Quality of Life of Children With Spinal Muscular Atrophy and Their Caregivers: A Chinese Cross-sectional Study

Mei Yao
Zhejiang University School of Medicine Children's Hospital
Ying Ma
Zhejiang University School of Medicine Children's Hospital
Ruiying Qian
Zhejiang University School of Medicine Children's Hospital
Yu Xia
Zhejiang University School of Medicine Children's Hospital
Changzheng Yuan
Zhejiang University
Guannan Bai
Guangzhou Women and Children's Medical Center
Shanshan Mao (6307003@zju.edu.cn)
Zhejiang University School of Medicine Children's Hospital https://orcid.org/0000-0001-6736-1407

Research

Keywords: spinal muscular atrophy, quality of life, disease-related characteristic, medical intervention, proxy-report

Posted Date: August 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-50728/v1

Version of Record: A version of this preprint was published on January 6th, 2021. See the published version at https://doi.org/10.1186/s13023-020-01638-8.

Abstract

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

Methods: 101 caregivers and children aged 0-14 years with SMA were recruited from a children hospital. 26 children had type I SMA, 56 type II and 19 type III. Children's QoL was measured by the Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL NMM) that was filled by caregivers. Caregiver's QoL was measured by the Pediatric Quality of Life Inventory Family Impact Module (PedsQL FIM). Information on sociodemographic, disease-specific characteristics, and treatments were collected by the proxy-reported questionnaire. Two independent t-tests and one-way ANOVA were applied to compare differences in scores of QoL across subgroups.

Results: Children with type III SMA had higher total score of PedsQL NMM, and scores in neuromuscular disease and family resources domain than those with type I and type II SMA ($p < 0.001$). Caregivers of children with type III SMA reported higher scores in domains of physical, emotional, social, and cognitive function of PedsQL FIM than those of children with types I and II ($p < 0.05$). In addition, disease-related characteristics (e.g. limited mobility, motor degeneration, skeleton deformity, and digestive system dysfunction) and respiratory support were associated with lower scores of PedsQL NMM and PedsQL FIM ($p < 0.05$). Exercise training, multidisciplinary team management and using the medication nusinersen were associated with higher scores of QoL in both PedsQL NMM and FIM ($p < 0.05$).

Conclusion: Our study has demonstrated the 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 than those with type III SMA. Our study called for attention from clinical physicians on measuring QoL in their clinical practices in order to enhance the understanding of impacts of SMA and make better decisions regarding treatment.

Introduction

Spinal muscular atrophy (SMA) is a rare, autosomal-recessive neuromuscular disease caused by genetic deletion or mutation in the survival of motor neuron 1 (SMN1) gene on chromosome 5q13, which results in reduced levels of the survival of motor neuron (SMN) protein, causing muscle weakness and atrophy [1–5]. SMA is traditionnally divided into five clinical subtypes (Type 0, I, II, III, IV) based on the age of symptom onset highest motor milestones archived [6, 7]. SMA Type 0 is the most severe subtype that onsets during prenatal period and the live birth survives less than one month after birth. SMA Type I is the most common and most severe subtype that usually presents before 6 months of age. The patient never learns to sit up independently, and his/her life expectancy is seldom more than two years without respiratory support. Type II usually onsets between 6 and 18 months of age. Patients can sit independently but never be able to walk. They can usually live into adulthood. Symptoms of SMA type III normally present after age 18 months; patients can acquire independent ambulation, although some patients may lose the ability to walk in adulthood due to the progressive nature of the disease. Their life spans are almost identical to that of the general population. SMA Type IV is rarest and with lowest morbidity and mortality, which occurs after 20 years of age. Their life span is similar to patients with Type III [8, 9].

SMN protein deficiency is detrimental to the functioning of other tissues including skeletal muscle, heart, autonomic and enteric nervous, metabolic/endocrine (e.g. pancreas), lymphatic, and reproductive systems [10–12]. Therefore, multiple organ system dysfunction may occur in SMA as the disease progresses, requiring daily medical care and nursing support for daily activities as well as for the long-term co-management of several medical devices [13, 14]. As the advanced clinical treatments have been emerged and developed in the last decades, the morbidity and mortality of SMA patients have been decreased and their life span has been significantly extended [15–17]. Accordingly, the quality of life (QoL) of SMA patients is supposed to be improved.

Quality of life (QoL) is a multidimensional concept, and is an important patient-reported outcome measure in clinical research and practice. Based on the definition by the World Health Organization (WHO). 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]. Investigating QoL in the clinical setting is important to understand patient's experience, to evaluate the effectiveness of treatments, and optimize the personized therapy plan, which ultimately improve patient's wellbeing [19, 20].

In the area of pediatric neurology research, attentions mostly have been focused on developing the novel technologies and pharmaceuticals for children with SMA. Few studies were 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 has highlighted patient's perspective in terms of treatment and living with SMA [21]. However, the above study used a self-developed questionnaire based on expert opinion instead of a validated instrument of measuring QoL. Based on literature review, we found that the PedsQL 3.0 Neuromuscular Module (PedsQL NMM) can be used to estimate the QoL of SMA patients, while the PedsQL Family Impact Module (PedsQL FIM) can reflect the caregivers' QoL and the family impact, as a supplement instrument to the PedsQL NMM. Weaver et al found that PedQL FIM captured the significant differences in functioning domains including physical, emotional, social, and family relations between SMA Type I and II [22]. In addition, this study also demonstrated significant differences in the communication domain of the proxy-reported PedsQL NMM [22]. Nusinersen use did not impact proxy-reported QoL, while gastrostomy tube and ventilation support decreased children's QoL [22]. The existing published studies in terms of QoL of SMA patients and caregivers were conducted in United States or Europe. To our best knowledge, there has been no similar study in China. Therefore, in the present study we aimed to evaluate QoL of children with SMA and their caregivers, and to identify the potential associated factors (such as SMA subtypes, disease-related characteristics and treatments) in a hospital-based cross-sectional study in China.

Methods

Participants and Design

A total of 101 caregivers were 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 diagnosis as SMA by genetic testing; (2) their child's age ranged from 0 to 18 years. Caregivers were excluded if they were not able to correctly understand or fill in the questionnaire. 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 final version of questionnaire (including PedsQL NMM and PedsQL FIM) was applied to the study, we conducted a preliminary test on the feasibility, comprehensibility, and acceptability of the question items and answer options, and revised the questionnaire according to the feedback results. All data were collected by trained physicians through a one-to-one internet survey with the participants. After logging onto the questionnaire website, the caregivers were asked to fill in the electronic questionnaire separately and then immediately submit the completed questionnaire.

Measures

PedsQL NMM and PedsQL FIM were used to measure QOL of patients with SMA and their caregivers. In addition, the questionnaire also include some questions to collect the information on sociodemographic characteristics, disease-related characteristics, and medical interventions/treatment plan of the patients. The PedsQL NMM is a proxy-reported, 25-item instrument to measure health-related QoL in children with neuromuscular disorders. It 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). Caregivers were asked to rate the influence of a certain problem in the past month by each question item; the answer options were scored from 0 (never a problem) to 4 (almost always a problem). Item scores were reversed and linearly transformed into a 0 to 100 scale (i.e. 0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0). Higher scores indicated better QoL. PedsQL NMN was a reliable instrument with the Cronbach's coefficient alpha of each dimension greater than 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 six scales measuring caregivers' 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). Additionally, the PedsQL FIM further explored two scales for primary caregivers reporting family functioning: daily activities (three items) and family relationships (five items). A five-point response scale is utilized (scale: 0 = never a problem; 4 = always a problem). The item scores were reversely graded and linearly converted into a 0-100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, 4 = 0) with higher scores indicating better functioning (or less negative impacts). In initial validation studies, PedsQL FIM scales demonstrated Cronbach's coefficient alpha scores > 0.70 [24].

Statistical analysis

Descriptive analysis was applied to describe the characteristics of the study population. Continuous variables were presented as means ± standard deviations (SDs), and categorical variables were shown as frequencies with percentages. Two independent samples t-test was used to compare the differences in the scores of QoL between two subgroups; while one-way ANOVA was used to compare the differences in the scores of QoL across more than two subgroups. In addition, we used the Cohen's effect size to assess the clinical relevance in terms of the between-groups difference. Effect size (Cohen's *d*) was calculated as: the absolute value of the difference in mean scores divided by the largest SD, and interpreted as (*d*): $0.2 \leq d < 0.5$ small difference, $0.5 \leq d < 0.8$ moderate, and $d \geq 0.8$ large [25].

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

Results

Characteristics of the study population

Table 1 presented the characteristics of socio-demographics andcharacteristics of disease and treatment of our study population. 101 caregivers with SMA children were involved in our study. 52 (51%) were female. All caregivers completed the PedsQL FIM questionnaire. Because the PedsQL NMM was only applicable for children aged from 2 to 18 years, a total of 87 caregivers completed NMM scale in our study. 46 (45.5%) patients were unable to sit alone; 39 (38.6%) able to sit alone but unable to walk alone; and 16 (15.8%) patients able to walk freely. 60 (59.4%) of patients had motor degeneration problems; 74 (73.3%) had skeletal deformity; and 23(22.8%) had a digestive system dysfunction. 39 (33.7%) patients sought for help regarding medical services, and 13 patients under multidisciplinary team (MDT) health management. Overall, 45(44.6%) of patients received exercise training in daily life; 26 (25.7%) received nutritional support; and 19 (18.8%) received respiratory support. Only two children in our study received scoliosis surgery, and nine children were using medication nusinersen.

Table 1
Participant demographics (n = 101)

Variable	*N* (%)
Child sex	
Male	49 (48.5)
Female	52 (51.5)
Child primary diagnosis	
SMA type I	26 (25.7)
SMA type II	56 (55.4)
SMA type III	19 (18.8)
Average age of SMA type (years)	Age range of SMA type (years)
SMA type I: 5.28	0.5–16.17
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 (0.17–15.5)
SMA type III	5.9 (1.0–13.67)
Mobility	
Non-sitter	46 (45.5)
Sitter	39 (38.6)
Walker	16 (15.8)
Motor degeneration	
No	41 (40.6)
Yes	60 (59.4)
Skeletal deformity	
No	27 (26.7)
Yes	74 (73.3)
Digestive system dysfunction	
No	78 (77.2)
Yes	23 (22.8)
Medical services	
No medical services	67 (66.3)
Medical services but not under MDT	21 (20.8)
Under MDT	13 (12.9)
Exercise training	
No	56 (55.4)
Yes	45 (44.6)
Respiratory support	
No	75 (74.3)
Yes	26 (25.7)
Nutritional support	
No	82 (81.2)
Yes	19 (18.8)

Variable	*N* (%)
Scoliosis surgery	
No	99 (98)
Yes	2 (2)
Nusinersen use	
No	92 (91.1)
Yes	9 (8.9)

Differences in quality of life scores of parents and children across SMA types

Table 2 presented the average scores of PedsQL NMM stratified by subtypes. Compared with the average total and domain scores in patients with SMA type I, the average total score and average scores of domains Neuromuscular disease and family resources were higher in patients with SMA type III (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, $p = 0.006$, $d = 0.74$). Compared with the average total and domain scores in patients with SMA type II, the average total score and average scores of domains Neuromuscular disease and family resources were higher in patients with SMA type III (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, $p < 0.001$, $d = 0.92$). There was no statistically significant difference in the average score of Communication domain across the three SMA subtypes.

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

Children's quality of life	SMA Type I Mean ± SD (*n* = 16)	SMA Type II Mean ± SD (n = 52)	SMA Type III Mean ± SD (*n* = 19)	Effect size *(d)*		
				□ *vs.*□	□ *vs.*□	□ *vs.*□
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**	**49.1 ± 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: ANOVA, analysis of variance; 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.						

Table 3 presented the differences in average scores of PedsQL FIM across SMA subtypes. The average total score and average domain scores of physical/emotional/social/cognitive functioning were higher in patients with SMA Type III compared with those in patients with type I or II ($p < 0.05$). The largest effect size was seen in the average domain scores of physical functioning when comparing parent self-reported physical functioning between subgroup type III and I ($d = 1.04$). There were no statistically significant differences in the above-mentioned average scores between type 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 Mean ± SD (*n* = 26)	SMA Type II Mean ± SD (*n* = 56)	SMA Type III Mean ± SD (*n* = 19)	Effect size *(d)*		
				□ *vs.*□	□ *vs.*□	□ *vs.*□
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: ANOVA, analysis of variance; 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

Table 4 presented the average score of PedsQL NMM and the difference across disease-specific characteristics. Children who were unable to walk alone and unable to sit and children who were able to sit but unable to walk were reported by their parents with relatively low total QoL score and low scores of

neuromuscular disease domain, and family resources domain compared with parents with patients who were able to walk independently ($p < 0.05$). Particularly, comparing children who were unable to sit nor walk with those who were able to walk, effect sizes were 1.19, 1.35 and 1.07 in terms of the differences in the average total score, the average score of neuromuscular disease domain and of family resources domain. The average total score, and the average scores of neuromuscular diseases domain and family resource domain were significantly higher in children without motor degeneration than those children with motor degeneration ($p < 0.01$); the effect size ranged from 0.29 to 0.64. The average total score, and the average scores of neuromuscular diseases domain and of family resource domain were significantly higher in children without motor skeleton deformity than those with skeleton deformity ($p < 0.05$); the effect size ranged from 0.46 to 0.49. The average total scores, the average score of neuromuscular disease domain and of family resources domain were higher among children with normal digestive system function than those with digestive system dysfunction ($p < 0.01$); the effect size 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						**Motor degeneration**			**Skeletal deformity**			**Digestive system dysfunction**	
Non-sitter ($n = 34$)	Sitter ($n = 37$)	Walker ($n = 16$)	Effect size *(d)*			No ($n = 33$)	Yes ($n = 54$)	Effect size*(d)*	No ($n = 21$)	Yes ($n = 66$)	Effect size*(d)*	No ($n = 70$)	Yes ($n = 17$)	Effect size*(d)*
			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**	**47.5 ± 15.8**	0.64	**57.67 ± 17.84**	**49.35 ± 15.48**	0.47	**54.2 ± 16.28**	**39.65 ± 10.77**
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	**57.56 ± 17.31**	**49 ± 16.83**	0.49	**54.52 ± 16.68**	**36.85 ± 11.48**
Communication	72.79 ± 28.89	69.82 ± 26.89	75 ± 30.28	0.10	0.07	0.17	76.77 ± 27.54	68.98 ± 28.2	0.28	73.41 ± 26.83	71.46 ± 28.61	0.07	71.07 ± 28.51	75.49 ± 26.59
Family resources	**34.56 ± 16.67**	**37.16 ± 23.99**	**59.38 ± 23.23[b,c]**	0.11	1.07	0.93	**46.67 ± 24.2**	**36.3 ± 21.44**	0.29	**49.52 ± 26.64**	**37.27 ± 21.02**	0.46	**43.29 ± 23.14**	**27.65 ± 17.69**

Abbreviations: ANOVA, analysis of variance.

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

Table 5 showed the average scores of PedsQL FIM across disease-specific characteristics and effect sizes. Parents with children who were unable to walk alone reported lower QoL in average total score and the average scores of physical, emotional, social, cognitive domains compared with those with children who were able to walk independently *(*$p < 0.05$); the largest effect size was 1.40 regarding the comparison between non-sitter and walker. The average score of physical and emotional domains were significantly lower reported by parents whose children had skeletal deformity than those whose children had no deformity ($p < 0.05$). Regarding digestive system dysfunction, the average total score and the average scores of physical, emotional, social, cognitive and daily activities domains were significantly lower among parents whose children had the dysfunction than those whose children did not have 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			Digestive system dysfunction Mean ± SD			
Non-Sitter (n = 46)	Sitter (n = 39)	Walker (n = 16)	Effect size *(d)*			No (n = 27)	Yes (n = 74)	Effect size *(d)*	No (n = 78)	Yes (n = 23)	Effect size *(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	0.35	**45.05 ± 19.63**	**29.92 ± 19.45**	0.77
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**	0.65	**50.37 ± 22.77**	**21.01 ± 23.25**	1.26
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 ± 23.0**	0.49	**41.15 ± 22.53**	**23.70 ± 26.94**	0.65
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	0.28	**42.15 ± 27.09**	**26.90 ± 25.45**	0.56
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	0.32	**51.22 ± 25.37**	**32.39 ± 22**	0.74
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	0.11	47.87 ± 27.01	37.32 ± 32.16	0.33
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	0.02	29.74 ± 22.75	27.83 ± 22.55	0.08
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	0.05	**38.35 ± 25.35**	**24.64 ± 20.79**	0.54
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	0.32	56.35 ± 22.94	47.61 ± 25.89	0.34

Abbreviations: ANOVA, analysis of variance.

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

Table 6 demonstrated the average scores of parent-reported QoL measured by PedsQL NMM. Regarding the exercise training, the average total score and the average score of neuromuscular disease were significant higher in children who had the training than those who did not have ($p < 0.001$); the effect sizes were 0.60 and 0.75, respectively. Regarding the respiratory support, the average total score and the average score of neuromuscular disease were significant lower in children who had the support than those who did not have ($p < 0.001$); the effect sizes were 0.57 and 0.79, respectively. Regarding MDT, significant differences in total score, neuromuscular disease, and family resources domain scores were seen between the MDT health management and control groups. Children accepted medical services but not under MDT were got significantly higher scores in total score, neuromuscular disease, and family resources domain than those without medical services ($p < 0.05$). And children under MDT have a significantly difference in total score, neuromuscular disease, and family resources domain than those without medical services groups ($p < 0.05$) or those accept medical services but not under MDT ($p < 0.05$). 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)	Effect size(d)		
N-MS *vs.* MS but not U-MDT	N-MS *vs.* U-MDT	MS but not U-MDT *vs.* U-MDT										
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]**	0.68	0.61	0.10
Neuromuscular disease	**45.38 ± 14.98**	**58.4 ± 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	0.65	0.47	0.19
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	0.09	0.28	0.30
Family resources	36.02 ± 17.02	45.66 ± 28.19	0.34	40.55 ± 23.45	39.35 ± 21.97	0.05	**33.1 ± 18.23**	**55.94 ± 25.44[a]**	**52.69 ± 25.38[b,c]**	0.90	0.77	0.13

Abbreviations: ANOVA, analysis of variance; N-MS: No medical services; Under MDT: U-MDT; Medical services but not under MDT: MS but not UMDT.

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.

[c]Post hoc significance between medical services but not under MDT and under MDT.

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.

.

Discussion

Our study found that quality of life of patients and caregivers differed across SMA types,disease-related and treatment characteristics. A significant difference among SMA types presented in the domain of neuromuscular diseases on the PedsQL NMM, with type III having the highest score and type I the lowest score. By contrast, Meaghann *et al.* found there was no significant difference among SMA types in the field 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 with SMA types II and I, patients with type III had significantly higher scores in family resources, which is in accordance with the previous study [22]. In contrast, our results showed there was no significant difference among SMA types in the communication domain. We infer that 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 further indicates that all members of Chinese society are concerned with children's health. In terms of the 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 indicating that SMA types reflect the physical function of patients. Additionally, we also found the effect sizes were large or moderate in different subtypes of SMA, which indicated that the differences in quality of life of patients has reached the threshold of clinical relevance, which worth attention from health professionals. And we found there is no statistical difference in neuromuscular disease domain between children with type I and type II, but the effect size was moderate, which indicated that there was a clinical difference in neuromuscular disease domain between children with type I and with type II.

Our results showed that the physical, emotional, societal, and cognition items in the Family Impact Module were effective for comparing patients with different types of SMA. Patients with SMA type III tend to have higher scores than the other two types, which is related to the patients' motor ability. The effect size SMA type III compared with type I and type II also indicated that there was a large clinical difference in the above functional domains. Most patients with SMA type III are able to walk alone, while patients with type II and type I cannot. However, because patients with type III can move their limbs freely and 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 patients with type III than patients with types I and II. Our research showed that there was no significant difference among SMA types in communication, worry, daily activities, and family relations domains, which may be caused by the characteristics of China's national social conditions, similar to the communication function 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, some complications such as skeletal malformation, digestive disorders, respiratory disorders, and motor function degeneration appear gradually. Our findings showed that the total score, neuromuscular disease score, and family score of PedsQL NMM were significantly lower in patients with these complications than in those without them. Our

results support the findings from previous study - that is, motor function is reduced in patients with skeletal deformities, which in turn affects all aspects of the patient's life [26]. Digestive disorders make malnutrition a higher risk in patients, which may cause fatal or serious disorders [27, 28]. The degeneration in motor ability and current movement ability can indirectly reflect the patient's survival condition, and all of the 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 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]. 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 patients' physical health, and reduces their caregivers' 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 the 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 to their own lives and increased stress on their own bodies, which in turn can lead to the onset of anxiety, fear, depression, and other physical or mental side-effects. In addition to the statistical significance, effect sizes in terms of the above-mentioned domains were moderate or large, which indicated disease-related characteristics may impact quality of life of patients and caregivers, which warranted attention from clinical professionals during their practice.

Our results suggest that clinical treatments improve QoL in patients with SMA from the caregivers' perception. Early exercise training is beneficial to improving the recovery of limb function, and muscle-strengthening activities help patients regain strength and stability [30, 31]. Various studies indicate that exercise training at the recovery stage can effectively lower the disability level of stroke patients with hemiplegia and improve their QoL [32–34]. They also suggest that exercise training can activate the motor neurons of the body to promote the recovery of and effectively improve the motor function of patients with neuromuscular degeneration disease, including Duchenne muscular dystrophy and SMA [33]. Studies have demonstrated that exercise training is safe and feasible, prolongs survival, diminishes muscle weakness, and enhances motor behavior [35]. While not statistically significant, we observed a strong trend for exercise training to greatly increase the neuromuscular disease and family resources scores. However, the effect size reflects that whether exercise training is carried out or not has a moderate difference in clinical works. This trend suggests that exercise training is 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.

Numerous studies have shown that the most common causes of death in patients with SMA involve respiratory complications [36, 37]. 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 [38]. However, our study suggests that patients with respiratory support have lower neuromuscular disease and family resources scores compared with those 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 as SMA is a progressive disease involving multiple system dysfunction, including respiratory complications, and patients with type I often die of respiratory failure. Based on our findings, we suggest that patients with SMA type I should adopt mechanical ventilation strategies early to maintain respiratory function effectively, preventing respiratory complications and pulmonary infections, and subsequently improving their QoL.

Recently, nusinersen became the first effective drug treatment for SMA available in China. As previous research noted, nusinersen treatment can improve the motor, respiratory, digestive, and other system functions in patients [39–42]. In our study, six caregivers of patients who were receiving nusinersen treatment complete the PedsQL NMM. Although the questionnaire results for these six patients showed that the neuromuscular diseases and family resource scores were higher than those of patients who did not use nusinersen, the caregivers of these six patients reported that drug treatment effectively improved the patients' QoL. We cannot make definite conclusions on whether their QoL was improved by nusinersen use because of 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 whether 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 and the new medical models and with the theories, techniques, and means of modern medicine and management [43]. Multidisciplinary management is composed of more than two related disciplines in order to implement clinical treatments for specific diseases [44, 45]. The results of this study showed that the total score of the PedsQL NMM for patients receiving multidisciplinary management 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. And the effect size between non-MDT management group and MDT group are moderate, combined the statistical difference were more confirmed reflects the 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, improving patients' daily life, reducing caregiver burden, and decreasing healthcare load [46–49]. 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.

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 the 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 there are few studies on the influence of clinical treatments on QoL in SMA. Considering the social, economic, and medical characteristics in China, which are different from other developed countries, the QoL survey of patients with SMA in China has become an interesting and emerging research field.

Our study had several limitations. First, the sample size included in this study is modest, reflecting the rarity of the disease, and the statistical effectiveness of our analysis is limited as well. A second limitation of this study is that patients were only sampled from central and east China. Given the lack of QoL survey data on patients with SMA in other regions, the study may not be representative of the QoL of patients with SMA across China. Nevertheless, our results may be generalized to patients from the areas mentioned above. Third, this study was a cross-sectional cohort study with data collected at a single time point, which precluded drawing conclusions regarding causality. Further, the study reflected the influence of disease-related characteristics on the QoL of children and the initial effect of medical measures only. Finally, although the PedsQL is designed to be used for all types of disease, it has not been specifically validated for proxy-reported use in children with SMA.

To sum up, further longitudinal follow-up of these patients should be conducted and QoL indicators should be used to investigate the effectiveness of clinical treatments for childhood SMA. Furthermore, future studies need larger sample sizes and should pursue multicenter enrollment to involve patients with SMA from all of China to obtain a database that reflects the QoL of patients across the country. In addition, with the continuous progress in the diagnosis and treatment of SMA, larger patient sample sizes, especially in the drug treatment group, should be included in subsequent studies to confirm the effectiveness of treatment approaches and to make the results more generalizable.

Conclusion

In summary, he more severe the SMA disorder was, the lower were the 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, improve patients' QoL, and 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; WHO: World Health Organization;

Declarations

Acknowledgement

We thanks all the patients and families for their contribution to this work. We also thank Mingjuan Jin for the contribution on the statistic methods and thank Bin Ma and Huanping Xing for the support of this work.

Funding

This work is supported by National Natural Science Foundation (81801490 & 81741076).

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.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Author details

[1]Department of Neurology, Children's Hospital, Zhejiang University School of Medicine, National Clinical Research Center for Child Health, Hangzhou 310052, China.

[2]School Public Health of Zhejiang University, Hangzhou 310000, China.

[3]Clinical Data Center, Guangzhou Women's and Children's Medical Center, Guangzhou 510000, China.

References

1. Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017;81:355-68.
2. Groen EJN, Talbot K, Gillingwater TH. Advances in therapy for spinal muscular atrophy: promises and challenges. Nature reviews. Neurology. 2018;14:214-24.
3. Schmalbruch H, Haase G. Spinal Muscular Atrophy: Present State. Brain Pathology. 2001;11:231-47.
4. Ahmad S, Bhatia K, Kannan A, Gangwan L. Molecular Mechanisms of Neurodegeneration in Spinal Muscular Atrophy. 2016;10:39-49.
5. Oskoui M, Kaufmann P. Spinal Muscular Atrophy. Neurotherapeutics. 2008;5:499-506.
6. Russman BS. Spinal Muscular Atrophy: Clinical Classification and Disease Heterogeneity. Journal of Child Neurology. 2016;22:946-51.
7. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. Lancet Neurol 2012;11:443-52.
8. Faravelli I, Nizzardo M, Comi GP, Corti S. Spinal muscular atrophy--recent therapeutic advances for an old challenge. Nat Rev Neurol. 2015;11:351-9.
9. Cynthia CJ, Suzanne FC, Jill J, Lisa B, Sandra PR, John S, et al. Spinal Muscular Atrophy (SMA) Subtype Concordance in Siblings: Findings From the Cure SMA Cohort. J Neuromuscul Dis. 2020;7:33-40.
10. 10. Shababi M, Lorson CL, Rudnik Schöneborn SS. Spinal muscular atrophy: a motor neuron disorder or a multi-organ disease? Journal of Anatomy. 2014;224:15-28.
11. 11. Hamilton G, Gillingwater TH. Spinal muscular atrophy: going beyond the motor neuron. Trends in Molecular Medicine 2013;19:40-50.
12. 12. Nash LA, Burns JK, Chardon JW, Kothary R, Parks RJ. Spinal Muscular Atrophy: More than a Disease of Motor Neurons? Curr Mol Med 2016;16:779-92.
13. 13. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders. 2018;28:197-207.
14. 14. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018;28:103-15.
15. 15. Grychtol R, Abel F, Fitzgerald DA. The role of sleep diagnostics and non-invasive ventilation in children with spinal muscular atrophy. Paediatric Respiratory Reviews. 2018;28:18-25.
16. 16. Takei S, Miyagi M, Saito W, Imura T, Inoue G, Nakazawa T, et al. Safety and Efficacy of Treatment for Scolios Is Secondary to Spinal Muscular Atrophy Fused to Lumbar 5 Level. Spine Surg Relat Res. 2018;2:294-8.
17. 17. Mehta NM, Newman H, Tarrant S, Graham RJ. Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy. Pediatr Neurol. 2016;57:80-3.
18. 18. Martinez Martin P. What is quality of life and how do we measure it? Relevance to Parkinson's disease and movement disorders. Movement Disorders. 2017;32:382-92.
19. 19. Vanleerberghe P, De Witte N, Claes C, Schalock RL, Verté D. The quality of life of older people aging in place: a literature review. Quality of Life Research. 2017;26:2899-907.
20. 20. Haraldstad K, Wahl A, Andenaes R, Andersen JR, Andersen MH, Beisland E, et al. A systematic review of quality of life research in medicine and health sciences. Qual Life Res. 2019;28:2641-50.
21. 21. Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients. Neuromuscular Disorders. 2017;27:428-38.
22. Hu J, Jiang L, Hong SQ, Cheng L, Kong M, Ye YZ. Reliability and validity for Chinese version of pediatric quality of life inventoryTM(PedsQLTM) 3.0 neuromuscular module. Journal of Chongqing Medical University. 2012;37:806-10.
23. 23. Chen RQ, Hao YT, Feng LF, Zhang YF, Huang The Chinese version of the Pediatric Quality of Life Inventory™ (PedsQL™) Family Impact Module: cross-cultural adaptation and psychometric evaluation. Health and Quality of Life Outcomes. 2011;9:16.
24. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edn. Hillsdale, New Jersey: L. Erlbaum; 1988.
25. 25. Weaver MS, Hanna R, Hetzel S, Patterson K, Yuroff A, Sund S, et al. A Prospective, Crossover Survey Study of Child- and Proxy-Reported Quality of Life According to Spinal Muscular Atrophy Type and Medical Interventions. J Child Neurol. 2020;35:322-30.
26. 26. Vai S, Bianchi ML, Moroni I, Mastella C, Broggi F, Morandi L, et al. Bone and Spinal Muscular Atrophy. Bone. 2015;79:116-20.
27. 27. Davis RH, Godshall BJ, Seffrood E, Marcus M, LaSalle BA, Wong B, et al. Nutritional Practices at a Glance. Journal of Child Neurology. 2013;29:1467-72.

28. 28. Mehta NMM, Newman HB, Tarrant SR, Graham RJM. Nutritional Status and Nutrient Intake Challenges in Children With Spinal Muscular Atrophy. Pediatric Neurology. 2016;57:80-3.
29. 29. Merlini L, Granata C, Bonfiglioli S, Marini ML, Cervellati S, Savini R. Scoliosis in spinal muscular atrophy: natural history and management. Dev Med Child Neurol. 1989;31:501-8.
30. 30. Veilleux L, Rauch F. Muscle-Bone Interactions in Pediatric Bone Diseases. Current Osteoporosis Reports. 2017;15:425-32.
31. 31. Coffey VG, Hawley JA. The molecular bases of training adaptation. Sports Med. 2007;37:737-63.
32. 32. Motl RW, Sandroff BM. Benefits of Exercise Training in Multiple Sclerosis. Current Neurology and Neuroscience Reports. 2015;15:1-9.
33. 33. Ng S, Manta A, Ljubicic V. Exercise Biology of Neuromuscular Disorders. Applied Physiology, Nutrition, and Metabolism. 2018;43:1194-1206.
34. 34. Case LE, Apkon SD, Eagle M, Gulyas A, Juel L, Matthews D, et al. exercise Management of the Patient With Duchenne Muscular Dystrophy. Pediatrics (Evanston).2018;142(Suppl 2):S17-33.
35. 35. Voet NB, van der Kooi EL, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease (Review. Cochrane Database of Systematic Reviews. 2019;12:CD003907.
36. 36. Mehta P, Melikishvili A, Carvalho KS. Neurological Complications of Respiratory Disease. Seminars in Pediatric Neurology. 2017;24:14-24.
37. 37. Boentert M, Wenninger S, Sansone VA. Respiratory involvement in neuromuscular disorders. Current Opinion in Neurology. 2017;30:529-37.
38. 38. Sansone VA, Pirola A, Albamonte E, Pane M, Lizio A, D'Amico A, et al. Respiratory Needs in Patients with Type 1 Spinal Muscular Atrophy Treated with Nusinersen. The Journal of Pediatrics. 2020;219:223-8.
39. 39. Corey DR. Nusinersen, an antisense oligonucleotide drug for spinal muscular atrophy. Nature neuroscience. 2017;20:497-9.
40. 40. Michelson D, Ciafaloni E, Ashwal S, Lewis E, Narayanaswami P, Oskoui M, et al. Evidence in focus: Nusinersen use in spinal muscular atrophy. Neurology. 2018;20:923-33.
41. 41. Darras BT, Farrar MA, Mercuri E, Finkel RS, Foster R, Hughes SG, et al. An Integrated Safety Analysis of Infants and Children with Symptomatic Spinal Muscular Atrophy (SMA) Treated with Nusinersen in Seven Clinical Trials. CNS Drugs. 2019;33:919-32.
42. 42. Pane M, Palermo C, Messina S, Sansone VA, Bruno C, Catteruccia M, et al. Nusinersen in type 1 SMA infants, children and young adults: Preliminary results on motor function. Neuromuscular Disorders. 2018;28:582-5.
43. 4 Swarthout M, Bishop MA. Population health management: Review of concepts and definitions. American Journal of Health-System Pharmacy. 2017;74:1405-11.
44. 44. Von Kodolitsch Y, Rybczynski M, Vogler M, Mir T, Schüler H, Kutsche K, et al. The role of the multidisciplinary health care team in the management of patients with Marfan syndrome. 2016;9:587-614.
45. 45. Brook J, McGraw C. Multidisciplinary perspectives: Application of the Consolidated Framework for Implementation Research to evaluate a health coaching initiative. Health & Social Care in the Community. 2018;26:e386-95.
46. 46. Auvin S, Bissler JJ, Cottin V, Fujimoto A, Hofbauer G, Jansen AC, et al. A step-wise approach for establishing a multidisciplinary team for the management of tuberous sclerosis complex: a Delphi consensus report. Orphanet J Rare Dis. 2019;14:91.
47. 47. Duis J, van Wattum PJ, Scheimann A, Salehi P, Brokamp E, Fairbrother L, et al. A multidisciplinary approach to the clinical management of Prader–Willi syndrome. Molecular Genetics & Genomic Medicine. 2019;7:e514.
48. 48. Abu-El-Haija M, Nathan JD. Pediatric chronic pancreatitis: Updates in the 21st century. Pancreatology. 2018;18:354-9.
49. Chan DS, Callahan CW, Moreno C. Multidisciplinary education and management program for children with asthma. Am J Health Syst Pharm. 2001;58:1413-7.