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Original Research Article

Health-related quality of life in patients with rheumatoid arthritis and the clinical associations of EQ-5D utility scores

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Abstract

Purpose: *To assess health-related quality of life (HR-QoL) and the clinical associations in patients with Rheumatoid Arthritis (RA).*

Methods: *A cross-sectional study on multi-ethnic RA patients was performed. Disease activity was assessed using DAS28-ESR. HR-QoL was measured by EQ5D, functional disability by HAQ-DI and fatigue by FACIT-F.*

Results: *A total of 214 predominantly female (86.9 %) patients were recruited. Median age was 62 years; Inter-quartile range (IQR): 53 – 68 years. Median and mean EQ-5D scores were 0.793 (IQR: 0.647 – 0.879) and 0.752 (SD: 0.165) respectively. Median EQ-5D scores for patients in remission, low, moderate, and high disease activity were 0.879 (IQR: 0.742 – 0.933), 0.795 (IQR: 0.645 – 0.880), 0.742 (IQR: 0.564 – 0.818) and 0.653 (IQR: 0.323 – 0.775) respectively. Median EQ-5D scores for patients with mild to moderate, moderate to severe, and severe to very severe disability were 0.795 (IQR: 0.714 – 0.933), 0.728 (IQR: 0.564 – 0.818) and 0.554 (IQR: 0.287 – 0.765) respectively. DAS28-ESR, HAQ-DI, ethnicity and FACIT-F correlated with HR-QoL. EQ-5D scores were lowest in patients requiring biologic disease-modifying anti-rheumatic drugs (DMARDs) compared to none or conventional DMARDs, although this was not significant.*

Conclusion: *HR-QoL declined as RA disease activity and disability increased. Treat-to-target strategies and preventing joint destruction may improve health-related outcomes of RA patients. It is recommended that future studies be conducted in multiple health centers across Malaysia to capture variations in HR-QoL of RA patients nationally.*

Keywords: *Health-related quality of life, EQ-5D, HAQ-DI, rheumatoid arthritis*

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory condition, with a global prevalence of 0.5 [1]. RA patients are at risk of developing irreversible erosive damage to the joints, resulting in significant deformities, loss of function, reduced health-related quality of life (HR-QoL) and productivity at work.

The EuroQol EQ-5D questionnaire is one of the most used generic HR-QoL instruments worldwide [2]. The EQ-5D-3L measures HR-QoL in a single summary score based on five health

domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each of these domains is rated on three levels of severity. The summary utility score ranges from zero (death) to 1.0 (full health), and a negative score indicates a health state 'worse than death'. The EQ-5D is widely used and its repeatability, validity, and responsiveness to changes in HR-QoL in patients with RA have been shown in several studies [3].

This study aimed to characterize HR-QoL utility values for patients with RA and to determine the clinical factors influencing the health state utility scores in a multi-ethnic cohort of RA patients.

METHODS

Patient recruitment

A cross-sectional study of patients with RA was conducted in a Malaysian tertiary medical center. Recruitment was performed consecutively from April 2018 to April 2019. The inclusion criteria consisted of patients aged 18 and over who met the European League Against Rheumatism/American College of Rheumatology 2010 RA criteria. Patients were excluded if there were overlapping connective tissue diseases, chronic liver disease, chronic infection, or active malignancy. Written informed consent was obtained from all patients. Ethics approval was obtained from the University of Malaya Medical Centre Medical Research Ethics Committee (Institutional Review Board no. 2017112-5774). This study was conducted in accordance with the Declaration of Helsinki [4].

Clinical assessments and data collection

A societal-based value set for Malaysia was used to convert the EQ-5D-3L health states to utility values [3]. Patient-reported data were obtained via face-to-face interviews while data on clinical and demographic characteristics were obtained through reviews of electronic medical records. HR-QoL utility values were assessed using the EQ-5D-3L questionnaire, which was available in validated translated versions in Malay, Mandarin and Tamil [2,3].

Disease activity was assessed using the Disease Activity Score of 28 joints – erythrocyte sedimentation rate (DAS28-ESR) by a study clinician, with patients categorized into remission (< 2.6), low disease activity (2.6 - 3.1), moderate disease activity (3.2 - 5.1) and high disease activity (> 5.1) [5]. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy (FACIT-F version 4) questionnaire, with Low FACIT-F scores indicate high levels of fatigue [6]. Functional disability was assessed using the Health Assessment Questionnaire – Disability Index (HAQ-DI) score, which classifies disability into three groups (mild to moderate, moderate to severe and severe to very severe [7]. Anemia and its severity (not anemic, mild, moderate and severe) were defined based on the World Health Organization's recommendations [8]. The Charlson Comorbidity Index (CCI) was utilized to measure the burden of comorbidity, where a greater score indicates more comorbidities and a higher risk of mortality [9].

Statistical analysis

Median (IQR: 25 – 75 %), mean and standard deviation (SD) were respectively reported for continuous and categorical or ordinal variables. Differences in the distribution of EQ-5D scores across categories of the variables were tested using Mann-Whitney U or Kruskal-Wallis test. Strength of the monotonic association between EQ-5D score with age, duration of illness, FACIT-F score, anemia level, DAS28 level and HAQ-DI was assessed using Spearman's rank correlation coefficient. Univariate beta regression analyses were performed on variables found significantly associated with EQ-5D scores. The association between these variables and EQ-5D scores was then considered jointly through the stepwise beta regression analysis. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS, IBM, version 27) software, with a *p*-value less than 0.05 considered statistically significant.

RESULTS

Patient demographics and clinical data

Table 1 presents the data of the 214 study patients, with median age of 62 years old (IQR: 53 – 68) and the majority were female (86.9 %). Median disease duration was 8 years (IQR: 4 – 15). Most patients were being treated with disease-modifying anti-rheumatic drugs (DMARDs; n = 194, 92.1 %). DAS28-ESR score revealed that 78 patients (36.4 %) were in remission, 48 (22.4 %) patients had low disease activity, 76 (35.5 %) patients had moderate disease activity, and 12 (5.6 %) patients had high disease activity. The HAQ-DI assessment indicated that majority of patients (152, 71.0 %) experienced mild difficulties to moderate disability while 10 (4.7 %) had severe to very severe disability. Median CCI score was 3 (IQR: 2 – 4) and median FACIT-F score was 113.22 (IQR: 93.08 – 130.17). Mean and median HR-QoL utility values show similar differences across

the different levels of disease activity and levels of disability (Table 1).

EQ-5D score and its associated factors

EQ-5D scores for the 214 RA patients were distributed with a median of 0.793 (IQR: 0.647 – 0.879) and a mode of 0.933 with 44 patients scoring this value (Figure 1). Only 11 (5.1 %) patients scored 0.40 and below. Statistically significant differences in median EQ-5D scores were seen across ethnic categories (p = 0.005), DAS28 score (p < 0.001), anemia level (p < 0.001), and HAQ-DI (p < 0.001). EQ-5D scores were not significantly different between the types of DMARD received, although those receiving biologic DMARD had the lowest scores.

Table 1: Demographics and characteristics of 214 patients with rheumatoid arthritis

Characteristic	Frequency, *n* (%)	EQ-5D score, mean (SD)	EQ-5D score, median (IQR: 25% – 75%)	*p*-value[#]
All RA patients (*n* = 214)		0.752 (0.165)	0.793 (0.647 – 0.879)	
Gender				
Female	186 (86.9)	0.746 (0.169)	0.752 (0.645 – 0.879)	0.241
Male	28 (13.1)	0.790 (0.135)	0.795 (0.742 – 0.879)	
Ethnicity				
Chinese	76 (35.5)	0.801 (0.141)	0.879 (0.742 – 0.933)	0.005
Indian	90 (42.1)	0.719 (0.179)	0.745 (0.564 – 0.879)	
Malay	48 (22.4)	0.737 (0.159)	0.742 (0.661 – 0.879)	
BMI				
Underweight (≤18.5)	15 (7.0)	0.741 (0.216)	0.826 (0.645 – 0.879)	0.347
Normal (≥18.5 – ≤24.5)	66 (30.8)	0.745 (0.166)	0.749 (0.598 – 0.879)	
Overweight (≥24.5 – ≤29.5)	83 (38.8)	0.777 (0.149)	0.795 (0.714 – 0.879)	
Obese (≥29.5)	50 (23.4)	0.724 (0.172)	0.742 (0.645 – 0.859)	
Seropositivity				
Positive	144 (67.3)	0.752 (0.176)	0.793 (0.646 – 0.879)	0.596
Negative	70 (32.7)	0.753 (0.142)	0.745 (0.657 – 0.879)	
DMARD				
No DMARD	17 (7.9)	0.727 (0.168)	0.745 (0.646 – 0.879)	0.254
cDMARD	182 (85.0)	0.762 (0.160)	0.793 (0.661 – 0.879)	
bDMARD	4 (1.9)	0.643 (0.244)	0.694 (0.392 – 0.845)	
cbDMARD	11 (5.1)	0.677 (0.205)	0.698 (0.472 – 0.933)	
Current Prednisolone use				
Yes	106 (49.5)	0.741 (0.165)	0.749 (0.645 – 0.879)	0.239
No	108 (50.5)	0.763 (0.166)	0.793 (0.661 – 0.879)	
DAS28-ESR score				
Remission (≤2.6)	78 (36.4)	0.820 (0.124)	0.879 (0.742 – 0.933)	<0.001
Low (≥2.6 –*than*)	48 (22.4)	0.766 (0.160)	0.795 (0.645 – 0.880)	
to	76 (35.5)	0.701 (0.159)	0.742 (0.564 – 0.818)	
Highthan 1)	12 (5.6)	0.580 (0.240)	0.653 (0.323 – 0.775)	
Anaemia				
Not anemic	110 (51.4)	0.783 (0.152)	0.811 (0.714 – 0.880)	<0.001
Mild anaemia	70 (32.7)	0.756 (0.166)	0.757 (0.645 – 0.893)	
Moderate to severe anemia*	34 (15.9)	0.645 (0.165)	0.653 (0.559 – 0.795)	
HAQ-DI				
Mild difficulties to moderate disability	152 (71.0)	0.788 (0.139)	0.795 (0.714 – 0.933)	<0.001
Moderate to severe disability	52 (24.3)	0.689 (0.176)	0.728 (0.564 – 0.818)	
Severe to very severe disability	10 (4.7)	0.539 (0.228)	0.554 (0.287 – 0.765)	

[#]p < 0.05 considered statistically significant for the difference in median EQ-5D scores distribution across categories (Kruskal-Wallis/Mann-Whitney U). *There was only one severely anemic patient (borderline value of 77 mg/dL) who was grouped as moderate to severe anemia for analysis.

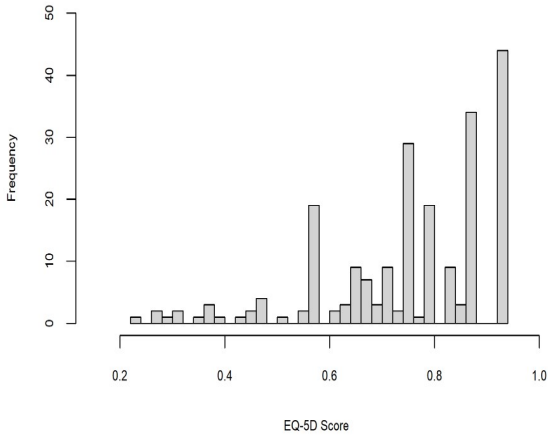

Figure 1: Distribution of EQ-5D scores from 214 RA patients

Table 2 shows that EQ-5D scores were significantly associated with anemia ($p < 0.001$), DAS28-ESR ($p < 0.001$) and HAQ-DI ($p < 0.001$) levels and FACIT-F score (all p values < 0.001). Patients with higher FACIT-F scores (less fatigue) tended to have higher EQ-5D scores, while patients with more severe HAQ-DI or anemia levels or higher DAS28-ESR scores were more likely to have lower EQ-5D scores.

Table 2: Monotonic association of continuous and ordinal independent factors with EQ-5D scores in RA patients

Property	Spearman's rank correlation with EQ-5D	*p*-value
Age (years)	0.054	0.431
Duration of illness (years)	-0.107	0.119
CCI	-0.042	0.538
FACIT-F score	0.622	<0.001
DAS28-ESR levels	-0.371	<0.001
HAQ-DI	-0.318	<0.001
Anaemia	-0.253	<0.001

Note: $p < 0.05$ is considered statistically significant for monotonic association

EQ-5D utility scores ranged between 0 to 1 with scores scattered along the straight line in the QQ plot of the beta distribution (Figure 2), modeled reasonably with the beta distribution. Beta regression modeling was then performed for the identified independent predictors significantly associated with the EQ-5D scores (from Table 1 and Table 2) separately and jointly.

Table 3 presents the results of the regression modeling, showing that ethnicity, DAS28, HAQ-DI and FACIT-F scores are significantly and jointly associated with EQ-5D scores. With higher FACIT-F total scores, patients have higher EQ-5D scores ($p < 0.001$). Patients who were of Indian ($p = 0.009$) and Malay ($p = 0.004$) ethnicities had lower EQ-5D scores compared to Chinese patients. Patients with low, moderate or high DAS28 scores had lower EQ-5D scores ($p < 0.001$, $p = 0.001$ and $p = 0.018$, respectively) compared to patients who were in remission. Patients with moderate to severe disability or severe to very severe disability exhibited EQ-5D scores that were significantly lower ($p < 0.001$) compared to patients with mild difficulties to moderate disability. After adjusting for other predictors, duration of illness and anemia levels had no significant association with EQ-5D scores and were not included in the final stepwise beta regression model in Table 3.

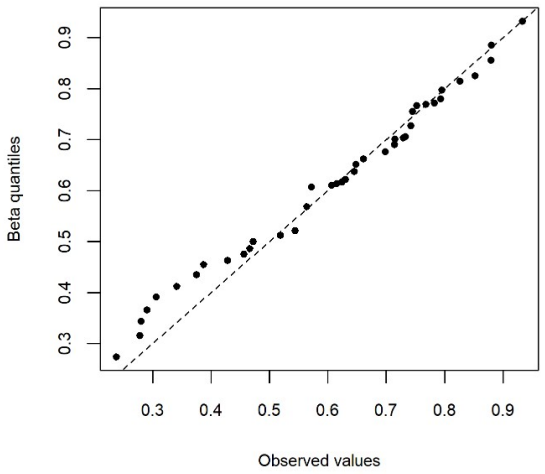

Figure 2: QQ plot of observed EQ-5D scores versus expected values from a beta distribution

DISCUSSION

RA treatment aims to improve health-related HR-QoL, with emphasis on treating-to-target [10]. This is the first study assessing HR-QoL of RA patients in Malaysia, with the only other studies in Southeast Asia conducted in Thailand [11-13]. The impact of RA on HR-QoL is significant and potentially greater compared to other more prevalent chronic diseases like diabetes mellitus and chronic obstructive pulmonary disease [14], which highlights the importance of optimizing RA treatment.

The mean EQ-5D score from this study (0.752 (SD: 0.165)) was higher than the pooled mean from a meta-analysis of EQ-5D utility scores in RA patients across Asia (0.66; 95 % confidence interval (CI): 0.63 – 0.69) [15].

Table 3: Univariate and multivariate analyses of factors associated with EQ-5D values

Predictor	Univariate		Multivariate	
	Coefficient (SE)	***p-value***	***Coefficient (SE)***	***p-value***
Ethnicity				
Chinese	Ref.		Ref.	
Indian	-0.370 (0.122)	0.002*	-0.254 (0.097)	0.009*
Malay	-0.306 (0.143)	0.033*	-0.323 (0.112)	0.004*
DAS28-ESR score				
Remission	Ref.		Ref.	
Low	-0.235 (0.140)	0.093	-0.081 (0.115)	0.483
Moderate	-0.568 (0.121)	<0.001*	-0.257 (0.101)	0.011*
High	-1.043 (0.216)	<0.001*	-0.661 (0.177)	<0.001*
HAQ-DI				
Mild difficulties to moderate disability	Ref.		Ref.	
Moderate to severe disability	-0.463 (0.117)	<0.001*	-0.121 (0.100)	0.226
Severe to very severe disability	-1.087 (0.223)	<0.001*	-0.575 (0.186)	0.002*
FACIT-fatigue score	0.0207 (0.0017)	<0.001*	0.0176 (0.0017)	<0.001*
Anaemia				
Not anemic	Ref.			
Mild anaemia	-0.108 (0.118)	0.357		
Moderate to severe anemia	-0.645 (0.143)	<0.001*		
Duration of illness	-0.012 (0.006)	0.049*		

SE: Standard error; Ref.: Reference category. Analysis was done using beta regression (univariate) and stepwise beta regression (multivariate; a range of EQ-5D values between 0 and 1). For the stepwise beta regression model, the intercept was -0.360 (SE: 0.228; $p = 0.1114$) and the Φ coefficient (from the identity link) is 14.053 (SE: 1.337; $p < 0.001$). *Statistical significance at $p < 0.05$

Most of the studies were conducted in Japan, Korea and China, with varying mean EQ-5D scores between countries [15]. Haridoss *et al* [15] found significant differences in the EQ-5D utility values across different study designs, with lower EQ-5D values for pooled findings of case-control (0.65; 95 % CI: 0.49 – 0.80) and cohort studies (0.60; 95 % CI: 0.54 – 0.66) compared to cross-sectional studies (0.72; 95 % CI: 0.68 – 0.75). The mean EQ-5D score observed in this study (0.752; SD: 0.165) was similar to the pooled utility values of the twelve cross-sectional studies conducted in Asia (0.72; 95 % CI: 0.68 – 0.75) [15]. This could be due to the different objectives of these studies with varied inclusion and eligibility criteria and timing of sampling, leading to observed differences in EQ-5D utility values.

The HR-QoL utility values from this study were in line with the trend from the pooled EQ-5D scores from a meta-analysis of RA patients [15], with utility values for patients with remission, low, moderate and high disease activity being 0.820 (SD: 0.124) vs 0.78 (95% CI: 0.65 – 0.90) from the meta-analysis, 0.766 (SD: 0.160) vs 0.73 (95% CI: 0.65 – 0.80), 0.701 (SD: 0.159) vs 0.53 (95% CI: 0.32 – 0.74) and 0.580 (SD: 0.240) vs 0.47 (95 % CI: 0.32 – 0.62), respectively (Table 1). This trend was also consistent for functional disability measured by HAQ-DI scores, where patients with severe to very severe disability had lower mean HR-QoL utility values (0.539; SD: 0.228) compared to those with mild difficulties to moderate disability (0.788; SD: 0.139) and moderate to severe disability (0.689; SD: 0.176; Table 1). The study population is past the initial early diagnosis period (median disease duration 8 years) and their higher EQ-5D scores may reflect advancements in RA treatment and the relative ease of access to specialist rheumatology services in urban cohort.

In the final multivariate analysis, DAS28-ESR, HAQ-DI, ethnicity and FACIT-F scores were all significantly and jointly associated with HR-QoL utility values. Similar to Haridoss *et al* [15], lower EQ-5D scores correlated with high disease activity. Consistent with other studies, EQ-5D values correlated with functional disability measured by HAQ-DI, which are expected as higher disease activity leads to poorer state of health and function due to inflammation in active RA disease [12].

In this study population, Chinese patients had significantly higher median EQ-5D scores compared to Malay and Indian ethnicities. Another single-center cross-sectional study of 371 RA patients in Malaysia reported a similar pattern of under-representation of Malay patients and over-representation of Indian patients, with 36% Chinese patients in this study compared to 49% in theirs, 22% Malay patients compared to 27% and 42 % Indian compared to 24 %) [16]. The study found that Malay patients (OR: 2.96; 95 % CI: 1.47 – 5.96) and the use of three DMARDs (OR: 2.14; 95 % CI: 1.06 – 4.35) were

linked to failure to achieve treatment target and concluded that Malay patients required more aggressive treatment adjustments to achieve optimal outcomes [16]. However, this study did not find a correlation between ethnicity and the level of disease activity (p = 0.787), potentially due to the different study design, objectives and distribution of ethnic groups.

Fatigue is a common yet complex multi-dimensional symptom in chronic diseases like RA. The relationship between RA disease activity and fatigue is inconsistent, with some studies reporting high levels of fatigue despite adequate treatment with DMARDs [17,18]. The relationship between fatigue and HR-QoL is more clearly established with greater reduction in HR-QoL reported in patients with more fatigue [19]. This study reports a significant correlation between fatigue and HR-QoL, highlighting the importance of addressing fatigue in managing RA to improve health outcomes for patients.

Median EQ-5D values were the lowest among patients treated with biologic DMARD (bDMRD) and a combination of conventional and biologics DMARDs (csDMARD) groups (although not statistically significant), possibly a reflection of moderate to active disease in these patients and, in line with findings that persistent disease may occur despite optimum treatment [19].

Strengths and limitations of this study

This study population represented RA patients who were being treated in real-world clinical practice, with efforts made to invite all eligible patients treated at the Rheumatology Clinic in University Malaya Medical Centre to participate during the one-year study period leading to 214 patients included. The cross-sectional design limited the assessment of whether EQ-5D values change with various disease activities over time. However, the trend of these findings is similar to twelve other cross-sectional HR-QoL studies in RA patients in Asia [15]. The single-center study reflected an urban population of RA patients in Malaysia with access to a rheumatology specialist clinic and may not reflect patients in rural areas with limited access to specialist treatment. Due to limited funding and resources, this study was focused on a single academic medical center which serves as a referral center.

CONCLUSION

This study reports the first EQ-5D data of RA patients in Malaysia and provides HR-QoL data for future pharmaco-economic studies. HR-QoL utility values in this patient population decreased with higher disease activity and greater disability. DAS28-ESR, HAQ-DI, ethnicity and FACIT-F and strongly correlated with EQ5D scores. The findings suggest that reducing disease activity and disability through treat-to-target strategies and preventing joint destruction may lead to better HR-QoL and overall health outcomes in RA patients. It is recommended that future studies be conducted in multiple health centers across Malaysia to capture variations in HR-QoL of RA patients nationally.

DECLARATIONS

Acknowledgement

None.

Funding

None provided.

Ethical approval

Approval was granted by the Medical Research Ethics Committee of the University of Malaya Medical Centre (no. 2017112-5774).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Lydia SL Pok and Fatiha H Shabaruddin are co-first authors. All authors contributed to the study's conception and design. Material preparation and data collection were performed by Lydia SL Pok and Hwai J Lee. Data analysis was performed by Choung M Ng. The first draft of the manuscript was written by Lydia SL Pok and Fatiha H Shabaruddin. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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