Australian Clinical Guideline for Physical Rehabilitation and Mobilisation in Adult Intensive Care Units

Technical Report

Monash University

Australian and New Zealand Intensive Care Research Centre (ANZIC-RC)

Table of Contents

1 Guideline Methodology 3
1.1 Identifying Scope and Systematic Guideline Review 3
1.2 Key Clinical Question 6
1.3 Systematic Searching of Evidence 6
1.3.1 Inclusion and Exclusion Criteria 8
1.3.2 Study Selection 8
1.3.3 Quality Assessment and Data Extraction 9
1.4 Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) 9
1.4.1 Evidence to Decision (EtD) Framework and Formulation of Recommendations 9
1.4.2 Guideline Development Meetings 10
1.5 Systematic Review Evidence Table 12
1.6 Forest Plots 24
1.7 Evidence Profile 27
Appendix A 29

This Technical Report accompanies the Australian Clinical Guideline for Physical Rehabilitation and Mobilisation in Adult Intensive Care Units (ICUs) and gives an account of the guideline development process and methodology, lists the clinical questions, and provides evidence summaries for all clinical questions addressed to date.

1 Guideline Methodology

Guideline development has been in accordance with the Standards prescribed by the National Health and Medical Research Council (NHMRC) under the direction of an interdisciplinary expert advisory panel. Full details of the NHMRC Standards are available at: https://www.nhmrc.gov.au/guidelinesforguidelines/standards.

1.1 Identifying Scope and Systematic Guideline Review

The Guideline Development Group (GDG) met on numerous occasions between 2021 and 2022 to discuss the scope of the guideline. The GDG agreed that there were several existing guidelines and resources that could be reviewed to inform the guideline development process and ensure complete, high-quality and consistent guidelines for safe and effective physical rehabilitation and mobilisation of adult patients critically ill in the ICU. A systematic review [1] of existing guidelines was performed and those deemed relevant were shortlisted, including:

- NICE – Rehabilitation after critical illness (2009) [2]
- German Society of Anaesthesiology and Intensive Care Medicine - S2e guideline: Positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders: Revision (2015)[3]
- Independent author group - Physiotherapy in the intensive care unit: An evidence-based, expert driven, practical statement and rehabilitation recommendations (2015)[4]
- Society of Critical Care Medicine (SCCM) - Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient (2016)[5]
- New South Wales Agency for Clinical Innovation - Physical activity and movement: A guideline for critically ill adults (2017)[6]
- American Thoracic Society and American College of Chest Physicians - Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests (2017)[7]
- SCCM - Clinical practice guidelines for the prevention and management of pain, agitation/ sedation, delirium, immobility, and sleep disruption in adult patients in the ICU (2018)[8]
- Associação Médica Brasileira - Brazilian guidelines for early mobilization in intensive care unit (2019)[9]
- European Respiratory Society and European Society of Intensive Care Medicine - Physiotherapy for adult patients with critical illness (2008)[10]
- Independent author group - The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: A synthesis of evidence and expert opinion and its translation into practice (2011)[11]

Table 1. Search terms used for systematic guideline review

Search Terms for Systematic Guideline Review
intensive care or artificial ventilation or pressure support ventilation or ventilator weaning or early goal-directed therapy or intensive care nursing or intensive care unit or burn unit or exp coronary care unit or neurological intensive care unit/ or surgical intensive care unit or critically ill patient or critical illness or ventilated patient or mechanical ventilator
critical* ill or illness*
critical care or intensive care or intensive treatment unit* or intensive therapy unit* or high dependenc* unit* or burn unit* or coronary care unit* or respiratory care unit* or ICU or Intensive therapy unit (ITU) or High dependency unit (HDU)
mechanical* or artificial* or noninvasive or non-invasive or positive-pressure (ventilat* or respirat*)
exp exercise or mobilization or physiotherapy or joint mobilization or exp walking or rehabilitation or functional assessment or functional training or muscle training or rehabilitation care or muscle weakness or limb weakness or muscle strength or exp kinesiotherapy or physical activity or weight bearing or weight lifting or endurance or fitness or physiotherapist or physiotherapy practice or exercise tolerance or "movement (physiology)" or locomotion or exp body movement or exp limb movement or patient mobility or physical mobility or "range of motion" or voluntary movement or occupational therapy or occupational therapist or occupational therapy practice
movement* or ambulation* or ambulate* or rehabilit* or mobili* or physical therap* or physiotherap* or kinesiotherap* or physical activit* or physical exertion* or exercis* or locomotion* or physical endurance or physical exertion* or walk* or occupational therap* or weight bear* or weight lift* or resistance train*
exp practice guidelines or evidence based medicine or protocol compliance
recommend* or guideline*
practic* or evidence* or clinical* statement* or protocol* or guide*
exp critical illness/rh [Rehabilitation]
standardization or standard or gold standard
critical* ill or illness* or critical care or intensive care or intensive treatment unit* or intensive therapy unit* or high dependenc* unit* or burn unit* or coronary care unit* or respiratory care unit* or ICU or ITU or HDU) or mechanical* or artificial* or noninvasive or non-invasive or positive pressure ventilat* or respirat* standard*
movement* or ambulation* or ambulate* or rehabilit* or mobili* or physical therap* or physiotherap* or kinesiotherap* or physical activit* or physical exertion* or exercis* or locomotion* or physical endurance or physical exertion* or walk* or occupational therap* or weight bear* or weight lift* or resistance train* standard*

Databases and websites searched from January 2008 to February 2020 included:

- Medline
- Embase
- CINAHL
- Cochrane
- Grey literature

Each guideline was appraised for their quality using the AGREE II tool by two separate appraisers. All ten of the guidelines were found to range from low to high quality and were assessed for adaptation, see Table 2.

Table 2. AGREE II Appraisal of existing clinical practice guidelines relevant to early mobilisation interventions, adapted from Lang et al.[1]

Guideline	Agree II Score	
	A1	A2
NICE – Rehabilitation after critical illness (2009)	5.9	5.8
German Society of Anaesthesiology and Intensive Care Medicine - aS2e guideline: Positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders: Revision (2015)	3.4	4.6
Independent author group - Physiotherapy in the intensive care unit: An evidence-based, expert driven, practical statement and rehabilitation recommendations (2015)	3.8	4.6
SCCM - Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient (2016)	5.5	5.3
New South Wales Agency for Clinical Innovation - Physical activity and movement: A guideline for critically ill adults (2017)	4.4	4.8
American Thoracic Society and American College of Chest Physicians - Liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests (2017)	5.2	4.8
SCCM - Clinical practice guidelines for the prevention and management of pain, agitation/ sedation, delirium, immobility, and sleep disruption in adult patients in the ICU (2018)	6.3	5.3
Associação Médica Brasileira - Brazilian guidelines for early mobilization in intensive care unit (2019)	3.7	3.9
European Respiratory Society and European Society of Intensive Care Medicine - Physiotherapy for adult patients with critical illness (2008)	2.9	4
Independent author group - The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: A synthesis of evidence and expert opinion and its translation into practice (2011)	4.9	4.9

**A1: Appraiser 1; A2: Appraiser 2.*

1.1.1 Systematic reviews on physical rehabilitation and mobilisation

There has been a number of comprehensive systematic reviews within the field of physical rehabilitation and mobilisation in adult ICU's[12-22]. The interpretation of this research is significantly challenged by the pronounced heterogeneity in study populations, variations in intervention strategies, and the lack of standardised definitions for 'early mobilisation'. Patient populations vary in terms of diagnoses and lengths of stay, while intervention approaches differ widely in scope and intensity. Additionally, the unclear distinction between 'early mobilisation' and 'standard care' across studies adds complexity. This diversity in patient characteristics and interventions makes it challenging to draw clear conclusions from the research, complicating our understanding of the effects of early mobilisation in the ICU.

1.2 Key Clinical Question

The GDG engaged in a comprehensive discussion to identify and prioritize critical topics, leading to the formation of the central clinical question and associated outcomes. Subsequent discussions and feedback from the GDG refined the clinical question to align with the guideline's scope. The key clinical question from the guideline - ***Should physical rehabilitation and/or mobilisation be used as a therapy in adult critically ill patients in ICU?***- was integrated with the key outcomes of interest.

Table 3. Guideline PICO (Population, Intervention, Comparison, Outcomes)

Population	Patients admitted to an adult ICU
Intervention	Active physical rehabilitation and/or mobilisation commenced in an ICU where the intervention includes an active component targeting whole body rehabilitation
Comparator	Standard care or no active physical rehabilitation and/or mobilisation
Outcomes	Mortality Health-related quality of life (HRQoL) Physical function Cognitive function Early mobilisation complications Economic outcomes

1.3 Systematic Searching of Evidence

A meta-analysis was conducted (Michelle Paton, Carol Hodgson) using the PICO process. The following databases were searched from inception until 16 March 2023: Medline (OVID), Embase (OVID), Cochrane Central Register of Controlled Trials (OVID), CINAHL Plus (EBSCOhost), SPORTDiscus (EBSCOhost), SCOPUS, Web of Science, PEDro. The reference lists of relevant primary research and review articles, trial registries for unpublished data (World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov), and published abstracts were also searched.

Table 4. Search terms used for systematic randomised controlled trial (RCT) review

Search Terms for Systematic RCT Review
intensive care/ or early goal-directed therapy/
intensive care unit/ or burn unit/ or coronary care unit/ or medical intensive care unit/ or neurological intensive care unit/ or surgical intensive care unit/
critical illness/ or critically ill patient/ or ventilated patient/
artificial ventilation/ or high frequency ventilation/ or interactive ventilatory support/ or intermittent mandatory ventilation/ or intermittent positive pressure ventilation/ or inverse ratio ventilation/ or positive end expiratory pressure/ or pressure support ventilation/ or ventilator weaning/
mechanical ventilator/ or adult respiratory distress syndrome/ or respiratory failure/ or acute respiratory failure/ or chronic respiratory failure/ or lung insufficiency/ or respiratory arrest/

(critical care or critically ill or critical illness or intensive care or intensive treatment unit* or intensive therapy unit* or high dependency unit* or burn? unit* or burn? ward* or coronary care unit* or critical coronary care ward* or recovery room or respiratory care unit* or critical respiratory care ward* or ICU or ITU or HDU or neurocritical*).mp.
(((ventilator* or respirat*) adj3 wean*) or (ventilat* support or ventilat* patient* or positive end expiratory pressure)).mp.
((mechanical* or artificial or high frequency or positive pressure or intermittent mandatory or inverse ratio or pressure support or invasive) adj (ventilat* or respirat*)).mp.
(respiratory distress syndrome or respiratory failure or respiratory insufficiency or lung insufficiency or respiratory arrest).mp.
mobilization/ or rehabilitation/
kinesiotherapy/ or plyometrics/ or stretching exercise/ or exp exercise/ or endurance training/ or resistance training/ or exp fitness/ or physiotherapist/ or physiotherapy practice/ or endurance/ or physical activity/ or physiotherapy/ or exercise tolerance/
"movement (physiology)"/ or body movement/ or limb movement/ or exp *locomotion/ or patient mobility/ or physical mobility/ or "range of motion"/ or motion/ or muscle weakness/ or muscle training/ or muscle strength/ or occupational therapy practice/ or occupational therapy/ or occupational therapist/
(mobili* or ambulation*).mp.
(rehab* adj7 (early or earlie* or initiat* or functional or gradual or delay* or time or timing or start* or commenc* or immediate or fast-track or rapid or accelerat*)).mp.
((exercise* or walking or movement or locomotion) adj10 (early or earlie* or functional or gradual or delay* or timing or start* or commenc* or immediate or fast-track)).mp.
(physiotherap* or kinesiotherap* or occupational therap* or physical rehab* or early physio* or early physical).mp.
((weight or strength* or resistance) adj3 (train* or lift*)).mp.
((exercise* or endurance or aerobic) adj2 (fitness or train* or intervention* or protocol* or program* or therap* or activit* or regim* or session* or technique* or rehabilitation)).mp.
(physical* adj2 (exercise* or exertion or endurance or therap* or train* or conditioning or activ* or fit* or effort* or movement*)).mp.
(bed* cycle or bedside cycling or cycle ergomet* or bicycle ergomet* or bed* ergomet* or lower body ergomet* or leg ergomet* or leg cycle* or leg cycling or FES cycling).mp.
((leg or limb or body) adj (movement* or exercise*)).mp.
(musc* training or strengthening exercise* or stretching exercise* or muscle strengthening or weightlifting or resistance exercise* or functional training).mp.
((recovery of function or functional recovery or range of motion or functional performance) and (early or earlie* or timing or immediate or fast-track or rapid or accelerat*)).mp.
critical illness/rh [Rehabilitation]

((immobili* or bedrest or bed-rest or atroph* or wasting or weakness or disabilit* or muscle* or muscular or neuromuscular or polyneuropath* or neuropath*) adj5 (critical care or critically ill or critical illness or intensive care or intensive treatment unit* or intensive therapy unit* or high dependency unit* or burn? unit* or burn? ward* or coronary care unit* or critical coronary care ward* or recovery room or respiratory care unit* or critical respiratory care ward* or ICU or ITU or HDU or neurocritical*)).mp.
((immobili* or bedrest or bed-rest or atroph* or wasting or weakness or disabilit* or muscle* or muscular or neuromuscular or polyneuropath* or neuropath*) adj5 ((mechanical* or artificial or high frequency or positive pressure or intermittent mandatory or inverse ratio or pressure support or invasive) adj (ventilat* or respirat*))).mp.
randomized controlled trial/ or randomization/ or single blind procedure/ or double blind procedure/ or crossover procedure/ or placebo/ or prospective study/
(randomi?ed controlled or RCT or randomly allocated or allocated randomly or random allocation or "allocated at random" or single blind* or double blind* or ((treble or triple) adj blind*) or placebo*).mp.
limit 30 to (randomized controlled trial or controlled clinical trial)
(exp animal/ or exp invertebrate/ or animal.hw. or nonhuman/) not exp human/
limit 38 to (conference abstract or editorial or letter or note)

1.3.1 Inclusion and Exclusion Criteria

Studies were included in the meta-analyses if they met the following criteria:

- Investigated the effect of early active mobilisation for adult participants (age ≥18 years) admitted to an ICU who required invasive mechanical ventilation (IMV)
- Available in the any language.
- RCT.

Studies were excluded if they were:

- Trials in cohorts with disease processes that would affect the outcome of an active interventional program (e.g., acute neurologic conditions, pre-existing or rapidly developing neuromuscular disease, spinal cord injury, advanced dementia)
- Non-randomised trials.
- Trials in which the intervention did not include active participation by the participant.
- Trials that did not occur in an acute ICU setting.

1.3.2 Study Selection

A systematic search of RCTs that compared physical rehabilitation and/or mobilisation to usual care in critically ill adults was conducted to inform the guideline. Title, abstract, and full text screen was performed. At each stage, two independent reviewers assessed the articles, and any conflicts were addressed through discussion or consultation with a third reviewer, as necessary, to achieve consensus. A total of 18,823 records and 3,100 registers were identified from systematic search. After removal of duplicates, 21,923 records were screened on eligibility based on title and abstract. 466 articles were selected for a full-text review. A total of 388 trials were excluded; there were 115 studies excluded for wrong study design, 101 duplicates, 42 ongoing trials with no results, 29 with the wrong outcomes, 27 wrong intervention, 26 in the wrong setting, 23 trials awaiting classification,

9 trials with the wrong comparator, 7 with the wrong patient population, 6 trials terminated with no results to share and 3 full texts unable to be obtained. Seventy-eight RCT published from 2009 to 2023 met eligibility criteria. See Table 7 for included studies.

1.3.3 Quality Assessment and Data Extraction

The Covidence systematic review software[23] was used to independently screen all RCTs meeting the inclusion criteria. Two unaffiliated reviewers independently extracted data from each included trial using a standardized data collection form. Extracted data included trial characteristics, design, population details, intervention specifics, and control group information. Unavailable data were requested from corresponding authors.

Methodologic quality was independently reviewed by two researchers using the Cochrane Risk of Bias tool[24] (version 1) with disagreements resolved through discussion or third reviewer involvement. Corresponding authors were consulted for clarification when trial methods were unclear. Statistical heterogeneity of effect size among trials was quantified by using the I^2 test, with a 50% threshold indicating substantial statistical heterogeneity. Continuous data were analysed with pooled mean difference (MD) or standardized MD (SMD), with 95% confidence interval (CI), using a random effects model. Where outcomes were reported as median interquartile range (IQR), they were converted to mean (± standard deviation, SD), and data presented with a 95% CI were converted to SD[25]. The analysis was performed using the restricted maximum likelihood (REML) and a prediction interval was calculated.

1.4 Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)

The critical outcomes were evaluated and presented utilizing the GRADE methodology. A succinct summary of findings from the body of evidence for each clinical question was presented in evidence profile tables. The GRADE evidence profile includes:

- A list of all outcomes deemed critical and significant for formulating a recommendation.
- The results for each outcome, expressed as the absolute and relative magnitude of effect (if applicable).
- The number of participants and studies contributing to the result for each outcome (the body of evidence).
- A GRADE assessment of the overall certainty of the body of evidence for each outcome (high, moderate, low, or very low certainty).
- An informative statement providing a lay description of the size of the effect and evidence certainty for each result (plain text summary).
- A rationale for any decision to downgrade the certainty of evidence (based on consideration of five GRADE domains: risk of bias, imprecision, inconsistency, indirectness, and publication bias-induced bias).

1.4.1 Evidence to Decision (EtD) Framework and Formulation of Recommendations

Guideline development meetings took place from June 2021 to May 2023. During each meeting, the GDG reviewed and discussed the evidence related to the clinical questions and outcomes. The GRADE Evidence to Decision (EtD) Framework guided the transparent decision-making process and

recommendation formulation, with leadership from experienced methodologist Sue Brennan and contributions from all panel members, including consumers. All evidence was digitally presented on the MAGICapp platform.

In formulating recommendations, the following factors were considered for each clinical outcome:

- Benefits and Harms – evaluating and balancing the desirable and undesirable effects.
- Certainty of evidence – a comprehensive assessment of quality of the evidence contributing to the evidence profile.
- Values – accounting for the priorities of critically ill people receiving mobilisation treatment in ICU (or others affected) concerning the primary outcomes based on qualitative systematic review. See appendix for search strategy
- Resources – considerations of the direct costs associated with the intervention.
- Acceptability – considering the acceptability for consumers, healthcare professionals and other stakeholders.
- Feasibility – determining the practicality of implementing the recommendation in clinical practice based on qualitative systematic review. See appendix for search strategy
- Equity – evaluating potential inequities arising from the intervention

1.4.2 Guideline Development Meetings

Each meeting featured a range of multidisciplinary expertise; however, it was deemed crucial to include at least one representative with lived experience at each meeting. During each guideline development meeting, the GDG voted on judgements for each of the above factors. Following review and discussion of the EtD framework, the GDG were requested to vote on the direction of the recommendation (i.e., for or against the intervention). Refer to Table 6 for the different types of recommendations.

While drafting the recommendations and good practice statements, relevant existing Australian guidelines were considered and aligned with when appropriate.

Table 5. GRADE definitions for ratings for quality of evidence[26].

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

Table 6. GRADE definitions for rating strength of recommendation[27].

Recommendation	Definition
Strong Recommendation for	A strong recommendation for an intervention is given when the certainty of evidence is high or moderate. The benefits outweigh harms for almost everyone and all or nearly all people would likely want the recommended intervention.
Strong Recommendation against	A strong recommendation against an intervention is given when the certainty of evidence is high or moderate. There are clear harms attributed to the intervention and they outweigh the benefits. Most people would decline the intervention.
Conditional Recommendation for	A conditional recommendation is given when it is considered that the benefits of the intervention are greater than the disadvantages, or the available evidence cannot rule out a significant benefit of the intervention while assessing that the adverse effects are few or absent. This recommendation is also used when patient preferences vary.
Conditional Recommendation against	A conditional recommendation is given against the intervention when it is judged that the disadvantages of the intervention are greater than the benefits, but where this is not substantiated by strong evidence. This recommendation is also used where there is strong evidence of both beneficial and harmful effects, but where the balance between them is difficult to determine. Likewise, it is also used when patient preferences vary.
Good Practice Statements	Good Practice Statements are ungraded statements that represent the GDG's view of optimal practice. Good practice statements are used in instances where high quality indirect evidence is available; however, conducting a formal evidence review would not be a good use of resources.

1.5 Systematic Review Evidence Table

Table 7. Early Mobilisation Trial Characteristics

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
Afxonidis 2021[28]	Surgical	Greece	2	39	63.5 ± 8.9	Goal-directed mobility	39	65.1 ± 8.9	Goal-directed mobility starting later & less frequent	- mortality - adverse events (commentary only) - length of stay (ICU & hospital) - pre- & post-intervention measurements	Overall: Some concerns -unclear risk of selection bias -high risk of performance bias -unclear risk of reporting bias
Amundadottir 2021[29]	Mixed	Iceland	2	29	62 [50-70]	Goal-directed mobility	21	64 [58-74]	Mobilisation starting later & less frequent	- mortality - physical function (Barthel, 6MWD) - strength (ICUAW, MRCSS) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination - time till mobility milestones	Overall: Low risk -high risk of performance bias
Baum 2022[30]	Surgical	Germany	1	10	55.5 [47-67]	Robotic assisted mobility	10	61 [56.75-68]	Usual care (progressive mobility)	- mortality - physical function (IMS, SOMS) - quadricep ultrasound - length of stay (ICU & hospital) - mechanical ventilation duration - HRQoL - disability	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -high risk of other bias
Berney 2021[31]	Mixed	Australia, America	4	80	59 ± 15	FES cycling & usual care	82	56 ± 14	Usual care (progressive mobility)	- mortality - adverse events - physical function (6MWD, PFIT, FSS-ICU, IMS, SPPB, Katz, IADL) -strength (MRCSS, ICUAW, grip, quadriceps force) - quadriceps cross-sectional area - HRQoL (EQ5D utility & VAS) - length of stay (ICU & hospital) - mechanical ventilation duration - cognitive impairment - delirium incidence & duration - anxiety & depression - post-traumatic stress disorder - discharge destination	Overall: Low risk -high risk of performance bias
Borges (RBR-29495g)[32]	Surgical	Brazil	1	31	54 [41.5-63]	Goal-directed mobility starting at highest level	33	57 [39-65]	Usual care (progressive mobility)	- mortality - adverse events - physical function (IMS) - strength (grip) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination	Overall: High risk -high risk of performance bias -unclear risk of attrition bias -high risk of other bias
Brummel 2014[33]	Mixed	America	1	1) 22	62 [48-67]	1) Goal-directed mobility	22	60 [51-69]		- mortality - adverse events (commentary only)	Overall: Low risk -High risk of performance bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
				2) 43	62 [54-69]	2) Goal-directed mobility & cognitive therapy			Goal-directed mobility starting later & less frequent	- physical function (TUGT, Katz, FAQ) - HRQoL (EQ5D VAS) - cognitive function (Tower test, DEX, MMSE) - delirium FD - length of stay (ICU & hospital) - mechanical ventilation duration & ventilator FD - discharge destination - time till mobility milestones - feasibility outcomes	
Burtin 2009[34]	Mixed	Belgium	1	45	56 ± 16	Cycling & usual care	45	57 ± 17	Usual care (progressive mobility & ROM exercises)	- mortality - adverse events (commentary only) - physical function (6MWD, Berg) - strength (quadricepsforce, grip) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination	Overall: High risk -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias
Cui 2020[35]	Surgical	China	1	89	65.1 ± 4.6	Enhanced recovery after surgery program	89	66.2 ± 4.4	Usual care (mobilisation education only)	- mortality - adverse events (commentary only) - length of stay (ICU & hospital) - incidence of early discharge - post-traumatic stress disorder - laboratory tests - multiple organ functioning	Overall: Low risk -High risk of performance bias -unclear risk of reporting bias
Cundiff 2012[36]	Medical	USA	1	Not reported	Not reported	Goal-directed mobility	Not reported	Not reported	Not reported	- length of stay (hospital; commentary only) - mechanical ventilation duration (commentary only)	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -high risk of reporting bias -high risk of other bias
da Costa Torres 2016[37]	Surgical	NS (Brazil)	1	33	Not reported	Cycling & Goal-directed mobility	33	Not reported	Respiratory management	- mortality - physical function (6MWD) - length of stay (hospital) - post-operative pulmonary complications - analgesia use & pain scores	Overall: High risk -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -unclear risk of reporting bias -high risk of other bias
Dantas 2012[38]	Mixed	Brazil	1	26	59.07 ± 15.22	Goal-directed mobility	33	50.43 ± 20.45	Passive or active ROM exercises	- mortality - physical function (% independent) - strength (MRCSS, respiratory muscle) - length of stay (ICU & hospital; commentary only) - mechanical ventilation duration (commentary only)	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -high risk of reporting bias -unclear risk of other bias
de Carvalho 2013[39]	Medical	Brazil	1	5	55.8 ± 19.7	Goal-directed mobility & usual care	5	62.5 ± 23.64	Usual care (position changes, progressive ROM exercises)	- mortality - physical function (FIM) - length of stay (ICU & hospital)	Overall: Some concerns -high risk of performance bias -unclear risk of attrition bias -unclear risk of other bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
Denehy 2013[40]	Mixed	Australia	1	74	61.4 ± 15.9	Goal-directed mobility & usual care	76	60.1 ± 15.8	Usual care (progressive mobility & respiratory management)	- mortality - adverse events (commentary only) - physical function (6MWD, TUGT, PFIT) - strength (ICUAW) - HRQoL (SF36, AQoL) - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination	Overall: Low risk -high risk of performance bias -unclear risk of other bias
Deng 2022[41]	Mixed	China	1	41	51.78 ± 16.85	Cycling & Goal-directed mobility	42	56.4 ± 14.93	Passive ROM exercises only	- mortality - adverse events (commentary only) - length of stay (ICU) - mechanical ventilation duration - gut motility, feeding tolerance & enteral feeding rates	Overall: Low risk -high risk of performance bias -unclear risk of other bias
Dong 2014[42]	Medical	China	1	30	55.3 ± 16.1	Goal-directed mobility	30	55.5 ± 16.2	Usual care (not described)	- mortality - adverse events (commentary only) - length of stay (ICU) - mechanical ventilation duration - time till mobility milestones - highest FiO2 - lowest PaO2/FiO2	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Dong 2016[43]	Surgical	China	1	53	62.6 ± 12.8	Goal-directed mobility	53	60.2 ± 15.1	Education only	- mortality - adverse events (commentary only) - length of stay (ICU & hospital) - mechanical ventilation duration - time till mobility milestones	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias
Dong 2021[44]	Mixed	China	1	39	59.05 ± 17.61	Goal-directed mobility	41	64.44 ± 14.72	Usual care (not described)	- adverse events (commentary only) - physical function (% recovered) - length of stay (ICU) - mechanical ventilation duration - diaphragmatic excursion &thickening fraction	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -high risk of reporting bias -unclear risk of reporting bias
Dos Santos 2020[45]	Medical	Brazil	1	1) 12 2) 13 3) 11	55.6 ± 10.8 55.3 ± 12.8 50.2 ± 12.8	1) NMES & limb exercises 2) Progressive ROM exercises 3) NMES*	15	51.8 ± 12.8	Passive ROM exercises only	- mortality - length of stay (ICU) - mechanical ventilation duration - sedation duration	Overall: Some concerns -unclear risk of selection bias -high risk of performance bias
Eggmann 2018[46]	Mixed	Switzerland	1	58	65 ± 15	Cycling & resistance exercises & Goal-directed mobility	57	63 ± 15	Progressive mobility program	- mortality - adverse events - physical function (6MWD, FIM, TUGT) - strength (MRCSS, grip, ICUAW, quadriceps force) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - delirium FD - discharge destination - time till mobility milestones	Overall: Low risk -high risk of performance bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- limitations to ROM - ICU complications	
Fagevik Olsén 2021[47]	Surgical	Sweden	1	42	66.8 ± 8	Mobilisation starting day 0	41	68 ± 10.2	Mobilisation starting later	- adverse events (commentary only) - length of stay (ICU & hospital) - blood gas analysis	Overall: Low risk -high risk of performance bias
Fangzheng 2018[48]	Not reported	China	1	30	42.77 ± 11.41	Goal-directed mobility & resistive exercises	30	42.33 ± 11.35	Passive ROM exercises	- adverse events - strength (MRCSS) - length of stay (ICU) - mechanical ventilation duration - unplanned extubation rate	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -unclear risk of reporting bias -unclear risk of other bias
Farzammanesh 2020[49]	Mixed	Iran	2	84	45.16 ± 16.83	ROM exercises	84	46.53 ± 19.11	Usual care (no exercise)	- mortality - length of stay (ICU) - mechanical ventilation duration - delirium duration & incidence	Overall: Some concerns -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of other bias
Files 2013[50]	Medical	America	1	50	Not reported	Goal-directed mobility & resistance exercises	50	Not reported	Progressive mobility program	- mortality - adverse events (commentary only) - physical function (SPPB) - strength (grip) - ICU, hospital, & ventilator FDs - cytokines - feasibility outcomes	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -high risk of reporting bias -high risk of other bias
Fossat 2018[51]	Mixed	France	1	158	65 ± 13	Cycling & NMES & usual care	154	66 ± 15	Progressive mobility program	- mortality - adverse events - physical function (IMS, Katz, Barthel) - strength (MRCSS) - HRQoL (SF36) - mechanical ventilation duration & FD - delirium incidence - time till mobility milestones - rectus femoris muscle thickness	Overall: Some concerns -high risk of performance bias -unclear risk of detection bias
Han 2022[52]	Surgical	China	1	47	64.1 ± 5.3	1) Respiratory exercises & mobilisation starting on ward*	46	63.0 ± 8.7	Usual care (respiratory education)	- adverse events (commentary only) - physical function (Barthel) - length of stay (ICU & hospital) - mechanical ventilation duration - post-operative pulmonary complications - atrial fibrillation during hospitalization - complications (till day 30 post discharge)	Overall: High risk -high risk of performance bias -high risk of detection bias -unclear risk of attrition bias -unclear risk of reporting bias -unclear risk of other bias
				47	63.6 ± 6.5	2) Goal-directed mobility starting in ICU					
He 2021[53]	Not reported	China	1	71	53.8 ± 20.0	Goal-directed mobility	62	55.9 ± 16.3	Usual care (Passive ROM exercises / turning)	- mortality - length of stay (ICU) - mechanical ventilation duration - immune regulators	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
Hickmann 2018[54]	Medical	Brussels	1	9	59 ± 19	Cycling & ROM exercises	10	57 ± 20	ROM exercises once daily	- mortality - adverse events - strength (MRCSS) - length of stay (ICU) - mechanical ventilation duration - histology & molecular effects of exercise in septic shock via muscle biopsies & electrophysiological testing - haemodynamics - feasibility outcomes	Overall: Some concerns -unclear risk of selection bias -High risk of performance bias
Hodgson 2016[55]	Mixed	Australia, NZ	5	29	64 ± 12	Goal-directed mobility starting at highest level	21	53 ± 15	Progressive mobility program	- mortality & DAOH to day 180 - adverse events (commentary only) - physical function (PFIT, FSS-ICU, IMS, IADL) - strength (MRCSS, ICUAW) - HRQoL (EQ5D, VAS, % return to work) - anxiety and depression - length of stay (ICU & hospital) - mechanical ventilation duration & FD - discharge destination - time till mobility milestones - feasibility outcomes	Overall: Low risk -high risk of performance bias
Hodgson 2020[56]	Mixed	Australia	3	10	49.3 ± 13.4	Goal-directed mobility starting at highest level	10	50.6 ± 17.1	Progressive mobility program	- mortality - adverse events - physical function (IMS, Katz, Barthel, IADL) - strength (MRCSS; commentary only) - HRQoL (EQ5D VAS) - cognition (MoCA) - length of stay (ICU & hospital) - mechanical ventilation duration - d/c destination - time till mobility milestones	Overall: Low risk -high risk of performance bias
Hui 2016[57]	Not reported	China	1	50	54.4 ± 12.7	Goal-directed mobility	50	54.2 ± 14	ROM exercises once daily	- physical function (Barthel) - strength (ICUAW, MRCSS) - length of stay (ICU & hospital) - mechanical ventilation duration - incidence of ventilator-associated pneumonia, deep vein thrombosis & pressure ulcers	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Kayambu 2015[58]	Mixed	Australia	1	26	62.5 [30-83]	Goal-directed mobility	24	65.5 [37-85]	Usual care (no other details)	- mortality & DAOH to day 180 - adverse events (commentary only) - physical function (ACIF, PFIT) - strength (MRCSS) - HRQoL (SF36) - cognition (ACIF) - anxiety - length of stay (ICU & hospital) - mechanical ventilation duration & FD - exercise capacity - inflammatory biomarker & lactate analysis	Overall: High risk -High risk of performance bias -high risk of attrition bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- fat-free mass	
Kho 2019[59]	Mixed	Canada	7	36	60 ± 16.8	Cycling & usual care	30	63.6 ± 17.1	Usual care (progressive mobility & respiratory management)	- mortality - adverse events - physical function (PFIT, PRFS, 30sec STS, Katz, 2MWD) - strength (MRCSS, ICUAW, quadriceps force) - HRQoL (EQ5D utility & VAS, IPAT) - length of stay (ICU & hospital) - mechanical ventilation duration - d/c destination - time till mobility milestones - feasibility outcomes	Overall: Some concerns -high risk of performance bias -unclear risk of attrition bias
Liu 2019[60]	Medical	China	1	32	52.8 ± 4.8	Cycling & NMES & massage	28	55.5 ± 3.3	Usual care (no exercise)	- mortality - adverse events (commentary only) - length of stay (ICU) - mechanical ventilation duration - return of normal gastric function	Overall: High risk -unclear risk of selection bias -high risk of performance bias -high risk of attrition bias -unclear risk of reporting bias -unclear risk of other bias
Maca 2023[61]	Mixed	Czech Republic	1	21	53.0 ± 16.02	Cycling & usual care	19	67.0 ± 12.59	Usual care (progressive mobility & respiratory management)	- mortality - adverse events (commentary only) - physical function (Barthel) - strength (grip, quadriceps force) - speed of muscle strength recovery - length of stay (ICU) - mechanical ventilation duration - feasibility outcomes - haemodynamics	Overall: Low risk -high risk of performance bias -unclear risk of other bias
Maffei 2017[62]	Surgical	France	1	20	52 ± 9	Goal-directed mobility	20	54 ± 9	Usual care (progressive mobility & ROM exercises)	- mortality - adverse events - length of stay (ICU & hospital) - mechanical ventilation duration - time to achieve mobility milestones - gut motility	Overall: Some concerns -high risk of performance bias -unclear risk of reporting bias
Malik 2021[63]	Mixed	India	1	29	37.72 ± 15.926	Early mobilisation & bundle of care	25	46.40 ± 18.053	Usual care (mobilisation once extubated)	- mortality - adverse events (commentary only) - strength (ICUAW) - length of stay (ICU & hospital) - mechanical ventilation duration - delirium incidence, duration & FD	Overall: Some concerns -high risk of performance bias -unclear risk of detection bias -unclear risk of other bias
McWilliams 2018[64]	Mixed	UK	1	53	62 [46-68]	Goal-directed mobility	50	61 [47-70]	Progressive mobility program	- mortality - adverse events - physical function (MMS, Barthel, % mobilised 30m) - strength (MRCSS, grip) - HRQoL (SF36) - hospital anxiety & depression - length of stay (ICU & hospital) - mechanical ventilation duration	Overall: Low risk -high risk of performance bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- time to mobility milestones - feasibility outcomes	
Mehani 2020[65]	Surgical	Egypt	1	24	45.8 ± 2.89	Cycling & IMT & ROM exercises & mobility	26	45.25 ± 3.62	Respiratory management	- mortality - physical function (FIM; commentary only) - strength (quadriceps force, peripheral and respiratory) - mechanical ventilation duration	Overall: High risk -high risk of performance bias -high risk of other bias
Moreira (RBR-92j6qf)[66]	Not reported	Brazil	1	67	Not reported	Goal-directed mobility	67	Not reported	Usual care (not described)	- mortality (commentary only) - physical function (% SOOB) - length of stay (ICU) - mechanical ventilation duration - time to mobility milestones - hospitalisation costs	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -high risk of reporting bias -high risk of other bias
Morris 2016[67]	Medical	America	1	150	55 ± 17	Goal-directed mobility & resistive exercises	150	58 ± 14	No rehabilitation unless ordered	- mortality - adverse events (commentary only) - physical function (SPPB, % walked, FPI) - strength (grip) - HRQoL (SF36) - cognitive function (MMSE) - delirium duration - length of stay (ICU & hospital) - mechanical ventilator FD - discharge destination	Overall: Some concerns -unclear risk of selection bias -high risk of performance bias
Moss 2016[68]	Mixed	America	5	59	26 ± 14	Goal-directed mobility program & resistive exercises	61	49 ± 15	Usual care (progressive mobility & ROM exercises)	- mortality & DAOH to day 180 - adverse events (commentary only) - physical function (TUGT, Berg, 5x STS, CS-PFP-10) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of attrition bias
Nickels 2020[69]	Mixed	Australia	1	37	56 ± 18	Cycling & usual care	37	57 ± 16	Usual care (progressive mobility & respiratory management)	- mortality & DAOH to day 180 - adverse events (commentary only) - physical function (IMS, FSS-ICU, 6MWD) - strength (MRCSS, grip) - muscle atrophy (ultrasound) - HRQoL (EQ5D VAS) - delirium incidence & duration - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination - time till mobility milestones	Overall: Low risk -high risk of performance bias
Nydal 2022[70]	Mixed	UK, Germany	5	26	64.4 ± 11.9	Mobilisation at night	20	60.8 ± 17.3	No mobilisation at night	- mortality - adverse events - physical function (IMS) - ICU & hospital FD - mechanical ventilation FD - delirium incidence & duration - feasibility outcomes	Overall: High risk -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -unclear risk of other bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- costs	
Patel 2022[71]	Mixed	USA	1	100	57·9 [42·3-66·8]	Early Physiotherapy & Occupational therapy	100	54·5 [41·9-64·7]	Usual care (therapy following extubation or earlier if requested)	- mortality & DAOH to day 365 - adverse events - physical function (% independent) - strength (ICUAW, MRCSS) - HRQoL (SF36) - delirium duration - cognition (MoCA, % impaired) - length of stay (ICU & hospital) - mechanical ventilation duration & FD - discharge destination - time till mobility milestones	Overall: Low risk -high risk of performance bias -unclear risk of reporting bias
Pinkaew 2020[72]	Not reported	Thailand	1	1) 25	69.08 ± 16.96	1) Goal-directed mobility	25	74.68 ± 15.23	Usual care (respiratory & limb exercises)	- mortality - strength (grip) - physical function (activity level) - mechanical ventilation duration	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
				2) 25	75.32 ± 14.28	2) Goal-directed mobility & resistance exercises					
Rahiminezhad 2022[73]	Medical	India	1	36	44.27 ± 13.61	Progressive range of motion	35	47.43 ± 17.36	Usual care (respiratory & limb exercises)	- mortality - adverse events - strength (grip)	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of attrition bias -unclear risk of reporting bias
Rezvani 2022[74]	Medical	Iran	1	30	53.92 ± 13.09	Goal-directed mobility	30	54.83 ± 10.89	Usual care (position change)	- length of stay (ICU) - mechanical ventilation duration - respiratory parameters & compliance	Overall: Some concerns -high risk of performance bias -unclear risk of detection bias -unclear risk of other bias
Ribeiro 2021[75]	Surgical	Brazil	1	1) 25	58.3 ± 7.7	1) Cycling & mobility & usual care	23 (16)	60.3 ± 8.3	Usual care (respiratory & circulation exercises)	- mortality - adverse events (commentary only) - length of stay (ICU & hospital) - mechanical ventilation duration - heart rate variability	Overall: High risk -unclear risk of performance bias -high risk of attrition bias -unclear risk of reporting bias
				2) 28	62.1 ± 9	2) Cycling & mobility & usual care & virtual reality games					
Sarfati 2018[76]	Surgical	France	1	72	62 [52-73]	Tilt table & usual care	73	67 [54-75]	Usual care (progressive mobility & ROM exercises)	- mortality - adverse events - strength (MRCSS, ICUAW) - length of stay (ICU & hospital) - mechanical ventilation duration - time till mobility milestones - sedative & NMBAs agent use - infections and serve ICU compilations	Overall: High risk -high risk of performance bias -high risk of attrition bias
Schaller 2016[77]	Surgical	Austria, Germany, USA	5	104	66 [48-73]	Goal-directed mobility & usual care	96	64 [45-76]	Usual care (progressive mobility)	- mortality - adverse events - physical function (SOMS, mmFIM, % mobilised) - strength (ICUAW) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation, delirium sedation, NMBAs, & vasopressor FD	Overall: High Risk -high risk of performance bias -high risk of detection bias -unclear risk of reporting bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- discharge destination - analgesia & steroid use - serum glucose & sodium concentrations	
Schujmann 2020[78]	Mixed	Brazil	1	68	48 ± 15	Goal-directed mobility & cycle ergometry & NMES & resistive exercises	67	55 ± 12	Usual care (progressive mobility)	- mortality - adverse events - physical function (Barthel, STS, TUGT, 2MWD, IMS, % independent) - strength (grip) - length of stay (ICU & hospital) - mechanical ventilation duration - sedation, vasoactive drug & NMBA use - respiratory & peripheral muscle strength	Overall: Low risk -high risk of performance bias
Schweickert 2009[79]	Mixed	America	2	49	55.7 [36.3-69.1]	Goal-directed mobility & occupational therapy	55	54.4 [46.5-66.4]	Usual care (minimal therapy)	- mortality - adverse events - physical function (Barthel, walk distance, % independent) - strength (grip, MRCSS, ICUAW) - delirium incidence & duration - length of stay (ICU & hospital) - mechanical ventilation duration & FD - time till mobility milestones - discharge destination	Overall: Low risk -High risk of performance bias
Shaaban 2022[80]	Medical	Egypt	1	58	66.30 ± 7.97	Pulmonary rehabilitation & usual care	62	65.82 ± 9.31	Usual care (not described)	- mortality (commentary only) - respiratory muscle strength - length of stay (ICU) - mechanical ventilation duration - weaning success - diaphragm thickness & excursion	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -high risk of reporting bias -unclear risk of other bias
Shirvani 2020[81]	Surgical	Iran	1	45	58.67 ± 9.01	Goal-directed mobility	45	62.18 ± 8.17	Usual care (minimal mobility in ICU)	- mortality - delirium incidence & severity - length of stay (ICU & hospital) - mechanical ventilation duration	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of other bias
Shosholcheva 2016[82]	Not reported	Macedonia	1	19	Not reported	Goal-directed mobility & IMT & limb exercises	15	Not reported	Later rehabilitation (not described)	- adverse events (commentary only) - length of stay (ICU) - mechanical ventilation duration - change in APACHE II scores	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -high risk of reporting bias -high risk of other bias
Sosnowski 2018[83]	Mixed	Australia	1	15	54.9 ± 15.9	ABCDE bundle	15	60.6 ± 11	Usual care (progressive mobility)	- mortality - adverse events (commentary only) - physical function (FIM, PFIT-s) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation duration - feasibility outcomes	Overall: Some concerns -High risk of performance bias -unclear risk of attrition bias -unclear risk of other bias
Suwardianto 2018[84]	Medical	Indonesia	1	32	59.39 ± 10.94	Physical-cognitive therapy	32	48.03 ± 11.4	No therapy	- physical function (PFIT; commentary only) - cognitive function (MMSE; commentary only)	Overall: High risk -unclear risk of selection bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
											-high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -high risk of reporting bias -unclear risk of other bias
Tariq 2017[85]	Surgical	Pakistan	1	87	Not reported	Mobilisation from day 0 post-op	87	Not reported	Usual care (mobilisation from day 1)	- length of stay (ICU) - haemodynamic and blood analysis	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
TEAM Study Investigators 2022[86]	Mixed	International (6 countries)	49	372	60.5 ± 14.8	Goal-directed mobility starting at highest level	378	59.5 ± 15.2	Usual care (variable at each site)	- mortality & DAOH to day 180 - adverse events - physical function (Barthel, IADL) - HRQoL (EQ5D utility & VAS, WHODAS) - cognitive function (MoCA) - ICU & mechanical ventilation FD	Overall: Low risk -high risk of performance bias
Thammata 2021[87]	Surgical	Thailand	1	15	61.27 ± 5.95	Goal-directed mobility & IMT & resistive exercises & usual care	15	65.75 ± 12.9	Usual care (respiratory & limb exercises)	- mortality - adverse events (commentary only) - strength (respiratory) - mechanical ventilation duration - body composition	Overall: Some concerns -high risk of performance bias -unclear risk of attrition bias -unclear risk of other bias
Varghese 2022[88]	Surgical	USA	1	5	Not reported	Physical therapy & NMES & protein supplementation	6	Not reported	Not reported	- length of stay (ICU & hospital) - mechanical ventilation duration - hypotaurine levels	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias
Verceles 2023[89]	Medical	USA	1	16	62 ± 9.3	Goal-directed mobility & NMES & protein supplementation	23	62 ± 9.3	Usual care (progressive mobility)	- delirium incidence - length of stay (ICU & hospital) - mechanical ventilation duration - discharge destination - muscle volume &cross sectional area - nitrogen balance	Overall: High risk -unclear risk of selection bias -High risk of performance bias -unclear risk of detection bias
Waldauf 2021[90]	Medical	Czech Republic	1	75	59.9 ± 15.1	FES assisted cycling & usual care	75	62.3 ± 15.4	Usual care (progressive mobility)	- mortality - adverse events - physical function (PFIT-s) - strength (MRCSS) - HRQoL (SF36) - length of stay (ICU & hospital) - mechanical ventilation FD - rectus femoris muscle thickness - nitrogen balance	Overall: Low risk -high risk of performance bias
Wang 2022[91]	Mixed	China	2	135	54.88 ± 12.29	Pain, agitation, and delirium bundle including goal-directed mobility	135	52.78 ± 10.83	Usual care (no mobility)	- mortality - adverse events (commentary only) - delirium incidence & duration - cognitive function (MoCA, % impaired) - length of stay (ICU) - mechanical ventilation duration	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -unclear risk of reporting bias -unclear risk of other bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
Windmoller 2020[92]	Surgical	Brazil	1	21	57 ± 8	Cycling & Continuous positive airway pressure & usual care	21	62 ± 6	Usual care (progressive mobility & respiratory management)	- mortality - physical function (1min STS, 6MWD) - length of stay (ICU & hospital) - mechanical ventilation duration - inspiratory muscle strength	Overall: High risk -High risk of performance bias -high risk of attrition bias
Winkelman 2018[93]	Not reported	America	4	25	52.68 ± 18.53	Goal-directed mobility	29	59.48 ± 15.56	Goal-directed mobility once daily	- mortality - adverse events (commentary only) - strength (grip, MRCSS) - length of stay (ICU) - mechanical ventilation duration - delirium incidence - inflammatory biomarker activity	Overall: Some concerns -High risk of performance bias -unclear risk of attrition bias -unclear risk of other bias
Wolfe 2013[94]	Medical	America	2	48	Not reported	Goal-directed mobility & occupational therapy	48	Not reported	Usual care (minimal therapy)	- mortality & DAOH to day 180	Overall: High risk -high risk of performance bias -unclear risk of detection bias -unclear risk of attrition bias -unclear risk of reporting bias -high risk of other bias
Wright 2018[95]	Mixed	UK	4	150	60 ± 16	Goal-directed mobility & resistive exercises	158	64 ± 16	Usual care (respiratory care & functional retraining)	- mortality - adverse events (commentary only) - physical function (Rivermead Mobility Index, FIM, 6MWD) - strength (grip) - HRQoL (SF36, EQ5D & SF6D utility) - length of stay (ICU & hospital) - mechanical ventilation duration	Overall: High risk -high risk of performance bias -high risk of detection bias -unclear risk of attrition bias
Wu 2022[96]	Surgical	China	1	48	58.1 ± 10.4	Goal-directed mobility	48	56.0 ± 11.5	Usual nursing care	- adverse events (commentary only) - physical function (Barthel, 6MWD) - length of stay (ICU & hospital) - mechanical ventilation duration - time till mobility milestones - lung function	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Xue 2020[97]	Medical	China	1	43	64.6 ± 6	Multimodal rehabilitation	43	65 ± 6.6	Usual Care (not described)	- mortality - adverse events (commentary only) - physical function (Barthel; commentary only) - length of stay (ICU) - mechanical ventilation duration - change in APACHE II scores	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Yosef-Brauner 2015[98]	Mixed	Israel	1	9	61.5 ± 12	Goal-directed mobility	9	51.6 ± 18	Progressive mobility program	- mortality - adverse events (commentary only) - physical function (sitting balance) - strength (grip, MRCSS, respiratory) - length of stay (ICU) - mechanical ventilation duration	Overall: High risk -unclear risk of selection bias -high risk of performance bias -high risk of detection bias -high risk of reporting bias -unclear risk of other bias
Yu 2020[99]	Not reported	China	1	55	59.98 ± 8.01	Cycling & ROM exercises	57	58.37 ± 7.35	Usual Care (Passive ROM)	- adverse events (commentary only) - physical function (Barthel) - strength (ICUAW) - length of stay (ICU)	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias

Reference	Diagnostic category	Countries	No sites	Intervention			Control				Risk of bias
				n	Age	Type	n	Age	Description	Outcomes	
										- mechanical ventilation duration	-unclear risk of reporting bias -unclear risk of other bias
Yu 2022[100]	Not reported	China	1	76	69.96 ± 8.14	Usual care & cycling	76	69.74 ± 8.13	Usual care (respiratory care & Goal-directed mobility)	- mortality - adverse events (commentary only) - length of stay (ICU & hospital) - mechanical ventilation FD - gastrointestinal function - nutritional status	Overall: Some concerns -high risk of performance bias -unclear risk of attrition bias -unclear risk of reporting bias -unclear risk of other bias
Yulan 2017[101]	Medical	China	1	30	Not reported	Goal-directed mobility & NMES & progressive ROM exercises & respiratory therapy	30	Not reported	Usual care (no exercise)	- adverse events (commentary only) - length of stay (ICU & hospital) - mechanical ventilation duration - incidence of ventilator associated pneumonia & sputum	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Zanini 2019[102]	Surgical	Brazil	1	1) 10	58 ± 5	1) Goal-directed mobility & IMT	10	61 ± 5	Usual care (respiratory therapy & education)	- mortality - adverse events (commentary only) - physical function (6MWD,CPET) - length of stay (ICU & hospital) - mechanical ventilation duration - lung capacity & respiratory muscle function	Overall: Low risk -high risk of performance bias -unclear risk of other bias
				2) 10	56 ± 7	2) Goal-directed mobility					
Zeng 2017[103]	Medical	China	1	37	62.89 ± 15.19	Goal-directed mobility & respiratory exercises	31	65.58 ± 14.13	Usual care (respiratory therapy)	- length of stay (ICU) - mechanical ventilation duration - incidence of ventilator-associated pneumonia, atelectasis & deep vein thrombosis - change in APACHE II score & respiratory function - blood & vital sign analysis	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias
Zhou 2022[104]	Mixed	China	2	1) 50	57.0 ± 15.3	1) Goal-directed mobility	50	57.3 ± 13.7	Usual care (Passive ROM)	- mortality - physical function (Barthel) - strength (ICUAW, MRCSS) - length of stay (ICU) - mechanical ventilation duration - change in SOFA score - nutritional status	Overall: Low risk -high risk of performance bias -unclear risk of detection bias -unclear risk of other bias
				2) 50	58.7 ± 14.9	2) Goal-directed mobility & early nutrition					
Zhu 2018[105]	Mixed	China	1	20	62 ± 14.3	Goal-directed mobility & respiratory exercises & NMES	20	57.3 ± 15.6	Usual care (no exercise)	- strength (ICUAW, MRCSS) - length of stay (ICU) - mechanical ventilation duration - ICU costs - rectus femoris & vastus intermediate muscle thickness	Overall: High risk -unclear risk of selection bias -high risk of performance bias -unclear risk of detection bias -unclear risk of reporting bias -unclear risk of other bias

*subgroup did not contribute to evidence analysis

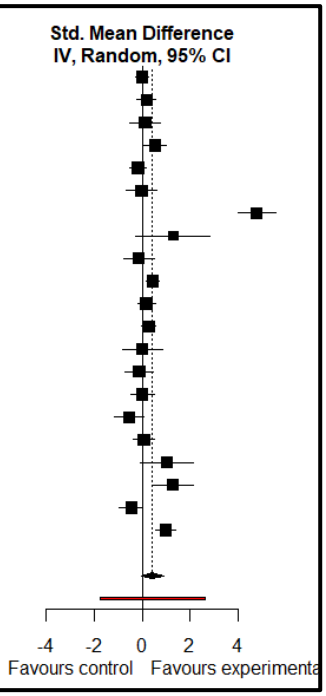
Abbreviations: *2/6MWD* two/six minute walk distance; *ABCDE* Awakening and Breathing Coordination, Delirium monitoring/management and Early exercise/mobility; *ACIF* Acute Care Index of Function; *APACHE* Acute Physiology and Chronic Health Evaluation; *AQoL* Assessment of Quality of Life; *CPET* cardiopulmonary exercises testing; *CS-PFP-10* Continuous Scale Physical Functional Performance; *DAOH* days alive and out of hospital; *DEX* Dysexecutive Questionnaire; *EQ5D* EuroQol-5 Dimension; *FAQ* Functional Activities Questionnaire; *FD* free days; *FES* functional electrical muscle stimulation; *FIM* Functional Independence Measure; *FiO2* fraction of inspired oxygen; *FSS-ICU* Functional Status Score for the Intensive Care Unit; *HRQoL* health related quality of life; *IADL* Lawton Instrumental Activities of Daily Living; *ICU* Intensive Care Unit; *ICUAW* Intensive Care Unit acquired weakness; *IMS* Intensive Care Mobility Scale; *IMT* inspiratory muscle training; *IPAT* Intensive Care Phycological Assessment Tool; *mmFIM* minimal modified Functional Independence Measure *MMSE* Mini-Mental State Examination; *MoCA* Montreal Cognitive Assessment; *MRCSS* Medical Research Council Sum Score; *NMBAs* neuromuscular blocking agents; *NMES* neuromuscular electrical stimulation; *PaO2* partial pressure of oxygen in arterial blood; *PFIT(s)* Physical Function in ICU Test (scored); *PRFS* Patient Reported Functional Scale; *ROM* range of motion; *SF36* Short-Form 36; *SOFA* Sequential Organ Failure Assessment Score *SOMS* Surgical Intensive Care Unit Optimal Mobilisation Score; *SPPB* Short Physical Performance Battery; *STS* sit to stand; *TUGT* Timed Up and Go Test; *VAS* visual analogue scale; *WHODAS* World Health Organisation Disability Assessment Schedule

1.6 Forest Plots

Outcome 1: Physical function - Hospital discharge

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Morris 2016	4.70	3.6800	106	4.70	3.5400	98	5.1%	0.00 [-0.27; 0.27]
Schweickert 2009	59.17	66.8300	49	46.67	64.7100	55	5.0%	0.19 [-0.20; 0.57]
Brummel 2014	1.67	3.7400	35	1.27	2.3300	14	4.8%	0.12 [-0.50; 0.74]
Burtin 2009	217.00	157.7700	31	135.33	145.9200	36	4.9%	0.53 [0.04; 1.02]
Denehy 2013	244.20	124.0000	59	266.70	136.8000	58	5.1%	-0.17 [-0.53; 0.19]
Moss 2016	-15.60	13.2000	21	-15.20	13.8000	19	4.8%	-0.03 [-0.65; 0.59]
Hui 2016	93.47	5.1700	50	61.82	7.7400	50	4.5%	4.77 [3.99; 5.55]
de Carvalho 2013	120.00	6.1600	5	90.50	30.4500	4	3.3%	1.28 [-0.25; 2.81]
McWilliams 2018	86.67	12.1300	17	88.33	11.9300	21	4.7%	-0.14 [-0.78; 0.51]
Schaller 2016	6.67	3.0000	104	5.00	4.5200	96	5.1%	0.44 [0.16; 0.72]
Eggmann 2018	86.56	39.3500	58	79.10	42.1900	57	5.1%	0.18 [-0.18; 0.55]
Wright 2018	113.00	17.0000	83	108.00	20.0000	75	5.1%	0.27 [-0.04; 0.58]
Sosnowski 2018	95.80	29.6000	9	95.20	24.7000	13	4.4%	0.02 [-0.83; 0.87]
Amundadottir 2021	76.83	42.3500	26	81.50	29.9200	20	4.8%	-0.12 [-0.71; 0.46]
Nickels 2020	204.67	232.6900	33	202.00	210.9800	32	4.9%	0.01 [-0.47; 0.50]
Kho 2019	3.67	3.9200	26	5.67	3.2200	18	4.8%	-0.54 [-1.15; 0.07]
Berney 2021	249.00	118.0000	39	240.00	140.0000	49	5.0%	0.07 [-0.35; 0.49]
Hodgson 2020	9.80	0.4000	6	8.90	1.0000	9	4.0%	1.03 [-0.09; 2.15]
Zanini 2019	383.00	68.8600	20	291.00	69.5700	10	4.5%	1.30 [0.46; 2.13]
Borges	9.10	2.5000	31	9.90	0.1000	33	4.9%	-0.45 [-0.95; 0.04]
Han 2022	89.10	15.5000	47	75.30	12.1000	46	5.0%	0.98 [0.55; 1.41]
Total (95% CI)			**855**			**813**	**100.0%**	**0.43 [-0.03; 0.88]**
Prediction interval								**[-1.76; 2.61]**

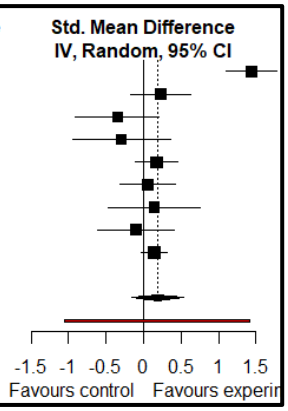
Heterogeneity: $Tau^2 = 1.0340$; $Chi^2 = 181.16$, df = 20 (P < 0.01); $I^2 = 89\%$
Test for overall effect: Z = 1.84 (P = 0.07)



Outcome 2: Physical function - 6 months post randomisation

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Morris 2016	9.00	0.7000	84	8.00	0.6800	84	12.0%	1.44 [1.10; 1.78]
Denehy 2013	-9.80	5.1000	47	-12.90	17.9000	48	11.5%	0.23 [-0.17; 0.64]
Moss 2016	-14.20	9.6000	27	-11.10	7.6000	24	10.1%	-0.35 [-0.90; 0.20]
Hodgson 2016	6.50	1.9000	21	7.00	1.3000	16	9.2%	-0.29 [-0.95; 0.36]
Fossat 2018	96.67	7.5300	90	95.00	11.2700	106	12.4%	0.17 [-0.11; 0.45]
Wright 2018	118.00	17.0000	64	117.00	16.0000	51	11.8%	0.06 [-0.31; 0.43]
Amundadottir 2021	97.67	5.5200	24	96.67	8.0400	18	9.6%	0.15 [-0.47; 0.76]
Berney 2021	6.70	2.4000	27	6.90	1.5000	31	10.5%	-0.10 [-0.62; 0.42]
TEAM Study Investigators 2022	7.00	1.7000	249	6.73	2.0000	250	13.0%	0.15 [-0.03; 0.32]
Total (95% CI)			**633**			**628**	**100.0%**	**0.19 [-0.16; 0.54]**
Prediction interval								**[-1.05; 1.42]**

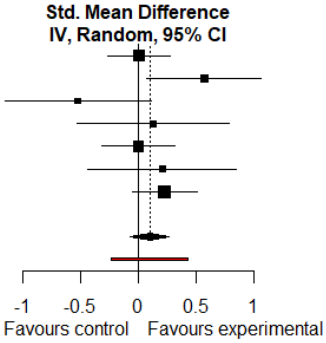
Heterogeneity: $Tau^2 = 0.2399$; $Chi^2 = 58.89$, df = 8 (P < 0.01); $I^2 = 86\%$
Test for overall effect: Z = 1.04 (P = 0.30)



Outcome 3: HRQoL – Hospital discharge

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Morris 2016	38.40	27.8400	108	38.30	28.0600	100	25.7%	0.00 [-0.27; 0.28]
Burtin 2009	20.60	3.8000	31	17.33	6.9400	36	10.2%	0.57 [0.08; 1.06]
Moss 2016	40.00	27.7000	21	54.70	27.4000	19	6.5%	-0.52 [-1.16; 0.11]
McWilliams 2018	32.10	7.6800	17	31.10	7.8500	19	6.1%	0.13 [-0.53; 0.78]
Wright 2018	34.00	8.0000	76	34.00	9.0000	76	20.6%	0.00 [-0.32; 0.32]
Kho 2019	69.80	16.7000	21	65.80	21.4000	17	6.3%	0.21 [-0.43; 0.85]
Patel 2023	43.67	19.4800	99	39.97	12.5600	99	24.7%	0.22 [-0.05; 0.50]
Total (95% CI)			**373**			**366**	**100.0%**	**0.10 [-0.07; 0.27]**
Prediction interval								**[-0.23; 0.43]**

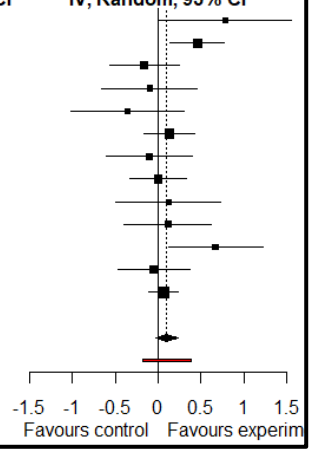
Heterogeneity: $Tau^2 = 0.0092$; $Chi^2 = 8.94$, df = 6 (P = 0.18); $I^2 = 33\%$
Test for overall effect: Z = 1.18 (P = 0.24)



Outcome 4: HRQoL – 6 months post randomisation

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kayambu 2015	81.80	22.2000	11	60.00	29.4000	19	2.5%	0.78 [0.01; 1.56]
Morris 2016	55.90	26.6200	82	43.60	27.2400	79	11.3%	0.45 [0.14; 0.77]
Denehy 2013	40.10	14.7000	48	42.40	13.7000	48	7.9%	-0.16 [-0.56; 0.24]
Moss 2016	58.80	27.4000	26	61.50	26.1000	24	4.6%	-0.10 [-0.65; 0.46]
Hodgson 2016	61.00	19.0000	21	68.00	19.0000	16	3.4%	-0.36 [-1.02; 0.30]
Fossat 2018	53.33	41.4700	86	48.33	37.6700	90	12.1%	0.13 [-0.17; 0.42]
Eggmann 2018	63.94	27.9500	36	66.83	25.7900	27	5.5%	-0.11 [-0.60; 0.39]
Wright 2018	37.00	11.4000	72	37.00	10.2000	68	10.4%	0.00 [-0.33; 0.33]
Amundadottir 2021	38.50	9.7100	24	37.30	9.9500	18	3.9%	0.12 [-0.49; 0.73]
Nickels 2020	75.00	18.0000	31	73.00	17.0000	29	5.4%	0.11 [-0.39; 0.62]
Berney 2021	76.30	13.8000	26	64.40	20.4000	28	4.7%	0.67 [0.12; 1.22]
Waldauf 2021	48.10	36.1900	42	50.00	33.5800	46	7.4%	-0.05 [-0.47; 0.36]
TEAM Study Investigators 2022	70.20	19.7000	246	69.00	20.1000	254	20.9%	0.06 [-0.12; 0.24]
Total (95% CI)			**751**			**746**	**100.0%**	**0.10 [-0.03; 0.23]**
Prediction interval								**[-0.18; 0.39]**

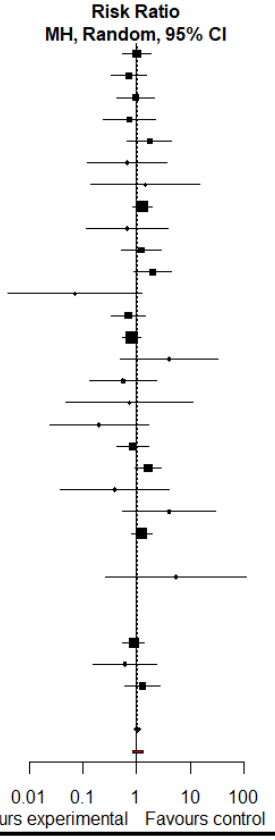
Heterogeneity: $Tau^2 = 0.0124$; $Chi^2 = 17.82$, df = 12 (P = 0.12); $I^2 = 33\%$
Test for overall effect: Z = 1.56 (P = 0.12)



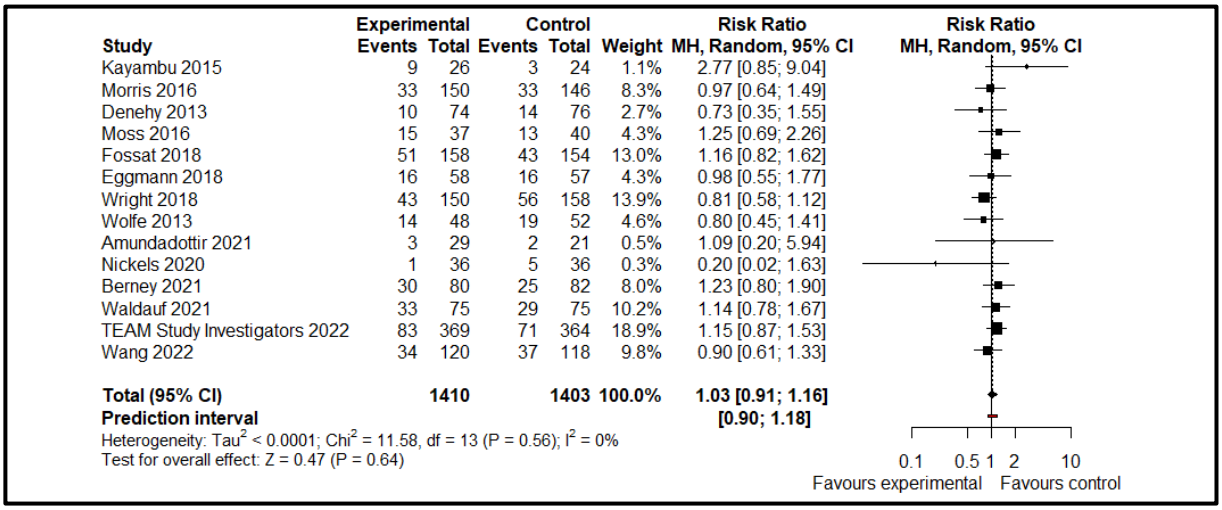
Outcome 5: Mortality – Hospital Discharge

Study	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio MH, Random, 95% CI
Morris 2016	18	150	18	150	5.9%	1.00 [0.54; 1.85]
Schweickert 2009	9	49	14	55	4.1%	0.72 [0.34; 1.52]
Brummel 2014	17	65	6	22	3.6%	0.96 [0.43; 2.12]
Denehy 2013	5	74	7	76	1.9%	0.73 [0.24; 2.21]
Moss 2016	10	59	6	61	2.5%	1.72 [0.67; 4.44]
Dong 2014	2	30	3	30	0.8%	0.67 [0.12; 3.71]
Hodgson 2016	2	29	1	21	0.4%	1.45 [0.14; 14.94]
Fossat 2018	42	158	32	154	12.7%	1.28 [0.86; 1.91]
Dong 2016	2	53	3	53	0.8%	0.67 [0.12; 3.83]
McWilliams 2018	10	52	8	50	3.2%	1.20 [0.52; 2.80]
Schaller 2016	17	104	8	96	3.6%	1.96 [0.89; 4.34]
Sarfati 2018	0	65	6	60	0.3%	0.07 [0.00; 1.23]
Eggmann 2018	10	58	14	57	4.3%	0.70 [0.34; 1.45]
Wright 2018	34	150	45	158	13.8%	0.80 [0.54; 1.17]
Sosnowski 2018	4	15	1	15	0.5%	4.00 [0.50; 31.74]
Hickmann 2018	2	9	4	10	1.1%	0.56 [0.13; 2.34]
Amundadottir 2021	1	29	1	21	0.3%	0.72 [0.05; 10.93]
Nickels 2020	1	36	5	36	0.5%	0.20 [0.02; 1.63]
Kho 2019	11	36	11	30	4.8%	0.83 [0.42; 1.65]
Berney 2021	24	80	15	82	6.8%	1.64 [0.93; 2.89]
Nydahl 2022	1	26	2	20	0.4%	0.38 [0.04; 3.95]
Hodgson 2020	4	10	1	10	0.6%	4.00 [0.54; 29.80]
Waldauf 2021	30	75	24	75	11.3%	1.25 [0.81; 1.92]
Zanini 2019	0	20	0	10	0.0%	
Borges	2	31	0	33	0.3%	5.32 [0.27; 106.50]
Shirvani 2020	0	45	0	45	0.0%	
Afxonidis 2021	0	39	0	39	0.0%	
Wang 2022	27	123	30	120	10.2%	0.88 [0.56; 1.38]
Xue 2020	3	43	5	43	1.2%	0.60 [0.15; 2.36]
Patel 2023	14	99	11	99	4.1%	1.27 [0.61; 2.66]
Total (95% CI)		**1812**		**1731**	**100.0%**	**1.04 [0.89; 1.21]**
Prediction interval						**[0.83; 1.29]**

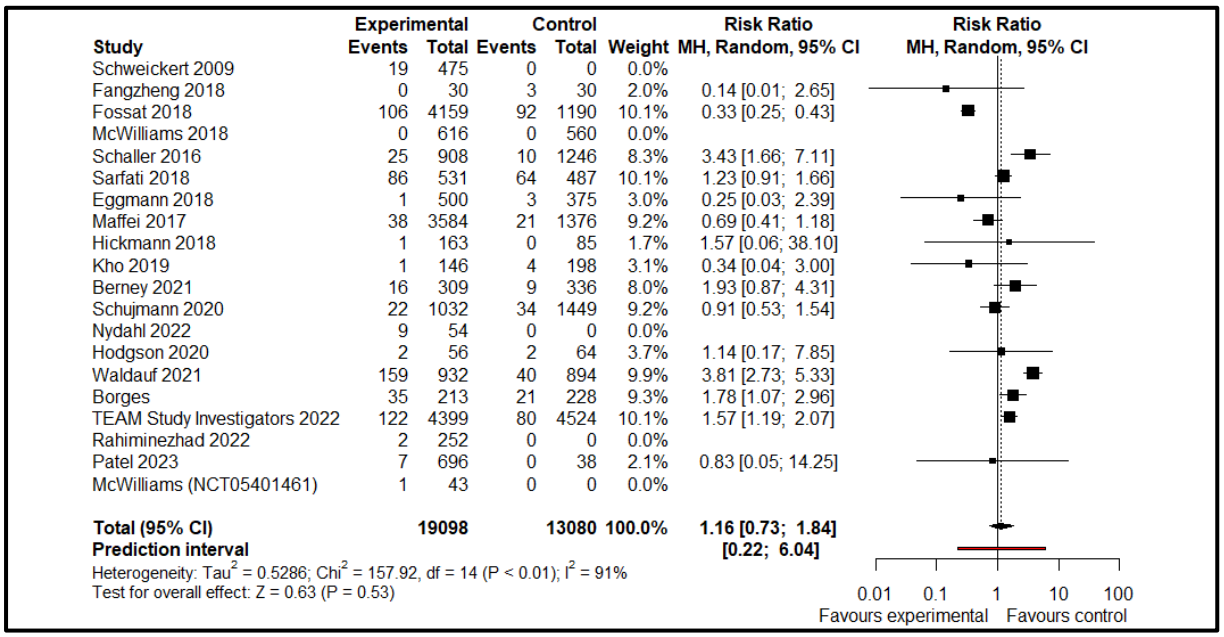
Heterogeneity: $Tau^2 = 0.0056$; $Chi^2 = 26.40$, df = 26 (P = 0.44); $I^2 = 2\%$
Test for overall effect: Z = 0.46 (P = 0.65)



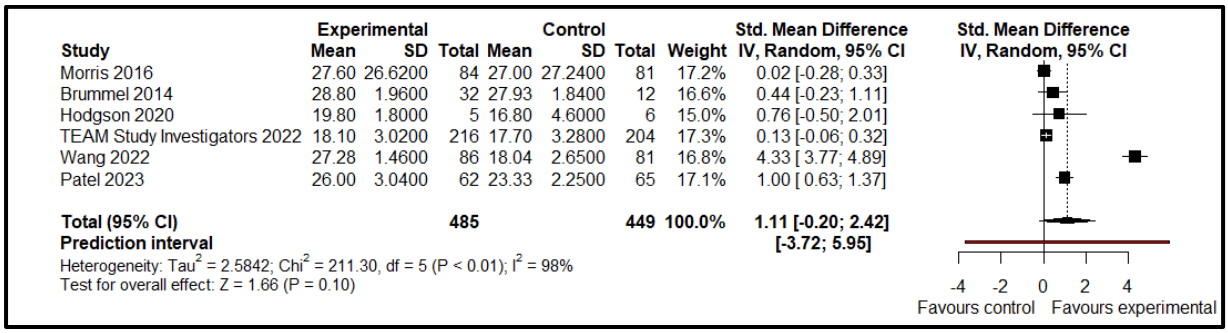
Outcome 6: Mortality – 6 months post randomisation



Outcome 7: Adverse events



Outcome 8: Cognitive Function – closest to 6 months post randomisation



1.7 Evidence Profile

Table 8. Evidence Statement form

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Usual care Rehabilitation and mobilisation	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality Hospital discharge	Relative risk: 1.04 (CI 95% 0.89 - 1.21) Based on data from 3543 participants in 30 studies	**163** per 1000 **170** per 1000 Difference: **7 more per 1000** (CI 95% 18 fewer - 34 more)	**Moderate** Due to serious imprecision[1]	Physical rehabilitation and/or mobilisation probably has little or no effect on hospital mortality in critically ill patients compared to standard care.
Mortality 6 month	Relative risk: 1.03 (CI 95% 0.91 - 1.16) Based on data from 2813 participants in 14 studies	**187** per 1000 **193** per 1000 Difference: **6 more per 1000** (CI 95% 17 fewer - 30 more)	**Moderate** Due to serious imprecision[2]	Physical rehabilitation and/or mobilisation probably has little or no effect on 6 month mortality in critically ill patients compared to standard care
Adverse events	Relative risk: 1.16 (CI 95% 0.73 - 1.84) Based on data from 2716 participants in 19 studies	**29** per 1000 **34** per 1000 Difference: **5 more per 1000** (CI 95% 8 fewer - 24 more)	**Very low** Due to very serious inconsistency, Due to very serious risk of bias.[3]	We are uncertain whether physical rehabilitation and/or mobilisation increases or reduces the number of adverse events in critically ill patients compared to standard care.
Physical function Hospital Discharge	Measured by: Scale: - High better Based on data from 1668 participants in 21 studies	Difference: **SMD 0.43 higher** (CI 95% 0.03 lower - 0.88 higher)	**Very low** Due to serious risk of bias, Due to serious inconsistency. Due to serious imprecision[4]	We are uncertain whether physical rehabilitation and/or mobilisation improves or worsens physical function at hospital discharge compared to standard care.
Physical Function 6 months	Measured by: Scale: - High better Based on data from 1261 participants in 9 studies	Difference: **SMD 0.19 higher** (CI 95% 0.16 lower - 0.54 higher)	**Very low** Due to serious risk of bias, due to very serious inconsistency, due to serious imprecision.[5]	We are uncertain whether physical rehabilitation and/or mobilisation improves or reduces physical function at 6 months compared to standard care.
HRQoL Hospital Discharge	Measured by: Scale: - High better		**Low**	Physical rehabilitation and/or mobilisation may have little or no difference on health

	Based on data from 739 participants in 7 studies	Difference: **SMD 0.10 higher** (CI 95% 0.07 lower - 0.27 higher)	Due to serious risk of bias, Due to serious inconsistency[6]	related quality of life at hospital discharge, compared to standard care.
HRQoL 6 months	Measured by: Scale: - High better Based on data from 1497 participants in 13 studies	Difference: **SMD 0.10 higher** (CI 95% 0.03 lower - 0.23 higher)	**Moderate** Due to serious risk of bias[7]	Physical rehabilitation and/or mobilisation probably has little or no effect on health related quality of life at 6 months compared to standard care.
Cognitive function closest timepoint to 6 months	Measured by: Scale: - High better Based on data from 934 participants in 6 studies	Difference: **SMD 1.11 higher** (CI 95% 0.20 lower - 2.42 higher)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[8]	We are uncertain whether physical rehabilitation and/or mobilisation improves or worsens cognitive function compared to standard care.
Economic Outcome				

1. **Imprecision: serious.** 95% confidence interval (CI) crosses the threshold for an important difference (2 deaths per 100);
2. **Imprecision: serious.** 95% CI crosses the threshold for an important difference (2 deaths per 100);
3. **Risk of Bias: very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: very serious.** Point estimates vary widely, the direction of the effect is not consistent between the included studies, the magnitude of statistical heterogeneity was high, with I^2:91%., The CI of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2 =89%.; **Imprecision: serious.** Cis cross the threshold for an important difference (SMD 0.4).;
5. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: very serious.** The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I^2: 86 %.; **Imprecision: serious.** CIs cross the threshold for an important difference (SMD 0.4);
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The direction of the effect is not consistent between the included studies;
7. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias;
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2:98 %.; **Imprecision: serious.** CIs cross the threshold for an important difference (SMD 0.4);

Appendix A

Qualitative Search strategies

Medline search strategy for:

Perspectives and experiences of those delivering and receiving Early Mobilisation in the ICU: a qualitative evidence synthesis.

Critical Care/
Intensive Care Units/
Critical Illness/
exp Respiration, Artificial/
((mechanical* or artificial* or non*invasive or (positive adj pressure)) adj2 (ventilat* or respirat*)).mp.
ICU.mp.
1 or 2 or 3 or 4 or 5 or 6
rehabilitation/ or early ambulation/ or exercise therapy/ or occupational therapy/ or exercise/
Muscle Weakness/
physical therapy modalities/ or exercise movement techniques/ or exercise therapy/ or musculoskeletal manipulations/
allied health occupations/ or occupational therapy/ or physical therapy specialty/
exp "Physical and Rehabilitation Medicine"/
(Earl* adj2 (mobil* or physio* or physical)).mp.
(mobili* or ambulation*).mp.
((early or earlie* or initiat* or functional or gradual or delay* or time or timing or start* or commenc* or immediate or fast-track or rapid or accelerat*) adj2 rehab*).mp.
((leg or limb or body) adj (movement* or exerci*)).mp.
8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
qualitative research/
grounded theory/
data collection/ or focus groups/ or interviews as topic/ or narration/ or "surveys and questionnaires"/ or health care surveys/ or patient reported outcome measures/ or health surveys/ or patient health questionnaire/
(("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "face-to-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)).mp.
(focus group* or qualitative or ethnograph* or fieldwork or "field work" or "key informant").mp.
((patient* or famil* or care*) adj2 (perspectiv* or attitud* or opinion* or perspective* or perception* or experience*)).mp.
18 or 19 or 20 or 21 or 22 or 23
7 and 17
24 and 25
limit 26 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
26 not 27

Barriers and enablers of early mobilisation in the ICU: a systematic review

1 Critical Care/
2 Intensive Care Units/
3 Critical Illness/
4 (ICU or ICUs).mp.
5 ("Intensive care" or "critical care" or "critical illness" or "critical condition").mp.
6 exp Respiration, Artificial/
7 ((mechanical* or artificial* or non-invasive or noninvasive or (positive adj pressure)) adj2 (ventilat* or respirat*)).mp.
8 1 or 2 or 3 or 4 or 5 or 6 or 7
9 rehabilitation/ or early ambulation/ or exercise therapy/ or occupational therapy/ or exercise/
10 Muscle Weakness/
11 physical therapy modalities/ or exercise movement techniques/ or exercise therapy/ or musculoskeletal manipulations/
12 allied health occupations/ or occupational therapy/ or physical therapy specialty/
13 exp "Physical and Rehabilitation Medicine"/
14 (Earl* adj3 (mobil* or physiotherap* or physical or rehab* or ambulat*)).mp.
15 (mobili* or ambulation*).mp.
16 ((early or earlie* or initiat* or functional or time or timing or start* or commenc* or immediate or fast-track or rapid or accelerat*) adj2 rehab*).mp.
17 ((leg or limb or body) adj (movement* or exerci*)).mp.
18 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19 Qualitative research/
20 qualitative research*.mp.

21 qualitative stud*.mp.
22 Grounded theory/
23 data collection/ or focus groups/ or interviews as topic/ or narration/ or "surveys and questionnaires"/ or health care surveys/ or patient reported outcome measures/ or health surveys/ or patient health questionnaire/
24 (("semi-structured" or semistructured or unstructured or informal or "in-depth" or indepth or "faceto-face" or structured or guide) adj3 (interview* or discussion* or questionnaire*)).mp.
25 (focus group* or qualitative or ethnograph* or phenomeno* or grounded theory or fieldwork or "field work" or "key informant").mp.
6
26 Organizational Case Studies/ or Organizational Culture/ or Organizational Innovation/ or Quality Improvement/ or Action Research/
27 (quality improvement* or action research*).mp.
28 (barrier* or facilitat* or enabl*).mp.
29 ((limit* or restrict* or environmen* or facilitat* or enabl*) adj2 factor*).mp.
30 Health Knowledge, Attitudes, Practice/ or "attitude of health personnel"/
31 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32 8 and 18 and 31
33 limit 32 to ("all infant (birth to 23 months)" or "all child (0 to 18 years)" or "newborn infant (birth to 1 month)" or "infant (1 to 23 months)" or "preschool child (2 to 5 years)" or "child (6 to 12 years)" or "adolescent (13 to 18 years)")
34 32 not 33

References

1. Lang JK, Paykel MS, Haines KJ, Hodgson CL. Clinical practice guidelines for early mobilization in the ICU: a systematic review. *Critical Care Medicine* 2020; **48**(11): e1121-e8.
2. Excellence NIfHaC. Rehabilitation After Critical Illness. 2009. https://www.nice.org.uk/guidance/CG83 (accessed 14 September 2023).
3. Bein T, Bischoff M, Brückner U, et al. S2e guideline: positioning and early mobilisation in prophylaxis or therapy of pulmonary disorders: revision 2015: S2e guideline of the German Society of Anaesthesiology and Intensive Care Medicine (DGAI). *Der Anaesthesist* 2015; **64**: 1.
4. Sommers J, Engelbert RH, Dettling-Ihnenfeldt D, et al. Physiotherapy in the intensive care unit: an evidence-based, expert driven, practical statement and rehabilitation recommendations. *Clinical rehabilitation* 2015; **29**(11): 1051-63.
5. Murray MJ, DeBlock H, Erstad B, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Critical care medicine* 2016; **44**(11): 2079-103.
6. Berry A, Beattie K, Bennett J, et al. Physical activity and movement: a guideline for critically ill adults. *SHPN Agency for Clinical Innovation, Chatswood* 2017.
7. Girard TD, Alhazzani W, Kress JP, et al. An official American Thoracic Society/American College of Chest Physicians clinical practice guideline: liberation from mechanical ventilation in critically ill adults. Rehabilitation protocols, ventilator liberation protocols, and cuff leak tests. *American journal of respiratory and critical care medicine* 2017; **195**(1): 120-33.
8. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical care medicine* 2018; **46**(9): e825-e73.
9. Aquim EE, Bernardo WM, Buzzini RF, et al. Brazilian guidelines for early mobilization in intensive care unit. *Revista Brasileira de terapia intensiva* 2020; **31**: 434-43.
10. Gosselink R, Bott J, Johnson M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on physiotherapy for critically ill patients. *Intensive care medicine* 2008; **34**: 1188-99.
11. Hanekom S, Gosselink R, Dean E, et al. The development of a clinical management algorithm for early physical activity and mobilization of critically ill patients: synthesis of evidence and expert opinion and its translation into practice. *Clinical rehabilitation* 2011; **25**(9): 771-87.
12. Wang YT, Lang JK, Haines KJ, Skinner EH, Haines TP. Physical rehabilitation in the ICU: a systematic review and meta-analysis. *Critical Care Medicine* 2021; **50**(3): 375-88.
13. Waldauf P, Jiroutková K, Krajčová A, Puthucheary Z, Duška F. Effects of rehabilitation interventions on clinical outcomes in critically ill patients: systematic review and meta-analysis of randomized controlled trials. *Critical care medicine* 2020; **48**(7): 1055-65.
14. Nydahl P, Sricharoenchai T, Chandra S, et al. Safety of patient mobilization and rehabilitation in the intensive care unit. Systematic review with meta-analysis. *Annals of the American Thoracic Society* 2017; **14**(5): 766-77.
15. Tipping CJ, Harrold M, Holland A, Romero L, Nisbet T, Hodgson CL. The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review. *Intensive care medicine* 2017; **43**: 171-83.
16. Kayambu G, Boots R, Paratz J. Physical therapy for the critically ill in the ICU: a systematic review and meta-analysis. *Critical care medicine* 2013; **41**(6): 1543-54.
17. Li Z, Peng X, Zhu B, Zhang Y, Xi X. Active mobilization for mechanically ventilated patients: a systematic review. *Archives of physical medicine and rehabilitation* 2013; **94**(3): 551-61.
18. Adler J, Malone D. Early mobilization in the intensive care unit: a systematic review. *Cardiopulmonary physical therapy journal* 2012; **23**(1): 5.

19. Zayed Y, Kheiri B, Barbarawi M, et al. Effects of neuromuscular electrical stimulation in critically ill patients: A systematic review and meta-analysis of randomised controlled trials. *Australian Critical Care* 2020; **33**(2): 203-10.
20. Connolly B, O'Neill B, Salisbury L, Blackwood B. Physical rehabilitation interventions for adult patients during critical illness: an overview of systematic reviews. *Thorax* 2016; **71**(10): 881-90.
21. Worraphan S, Thammata A, Chittawatanarat K, Saokaew S, Kengkla K, Prasannarong M. Effects of inspiratory muscle training and early mobilization on weaning of mechanical ventilation: a systematic review and network meta-analysis. *Archives of Physical Medicine and Rehabilitation* 2020; **101**(11): 2002-14.
22. Clarissa C, Salisbury L, Rodgers S, Kean S. Early mobilisation in mechanically ventilated patients: a systematic integrative review of definitions and activities. *Journal of intensive care* 2019; **7**(1): 1-19.
23. Covidence. Covidence: better systematic review management. 2020.
24. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011; **343**.
25. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC medical research methodology* 2014; **14**: 1-13.
26. Hultcrantz M, Rind D, Akl EA, et al. The GRADE Working Group clarifies the construct of certainty of evidence. *Journal of clinical epidemiology* 2017; **87**: 4-13.
27. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj* 2008; **336**(7650): 924-6.
28. Afxonidis G, Moysidis DV, Papazoglou AS, et al. Efficacy of Early and Enhanced Respiratory Physiotherapy and Mobilization after On-Pump Cardiac Surgery: A Prospective Randomized Controlled Trial. *Healthcare (Basel)* 2021; **9**(12).
29. Amundadottir OR, Jónasdóttir RJ, Sigvaldason K, et al. Effects of intensive upright mobilisation on outcomes of mechanically ventilated patients in the intensive care unit: a randomised controlled trial with 12-months follow-up. *European journal of physiotherapy* 2021; **23**(2): 68-78.
30. ESICM LIVES 2022: part 1. *Intensive Care Medicine Experimental* 2022; **10**(2): 39.
31. Berney S, Hopkins RO, Rose JW, et al. Functional electrical stimulation in-bed cycle ergometry in mechanically ventilated patients: a multicentre randomised controlled trial. *Thorax* 2021; **76**(7): 656-63.
32. Borges MGB LL, Cardoso RAM, Costa Júnior JS, Silva ASC, Guterres DMS, da Rocha Rodrigues L, Lima CMA, Borges DL, da Silva Nina VJ. Application of exercises after cardiovascular surgery. The Brazilian Clinical Trials Registry; 2020.
33. Brummel NE, Girard TD, Ely EW, et al. Feasibility and safety of early combined cognitive and physical therapy for critically ill medical and surgical patients: the Activity and Cognitive Therapy in ICU (ACT-ICU) trial. *Intensive Care Med* 2014; **40**(3): 370-9.
34. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med* 2009; **37**(9): 2499-505.
35. Cui Z, Li N, Gao C, et al. Precision implementation of early ambulation in elderly patients undergoing off-pump coronary artery bypass graft surgery: a randomized-controlled clinical trial. *BMC Geriatr* 2020; **20**(1): 404.
36. E C. Effect of a Nurse-Implemented Early Progressive Activity Program on Duration of Intubation. *Am J Crit Care* 2012; **21**(e79-e79).
37. da Costa Torres D, Dos Santos PM, Reis HJ, Paisani DM, Chiavegato LD. Effectiveness of an early mobilization program on functional capacity after coronary artery bypass surgery: A randomized controlled trial protocol. *SAGE Open Med* 2016; **4**: 2050312116682256.
38. Dantas CM dSSP, de Siqueira FHT, Pinto RMF, Matias S, MacIel C, de Oliveira MC, de Albuquerque CG, Dias Andrade FM, Ramos FF, França EET. Influence of early mobilization on

respiratory and peripheral muscle strength in critically ill patients. *Rev Bras Ter Intensiva* 2021; **24**(2): 173-8.
39. de Carvalho TG SA, Santos ML, Schafer J, Cunha LS, Santos LJ. Avaliation between precocious out of bed in the intensive care unit and functionality after discharge: a pilot study [Relação entre saída precoce do leito na unidade de terapia intensivae funcionalidade pós-alta: um estudo piloto]. *Rev Epidemiol Control Infect* 2013; **3**(3): 82-6.
40. Denehy L, Skinner EH, Edbrooke L, et al. Exercise rehabilitation for patients with critical illness: a randomized controlled trial with 12 months of follow-up. *Critical Care* 2013; **17**.
41. Deng LX, Lan C, Zhang LN, et al. The effects of abdominal-based early progressive mobilisation on gastric motility in endotracheally intubated intensive care patients: A randomised controlled trial. *Intensive Crit Care Nurs* 2022; **71**: 103232.
42. Dong ZH, Yu BX, Sun YB, Fang W, Li L. Effects of early rehabilitation therapy on patients with mechanical ventilation. *World J Emerg Med* 2014; **5**(1): 48-52.
43. <Dong 2016.pdf>.
44. Dong Z, Liu Y, Gai Y, et al. Early rehabilitation relieves diaphragm dysfunction induced by prolonged mechanical ventilation: a randomised control study. *BMC Pulm Med* 2021; **21**(1): 106.
45. Dos Santos FV, Cipriano G, Jr., Vieira L, et al. Neuromuscular electrical stimulation combined with exercise decreases duration of mechanical ventilation in ICU patients: A randomized controlled trial. *Physiother Theory Pract* 2020; **36**(5): 580-8.
46. Eggmann S, Verra ML, Luder G, Takala J, Jakob SM. Effects of early, combined endurance and resistance training in mechanically ventilated, critically ill patients: A randomised controlled trial. *PLoS One* 2018; **13**(11): e0207428.
47. Fagevik Olsen M, Becovic S, Dean E. Short-term effects of mobilization on oxygenation in patients after open surgery for pancreatic cancer: a randomized controlled trial. *BMC Surg* 2021; **21**(1): 185.
48. Fangzheng J YY, Xianghong Y, Lili W, Weigin L, Yunzhao Z, Jianan R. Application of daily awakening combined with early functional exercise in patients with ICU-acquired mechanical ventilation [每日唤醒联合早期功能锻炼在ICU获得性肌无力机械通气病人中的应用效果]. *Journal Nursing Research* 2018; **32**(21): 150-3.
49. Farzammanesh A JS, Rashidi M, Maraghi E, Ravanbakhsh M. The Effect of Joints Range of Motion Exercises on Delirium Prevention in Patients Admitted to Intensive Care Units. *International Journal of Pharmaceutical and Phytopharmacological Research* 2020; **10**(1): 105-13.
50. Files D, Morris P, Shrestha S, et al. Randomized, controlled pilot study of early rehabilitation strategies in acute respiratory failure. *Crit Care* 2013; **17 Suppl 2**(Suppl 2): P1-545.
51. Fossat G, Baudin F, Courtes L, et al. Effect of In-Bed Leg Cycling and Electrical Stimulation of the Quadriceps on Global Muscle Strength in Critically Ill Adults: A Randomized Clinical Trial. *JAMA* 2018; **320**(4): 368-78.
52. Han P, Yu H, Xie F, et al. Effects of early rehabilitation on functional outcomes in patients after coronary artery bypass graft surgery: a randomized controlled trial. *J Int Med Res* 2022; **50**(3): 3000605221087031.
53. He R XC, Yanling T, Suzhen C, Shou O. Application of early activities in rehabilitation of mechanically ventilated patients in ICU [早期活动在ICU 机械通气病人康复中的 应用]. *Chinese Nursing Research* 2021; **35**(10): 1803-6.
54. Hickmann CE, Castanares-Zapatero D, Deldicque L, et al. Impact of Very Early Physical Therapy During Septic Shock on Skeletal Muscle: A Randomized Controlled Trial. *Crit Care Med* 2018; **46**(9): 1436-43.
55. Hodgson CL, Bailey M, Bellomo R, et al. A Binational Multicenter Pilot Feasibility Randomized Controlled Trial of Early Goal-Directed Mobilization in the ICU. *Crit Care Med* 2016; **44**(6): 1145-52.

56. Investigators E-PS, International EN. Early mobilisation during extracorporeal membrane oxygenation was safe and feasible: a pilot randomised controlled trial. *Intensive Care Med* 2020; **46**(5): 1057-9.
57. Hui K HH. Effect observation on four stage early activity and rehabilitation exercise therapy for prevention of patients with ICU acquired weakness [四级早期活动与康复锻炼疗法预防病人ICU获得性衰弱的效果观察]. *Chinese Nursing Research* 2016; **18**: 2202-5.
58. Kayambu G, Boots R, Paratz J. Early physical rehabilitation in intensive care patients with sepsis syndromes: a pilot randomised controlled trial. *Intensive Care Med* 2015; **41**(5): 865-74.
59. Kho ME, Molloy AJ, Clarke FJ, et al. Multicentre pilot randomised clinical trial of early in-bed cycle ergometry with ventilated patients. *BMJ Open Respir Res* 2019; **6**(1): e000383.
60. Liu D XZ, Qu C, Huo B, Lai H, Li Y, Liu B, Deng H, Wang Q, Li D, Chang P, Li S, Wang H. Efficacy and safety of early physical therapy for acute gastrointestinal injury during mechanical ventilation in patients with sepsis: a randomized controlled pilot trial [早期胃肠康复治疗机械通气的脓毒症伴急性胃肠损伤患者的有效性和安全性：34例前瞻性、随机对照、先导试验]. *Nan Fang Yi Ke Da Xue Xue Bao* 2019; **39**(11): 1298-304.
61. Maca J, Iva, C, Fiedorova, I, Knapkova, L, Marketa, K, Nytra, I, Kucerova, Z, Zoubkova, R. The effect of the addition of in-bed leg cycling using a MOTOmed device to standard rehabilitation on the length of mechanical ventilation: a randomized clinical trial. *Signa Vitae* 2022.
62. Maffei P, Wiramus S, Bensoussan L, et al. Intensive Early Rehabilitation in the Intensive Care Unit for Liver Transplant Recipients: A Randomized Controlled Trial. *Arch Phys Med Rehabil* 2017; **98**(8): 1518-25.
63. Malik AK BD, Anand RK, Subramaniam R. A New ICU Delirium Prevention Bundle to Reduce the Incidence of Delirium: A Randomized Parallel Group Trial. *Indian J Crit Care Med* 2021; **25**(7): 754-60.
64. McWilliams D, Jones C, Atkins G, et al. Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. *J Crit Care* 2018; **44**: 407-12.
65. Mehani SHM, Elmoutaz H, Rahmy AF, Eldin AMSN, Fouad AZ. Comprehensive Rehabilitation Program Versus Traditional Chest Physiotherapy for Weaning from Mechanical Ventilator ; randomized clinical trial. *Research Square* 2020; **1:1**: 1-21.
66. Moreira R. Early mobilization of patients hospitalized in the intensive care unit. The Brazilian Clinical Trials Registry / Registro Brasileiro de Ensaios Clínicos (reBEC); 2018.
67. Morris PE, Berry MJ, Files DC, et al. Standardized Rehabilitation and Hospital Length of Stay Among Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2016; **315**(24): 2694-702.
68. Moss M, Nordon-Craft A, Malone D, et al. A Randomized Trial of an Intensive Physical Therapy Program for Patients with Acute Respiratory Failure. *Am J Respir Crit Care Med* 2016; **193**(10): 1101-10.
69. Nickels MR, Aitken LM, Barnett AG, et al. Effect of in-bed cycling on acute muscle wasting in critically ill adults: A randomised clinical trial. *J Crit Care* 2020; **59**: 86-93.
70. Nydahl P, McWilliams D, Weiler N, et al. Mobilization in the evening to prevent delirium: A pilot randomized trial. *Nurs Crit Care* 2022; **27**(4): 519-27.
71. Patel BK, Wolfe KS, Patel SB, et al. Effect of early mobilisation on long-term cognitive impairment in critical illness in the USA: a randomised controlled trial. *The Lancet Respiratory Medicine* 2023.
72. Pinkaew D WK, Ueawattanasirikul C , Wongpalee T , Chanritwattana S , Jaiwongpeng P , Chiamdamrat O , Wiengmoon K , Pramason N , Inpunkaew N. The Effect of Early Mobilization with Elastic Band Exercise on the Duration of Mechanical Ventilator Weaning of Critically Ill Patients. *Indian Journal of Public Health Research & Development* 2020; **11**(8): 237-43.

73. Rahiminezhad E, Sadeghi M, Ahmadinejad M, Mirzadi Gohari SI, Dehghan M. A randomized controlled clinical trial of the effects of range of motion exercises and massage on muscle strength in critically ill patients. *BMC Sports Sci Med Rehabil* 2022; **14**(1): 96.
74. Rezvani H EM, Maroufizadeh S, Rahimi B. The Effect of Early Mobilization on Respiratory Parameters of Mechanically Ventilated Patients With Respiratory Failure. *Crit Care Nurs* 2022; **45**(1): 74-82.
75. Ribeiro BC PJ, Rocha AMC, Cunha CNSd, Cunha KdC, Falcão LFM, Torres DdC, Rocha LSdO, Rocha RSB. Different physiotherapy protocols after coronary artery bypass graft surgery: A randomized controlled trial. *Physiother Res Int* 2021; **26**(e1882).
76. Sarfati C, Moore A, Pilorge C, et al. Efficacy of early passive tilting in minimizing ICU-acquired weakness: A randomized controlled trial. *J Crit Care* 2018; **46**: 37-43.
77. Schaller SJ, Anstey M, Blobner M, et al. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet* 2016; **388**(10052): 1377-88.
78. Schujmann DS, Teixeira Gomes T, Lunardi AC, et al. Impact of a Progressive Mobility Program on the Functional Status, Respiratory, and Muscular Systems of ICU Patients: A Randomized and Controlled Trial. *Crit Care Med* 2020; **48**(4): 491-7.
79. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet* 2009; **373**(9678): 1874-82.
80. Shaaban L, Abdeen A, Saleh HM, Mahran SA, Farghaly S. Early rehabilitation program and weaning outcomes in critically ill chronic obstructed airway disease patients: a randomized trial. *The Egyptian Journal of Bronchology* 2022; **16**(1).
81. Shirvani F, Naji SA, Davari E, Sedighi M. Early mobilization reduces delirium after coronary artery bypass graft surgery. *Asian Cardiovasc Thorac Ann* 2020; **28**(9): 566-71.
82. Shosholcheva M JN, Kartalov A, Kuzmanovska B. Early physical rehabilitation improves outcome at mechanical ventilated patients. *Anesthesia & Analgesia* 2016; **123**(168).
83. Sosnowski K, Mitchell ML, White H, et al. A feasibility study of a randomised controlled trial to examine the impact of the ABCDE bundle on quality of life in ICU survivors. *Pilot Feasibility Stud* 2018; **4**: 32.
84. Suwardianto H PA, Utami RS. Effects of physical-cognitive therapy (PCT) on critically ill patients in intensive care unit. *Hiroshima J Med Sci* 2018; **67**: 63-9.
85. Tariq MI KA, Khalid Z, Farheen H, Siddiqi FA, Amjad I. Effect of Early ≤ 3 Mets (Metabolic Equivalent of Tasks) of Physical Activity on Patient's Outcome after Cardiac Surgery. *J Coll Physicians Surg Pak* 2017; **27**(8): 490-4.
86. Team Study Investigators, Group ACT, Hodgson CL, et al. Early Active Mobilization during Mechanical Ventilation in the ICU. *N Engl J Med* 2022; **387**(19): 1747-58.
87. Thammata A, Worraphan, S, Chittawatanarat, K, Juntaping, K, Prasannarong, M. Impact of inspiratory muscle training and early mobilization program during the peri-weaning period on body composition in critically ill surgical patients: A pilot randomized controlled trial. *Journal of Associated Medical Sciences* 2021; **54**(1): 58-66.
88. Varghese A RA, Wells C, Li G, Baer D, Parker EA, Buko A, Kaza V, Banga A, Bollineni S, Mahan LD, Mohanka M, Lawrence A, Joerns J, Torres F, Wait M, Iacono A, Verceles AC, Terada L, Terrin M, Timofte I. Post-Transplant Metabolomics Profiles in Patients Undergoing Lung Transplantation. *Elsevier Inc 4 edition* 2022; **41**.
89. Verceles AC, Serra M, Davis D, et al. Combining exercise, protein supplementation and electric stimulation to mitigate muscle wasting and improve outcomes for survivors of critical illness-The ExPrES study. *Heart Lung* 2023; **58**: 229-35.
90. Waldauf P, Hruskova N, Blahutova B, et al. Functional electrical stimulation-assisted cycle ergometry-based progressive mobility programme for mechanically ventilated patients: randomised controlled trial with 6 months follow-up. *Thorax* 2021; **76**(7): 664-71.

91. Wang XP, Lv D, Chen YF, et al. Impact of Pain, Agitation, and Delirium Bundle on Delirium and Cognitive Function. *J Nurs Res* 2022; **30**(4): e222.
92. Windmoller P, Bodnar ET, Casagrande J, et al. Physical Exercise Combined With CPAP in Subjects Who Underwent Surgical Myocardial Revascularization: A Randomized Clinical Trial. *Respir Care* 2020; **65**(2): 150-7.
93. Winkelman C, Sattar A, Momotaz H, et al. Dose of Early Therapeutic Mobility: Does Frequency or Intensity Matter? *Biol Res Nurs* 2018; **20**(5): 522-30.
94. Wolfe K S WBN, Patel S B, Patel B K, Greenberg J A, Pohlman A S, Hall J B, Kress J P. Long-term survival and health care utilization of mechanically ventilated patients in a randomized controlled trial of early mobilization. *Am J Respir Crit Care Med* 2013; **187**https://www.atsjournals.org/doi/abs/10.1164/ajrccm-conference.2013.187.1_MeetingAbstracts.A5235.
95. Wright SE, Thomas K, Watson G, et al. Intensive versus standard physical rehabilitation therapy in the critically ill (EPICC): a multicentre, parallel-group, randomised controlled trial. *Thorax* 2018; **73**(3): 213-21.
96. Wu T, Zhou S, Wu B, Chen J, Zhu X, Cai Y. The effect of early tracheal extubation combined with physical training on pulmonary rehabilitation of patients after lung transplantation: a randomized controlled trial. *J Thorac Dis* 2022; **14**(4): 1120-9.
97. Xue F LW, Zhang C, Zhang J, Yuan J, Ren B, He Q. Rehabilitation Therapy for Better Control of Critically Ill Patients. *Indian Journal of Pharmaceutical Sciences* 2020; **6**.
98. Yosef-Brauner O, Adi N, Ben Shahar T, Yehezkel E, Carmeli E. Effect of physical therapy on muscle strength, respiratory muscles and functional parameters in patients with intensive care unit-acquired weakness. *Clin Respir J* 2015; **9**(1): 1-6.
99. Yu L, Jiang JX, Zhang Y, Chen YZ, Shi Y. Use of in-bed cycling combined with passive joint activity in acute respiratory failure patients receiving mechanical ventilation. *Ann Palliat Med* 2020; **9**(2): 175-81.
100. Yu T, Cai F, Jiang R. Effects of Early Bedside Cycle Exercise on Gastrointestinal Function in Intensive Care Unit Patients Receiving Mechanical Ventilation. *Front Med (Lausanne)* 2022; **9**: 823067.
101. Yulan J HN, Liqin X. Early rehabilitation activities during mechanical ventilation should be used Analysis of curative effect in patients with severe AECOPD [**机械通气期**间早期康复活动应用于重度ＡＥＣＯＰＤ**病人的**疗效分**析**]. *Chinese Nursing Research* 2017; **32**(16): 1994-6.
102. Zanini M, Nery RM, de Lima JB, Buhler RP, da Silveira AD, Stein R. Effects of Different Rehabilitation Protocols in Inpatient Cardiac Rehabilitation After Coronary Artery Bypass Graft Surgery: A RANDOMIZED CLINICAL TRIAL. *J Cardiopulm Rehabil Prev* 2019; **39**(6): E19-E25.
103. Zeng H, Zhang Z, Gong Y, Chen M. [Effect of chest physiotherapy in patients undergoing mechanical ventilation: a prospective randomized controlled trial]. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2017; **29**(5): 403-6.
104. Zhou W, Yu L, Fan Y, et al. Effect of early mobilization combined with early nutrition on acquired weakness in critically ill patients (EMAS): A dual-center, randomized controlled trial. *PLoS One* 2022; **17**(5): e0268599.
105. Zhu C LB, Yang T, Mei Q, Pan A, Zhao D. Effect of early rehabilitation physiotherapy on muscle quality and function in critically ill patients. [**早期康复理**疗对危重症患者肌肉质量和功能的影响]. *Chinese Crit Care Med* 2018; **30**(6): 569-72.