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Disease burden and health-related quality of life among children with X-linked hypophosphataemia in China: a national cross-sectional survey

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ABSTRACT

Background X-linked hypophosphataemia (XLH) is a rare inherited disorder often misdiagnosed and lacking sufficient aetiological treatment. Previous studies have shown that XLH is associated with worse health-related quality of life (HRQoL) and greater economic burden for children and their families compared with the general population, but evidence from China is scarce. This study aimed to comprehensively explore the burden and HRQoL of XLH children in China.

Methods An online retrospective survey of paediatric patients with XLH and their caregivers was conducted nationwide during March to June 2021. A self-administered questionnaire was used to collect socio-demographic, clinical and economic data. The EQ-5D-Y-3L instrument was employed to assess HRQoL, and the health utility score was calculated. Direct medical, non-medical and indirect costs were determined. Multivariate regression analysis was performed to explore potential associations between HRQoL and identified influencing factors.

Results The study included 221 subjects with a mean age of 7.25 years, of whom 119 (53.8%) were girls. Most XLH children (63.8%) lived in rural areas, and 39.4% reported a family history. Over 70% experienced misdiagnosis. The average total annual cost per patient was found to be 34 657.85 CNY. Of direct medical costs, patients' out-of-pocket expenses were substantial. The incidence of catastrophic health expenditure was 19.9%. The means (SD) of EQ-5D-Y-3L health utility and EQ-5D VAS scores were 0.83 (0.14) and 56.07 (10.95). Both univariate and multivariate analyses found older age and lower economic affordability were associated with poorer HRQoL.

Conclusions The study underscores the significant burden of XLH on paediatric patients and their families in China, both in terms of HRQoL and economic costs. The findings emphasise the importance of early detection, accurate diagnosis, cost-effective targeted interventions and long-term multidisciplinary management strategies to improve the lives of XLH children and their families.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Previous studies have found that children with X-linked hypophosphataemia (XLH) had poorer health-related quality of life (HRQoL) than the local general population. And the disease also placed a heavy economic burden on the children's family.

WHAT THIS STUDY ADDS

⇒ This survey included the largest number of paediatric patients with XLH so far worldwide. It provides baseline real-world data on the average costs and health utilities of treated children with XLH in China, which are useful for future long-term follow-up comparisons and cost-effectiveness evaluation for targeted therapy like burosumab.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our study highlights the importance of early detection, accurate diagnosis, cost-effective targeted interventions and long-term multidisciplinary management strategies to improve the lives of XLH children and their families.

INTRODUCTION

X-linked hypophosphataemia (XLH) is the most common form of heritable hypophosphataemic rickets, accounting for approximately 80% of all inherited cases.[1] The aetiology of this disease is attributed to the mutation in the *PHEX* gene, leading to elevated levels of the hormone fibroblast growth factor 23 (FGF23), which subsequently results in renal phosphate depletion and abnormal bone mineralisation.[2] The international incidence of the disease is 5/100 000 live births, and the reported prevalence was 1.4 per 100 000 in the UK[3] and 1.7 per 100 000 in Norway,[4] respectively. There is a lack of epidemiology data of XLH disease in China currently. China has about 12 million births (year 2020) and 253 million growing children (<15 years) according to the seventh national population census data.[5] Extrapolation of the ~1:20,000 incidence and the ~1:50,000 prevalence would imply that this rare disease has an

incidence of about 600 cases in newborns annually and a prevalence of 5060 cases in the paediatric and adolescent population. In 2018, XLH had already been included in China's First National List of Rare Diseases as a subtype of hypophosphataemic rickets.[6]

XLH is a lifelong progressive rare disease primarily affecting the kidneys and bones. As the disease often develops in childhood, it can progress to rickets, skeletal malformations and growth retardation.[7] The musculoskeletal symptoms, such as stiffness, bone and joint pain, greatly impair physical function and affect the health-related quality of life (HRQoL) of patients throughout their lives. Besides, multi-systemic complications of XLH can lead to craniosynostosis, hearing loss, dental and periodontal recurrent lesions and psychiatric disorders.[8] While there has been extensive research on the disease mechanism and clinical manifestations,[9 10] few studies have explored the living status of patients with XLH symptoms and the impact of current treatments from the patient's perspective.[11] The XLH Burden of Disease Study, a large global online survey of 90 children and 232 adults with XLH was conducted from 2014 to 2016, while no Chinese population was included.[12] Thus, knowledge of the disease burden of the XLH population in China remains limited.

Over the past 40 years, the management of XLH mainly relied on the conventional therapy with oral phosphate supplementation and active vitamin D analogues to offset its renal loss.[13] The treatment goal is to improve rickets, reduce skeletal deformities and avoid the need for surgery, but the clinical outcomes varied related to the age at diagnosis and onset of treatment, and the efficacy seemed often insufficient.[8 14–16] The treatment rates among adults are also significantly low. Since conventional therapy requires multiple daily oral doses, it places a burden on XLH patients, especially children. In January 2021, burosumab, a recombinant human immunoglobulin G-1 (IgG1) monoclonal antibody that inhibits excess FGF23 activity, was approved by the National Medical Products Administration for the treatment of XLH in adults and children 1 year of age and older in China.[17] As an emerging therapeutic alternative for XLH, burosumab remains prohibitively expensive, with annual treatment costs reaching millions of Chinese Yuan (CNY), a figure more than 10 times GDP per capita. Therefore, its use in Chinese patients is limited. Drug reimbursement policies informed by utility-based economic evaluations require reliable estimates of utility and cost of illness.[18] Hence, the collection of data on diagnosis, cost and HRQoL of Chinese patients is key to understanding the challenges of living with XLH and providing the primary inputs in cost-utility analysis to support evidence-based policy-making in the care of patients with rare XLH disease.

Therefore, this study aims to provide a comprehensive understanding of the disease burden faced by the children with XLH in China by conducting a nationwide survey and providing baseline data on the costs and health outcomes of current treatments.

METHODS

Study design and patient involvement

A national cross-sectional online survey of XLH disease burden was conducted in 27 cooperative hospitals (see the Contributors section for details) under the coordination of the Joint Meeting of Directors of National Academic Societies for Rare Diseases and the Shanghai Foundation for Rare Diseases, with the approval of the Ethics Committee of Shanghai Health Development Research Centre (No. 2021001). Data were collected with the snowball sampling approach during March to June 2021. Inclusion/exclusion criteria for the survey were patients clinically diagnosed with XLH with no serious comorbidities and agreed to participate. The electronic questionnaire was administered using the Wenjuanxing software and completed online by patients or the caregivers of children with XLH (aged ≤18 years) with informed consent. The follow-up telephone calls of each respondent were made to ensure the quality of data by the research group, especially for the medical/non-medical cost. Data from paediatric patients with XLH (aged ≤18 years) in the national survey were extracted and analysed for this study.

Questionnaire

A self-designed questionnaire consisting of two parts, gathering individual information and patient-reported outcomes, was administered, taking approximately 20 min to complete. Items on the patient's socio-demographic information (ie, gender, age, height, weight, medical insurance, residence, guardian's educational level and annual income of the family) were surveyed. Clinical data about family history, diagnostic history, surgical history, medications, disease-specific clinical symptoms and economic costs related to the disease were also collected.

The economic burden of XLH during the previous year (specifically, the year 2020 as referenced in this study) was estimated by calculating direct medical costs (ie, hospitalisation, outpatient and out-of-hospital expenses, including out-of-pocket cost and insurance payments if covered), non-medical costs (ie, traffic and accommodation costs) as well as indirect costs. Indirect costs were estimated by the loss of labour time caused by unemployment or loss of work due to illness for patients and their caregivers.

HRQoL was assessed by different versions of the widely used EuroQol Five-Dimensional Questionnaire with three response levels (EQ-5D-3L) according to the age of XLH patients along with the EQ-5D visual analogue scale (VAS). The five core health dimensions were 'Mobility (walking about)', 'Looking After Myself (like washing or dressing themselves)', 'Doing Usual Activities (for example, going to school, hobbies, sports, playing, doing things with family or friends)', 'Having Pain or Discomfort' and 'Feeling Worried, Sad or Unhappy' with each dimension categorised into three severity levels (no problems, some problems and a lot of problems).[19] The Youth version (EQ-5D-3L-Y) was used for children aged from 8

to 18 years old and a proxy version for children aged 4 to 7 years.[20]

Data analysis

The STROBE cross-sectional reporting guidelines were used.[21] The frequency (percentage) and means (SD) were used for descriptive analyses of socio-demographic and clinical characteristics of the sample. According to the growth standards for children issued by the National Health Commission,[22 23] Height-for-age Z (HAZ) scores were calculated for children with XLH. Those with HAZ scores of below −2 were classified as having short stature (height < median −2 SD). Then, the incidence of catastrophic health expenditure (CHE) was measured by out-of-pocket medical expenses as a proportion of household income that reaches or exceeds 40%.[24] HRQoL was illustrated by the proportions of 'reporting problems' on the five dimensions. In addition, the latest Chinese value set of the EQ-5D-Y-3L was applied to calculate the health utility score (HUS) for each health state of XLH children in this study.[25] The overall HRQoL was shown as the means (SD) of EQ-5D-Y-3L HUS and EQ-5D VAS scores, with higher scores of EQ-5D-Y-3L utility and EQ-5D VAS indicating better health status.

The analysis of variance (ANOVA) was used to compare health outcomes among different levels of each variable. A multivariate beta regression model was built on the EQ-5D-Y-3L HUS to explore its associations with potential risk factors, including demographic characteristics (age, gender, residence, educational status, parental education, etc), clinical characteristics (misdiagnosis, genetic testing, family history of XLH, etc) and economic characteristics (income, economic affordability, etc). This model is specifically designed to analyse continuous variables within the open interval (0, 1) and is particularly well-suited for handling skewed distributions.[26] Regression coefficients (beta) and marginal effect were calculated with 95% CIs. The statistical analyses were performed using STATA 18.0 at a significance level of 0.05.

RESULTS

Basic information of participants

A total of 221 paediatric patients with XLH were included in this study. The socio-demographic and clinical characteristics of the study population are shown in table 1. The average age of patients was 7.25±3.87 years, with a majority of 73.8% being under 10 years old. There was a slightly higher proportion of females than males (53.8% vs 46.2%). In terms of educational status, nearly half of the patients (48.4%) were currently in school, while a similar proportion (48.0%) had not yet reached school age. Most patients' parents had attained a middle school educational level (62.4%), with 22.6% having completed college or higher. The study population predominantly resided in rural areas (63.8%).

The vast majority of XLH children (98.2%) were covered by the urban and rural resident basic medical insurance, while only 16.3% of them had additional commercial medical insurance. More than half of the patients (59.6%) belonged to households with more than three members. The household per capita disposable income groups were classified according to the China Statistical Yearbook 2021. The distribution of patients across these income groups revealed that the highest proportion (43.0%) belonged to the highest income category (≥44 9490.0 CNY ≈ 6278 USD), followed by the middle (19.5%) and upper middle (19.0%) income

Table 1 Socio-demographic and clinical characteristics of the study population (n=221)

Variables	Category	N	%
Age (years)	< 10	163	73.8
Gender	Female	119	53.8
Educational status	In school	107	48.4
	Not yet of school age	106	48.0
	Enrolled with classmates	7	3.2
	Dropped out	1	0.5
Parental educational level	High school or college above	50	22.6
	Middle school	138	62.4
	Primary school or below	33	14.9
Residence	Rural area	141	63.8
Urban and rural resident basic medical insurance*	Yes	217	98.2
Commercial medical insurance	Yes	36	16.3
Household members	≤3	89	40.5
Household per capita disposable income group	Lowest (0–8333 CNY)	6	2.7
	Lower middle (8333–18,445 CNY)	35	15.8
	Middle (18 445–29,053 CNY)	43	19.5
	Upper middle (29 053–44,949 CNY)	42	19.0
	Highest (≥44 9490.0 CNY)	95	43.0
Family history of XLH	Yes	87	39.4
Presence of complications	Yes	124	56.1
Types of complications	Hyperparathyroidism	57	25.8
	Kidney dysfunction	38	17.2
	Renal calcinosis	26	11.8
	Kidney stones	21	9.5
	Others	13	5.9

*Reimbursement covers general outpatient expenses incurred at designated medical institutions, comprehensive hospitalisation (with the exception of accidental injuries and childbirth) and substantial illness expenses (annual medical costs exceed a certain range).
XLH, X-linked hypophosphataemia.

Table 2 Diagnostic journey of paediatric XLH patients

Variables	Category	N	%
Symptom for first visit	Lower limb deformity (X- or O-shaped legs)	147	66.5
	Gait abnormalities	29	13.1
	Growth retardation	19	8.6
	Muscle weakness	9	4.1
	Skeletal pain	5	2.3
	Others	12	5.4
First diagnosis department	Orthopaedics	98	44.3
	Child healthcare	39	17.7
	Paediatrics	32	14.5
	Paediatric endocrinology	25	11.3
	Endocrinology (including osteoporosis)	10	4.5
	Paediatric nephrology	6	2.7
	Nephrology	5	2.3
	Others (rehabilitation, internal medicine, etc)	6	2.7
Diagnosis on first visit	Yes	65	29.4
Genetic Testing	Yes	180	81.5
Self-reported misdiagnosis	Yes	132	59.7
Misdiagnosed Disease	Vitamin D deficiency Rickets	71	53.8
	Calcium deficiency	18	13.6
	Osteoporosis	4	3.0
	Growth retardation	2	1.5
	Others	37	28.0

categories. A family history of XLH was reported in 39.4% of participants. Over half of the participants (56.1%) had complications, which included hyperparathyroidism (25.8%), kidney dysfunction (17.2%), renal calcinosis (11.8%) and kidney stones (9.5%).

Diagnosis and treatment

Diagnosis

Table 2 and figure 1 illustrate the diagnostic journey of paediatric XLH patients. The most common self-reported symptom that led to the first visit to hospitals was lower limb deformity (X or O-shaped legs), affecting 66.5% of patients. Gait abnormalities (13.1%) and growth retardation (8.6%) were the next prevalent symptoms that prompted patients to seek medical attention. The initial diagnostic evaluations were primarily conducted in orthopaedics (44.3%), child healthcare (17.7%) and paediatrics (14.5%). Genetic testing, the gold standard in confirming XLH, was used in 81.5% of cases.

However, only 29.4% of the patients received an accurate diagnosis during their first healthcare encounter, while a staggering 70.6% were subjected to misdiagnosis. Overall, 59.7% of the patients in the survey experienced misdiagnosis. Misdiagnosed patients visited an average of 2.8 hospitals, with some patients seeking medical care at up to 10 different institutions. The average time to diagnosis was 10.9 months (≈0.9 years), with a median time of 3 months. The longest diagnostic journey spanned 127 months (≈10.6 years). Among the misdiagnosed cohort, vitamin D deficiency rickets was the most common misdiagnosis, assigned to 53.8% of the patients.

Current treatment for XLH

At the time of the survey, since burosumab was not commercially available in mainland China, 217 (98.2%) patients were receiving conventional treatment for XLH, while four had discontinued treatment due to poor efficacy. The majority of paediatric patients were receiving oral phosphate (99.1%) and/or active vitamin D (92.8%). Furthermore, 18.6% of the cases had undergone surgery as part of their treatment plan.

Economic burden

The economic burden for patients with XLH in this study was categorised into direct medical cost, direct non-medical cost and indirect cost, as presented in table 3. In 2020, 200 children with XLH incurred outpatient costs, 34 of whom incurred inpatient costs, and 143 incurred out-of-hospital costs. The mean annual total cost per patient was found to be 34 657.85 CNY, with direct medical costs constituting the largest proportion at 47.5% (16 451.97 CNY). Remarkably, patients' out-of-pocket expenses accounted for a substantial 97.1% and 71.6% of outpatient and inpatient medical costs, respectively. With regard to the capacity to pay for medical expenses, the median proportion of total out-of-pocket

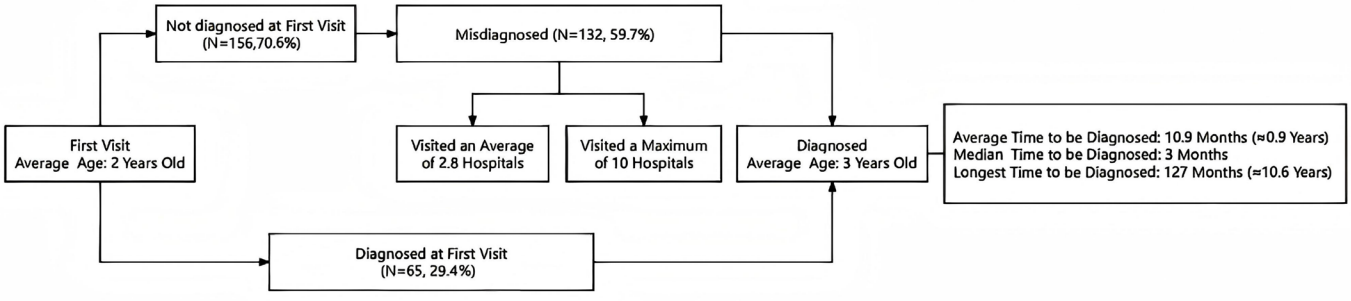

Figure 1 Diagnostic journey for X-linked hypophosphataemia children.

Table 3 Economic burden for patients with X-linked hypophosphataemia in 2020 (n=221)

Cost category (CNY*)	Mean	%	Median (IQR)
Direct medical cost	16 451.97	47.5	9829.00 (6000.00,15 000.00)
Outpatient medical cost	7792.57	47.4	5500.00 (2850.00, 8450.00)
Out-of-pocket cost	7563.04	97.1	5500.00 (2600.00, 8000.00)
Inpatient medical cost	4587.63	27.9	0.00 (0.00, 0.00)
Out-of-pocket cost	3284.46	71.6	0.00 (0.00, 0.00)
Out-of-hospital medical cost	4071.78	24.8	2500.00 (0.00, 6000.00)
Direct non-medical cost	3797.42	11.0	2000.00 (600.00, 4050.00)
Outpatient non-medical cost	3140.86	82.7	2000.00 (550.00, 3800.00)
Inpatient non-medical cost	656.56	17.3	0.00 (0.00, 0.00)
Indirect cost	14 408.46	41.6	2100.00 (0.00, 24 500.00)
Full-time care loss	12 159.28	84.4	0.00 (0.00, 20 000.00)
Work absence loss	2249.19	15.6	0.00 (0.00, 1200.00)
Total cost	34 657.85	100.0	21 300.00 (11 800.00, 49 500.00)

*1 USD ≈ 6.9 CNY.

medical expenses to annual household income was 15.9%. However, this proportion reached a maximum of 692%, which is close to seven times the annual household income. The incidence of CHE in XLH families was 19.9%. Direct non-medical costs, including transportation and accommodation expenses, accounted for 11.0% (3797.42 CNY) of the total cost. Outpatient non-medical expenses (3140.86 CNY, 82.7%) exceeded inpatient expenses (656.56 CNY, 17.3%). Indirect costs, which include the productivity loss of parents with XLH children due to caregiving and work absences, accounted for a significant 41.6% (14408.46 CNY) of the total burden. The primary factor was the need for full-time care.

Patient-reported outcomes

Physical function

Table 4 showed the distribution of HAZ and growth status in children with XLH. The heights of most children in their age group were below age-appropriate norms.[22 23] Overall, the median (IQR) of HAZ was −2.20 (−3.17, −1.38), with 57.5% of the children classified as having short stature, highlighting the significant growth challenges faced by those with XLH. Furthermore, the median (IQR) of HAZ for boys aged 7 to 12 years was −2.54 (−4.87, −1.28), while for those aged 13 to 18 years, it was −3.68 (−5.28, −2.36), indicating a worsening trend in growth impairment as age increases. Additionally, this phenomenon of growth and developmental retardation is more pronounced in males than in females. Thus, parts of the surveyed subjects (17.2%) possessed a disability certificate, and 31.7% had to use assistive devices.

In addition to short stature and leg deformity, widespread and diverse health challenges were faced by XLH patients (see online supplemental figure 1). Other significant issues were bone pain (68.3%), osteomalacia

Table 4 The distribution of height-for-age Z scores and growth status among children with X-linked hypophosphataemia (n=221)

Age (years old)	Total			Male		Female	
	N	HAZ Median (IQR)	Short N (%)	HAZ Median (IQR)	Short N (%)	HAZ Median (IQR)	Short N (%)
<7	117	−2.15 (−3.00 to −1.45)	68 (58.1)	−2.38 (−3.06 to −1.35)	34 (61.8)	−2.10 (−2.92 to −1.46)	34 (54.8)
7–12	76	−2.27 (−3.12 to −1.17)	43 (56.6)	−2.54 (−4.87 to −1.28)	23 (65.7)	−1.81 (−2.86 to −1.07)	20 (48.8)
13–18	28	−2.39 (−3.76 to −1.54)	16 (57.1)	−3.68 (−5.28 to −2.36)	10 (83.3)	−1.80 (−3.18 to −1.48)	6 (37.5)
Total	221	−2.20 (−3.17 to −1.38)	127 (57.5)	−2.47 (−3.65 to −1.39)	67 (65.7)	−2.00 (−2.92 to −1.38)	60 (50.4)

Note: HAZ= (height-median)/SD Short: HAZ<-2.
HAZ, height-for-age Z scores.

Table 5 Health-related quality of life of paediatric X-linked hypophosphataemia patients assessed by EQ-5D-Y-3L

EQ-5D-Y-3L	N(%)		
Domain	No problems	Moderate problems	A lot of problems
Mobility(walking about)	107 (63.7%)	52 (31.0%)	9 (5.4%)
Looking After Myself	148 (88.1%)	17 (10.1%)	3 (1.8%)
Doing Usual Activities	98 (58.3%)	62 (36.9%)	8 (4.8%)
Having Pain or Discomfort	47 (28.0%)	114 (67.9%)	7 (4.2%)
Feeling Worried, Sad or Unhappy	81 (48.2%)	80 (47.6%)	7 (4.2%)
Score	N	Range (min-max)	Mean±SD
EQ-5D-Y-3L HUS	168	0.19–0.99	0.83±0.14
EQ-5D-Y-3L VAS	209	25–81	56.07±10.95

HUS, health utility score; VAS, visual analogue scale.

(64.6%) and muscle weakness (62.9%) as well as tooth abscess (53.9%), kidney dysfunction (44.8%), digestive symptoms (32.6%) and hearing loss (12.2%).

HRQoL

HRQoL scores of 168 children with XLH (76.0%) were responded to by their caregivers. The majority of the participants reported no problems in the Mobility (63.7%) and Looking After Myself (88.1%) domains. However, some and a lot of problems were more prevalent in the Doing Usual Activities (41.7%), Feeling Worried, Sad or Unhappy (51.8%) and Having Pain or Discomfort (72.0%) domains. The proportion of participants experiencing a lot of problems was relatively low across all five domains, ranging from 1.8% in Looking After Myself to 5.4% in Mobility. The mean value of EQ-5D-Y-3L health utility and VAS for XLH children was found to be 0.83 (SD=0.14) and 56.07 (SD=10.95), respectively (see table 5).

Association between the EQ-5D-Y-3L utility scores and patient characteristics

According to the ANOVA results presented in table 6, age and parental educational level, among the sociodemographic factors, were found to exhibit a significant association with EQ-5D-Y-3L HUS. Participants younger than 10 years old reported higher scores (0.86±0.10) compared with those aged 10 years and above (0.78±0.18) (F=13.771, p<0.001). Participants whose parents had a high school or college education and above reported the highest EQ-5D-Y-3L HUS of 0.87, followed by those with middle school (0.83) and primary school or below

Table 6 Results of analysis of variance for health utility scores among X-linked hypophosphataemia children (n=168)

		EQ-5D-Y-3L HUS		
Variables	N	Mean±SD	*F*	P†
Age (years)			13.771	0.000***
<10	114	0.86±0.10		
≥10	54	0.78±0.18		
Parental educational level			3.090	0.048*
High school or college above	39	0.87±0.10		
Middle school	103	0.83±0.13		
Primary school or below	26	0.79±0.18		
Economic affordability			3.510	0.009**
Completely unable	29	0.75±0.10		
Somewhat unable	72	0.84±0.12		
Fairly able	57	0.86±0.10		
Mostly able	6	0.84±0.10		
Completely able	4	0.90±0.17		

*p < 0.05.
**p < 0.01.
***p < 0.001.
†P value was calculated from mean.

(0.79) education (F=3.090, p<0.05). Besides, economic affordability was also found to have a significant effect on the EQ-5D-Y-3L HUS (F=3.510, p<0.01). Participants who reported being completely able to afford treatment had the highest EQ-5D-Y-3L (0.90±0.17), while those who were completely unable to afford treatment had the lowest scores (0.75±0.12). Furthermore, the multivariate beta regression analysis identified genetic testing with a positive significant association (β=0.303, p=0.044, ME=0.045). However, other socio-demographic characteristics (ie, gender, residence, patients' educational status, basic and commercial medical insurance, number of household members), clinical factors (ie, expercience of misdiagnosis, family history of XLH, phosphate supplement, vitamin D treatment, surgery history) and economic factors (ie, household per capita disposable income, out-of-hospital medical treatment) were found to be not significantly associated with EQ-5D-Y-3L utility scores.

DISCUSSION

To our knowledge, the disease burden survey of XLH was first carried out in China and has included the largest number of 221 paediatric patients to date worldwide. This study provides the most comprehensive baseline data on the diagnosis, treatment, HRQoL and economic costs of Chinese children with XLH and reveals the substantial burden of XLH in China.

In the context of the Chinese paediatric population, the prevalence of XLH is observed to be higher in girls than in boys, a finding that is consistent with the results of previous global studies[12 27] and other studies that investigate Chinese populations.[28] As XLH is a hereditary disorder, the prevalence of a family history of the condition in this study was found to be approximately 40%. This finding is supported by another study, which has reported a comparable prevalence rate of 33%.[29] Furthermore, the majority of patients reside in rural areas, and their parents are often poorly educated. The inter-generational inheritance of the disease may be an inevitable contributing factor to the poor socioeconomic status of XLH families, emphasising the need for routine screening of at-risk families.

It was demonstrated that the average time taken from the onset of symptoms (the first visit to the doctor) to the first diagnosis of children with XLH in China was nearly 1 year, while surveys in Japan and Korea showed that this time was around 0.4 years.[26] Following the release of rare disease diagnosis and treatment guidelines by the National Health Commission in 2019, the standardised level of rare disease diagnosis and treatment in China has been gradually improving, but there is still a gap between China and developed Asian countries, suggesting that policymakers and clinicians should consider early genetic testing as an effective means of improving diagnosis rates and reducing misdiagnosis.

The economic burden of XLH in China is likely significant, given the costs associated with long-term medical care and the potential loss of productivity for patients and caregivers. The real-world survey indicates that the mean annual direct medical costs of XLH (16452 CNY) represent a significant source of economic burden, with expenditures approaching 96% of the national disposable income per capita of rural residents (17131 CNY) and three times exceeding the overall annual cost of healthcare per capita (5146 CNY) in 2020.[30] In addition, patient out-of-pocket payments exceeded 90% for outpatient services, owing mainly to the fact that phosphate preparations were hospital-made and not reimbursed by health insurance. Patients also reported purchasing vitamin D online, which is not covered by basic insurance. Thus, the XLH family suffered a higher CHE incidence of nearly 20%, while the overall incidence of CHE for people with health insurance in China was found to be around 13%.[31] It is recommended that the inclusion of non-fatal, chronic, rare diseases be explored in outpatient special chronic disease management, with a view to further improving the reimbursement rate of related drugs and preventing poverty due to illness.

It has been previously reported that regular treatment with phosphate supplements and active vitamin D can significantly improve the symptoms except for the height.[27] Prior qualitative interviews have demonstrated that being shorter than average has a detrimental impact on the psychological well-being of affected children, who consistently find themselves at the lower end of the height distribution within their peer groups.[32] A low percentage of normal height (12.7%) was also observed in XLH children included in the study, which may be a contributing factor to their poor mood. Of the patients, 51.8% reported feelings of sadness, worry or unhappiness. Moreover, a range of complications, such as hyperparathyroidism and renal calcinosis, are also frequently observed. One of the other most common clinical manifestations of osteomalacia is generalised or localised bone pain. The occurrence of bone pain in children with XLH (68.3%) was also reported by caregivers, which was reaching 100% in previous studies on XLH.[33] Furthermore, it was observed that children predominantly reported problems (72.0%) in the domain of Having Pain or Discomfort.

Regarding HRQoL scores, the mean EQ-5D-Y-3L HUS and VAS for XLH children were 0.83±0.14 and 56.07±10.95, which were both lower than the norm scores of the general Chinese population, which were 0.985 and 80.91.[34] Compared with Spanish children, the EQ-5D-3L VAS scores were lower (68.33±16.06), while the index score was higher (0.788±0.153).[35] Compared with other rare diseases, the mean EQ-5D VAS was much lower than Gaucher receiving therapy, but comparable with Fabry, Pompe disease and Mucopolysaccharidosis in previous surveys.[36] Our study also found that older children and adolescents with XLH experienced a more pronounced reduction in HRQoL, and patients who had undergone genetic testing had significantly higher scores than those

who had not, implying that genetic confirmation of the XLH diagnosis may have contributed to improved HRQoL, possibly through earlier access to appropriate care and management.

The high prevalence of complications and impaired HRQoL in this study may be explained by delayed diagnosis, limited access to specialised treatments and inadequate disease management. For clinicians, this underscores the importance of early screening, accurate diagnosis and proactive management strategies to prevent or mitigate complications and improve patient outcomes. The management of XLH necessitates a therapeutic approach that targets disease mechanisms and is capable of modifying the disease's natural history. In this regard, burosumab represents a promising intervention that has demonstrated efficacy in alleviating multiple XLH complications and helping improve HRQoL in paediatric populations.[37 38] Policymakers should consider implementing measures to improve insurance coverage, access to specialised care medications and genetic counselling, as well as increasing public awareness about XLH to reduce stigma, which can impact the experience of XLH for patients and their families in China.

Several limitations should be noted in our study. First, despite our efforts to include as many of the nation's XLH children as possible, the low rate of diagnosis may have meant that the current samples collected represent only a small proportion of children in China. Second, the EQ-5D-Y-3L is generally recommended for children aged 8–15 years, and for older adolescents who were 16–18 years old in our study, it may be more appropriate to use the adult version and its corresponding value set.[39] However, depending on the study design and considering the convenience of the survey, the EQ-5D-Y-3L and the latest Chinese value set were only used. Nonetheless, EQ-5D has been recognised as being inaccurate for measuring quality of life, particularly for rare diseases. Our study chose the EQ-5D instrument because it has been used in other studies of HRQoL in patients with XLH.[35 40] Third, since the first prescription of burosumab in Mainland China was issued in September 2021, a date later than the time of our cross-sectional survey, this study did not include children treated with burosumab. Therefore, the limited available data do not allow us to make any inferences about the effect of burosumab on the burden of XLH and compare to conventional therapy. Further research is needed to evaluate the effectiveness and cost-effectiveness of new treatment options like burosumab, taking into account the local context and healthcare systems in China.

CONCLUSION

This study offers crucial foundational data for comprehending the disease burden, quality of life and its influencing factors among children with XLH in China. The paediatric patients with XLH mainly suffered from pain, discomfort and felt sad, worried or unhappy, and many of them still had impaired physical function after conventional therapy. Age and family economic affordability were significantly affecting HRQoL, and the economic burden of the disease was heavy for over half of the patients' families. Genetic testing should be carried out as early as possible to reduce misdiagnosis and delayed diagnosis and improve the quality of life of XLH patients. These findings highlight the importance of early detection, accurate diagnosis, cost-effective targeted interventions and long-term multidisciplinary management strategies to improve the lives of XLH children and their families.

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