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Interventions for the management and prevention of sarcopenia in the critically ill: a systematic review.

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Purpose: In the critically ill, sarcopenia is associated with a variety of adverse outcomes however there is no consensus regarding its management. This study aimed to systematically review the evidence for interventions for the management and prevention of sarcopenia in critically ill patients.

Materials and Methods: Bibliographic databases were searched according to pre-specified criteria (PROSPERO-CRD42018086271). Randomised controlled trials (RCTs) investigating interventions to preserve muscle mass and/or function in critically ill patients were included. Two independent authors selected the articles and assessed bias using the Cochrane Risk of Bias Tool.

Results: Twenty-two eligible RCTs were identified comprising 2792 patients. Three main groups of interventions were implemented in these trials: neuromuscular electrical stimulation (NMES), exercise-based and nutritional. Both the interventions and outcomes measured varied significantly between studies. NMES

was most frequently studied as an intervention to preserve muscle mass whilst exercise-based treatments were evaluated as interventions to preserve muscle function. There was significant variation in the efficacy of the interventions on sarcopenia markers and secondary outcomes.

Conclusions: NMES and exercise-based interventions may preserve muscle mass and function in patients with critical illness. There is a lack of consistency seen in the effects of these interventions. Further, large, high quality RCTs are required.

Keywords: sarcopenia; muscle wasting; critical illness; intensive care; intensive care unit acquired weakness; ICU-AW.

Introduction:

Sarcopenia is defined as a decline in skeletal muscle mass and function [1]. Sarcopenia can be further classified as primary, age-related sarcopenia and secondary sarcopenia which is associated with a variety of risk factors including malnutrition, immobilisation, disease and inflammation [2,3]. Sarcopenia primarily results from the deterioration of fast twitch type II muscle fibres which are crucial to muscle strength and performance [4]. Observational studies have reported a high prevalence of sarcopenia in hospitalised patients and in as many as 60% of patients admitted to critical care for mechanical ventilation [5-7]. Crucially, patients with sarcopenia have been shown to be at increased risk of mortality, longer hospital stay and a greater readmission rate [7-13]. Mechanically ventilated, critically ill patients with low skeletal muscle-area have been shown to have a 25% increased risk of in-hospital mortality compared to patients with normal skeletal muscle area [7]. Furthermore, sarcopenia has been shown to result in significant morbidity including a loss of functional independence in patients surviving to hospital discharge [8].

Currently, there is no gold standard for the assessment of patients at risk of sarcopenia in critical care. Computed tomography (CT) and magnetic resonance imaging (MRI) are often used to assess muscle mass however these techniques are expensive and cannot be performed at the bedside [14,15]. Hand grip strength (HGS) is frequently used to assess muscle function and is strongly correlated with other measures of strength [16]. Other metrics include the 6-minute walk test (6MWT) and Medical Research Council (MRC) muscle scale [17]. Several interventions have been investigated to manage sarcopenia. Exercise-based

interventions such as early mobilisation have been shown to help prevent muscle wasting in addition to having a positive impact on mood, quality of life and mobility in patients recovering from critical illness [18]. For patients unable to engage in exercise-based interventions, neuromuscular electrical stimulation (NMES) has emerged as an alternative treatment [19].

Despite the adverse outcomes experienced by critically ill patients with sarcopenia, there is no consensus regarding its management. This study aimed to systematically review the evidence for the management and prevention of sarcopenia in critically ill patients, with a view to describing those that are clinically effective. Through this process we aim to suggest further work that may be required prior to introduction of therapies targeting sarcopenia in routine clinical practice in patients with critical illness.

Materials and Methods:

Standard systematic review methodology was performed according to a pre-specified study protocol (PROSPERO-CRD42018086271). Searches were carried out using the Medline/PubMed and Embase bibliographic databases. In addition, the Cochrane Database of Systematic Reviews and PROSPERO were checked to avoid redundant repetition of review and trials registers searched to identify ongoing studies.

Search strategy

Our search strategy focussed on two keywords: sarcopenia and critical illness. Search terms were extrapolated from the keywords and MeSH headings were included to ensure that no papers using non-standard terms were missed (see supplement 1 for full search strategy). Intensive care unit-acquired weakness (ICU-AW) was a term that appeared frequently during background reading. ICU-AW shares many similarities with sarcopenia and as such we decided to include it in our search terms to ensure that papers relevant to sarcopenia were not missed. Searches were limited to English language articles.

Study selection

The population of interest was patients with critical illness. We defined this as patients who were admitted to a high dependency unit (HDU) or intensive care unit (ICU) for level 2 or level 3 care. Only randomised controlled trials evaluating an intervention that aimed to treat sarcopenia by improving or maintaining muscle mass/size and/or muscle function (strength or performance) were included. The comparator of interest was

usual care or placebo/sham intervention. Primary outcomes of interest included any measure of muscle mass/size and muscle function. Secondary outcomes included length of ICU/hospital stay, days mechanically ventilated, rate of hospital readmission or mortality. Studies were checked for duplication between databases. Following this, titles and abstracts were screened against the inclusion and exclusion criteria by two reviewers (NB and SPT). Any disparities were discussed and if required, referred onto a third reviewer for final decision. Following initial screening, full papers were obtained and examined to ensure eligibility for data extraction.

Data extraction, risk of bias assessment and evidence synthesis

A data extraction form, modelled on the Cochrane data extraction pro-forma, was used. Data was extracted by one reviewer and checked by another. All studies that met the inclusion criteria were assessed using the Cochrane risk of bias tool. This assessed six areas: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Each of these areas was classified as high risk, low risk or unclear risk of bias. Narrative synthesis of evidence was undertaken for all included studies. Meta-analysis was not possible due to heterogeneity of study design and outcomes.

Results:

The PRISMA flow diagram in Figure 1 illustrates the process of article selection. Searches of the PubMed/Medline and Embase databases resulted in 204 and 116 papers being returned respectively. Forty-eight duplicates were found between databases leaving 272 unique papers. An additional 4 papers were identified from reference lists. Following title/abstract screening 37 papers underwent full review. Fifteen papers did not meet inclusion criteria leaving 22 full papers included for evidence synthesis. Characteristics of included studies are summarised in Table 1. In total, the 22 studies comprised 2792 patients. Study size varied from 8 patients to 1372 patients, with recruitment occurring primarily within the first 24-48 hours of ICU admission. Eighteen studies described the severity of critical illness using established scores such as Sequential Organ Failure Assessment (SOFA) and Acute Physiology And Chronic Health Evaluation II (APACHE II).

Interventions

NMES was evaluated in 11 studies [20-30]. There was wide variation in protocols for NMES administration, summarised in Table 1. Exercise-based interventions were evaluated in 11 studies [25,26,30-38]. Exercise-based interventions encompassed a variety of different techniques with significant heterogeneity of intervention protocols. Nutrition-based therapy by means of early enteral or parenteral feeding was evaluated in 3 studies and essential amino acid supplementation was evaluated in 1 study [35,39-41]. For the purposes of this review, we categorised interventions into 4 groups: NMES, exercise-based, nutritional and combined interventions.

Comparators

The comparator in most studies was 'usual care' (n=17), the remainder utilised a placebo/sham intervention (n=5). In studies of NMES, the use of sham intervention occurred whereby electrodes were attached, but no current was passed through the target muscle. Several studies of NMES used a patient's contralateral limb as a paired control by only stimulating one quadriceps (n=4). Placebo/sham did not occur with the exercise-based interventions, as this was not feasible.

Outcomes

Only 4 studies measured both components of sarcopenia – muscle mass/size and muscle function. The remainder of studies measured either muscle mass/size or muscle function. Muscle function alone was assessed in 12 studies and muscle mass/size alone was assessed in 6 studies. Table 2 summarises the different sarcopenia related outcomes used in these studies. A variety of additional clinical outcomes were reported including: in-hospital mortality, number of days mechanically ventilated, length of ICU/hospital stay, readmission rate and post-discharge mortality.

Risk of Bias

An overview of the risk of bias assessment is presented in Table 2. Some studies were well conducted using large cohorts with adequate blinding of both patients and personnel and clear presentation of their methods of blinding. However, many studies were subject to a high risk of bias due to small cohort size or insufficient

blinding of patients or personnel. Many papers did not describe their methodology of randomisation or suffered from attrition (e.g. due to withdrawal from the study or death) resulting in incomplete data capture. Selective outcome reporting was seen in three studies and several studies did not present raw data or average values of outcome measures.

Neuromuscular electrical stimulation

Eight studies investigated the efficacy of NMES in addition to usual care [20-24,27-29]. Three of these studies assessed both muscle mass/size and muscle function as outcomes [21,22,28], one study assessed muscle function alone and 4 studies assessed muscle mass/size alone [20,23-27,29,30].

Of the 3 studies evaluating both muscle mass/size and function, Fischer et al. [22] observed a faster rate of improvement of quadriceps muscle strength as measured by mean MRC score during ICU stay in patients treated with NMES, however there were no differences in mean MRC score, quadriceps muscle layer thickness (MLT), HGS or functional outcomes at hospital discharge. Falavigna et al. [21] found an increased range of movement of active dorsiflexion following NMES treatment, however there were no differences in leg or thigh circumference or MRC score. Rodriguez et al. [28] found greater preservation of muscle strength as measured by MRC score following NMES treatment, however there were no differences in leg or arm circumference or bicep thickness.

In the largest of 5 studies evaluating either muscle mass/size or muscle function, Routsi et al. [29] demonstrated greater preservation of muscle strength as measured by MRC score (median [range]: 58 points [33-60 points] vs. 52 points [2-60 points], p=0.04), a shorter duration of weaning from mechanical ventilation (median [range]: 1 day [0-16 days] vs. 4 days [0-44 days], p=0.003) and a shorter time off mechanical ventilation (median [range]: 4 days [0-16 days] vs. 6 days [0-41 days], p=0.003) in patients treated with NMES. However, there were no differences in ICU length of stay (ICU LOS) or total number of days on mechanical ventilation. Gerovasili et al. [23] found treatment with NMES lead to a greater preservation of quadriceps muscle cross sectional diameter as measured by ultrasound. Similarly, Dirks et al. [20] observed greater preservation of quadriceps muscle fibre cross sectional area with NMES treatment. However, Poulsen et al. [27] observed no difference in quadriceps muscle volume with NMES treatment and Gruther et al. [24] demonstrated no difference in quadriceps MLT in an acute ICU group (admission <7days),

however they did find greater preservation of quadriceps MLT in the long-term ICU group (admission >14days).

Exercise-based interventions

Seven studies investigated the efficacy of exercise-based interventions in addition to usual care [31-34,36-38]. None of these studies assessed muscle mass/size as an outcome. The comparator in these studies was usual care. Conolly et al. [32] found that an enhanced rehabilitation programme had no effect on 6MWT or functional outcomes compared to usual care. Similarly, Denehy et al. [33] found there were no between group differences in 6MWT, timed up-and-go test (TUAG) or health related quality of life (HRQoL) at 12 months post-ICU discharge following a phased rehabilitation programme. Conversely, Burtin et al. [31] found that, compared to usual care, patients treated with daily cycle ergometer sessions until ICU discharge had greater 6MWT (median [range]: 196m [126-329m] vs.143m [37–226m], $p<0.05$), improved self-reported physical performance (median [range]: 21 points [18–23 points] vs. 15 points [14–23 points], $p<0.01$) and greater improvement in quadriceps force at hospital discharge. However, in this trial there were no differences in HGS, duration of weaning from mechanical ventilation, ICU LOS, hospital LOS or 1-year mortality.

Yosef-Brauner et al. [38] found that twice daily intensive physical therapy until discharge resulted in a faster initial rate of improvement in MRC score and a shorter ICU LOS however the intervention had no effect on MRC score improvement or HGS at ICU discharge or duration of mechanical ventilation. In patients treated with early, daily physical and occupational therapy sessions, compared to usual care, Schweickert et al. [37] observed a greater return to independent functional status (number [%]: 29 [59%] vs. 19 [35%], p=0·02), greater maximum walking distance at hospital discharge (median [range]: 33·4m [0–91·4m] vs. 0m [0–30·4m], p=0·004) and a greater number of ventilator-free days (median [range]: 23·5 days [7·4–25·6 days] vs. 21·1 days [0·0–23·8 days], p=0·05). The authors found no differences in MRC score, HGS, ICU LOS, hospital LOS or hospital mortality.

Morris et al. [36] found that a programme of standardised rehabilitation therapy sessions three times per day had no effect on short physical performance battery (SPPB) score, HGS, hospital LOS, ventilator-free days, self-reported physical performance, HRQoL or functional outcomes measured at hospital discharge.

Hodgson et al. [34] found that early, goal-directed mobilisation resulted in higher ICU mobility scale score compared to usual care however there were no differences in strength or functional outcomes at ICU discharge, duration of mechanical ventilation, ventilator-free days, in-hospital mortality, ICU LOS or hospital LOS.

Nutrition-based intervention

Three studies evaluated nutrition-based interventions consisting of early parenteral nutrition or immediate postoperative enteral feeding. Watters et al. [41] found that immediate post-op enteral feeding continued for 6 days, compared to usual care (enteral feeding no sooner than day 6 post-op) had no effect on HGS measured 6 days post-op. There were also no differences in ICU LOS, hospital LOS or post-op maximal inspiratory capacity between treatment groups however there was greater impairment of post-op forced expiratory volume in 1 second and forced vital capacity in the immediate post-op enteral feeding group. Caesar et al. [39] found that early parenteral nutrition (starting ≤48hrs after ICU admission) continued for 9 days compared to late parenteral nutrition (started ≥8 days after ICU admission) had no effect on femoral muscle volume, ICU LOS or 90-day mortality. Doig et al. [40] found that early parenteral nutrition (starting day 1 of ICU admission) continued until ICU discharge compared with usual care resulted in a shorter duration of invasive mechanical ventilation (number of days, adjusted for duration of ICU stay: 7.26 vs. 7.73 days per 10 patient x ICU days, p=0.01) and reduced self-reported muscle wasting and fat loss. However, the authors observed no difference in mid-arm muscle circumference, 60-day mortality, ICU LOS, hospital LOS or hospital mortality between groups.

Combined interventions

Four studies evaluated a combination of two interventions for preservation of muscle mass/size or muscle function [25,26,30,35]. Kayambu et al. [25] evaluated early, targeted physical rehabilitation and/or NMES continued until ICU discharge, compared with usual care. The authors observed an improvement in HRQoL in the domains of 'physical function' (mean score ±SD: 81.8 ±22.2 vs. 60.0 ±29.4, p=0.04) and 'physical role' (mean score ±SD: 61.4 ±43.8 vs. 17.1 ±34.4, p=0.005) measured at 6 months post-ICU discharge in the treatment group. However, there were no differences in acute care index of function (ACIF), physical function ICU test (PFIT), fat-free mass or MRC score at ICU discharge. Furthermore, there were no differences in duration of mechanical ventilation, ICU LOS or ICU readmission rate.

Jones et al. [35] evaluated a supervised physiotherapy and exercise programme combined with glutamine and essential amino acid supplementation twice daily for 3 months. The authors observed a greater improvement in 6MWT at 3 months in the exercise plus nutrition intervention group. However, they observed a shorter ICU LOS in the exercise plus placebo group. There was no difference in duration of mechanical ventilation between groups. Patsaki et al. [26] evaluated daily NMES combined with a targeted physical rehabilitation programme until hospital discharge compared with sham NMES and usual care. The authors found no differences in MRC score, HGS, Functional Independence Measure or hospital LOS between groups. Finally, in a small trial, Zanotti et al. [30] found that NMES combined with active limb mobilisation 5 days/week for 28 days resulted in greater improvement in muscle strength score compared with usual care.

Discussion:

To our knowledge, this is the first systematic review of interventions for the management and prevention of sarcopenia in critically ill patients. In total, we identified 22 RCTs which evaluated the impact of an intervention on at least one marker of sarcopenia in critically ill patients. We categorised interventions into 4 groups: NMES, exercise-based, nutritional and combined interventions. Despite several studies showing promising results, the efficacy of interventions for the preservation of muscle mass/size and muscle function was variable. NMES represents an appealing intervention to utilise in patients unable to engage in physical therapies due to its ability to be performed at the bedside without any need for patient interaction. However, this systematic review suggests more evidence is needed before NMES can be integrated into routine clinical practice. Similarly, exercise-based interventions showed variable results and require further evaluation.

Neuromuscular electrical stimulation

Overall, the impact of NMES on sarcopenia markers was inconsistent. NMES may potentially improve muscle strength and preserve muscle mass in critically ill patients. It is important to note however, that protocols of NMES administration varied significantly between studies. Protocols consisted of daily or twice-daily NMES sessions of varying duration (typically <60 minutes), applied to different muscles, started at different times during admission and continued for different lengths of time. Furthermore, comparators included a mixture of other patients receiving sham treatment/usual care or the intervention patient receiving NMES to one leg only, with their contralateral leg as the comparator.

Measurement of muscle mass/size was not consistent across studies. Some studies used indirect measures (leg and arm circumference) while others used ultrasonography and CT imaging techniques to more accurately determine muscle mass/size. Whilst these studies were limited by small numbers there was a suggestion that any benefit with NMES probably occurs in patients whose ICU stay is longer, as demonstrated by Gruther et al. [24]. This would be consistent with the mechanism by which muscle wasting accrues in critical illness. Prolonged bed-rest, inactivity and systemic inflammation are thought to play key roles in the development of sarcopenia [2]. Patients with prolonged critical illness and a longer duration of admission are therefore more at risk of developing sarcopenia and may benefit from interventions such as NMES. The benefit of NMES in the acute phase of critical illness is less clear.

Several studies appeared to show a modest effect of NMES on muscle function. Fischer et al. [22] observed a faster initial rate of improvement of quadriceps muscle strength in patients treated with NMES, however this effect did not translate into improved quadriceps muscle strength at discharge, nor were there any differences in HGS or functional outcomes. Conversely, both Rodriguez et al. [28] and Routsi et al. [29] found greater preservation of muscle strength as measured by MRC score in NMES treated patients. The effects of NMES on muscle strength seen in these trials might be expected to translate into a shorter duration of weaning from mechanical ventilation or reduced disability at hospital discharge, however the evidence for this was limited and definitive trials might require powering against such 'harder' clinical outcomes.

Optimal timing of when to initiate treatment with NMES, frequency of sessions and for how long NMES should be continued both during and post-critical care admission requires further research. Similarly, protocol standardisation is required regarding choice of target muscles, stimulation intensity, timing and duration of individual NMES sessions. Finally, the effect of NMES on meaningful patient centred outcomes such as HRQoL and functional outcomes was lacking in these trials and requires further investigation.

Exercise-based interventions

The impact of exercise-based interventions on muscle function varied, with studies showing conflicting results. The exercise protocols used in these trials also varied in timing, frequency and content. Again, small

numbers limit the breadth of conclusions which can be drawn but the available evidence suggests that daily therapy is required, since two studies (n=194 patients in total) using this frequency of treatment demonstrated improvements in walking distance at hospital discharge [31,37]. Furthermore, 6MWT is a validated measure of exercise capacity and may represent a more clinically useful marker of muscle function and of cardiovascular fitness than simple measures of muscle strength such as MRC score and HGS. 6MWT may therefore be a more clinically relevant marker of response to exercise-based interventions in future studies.

Exercise-based interventions had little impact on secondary clinical outcomes. Most studies found no effect of exercise-based interventions on ICU LOS, hospital LOS, ventilator-free days or mortality [31,34,36-38]. This suggests that future work on exercise-based interventions should focus on intensive treatment in appropriately selected patients. Ongoing trials, such as the evaluation of in-bed cycling sessions in addition to usual care [42], will provide important new information about the efficacy of exercise-based interventions on sarcopenia markers in critically ill patients

Nutrition-based and combined interventions

Few studies evaluated the impact of nutrition-based interventions on muscle mass/size and function. Early enteral and parenteral nutrition had no significant effects on objective measures relevant to sarcopenia in these studies [39-41]. In the largest RCT, Doig et al. [40] found that early parenteral nutrition resulted in a shorter duration of mechanical ventilation. However, since the authors observed no difference in mid-arm muscle circumference, and the only other measure of muscle wasting was self-reported (and thus potentially inaccurate), whether this was due to amelioration of sarcopenia or some other mechanism is far from clear.

Combination interventions also showed varied results. Two of three studies combining NMES and conventional exercise appeared to show no effect on muscle strength [25,26]. The single study that showed benefit must be viewed cautiously due to its small size [30]. In a trial of supervised physiotherapy and exercise combined with glutamine and essential amino acid supplementation, Jones et al. [35] observed a greater improvement in 6MWT at 3 months post-ICU discharge in the dual intervention group. This study suggests that the greatest benefit from combined nutrition and exercise-based interventions may be seen in older patients with prolonged ICU admission. In addition, the benefit appears cumulative over time and future

trials may wish to investigate the impact of interventions continued for longer periods of time both as an inpatient and an outpatient. Finally, none of the combined intervention trials observed any differences in secondary clinical outcomes including hospital LOS or duration of mechanical ventilation.

Management and prevention of sarcopenia in non-critically ill patients

Interventions for the management and prevention of sarcopenia in elderly patients without critical illness have been extensively studied; interventions including NMES, exercise-based, nutrition-based and multimodal approaches have all previously shown promise in non-critically ill older adults [43, 44, 45]. Studies included in this systematic review comprised a heterogenous population of critically ill patients with a variety of co-morbidities. The aetiological differences in these patients and the heterogeneity of mechanisms underlying sarcopenia may partly explain some of the differences observed in the efficacy of the interventions on measures of muscle mass and function. Further research examining specific sub-populations of critically ill patients with, for example, respiratory failure related to underlying chronic obstructive pulmonary disease, may provide valuable information regarding the efficacy of interventions in specific patient groups [46].

Limitations

Studies included in this review did not explicitly report metrics on sarcopenia diagnosis/severity, rather they reported measures of sarcopenia: muscle mass/size and muscle function. Only 4 studies evaluated both components of sarcopenia, making it difficult to draw definitive conclusions about the impact of the interventions on sarcopenia. Due to heterogeneity of study design, interventions used, and outcomes measured, meta-analysis was not possible. Furthermore, although all patients included in this study met our inclusion criteria of being critically ill, this systematic review represents a heterogeneous cohort. There was a high risk of bias in many of the studies, particularly in the domains of performance bias, due to a lack of blinding of patients and personnel to interventions, and attrition bias due to high numbers of patient withdrawal resulting in small study size and a lack of statistical power.

Recommendations for further research

Larger, high quality RCTs are required which evaluate the impact of interventions on accepted measures of sarcopenia. Our review suggests that the most promising interventions are NMES and daily exercise, which

might be used in combination, or in different patient groups. Since benefits may accrue more in older patients with prolonged ICU stay, this would be a priority group in whom to obtain specific data. Future studies should also be wary of the risk of attrition, as seen in many of the studies included in this review, which may affect statistical power. To facilitate data comparison and quantitative synthesis of findings, mechanistic studies should seek to standardise techniques for the measurement of muscle mass/size and muscle function in critical care, or to enhance their clinical relevance by use of a functional outcome, such as duration of ventilation, or walk distance at discharge from hospital as their primary outcome. The methodological challenges of measuring muscle mass and function remain an important area for future research in both patients with critical illness and in older adults with aging-related sarcopenia [47].

Conclusions

NMES and exercise-based interventions may help preserve muscle mass and function in critically ill patients. The lack of high quality methodology and small cohort size in many of the studies limits the confidence in these findings. Standardisation of sarcopenia outcome measurement in critical care is needed to ensure validity and reproducibility and to facilitate quantitative synthesis of study findings. Further, large, high quality RCTs are required to identify the most effective interventions for the management and prevention of sarcopenia in critically ill patients.

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Table 1. Summary of randomised controlled trials.

Source	No of patients	Age (years)		Intervention	Comparator	Outcomes – Muscle Mass	Outcomes – Muscle Function	Outcomes - Other	Main findings
Fischer 2016	54	C: 69.7 (±13.1)	I: 63.3 (±15.5)	NMES - Twice daily 30-min sessions on quadriceps (bilateral) started day 1 post-op, continued until	Sham NMES	Quadriceps MLT	MRC score; HGS	Functional Independence Measure; TUAG	Faster rate of improvement of MRC score during ICU stay in intervention group. No significant differences in

				discharge or max 14 days					quadriceps MLT, mean MRC score or HGS at hospital discharge. No significant differences in functional outcomes.
Falavigna 2014	25	34.0 (±17.3)		NMES - Daily 20-min sessions on quadriceps and tibialis anterior (unilateral) until a force of 4 on the MRC scale obtained	Contralateral leg - usual care	Leg and thigh circumference	MRC score; ankle joint movement		Increased range of movement of active dorsiflexion in intervention leg. No significant differences in leg or thigh circumference or MRC score.
Rodriguez 2012	16	72 [63-80]		NMES - Twice daily 30-min sessions on biceps brachii and vastus medialis (unilateral) until successful extubation	Contralateral leg - usual care	Leg and arm circumference; biceps thickness	MRC score		Greater preservation of muscle strength as measured by MRC score in intervention leg. No significant differences in leg or arm circumference or bicep thickness.
Routsi 2010	140	C: 58 (±18)	I: 61 (±19)	NMES - Daily 55-min sessions on quadriceps and peroneus longus (bilateral) started on day 2 post-admission, continued until discharge	Usual care		MRC score	ICU LOS; MV days; duration of weaning period from MV; days off ventilator	Greater preservation of muscle strength as measured by MRC score in intervention group. Shorter duration of weaning period from MV and days off ventilator in intervention group. No significant differences in ICU LOS or MV days.
Dirks 2015	9	63 (±6)		NMES - Twice daily 40-min sessions on quadriceps (unilateral) until awoken	Contralateral leg – sham NMES	Leg circumference; quadriceps muscle fibre CSA			Greater preservation of quadriceps muscle fibre CSA in intervention leg.

				from sedation					
Gerovasili 2009	49	C:56 (±19)	I: 59 (±23)	NMES - Daily 55-min sessions on quadriceps and peroneus longus (bilateral) started on day 2 post-admission, continued until day 9	Usual care	Quadriceps CSD			Greater preservation of quadriceps CSD in intervention group.
Poulsen 2011	8	67 [64-72]		NMES - Daily 60-min sessions on quadriceps (unilateral) for 7 days	Contralateral leg - usual care	Quadriceps muscle volume			No significant differences in quadriceps muscle volume.
Gruther 2010	46	C-A: 48(±12) C-L: 64(±8)	I-A: 52(±10) I-L: 61(±10)	NMES - Daily 30-min sessions in week one followed by daily 60-min sessions on quadriceps (bilateral) treatment 5 days a week for a total of 4 weeks	Sham	Quadriceps MLT			Greater preservation of quadriceps MLT in long-term patient intervention group. No significant differences in quadriceps MLT in acute patient group.
Connolly 2015	20	C: 68.5 [64.3-79]	I: 63 [46.8-71.8]	Exercise - Rehabilitation programme: 2 x 40-min sessions/week for 3 months	Usual care		6MWT; incremental shuttle walk test	SF-36	No significant differences in primary or secondary outcomes.
Denehy 2013	150	C: 60.1 (±15.8)	I: 61.4 (±15.9)	Exercise - Phased rehabilitation programme: 2 x 15-min sessions/day on ICU, 2 x 30-min sessions/day on ward followed by 2 x 60-min sessions/week as outpatient for further 8 weeks	Usual care		6MWT	TUAG; HRQoL	No significant differences in 6MWT, TUAG or HRQoL at 12 months post-ICU discharge.
Burtin 2009	90	C: 57 (±17)	I: 56 (±16)	Exercise - Daily 20-min bedside cycle ergometer sessions starting no earlier than day 5 of	Usual care		6MWT; HGS; quadriceps force	SF-36 PF; weaning time, ICU LOS; hospital LOS; 1-yr mortality	Greater 6MWT, SF-36 PF and improvement in quadriceps force at

				admission, 5 times/week until ICU discharge					hospital discharge in the intervention group. No significant differences in HGS, weaning time, ICU LOS, hospital LOS or 1-yr mortality.
Yosef-Brauner 2013	18	C: 61.5 (±12)	I: 51.6 (±18)	Exercise - Twice daily intensive physical therapy until discharge	Usual care		MRC score; HGS	ICU LOS; MV days	Faster initial rate of improvement in MRC score in intervention group. Shorter ICU LOS in intervention group. No significant differences in MRC score improvement or HGS at ICU discharge. No significant difference in MV days.
Schweickert 2009	104	C: 54·4 (46·5–66·4)	I: 57·7 (36·3–69·1)	Exercise - Early, daily physical and occupational therapy sessions until functional baseline reached or discharged from hospital	Usual care		Functional Independence Measure; MRC score; HGS; maximum walking distance	Ventilator-free days; ICU LOS; hospital LOS; hospital mortality	Increased return to independent functional status, maximum walking distance and ventilator-free days in intervention group. No significant differences in MRC score, HGS, ICU LOS, hospital LOS or hospital mortality.
Morris 2016	300	C: 58 (±14)	I: 55 (±17)	Exercise - Standardised rehabilitation therapy: sessions three times/day	Usual care		SPPB; HGS	Hospital LOS; ventilator free days; SF-36 PF; Functional Performance Inventory;	No significant differences in any of the outcomes measured at hospital

				including passive range of motion, physical therapy, and progressive resistance exercises				HRQoL	discharge.
Hodgson 2016	50	C: 53 (15)	I: 64 (12)	Exercise - Early goal-directed mobilization: daily 30-60-min sessions comprising active functional activities	Usual care		ICU mobility scale; PFIT; Functional Status Score in ICU test; MRC score	In-hospital mortality; MV days; ICU LOS; hospital LOS; ventilator free days	Higher maximum ICU mobility scale score in intervention group. No significant differences in strength or functional outcomes at ICU discharge, MV days, ventilator free days, in-hospital mortality, ICU LOS or hospital LOS
Watters 1997	31	C: 61 (±12)	I: 64 (±11)	Nutrition - Immediate post-op enteral feeding 20mL/hr max 2500ml/day for 6 days	Usual care - Enteral feeding no sooner than day 6 post-op		HGS; FEV1; FVC; maximal inspiratory pressure	ICU LOS; hospital LOS	No significant difference in HGS 6 days post-op. No significant differences in ICU LOS, hospital LOS or post-op maximal inspiratory capacity. Greater impairment of post-op FEV1 and FVC in intervention group.
Casaer 2013	15	C: 50 (±16)	I: 44 (±14)	Nutrition - Early parenteral nutrition (≤48hrs after ICU admission) daily for 9 days	Late Parenteral nutrition (≥8 days after ICU admission)	Femoral muscle volume		ICU LOS; 90-day mortality	No significant difference in femoral muscle volume. No significant differences in ICU LOS or 90-day mortality.
Doig 2013	1372	C: 68.6 (±14.3)	I: 68.4 (±15.1)	Nutrition - Early parenteral nutrition (starting day 1	Usual care	Mid-arm muscle circumferenc e; muscle w asting and		60-day mortality; ICU LOS; hospital LOS;	Few er MV days and reduced muscle

				of ICU admission) until ICU discharge		fat loss (subjective)		hospital mortality; MV days	w asting and fat loss (subjective) in intervention group. No significant differences in mid-arm muscle circumferenc e, 60-day mortality, ICU LOS, hospital LOS or hospital mortality.
Jones 2015	93	C: 60 (±12) E: 64 (±18)	CP: 64 (±13) EP: 62 (±14)	Combined - Supervised physiotherapy and exercise programme, 3 times/w eek as IP follow ed by w eekly sessions as OP for 6 w eeks ± glutamine and essential amino acid supplementati on tw ice daily for 3 months	Usual care or placebo		6MWT	ICU LOS; MV days	Greater improvemen t in 6MWT at 3 months in the exercise + nutrition intervention group. Shorter ICU LOS in the exercise + placebo group. No significant differences in MV days.
Patsaki 2017	128	C: 53 (±16)	I: 53 (±15)	Combined - Daily 55-min NMES sessions on rectus femoris and peroneus longus (bilateral) + targeted physical rehabilitation programme 5 days/week until hospital discharge	Sham NMES and usual care		MRC score; HGS	Hospital LOS; Functional Independen ce Measure	No significant differences in MRC score, HGS, Functional Independen ce Measure or hospital LOS.
Zanotti 2003	24	C:64.5 (±4)	I:66.2 (±8)	Combined - 30-min NMES sessions on quadriceps and vastus gluteus 5 days/week for 28 days + 30-min active limb mobilisation sessions 5 days/week for 28 days	Usual care		Muscle strength score		Greater improvemen t in muscle strength score in the intervention group.

Kayambu 2015	50	C: 65.5 [37-85]	I: 62.5 [30-83]	Combined - Early, targeted physical rehabilitation: 30-min sessions 1-2 times/day consisting of exercise and/or NMES to quadriceps, tibialis anterior and brachioradialis, continued until ICU discharge	Usual care	Fat-free mass	ACIF; PFIT; MRC score	ICU LOS; ICU readmission; MV days; SF-36; physical functional ICU test	Improvement in HRQoL at 6 months post-ICU discharge in 'physical function' and 'physical role' in intervention group. No significant differences in ACIF, physical function ICU test, fat-free mass or MRC score at ICU discharge. No significant differences in MV days, ICU LOS or ICU readmission.

Abbreviations: NMES, neuromuscular electrical stimulation; MLT, muscle layer thickness; HGS, hand grip strength; TUAG, timed up and go test; MRC, Medical Research Council muscle strength score; LOS, length of stay; MV, mechanical ventilation; CSA, cross sectional area; CSD, cross sectional diameter; 6MWT, 6 metre walk test; SF-36, 36-item short form survey; HRQoL, health related quality of life; SF-36 PF, physical function component of the 36-Item Short-Form Health Survey; ACIF, acute care index of function; PFIT, Physical Function in ICU Test; SPPB, short performance physical battery.

Table 2. Sarcopenia related outcomes used in the randomised controlled trials.

Muscle Mass	**Muscle Function**
Quadriceps muscle layer thickness (MLT)*	MRC score
Quadriceps muscle cross sectional diameter (CSD)*	Hand grip strength (HGS)
Biceps thickness*	6-minute walk test (6MWT)
Quadriceps muscle fibre cross sectional area (CSA)**	Maximum walking distance
Quadriceps muscle volume***	Quadriceps force
Femoral muscle volume***	Ankle joint movement
Fat-free mass****	Incremental shuttle walk test
Mid-arm muscle circumference	Muscle strength score
Leg and arm circumference	Short physical performance battery (SPPB)
Muscle wasting and fat loss score (subjective)	Physical function outcome measure (PFIT)
	Acute care index of function (ACIF)
	Functional independence measure
	ICU mobility scale
	Functional Status Score in ICU test

*Quadriceps MLT, quadriceps CSD and biceps thickness were measured using ultrasonography; **Quadriceps CSA was measured using muscle biopsy; ***Quadriceps muscle volume and femoral muscle volume were measured using computed tomography; **** Fat-free mass was measured using multi-frequency bioelectrical impedance spectroscopy.

Figure 1. PRISMA flow diagram illustrating study selection.
Figure 2. Risk of bias summary.

Highlights

- NMES and exercise-based interventions may preserve muscle mass and function.
- A lack of consistency is seen in the effects of these interventions.
- Standardisation of sarcopenia outcome measurement is needed.

- Further, large, high quality randomised controlled trials are required.

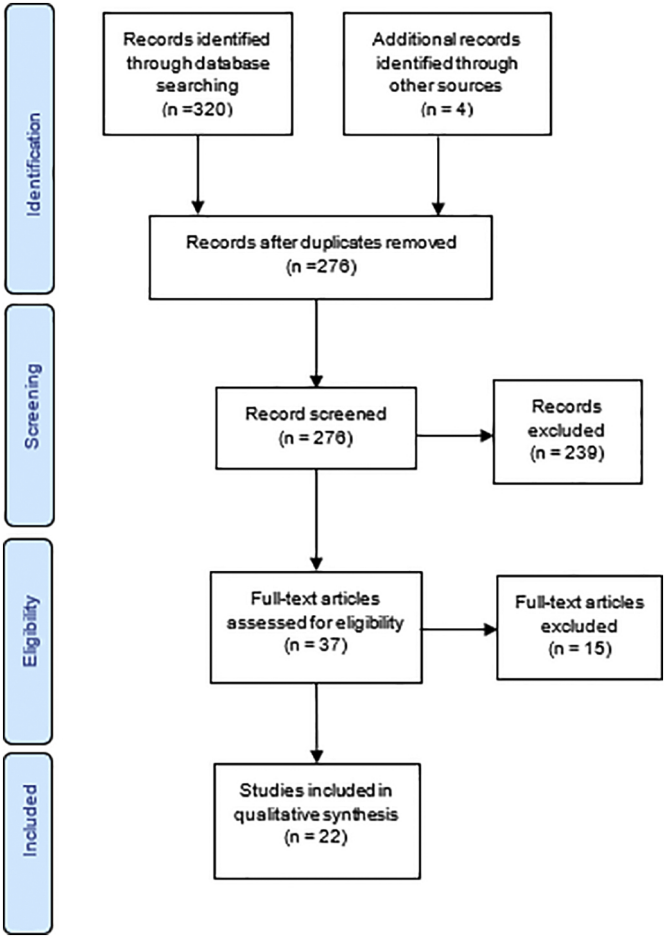
Identification
Screening
Eligibility
Included
Records identified through database searching (n =320)
Additional records identified through other sources (n = 4)
Records after duplicates removed (n =276)
Record screened (n = 276)
Records excluded (n = 239)
Full-text articles assessed for eligibility (n = 37)
Full-text articles excluded (n = 15)
Studies included in qualitative synthesis (n = 22)

Figure 1

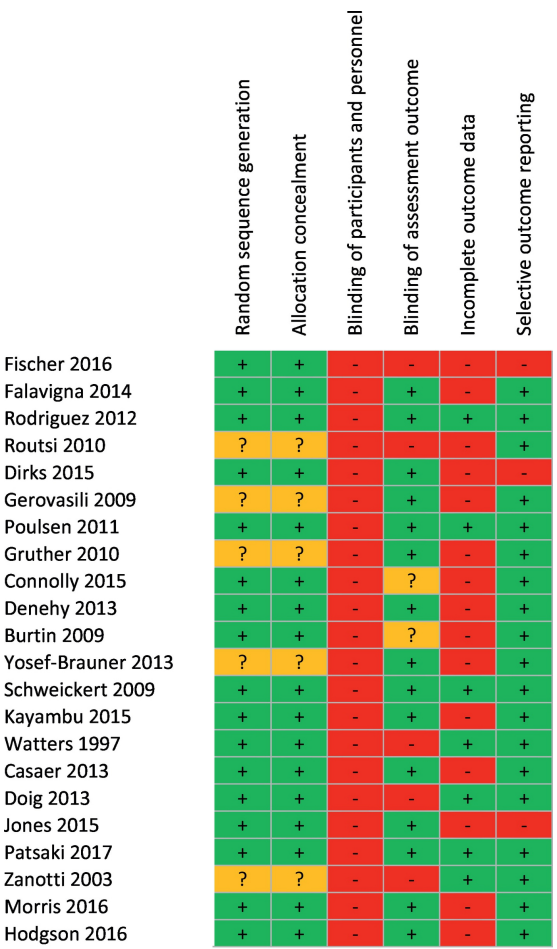
Random sequence generation
Allocation concealment
Blinding of participants and personnel
Blinding of assessment outcome
Incomplete outcome data
Selective outcome reporting
Fischer 2016 + + - - - -
Falavigna 2014 + + - + - +
Rodriguez 2012 + + - + + +
Routsi 2010 ? ? - - - +
Dirks 2015 + + - + - -
Gerovasili 2009 ? ? - + - +
Poulsen 2011 + + - + + +
Gruther 2010 ? ? - + - +
Connolly 2015 + + - ? - +
Denehy 2013 + + - + - +
Burtin 2009 + + - ? - +
Yosef-Brauner 2013 ? ? - + - +
Schweickert 2009 + + - + + +
Kayambu 2015 + + - + - +
Watters 1997 + + - - + +
Casaer 2013 + + - + - +
Doig 2013 + + - - + +
Jones 2015 + + - + - -
Patsaki 2017 + + - + + +
Zanotti 2003 ? ? - - + +
Morris 2016 + + - + - +
Hodgson 2016 + + - + - +
Key:
Low risk of bias +
Unclear risk of bias ?
High risk of bias -

Figure 2