Scientific Research Publishing

Health, 2025, 17(10), 1230-1241
https://www.scirp.org/journal/health
ISSN Online: 1949-5005
ISSN Print: 1949-4998

Nusinersen as a Leading Therapy for Spinal Muscular Atrophy: A Bibliometric Analysis of Leading Treatments

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How to cite this paper: Khan Lookmanji, F., Bhat, D., Smith, G., Dinarvand, D., Susoeff, J., Keerthana Beerakayala, S., Li, A., Cordeiro Larkin, H. and Yan, M. (2025) Nusinersen as a Leading Therapy for Spinal Muscular Atrophy: A Bibliometric Analysis of Leading Treatments. *Health*, **17**, 1230-1241.
https://doi.org/10.4236/health.2025.1710081

Received: September 5, 2025
Accepted: October 19, 2025
Published: October 22, 2025

Abstract

Spinal muscular atrophy (SMA) is a genetic disorder caused by mutations in the SMN1 (survival motor neuron 1) gene, leading to muscle weakness and impaired motor function. SMA generally affects infants and children but can develop during adulthood. Well-researched treatments such as nusinersen, onasemnogene abeparvovec-xioi, and risdiplam aim to restore SMN protein and improve patient outcomes. In order to identify research trends, leading therapies, and clinical outcomes for SMA, a bibliometric analysis of the 100 most-cited articles on SMA treatments in Web of Science (WoS) was performed. Nusinersen emerged as the most frequently studied treatment, with robust evidence supporting its role in improving patient quality of life and outlook. The bibliometric insights gathered may inform future research directions and support clinicians and patients in evidence-based decision-making.

Keywords

Spinal Muscular Atrophy, Patient-Reported Outcomes, and Treatments

1. Introduction

Spinal muscular atrophy (SMA), the leading cause of hereditary death in infancy, is a genetic condition that affects the nerves controlling muscle movement. Children with SMA frequently experience worsening muscle weakness, which can

make routine activities such as sitting, standing, or walking more challenging over time. It is caused by mutations in the SMN1 (survival motor neuron 1) gene, which leads to a lack of SMN protein production, an essential protein for motor neuron health [1]-[3]. Without enough of this protein, motor neurons can break down, causing muscle weakness, difficulty moving, and, in severe cases, difficulty breathing [1]. The severity of SMA is often categorized by symptom onset and what motor skills a person can develop [4]. The disease presents on a spectrum, with severity often determined by the age of symptom onset and the highest motor milestones achieved. Type 1 SMA stands as the most aggressive, often leading to death or permanent ventilation by two years of age if left untreated [1]. Milder forms, such as types 2 and 3, still cause significant disability, with many patients losing the ability to walk or experiencing complications like scoliosis and contractures over time [1] [5]. Additionally, individuals with type 1 SMA are shown to have a higher amount of phosphorylated neurofilament heavy chain (pNfH) present in their cerebrospinal fluid (CSF) and/or blood, which is a protein released by neurons when they become damaged [6]. Biomarkers such as pNfH are increasingly recognized as important tools in SMA research and clinical care. They provide measurable indicators of neuronal injury and can help monitor both disease progression and response to treatment. This makes them especially valuable for assessing how well new therapies work and determining when treatment should begin [6]. Previously, treatment for SMA was limited to supportive care and symptom management, without targeting the underlying genetic cause. However, recent developments in genetic and molecular therapies have revolutionized SMA treatment, offering new methods that improve mobility, increase survival rates, and enhance the overall quality of life. As a result, several advanced therapies, including combination approaches like protein inhibitors, have been developed to target the root causes of SMA [7].

Among these treatments, onasemnogene abeparvovec-xioi, nusinersen, and risdiplam are leading therapies and demonstrate significant clinical benefits [8]. Onasemnogene abeparvovec-xioi is a gene therapy designed to provide a functional copy of the SMN1 gene, directly targeting the underlying cause of SMA. Administered as a one-time treatment, it is specifically intended for patients under the age of 2 years at the time of administration [9]. In clinical trials, it has shown remarkable efficacy in infants with SMA type 1, with over half achieving independent sitting, an otherwise unattainable milestone for untreated patients. Additionally, survival rates without permanent ventilation have dramatically improved following treatment, providing hope for a condition that was once considered fatal in infancy [2]. Another notable SMA treatment is nusinersen, an antisense oligonucleotide that increases the expression of the SMN2 gene. Nusinersen is approved for all types of SMA and shows long-lasting improvements in motor function across various age groups, including adults [10]. This is in part due to the fact that nusinersen reduces the level of pNfH in individuals with SMA, allowing them to achieve increased motor function as a result [11]. Risdiplam, an oral

treatment for SMA that boosts SMN protein production, is the first prescription medicine approved by the FDA for patients of all ages [9]. Even more, risdiplam was recently administered to a baby girl in utero. After genetic testing confirmed the baby Type 1 SMA diagnosis, the most severe form, she received the first-ever prenatal treatment during the final six weeks of pregnancy and now exhibits no signs of the disease at age two, offering hope that early genetic intervention can prevent its severe effects [12].

Despite these advances, significant challenges remain in the treatment and management of SMA. Delayed diagnosis continues to be a major obstacle, and early intervention is critical for maximizing treatment benefits [1]. Obtaining an SMA diagnosis is often a long and difficult journey for families, filled with uncertainty and frustration. Families experience challenges to finding therapy due to factors including geography, insurance coverage, and/or cost [13]. On top of these challenges, SMA also has a profound emotional and financial impact on families, affecting their daily lives, social interactions, and overall well-being [14]. The long-term effectiveness of the treatments discussed is still largely unknown, particularly in elderly patients who have already seen a major loss in motor neuron function [10].

Because SMA is a lifelong condition, identifying the most effective treatment strategies is important for improving long-term outcomes. In addition to the clinical endpoints like survival and motor milestones, patient-reported outcomes (PROs) are critical for understanding how treatments impact daily life. PROs better capture the patient and family perspective on physical function, emotional health, social participation, and overall well-being for individuals living with SMA, offering insight into dimensions of health that may not be fully reflected in motor assessments alone [14]. Beyond simply prolonging survival, effective therapies must preserve motor function, reduce complications, and enhance quality of life for patients of all ages. Research on the natural history of SMA shows that untreated individuals inevitably experience motor decline, reinforcing the need for therapies that provide lasting stability and functional preservation [1]. Further, patient-reported outcomes emphasize the importance of treatments that go beyond motor function alone, addressing the broader physical, psychological, and social aspects of living with SMA [14]. Although biomarkers like pNfH may help monitor disease progression and therapeutic response, patient-reported outcomes remain essential for understanding the broader impact of treatments on quality of life.

As SMA treatments continue to evolve, it is critical to evaluate their relative benefits to guide both clinical decision-making and choice for patients navigating this difficult diagnosis. This study reviews the current research landscape on SMA therapies including onasemnogene abeparvovec xioi, nusinersen, risdiplam, and others to identify which offer the most meaningful long-term benefits in survival, motor function, and quality of life. By identifying the most researched treatments and evaluating the current research landscape, this analysis aims to support in-

formed medical choices and improve care strategies for patients with SMA.

2. Methods

A bibliometric analysis was conducted to evaluate the research landscape on patient-reported treatment outcomes for SMA. Data collection was performed using the Web of Science (WOS) Core Collection database, employing a combination of search terms, including "spinal muscular atrophy," "treatments," and "patient-reported outcomes." The search was not restricted by publication year but was limited to peer-reviewed articles to ensure the quality and reliability of the data. The initial search yielded 156 articles. These results were subsequently sorted in descending order based on citation count, and the 100 most relevant articles were selected for further analysis (Figure 1).

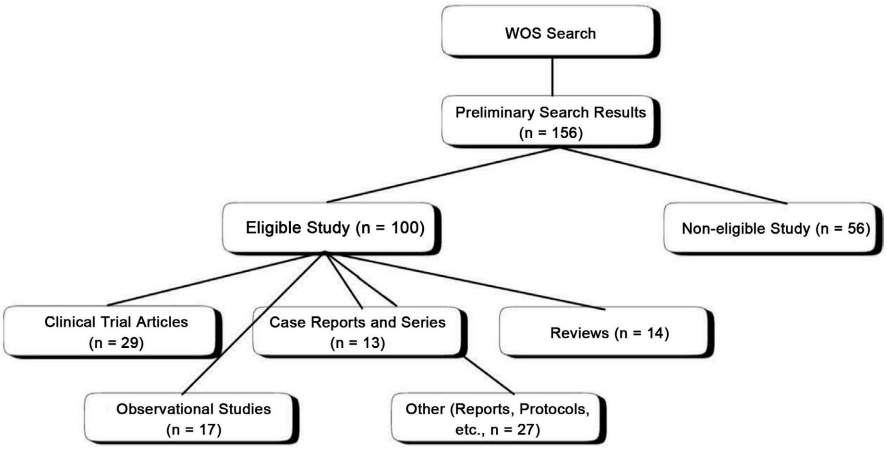

Figure 1. Flowchart summarizing the literature search and selection process, including the number of articles identified, included, and excluded through each stage.

The choice to analyze the 100 most-cited articles was based on the premise that citation count serves as a proxy for research impact, reflecting its recognition in the body of scientific literature. This approach provides a logical foundation for selecting articles that have shaped the field of SMA treatments and ensures that the analysis focuses on the most impactful research.

Articles were included if they met the following criteria: 1) published in a peer-reviewed, WOS-indexed journal, 2) directly relevant to SMA treatment and patient outcomes based on the search keywords, and 3) available in full-text format.

Articles were excluded if they 1) were not published in a peer-reviewed journal, 2) did not focus on SMA treatment or long-term outcomes, or 3) lacked full-text access, such as abstracts or posters only. Discrepancies in study inclusion were resolved through discussion among the research team until a consensus was reached.

Following the selection of the 100 most-cited articles, bibliometric methods were used to extract and analyze key research indicators. Data processing and analysis were conducted using R (R Core Team, 2024) with the Bibliometrix pack-

age (Aria & Cuccurullo, 2017).

The following bibliometric parameters were recorded for each study: article title, publication year, senior author, senior author affiliations, senior author publication count, journal title, and the most frequently studied SMA treatments. Descriptive statistics were used for univariate analysis to identify patterns and research trends within the dataset.

3. Results

The 100 articles on spinal muscular atrophy with the most references were selected from 156 papers that correlated with our search terms "spinal muscular atrophy", "patient-reported outcomes", "treatments." The article "Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STR1VE): an open-label, single-arm, multicentre, phase 3 trial" with Jerry Mendell as the senior author was most cited, with 271 citations. In addition, we identified 25 of our papers that were published most recently in 2024 and one paper, "Efficacy and safety of dutasteride in patients with spinal and bulbar muscular atrophy: a randomized placebo-controlled trial," published the earliest in 2011.

3.1. Most Relevant Authors

A total of 1513 unique authors contributed to the 100 most cited papers. Only 10 of these authors contributed to five or more articles. Figure 2 enumerates these authors' names and their respective number of contributions. Among them, Tina Duong was recognized as the most prolific author with eight articles. Tim Hagenacker had the second largest number of contributions with seven articles.

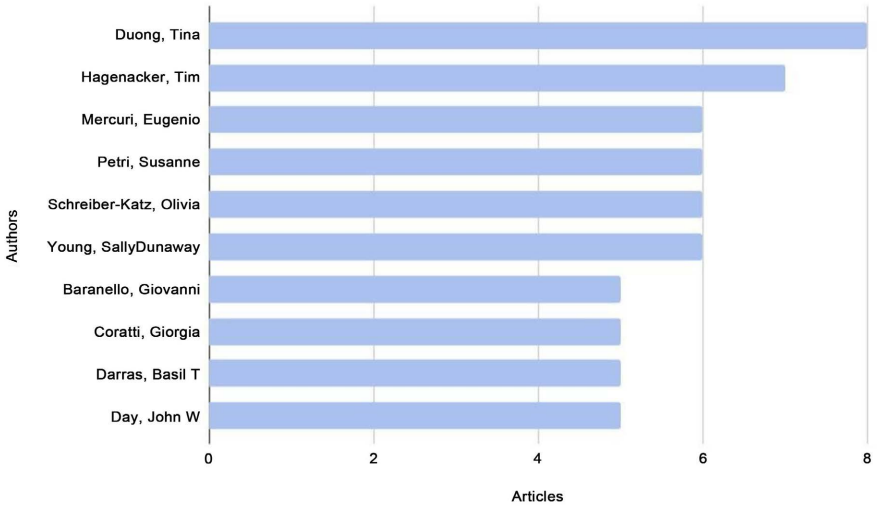

Figure 2. Authors with the most publications in the top 100 most cited SMA articles.

3.2. Senior Author Institutions

From the 100 most cited articles, senior authors from 15 different institutions

contributed at least two publications on patient-reported outcomes for SMA. Hannover Medical School leads the distribution with six papers, followed by the University of Freiburg, the Catholic University of the Sacred Heart, and Roche Holding each with three, per Figure 3.

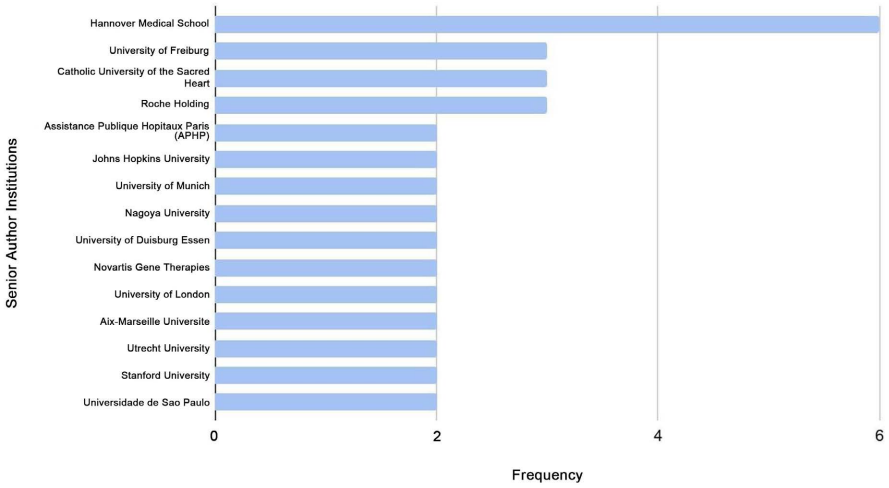

Figure 3. Institutions with the most senior author affiliations in the top 100 most cited SMA articles.

3.3. Most Relevant Affiliations

Among 427 unique author affiliations, 10 institutions contributed at least eight articles. Essen University Hospital in Germany leads the institutional output with 15 authors affiliated, followed by Columbia University and University of Freiburg with 14 articles each, as shown by Figure 4.

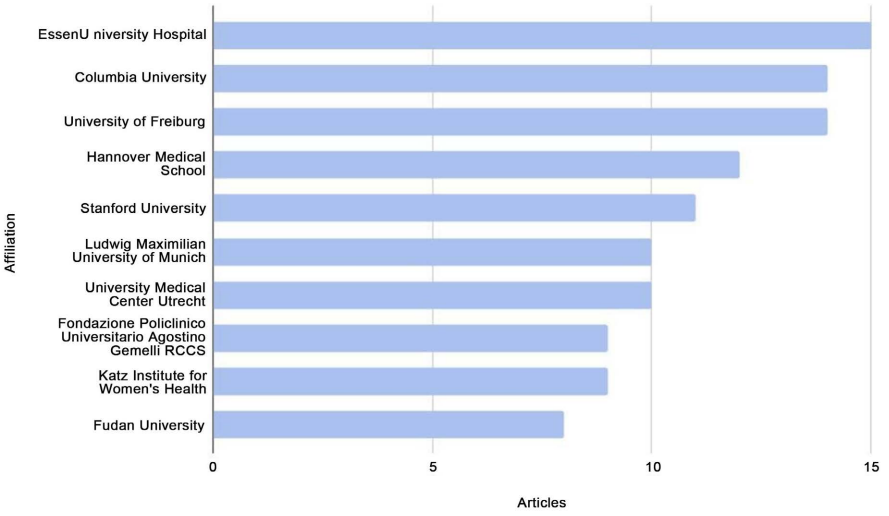

Figure 4. Institutions with the most publications in the top 100 most cited SMA articles.

3.4. Most Relevant Sources

There were 55 total journals represented among the top 100 cited articles, with 15

journals having at least two publications. The Orphanet Journal of Rare Diseases was the most contributed journal (n = 8), followed by Frontiers in Neurology and the Journal of Neuromuscular Diseases with seven publications, and the Journal of Neurology and Muscle & Nerve with six each, per Figure 5.

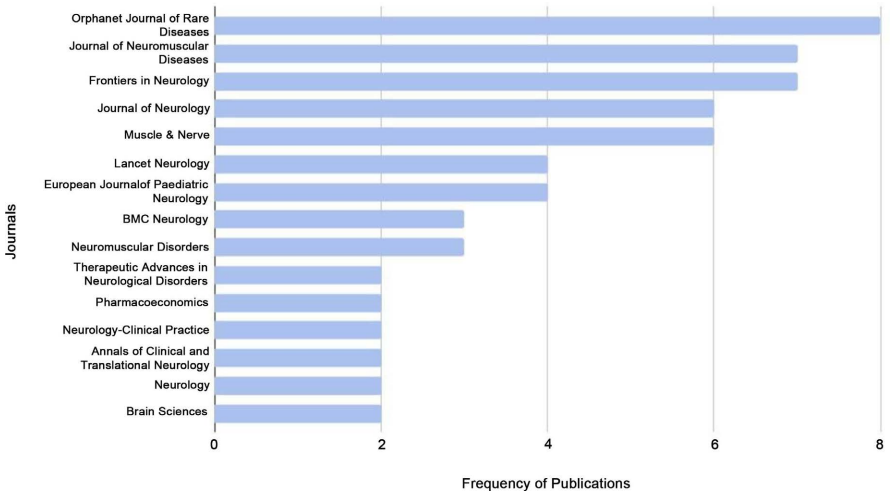

Figure 5. Journals with the most publications in the top 100 most cited SMA articles.

3.5. Most Relevant Treatments

There were a total of 18 treatments mentioned in the top 100 articles. Nusinersen, onasemnogene abeparvovec-xioi, cyborg hybrid assistive limb, and risdiplam were frequently mentioned, with nusinersen heavily being the most common, appearing in 43 articles, as shown by Figure 6.

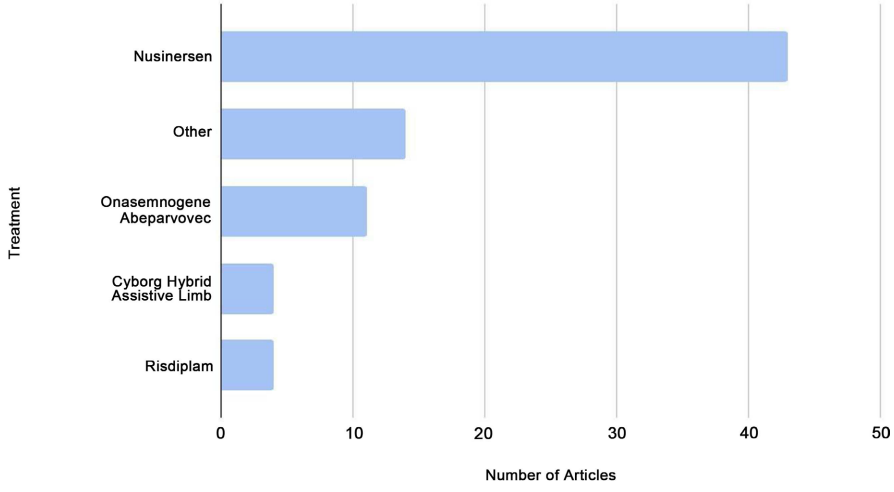

Figure 6. Most mentioned SMA treatments in the top 100 most cited SMA articles.

3.6. Years of Publication

Within the top 100 most cited articles, there was a 13-year span (from 2011-2024) between the oldest and newest published articles. Results show that 2024 had the

highest number of publications (n = 25), followed closely by 2021 (n = 23). Other notable years were 2023 with 16, and 2022 with 15 publications (See Figure 7).

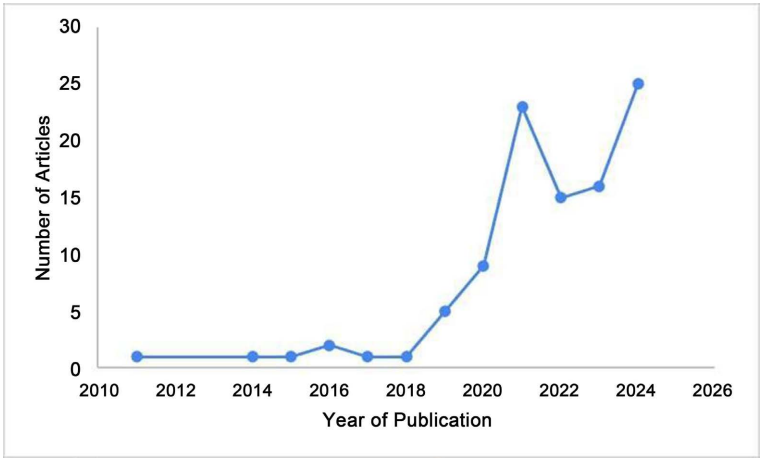

Figure 7. Number of articles vs. year of publication of the top 100 most cited SMA articles.

4. Discussion

In our analysis, we collected our data through the Web of Science Core Collection (WoSCC) using the keywords "spinal muscular atrophy," "patient reported outcomes," and "treatments." These search terms resulted in a total of 156 papers. Out of the top 100 most-cited papers, Dr. Tina Duong appeared as the most frequent author on our topic, with eight articles published. Dr. Duong, a senior research scientist and physical therapist at Stanford University, has over two decades of experience leading neuromuscular clinical research aimed at improving patient outcomes through innovative measures. Her work has had a profound impact on the treatment of SMA, particularly with therapies like nusinersen.

Understanding the burden SMA places on individuals and families highlights the importance of these advancements. Many individuals with SMA, including adults with milder forms, struggle with independence, placing a burden on their caretakers. Furthermore, treatment is able to improve other bodily functions, such as respiration and swallowing, significantly enhancing quality of life in those with SMA [10]. The most common and researched form of treatment (n = 43), nusinersen, is now available in many medical centers across the United States and has greatly improved the health of individuals with SMA. Approved by the FDA in 2016, nusinersen was the first disease-modifying therapy for SMA, marking a turning point in clinical care and sparking a rapid development in the treatment research landscape. Despite nusinersen becoming a cornerstone treatment for those with SMA, there is still more research that needs to be conducted regarding its effectiveness in specific populations like pregnant women. This gap in the literature, identified by our bibliometric analysis, highlights the need for future studies to better understand the safety and efficacy of SMA treatments in this unique group. With the increasing prevalence of SMA, especially Type 1, the need for

effective, long-term treatments remains critical. In uteri treatment of SMA is an increasingly promising option for stopping the course of SMA by preventing its onset [12]. Additionally, early evidence suggests that nusinersen may offer benefits when used during pregnancy. In women with type three SMA, researchers noted that nusinersen might have benefits when administered during pregnancy, however, it is critical to recognize the lack of research regarding this treatment in mothers [15]. Ongoing research is likely to improve the effectiveness of SMA therapies and broaden their availability to patients.

The top 5 most-cited articles regarding SMA treatments were all published from 2020 or later, which aligns with the surge in publications following nusinersen's FDA approval in 2016. Our analysis revealed that a small number of institutions are driving a significant portion of the research output, highlighting key centers of expertise in SMA treatments. Notably, Essen University Hospital emerged as the top institutional contributor with 15 articles, indicating its leadership in neuromuscular research, with Columbia University and the University of Freiburg also playing major roles in advancing the literature with 14 articles published per **Figure 4**. In regards to senior author institutions, Hannover Medical School leads the institutional output with six articles as shown in **Figure 3**. Using the same keywords we used for our bibliometric analysis through WosCC, The Orphanet Journal of Rare Diseases contains a multitude of sources on SMA treatment (n = 67).

Our results also showed that 18 treatment methods were mentioned in the top 100 articles for SMA treatments, but only four appeared consistently across the scientific literature. The most frequently discussed was nusinersen, cited in 43 articles, reflecting its central role in reshaping SMA treatment. Nusinersen was found to help reduce the impacts of SMA as it improved motor function across all ages. Considering that SMA is a progressive neurological disorder affecting the muscles, early nusinersen intervention is necessary to have full effect [7]. Further support for positive impact of nusinersen can be found in an observational study on its perception. An observational study of 151 adult SMA patients treated with nusinersen showed improvements in symptoms, daily activity, and motor function across all ages, with 64% responders and a Net Promoter Score of +51, reinforcing not only its clinical impact but positive perception among patients [16]. While our search included "patient-reported outcomes" as a key term, the bibliometric analysis focused on trends in publication, authorship, and treatment mentions rather than a detailed evaluation of PRO data. Nonetheless, the presence of this keyword across all articles indicates that patient-centered outcomes are a consistent focus in SMA treatment research.

Other than nusinersen, onasemnogene abeparvovec-xioi, cyborg hybrid assistive limb, and risdiplam were the next most frequently mentioned treatment options. Treatments categorized as "other" were far less common, reflecting approaches that differed from these widely adopted options.

5. Limitations

A primary limitation of our bibliometric study is the inherent age bias. Older ar-

ticles have had more time to accumulate citations, which can disadvantage newer studies that may be highly impactful but not yet widely cited. Our bibliometric study, conducted in 2024, did not restrict by publication year, which amplifies this effect. Since SMA was first described in the scientific literature in the 1890s, early research may reflect historical understandings that are now outdated, while later studies, especially following the introduction of nusinersen in 2016, the first disease-modifying therapy, have driven a surge in citations. Lastly, because our analysis only included the top 100 most-cited articles, recently published studies may have been excluded simply because they have had less time to be referenced. As SMA treatment research continues to evolve, this study provides a snapshot of the research landscape at the time of data collection.

6. Conclusions

Our analysis identified the top 100 most-cited publications on spinal muscular atrophy (SMA) treatments and patient-reported outcomes, providing insight into the most influential research in the field. Among the therapies studied, nusinersen emerged as the most thoroughly researched and widely used, with strong evidence supporting its long-term efficacy and role in improving the quality of life for individuals with SMA. Our analysis also revealed key contributors to SMA research, with Essen University Hospital leading institutional output and the Orphanet Journal of Rare Diseases publishing the most relevant articles.

These findings emphasize the rapid advancements in SMA treatment and the need for continued research on long-term patient outcomes. As research on treatment options continues to expand, understanding the most effective treatments is crucial for guiding clinical decision-making and improving quality of life for SMA patients. By identifying the most impactful studies, this analysis aims to support informed choices for patients, caregivers, and clinicians navigating a diagnosis of SMA.

Acknowledgements

A great thanks to ThinkNeuro, LLC for providing mentorship, research guidance, and resources that supported the development of this work.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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