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REVIEW ARTICLE (META-ANALYSIS)

Active Mobilization for Mechanically Ventilated Patients: A Systematic Review

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Abstract

Objective: To investigate the effectiveness and safety of active mobilization on improving physical function and hospital outcomes in patients undergoing mechanical ventilation for more than 24 hours.

Data Sources: PubMed, Embase, CINAHL, CENTRAL, Physiotherapy Evidence Database, SinoMed, and ISI Web of Knowledge were searched for randomized controlled trials (RCTs), quasi-RCTs, other comparative studies, and case series with 10 or more consecutive cases. Additional studies were identified through references, citation tracking, and by contacting the authors of eligible studies.

Study Selection: Two reviewers independently selected potential studies according to the inclusion criteria.

Data Extraction: Two reviewers independently extracted data and assessed the methodologic quality.

Data Synthesis: A narrative form was used to summarize study characteristics and outcomes, because the substantial heterogeneity between the individual studies precluded formal meta-analyses. Among the 17 eligible studies, 7 RCTs, 1 quasi-RCT, 1 prospective cohort study, and 1 history controlled study were used to examine the effectiveness; and 2 RCTs, 1 prospective cohort study, and 7 case series were used to examine the safety of active mobilization in patients receiving mechanical ventilation for more than 24 hours. We found that active mobilization may improve muscle strength, functional independence, and the ability to wean from ventilation and may decrease the length of stay in the intensive care unit (ICU) and hospital. However, only 1 study reported that active mobilization reduced the 1-year mortality rate. No serious adverse events were reported among included studies.

Conclusions: Active mobilization appears to have a positive effect on physical function and hospital outcomes in mechanical ventilation patients. Early active mobilization protocols may be initiated safely in the ICU setting and continued in post-ICU settings. However, the current available studies have great heterogeneity and limited methodologic quality. Further research is needed to provide more robust evidence to support the effectiveness and safety of active mobilization.

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An increasing number of critically ill patients survive the acute phase of their illness with the aid of intensive care unit (ICU) interventions. Survivors of a critical illness frequently suffer long-term physical and psychological complications,[1,2] and ICU-acquired weakness is a common complication of critical illness, occurring in 25% of patients who are mechanically ventilated for more than 7 days.[3] This weakness affects both skeletal and diaphragmatic muscles, extends the duration of mechanical ventilation, prolongs the length of stay (LOS) in the ICU and hospital, and increases mortality.[3-5] Weakness can persist for years after hospital discharge, limiting functional status, preventing return to work, and increasing health care needs.[1,6]

Although the etiology of ICU-acquired weakness is multifactorial, prolonged immobilization and bed rest play important roles. Experimental trials in healthy subjects have shown a muscle strength loss of up to 4% to 5% per week with bed rest.[7] In cases where nerve to muscle connections have been destroyed, the progression of muscle strength loss can be even faster.[8] Mechanically ventilated patients often remain relatively motionless for days

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to weeks. This state of immobilization typically occurs because of the underlying severe illness of the patient, in combination with the sedatives that are administered during mechanical ventilation.

The use of mobilization therapy in patients with acute illness is not a novel intervention.[9] However, only recently has the practice of complete bed rest in mechanically ventilated patients been challenged. Several surveys of international ICU physiotherapy practice have been published.[10-14] Only lower-intensity mobilization therapies were commonly employed in a population of 56% Canadian and 55% Australian respondents.[10,11]

In spite of active attitude changes, no systematic reviews are yet available on active mobilization for mechanically ventilated patients. Therefore, this systematic review was undertaken, in accordance with PRISMA guidelines,[15] to assess the effectiveness and safety of active mobilization intervention in patients who have been mechanically ventilated for more than 24 hours.

Methods

Inclusion criteria

For inclusion, the articles had to fulfill all of the following criteria: (1) the study population consisted of adults (mean age ≥18y), at least 60% of whom were mechanically ventilated for 24 hours or more; (2) the study design was a randomized controlled trial (RCT), quasi-RCT, or other comparative study with or without concurrent controls. To further assess safety, case series with 10 or more consecutive cases were also included. The studies were defined as a National Health and Medical Research Council Classification[16]; (3) active mobilization was conducted in an ICU or high dependency unit (HDU) setting. Active mobilization was defined as assisted training such as in-bed exercises (eg, weights, cycling), sitting on the edge of the bed, standing beside the bed, transferring to a chair, and assisted or independent ambulation. Excluded studies included those in which intervention started at home or was conducted both during hospital stay and hospital-discharge; as well as studies which only assessed the effects of passive mobilization (for example passive limb movements, side-to-side turning in bed, chair or standing hoist therapy, tilt table therapy, and electrical interferential therapy); and (4) primary outcome measure was physical function (eg, muscle strength, physical activity, mobility and functional ability, and health-related quality of life). Secondary outcome measures were hospital outcomes, such as weaning rate, duration of mechanical ventilation, ventilator-free days, LOS in the ICU/HDU and hospital, mortality, discharge destination after hospitalization, and costs associated with patient care and adverse events (eg, deterioration of physical signs and/or symptoms, removal of support equipment, falls, musculoskeletal injury, and patient mortality related to mobilization).

List of abbreviations:

ADL	**activities of daily living**
BI	**Barthel Index**
HDU	**high dependency unit**
ICU	**intensive care unit**
LOS	**length of stay**
RCT	**randomized controlled trial**
6MWD	**six-minute walk distance**

Search strategy

Seven electronic databases were searched (PubMed, Embase, CINAHL, CENTRAL, Physiotherapy Evidence Database, SinoMed, and ISI Web of Knowledge) from the earliest available date until May 2012. Additional studies were identified through reference and citation tracking and by contacting the authors of eligible studies. A search strategy was developed for PubMed (appendix 1) and adopted to the other databases. In addition, there were no language restrictions.

Study selection

Primary studies were selected based on the inclusion criteria previously described. Two reviewers independently performed an assessment of the identified records by reading the title/abstract. If a reason for exclusion was not evident, the full paper was obtained. Two reviewers independently evaluated the full text of each record. They used a predeveloped inclusion form. Differences in assessment screening were discussed until consensus was reached. If consensus could not be reached, a consulting group including 2 experts resolved the disagreements. The main reason for exclusion at this stage was recorded for each record, and a list of excluded records (with reasons) was created. When the same study had more than 1 record, all potential exclusion factors were included, but the most relevant factor became the main record.

Data extraction

Two reviewers independently extracted data from the published sources using a predesigned data extraction form. After independent extraction of data, the 2 reviewers compared their forms and resolved any discrepancies by consulting experts.

Quality assessment

RCTs, quasi-RCTs, and other comparative studies were independently rated for quality by 2 reviewers using the PEDro scale, which is a checklist used to measure the quality of reports from RCTs of physiotherapy developed by the Physiotherapy Evidence Database.[17] The PEDro scale included eligibility criteria (not used to calculate score), random allocation, concealment of allocation, similarity at baseline, subject blinding, therapist blinding, assessor blinding, adequacy of follow-up, intention-to-treat analysis, between-group statistical analysis, and reports of both point estimates and measures of variability. Trials were rated on the basis of what they reported. Items were marked as either present (yes/1) or absent (no/0), and a score out of 10 was obtained. For case series, recommendations from the Centre for Reviews and Dissemination were used.[18] Differing opinions between independent reviewers were resolved through discussion including a third independent reviewer, when necessary.

Literature synthesis

Information was abstracted from each included study about the author, country and setting, study design, sample size, participant characteristics, intervention and dosage (frequency, intensity, and duration), and outcome measures. The primary comparison of the effects of active mobilization was explored. However, substantial variation of methods (characteristics of participants, types of intervention, follow-up periods, and outcome measurements of the included studies) among individual studies precluded formal meta-analyses. Therefore, the results are presented in narrative form.

Results

Description of studies

The search strategy retrieved 14,678 potentially relevant articles. After screening the title and/or abstract, 29 articles remained and were obtained in full text. Twelve studies failed to meet the inclusion criteria as described, therefore 17 studies[19-35] were included in this systematic review. All included studies were published in English. No relevant unpublished studies were obtained. Figure 1 presents the study selection process.

Of the 17 studies, the sample sizes ranged from 17 to 510 participants. Participant inclusion and exclusion criteria differed across studies. Eleven studies took place in the medical/surgical ICU[25-35] and 6 in the HDU.[19-24] The studies were conducted at hospitals in the United States,[25,27,30,31,33,35] Italy,[19,20,24] Belgium,[26] Turkey,[29] Australia,[32] France,[34] and Taiwan.[21-23,28] The design of the active mobilization program differed between the included studies. Of the 17 studies, 15 studies[19,21-25,27-35] examined whole-body physical therapy, and 2 studies[20,26] tested arm exercise training. The effectiveness of active mobilization was assessed in 10 comparative studies,[19-23,25-29] and the safety profile was assessed in 3 comparative studies[25-27] and 7 case series studies.[24,30-35] Table 1 summarizes the basic characteristics of included studies in this systematic review.

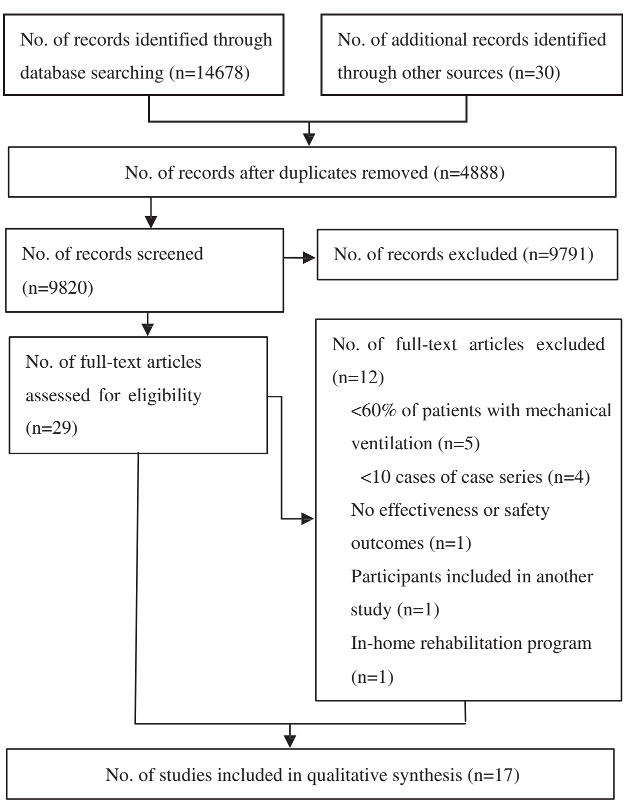

Fig 1 Process for identification of the included studies.

Risk of bias in included studies

For the comparative studies,[19-23,25-29] the number of eligible items among the individual studies ranged from 4 to 8 with a mean PEDro score of 5 (table 2). Seven of the included studies[19,20,22,23,26-28] were considered adequately randomized. One quasi-RCT study[21] used alternate numbers to allocate patients. One prospective cohort study[25] assigned consecutively eligible patients by unit to receive the mobility protocol using a block allocation design. One study[29] was a historical control study. Four studies[23,26-28] provided adequate detail to consider that concealed allocation occurred. All except 2 studies[23,26] had a similar baseline regarding important outcomes. Blinding of subjects was difficult to implement in the mobilization intervention studies, because blinding of the therapist that provided mobilization was neither possible, nor appropriate. Therefore, none of the studies reported therapist blinding. Assessor blinding was reported for at least 1 key outcome in 4 studies.[20,21,23,27] Four studies[22,25,27,29] reported at least 85% of the hospital discharge data for 1 key outcome, and only 1 study[27] reported an intention-to-treat analysis. Between-group statistical comparison data and point estimates, as well as measures of variability for outcomes, were provided for each trial.

For the case series, risk of bias was assessed according to the 6 criteria suggested by the Centre for Reviews and Dissemination (table 3).[18] Four studies[24,30,31,34] enrolled all consecutively eligible ICU or HDU patients. The patients in 2 studies[32,33] were identified to not be representative samples because of the small sample size and the high proportion of attrition before the intervention. In 1 study,[35] it was impossible to determine if the patients enrolled comprised the total population or the random sample. All case series studies clearly presented the inclusion criteria for participants. The point of disease progression was not the same in terms of severity, duration of mechanical ventilation, or LOS in the ICU before enrollment. The follow-up was long enough to include important short-term adverse events. Criteria for outcome measures for adverse events were objective in all case series. No subseries were made. The results from the case series studies were assessed as low quality evidence because of the study designs and the methodologic limitations.

Effectiveness of interventions

Muscle strength outcomes

Muscle strength was measured in 6 studies (table 4),[19-21,26-28] including respiratory muscle force[19-21,23,28] and upper and lower limbs muscle force.[20,21,26,27] Four studies[19-21,28] reported pre-post improvements on maximal inspiratory pressure in the mobilization group, but only 1 study[21] found a significant difference between 2 groups. Upper limbs muscle force was assessed in 4 studies.[20,21,26,27] Pre-post differences within and between groups were noted in 2 studies,[20,21] but other studies[26,27] did not find a significant difference between groups. Chiang et al[21] found a significant improvement in knee extensors in both groups; however, the improvement in the active mobilization group was greater. Burtin et al[26] observed that quadriceps force improved more between ICU discharge and hospital discharge in the mobilization group than in the control group. However, Schweickert et al[27] did not find a significant difference between groups in Medical Research Council examination scores at hospital discharge.

Table 1 Characteristics of included studies

Study	Study Design	County, Setting	Sample Size	Patients Enrollment	Female (%)	Age (y)	APACHE II Score	Intervention Delivered
Nava[19]	RCT	Italy, RICU	80	100% COPD, 48% IPPV, 29% NIPPV 5–19d from intubation to admission to RICU 3–5d after admission to RICU	Exp: 36.7 Con: 35.0	Exp: 65.0 (6.0) Con: 67.0 (9.0)	NR	Exp: passive mobilization (step I); walking retraining (step II); bicycle/stair training (step III); treadmill walking (step IV) 30–45min/session daily for 18d Con: standard medical therapy
Porta et al[20]	RCT	Italy, RIICU	66	70%–78% COPD 4–87d from intubation to admission to RIICU >48h after weaning from MV	Exp: 31.3 Con: 32.4	Exp: 70.0 (6.0) Con: 72.0 (5.0)	NR	Exp: supported arm exercise training and general physiotherapy 20min/session daily for 15d Con: general physiotherapy only
Chiang et al[21]	Quasi-RCT	Taiwan, RCC	39	46–52d after start of MV	Exp: 25.0 Con: 15.8	Exp: 75.0 (63.0–80.0)* Con: 79.0 (73.0–83.0)*	NR	Exp: limbs ROM exercise; bed to chair transfers; standing training; ambulation; diaphragmatic breathing exercises 5 sessions/wk for 6wk Con: standard therapy
Chen et al[22]	RCT	Taiwan, RCC	34	>14d after start of MV	Exp: 31.2 Con: 22.2	Exp: 75.0 (63.0–81.0)* Con: 79.0 (72.5–82.8)*	NR	Exp: diaphragmatic breathing exercises; limbs exercises; transfer training; standing training; functional activity training 5 sessions/wk for 12wk Con: standard care
Chen et al[23]	RCT	Taiwan, RCC	27	>21d after start of MV	Exp: 41.7 Con: 53.3	Exp: 64.9 (21.3) Con: 66.5 (18.7)	NR	Exp: stretching exercises; muscle strengthening exercise; cardiopulmonary endurance training 30–40min/session; 4–6 sessions/wk for 10 sessions Con: standard therapy (no exercise training)
Clini et al[24]	Case series	Italy, RICU	77	>14d after start of MV 24d ICU stay prior to enrollment	40.3	75.0 (7.0)	11.5 (4.4)	Active ROM; trunk control; maintenance of body posture; supported or unsupported limb training, transfer training; standing; walking 30min/session (supported limb training) daily for >15 sessions
Morris et al[25]	Prospective cohort study	USA, MICU	330	Within 48h of intubation	Exp: 43.6 Con: 46.7	Exp: 54.0 (17.0) Con: 55.0 (17.0)	Exp: 24.0 (9.0) Con: 22.0 (8.0)	Exp: passive ROM; sitting in bed/resistance limb training; sitting on bed edge; bed to chair transfer 20–60min/sessions daily until patient transferred to a regular bed Con: standard therapy

(*continued on next page*)

Table 1 (*continued*)

Study	Study Design	County, Setting	Sample Size	Patients Enrollment	Female (%)	Age (y)	APACHE II Score	Intervention Delivered
Burtin et al[26]	RCT	Belgium SICU/MICU	67	80% postoperative patients by day 5 in SICU/MICU	Exp: 29.0 Con: 27.8	Exp: 56.0 (16.0) Con: 57.0 (17.0)	Exp: 26.0 (6.0) Con: 25.0 (4.0)	Exp: training using with cycle ergometer and standard physiotherapy 20min/session; 5 sessions/wk until ICU discharge Con: standard physiotherapy only
Schweickert et al[27]	RCT	USA, MICU	104	<72h after start of MV	Exp: 59.2 Con: 41.8	Exp: 57.7 (36.3–69.1)* Con: 54.4 (46.5–66.4)*	Exp: 20.0 (15.8–24.0)* Con: 19.0 (13.3–23.0)*	Exp: passive/active ROM; sitting balance activities; activities of daily life; transfer; pregait/walking training 19.2min/session daily throughout hospital stay Con: standard care
Chang et al[28]	RCT	Taiwan, SICU	34	>72h of requiring MV	Exp: 44.4 Con: 31.3	Exp: 65.0 (13.0) Con: 70.0 (17.0)	Exp: 17.0 (8.0) Con: 15.0 (8.0)	Exp: bed-to-chair mobilization 30–120min/session daily (n=15)/3 sessions/wk (n=3) for 6d Con: no bed-to-chair mobilization
Malkoç et al[29]	Historical controlled study	Turkey, MICU	510	Medical ICU patients	Exp: 37.2 Con: 48.9	Exp: 55.7 (4.6) Con: 56.7 (3.2)	Exp: 19.2 Con: 18.7	Exp: chest physiotherapy and mobilization twice daily, 5 sessions/wk Con: no physical therapy
Bailey et al[30]	Case series	USA, RICU	103	>4d after start of MV	42.7	62.5 (15.5)	17.0 (4.8)	Sitting on bed edge; bed-to-chair transfers; walking twice daily; until respiratory ICU discharge
Needham et al[31]	Case series	USA, MICU	57	>4d after start of MV	Pre-QI: 70.4 QI: 70.0	Pre-QI: 50.0 (43.0–59.0)* QI: 53.0 (43.0-69.0) *	Pre-QI: 26.0 (21.0–29.0)* QI: 27.0 (21.0–32.0)*	Supine to sit; sitting on bed edge; bed-to-chair transfer; sit-to-stand transfer; walking
Zafiropoulos et al[32]	Case series	Australia, GICU	17	Intubated, ventilated abdominal surgical patients	52.9	71.4 (7.1)	NR	Sitting on bed edge; standing; walking on the spot; sitting
Zanni et al[33]	Case series	USA, MICU	32	>4d after start of MV	62.5	49.0 (42–57.0)*	27.0 (21.0–30.0) *	Stretching; strengthening; balance training; functional activities (rolling, sitting on bed edge, sit-to-stand transfer, ambulation, grooming, bathing)
Bourdin et al[34]	Case series	France, MICU	20	>7d of ICU stay and >2d of start of MV	30.0	68.0 (32.0–85.0)*	NR	Chair-sitting, tilting-up; walking
Winkelman[35]	Case series	USA, MICU and SDU	17	COPD patients 48–60h after admission to MICU	82.4	60.0 (8.8)	39.0 (14.4)	Turning in the bed; ROM; sitting on bed edge; sitting in the chair; ambulation 20min/session

NOTE. Data are presented as no. (%) or mean ± SD unless otherwise indicated.
Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation II; Con, control group; COPD, chronic obstructive pulmonary disease; Exp, experiment group; GICU, general ICU; IPPV, invasive positive pressure ventilation; MICU, medical ICU; MV, mechanical ventilation; NIPPV, noninvasive positive pressure ventilation; NR, no report; QI, quality improvement; RCC, respiratory care center; RICU, respiratory ICU; RIICU, respiratory intermittent ICU; ROM, range of motion; SICU, surgical ICU; SDU, step down unit.
* Median (interquartile range).

Table 2 Assessment of quality for comparative studies by the PEDro score

Study	Eligibility Criteria	Random Allocation	Concealed Allocation	Similarity at Baseline	Subject Blinding	Therapist Blinding	Assessor Blinding	>85% Follow-Up	ITT Analysis	Between-Group Difference Reported	Point Estimate and Variability Reported	Total (0–10)
Nava[19]	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Porta et al[20]	Yes	Yes	No	Yes	No	No	Yes	No	No	Yes	Yes	5
Chiang et al[21]	Yes	No	No	Yes	No	No	Yes	No	No	Yes	Yes	4
Chen et al[22]	Yes	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5
Chen et al[23]	Yes	Yes	Yes	No	No	No	Yes	No	No	Yes	Yes	6
Morris et al[25]	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4
Burtin et al[26]	Yes	Yes	Yes	No	No	No	No	No	No	Yes	Yes	4
Schweickert et al[27]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8
Chang et al[28]	Yes	Yes	Yes	Yes	No	No	No	No	No	Yes	Yes	5
Malkoç et al[29]	Yes	No	No	Yes	No	No	No	Yes	No	Yes	Yes	4

Abbreviation: ITT, intention-to-treatment.

Functional status outcomes

Walking ability was tested in 3 studies (see table 4).[19,26,27] Nava[19] found that most patients regained the ability to walk, either unaided or aided, and six-minute walk distance (6MWD) results were significantly improved in the mobilization group at hospital discharge. Burtin et al[26] reported 6MWD results that were significantly higher in the mobilization group, but the proportion of patients with the ability to stand and walk independently did not differ at ICU and hospital discharge. Another study by Schweickert[27] showed that patients in the mobilization group had a greater unassisted walking distance score at hospital discharge than the controls.

Four trials[21-23,27] assessed changes in independence with activities of daily living (ADL) (see table 4). Chiang et al[21] found that total Barthel Index (BI) and FIM scores increased significantly in the mobilization group and remained unchanged in the control group. Chen et al[22] reported scores for total FIM, motor domain, cognitive domain, and some subitems. All scores except for the walking/wheelchair subitem increased significantly in the mobilization group at 6 months postenrollment, but remained unchanged for the control group. Chen et al[23] found that FIM scores improved significantly more in the mobilization group than the control group. Schweickert[27] noted that return to independent functional status at hospital discharge occurred in more patients in the mobilization group than in the control group. Moreover, patients in the mobilization group had higher BI scores and a higher number of independent ADL.

Burtin[26] reported a significantly higher health-related quality of life Medical Outcomes Study 36-Item Short-Form Health Survey Physical Functioning score for the mobilization group than the control group at the time of hospital discharge. Dyspnea scores, measured by a visual analog scale and Borg scale, were assessed in 2 studies in the HDU settings.[19,20] Although both studies demonstrated a decrease in dyspnea ratings at posttraining in both the mobilization and control groups, only 1 study[19] identified differences in the magnitude of change between the 2 groups (see table 4).

Hospital outcomes

Nine studies[19,21-23,25-29] reported data for the mechanical ventilation domain concerning weaning rate, ventilator-free time, and duration of ventilation (see table 4). Three studies[21,27,29] noted a significantly shorter duration of mechanical ventilation and more ventilator-free time in the mobilization group.

Seven studies[19,23,25-29] included in this systematic review provided ICU/HDU and total hospital LOS data (see table 4). Five of the studies[19,23,26-28] indicated no significant effect from active mobilization intervention on reducing ICU/HDU and total hospital LOS. The 2 exceptions were the nonrandomized studies by Morris,[25] Malkoç,[29] and colleagues, which found the LOS in the ICU or hospital was significantly shorter in the mobilization group than the control group.

Five studies[19,23,25-27] provided mortality data at hospital discharge, and 2 studies[22,26] provided 1-year mortality data (see table 4). All studies indicated no effect on patient mortality at the time of hospital discharge for active mobilization intervention. One study[22] showed a significant reduction in 1-year mortality from active mobilization intervention. However, data from another study[26] indicated no significant difference in 1-year mortality between the control group and the mobilization group.

Four studies[22,25-27] reported discharge destination data at hospital discharge (see table 4). No studies detected significant

Table 3 Assessment of quality for case series by Centre for Reviews and Dissemination's guidance

Study	Representative Sample	Explicit Indication for Inclusion	Similar Point in Disease Progression	Sufficient Length of Follow-Up	Outcome Assessment with Objective Criteria or Blinding	Sufficient Description of the Series
Clini et al[24]	Yes	Yes	No	Yes	Yes	No subseries
Bailey et al[30]	Yes	Yes	No	Yes	Yes	No subseries
Needham et al[31]	Yes	Yes	No	Yes	Yes	No subseries
Zafiropoulos et al[32]	No	Yes	No	Yes	Yes	No subseries
Zanni et al[33]	No	Yes	No	Yes	Yes	No subseries
Bourdin et al[34]	Yes	Yes	No	Yes	Yes	No subseries
Winkelman[35]	Not clear	Yes	No	Yes	Yes	No subseries

differences between groups when comparing the number of patients discharged to home. However, the study by Schweickert et al[27] observed a trend toward better discharge rates to home compared with all other possible locations for both groups.

The 1 study[25] that provided hospital cost data found no statistical difference between groups. However, the absolute difference in cost appeared to be less for the mobilization group, including the cost for the mobility team (see table 4).

Safety

Of the 17 studies included in this review, 10[24-27,30-35] reported safety profile data (table 5). The most commonly cited adverse events were oxygen desaturation,[26,27,30,33,34] change of heart rate or blood pressure,[25,26,30,32-34] accidental removal of patient support equipment,[27,30,31,34] muscle tone,[34] and falls.[30] Burtin et al[26] reported 1 Achilles′ tendon rupture in the mobilization group that used in-bed cycle ergometry. There were no serious adverse events that required life saving measures or alterations in the patient's medical care.

Discussion

This narrative systematic review describes an assessment of active mobilization intervention on physical function and hospital outcomes in ICU/HDU settings. Seven RCTs,[19,20,22,23,26-28] 1 quasi-RCT,[21] 1 prospective cohort study,[25] and 1 history controlled study[29] were identified to examine the effectiveness, and 2 RCTs,[26,27] 1 prospective cohort study,[25] and 7 case series[24,30-35] were examined to assess the safety of active mobilization intervention in patients who had been mechanically ventilated more than 24 hours. We found that active mobilization may improve muscle strength[19-21,26,28] and functional independence,[19,21-23,26,27] enhance weaning ability,[21,27,29] and shorten ICU and hospital LOS.[25,29] However, no robust evidence was found to support the effectiveness of active mobilization for improving mortality. No serious adverse events were reported in the 17 studies.[24-27,30-35]

It is generally accepted that mechanical ventilation patients within critical care settings for prolonged periods of time are often bed ridden and deconditioned and have weak muscle strength. And the testing of muscle strength is widely used by clinicians to assess neuromuscular deficits in patients. In our systematic review, 6 studies[19-21,26-28] compared muscle strength in mobilization groups with that in control groups. Muscle strength was consistently better in patients in the HDU settings. Two studies, Burtin et al[26] and Schweickert et al,[27] found that muscle strength measured by a handheld dynamometer was not significantly better in the ICU settings. Although the handheld dynamometer muscle test is a common measurement of strength and has been used in many different noncritically ill populations,[36-38] it may not be a sensitive enough detection measure for mechanically ventilated patients who are often unconscious or have a suboptimal level of cooperation. Future studies with muscle biopsies[39] or ultrasound assessments of muscle bulk[40] may give us more insight into the effect of mobilization intervention at the muscular level.

The improvement in functional status could possibly be a consequence of a partial prevention of muscle atrophy, a larger increase of muscle force, better muscle coordination, or an enhanced psychological status. With the benefits of active mobilization training, patients are capable of walking greater distances and performing a higher level of ADL with lower ventilation demands and fewer symptoms of dyspnea and/or fatigue. The studies reviewed in this systematic review support improvements in functional status after active intervention in ICU/HDU settings, but the measurement of this outcome was not uniform across the studies. The 6MWD is a common measure of functional exercise capacity performed as a self-paced test, but disabled patients in the ICU or after ICU discharge are often too weak to walk. For example, almost 40% of patients were not able to walk or required 2 or more assistants at 4 days after ICU discharge.[41] ADL have advantages over walk tests for both assessment of upper and lower limb function. Although ADL have been used in more recent ICU research,[27,33] the validity and sensitivity should be confirmed in future studies. The Medical Outcomes Study 36-Item Short-Form Health Survey has been widely used to assess health-related quality of life and is recommended for critical illness.[42,43] Although health-related quality of life was assessed by the Medical Outcomes Study 36-Item Short-Form Health Survey PF score in only 1 study in this review,[26] it can be assumed that patients in the active mobilization group with higher weaning and survival rates have a better quality of life. Various studies have proven that patients who successfully wean from mechanical ventilation may have a better quality of life.[44,45]

The relation between respiratory and limb muscle strength in mechanically ventilated patients has been examined by De Jonghe et al.[3] The authors demonstrated that both respiratory muscle strength and lung volume significantly correlate with limb muscle strength, and respiratory muscle weakness is associated with delayed extubation and prolonged mechanical ventilation. In this systematic review, 3 trials[21,27,29] noted a significantly shorter duration of mechanical ventilation and more ventilator-free time after an active mobilization intervention, which may contribute to

Table 4 Effectiveness of active mobilization among included trials

Outcomes	Study	Experiment Group	Control Group	MD or RR (95% CI)	P
Respiratory muscle force					
MIP (cm H_2O)	Nava[19]	↑16.0*	NR		NR
	Porta et al[20]	↑9.8*	↑4.8*	4.9 (−0.62 to 10.6)	.080
	Chiang et al[21]	↑14.0*†	↓8*†	1.45 (0.63 to 2.18)	<.050
	Chang et al[28]	↑20.0*	↑14*		NS
Limbs muscle force					
Arm incremental test (W)	Porta et al[20]	↑7.3*	↑2.6*	4.7 (1.69 to 7.75)	.003
Arm endurance test (min)	Porta et al[20]	↑8.0*	↑4*	4.12 (0.68 to 7.56)	.021
Shoulder flexors (kg)	Chiang et al[21]	↑1.3*†	↓1.1*†	1.48 (0.66 to 2.22)	<.050
Elbow flexors (kg)	Chiang et al[21]	↑3.0*†	↓3.4*†	1.82 (0.95 to 2.59)	<.050
Handgrip force (%)	Burtin et al[26]	↑51 (16)	↑59 (25)	−8.0 (−17.92 to 1.92)	.110
(kg)	Schweickert et al[27]	39 (10−58)†	35 (0−57)†		.670
Knee extensors (kg)	Chiang et al[21]	↑3.2*†	↓2.3*†	1.26 (0.47 to 1.99)	<.050
Quadriceps force (N/kg)	Burtin et al[26]	↑0.54*	↑0.17		<.050
MRC score	Schweickert et al[27]	52 (25−58)†	48 (0−58)†		.380
Walking ability					
6MWD (m)	Nava[19]	↑*	↑		<.001
	Burtin et al[26]	196 (126−329)†	143 (37−226)†		<.050
Greatest walking distance (m)	Schweickert et al[27]	33.4 (0−91.4)†	0 (0−30.4)†		.004
Walking autonomy (n)	Nava[19]	52/60	14/20	1.24 (0.91 to 1.68)	.170
	Burtin et al[26]	23/31	20/36	1.34 (0.93 to 1.91)	.110
ADL					
BI score	Chiang et al[21]	↑30*†	↑0†	2.02 (1.12 to 2.81)	<.050
	Schweickert et al[27]	75 (7.5−95)†	55 (0−85)†		.050
	Chen et al[23]	↑8.8	NR		NS
FIM score	Chiang et al[21]	↑15*†	↓7†		<.050
	Chen et al[22]	↑44*†	↓0.5†		<.010
	Chen et al[23]	↑16.5 (16.5)	↑4.6 (7.9)		.020
Health-related quality of life					
Dyspnea score	Nava[19]	↓*	↓*		<.010
	Porta et al[20]	↓−1.24*	↓−1.5*	0.26 (−0.97 to 1.49)	.590
		↓−2.12*	↓−0.66	−1.46 (−2.93 to 0.014)	.070
Independent functional status (n)	Schweickert et al[27]	29/49	19/55	1.71 (1.11 to 2.64)	.010
SF-36 PF score	Burtin et al[26]	21 (18−23)†	15 (14−23)†		<.010
Hospital outcomes					
Weaning rate (n)	Nava[19]	39/47	11/14	1.06 (0.78 to 1.43)	.720
	Chen et al[22]	4/18	1/16	3.56 (0.44 to 28.61)	.230
	Chen et al[23]	8/12	8/15	1.25 (0.67 to 2.32)	.480
	Chang et al[28]	15/18	13/16	1.03 (0.75 to 1.40)	.870
Ventilator-free time (d)	Schweickert et al[27]	23.5 (7.4−25.6)†	21.1 (0.0−23.8)†		.050
Ventilator-free time (h)	Chiang et al[21]	↑6*†	↑0†		>.050
Duration of ventilation (d)	Chen et al[23]	32.7 (23.4)	54.6 (46.2)	−21.9 (−48.77 to 4.97)	.110
	Morris et al[25]	8.8 (7.4−10.3)†	10.2 (8.7−11.7)†		.163
	Burtin et al[26]	6.0 (3.0−13.0)†	6.0 (3.0−16.0)†		.400
	Schweickert et al[27]	3.4 (2.3−7.3)†	6.1 (4.0−9.6)†		.020
	Chang et al[28]	6.4 (4.0)	6.9 (5.3)	−0.5 (−3.69 to 2.69)	.760
	Malkoç et al[29]	14.0 (5.9)	20.0 (6.1)	−6.0 (−7.1 to −5.0)	<.001
LOS in ICU/HDU (d)	Nava[19]	38.1 (14.3)	33.2 (11.7)	4.9 (−0.63 to 10.43)	.080
	Chen et al[23]	35.4 (21.9)	56.9 (45.6)	−22.7 (−51.1 to 5.8)	.100
	Morris et al[25]	5.5 (4.7−6.3)†	6.9 (5.9−8.0)†		.025
	Burtin et al[26]	25.0 (15.0−37.0)†	24.0 (17.0−34.0)†		.140
	Schweickert et al[27]	5.9 (4.5−13.2)†	7.9 (6.1−12.9)†		.080
	Chang et al[28]	17.5 (9.8)	17.5 (11.8)	0.00 (−7.34 to 7.34)	1.000
	Malkoç et al[29]	15.8 (8.5)	25.5 (4.5)	−9.7 (−10.9 to −8.5)	<.001
LOS in hospital (d)	Morris et al[25]	11.2 (9.7−12.8)†	14.5 (12.7−16.7)†		.006
	Burtin et al[26]	36.0 (28.0-47.0)†	40.0 (28.0−19.0)†		.130
	Schweickert et al[27]	13.5 (8.0-23.1)†	12.9 (8.9−19.8)†		.930

(*continued on next page*)

Table 4 (*continued*)

Outcomes	Study	Experiment Group	Control Group	MD or RR (95% CI)	*P*
Hospital mortality (n)	Nava[19]	12/60	4/20	1.00 (0.36 to 2.75)	1.000
	Chen et al[23]	0/12	3/15	0.18 (0.01 to 3.11)	.200
	Morris et al[25]	20/165	30/165	0.67 (0.10 to 1.12)	.130
	Burtin et al[26]	11/45	7/45	1.57 (0.67 to 3.69)	.300
	Schweickert et al[27]	9/49	14/55	0.72 (0.34 to 1.52)	.390
1-year mortality (n)	Chen et al[22]	7/18	12/16	0.52 (0.27 to 0.99)	.040
	Burtin et al[26]	3/31	3/36	1.16 (0.25 to 5.34)	.850
Home discharge (n)	Chen et al[22]	5/18	1/16	4.44 (0.58 to 34.14)	.130
	Morris et al[25]	107/145	98/135	1.02 (0.88 to 1.17)	.820
	Burtin et al[26]	23/31	24/36	1.11 (0.82 to 1.52)	.500
	Schweickert et al[27]	21/40	13/41	2.38 (0.96 to 5.88)	.060
Hospital costs ($)					
Total direct costs	Morris et al[25]	6,805,082	7,309,871		NS
Average costs per patient	Morris et al[25]	41,142	44,302		.262

NOTE. Data are presented as no. (%) or mean (SD) unless otherwise indicated.
Abbreviations: CI, confidence interval; MD, mean difference; MIP, maximum inspiratory pressure; MRC, Medical Research Council; NR, no report; NS, no significance; RR, risk ratio; SF-36 PF score, 36-item short form physical functioning score; ↑, increase; ↓, decrease.
* Significant difference in pre-post comparison.
† Median (interquartile range).

improvement in muscle strength and functional status. However, reduced LOS was observed in only 2 nonrandomized trials.[25,29] Therefore, the results need to be interpreted with caution considering methodologic design and differing discharge policies. To date, only 1 study[22] demonstrated a significant 1-year mortality benefit after active mobilization in the HDU. However, the result was limited by a small and uneven sample size (only 4 patients in the control group and 11 patients in the mobilization group). From a clinical and economic point of view, every patient referred to home instead of a rehabilitation center is an important accomplishment. Unfortunately, only 1 study, Schweickert et al,[27] showed better discharge rates to home, and the difference was not significant.

The number of adverse events was low, and no event was serious. Early mobilization had a low risk of complications, even though a majority of activity events occurred when patients had an

Table 5 Safety outcomes in included trials

Study	Safety Profile
Clini et al[24]	None of the patients had an adverse event related to physical activities.
Morris et al[25]	Of all sessions, only 1.4% was not initiated because of either a high or low BP, and 0.9% of sessions were not initiated because of either too high or too low HR. The most frequent reason for ending a session was patient fatigue occurring without a significant change in the patient's vital signs.
Burtin et al[26]	425 sessions: 16 (<4%) sessions terminated because of desaturation <90% (n=8) or SBP >180mmHg (n=6), or a >20% decrease of DBP (n=2); 3 subjects dropped out because of Achilles' tendon rupture (n=1) and cardiorespiratory instability (n=2).
Schweickert et al[27]	498 sessions: 1 desaturation <80%; 1 radial artery line removed; 19 (4%) sessions discontinued for patient instability.
Bailey et al[30]	14 events (0.96%) occurred during 1449 sessions: falls to knees (n=5); desaturation <80% (n=3); SBP <90mmHg (n=4); SBP >200mmHg (n=1); nasogastric tube removal (n=1)
Needham et al[31]	rectal/feeding tube displaced/removed (n=4).
Zafiropoulos et al[32]	Increased minute ventilation, tidal volume, and RR in standing and no additional increase in walking; increased inspiratory flow rates and rib cage displacement and no significant increase in abdominal displacement compared with supine values; increased HR/BP/MAP from supine to sitting; no improvements in arterial blood gases.
Zanni et al[33]	Physiological changes in HR, BP, and oxygen saturation during treatment sessions were minimal, with no unexpected events occurring during therapy.
Bourdin et al[34]	Adverse events were observed in 13 cases (3% of the 424 interventions): drop-in muscle tone (n=7); hypoxemia (n=4); unscheduled extubation (n=1), and orthostatic arterial hypotension (n=1); none of the adverse events was associated with death, pulmonary embolism, dysrhythmia, or myocardial infarction.
Winkelman[35]	No episodes of hypoxia and >20% variation occurred in HR, SBP or MBP, or RR; no episode of fall or line dislodgement.

Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; HR, heart rate; MAP, mean blood pressure; SBP, systolic blood pressure; RR, risk ratio.

artificial airway in place. Adverse events did not result in extubation, complications that required additional therapy, additional cost, or longer LOS. Therefore, early active mobilization can begin immediately on stabilization of hemodynamic and respiratory physiology, which may occur 48 hours after ICU admission.[27] Although a low incidence of adverse events was found in these studies, it is imperative to stress that a comprehensive screening process was used to select suitable patients for mobilization. Additionally, appropriate precautions should be taken prior to, during, and after mobilization.

Study limitations

To our knowledge, this is the first systematic review to examine the effectiveness and safety of active mobilization in mechanically ventilated patients and that has been performed using a rigorous, yet broad, search in different languages. However, several limitations need to be addressed. First, as with any systematic review, the potential for selection bias existed; however, a comprehensive search strategy was used that included publications in any language. In addition, 2 independent reviewers were used, and reasons for study exclusions were clearly documented. Second, a number of the published studies had substantial limitations in their methods. The PEDro scores were lowered by a lack of insufficient randomization and allocation concealment, appropriate blinding of patients, caregivers, and/or assessors, substantial losses in follow-up, and intention-to-treat analysis. The vast majority of studies that were included to assess safety in this review were case series from single interventions with several limitations related to methodologic quality. In addition, testing the pre-post effectiveness change in most included studies may be not appropriate for the RCT study. Third, the heterogeneity between the studies, particularly with respect to participants, enrollment rate, and study intervention, was a challenge for this review. This diversity prevented us from conducting a meta-analysis and highlights the need for further research. Finally, the relatively small sample size[21-23,28,32-35] may lack the statistical power necessary for detecting differences between groups in some outcome measures. In addition, an unexpected loss of subjects, caused by episodes of acute illness and poor participant adherence, further contributed to the low statistical power.

Conclusions

Active mobilization therapy for patients who have undergone mechanical ventilation in ICU/HDU settings appears to have a positive effect on physical function and hospital outcomes with no severe adverse events. Furthermore, early active mobilization protocols may be initiated in the ICU setting and continued in the post-ICU setting. However, the heterogeneity and limited methodologic quality of the studies retrieved prevented a firm conclusion. Further research should be conducted to better define the population most likely to benefit from mobilization therapy, by using appropriate measure and assessment instruments, and by examining the ideal dosage and frequency of mobilization therapy to suit individual patient needs.

Keywords

Critical illness; Exercise therapy; Rehabilitation; Respiration, artificial; Review literature as topic

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Appendix 1

PubMed search strategy

#1randomized controlled trial [pt]OR controlled clinical trial [pt]OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) OR non-randomi*[tw] OR before after study[tw] OR time series[tw] OR case control[tw] OR prospective cohort[tw] OR retrospective cohort[tw] OR cross-section*[tw] OR prospective[tw] OR retrospective[tw] OR research design [mh:noexp] OR comparative study[pt] OR evaluation studies[pt] OR followup studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer* [tw] OR longitud*[tw] OR descripti*[title/abstract] OR study [title/abstract] OR evaluat*[title/abstract]OR pre-post[tw] OR (pre-test[tw] AND post-test[tw]) NOT (animals [mh] NOT human [mh]).

#2exercise[mh] OR exercise[tw] OR exercise movement techniques[mh] OR exercise therapy[mh] OR Physical Medicine[mh] OR occupational therapy[mh] OR occupational therapy[tw] OR early ambulation[mh] OR ambulation[tw] OR rehabilitation[mh] OR rehabilitation[tw] OR physical therapy[tw] OR physiotherapy [tw] OR mobilization[tw] OR mobilisation[tw] OR mobility[tw].

#3critical care[mh] OR critical care[tw] OR critical illness[mh] OR critical illness[tw] OR intensive care[mh] OR intensive care[tw] OR intensive care units[mh] OR intensive care units[tw] OR (ICU [title/abstract]) OR HDU[title/abstract] OR respiration, artificial [mh] OR mechanical ventilation[tw] OR ventilators, mechanical [mh] OR ventilat*[title/abstract].

#4 #1 and #2 and #3.

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