Measuring parent proxy-reported quality of life of 11 rare diseases in children in Zhejiang, China

Qisheng Gao (mooshaa@163.com)
Hangzhou medical college https://orcid.org/0000-0002-8347-2577
Shanshan Wang
Departement of Health Management, School of Medicine,Hangzhou Normal University
Jianping Ren
Department of Health Management,School of Medicine,Hangzhuo Normal University
Xin Wen
Center for medical science,technology and education of Zhejiang Province

Research

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Abstract

Background: It becomes increasingly important to measure the health-related quality of life (HRQoL) of rare diseases in children and adolescents in recent decades. Much attention has been paid to investigate the HROoL of one specific rare disease by self-report in previous studies. This study aimed to evaluate and compare the HROoL of 11 rare diseases in Chinese children by parent proxy-report, to explore the factors associated with HROoL of patients and to know the problems of most concern.

Methods: A total of 651 children aged from 2 to 18 were enrolled from the Children's Hospital Affiliated Zhejiang University in 2018. Their parents completed the parent proxy-reports version of the Pediatric Quality of Life Inventory™ 4.0 (PedsQL™). Independent samples *t*-test, one-way ANOVA, or Kruskal-Wallis *H* test was used to compare HROoL scores between groups. Multilevel linear regression models with random intercept were applied to analyze the relationship between socioeconomic variables and both the total score and sub-domain scores.

Results: The total PedsQL scores of Patent ductus arteriosus, Infantile agranulocytosis, Autoimmune thrombocytopenia, Polysyndactyly, Hirschsprung disease, Cleft lip and palate, Tetralogy of fallot, Myasthenia gravis, Guillain-barre syndrome, Glycogen storage disease, and Langerhans cell histiocytosis children were 79.65±5.46, 95.88±3.48, 71.39±3.27, 91.77±6.35, 76.18±6.92, 96.33±4.22, 77.85±8.90, 95.99±3.31, 85.77±4.56, 82.97±4.13 and 77.6±5.15, respectively. Age was significantly associated with physical functioning, school functioning, and psychosocial health score. Gender and The household registration place was significantly associated with the overall score. The most urgent desire of patients was reducing the overall medical costs.

Conclusions: These data show that Patent ductus arteriosus scores lowest in physical functioning, Autoimmune thrombocytopenia (ITP) ranks the lowest in the emotional functioning score, social functioning score, school functioning score, psychosocial health score, and total score. Incentive policies should be further taken to improve orphan drug availability and reduce the financial burden of rare diseases.

Background

Rare diseases, also known as "orphan diseases", refer to diseases with a low prevalence but which are seriously debilitating or even life-threatening[1] There is no universal definition of rare diseases worldwide. Different countries or regions have distinct definitions depending on disease incidence or prevalence, the severity of the disease, and the existence of adequate treatments or drugs. The average prevalence threshold used to define rare diseases across different organizations within individual jurisdictions ranged from 5 to 76 cases/100,000 people, with a global average prevalence threshold of 40 cases/100,000 people[2]. In China, rare diseases have not been officially defined until now. In 2010, experts in the seminar held by the Chinese Society of Genetic Medicine of the Chinese Medical Association reached a consensus that a rare disease is defined by a prevalence of less than 1/500,000 or neonatal morbidity of less than 1/10,000. It is estimated to exceed 16.8 million rare disease patients in China with a population of 1.4 billion according to this prevalence[3]. There are an estimated 6000–8000 rare diseases globally[4], and 75% of rare diseases affect children, 30% of rare diseases patients die before the age of 5[5]. In 2018, the National Health Commission of China and other 4 government departments jointly formulated and published *China's First List of Rare Diseases*, which included 121 rare diseases[6], the onset age of 43 rare diseases are during an infant and child's stage, such as Albinism, Angelman syndrome, Arginase deficiency and so on. Most rare diseases are the result of small genetic changes and severely impair physical, emotional, and mental abilities. These disabilities can decrease the quality of life considerably and cause a tremendous burden on the affected families and health care systems[7]. In recent decades, it has become increasingly important to measure the health-related quality of life (HRQoL) of rare diseases in children and adolescents. Generic instruments and disease-specific instruments may be applied to measure HRQoL in children and adolescents with the same rare diseases[8]. The generic instruments can measure HRQoL domains universally important across diseases and can be used in different populations or diseases[9]. Among generic instruments, the Pediatric Quality of Life Inventory™ (PedsQL™) was one of the widely used instruments in young people[10]. To evaluate patients' HRQoL, many previous studies on rare diseases randomly chose healthy controls subjects for comparisons[11-14]. However, there is a paucity in the literature documenting differences in HRQoL among different rare diseases.

The main purpose of this study was to evaluate and compare HRQoL by surveying parents of children with 11 different rare diseases aged between 2 to 18 years using PedsQL™ instrument which can assess the domains outlined by the WHO[15], to identify the association between potentially confounding factors on HRQoL summary scores and to know the problems of most concern of patients.

Methods

Participants and procedures

The study was a cross-sectional, observational study performed at the Children's Hospital Affiliated Zhejiang University in 2018. We signed a confidentiality agreement with the hospital that the patient's information would be kept strictly confidential. Patients diagnosed with rare diseases included in the *List of Rare Diseases in the European Union* between 2013 to 2017 were recruited from the hospital [16]. The criteria for inclusion were as follows:1) The age of patients were between 2 to 18 years; 2)The patients were diagnosed with no other diseases severely affecting quality of life;3)The parents were capable of understanding and expressing normally; 4)Consent of parents. The exclusion criteria were: 1)Patients were younger than 2 years or older than 18 years at the time of interview; 2) Patients had other unrelated serious diseases. The parents were informed of the purpose, significance and main content of the investigation orally before the telephone interview, and asked for their consent. The investigators were trained before the interview by the project manager to be very familiar with the questionnaire and using the normative expression. Besides, the investigators were responsible for ensuring there were no missing data or logical errors in the questionnaire.

Instruments

The Pediatric Quality of Life Inventory™ 4.0 (PedsQL™), which includes parallel child self-reports(age range 5-18 years) and parent proxy-reports(age range 2-18 years) is a reliable, valid and sensitive instrument which is widely used to assess HRQoL among the healthy and patient population[17,18]. While child self-reports should be considered the gold standard for measuring HRQoL, there may be circumstances when the child is unable to complete a questionnaire directly themselves due to energy or cognitive impairment or the disease-specific instruments are not available, and parent proxy report may be one strategy to assess HRQoL of a child or adolescent[19,20]. The items for child self-reports and parent proxy-reports are essentially consistent, except that they are different in the developmentally appropriate language and first or third person tense [17,21]. Previous empirical studies confirmed the validity of parental reports[22,23]. Besides, it is generally the parents' perceptions of their children's HRQoL that influences healthcare utilization [24,25]. In this study, the Chinese parent proxy-reports version of the PedsQL™ 4.0 which has been validated for Chinese children was applied to evaluate children's quality of life [26-29]. This scale was composed of 23 items which divided into 4 dimensions, Physical Functioning(8 items), Emotional Functioning(5 items), Social Functioning(5 items) and School Functioning(5 items), The latter 3 dimensions can also be united and called psychosocial health. Each item was scored using a 5-point response scale where 0=never a problem,1=almost never a problem,2=sometime a problem,3=often a problem,4=almost always a problem. Items were reverse-scored and linearly transformed to a score on a 0-100

scale(0=100,1=75,2=50,3=25,4=0) with higher scores indicated better HRQoL. Scale scores are computed as a sum of the items divided by the number of items answered. If more than 50% of the items in the scale are missing, the scale score is not computed. The physical, emotional, social, school, psychosocial, and total scale scores were used in this report. In addition to PedsQL™, all parents were required to complete a brief questionnaire concerning children's socio-demographic characteristics, e.g. gender, age group, household registration place, household type, and monthly family income per capita.

Statistical analysis

Categorical data were presented as counts and percentages. Quantitative data were described by the mean and standard deviation. The distribution of the HRQoL scores was tested for normality using the Shapiro-Wilk test. Comparisons between two groups were made using independent t-test. When there were more than two groups, differences were assessed using one-way ANOVA and Kruskal-Wallis *H* test depending on the homogeneity of variance. Dunn's post hoc test or least significant difference test(LSD) was used for multiple comparisons~~ in types of rare diseases~~. The multilevel linear regression models with random intercepts were applied to analyze the relationship between socioeconomic variables and both the total score and sub-domain scores. Initially, a model was estimated with the intercept only, to estimate the proportion of variance due to the diseases concerning the individuals. This model served as the basis for evaluating the reduction in the variance of the other models studied. After this, individual socioeconomic variables were tested. The two-tailed P <0.05 was considered to be statistically significant. Data were processed and analyzed using R 3.6.1 for windows.

Results

Participants' characteristics

A total of 651 children's parents completed the questionnaire. The socio-demographic characteristics of their children were presented in Table 1. The most frequently presenting rare disease was Autoimmune thrombocytopenia (18.4%). Among the children, 373(57.3%were male, 310 (47.6%) aged between 2 to 4 years, 474(72.8%) came from urban areas, 288(44.2%) of the monthly family income per capita less than 5000 CNY. The children came from 9 different cities in Zhejiang province, which were Hangzhou 350(53.8%),Ningbo105(16.1%),Shaoxing67 (10.3%),Wenzhou25 (3.8%),Jinhua51 (7.8%), Lishui10 (1.5%),Quzhou29 (4.5%),Taizhou11 (1.7%),Zhoushan3 (0.5%). The 8 cities except for Hangzhou which is the capital city were integrated into one group due to the discrepancy of sample size in different cities.

Table 1 Socio-demographic characteristics of the total participants

Variables	Frequency（%）
Types of rare diseases	
Patent ductus arteriosus	40(6.1)
Infantile agranulocytosis	67(10.3)
Autoimmune thrombocytopenia	120(18.4)
Polysyndactyly	66(10.1)
Hirschsprung disease	118(18.1)
Cleft lip and palate	51(7.8)
Tetralogy of fallot	56(8.6)
Myasthenia gravis	42(6.5)
Guillain-barre syndrome	33(5.1)
Glycogen storage disease	30(4.6)
Langerhans cell histiocytosis	28(4.3)
Gender	
Male	373(57.3)
Female	278(42.7)
Age group	
2-4 year	310(47.6)
5-7 year	220(33.8)
8-12year	103(15.8)
13-18 year	18(2.8)
Household registration place	
Hangzhou	350(53.8)
Other cities	301(46.2)
Household type	
Urban areas	474(72.8)
Rural areas	177(27.2)
Family monthly income per capita	
￼5000	288(44.2)
￼5000-￼10000	259(39.8)
￼￼10000	104(16.0)
Total	651(100)

PedsQL^{TM} scores of children

Univariate analysis of categorical variables relative to PedsQL total score and sub-domain scores were summarized in Table 2. There were significant differences on the total scale and each subscale in different rare diseases, household registration place and monthly family income per capita(all P<0.05).Patent ductus arteriosus was significantly lower in the physical functioning score than Infantile agranulocytosis, Polysyndactyly, Hirschsprung disease, Cleft lip and palate and Myasthenia gravis(all P<0.05). Autoimmune thrombocytopenia was significantly lower in the emotional functioning score, school functioning score and total score than other rare diseases except for Langerhans cell histiocytosis(all P<0.05). Autoimmune thrombocytopenia was significantly lower in the social functioning score than other rare diseases except for Hirschsprung disease(all P <0.001). Autoimmune thrombocytopenia was significantly lower in the psychosocial health score than other rare diseases(all P<0.001). Females reported significantly higher scores than male in the physical functioning(t=-3.29, P=0.001) and total score(t=-2.43, P =0.015). The 2-4 year group was significantly higher than 8-12 year group in the emotional functioning(t=2.917, P=0.004). The 2-4 year group was significantly higher than the 5-7 year group(Z=2.979,P=0.017) and the 8-12 year group(Z=5.512,P<0.001) in the school functioning. The 8-12 year group was significantly lower than other age groups in the psychosocial health score(all P<0.05). The 2-4 year group was significantly higher than the 8-12 year group(Z=3.436,P=0.004) in the total score. Children whose household registration place in Hangzhou showed higher scores than those whose household registration place in other cities in each subscale and total scale(all P<0.001). Children in urban areas reported significantly higher scores than rural areas in physical functioning(t=3.31, P=0.001) , school functioning(t=3.24, P=0.001),psychosocial health(t=2.45, P=0.015) and total score(t=3.05, P=0.002). Family monthly income per capita over 10000 CNY was significantly higher in the total score and each sub-domain score than low-income groups(all P<0.05).

Table 2 Comparisons of PedsQL scores reported by parents

Variables	Physical functioning	Emotional functioning	Social functioning	School functioning	Psychosocial health	Total
Types of rare diseases						
Patent ductus arteriosus	65.86±8.88	84.38±8.18	87.75±8.91	88.88±8.95	87.00±6.16	79.65±5.46
Infantile agranulocytosis	97.01±3.86	94.93±6.18	97.76±5.02	93.13±9.8	95.27±4.55	95.88±3.48
Autoimmune thrombocytopenia	73.33±4.72	73.04±6.16	75.75±3.47	62.25±7.21	70.35±3.81	71.39±3.27
Polysyndactyly	90.39±9.76	91.59±9.49	94.09±7.99	91.82±9.27	92.50±6.78	91.77±6.35
Hirschsprung disease	74.84±10.44	78.56±8.80	77.84±10.16	74.28±10.38	76.89±7.20	76.18±6.92
Cleft lip and palate	99.02±2.38	96.47±6.35	92.75±11.42	95.49±7.09	94.9±6.160	96.33±4.22
Tetralogy of fallot	72.38±11.8	80.54±10.77	84.38±11.64	77.41±9.72	80.77±8.72	77.85±8.90
Myasthenia gravis	96.58±4.72	94.29±5.90	98.69±3.83	94.05±7.90	95.67±3.97	95.99±3.31
Guillain-barre syndrome	74.34±10.39	86.21±8.48	96.52±5.23	92.88±4.68	91.87±3.25	85.77±4.56
Glycogen storage disease	76.15±6.69	85.50±9.04	90.33±6.81	84.00±8.14	86.61±4.58	82.97±4.13
Langerhans cell histiocytosis	73.10±10.74	79.29±11.44	90.89±8.50	69.82±8.44	80.00±5.72	77.60±5.15
χ^2	400.95*	338.69*	371.83*	430.23*	471.05*	483.00*
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Sex						
Male	79.41±13.45	83.67±11.24	86.42±11.63	80.44±14.72	83.51±10.86	82.08±10.51
Female	82.94±13.65	84.98±11.85	87.59±11.77	81.94±15	84.84±11.25	84.18±11.12
t	-3.29	-1.44	-1.26	-1.28	-1.52	-2.43
P	0.001	0.151	0.207	0.202	0.130	0.015
Age group						
2-4 year	81.99±14.39	85.45±11.5	86.87±12.43	83.92±13.81	85.41±10.78	84.22±10.98
5-7 year	80.24±13.08	83.64±11.87	87.11±10.86	79.93±15.59	83.56±11.35	82.41±10.85
8-12year	79.58±12.63	81.65±10.72	85.53±11.18	74.76±14.41	80.65±10.73	80.28±10.19
13-18 year	78.30±11.96	85.28±9.31	93.33±9.70	82.50±13.2	87.04±9.07	84.00±8.03
F/χ^2	3.78*	3.16	2.32	32.11*	5.53	13.36*
P	0.287	0.024	0.074	<0.001	0.001	0.004
Household registration place						
Hangzhou	85.24±13.48	86.43±11.96	89.49±11.04	84.14±14.58	86.69±11.08	86.18±11.13
Other cities	75.88±12.01	81.68±10.42	83.94±11.74	77.52±14.38	81.05±10.2	79.25±9.14
t	9.37	5.42	6.21	5.81	6.72	8.73
P	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Household types						
Urban areas	81.96±13.72	84.66±11.59	87.28±11.82	82.23±14.56	84.72±10.95	83.76±10.89
Rural areas	78.11±13.06	83.08±11.27	85.96±11.33	78.02±15.22	82.35±11.12	80.88±10.35
t	3.31	1.56	1.28	3.24	2.45	3.05
P	0.001	0.119	0.201	0.001	0.015	0.002
Family monthly income per capita						
□□5000	79.42±13.79	83.44±10.95	86.46±11.69	81.77±13.55	83.89±10.32	82.33±10.26
□5000-□10000	79.72±12.82	83.53±11.78	85.6±11.69	78.71±15.69	82.61±11.48	81.61±10.74
□□10000	88.04±13.08	88.17±11.68	91.49±10.68	85.1±15.18	88.25±10.91	88.18±11.08
F/χ^2	17.81	14.352*	20.343	15.451*	20.405*	15.26
P	<0.001	0.001	<0.001	<0.001	<0.001	<0.001

*χ^2 of Kruskal-Wallis *H* test

Factors associated with HRQoL

The multilevel linear regression models were shown in Table 3. Children at the age of 8-12 had higher physical functioning score than children who at the age of 2-4 (*P*<0.001). There was a reduction in the school functioning score with the increase in children's age(*P*<0.05).

Children at the age of 8-12 reported less psychosocial health score than children who at the age of 2-4 (*P*=0.019). A higher score on the overall score was observed among the children whose household registration place was in Hangzhou compared to those whose household registration places were in other cities(*P* =0.027).

Table 3 Multilevel regression coefficients and *P* value between variables and PedsQL scores

	Physical functioning		Emotional functioning		Social functioning		School functioning		Psychosocial health		
	β(SE)	*p* value	*β*(SE)	*p* value	*β*(SE)	*p* value	*β*(SE)	*p* value	*β*(SE)	*p* value	
Intercept	80.85(3.82)	<0.001	85.62(2.45)	<0.001	90.99(2.37)	<0.001	86.79(3.46)	<0.001	87.92(2.59)	<0.001	8
Sex(ref=Male)											
Female	0.25(0.51)	0.619	-0.75(0.65)	0.247	-0.23(0.59)	0.692	-0.64(0.64)	0.317	-0.83(0.43)	0.057	-
Age group(ref=2-4 year)											
5-7 year	1.10(0.64)	0.084	0.07(0.82)	0.936	-0.47(0.74)	0.530	-2.46(0.81)	0.002	-1.01(0.55)	0.065	-
8-12 year	3.04(0.85)	<0.001	0.26(1.06)	0.804	-0.74(0.97)	0.445	-4.50(1.05)	<0.001	-1.67(0.71)	0.019	
13-18 year	1.09(1.66)	0.514	-0.29(2.09)	0.889	0.26(1.90)	0.891	-6.66(2.07)	0.001	-2.15(1.40)	0.125	-
Household registration place(ref=Hangzhou)											
Other cities	-0.79(0.56)	0.158	-0.11(0.71)	0.882	-0.94(0.65)	0.152	-1.28(0.71)	0.070	-0.57(0.48)	0.235	-
Household type(ref=cities and towns)											
Rural areas	-0.99(0.59)	0.096	0.82(0.75)	0.279	0.69(0.69)	0.320	-0.44(0.75)	0.555	-0.07(0.51)	0.895	-
Family monthly income per capita (ref=<□5000)											
□5000-□10000	-1.05(0.61)	0.084	0.76(0.78)	0.328	-1.11(0.71)	0.117	0.25(0.78)	0.748	0.06(0.53)	0.909	-
□□10000	0.50(0.81)	0.538	1.12(1.02)	0.276	1.00(0.94)	0.287	1.88(1.02)	0.064	1.20(0.69)	0.081	
conditional R^2	0.812		0.486		0.523		0.678		0.719		

Reimbursement rates and the most urgent desires

The reimbursement rates of medical insurance for rare diseases was set to four grades: 0%-20%, 20%-40%, 40%-60%, 60%-80%, ≥80%. The proportion of patient who chose these four levels were 47.2%, 30.1%, 17.2%, 4.9% and 0.6%, respectively. The choice proportions of the most urgent desires were 28.2%,21.1%,18.3%,15.5%,14.4% and 2.5% for a decrease in overall medical costs, improve diagnosis and treatment techniques, increase reimbursement rate, improve drug availability, service organizations can provide nursing services, not be discriminated at school, respectively.

Discussion

In the current study, used the parent proxy-reports version of the PedsQL 4.0 instrument to assess and compare the quality of life of patients with 11 kinds of rare diseases. Many studies proved that there was no statistically significant difference between child self-report and parent-proxy report of the PedsQL 4.0 scales, and moderate to good concordance was found between the child and parent-proxy scores[8,15,30-33]. However, other studies showed inconsistencies between parent-proxy and child-reporting of HRQoL, especially in the subjective domains such as emotional and social functioning[23,34-36]. Collins *et al.* pointed out that parent-proxy questionnaires may potentially reduce the accuracy of the child's experience[37]. Most authors agree that parent-proxy report should be used as a supplement to child self-report as a secondary outcome measure[15].

The present study has demonstrated that Patent ductus arteriosus(PDA) was the lowest in the physical functioning score, Autoimmune thrombocytopenia (ITP) ranked the lowest in the emotional functioning score, social functioning score, school functioning score, psychosocial health score and total score. Autoimmune thrombocytopenia is an acquired autoimmune disease associated with some symptoms such as spontaneous bruising, mucosal bleeding, epistaxis, or even fatal bleeding events[32]. The extremely low quality of life of Autoimmune thrombocytopenia most notable with regards to incessant worries of unpredictable bleeding, fears of invasive procedures and risk of splenectomy. Additionally, the serious side effects of corticosteroid therapy and daily life restrictions could worsen it[38,39]. Sood *et al.* summarized that the means of physical function score, psychosocial health score and total score measured by parent proxy-reports version of PedsQL 4.0 for 11-18 year patients with Hirschsprung disease were 89.17(SD=14.40), 82.53(SD=17.61) and 84.84(SD=14.91), respectively[8], which were all more than the results revealed by the current study and Collins [37] who reported that the psychosocial health score of children with Hirschsprung disease aged between 2 and 10 years(mean=76.0) was significantly less than the healthy control group(mean=81.2). Kwon *et al.* reported that the means of physical function score, emotional function score, social function score, school function score and total score measured by parent proxy-reports version of PedsQL 4.0 of patients for 8.4-18.7 year old with Repaired tetralogy of fallot were 78.00(SD=19.30),76.00(SD=17.60),73.00(SD=22.40),73.50(SD=17.90) and 77.40(SD=15.00), respectively[40], which were all significantly lower than the normal group except the emotional function score(all P<0.05), and the total score was very close to the present study.

Collett *et al.* found that the physical function score and psychosocial health score of children with Orofacial Clefts were 85.68(SD=17.57) and 81.03(SD=15.20) ,respectively, which were both less than the results of this study, and negligible differences were found in psychosocial outcomes between children with and without orofacial clefts[41]. Storch *et al.* reported that the means of physical function score, emotional function score, social function score, school function score, psychosocial health score and total score measured by parent proxy-reports version of PedsQL 4.0 of patients whose ages ranged from 3 to 25years with Glycogen storage disease Type I were 76.45(SD=19.63),76.93(SD=19.24),74.23(SD=20.33),71.92(SD=18.28), 74.36(SD=15.07) and 74.88(SD=15.64) ,respectively, which were all lower than that of the current study except for the physical functioning score[14], and the healthy control sample were significantly higher than the GSD sample in these domains(all P<0.05).

HRQoL is a broad multidimensional concept influenced by numerous factors. The result of multilevel linear regression showed that children at the age of 8-12 reported higher physical functioning scores and less psychosocial health scores than children who at the age of 2-4. Although there was no significant difference between the 13-18 age group, the 5-7 age group and the 2-4 age group, the regression coefficients indicated that the score of psychosocial health decreased with age.Collins *et al* reported a similar result that psychosocial functioning was negatively affected by increasing age in the children with Hirschsprung disease [37]. Peer teasing has been shown to be a strong predictor of self-concept and parent-reported behavior problems[42]. Collett *et al* found that many pre-school children with orofacial clefts are quite resilient, despite the potential for social stigmatization. However, as children develop and peer groups become more important, this situation may become more difficult to maintain[41]. This study also showed that increasing age negatively affected school functioning score. Miatton *et al* reveled that children with tetralogy of fallot showed significantly lower scores on the school performances than healthy peers[43]. Roodbol *et al* reported that many children were held back in class or dropped out of school after developing Guillain-Barré syndrome[44]. Khalil found that age at time of surgery was negatively affecting school functioning ($ß$ =-0.907) in children with Hirschsprung's disease[45].

The results of the multivariate analysis show that gender was not an influencing factor of HRQol. Though Mills et al. found that girls with Hirschsprung's disease had higher scores across all HRQol scales, the difference was not significant(P<0.05) [33]. Many previous studies also indicated that gender did not have a significant effect on aspects of the global HRQol in children with Hirschsprung's disease[8,37,45]. Children whose household registration place was in Hangzhou got significantly higher scores than in other cities, which was highly likely that Hangzhou is the capital city with the highest GDP per capita which represent a higher level of socioeconomic status that means children there have access to better health services and education and develop positive coping mechanisms to management the adversities. Moreover, Damiano *et al.* measured HRQoL using the PedsQL 4.0 and reported better physical, psychosocial, and total health score in cleft lip and palate patients in households with a higher income[46].

One study investigated 1771 patients covered with 142 rare diseases in 2016 in China reported that 66% patients were misdiagnosed before, and the most serious problem in the process of treatment was high medical cost(32.07%), the other problems were few types of drugs and rehabilitation(15.81%), poor treatment effect(12.25%), low reimbursement rate(12.14%), poor accessibility to health service(11.80%), respectively[47]. Among the 121 rare diseases included in *China's First List of Rare Diseases*, 9 rare diseases have no medication, and all the related medications of 13 rare diseases are excluded in the coverage of medical insurance[48]. Another study revealed similar results with the present study that the reimbursement rate of medical insurance is between

10% to 50%, and 80% of patients have no commercial insurance[49]. Therefore, the Chinese government should strengthen support to carry out fundamental research on the treatment and drugs of rare diseases and formulate and carry out incentive policies for the production or importation of orphan drugs. Moreover, it is recommended to include more rare disease drugs in medical insurance and raise the reimbursement rate to enhance orphan drug availability and reduce the financial burden of rare diseases.

Conclusions

This study reveals that the HRQoL of children with autoimmune thrombocytopenia (ITP) is relatively lower compared with other rare diseases. We should pay more attention to the child's mental health and school functioning with age. Patients still face a lot of problems when seeking treatment, such as a lack of effective medicine and unable to afford medical expenses. Therefore, further measures should be adopted to improve the efficiency of diagnosis and the effect of treatment, to improve the availability of health services, and to alleviate the economic burden.

Abbreviations

HRQoL: health-related quality of life; PedsQL™: pediatric quality of life inventory™; LSD: least significant difference; ITP: autoimmune thrombocytopenia. PDA: Patent ductus arteriosus;GSD: Glycogen storage disease

Declarations

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Availability of data and material

Please contact author for data requests.

Authors' contributions

XW and JR participated in the design of the study. SW collected and processed the data. QG performed the statistical analysis and drafted the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable

Ethics approval and consent to participate

The respondents were anonymous, voluntary and consent for participation.

All study procedures were approved by the Ethics Committee of Center for Medical science, technology and education of Zhejiang Province

Author details

[1]Department of Public Health, Hangzhou Medical College, No.481 Binwen Road, Hangzhou 310053, Zhejiang Province, China.[2] Department of Health Management, School of Medicine, Hangzhou Normal University,No.2318 Yuhangtang Road, Hangzhou 311121, Zhejiang Province, China.[3]Center for Medical science, technology and education of Zhejiang Province, No,60 Hefang Street, Hangzhou 310006, Zhejiang Province, China

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Figures

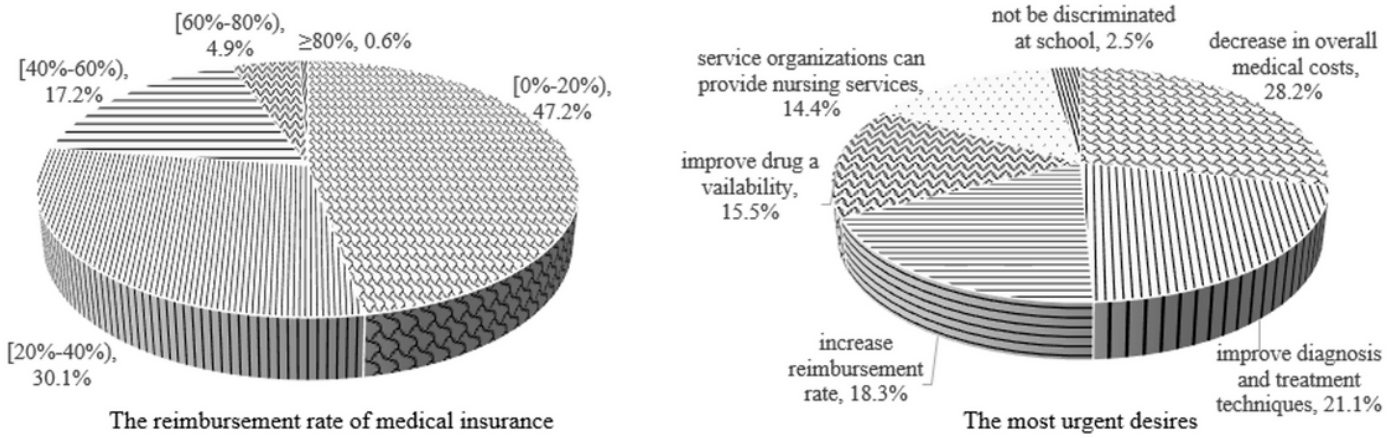

Figure 1

The choice proportions of the reimbursement rate of medical insurance and the most urgent desires