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Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures

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Glossary

CI = confidence interval; **DMT** = disease-modifying treatment; **IPD** = individual patient data; **N/R** = not reported; **NR** = not reached; **SLR** = systematic literature review; **SMA** = spinal muscular atrophy; **SMN** = survival of motor neuron.

Abstract

Background and Objectives

Spinal muscular atrophy (SMA) is a progressive neuromuscular disorder associated with continuous motor function loss and complications such as scoliosis and contractures. Understanding the natural history of SMA is key to demonstrating the long-term outcomes of SMA treatments. This study reviews the natural history of motor function, scoliosis, and contractures in patients with SMA.

Methods

Electronic databases were searched from inception to June 27, 2022 (Embase, MEDLINE, and Evidence-Based Medicine Reviews). Observational studies, case–control studies, cross-sectional studies, and case series reporting on motor function (i.e., sitting, standing, and walking ability), scoliosis, and contracture outcomes in patients with Types 1–3 SMA were included. Data on study design, baseline characteristics, and treatment outcomes were extracted. Datasets were generated from studies that reported Kaplan–Meier (KM) curves and pooled to generate overall KM curves.

Results

Ninety-three publications were included, of which 68 reported on motor function. Of these, 10 reported KM curves (three on the probability of sitting in patients with Types 2 and 3 SMA, and eight on the probability of walking/ambulation in patients with Type 3 SMA). The median time to loss of sitting (95% confidence interval [CI]) was 14.5 years (14.1–31.5) for the Type 2 SMA sitter population (their maximum ability was independent sitting). The median time to loss of ambulation (95% CI) was 13.4 years (12.5–14.5) for Type 3a SMA (disease onset at age <3 years) and 44.2 years (43.0–49.4) for Type 3b SMA (disease onset at age ≥3 years). Studies including scoliosis and contracture outcomes mostly reported non-time-to-event data.

Discussion

Results demonstrate that a high degree of motor function loss is inevitable, affecting patients of all ages. Additionally, data suggest that untreated patients with Types 2 and 3 SMA remain at risk of losing motor milestones during late adulthood, and patients with Types 3a and 3b SMA are at risk of loss of ambulation over time. These findings support the importance of stabilization of motor function development even at older ages. Natural history data are key for the evaluation of SMA treatments as they contextualize the assessment of long-term outcomes.

Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive, progressive neuromuscular disease and the leading genetic cause of infant mortality in the absence of treatment, with an estimated incidence of 1 in 10,000 live births.[1] SMA is characterized by a deficiency in the survival of motor neuron (SMN) protein leading to progressive muscle denervation, skeletal muscular atrophy, overall weakness, and motor function loss.[2] SMA severity varies among patients, but is generally inversely correlated to the number of copies of the centromeric form of the SMN encoding gene, *SMN2*, although this is not absolute due to additional genetic and epigenetic disease modifiers.[2, 3]

Patients with SMA are typically classified into Types 0–4 based on the age at symptom onset, clinical severity, and maximum motor function achievement.[4] Type 0 is the most severe form of SMA, resulting in fetal or neonatal death, whereas Type 4 manifests during adulthood as mild muscle weakness.[2, 5] Type 1 is the most common SMA type, accounting for approximately 50–80% of patients.[2, 6] Type 1 manifests at 0–6 months of age[2] and is characterized by symmetrical skeletal weakness, profound hypotonia, and respiratory deficiency; patients are generally unable to sit or walk and death typically occurs by 2 years of age if left untreated.[2, 5] Type 2 is generally diagnosed at 7−18 months of age, characterized by muscle weakness in which patients can sit but typically not walk and associated with a reduced life expectancy when untreated.[2, 5] Type 3 manifests after 18 months of age. Life expectancy is not affected and patients are typically ambulatory, although loss of ambulation is common if untreated.[2, 5] Complications including scoliosis and joint contractures are frequent in Types 1− 3 SMA; the occurrence of scoliosis has been associated with mobility difficulties, with patients who are unable to sit independently experiencing the highest rates.[7] Frequency of contractures increases with SMA severity, and in joints that are important for mobility such as knees, hips, and elbows.[7] Recent

recommendations suggest a reclassification of patients with SMA would be appropriate to acknowledge the disease spectrum and current clinical status, including mobility, particularly with the advent of disease-modifying treatments (DMTs).[7]

Since 2016, three DMTs with different treatment mechanisms to increase SMN protein levels have been introduced, leading to both short- and long-term improvements in patients with SMA.[8] Significantly improved lifespan and quality of life, greater achievement of motor milestones, reduced reliance on healthcare resources, and decreased symptom progression have been reported in patients treated with DMTs compared with untreated patients.[9, 10] The impact of DMTs on long-term significant life events such as the occurrence of severe scoliosis or loss of ambulation is still unknown. As adoption of DMTs becomes more widespread, SMA natural history data will become more difficult to obtain. However, these data remain critical to understand and effectively demonstrate long-term treatment outcomes, and to evaluate the physical, social, and economic burden of the disease for patients and caregivers.[11, 12]

The aim of this systematic literature review (SLR) was to identify studies reporting on motor function development, scoliosis, and contractures in the natural history of patients with Types 1–3 SMA. Additionally, pooled datasets were generated for key time-to-event data to inform the occurrence of disease-related events (e.g., motor milestone gains and losses, scoliosis, and contractures).

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This SLR was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2020 guidelines.[13] The pre-defined protocol was not

registered. Ethical approval was deemed not necessary as data were analyzed from published studies in which informed consent was obtained by primary investigators.

Search Strategy and Selection Criteria

The search was performed on May 29, 2021 and updated on June 27, 2022. The following electronic databases were accessed via the Ovid platform: Embase, MEDLINE (including: MEDLINE Epub ahead of print, MEDLINE in-process & other non-indexed citations, and MEDLINE daily), Evidence-Based Medicine Reviews (incorporating: the Health Technology Assessment Database, National Health Service Economic Evaluation Database, Cochrane Central Register of Controlled Trials, Database of Abstracts of Reviews of Effects, and the Cochrane Database of Systematic Reviews). Full search strategies are provided in Supplement: eTables 1 and 2. Results were screened based on their title and abstract, and the full texts of potentially relevant citations were reviewed. Additional hand searches of conference proceedings from 2018–2022, reference lists of included publications, and searches of health technology assessment body websites were conducted (Supplement: eTable 3).

Eligibility criteria were based on the population, interventions, comparators, and outcomes framework[14] to identify relevant data (Supplement: eTable 4). Observational studies, case–control studies, cross-sectional studies, and case series reporting on motor function (i.e., sitting, standing, and walking ability), scoliosis, and contracture outcomes in patients with Types 1–3 SMA were included.

Data Extraction

Data on study design, baseline characteristics, and outcomes were extracted into summary tables by a reviewer. Data inputs were independently checked against the source document by a second reviewer, and disputes were resolved by consensus.

Assessment of Bias and Quality of Evidence

To assess the degree of bias of eligible studies in the pooled analysis, the appropriate checklist from the Joanna Briggs Institute[15] was used.

Data Synthesis and Analysis

Although the search covered several functional outcomes, only studies reporting motor functions, scoliosis, and contractures were considered for data analysis (Supplement: eTable 4). Numerical time-to-event data (i.e., mean or median time-to-event) were extracted and summarized. Additionally, studies reporting non-time-to-event data (i.e., rates, mean baseline, follow-up, or change from baseline score) relating to the relevant outcomes were identified and described qualitatively (Supplement: eTable 4).

Studies reporting time-to-event data as Kaplan–Meier (KM) curves for comparable outcomes were identified. A digitization process was conducted by scanning published KM curves from relevant reviewed studies. GetData Graph Digitizer v2.26.0.20 (available from: http://getdata-graph-digitizer.com) was used to estimate a set of coordinates from each KM curve. Following digitization, recreation of virtual individual patient data (IPD) was performed using the algorithm published by Guyot et al (2012)[16] in R statistical software.[17] This was completed using the digitized coordinates and number of patients at risk at the beginning of the follow-up period. A dataset was created from each study arm comprising recreated time-to-event data including a follow-up time variable and event status for all patients. Using the virtual IPD, KM curves were recreated for all study arms and compared with the figures in the publications.

To quality check the digitization process, summary statistics from the virtual IPD and original publication figures were compared, including estimates of median time to no

longer sitting and time to loss of ambulation, and other KM percentages at specific time points.

Scenario analyses were conducted to explore the impact of differences in study populations in terms of maximum function, age, and time axis definitions of the KM curves.

Data Availability

Data from this SLR are available within this manuscript and in the Supplement. The search strategy is also available in the Supplement and the studies excluded based on full-text analysis are available on request.

Results

The original electronic database searches conducted in May 2021 identified 6,475 records (Supplement: eFigure 1). Following removal of 1,448 duplicates, 5,027 titles and abstracts were screened, and 91 articles were deemed potentially relevant before 26 were excluded based on the population, interventions, comparators, and outcomes framework criteria.[14] Three additional records were identified via handsearching. The update search in June 2022 yielded an additional 23 records eligible for inclusion (Figure 1). A total of 91 publications were included in the SLR.

The reviewed studies were typically based on national registries with global coverage across Europe, Asia, the USA, and Canada. Their publication date ranged from 1989–2022, with 33% of the studies published in 2001 or earlier. Studies included patients with a range of SMA types including Types 0/1–4, Types 1–3, Type 2 or 3, or Type 1 SMA, with a single study reporting outcomes by *SMN2* copy number rather than SMA type. Definitions of SMA types, SMA phenotype, patient characteristics, and study designs (e.g., timing of clinical assessments or confirmation of functional milestones) were inconsistent across the

reviewed studies, and reporting of patient characteristics was limited. In addition, methods to assess motor milestones varied across the reviewed studies (e.g., patient questionnaires, review of medical records, or functional evaluations). Definitions of motor milestones also varied (e.g., inability to walk 100 m, or the need for patients to use a wheelchair for outdoor activities). Loss of sitting and loss of walking/ambulation were not defined beyond the statement of loss of the corresponding ability. Studies reporting KM curves defined the time axis (in months or years) as age or duration of disease, and in Kaneko et al (2017) as the time from sitting independently.[18]

There were 68 studies reporting on motor function gain or loss; of these, 10 reported KM curve data, primarily for motor function loss, 11 reported numerical time-to-event data, and 65 reported non-time-to-event data on motor function. For scoliosis, one study reported KM curves, nine reported numerical time-to-event data, and 24 reported non-time-to-event data. No KM curves or numerical time-to-event data were identified for contractures; however, four studies reported non-time-to-event data.

The studies reporting KM curves (n = 11) are indicated in Supplement: eTable 5; in total, these studies included 12 KM curves. The studies reporting numerical time-to-event data (n = 19) and non-time-to-event data (n = 76) are indicated in Supplement: eTables 6 and 7, respectively. A total of 16 studies reported only respiratory and bulbar outcomes and were not considered further in this manuscript.

Motor Function Outcomes

Kaplan–Meier Curve Data

Two studies reported KM curve data for motor function gain. Carson et al (2018)[19] reported KM curves for the ability to roll back to front, sit independently, crawl on all fours, walk with assistance, walk independently, and ascend stairs in a specific population of Mennonite

and Amish patients (SMA type not specified). Rudnik-Schöneborn et al (2001)[20] restricted inclusion of patients to those who had achieved motor function outcomes, with KM curves reaching 100% for the normal sitter and late sitter populations. Due to differences in the enrolled populations and SMA type reporting, KM curve pooling of these two studies was not deemed appropriate.

Eight studies reported KM curve data for multiple motor function loss outcomes.[18, 21-27] These KM curves (Supplement: eFigures 2 and 3) provided sufficient data to permit the generation of pooled datasets for the outcomes of loss of sitting and loss of ambulation. Due to likely patient population overlap in two studies,[26, 27] only Zerres et al (1997)[27] was included in the pooled analysis. No publications were excluded from pooling based on high risk of bias.

Only one study by Wadman et al (2017)[21] reported a KM curve for the loss of standing in patients with Types 2b, 3a, and 3b SMA; patients with Types 2b and 3a showed a loss of standing largely in childhood, and patients with Type 3b predominantly maintained the ability to stand during late adulthood.

Pooled Data for Median Time to Loss of Sitting: Base-Case Analysis

The median time to loss of sitting was evaluable for patients with Types 2 and 3 SMA using pooled data from KM curves reported over seven arms across three studies (**Error! Reference source not found.** and Supplement: eFigures 2A–2D).[18, 21, 22] The median time to loss of sitting was not reached in the overall population (Types 2 and 3 SMA; Figure 2A). In Type 2 SMA (n = 182), median time to loss of sitting was estimated to be 31.5 years (95% confidence interval [CI] 31.5–not reached [NR]; Figure 2B). In the Type 2 SMA sitter population (whose maximum ability was sitting independently, i.e., they were never able to stand or walk; n = 144), median time to loss of sitting was estimated to be

14.5 years (95% CI 14.1–31.5; Figure 2C). In Type 3 SMA (n = 66), median time to loss of sitting was not reached using pooled data from two arms in one study[21] (Figure 2D). The 25th percentiles for the time to loss of sitting ranged from 10.1 years to not reached across pooling scenarios (**Error! Reference source not found.**).

Pooled Data for Median Time to Loss of Ambulation: Base-Case Analysis

The median time to loss of ambulation was evaluable for patients with Type 3 SMA using pooled data from KM curves reported over 22 arms across seven studies (**Error! Reference source not found.** and Supplement: eFigures 3A–3C); in this overall population (n = 1,327), the median time to loss of ambulation was 13.4 years (95% CI 12.6–14.5; Figure 3A). For Type 3a SMA (n = 413), median time to loss of ambulation was 13.4 years (95% CI 12.5–14.5), with seven arms across six unique studies (Figure 3B).[18, 21, 22, 24, 25, 27] For Type 3b SMA (n = 331), median time to loss of ambulation was 44.2 years (95% CI 43.0–49.4), with eight arms across six unique studies (Figure 3C)[18, 21, 22, 24, 25, 27] The 25th percentiles for the probability of loss of ambulation ranged from 7.0–25.0 years across pooling scenarios (Table 1).

Pooled Data for Motor Function Loss: Sensitivity Analyses

The study by Kaneko et al (2017)[18] defined the time axis as time from sitting independently, as opposed to age or duration of disease, as reported across the rest of studies. The sensitivity analysis of the sitter population, which excluded Kaneko et al (2017),[18] increased the median time to loss of sitting by 5 years to 19.5 years (95% CI 13.5–31.5) compared with the base-case analysis. However, the pooled curves indicated a similar trend with both the presence and absence of these data (Table 1 and Supplement: eFigure 2C).

For the analysis of ambulation, to separate Type 3a SMA from Type 3b SMA, sensitivity analyses excluded the study by Russman et al (1996),[22] as this study included a cut-off age at SMA onset of 2 years compared with 3 years in the other studies. This exclusion resulted in a small increase in the median time to loss of ambulation from 13.4 (95% CI 12.5–14.5) to 14.0 years (95% CI 12.5–14.9) in Type 3a SMA and from 44.2 (95% CI 43.0–49.4) to 46.1 years (95% CI 43.0–58.4) in Type 3b SMA (**Error! Reference source not found.**).

Visual inspection of the recreated KM datasets identified outliers, most notably in the pooled analysis of the probability of maintaining ambulation in Type 3 SMA. Three KM curves extracted from the study by Bladen et al (2014)[23] covering populations in Argentina, Hungary, and Serbia showed a decreased probability of maintaining ambulation compared with the KM curves from the other study, highlighting regional differences in patient outcomes. The KM curve for Type 3b with a disease onset after 12 years of age from Wadman et al (2017)[21] was a visual outlier with no function loss observed before 60 years. However, this curve was based on a small population (n = ~12) and removal of these data had minimal impact on the pooled curve and the median time-to-event (44.2 years [95% CI 43.0–49.4] with Wadman et al (2017)[21] included vs 44.2 years [95% CI 39.9–46.0] after exclusion).

Numerical Time-to-Event Data

Numerical time-to-event data for motor function gain were reported across four studies.[18-21] Of those, three studies reported median times to sitting in Type 2 SMA (5.5–10 months) and median time to ambulation in Type 3 SMA (10–18 months) (Tables

Table 1. Summary of Pooled Datasets for Motor Milestone Losses

Outcome	SMA type	Number of studies (number of individual curves)	N	25th percentile time-to-event (95% CI), years	Median time-to-event (95% CI), years
Probability of maintaining the ability to sit	2/3	3 (7)	248	14.1 (12.0–16.4)	NR
	2	3 (5)	182	12.0 (10.1–14.1)	31.5 (31.5–NR)
	2 (sitter population*)	3 (4)	144	10.1 (6.5–12.0)	14.5 (14.1–31.5)
	2 (sitter population*) sensitivity analysis†	2 (2)	102	7.0 (5.5–12.0)	19.5 (13.5–31.5)
	3	1 (2)	66	NR	NR
Probability of maintaining ambulation	3	7 (22)	1,327	7.0 (6.2–7.7)	13.4 (12.6–14.5)
	3a	6 (7)	413	7.8 (6.4–8.9)	13.4 (12.5–14.5)
	3a – sensitivity analysis‡	5 (6)	384	7.8 (6.5–9.0)	14.0 (12.5–14.9)
	3b	6 (8)	331	25.0 (22.2–28.1)	44.2 (43.0–49.4)
	3b – sensitivity analysis‡	5 (7)	301	26.0 (23.5–30.1)	46.1 (43.0–58.4)

*Maximum function to sit independently.
†Excluding Kaneko 2017[18] due to different definition of the time axis (i.e., Kaneko 2017[18] defined the time axis as time from sitting independently, while the rest of studies defined it as time in years of age).
‡Excluding Russman 1996[22] as this is the only curve that has the age cut-off at 2 years instead of 3 years in the analysis.

CI = confidence interval; NR = not reached; SMA = spinal muscular atrophy.

Table).[18-20] All median values for time-to-event data on motor function gain were of similar magnitude, with overlapping ranges, suggesting that most patients fit within normal World Health Organization-defined motor milestone acquisitions.[28] However, the associated upper ranges of median milestone acquisition indicated that there was a proportion of patients with delayed milestones.

Numerical time-to-event data for motor function loss were reported across eight studies.[18, 22-27, 29] The median time to loss of sitting in Type 2 SMA was reported at 11 years of age in Type 2a SMA[18] and 14 years of age in Type 2b SMA.[22] There was notable variability in the mean/median time to loss of ambulation across these studies (range 11.9–522 months) which is likely due to patient population heterogeneity, changes in standard of care over time, territories, and differing definitions of time to loss of ambulation (i.e., age at loss, time since gaining ambulation function, or interval between disease onset and loss of ambulation).[18, 22-27, 29] The percentage of patients remaining ambulatory at 10 years ranged from 58%[25]–73%[26] for Type 3a, and 89%[25]–97%[26] for Type 3b SMA. The probability of maintaining ambulation after 10 years generally increased with the age of onset.[27]

Non-Time-to-Event Data

Reporting of non-time-to-event data across 65 studies included motor function scores and/or the proportion of patients achieving, maintaining, or losing motor milestones, with ambulation and sitting most frequently reported. However, the parameters and populations assessed varied across studies.

The proportion of patients achieving the ability to sit independently and ambulation was reported in 10 studies. In patients with Type 1 SMA, one study reported that 11.8% of patients achieved sitting and none achieved ambulation.[30] For Type 2 SMA, achievement of sitting and ambulation was reported for 47.0%–98.0% and 0%–2.5% of patients,

respectively, across seven studies.[27, 30-35] In patients with Type 3 SMA, who typically learn to sit and walk in most cases, 42.4%–100% achieved sitting and 30.3%–100% achieved ambulation across eight studies.[25, 30-33, 35-37] These broad ranges reflected the heterogeneous nature of the available datasets, which included young patients with delayed motor function. The proportion of patients achieving standing was sparsely reported, with 24.4% of 168 patients with Type 2 SMA achieving standing in a study by Zerres et al (1997),[27] and 50% of eight patients with Type 3 SMA in Kroksmark et al (2001).[36] A limited number of studies reported on the proportion of patients losing motor functions.[38-40] Due to the heterogeneity in follow-up duration and population demographics in reporting these values, no trends were identified. While many of the studies reported motor function scores, these have been reviewed recently for patients with Types 2 and 3 SMA by Coratti et al (2021),[41] identifying a trend towards negative changes in motor function scores for untreated pediatric and adult patients.

Scoliosis Outcomes

Wijngaarde et al (2019)[42] reported KM-estimated median age at scoliosis surgery for patients with Types 1c, 2a, and 2b SMA of 14.6, 9.6, and 13 years, respectively.[42] Due to the limited data on scoliosis outcomes, pooled analysis was not feasible.

Nine studies reported numerical time-to-event data on the mean or median age at scoliosis surgery in patients aged 7.9–25.1 years, with most patients aged <15 years.[21, 34, 38, 40, 42-46] No consistent trends were identified for studies reporting data by SMA type, highlighting heterogeneity across datasets.

Non-time-to-event data were reported in 24 studies. Generally, these studies indicated that a more severe SMA phenotype was associated with a higher probability of developing scoliosis and undergoing scoliosis surgery.[21, 23, 34, 38, 42, 43] Wijngaarde et al (2019)[42]

reported that patients with more severe SMA (Types 1c and 2) had an approximately 80% lifetime probability of scoliosis surgery. Ambulatory ability was associated with an older age at scoliosis surgery and reduced risk of surgery;[42] 71% of patients who lost the ability to walk under 10 years of age and 22% of patients who remained ambulatory at 10 years of age were at risk of scoliosis surgery.[42] Preservation of ambulation for 1 extra year in these patients reduced the risk of scoliosis surgery by 15%.[42] Coratti et al (2020)[38] reported that the mean age at scoliosis surgery was higher in ambulatory versus non-ambulatory patients with Type 3 SMA (mean 16 vs 12 years).

Contractures

Limited non-time-to-event data, predominantly flexion angles and the proportion of patients with contractures, were reported across four studies[31, 36, 37, 47] which showed that the proportion of patients with upper limb contractures (fingers, wrist, elbow) and limitations in the range of movement across all contractures was larger in patients with Type 2 versus Type 3 SMA (Supplement: eTable 7).

Discussion

Natural history data on SMA are essential to fully understand the impact of SMA treatment on long-term outcomes.[11] This SLR aimed to identify data on motor function, scoliosis, and contractures associated with SMA, and generate pooled datasets for key outcomes. As such, this article summarizes the breadth of natural history evidence related to motor function, scoliosis, and contractures in Types 1–3 SMA over patients' lifetimes.

In this study, pooled datasets for time-to-event data showed that a high degree of motor function loss is inevitable over time in untreated patients, especially in the Type 2 SMA sitter population, ambulatory patients with Type 3 SMA, and across all ages. Analysis of the 25th percentiles from the pooled datasets also highlighted a motor function loss over

the early years of patient follow-up. Identified trends were consistent with the known SMA phenotypes, with patients with Type 2 SMA able to sit but unlikely to achieve ambulation and patients with Type 3 SMA more likely to achieve ambulation. Our study showed that patients with Types 2 and 3 SMA continued to be at risk of losing motor milestones during late adulthood and supported the importance of stabilization of motor milestones even at older ages. Despite a perception that patients with Type 3 SMA are at lower risk of motor function loss, the identified literature showed that these patients were at risk of losing sitting, standing, and ambulation function over time.

This study highlighted the importance of acknowledging differences in SMA management across countries and the potential effect such differences could have on international studies. This is particularly relevant in the management of mild SMA symptoms where treatment guidelines are less stringent, and interventions depend on the evaluation of the treating physician.[48] Prior to the introduction of DMTs, international guidelines were published in an attempt to help standardize the multidisciplinary care required for patients globally.[48] However, access to relevant clinical specialists, scoliosis surgery, and other treatments is not conceivable for some regions.

This analysis was associated with several limitations. The clinical classification of SMA was established in the 1980s and the gene locus for 5q SMA was identified in the 1990s. Although many of the studies did not explicitly confirm the 5q SMA genotype, only two were published prior to 1995, both reporting scoliosis outcomes.[40, 49] Therefore, the data included in the current review can be confidently related to 5q SMA in most cases. Some reviewed studies partly included data collected after the introduction of DMTs in December 2016 (Supplement: eTables 5 and 6).[25, 34, 38, 45] These studies may partially represent the natural history of selected groups of patients who were not eligible to receive DMTs, which

may have biased their results compared with earlier studies, and this may consequently be reflected in this SLR.

Several assumptions were required when creating the virtual IPD; studies used different time units (for age) and all IPD were recreated in years, the sample sizes were estimated for the relevant subgroups of patients in two studies, and only the total number of patients was reported rather than the number of patients at risk at specified time points. Due to the nature of the reviewed studies, there was a risk of potential overlap in study populations which may have led to some patients being included multiple times in the pooled analyses. Where potential overlap could be identified, only one study was included.

The outcomes of interest for the current work are non-fatal events and the correct analysis of the data would incorporate the handling of the competing risk of death. However, the KM estimator used in the current analysis is known to inflate the outcome probability in the presence of competing events such as death; using the Aalen-Johansen estimator would have been more appropriate as it accounts for the competing risk of death.[50]

Limited data were available for the outcomes of interest, particularly for scoliosis and contractures. Notably, scoliosis data were most reported as age at scoliosis surgery. This is unlikely to accurately reflect the timeline of development of scoliosis in all patients, as those who did not undergo surgery due to expense, access, or disease severity were not considered in these data. However, given the paucity of reliable scoliosis data, it may be useful as a proxy for severe scoliosis in some countries. Regional differences in SMA management between countries (e.g., in rates of, and access to, scoliosis surgery) are likely to impact the outcomes of interest.

Despite limiting eligibility of publications to Types 1–3 SMA, the included studies were heterogeneous in the definition of SMA phenotype and patient characteristics. Limited

reporting of patient characteristics across the studies (e.g., baseline *SMN2* copy number [Supplement: eTable 5]), precluded a robust assessment of inter-trial heterogeneity of the patient populations. Thus, cross-study differences in the KM estimates of the pooled dataset could not be adjusted for and observations were treated as if they came from a single study, likely underestimating the variability of the estimates.

The methods of assessing motor milestones were generally extracted from medical records and questionnaires which may have been subject to observer and recall bias. Comparison across results was challenging due to the variability in reported data, and pooled datasets could only be generated from data on the loss of sitting and loss of ambulation. A coherent summary of non-time-to-event data, particularly in terms of motor function, was not possible due to the inherent heterogeneity of these data.

Differences in study designs, patient populations, data collection methods, and outcome definitions were a key limitation. Finally, inconsistent definitions of SMA types were reported, thus careful consideration of comparable SMA definitions was ensured prior to the selection of the KM curves included in the pooled analyses. Differences in severity and motor function between SMA types limited the relevance of pooled data. Further pooled analyses by SMA type were therefore conducted which provided more meaningful results.

This is the first study, to the authors knowledge, to present pooled datasets for time-to-event data on SMA natural history. A strength of this study was the accuracy of the estimation of time-to-outcome achievement for the generation of pooled datasets via virtual IPD, as demonstrated by the similar values of the median times obtained from time-to-event data. Additionally, this study highlighted the substantial quantity of evidence related to motor function, especially loss of sitting and loss of ambulation. However, a

paucity of natural history data on outcomes such as standing and heterogeneity in reporting limited further conclusions.

This study provided a comprehensive repository of the natural history data of patients with Types 1–3 SMA. Pooled data from KM curves of published studies showed that patients with Type 2 and Type 3 SMA continued to be at risk of losing motor milestones during late adulthood.

Natural history data represent an important decision-making basis for the acceptance of new treatments and allow assessment of long-term treatment outcomes, which are currently relevant with the introduction of new DMTs to markets worldwide. Further research on SMA natural history would benefit from time-to-event data as opposed to non-time-to-event data which have been most frequently reported in the literature.

WNL-2023-001195_sup --- http://links.lww.com/WNL/D158

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Tables

Table 1. Summary of Pooled Datasets for Motor Milestone Losses

Outcome	SMA type	Number of studies (number of individual curves)	N	25th percentile time-to-event (95% CI), years	Median time-to-event (95% CI), years
Probability of maintaining the ability to sit	2/3	3 (7)	248	14.1 (12.0–16.4)	NR
	2	3 (5)	182	12.0 (10.1–14.1)	31.5 (31.5–NR)
	2 (sitter population*)	3 (4)	144	10.1 (6.5–12.0)	14.5 (14.1–31.5)
	2 (sitter population*) sensitivity analysis†	2 (2)	102	7.0 (5.5–12.0)	19.5 (13.5–31.5)
	3	1 (2)	66	NR	NR
Probability of maintaining ambulation	3	7 (22)	1,327	7.0 (6.2–7.7)	13.4 (12.6–14.5)
	3a	6 (7)	413	7.8 (6.4–8.9)	13.4 (12.5–14.5)
	3a – sensitivity analysis‡	5 (6)	384	7.8 (6.5–9.0)	14.0 (12.5–14.9)
	3b	6 (8)	331	25.0 (22.2–28.1)	44.2 (43.0–49.4)
	3b – sensitivity analysis‡	5 (7)	301	26.0 (23.5–30.1)	46.1 (43.0–58.4)

*Maximum function to sit independently.
†Excluding Kaneko 2017[18] due to different definition of the time axis (i.e., Kaneko 2017[18] defined the time axis as time from sitting independently, while the rest of studies defined it as time in years of age).
‡Excluding Russman 1996[22] as this is the only curve that has the age cut-off at 2 years instead of 3 years in the analysis.

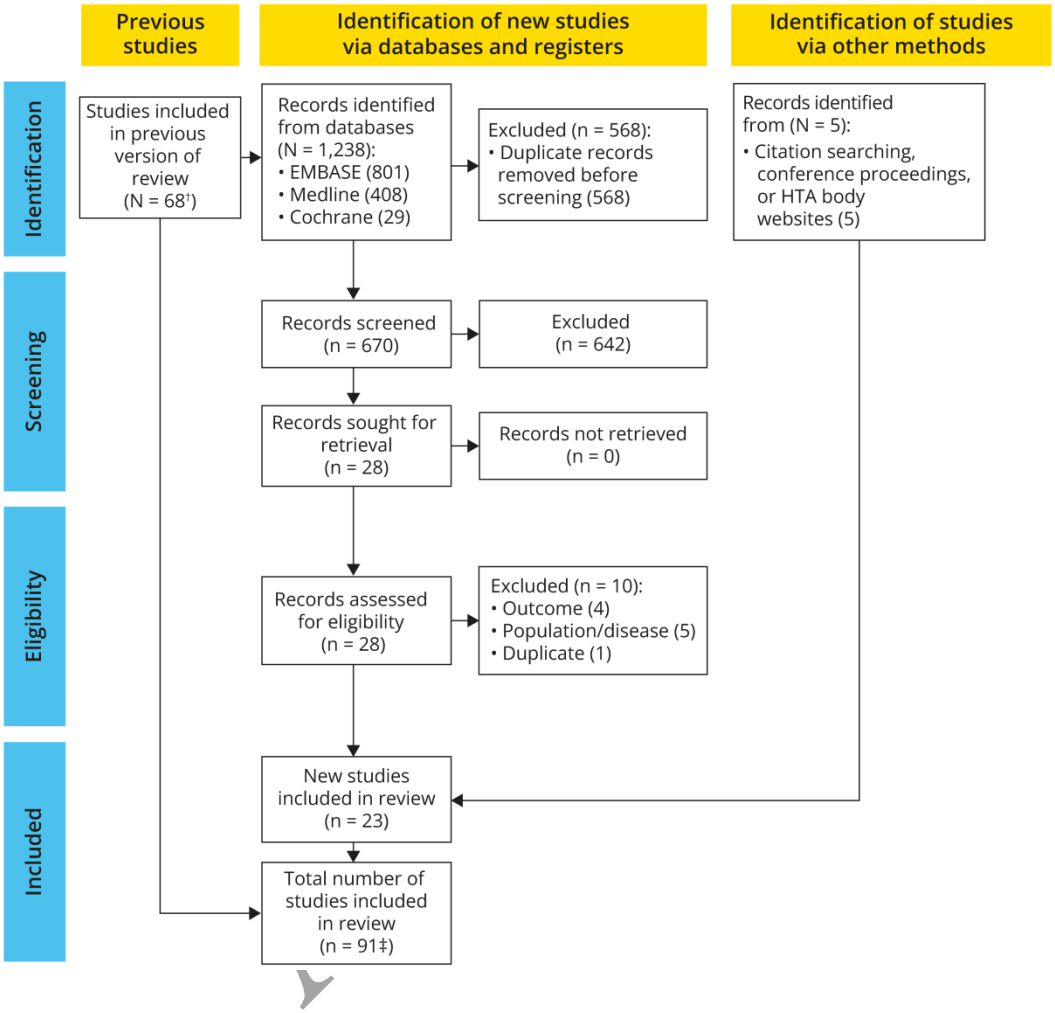
CI = confidence interval; NR = not reached; SMA = spinal muscular atrophy.

Table 2. Median Time-to-Event Data for Achievement of Sitting and Ambulation

Source	SMA type	n	Median time-to-event, months (range)
Sitting			
Carson 2018[19]	N/R, 3 copies of *SMN2*	9	7 (6–8)
Carson 2018[19]	N/R, 4 copies of *SMN2*	3	5.5 (5.4–6)
Kaneko 2017[18]	2a	10	10 (9–30)
Kaneko 2017[18]	2b	32	7 (4–8)
Rudnik-Schöneborn 2001[20]	2	175	7 (4–30)
Ambulation			
Carson 2018[19]	N/R, 3 copies of *SMN2*	9	18 (12–42)
Carson 2018[19]	N/R, 4 copies of *SMN2*	3	10 (N/R)
Kaneko 2017[18]	3a	10	13 (11–24)
Kaneko 2017[18]	3b	13	13 (10–22)
Rudnik-Schöneborn 2001[20]	3	170	13 (9–53)

N/R = not reported; SMA = spinal muscular atrophy; *SMN2* = survival of motor neuron 2.

Figure 1. PRISMA Flow Diagram for the Systematic Literature Review (June 2021)



For more information, visit: http://www.prisma-statement.org/.
*A PRISMA flow diagram of the original search conducted in May 2021 is provided in Supplement: eFigure 1.
†A total of 16 studies included in the review reported only respiratory and bulbar outcomes and are not considered further in this manuscript.
HTA = health technology assessment; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure 2. Recreated Kaplan–Meier Curves for the Probability of Maintaining the Ability to Sit

*The pooled curve across all seven study arms (i.e., Kaneko 2017 [Types 2a and 2b], Russman 1996 Type 2, and Wadman 2017 [Types 2a, 2b, 3a, and 3b]), which is based on a total of 248 patients, is presented (along with the corresponding 95% CI). The follow-up length was variable across study arms, ranging from 1 year (Kaneko 2017 [Type 2a SMA]) to 79 years (Wadman 2017 [Type 3b]). The median time to no longer sitting in all pooled study arms was not reached.
†The pooled curve across all five study arms (i.e., Kaneko 2017 [Types 2a and 2b], Russman 1996 [Type 2], and Wadman 2017 [Types 2a and 2b]), which is based on a total of 182 patients, is presented (along with the corresponding 95% CI). The median time to no longer sitting based on pooled study arms was estimated to be 31.5 years (95% CI 31.5–NR).
‡The pooled curve across all four study arms (i.e., Kaneko 2017 Type 2a, Kaneko 2017 Type 2b, Russman 1996 Type 2, and Wadman 2017 Type 2a), which is based on a total of 144 patients, is presented (along with the corresponding 95% CI). The median time for the sitter population based on the pooled curve across all four study arms was estimated to be 14.5 years (95% CI 14.1–31.5). In the sensitivity analysis (which excluded Kaneko 2017 [Types 2a and 2b SMA]), the median time to no longer sitting based on the pooled curve across the two study arms is estimated to be 19.5 years (95% CI 13.5–31.5). Compared with the base-case analysis, in the sensitivity analysis the median increased by 5 years; however, the pooled curves appeared very similar both with and without the data from Kaneko 2017 (Types 2a and 2b SMA).
§The pooled curve across both study arms, which is based on a total of 66 patients, is presented (along with the corresponding 95% CI). The data are immature for both Type 3a and Type 3b SMA, with no events observed in patients with Type 3b SMA, and the median time to no longer sitting in Type 3 SMA based on pooled study arms was not reached.
CI = confidence interval; NR = not reached; SMA = spinal muscular atrophy.

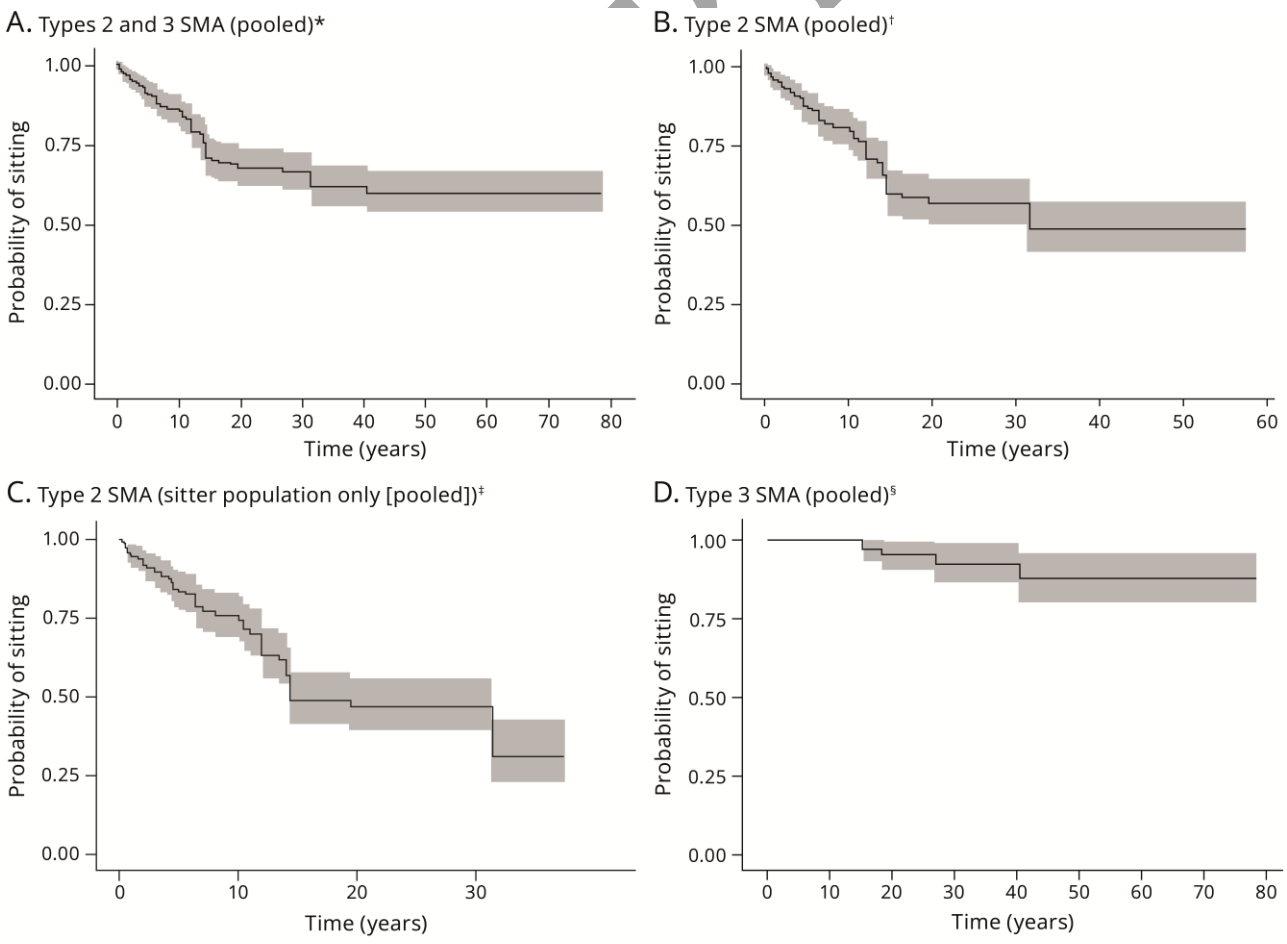
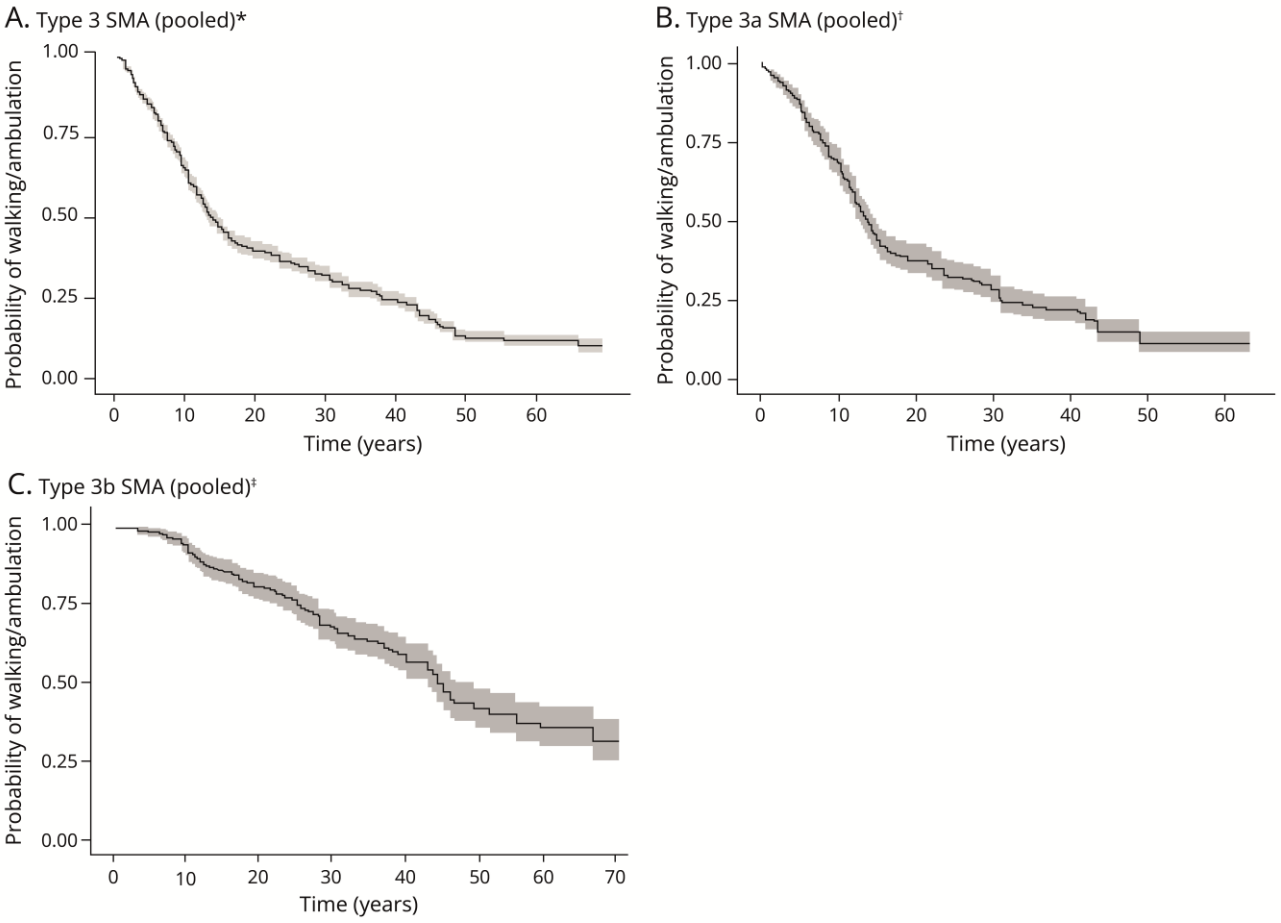


Figure 3. Recreated Kaplan–Meier Curves for the Probability of Maintaining Ambulation

*The pooled curve for the seven individual studies (i.e., Bladen 2014, Chung 2004, Kaneko 2017, Lusakowska 2021, Russman 1996, Wadman 2017, and Zerres 1997) is presented (along with the corresponding 95% CI). The pooled curve across all 22 study arms (i.e., Bladen 2014 [Argentina, Germany and Austria, Hungary, Serbia, Switzerland, UK, and Ukraine], Chung 2004 [Type 3a and Type 3b], Kaneko 2017 [Type 3a onset <3 years old and Type 3b onset ≥3 years old], Lusakowska 2021 [Type 3a 3 copies, Type 3a 4 copies, Type 3b 3 copies, and Type 3b 4 copies], Russman 1996 [Type 3b <2 years old, Type 3b ≥2 years old], Wadman 2017 [Type 3a, Type 3b onset <12 years old, and Type 3b onset >12 years old], and Zerres 1997 [Type 3a and Type 3b]), which is based on a total of 1,327 patients, is presented.
†The pooled curve across all seven study arms (i.e., Chung 2004 [Type 3a] and Kaneko 2017 [Type 3a onset <3 years old], Lusakowska 2021 [Type 3a 3 copies and Type 3a 4 copies], Russman 1996 [Type 3b onset <2 years old], Wadman 2017 [Type 3a], and Zerres 1997 [Type 3a]), which is based on a total of 413 patients, is presented (along with the corresponding 95% CI). The median time to loss of walking/ambulation based on pooled study arms was estimated to be 13.4 years (95% CI 12.5–14.5). In the sensitivity analysis (which excluded Russman 1996 [Type 3b onset <2 years old]), the median time to loss of walking/ambulation across pooled study arms is estimated to be 14.0 years (95% CI 12.5–14.9). Compared with the base-case analysis, in the sensitivity analysis the median increased by 7 months.
‡The pooled curve across all eight study arms (i.e., Chung 2004 [Type 3b], Kaneko 2017 [Type 3b onset ≥3 years old], Lusakowska 2021 [Type 3b 3 copies and Type 3b 4 copies], Russman 1996 [Type 3b onset ≥2 years old], Wadman 2017 [Type 3b onset <12 years old and Type 3b onset >12 years old], and Zerres 1997 [Type 3b]), which is based on a total of 331 patients, is presented (along with the corresponding 95% CI). The median to loss of walking/ambulation based on pooled study arms was estimated to be 44.2 years (95% CI 43.0–49.4). In the sensitivity analysis (which excluded Russman 1996 Type 3b ≥2 years old), the median time to loss of walking/ambulation across pooled study arms is estimated to be 46.1 years (95% CI 43.0–58.4). Compared with the base-case analysis, the median increased by 1.9 years.
CI = confidence interval; SMA = spinal muscular atrophy.



Systematic Literature Review of the Natural History of Spinal Muscular Atrophy: Motor Function, Scoliosis, and Contractures

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