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ORIGINAL RESEARCH INTENSIVE CARE

Impact of neuromuscular electrical stimulation (NMES) on duration of mechanical ventilation in ICU patients: A systematic review and meta-analysis

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ABSTRACT

Background: Intensive care unit acquired weakness (ICUAW) is associated with prolonged mechanical ventilation (PMV), increasing risk and mortality in intensive care unit (ICU) patients. Early mobilization along with neuromuscular electrical stimulation (NMES), has shown potential in reducing mechanical ventilation duration, but remains inconclusive**.** This study evaluates the impact NMES on the mechanical ventilation duration in ICU patients.

Methodology: A systematic literature search was conducted using Cochrane, EBSCOhost, Scopus, and PubMed databases, employing specific keywords and Boolean operators. The inclusion criteria were randomized controlled trials (RCTs) assessing NMES and the duration of mechanical ventilation. The included studies were evaluated for bias using the Cochrane Risk of Bias tool 2.0 (RoB 2). The effect size was estimated using a random-effects model in Review Manager 5.4 software.

Results: A total of 320 patients from 9 RCTs were included in this meta-analysis. Pooled data indicated that NMES administration significantly reduced the duration of mechanical ventilation (MD -1.68 days; 95% CI: -3.09 to -0.27, P = 0.02), with moderate heterogeneity (I^2 = 30%).

Conclusion: NMES administration appears to reduce the mechanical ventilation duration in ICU patients. However, further large-scale RCTs and inclusion of grey literature are necessary to confirm these findings.

Abbreviations: ICU: Intensive care unit, ICUAW: Intensive care unit acquired weakness, NMES: neuromuscular electrical stimulation, RCT: randomized controlled trials

Keywords: Neuromuscular electrical stimulation; duration of mechanical ventilation; ventilator duration; ICU-acquired weakness; prolonged mechanical ventilation

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1. INTRODUCTION

The demand for life support therapy for critically ill patients in the intensive care unit (ICU) was substantial, with an estimated 13 to 20 million patients requiring such care globally each year.[1] Among the complications encountered in these patients, intensive care unit-acquired weakness (ICUAW) was particularly concerning.

ICUAW is characterized by diffuse, symmetrical muscle weakness, including the respiratory muscles. This condition could arise from various pathologies, including Critical Illness Myopathy (CIM), Critical Illness Polyneuropathy (CIP), or combination of both.[2] The incidence of ICUAW exceeded 50% among ICU patients, highlighting the prevalence and significance of muscle weakness in critically ill patients.[3] ICUAW was associated with 30% reduction in post-discharge survival, with a 13% increase in mortality within a year.[4]

Chronic critical illness and ICUAW were associated with prolonged mechanical ventilation (PMV), defined as ventilator use for more than six hours per day over at least 21 consecutive days.[5-7] Patients requiring PMV had higher mortality rates, longer duration of stay in ICU, and complications such as pulmonary embolism, muscle weakness, acute respiratory distress syndrome (ARDS), nosocomial sepsis, upper gastrointestinal tract bleeding, and pressure ulcers.[8]

Early mobilization, both active and passive, had emerged as a strategy for preventing ICUAW. For patients on mechanical ventilation, passive mobilization techniques such as manual exercise, ergometer cycling, continuous passive motion, and neuromuscular electrical stimulation (NMES) were often preferred due to their feasibility. Early mobilization is safe enough to be done on the first day of ICU admission, even with ventilator use. Undesirable events are reported to be 0–3% of the cases and are usually not serious, such as a fall or a loose tube. NMES, which delivers low-intensity electrical impulses to stimulate tetanic muscle contractions, mimics active exercise therapy and has shown potential benefits in critically ill patients.[9] Several studies related to NMES have shown an increase in the strength of stimulated muscles compared to controls.[10] However, there are currently not enough studies focused on reviewing the effect of NMES on mechanical ventilation duration. Therefore, This study aims to evaluate the impact of NMES on the duration of mechanical ventilation in ICU patients.

2. METHODOLOGY

The systematic review protocol was registered in the PROSPERO database (registration number: CRD42022318931).

2.1. Search strategy

We conducted a comprehensive literature search in English across multiple electronic databases, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The databases used included Cochrane, EBSCOhost, Scopus, and PubMed, utilizing a combination of medical subject keywords and text terms (detailed in Supplementary Table S1). Boolean operators were employed to both broaden and refine the search. The search was limited to studies involving human subjects published in English. To ensure up-to-date evidence, we only included studies published from 2010 onwards.

2.2. Eligibility Criteria

We applied the following inclusion criteria: (1) randomized controlled trials (RCTs) involving adult patients (≥18 years old), (2) patients requiring mechanical ventilation for ≥24 hours, and (3) ICU admissions lasting >48 hours. Exclusion criteria included: (1) studies published prior to 2010, (2) patients with neurological conditions such as stroke, traumatic brain injury, multiple sclerosis, or neuromuscular diseases, (3) patients who had undergone rehabilitation prior to ICU admission, (4) patients with trauma, disability, or vascular disorders that might affect rehabilitation, and (5) studies where ventilator duration was not a primary outcome.

2.3. Data Synthesis and Quality Assessment

Two independent investigators screened the search results. Duplicates were removed using Mendeley software (version 1803), and titles, abstracts, and full texts were reviewed for eligibility based on the Participants, Intervention, Control, Outcome, and Study Design (PICOS) framework. Discrepancies in study selection were resolved by consensus. Risk of bias in the included studies was assessed using the Cochrane Risk of Bias tool 2.0 (RoB 2), and evidence quality was evaluated according to the Oxford 2011 Levels of Evidence. Data extracted included study design, patient demographics, ventilator duration, and p-values for outcomes.

2.4. Statistical Analysis

Meta-analyses were conducted using Review Manager 5.4 (Cochrane Collaboration). Pooled data were analyzed using weighted mean differences (IV) and 95% confidence intervals (CI). Heterogeneity was quantified using the I^2 statistic. A random-effects model was employed due to observed inter-study variability in interventions.

3. RESULTS

3.1. Overview of Literature Search

Our initial search identified 446 studies, of which 53 were duplicates. After screening titles and abstracts, 340 studies were excluded, leaving 53 for full-text assessment. Following full-text review, 44 studies were excluded for not meeting eligibility criteria, resulting in 9 studies being included in the qualitative and quantitative analyses (Figure 1).

3.2. Characteristics and Eligibility of Selected Studies

Nine RCTs, involving 320 mechanically ventilated ICU patients, were included. These studies were published between 2010 and 2020. Three were double-blind RCTs, two were single-blind, and four were open-label RCTs. One study was conducted in multiple centers across Europe and Australia, while the others were single-center studies in North America, South America, Europe, Africa, and Asia. Sample sizes ranged from 20 to 80 patients, with a mean age range of 51.12 to 77.28 years.

The intervention across studies was neuromuscular electrical stimulation (NMES) compared with usual care or passive mobilization. The NMES protocols varied in terms of duration and site of application. The detailed characteristics were listed in Table 1 and the outcome of ventilator duration were listed in Table 2. Bias assessment revealed three studies with low risk, two with unclear risk, and four with high risk (Supplementary Figure S1).

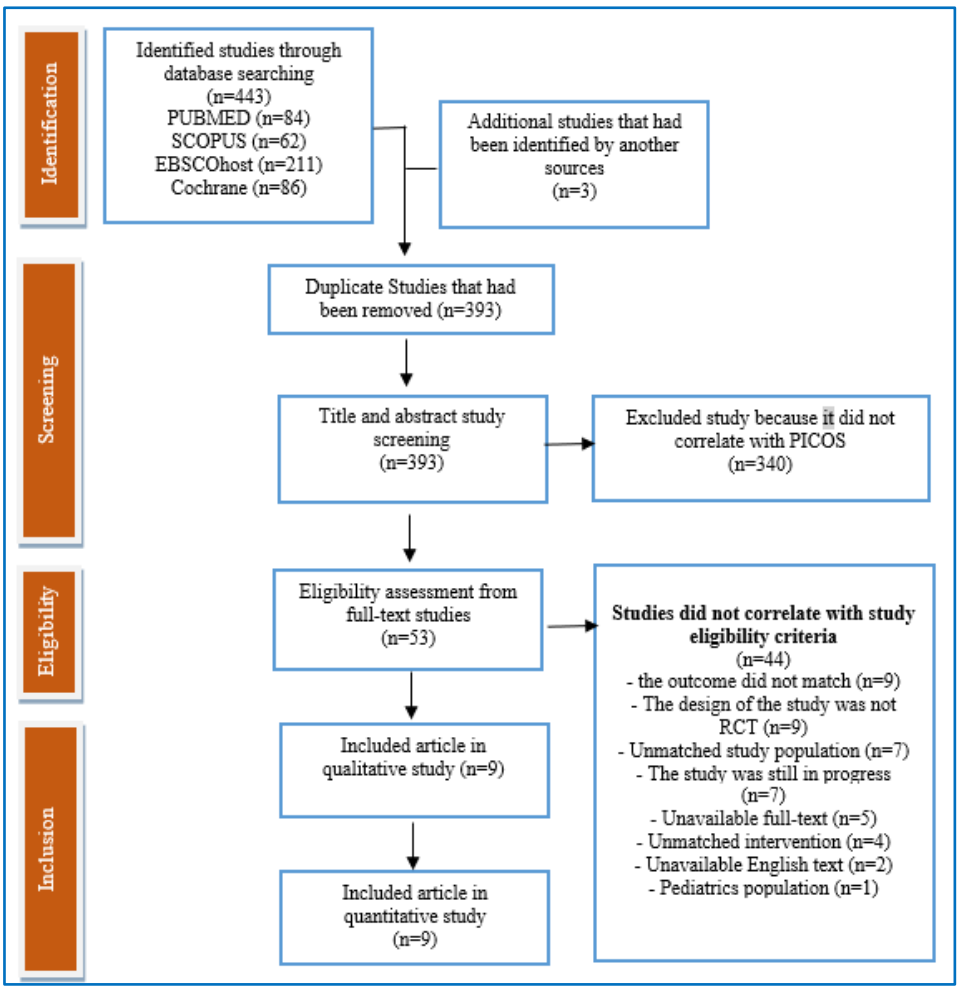


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart

[Legend: PICOS = participants, intervention, control, outcome, study; RCT = randomized controlled trial]

3.2. NMES and Duration of Ventilator Use in the ICU

The meta-analysis of nine studies (n = 320) demonstrated that NMES was associated with a significant reduction in ventilator duration (mean difference: -1.68 days; 95% CI: -3.09 to -0.27, P = 0.02; I^2 = 30%; random-effects model) (Figure 2).

3.3. Publication Bias

The funnel plot analysis was symmetrical, and the Begg and Mazumdar rank-correlation test (P = 0.5736) indicated no significant publication bias (Figure 3).

4. DISCUSSION

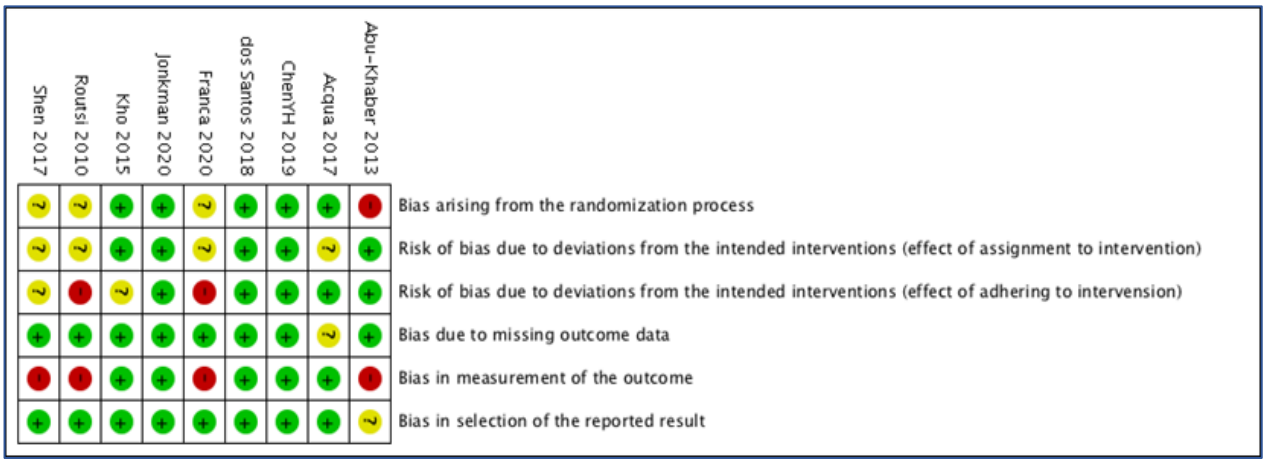
Patients requiring mechanical ventilation in the ICU often experience prolonged immobilization, leading to muscle atrophy and protein breakdown.[11] Early mobilization has been shown to improve muscle perfusion and metabolism, promoting muscle protein synthesis, enhancing muscle fiber recruitment, and reducing the duration of mechanical ventilation.[12,13] NMES is one of the early passive interventions that could be considered for patient mobilization in ICU. Previous systematic reviews yielded inconsistent results on the effects of NMES. Limitations in these studies included heterogeneity in disease severity, interventions, and small sample sizes. For instance, Hermans et al.[14] reported low-quality evidence due to differences in patient populations, while Anekwe et al.[15] provided ambiguous findings due to inconsistent evidence. Zayed et al.'s

TABLE 1: SUMMARY OF INCLUDED STUDIES

Author/Title of Study (NCT ID); publication year	Study						Subject Characteristics			Level of Evid	RoB2 score
	Study design (Recruitment period)	Masking	Location	Intervention	NMES position	Frequency/ Intensity (duration); Total duration/day	Sample size	Age; year ± SD	Male; n (%)		
Abu-Khaber; 2013	Randomized controlled trial	Open-label	Single-center (Egypt)	NMES vs Usual care	Quadriceps femoris bilateral	50 Hz, 200 µsec (15" on); 60'/day	80 (40 I, 40C)	58.32±6.11	51 (63.75%)	2	+
Acgua (NCT02298114); 2017	Randomized controlled trial (Aug 2013–Aug 2014)	Double-blind	Single-center (Brazil)	NMES vssham NMES	Pectoralis major, rectusabdominis	50 Hz, 300 µsec (3" on, 10" off); 30'/day	25 (11 I, 14 C)	58.8±14.10	16 (64%)	2	?
Chen (NCT02227810); 2019	Randomized controlled trial	Single-blind	Single-center (Taiwan)	NMES vsusual care	VL,rectus femoris bilateral	50 Hz 400 µsec (2" on, 4" off); 30'/day	23 (16 I, 17 C)	75.6±16.06	17 (51%)	2	-
dos Santos etal; 2018	Randomized controlled trial (Mar 2012–Apr 2014)	Double-blind	Single-center (Brazil)	NMES vsusual care	VM,VL,Rectus femoris	45 Hz, 500 µsec (12" on, 6" off); 55'/day	26 (11 I, 15 C)	51.1±12.57	18 (69.23%)	2	-
Franca; 2020	Randomized controlled trial (Dec 2013–Feb 2016)	Open-label	Single-center (Brazil)	NMES vsusual care	Quadriceps femoris bilateral	50 Hz, 500 µsec (4.5" on, 4.5" off); 20'/day	19 (10 I, 9 C)	60.2±15.96	Not reported	2	+
Jonkman (NCT03453944); 2020	Randomized controlled trial	Double-Blind	Multi- center (Netherlands & Australia)	NMES vssham NMES	EO, IO, Transversus abdominis	30 Hz, 352 µsec; 60'/day	40 (20 I, 20 C)	63.4±14	26 (65%)	2	-
Kho et al (NCT00709124); 2015	Randomized controlled trial (2008–2009, 2010–2013)	Single-blind	Single-center (Canada)	NMES vs. sham NMES	VM,VL, Tibialis anterior, Gastrocnemius.	50 Hz, 400 µsec (5" on, 10" off); 60'/day	34 (16 I, 18C)	55±16	17 (50%)	2	?
Routsi et al (NCT00882830); 2010	Randomized controlled trial (Sep 2007–Jun 2009)	Open-label	Single-center (Greece)	NMES vs. Usual care	VM,VL, Peroneous longus.	45 Hz, 400 µsec (12" on, 6" off); 55'/day	52 (24 I, 28C)	57.15±20.44	41 (78.84%)	2	+
Shen et al (NCT01895647A); 2017	Randomized controlled trial (Aug 2013–Sept 2015)	Open-label	Single-center (Taiwan)	NMES vs passive mobilization	VM,biceps femoris	1500 Hz; 32'/day	25 (18 I, 7 C)	77.28±2.42	14 (56%)	2	+

Legend: *NCT ID - National clinical trial identification; RoB2: revised Cochrane risk of bias tools for randomized trials; NMES - neuromuscular electrical stimulation; SD - standard deviation; I - intervention group; C - control group*

VM - Vastus medialis,VL - Vastus lateralis,RF - Rectus femoris, EO - External oblique, IO - Internal oblique, TA - Transversus abdominis



Supplementary Figure S1: Risk of bias assessment in the included studies

(Legend: green - low risk of bias; yellow - unclear risk of bias; red - high risk of bias)

Table 2: Outcome summary of included studies

First author / Title of Studies; Year of publication	Sample Size	Duration of ventilator use (days)		P-Value
		Intervention group (days)	Control group (days)	
Abu-Khaber; 2013	80 (40 I, 40 C)	9.01 ± 8.01	11.97 ± 8.07	0.048
Acqua; 2017	25 (11 I, 14 C)	7.0 ± 2	8.0 ± 3	0.67
Chen; 2019	33 (16 I, 17 C)	24.2 ± 7.95	23.88 ± 7.63	0.89
dos Santos; 2018	26 (11 I, 15 C)	9.0 ± 7.0	14.8 ± 5.4	< 0.01
Franca; 2020	19 (9 I, 10 C)	5.67 ± 3.35	4.9 ± 2.80	0.174
Jonkman; 2020	26 (16 I, 10 C)	8.7 ± 1.65	12.98 ± 5.88	0.60
Kho; 2015	34 (16 I, 18 C)	20 ± 18	16 ± 15	0.492
Routsi; 2010	52 (24 I, 28 C)	14.3 ± 11.3	20.8 ± 17.6	0.075
Shen; 2017	25 (18 I, 7 C)	7.0 ± 1.25	8.25 ± 2.64	0.85

Legend: *I - Intervention group; C - Control group*

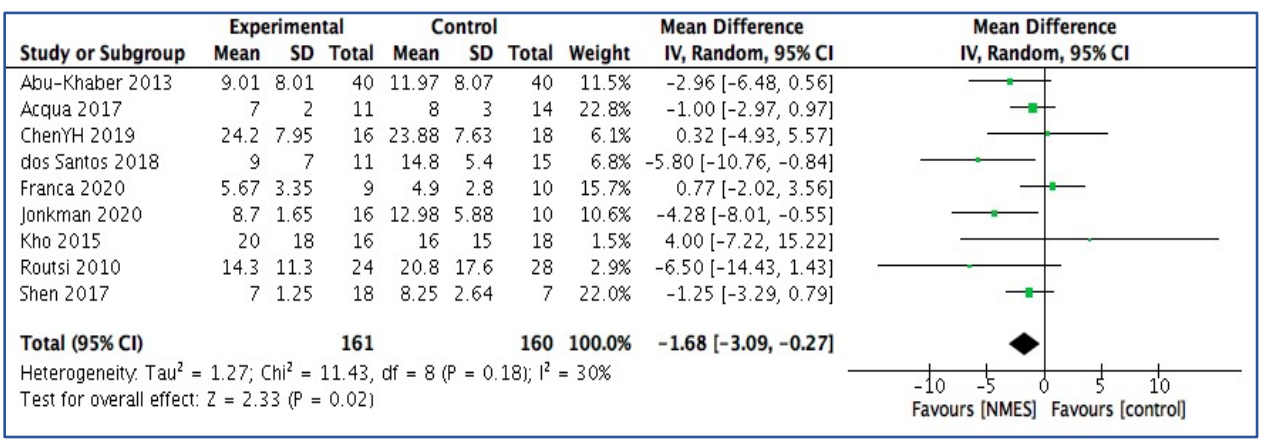


Figure 2:. Forest Plot of NMES therapy on the outcome of decreasing the duration of ventilator use

Legend: *SD - standard deviation; IV - weighted mean difference; CI - confidence interval; df - degrees of freedom; Chi2 - chi-square statistic; P - P-value; I2 - I-square heterogeneity statistic; Z - Z statistic*

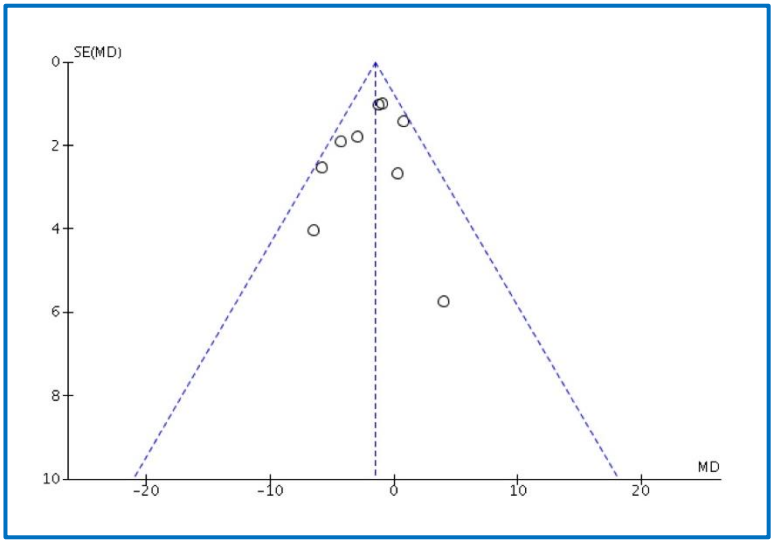


Figure 3: Funnel Plot analysis of NMES therapy on the outcome of decreasing the duration of ventilator use

review was hampered by the small number of included trials.[16]

Our meta-analysis demonstrated that NMES reduced the duration of mechanical ventilation in ICU patients. This effect was likely related to improvements in muscle strength. Notably, two studies showed significant reductions in ventilator duration when NMES was combined with physiotherapist-assisted rehabilitation.[17,18] Combining NMES with other rehabilitation interventions was reported to reduce the duration of both mechanical ventilation and sedation than NMES or other therapies used alone.[18] The studies that achieved the most notable reductions in ventilator time typically administered NMES for over 50 minutes per session. By contrast, studies where NMES was applied for only 30 minutes reported improvements in muscle strength and preservation of muscle thickness, but these shorter sessions did not result in a significant reduction in ventilator use. However, not all studies reported consistent results. Routsi et al.[19] found no significant reduction in ventilator duration, although NMES appeared to facilitate short-term weaning and reduce ICU discharge times.

The included studies primarily focused on NMES applied to the lower extremities, which are more prone to atrophy during prolonged bed rest; up to 30% fall in 16 weeks with 15% happening in the first week.[20] Studies also explored NMES applied to respiratory muscles, but this did not significantly impact ventilator duration, possibly due to disuse atrophy from mechanical ventilation itself.

In the studies included in our analysis, the most frequently targeted muscles for NMES were those of the lower extremities. These muscles are often prioritized in NMES interventions as they tend to experience the most significant atrophy during prolonged bed rest in ICU patients, with muscle mass reductions of up to 30% over 16 weeks, and 15% of this loss occurring in the first week alone.[20] However, muscle wasting is not confined to the peripheral muscles or lower extremities; it can also affect core muscles such as the rectus abdominis and pectoralis major, both of which are involved in respiratory function.

Acqua et al.[21] demonstrated that the thickness of the pectoralis major and rectus abdominis muscles was better maintained in patients who received NMES combined with proprioceptive neuromuscular facilitation (PNF) compared to those who received sham NMES with PNF. Similarly, Jonkman et al.[22] reported that NMES could increase the overall thickness of expiratory abdominal muscles. Despite these findings, NMES applied to respiratory muscles did not significantly reduce the duration of mechanical ventilation in ICU patients. This may be due to disuse atrophy of the expiratory muscles, which are often underused during mechanical ventilation. Although this hypothesis has not been extensively explored, it is well-known that controlled mechanical ventilation can suppress the activity of respiratory centres in the brainstem, leading to disuse of both inspiratory and expiratory muscles.[23] Other factors, such as the duration of NMES sessions or the specific characteristics of patients' illnesses, may also contribute to these outcomes.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a widely used metric to assess the mortality risk in ICU patients. In our meta-analysis, three studies that included patients with APACHE II scores above 25 reported that NMES was effective in maintaining muscle thickness, but only one study observed a reduction in ventilator duration.[17,21,24] In contrast, patients with APACHE II scores below 16 exhibited better muscle responses to NMES. This suggests a potential correlation between NMES efficacy and disease severity, as illustrated by the study conducted by Dos Santos et al.[18], which found a shorter duration of mechanical ventilation in patients with lower APACHE II scores. Other factors, such as age and underlying illness, may also influence the effectiveness of NMES in reducing ventilator dependency. Shen et al.[25] found that NMES did not significantly reduce the duration of mechanical ventilation in critically ill elderly septic patients, likely due to the high prevalence of muscle atrophy in this population. Sepsis, a leading cause of ICU admission, is associated with protein hypercatabolism in muscle tissue, which accelerates muscle loss.[26] The combination of

drowsiness, muscle weakness, severe sepsis, and acute respiratory failure can further diminish the benefits of NMES in this group.

Additionally, prolonged mechanical ventilation (PMV) and extended bed rest are known to contribute to complications such as pneumonia, which is associated with elevated inflammatory mediators, abnormal metabolic states, and oxidative stress—all of which are linked to muscle weakness and prolonged ventilator use. Chen et al.[27] showed that a two-week course of NMES in elderly PMV patients did not significantly reduce the duration of mechanical ventilation or improve lung function, indicating that these patients may be at higher risk for muscle atrophy. However, NMES may still play a role in mitigating some of the negative effects of prolonged immobility. Franca et al.[28] reported that NMES, particularly functional electrical stimulation (FES), could reduce oxidative stress by lowering nitric oxide levels in muscle tissue after one hour of stimulation. This suggests that NMES may have anti-inflammatory effects that improve muscle perfusion not only locally but also in distant muscles via the bloodstream. Further research is needed to determine whether prolonged NMES use could lead to greater improvements in physical function.

Our analysis is limited by the moderate heterogeneity of the included studies. This variability can be attributed to several factors, including small sample sizes, differences in the intervention and control groups, and variations in patient characteristics (e.g., severity of illness, age, and diagnosis), all of which may influence the duration of mechanical ventilation. Additionally, differences in NMES intensity, session duration, and the targeted muscles (e.g., lower extremities versus respiratory muscles) may also contribute to inconsistent findings. Further research is needed to explore the relationship between NMES, extremity muscle strength, and respiratory muscle weakness in ICU patients.

Other independent factors, such as positive end-expiratory pressure (PEEP), postoperative conditions, and Sequential Organ Failure Assessment (SOFA) scores, may also influence ventilator duration. However, NMES remains a safe and feasible intervention for ICU patients, even those who are sedated, delirious, or experiencing decreased consciousness, as it does not require active patient participation. NMES is most effective when initiated early, before significant muscle mass and function are lost, which typically occurs within the first two weeks of ICU stay.[28]

5. LIMITATIONS

This meta-analysis has several limitations. First, we only included English-language studies, which may introduce selection bias. Second, gray literature was not included. Third, the analysis exhibited moderate heterogeneity, potentially due to variations in patient populations, interventions, and study designs. Finally, many included studies had moderate to high risk of bias, particularly regarding the difficulty of blinding participants and investigators in NMES trials.

6. CONCLUSION

Although research on NMES in ICU patients is limited, available evidence suggests that NMES can be a valuable intervention for patients requiring mechanical ventilation. By helping to prevent prolonged ventilation, NMES may contribute to reducing the risk of associated complications, lowering mortality rates, shortening ICU stays, and decreasing healthcare costs. However, further well-designed systematic studies and meta-analyses are necessary to better understand the broader impacts of NMES. Future research should explore additional outcomes, such as ICU length of stay, patient mortality, and the potential benefits of combining NMES with other passive mobilization therapies. Such studies could provide important insights to optimize the care of critically ill patients and improve their overall medical outcomes.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

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9. Conflict of interest

None was declared by the authors. The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

RES: Conducted the literature search, performed statistical analysis, and contributed to manuscript editing

ASM: Conceptualized the study, supervised the research process, and assisted in manuscript editing

RS: Contributed to the literature search, conducted the statistical analysis, and drafted sections of the manuscript

MM: Provided critical revisions of the manuscript, ensured compliance with journal guidelines, and assisted in the interpretation of results

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