Review article:

Efficacy of Rehabilitation Interventions in Children with Spinal Muscular Atrophy to Improve Their Motor Function: Systematic Review

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Abstract:

Spinal Muscular Atrophy (SMA) is a rare genetic disorder characterized by progressive muscle weakness and atrophy due to motor neuron degeneration. Rehabilitation plays a crucial role in managing the disease and improving quality of life. This systematic review aims to investigate the effectiveness of specific rehabilitation interventions in improving motor function, including muscle strength, lung function, and range of motion, for individuals with SMA. A systematic literature search was conducted in major databases (CINAHL, PubMed, MEDLINE, Scopus, and PEDro) from 2014 to 2024 using relevant keywords. Five studies met the inclusion criteria. The findings suggest that physical therapy, occupational therapy, and transcutaneous spinal cord stimulation (tSCS) combined with physiotherapy demonstrated the most positive effects on gross and fine motor function, muscle strength, and respiratory function in SMA patients. However, the overall quality of evidence was moderate, with key limitations including small sample sizes, high heterogeneity in study design, and lack of blinding in some trials. While rehabilitation interventions show promise, further well-designed randomized controlled trials with larger sample sizes are needed to strengthen the evidence base and optimize rehabilitation strategies for this populations.

Keywords:

Spinal Muscular Atrophy; Rehabilitation; Physical Therapy; Occupational Therapy; Assistive Technology; Systematic Review

Introduction:

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disease[1,2]. It is a progressive disease characterized by motor neuron degeneration, muscle atrophy and reduced muscle control [1,3]. SMA is caused by deficiency of the survival of motor neuron (SMN) protein due to homozygous deletions and/or mutations of the SMN1 gene [1,2]. SMN2 is a similar gene, which produce functional SMN protein at insufficient levels to fully compensate for the deficiency of SMN1 gene [1,4].

The number of protein copies produced by SMN2 gene is inversely correlated with the disease severity, it can produce a milder phenotype as the number of copies increases [3]. Nonetheless, due to other genetic disease modifiers, this correlation is not absolute. SMA are classified into five phenotypes that is vary in onset age, life span, motor milestones, which are: SMA0, SMA I, SMA II, SMA III, and SMA IV [4].

SMA0 is characterized by early prenatal onset, severe hypotonia, and weakness. Affected fetuses often exhibit reduced movements, and infants born with SMA0 may experience respiratory distress, areflexia, facial diplegia, atrial septal defects, and joint contractures. Without supportive care, life expectancy is typically less than six months[5,6].

SMA I, also known as Werdnig-Hoffmann disease, typically presents before six months of age with severe hypotonia and poor head control. Despite normal cognitive development, affected individuals exhibit severe muscle weakness, difficulty swallowing and speaking, and respiratory issues. Respiratory failure usually occurs before age two [7,8].

SMA II typically begins between 6 and 12 months, with gradual motor milestone development until age five. Affected individuals have hypotonia, muscle weakness (more pronounced in the lower body), and may develop joint contractures, scoliosis, and respiratory issues [9]. While they can typically sit independently, walking is not possible. Cognitive function remains normal, but motor skills decline over time, with loss of independent sitting by the mid-teens [10,11].

SMA III (Kugelberg-Welander disease) begins after 18 months, primarily affecting lower limb muscles. While individuals can initially walk independently, weakness gradually worsens, leading to difficulty walking and eventual wheelchair use [12]. Unlike other SMA types, scoliosis and re-

spiratory problems are less common. Furthermore, cognitive function remains normal [13,14]. However, The age at which SMA III begins affects when walking is lost. People with an onset before age three typically lose the ability to walk within their twenties [13]. If symptoms start between three and twelve years old, they usually lose the ability to walk in their forties [13].

SMA IV is the rarest form of SMA, affecting less than 5% of patients. It is characterized by mild symptoms with an adult onset, typically between the ages of 30 and 40. Individuals with SMA Type IV can walk independently. Unique features include weakness in the deltoid, triceps, and quadriceps muscles, absent knee-jerk reflexes (patellar areflexia), reduced reflexes in the arms and ankles, and potential hand tremors [7,13,14].

Globally, SMA is estimated to have an incidence of approximately 1 in 10,000 newborns. While many people carry the SMA gene, the condition is relatively uncommon, with 1 to 2 cases per 100,000 individuals. The occurrence of SMA varies globally due to factors like population size and genetics [15–17]. Notably, in Saudi Arabia, the prevalence of SMA is calculated to be 1 in 6,000 live births, while the estimated incidence is approximately 32 cases per 100,000 live births. This is largely due to the high rate of consanguineous marriages in the region, which increases the chances of children inheriting the SMA gene [18].

SMA treatment options have significantly advanced. Gene-based therapies, such as Zolgensma, Spinraza, and Evrysdi, target the underlying genetic cause of the disease. While there's no cure yet, these treatments, combined with supportive care including physical, occupational, and speech therapy, respiratory support, and assistive devices, can significantly improve quality of life for individuals with SMA [19].

Rehabilitation for SMA focuses on improving physical abilities, managing symptoms, and enhancing quality of life. Tailored treatment plans are developed based on thorough patient assessments. These assessments often include the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) [20] and Hammersmith Functional Motor Scale-Expanded (HFMSE) [21] to evaluate gross motor skills, the Six-Minute Walk Test (6MWT) for endurance [22], and the Revised Upper Limb Module (RULM) for fine motor function [23].

Rehabilitation intervention emphasiz-

es stretching, strengthening, balance, and aerobic exercises to maintain function and prevent deformities[24,25]. Assistive devices and proper positioning are essential, especially for those unable to sit independently[26]. While head-pods and cervical braces might be considered, their use should be individualized [25]. The effectiveness of these interventions varies based on SMA severity [24].

Current rehabilitation approaches for SMA involve a multidisciplinary team and typically include physical therapy, occupational therapy, respiratory therapy, and the use of assistive devices [25]. Physical therapy focuses on maintaining muscle strength and preventing contractures through targeted exercises and stretching [26]. Occupational therapy aims to enhance independence in daily activities by providing adaptive equipment and strategies [27]. Respiratory therapy is crucial for managing respiratory complications, a leading causes of morbidity in SMA [28]. However, current rehabilitation practices are often characterized by a lack of standardized protocols, leading to significant variability in interventions delivery [29]. Furthermore, the evidence base supporting the effectiveness of specific rehabilitation strategies for motor function improvement remains limited [29].

Despite advances in pharmacological treatments, rehabilitation remains a key component in SMA management. However, there is no standardized approach to optimize motor function rehabilitation, and existing studies show high variability in intervention protocols and outcome measures[25, 26]. Previous reviews have primarily focused on disease-modifying therapies, while the role of rehabilitation in motor function preservation and enhancement remains underexplored[35,37]. However, existing research on SMA rehabilitation is often fragmented, with studies employing diverse interventions, outcome measures, and methodologies. Previous reviews have largely focused on disease-modifying therapies, leaving a gap in our understanding of the most effective rehabilitation approaches for motor function improvement.

This systematic review aims to examine the effectiveness of specific rehabilitation interventions in improving motor function including muscle strength, lung function, and range of motion for individuals with SMA. By identifying evidence-based practices and tailoring rehabilitation programs to individual needs, this research seeks to contribute to improved care and quality of

life for individuals living with SMA.

Methodology:

This study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [27].

1. Search Strategy:

A comprehensive electronic search was conducted across four major databases: CINAHL, PubMed, ScienceDirect, and PEDro, convering studies published from2014 to 2024. This search focused on rehabilitation interventions for SMA. To ensure a thorough capture of relevant literature, particularly those addressing motor function improvement, the search strategy utilized a combination of Medical Subject Headings (MeSH) terms and a broad range of keywords. These keywords include "Spinal Muscular Atrophy", "SMA", "Physical Therapy", Rehabilitation", "Physiotherapy", "Intervention", "Motor Function", "Motor Skills", Functional Mobility", Neuromuscular Function", and "Motor Development". Boolean operators (AND, OR) were employed to refine the search and combine terms effectively. The specific searc strings used for each database are detailed in (Table 1), which has been revised to reflect the inclusion of motor function-related terms.

Table 1: Keywords/terms used for electronic database search.

Database	Keywords
PubMed	("Spinal Muscular Atrophy" OR "SMA") AND ("Physical Therapy" OR "Rehabilitation" OR "Physiotherapy") AND ("Motor Function" OR "Motor Skills" OR "Functional Mobility" OR "Neuromuscular Function")
CINAHL	("Spinal Muscular Atrophy" OR "SMA") AND ("Intervention" OR "Rehabilitation") AND ("Motor Function" OR "Motor Development" OR "Functional Mobility")
ScienceDirect	("Spinal Muscular Atrophy" OR "SMA") AND ("Physiotherapy Intervention" OR "Rehabilitation") AND ("Motor Function" OR "Neuromuscular Function" OR "Motor Skills")
PEDro	("Spinal Muscular Atrophy" OR "SMA") AND ("Physical Therapy" OR "Rehabilitation") AND ("Motor Function" OR "Functional Mobility")

2. Inclusion Criteria:

The included studies were selected according to the following inclusion criteria: (1) children diagnosed with SMA with different phenotypes; (2) studies that were published from 2014 to 2024; to focus in recent technologies; and (3) studies measured the functional outcomes whether upper limbs functions or lower limbs func-

tions.

3. Exclusion Criteria:

Only records that written in English were included, any other languages were excluded. Further, animal studies, assessment or diagnostic studies, studies that focused in other outcomes such as cost-effectiveness of the intervention, and studies that published prior to 2014 were also excluded.

4. Data Extraction:

The extracted data from the selected studies include the citation details, study design, participants characteristics (Number of participants, Age, Gender, and Condition), the concluded outcomes, and the parameters and the duration of the intervention, and the outcome measures used in the selected studies.

5. Quality Assessment:

Two independent assessors evaluated the selected studies using different scales based on the study design. Randomized Controlled Trials (RCTs) were assessed using the PEDro scale, while other study designs were evaluated with the National Heart, Lung, and Blood Institute's quality assessment tool.

The PEDro scale is a tool used to assess the quality of clinical trials, especially in physiotherapy research. It evaluates factors like randomization, blinding, and statistical reporting. A higher score indicates a higher-quality study, making it easier to identify reliable evidence. The scale has been shown to be reliable and valid for assessing research quality [28,29].

The National Heart, Lungs, and Blood Institute (NHLBI) provided a variety of quality assessment tools for different study designs. The tools were developed to screen for potential problems in the implementation or use of certain study designs. NHLBI offers the tools through the website (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).

Results:

1. Study Selection:

The initial literature search identified 295 articles. After removing duplicates, 265 articles underwent title and abstract screening. Following a full-text assessment of 11 shortlisted articles, we excluded 6

studies due to irrelevant outcomes, unsuitable study designs, or not being original research. Ultimately, 5 studies [30–34] were included for qualitative analysis (Figure 1).

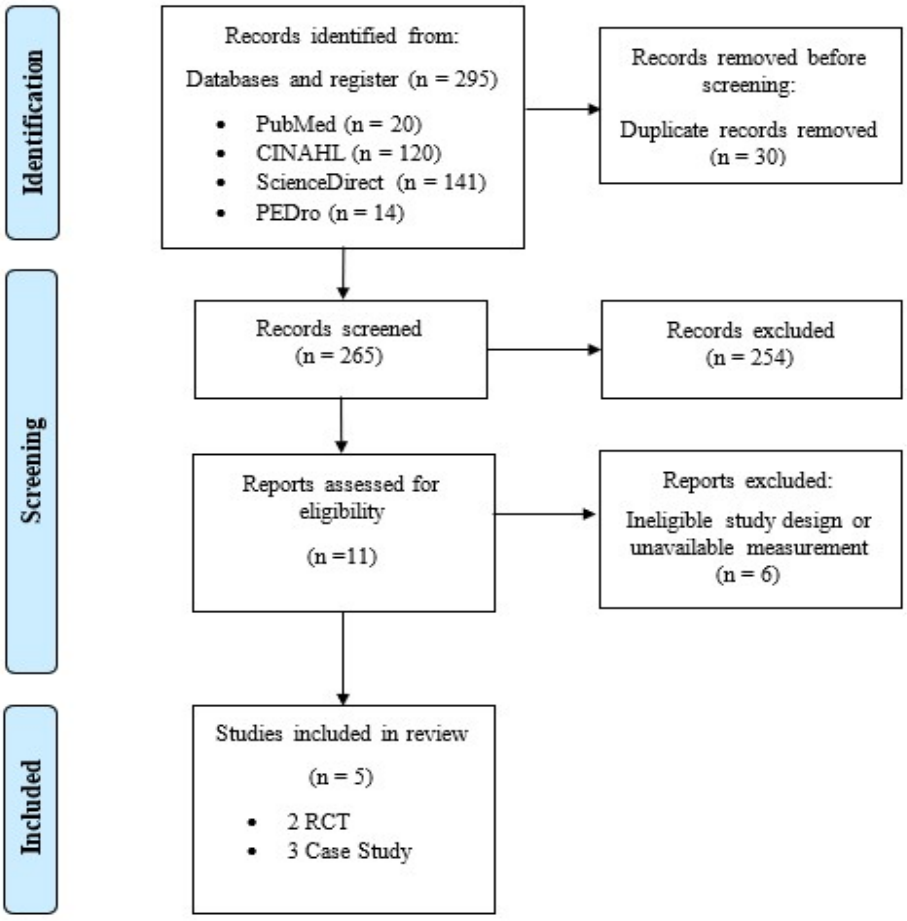


Figure1: Flow diagram of the study selection process.

2. Study characteristics:

A total of 109 participants (91 males and 18 females) were included across 5 studies. Gross motor function was assessed using the HFMSE in studies [32, 33], and [34], while fine motor function was assessed using the RULM in studies [32] and [34]. Lung function was assessed using Forced Vital Capacity (FVC) and range of motion were assessed in studies [32] and [34]. Functional status and endurance were assessed using the Adult Myopathy Assessment (AMAT) in study[33]. Study [30] compared conventional physical therapy and medication on gross motor function using CHOP-INTEND and Hammersmith Infant Neurological Examination (HINE-2). Muscle power was measured using Quantitative Muscle Assessment (QMA) in study [31] (Table 2).

Table 2: Study characteristic of included studies.

Author	Design	Participation	Age	Condition	Intervention	Outcome measures	Summary result
30	RCT	12 M= 12 F= 0	8-50Y	Spinal muscular atrophy	Exercise group (n=5): Muscles strength program combined recumbent cycle ergometry aerobic exercise program Control group (n=7): Usual care	*6 Minute walk test *Generic quality of life inventory	12 participants completed the initial 7-months phase, while 9 successfully completed the entire 19-months study. baseline assessments revealed no significant differences between the groups across all clinical variables. No group-level changes were observed in 6MWT performance, fatigue, or overall functional status throughout the study. However, a 4.9% improvement in percent-predicted VO2 man was noted in all participants within the first 6 months (p=0.036), with data from10 participants contributing to this finding.
31	Case Study	1 F=1	8M	SMA type I	Nusinersen with physical therapy	*CHOP INTEND *HINE -2	This report highlighted the potential benefits of combined approach to treating SMA type I, showcasing improved motor function in a child who received both physiotherapy and Nusinersen. This case may encourage collaborative efforts between physiotherapists and physicians to optimize long-term motor outcomes for children with SMA.

32	Case Study	5 M= 4 F= 1	9-13Y	Spinal muscular atrophy	Transcutaneous spinal cord stimulation (tSCS) combined with physical therapy	* Goniometry of joint with contraction *Result of upper extremity motor function (RULM) *HFMSE scale *Forced vital capacity (FVC)	Children with SMA treated with Nusinersen who received a combined intervention of non-invasive electrical spinal cord stimulation and physical therapy experienced a reduction in muscle contractures, increased muscle strength, improved lung capacity, and expanded range of motion or acquired new motor skills.
33	RCT	54 M=54 F=0	Over 18Y	Spinal and bulbar muscular atrophy	Intervention group (n= 27): Functional exercise Control group (n=27): Stretch exercise	*Adult myopathy assessment tool (AMAT) *Quantitative muscle assessment (QMA)	Participants tolerated the functional exercise program well, but no significant differences were observed between the functional exercise and stretching groups in terms of primary outcomes or any of the secondary outcomes. The functional exercise did not result in a higher incidence of adverse events compared to stretching and was not perceived as excessively difficult. Th further investigate potential benefits, a subgroup analysis was conducted based on baseline functional status, dividing participants into high and low-functioning scale.

34	Case Study	37 M=21 F=16	6-24Y	SMA type II and III	Transcutaneous spinal cord stimulation (tSCS) combined with physical therapy	*Joint Goniometry *RULM *HFMSE *FVC	The study demonstrated significant improvements in motor function, respiratory function, and a reduction in muscle contractures among both type II and type III SMA participants. Importantly, these functional improvements were observed regardless of the participants.

3. Quality assessment:

To assess the methodological quality of the included studies, the PEDro scale was used for RCTs, and the NHLBI quality assessment tool was used for case studies. Overall, the included studies had a moderate risk of bias. Most studies had a low risk of selection bias but a high risk of performance bias due to the lack of blinding. Additionally, several studies had a high risk of detection bias, as outcome assessment was not blinded.

While there limitations may have influenced the results of the review, the consistent findings across multiple studies suggest that the interventions may have a positive effect. The PEDro scale indicated that studies [33] and [30] were of fair quality. Common reasons for this rating included issues with concealed allocation, blinding of subjects, therapists, and assessors, and the use of intention-to-treat analysis (Table 3).

Table 3: PEDro Scale Risk of Bias Assessment.

Included studies	30	33
Eligibility criteria	No	Yes
Random allocation	Yes	Yes
Concealed allocation	No	No
Baseline comparability	No	Yes
Blind subjects	No	No
Blind therapists	No	No
Blind assessors	Yes	Yes
Adequate follow-up	Yes	Yes
Intention-to-treat analysis	No	No
Between-group comparisons	Yes	Yes
Point estimates and variability	Yes	Yes
Total score for each study	5/10	6/10
Overall Quality	Fair	Fair

In contrast, the NHLBI assessment yielded different results. Studies [32] and [34] were rated as good quality, while study [31] was rated as fair quality. The common reasons for the identified risks of bias were inadequate follow-up duration and lack of comparability between study subjects (Table 4).

Table 4: NHLBI Assessment:

Appraisal Question	31	32	34
Was the study question or objective clearly stated?	Yes	Yes	Yes
Was the study population clearly and fully described, including a case definition?	Yes	Yes	Yes
Were the cases consecutive?	N/A	Yes	Yes
Were the subjects comparable?	N/A	No	No
Was the intervention clearly described?	Yes	Yes	Yes
Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes
Was the length of follow-up adequate?	No	No	Yes
Were the statistical methods well-described?	N/A	Yes	Yes
Were the results well-described?	Yes	Yes	Yes
Total score	5/9	7/9	8/9
Overall quality	Fair	Good	Good

A discrepancy was observed between the two tools. While the PEDro scale rated studies [30] and [33] as "fair quality", the NHLBI tool rated studies [32] and [34] as "good quality" and study [31] as "fair quality" (Table 3 & 4). These differences primarily arose due to the following factors; Blinding Differences The PEDro scale places strong emphasis on blinding of participants, therapists, and assessors, which was lacking in most included studies. In contrast, the NHLBI tool does not penalize studies as heavily for blinding issues, particularly in observational and case studies. Follow-up Duration, The NHLBI tool penalized studies with short follow-up periods, contributing to the lower rating of study [31]. Study Design Sensitivity, The PEDro scale is specifically designed for RCTs, while the NHLBI tool accommodates different study designs, leading to different ratings for the same studies. Despite these discrepancies, the overall risk of bias across studies remained moderate, with consistent findings across multiple studies supporting the effectiveness of rehabilitation interventions. The methodological limitations, particularly related to blinding and follow-up duration, should be considered when interpreting the results. Future research should address these issues by incorporating better blinding strategies and longer follow-up periods to enhance study quality.

4. Data analysis:

A meta-analysis was considered but deemed not feasible due to substantial heterogeneity across studies in terms of study design, interventions, outcome measures, and population characteristics. The included studies utilized different reha-

bilitation approaches, including physical therapy, transcutaneous spinal cord stimulation, and multidisciplinary interventions, making direct comparisons challenging. To further quantify this heterogeneity, we attempted to calculate the I^2 statistic, which assesses statistical heterogeneity across studies. However, due to the small number of included studies (n = 5) and variability in study designs (RCTs vs. case studies), pooling the data was not methodologically appropriate. Differences in outcome measures, such as HFMSE, RULM, FVC, CHOP INTEND, and AMAT, also contributed to the inability to generate a meaningful combined effect estimate. Given these limitations, we adopted a narrative synthesis approach, summarizing the findings qualitatively to provide a comprehensive interpretation of the available evidence. Future research with standardized intervention protocols and outcome measures will be necessary to facilitate meta-analysis and strengthen the evidence base.

Discussion:

This systematic review aimed to evaluate the effectiveness of rehabilitation interventions in individuals with SMA. Five studies were included, investigating a variety of interventions across different SMA phenotypes and age groups. The findings suggest that rehabilitation interventions may have positive effects on various functional outcomes in SMA patients, including gross motor function, fine motor function, muscle strength, lung function, and range of motion. However, the overall quality of evidence was moderate due to limitations in the included studies.

Several studies reported improvements in gross motor function, as measured by HFMSE, indicating that rehabilitation can enhance mobility and daily activities in individuals with SMA. Notably, studies [32] and [34] demonstrated tSCS combined physical therapy resulted in significant improvement in HFMSE scores. This suggests that tSCS may potentiate the effects of physical therapy, leading to enhanced motor function. Clinically, these improvements could translate to patients being able to perform activities of daily living with greater ease, such as transferring, dressing, or ambulating [37]. Additionally, these improvements were observed across different interventions, including physical therapy, occupational therapy, and assistive technology, suggesting that multidisciplinary approach may be beneficial [35].

Furthermore, studies employing Quantitative Muscle Assessment (QMA) and Non-Invasive Electrical Spinal Cord Stimulation (NES) observed increased mus-

cle strength. Specifically, study [31] reported improvements in muscle power following a combined approach of Nusinersen and physical therapy, as measured by QMA. From a clinical standpoint, increased muscle strength can lead to improved endurance, reduced fatigue, and enhanced ability to perform functional tasks, suggesting potential benefits for muscle function and endurance [38]. This is particularly important for individuals with SMA, as muscle weakness is a hallmark of the disease [1]. [32] and [34] reported increased FVC after a combined intervention of NES and physical therapy, indicating potential improvements in respiratory function. This finding is significant, as respiratory complications are a major cause of morbidity and mortality in individuals with SMA [36]. Clinically, improvements in FVC suggest enhanced respiratory muscle function, potentially reducing the risk of respiratory failure and improving overall quality of life [40].

A decrease in muscle contractures was observed following NES intervention in both studies, highlighting the potential of rehabilitation to improve joint flexibility and range of motion. Clinically, reducing muscle contractures can prevent or delay the onset of secondary complications such as scoliosis, improve posture, and enhance comfort and mobility [37].

It is important to note that the impact of rehabilitation may vary depending on the specific SMA type and disease severity. Individuals with milder forms of SMA may experience greater benefits from certain interventions compared to those with more severe forms [38]. For example, individuals with SMA type III may benefit more from strengthening exercises, while those with SMA type 1 may require a greater focus on respiratory support and positioning strategies. Furthermore, the role of caregiver involvement and support cannot be underestimated. Family members and caregivers play a crucial role in implementing and supporting rehabilitation program at home [39]. Providing education and training to caregivers on appropriate exercise techniques, positioning strategies, and the use of assistive devices can significantly enhance the effectiveness of rehabilitation [25].

This systematic review has several limitations that should be considered when interpreting the findings. While the small sample sizes and lack of blinding in many studies were acknowledged, additional potential confounders may have influenced the results, variability in intervention protocols, the included studies employed different rehabilitation approaches, frequencies, and durations, making direct comparisons challenging. For example, studies [32],

[33], and[34] used tSCS combined with physiotherapy, while studies[30],[33]implemented functional and strengthening exercises. These variations may have contributed to differences in reported outcomes. Heterogeneity in patient characteristics, participants varied in SMA type, disease severity, and age range, which could affect their response to rehabilitation. Studies with older participants. [33] reported less pronounced improvements, possibly due to disease progression. Differences in outcome measures while some studies used HFMSE and RULM to assess motor function, others relied on 6MWT, AMAT, or CHOP-INTEND, limiting cross-study comparability.

These findings have important clinical implications for the management of children with SMA. The results suggest that incorporating a comprehensive rehabilitation program, which may include physiotherapy, occupational therapy, and assistive technology, into the overall treatment plan for children with SMA can be beneficial in improving their physical function and quality of life [35]. However, further research is needed to address the limitations of existing studies and to optimize rehabilitation strategies for individuals with SMA.

It is crucial to emphasize the importance of individualized rehabilitation plans. Given the variability in disease severity and individual needs, a personalized approach is essential for optimizing outcomes. This may involve incorporating patient preferences, caregiver involvement, and regular reassessment of treatment goals [26].

Furthermore, this review highlights the need for ongoing research to address the limitations of existing studies and to optimize rehabilitation strategies for individuals with SMA. Further research should consider employing larger sample sizes and robust methodologies, including randomization and blinding, in well-designed RCTs. Utilizing standardized protocols for rehabilitation interventions and outcome measures would facilitate comparisons across studies. Studies with longer follow-up periods are needed to assess the sustainability of rehabilitation benefits. Tailoring rehabilitation programs to specific SMA phenotypes and age groups may optimize outcomes. Finally, evaluating the cost-effectiveness of different rehabilitation approaches can inform healthcare decision-making.

Conclusion:

In conclusion, this systematic review suggests that rehabilitation interventions have the potential to improve various functional outcomes in individuals with SMA. However, the quality of evidence

is moderate due to limitations in the included studies. Further research is necessary to strengthen the evidence base and optimize rehabilitation strategies for this population. By incorporating the recommendations for future research, healthcare professionals can develop more effective individualized rehabilitation programs to improve the quality of life for individuals with SMA.

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