PharmacoEconomics - Open (2024) 8:459–469
https://doi.org/10.1007/s41669-023-00468-1

ORIGINAL RESEARCH ARTICLE

Health-Related Quality of Life and Economic Burden Among Hospitalized Children with Hand, Foot, and Mouth Disease: A Multiregional Study in China

Ting Zhou[1] · Hongfei Hu[1] · Junyang Gao[2,3] · Hongjie Yu[2] · Mark Jit[4] · Pei Wang[2,3]

Accepted: 17 December 2023 / Published online: 9 January 2024

Abstract

Background Hand, foot, and mouth disease (HFMD) is an infectious disease with high morbidity and mortality rates among children under 5 years old. This study aimed to explore the health-related quality of life (HRQOL), economic burden, and related influencing factors among Chinese HFMD patients.

Methods From January to October 2019, a longitudinal cohort study of 296 hospitalized patients (≤ 5 years old) with HFMD and their guardians was conducted using the proxy version of the 5-level EQ-5D-Y (EQ-5D-Y-5L, Y-5L) in face-to-face interviews in Shanghai, Zhengzhou, and Kunming, representing three regions with different economic development levels. Multiple linear regression was used to explore the factors associated with HRQOL and costs.

Results The mean Y-5L health utility score (HUS) (standard deviation, SD), and visual analogue scale (VAS) score (SD) were 0.730 (0.140) and 60.33 (16.52) at admission and increased to 0.920 (0.120) and 89.95 (11.88) at discharge, respectively. The children from Shanghai had the lowest HUSs at admission and had the best health improvement. The mean hospitalization cost and total cost were 4037 CNY and 5157 CNY, respectively. The children from Shanghai had the highest hospitalization cost (4559 CNY) and total cost (5491 CNY). Multiple regression analysis suggested that medical insurance status, type of employment, residence type, and religious status were significantly associated with the baseline HUS and improvement in the HUS after treatment. Region, loss of work time, and length of stay had a significant impact on the hospitalization cost and total cost.

Conclusion Our findings demonstrate that HFMD could lead to poor HRQOL and the economic burden varies in different regions in China. Many pediatric patients still have physical or mental health problems shortly after treatment.

Key Points for Decision Makers

Children with hand, foot, and mouth disease (HFMD) have poor health-related quality of life in China. The health utility score (HUS) difference of these patients between baseline and at discharge was varied in different regions.

The improvement in HUS after treatment was significantly associated with region, type of the guardians' employment, residence type, and age of patients.

The family of children with HFMD suffered heavy economic burden in China. The factors of region, loss of work time, and length of stay significantly impacted the total cost.

✉ Pei Wang
wang_p@fudan.edu.cn

1 School of International Pharmaceutical Business, China Pharmaceutical University, Nanjing, China

2 School of Public Health, Fudan University, 130 Dong An Road, Shanghai 200032, China

3 Key Lab of Health Technology Assessment, National Health Commission of the People's Republic of China (Fudan University), Shanghai, China

4 Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, UK

1 Introduction

Hand, foot, and mouth disease (HFMD) is an infectious disease caused by an enterovirus (EV). It mainly manifests as fever, oral ulcers, hand and foot blisters, and rash, which can be life threatening in severe cases [1–3]. Most HFMD cases occur in children under 5 years old [2, 4].

Numerous HFMD outbreaks and deaths have been reported in the Asia–Pacific region, including China [5]. From 2011 to 2018, children under 5 years old accounted for the largest proportion of all patients with HFMD in China, ranging from 92.76 to 95.32% [6]. According to a report of the Chinese Center for Disease Control and Prevention, the incidence and mortality rates of HFMD in China were 96.08 per 100,000 and 0.006 per 100,000 in 2021, respectively [7].

Previous studies have suggested that the patients with HFMD are more likely to report a worse health status and suffer a heavier economic burden than healthy children without HFMD in China [4, 8–12]. The three-level EuroQol-five dimensions (EQ-5D-3L) proxy 2 questionnaire [9] and TNO-AZL Preschool Quality of Life (TAPQOL) scale [10] were used to assess the health-related quality of life (HRQOL) of pediatric patients with HFMD. The results suggested that HFMD impaired the patients' health in terms of both psychological and physical aspects [9, 10], and thus reduced their HRQOL. However, few studies have used child-specific HRQOL instruments and compared health status changes before and after treatment. In terms of economic burden in China, previous studies focused on high-income provinces (i.e., Jiangsu and Guangzhou) and mainly focused on severe patients [4, 8–12]. In addition, cost data were collected almost 10 years ago [4, 9]. More information is needed to reflect the current HRQOL of HFMD patients and their economic burden in China.

Hence, this study aimed to assess HRQOL in children with HFMD before and after treatment and explore the sociodemographic characteristics associated with HRQOL. Furthermore, we estimated the economic burden and identified the factors that affect cost by performing a survey in children with HFMD in three regions with different levels of economic development in China.

2 Methods

2.1 Study Design and Study Population

In this study, the HRQOL and cost of hospitalized children with HFMD were estimated, and data were collected by face-to-face interviews from January to October 2019. The inclusion criteria for patients were as follows: (i) children aged no more than 5 years, (ii) children with a clinical diagnosis of HFMD, (iii) children who were hospitalized, and (vi) children with no concomitant diseases. The inclusion criteria for the guardians included (i) being the parents or the primary caregiver of the patient and (ii) being able to understand the questionnaire. After providing explicit informed consent, eligible patients and their guardians were invited to participate in the study. This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of School of Public Health, Fudan University (IRB00002408).

The study adopted a stratified sampling method to make the survey results more representative. Three provincial capital cities located in the eastern (Shanghai), central (Zhengzhou), and western (Kunming) regions of China were sampled to represent high, middle, and low socioeconomic levels, respectively. Then, we sampled a tertiary general hospital or children's specialized hospital as study sites in each city.

Respondents introduced by doctors were recruited for this research and received a 50 CNY voucher as an incentive if they completed the survey. Two face-to-face surveys with consenting patients and their guardians were conducted to collect data at different time points. The first interview was performed within the first 2 days after hospitalization. A questionnaire was used to collect data on the sociodemographic characteristics of the children and their guardians and to assess the patients' HRQOL via the proxy youth version of the 5-level EQ-5D questionnaire (EQ-5D-Y-5L, Y-5L). The sociodemographic characteristics of the patients included age, sex, and medical insurance status. The guardians' sociodemographic characteristics included age, sex, relationship with the child, education level, marital status, employment status, monthly income level, ethnicity, residence type, and religious status. The second interview was conducted when the child was discharged, assessing the change in patients' HRQOL with the Y-5L questionnaire and recording total hospitalization costs, out-of-pocket costs, insurance costs (if covered by insurance), traffic costs, lost work time, and the length of stay in the hospital.

2.2 Health-Related Quality of Life Measurement

The Y-5L questionnaire is based on the widely used EQ-5D-5L questionnaire with more child-friendly wording and is specifically designed to measure the HRQOL of children and adolescents.

The questionnaire contains two parts: a descriptive system and the EQ visual analogue scale (VAS). The descriptive system consists of five dimensions: mobility (walking about); looking after myself; doing usual activities; having pain or discomfort; and feeling worried, sad, or unhappy

[13]. Each dimension has five response levels, including no problems (level 1), a little bit of problems (level 2), some problems (level 3), a lot of problems (level 4), and extreme problems (level 5) [13]. The system thus defines 3125 (5^5) different health states. Each health state can be summarized into an index value (health utility score, HUS) by applying a country- or region-specific formula (value set) estimated from the general population that assigns a value corresponding to each of the levels in each dimension. Given that the Chinese Y-5L questionnaire value set is not currently available, a Chinese EQ-5D-5L questionnaire value set (adult version) was an alternative formula used to calculate HUS in the study [14].

The EQ-VAS score can also be used as a quantitative indicator of health outcomes. The EQ-VAS records a respondent's self-rated health status on a vertical scale. The scale ranges from 0 to 100, with 0 for "the worst health you can imagine" and 100 for "the best health you can imagine."

In the study, we assumed that the "self-care" dimension was not relevant, considering that children aged 0–5 years often need to be cared for by their parents. Therefore, we did not ask respondents to report the response of this dimension and set the responses at level 1. We also assumed that the "mobility (walking about)" dimension was insignificant for children under 18 months of age who could not stand (the response set at level 1), which is in line with a previous study [9]. For children over 18 months, their guardians were asked to report the level of "mobility (walking about)" dimension.

2.3 Economic Burden of HFMD

We retrospectively evaluated the total hospitalization cost and total cost of HFMD. The hospitalization cost was defined as the direct medical costs, including out-of-pocket costs, and insurance costs (if any). The total cost consisted of the total hospitalization costs, traffic costs, and indirect costs. Hourly wage was calculated from the latest published annual average income in China in 2021 (8 h per work day and 250 work days per year) [15, 16]. Indirect costs were estimated using the human capital approach, which was calculated by multiplying the loss of work time by the hourly wage. The remaining costs were directly obtained from the respondent's reported information. All cost data were adjusted to 2021 Chinese Yuan (CNY) using China's annual consumer price index [17].

2.4 Statistical Analysis

Descriptive analysis was performed to present the social demographic characteristics, distributions of Y-5L dimension responses, summary of the Y-5L HUS, the EQ-VAS score and various costs related to HFMD. A *t*-test or ANOVA was used to compare differences when continuous variables followed a normal distribution; otherwise, the Wilcoxon-Mann−Whitney test or Kruskal−Wallis *H* test was used for difference analysis. Continuous variables are presented as the mean, standard deviation (SD) and range or median and interquartile range (IQR). The chi-square test was used to compare the categorical variables, which are described by the number and percentage of the total sample. The HUS, EQ-VAS score and costs were further compared between different region samples using the kwAllPairsDunn (post hoc analysis) test to determine which pairwise groups differed [18]. Bonferroni correction was applied for multiple comparisons.

The important factors associated with the HUS and economic burden were explored by multiple linear regression models. In the HUS analysis, the dependent variables in the models were the baseline HUS and HUS difference. For economic burden analysis, the dependent variables in the models were hospitalization costs and total costs. All the models were adjusted with the independent variables including region, age, sex, ethnicity, residence type, and the number of hospital days for children and religious status, education level, marital status, employment status, monthly income level, and lost work time for guardians. All predictors were tested in the models using forward and backward selection to determine the final models. Given the heteroscedasticity and nonnormal distribution of cost data, a natural logarithmic transformation of the costs was performed.

All statistical analyses were conducted using R software (version 4.2.2). A two-tailed *P*-value less than 0.05 was considered statistically significant.

3 Results

3.1 Characteristics of Study Subjects

A total of 296 patients with a diagnosis of HFMD were included in the analysis. Of these, 120, 120, and 56 patients were from Shanghai, Zhengzhou, and Kunming, respectively. The characteristics of the enrolled patients and their guardians are presented in Table 1. In this cohort, 49.7% (147/296) of the patients were boys, and 50.3% (149/296) were girls. The mean (SD) age of the patients was 3.07 (1.50) years old. A total of 69.9% (207/296) of the guardians reported that they did not use any medical insurance, with the highest being for patients in Kunming (89.3%). A total of 73.6% of the guardians were female, and most of them were the mothers of the children (71.6%). The mean (SD) age of the guardians was 31.30 (5.48) years old, and most of them were married (97.6%). More than half of the guardians had received a university education or above (52.0%), and most of them worked in enterprises or were self-employed (53.9%). In terms of income, 35.1% of the guardians earned 20,000–30,000 CNY per month, and 38.9% earned 10,000–20,000 CNY

per month. Almost all of the guardians were Han Chinese (97.0%), and nearly two-thirds of them were living in cities (63.5%) and were not religious (97.3%). The characteristics of the patients and their guardians statistically differed among the three regions except for the sex of the guardian ($P = 0.117$), marital status ($P = 0.071$), and religious status ($P = 0.258$).

3.2 Health-Related Quality of Life of the Children

The responses for each dimension of the Y-5L questionnaire at admission and discharge are presented in Table 2. At admission, the highest proportion of the respondents with problems was in the *having pain or discomfort* dimension (97.6%). For the *mobility* (*walking about*) ($P = 0.009$) and *having pain or discomfort* ($P = 0.031$) dimensions, there were significant differences among the three regions. Moreover, the patients and guardians from Shanghai had the highest proportion of reported problems in the *mobility* (*walking about*) dimension, while the children and guardians from Zhengzhou had the highest proportion of problems in the *having pain or discomfort* dimension. At discharge, the HRQOL of the patients improved significantly after treatment. For all samples, over half of respondents reported no problems in all dimensions (from 62.8 to 74.0%). There were significant differences in responses among the three regions in the dimensions of *having pain or discomfort* ($P < 0.001$) and *feeling worried, sad, or unhappy* ($P < 0.001$). In addition, the guardians from Kunming reported the fewest problems in these two dimensions.

Table 3 presents the Y-5L HUS and EQ-VAS scores of the children with HFMD in the three regions. Regardless of admission, discharge, and admission-and-discharge differences, the HUS and VAS score among the three regions were significantly different ($P < 0.05$). At admission, the mean (SD) HUS of the patients was 0.730 (0.140), and the patients from Shanghai had the lowest HUS (0.710). The mean (SD) VAS score of all respondents was 60.33 (16.52), and similarly, the children from Shanghai had the lowest score (57.38). At discharge, patients' HUS and VAS scores both improved substantially, increasing to 0.920 (0.120) and 89.95 (11.88), respectively. The children from Kunming reported the highest HUS (0.950) and VAS score (96.95). For admission-and-discharge differences, the HUS improved by an average value of 0.180. In terms of regions, the HUS increased by 0.210, 0.150 and 0.200 in children from Shanghai, Zhengzhou, and Kunming, respectively. Similarly, the children from Shanghai reported the largest VAS score improvement (31.55).

On post hoc analysis, the HUS reported by the children from Shanghai and Zhengzhou were significantly different at admission (0.710 versus 0.750, $P = 0.041$) and at discharge (0.210 versus 0.150, $P < 0.001$). In addition, there were significant differences in VAS scores between patients from Shanghai and Kunming at admission (57.38 versus 72.05, $P < 0.001$) and at discharge (88.92 versus 96.95, $P < 0.001$). The change in the VAS score was also significant (31.55 versus 24.89, $P < 0.020$). When comparing the VAS score and HUS of children from Zhengzhou and Kunming, there were significant differences in the VAS score at admission (57.83 versus 72.05, $P < 0.001$), the VAS score at discharge (87.71 versus 96.95, $P < 0.001$), the HUS at discharge (0.900 versus 0.950, $P = 0.034$), and the change in the HUS before and after receiving treatment (0.150 versus 0.200, $P = 0.003$) (Table 3).

3.3 Economic Burden of HFMD

The cost of patients with HFMD is presented in Table 4. The mean (SD) total economic burden of HFMD was 5157 (2175) CNY per patient. The patients from Shanghai and Kunming reported the average highest (5491 CNY) and lowest total cost (3875 CNY), respectively. The mean (SD) hospitalization cost was 4037 (2434) CNY. The mean hospitalization cost was 4559 (2364) CNY, 4488 (2463) CNY and 1951 (1048) CNY in Shanghai, Zhengzhou, and Kunming, respectively. The mean length of stay was 5.2 (2.1) days, and the patients from Kunming reported the shortest hospitalization stays (4.4 days). However, the average hours of loss of work for guardians in Kunming (44.5 h) was approximately twice that of guardians in Shanghai (20.5 h) and Zhengzhou (20.7 h). Therefore, the guardians from Kunming reported the highest indirect cost (1887 CNY), followed by those from Zhengzhou (878 CNY) and Shanghai (872 CNY).

3.4 Regression Analyses

The results of the multiple linear regression model illustrating the association between the baseline HUS and sociodemographic variables are presented in Table 5. Compared with the patients covered by any medical insurance, those who paid all by themselves were associated with a significant reduction in the HUS by 0.04 (95% CI, − 0.07 to 0.00, $P = 0.039$). Compared with that for children from Shanghai, there was a significant increase in the HUS for patients from Zhengzhou (0.05, 0.01 to 0.08, $P = 0.045$) and Kunming (0.05, 0.00 to 0.10, $P = 0.045$).

For the change in the HUS at discharge, younger children had significantly lower HUS difference than older children. Compared with patients from Shanghai, there was a significant smaller reduction in HUS difference for patients from Zhengzhou. The same results were also found in the comparison of rural patients to city patients. Additionally, compared with children whose guardians worked in enterprises or

Table 1 Sociodemographic characteristics of the children with HFMD and their guardians in three regions

Characteristics	Total *N* = 296	Shanghai *N* = 120	Zhengzhou *N* = 120	Kunming *N* = 56	*P*-value[a]
Sex					0.021
Boys	147 (49.7%)	57 (47.5%)	53 (44.2%)	37 (66.1%)	
Girls	149 (50.3%)	63 (52.5%)	67 (55.8%)	19 (33.9%)	
Age (year)					< 0.001
Mean (SD)	3.07 (1.50)	3.45 (1.53)	2.83 (1.29)	2.77 (1.71)	
Median (IQR)	3.17 (1.81–4.33)	3.42 (2.17–4.96)	3.12 (1.67–3.96)	2.54 (1.46–3.50)	
Range	0.50–10.00	0.75–5.75	0.50–5.00	0.83–10.00	
Medical insurance					0.002
Yes	83 (28.0%)	37 (30.8%)	41 (34.2%)	5 (8.9%)	
No	207 (69.9%)	79 (65.8%)	78 (65%)	50 (89.3%)	
Unknown/refuse to answer	6 (2.0%)	4 (3.3%)	1 (0.8%)	1 (1.8%)	
Guardian's age (year)					0.001
Mean (SD)	31.30 (5.48)	30.46 (3.2)	31.55 (3.35)	32.55 (10.56)	
Median (IQR)	30 (28-32)	30 (28-32)	31 (30-34)	29 (27-32)	
Range	24–67	25–40	25–39	24–67	
Guardian's sex					0.117
Male	78 (26.4%)	32 (26.7%)	37 (30.8%)	9 (16.1%)	
Female	218 (73.6%)	88 (73.3%)	83 (69.2%)	47 (83.9%)	
Relationship					< 0.001
Father	77 (26.0%)	32 (26.7%)	37 (30.8%)	8 (14.3%)	
Mother	212 (71.6%)	88 (73.3%)	82 (68.3%)	42 (75%)	
Others[b]	7 (2.4%)	0 (0.0%)	1 (0.8%)	6 (10.7%)	
Education level					< 0.001
Uneducated	3 (1.0%)	0 (0.0%)	0 (0.0%)	3 (5.4%)	
Primary school	12 (4.1%)	1 (0.8%)	2 (1.7%)	9 (16.1%)	
Junior high school	14 (4.7%)	0 (0.0%)	1 (0.8%)	13 (23.2%)	
Senior high school	52 (17.6%)	15 (12.5%)	17 (14.2%)	20 (35.7%)	
Junior college	61 (20.6%)	26 (21.7%)	29 (24.2%)	6 (10.7%)	
University and above	154 (52.0%)	78 (65%)	71 (59.2%)	5 (8.9%)	
Marital status					0.071
Married	286 (97.6%)	118 (98.3%)	119 (99.2%)	52 (92.9%)	
Separated	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	
Divorced	6 (2.0%)	2 (1.7%)	1 (0.8%)	3 (5.4%)	
Employment status	*N* = 188	*N* = 120	*N* = 12	*N* = 56	< 0.001
No	38 (20.2%)	12 (10.0%)	12 (100.0%)	14 (25.0%)	
Yes	150 (79.8%)	108 (90.0%)	0 (0.0%)	42 (75.0%)	
Employment	*N* = 295	*N* = 119	*N* = 120	*N* = 56	< 0.001
Enterprise/self-employed	159 (53.9%)	69 (58%)	77 (64.2%)	13 (23.2%)	
Government/institution employee	71 (24.1%)	37 (31.1%)	30 (25.0%)	4 (7.1%)	
Full-time stay at home/housewife	25 (8.5%)	7 (5.9%)	6 (5.0%)	12 (21.4%)	
Retire	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	
Farming	18 (6.1%)	1 (0.8%)	3 (2.5%)	14 (25%)	
Temporary worker	20 (6.8%)	5 (4.2%)	4 (3.3%)	11 (19.6%)	
Unemployed	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	
Monthly income (CNY)					< 0.001
< 5000	18 (6.1%)	2 (1.7%)	6 (5.0%)	10 (17.9%)	
5000–10,000	59 (19.9%)	18 (15.0%)	22 (18.3%)	19 (33.9%)	
10,000–20,000	115 (38.9%)	51 (42.5%)	42 (35.0%)	22 (39.3%)	
20,000–30,000	104 (35.1%)	49 (40.8%)	50 (41.7%)	5 (8.9%)	

Table 1 (continued)

Characteristics	Total $N = 296$	Shanghai $N = 120$	Zhengzhou $N = 120$	Kunming $N = 56$	P-value[a]
Guardian's ethnicity					0.037
Han	287 (97.0%)	118 (98.3%)	118 (98.3%)	51 (91.1%)	
Others	9 (3.0%)	2 (1.7%)	2 (1.7%)	5 (8.9%)	
Residence type					< 0.001
City	188 (63.5%)	92 (76.7%)	93 (77.5%)	3 (5.4%)	
Town	44 (14.9%)	18 (15.0%)	17 (14.2%)	9 (16.1%)	
Rural	63 (21.3%)	9 (7.5%)	10 (8.3%)	44 (78.6%)	
Unknown/refuse to answer	1 (0.3%)	1 (0.8%)	0 (0.0%)	0 (0.0%)	
Religious status					0.258
No	288 (97.3%)	114 (95.0%)	119 (99.2%)	55 (98.2%)	
Yes	5 (1.7%)	4 (3.3%)	1 (0.8%)	0 (0.0%)	
Unknown/refuse to answer	3 (1.0%)	2 (1.7%)	0 (0.0%)	1 (1.8%)	

SD standard deviations, *IQR* interquartile range, *CNY* Chinese Yuan

[a]Comparison of population characteristics among the three regions. Categorical variables and continuous variables were analyzed using chi-square test and Kruskal–Wallis H test, respectively

[b]This refers to a guardian such as a nonparental relative of the affected child

were self-employed, the children whose guardians engaged in other professions involving government or institution employees, full-time stay-at-home parents or housewives, and farmers showed a significantly lower HUS difference (Table 5).

Similar regression models were performed to assess the association of the total cost and hospitalization costs with the sociodemographic characteristics (Table 6). The total cost was significantly associated with region, loss of work time, and length of stay, while the hospitalization cost of HFMD patients was significantly associated with region and length of stay.

4 Discussion

This study used the Y-5L questionnaire to compare the HRQOL of children with HFMD before and after treatment. A face-to-face interview was conducted with guardians of HFMD patients from three regions representing different socioeconomic statuses in China. In addition to measuring the HUS, we also estimated the costs of HFMD patients and further explored the important factors affecting the HUS and costs. The results suggest that children with HFMD could have both worse physical and psychological health, with an average HUS of 0.730 and 0.920 before and after treatment, respectively. We also found that the total cost per HFMD patient ranged from approximately 827 CNY to 14,593 CNY among different regions, which was mainly attributed to hospitalization costs. Key factors that had a significant influence on health status and economic burden were identified.

Some published studies have focused on the HRQOL of HFMD patients [4, 8–10]. Three studies [4, 8, 10] reported disability-adjusted life-years (DALYs) and TAPQOL scale scores of patients with HFMD. Moreover, our results cannot be directly compared with their results because different measurement methods and indicators were applied. Zheng et al. [9] used the EQ-5D-3L proxy 2 questionnaire to measure the HUS of children with HFMD aged 6 months to 5 years in 31 provinces in China. The average HUS and VAS scores for mild outpatients were 0.83 (95% CI 0.80–0.83) and 75 (74–76), respectively. For mild hospitalized patients, the mean HUS and VAS score was 0.74 (0.73–0.75) and 68 (67–69), respectively. In terms of severe patients, the mean HUS was 0.61 (0.59–0.62). Similar results were observed in our analysis, which demonstrates the health deterioration of children with severe HFMD. Therefore, it is important to improve the HRQoL of HFMD patients to reduce their disease burden.

For patients at discharge, *doing usual activity* was the dimension with the highest proportion of reported problems. However, the remaining dimensions were only slightly better. It was suggested that HFMD may reduce the vitality of children even after treatment. In addition, guardians might be more aware of the direct changes in the *doing usual activity* dimension than other dimensions. Thus, the psychological condition of HFMD patients who have received therapy should be given more attention. The study also found that children from Kunming covered by medical insurance

Table 2 Guardians' responses to the proxy EQ-5D-Y-5L dimensions at admission and discharge

Dimension	At admission				*P*-value[a]	At discharge				*P*-value[a]
	Total	Shanghai	Zhengzhou	Kunming		Total	Shanghai	Zhengzhou	Kunming	
	N = 296	*N* = 120	*N* = 120	*N* = 56		*N* = 296	*N* = 120	*N* = 120	*N* = 56	
Mobility (walking about)					0.009					0.372
No problems	159 (53.7%)	54 (45.0%)	67 (55.8%)	38 (67.9%)		219 (74.0%)	85 (70.8%)	90 (75.0%)	44 (78.6%)	
Mild problems	108 (36.5%)	48 (40.0%)	45 (37.5%)	15 (26.8%)		68 (23.0%)	31 (25.8%)	28 (23.3%)	9 (16.1%)	
Moderate problems	28 (9.5%)	18 (15.0%)	8 (6.7%)	2 (3.6%)		8 (2.7%)	4 (3.3%)	2 (1.7%)	2 (3.6%)	
Severe problems	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Extreme problems	1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.8%)		1 (0.3%)	0 (0.0%)	0 (0.0%)	1 (1.8%)	
Doing usual activity					0.363					0.431
No problems	85 (28.7%)	29 (24.2%)	35 (29.2%)	21 (37.5%)		186 (62.8%)	77 (64.2%)	74 (61.7%)	35 (62.5%)	
Mild problems	161 (54.4%)	64 (53.3%)	69 (57.5%)	28 (50.0%)		92 (31.1%)	35 (29.2%)	41 (34.2%)	16 (28.6%)	
Moderate problems	41 (13.9%)	22 (18.3%)	14 (11.7%)	5 (8.9%)		14 (4.7%)	7 (5.8%)	4 (3.3%)	3 (5.4%)	
Severe problems	6 (2.0%)	4 (3.3%)	1 (0.8%)	1 (1.8%)		2 (0.7%)	1 (0.8%)	1 (0.8%)	0 (0.0%)	
Extreme problems	3 (1.0%)	1 (0.8%)	1 (0.8%)	1 (1.8%)		2 (0.7%)	0 (0.0%)	0 (0.0%)	2 (3.6%)	
Having pain or discomfort					0.031					< 0.001
No problems	7 (2.4%)	3 (2.5%)	2 (1.7%)	2 (3.6%)		203 (68.6%)	79 (65.8%)	69 (57.5%)	55 (98.2%)	
Mild problems	183 (61.8%)	73 (60.8%)	85 (70.8%)	25 (44.6%)		80 (27.0%)	37 (30.8%)	42 (35.0%)	1 (1.8%)	
Moderate problems	92 (31.1%)	37 (30.8%)	28 (23.3%)	27 (48.2%)		13 (4.4%)	4 (3.3%)	9 (7.5%)	0 (0.0%)	
Severe problems	14 (4.7%)	7 (5.8%)	5 (4.2%)	2 (3.6%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Extreme problems	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Feeling worried, sad, or unhappy					0.215					< 0.001
No problems	9 (3.0%)	5 (4.2%)	3 (2.5%)	1 (1.8%)		210 (70.9%)	83 (69.2%)	73 (60.8%)	54 (96.4%)	
Mild problems	158 (53.4%)	54 (45%)	72 (60%)	32 (57.1%)		71 (24.0%)	31 (25.8%)	38 (31.7%)	2 (3.6%)	
Moderate problems	96 (32.4%)	43 (35.8%)	32 (26.7%)	21 (37.5%)		10 (3.4%)	4 (3.3%)	6 (5.0%)	0 (0.0%)	
Severe problems	30 (10.1%)	16 (13.3%)	12 (10%)	2 (3.6%)		5 (1.7%)	2 (1.7%)	3 (2.5%)	0 (0.0%)	
Extreme problems	3 (1.0%)	2 (1.7%)	1 (0.8%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

EQ-5D-Y-5L Youth version of the Five-level EuroQol-five dimensions questionnaire

[a]Calculated using the chi-square test

[b]Children younger than 18 months were assumed to have no problem on walking about dimension

Table 3 EQ-5D-Y-5L HUS and EQ VAS scores of children with HFMD in the three regions

	Total $N = 296$	Shanghai $N = 120$	Zhengzhou $N = 120$	Kunming $N = 56$	Post hoc analysis[a]	P-value[b]
HUS baseline					SH < ZZ	0.032
Mean (SD)	0.730 (0.140)	0.710 (0.150)	0.750 (0.130)	0.750 (0.140)		
Median (IQR)	0.782 (0.647–0.848)	0.760 (0.613–0.824)	0.782 (0.713–0.848)	0.782 (0.699–0.848)		
Range	0.170–1.000	0.220–0.950	0.270–0.950	0.170–1.000		
VAS baseline					SH < KM, ZZ < KM	< 0.001
Mean (SD)	60.33 (16.52)	57.38 (16.39)	57.830 (16.09)	72.05 (12.24)		
Median (IQR)	64 (50–74)	60 (46.25–70.25)	62.5 (45–70)	75 (60–80)		
Range	18–85	18–80	22–80	40–85		
HUS discharge					ZZ < KM	0.039
Mean (SD)	0.920 (0.120)	0.910 (0.120)	0.900 (0.120)	0.950 (0.100)		
Median (IQR)	0.955 (0.848–1.000)	0.978 (0.840–1.000)	0.951 (0.840–1.000)	1.000 (0.936–1.000)		
Range	0.295–1.000	0.460–1.000	0.300–1.000	0.420–1.000		
VAS discharge					SH < KM, ZZ < KM	< 0.001
Mean (SD)	89.95 (11.88)	88.92 (11.91)	87.71 (12.92)	96.95 (5.09)		
Median (IQR)	94 (85.75–100)	92 (83–97)	90 (83.75–97.25)	100 (95–100)		
Range	30–100	30–100	37–100	75–100		
HUS difference					SH > ZZ, ZZ < KM	< 0.001
Mean (SD)	0.180 (0.120)	0.210 (0.130)	0.150 (0.110)	0.200 (0.080)		
Median (IQR)	0.176 (0.107–0.256)	0.198 (0.112–0.287)	0.126 (0.068–0.218)	0.197 (0.152–0.256)		
Range	0.000–0.618	0.000–0.620	0.000–0.580	0.000–0.430		
VAS difference					SH > KM	0.022
Mean (SD)	29.61 (14.53)	31.55 (14.46)	29.88 (15.44)	24.89 (11.55)		
Median (IQR)	25 (18.75–40.00)	27 (20–41.25)	25 (17–41)	22.5 (15–31.25)		
Range	0.00–76.00	11–76	9–75	0–50		

EQ-5D-Y-5L Youth version of the Five-level EuroQol-five dimensions questionnaire; *HUS* health utility score; *EQ VAS* EuroQol Visual analog scale; *HFMD* gand, foot and mouth disease; *SD* standard deviations; *IQR* interquartile range; *SH* Shanghai; *ZZ* Zhengzhou; *KM* Kunming

[a]Comparison using kw All Pairs Dunn test by Bonferroni correction

[b]Calculated using Kruskal–Wallis *H* test

had higher baseline HUSs than those from other regions. Kunming is located in western China and has a relatively low socioeconomic level, fewer risk factors for HFMD in low economic regions, and better satisfaction due to medical insurance coverage [19]. Children from Shanghai living in city areas whose guardians worked in enterprises or were self-employed were more likely to show much higher HUS differences. Usually, regions with good economic status, such as Shanghai, allocate better medical resources and provide better health care, which leads to better health improvement.

Several studies have explored the economic burden of HFMD patients in China [4, 10–12, 20]. Compared with the studies that included inpatients with worse conditions [4, 10, 20], in our study, lower average hospitalization and total costs were reported. However, the costs of patients in this study were higher than the outpatient costs calculated in previous studies [11, 12]. The costs of hospitalization in our study were similar to those of general inpatients (3312–5520 CNY) after being adjusted to 2021 CNY [12]. The gross domestic product (GDP) per capita of Shanghai, Zhengzhou, and Kunming was 173,600 CNY, 100,563 CNY, and 85,400 CNY in 2021, respectively [21]. Correspondingly, the total cost accounts for 3.16%, 5.39%, and 4.53% of the local GDP per capita, respectively.

The guardians in Kunming reported the highest loss of work time. Compared with other regions in China, in Kunming, the level of social and economic development is relatively low [22]. However, medical resources are more scarce in other cities in Yunnan Province. Patients living in Yunnan outside of Kunming are willing to seek better treatment and travel to Kunming, resulting in an increased loss of time but a shorter length of stay.

This study has some limitations. First, only hospitalized patients without complications were included. Second, the Y-5L questionnaire is mainly designed for children over

Table 4 Economic burden of disease in children with HFMD per person

	Total *N* = 296	Shanghai *N* = 120	Zhengzhou *N* = 120	Kunming *N* = 56	Post hoc analysis[b]	*P*-value[a]
Traffic cost (CNY)					–	0.287
Mean (SD)	54 (109)	61 (134)	55 (103)	38 (36)		
Median (IQR)	29 (12–47)	26 (10–45)	31 (20–48)	26 (12–54)		
Range	0–724	0–724	0–654	0–155		
Out-of-pocket cost (CNY)					SH > KM, ZZ > KM	< 0.001
Mean (SD)	1854 (1278)	2000 (1269)	2022 (1281)	1180 (1078)		
Median (IQR)	1462 (896–2427)	1600 (1098–2614)	1688 (1037–2563)	890 (808–1014)		
Range	182–6721	414–6721	424–6516	182–5171		
Hospitalization cost (CNY)					SH > KM, ZZ > KM	< 0.001
Mean (SD)	4037 (2434)	4559 (2364)	4488 (2463)	1951 (1048)		
Median (IQR)	3278 (2068–5414)	3858 (2633–6196)	3951 (2640–6021)	1659 (1478–1948)		
Range	542–12,411	1345–12,411	1241–11,790	542–5171		
Insurance cost (CNY)	*N* = 83	*N* = 37	*N* = 41	*N* = 5	–	0.499
Mean (SD)	1498 (1009)	1554.1 (1273.3)	1435 (776)	1593 (398)		
Median (IQR)	1329 (775–1854)	1068 (770–1655)	1362 (775–1847)	1551 (1448–1862)		
Range	362–6205	362–6205	465–4477	1034–2069		
Indirect cost (CNY)[c]					–	0.075
Mean (SD)	1066 (1079)	872 (498)	878 (451)	1887 (2101)		
Median (IQR)	806 (509–1358)	721 (509–1061)	764 (583–1114)	1697 (0–2546)		
Range	0–10,183	212–2376	212–2037	0–10,183		
Total cost (CNY)[d]					SH > KM, ZZ > KM	< 0.001
Mean (SD)	5157 (2715)	5491 (2689)	5421 (2685)	3875 (2495)		
Median (IQR)	4630 (3124–6793)	4922 (3350–7083)	4914 (3364–6771)	3326 (1759–5346)		
Range	827–14,593	1653–14,593	1527–13,420	827–11,822		
Loss of work time (h)					–	0.075
Mean (SD)	25.1 (25.4)	20.5 (11.8)	20.7 (10.6)	44.5 (49.5)		
Median (IQR)	19 (12–32)	17 (12–25)	18 (13.75–26.25)	40 (0–60)		
Range	0–240	5–56	5–48	0–240		
Length of stay (days)					–	0.072
Mean (SD)	5.2 (2.1)	5.3 (2.1)	5.4 (2.1)	4.4 (1.7)		
Median (IQR)	5 (3–7)	5 (3–7)	5 (3–7)	5 (4–5)		
Range	0–10	3–10	3–10	0–8		

HFMD Hand, foot, and mouth disease; *SD* standard deviations; *IQR* interquartile range; *SH* Shanghai; *ZZ* Zhengzhou; *KM* Kunming; *CNY* Chinese Yuan

[a]Comparison using kw All Pairs Dunn test by Bonferroni correction

[b]Calculated using Kruskal–Wallis *H* test

[c]Indirect cost: loss of work hour multiples income per hour that converted from annual average income in China 2021 (8 h per work day, and 250 work days per year)

[d]Total cost includes hospitalization cost, traffic cost and indirect cost. All cost data were adjusted to 2021 Chinese Yuan (CNY) using China's annual consumer price index

6 years old, and the reliability and validity of its proxy version for guardians of children under 5 years old need to be further tested. Third, the survey was answered by the guardians of the patients, and the results may be influenced by respondents' preferences. Fourth, without the Chinese Y-5L questionnaire value set, the standard Chinese EQ-5D-5L questionnaire value set was used to calculate the HUS, and future exploration should be performed when it is available. Fifth, the costs were mainly reported by guardian recall of treatment-related costs and recall bias may occur. Last, the guardians of children did not know the specific clinical characteristics when we surveyed. The absence of data on specific clinical characteristics such as disease severity and treatment methods prevent the evaluation of their impact on HRQOL and economic burden.

Table 5 Multiple regression analysis of significant factors of the baseline HUS and HUS difference between baseline and follow-up

	Coefficient	95% CI		*P*-value[a]	Coefficient	95% CI		*P*-value[a]
		LCI	UCI			LCI	UCI	
		Utility baseline				Utility difference		
Region (Shanghai[b])								
Zhengzhou	0.05	0.01	0.08	0.013	− 0.06	− 0.09	− 0.03	< 0.001
Kunming	0.05	0.00	0.10	0.033	− 0.03	− 0.09	0.02	0.233
Age (year)	–	–	–	–	0.01	0.00	0.02	0.037
Medical insurance (yes[b])								
No	− 0.04	− 0.07	0.00	0.039	–	–	–	–
Employment (enterprise/self-employed[b])								
Government/institution employee	–	–	–	–	− 0.06	− 0.10	− 0.03	< 0.001
Full-time stay at home/housewife	–	–	–	–	− 0.05	− 0.10	0.00	0.060
Retire	–	–	–	–	0.07	− 0.16	0.30	0.528
Farming	–	–	–	–	− 0.07	− 0.14	0.00	0.036
Temporary worker	–	–	–	–	− 0.05	− 0.11	0.01	0.133
Unemployed	–	–	–	–	− 0.14	− 0.38	0.10	0.247
Residence type (city[b])								
Town	–	–	–	–	0.00	− 0.04	0.04	0.886
Rural	–	–	–	–	0.06	0.01	0.11	0.016
Religious status (no[b])								
Yes	0.09	− 0.04	0.21	0.172	− 0.08	− 0.18	0.02	0.118
Unknown/refuse to answer	0.15	− 0.04	0.35	0.126	− 0.12	− 0.28	0.04	0.139

HUS health utility score, *CI* confidence interval, *LCI* lower confidence interval, *UCI* upper confidence interval

[a]Calculated using multiple linear regression

[b]Reference category

Table 6 Multiple regression analysis results of significant factors of the total cost and hospitalization costs

	Coefficient	95% CI		*P*-value[b]	Coefficient	95% CI		*P*-value[b]
		LCI	UCI			LCI	UCI	
		Total cost[a]				Hospitalization cost		
Region (Shanghai[c])								
Zhengzhou	− 0.03	− 0.11	0.05	0.498	− 0.05	− 0.15	0.05	0.335
Kunming	− 0.54	− 0.65	− 0.43	< 0.001	− 0.67	− 0.80	− 0.55	< 0.001
Loss of work time (h)	0.01	0.01	0.01	< 0.001	–	–	–	–
Length of stay (days)	0.14	0.12	0.16	< 0.001	0.17	0.15	0.20	< 0.001

CI confidence interval

[a]Total cost includes hospitalization costs, traffic costs, and indirect costs

[b]Calculated using multiple linear regression

[c]Reference category

5 Conclusion

HFMD deteriorates HRQOL and increases the economic burden of patients in China. The main problems after treatment occur in the doing usual activity activities dimension. Regional variations in health utility and costs are observed across China.

Author Contributions TZ: Conceptualization, methodology, data analysis, and writing (original draft and revision). HFH: Methodology, data analysis, manuscript writing, and revision. JYG: Methodology, data analysis, and manuscript revision. HJY: data collection and manuscript revision. MJ: manuscript revision. PW: Conceptualization, methodology, critical manuscript revision, supervision, and project administration. All authors critically revised the manuscript and approved the final version of manuscript.

Funding This research was funded by the National Institute for Health and Care Research (GHR 16/137/09) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the author(s) and not necessarily those of the NIHR or the UK government.

Data Availability The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Code Availability The code for the current study may be available from the corresponding author on reasonable request.

Declarations

Conflict of Interest All the authors declare no competing interests.

Ethical Approval This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of School of Public Health, Fudan University (IRB00002408).

Informed Consent to Participate Informed consent was obtained from the parent/guardian of each participant prior to enrolment in this study.

Consent for Publication The participants gave their consent for the data to be analyzed and published in aggregated data.

References

1. Xing WJ, Liao QH, Viboud C, et al. Hand, foot, and mouth disease in China, 2008–12: an epidemiological study. Lancet Infect Dis. 2014;14(4):308–18. https://doi.org/10.1016/S1473-3099(13)70342-6.
2. Cox B, Levent F. Hand, foot, and mouth disease. JAMA. 2018;320(23):2492. https://doi.org/10.1001/jama.2018.17288.
3. Wu Y, Yeo A, Phoon MC, et al. The largest outbreak of hand; foot and mouth disease in Singapore in 2008: the role of enterovirus 71 and coxsackievirus A strains. Int J Infect Dis. 2010;14(12):e1076–81. https://doi.org/10.1016/j.ijid.2010.07.006.
4. Gan ZK, Jin H, Li JX, et al. Disease burden of enterovirus 71 in rural central China: a community-based survey. Hum Vaccin Immunother. 2015;11(10):2400–5. https://doi.org/10.1080/21645515.2015.1059980.
5. Solomon T, Lewthwaite P, Perera D, et al. Virology, epidemiology, pathogenesis, and control of enterovirus 71. Lancet Infect Dis. 2010;10(11):778–90. https://doi.org/10.1016/S1473-3099(10)70194-8.
6. Wu YZ, Wang TW, Zhao MY, et al. Spatiotemporal cluster patterns of hand, foot, and mouth disease at the province level in mainland China, 2011–2018. PLoS One. 2022;17(8): e0270061. https://doi.org/10.1371/journal.pone.0270061.
7. China national administration of disease prevention and control. Overview of the epidemic situation of statutory infectious diseases in 2021. http://www.nhc.gov.cn/jkj/new_index.shtml. Accessed 20 Mar 2023.
8. Koh WM, Badaruddin H, La H, et al. Severity and burden of hand, foot and mouth disease in Asia: a modelling study. BMJ Glob Health. 2018;3(1):e000442. https://doi.org/10.1136/bmjgh-2017-000442. (**Published 2018 Jan 26**).
9. Zheng YM, Jit M, Wu JT, et al. Economic costs and health-related quality of life for hand, foot and mouth disease (HFMD) patients in China. PLoS One. 2017;12(9):e0184266. https://doi.org/10.1371/journal.pone.0184266. (**Published 2017 Sep 21**).
10. Han Y, Ji H, Shen WQ, et al. Disease burden in patients with severe hand, foot, and mouth disease in Jiangsu Province: a cross-sectional study. Hum Vaccin Immunother. 2022;18(5):2049168. https://doi.org/10.1080/21645515.2022.2049168.
11. Wang H, Jiang SQ, Chen C, et al. Economic burden of outpatients with different subtypes of HFMD in Guangzhou. Modern Prevent Med. 2022;49(01):152–7 (**Published in Chinese**).
12. Wang XL, Wei HX, Jia L, et al. Summary of research in economic burden of hand, foot, and mouth disease in China. Chin J Epidemiol. 2020;41(2):273–9. https://doi.org/10.3760/cma.j.issn.0254-6450.2020.02.023. (**Published in Chinese**).
13. Kreimeier S, Greiner W. EQ-5D-Y as a health-related quality of life instrument for children and adolescents: the instrument's characteristics, development, current use, and challenges of developing its value set. Value Health. 2019;22(1):31–7. https://doi.org/10.1016/j.jval.2018.11.001.
14. Pan CW, Zhang RY, Luo N, et al. How the EQ-5D utilities are derived matters in Chinese diabetes patients: a comparison based on different EQ-5D scoring functions for China. Qual Life Res. 2020;29(11):3087–94. https://doi.org/10.1007/s11136-020-02551-0.
15. National Bureau of Statistics of China. The average annual wage of persons employed in urban non-private units in 2021. http://www.stats.gov.cn/sj/zxfb/202302/t20230203_1901472.html. Accessed 1 Apr 2023.
16. National Bureau of Statistics of China. The average annual wage of persons employed in urban private units in 2021. http://www.stats.gov.cn/xxgk/sjfb/zxfb2020/202205/t20220520_1857636.html. Accessed 1 Apr 2023.
17. National Bureau of Statistics of China. Consumer price index. http://www.stats.gov.cn/. Accessed 1 Apr 2023.
18. Dunn OJ. Multiple comparisons using rank sums. Technometrics. 1964;6:241–52. https://doi.org/10.1080/00401706.1964.10490181.
19. Zhang J, Li XH, Li L, et al. Etiology and epidemiology of hand, foot and mouth disease in China. Chin J Epidemiol. 2022;43(5):771–83. https://doi.org/10.3760/cma.j.cn112338-20211012-00788. (**Accessed in Chinese**).
20. Zheng YM, Yang J, Liao QH, et al. Direct medical costs and influencing factors in severe hand, foot and mouth disease in children aged between six months and five years old. Chin J Prev Med. 2017;51(1):87–92. https://doi.org/10.3760/cma.j.issn.0253-9624.2017.01.017. (**Published in Chinese**).
21. National Bureau of Statistics of China. http://www.stats.gov.cn. Accessed 20 Mar 2023.
22. National Bureau of Statistics of China. China city statistical yearbook. http://www.stats.gov.cn/sj/ndsj/2022/indexch.htm. Accessed 9 Apr 2023.