab or physiotherapy

#3 early mobili\*:ab or late mobili\*:ab ΟR early intervention

#4 meta-analysis:ab OR metaanalysis ΟR network:ab OR Cochrane review:ab or review

#5 (#1) AND ( # 2) AND (#3) AND (#4)

Two researchers will independently search the databases for relevant systematic reviews. Any discrepancies will be resolved by discussion with a third investigator.

# Study Selection

Two reviewers will independently screen the retrieved records, review full-text articles, and verify the inclusion criteria. Initially, the title and abstract of each citation will be evaluated, and subsequently, potentially eligible articles will be chosen for a detailed examination of the full text.

# Data Extraction

Data will be collected using standardized extraction templates in Excel to maintain consistency in information and evaluation for each eligible study. A member of the review team will gather the relevant data, which will then be verified for accuracy by a senior team member. If any information is missing regarding methods, outcome data is incomplete, or discrepancies arise (e.g. when data from the same primary study is reported differently across systematic reviews), an effort will be made to contact the corresponding authors. The following data items will be extracted: first author, journal, year of publication, funding, conflict of interest, number of included studies, number of participants, protocol availability, intervention group, control group, and outcomes.

# Data Synthesis & Analysis

A detailed table will be provided to summarize the findings extracted from the eligible systematic reviews. The table will include key characteristics of each eligible study, such as interventions, summarized outcomes according to the different techniques that could be used for the early mobilization process of the ICU-admitted patients, quality assessments, and major conclusions. Additionally, we will create a summary table for the effect estimates of every outcome and accompany it with a meta-analysis visualization to show the overall effect for each outcome in our study, alongside the appropriate metrics for the heterogeneity, the confidence interval and the p-value for the potential subgroup comparisons. Early mobilization for the patients’ health status will be assessed at different timepoints described in the pertinent studies:

* during their ICU stay
* after their ICU departure
* during their hospital stay
* after their hospital discharge
* several days (or months) after their hospital discharge

In the case of various scores or tests regarding the mobility status of the patients, we will perform a qualitative analysis for the overall effectiveness of the early mobilization techniques. Additionally, we will pay attention to the circumstances of the mobilization process and the correspondence from the patients, in terms of their physical and mental health, as we appreciate the mental issues a person could come across (delirium, etc.) if he/she remains stationary during their ICU admission. Additionally, we will analyze separately the potential bundles (ABCDEF, etc.) that we may come across and include in our paper, and their evaluation will be at a different group, due to the nature of a multidimensional treatment procedure and its effect on the patients.

Although there are multiple levels of early mobilization treatment, we will focus on the total effectiveness of the procedure for the patients of our study. There will be a distinction between the control and intervention groups, but there will also be a distinction between the intervention groups, based on the treatment level the patients received on each occasion.

# Discussion

This protocol describes the approach for reviewing systematic reviews to evaluate the effects of early mobilization on adult patients in the intensive care unit (ICU). It emphasizes the importance of addressing ICU-acquired weakness (ICUAW), the length of stay (LOS) in the ICU and hospital, and other outcomes such as ICU mortality, ICU morbidity (health-functional status), quality of life (QoL), and ICU complications or adverse events, reflecting the increasing focus on interventions that enhance critical care results. Early mobilization has been recognized as a beneficial strategy to mitigate the harmful consequences of extended immobilization, which can lead to ICU-AW, functional descent, and long-lasting reductions in quality of life (19,20). However, the different clinical practices by healthcare professionals, the various patient demographics, and the quality of methodologies across various studies highlight the need for a thorough synthesis of the available evidence (6). This overview aims to consolidate findings from systematic reviews, clarify the overall evidence, identify research gaps, and provide support for clinical decision-making.

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