Investigation on the Current Situation and Health-Related Quality of Life of Children and adolescents with OI in southwest China

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Research

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Abstract

Background: Osteogenesis imperfecta（OI）is a chronic, non-infectious disease that accompanies the patient for life. OI will result in reduced bone mass, fractures, thereby leading to bone deformities and reduced patient the health-related quality of life (HRQoL). With the endocrine therapy and surgical orthopedic had been recommended, the disease was effectively controlled. The disease status is discrepancy in different regions. This study aims to assess the diagnosis and treatment status, evaluate the HRQoL of children and adolescents with OI in southwest China, and analyze the influencing factors, so as to provide reference for health care consideration for OI population in southwest China.

Methods: This cross-sectional study was performed using the Pediatric Quality of Life Inventory™ (PedsQL ™) to assess the HRQoL of children and adolescents with OI. The demographic and clinical data were collected. This study was conducted in Children's Hospital of Chongqing Medical University, the National Children's Regional Medical Centre (SOUTH-WEST) and the National Clinical Research for child health. Healthy children and adolescents aged 2 to 18 years lived in southwest China as a reference.

Results: A total of 27 children and adolescents with OI were included in this study. The current status of diagnosis and treatment such as the treatment, education, family, BMI, pain, steep walking and friends and so on had been investigated. The PedsQL™ of OI population was lower in all dimensions, and they were significantly different in physiological and social functioning and the total score, compared with 54 healthy children and adolescents. Factors associated with HRQoL of OI patients were the steep walking and fixing a playmate at less.

Conclusions: The HRQoL of children and adolescents with OI had been improved with the endocrine therapy and surgical orthopedic. But there was an imbalance around the world for the less effective management. Health care education should be more professional, effectively and continuously. Training patients to gain steep walking ability and peer companionship could be a way to improve the HRQoL of children and adolescents with OI in southwest China. The medical staff also should pay attention to their life and growth after discharge.

Background

Osteogenesis Imperfecta (OI), also known as Brittle Bone Disease, is an autosomal dominant genetic disease caused by gene mutation, and the incidence is 1/10000 to 20000[1]. OI has been defined as a rare disease in 2018 in China. The incidence has been calculated as 1.13/10000 by DISMOD Ⅱ model in eight provinces of China[2]. OI is a chronic non-communicable disease, and the main clinical manifestations are blue sclera, skeletal malformation, tooth dysplasia, etc. The main goals of the treatment are to decrease fracture incidence, relieve bone pain, and promote mobility and growth. These objectives require a multi-disciplinary approach, utilizing pharmacological interventions, physical therapy, orthopedic surgery, and monitoring nutrition with appropriate calcium and vitamin D supplementation. Bisphosphonate therapy has been proved beneficial in increasing bone mass, and to some extent reducing fracture risk[3]. The OI population have to face a high cost of treatment. The disease burden is 1.2 DALYs /1000000, the burden of disease is higher than the burden caused by death (disability adjusted life year, DALYs)[2].

With the improvement of disease treatment and management, the current situation of the diagnosis and treatment had been changed, and the quality of life (QoL) also had been improved. The HRQoL had been used as a subjective evaluation method for individuals with OI to evaluate the outcome of treatment[4]. The HRQoL was also essential for evaluation of patients' well-beings[1]. The HRQoL of children and adolescents with OI had been reported in some countries. HRQoL as a subjective evaluation index, there are differences among different regions and cultures. The research conclusion is only of reference significance. Different tools and methods had been used to assess the HRQoL, such as Inventory of Subjective Life Quality(ISLQ)[6], PedsQL[1][7], Pediatric Evaluation of Disability Inventory(PEDI)[8][9],

Functional Independence Measure for Children(WeeFIM)[10][11], Short From-36 for health(SF-36)[12],a quality report[13] and patient-reported outcomes(PROs)[14].

The aim of this study was to report the current situation of diagnosis and treatment, assess the HRQoL of children and adolescents with OI, and analyze the factors in southwest China. In order to reflect the actual situation, all the children and adolescents diagnosed with OI only were selected, no matter which treatment they had received or not. This has not been found in southwest China. It was helpful to summarize the current problems about the management of OI in southwest China. The HRQoL data of healthy children and adolescents in southwest China were used as a norm for comparison.

Methods

Participants

This was a cross-sectional study. Participants aged from 2 years to 18 years and diagnosed with OI only based on their medical records were recruited by convenience sampling between December 2018 to January 2020 in the Department of Orthopaedic and Endocrinology at Children's Hospital of Chongqing Medical University, the National Children's Regional Medical Centre (SOUTH-WEST), the National Clinical Research for child health. Informed consent was obtained from all participants.

Measures

Demographic information was obtained by a questionnaire. A lot of questions about these patients and their families were included, such as "the frequency of fracture in the past one year", "whether they have a pain in the last month and the location", "whether they had a fixed friend", "how about the step walking and education" and so on. Clinical information was achieved from the medical records.

HRQoL was evaluated by the Pediatric Quality of Life Inventory (PedsQL™ 4.0 Generic Core),which was approved by the author. This instrument consists of 23 items in four domains: physical functioning (8 items), emotional functioning (5 items), social functioning (5 items), and school functioning (5 items). The PedsQL Measurement Model consisted of developmentally appropriate forms for children aged 2–4,5–7,8–12, and 13–18 years old. Responses are used to calculate total, psychosocial health, and physical summary scores. Scores are summarized according to a statistical model established by the authors of PedsQL™4.0. They were expressed as transformed scores on a 0-100 scale, with higher scores indicating better HRQoL. The guardians filled out this questionnaire in this study.

Healthy children and adolescents aged from 2 to 18 years living in southwest China were taken as control. It was twice as large as the OI group. Two researchers checked clinical data twice.

Statistical analyses

Continuous data was described by mean and standard deviation. Categorical data were presented as counts and percentages. All statistical analyses were performed with SPSS version 22. Statistical significance was set at $p < 0.05$. The PedsQL score followed a nearly symmetrical distribution was analyzed by independent samples T test. Risk factors in OI group were analyzed by the single factor (the independent sample T test) and the multiple factor analysis (Logistic regression).

Results

A total of 27 children and adolescents with OI and 54 healthy children and adolescent from 2 to 18 years old coming from southwest of China were included in this study. The mean ages and sex distributions did not differ significantly between the two groups (Table 1). The mean age of the OI group was 10.00 ± 3.53 years compared to 9.11 ± 3.88 years in control group.

Table 1
Demographic characteristics for OI and control groups

	OI group	Control group	*t*	*P value*
Age (mean ± SD)	10.00 ± 3.53	9.11 ± 3.88	1.033	0.306
2–4 years(n)	2(7.41%)	9(16.67%)		
5–7 years(n)	4(14.81%)	9(16.67%)		
8–12 years(n)	16(59.26%)	26(58.15%)		
13–18 years(n)	5(18.52%)	10(18.52%)		
Sex			0.477	0.636
Male(n)	16(59.26%)	33(61.11%)		
Female(n)	11(40.74%)	21(38.89%)		
P value is derived from independent sample Student t test statistic.				

The demographic and clinic characteristics of OI populations

The sample was composed of 27 children and adolescents with OI. The demographic characteristics is summarized in Table 1 and Table 2. In this study,18(75%) school-age patients went to school;6(25%) school-age patients dropped out of school. 25(92.59%) were taken care of by their parents; 2(7.41%) were their grandparents. In China, a nuclear family consisted of parents and children; a joint family consisted of parents, children and grandparents; a single parent family consisted of one parent and children.13(48.15%) had only one child or adolescent in their family;19(70.37%) had a friend at less. 3(11.11%) did not had any treatment, because in their parents' opinions, OI could not be cured; 15 (55.56%) had received endocrine therapy regularly; 21(77.78%) had received surgical therapy in their long bone; 9(33.33%) had received both endocrine and surgical therapy. 10(37.04%) guardians had not finished the nine-year compulsory education.13(48.15%) could walk on their feet;14(51.85%) could move with an assistance device, but 3 didn't have a professional device. The OI patients were generally shorter and thinner than their peer. In comparison to Chinese norms published in 2005,23(85.19%) were below median height,13(48.15%) were below median weight, 13(48.15%) had a median weight, 17(62.96%) had normal BMI, 5(18.52%) were overweight and 5(18.52%) were fat. 4(14.81%) suffered from pain without a fracture in the past one month. 10(37.04%) have suffered from a fracture in the past one year. 19(70.37%) did not have a systematic functional exercise. 11(40.70%) did not receive a regular outpatient.

Table 2
Clinic characteristics of OI populations (n = 27)

Variables	*N* (%)
Education	
School(>6yesrs)	18(66.67)
Dropout(>6yesrs)	6(22.22)
Self-study(3-6years)	3(11.11)
Guardian	
Parents	25(92.59)
Grandparents	2(7.41)
Homestyle	
Nuclear family	20(74.08)
Joint family	6(22.22)
Single parent family	1(3.70)
The status of treatment	
Sodium pamidronate	15(55.56)
Surgical therapy	21(77.78)
No treatment	3(11.11)
Education of caregivers	
Undergraduate education	1(3.70)
Senior high school	6(22.22)
Junior high school	10(37.04)
Primary school	10(37.04)
Step walking	
Walk on feet	13(48.15)
Walk with an assistance device [a]	14(51.85)
High [b]	
-3SD	15(55.57)
-2SD	4(14.81)
-1SD	4(14.81)

[a] 3 of them did not purchase a professional device, a chair replaced professional device.

[b] Height, weight and BMI were relative to Chinese norms which has was published in 2005

[c] Pain in the last one month without a fracture

Variables	*N* (%)
Median	4(14.81)
Weight [b]	
-3SD	5(18.52)
-2SD	4(14.81)
-1SD	4(14.81)
Median	13(48.15)
+ 1SD	1(3.70)
BMI [b]	
Normal	17(62.96)
Over weight	5(18.52)
Fat	5(18.52)
Pain in the last month [c]	
YES	4(14.81)
NO	23(85.19)
Regular functional exercise	
YES	8(29.63)
NO	19(70.37)
Regular outpatient	
YES	16(59.26)
NO	11(40.70)
Fracture in the past one year	
YES	10(37.04)
NO	17(62.96)
Single-child family	
YES	13(48.15)
NO	14(51.85)
Fixed a playmate at less	
YES	19(70.37)

[a] 3 of them did not purchase a professional device, a chair replaced professional device.

[b] Height, weight and BMI were relative to Chinese norms which has was published in 2005

[c] Pain in the last one month without a fracture

Variables	*N* (%)
NO	8(29.63)
Treatment	
No therapy	3(11.11)
endocrine therapy	15(55.56)
surgical therapy	21(77.78)
[a] 3 of them did not purchase a professional device, a chair replaced professional device.	
[b] Height, weight and BMI were relative to Chinese norms which has was published in 2005	
[c] Pain in the last one month without a fracture	

The HRQoL between the two groups

OI patients had lower HRQoL. There were significant differences between physical functioning, social functioning and the total scores. (Table 3).

Table 3
Comparison of PedsQL ^{TM} 4.0 scores between two group

PedsQL™ score	OI group	Control group	P
physical functioning	39.59 ± 24.54	82.16 ± 12.84	0.000*
emotional functioning	69.26 ± 21.02	71.67 ± 16.92	0.590
social functioning	64.62 ± 23.23	83.54 ± 12.71	0.001*
school functioning	64.05 ± 17.37	68.95 ± 15.91	0.233
Total	55.30 ± 19.15	77.25 ± 11.46	0.000*
Data are presented as mean ± standard deviation.			
*the level of significant set was <0.05			

The Factors Affecting The Hrqol Of Oi Populations

All the clinic characteristics were taken as the grouping factors for monofactor analysis. Step walking, pain in the last month, and fixed a playmate at less were proved to be have a negative effect on the HRQoL in the independent sample T test. Monofactor analysis showed that step walking affected physiological function; step walking and fixing a playmate at less affected emotional function; step walking, pain in the last month, and fixing a playmate at less affected social function; pain in the last month affected school function. The total score had a relationship with step walking and fixed a playmate at less ($P < 0.05$), in Table 4.

Table 4

The monofactor analysis for clinic variables in PedsQL™ scores

PedsQL ™ domain variables	Score		P
	NO	YES	
physical functioning			
Step walking	26.79 ± 18.17	53.37 ± 23.47	0.003*
Pain in the last month	42.53 ± 24.31	22.66 ± 20.94	0.138
Fixed a playmate at less	29.69 ± 25.39	43.75 ± 23.62	0.179
emotional functioning			
Step walking	60.00 ± 18.71	79.23 ± 19.24	0.014*
Pain in the last month	69.56 ± 19.94	67.50 ± 30.14	0.860
Fixed a playmate at less	52.50 ± 20.70	76.32 ± 17.15	0.005*
social functioning			
Step walking	51.92 ± 23.23	77.31 ± 15.36	0.003*
Pain in the last month	68.86 ± 20.46	41.25 ± 26.58	0.025*
Fixed a playmate at less	43.57 ± 23.75	72.37 ± 18.06	0.003*
school functioning			
Step walking	58.33 ± 17.68	68.33 ± 16.56	0.199
Pain in the last month	68.24 ± 14.25	46.25 ± 20.16	0.028*
Fixed a playmate at less	54.00 ± 21.62	67.19 ± 15.27	0.142
Total			
Step walking	44.29 ± 15.42	67.15 ± 15.59	0.001*
Pain in the last month	57.65 ± 18.07	41.75 ± 22.25	0.128
Fixed a playmate at less	40.75 ± 18.79	61.42 ± 16.08	0.008*
Data are presented as mean ± standard deviation.			
*the level of significant set was <0.05			
Variable that were significant at a P value of < 0.05 in the monofactor analysis were selected for the Multiple linear regression analysis. It showed that step walking and fixing a playmate at less were the influencing factors of the total HRQoL (P < 0.05), in Table 5.			

Table 5
The multiple stepwise regression analysis for step walking, pain in the last month, and fixed a playmate at less in PedsQL™ scores

variables	*B*	*SE*	*β*	*t*	*P*
Step walking	18.067	5.864	0.480	3.081	0.005*
Pain in the last month	-7.739	8.006	-0.146	-0.967	0.344
Fixed a playmate at less	13.608	6.408	0.331	2.124	0.045*
*the level of significant set was <0.05					

Discussion

To reflect the HRQoL, the actual diagnosis and treatment status of the OI populations in southwest China. All the patients with OI under 18 years old were included. Only one OI child suffered from kidney stones caused by melamine-tainted milk powder was excluded. Published studies have used different tools to assess the HRQoL in children and adolescents with OI, such as the PedsQL^{TM}4.0, PEDI, WeeFIM, ISLQ, Form-36, The EQ-5D-5L, and a qualitative research. There was no specialist scale for OI. To make a comparison with healthy populations, a lot of studies had used PedQoL^{TM}4.0 to assess the HRQoL in OI populations around the world.

Low educational level and their family

Dropping out of school would be an important reason for the low educational level, which could lead to a discriminated in employment and a low income in OI adult populations. In a 2013 report of China, the education level of OI adults are generally low, accounting for 13.5% of college degree or above[15]. In this study, all the preschool children with OI did not go to kindergarten as usually. One quarter (6/24) of school-age OI patients had dropped out for the self and external factors. Some parents of OI rejected to go to school for safety or hospitalization. In their opinions, children are prone to a fracture without their supervision. Some of them had been rejected by the school. Adopting a student with OI would increase the teaching cost due to added accessible facilities or accidents. Low education would reduce the employment opportunities for OI adults. A survey of the OI population in China shows that OI adults are discriminated in employment and have low incomes, with the exception of self-employment[15]. People with OI mostly engage in simple work and have low income, while self-employed people have high income [15].

Low education of parents made it more difficult to understand this disease, ignored the severity of OI, thus it would limit the treatment of disease. Education level of OI patients' caregivers was under the average in China. Compared with the data in 2019 China Yearbook[16]. 34.03% were senior high school vs 22.22% in OI population, 14.95% were junior high school vs 37.04% in OI population, 14.14% were primary school vs 37.04% in OI population. Compared with the Song's study conducted in Beijing[4], 34.8% were University and above vs 3.70% in this study, 22.6% was senior high school vs 22.22% in this study, 39.1% were junior high school vs 37.04% in this study, 3.5% were primary school vs 37.04% in this study. The lack of genetic knowledge about OI could lead to a family cluster. In this study, 2 families have more than 2 kids with OI, because their parents did not know OI could be inherited by birth. In Song's[4] study conducted in Beijing, the patients receiving endocrine therapy was more (77% vs 55,56%) than that in this study, whether the patients receiving surgical correction was not been reported, this was 77.78% in this study. The patients with guardian in low education level or a lack of disease information would decrease their opportunities to get the standardized treatment. A lot of guardians whose children and adolescents did not have the endocrine therapy complained a lack of the information about the endocrine therapy in this study. Health care education and management of diseases are important for OI families, especially in low education and marginal areas.

Families play an important role in chronic disease management. In this study, 92.59% were taken care of by their parents, 3.7% lived in a single family with his mother divorced for the disease. 74.08% lived in a nuclear family, 22.22% lived in a joint family. 51.85% had more than one kid in their family. Children and adolescents with OI need to be taken care of by at least one person throughout the daily life. This had led to a reduction in household income. The lack of money would interrupt the treatment, which could aggravate the severity of OI. The more severity of the disease would lead to more cost of treatment, even give up, or give birth to a second or third child in their family. Patients with severe phenotypes had poorer HRQoL values than those with mild OI[1]. It is particularly important to establish a correct concept of disease management.

Walking ability, Height, Weight, BMI, dietary habit

With a regular treatment, OI patient could regain their walking ability. It was more difficult to have an assistant device in rural areas, especially an assistant device with suitable size for younger. Children and adolescents with OI were shorter and thinner, with a trend towards obesity for a lack of exercise. Childhood obesity creates a situation where bone is unable to fully adapt to the stresses placed upon it[17].The linear growth patterns, in addition to the marked increase in weight over time, indicate a need for lifestyle modifications early in childhood, especially a need for weight control. Further definition of the anthropometric measures in OI enables patients to begin modifications as early as possible[18]. OI limits the activity of the patients, thus controlling their weight from the diet. Chinese with a diet of carbohydrates, it is necessary to adjust the diet structure, reducing the intake of carbohydrates and increasing the intake of high-quality protein, fresh fruits and vegetables. Surgery to control weight had been reported. Weight loss surgery effectively treated severe obesity in 2 OI patients and substantially improved mobility and HRQoL, theoretically reducing fracture risk[19]. Moderate exercise is recommended for OI populations, such as swimming and walking. Feasible exercise without accident was difficult for OI children. A customized rehabilitation for muscular strengthening and walking was necessary for OI patient in different stage of illness.

Treatment

The treatment of the disease improved over time. 50% and 36.5% of patients had received endocrine therapy and physiotherapy in a study in southern Brazil in 2018[1]. In a report of China in 2012[15], 34.9%,34.9% and 5.3% had received endocrine therapy, surgical therapy, and physiotherapy, and 41% did not receive therapy. The status of treatment is related to the cognition of doctors and patients' families. In these opinions of these families with the patients without any treatment, OI could not be cured, it was no need to relieve the symptoms. Patients who only received endocrine therapy was informed that there was no need to receive surgical therapy. And the parents of OI patients received surgical therapy only did not know about the endocrine therapy. Failure to achieve the therapeutic effect expected by their families and lack of information about OI would reduce the treatment compliance. Families with insufficient understanding of diseases have serious misconceptions about the treatment of diseases. The following misconceptions about OI were mentioned frequently. Such as, “no fresh fracture, no regular outpatient”, “no walking, no fracture”, “There was no need to receive any treatment, if there was no severe fracture, because OI could not be cured, ,”.

In comparison to the medical and surgical therapy, the physical therapy needed to be improved. A lack of professional tools and guidance personnel, or too young to comply physical therapy were always mentioned by their parents. Physical therapy programs and equipment for younger children need to be available.

The HRQoL of children and adolescent with OI

As far as we know, there are litter study focusing on the HRQoL of children and adolescents with OI.As reported by Fano and Vanz, patients with OI had impaired physical functioning in HRQoL, and patients with severe phenotypes had poorer

HRQoL values than those with mild OI[1].Bone pain, scoliosis, and activity limitations were postulated to be related to worse physical QOL scores[20]. In a qualitative study about the QOL in children and adolescents with OI, six main themes were identified, being safe and careful, reduced function, pain, fear, isolation, independence[13]. Physical functions were significantly impaired in OI patients, and the disease severity was correlated to HRQoL scores. The physical functions were positively correlated to family income, height Z-score, BMD Z-score at the LS and FN, and negatively correlated to disease severity and fracture frequency in OI patients[7]. For adult, individuals with OI have worse symptom burden and functioning, the scores from most domains differ significantly from the general US population by the Patient-Reported Outcome Measurement Information System (R) (PROMIS (R)[14].

In our study, associated with healthy populations, the HRQoL was lower in all latitude and total score, and the differences in physiological and social functioning and total score were statistically significant. In another study, the HRQoL of OI children were lower than that of healthy children in all latitude and total score, and the differences in all latitude and total score were statistically significant[4]. Patients with severe phenotypes had poorer HRQoL values than those with mild OI[1]. With the proper treatment, the severity of OI had been effectively reduced, the HRQoL had been improved.

Pain

What is known: Pain remains a major issue in OI population. Pain has a negative impact on the HRQoL. But in this study, as the consequence of the multiple-factor analysis, pain caused not by a fracture in the past month did not affect the HRQoL of children and adolescents with OI. “No fracture, no pain” always been talked in OI families. Only 4 of 27 patients had experienced chronic pain in the past one month, pain had been located in the extremities, joints and lower back. One child did not point the location of pain. The proportion of pain was lower than other studies for many reasons. In the study, three of them who experience pain in the last month had surgical orthopedic only, while one of them had endocrine therapy only. The endocrine therapy also had been proved to relieve pain[21]. Compared with another study,19 of 44 patients could feel pain in the past one month, and the multiple linear regression analysis showed that pain score was statistically associated with all PedsQL domains except schooling[1].The different definitions of pain could lead to different findings. In their study, pain means chronic and acute pain. In this study, pain means chronic pain. Children and adolescents with OI experience pain intensity that is mild, yet complex in quality and localized across several body areas[22]. There was no standard method of assessing pain in children and adolescents with OI[23].Children and adolescents at different ages expressed pain differently. Younger children talked about pain in terms of “ouchys” and things “hurting”; older children described pain, hurt and ache, often relating to fractures, but occasionally just the general aches and experience by people with OI[13]. With the chronic pain control is necessary to improve the QOL of OI adults[24],the management of chronic pain was important.

Steep Walking

In the multi-factor analysis, whether a patient was able to walk on feet affected the HRQoL in all domains except school functioning. Fractures aggravate bone deformities and affected the walking ability. Whether there is a fracture in the past one year could not reduce the HRQoL of OI children and adolescents. A study found a negative correlation between HRQoL and number of fractures in OI patients[4].Multiple fractures could lead to bone deformities, which would reduce the steep walking ability. A negative association was observed between hypotonia, number of fractures, and independent walking[25]. It always took more time for OI patients to regain walking ability after lower limb long-bone fracture. The relative risk of fractures generally declines with age[26]. Avoiding fractures was more important in childhood. Avoiding fractures and restoring the ability to steeping independently was of equally important. The presence

of impaired bone and muscle in OI leads to a continuous cycle of altered muscle–bone crosstalk with weak muscles further compromising bone and vice versa[27].

Fixing a playmate at less

Fixing a playmate at less was a factor which affected the total score and the social and emotional function of the HRQoL. This was firstly been found in the HRQoL of children and adolescents with OI. Fixing a playmate at less was an objective evaluation index to be measured more easily in clinic. Being able to rank reciprocal friendships, and that having more than one reciprocal friendship increases HRQoL, are important and could be beneficial for developing programs that promote high HRQoL, hence preventing possible maladjustments in a long-term perspective[28].Whether the children and adolescents with OI are the only child of their family had no significant influence on the HRQoL. Kinship was no substitute for friendship. It was easier for a child or adolescent with OI to fix a playmate at less in the schoolyard or neighborhood. School attendance always be associated with the ability to walk independently for children and adolescents with OI.

To sum up, the current status of diagnosis and treatment of OI had an imbalance around the world. In the southwest China, the health care for OI population should be improved, especially for their life and growth after discharge, and the communication with their peers. Training patients to gain steep walking ability and peer companionship could improve the HRQoL of children and adolescents with OI.

Abbreviations

OI
Osteogenesis imperfecta
QOL
Quality of life
PedsQL
the Pediatric Quality of Life Inventory
HRQOL
the health related quality of life
ISLQ
Inventory of Subjective Life Quality
PEDI
Pediatric Evaluation of Disability Inventory
WeeFIM
Functional Independence Measure for Children
SF-36
Short From-36 for health
PROs
patient-reported outcomes
DALYs
disability adjusted life year,

Declarations

Ethics approval and consent to partcipate

The Ethics Committee of Children's hospital of CHONGQING Medical University approved the study and all participants gave written or oral informed consent.

Consent for publication

Not applicable.

Availability of supporting data

The datasets generated and/or analyzed during the current study are not publicly available due to the institution's policy, but are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Conception and design: MO lin, DU Fanyan; acquisition of data: DU Fanyan; data analysis: DU Fanyan; Data interpretation: DU Fanyan; drafting the manuscript: MO lin, DU Fanyan; revising manuscript critically: DU Fanyan; given final approval of the version to be published: MO lin, DU Fanyan; Agreed to be accountable for all aspects of the work: MO lin, DU Fanyan. All authors read and approved the final manuscript.

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Declaration of Conflicting Interest

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