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BRIEF REPORT

Are extra-spinal symptoms associated with quality of life in patients with axial spondyloarthritis? A 1-year follow-up study

Yu Heng Kwan[1] · Warren Fong[2,3,4] · Ying Ying Leung[2] · Nai Lee Lui[2] · Chuen Seng Tan[5] · Rahul Malhotra[1] · Truls Østbye[1] · Julian Thumboo[1,2,4]

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Abstract

To assess the extent to which a history of extra-spinal symptoms (including peripheral arthritis, heel enthesitis, or dactylitis) (HPED) is associated with quality of life (QoL) in patients with axial spondyloarthritis (axSpA) at baseline and 1-year follow-up. We analyzed data from 138 patients with axSpA from a tertiary referral center in Singapore, seen between 2011 and 2015. Demographic, clinical variables, and patient-reported outcomes [Ankylosing Spondylitis Quality of Life (ASQoL) and SF-36] at baseline and 1-year follow-up were collected. We used linear mixed models to assess the association of HPED with QoL at baseline and 1 year post-baseline. Among 138 patients (mean age 39.3 years, 74.6% males, 87.6% Chinese, disease duration 7.4 years), at baseline, HPED was associated with poorer QoL for 3 of 8 SF-36 domains [role physical (RP) scores $\beta - 8.38$, $p < 0.05$; social functioning (SF) scores $\beta - 6.74$, $p < 0.05$; role emotional (RE) scores $\beta - 9.37$, $p < 0.01$] and SF-36 Physical Component Summary (PCS) ($\beta - 4.52$, $p < 0.01$) scores, but not ASQoL scores. At 1 year post-baseline, HPED was associated with poorer ASQoL (β 1.61, $p < 0.05$) scores, SF-36 PCS ($\beta - 5.61$, $p < 0.01$) scores, and three out of eight SF-36 domains (physical functioning (PF) $\beta - 9.60$, $p < 0.01$; RP $\beta - 12.17$, $p < 0.01$; RE $\beta - 7.87$, $p < 0.05$) scores. HPED was associated with QoL in patients with axSpA. After 1-year, patients with HPED have poorer QoL especially for physical health domains than patients without HPED.

Keywords Dactylitis · Extra-spinal symptoms · Heel enthesitis · Peripheral arthritis · Quality of life · Spondyloarthritis

Introduction

Axial spondyloarthritis (axSpA) is a heterogeneous group of inflammatory chronic diseases that can cause severe limitations in physical function [1]. Patients with axSpA experience fatigue and pain [2], and some patients experience limited spinal mobility. Furthermore, as much as 60% of patients with axSpA have a history of extra-spinal symptoms [including peripheral arthritis, heel enthesitis, or dactylitis] (HPED) [3].

As there are few if any disease-modifying drugs for axSpA, management of patients with axSpA currently focuses on improving function and reducing pain to improve quality of life (QoL) [4]. QoL refers to a patient's subjective perception of well-being [5] and can be measured using generic or disease-specific instruments [6]. Generic instruments allow for comparison across diseases, while disease-specific instruments are generally more sensitive to detecting and quantifying smaller changes than generic instruments [7, 8]. Out of the possible domains encompassed by QoL, physical function, fatigue, pain, and patient global assessment have been identified as the core domains for Assessment of Spondyloarthritis International Society (ASAS) outcome measures for ankylosing spondylitis [9]. These core domains have also been found to be relevant to QoL among patients with SpA [6].

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✉ Julian Thumboo
julian.thumboo@singhealth.com.sg

[1] Program in Health Services and Systems Research, Duke-NUS Medical School, Singapore, Singapore

[2] Department of Rheumatology and Immunology, Singapore General Hospital, Level 4, 20 College Road, Bukit Merah 169856, Singapore

[3] Duke-NUS Medical School, Singapore, Singapore

[4] Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

[5] Saw Swee Hock School of Public Health, National University of Singapore, Singapore, Singapore

Patients with peripheral arthritis in ankylosing spondylitis have poorer QoL than patients without peripheral arthritis [10]. Our previous qualitative study showed that patients with axSpA who have extra-spinal symptoms have greater number of adversely affected QoL domains (i.e., body image and appearance, personal relationship and thinking, learning, memory, and concentration) than patients without extra-spinal symptoms [11]. Furthermore, extra-spinal symptoms have high recurrence rates [12]. Therefore, understanding the influence of HPED on QoL longitudinally is important to develop useful interventions to improve the QoL in patients with axSpA [5].

There are no studies investigating the association of HPED with QoL in patients with axSpA. Therefore, we aimed to assess whether HPED is associated with poorer QoL in patients with axial spondyloarthritis (axSpA) at baseline and 1 year post-baseline.

Materials and methods

Study design

We used data from the precision medicine in spondyloarthritis for better outcomes and disease remission (PRESPOND) registry, from a tertiary referral center in Singapore, collected from January 2011 to July 2015. PRESPOND was developed to monitor the disease progression of all consenting patients with axSpA in Singapore. This study was conducted in accordance with the ethical standards of the SingHealth Centralized Institutional Review (CIRB Ref 2012/498/E) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Written informed consent was obtained from all patients before commencement of the study.

Subjects

All patients recruited into the PRESPOND registry were over 18 years old and fulfilled the 2009 ASAS criteria for axSpA. We limited the analysis to patients who had completed QoL data at both baseline and 1 year to reduce potential bias due to dropout. Our dropout rate of 37.6% is similar to other registries [13, 14].

Data collection

We prospectively collected demographic characteristics, clinical data, and patient-reported outcome measures (PROMs) at point of recruitment (baseline) and 1 year later using a standardized, pre-tested data collection form. If a patient had problem reading, an interviewer administered the questionnaire.

Demographic data that included age, gender, and ethnicity were collected.

Disease duration, erythrocyte sedimentation rate, comorbidities, HLA-B27, extra-articular and extra-spinal features of SpA, family history of SpA, current treatment, and Bath Ankylosing Spondylitis Metrology Index (BASMI) (range 0–10 numerical rating scores, higher scores reflect poorer metrological measurement) were collected as part of the clinical assessment.

The following PROMs were collected:

- Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (range 0–10 numerical rating scores, higher scores reflect higher disease activity)
- Bath Ankylosing Spondylitis Functional Index (BASFI) (range 0–10 numerical rating scores, higher scores reflect poorer functioning)
- Bath Ankylosing Spondylitis Global Score (BASG) (range 0–10 visual analogue scale, higher scores reflect poorer patient's opinion of disease)
- Pain visual analog scale (VAS) (range 0–100 VAS, higher scores reflect more pain)
- Health Assessment Questionnaire (HAQ) (range 0–3, higher scores reflect poorer functioning)

Independent variable: HPED

HPED was the independent variable in this study. HPED was defined as the description of peripheral arthritis, heel enthesitis, or dactylitis (or some combinations of these three) in the clinical records. Heel enthesitis refers to pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus [15]. HPED was selected because we found in our previous qualitative study that patients with HPED experienced a wider impact on QoL than patients without HPED [11]. As we were interested in the impact of HPED at baseline on QoL in patients with axSpA, classification of HPED was only conducted at baseline.

Outcome: QoL

The primary outcome was ASQoL score, and the secondary outcomes were the eight domains of the SF-36 and the physical and mental component summary scores of the SF-36. Both ASQoL and SF-36 were validated PROMs to measure QoL in Singapore [16, 17].

ASQoL

ASQoL is a patient-derived and disease-specific measure of QoL for AS. It consists of 18 items with a yes (scored as 1) or no (scored as 0) response to each item. All item scores are summed to a total 0–18 score [18], with *higher* scores indicating *worse* QoL.

SF-36

The SF-36 version 2 is a self-reported generic health-related quality of life (QoL) questionnaire. It comprises of eight health domains: physical functioning (PF), physical role functioning (RP), emotional role functioning (RE), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), and mental health (MH). The eight domains are further summarized into physical component summary (PCS) and mental component summary (MCS) scores. PCS and MCS are norm-based scores with a mean of 50 and a standard deviation of 10, with *higher* scores indicating *better* QoL [19].

The ASQoL and SF-36 were self-administered in English as PROMs.

Statistical analysis

Descriptive statistics are presented as frequencies and percentages or means and standard deviations. Shapiro-Wilk test was used to determine normality. Continuous data were analyzed using independent samples Student's t test or Mann-Whitney U test as appropriate, while categorical data were analyzed using either chi-square test or Fisher's exact test as appropriate.

To assess the association of HPED with QoL in patients with axSpA at baseline (i.e., cross-sectionally), Student's t test or Mann-Whitney U test was used as appropriate to assess the difference of QoL scores between the patients with or without HPED at baseline.

To assess the association of HPED with QoL in patients with axSpA, a linear mixed model with random subject effect was developed in stages. The initial model included HPED as the sole independent variable (Model 1) and QoL (ASQoL or SF-36) as the outcome variable separately. The model was then adjusted with age, gender, comorbidities, disease activity, treatment, and disease duration as confounders (Model 2) [20]. These confounders were chosen because they had been shown to be associated with QoL in the literature and were tested to be associated with HPED and QoL in our univariate analyses. We checked for collinearity and ensured that all variables have variance inflation factor less than 5 before inclusion in the model. In the linear mixed model, we presented β which represents the change in QoL when the independent variable increases by 1.

To assess the association of HPED with QoL at baseline and 1 year post-baseline, the time of assessment (baseline or 1 year) and an interaction term between HPED at baseline and time of assessment were added as independent variables (Model 3). The mathematical equation representing Model 3 can be found in the Supplementary Figure 1.

STATA SE15.0 was used for all analyses and p values less than 0.05 were considered statistically significant.

Results

Study sample

This study included 138 patients with axSpA, of whom 85 (61.5%) had HPED (or some combination of these three). As shown in Table 1, there were less males (67.0% vs 86.7%; $p = 0.01$), more patients were on sulfasalazine (27.0% vs 7.5%; $p < 0.01$), and more patients with higher BASDAI scores (3.7 ± 1.8 vs 2.6 ± 1.6; $p < 0.01$) when comparing patients with and without HPED, respectively. At baseline, 83 (60.1%) patients had HPED, while at 1 year post-baseline, 85 (61.5%) patients had HPED.

Differences in QoL between patients with and without HPED at baseline

As shown in Table 2, patients with HPED had poorer QoL as shown by higher ASQoL scores (4.6 ± 4.5 vs 2.3 ± 2.9; $p < 0.01$) when compared to patients without. Patients with HPED also had lower scores for all SF-36 domains except GH (51.5 ± 21.5 vs 58.1 ± 21.8; $p = 0.08$), MH (69.4 ± 17.4 vs 75.2 ± 16.5; $p = 0.05$), and MCS (42.7 ± 11.5 vs 46.3 ± 12.2; $p = 0.08$) as compared to patients without HPED.

Association of HPED with QoL at baseline and 1 year post-baseline in patients with axSpA using linear mixed model: longitudinal analyses

The multivariable analysis using linear mixed model in Table 3 (Model 1) showed that HPED was associated with ASQoL and 6 SF-36 domains (PF, RP, BP, VT, SF, and RE) and PCS. After adjustments with confounders (Model 2), HPED was associated with ASQoL and 4 SF-36 domains (PF, RP, SF and RE) and PCS.

After inclusion of the time of assessment and interaction between HPED and time of assessment (Model 3), HPED was associated with 3 SF-36 domains (RP, SF, and RE) and PCS at baseline. At 1 year post-baseline, HPED was associated with ASQoL, 3 SF domains (PF, RP and RE) and PCS. BP, GH, VT, MH, and MCS were not associated with HPED at baseline or at 1 year post-baseline. Although the interaction term between HPED and time of assessment was significant only for PF, the directions of the associations were largely positive for physical domains of QoL while negative for mental domains of QoL (Model 3).

Discussion

This is the first study to examine the association between HPED and QoL among patients with axSpA over a 1-year period. In the cross-sectional analyses, HPED in patients

Table 1 Characteristics of axSpA patients with and without extra-spinal features (HPED)

Characteristics	Total ($n = 138$)	With HPED ($n = 85$)	Without HPED ($n = 53$)	P value
Age	39.3 ± 17.1	39.3 ± 9.3	39.4 ± 25.2	0.22
Male	103 (74.6)	57 (67.0)	46 (86.7)	*0.01*
Chinese ethnicity	121 (87.6)	75 (88.2)	46 (86.7)	0.80
Disease duration (years)	7.4 ± 8.7	8.3 ± 9.2	5.8 ± 7.6	0.09
Disease subtypes				
Ankylosing spondylitis	121 (87.6)	74 (87.0)	47 (88.6)	0.77
Non-radiographic axSpA	17 (12.4)	11 (13.0)	6 (11.4)	
BASMI (0–10)	2.8 ± 2.2	2.9 ± 2.3	2.6 ± 2.0	0.49
Presence of HLA-B27 allele	116 (84.6)	76 (89.4)	40 (76.9)	0.05
Peripheral arthritis[a]	64 (46.3)	64 (75.2)	0 (0)	< *0.01*
Dactylitis[a]	10 (7.2)	10 (11.7)	0 (0)	< *0.01*
Heel enthesitis[a,b]	46 (33.3)	46 (54.1)	0(0)	< *0.01*
Uveitis[a]	43 (31.1)	30 (35.2)	13 (24.5)	0.18
Psoriasis[a]	4 (2.9)	2 (2.3)	2 (3.7)	0.63
Inflammatory bowel disease[a]	7 (5.0)	5 (5.8)	2 (3.7)	0.70
Family history of SpA	21 (15.2)	13 (15.2)	8 (15.0)	0.97
On biologics currently	10 (7.2)	8 (9.4)	2 (3.8)	0.21
On sulfasalazine currently	27 (19.5)	23 (27.0)	4 (7.5)	< *0.01*
PROMs				
BASDAI (0–10)	3.3 ± 1.8	3.7 ± 1.8	2.6 ± 1.6	< *0.01*
BASFI (0–10)	2.0 ± 2.0	2.4 ± 2.2	1.4 ± 1.5	*0.01*
BASG (0–100)	36.4 ± 21.1	39.5 ± 21.3	31.3 ± 19.8	*0.03*
Pain (0–100)	32.4 ± 23.8	38.1 ± 23.6	22.7 ± 20.9	< *0.01*
HAQ Score (0–3)	0.2 ± 0.3	0.3 ± 0.4	0.1 ± 0.2	*0.02*

Data presented as frequency (%) or mean ± standard deviation. Statistically signifcant p values were italicised

[a] Ever presence of symptoms (by clinical examination)

[b] Heel enthesitis refers to pain or tenderness at examination of the site of the insertion of the Achilles tendon or plantar fascia at the calcaneus

HPED presence of peripheral arthritis, enthesitis, or dactylitis at baseline, ever; *axSpA* axial spondyloarthritis; *SpA* spondyloarthritis; *ESR* erythrocyte sedimentation rate; *PROMs* patient-reported outcomes measures; *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index; *BASFI* Bath Ankylosing Spondylitis Functional Index; *BASMI* Bath Ankylosing Spondylitis Metrology Index; *BASG* Bath Ankylosing Spondylitis Global Score; *PGA* Patient Global Assessment; *HAQ* Health Assessment Questionnaire

with axSpA was associated with poorer QoL across all outcomes except SF-36 GH, MH, and MCS. Also, HPED was associated with poorer physical health at 1 year post-baseline. Our findings were consistent with the results of a study by van der Heijde et al. which has shown that improvement in extra-spinal symptoms may indirectly improve QoL [21].

We showed that HPED in axSpA has a negative impact on most domains of QoL. This was similar to the finding by Yilmaz et al. that peripheral arthritis in patients with ankylosing spondylitis resulted in poorer QoL [10]. Patients with HPED experience pain in areas such as hands or feet which may adversely affect QoL during walking, locomotion, and usage of hands [6]. Our cross-sectional analyses did not show an association between HPED and SF-36 GH, MH, and MCS—this may be due to the fact that patients in our cohort already had low SF-36 GH, MH, and MCS scores, as axSpA has a strong impact on GH, MH, and MCS due to the systemic nature of the disease [16]. Patients with axSpA have mental health scores comparable to patients on dialysis [22] as well as a higher prevalence of depression and anxiety compared to the general population [23]. As our patients had low HAQ and BASMI scores suggesting good functioning and metrology measurements, respectively, the poor QoL observed in this study demonstrated that other factors such as pain and HPED may be influencing QoL. Therefore, clinicians should try to screen for HPED, as this can result in poorer QoL in patients with axSpA. Also, the presence of enthesitis and dactylitis might not result in the patient having a BASDAI greater than 4, but these patients might still benefit from biologics, thus improving their QoL.

Table 2 Quality of life of patients with axSpA with and without extra-spinal features (HPED) at baseline: cross-sectional analyses

Characteristics	Total ($n = 138$)	HPED ($n = 85$)	Without HPED ($n = 53$)	P value
Primary outcome (0–18, lower value indicates better QoL)				
ASQoL	3.7 ± 4.1	4.6 ± 4.5	2.3 ± 2.9	*< 0.01*
SF-36 Eight domains (0–100, higher value indicates better QoL)				
Physical function	77.6 ± 20.9	72.7 ± 22.1	85.5 ± 16.1	*< 0.01*
Role physical	76.3 ± 23.5	70.1 ± 24.4	86.3 ± 18.3	*< 0.01*
Bodily pain	60.3 ± 21.0	55.4 ± 21.7	68.1 ± 17.4	*< 0.01*
General health	54.0 ± 21.8	51.5 ± 21.5	58.1 ± 21.8	0.08
Vitality	58.1 ± 19.8	54.1 ± 19.2	64.5 ± 19.1	*< 0.01*
Social functioning	80.0 ± 19.9	74.7 ± 20.1	88.6 ± 16.4	*< 0.01*
Role emotional	81.8 ± 22.3	76.5 ± 24.3	90.6 ± 15.0	*< 0.01*
Mental health	71.7 ± 17.2	69.4 ± 17.4	75.2 ± 16.5	0.05
SF-36 Norm-based summary (0–100, higher value indicates better QoL)				
Physical component summary	43.8 ± 11.3	40.5 ± 11.6	49.3 ± 8.4	*< 0.01*
Mental component summary	44.1 ± 11.9	42.7 ± 11.5	46.3 ± 12.2	0.08

Data presented as mean ± standard deviation. Statistically signifcant p values were italicised

HPED presence of peripheral arthritis, enthesitis, or dactylitis, ever; *ASQoL* Ankylosing Spondylitis Quality of Life; *axSpA* axial spondyloarthritis; *QoL* quality of life; SF-36 Short Form-36 Health Surveys (SF-36)

Disease activity, as expected, was the main driver of QoL [24]. Despite this, at 1 year, HPED was still shown to have a persistent negative impact on QoL especially the physical domains. This showed that over 1 year, the impact of HPED on physical health increased, while the impact of HPED on mental health decreased. Possible reasons could be due to response shift seen or development of coping strategies in

Table 3 The association of extra-spinal symptoms (HPED) with quality of life outcomes: linear mixed model analyses

Outcome	Model 1 ($n = 138$)	Model 2 ($n = 138$)	Model 3 ($n = 138$)		
	HPED on QoL at baseline	HPED on QoL at baseline	β_1	$\beta_1 + \beta_3$	β_3
ASQoL	2.20**	1.24*	0.85	1.61**	0.76
PF	− 12.50**	− 6.72*	− 3.64	− 9.60**	− 5.96*
RP	− 14.15**	− 10.34**	− 8.38*	− 12.17**	− 3.79
BP	− 8.94**	− 3.57	− 3.35	− 3.79	− 0.44
GH	− 3.50	− 1.25	− 1.36	− 1.14	0.22
VT	− 7.12*	− 3.13	− 4.03	− 1.78	2.25
SF	− 10.57**	− 6.11*	− 6.74*	− 5.42	1.32
RE	− 10.67**	− 8.58**	− 9.37**	− 7.87*	1.50
MH	− 2.82	0.32	− 0.64	1.25	1.89
PCS	− 7.34**	− 5.06**	− 4.52**	− 5.61**	− 1.09
MCS	− 1.34	0.59	− 0.25	1.46	1.71

Data presented as β. Time referred to time of assessment (baseline or 1-year). β_1, $\beta_1 + \beta_3$, and β_3 represented the effect of HPED on QoL at baseline, 1 year, and that of the interaction with time, respectively. Higher ASQoL β refers to poorer quality of life, while higher PF, RP, BP, GH, VT, SF, RE, MH, and PCS, and higher MCS β refer to better quality of life

HPED presence of peripheral arthritis, enthesitis, or dactylitis, ever; *PF* physical function; *RP* role physical; *BP* bodily pain; *GH* general health; *VT* vitality; *SF* social functioning; *RE* role emotional; *MH* mental health; *PCS* physical component summary of SF-36; *MCS* mental component summary of SF-36; *ASQoL* Ankylosing Spondylitis Quality of Life; *axSpA* axial spondyloarthritis; *QoL* quality of life

*$p < 0.05$; **$p < 0.01$

Model 1 Unadjusted analysis

Model 2 Model 1 with adjustment for age, gender, comorbidities, disease duration, disease activity, and treatment

Model 3 Model 2 with inclusion of time of assessment and interaction between time of assessment and HPED

patients with HPED [25]. Nevertheless, patients should be followed up over a longer duration, and more qualitative studies are needed to understand the true impact of HPED on the QoL of patients with axSpA in order to develop suitable interventions to improve their QoL.

The strength of our study is that we utilized both generic (SF-36) and disease-specific QoL PROMs (ASQoL) which allow further comparison of QoL with other diseases in the future. Our study has several limitations. Firstly, the number of Malay and Indian patients in our cohort was relatively small; therefore, we could not adjust fully for the effect of ethnicity. However, the low representation of minorities in our study is comparable to the ethnic composition of the axSpA cohort in our center and in Singapore [16, 26, 27]. Also, no significant difference in QoL was found among different ethnic groups in patients with rheumatoid arthritis and psoriatic arthritis [28, 29]. Furthermore, we re-analyzed the data with BASMI as a confounder, and the results were similar to that presented in this manuscript. Secondly, we did not adjust for structural changes in the spine in our modeling. However, we believe that this was appropriate in our study because structural changes are known to be very slow and are reported to be not associated with QoL [20]. Thirdly, less than 10% of our patients were on biologics at the time of analysis, as our patients have generally lower disease activity (mean BASDAI of 3.3 as compared to 4.6 in the DESIR cohort) [30] and Singapore has a healthcare system whereby patients have to co-pay, thus limiting financial accessibility to biologics [31]. Fourthly, HPED did not reflect extra-spinal symptoms at the time of assessment but rather the presence of extra-spinal symptoms ever. However, only five patients developed extra-spinal symptoms over the 1 year follow-up. The results of our sensitivity analysis, when we excluded these patients, were similar to those shown in Table 3. Finally, we did not analyze the separate effects of peripheral arthritis, heel enthesitis, and dactylitis because of the limited number of patients with single symptoms, and treatment algorithm currently hinges on whether patients presented with peripheral symptoms [9].

In conclusion, HPED was associated with poorer QoL outcomes in patients with axSpA. After 1 year, patients with HPED have poorer QoL especially for physical health domains than patients without HPED.

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Compliance with ethical standards

Disclosures None.

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