Multiple organ dysfunction syndrome (MODS) is defined as altered organ function in an acutely ill patient (1). MODS usually involves 2 or more organ systems among the respiratory, cardiovascular, renal, hepatic, gastrointestinal, haematological, endocrine, and central nervous system (2). Once the syndrome has developed, there is no effective therapy for modulating the inflammatory response and reducing the severity of MODS. Therefore, treatment is focused on prevention and treating individual organ dysfunction as it develops, and supportive measures are required (3).

The survival of critically ill patients is frequently associated with significant functional impairment and reduced health-related quality of life (4). Although the pathophysiology of MODS is not entirely understood, the dysregulated immune response to critical illness plays a central role in determining the severity of the disease (3). MODS can be classified as primary (immediately after several specific traumas, such as extensive injuries of tissues, hypoxia and the ischaemia-reperfusion syndrome) or secondary (end-stage of a systemic inflammatory response syndrome, commonly involving sepsis) (5). The clinical course of MODS is divided by the Sequential Organ Failure Assessment (SOFA) score system into 4 stages, according to the degree of dysfunction of 6 organ systems (respiration, coagulation, liver, cardiovascular, central nervous system, renal). The SOFA score is instrumental in predicting the outcome (6). Independent of the initial score, an increase in SOFA during the first 48 h in the intensive care unit (ICU) predicts a mortality rate of at least 50% (7). The first clinical objective in MODS is always patient survival. Having assured survival, the objective shifts into improvement in as much as possible of health-related quality of life, reducing any organ dysfunction, and preventing all the possible sequelae of MODS or a long period of hospitalization (8). Therefore, rehabilitation interventions could cover an essential role in the accomplishment of functional recovery.

MODS is one of the worst possible manifestations of COVID-19, along with respiratory failure, neuro-
A rapid review of rehabilitation interventions in adults with MODS was performed. The review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (12) and the Interim Guidance from the Cochrane Rapid Reviews Methods Group (13). The protocol was registered on PROSPERO (CRD42020222599).

**Selection criteria**

Type of study: The review included only randomized controlled trials (RCTs) addressing the effects of rehabilitation interventions in patients with multiple organ failure.

Population. Considering the high variability in the definition of MODS in epidemiology and in the clinical outcomes in diverse healthcare settings, the review included studies involving adults with 2 or more organ dysfunctions diagnosed with SOFA (14).

Interventions. The review included studies addressing rehabilitation interventions, defined according to the classificatory items relevant to rehabilitation defined by Cochrane Rehabilitation (15): “all interventions provided or prescribed by rehabilitation professionals to enable people with disabilities to attain, or maintain, their maximum independence; all the interventions provided by rehabilitation professionals to prevent secondary health conditions or complications arising from a primary health condition, and all physical modalities, manual therapies, exercise therapies, prosthetic and orthotic interventions and adaptive technologies for disabilities”. Interventions aiming to prevent or delay complications arising from a primary health condition were regarded as part of primary interventions, whereas interventions designed to prevent or delay complications arising from a primary health condition were regarded as part of secondary interventions. Pharmacological or surgical interventions were not considered rehabilitation approaches and were therefore excluded.

Comparator(s). The review included studies that compared the rehabilitation interventions with any other type of intervention or with no intervention.

Outcomes. Considering the complexity and heterogeneity of outcomes related to the improvement in MODS in a rehabilitation context, it was decided to categorize the primary outcomes according to the International Classification of Functioning, Disability and Health (ICF) (16), as follows:

- Primary outcomes:
  - Body functions: mobility and muscle power (e.g. Medical Research Council scale); functions of cardiovascular, haematological, respiratory, metabolic and endocrine systems.
  - Secondary outcomes:
    - Mortality rate reduction, medical complications’ risk mitigation, and prevention of worsening of symptoms.
    - Quality of life: e.g. Short Form 36 (SF-36) questionnaire.

**Search strategy and screening**

The search was performed by an information specialist (SGL) on 30 November 2020 in the following databases: PubMed, Embase and Cochrane Central Register of Controlled Trials in the Cochrane Library, using the following key words: “rehabilitation interventions”, “multi-organ dysfunction syndrome, adult” and “randomized controlled trial”. The full search strategy is shown in Table I. A review author (EP) screened the title abstracts and full-text articles, with conflict resolution performed by another review author (CA). The review excluded conference abstracts, conference proceedings, abstracts, protocol stages, pilot or crossover designs and full-text articles in non-English languages.

**Assessment of risk of bias in included studies**

The risk of bias in included randomized controlled trials was assessed using the Cochrane “Risk of Bias” tool, described in the Cochrane Handbook for Systematic Reviews of Interventions (17). The tool was applied to the included studies for each outcome, by 1 author (EP), and a second author (SGL) verified her judgements. Any disagreements were solved by consensus or by consultation with the third review author (CA).

The following domains were assessed: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), other sources of bias. Each domain of the studies was classified as “low risk”, “high risk” or “unclear risk”, and the bias of individual items was evaluated as described in the Cochrane Handbook for Systematic Reviews of Interventions (17). For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), the risk of bias was evaluated only for the primary outcome.

**Summary of findings and assessment of the certainty of the evidence**

A “Summary of findings” table was proposed using standard Cochrane methodology to present results for each outcome (18). The GRADE approach was used to assess the body of evidence’s certainty to all outcomes of interest. A single review author (EP) applied GRADE and the second review author (MP) verified all judgements and added rationales for judgements to footnotes.

**Data extraction**

One review author (EP) extracted data on study characteristics using Microsoft Excel before comparing findings. A predetermined data form was used to extract the features of the selected papers, including:

- Report characteristics (year, authors, title and journal)
- Study design (location, groups and number of participants)
- Intervention characteristics (type, dose, intensity and frequency)
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Table I. Search strategy

| Database | Search strategy |
|----------|----------------|
| PubMed   | "Multiple Organ Failure"[Mesh] OR "Multiple Organ Dysfunction Syndrome"[tiab] OR "Multiple Organ OR "multi-organ"[tiab] OR MODS[tiab] OR "organ failure*"[tiab] OR "rehabilitation"[Mesh] OR "physical therapy"[Mesh] OR "exercise"[Mesh] OR "electrical stimulation"[Mesh] OR "patient positioning"[Mesh] OR "moving and lifting patients"[Mesh] AND (moving*[tiab] OR positioning*[tiab] OR repositioning*[tiab] OR lifting*[tiab] OR Handling*[tiab]) #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 |
| Embase (via Embase.com) | "randomized controlled trial"[pt] OR randomized[ti] OR "randomization"[de] OR "controlled clinical trial"[de] OR "randomly assigned"[tiab] OR placebo[tiab] OR "random group allocation"[tiab] OR "randomly assigned[tiab] OR (compare:ab OR comparison:tt OR compare:ab OR comparison:tiab) AND (open[tt] OR double blind procedure[de] OR "double blind procedure"[de] OR parallel[ti] OR crossover[ti] OR "cross over" OR "cross over" OR "cross over") OR (assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants) OR (assigned:ab OR allocated:ab) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR (volunteer:ab OR volunteers:ab OR "human experiment":de) OR (trial:ti OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) |
| CENTRAL (via Cochrane Library) | "randomized controlled trial"[pt] OR randomized[ti] OR "randomization"[de] OR "controlled clinical trial"[de] OR "randomly assigned"[tiab] OR placebo[tiab] OR "random group allocation"[tiab] OR "randomly assigned[tiab] OR (compare:ab OR comparison:tt OR compare:ab OR comparison:tiab) AND (open[tt] OR double blind procedure[de] OR "double blind procedure"[de] OR parallel[ti] OR crossover[ti] OR "cross over" OR "cross over" OR "cross over") OR (assign* OR match OR matched OR allocation) NEAR/6 (alternate OR group OR groups OR intervention OR interventions OR patient OR patients OR subject OR subjects OR participant OR participants) OR (assigned:ab OR allocated:ab) OR (controlled NEAR/8 (study OR design OR trial)):ti,ab,tt OR (volunteer:ab OR volunteers:ab OR "human experiment":de) OR (trial:ti OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26) |

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• Comparator characteristics (type, dose, intensity and frequency)
• Outcomes assessed and measures
• Numerical data for outcomes of interest (effect size between groups and statistical significance).

Differences of opinion regarding study characteristics and methodological limitations of the studies were resolved by consensus with the second review author (SGL).

Data synthesis

Given the heterogeneity of the included studies’ comparisons and outcomes, meta-analysis was not performed. Consequently, the results have been synthesized narratively and reported at the study level.

RESULTS

A total of 404 papers were identified through the database search, and 346 remained after removal of duplicates. After screening by title and abstract, 17 full-text articles were evaluated for eligibility. Three studies (90 participants) ultimately met the inclusion criteria for assessing the study question. Fig. 1 reports details of the screening process.

The 3 included studies (19–21) were RCTs with 90 critically ill patients with MODS, measured using the SOFA score, admitted to the intensive care unit (ICU) for at least 48 h. These studies aimed to prevent the loss of muscle mass and to improve muscle strength and functional outcomes in critically ill patients with MODS during their period of hospitalization before and after awakening, using neuromuscular electrical stimulation (NMES), alone or in combination with whole-body vibration (WBV), added to no treatment or usual care, such as early protocol-based physiotherapy.

Gerovasili (19) included 26 patients (13 per group) with admission scores of Acute Physiology and Chronic Health Evaluation (APACHE) II of 13 or higher. SOFA mean admission scores were 10 and 8 for NMES and control groups, respectively. This study compared daily NMES session simultaneously implemented on quadriceps muscles of both lower extremities, with control intervention for 7 days after admission to preserve muscle mass loss. They assessed the results with ultrasound, measuring the cross-sectional diameter (CSD) of the quadriceps muscles at baseline and end of treatment (7/8 days after the assessment). The duration of sessions was 55 min, including 5 min of warm-up and 5 min of recovery.

Rodriguez (20) included 14 intubated patients with baseline APACHE II and SOFA scores of 20 (interquartile range (IQR) 18–27) and 10 (IQR, 9–12), respectively. This study compared NMES applied on one side of the brachial biceps and vastus medialis with the other side. The authors evaluated the level of muscle strength after awakening and on the last day of treatment. NMES intensity was gradually increased until the achievement of 1 of these 3 outputs: visible contraction of the muscle mass, pain onset, or maximal tool intensity stimulation. Each session lasted 30 min.

Finally, Wollersheim (21) included 50 participants (33 intervention, 17 control) with sepsis at admission and a me-

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**Fig. 1.** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study.

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This study compared NMES and (not better specified in the original study) WBV in addition to early protocol-based physiotherapy applied twice a day. The aim was to improve muscle strength and physical performance at first awakening and ICU discharge. NMES was performed bilaterally on 8 muscle groups for 20 min; WBV was performed daily for 20 cycles. The study also performed a molecular analysis, but these results were not reported, due to the aim of the current systematic review. Full details of the study are reported in Table II.

Risk of bias in included studies

Fig. 2 provides an overview of the risk of bias for the considered domains.

Random sequence generation (selection bias)

Two studies (19, 20) did not provide enough information about the sequence generation process. Another study (21) reported the method of random sequence generation with sealed opaque envelopes.

Allocation concealment (selection bias)

Two studies (19, 21) did not provide enough information on the concealment method to permit assessment of whether the allocation sequence was concealed. One study (20) reported the allocation side selection randomized method: to balance previous minor muscle strength and mass differences between sides, the authors used sealed envelopes according to cerebral dominance.

Blinding of participants and personnel (performance bias)

Blinding of participants and providers was not possible for any study (19–21) because of the physical nature of the interventions. No studies reported whether data analysts were blinded to the treatment allocation.

Blinding of outcome assessor (detection bias)

None of the studies (19–21) provided sufficient information about the blinding of outcome assessor, but the outcome measured was objective and, consequently, unlikely to be influenced by the lack of blinding.

Incomplete data outcome (attrition bias)

Two studies (19, 20) reported dropouts and loss to follow-up. Data from these participants were excluded from the analysis in either study. Another study (21) reported no missing data to follow-up into the clinical analysis.

Selective reporting

One study (19) did not report all outcome measures mentioned in the registered protocol. Two other studies (20, 21) reported insufficient information to permit any judgement of risk of bias.

Effects of interventions

All studies (19–21) compared intervention with no treatment or standard physiotherapy, and reported positive effects of NMES on muscle mass measurements and strength.

Gerovasili (19) showed that the CSD of quadriceps muscles (rectus femoris and vastus intermedius) decreased significantly less in the NMES group than in the control group. Considering the right side, the CSD values of rectus femoris were \(-0.11\pm0.06\) cm \((-8\pm3.9\%)\) in the NMES group and \(-0.21\pm0.10\) cm \((-13.9\pm6.4\%)\) in the control group \((p=0.009\) for the absolute and \(p=0.029\) for the relative difference); corresponding values of vastus intermedius were \(-0.10\pm0.05\) cm.
Table II. Characteristics of included studies

| Study                        | Title                                                                 | Population       | Intervention                                                                 | Comparison                                                                 | Outcomes                                                                 | Outcome measures                                                                 | Participants analysed, n | Statistical significance | Effect size between groups |
|------------------------------|-----------------------------------------------------------------------|------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------------|----------------------------|--------------------------|--------------------------|
| Gerovasili et al. 2009 (19)  | Electrical muscle stimulation preserves the muscle mass of critically ill patients: a randomised study | 49               | Adult patients with an APACHE II admission score of 13 or higher and an ICU stay of more than 48 h | Daily EMS sessions of both lower extremities                              | Preservation of muscle mass                                              | CSD right rectus femoris evaluated with US                           | 26                         | SS p = 0.009             | EMS group: –0.114±0.06 cm. Control group: –0.214±10 cm. |
|                              |                                                                       |                  |                                                                               |                                                                            | CSD right vastus intermedius evaluated with US                          | SS p = 0.034                                                           |                            |                          | EMS group: –0.10±0.05 cm. Control group: –0.294±28 cm. |
|                              |                                                                       |                  |                                                                               |                                                                            | CSD left rectus femoris evaluated with US                                | NS p = 0.07                                                            |                            |                          | EMS group: –0.13±0.10 cm. Control group: –0.19±0.16 cm. |
|                              |                                                                       |                  |                                                                               |                                                                            | CSD left vastus intermedius evaluated with US                          | SS p = 0.018                                                            |                            |                          | EMS group: –0.009±0.05 cm. Control group: –0.22±0.26 cm. |
| Rodriguez et al. 2012 (20)   | Muscle wasting in septic patients requiring mechanical ventilation: a protective effect of transcutaneous neuromuscular electrical stimulation. | 32               | Adult patients with sepsis requiring MV and presenting 1 or more organ failure and an ICU stay of more than 48 h | Two daily sessions of NMES only applied to the muscles of 1 side of the body | Quadriceps muscle strength after awakening | Medical Research Council (MRC) scoring system | 28                         | SS p = 0.025             | EMS group: at awakening 2 (2–3), on the last day of NME 3 (3–4). Control group: at awakening 2 (2–3), on the last day of NME 3 (3–4). |
|                              |                                                                       |                  |                                                                               |                                                                            | Biceps muscle strength after awakening                                  | Medical Research Council (MRC) scoring system                           | SS p = 0.014                                                            |                            |                          | EMS group: at awakening 2 (2–3), on the last day of NME 3 (3–4). Control group: at awakening 2 (2–3), on the last day of NME 3 (3–4). |
|                              |                                                                       |                  |                                                                               |                                                                            | Arms circumference                                                      | Medical Research Council (MRC) scoring system                           | SS p = 0.065                                                            |                            |                          | EMS group: –1.3±0.5 cm. Control group: –2.5±0.0 cm. (From enrolment to the last day of NME) |
|                              |                                                                       |                  |                                                                               |                                                                            | Thigh circumference                                                     | Medical Research Council (MRC) scoring system                           | NS p = 0.979                                                            |                            |                          | EMS group: –0.4±0 cm. Control group: –1.0±1.9 cm. (From enrolment to the last day of NME) |
|                              |                                                                       |                  |                                                                               |                                                                            | Biceps thickness                                                       | Medical Research Council (MRC) scoring system                           | NS p = 0.290                                                            |                            |                          | EMS group: 0 (–2–2). Control group: 0 (–3–0). (From enrolment to the last day of NME) |
| Wollersheim et al. 2019 (21) | Muscle wasting and function after muscle activation and early protocol-based physiotherapy: an explorative trial | 50               | Mechanically ventilated patients ≥18 years of age with sepsis-related MODS indicated by a sepsis-related organ failure assessment (SOFA) score ≥9 within the first 72 h after ICU admission were eligible for enrolment | Muscle activating measures (NMEs and whole-body vibration (WBV)) in addition to protocol-based physiotherapy | Muscle strength                                                          | Medical Research Council (MRC) score                                    | 50                         | NS p > 0.05              | MRC median [IQR]. At awakening, control 3.0 [2.7–3.4]. intervention 3.0 [2.1–3.8]. At ICU discharge, control 3.9 [3.3–4.0]. intervention 3.6 [2.8–4.0]. At 12-month follow-up, control 5.0 [4.3–5.0]. |
|                              |                                                                       |                  |                                                                               |                                                                            | Muscle strength                                                         | Handgrip dynamometry/ 6 min-walking test                               | NS p > 0.05                                                            |                            |                          | Control: –.84 (–1.5–0). |
|                              |                                                                       |                  |                                                                               |                                                                            | Muscle strength                                                         | Functional Independence Measure (FIM)                                   | NS p > 0.05                                                            |                            |                          | Control: –.84 (–1.5–0). |

APACHE II: Acute Physiologic Assessment and Chronic Health Evaluation; ICU: Intensive Care Unit; EMS: Electrical Muscle Stimulation; NR: Not Reported; CSD: Cross Sectional Diameter; US: Ultrasound; SS: Statistical Significance; NS: Non Significance; V: Mechanical Ventilation; NMES: Neuromuscular Electrical Stimulation; MRC: Medical Research Council; MODS: Multiple Organ Dysfunction Syndrome; SOFA score: Sequential Organ Failure Assessment score; WBV: Whole-Body Vibration; FIM: Functional Independence Measure; CI: Confidence Interval.
The immobilization caused by this health condition affects the muscles, while their stimulated side showed enough strength to move against gravity at the end of treatment. Wollersheim (21) reported a significant muscle weakness in patients before awakening. Muscle strength and functional mobility did not differ significantly between intervention and control groups at ICU discharge. However, muscle strength showed a significant increase for the control (p = 0.008), intervention (p = 0.009), and usual physiotherapeutic practise group (p = 0.036) from the first awakening until discharge, with no difference between the groups at either time-point. Compared with common physiotherapeutic practise, the function outcome showed no significant improvement in the control or in the intervention group. At the 12-month follow-up visit, muscle strength and functional independence measure (FIM) scores returned to normal values in both groups independently of the study intervention.

The overall quality of evidence was low, due to high risk of bias and the imprecision of the small number of included studies (3) and participants (90) (see Supplementary Tables SI–SIII).

This rapid review investigated the effectiveness of rehabilitation interventions to improve functional outcomes in critically ill patients with MODS. The results show that NMES may be a potential preventive and rehabilitative intervention to preserve the muscle mass of the lower extremities, reduce muscle weakness, and improve muscle strength and function outcome in critically ill patients with MODS.

Muscle weakness is a frequent complication of MODS, and is associated with high morbidity and mortality (22). It involves functional and structural alterations in both muscles and nerves, and muscle atrophy can occur early during hospitalization (23). Critically ill patients with MODS undergo a state of hypermetabolism, characterized by increased energy expenditure, associated with increased protein loss (24). The immobilization caused by this health condition has damaging effects on skeletal muscles in healthy subjects and critically ill patients (23). Therefore, it is crucial to contain MODS sequelae, reducing the recovery period and increasing the capability to preserve and strengthen muscle mass in patients with complete or relevant functional impairments (25). Reducing duration of immobilization with early mobilization is recommended in international guidelines because it improves safety, intensity, and degree of mobility (26).

Compared with patients receiving standard physiotherapy, quadriceps strength at hospital discharge improved in long-stay patients receiving passive or active exercise training using a bedside ergometer (25). Passive range-of-motion exercises in unresponsive patients, progressing to active range-of-motion exercises, bed mobility, sitting upright, transfer training, and eventually walking, can improve functional status and health-related quality of life in these patients (27). Therefore, rehabilitation interventions might deliver tangible improvements in several aspects in the recovery from MODS and other pathologies causing similar impairments, such as COVID-19.

**Quality of evidence**

There are several potential sources of bias in this review: selection bias, attrition bias and selective reporting were common to all studies. These critical issues regard patient selection process, differences between participants who leave or continue the study, particularly between study groups (28), and missing protocol registration (29). Review outcomes were rated as low-quality using the GRADE system. Indeed, poor reporting of methods increased the risk of bias, and the small number of included studies and participants contributing to each outcome increased imprecision. All these methodological issues can lead to overestimation of intervention effects (30).

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1. [http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2846](http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2846)
CONCLUSION

NMES may be a potential rehabilitation intervention for preventing muscle volume loss and improving muscle strength and function in critically ill patients with MODS. However, no firm conclusion can be drawn, due to a lack of evidence on the effectiveness of rehabilitation interventions in improving or maintaining the clinical condition in critically ill patients with MODS. Further studies, with adequate sample size and methodological rigour, are needed to investigate the effectiveness of this approach and to support these preliminary findings. Moreover, other studies on other possible interventions are also needed.

The authors have no conflicts of interest to declare.

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