Effects of Rehabilitation Interventions on Clinical Outcomes in Critically Ill Patients: Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Objectives: To assess the impact of rehabilitation in ICU on clinical outcomes.

Data Sources: Secondary data analysis of randomized controlled trials published between 1998 and October 2019 was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Study Selection: We have selected trials investigating neuromuscular electrical stimulation or cycling exercises or protocolized physical rehabilitation as compared to standard of care in critically ill adults.

Data Extraction: Mortality, length of stay in ICU and at hospital, days on mechanical ventilator, and adverse events.

Data Synthesis: We found 43 randomized controlled trials (nine on cycling, 14 on neuromuscular electrical stimulation alone and 20 on protocolized physical rehabilitation) into which 3,548 patients were randomized and none of whom experienced an intervention-related serious adverse event. The exercise interventions had no influence on mortality (odds ratio 0.94 [0.79–1.12], $n = 38$ randomized controlled trials) but reduced duration of mechanical ventilation (mean difference, −1.7 d [−2.5 to −0.8 d], $n = 32$, length of stay in ICU (−1.2 d [−2.5 to 0.0 d], $n = 32$) but not at hospital (−1.6 [−4.3 to 1.2 d], $n = 23$). The effects on the length of mechanical ventilation and ICU stay were only significant for the protocolized physical rehabilitation subgroup and enhanced in patients with longer ICU stay and lower Acute Physiology and Chronic Health Evaluation II scores. There was no benefit of early start of the intervention. It is likely that the dose of rehabilitation delivered was much lower than dictated by the protocol in many randomized controlled trials and negative results may reflect the failure to implement the intervention.

Conclusions: Rehabilitation interventions in critically ill patients do not influence mortality and are safe. Protocolized physical rehabilitation significantly shortens time spent on mechanical ventilation and in ICU, but this does not consistently translate into long-term functional benefit. Stable patients with lower Acute Physiology and Chronic Health Evaluation II at admission (<20) and prone to protracted ICU stay may benefit most from rehabilitation interventions. (*Crit Care Med* 2020; XX:00–00)

Key Words: cycling; critically ill; exercise; neuromuscular electrical stimulation; outcome; physical rehabilitation

Mortality from most ICU syndromes is decreasing despite the increasing frailty and age of the patients being admitted to intensive care. Growing number of survivors suffer from poor long-term functional outcomes related to neuromuscular weakness and fatigability (1–4). Although ICU-acquired weakness is multifactorial (5), immobility plays an important role in its pathophysiology (6–9). Over the last two decades, there has been a paradigm shift away from providing "rest for recovery" to early mobility for patients in the ICU (5, 10–12). Since the landmark study by Schweickert et al (13), the concept of protocolized physical rehabilitation (PPR) has been shown to be safe (14–17) and physiologically plausible (13, 16–26). In addition, semiautomated instruments have been developed to deliver exercise to critically ill patients independently on their level of consciousness or constant presence of a physiotherapist. Namely, passive and active supine cycling on a bicycle ergometer (18, 25, 27–29) or neuromuscular electrical stimulation (NMES) (30–38), during which cutaneous electrodes placed over specific muscle groups electrically trigger muscle contractions.

As of today, it is difficult to offer a clear clinical guidance as to how and in whom to use which rehabilitation techniques

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DOI: 10.1097/CCM.0000000000004382

at the bedside in ICU. Data from randomized controlled trials (RCTs) are quickly emerging as 14 new RCTs have been published since the topic has been last reviewed (39, 40), but a lot remained to be done regarding the individualized approach that could have been tailored to the patient's need and circumstances In light of this, we set out to systematically review all RCTs reporting clinical outcomes investigating all types of rehabilitation interventions in adult critically ill patients. In order to gain insight into the sources of heterogeneity of the results, we also performed a meta-regression analysis of factors that may have influenced the results of the RCTs.

METHODS

Registration

This meta-analysis is fully compliant with Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (41), and systematic review has been prospectively registered in an international database of prospectively registered systematic reviews Prospero (No CRD42019132255, http: https://www.crd.york.ac.uk/prospero/).

Eligibility Criteria

We searched for RCTs in critically ill patients, which investigated a rehabilitation intervention defined as any form of PPR, NMES, or supine cycling. RCTs were included if they reported on at least one clinical endpoint such as mortality, days on mechanical ventilation (or ventilator-free days), lengths of stay in intensive care or in hospital, or long-term functional outcome. We have included all papers without language limitation that were accepted for publication or published between 1 January 1998 and 1 October 2019.

Information Sources and Search Strategy

Two researchers (A.K., K.J.) independently conducted a comprehensive literature search using PubMed, the Cochrane Central Register of Controlled Trials, MEDLINE, Web of Science, Physiotherapy Evidence Database, Scientific Electronic Library Online and Latin American & Caribbean Health Sciences Literature databases. Additionally, we searched the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov via their dedicated search portal for studies that might have been missed. Step-by-step strategy and full search terms sequence used in PubMed database can be found in **Supplemental Data File—Detailed Search Strategy** (Supplemental Digital Content 1, http://links.lww.com/CCM/F484). We adopted the PubMed search strategy when searching in other databases.

Selection of Studies and Data Extraction

Two authors (A.K., K.J.) independently extracted the data from the full text of papers into sheets designed a priori by the data analyst (P.W.). The two versions were compared, and any discrepancies are resolved by a third assessor (F.D.). Rationales for study exclusion are given in **Figure 1**.

Data Items

We extracted patients' age, sex, disease severity (Acute Physiology and Chronic Health Evaluation [APACHE] II, mortality in the control group), diagnostic category (medical, surgical, mix, specific disease only), and the proportion of patients with sepsis. We categorized the type of intervention as cycling, NMES or any form of PPR), timing (days after ICU admission or beginning of mechanical ventilation [MV]), and per-protocol exercise dose (in min/d, days/patient and whether or not the intervention was delivered >5 d per week). Outcomes included ICU- and end-of-study mortality (defined as mortality at the last follow-up point), the length of stay (LOS) in ICU and in hospital, the duration of mechanical ventilation and/or ventilator-free days at day 28, and any long-term functional outcome.

Risk of Bias

Risk of publication bias (small study effect) was assessed by Eggers test (with $p < 0.05$ considered significant) and by funnel plots, which were constructed in addition to forest plots for all meta-analyses (**Supplemental Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F485; and **Supplemental Additional Results**, Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

Summary Measures

Mantel-Haenzel odds ratios (ORs) and 95% CIs were calculated for death in ICU and death at the end of the study for each RCT. The OR was chosen because of the large variation in baseline event rates between the RCTs (mortality in the control groups ranges from 0% to 78%), implying that the relative risk would not be a good summary measure. Differences in means (95% CIs) between intervention and control groups were calculated for the LOS in ICU, LOS at hospital, duration of MV, and ventilator-free days. Where these outcomes were reported as median (interquartile range [IQR]) or median (range) and in the absence of access to record-level data, we used transformation to means (SD) as described by Wan et al (42).

Synthesis of Results and Measures of Consistency

Apart from the synthesis of the outcomes from all the RCTs, we separately analyzed three prespecified subgroups of RCTs based on the intervention studied: (NMES, cycling, and PPR). Heterogeneity of treatment effect between RCTs was assessed using a standard chi-square test, and, if appropriate, a weighted estimate of the typical treatment effect across all RCTs was calculated.

Additional Analyses

In order to gain insight into the sources of heterogeneity, prespecified subgroup analyses were performed to determine whether the treatment effect varies with the following: 1) intervention exposure (defined as mean ICU-LOS multiplied by per-protocol daily dose of rehabilitation [min]) and timing of initiation (>72 vs ≤72 hr within ICU admission),

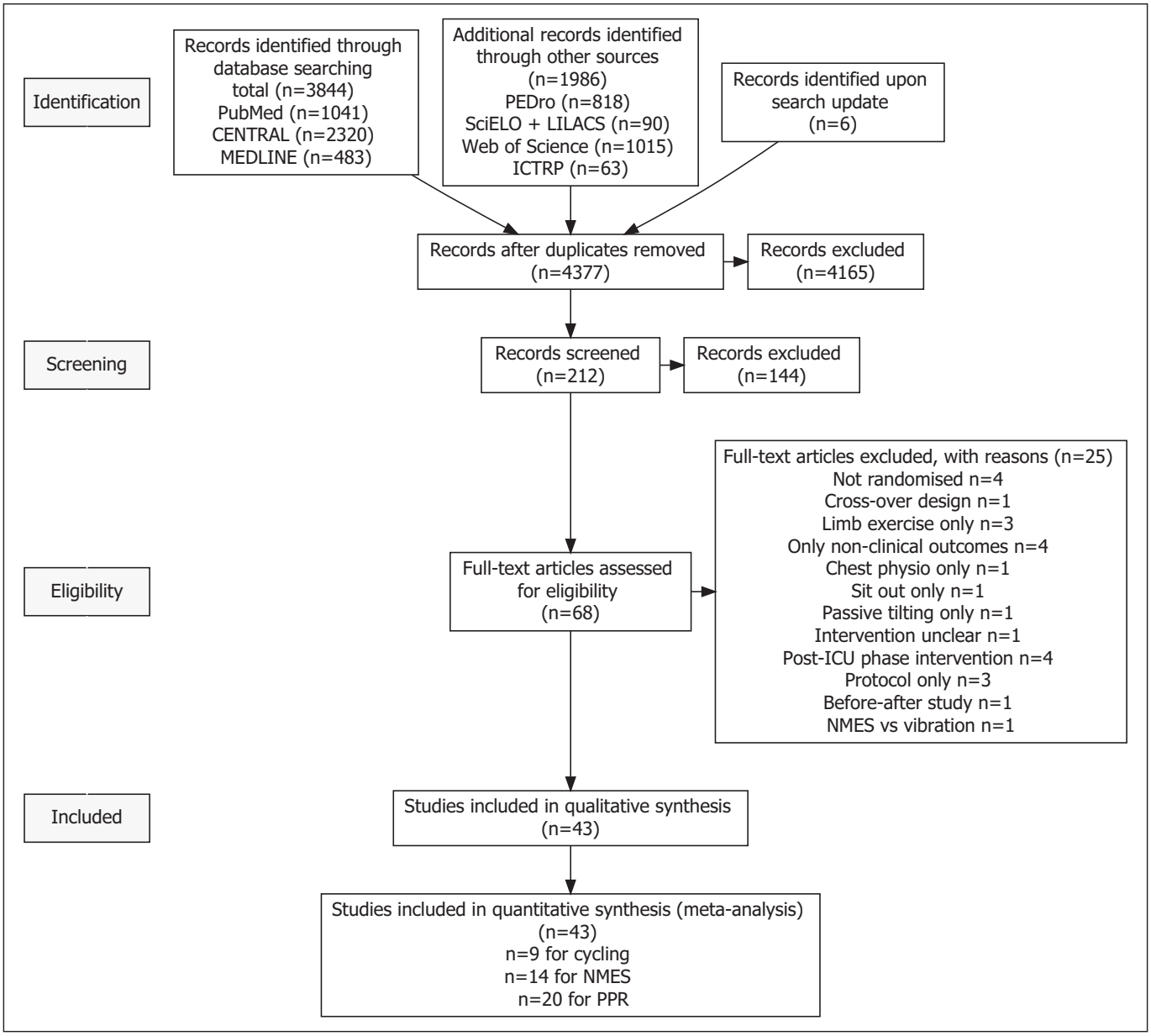

Figure 1. Search and selection process flowchart. Other sources include Physiotherapy Evidence Database (PEDro [*n* = 818]), Scientific Electronic Library Online (SciELO) and Latin American & Caribbean Health Sciences Literature (LILACS) databases (*n* = 90), World Health Organization International Clinical Trials Registry Platform (ICTRP), and ClinicalTrials.gov (*n* = 63) and secondary search within references of retrieved full texts (*n* = 6). CENTRAL = Cochrane Central Register of Controlled Trials, NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

2) patient characteristics (sex, disease severity expressed as APACHE II score, proportion of patients with sepsis), and 3) risk of bias (whether MV duration or ICU and hospital LOS were reported in intention-to-treat population or only in survivors). Test for differences in subgroups were based on random effect models and DerSimonian-Laird method to calculate τ^2 (underlying between-study variability). In addition, for continuous independent variables, we also performed meta-regression to estimate its influence on the treatment effect.

All calculations were performed using statistical packages meta_4.9-5 (43) and metafor_2.1-0 (44) programmed in R, version 3.6.1 2019-07-05 R.app 1.65 (45). Further details of the methods and step-by-step analyses can be found in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

RESULTS

Characteristics of Studies Analyzed

The search strategy (Fig. 1) yielded 43 RCTs. Of these, nine investigated some form of in-bed cycling, 14 NMES, and 20 PPR. One RCT (17) investigated combination of PPR with NMES, and it was further grouped with PPR. Individual RCTs processed in this meta-analysis are summarized in **Supplemental Table 2** (Supplemental Digital Content 4,

http://links.lww.com/CCM/F487). The RCTs were relatively small (median number of subjects is 55) and selective (median of 13% of admitted patients were recruited), often excluding patients with common comorbidities such as obesity (18, 25, 32, 46). Randomized patients (n = 3,548) were 59.5 years old (IQR, 56.5–62.5 yr old), had APACHE II score 19.6 (IQR, 17.9–23.7), and spent a median of 15 days (IQR, 10–21 d) in ICU and 10 days (IQR, 7–13 d) on mechanical ventilation.

Treatment Effects on In-Hospital Clinical Outcomes

Exercise interventions had no influence on ICU mortality (OR 1.02 [0.84–1.24]) or end-of-study mortality (OR, 0.94 [0.79–1.12]) (**Fig. 2**). This lack of effect on survival was homogenous in pooled RCTs (n = 38 RCTs, p for heterogeneity = 0.73 and 0.50, respectively) and across subgroups according to the type of exercise delivered. None of the RCTs reported a severe or life-threatening complication of the intervention. "ICU LOS" was marginally shorter in the intervention group as compared to controls (mean difference, –1.2 [–2.5 to 0.0] days, n = 31 RCTs), mostly due to the effect of RCTs investigating PPR (n = 16 RCTs, mean difference –2.0 [–3.6 to –0.3] days). The "duration of MV" reflected the treatment effects on ICU LOS (mean difference –1.7 d [–2.5 to –0.8 d], heterogeneity $p < 0.01$, n = 32 RCTs) (**Fig. 3**). "Hospital LOS" was not significantly different (mean difference –1.6 d [–4.3 to 1.2 d], n = 23 RCTs). See also Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486).

Treatment Effects on Long-Term Functional Outcomes

Twelve RCTs reported on some form of functional outcomes (Supplemental Table 2, Supplemental Digital Content 4, http://links.lww.com/CCM/F487). The timeframes and outcomes reported were diverse. In nine RCTs, there was no measurable effect of the intervention on functional variables, whereas three RCTs reported an improvement in physical function (17, 47) or the degree of independence (48). Most commonly reported parameter (in seven RCTs (17, 18, 24, 28, 47, 49) available from 768 patients) was physical component summary score component of The 36-Item Short Form Health Survey at 6 months, which was not significantly changed by rehabilitation intervention (mean difference, where positive value favors intervention 1.5 [-2.1; 5.1]). Other important patient-oriented outcomes such as return to work of cognitive function were only reported in few RCTs (19, 22, 50, 51).

Patients' Factors Influencing the Treatment Effect

Patients' age, male-to-female ratio, and proportion of septic patients did not influence the treatment effect on ICU LOS (p = 0.53, p = 0.49, p = 0.56, respectively). The meta-regression analyses suggest that the treatment effect on ICU LOS (**Fig. 4*A***) and MV duration (**Fig. 4*B***) might be reduced in RCTs on patients with higher APACHE II score. In line, the treatment reduced MV duration and ICU LOS in subgroup of RCTs enrolling patients with mean APACHE II below the median of 20 (mean differences –1.7 d [–3.3 to –0.1 d], –2.9 d [–4.4 to –1.3 d], respectively), whereas the treatment effect was not seen in RCTs on patients with APACHE II greater than or equal to 20 (mean differences –1.4 d [–3.3 to 0.5 d] and –0.4 d [–2.5 to 1.6 d], respectively). Importantly, there was no relation between APACHE II score in treatment effect on mortality (**Fig. 4*E***).

Intervention Characteristics Influencing the Treatment Effect

There is a strong association between the length of exposure to intervention and treatment effect on MV duration and ICU LOS ($p < 0.05$ for both) (**Fig. 4 C, D**). We have not found, however, any differences in treatment effects on ICU LOS between prespecified subgroups of the RCTs with or without early start (within 3 d of ICU admission, p = 0.46) (**Fig. 4*F***) or with the total per protocol extra rehabilitation dose in the intervention arm (p = 0.97). Nonetheless, only few RCTs monitored and reported delivered dose of intervention (19, 34, 47, 51–53), and in these, the delivered dose was invariably smaller than the dose prescribed in the protocol, sometimes as low as 25% of prescribed dose (19).

Risk of Bias

Risk of bias within RCTs is shown **Figure 5**, with details for individual RCTs in Supplemental Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/F485). For neither of four main outcomes (mortality, ICU and hospital LOS, MV duration), the risk of publication bias (small study effect) was significant. Funnel plots can be seen with each forest plot in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486). Only 10 RCTs reported ventilator-free days. There was no influence of study subjects' mortality on ICU LOS (p = 0.48), and MV duration was shortened in RCTs reporting it in intention-to-treat population (n = 19, mean difference –1.7 d [–2.5 to –0.8 d]) similarly to the RCTs reporting it only in survivors (n = 13, mean difference –1.4 d [–2.9 to 0.12 d]). Three RCTs (14, 17, 34) were stopped prematurely. Primary outcome was measured on average in 71% (range 31%–100%) of enrolled patients, but assessor was blinded to subject's treatment allocation only in three of 43 RCTs.

DISCUSSION

The main finding of this meta-analysis is that rehabilitation interventions in ventilated critically ill patients significantly reduce the duration of mechanical ventilation and the LOS in ICU by 1.7 and 1.2 days, respectively. Protocolized physical therapy (i.e. individualized physical exercise that is adjusted according to patient's tolerance and performance capacity) was more efficient that NMES alone or supine cycling-based treatment in reducing MV or ICU days. All forms of exercise seem to be safe, as none of the RCTs reported a serious or life-threatening complication. RCTs focused on physiologic outcomes showed no effect (54–56) or a reduction (29) in systemic inflammation, very modest changes in gas exchange and hemodynamics (38, 55, 57), and preservation or improvement

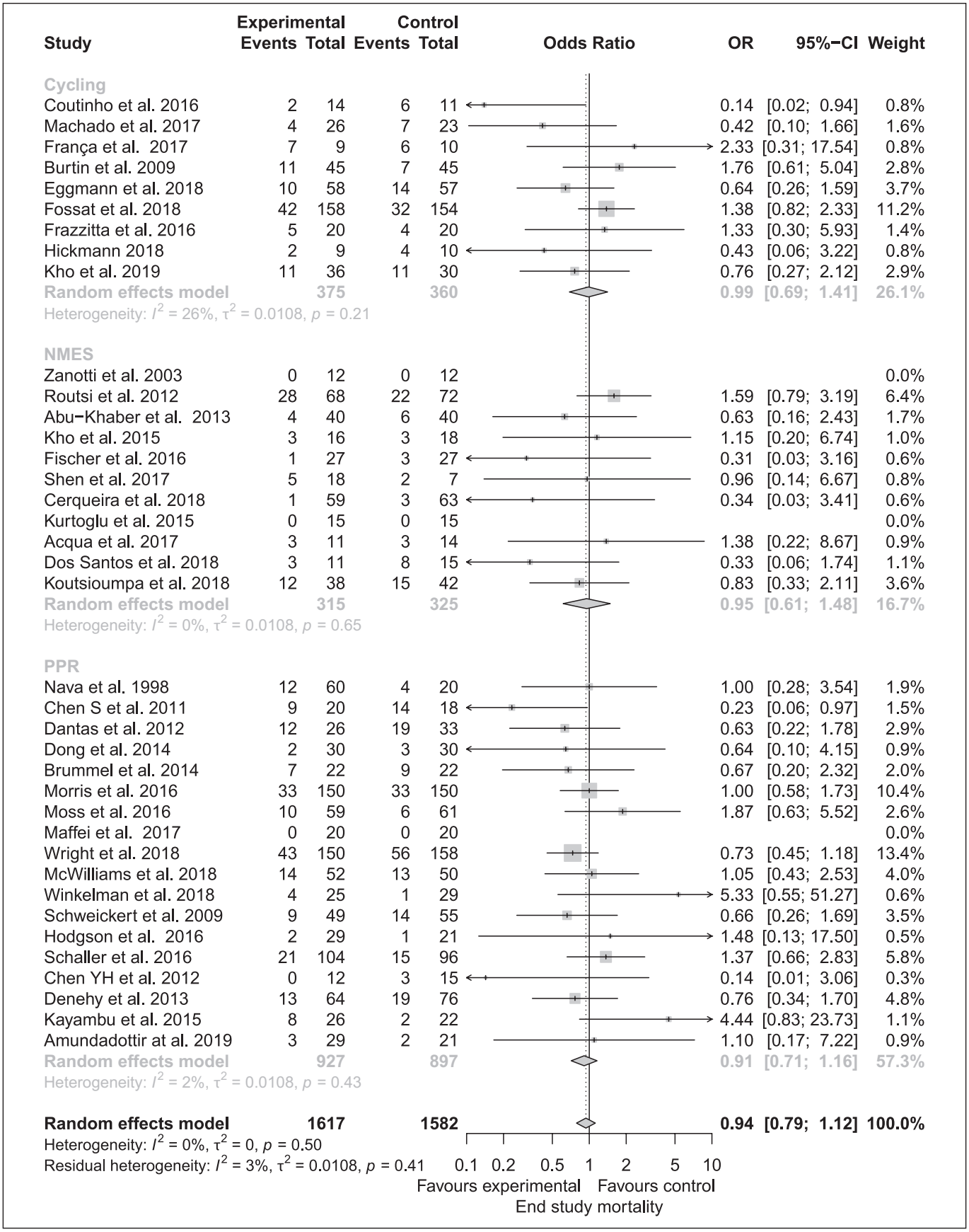

Figure 2. Forrest plot of the influence of intervention on end-of-study mortality. NMES = neuromuscular electrical stimulation, OR = odds ratio of death, PPR = protocolized physical rehabilitation.

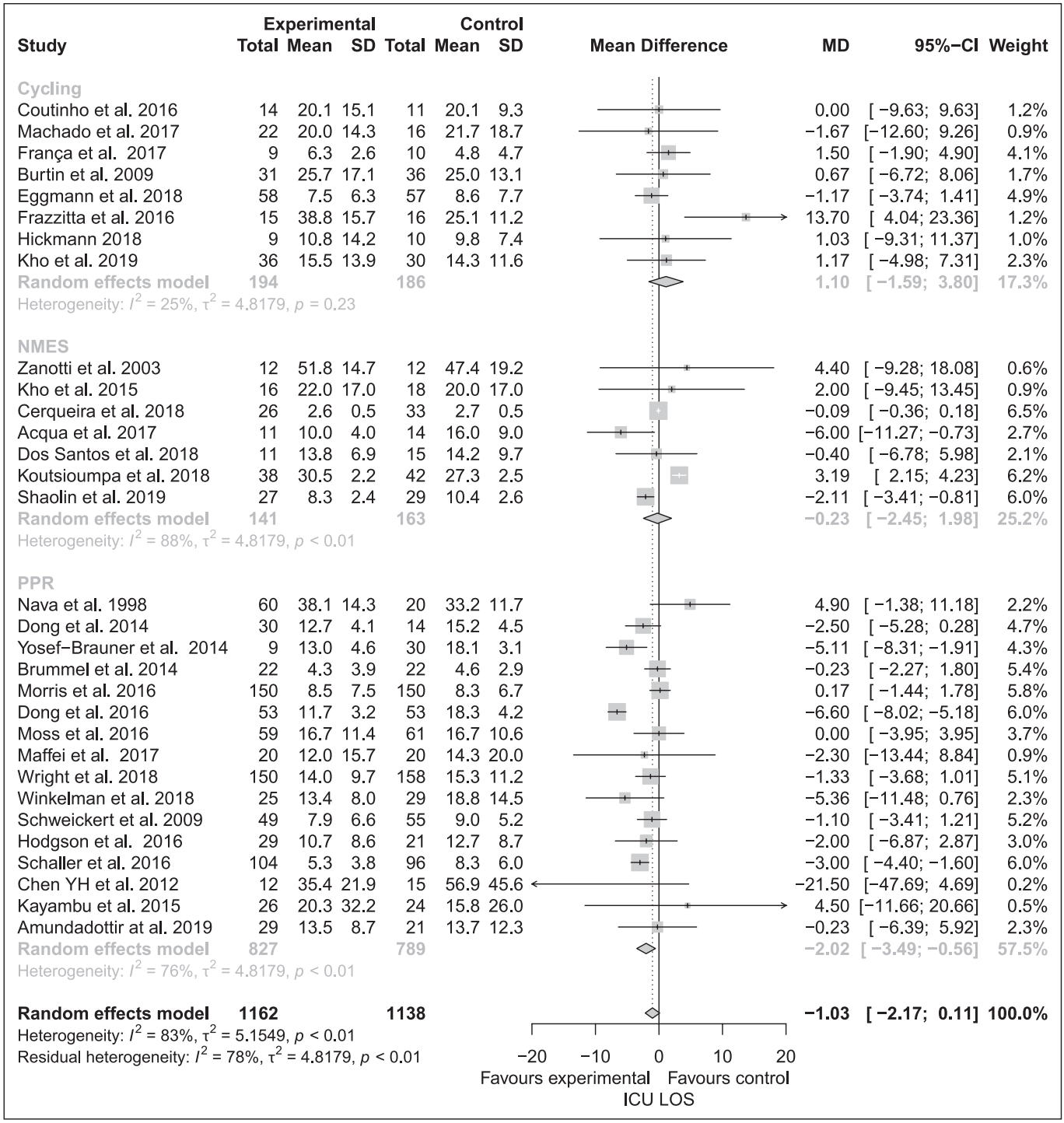

Figure 3. Forrest plot of the influence of intervention on ICU length of stay. LOS = length of stay, NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

of muscle power in some (27, 30, 32, 35, 36), but not all (28, 33, 34) RCTs.

The meta-regression analysis suggests that patients with lower APACHE II scores at admission might gain more benefit (in terms of a reduction of MV and ICU days) than sicker patients. The lack of association of intervention with mortality is consistent across RCTs recruiting patients with a range of mean APACHE II scores (Fig. 4E). There was no signal of difference in treatment effect with any other patients' characteristics. Most benefit was seen in patients that stayed in ICU long enough to receive effective dose of the intervention. For example, for any additional day on MV in the control group, exercise intervention was able to shorten it by 0.3 d (0.1–0.5 d). The length of exposure could

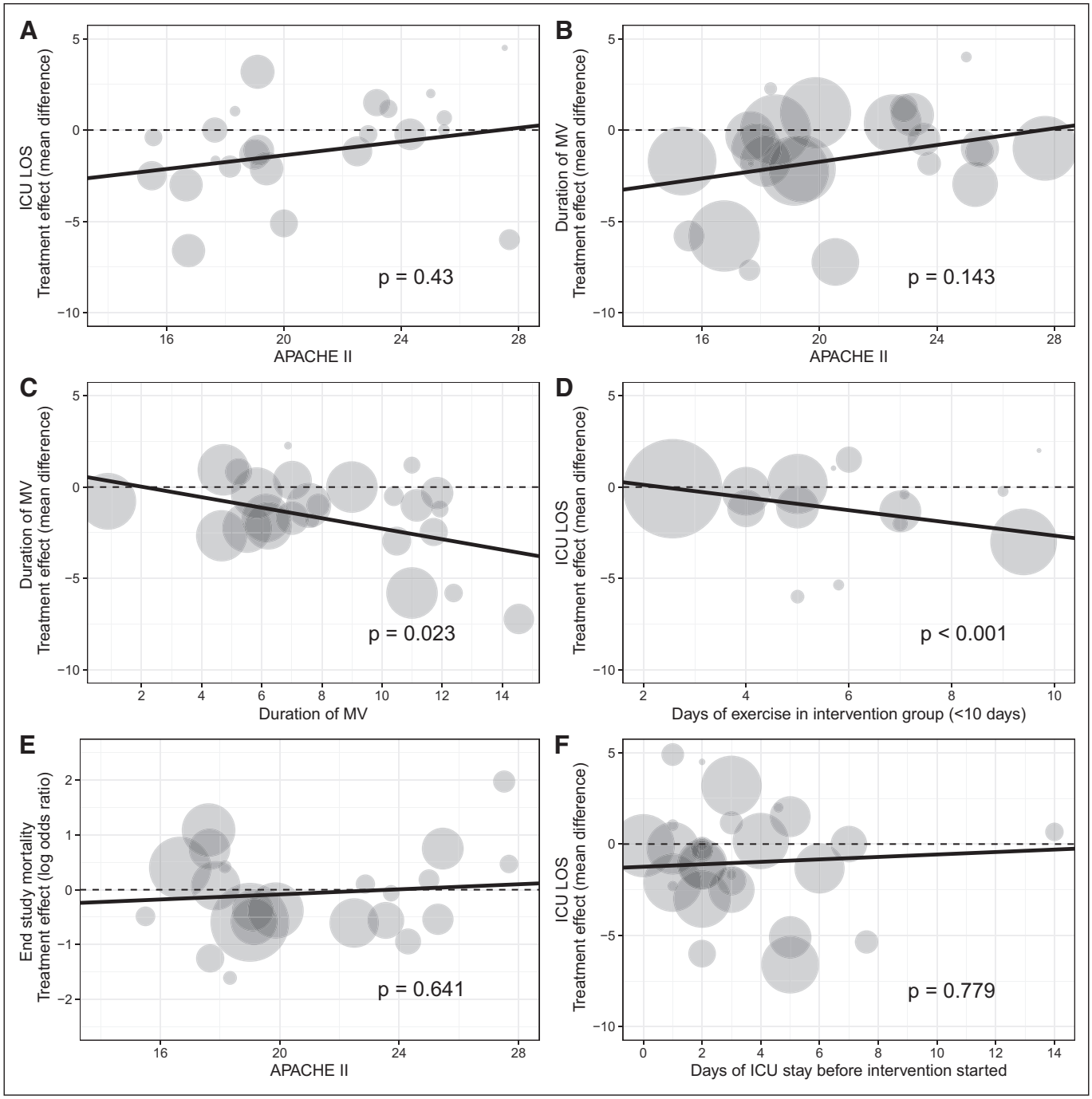

Figure 4. Meta-regression bubble plots. **A**, Acute Physiology and Chronic Health Evaluation (APACHE) II score versus treatment effect on ICU length of stay (LOS). **B**, APACHE II score versus treatment effect on mechanical ventilation (MV) duration. **C**, MV duration versus treatment effect on MV duration. **D**, Days of exercise versus treatment effect on ICU stay. **E**, APACHE II score versus treatment effect on study subjects' mortality. **F**, Mean number of days in ICU before intervention started versus treatment effect on ICU LOS.

not be compensated by more frequent rehabilitation (>5 d/wk), early start, or increased prescribed daily dose of exercise (measured in min/day). Yet, the shortening the time on ventilator and in ICU did not translate into a significant shortening of hospital LOS or consistent improvements of long-term functional outcomes. This suggests that for a lasting effect, rehabilitation intervention may need to be extended beyond ICU (14)

The evidence summarized in this review is limited to RCTs. In addition, 73% of patients in this meta-analysis were recruited into single-center phase II RCTs with less than 150 patients, testing primarily physiologic endpoints and safety or feasibility of interventions in diverse patient populations. Only five RCTs had greater than 150 subjects (14, 19, 22, 28, 50), and only two (19, 47) were adequately powered to investigate the effect of interventions on the patient-centered outcomes. Furthermore,

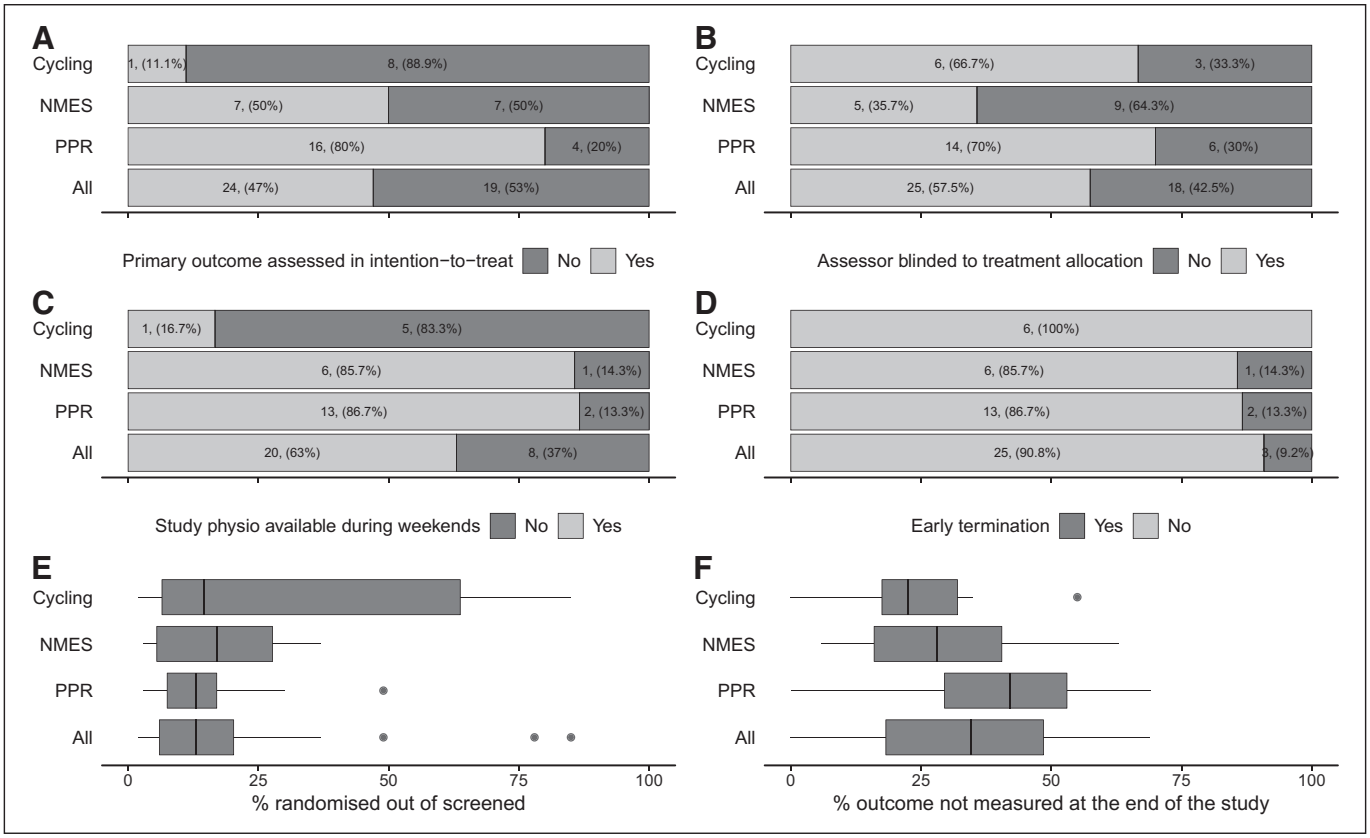

Figure 5. Risk of bias in individual randomized controlled trials displayed as the proportion at risk. **A**, Primary outcome assessed in intention-to-treat population. **B**, Assessor of primary outcome blinded to patient's treatment allocation. **C**, Study physiotherapist was reported to be available during the weekend. **D**, The randomized controlled trial was terminated early, that is, before reaching prespecified target number of participants. **E**, Proportion of randomized patients out of screened. **F**, Proportion of patients in whom the primary outcome was not measured for any reason. Detailed table with risk of bias for individual RCTs is available in the table S208 in Supplemental Additional Results (Supplemental Digital Content 3, http://links.lww.com/CCM/F486). NMES = neuromuscular electrical stimulation, PPR = protocolized physical rehabilitation.

37 RCTs did not monitor and report rehabilitation dose delivered to patients, and in six RCTs that did (19, 34, 47, 51–53), it was invariably smaller than the dose prescribed per protocol. Indeed, the lack of treatment effect even in adequately powered studies may either be true or represent a failure of protocol implementation. In addition, implementation failures could lead to superimposed selection bias, that is, that even physiotherapists consciously or subconsciously may have selected less sick patients for rehabilitation and in turn, within each trial less sick patients might have received more rehabilitation. This is an alternative explanation of the inverse relation of treatment effect and APACHE II score seen in the meta-regression analysis. Further confounding factor was the variability of per-protocol rehabilitation in the control groups. It ranged from no exercise at all (13, 29, 58), through passive limb movements (30, 46, 48, 59) to once-daily PPR (22, 53, 54, 60, 61) up to 60 minutes per day of exercise (62).

Meta-regressions results should be interpreted with caution and only as hypothesis generating. Although the original studies are RCTs, the meta-regression is across RCTs and is prone to the effect of confounders and aggregation bias, that is, the relationship with patient averages across RCTs may not be the same as the relationship for patients within RCTs. Further limitation of meta-regression analysis is inherent to the quality and completeness of source data. Important cofounders to the treatment effect might have been missed because they are were not reported by RCTs (such as preadmission frailty or functional status) or failures of protocol implementation render them invalid (such as per-protocol daily rehabilitation dose or early start). In addition, most trials only included patients with a certain pre-specified expected LOS—however understandable, this fact introduced selection bias and left the study population skewed toward long-stay patients.

From clinical point of view, it is important to notice that 24 of 43 RCTs report having a physiotherapist available 7 days a week, which is unlikely to be reproduced in routine clinical care, where a physiotherapist is often a scarce resource. At this time, there is no evidence from the pooled data to support the use of automated devices such as NMES or cycling-based interventions (18, 25, 27, 55, 56) even combined (28) or coordinated (63, 64). Hence, the individualized physical rehabilitation remains the only intervention with proven benefit in critically ill patients. With limitations noted above, it is likely that patients, regardless of age or sex, who are already stable and likely to require protracted stay in the ICU are those who benefit most from exercise interventions. On the other hand, goal-directed rehabilitation is safe and potentially beneficial for all ICU patients meeting the established safety criteria (65).

TABLE 1. Recommendation for Future Clinical Trials in Critical Care Rehabilitation

Patients	Report Patient's Premorbid Functional Status and Trajectory Report Reason for Admission Diagnosis
Intervention	Monitor and report on protocol implementation, that is,. the dose of exercise delivered to individual patients.
	Consider qualitative aspects/studies, that is, analyzing barriers to protocol implementation as a part of routine care.
	Consider studying rehabilitation interventions extending beyond ICU.
Control	Measure and report on rehabilitation intervention delivered in the control group.
	Monitor and report on sedation holds planned and performed.
Outcomes	Adhere to recommended core outcome set for trials in critical care rehabilitation (66).
	Make anonymized patient-level data set available in public databases accessible to secondary analyses.

The evidence in the field of critical care rehabilitation consists mainly of small single centre studies, often underpowered to measure the effect of intervention on patient-centered outcomes and even more often failing to implement the protocol and report on the dose of exercise and other important information. Indeed, performing RCTs in the critically ill is challenging mainly due to the inherent heterogeneity in these patients and due to the presence of many confounders mitigating the casual link between the immobility (or lack of exercise) and clinical outcomes. Based on our analysis of existing data, we formulated several recommendations for the design of future trials, which are summarized in **Table 1**.

CONCLUSIONS

The evidence available in the field is mostly derived from the synthesis of the results of small, single-center RCTs. PPR, but not supine cycling or NMES alone, shortens the time spent on MV and in the ICU. Long-term ICU patients with lower APACHE II scores seem to benefit most, and exposure time to rehabilitation may be more important than the acuteness of intervention initiation. Summary of evidence for the main finding is provided in **Supplemental GRADE Table** (Supplemental Digital Content 5, http://links.lww.com/CCM/F488).

ACKNOWLEDGMENTS

We thank Natalia Hrušková, Kamila Řasová, Barbora Blahutová, and Magda Šlehoferová for their assistance with source data search and extraction.

Drs. Waldauf, Puthucheary, and Duška are the authors of the original idea. Drs. Jiroutková and Krajčová searched for the sources and extracted the data. Dr. Waldauf performed independent data check and all statistical analyses. Drs. Puthucheary and Duška wrote first draft of the article, to which all the authors contributed. All authors contributed to data interpretation.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (http://journals.lww.com/ccmjournal).

Supported solely by Agency for Healthcare Research of the Czech Ministry of Health grant number AZV 16-28663A.

Drs. Jiroutková's and Duška's institutions received funding from Czech Government-funded grant agency AZV, grant no 16-28663A. Dr. Puthucheary received funding from Faraday Pharmaceuticals, Fresenius Kabi, and Lyric Pharmaceuticals. The remaining authors have disclosed that they do not have any potential conflicts of interest.

All authors have approved the final version of the article and gave their consent with the intention to publish.

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