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SYSTEMATIC REVIEW

# The effects of active mobilisation and rehabilitation in ICU on mortality and function: a systematic review

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**Abstract**

**Purpose:** Early active mobilisation and rehabilitation in the intensive care unit (ICU) is being used to prevent the long-term functional consequences of critical illness. This review aimed to determine the effect of active mobilisation and rehabilitation in the ICU on mortality, function, mobility, muscle strength, quality of life, days alive and out of hospital to 180 days, ICU and hospital lengths of stay, duration of mechanical ventilation and discharge destination, linking outcomes with the World Health Organization International Classification of Function Framework.

**Methods:** A PRISMA checklist-guided systematic review and meta-analysis of randomised and controlled clinical trials.

**Results:** Fourteen studies of varying quality including a total of 1753 patients were reviewed. Active mobilisation and rehabilitation had no impact on short- or long-term mortality ($p > 0.05$). Meta-analysis showed that active mobilisation and rehabilitation led to greater muscle strength (body function) at ICU discharge as measured using the Medical Research Council Sum Score (mean difference 8.62 points, 95% confidence interval (CI) 1.39–15.86), greater probability of walking without assistance (activity limitation) at hospital discharge (odds ratio 2.13, 95% CI 1.19–3.83), and more days alive and out of hospital to day 180 (participation restriction) (mean difference 9.69, 95% CI 1.7–17.66). There were no consistent effects on function, quality of life, ICU or hospital length of stay, duration of mechanical ventilation or discharge destination.

**Conclusion:** Active mobilisation and rehabilitation in the ICU has no impact on short- and long-term mortality, but may improve mobility status, muscle strength and days alive and out of hospital to 180 days.

**Registration of protocol number:** CRD42015029836.

**Keywords:** Intensive care units, Critical illness, Early mobility, Rehabilitation, Mortality

## Introduction

Patients admitted to intensive care units (ICUs) often require multiple treatments that result in immobility and bed rest [1]. One of the consequences of bed rest in critically ill patients is profound muscle weakness, termed ICU acquired weakness (ICU-AW) which occurs within 24 h and continues to progress [2]. ICU-AW is not yet fully understood, but is likely due to a combination of muscle atrophy and inflammatory processes [3, 4]. Patients at ICU discharge have significant muscle weakness and decreased functional status [5] and it can take 1–2 years to reach peak functional recovery [6] and in some cases patients never fully recover [7].

There are many factors which may impact on functional recovery post critical illness, including premorbid health status (i.e. frailty [8], co-morbidities [9, 10] and

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functional status) and factors occurring during critical illness (i.e. medications provided, presence of sepsis [7], length of mechanical ventilation) [11].

The use of mobilisation as an intervention to improve muscle strength and function in ICU patients is feasible and safe, with very few adverse events recorded [12, 13]. A previous meta-analysis found that there was no significant association between mobilisation in the ICU and improvements in functional status, muscle strength, quality of life or healthcare utilization [14]. However mobility in the ICU was associated with improved walking ability compared to usual care at hospital discharge [14]. There have been several recently published randomised controlled trials (RCTs) that have not yet been included in a systematic review or meta-analysis.

Because of the complexity of acute and critical illness it is possible that there may be adverse outcomes of rehabilitation starting early in the ICU stay [15]. Although the mechanism by which rehabilitation in ICU might impact on mortality and morbidity is not clear, it is important to establish whether rehabilitation during critical illness results in beneficial or harmful effects and whether it differs for interventions commenced early or later during the ICU stay or in higher or lower doses.

The aims of this systematic review and meta-analysis were to determine the impact of active mobilisation and rehabilitation in the ICU on (1) patient mortality (measured at ICU discharge, hospital discharge, 3 and 6 months) compared to standard care; (2) patient's functional status, mobility status, muscle strength, quality of life, number of days alive and out of hospital to 180 days, duration of mechanical ventilation, ICU and hospital length of stay and discharge destination compared to standard care.

## Methods

The PRISMA guidelines for systematic reviews and meta-analysis [16] (Electronic Supplementary Material (ESM) 1, Table 1) and the Cochrane Handbook [17] were followed and the protocol was registered [18].

### Search strategy

A comprehensive electronic search of MEDLINE, CINAHL, EMBASE, LILACS, Scopus and Web of Science was undertaken, using a detailed search strategy (ESM 2, Table 1). Clinical trials websites [19, 20] were also searched. All resources were searched from inception to June 2016. The reference list of included articles and systematic reviews were searched for additional studies. Authors of eligible studies were contacted for clarification of methodology and results in the case of unpublished or missing data.

### Inclusion and exclusion criteria

#### *Types of studies*

Studies were included if they were randomised or controlled clinical trials written in English.

#### *Type of patients*

Adult patients admitted to the ICU for greater than 24 h.

#### *Interventions*

Active mobilisation and rehabilitation delivered in the ICU by any members of the ICU team. This could include any combination of active exercises in bed, bed mobility practice, progression of mobility from sitting, to standing and ambulation, tilt table therapy or hoisting to a chair.

Studies were excluded if they investigated passive therapies only, started rehabilitation after discharge from the ICU, or were conducted in long-term weaning centres or rehabilitation facilities. Cycle ergometry and functional electrical muscle stimulation used as the sole rehabilitation therapy were not included, as they do not involve the same complexities surrounding sedation and cardiovascular and respiratory stability that are encountered with out-of-bed active exercise.

#### *Control*

For studies to be eligible the control group needed to be receiving standard physical therapy as determined by the treating centre during the ICU admission and standard medical and nursing care.

#### *Types of outcome measures*

The primary outcome was mortality measured at hospital discharge. The secondary outcomes were mortality at ICU discharge and 6 and 12 months after admission; functional status, mobility, muscle strength and quality of life and mood state at ICU discharge, hospital discharge and 6 and 12 months follow-up (ESM 2). Days alive and out of hospital to 180 days, length of stay (ICU and hospital), duration of mechanical ventilation and discharge destination were also included. Outcomes were categorised using the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF) components into Body Functions (b1-8), Activity Limitation (d1-4) and Participation Restriction (d5-9) [21].

### Selection of studies

Titles and abstracts were screened by two independent reviewers (CT, TN). Disagreements were resolved by consensus. Covidence was used to manage and review citations [22]. The full text of eligible and uncertain references were then reviewed (CT, TN), with a third reviewer (CH) as necessary.

### Data extraction

A data extraction form was developed and piloted (CT). Data were extracted by two independent researchers. Disagreements were resolved using consensus, and by a third reviewer if necessary. Where the data extraction was unclear or required further detail, study authors were contacted by email for clarification of results. One of the included studies [23] was co-authored by three of the authors on this paper; therefore two external independent reviewers completed data extraction and the risk of bias assessment.

### Assessment of methodological quality

The studies were independently assessed by two researchers for methodological quality using the Cochrane risk of bias tool [17]. This tool assesses seven domains of bias as high, low or unclear risk; selection, performance, detection, attrition and reporting bias. Any other potential bias can also be reported [17].

### Data synthesis and analysis

Meta-analysis was performed using Review Manager 5.3 (RevMan 5.3). Dichotomous variables were presented as relative risks or odds ratios, whilst continuous variables were expressed as mean differences between groups and associated confidence intervals (CI).

Data that were presented non-parametrically were assessed for suitability for conversion to parametric statistics to allow for meta-analysis [17]. The data were converted by replacing the median with mean, and the standard deviation (SD) was calculated by dividing the interquartile range by 1.35. The skew was then assessed by calculating the ratio of mean/SD. A ratio less than 2 demonstrates some skew, and less than 1 demonstrates strong evidence of skewed deviation and data was not converted [24].

Meta-analysis was performed when data were presented for the same outcome at the same time point, providing the studies were clinically and statistically homogenous. Clinical heterogeneity was determined by reviewing the setting, participants, intervention and control therapies and statistically by assessing the $I^2$ value [17]. $I^2$ values were interpreted as 0–40% might not be important, 30–60% may represent moderate heterogeneity, 50–90% may represent substantial heterogeneity and 75–100% considerable heterogeneity [17]. As a result of the high level of heterogeneity across all studies, random effects methods were used for all meta-analysis.

Subgroup analyses were undertaken for all outcomes, where able, in two predefined subgroups:

- Early active mobilisation and rehabilitation defined as commencing ≤3 days of admission, compared to late starting after the first 3 days of ICU admission
- High dose of rehabilitation defined as completing over 30 min of active rehabilitation daily, compared to those receiving less than 30 min daily

Subgroups were determined on the basis of the positive results of trials commencing rehabilitation early [12] and preliminary data on inflammatory changes in early rehabilitation [25] and from the results of high dosage rehabilitation studies [15].

A post hoc analysis was completed to determine if methodological quality was a cause for the statistical heterogeneity observed in the meta-analysis. This is described in detail in ESM 2.

## Results

### Study selection

The search of all databases resulted in 8380 articles, of which 13 studies of active mobilisation and rehabilitation in the ICU were included (Fig. 1) [12, 23, 25–35]. There were five studies identified from clinical trials registries; one of these studies was completed prior to publication of this systematic review and therefore was included [36] (ESM 2, Table 2).

No further articles were found from hand searches. One study [12] was published in two reports, one for inpatient hospital data [12] and another for the long-term follow-up [37] and both were reported in Fig. 2 risk of bias assessment.

### Risk of bias assessment

The risk of bias assessment is outlined in Fig. 2. Three studies were of low quality with four or five sources of bias [28, 31, 32], two studies were controlled clinical trials and therefore had a high risk of bias for many of the criteria [29, 35], four studies were of moderate quality with three sources of bias [25, 33, 34, 36], and the remaining studies had minimal sources of bias [12, 23, 26, 27, 30].

### Patients

In total, 1753 patients were represented across the 14 studies (880 intervention and 873 control). They represented a range of medical, surgical and trauma patients, recruited in nine different countries and across 25 sites. Patient demographics are presented in Table 1 and details of the study centres and further patients demographics in ESM 2, Table 3. The patients in the intervention and control groups in each study were similar at baseline, except for two studies where the intervention patients were significantly older [23, 30] and had poorer muscle strength and bed mobility on enrolment; however this difference was not significant [30].

### Intervention therapy

Details of the therapies received are outlined in Table 1. Commencement of the intervention ranged from 1 to

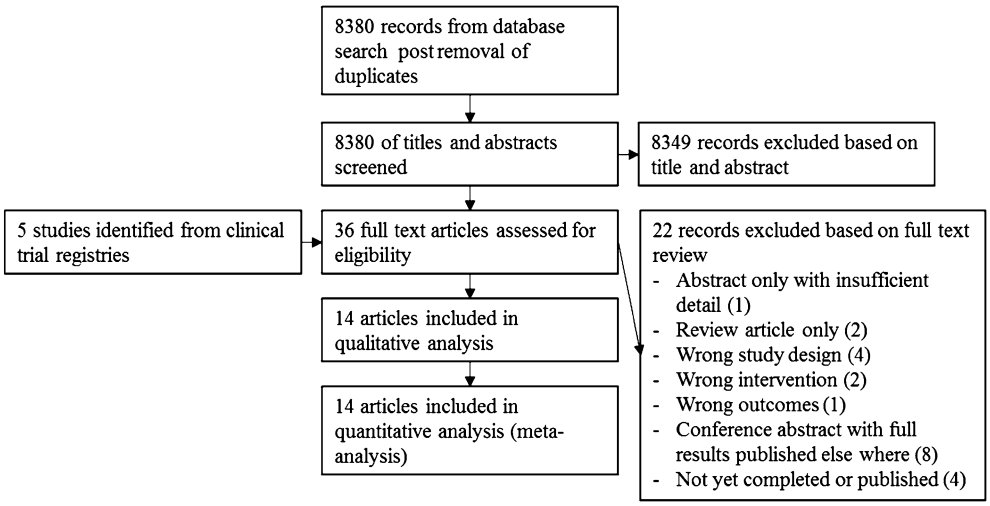


**Fig. 1** Consort diagram

8 days after admission to the ICU. Therapy was provided at least daily in the intervention groups and ranged from an average of 15 to 31 min of therapy per day. Further details of timing and duration of the interventions delivered in the studies are outlined in ESM 2, Table 3. Eleven studies used a protocol to guide the intervention therapies [23, 26, 27, 29–36], whilst the other three individually tailored therapy to each patient [12, 25, 28]. Progression of exercise was determined by sedation [25, 26, 34], strength [30–32, 35], fatigue [33], level of mobility (IMS [38]) [23], function [27] or a combination of these factors [36]. One study aimed to exercise patients at an intensity of 3–5 on the modified Borg scale whilst in the ICU [27], whilst another aimed for 12–13 on the Borg scale [32].

One study had two intervention arms, namely physical therapy alone and physical therapy combined with cognitive therapy [26]; results from the cognitive therapy group were not included. Five of the studies had little detail regarding the timing of the intervention [31, 32, 34–36] and seven studies had little detail regarding duration of intervention [28, 31–36] and therefore, despite attempts to contact the corresponding authors, were not included in the subgroup analyses. A post hoc analysis was completed to investigate whether methodological quality was a cause for the detected statistical heterogeneity across the studies. These results are outlined in ESM 2.

### Control therapy

There was large variation in the standard therapy provided in the control groups. The control group in six studies received daily therapy as part of standard care [23, 25, 27, 31, 32, 35]. This mainly involved passive or active assisted range of motion and was individually tailored. The other eight studies received therapy one to three times a week, with limited resources [12, 26, 28–30, 33, 34, 36]. One study reported that physical therapy was not routinely provided in patients mechanically ventilated for less than 2 weeks [12].

### Effects of intervention

#### *Mortality*

All studies reported mortality at one or more time points (Fig. 3). One study reported the *p* value only and therefore could not be included in the meta-analysis [29]. As not all centres used central death registries to report mortality, no assumptions were made for the patients who were not followed up at 6 months. Mortality was calculated by the number of patients at risk and therefore at 6 months was influenced by the number of patients who withdrew or were lost to follow-up. In a pooled analysis no significant difference was found in mortality at any time point (Fig. 3). Subgroup analysis showed that early mobilisation and high dose rehabilitation had no significant effect on mortality (ESM 2, Table 4).

#### *Measures of body function*

Five of the studies reported three different measures of body functions at relevant time points [12, 23, 25, 31, 32] (ESM 2, Table 5). Four studies reported MRC-SS at ICU discharge [23, 25, 31, 32]; however, raw results for one study were unable to be obtained and could not be included in the meta-analysis [31]. Analysis of the three studies demonstrated an improvement in muscle strength favouring rehabilitation in the ICU (pooled mean difference (MD) 8.62, 95% CI 1.39–15.86, $p = 0.02$,

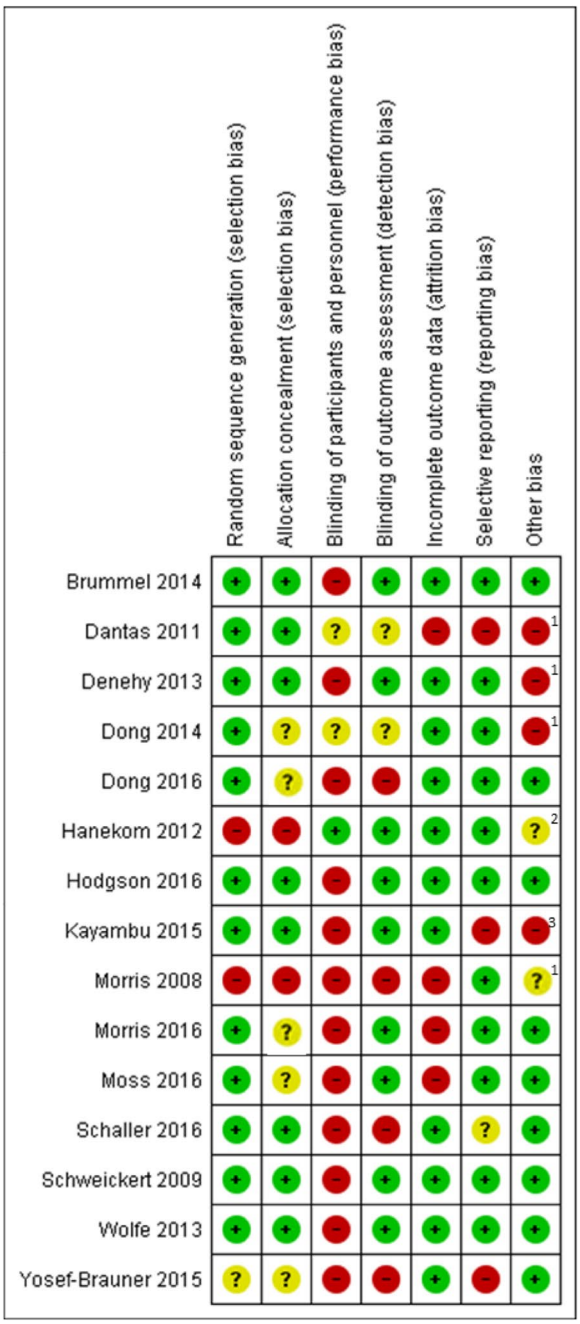


**Fig. 2** Risk of bias assessment. *Red* denotes high risk, *yellow* unclear risk and *green* low risk. [1]Very little detail given regarding the therapy received in the control group. No details given regarding the duration and intensity of the therapy. [2]Historical controls, therefore could be some added bias. [3]Health-related quality of life outcome does not account for non-survivors

$I^2 = 73\%$, three studies, $n = 120$) [23, 25, 32]. When one study of high risk of bias was removed the $I^2$ decreased to 0% and the result was still significant (ESM 2, Fig. 1). Three studies reported strength using the hand-held dynamometer at ICU discharge [12, 31, 34]; however, the raw values could not be obtained for one study [31] and the data from one study was severely skewed and was not appropriate for conversion to mean and SD [12]. No other meta-analyses were appropriate.

#### *Measures of activity limitation*

Nine studies reported 14 different measures of activity limitations (ESM, Table 6) [12, 23, 25–27, 30, 31, 34, 36]. Two studies reported ability to walk independently at hospital discharge [12, 29]. One study presented the information graphically [12]; therefore the numerical results were gathered from a previous systematic review [14]. In a pooled analysis, patients in the rehabilitation group had a higher probability of mobilising without assistance at hospital discharge (OR 2.13, 95% CI 1.19–3.83, $p = 0.01$, $I^2 = 0\%$, two studies, $n = 189$). Three studies reported the PFIT at ICU discharge. Pooled analysis demonstrated no significant difference between the intervention and control group (MD −0.19, 95% CI −0.69 to 0.32, $I^2 = 0\%$, three studies, $n = 207$) [23, 25, 27]. There were no differences between groups for any of the subgroup analysis [23, 25, 27] (ESM 2, Table 4).

Two studies report TUG at hospital discharge [26, 27] and two studies at 6 months [27, 30]. The data from one of the studies at hospital discharge was highly skewed [26] and not appropriate for meta-analysis. The pooled analysis at 6 months showed no difference between the rehabilitation and standard care groups (MD 0.11, 95% CI −5.96 to 6.19, $I^2 = 66\%$, two studies, $n = 146$) [27, 30]. No subgroup analysis or other meta-analysis could be performed.

#### *Measures of participation restriction*

Nine studies reported 13 different measures of participation restriction at the time points of interested for this review (ESM 2, Table 7) [12, 23, 25–27, 29, 30, 34, 36]. Four studies reported the SF-36 at 6 months [25, 27, 30, 34]; however, one study only reported physical function and the physical and mental component score [34]. One study reported non-parametric results which were converted to mean and standard deviation for meta-analysis [17, 30]. The pooled analysis of the four studies showed no significant difference between the intervention and control groups (ESM 2, Table 8) [25, 27, 30, 34]. In the social functioning domain, when one study of high risk of bias was removed the $I^2$ value decreased to 0%. There was no change in the $I^2$ when separating by methodological quality in the other three domains (ESM 2, Table 8). The subgroup analysis of three studies ($n = 177$) showed significantly higher SF-36 results favouring the intervention group in the role physical and role emotional domains for high dose rehabilitation [25, 30], compared to low dose

**Table 1 Demographic characteristics of patients and description of therapy from studies included in the systematic review**

| References, type of study | Population | Group allocation | Number | Age, mean ± SD or median (IQR) | Sex, *n* (%) females | Description of therapy |
|---|---|---|---|---|---|---|
| Brummel et al. [26] Feasibility RCT | Adult patients with respiratory failure, sepsis or shock and likely to benefit from rehabilitation | Intervention | 22 | 62 (48–67) | 9 (41) | Therapy commenced early, delivered daily by nurses and physicians or physical therapists and OT. Exercise guided by RASS, and titrated to allow patients to reach their maximal functional milestones as rapidly as possible |
| | | Control | 22 | 60 (51–69) | 14 (64) | Physical therapy once ordered by the treating clinicians (approx. 1–2 sessions per week) |
| Dantas et al. [32] RCT | Adult MV patients, with adequate cardiovascular reserve and independent mobility prior | Intervention | 14 | 59.07 ± 15.22 | 7 (50) | Patients received a systematic mobilisation protocol, 2× a day, every day of the week |
| | | Control | 14 | 50.43 ± 20.45 | 10 (71) | Received passive mobilisation 5 × a week and active-assisted exercises according to patient improvement and cooperation |
| Denehy et al. [27] RCT | Adult patients, with ICU stay >5 days and nothing preventing physical rehabilitation | Intervention | 74 | 61.4 ± 15.9 | 31 (41.9) | Therapy commence early, using set protocol for active exercise, 1–2 times a day based on the PFIT score in the ICU and 6WMT, cycle ergometery and 5RM for ward and outpatients. Also received standard therapy |
| | | Control | 76 | 60.1 ± 15.58 | 24 (31.6) | Standard PT was provided based on individual patient assessment. Service was available 7 days a week for 12 h a day |
| Dong et al. [28] RCT | MV for >48 h but <72 h, duration of MV expected to be ≥1 week and independent function prior | Intervention | 30 | 55.3 ± 16.1 | 9 (30) | Therapy commenced early, delivered by physician and nurse 2 times a day. Training time and intensity individually adjusted<br>Position changed every 2 h. Therapy ceased on hospital discharge or once returned to premorbid level of function |
| | | Control | 30 | 55.5 ± 16.2 | 10 (33) | Not reported |
| Dong et al. [33] RCT | Patients post coronary artery bypass graft, MV >72 h | Intervention | 53 | 62.6 ± 12.8 | 33 (62) | Consisted of six steps, heading up, transferring to sitting, sitting on edge of bed, sitting out of bed, transferring to standing, walking along the bed |
| | | Control | 53 | 60.2 ± 15.1 | 31 (58) | Rehabilitation therapy with the help of family after leaving the ICU |
| Hanekom et al. [29] Controlled clinical trial | >16 years of age and admitted to the surgical ICU | Intervention | 96 | 52.1 ± 18.5 | 37 (38.5) | Therapy was commenced early and provided by research therapists. Exercise prescription based on a documented protocol and algorithm |
| | | Control | 97 | 50.2 ± 17.9 | 36 (37.1) | Usual care provided by one PT, with limited resources |

**Table 1 continued**

| References, type of study | Population | Group allocation | Number | Age, mean ± SD or median (IQR) | Sex, *n* (%) females | Description of therapy |
|---|---|---|---|---|---|---|
| Hodgson et al. [23] Pilot RCT | MV >24 h, expected to be MV for another 72 h, independent mobility prior to admission | Intervention | 29 | 64 ± 12 | 8 (38) | Therapy commenced early. Daily active exercise with the goal to mobilise at the highest level of activity for a long as possible. Sedation was adjusted to allow active participation. Duration and exercise type depended on the patients IMS score |
| | | Control | 21 | 53 ± 15 | 12 (41) | Standard care. All ICUs had dedicated PT, generally PROM for 5–10 min a day |
| Kayambu et al. [25] Pilot RCT | MV ≥48 h with sepsis | Intervention | 26 | 62.5 (30–83) | 8 (16) | Therapy commenced early and was individualised physical rehabilitation prescribed by a PT for 30 min, 1–2 times a day. Including EMS, AROM, PROM, sitting out of bed, transfers and ambulation |
| | | Control | 24 | 65.5 (37–85) | 10 (20) | Standard care provided by unit staff |
| Morris et al. [35] Controlled clinical trial | MV via ETT, enrolled within 48 h of intubation and 72 h of admission to MICU | Intervention | 165 | 54.0 ± 16.8 | 72 (43) | Four-level protocol therapy, progressing from PROM to mobilising out of bed, based on patients level of strength |
| | | Control | 165 | 55.4 ± 166.8 | 77 (46) | Usual care including PROM and repositioning |
| Morris et al. [34] RCT | MV via ETT or NIV mask, P/F ratio <300 | Intervention | 150 | 55 ± 17 | 84 (56) | Three exercise types: PROM, physical therapy and progressive resistance exercise, administered by a research team. Level consciousness and strength helped to determine suitability and progression |
| | | Control | 150 | 58 ± 14 | 82 (5) | Usual care received no rehabilitation as per protocol, physical therapy could be ordered as part of routine care Monday to Friday |
| Moss et al. [30] RCT | MV ≥5 days. Changed to ≥4 days after 78 patients were enrolled | Intervention | 59 | 56 ± 14 | 23 (39) | Therapy commenced early. Protocol exercise by a physical therapist daily for up to 28 days, or until program completed. 30 min daily whilst in the ICU and 60 min daily on ward. Consisted of breathing exercises and active exercises. Continued as an outpatient 3 days a week |
| | | Control | 61 | 49 ± 15 | 26 (43) | Based on a national survey. Received control intervention for 28 days, 3× weekly for 20 min (ICU and ward). Outpatients received an educational pamphlet and telephone calls 3× weekly |

**Table 1 continued**

| References, type of study | Population | Group allocation | Number | Age, mean ± SD or median (IQR) | Sex, *n* (%) females | Description of therapy |
|---|---|---|---|---|---|---|
| Schaller et al. [36] RCT | Functionally independent (BI ≥70), MV <48 h, expected to be MV for further 24 h | Intervention | 104 | 66 (48–73) | 39 (38) | Therapy commenced no later than 1 day after enrolment. Progression through five levels of activities based on strength and medical stability, using facilitator closed loop communication |
| | | Control | 96 | 64 (45–76) | 35 (37) | Individually tailors, based on each centres practice guidelines for mobilisation and physical therapy |
| Schweickert et al. [12] RCT | MV <72 h, expected to be MV for ≥24 h, independent function prior to admission | Intervention | 49 | 57.7 (36.3–69.1) | 29 (59) | Therapy commenced early. Progression was individually tailored with sedation break. Therapy ceases once patient reached previous functional level or at ICU discharge |
| | | Control | 55 | 54.4 (46.5–66.4) | 23 (42) | Standard care. Neither site routinely provides physical therapy for patients who are MV <2 weeks |
| Yosef-Brauner et al. [31] RCT | MV ≥48 h and expected to be MV for further 48 h, independent prior to admission, follows commands and has ICU AW | Intervention | 9 | 51.6 (18) | 6 (67) | Three-phrase protocol therapy. Progressed by strength and sitting balance ability |
| | | Control | 9 | 61.5 (12) | 5 (56) | Standard care consisted of protocol therapy delivered daily |

*6MWT* 6 min walk test, *BI* Barthel Index, *EMS* electrical muscle stimulation, *ETT* endotracheal tube, *ICU* intensive care unit, *IMS* ICU mobility scale, *IQR* interquartile range, *MV* mechanical ventilation, *n* number (sample size), *NIV* non-invasive ventilation, *RASS* Richmond agitation and sedation scale, *RCT* randomised control trial, *RM* repetitions maximum, *SD* standard deviation, *OT* occupational therapist, *PFIT* physical function ICU tests, *P/F ratio* partial pressure of arterial oxygen to fractional inspired oxygen ratio, *PROM* passive range of motion and *PT* physiotherapist

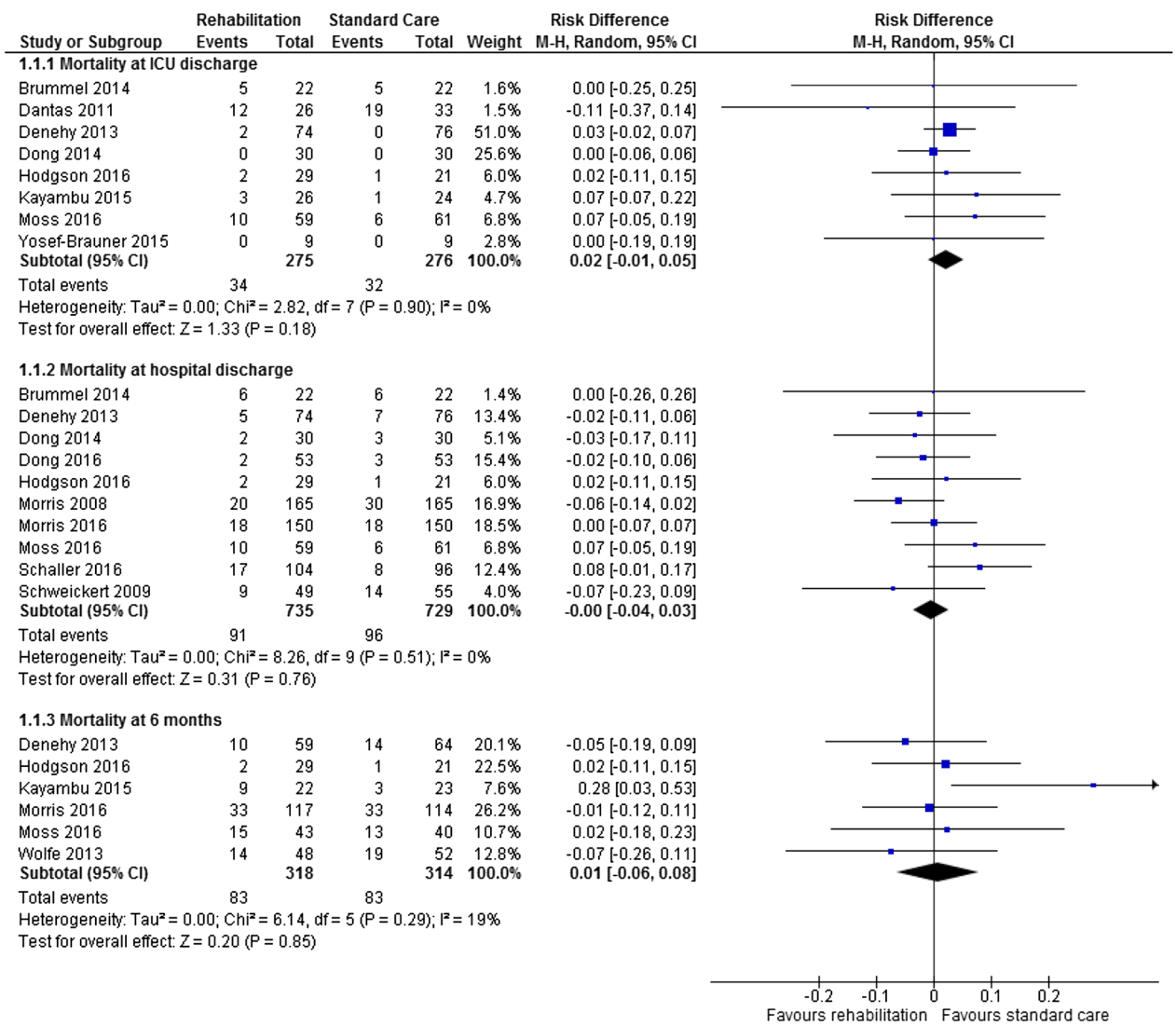


**Fig. 3** Forest plot for mortality at intensive care discharge, hospital discharge and 6-month follow-up

rehabilitation (ESM 2, Table 8). SF-36 results at 6 months had large statistical heterogeneity for the physical functioning, role physical, social functioning and role emotional domains.

Five studies reported days alive and out of hospital to 6 months [23, 25, 29, 30, 37]. A pooled analysis of the five studies showed a significant mean difference favouring the rehabilitation group (MD 9.63, 95% CI 1.68–17.57, $p = 0.02$, $I^2 = 0$, five studies, $n = 509$). However the data from one of the studies was highly skewed and required conversion to mean and SD to allow meta-analysis [25]. Therefore a pooled analysis was also completed for the remaining four studies, demonstrating a significant MD of 9.69 (Fig. 4) favouring the rehabilitation group [23, 29, 30, 37]. No subgroup differences were identified (Fig. 4).

### *Length of stay, mechanical ventilation duration and discharge destination*

The individual results of each study are outlined in ESM 2, Table 8. Because the majority of the length of stay and duration of mechanical ventilation data were significantly skewed, a meta-analysis was not able to be performed. Several studies did not report LOS for survivors and non-survivors separately, thereby introducing bias [23, 25–27, 29, 30, 32–34, 36]. Two studies had no deaths in ICU and reported significantly shorter ICU length of stay in the rehabilitation group compared to the standard care group (ESM Table 9) [28, 31].

No difference was found in the pooled analysis of discharge destination (proportion of patients discharged home, OR 1.35, 95% CI 0.98–1.87, $p = 0.07$ $I^2 = 40\%$,

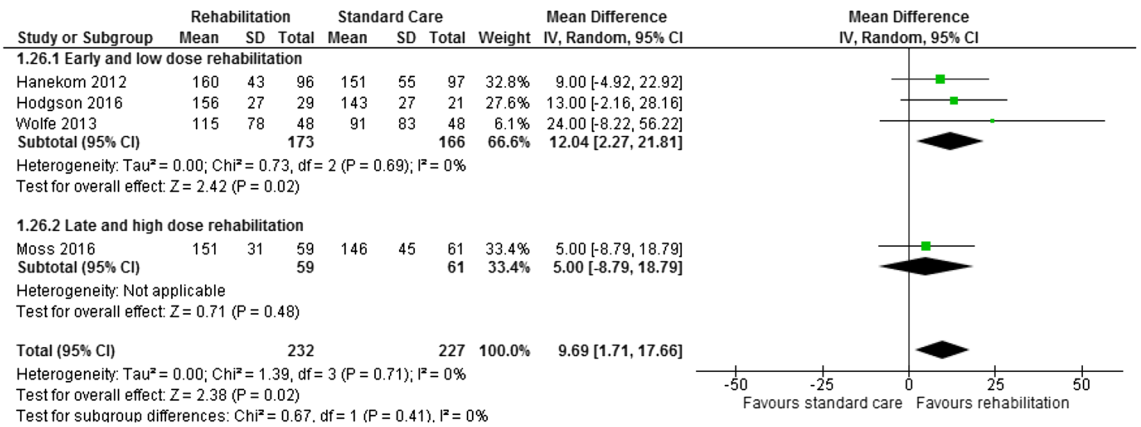


**Fig. 4** Forest plot for days alive and out of hospital to 180 days

eight studies, $n = 1255$) [12, 23, 26, 27, 30, 34–36]. The subgroup analysis showed no difference in proportion of patients discharged home (ESM 2, Table 4).

#### *Adverse events*

One serious adverse events was reported (desaturation less than 80%) [12]. Six studies reported adverse events during the intervention; these are described in ESM 2.

## Discussion

### Key findings

This meta-analysis found that active mobilisation and rehabilitation in the ICU had no effect on patient mortality [12, 23, 25–37]. However, the intervention improved body function (muscle strength) at ICU discharge [23, 25, 32], reduced activity limitations (walking ability) at hospital discharge [12, 29] and reduced participation restriction (days alive and out of hospital) at 6 months [23, 29, 30, 37]. Studies of high dose rehabilitation showed that rehabilitation in the ICU may lead to improved quality of life at 6 months in the role physical and role emotional domain [25, 30]. Meta-analysis showed no difference in function at ICU discharge or discharge destination.

### Clinical implications of results

This meta-analysis demonstrates that active mobilisation and rehabilitation in the ICU does not increase mortality in a research setting. However, there is still not enough evidence to determine long-term morbidity. In clinical practice active mobilisation and rehabilitation in the ICU may be an appropriate treatment strategy, when safety consensus guidelines are followed and a team approach is used to ensure safety [39].

There was very limited information available regarding the dosage provided in many of the studies and this limited the meta-analysis. There was a trend for higher SF-36 results in the role physical and role emotional domains in a pooled analysis of studies of high dose rehabilitation [25, 30]. However there was only one study in the low dose subgroup and therefore it may have been underpowered [27]. More studies are needed to specifically assess appropriate dosages and timing of therapy. This information will better inform clinicians and assist in prescribing therapy in clinical practice.

### Relationship to other studies

This review showed that mobilisation and rehabilitation in ICU does not increase short- or long-term mortality but has shown promising improvements in patient-centred outcomes across three components of the WHO ICF framework [21]; however, its full impact is not yet understood, particularly in regards to long-term outcomes. An RCT of early rehabilitation in acute exacerbations of chronic obstructive pulmonary disease showed higher 1-year mortality in the early rehabilitation group compared to the control group [40]. Similarly a recent early rehabilitation study in stroke patients found that patients in the intervention group had a higher level of disability compared to the patients in the control group at 3 months after stroke [15]. As a result of the complexity of acute and critical illness it is possible that there may be adverse outcomes of rehabilitation commenced in the ICU, and large RCTs need to be completed in the ICU setting to appropriately determine the impact of active mobilisation and rehabilitation in this patient population.

Premorbid status can influence functional recovery following critical illness, with frail patients and those with co-morbidities having worse long-term function [8, 10]. Whilst the studies included in this review did not measure frailty, six of the studies only included patients who had independent mobility prior to ICU admission [12, 23, 30–32, 34, 36] and therefore may have been more responsive

to rehabilitation, thereby influencing the results. One of the RCTs included in this review [27] has since completed a secondary analysis of their cohort, showing significant benefits both in previously healthy patients and those with pre-existing chronic disease [9]. It is possible that those with pre-existing chronic disease may require targeted rehabilitation tailored to their premorbid functional status [9, 10].

Previous meta-analyses have assessed the short-term effect of rehabilitation in the ICU. The inclusion criteria for these previous meta-analyses differed from this current study, in regards to the types of interventions included (cycling and electrical muscle stimulation [14, 41], compared to functional active rehabilitation only) and the timing of therapy (commencing early in hospital stay compared to late). Castro-Avila et al. [14] showed in a meta-analysis that, despite some conflicting individual study results, rehabilitation in the ICU was associated with an increased probability of walking without assistance at hospital discharge. Kayambu et al. [41] reported increased function and quality of life at hospital discharge and more ventilator-free days in the intervention group. However, the meta-analysis pooled a wide range of treatment techniques in the intervention group and had varying time of commencement of the therapy. Our meta-analysis focused specifically on the effect of active mobilisation and rehabilitation within the ICU and included several recently published studies, and the results highlight a significant improvement in muscle strength at ICU discharge and increased number of days alive and out of hospital to day 180.

### Strengths and limitations

The strengths of this study stem from a comprehensive search strategy, clear and targeted inclusion and exclusion criteria and rigour in the data extraction and risk of bias assessment. The results of this review are highly generalisable owing to nine countries being represented and detailed patient demographic data presented. This review specified studies that included patients during acute critical illness and ICU stay, as we wanted the results to be relevant to the care provided and the challenges associated with managing an acutely unwell patient population.

Nine of the studies included in this review have not yet been included in other systematic reviews of active mobilisation and rehabilitation in the ICU [23, 25, 28, 30–32, 34–36]; there were also five studies identified that are still being completed. The results contributing to the meta-analysis in this review were mostly from moderate to high quality studies [12, 23, 25, 30, 36, 37] and the outcome measures reported in this review have been linked to the WHO ICF framework.

Weaknesses include the small sample size of the included studies ($n \leq 50$ in five of the studies [23, 25, 26, 31, 32]) and heterogeneity was present with a range of outcome measures collected at varying time points, limiting the ability to complete meta-analysis. Subgroup analysis in this systematic review was limited as the timing, amount and intensity of therapy received by both the intervention and control groups across the studies were varied and in some cases details were unavailable. The full impact of early or late mobilisation and rehabilitation on patients in the ICU remains unknown.

The range of admission diagnoses represented across the studies could limit the validity of the results as particular patient populations may have a different likelihood and trajectories of recovery. Mortality collected at 6 months may have been affected by loss to follow-up in some studies; however, the primary outcome was not affected by loss to follow-up. Length of stay data were highly skewed and not always reported for both survivors and non-survivors, making it difficult to interpret, as death can influence the results.

### Future directions

Currently there is limited evidence on the long-term effect of active mobilisation and rehabilitation in the ICU on morbidity or the appropriate dosage, intensity and progression of exercise. It remains unclear whether there are particular patient population that may show greater benefits from physical rehabilitation during ICU. Ideally a well-designed large multi-centre RCT needs to be conducted, with appropriate sample size to determine the effect of active mobilisation and rehabilitation in the ICU on long-term patient-centred outcomes. In order for better comparison of results across studies, future trials would benefit from a core set of outcome measures [42] collected at consistent time points.

## Conclusion

Active mobilisation and rehabilitation in the ICU improved body function, reduced activity limitation and improved participation measured using muscle strength, walking ability and days alive and out of hospital respectively. No differences in short- or long-term mortality were evident.

Further research should determine the overall impact of mobilisation and rehabilitation in the ICU on long-term patient-centred outcomes. Specific studies also need to determine the most effective protocols, intensity and progression of rehabilitation.

**Electronic supplementary material**
The online version of this article (doi:10.1007/s00134-016-4612-0) contains supplementary material, which is available to authorized users.

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**Compliance with ethical standards**

**Conflicts of interest**
None of the authors have any financial conflicts of interest. Three of the authors (CT, MH and CH) are authors on one of the randomised controlled trials included in the review. The data extraction and risk of bias assessment for this study were completed by two independent researchers.

**Ethics approval**
Not applicable.

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