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ORIGINAL RESEARCH

Health related quality of life impact from rotavirus diarrhea on children and their family caregivers in Thailand

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ABSTRACT

Background: Rotavirus diarrhea is a major health problem among young children worldwide with potential negative impacts on health-related quality of life (HRQoL). This study assessed the impact of rotavirus diarrhea on HRQoL of children and their caregivers.

Methods: We performed a cross-sectional study among 460 hospitalized children with diarrhea aged under 5 years and their family caregivers at three hospitals in Phetchabun province, Thailand during May 2013 and February 2014. The severity of diarrhea was assessed using the Vesikari severity scoring system while the HRQoL was assessed using the EQ-5D-3L.

Results: The mean EQ-5D utility of children with all-causes diarrhea was 0.604. The utility of the rotavirus diarrhea group was significantly lower than that of the non-rotavirus diarrhea group (0.593 vs. 0.612; p-value = 0.040). The family caregiver's utility was 0.964 at baseline and significantly decreased to 0.620 (p-value = 0.041) when their children were hospitalized with diarrhea. In multiple regression analyses, severity but not rotavirus infection had significant negative impacts on the utility of both the children and their caregivers.

Conclusion: Diarrhea, either caused by rotavirus or non-rotavirus infection, resulted in substantial negative impacts on the quality of life of both the children and their caregivers.

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Rotavirus; diarrhea; quality of life; child; caregiver; utility

1. Introduction

Globally, diarrhea is the cause of 578,000 deaths of children aged under 5 years annually [1]. In developing countries, it is one of the leading causes of morbidity and mortality among children in this age group. Rotavirus is the most common cause of diarrhea, especially among infants and young children. It is transmitted primarily via the fecal-oral transmission from person to person or through contaminated food, water, and toys. Rotavirus diarrhea is associated with severe symptoms, which may lead to significant loss of water and electrolytes to dehydration and death if oral/intravenous rehydration solution is not administered as soon as possible. Approximately 37% of hospitalizations due to diarrhea or 215,000 deaths annually in children under the age of five worldwide were caused by rotavirus [2].

In Thailand, the reported incidence of diarrhea among children under 5 years (Bureau of Epidemiology, Ministry of Public Health) has decreased over the past five years from 10,000 cases in 2010 to 7595 cases per 100,000 populations in 2014. Similarly, diarrhea-related mortality rate has been reduced to 0.10 per 100,000 population in 2012 [3,4]. In Thailand, it was found that the proportion of rotavirus positive stool samples varied from 27% to 50% of hospitalized children with diarrhea [5–8].

Childhood diarrhea significantly affects impairment of physical and physiological function and may delay growth development through the decrease in absorption of nutrients [9,10]. Likewise, caregivers face various challenges related to caring for these children concerning disruptions in social life, stress, anxiety, and also economic consequences. Several evidences consistently reported the negative impacts of diarrhea, especially of rotavirus gastroenteritis, on both children and their caregivers [11–17].

Although disability-adjusted life year was used to measure disease burden especially among Low -and middle-income countries (LMICs), the use of health-related quality of life (HRQoL) in terms of utility is more common in conducting economic evaluation. Measuring the impact of rotavirus diarrhea on HRQoL in terms of utility is important in evaluating the effectiveness and cost-effectiveness of treatments for rotavirus diarrhea. To date, very few studies exist that have examined the utility among children with rotavirus diarrhea [13,16–18]. Furthermore, it should be noted that none were conducted in less developed countries, where the mortality caused by rotavirus is the greatest. In addition, the comparison of HRQoL between rotavirus diarrhea and non-rotavirus diarrhea is unknown.

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At present, the effect of rotavirus diarrhea on the quality of life of these children and their caregivers has not yet been studied in Thailand. The objectives of this study were to estimate HRQoL in terms of utility scores for children with rotavirus diarrhea and their caregivers, to compare utility scores between rotavirus diarrhea and non-rotavirus diarrhea, and to identify the factors associated with the utility scores of children with diarrhea and their caregivers.

2. Patients and methods

2.1. Participants and setting

Study participants were children hospitalized in the inpatient department with diarrhea and their corresponding caregivers. Decision on hospitalization depends mainly on physicians with agreement from parents. In this study, a caregiver was defined as a family member or a legal guardian or unpaid volunteer/friend, who provided direct care for the child. Diarrhea was defined as the presence of three or more watery or looser stools within a 24-hour period. Participants were recruited from one general hospital in urban area (Phetchabun hospital) and two community hospitals in rural area (Lomsak hospital and Nhongpai hospital), located in Phetchabun province, which was one of the study sites of the 'Effectiveness and Cost-effectiveness of Rotavirus Vaccination' study in Thailand [19] during May 2013 and February 2014.

The ward nurses recruited study participants according to the following eligible criteria: (i) children hospitalized with diarrhea, (ii) aged 2–59 months, (iii) living in Phetchabun province, (iv) availability of one caregiver, who can communicate in the Thai language, and (v) willing to participate in this study. Children who had underlying disease (e.g. bowel disease, immune deficiency, or cardiovascular disease) were excluded.

The sample size was calculated using the formula derived from Lemeshow et al. [20]. By using a standard deviation of 0.38 [18], setting the precision of estimate at 0.1, and adjusting for 10% loss to follow-up, the required sample size for children with rotavirus diarrhea was 55. With the assumption that 40% of diarrhea cases were caused by rotavirus infection [8,21], a minimal number of 153 children with all-cause diarrhea and their caregivers were to be recruited.

2.2. Study instruments

Measurement of the quality of life, especially in terms of utility among very young children, is challenging [22,23]. Using proxies (e.g. parents, physician, and teacher) is an alternative approach to assess the quality of life of these children. In this study, the family caregivers were used as proxies in assessing the quality of life of the children. The EQ-5D-3L (Thai version) was chosen as the instrument to measure quality of life among children and their caregivers not only because it had acceptable psychometric properties [24,25], but also as it is widely used and recommended by many health technology assessment guidelines, including the Thai's guideline [24,26]. In addition, recent systematic review found that EQ-5D was the most commonly used instrument for the measurement of health utility values in children and adolescents [27].

The EQ-5D questionnaires consist of two parts [28]. The first part is the health status measurement, which includes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels: no problems, some problems, and extreme problems. The second part is a direct valuation using the visual analog scale (VAS) that records the health status on a scale from 0 (the worst health state) to 100 (the best health state). For both parts, the caregivers were asked to rate the health states of children as proxies and then of themselves. Unlike the children, the caregivers were required to rate their own health status in two situations: (1) current situation while their child hospitalized and (2) the previous situation before the hospitalization of their child

In addition to EQ-5D-3L, general characteristics of the children (e.g. age, gender, weight, and duration of breastfeeding) and of the caregivers (e.g. gender, level of education, occupation, and underlying disease) were also collected. The Vesikari score, a 20-point scale [29], was used to assess the clinical severity of children with diarrhea. It consists of seven clinical parameters: maximum number of stools per day, duration of diarrhea, maximum number of vomiting per day, duration of vomiting, fever, dehydration, and treatment status. A Vesikari score of 6 or less than indicates a mild condition, while scores 7–10 and ≥11 represent moderate and severe conditions, respectively.

2.3. Data collection

On the first day of hospitalization, the ward staffs informed the caregivers about all the details of this study and invited them to participate in the study. After informed consents were given, caregivers were interviewed face-to-face. Stool samples were collected from all the recruited children and were sent to the laboratory of the National Institute of Health Department of Medical Science, Ministry of Public Health, to be tested for rotavirus antigens using polyacrylamide gel electrophoresis (PAGE). The study was approved by the Ethics Committee of the Institute for the Development of Human Research Protections, Ministry of Public Health, Thailand.

2.4. Data analysis

Proportions of participants reporting having problems in each health dimension of the EQ-5D questionnaire were presented and were converted to the EQ-5D index or utility value using the Thai algorithm [30]. In general, utility values range from 0 (worst health condition) to 1 (full health). When comparing between rotavirus and non-rotavirus diarrhea, a chi-square test or Fisher's exact test was used for categorical variables while *t*-tests were used for continuous variables. Differences across severity of diarrhea were examined using analysis of variance. Non-parametric statistics were employed if data was not normally distributed. Multiple linear regression analysis was used to assess the factors associated with utility scores of children with diarrhea and those of their caregivers. The level of statistical significant was set at 0.05.Statistical analyses were performed by STATA14 software.

3. Results

From a total of 470 interviewed participants, 460 diarrheal children and their caregivers were included in this study due to the availability of stool samples. Of 460 collected stools, 195 stools (42.4%) were rotavirus-positive. The demographic and clinical characteristics of the children and their caregivers relating to their rotavirus infection status are shown in Table 1. Mean age of the patients was 22.5 months. It was found that the mean age of the rotavirus diarrhea group (26.4 months) was significantly higher than that of the non-rotavirus diarrhea group (19.71 month) (p-value < 0.001). No significant difference was found between the rotavirus and non-rotavirus diarrhea groups in terms of gender, nutritional status, and breastfeeding status. In terms of caregiver's characteristics, no significant

Table 1. Baseline and clinical characteristics of children and caregivers.

Characteristics		N (%) Rotavirus (n = 195)	N (%) Non-rotavirus (n = 265)	p-Value
Children				
Age (months)	Mean (SD)	26.24 (14.01)	19.71 (14.00)	<0.001
Age group(months)	≤ 24	107 (54.87)	185 (69.81)	<0.001
	> 24	88 (45.13)	80 (30.19)	
Gender	Male	103 (52.82)	139 (52.45)	0.938
	Female	92 (47.18)	126 (47.55)	
Nutrition status[a]	Normal	160 (82.05)	223 (84.15)	0.551
	Abnormal	35 (17.95)	42 (15.85)	
Breastfeeding status	No	4 (2.05)	9 (3.40)	0.390
	Yes	191 (97.95)	256 (96.60)	
Caregivers				
Relationship with children	Father/mother	142 (72.82)	184 (69.43)	0.236
	Grandmother/father	51 (26.15)	75 (28.30)	
	Uncle/aunt	1 (0.51)	6 (2.26)	
	Brother/sister	1 (0.51)	0 (0.00)	
Gender	Male	14 (7.18)	14 (5.28)	0.401
	Female	181 (92.82)	251 (94.72)	
Education	No formal education	2 (1.03)	12 (4.53)	0.082
	Below bachelor's degree	174 (89.23)	232 (87.55)	
	Bachelor's degree or higher	19 (9.74)	21 (7.92)	
Employment status	Housewife	21 (10.88)	41 (15.07)	0.028
	Agriculture	58 (30.05)	105 (39.62)	
	Government officer	87 (45.08)	90 (33.96)	
	Self-employed	5 (2.59)	2 (0.75)	
	Employee	22 (11.40)	27 (10.19)	
Underlying disease	No	161 (82.56)	220 (83.02)	0.898
	Yes	34 (17.44)	45 (16.98)	
Clinical characteristics				
Length of stay (days)	Median (IQR)	4.00 (2.00)	3.00 (2.00)	0.154
Vesikari score	Mean (SD)	14.37 (2.09)	12.51 (2.73)	<0.001
Level of severity				
Mild (Vesikari score ≤6)		0 (0.00)	3 (1.13)	<0.001
Moderate (Vesikari score 7–10		4 (2.05)	62 (23.40)	
Severe (Vesikari score ≥11)		191 (97.95)	200 (75.47)	
Frequency of diarrhea per day				
1–3		22 (11.28)	46 (17.36)	0.124
4–5		47 (24.10)	69 (26.04)	
≥ 6		126 (64.62)	150 (56.60)	
Duration of diarrhea (days)				
1–4		125 (64.10)	158 (59.62)	0.605
5		30 (15.38)	44 (16.60)	
≥ 6		40 (20.51)	63 (23.77)	
Presence of vomiting		190 (97.44)	188 (70.94)	<0.001
Frequency of vomiting per day				
1		2 (1.03)	19 (7.17)	<0.001
2–4		62 (31.79)	89 (33.58)	
≥ 5		126 (64.62)	80 (30.19)	
Duration of vomiting (days)				
1		37 (18.97)	70 (26.42)	<0.001
2		65 (33.33)	55 (20.75)	
≥ 3		88 (45.13)	63 (23.77)	
Temperature (°C)				
< 37		6 (3.08)	16 (6.04)	0.400
37.1–38.4		96 (49.23)	136 (51.32)	
38.5–38.9		32 (16.41)	36 (13.58)	
≥ 39		61 (31.28)	77 (29.06)	
Dehydration				
None		57 (29.23)	60 (22.64)	0.046
1–5%		136 (69.74)	205 (77.36)	
≥6%		2 (1.03)	0 (0.00)	

[a]Using recommended weight-for-age for Thai children.

difference was found between the rotavirus and non-rotavirus diarrhea groups, except for occupation. When comparing clinical presentations between the different the two groups, children with rotavirus diarrhea had significantly higher severity scores than children with non-rotavirus diarrhea (14.37 vs. 12.51; p-value < 0.001), but there was no difference in the length of stay (median = 4 days). Rotavirus diarrhea resulted significantly more frequent in the presence of vomiting (p-value < 0.001) and the degree of dehydration (p-value = 0.046) than non-rotavirus diarrhea.

Table 2 presents the responses for each dimension of the EQ-5D questionnaires. Among the children, we found that pain/discomfort, anxiety/depression, and usual activities were the three main dimensions mostly affected by diarrhea. It was found that 94%, 83%, and 56% of the children reported having problems in pain/discomfort, anxiety/depression, and usual activity dimensions, respectively. When comparing the rotavirus and non-rotavirus diarrhea groups, significant differences were found in usual activities (p-value = 0.003) and anxiety/depression (p-value = 0.002) dimensions. A similar pattern was reported among the caregivers, as shown in Table 2. Among the caregivers, a significant difference between the rotavirus and non-rotavirus diarrhea groups was found only in usual activities (p-value = 0.008).

As shown in Table 3, the average EQ-5D index and VAS among children with all-cause diarrhea was 0.604 (SD = 0.12) and 61.09 (SD = 13.39), respectively. The EQ-5D index score of children with rotavirus diarrhea was significantly lower than that of the non-rotavirus diarrhea group (0.593 vs. 0.612; p-value = 0.040). For caregivers, the EQ-5D index decreased significantly from baseline (0.964) when their children became hospitalized (0.620) (p-value < 0.0001).Similar to those of children, the EQ-5D index of caregivers of children with rotavirus diarrhea was significantly lower than that of non-rotavirus diarrhea (0.606 vs. 0.630; p-value = 0.041).

The utility scores of the children and their caregivers, categorized by rotavirus infection and disease severity, are reported in Table 4. Among children, EQ-5D index was significantly different across severity groups with the reported value of 0.685 for mild, 0.649 for moderate, and 0.595 for severe group (p-value = 0.0003). However, within the same severity level, there was no statistically significant difference in terms

Table 2. Distribution of EQ-5D responses of children with diarrhea and their caregivers.

Domain	Baseline	Rotavirus (n = 195)	Non-rotavirus (n = 265)	Total (n = 460)	p-Value[a]
Children					
Mobility, n (%)					
No problem	n/a	186 (95.38)	248 (93.56)	434 (94.35)	0.409
Some problem	n/a	9 (4.62)	17 (6.42)	26 (5.65)	
Severe problem	n/a	0 (0.00)	0 (0.00)	0 (0.00)	
Self-care n (%)					
No problem	n/a	166 (85.13)	231 (87.17)	397 (86.30)	0.241
Some problem	n/a	29 (14.87)	31 (11.70)	60 (13.04)	
Severe problem	n/a	0 (0.00)	3 (1.13)	3 (0.65)	
Usual activities, n (%)					
No problem	n/a	69 (35.38)	133 (50.19)	202 (43.91)	0.003
Some problem	n/a	124 (63.69)	129 (48.68)	253 (55.00)	
Severe problem	n/a	2 (1.03)	3 (1.13)	5 (1.09)	
Pain/discomfort, n (%)					
No problem	n/a	11 (5.64)	16 (6.04)	27 (5.87)	0.926
Some problem	n/a	159 (81.54)	218 (82.26)	377 (81.96)	
Severe problem	n/a	25 (12.82)	31 (11.70)	56 (12.17)	
Anxiety/depression, n (%)					
No problem	n/a	38 (19.49)	42 (15.85)	80 (17.39)	0.002
Some problem	n/a	142 (72.82)	219 (82.64)	361 (78.48)	
Severe problem	n/a	15 (7.69)	4 (1.51)	19 (4.13)	
Caregivers					
Mobility, n (%)					
No problem	459 (99.78)	195 (100.00)	263 (99.25)	458 (99.57)	1.000
Some problem	1 (0.22)	0 (0.00)	2 (0.75)	2 (0.43)	
Severe problem	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Self-care, n (%)					
No problem	452 (98.26)	168 (86.15)	230 (86.79)	398 (86.52)	0.824
Some problem	8 (1.74)	26 (13.33)	34 (12.83)	60 (13.04)	
Severe problem	0 (0.00)	1 (0.51)	1 (0.38)	2 (0.43)	
Usual activities, n (%)					
No problem	442 (96.09)	71 (36.41)	130 (49.06)	201 (43.70)	0.008
Some problem	18 (3.91)	96 (49.23)	118 (44.53)	214 (46.52)	
Severe problem	0 (0.00)	28 (14.36)	17 (6.42)	45 (9.78)	
Pain/discomfort, n (%)					
No problem	421 (91.52)	85 (43.59)	90 (33.96)	175 (38.04)	0.144
Some problem	39 (8.48)	106 (54.36)	169 (63.77)	215 (59.78)	
Severe problem	0 (0.00)	4 (2.05)	6 (2.26)	10 (2.17)	
Anxiety/depression, n (%)					
No problem	455 (98.91)	7 (3.59)	10 (3.77)	17 (3.70)	0.439
Some problem	5 (1.09)	158 (81.03)	224 (84.53)	382 (83.04)	
Severe problem	0 (0.00)	30 (15.38)	31 (11.70)	61 (13.26)	

n/a: not available.
[a]Comparing rotavirus and non-rotavirus group.

Table 3. Utility score of children and caregivers.

	Utility score								
			Hospitalization period						
	Baseline		Rotavirus (n = 195)		Non-rotavirus (n = 265)		Total (n = 460)		
EQ-5D	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	p-Value[a]
Children									
EQ-5D index	n/a	n/a	0.593 (0.12)	0.635 (0.514–0.694)	0.612 (0.12)	0.635 (0.546–0.694)	0.604 (0.12)	0.635 (0.514–0.694)	0.040
EQ-VAS	n/a	n/a	58.59 (12.90)	60 (50–70)	62.92 (13.46)	70 (50–70)	61.09 (13.39)	60 (50–70)	0.0003
Caregivers									
EQ-5D index	0.964 (0.10)	1 (1–1)	0.606 (0.12)	0.635 (0.509–0.694)	0.630 (0.12)	0.635 (0.549–0.707)	0.620 (0.12)	0.635 (0.514–0.694)	0.041
EQ-VAS	97.09 (6.97)	100 (100–100)	63.23 (11.36)	65 (55–70)	66.70 (10.83)	70 (60–75)	65.23 (11.18)	70 (60–70)	0.002

n/a: not available.
[a]Comparison of the utility scores between rotavirus and non-rotavirus group using the Mann–Whitney U test.

Table 4. Utility score of children and their caregivers categorized by rotavirus infection and disease severity.

	Utility score						
	Rotavirus (n = 195)		Non-rotavirus (n = 265)		Total (n = 460)		
Group	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	p-Value[a]
Children							
EQ-5D index							
Mild	-	-	0.685 (0.015)	0.694 (0.667–0.694)	0.685 (0.016)	0.694 (0.667–0.694)	n/a
Moderate	0.660 (0.106)	0.681 (0.591–0.730)	0.649 (0.101)	0.681 (0.635–0.707)	0.649 (0.101)	0.681 (0.635–0.707)	0.795
Severe	0.591 (0.124)	0.635 (0.514–0.694)	0.599 (0.126)	0.635 (0.514–0.694)	0.595 (0.125)	0.635 (0.514–0.694)	0.373
EQ-VAS							
Mild	-	-	70 (0)	70 (70–70)	70 (0)	70 (70–70)	n/a
Moderate	66.25 (7.50)	70 (62.5–70)	67.74 (13.48)	70 (60–80)	67.65 (13.16)	70 (60–80)	0.506
Severe	58.43 (12.95)	60 (50–70)	61.33 (13.20)	60 (50–70)	59.91 (13.14)	60 (50–70)	0.031
Caregivers							
EQ-5D index							
Mild	-	-	0.698 (0.008)	0.694 (0.694–0.707)	0.698 (0.008)	0.694 (0.694–0.707)	n/a
Moderate	0.701 (0.054)	0.701 (0.665–0.737)	0.641 (0.108)	0.635 (0.586–0.726)	0.645 (0.107)	0.635 (0.586–0.726)	0.301
Severe	0.604 (0.123)	0.635 (0.549–0.694)	0.626 (0.120)	0.635 (0.549–0.694)	0.615 (0.122)	0.635 (0.549–0.694)	0.086
EQ-VAS							
Mild	-	-	71.67 (7.64)	70 (65–80)	71.67 (7.64)	70 (65–80)	n/a
Moderate	66.25 (7.50)	70 (62.5–70)	67.18 (10.11)	70 (60–75)	67.12 (9.93)	70 (60–75)	0.792
Severe	63.17 (11.43)	65 (55–70)	66.48 (11.10)	70 (60–75)	64.86 (11.37)	70 (60–70)	0.005

n/a: not available.
[a]Comparison of the utility scores between rotavirus and non-rotavirus group using the Mann–Whitney U test.

Table 5. Multiple linear regression analysis of EQ-5D index score.

Variables	β	p-Value	Lower CI	Upper CI
Child[a]				
Age (Ref: ≤ 24 mo)	−0.036	0.001	−0.058	−0.014
Gender (Ref: Male)	0.018	0.081	−0.002	0.039
Rotavirus infection (Ref: No)	0.019	0.106	−0.004	0.042
Vesikari score	−0.017	<0.001	−0.022	−0.013
Caregiver[b]				
Gender (Ref: Male)	−0.013	0.581	−0.058	0.033
Occupation (Ref: Housewife)				
Agriculture	−0.003	0.890	−0.037	0.032
Government officer	−0.031	0.076	−0.065	0.003
Self-employed	0.023	0.650	−0.071	0.114
Employee	−0.057	0.012	−0.102	−0.013
Vesikari score	−0.006	0.004	−0.010	−0.002

[a]Adjusted R^2 = 0.142.
[b]Adjusted R^2 = 0.030.

of the EQ-5D index between rotavirus and non-rotavirus diarrhea groups. Similar patterns in the EQ-5D index were also found among the caregivers.

Table 5 displays the variables affecting quality of life of the children and caregivers. As shown in the table, child's age and disease severity had significantly negative impacts on the children's quality of life. It was found that older children with more severe condition were more likely to give lower utility scores. After adjustments for other variables, it was found that rotavirus infection did not significantly affect quality of life of

the children. For the caregivers, their occupation and their child's severity score were significant factors associated with quality of life. Caregivers who were employed reported having a lower utility value compared to caregivers who worked at home as housewives. As expected, the utility values of caregivers of children with more severe diarrhea conditions were significantly lower than those of children with mild diarrhea conditions.

4. Discussion

Our study is the first study that reported and compared utility values of children with rotavirus diarrhea and non-rotavirus diarrhea and their caregivers in a developing country. Rotavirus, a leading cause of morbidity in young children, was detected in 42.4% of children with diarrhea in our study, which was in line with the findings from the previous studies [31].

Similar to previous studies, our study indicated that the rotavirus diarrhea group was associated with more vomiting and dehydration than the non-rotavirus diarrhea group [32–34]. This is also consistent with the previous two studies conducted in Thailand, which reported that Thai children with rotavirus diarrhea suffered from more vomiting and dehydration [21,35].

Both rotavirus diarrhea and non-rotavirus diarrhea had negative impacts on the quality of life of children and their caregivers. Our study found that diarrhea affected three domains of quality of life of children (anxiety/depression, pain/discomfort, and usual activities). A similar pattern was also found amongst the caregivers. This is probably due to the fact that caregivers spent a lot of time providing care for their sick children and also became worried and stressed when their children were sick. These results were consistent with those of previous studies, which reported that pain/discomfort and emotion were the main affected attributes among diarrheal children and parents and that the parents faced the disruption in their daily activities and working task [12–14].

At present, no generic instrument has been developed to assess utility values among children aged <5 years. According to our literature review, the health utility index (HUI), VAS, and EQ-5D were used in measuring utility among children aged <6 years old with diarrhea. As in previous studies, our study used EQ-5D [17,18] and VAS [11] in measuring utility values among these children. On the other hand, HUI was used in the study by Brisson et al. [13] and Marlow et al. [16]. A study conducted in diarrheal children aged <2 years in Germany found that VAS scores of mild and severe diarrhea patients were 54.6 and 33.9, respectively [11]. In our study, average VAS scores for diarrhea children were higher with an estimate of 70.0 for mild, 67.7 for moderate, and 59.9 for severe case. This can be partly explained by the age of the children, which was very young (< 2 years) in the previous study [11].

In terms of utility values, our study reported that utility of hospitalized children with rotavirus diarrhea was significantly lower than non-rotavirus diarrhea (0.593 vs. 0.612; p-value = 0.04). Nevertheless, it should be noted that this difference is not greater than the minimal clinically important difference of 0.03, which found from the recent review [36]. When comparing with the previous study that used EQ-5D [17,18], our findings were in line with those of a study conducted in UK, using general practitioner as proxies, which found that utility values of hospitalized children with rotavirus were 0.634 for those aged 18–60 months [18]. This was also consistent with another study conducted in Denmark, which found that the median utilities of hospitalized and non-hospitalized children with diarrhea were 0.531 and 0.756, respectively [17].

When looking at severity, our study was comparable to the study by Huppertz et al. [11] which found that more severe diarrhea case was associated with lower utility values. With respect to the effect of age on utility, our study found that diarrhea had a higher negative impact on quality of life of older children. This could be due to the fact that older children are more likely to exhibit outward signs of HRQoL decreases, and that the sleeping hour of older children is relatively shorter; therefore, caregivers may notice more changes in both physical and psychological function among older children than in younger children. Our results were consistent with previous study [18] using general physicians as proxies while being contradicted by pediatricians as proxies. The different proxies used in measuring the utility may account for this inconsistence.

In contrast to bivariate analysis, rotavirus infection was not significantly associated with the utility of children with diarrhea in multivariate analysis. For multivariate analysis, we found that only the severity and age of the children significantly predicted the utility values of children. This can be explained by the fact that rotavirus diarrhea usually resulted in more severe cases than non-rotavirus diarrhea; however, the utility values of children in the same severity levels were similar regardless of rotavirus infection. In case of the caregivers, it was also found that their occupations of caregivers significantly affected their utility values. As reported earlier, usual activity was one of the most affected dimensions among caregivers; however, caring for children with diarrhea might have affected the work roles of caregivers who were employed more than those who were housewives.

There are some limitations of this study that should be acknowledged. Firstly, the data were collected in three districts of Phetchabun province among hospitalized patients where 85% of cases were classified as severe, therefore generalizability should be made with caution. Secondly, this study was a cross-sectional study, in which the caregivers were interviewed only once and were asked to use their memories to establish a baseline. Thirdly, our participants were interviewed on the first day of admission, and, as the result, the utility scores might tend to be low. Fourthly, as there was no standard instrument developed to measure utility among young children, EQ-5D was used in our study; however, it should be noted that the EQ-5D was a generic instrument which was designed for measuring health related quality of life in adults and children aged 12 years and above [37]. In addition, measuring anxiety/depression and differentiate it from pain/discomfort and usual activities among very young children is quite challenging. In fact, for children

under 2 years of age, anxiety is more common than depression. Anxiety among these very young children may be expressed as worrying of being apart from their parents, clinging to parents, whimpering, and fearful. In terms of depression, children may show decrease interests in activities or inability to joy previous activities, feeling sad, and crying. On the other hand, pain/discomfort among these very young children can be recognized from facial expression, gasping of breath, sweating, and crying with high-pitched voice. Lastly, as the children in our study were very young, the caregivers were interviewed on behalf of their children. Although the caregivers may best report their child's quality of life, it should be noted that validity of using proxies depends on several factors, such as patient and proxy characteristics. In addition, it should be noted that the highest agreement is usually found for concrete domains than subjective domains [38].Given the current challenge in measuring utility values among young children [22], more research efforts are required to develop methods to measure utility among this group of population. Furthermore, given the family relationship, it might be appropriate to consider a 'family perspective' rather than an individual perspective in child health state evaluation [23]. Nevertheless, our study had several strengths as we employed face-to-face interview with a high response rate. In addition, all stool samples were tested by PAGE to confirm for rotavirus infection.

5. Conclusion

Diarrhea, whether caused by rotavirus or non-rotavirus, had significant negative impacts on quality of life of both children and their caregivers, especially in terms of anxiety/depression, pain/discomfort, and usual activities. The main factor affecting quality of life was the severity of diarrhea. Although rotavirus infection resulted in more severe diarrhea conditions and a lower quality of life, in bivariate analysis, it was not associated with differing utility scores anymore when adjusting for other factors. Our findings provide useful information for future cost-effectiveness analysis of treatment and prevention interventions for rotavirus diarrhea.

Key issues

- Rotavirus diarrhea is the main cause of diarrhea among young children with a significant impact on quality of life of both the children and their caregivers.
- There are the inapplicable instruments for measuring the health utility values for young children, thus the use of proxy respondents is preferable to evaluate their child's health.In this study, the EQ-5D, a psychometrically and accepted questionnaire, was applied to assess the quality of life of children with diarrhea and their caregivers.
- Severity of diarrhea significantly correlated with lower health utility values.
- No difference in utility values with and without rotavirus infection were noted under the adjusted variables.
- These health utilities will be useful in future cost-effectiveness analysis of treatment and prevention interventions for rotavirus diarrhea.

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