Quality of life of children with spinal muscular atrophy and their caregivers from the perspective of caregivers : a Chinese cross-sectional study

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Research

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Abstract

Background: Spinal muscular atrophy (SMA) is an autosomal-recessive motor neuron disease leading to dysfunction of multiple organs. SMA can impair the quality of life (QoL) of patients and family. We aimed to evaluate the QoL of children with SMA and their caregivers and to identify the factors associated with QoL in a cross-sectional study conducted in China.

Methods: We recruited 101 children aged 0-17 years with SMA and their caregivers from a children's hospital in China. Twenty-six children had type I SMA, 56 type II and 19 type III. Each child's QoL was measured by the Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL NMM), which was completed by the child's caregivers. The caregiver's QoL was measured by the Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM). Information on sociodemographic characteristics, disease-specific characteristics, and treatments were collected using the proxy-reported questionnaire. Two-sample t-tests and one-way ANOVA were used to compare differences in average scores of QoL across subgroups.

Results: Children with type III SMA had a higher average Total score of PedsQL NMM and higher average scores in domains Neuromuscular disease and Family resources than children with type I or type II SMA ($p < 0.001$). Caregivers of children with type III SMA reported higher average scores in the domains of Physical, Emotional, Social, and Cognitive functioning of the PedsQL FIM than those of children with types I or II SMA ($p < 0.05$). In addition, disease-related characteristics (e.g. limited mobility, stable course of disease, skeleton deformity, and digestive system dysfunction) and respiratory support were associated with lower average scores of PedsQL NMM and PedsQL FIM ($p < 0.05$). Exercise training, multidisciplinary team management and use of the medication Nusinersen were each associated with higher average scores in both PedsQL NMM and FIM ($p < 0.05$).

Conclusion: Our study has demonstrated factors that may impair or improve QoL of children patients with SMA and their parents. Particularly, QoL was relatively poor in children with type I and type II SMA as well as in their caregivers compared to those with type III SMA. We strongly recommend that standard of care in a multidisciplinary team (MDT) be strengthened to improve the QoL of SMA patients. Our study called for increased attention from clinical physicians on measuring QoL in their clinical practices in order to enhance the understanding of impacts of SMA and to make better decisions regarding treatment.

Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal-recessive neuromuscular disease caused by genetic mutation of the survival motor neuron (SMN) 1 gene on chromosome 5q13. This mutation results in reduced levels of the SMN protein, causing muscle weakness and atrophy [1-5]. SMA is traditionally divided into five clinical subtypes (type 0, I, II, III, IV) based on the age of onset of symptoms and on the highest achieved motor-function milestones [6,7]. Type 0 is the most severe subtype that onsets during the prenatal period and survives less than one month after birth. Type I is the most common subtype in living patients; it usually presents before 6 months of age. Non-sitter always refer to type I patients who were never learn to sit up independently, and their life expectancy is seldom more than two years without respiratory support. Type II usually onsets between 6 and 18 months of age. Sitter was defined as who can sit independently but are never be able to walk. Type II patients usually can live to adulthood. Symptoms of type III normally present after age 18 months; walker refer to some patients can acquire independent ambulation, although some may lose the ability to walk in adulthood owing to the progressive nature of the disease. Life spans of these patients are almost identical to those of the general population. Type IV is the rarest, has the lowest morbidity and mortality, and occurs after 20 years of age. Life span of type IV patients is similar to that of type III patients [8, 9].

In addition to causing damage of motor neurons, SMN protein deficiency is also detrimental to the functioning of multiple tissues including those found in skeletal muscle, heart, autonomic and enteric nervous systems, metabolic/endocrine system, lymphatic systems, and reproductive system [10-12]. Therefore, dysfunction of multiple organ systems may occur in a SMA patient as the disease progresses. SMA patients may need medical care and nursing support for daily activities as well as for long-term co-management of several medical devices [13, 14]. Current treatment options in SMA include (1) ventilatory support including non-invasive and invasive ventilation, (2) management of secretions including inhalational therapies and section, (3) feeding support including nasal feeding or placement of a percutaneous endoscopid gastrostomy and (4) supply with medical devices and orthosis [15-17]. Improvements regarding survival and QoL of SMA patients could be achieved by these options [7].

QoL is a multidimensional concept and is an important patient-reported outcome measure in clinical research and practice. According to the World Health Organization, QoL is defined as "an individual's perception of their position in the life in the context of the culture in which they live and in relation to their goals, expectations, standards and concerns" [18]. While investigating QoL in the clinical setting, it is important to understand the patient's experience, to evaluate the effectiveness of treatments, and to optimize individual therapy plans, which ultimately improve the patient's well-being [19, 20].

In pediatric neurology research, attentions mostly has focused on developing novel technologies and pharmaceuticals for children with SMA. Few studies have focused on investigating the impacts of these clinical treatments on the QoL of patients and caregivers. One study conducted in Europe by Rouault et al. described the disease impact on general well-being and therapeutic expectations of SMA type II and III patients [21]. This study highlighted the patient's perspective in terms of treatment and living with SMA [21]. However, the study used a self-developed questionnaire based on expert opinion instead of a validated survey instrument for measuring QoL. Based on a literature review, we found that the PedsQL 3.0 Neuromuscular Module (PedsQL NMM) can be used to estimate the QoL of SMA patients, whereas the PedsQL Family Impact Module (PedsQL FIM) can be used as a supplement of the PedsQL NMM to reflect the caregivers' QoL and the family impact. Weaver et al found that PedQL FIM captured significant differences in functioning domains of QoL including physical, emotional, social, and family relations between SMA Type I and II [22]. In addition, this study demonstrated significant differences in the communication domain of the proxy-reported PedsQL NMM [22]. Nusinersen treatment did not impact proxy-reported QoL, whereas gastrostomy tube and ventilation support decreased children's QoL [22]. The analysis of parents' questionnaires revealed that different types of SMA and clinical treatment can significantly affect the QoL of SMA patients. Published studies of the QoL of SMA patients and caregivers have been conducted in the United States or in Europe. To our best knowledge, no similar study has been conducted in China. Therefore, in the present study we aimed to evaluate the QoL of children with

SMA and their caregivers and to identify the factors associated with QoL (such as SMA subtypes, disease-related characteristics and treatments) for patients and caregivers that participated in a hospital-based, cross-sectional study in China.

Methods

Participants and design

During 16-28 March 2020 we conducted a questionnaire-based survey of 101 caregivers, which included the parents or grandparents of SMA patients recruited from the Department of Neurology of the Children's Hospital of Zhejiang University School of Medicine in Hangzhou, China. The inclusion criteria for caregivers were (1) their child was diagnosed as SMA by genetic testing and (2) their child's age ranged from 0 to 18 years. Caregivers were excluded if they could not understand or complete the questionnaire correctly. In accordance with the principle of voluntary participation, the study questionnaire was sent by website to the caregivers with detailed information about the purpose and methods of this study. All eligible participants provided signed, informed consent before they completed the questionnaire, and the study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine (2019-IRB-171).

Before the questionnaire was used, we conducted a preliminary test of the feasibility, comprehensibility, and acceptability of the questions (survey items) and their multiple-choice answers. During this test 25 questionnaires were sent out, 24 were received yielding an effective recovery of 96%. The results of the preliminary test showed that the population response rate was very high and that our investigation was feasible. It took the caregiver 20-30 minutes to fill in the questionnaire, so we set the recommended length of time of completion of questionnaire as 35 minutes in the instruction texts of the final survey questionnaire. During the survey of all participants, the data were collected by trained physicians using a one-to-one internet survey. After logging onto the questionnaire website, all caregivers were asked to complete the PedsQL FIM section. In addition, the caregivers of SMA patients aged 5 years and older were asked to complete the PedsQL NMM section. All caregivers immediately submitted their answers upon completion of the questionnaire.

QoL measures

PedsQL NMM and PedsQL FIM were used to measure QoL of patients with SMA and their caregivers. In addition, the questionnaire included some questions to collect the information on socio-demographic characteristics, disease-related characteristics, and medical interventions/treatment plan of the patients. Several terms were used in these additional questions. For example, a non-Sitter was defined as a patient who was unable to sit. A sitter was defined as a patient who could sit without aid but could not walk alone, whereas a patient who could walk alone was defined as walker. Skeletal dysfunctions were defined as structural changes in the skeletal system that result in functional changes, such as scoliosis, hip dislocation, tendon contracture, joint deformation, etc. Digestive system dysfunctions were defined as disordered functions of digestive organs including the gastrointestinal tract, the liver and biliary system, and the pancreas. The main symptoms of digestive system dysfunctions included salivation, difficulty swallowing, constipation, etc. Stable course of disease was defined as a state of disease progression wherein patient's athletic ability and intensity keep no progressive levels during past 6 months. For example, a patient who was 9 months old but was unable to hold her/his head up steadily from 3 months old. Exercise training was defined as rehabilitation training in professional institutions. A patient that had not accepted any medical service was defined as no-medical service (N-MS). A patient that only accepted a neurology doctor but was not under multidisciplinary team (MDT) was defined as medical service (MS). A patient that accepted MDT was defined as accepted standard of care (SOC) in a MDT management program.

We used PedsQL NMM, a proxy-reported, 25-item survey instrument, to measure health-related QoL in children with neuromuscular disorders. This instrument contains three dimensions: About My Child's Neuromuscular Disease (17 items, with emphasis on physical functioning), Communication (three items), and About Our Family Resources (five items). For each item, caregivers were asked to rate the influence of a certain problem in the past month. Each multiple-choice answer was scored from 0 (never a problem) to 4 (almost always a problem). Item scores were reversed and linearly transformed to a 0 to 100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0); therefore, a higher scores indicated a higher QoL. PedsQL NMN is a reliable survey instrument, and Cronbach's alpha for each dimension exceeds 0.70 [23].

The PedsQL FIM was designed to assess the impact of pediatric chronic health conditions on caregivers' QoL and family functions in the past month. The PedsQL FIM includes the following six scales of a caregiver's self-reported functioning: physical functioning (six items), emotional functioning (five items), social functioning (four items), cognitive functioning (five items), communication (three items), and worry (five items). In addition, the PedsQL FIM explored the following two scales of family functioning reported by the primary caregiver: daily activities (three items) and family relationships (five items). Each item included a five-point, multiple-choice response ranging from 0 (never a problem) to 4 (always a problem). These item scores were reversely graded and linearly transformed to a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0); therefore, higher scores indicated better functioning or less negative impacts. Initial validation studies indicated that PedsQL FIM has a relatively high internal consistency with Cronbach's alpha values exceeding 0.70 [24].

Statistical analysis

Descriptive analysis was applied to describe the characteristics of the study population. Continuous measurements were summarized as means ± standard deviations (SDs), and categorical measurements were summarized using frequencies with percentages. A normal distribution of our data was tested using the normality test and distribution curve. A two-sample t-test was used to compare the difference in average scores of QoL between two subgroups; whereas a one-way ANOVA was used to compare average scores of QoL among three or more subgroups. In addition, we used Cohen's effect size (Cohen's *d*) to assess the clinical relevance in terms of pairwise differences in average score between groups (including differences between subtypes of SMA, disease-related characteristics, and acceptance categories of clinical treatments). Cohen's *d* was calculated as the absolute value of the difference in average scores divided by the largest SD and was interpreted as follows: $0.2 \leq d < 0.5$, small difference; $0.5 \leq d < 0.8$, moderate difference; and $d \geq 0.8$, large difference [25].

All statistical tests were two-tailed and their significance was indicated by $p < 0.05$. All the analyses were conducted using SPSS version 22 (IBM Corp. NY, USA).

Results

Characteristics of the study population

Socio-demographics characteristics, disease-related characteristics and medical interventions/treatment plan of the patients in our study are summarized in Table 1. A total of 101 caregivers with SMA children participated in our study. All caregivers completed the PedsQL FIM questionnaire; however, only 87 caregivers completed the PedsQL NMM questionnaire because this survey instrument applies only to children of ages 2 to 18 years. Ten patients depended on invasive ventilation, 23 patients used a suction tube and only 1 child received a non-invasive ventilator treatment. Sixteen patients were treated by special formula feeding, 2 patients used nasal feeding tube and 1 child received gastrostomy in nutritional support.

Table 1 The demographics characteristics of SMA patients (n = 101)

Variable	*N* (%
Child sex	
Male	49 (48.50)
Female	52 (51.50)
Child primary diagnosis	
SMA type I	26 (25.70)
SMA type II	56 (55.40)
SMA type III	19 (18.80)
Average age of SMA type (years	Age range of SMA type (years)
SMA type I: 5.28	0.50–16.17
SMA type II: 6.90	0.92–16.00
SMA type III: 9.35	2.08–13.67
Disease duration	Age range of disease duration (years)
SMA type I	4.86 (0.33–15.58)
SMA type II	6.12 (0.17–15.50)
SMA type III	5.9 (1.00–13.67)
Mobility	
Non-sitter	46 (45.50)
Sitter	39 (38.60)
Walker	16 (15.80)
Stable course of disease	
No	41 (40.60)
Yes	60 (59.40)
Skeletal deformity	
No	27 (26.70)
Yes	74 (73.30)
Digestive system dysfunction	
No	78 (77.20)
Yes	23 (22.80)
Medical services	
N-MS	67 (66.30)
MS but not U-MDT	21 (20.80)
U-MDT	13 (12.90)
Exercise training	
No	56 (55.40)
Yes	45 (44.60)
Respiratory support	
No	75 (74.30)
Yes	26 (25.70)
Nutritional support	
No	82 (81.20)
Yes	19 (18.80)
Scoliosis surgery	
No	99 (98.00)
Yes	2 (2.00)
Nusinersen treatment	

No	92 (91.10)
Yes	9 (8.90)

Abbreviations: SMA, spinal muscular atrophy; N-MS, no medical services; MS but not U-MDT: medical services but not under multidisciplinary team; U-MDT: Under multidisciplinary team;

Differences in the average scores of PedsQL NMM across SMA subtypes

The average scores of PedsQL NMM stratified by SMA subtypes are summarized in Table 2. The average total score and average scores of domains Neuromuscular diseases and Family resources were significantly higher in patients with SMA type III than in those with SMA type I (64.89 vs. 43.63, $p < 0.001$, $d = 1.08$; 65.32 vs. 40.53, $p < 0.001$, $d = 1.23$; and 58.68 vs. 38.75, $p = 0.006$, $d = 0.74$). Similarly, the average total score and average scores of domains Neuromuscular diseases and Family resources were significantly higher in patients with SMA type III than in those with SMA type II(64.89 vs. 48.79, $p < 0.001$, $d = 0.82$; 65.32 vs. 49.10, $p < 0.001$, and 58.68 vs. 33.94, $p < 0.001$, $d = 0.92$). In contrast, no statistically significant differences were found among SMA subtypes in the average score of domain Communication.

Table 2 Average scores of proxy-reported PedsQL 3.0 Neuromuscular Module across SMA subtypes (n = 87)

Children's QoL accessed from the caregiver-	SMA Type I	SMA Type II	SMA Type III	*Effect size (d)*		
	Mean ± SD	Mean ± SD	Mean ± SD	□ *vs.*□	□ *vs.*□	□ *vs.*□
	(*n* = 16)	(n = 52)	(*n* = 19)			
Total score	**43.63±13.08**	**48.79±13.04**	**64.89±19.75**[b,c]	0.39	1.08	0.82
Neuromuscular disease	**40.53±13.86**	**49.10±13.65**	**65.32±20.21**[b,c]	0.62	1.23	0.80
Communication	69.27±33.85	71.79±26.72	74.56±27.70	0.07	0.16	0.10
Family resources	**38.75±13.60**	**33.94±20.28**	**58.68±26.87**[b,c]	0.24	0.74	0.92

Abbreviations: SMA, spinal muscular atrophy.

Bold prints indicate $P<0.05$

[a]Post hoc significance between type I and type II.

[b]Post hoc significance between type I and type III.

[c]Post hoc significance between type II and type III.

Effect size (Cohen's *d*) is interpreted as : $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large.

The average scores of PedsQL FIM stratified by subtype are summarized in Table 3. The average total score and the average scores of domains Physical, Emotional, Social, Cognitive functioning were significantly higher in patients with SMA type III than in those with SMA types I or II ($p < 0.05$). The largest effect size was seen in the average scores of domain Physical functioning when comparing patients of SMA types III and I ($d = 1.04$). No statistically significant differences were found in the above-mentioned average scores between patients of SMA types I and II ($p > 0.05$).

Table 3 Average scores of PedsQL Family Impact Module across SMA subtypes (n = 101)

Caregivers' quality of life	SMA Type I	SMA Type II	SMA Type III	*Effect size (d)*		
	Mean±SD	Mean±SD	Mean±SD	□ *vs.*□	□ *vs.*□	□ *vs.*□
	(*n* = 26)	(*n* = 56)	(*n* = 19)			
Total score	**34.97±21.97**	**40.56±17.76**	**53.80±21.87**[b,c]	0.25	0.86	1.45
Physical functioning	**29.01±25.18**	**45.16±21.52**	**59.43±29.23**[a,b,c]	0.64	1.04	0.49
Emotional functioning	**31.54±28.42**	**33.93±20.64**	**54.47±23.27**[b,c]	0.08	0.81	0.88
Social functioning	**29.33±26.15**	**37.28±25.11**	**55.59±29.16**[b,c]	0.30	0.90	0.63
Cognitive functioning	**40.00±24.78**	**45.18±24.77**	**61.58±25.71**[b,c]	0.21	0.84	0.64
Communication	41.99±31.49	43.75±25.69	55.26±31.21	0.06	0.42	0.37
Worry	30.00±26.87	26.16±17.94	37.63±27.35	0.14	0.28	0.42
Daily activities	28.20±25.94	36.61±24.40	40.79±24.52	0.32	0.49	0.17
Family relationships	49.81±28.02	54.46±21.78	60.26±23.24	0.17	0.37	0.25

Abbreviations: SMA, spinal muscular atrophy.

Bold prints indicate $P<0.05$

[a]Post hoc significance between type I and type II.

[b]Post hoc significance between type I and type III.

[c]Post hoc significance between type II and type III.

Effect size (Cohen's d) is interpreted as: $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large.

Differences in the average scores of PedsQL NMM across disease-specific characteristics

The average score of PedsQL NMM stratified by disease-related characteristics are summarized in Table 4. Patients categorized as non-sitter or sitter were reported by their parents to have relatively average scores (Total and domains Neuromuscular disease and Family resources) compared to parents that were able to walk independently ($p < 0.05$). In particular, in comparisons of Non-sitter or Walker, the effect sizes were 1.19, 1.35 and 1.07 for differences in average Total score, average score of domain Neuromuscular disease, and average score of domain Family resources, respectively. The average Total score and the average scores of domains Neuromuscular disease and Family resources were significantly higher in children without stable course of disease than in those with stable course of disease ($p < 0.01$); the effect sizes ranged from 0.29 to 0.64. The average Total scores and the average scores of domains Neuromuscular disease and Family resources were significantly higher in children without motor skeleton deformity than in those with skeleton deformity ($p < 0.05$); the effect sizes ranged from 0.46 to 0.49. The average Total scores and the average scores of domains Neuromuscular disease and Family resources were significantly higher among children with normal digestive system function than in those with digestive system dysfunction ($p < 0.01$); the effect sizes ranged from 0.68 to 1.06.

Table 4 Average scores of proxy-reported PedsQL 3.0 Neuromuscular Module across disease-related characteristics (n = 87)

	Mobility						Stable course of disease			
	Non-sitter (n=34)	Sitter (n=37)	Walker (n=16)	*Effect size (d)*			No (n=33)	Yes (n=54)	*Effect size(d)*	No (n=
				Non-sitter *vs.* sitter	Non-sitter *vs.*Walker	Sitter *vs.*Walker				
Total score	**43.03±11.98**	**52.51±13.48[a]**	**66.38±19.58[b,c]**	0.70	1.19	0.71	**57.67±15.51**	**47.50±15.80**	0.64	**57**
Neuromuscular disease	**40.27±12.70**	**53.97±12.68[a]**	**67.28±19.98[b,c]**	1.08	1.35	0.67	**57.53±16.46**	**47.11±16.65**	0.63	**57**
Communication	72.79±28.89	69.82±26.89	75.00±30.28	0.10	0.07	0.17	76.77±27.54	68.98±28.20	0.28	73
Family resources	**34.56±16.67**	**37.16±23.99**	**59.38±23.23[b,c]**	0.11	1.07	0.93	**46.67±24.20**	**36.30±21.44**	0.29	**49**

Values in the table are means, standard deviations and effect sized. Bold prints indicate $P<0.05$

[a]Post hoc significance between non-sitter and sitter.

[b]Post hoc significance between non-sitter and walker.

[c]Post hoc significance between sitter and walker.

Effect size (Cohen's d) is interpreted as: $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large.

Differences in the average scores of PedsQL FIM across disease-specific characteristics

The average scores of PedsQL FIM stratified by disease-related characteristics are summarized in Table 5. Parents with children categorized as Non-sitter or Sitter reported significantly lower average Total scores and average scores of domains Physical, Emotional, Social, Cognitive functioning compared with the same scores of children categorized as Walker ($p < 0.05$); the largest effect size was 1.40 in the comparison between Non-sitter and Walker categories. The average scores of domains Physical and Emotional functioning were significantly lower for children with skeletal deformity than for those without skeletal deformity ($p < 0.05$). Regarding digestive system dysfunction, the average Total score and the average scores of domain Daily activities and domains Physical, Emotional, Social, Cognitive functioning were significantly lower in children with the dysfunction than in those that lacked the dysfunction ($p < 0.01$); the effect sizes ranged from 0.56-1.26.

Table 5 Average scores of PedsQL Family Impact Module across disease-related characteristics (n = 87)

Caregivers' QoL	Mobility Mean±SD						Skeletal deformity Mean±SD		
	Non-Sitter (*n*=46)	Sitter (*n*=39)	Walker (*n*=16)	*Effect size (d)*			No (*n*=27)	Yes (*n*=74)	*Effe siz (d*
				Non-sitter *vs.* Sitter	Non-sitter *vs.* Walker	Sitter *vs.*walker			
Total score	**50.43±24.33**	**56.28±24.03**	**60.94±20.83**[b,c]	0.24	0.43	0.19	47.94±24.78	39.29±18.37	0.3
Physical functioning	**34.33±24.89**	**45.30±23.14**[a]	**66.67±20.53**[b,c]	0.44	1.40	0.86	**55.86±23.58**	**39.25±25.43**	0.6
Emotional functioning	**31.30±25.96**	**36.92±21.29**	**54.69±20.69**[b,c]	0.22	1.10	0.68	**46.67±26.67**	**33.72±23.00**	0.4
Social functioning	**32.34±26.46**	**37.34±24.81**	**60.16±26.70**[b,c]	0.19	1.04	0.85	46.07±35.45	35.98±23.47	0.2
Cognitive functioning	**42.07±23.13**	**46.03±26.39**	**63.13±26.64**[b,c]	0.15	0.79	0.64	53.89±29.40	44.40±24.06	0.3
Communication	43.48±29.91	42.31±24.29	58.85±31.40	0.04	0.49	0.53	48.15±33.60	44.48±26.50	0.1
Worry	29.57±22.85	24.62±18.79	40.00±27.69	0.22	0.38	0.56	29.81±29.92	29.12±19.52	0.0
Daily activities	32.43±24.48	35.04±25.30	43.75±25.18	0.10	0.45	0.34	36.42±30.24	34.79±22.97	0.0
Family relationships	50.43±24.33	56.28±24.03	60.94±20.83	0.2	0.44	0.19	60.18±25.02	52.23±23.15	0.3

Values in the table are means, standard deviations and effect sized. Bold prints indicate $P<0.05$

[a]Post hoc significance between non-sitter and sitter.

[b]Post hoc significance between non-sitter and walker.

[c]Post hoc significance between sitter and walker.

Effect size (Cohen's *d*) is interpreted as: $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large.

Differences in the average scores of PedsQL NMM across the clinical treatments

The average scores of PedsQL NMM stratified by clinical treatments are summarized in Table 6. The average Total scores and the average scores of domain Neuromuscular disease were significant higher in children that received Exercise training than in those which did not ($p < 0.001$); the effect sizes were 0.60 and 0.75, respectively. The average Total scores and the average scores of domain Neuromuscular disease were significant lower in children that received Respiratory support than in those which did not ($p < 0.001$); the effect sizes were 0.57 and 0.79, respectively. Regarding MDT, significant differences in average Total score and in average scores of domains Neuromuscular disease and Family resources were detected between groups with SOC in MDT and groups without MDT (N-MS and MS groups). Children in the MS group had significantly higher average Total scores and average scores in domains Neuromuscular disease and Family resources than children in N-MS group ($p < 0.05$). Children under MDT had significantly higher average Total scores and average scores in domains Neuromuscular disease and Family resources than children in N-MS groups ($p < 0.05$) or those in MS group ($p < 0.05$). Effect sizes ranged from 0.13 to 0.90.

Table 6 Average scores of proxy-reported PedsQL 3.0 Neuromuscular Module across subgroups of clinical treatments (n = 87)

	Exercise training			Respiratory support			MDT		
	No (*n*=49)	Yes (*n*=38)	Effect size *(d)*	No (*n*=64)	Yes (*n*=23)	Effect size *(d)*	N-MS (*n*=58)	MS but not U-MDT (*n*=16)	U-MDT (*n*=13)	N
Total score	**46.51±12.83**	**57.61±18.39**	0.60	**53.84±16.62**	**44.43±13.72**	0.57	**47.26±13.45**	**60.44±19.48**[a]	**58.46±18.46**[b,c]	
Neuromuscular disease	**45.38±14.98**	**58.40±17.38**	0.75	**54.62±17.00**	**41.18±14.02**	0.79	**47.26±14.66**	**60.39±20.11**[a]	56.56±19.67	
Communication	71.09±26.58	73.03±30.17	0.06	72.14±28.10	71.38±28.52	0.03	71.41±27.00	68.23±35.12	78.85±23.72	
Family resources	36.02±17.02	45.66±28.19	0.34	40.55±23.45	39.35±21.97	0.05	**33.10±18.23**	**55.94±25.44**[a]	**52.69±25.38**[b,c]	

Abbreviations: N-MS: No medical services; U-MDT: Under multidisciplinary team; MS but not U-MDT: Medical services but not under multidisciplinary team: .

Values in the table are means, standard deviations and effect sized. Bold prints indicate $P<0.05$

[a]Post hoc significance between no medical services and medical services but not under MDT.

[b]Post hoc significance between no medical services and under MDT.

Discussion

Our study found that quality of life of patients and caregivers differed across SMA subtype, disease-related characteristics, and treatment characteristics. We found a significant difference among SMA subtypes in the PedsQL NMM domain of Neuromuscular diseases, with type III having the highest average score and type I having the lowest average score. By contrast, Meaghann *et al.* found no significant difference among SMA subtypes in the domain of Neuromuscular diseases in the proxy-report of the PedsQL NMM [22]. A reasonable explanation for this finding is that in our study the sample size was larger than in the previous study and the children's physical function was worse in severe types, indirectly reflecting the severity of the disease. Compared with patients of SMA types II and I, patients of type III had significantly higher average scores in the Family resources domain, which is consistent with the previous study [22]. In contrast, our results revealed no significant difference among SMA subtypes in the Communication domain. These negative results may be related to social and humanistic characteristics in China - that is, all patients received care and concern from their relatives, friends, community, and medical staff. This result also suggests that all members of Chinese society are concerned with children's health [26]. In terms of the average Total score of PedsQL NMM, patients with type III showed a significant difference compared with types II and I. These results are consistent with previous reports, which indicate that SMA subtypes reflect the physical function of patients [22]. Additionally, we also found that effect sizes were large or moderate in different subtypes of SMA, which indicated that the differences in quality of life of patients had reached the threshold of clinical relevance and was worthy of attention from health professionals. We found no significant difference in the Neuromuscular disease domain between children with type I and type II; however, but the effect size was moderate and indicated a clinical trend with the QoL of type II being higher than that of type I in the Neuromuscular disease domain. These results suggest that more attention to this trend should be paid to improve the QoL of SMA patients.

Our results showed that the physical, emotional, societal, and cognition functioning domains of the Family Impact Module were effective for comparing patients with different subtypes of SMA. Type III patients tended to have higher scores than the other two subtypes, which is related to the patients' motor ability because most type III patients have the ability to move autonomously and the large scope of activities can improve their physical and mental health. The effect size SMA type III compared with type I and type II also indicated a large clinical difference in the above functional domains. Most patients with SMA type III are able to walk alone, whereas patients with type II and type I cannot. Because patients with type III can move their limbs freely and can complete various functional exercises by themselves, their caregivers put less time and energy into their care, resulting in significantly higher Family Influence Module scores in type III patients than in patients with types I or II. Our research showed no significant difference among SMA types in the Communication, Worry, Daily activities, or Family relations domains. This result may have been caused by the characteristics of China's national social conditions, similar to the Communication domain outcomes seen in the PedsQL NMM.

Disease-related characteristics of patients with SMA, such as skeletal malformation, digestive dysfunction, motor degeneration, and current motor ability, obviously influence the PedsQL NMM and PedsQL FIM results. SMA is a disease often involving dysfunction of multiple systems, as seen in the reduction in the distribution of SMN protein to the body's multiple organs and tissues [10, 11]. As SMA is a progressive disease, complications such as skeletal malformation, digestive disorders, respiratory disorders, and motor function degeneration appear gradually. Our findings showed that the average Total score and the average scores of domains Neuromuscular diseases and Family resources of PedsQL NMM were significantly lower in patients with these complications than in those without them. Our results support the findings from a previous study - that is, motor function is reduced in patients with skeletal deformities, which in turn affects all aspects of the patient's life [27]. Digestive disorders make malnutrition a higher risk in patients, which may cause fatal or serious disorders [28, 29]. The degeneration in motor ability and current movement ability can indirectly reflect the patient's survival condition, and all of these disease-related characteristics can have a significant effect on QoL. In the PedsQL FIM, the physical and emotional functions of the caregivers of patients with skeletal malformations were worse than those of the caregivers of patients without skeletal malformations. The disease status of skeletal malformation in SMA patients with progressive muscular atrophy and muscle weakness is a cumulative effect of a causal chain. The skeletal malformations of patients with SMA often include scoliosis, muscle contracture, dislocation of hip joint, and other conditions, which often lead to the degeneration or loss of motor ability [29]. In the meantime, severe progressive muscle weakness and muscle atrophy lead to skeletal malformations in SMA patients, which can further worsen the regression of motor ability in SMA patients. In this way, a kind of progressive circulation and accumulated effect is formed between skeletal malformations and the degeneration or loss of motor ability [13,14,30]. Faced with this situation, caregivers have to increase the daily nursing level of patients to achieve a high QoL. For so long caregivers' physical health and mental health are greatly affected. Dysphagia and other digestive disorders often appear in the last stage of SMA, which seriously affects the patient's physical health and reduces the caregiver's QoL and family relationships. Individual physical and psychological functions may be significantly affected by mobility, and the caregivers of patients who can walk freely require less care and energy than caregivers of patients who have lost the motor ability to walk. This means that when caregivers concentrate their energy on their children, the caregivers have frequent and serious limits placed on their own lives and have increased stress on their own bodies. These detrimental effects can lead to the onset of anxiety, fear, depression, and other physical or mental side-effects [31]. In addition to the statistical significance, the effect sizes in that we estimated for the above-mentioned domains were moderate or large, indicating that disease-related characteristics may impact the QoL of patients and caregivers, which warrant attention from clinical professionals during their practice.

Our results suggest that clinical treatments improve QoL of patients with SMA from the caregivers' perception. Early exercise training is beneficial for improving the recovery of limb function, and muscle-strengthening activities help patients regain strength and stability [32, 33]. Various studies indicate that exercise training at the recovery stage can effectively lower the disability level of stroke patients with hemiplegia and can improve their QoL [34-36]. These studies also suggest that exercise training can activate the motor neurons of the body to promote the recovery of and to effectively improve the motor

function of patients with neuromuscular degeneration disease, including Duchenne muscular dystrophy and SMA [35]. Studies have demonstrated that exercise training is safe and feasible, prolongs survival, diminishes muscle weakness, and enhances motor behavior [37]. While not statistically significant, we observed a strong trend for exercise training to increase average scores in the domains Neuromuscular disease and Family resources. However, the effect sizes reflected that whether exercise training was carried out or not had a moderate difference. This trend suggests that exercise training may be helpful in the recovery of motor function in patients with SMA and may delay the degradation of motor function, which can effectively improve the QoL of patients.

Several studies have shown that the most common causes of death in patients with SMA involve respiratory complications [38, 39]. As the disease progresses, patients may experience changes in their organ systems, especially the respiratory dysfunction, which occurs later. Without respiratory support, most patients with SMA type I die of pneumonia and respiratory failure before the age of 2 years [40]. However, our study suggests that patients with respiratory support had lower average scores in the domains Neuromuscular disease and Family resources compared to patients without respiratory support. One possible explanation for this unexpected result is that patients receive respiratory support when their condition has deteriorated, which in turn seriously affects their QoL and simultaneously requires caregivers to spend more energy in managing daily life. Many studies have confirmed that respiratory support is helpful in improving pulmonary function because SMA is a progressive disease involving multiple system dysfunction, including respiratory complications. Patients with type I often die of respiratory failure. Based on our findings, we suggest that patients with SMA type I adopt mechanical ventilation strategies early to maintain effective respiratory function, preventing respiratory complications and pulmonary infections, and subsequently improving QoL.

Recently, Nusinersen became the first effective drug treatment for SMA available in China. As noted in previous research, Nusinersen treatment can improve the motor, respiratory, digestive, and other system functions in patients [41-44]. In our study, six caregivers of patients who were receiving Nusinersen treatment and also receiving SOC completed the PedsQL NMM. Although the questionnaire results for these six patients showed that the average scores of domains Neuromuscular diseases and Family resources were higher than those of patients who did not accept Nusinersen treatment, the caregivers of these six patients reported that drug treatment effectively improved the patients' QoL. We cannot make definitive conclusions on whether their QoL was improved by Nusinersen treatment owing to the small sample size. These patients also received exercise training, so it is possible that a combination of the two factors increased QoL. The sample size should be increased in follow-up studies and should include an extended course of Nusinersen treatment to verify if this treatment improves patients' QoL.

Health management has been defined as an integrated approach to assess, guide, and intervene in the risk factors affecting the health of a group or an individual, based on the modern concept of health, new medical models, and the theories, techniques, and means of modern medicine and management [45]. Multidisciplinary team (MDT) management is composed of more than two related disciplines in order to implement clinical treatments for specific diseases [46, 47]. The results of this study showed that the average Total score of the PedsQL NMM for patients receiving MDT intervention was superior to that of the non-MDT management group ($p < 0.05$), indicating that MDT management can effectively improve the QoL of patients with SMA. The effect size between non-MDT management group and MDT group was moderate, but still indicates significant clinical benefits of participation in the MDT group. As shown in previous studies of MDT management in other chronic diseases, such as tuberous sclerosis complex (TSC), Prader-Willi syndrome, pediatric chronic pancreatitis, pediatric medulloblastoma, and asthma, this approach is conducive to ensuring the best outcomes of disease, to improving patients' daily life, to reducing caregiver burden, and to decreasing healthcare load [48-51]. Low awareness of MDT health management interventions among caregivers often results in ignoring other system dysfunction symptoms, which may lead to delayed treatment of SMA. Based on our observations and previous studies, we suggest that raising the caregivers' awareness of MDT health management, monitoring the status of system dysfunction, guiding patients treated with related systems concerning the progress of disease, and improving the patients' QoL can substantially improve the lives of patients and their caregivers [13,14].

The highlights of this study are that it is the first to evaluate and investigate the QoL of Chinese patients with SMA and to reflect the QoL of these children according to the perceptions of the caregivers. Moreover, this study analyzed the disease-related characteristics of the patients and the influence of clinical treatments on the QoL and the family impact. Previous studies have not provided data on the QoL of patients with SMA in China, and few studies exist on the influence of clinical treatments on QoL in SMA. Considering the social, economic, and medical characteristics in China, which are different from those of other developed countries, the QoL survey of patients with SMA in China has become an interesting and emerging research field.

Except for the Communication module, our survey was given a lower mark than those of previous studies conducted in foreign populations. The present situation can be explained by the following reasons: First, China is a developing country while American/European countries are developed ones. The cost of treatment is prohibitive for most SMA patients in China, and they cannot receive the early diagnosis and treatments obtained by patients of foreign countries. Second, the development of diagnosis and treatment of SMA in China is slower than that in foreign countries, drugs on the market later than foreign countries. Third, the United States has incorporated SMA into newborn screening and has attached great importance to the diagnosis and treatment of SMA; whereas China is still in early stages. However, the average score of the Communication domain in our research was higher than that of foreign studies.

Our study had several limitations. First, the sample size included in this study is modest, reflecting the rarity of the disease. We have not applied self-report in our study because the sample size would be even smaller if we only included children older than five years. In the future study, we recommended more larger samples could apply both self-reported and proxy-reported QOL measurements among patients with SMA to get a full picture of patient's QOL. A second limitation of this study is that patients were only sampled from central and east China. Given the lack of QoL surveys on SMA patients in other regions, the study may not be representative of the QoL of SMA patients across China. Nevertheless, our results may be generalized to patients from the areas mentioned above. Third, this study was a cross-sectional study with data collected at a single time point, which precluded drawing conclusions regarding causality. Fourth, owing to less data of specific items of clinical treatments, our study cannot provide a more in-depth analysis; so future research is needed with a larger sample that includes subsets of clinical treatments. In addition, our study reflected the influence of disease-related characteristics on the QoL of children and only the initial effect of medical measures. Finally, although the PedsQL is designed to be used for all types of neuromuscular diseases, this survey instrument has not been specifically validated for proxy-reported use in children with SMA in China.

In summary, further follow-ups of these patients should be conducted and QoL indicators should be used to investigate the effectiveness of clinical treatments for childhood SMA. In addition, future studies need larger sample sizes and should pursue multicenter enrollments to involve patients with SMA from all of China to generate a database that reflects the QoL of patients across the country. To confirm the effectiveness of treatment approaches and to make the results more generalizable, subsequent studies should continue research in the diagnosis and treatment of SMA, and should include larger numbers of patients, especially in the drug treatment group.

Conclusion

To conclude, the more severe the SMA disorder was, the lower were the average scores on the PedsQL NMM and PedsQL FIM as reported by the patients' caregivers, and the poorer was the patients' QoL. Disease-related clinical features and clinical treatments have a significant influence on the QoL of patients with SMA. We recommend implementing clinical treatments, supplemented by exercise training and respiratory support, regularly assessing the functional status of various systems, and establishing MDT health management in patients as early as possible, which can effectively prevent or delay the emergence of disease-related clinical characteristics, can improve patients' QoL, and can relieve caregivers' psychological pressures and overall life burden.

Abbreviations

SMA: Spinal muscular atrophy; QoL: quality of life; SMN1: survival motor neuron 1; SMN: survival of motor neuron; PedsQL NMM: Pediatric Quality of Life Inventory 3.0 Neuromuscular Module; PedsQL FIM: Pediatric Quality of Life Inventory Family Impact Module; MDT: multidisciplinary team; SD: Standard deviation; SOC: Standard of care;

Declarations

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Availability of data and materials

All data generated during this study are included in this published article.

Authors' contributions

MY, YM, SSM and YX designed the study questionnaire with input from the other authors. MY and SSM coordinated ethics application. YM managed the acquisition of data. MY, YM and RYQ analyzed data and interpreted findings with input from the other authors. MY drafted the manuscript. CZY and GNB substantially revised and edited the manuscript. All authors reviewed the final manuscript and approved the decision to submit for publication. MY and YM as first authors and SSM and GNB as last authors equally contributed to this manuscript.

Ethics approval and consent to participate

This study was approved by Ethical Committee of Children's Hospital, Zhejiang University School of Medicine (2019-IRB-171). Informed consent was obtained from all participants before the study questionnaires were completed.

Consent for publication

The consent for publication has been obtained from all authors.

Competing interests

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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