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Preference-Based Assessments

Evaluating the Health-Related Quality of Life of the Rare Disease Population in Hong Kong Using EQ-5D 3-Level

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ABSTRACT

Objectives: This study aimed to establish a normative profile of health-related quality of life (HRQOL) of the rare disease (RD) population in Hong Kong (HK) and identify potential predictors.

Methods: Between March 2020 and October 2020, patients with RD and caregivers were recruited through Rare Disease Hong Kong, the largest RD patient group alliance in HK. HRQOL was derived using the EQ-5D 3-Level with reference to the established HK value set. Utility scores were stratified according to demographics and disease-related information. Multiple linear regression was performed to explore the associations between patient characteristics and HRQOL.

Results: A total of 286 patients, covering 107 unique RDs, reported a mean utility score of 0.53 (SD 0.36). Thirty patients (10.5%) reported negative utility scores, indicating worse-than-death health states. More problems were recorded in the "usual activities" and "self-care" dimensions. Univariate analyses revealed that neurologic diseases, high out-of-pocket expenditure, home modification, and living in public housing or subdivided flats/units were significantly associated with lower HRQOL. A total of 99 caregivers reported a mean utility score of 0.78 (SD 0.17), which was significantly associated with the utility score of patients they took care of ($r = 0.32$; $P = .001$).

Conclusions: The normative profile of the RD population was established, which revealed lower HRQOL in the RD population than other chronic disease groups and general population in HK. Findings were corroborated by evidence from other cohorts using EQ-5D, combined as part of a meta-analysis. Identifying predictors highlight areas that should be prioritized to improve HRQOL of RD population through clinical and psychosocial dimensions.

Keywords: EQ-5D, health-related quality of life, rare disease caregivers, rare disease patients, rare diseases, utility score

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Introduction

Rare diseases (RDs) are characterized by its small prevalence in a population. Although a universal definition is lacking, approximately 40 in 100 000 people are affected by a RD.[1,2] Despite 6000 to 8000 RDs being discovered, limited medical knowledge on their complexities remains a key barrier to effective clinical management.[3] On average, each patient receives 3 misdiagnoses.[4] Long diagnostic odysseys and treatment uncertainty detrimentally influences economic and psychosocial aspects of patients' lives.[1,5–15] Impacts on caregivers, particularly parents of pediatric patients with RD, are also significant. Lifelong caring, high dependency of patient, and economic strain all decrease the well-being of patients' caregivers. These are known as "spillover effects" and must be considered when evaluating the impact of RDs.[16]

The impact of diseases can be determined by quantifying the health-related quality of life (HRQOL). HRQOL is an individual's perception of his/her living quality, encompassing physical, mental, and social wellbeing, and is relative to culture, value systems, and expectations.[17,18] EQ-5D quantifies HRQOL. It is a generic preference-based patient-reported outcome measure developed by the EuroQol group and recommended by the National Institute for Health and Care Excellence guidelines for clinical and economic assessment.[19,20] Given the rarity of RDs, most of the existing studies target patients with relatively "common" RDs. Many challenges are experienced by all patients with RD, resulting in health and policy planning considering RDs as a collective disease group. Therefore, it is important to investigate the HRQOL of patients with RD as a whole to provide a large enough sample for statistical power while analyzing similarities and heterogeneities within the disease group.[21]

To date, only 3 other studies have investigated the HRQOL of the RD population as a whole using EQ-5D.[5,22,23] All 3 studies highlighted significantly lower HRQOL than the general population and other chronic illnesses. Nevertheless, there is an apparent

gap in existing literature on HRQOL of patients with RD in Asia and cohorts with a variety of RDs. To fully assess the impact of RDs as a whole, more studies on the HRQOL of the RD population using the same EQ-5D measure must be conducted.

In Hong Kong (HK), 1 in 67 individuals lives with an RD, in which 35% are pediatric patients.[1] Despite patients with RD only accounting for 1.5% of the population, they contribute 4.3% of all inpatient costs locally.[1] The disparity between prevalence of RDs and healthcare utilization is suggestive of significant burden on the RD population in HK. Most RDs are chronic, progressive, degenerative, and life threatening, with effective drugs being costly and scarce.[24] Social exclusion and discrimination based on RD health conditions further deplete available resources for coping with RDs.[25] Therefore, it is crucial to identify the impact of RDs on patient's HRQOL. Although previous studies have shown that common chronic diseases negatively affect the HRQOL of patients, similar evidence is still lacking for the RD population.[26] In HK, the HRQOL of specific RD groups has only been studied in patients with tuberous sclerosis complex.[27] Nevertheless, the existing literature does not describe the full impact of the 470 types of RDs within the local population. Additionally, the "spill-over effects" on the families and caregivers of patients with RD have yet to be investigated in HK. Therefore, this study aims to assess the HRQOL of patients with RD and caregivers, establish a normative profile, and identify potential predictors for the RD population. A systematic review was also conducted to review the HRQOL of patients with RD across existing literatures and compare the RD population in HK with other international cohorts.

Methodology

Participants and Study Design

This was a prospective study conducted between March and October 2020. Due to the lack of patient registries at a national level, patients with RD were recruited through the largest alliance for RD patient groups in HK, Rare Disease Hong Kong (RDHK), and 8 other affiliated RD patient groups. A total of 527 patients with RD and their family members were registered under RDHK by the end of 2020, covering 149 different RDs.[28] Caregivers were recruited for patients with RD who were physically or mentally unable to self-complete the EQ-5D questionnaire. The EQ-5D questionnaire, available in both English and traditional Chinese, was distributed to participants through RDHK. A self-complete version for patients and a validated proxy version 2 for caregivers to complete on their patients' behalf were provided.[29] For patients requiring a proxy, data on HRQOL of caregivers were also collected. An informed consent was obtained and participation was strictly voluntary. All data were kept confidential and anonymous. Ethics approval was granted by the Institutional Review Board, the University of Hong Kong/Hospital Authority Hong Kong West Cluster (UW 19-609).

Measures

EQ-5D measures the HRQOL in 5 dimensions of health: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.[30] EQ-5D 3-Level (EQ-5D-3L) was used as the instrument of measure in this study because the proxy version 2 is only validated for HK in traditional Chinese for EQ-5D-3L measure.[29] The levels selected indicate severity of the problems in each dimension: "level 1" indicates absence of problems, "level 2" indicates some problems, and "level 3" indicates extreme problems. Combined, they form 234 possible 5-digit health profiles, ranging from the best and worst health state of "11111" and "33333," respectively.[31]

Value sets are required to convert the 5-digit health profiles into utility scores. Given that the HK value set was only available for EQ-5D 5-Level (EQ-5D-5L), a reverse crosswalk algorithm was used to generate EQ-5D-5L utility scores from the EQ-5D-3L measure.[32,33] This algorithm generates utility scores comparable with the data from other studies using EQ-5D-5L-HK, thus producing an objective measure of HRQOL. Utility scores ranged from −0.685 to 0.955, with 0.955 representing perfect health, 0 representing a health state equivalent to death, and negative values representing worse-than-death health states.

The EuroQol visual analog scale is an analog scale, ranging from 0 (worst health) to 100 (perfect health). It is a self-reported perception of health on the day of participation.[30]

Socioeconomic Characteristics and RD-Related Information

Socioeconomic characteristics included age, gender, marital status, type of housing, education level, employment status, monthly income, and whether patient received government allowance. RD-related information including the name of RD, year of diagnosis, number of family members with RDs, home modification, and out-of-pocket (OOP) expenditures associated with RDs was also collected. In the proxy-complete version, information on the relationship between the caregiver and patient and whether the caregiver was the main caregiver was collected.

Data Analysis

Descriptive statistics were reported for socioeconomic characteristics and health profiles. Mean utility scores were stratified according to socioeconomic characteristics. Mann-Whitney *U* tests and Kruskal-Wallis tests compared the mean utility scores among subgroups of respondents. The Mann-Whitney *U* test was used for binary variables (eg, gender, government allowance, and home modification). The Kruskal-Wallis tests was used for categorical data with 2 or more groups (eg, employment status and type of housing). Spearman correlation tested the correlation between continuous (eg, age, age of diagnosis, OOP expenditures and number of family members with RDs) and ordinal variables (eg, education level and monthly income level) with utility scores. Univariate association of independent variables against utility score was analyzed using simple linear regression. Variables with significant associations from univariate analyses were combined in multivariate analysis. Results were considered statistically significant at $P < .05$. All data analyses were performed with IBM SPSS Statistics version 27.0.

Systematic Review

A systematic review was conducted for studies on HRQOL of RD populations that used EQ-5D and included patients from >1 RD category. The full search strategy is included in the Appendix S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.04.1725. A meta-analysis was performed to determine a pooled estimate of the HRQOL of patients with RD using a random-effects model, conducted with RStudio (2009).

Results

Between March 26, 2020, and October 16, 2020, a total of 323 responses were collected. After removal of 37 invalid, incomplete, or duplicated responses, 286 independent valid responses remained, including 159 patients who self-completed and 127

patients who required a proxy to complete. Almost all patients (98.1%) who self-completed were aged ≥18 years, whereas 68.5% of proxy-reported patients were aged <18 years. Of the 196 adult patients, 40 (20.4%) required a proxy to complete, whereas almost all of the 89 patients aged <18 years (97.8%) required a proxy to complete. The HRQOL of 99 caregivers was also reported.

Demographics of Patients With RD

The demographics of the 286 patients with RD are presented in Table 1. The male-to-female ratio was 1:1.1. The mean patient age was 31.4 (SD 19.7), and 31.1% were <18 years old. The mean age of patients who self-completed was 43.3 years old (SD 12.9), which was significantly higher than patients who required a proxy to complete (16.6; SD 16.5) ($P < .001$).

In total, 107 distinct RDs were reported. These were classified into 13 RD categories with reference to existing literature.[1,34] "Rare neurologic disease" was the most reported RD (n = 106, 37.1%), followed by "rare developmental defects during embryogenesis" (n = 69, 24.1%) and "rare inborn errors of metabolism" (n = 31, 10.8%). Three patients were diagnosed of >1 RD from different categories. The mean age of diagnosis was at 20.5 years old (SD 19.5), and the mean time since patients received the diagnosis was 11.6 years (SD 10.6).

EQ-5D-3L Profile of Patients With RD

In total, 286 EQ-5D-3L profiles were collected from all patients with RD, with 70 unique combinations reported. The 3 most reported profiles were "11111" (16.1%), "11112" (6.3%), and "22222" (5.9%). The distribution of patients with RD with each level of the 5 health dimensions is presented in Table 2. The mean levels reported by patients with RD were 1.6 (mobility), 1.7 (self-care), 1.7 (usual activities), 1.6 (pain/discomfort), and 1.5 (anxiety/depression). Compared with pediatric patients with RD, adult patients with RD reported fewer problems regarding self-care, but more problems in pain/discomfort and anxiety/depression.

Utility Scores of Patients With RD

The mean and median utility score of patients with RD was 0.53 (SD 0.36) and 0.56 respectively, ranging from −0.69 ("33333" profile) to 0.96 ("11111" profile). Overall, 30 patients with RD (10.5%) reported negative utility scores, representing worse-than-death health states. The utility scores of patients who self-completed (mean 0.58; SD 0.29; median 0.62) were significantly higher than that of patients who required a proxy (mean 0.45; SD 0.42; median 0.53) ($P = .004$). The difference between the utility scores of patients aged <18 years (mean 0.46; SD 0.41; median 0.53) and patients aged ≥18 years (mean 0.56; SD 0.32; median 0.62) was not significant ($P = .114$). Patients with rare neurologic diseases had the lowest mean utility score (0.33; SD 0.32; median 0.54), which was significantly lower than patients with non-neurologic RDs (0.64; SD 0.33; median 0.72) ($P < .001$). The mean utility scores of patients with RD stratified according to selected background characteristics are presented in Table 3.

Univariate analysis revealed that patients living in public housing or subdivided flats/units (mean 0.45; SD 0.33; median 0.43) had significantly lower utility scores than patients living in bought flats (mean 0.61; SD 0.35; median 0.72) ($P = .001$). Furthermore, patients who had home modification made because of RD condition (mean 0.35; SD 0.35; median 0.33) had significantly lower utility score than patients who did not (mean 0.64; SD 0.31; median 0.72) ($P < .001$). Patients' utility score was also positively correlated with education level (r = 0.32; $P < .001$) and number of family members with RDs (r = 0.17; $P = .005$). Contrastingly, patients' utility score was negatively correlated with the OOP expenditure (r = −0.23; $P < .001$).

Multivariate analysis adjusted for each of the significant factors from univariate analyses revealed that patients with RD living in public housing or subdivided flats/units and those who had home modifications because of the RD condition were significantly associated with a lower utility score (Table 4).

EuroQol Visual Analog Scale Score

The mean and median VAS scores reported for patients with RD were 67 and 70, respectively, ranging from 0 to 100. VAS scores were significantly correlated to their utility scores (r = 0.48; $P < .001$).

HRQOL of Caregivers

In total, 125 caregivers of the patients with RD who required a proxy provided demographic information. Most of the caregivers were female (83.8%), and the mean age was 44.6 years (SD 11.0). Most caregivers (44.4%) were housewives or househusbands, and 74.5% were mothers of the patient. A total of 99 valid EQ-5D-3L caregiver profiles were collected. The 3 most reported profiles were "11111" (33.3%), "11112" (23.2%), and "11122" (17.2%). The mean and median utility score of the caregivers was 0.78 (SD 0.17) and 0.84, respectively. Caregivers reported the most problems in the anxiety/depression dimension (Table 2). Caregivers of patients with rare neurologic diseases also had the lowest utility score among all caregivers (mean 0.75; SD 0.18; median 0.83). Caregivers' utility scores were positively correlated with their monthly income (r = 0.41; $P = .011$), education level (r = 0.39; $P < .001$), and their patient's utility score (r = 0.32; $P = .001$). The mean and median VAS score reported were 76 and 78, respectively, ranging from 7 to 100. Caregiver's VAS scores were significantly correlated to both their own utility score (r = 0.5; $P < .001$) and their patient's utility score (r = 0.285; $P = .004$).

Meta-Analysis

Using the search strategy (Appendix S1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.04.1725), 4 studies were included in the meta-analysis. The studies included a total of 2079 patients with RD with a pooled utility score of 0.57 (SD 0.09; $I^2 = 95.29\%$; Q = 67.2), ranging from 0.46 to 0.65 (Fig. 1).

Linear regression revealed no significant relationships between the mean patient age, number of RDs included, and sample size on mean utility score ($P > .05$ for all variables).

Discussion

This study investigated the HRQOL of patients with RD using a large and heterogeneous sample of 286 patients and 99 caregivers, spanning across 107 unique RDs. These participants represented more than half of all patients and RDs within RDHK. Given that this cohort included both adult and pediatric patients, with the distribution of participants in age and disease categories reflecting numbers previously reported, the sample is likely to be representative the RD population in HK.[1] Overall, patients with RD and their caregivers recorded low mean utility scores, 0.53 (SD 0.36) and 0.80 (SD 0.17), respectively, with 1 in 10 patients with RD reporting worse-than-death health states. Additionally, patients diagnosed with rare neurologic disorders were revealed to have the lowest mean utility score across all RD categories.

Table 1. Demographic characteristics of patients with RD.

Characteristics	Number of patients with RD (n = 286), n (%)
Gender*	
Male	135 (47.2)
Female	150 (52.4)
Age*	
0-9	61 (21.3)
10-19	33 (11.5)
20-29	35 (12.2)
30-39	53 (18.5)
40-49	48 (16.8)
50-59	30 (10.5)
60-69	19 (6.6)
≥70	6 (2.1)
Employment/education status*	
Student	89 (31.1)
Employed (full time/part time)	59 (20.6)
Unemployed/nonstudent	83 (29.0)
Housewife/househusband	15 (5.2)
Retired	23 (8.0)
Allowance(s) patient receiving from government schemes*	
Yes (patients can receive >1 type of allowance)	173 (60.5)
Comprehensive social security assistance	41 (14.3)
Social security allowance: normal disability allowance	78 (27.3)
Social security allowance: higher disability allowance	59 (20.6)
Social security allowance: normal old age living allowance/higher old age living allowance	2 (0.7)
Others	16 (5.6)
No	107 (37.4)
RD category (patients can be affected by >1 RD)	
Rare bone disease	17 (5.9)
Rare developmental defects during embryogenesis	69 (24.1)
Rare endocrine disease	4 (1.4)
Rare eye disease	5 (1.7)
Rare gastroenterologic disease	2 (0.7)
Rare hematologic disease	9 (3.1)
Rare immune disease	6 (2.1)
Rare inborn errors of metabolism	31 (10.8)
Rare neoplastic disease	3 (1.0)
Rare neurologic disease	106 (37.1)
Rare respiratory disease	8 (2.8)
Rare skin disease	4 (1.4)
Rare systemic or rheumatologic disease	25 (8.7)
Age of diagnosis*	
0-9	107 (37.4)
10-19	18 (6.3)
20-29	28 (9.8)
30-39	39 (13.6)
40-49	27 (9.4)
50-59	15 (5.2)
≥60	7 (2.4)
Number of family member(s) with RD(s)*	
0	202 (70.6)
1	36 (12.6)
2	16 (5.6)
3	6 (2.1)
4	8 (2.8)
≥5	7 (2.4)
Patient is a member of patient group(s)*	
Yes	223 (79.0)
No	57 (20.0)

Continued in the next column

Table 1. Continued

RD indicates rare disease.
*Missing data observed.

Normative Profile of HRQOL for Patients With RD in HK

The results establish a normative profile of the HRQOL for encompassing a variety of patients with RD in HK. This serves as a baseline for comparisons with other populations within the jurisdiction and to evaluate the effectiveness of healthcare utilization and the impact of policies on the RD population.[35]

Based on the systematic review of existing literature, this is the first study to investigate the HRQOL of the RD population as a whole in HK. Only 3 other studies have attempted to determine HRQOL of patients across several RD categories using the EQ-5D measure.[5,22,23] Findings from the current study were corroborated with evidence from the 3 published cohorts, combined as part of a meta-analysis. The pooled utility score was 0.57 (SD 0.09) across 4 studies. Although no significant relationship was identified among the mean patient age, number of RDs included, and sample size on mean utility score, this meta-analysis serves as the first comprehensive review and provides a pooled HRQOL estimate across different cohorts. We hypothesize that the heterogeneity may arise from variability in social support and healthcare systems among jurisdictions. The HRQOL of patients with RD in HK is comparable with or even slightly lower than values in some jurisdictions. Therefore, it is necessary for similar studies to be conducted across different jurisdictions using the same instrument to determine the impact of region-specific variables on the HRQOL of patients with RD.

The mean utility score of patients with RD, 0.53 (SD 0.36), is significantly lower than that of the general population in HK (0.92; SD 0.12) ($P < .001$).[35] When comparing the HRQOL of patients in HK with other chronic illnesses, such as heart disease, diabetes, hypertension, and cancer,[26] patients with RD and their caregivers consistently reported the lowest utility scores (Fig. 2[26,35]). This highlights the disproportionately large negative impact of RDs and its significant adverse spillover effects.

Dimensions of HRQOL

With the EQ-5D encompassing 5 dimensions of HRQOL, the impacts of disease-related and psychosocial elements could be assessed.[36,37] Disease-related factors include severity and prognosis of the disease, medical complications, and a lack of treatment availabilities. Psychosocial factors include psychological wellbeing, coping mechanisms, and illness perception.[36] Overall, our findings suggest that disease-related factors are more likely to negatively affect HRQOL. This is indicated by patients with rare neurologic disorders having the lowest utility score and patients recording more problems associated with usual activities, pain/discomfort, and self-care compared with anxiety/depression (Table 2).

Table 2. Distribution of patients with RD and caregivers in each level of the EQ-5D-3L health dimensions.

Level in each EQ-5D health dimension	All patients (n = 286)*		Number of pediatric patients with RD (n = 89)		Number of adult patients with RD (n = 196)		Number of caregivers (n = 99)	
	n	%	n	%	n	%	n	%
Mobility								
1	140	49.0	47	52.8	93	47.4	89	89.9
2	125*	43.7	29	32.6	95	48.5	10	10.1
3	21	7.3	13	14.6	8	4.1	0	0
Self-care								
1	162	56.6	28	31.5	134	68.4	88	88.9
2	60*	21.0	21	23.6	38	19.4	9	8.1
3	64	22.4	40	44.9	24	12.2	2	2.0
Usual activities								
1	114	39.9	32	36.0	82	41.8	85	85.9
2	135*	47.2	36	40.4	98	50.0	13	13.1
3	37	12.9	21	23.6	16	8.2	1	1.0
Pain/discomfort								
1	139	48.6	56	62.9	83	42.3	66	66.7
2	133	46.5	30	33.7	103	52.6	33	33.3
3	14*	4.9	3	3.4	10	5.1	0	0
Anxiety/depression								
1	154	53.8	64	71.9	90	45.9	47	47.5
2	116	40.6	23	25.8	93	47.4	49	49.5
3	16*	5.6	2	2.2	13	6.6	3	3.0

EQ-5D-3L indicates EQ-5D 3-level; RD, rare disease.
*Missing data on age for 1 patient.

Disease-Related Determinants of HRQOL

Similar to this study, patients with rare neurologic diseases consistently report the lowest utility scores among all RD categories in other studies.[5,21,22,38-40] Neurologic diseases are characterized by dysfunction in the brain or nervous system, resulting in poor physical or mental functioning.[41] Progressive muscle degeneration, fatigue, and difficulty in respiration and ambulation drastically decrease the HRQOL in these patients.[21,38,40] Studies have also shown that the lack of coordination in the healthcare system prevents alleviation of the symptoms of rare neurologic diseases.[42] This may explain the hindered self-care ability and participation in usual activities as observed in this study.

Moreover, patients with RD as a whole share similar obstacles. The low prevalence of RDs in the global population limits the medical knowledge on RDs within the healthcare system. Currently <10% of patients with RD are effectively treated globally.[5,43] Infrequent research activities and lack of clear diagnostic guidelines and available treatments prevent many patients from receiving the necessary care.[37,44] Additionally, manufacturers have exploited the limited market for RD drugs, selling them at prices 25 times higher than traditional drugs.[45] As indicated by our analysis and several other studies, high OOP expenditure further lowers HRQOL.[35,39] Orphan drugs are also highly inaccessible, as indicated by a study showing that at least 40% of available orphan drugs were not readily available to patients with RD in several European countries.[46] In consideration of these barriers to treating RDs, debilitating disease symptoms persist, further decreasing the HRQOL of patients with RD.

Psychosocial Determinants of HRQOL

The impacts of RDs are not limited to the clinical domain. Although patients with RD in our cohort did not experience the most problems in the anxiety/depression dimension, stress and anxiety were reported in 33%, 82%, and 86% of patients with RD in New Zealand, the United Kingdom, and the United States, respectively.[4,47] In the face of clinical uncertainties, negative psychological responses manifest from patients' frustration and loss of confidence in the medical system.[48] Nevertheless, the social challenges cannot be ignored. Patients with RD have been reported to be highly conscious of the public's perception of their disorder, fueling negative psychosocial responses.[37,49,50] This is particularly evident for more visible RDs, such as achondroplasia and muscular dystrophy.[51] Inadequate public awareness on RDs means that little to no accommodations are made to education and work sectors. Thus, the social stigma surrounding RDs socially excludes patients with RD, contributing to increased feelings of depression, stress, and anxiety.[47]

Nevertheless, psychological mechanisms, namely perception of disease and coping mechanisms, have the power to reduce, or completely negate, loss of HRQOL. In concordance with another study, patients with "rare developmental defects during embryogenesis" in our cohort reported relatively better HRQOL than patients in other categories.[39] Early adaptation or "acceptance of disability" suggests that patients born with congenital disabilities do not have to adapt or experience a change in identity as much as patients with acquired conditions.[21,52] Surprisingly, adolescents with muscular dystrophy reported higher perceived living quality than unaffected peers despite living with physical disabilities, suggesting that the adaptation process can lead to positive shifts in perspectives.[53] Intervention in promoting positive perception of self and management of RD-related stressors can indeed foster feelings of control over consequences of the disease.[37,54] These illustrate the undeniable impact of acceptance, optimism, and improved self-esteem as effective coping strategies to improve HRQOL.[48]

Table 3. Mean utility score of patients with RD and caregivers stratified by different characteristics.

Characteristics	All patients with RD			All caregivers		
	n	Mean utility score (SD)	*P* value	n	Mean utility score (SD)	*P* value
Overall	286	0.53 (0.36)		99	0.80 (0.17)	
Gender	285*		.580†	99		.028†
Male	135	0.51 (0.37)		16	0.78 (0.17)	
Female	150	0.54 (0.34)		83	0.88 (0.07)	
Age group	285*		.854‡	97*		.983‡
0-9	61	0.45 (0.42)		-		
10-19	32	0.52 (0.39)		1	0.84 (-)	
20-29	36	0.57 (0.36)		3	0.78 (0.13)	
30-39	53	0.58 (0.33)		36	0.81 (0.18)	
40-49	48	0.59 (0.32)		28	0.78 (0.18)	
50-59	30	0.56 (0.25)		20	0.80 (0.17)	
60-69	19	0.38 (0.31)		9	0.79 (0.12)	
≥70	6	0.33 (0.37)		–		
Employment/education status	269*		<.001§	95*		.007§
Student	89	0.52 (0.39)				
Normal education	40	0.69 (0.26)				
Special education	49	0.39 (0.43)				
Employed	59	0.69 (0.24)		38	0.84 (0.14)¶	
Full-time employment	42	0.74 (0.23)		35	0.84 (0.14)	
Part-time employment	17	0.56 (0.24)		3	0.88 (0.06)	
Unemployed/nonstudent	83	0.42 (0.38)		5	0.76 (0.20)	
Housewife/househusband	15	0.45 (0.22)		44	0.69 (0.31)	
Retired	23	0.50 (0.24)		8	0.90 (0.12)	
Allowance(s) patient receiving from government schemes	281*		<.001†	95*		.020†
Yes	175	0.46 (0.35)		72	0.77 (0.18)	
CSSA	41	0.43 (0.34)		17	0.72 (0.14)	
Social security allowance: normal disability allowance	78	0.58 (0.26)		36	0.79 (0.17)	
Social security allowance: higher disability allowance	69	0.24 (0.37)		17	0.76 (0.21)	
Social security allowance: normal old age living allowance/higher old age living allowance	2	0.48 (0.08)				
Others	16	0.52 (0.41)		9	0.81 (0.25)	
No	106	0.65 (0.33)		23	0.80 (0.17)	
RD category (patients can be affected by >1 RD)	289		<.001‖,†	100		.184‖,†
Rare bone disease	17	0.65 (0.25)		8	0.78 (0.22)	
Rare developmental defects during embryogenesis	69	0.62 (0.31)		48	0.77 (0.20)	
Rare endocrine disease	4	0.67 (0.24)				
Rare eye disease	5	0.71 (0.16)		3	0.92 (0.06)	
Rare gastroenterologic disease	2	0.41 (0.19)				
Rare hematologic disease	9	0.81 (0.18)		4	0.81 (0.11)	
Rare immune disease	6	0.76 (0.32)				
Rare inborn errors of metabolism	31	0.45 (0.50)		16	0.84 (0.16)	
Rare neoplastic disease	3	0.82 (0.15)		1	0.84 (-)	
Rare neurologic disease	106	0.33 (0.32)		18	0.75 (0.18)	
Rare respiratory disease	8	0.57 (0.17)		1	0.84 (-)	
Rare skin disease	4	0.67 (0.13)				
Rare systemic or rheumatologic disease	25	0.81 (0.17)		1	0.95 (-)	
Home modification	284*		<.001†	98*		.131†
Yes	116	0.35 (0.35)		38	0.77 (0.16)	
No	168	0.64 (0.31)		60	0.81 (0.17)	
Age of diagnosis	246*		.617‡	83*		.437‡
0-9	107	0.46 (0.41)				
10-19	18	0.61 (0.32)		72	0.82 (0.15)	
20-29	28	0.59 (0.39)		5	0.73 (0.18)	
30-39	39	0.59 (0.27)		1	0.84 (-)	
40-49	27	0.50 (0.33)		2	0.72 (0.15)	
50-59	15	0.52 (0.27)		1	0.72 (-)	
≥60	7	0.38 (0.36)		1	0.52 (-)	
Not sure	5	0.49 (0.23)		1	0.31 (-)	
Housing	286		<.001§	99		<.001§
Public housing or subdivided flats/units	122	0.45 (0.33)		33	0.72 (0.14)	
Rented	37	0.56 (0.40)		17	0.83 (0.14)	

continued on next page

Table 3. Continued

Characteristics	All patients with RD			All caregivers		
	n	Mean utility score (SD)	*P* value	n	Mean utility score (SD)	*P* value
Bought	118	0.61 (0.35)		45	0.82 (0.18)	
Others	9	0.33 (0.42)		4	0.93 (0.06)	

CSSA indicates comprehensive social security assistance; RD, rare disease.
*Missing data observed.
†Differences between binary variables; *P* values of Mann-Whitney *U* test reported.
‡Differences between ordinal variables tested; *P* values of Spearman correlation test reported.
§Differences between multiple categories tested; *P* values of Kruskal-Wallis test reported.
‖*P* value for the difference between utility scores of patients with neurologic RDs and nonneurologic RDs.

Spillover Effects Onto Caregivers

The impact of RDs on caregivers is often overlooked. Several studies have described this effect. Lopez-Bastida et al. (2016)[5] illustrated that caregivers of patients with Duchenne muscular dystrophy, fragile X syndrome, and mucopolysaccharidosis reported utility scores significantly lower than the general population. Parents have also been reported to express higher levels of anxiety from the complications of RDs than the children with immune thrombocytopenia themselves.[55] The current study also indicated significant loss of HRQOL in caregivers of patients with RD that was significantly correlated with their patients' utility scores.[16,56,57] Surprisingly, caregivers of patients with RD had significantly lower utility scores than patients with other chronic diseases.[58] The distribution of RD caregivers in each level of the EQ-5D health dimensions in this study identified that RD caregivers reported more problems with anxiety and depression (Table 2), suggestive of significant psychological burden of the caretaking role. Undoubtedly, diagnostic uncertainties, low social support, and ineffective communication with medical professionals may cause hopelessness and loneliness.[57,58] As such, RD caregivers often develop health problems because of mental and physical exhaustion, ultimately becoming the "hidden patients".[59] Therefore, interventions and holistic healthcare services should be provided to support and care for both patients with RD and their caregivers.

Future Directions: A Holistic Approach

This study identified both clinical and psychosocial factors associated with the loss of HRQOL in patients with RD and their caregivers. HRQOL has also been conceptualized as an outcome of adaptation.[36] Hence, healthcare professionals and policy makers who aim to ameliorate the living quality of patients with RD and caregivers should strive to facilitate the adaptation process through a holistic approach.[16] Increased engagement among patients, healthcare professionals, policy makers, and the community could promote coordinated care models for patients with RD.[16,49] This includes providing effective diagnostic tests and trained professionals to identify RDs, providing medical services that alleviate the symptoms of RD conditions, and establishing patient support groups.[48,50] Raising public awareness would also be beneficial for society to recognize and accept the needs of the RD population. Finally, this study highlights the substantial impact on caregivers. EQ-5D profiles of caregivers are an invaluable tool in future decision making on resource allocation. In particular, results from this study could be used to justify the provision of respite services and financial support for RD caregivers. This holistic approach could foster multidisciplinary and collaborative services, effectively improving the HRQOL of the RD population from all dimensions.

Strengths and Limitations

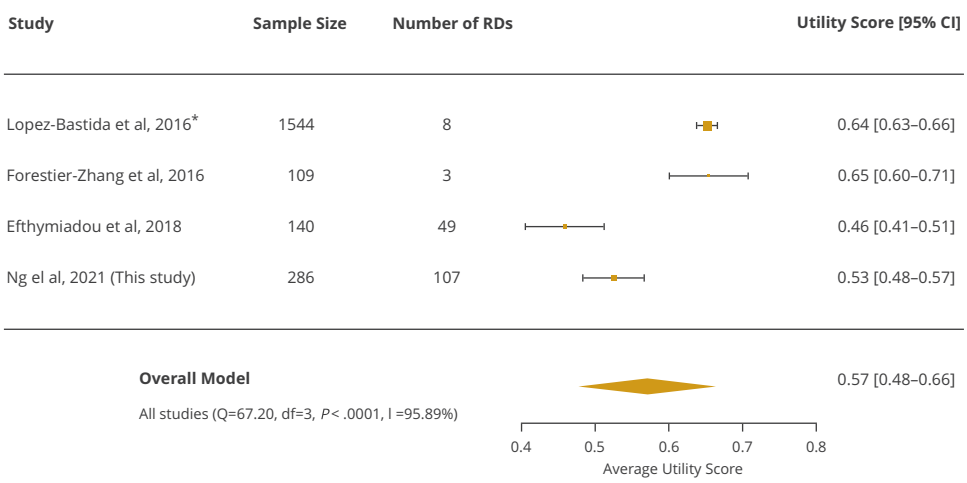
This study was the first to assess the HRQOL of patients with RD in HK inclusive to all patients with RD from any socioeconomic background and disease category. Our study also investigated the "spillover" effect onto RD caregivers by assessing their HRQOL. These results establish a normative profile of the HRQOL for the RD population in HK. It can serve as a baseline for comparisons with other populations within the jurisdiction and

Table 4. Full multivariate model for variables associated with utility scores of patients with RD.

Variable	Unit/coding	Standardized coefficient (β)	*t*	*P* value
Total annual OOP*	$HKD	−0.196	−1.932	.060
Monthly income level	$HKD	0.151	1.302	.200
Receiving government allowance	0, 1	−0.167	−1.488	.144
Home modification	0, 1	−0.405	−3.429	.001
Number of family members with RD	0, 1,2, 3, 4, 5	0.019	0.177	.860
Type of housing	0, 1, 2	0.253	2.305	.026
Education level	0, 1, 2, 3, 4	0.073	0.647	.521

Note. Coding for variables: receiving government allowance, home modification: 0 (no), 1 (yes); number of family members with RD: 0 (none), 1 (one), 2 (two), 3 (three), 4 (four), 5 (five or more); type of housing: 0 (public housing or subdivided flats/units), 1 (rented), 2 (bought); education level: 0 (primary school or below), 1 (secondary school), 2 (tertiary education), 3 (bachelor's degree), 4 (postgraduate degree or above).
HKD indicates Hong Kong dollar; OOP, out-of-pocket; RD, rare disease.
*OOP expenditures includes all health costs associated with inpatient and outpatient care, accident and emergency care, day care, surgery, procedure, treatment, residential health services, allied health services, medications, and medical resources/consumables.

Figure 1. Forest plot of meta-analysis of 4 studies measuring utility scores of patients with RD using EQ-5D. *Summary values of "Social Economic Burden and Health-Related Quality of Life in Patients with Rare Diseases in Europe" (BURQOL-RD) studies were used in meta-analysis (see Appendix S2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.04.1725 for methodology used).

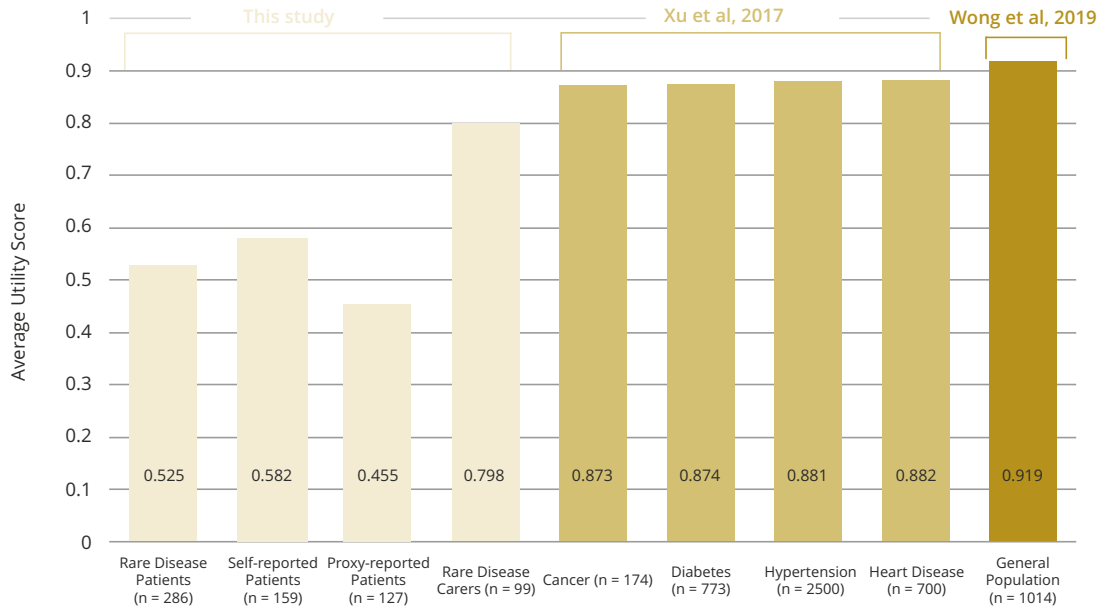


CI indicates confidence interval; RD, rare disease.

to evaluate the impact of policies on the RD population in the future.

Nevertheless, several limitations should be acknowledged. First, the study period coincided with the COVID-19 pandemic in HK. It is possible that the pandemic affected the psychologic and physical health of patients with RD and that utility scores represent the impact of RDs and the pandemic. Despite this, the meta-analysis revealed that our results were comparable with international studies. Second, using generic patient-reported outcome measures may be inaccurate for pediatric patients because problems reported in health dimensions may also be due to their young age. Nevertheless, given that pediatric patients represent a significant proportion of the RD population of HK, including patients from all ages is necessary to derive a representative utility score of RD patient in HK. Third, results of caregivers in this study may not be generalizable, given that only caregivers of patients who were incapable of self-reporting were invited to report their own HRQOL. Fourth, proxy reports of HRQOL of patients with RD may not be as accurate because they reflect the caregiver's beliefs about the effects of the disease rather than actual states of the patients. Given that children's perspective of the different dimensions is likely to differ from adults, pediatric utility scores proxied by adults may not be accurate.[60,61] Nevertheless, the proxy version of EQ-5D has been

Figure 2. Average utility scores of patients with RD (overall/self-reported/proxy reported) and caregivers (light yellow), patients with chronic illnesses (yellow), and the general population (dark yellow) in HK using EQ-5D.[26,35]



HK indicates Hong Kong; RD, rare disease.

validated in HK and >60 other jurisdictions and is well recognized in international studies.[30]

Conclusions

This study was the first to examine HRQOL in a heterogeneous sample of patients with RD using a globally validated measure, adding new information across different RD types to existing literatures. In addition to establishing a normative profile of HRQOL of patients with RD in HK, the results demonstrated the significant impact of RDs on patients and their caregivers compared with the general population and patients with chronic diseases. Identifying potential solutions that facilitate patients' adaptation and implementing respective policies would be crucial to improve the living quality of the RD population.

Supplemental Materials

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.04.1725.

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