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Does enhanced physical rehabilitation following intensive care unit discharge improve outcomes in patients who received mechanical ventilation? A systematic review and meta-analysis

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ABSTRACT

Objective We aimed to determine whether enhanced physical rehabilitation following intensive care unit (ICU) discharge improves activities-of-daily-living function, quality of life (QOL) and mortality among patients who received mechanical ventilation in the ICU.

Design Systematic review and meta-analysis using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Data sources MEDLINE, Embase, CENTRAL, PEDro and WHO International Clinical Trials Registry Platform searched through January 2019.

Eligibility criteria for selecting studies We included randomised controlled trials assessing the effect of post-ICU rehabilitation designed to either commence earlier and/or be more intensive than the protocol employed in the control group. Only adults who received mechanical ventilation for >24 hours were included.

Data extraction and synthesis Two independent reviewers extracted data and assessed risk of bias. Standard mean differences (SMDs) with 95% CIs were calculated for QOL, and pooled risk ratios (RRs) with 95% CIs are provided for mortality. We assessed heterogeneity based on I^2 and the certainty of evidence based on the GRADE approach.

Results Ten trials (enrolling 1110 patients) compared physical rehabilitation with usual care or no intervention after ICU discharge. Regarding QOL, the SMD (95% CI) between the intervention and control groups for the physical and mental component summary scores was 0.06 (−0.12 to 0.24) and −0.04 (−0.20 to 0.11), respectively. Rehabilitation did not significantly decrease long-term mortality (RR 1.05, 95% CI 0.66 to 1.66). The analysed trials did not report activities-of-daily-living data. The certainty of the evidence for QOL and mortality was moderate.

Conclusions Enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation in the ICU. Given the wide CIs, further studies are needed to confirm the efficacy of intensive post-ICU rehabilitation in selected populations.

PROSPERO registration number CRD42017080532.

Strengths and limitations of this study

- This is the first meta-analysis focused on enhanced physical rehabilitation to review randomised controlled trials in which the study intervention was conducted only after intensive care unit discharge.
- The conclusions are based on moderate-certainty evidence.
- The main limitations of this meta-analysis are that (i) few studies had a follow-up >6 months and (ii) medical resources and costs associated with each intervention were not considered.
- We employed rigorous methodology that followed a protocol developed a priori according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement, and used the Grading of Recommendations Assessment, Development and Evaluation approach in the review process.

INTRODUCTION

In critically ill patients, rehabilitation mainly aims to enhance quality of life (QOL) by improving activities-of-daily-living (ADL) function,[1 2] which may be severely impaired also due to postintensive care syndrome (PICS).[3–5] According to the guidelines issued by the National Institute for Health and Care Excellence, provision of rehabilitation should be seamlessly integrated with the patient's transition from the intensive care unit (ICU) to the ward and then to out-of-hospital care.[6] However, at the time the guidelines were issued, there was little evidence from clinical trials to support the use of enhanced physical rehabilitation following ICU discharge. Some experts do recommend physical rehabilitation following ICU discharge to improve ADL function and QOL.[7] With regard to sepsis survivors, the findings of a large observational

study suggested that physical rehabilitation following ICU discharge improves long-term mortality.[8 9]

A recent systematic review by Connolly *et al*[10] focused on randomised controlled trials (RCTs) regarding the effectiveness of enhanced exercise rehabilitation following ICU discharge in adult ICU survivors who had been mechanically ventilated for longer than 24 hours in the ICU. Despite the comprehensive search, this previous systematic review included only six RCTs with conflicting results, and no clear effect of the intervention on QOL, mortality, functional exercise capacity or incidence of adverse events could be established at the time. Additionally, ADL, pain, return-to-work rate, muscle strength and duration of delirium were not considered in that review.[10] Several RCTs assessing the effect of enhanced physical rehabilitation following ICU discharge on clinically relevant outcomes[11–15] have been published since Connolly *et al* conducted their Cochrane review.[10] Therefore, in the present study, we aimed to re-evaluate the available literature and determine whether enhanced physical rehabilitation following ICU discharge improves clinically relevant outcomes among critically ill adults who received mechanical ventilation.

MATERIALS AND METHODS

Compliance with reporting guidelines

Using a prespecified protocol (PROSPERO registry ID: CRD42017080532),[16] we conducted a systematic review of the relevant literature in agreement with the recommendations listed in the Cochrane Handbook[17] and the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[18] We confirmed that this systematic review was PRISMA-compliant by consulting the PRISMA 2009 checklist[19] (details provided in online supplementary file 1).

Research question and eligibility criteria

The research question addressed in this study was: 'Does enhanced physical rehabilitation following ICU discharge result in improved QOL, ADL function and mortality (compared with those achievable with usual care) among patients who received mechanical ventilation in the ICU?' We included all published and unpublished prospective RCTs involving adult human subjects (age ≥18 years) who had been discharged from an ICU or critical care environment after a stay of at least 48 hours during which mechanical ventilation was provided for at least 24 hours. Crossover trials, as well as cluster-randomised, quasi-randomised and non-randomised trials were excluded. Studies were included regardless of the intervention setting (in-hospital or out-of-hospital), follow-up duration and country of origin. We included patients of any sex and race, but excluded those receiving palliative care and those with head or spinal cord injuries, or unstable fracture diminishing mobility.

Intervention was defined as any protocolised rehabilitation following ICU discharge, designed to either commence earlier and/or be more intensive than the care received by the control group. To determine whether enhanced physical rehabilitation following ICU discharge improved clinically relevant outcomes, we excluded studies in which the patients in the intervention group received earlier and/or more intensive physical rehabilitation (compared with the care received by the control group) during their stay in the ICU. However, while we excluded studies in which enhanced rehabilitation was provided in the ICU, we did not exclude studies in which the same rehabilitation programme was provided in the ICU as standard care for both the intervention group and the control group. Protocolised rehabilitation consisting of one or more of the following activities was considered as a form of enhanced physical rehabilitation: neuromuscular stimulation, inspiratory or respiratory muscle training, passive range-of-motion exercise, cycle ergometer exercise, active-assisted exercises, active range-of-motion exercises, bed mobility activities (eg, bridging, rolling, lying-to-sitting exercise), ADL training, transfer training, pregait exercises (including marching in place) and walking exercise.

Outcomes of interest

The primary outcomes were QOL, ADL function and mortality. Secondary outcomes included functional exercise capacity, pain, return-to-work rate, muscle strength, duration of delirium and incidence of adverse events (defined by the trialists). We defined the intervention outcomes according to the timing of their evaluation postintervention, as short-term (evaluated at 28–35 days) or long-term (evaluated at 6 months).

Search strategy and selection of studies

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, Excerpta Medica Database (EMBASE) via Elsevier, the Physiotherapy Evidence Database (PEDro) and the WHO International Clinical Trials Registry Platform (WHO ICTRP) via their dedicated search portal. The search, which employed a set of suitable search terms (details provided in online supplementary file 2), was performed in December 2017 and updated in January 2019. We hand-searched reference lists for the guidelines for rehabilitation after critical illness.[6] We attempted to identify other relevant research by hand-searching the reference lists of the studies returned by the search and those of articles citing such studies (based on citation information from the Web of Science). If the database entry for a candidate study did not contain the necessary information, we contacted the study authors. Two reviewers (ST and KY) independently screened the title and abstract of each study returned by the search to determine whether the inclusion criteria were met. The two reviewers performed a full-text review to assess the eligibility of each candidate study. Disagreement was resolved by discussion between the two reviewers, occasionally with arbitration by a third reviewer (YK).

Data abstraction and quality assessment

Two reviewers (ST and KY) independently abstracted trial-level data using prespecified forms. Disagreements regarding data extraction were resolved through discussions. Where necessary, we contacted the authors of studies that did not provide sufficient information. The risk of bias in each study was assessed independently by two reviewers (ST and KY) using the Cochrane risk-of-bias assessment tool.[17] Differences in opinion regarding the assessment of risk of bias were resolved through discussion between the two reviewers, occasionally with arbitration by a third reviewer (KY).

Data analysis

All analyses were conducted using the Cochrane Review Manager software (RevMan V.5.3; Cochrane Collaboration, Copenhagen, Denmark). For the dichotomous variables of mortality and return-to-work rate, pooled risk ratios (RRs) with 95% CIs are provided. For continuous outcomes including QOL scores, ADL function scores, pain, muscle strength and duration of delirium (expressed in days of ICU or hospital stay), the standardised mean differences or the mean differences with 95% CIs were calculated, as recommended by the Cochrane Handbook.[17] Adverse events were narratively summarised because their definition often varies across studies. We used the random-effects models for all analyses.

We calculated I^2 as a measure of variation across studies that is due to heterogeneity rather than chance, and interpreted the values as follows: 0%–40%, negligible heterogeneity; 30%–60%, mild-to-moderate heterogeneity; 50%–90%, moderate-to-substantial heterogeneity; 75%–100%, considerable heterogeneity. If heterogeneity was identified for an outcome (I^2 >50%), we investigated the underlying reasons and conducted the χ^2 test, with a p value of <0.10 being considered to indicate statistical significance. We investigated reporting bias by checking the WHO ICTRP to detect trials that had been completed but not published at the time of the review.

We planned the following prespecified sensitivity analyses for the primary outcomes: (i) exclusion of studies using imputed statistics and (ii) exclusion of studies with high or unclear risk of bias. We also carried out prespecified subgroup analyses according to the type of rehabilitation involved (neuromuscular stimulation vs other types of rehabilitation), rehabilitation provision in the ICU (received vs did not receive protocolised physical rehabilitation in the ICU), timing of commencement of the intervention (in-hospital or after hospital discharge), intervention duration (≤8 vs >8 weeks), treatment frequency (<5 vs ≥5 times/week) and type of control (no intervention vs standard rehabilitation). Statistical significance was also set at p<0.05. We created a summary-of-findings table that included an overall grading of the certainty of evidence for each of the main outcomes, which was evaluated using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[20 21]

Patient and public involvement

The patients or public were not involved in this meta-analysis.

RESULTS

Characteristics of trials on rehabilitation in ICU survivors

After removing duplicates, we identified 3589 records during the search conducted in December 2017 and updated the electronic searches in January 2019. We identified 10 unique RCTs[11–13 15 22–27] that fulfilled all eligibility criteria and were included in the qualitative synthesis (figure 1; details provided in online supplementary file 3). The 10 RCTs provided a pooled sample of 1110 critically ill patients with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours. Eight studies were performed in the UK, one in Australia and one in India. The mean or median age in the analysed studies ranged from 40.5 to 68.5 years, while the mean or median Acute Physiology and Chronic Health Evaluation II score ranged from 15.2 to 31. Only one RCT included participants with PICS symptoms or ICU-acquired weakness.[11] Three RCTs[25–27] did not have sufficient outcome data for meta-analysis (details provided in online supplementary file 4), leaving a total pooled sample of 1000 patients (506 patients in the intervention groups; 494 controls) represented across seven studies to be included in the quantitative synthesis. Of the 10 trials analysed, 6 evaluated the effect of physical rehabilitation including self-directed exercise and/or supervised exercise following hospital discharge, while 4[12 22–24] focused on rehabilitation started during hospitalisation. The duration of intervention ranged from 6 weeks to 3 months, while the frequency of intervention ranged from three times per week to once daily. No study considered intensive intervention (>30 min of active rehabilitation daily) or intervention with neuromuscular stimulation. Two studies[12 23] had a follow-up >6 months. We did not identify any ongoing studies.

Most studies were at high or unclear risk of bias, as determined using the Cochrane risk-of-bias assessment tool[17] (details provided in online supplementary file 5). All 10 studies demonstrated adequate random sequence generation and allocation concealment, but participants and personnel were not blinded to the intervention. One study[11] demonstrated a high risk of detection bias for all outcomes except mortality, and another study[27] did not report whether or not the outcome assessor was aware of group allocation. Five studies had high risk of incomplete outcome data. Four studies had high risk of selective reporting bias, and two studies had unclear risk of bias because the protocols were not published. High or unclear risk of other bias was noted for all studies because of insufficient information regarding the intervention and control protocols.

Primary outcomes

QOL was measured in nine trials (see online supplementary file 3), but the short-term and long-term QOL

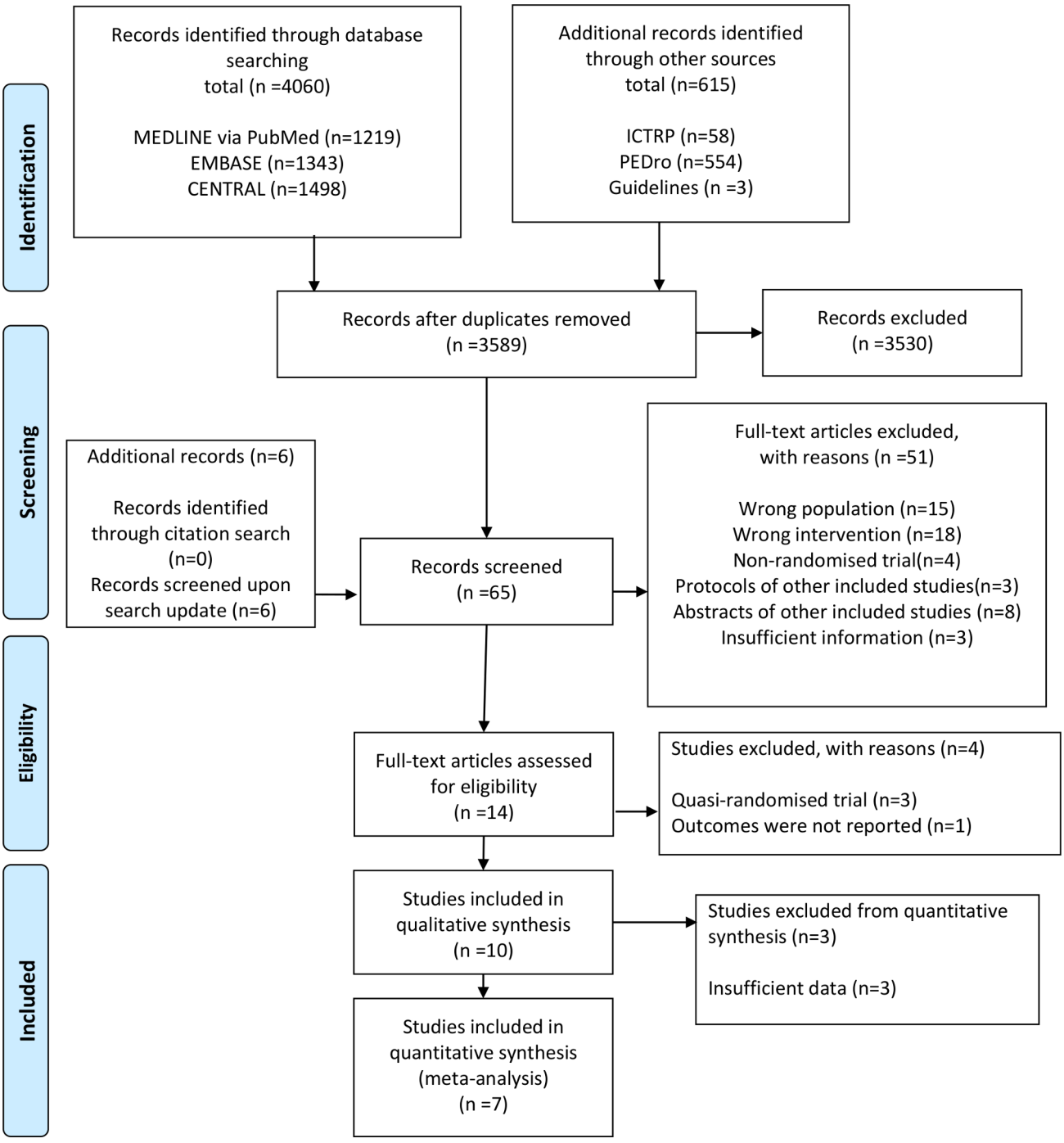
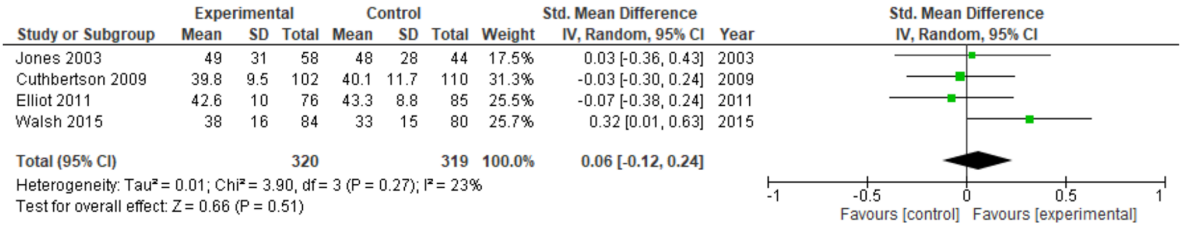


Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flow diagram.

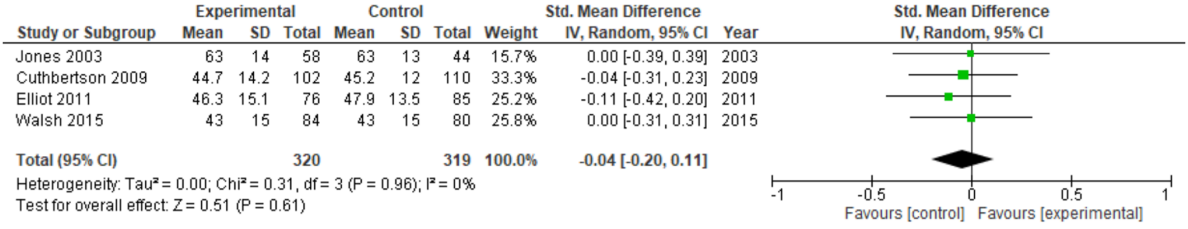
scores were only available in four trials,[12 22–24] whereas the other five trials measured these outcomes at a different time or had insufficient outcome data for meta-analysis. ADL function was measured in one trial,[11] but the short-term and long-term data were not available. Short-term mortality was reported in two trials,[11 13] while long-term mortality was reported in five trials.[12 15 22–24]

The standard mean deviation between intervention and control regarding the physical and mental component summary scores measured using QOL questionnaires (Short Form 36 or Short Form 12) were 0.06 (95% CI −0.12 to 0.24) and −0.04 (95% CI −0.20 to 0.11), respectively (figure 2A,B respectively). Rehabilitation did not significantly decrease short-term mortality (RR 0.71; 95% CI 0.05 to 9.80, I^2=33%; n=93) (figure 2C) or long-term mortality (RR 1.05; 95% CI 0.66 to 1.66, I^2=0%; n=907) (figure 2D). The certainty of evidence for QOL and long-term mortality was moderate, while that for short-term mortality was low (table 1). The lack of benefit of enhanced physical rehabilitation after ICU discharge was confirmed on additional analysis of QOL scores and mortality at 12 months postintervention (see details provided in online supplementary file 6).

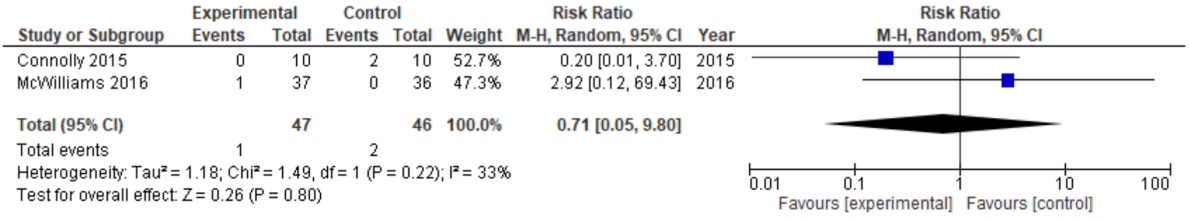
A Quality of life: physical component summary



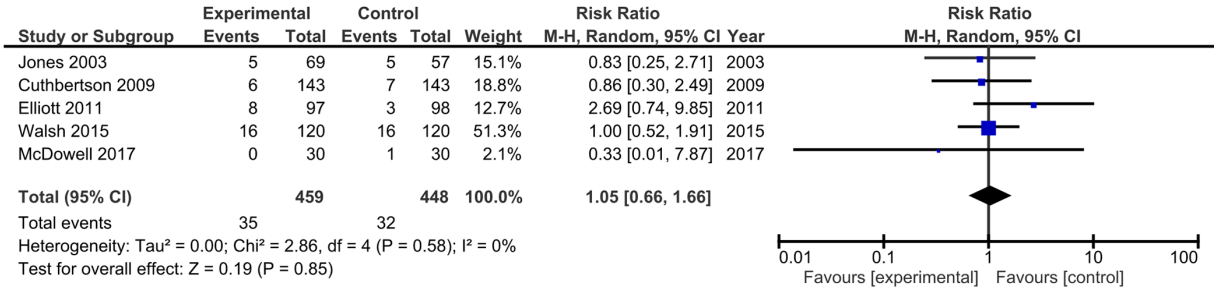
B Quality of life: mental component summary



C Short term mortality



D Long term mortality



We converted median (inter quartile range) of QOL score in Walsh's study to mean (standard deviation).

Figure 2 Forest plot for quality of life and mortality.

We could not carry out all prespecified sensitivity analyses because there was no study using imputed statistics, and we judged that the risk of bias of all included studies was similar in terms of random sequence generation, allocation concealment, incomplete outcome data and other bias. The prespecified subgroup analyses for the primary outcomes revealed no significant differences among subgroups (see details provided in online supplementary file 7).

Secondary outcomes

Functional exercise capacity was measured in two trials,[11 24] pain was measured in one trial[12] and muscle strength was measured in one trial,[11] but short-term and long-term data were not available. No trials evaluated return-to-work rate or incidence of delirium.

Adverse events were measured in three trials.[11 13 15] Two studies[11 13] reported no adverse events. One study[15] reported 18 events in the intervention group and 5 events in the control group. Among the 18 adverse events reported in the intervention group, 12 were mild or moderate (musculoskeletal pain higher than expected or muscle soreness potentially indicating injury, 3 cases; any pain higher than expected, 1 case; cardiac symptoms or chest pain, 1 case; any other event considered by the researcher to be of concern, 7 cases; 6 of 12 events were considered to be related or possibly related to study participation), while 6 were serious (hospitalisation or prolonged hospitalisation, with one event related/possibly related to study participation). In the control group, there was one adverse event (musculoskeletal

Table 1 Findings from 10 trials focused on post-ICU rehabilitation of critically ill patients who received mechanical ventilation

Overview of study design

***Patients or study population*: adult patients who have been discharged from an ICU or critical care environment during which mechanical ventilation was provided for at least 24 hours.**
***Setting*: any.**
***Intervention*: protocolised physical rehabilitation following ICU discharge, designed to be more intensive than the care received by the control group.**
***Comparison*: no intervention or usual care.**

Outcome	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk Control	Corresponding risk Intervention				
Quality of life Physical component summary score (6 months)	**Study population**	**SMD: 0.06** (–0.12 to 0.24)		639 (4 RCTs)	⊕⊕⊕⊖ **Moderate**†	
Quality of life Mental component summary score (6 months)	**Study population**	**SMD: –0.04** (–0.20 to 0.11)		639 (4 RCTs)	⊕⊕⊕⊖ **Moderate**†	
Mortality Short term (28–35 days)	**Study population** **43 per 1000**	**31 per 1000** (2 to 426)	**RR: 0.71** (0.05 to 9.80)	93 (2 RCTs)	⊕⊕⊖⊖ **Low**‡§	
Mortality Long term (6 months)	**Study population** **71 per 1000**	**75 per 1000** (47 to 119)	**RR: 1.05** (0.66 to 1.66)	907 (5 RCTs)	⊕⊕⊕⊖ **Moderate**¶	
Adverse events	**Study population** Two studies reported no adverse events. One study reported 18 and 5 events in the intervention and control groups, respectively.			153 (3 RCTs)	⊕⊕⊖⊖ **Low****††	

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: 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 a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.
*The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect (and its 95% CI) estimated for the intervention group.
†Downgraded one point because of high risk of bias associated with the lack of information regarding the dose of physical rehabilitation and adherence in the intervention group (other bias).
‡Downgraded one point because of high risk of bias associated with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).
§Downgraded because of imprecision (only two small studies).
¶Downgraded one point because of high risk of bias associated with incomplete outcome data and lack of information regarding the dose of physical rehabilitation and adherence in the intervention group, as well as with the fact that the intervention included nutritional therapy but the study provided very little detail regarding the therapy received in the control group (other bias).
**Downgraded one point because of high risk of bias associated with the fact that very little detail was given regarding the therapy received in the control group, and the adherence in the intervention group was 70% (other bias).
††Downgraded because of imprecision (only three small studies).
GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; RCT, randomised controlled trial; RR, risk ratio; SMD, standardised mean difference.

pain higher than expected, muscle soreness potentially indicating injury, related/possibly related to study participation) and four serious adverse events (hospitalisation or prolonged hospitalisation, with one event related/possibly related to study participation). The certainty of evidence for adverse events was low (table 1).

DISCUSSION

The results of this up-to-date review covering 10 RCTs and 1110 patients suggest that enhanced rehabilitation following ICU discharge might not improve QOL or reduce mortality at 6 or 12 months postintervention among patients who received mechanical ventilation in the ICU. We could not confirm the effect of enhanced physical rehabilitation even though all included studies exhibited performance bias potentially increasing the observed effect of the intervention. Furthermore, despite the large sample size in the meta-analysis for QOL and long-term mortality, limited data for these outcomes were available, and the certainty of evidence was only low or moderate.

Furthermore, subgroup meta-analyses revealed no differences among subgroups defined according to the nature or timing of the intervention. The previous review by Connolly *et al*[10] did not conduct meta-analysis due to the limited number of included studies. A recent systematic review of ICU rehabilitation[28 29] also reported no significant difference in QOL between the intervention and control groups. Thus, neither enhanced rehabilitation in the ICU nor rehabilitation following ICU discharge appear to be superior to standard care in terms of QOL outcomes. In addition, we found no benefit in terms of short-term or long-term mortality regardless of timing of commencement, which is consistent with previous findings that ICU rehabilitation did not decrease mortality at ICU discharge, at hospital discharge or at 6 months after discharge.[28 30] On the other hand, rehabilitation may be detrimental in acute conditions. Specifically, intensive physical rehabilitation started within 48 hours of admission for exacerbations of chronic respiratory disease increased mortality at 12 months,[31] and higher-dose physical rehabilitation very early after stroke decreased favourable outcomes at 3 months.[32] Thus, implementation of an intensive rehabilitation programme might not be indicated in all patients who received mechanical ventilation in the ICU.

Subgroup analysis in a previous systematic review[28] indicated that, compared with low-dose rehabilitation, high-dose active rehabilitation for >30 min daily was associated with significantly higher QOL. Dose-response analysis of early physical rehabilitation[33] in patients with stroke enrolled in A Very Early Rehabilitation Trial[32] determined that intervention in such acute cases improved the odds of a favourable outcome with each episode of activity per day. Our present review did not include studies comparing high-dose rehabilitation and usual care, and thus the QOL effect of high-dose rehabilitation remains unclear. Additionally, we could not perform subgroup analysis for PICS symptoms with effect on QOL[3–5] or for sepsis, which is a risk factor for PICS.[34 35] It remains unclear which population of critically ill patients may truly benefit from intensive physical rehabilitation.

The studies included in our review did not cover all important outcomes included in the core outcome set of rehabilitation after critical illness,[7] including ADL function, functional exercise capacity, pain, return-to-work rate, muscle strength or delirium incidence. Nonetheless, our findings regarding QOL and mortality suggest that, even if future studies report improvement in these other aspects, the amount of improvement would likely be too small to affect QOL.

The present review has several strengths. First, we employed rigorous methodology that followed a written protocol developed a priori according to the PRISMA statement, including a comprehensive search for evidence. Second, we performed duplicate assessment of eligibility, risk of bias and data abstraction. Third, we used the GRADE approach for assessing the certainty of evidence. In addition, we only included RCTs, most of which were multicentre studies. We could thus conduct an intention-to-treat analysis to understand the effect of intensive physical rehabilitation or standard care, which gives a pragmatic estimate of the benefit of a change in treatment policy. Fourth, the cohorts of ICU survivors are heterogeneous in terms of demographics and pathologies. To confirm the effect of enhanced physical rehabilitation for a particular group, we selected studies including only participants with an ICU stay of >48 hours during which mechanical ventilation was provided for at least 24 hours.

This systematic review has several potential limitations. First, few studies[12 23] had a follow-up >6 months, and thus we could not consider longer follow-up data for primary analysis. The meta-analysis should be updated as the outcomes of further studies with follow-up beyond 6 months become available. Second, none of the studies included in our meta-analysis reported mortality outcomes as time-to-event data, which is the preferred approach for reporting mortality data. Future studies should report time-to-event data for mortality. Third, we could not take into account the medical resources and costs associated with each intervention. However, since studies included in this review compare rehabilitation intervention against standard care or no intervention, it is obvious that intensive physical rehabilitation would be associated with increased medical resources and costs. Fourth, the outcome measures might be not sufficiently sophisticated. For example, the RECOVER (Evaluation of a Rehabilitation Complex Intervention for Patients Following Intensive Care Discharge) trial[12] did not demonstrate an improvement in the primary quantitative outcome, but showed evidence of benefit of the intervention in a parallel qualitative evaluation.[36] Fifth, we could not consider the psychological aspects that are likely to affect the outcomes of rehabilitation. While our findings

indicate a lack of benefit of enhanced post-ICU rehabilitation in the evaluated population, highly self-motivated individuals might have derived benefit from such therapies. Further studies should collect data on motivation and engagement, which are crucial in maximising the benefits of rehabilitation.[37] Lastly, the patient characteristics, follow-up timing and types of outcomes reported might exhibit substantial heterogeneity across trials and within each individual trial, an aspect we did not examine in the present analysis. However, on reviewing the best available evidence based on a standardised approach, we confirmed that the direction of the effect and the effect size of enhanced post-ICU physical rehabilitation were similar in pooled studies, as reflected in the forest plots (see details in online supplementary file 7).

Taken together, the findings of the present meta-analysis indicate that enhanced physical rehabilitation following ICU discharge may make little or no difference to QOL or mortality among patients who received mechanical ventilation in the ICU. Given the wide CIs, further studies are needed to determine the efficacy of enhanced rehabilitation in selected populations of ICU survivors.

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