Association between Patient Acceptable Symptom State and disease activity in psoriatic arthritis is disrupted by confounders, including comorbid fibromyalgia

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Abstract

Objective

Due to the prevalence of fibromyalgia in psoriatic arthritis (PsA) patients, any evaluation about PsA-specific patient-reported outcomes (PROs) should take in account the possible bias related to this comorbidity. Patient acceptable symptom state (PASS) is a patient-reported measure evaluating the acceptable and/or satisfactory level of symptoms in rheumatic diseases, which has been proposed as a disease activity index, in patients with PsA. Thus, this study was designed to analyse if the association between PASS and PsA disease activity may be biased by the presence of comorbid fibromyalgia.

Methods

A multi-centre, cross-sectional, observational study enrolling consecutive PsA participants has been conducted from July 2021 to November 2021. The Disease Activity for Psoriatic Arthritis (DAPSA) was collected; the following formulation of PASS question: 'Think about all the ways your PsA has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable to you?', was submitted to our participants.

Results

Multivariable logistic regressions, adjusted for the presence of fibromyalgia, did not show any significant association between PASS and DAPSA low disease activity, DAPSA as nominal variable (remission, low disease activity, moderate disease activity, high disease activity) and DAPSA as continuous variable.

Conclusion

Our data suggest that fibromyalgia influences the patient's perception of the disease and has a negative impact on PASS status independently of disease activity, thus limiting the utility of this Patient reported outcome in real world clinical practice.

Key words

psoriatic arthritis, fibromyalgia, Patient Acceptable Symptom State (PASS), disease activity

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Introduction

Psoriatic arthritis (PsA) is a complex chronic inflammatory disease, characterised by psoriasis, heterogenous musculoskeletal manifestations, such as peripheral and axial arthritis, enthesitis and dactylitis, extra-articular involvement, including uveitis and inflammatory bowel diseases, and finally cardiovascular, metabolic, and psychological comorbidities (1-3).

The achievement of disease remission or, alternatively, low disease activity should be the targets in the management of PsA (4, 5). A large number of disease activity scores for PsA assessment are currently used in clinical settings (6). Moreover, in the last years, the patients-related perspective emerged as an important tool, and different patient-reported outcomes (PROs) were developed (7). PROs, regarding both PsA severity and quality of life, may differ from different physicians' point of view, generally more influenced from biologic variables, such as swollen joints count and C-reactive protein (8, 9). Indeed, psychologic factors are considered as important determinants of the pain experience in patients with inflammatory arthritides, and among them, pain catastrophising and depression, garnered specific attention (10, 11). All these factors, influencing the patient's perception of the disease, may negatively impact the achievement of remission or low disease activity, after specific treatments, altering the patients' perception of drugs efficacy (12).

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) prospected the assessment of patients' well-being, according to a dichotomous condition: satisfactory *versus* unsatisfactory status (13). In this context, the Patient Acceptable Symptom State (PASS), a tool evaluating the level of symptoms considered acceptable by patients, has been suggested an useful instrument to be adopted in real world clinical practice (14). PASS is clearly fast and easy to use, consisting in a single question ('Think about all the ways your PsA has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable to you?), and it has been evaluated in patients with a broad spectrum of rheumatic diseases (15-17). As far as PsA is concerned, PASS mirrors the results of Disease Activity of Psoriatic Arthritis (DAPSA) score - low disease activity, but shows poor specificity when compared with: i. minimal disease activity (MDA); ii. very low disease activity (VLDA); iii. DAPSA remission (17).

It must be pointed out that, in this setting, many studies have shown a high prevalence of fibromyalgia, ranging from 17% to 53.3%, in different subtypes of PsA (18). It is well-known how fibromyalgia may dramatically impact the perception of pain and discomfort in the affected patients, thus possibly influencing also the PsA specific PROs, including the PASS, independently from disease activity.

Due to the prevalence of fibromyalgia in PsA patients, any evaluation about PsA-specific PROs should take in account the possible bias related to this comorbidity. Thus, this study was designed to analyse if the association between PASS and PsA disease activity may be biased by the presence of comorbid fibromyalgia.

Materials and methods

A multi-centre, cross-sectional study enrolling consecutive PsA participants has been conducted from July 2021 to November 2021. At baseline, PsA participants who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) and followed at least for 6 months during treatment with conventional and/or biologic disease-modifying antirheumatic drugs were considered potentially eligible for the study.

The study was approved by the Ethics committee of the University Campus Bio-Medico of Rome, Italy (approval number 78.20 OSS), and conducted in conformity with the Declaration of Helsinki and its later amendments.

Inclusion criteria were both genders, age >18 years, and the fulfilment of CASPAR criteria. The exclusion criteria were history of any psychiatric disorder according to DSM-V prior the recruitment, history of any malignancy,

pregnancy, age >85 or inability to express informed consent to participate in the study.

Clinical assessment encompassed the number of tender joints (of the 68 assessed joints) and swollen joints (total of 66 joints), enthesitis and dactylitis. Enthesitis was assessed using the Leeds Enthesitis Index (LEI), and dactylitis assessed as number of them in both hands and feet. Skin assessment was performed using the Psoriasis Area Severity Index (PASI).

The following PsA disease activity scores were collected: Disease Activity for Psoriatic Arthritis (DAPSA), Composite Psoriatic Disease Activity Index (CPDAI), Minimal Disease Activity (MDA) and very low disease activity (VLDA), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Patients were considered in MDA when they satisfied five of the following seven criteria: tender joint count ≤1; swollen joint count ≤1; BSA ≤3%; VAS pain score of ≤15; PtGA VAS score of ≤20; HAQ score ≤0.5; and tender entheseal points ≤1.

Axial involvement was evaluated according to magnetic resonance imaging (MRI) or x-Rays studies of the sacroiliac joints and the spine.

Patients were considered in VLDA when all seven criteria were met. A DAPSA score of ≤4 means disease remission, while a DAPSA score of ≤14 means a condition of low disease activity.

The Health Assessment Questionnaire (HAQ) and the Psoriatic Arthritis Impact of Disease (PsAID) were evaluated as measures of function and quality of life. Patients fulfilling the 2016 American College of Rheumatology revised criteria were identified as affected by concomitant fibromyalgia.

As reported in other papers, the following formulation of PASS question: 'Think about all the ways your PsA has affected you during the last 48 hours. If you were to remain in the next few months as you were during the last 48 hours, would this be acceptable to you?', was submitted to our participants. The yes/no response was used as a dichotomic variable.

Continuous data are described as median (25-75th Pctl), whilst categorical

Table I. PsA and axSpA demography and clinical characteristics.

Variables	Entire population (n=221)	PASS = 1 (n=139)	PASS = 0 (n=82)	*p*
Age (years)	56 (48 – 63)	57 (49 – 64)	54.5 (48 – 62)	0.4
Male/female (%)	63.96% - 36.04%	56.12% - 43.88%	78.05%- 21.95%	**0.001**
Disease duration (months)	100 (56 – 144)	96 (48 – 144)	108 (62 – 144)	0.6
BMI	26.5 (23.85 - 29.55)	27.15 (24.3 - 30.9)	25.95 (23.5 - 28.6)	0.057
Elementary school (%)	6.33%	60.00%	40.00%	0.6
Junior High school (%)	29.75%	68.09%	31.91%	
High school (%)	44.30%	64.29%	35.71%	
University (%)	18.35%	75.86%	24.14%	
Post-graduate (%)	1.27%	100.00%	0.00%	
Charlson Comorbidity Index	2 (1 – 3)	2 (1 – 3)	2 (1-3)	0.4
Fibromyalgia (%)	36.53%	32.50%	67.50%	**0.001**
Smoke habits (no/yes/ex)	73.50/22.50/ 4.00 %	71.76/ 23.66/ 4.58%	76.81/ 20.29/ 2.90%	0.7
Peripheral arthritis (%)	98.20%	97.84%	98.78%	0.6
Axial involvement (%)	53.67%	46.72%	65.43%	**0.007**
Enthesitis (%)	50.93	51.47	50.00	0.8
Dactylitis (%)	20.64	24.82	13.75	0.052
Psoriasis (%)	66.67	71.74	57.50	**0.03**
csDMARDs no use (%)	49.32	46.04	54.88	0.3
Methotrexate (%)	32.13	35.97	25.61	
Sulfasalazine (%)	8.14	6.47	10.98	
Leflunomide (%)	6.79	7.91	4.88	
Cyclosporine (%)	1.36	1.44	1.22	
Hydroxychloroquine (%)	2.26	2.16	2.44	
b/tsDMARDs no use, (%)	30.63	31.65	29.27	0.2
Infliximab (%)	1.80	2.88	0.00	
Adalimumab (%)	27.93	25.18	31.71	
Etanercept (%)	13.06	15.83	8.54	
Golimumab (%)	6.31	6.47	6.10	
Certolizumab-pegol (%)	0.90	1.44	0.00	
Secukinumab (%)	4.95	5.76	3.66	
Ixekizumab (%)	2.70	2.88	2.44	
Ustekinumab (%)	7.21	4.32	12.20	
Apremilast (%)	4.50	3.60	6.10	
CCS (%)	18.18	16.79	20.73	0.4
NSAIDs (%)	36.82	29.93	48.78	**0.005**
SNRI	7.73	6.52	9.88	0.3
Tryciclic antidepressant drugs use (%)	2.27	2.16	2.50	0.8
Other antidepressant drugs use (%)	5.91	2.16	12.50	**0.002**
Anticonvulsant drugs use (%)	13.57	7.19	24.69	**<0.001**
Antispasmodic drugs use (%)	21.46	15.11	32.91	**0.002**
Hypnotic drugs use (%)	5.41	4.32	7.32	0.3
TJ	2 (0 – 5)	1 (0 – 4)	4 (1 – 6)	**<0.001**
SJ	0 (0 – 1)	0 (0 – 0)	0 (0 – 1)	0.1
PP	6 (2 – 8)	4 (1 – 7)	7.5 (6 – 8)	**<0.001**
PtGA	5.5 (3 – 7)	4 (1 – 7)	7 (6 – 8)	**<0.001**
EGA	1 (0 – 1)	0 (0 – 1)	1 (0 – 2)	**0.03**
LEI	0 (0 – 0)	0 (0 – 0)	0 (0 – 1)	**0.02**
Dactylitis	1.36%	1.45	1.22	0.8
CRP mg/dl	0.3 (0.17 - 0.58)	0.3 (0.14 - 0.56)	0.3 (0.2 - 0.6)	0.4
ESR	13 (8 – 22)	14 (8 – 25.5)	12 (7 - 1 8)	0.1
HAQ	0.88 (0.25 - 1.5)	0.63 (0 – 1.25)	1.5 (1 – 2)	**<0.001**
PSAID	3.86 (1.5 - 5.99)	2.5 (0.8 - 4.3)	5.97 (3.9 - 7.25)	**<0.001**
PASI	0 (0 – 0.4)	0 (0 – 0.4)	0 (0 – 0)	0.7
DAPSA	14.29 (7.04 - 20.87)	10.09 (3 – 18.03)	19.18 (13.5 - 22.75)	**<0.001**
MDA	73.97 - 26.03	63.24 - 36.76	91.46 - 8.54	**<0.001**
DAPSA-patient	0.94 (0.85-0.98)	0.91 (0.8-0.98)	0.96 (0.93-0.98)	**<0.001**

PsA: psoriatic arthritis; axSpA: axial spondyloarthritis); PASS: Patient Acceptable Symptom State; BMI: body mass index; IBD: inflammatory bowel diseases; csDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; ts/bDMARDs: targeted synthetic/biologic disease-modifying anti-rheumatic drugs; CCS: corticosteroids; NSAIDs: non-steroidal anti-inflammatory drugs; SNRI: serotonin-norepinephrine reuptake inhibitor; TJ: tender joints; SJ: swollen joints; PP: patient pain; PtGA: patient global assessment; EGA: evaluator global assessment; LEI: Leeds enthesitis Index; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PSAID: psoriatic arthritis impact of disease; PASI: Psoriasis Area Severity Index; DAPSA: Disease Activity in PSoriatic Arthritis; MDA: minimal disease activity.

variables are described as percentages (%). The Shapiro-Wilk test was used to evaluate the normality of data. Patients reporting an acceptable symptoms state (PASS-yes) were compared with patients reporting an unacceptable symptoms state (PASS-no). Chi2 was used for the analysis of contingency tables, while Mann-Whitney test was used to compare ranks.

Furthermore, univariable and multivariable analyses were used to assess the potential role of demography and disease characteristics in influencing the PASS response of our patients, considering for the multivariable analysis every variable with $p<0.05$ in the univariate analysis.

The whole statistical analysis was performed using Stata v.14. p-values <0.05 have been considered as significant.

Table II. Univariable logistic regression; PASS as dependent variable.

Independent variables	OR	95%CI	*p*
Female sex	0.36	0.19 - 0.67	0.001
Fibromyalgia	0.11	0.07 - 0.27	<0.001
Axial involvement	0.45	0.25 - 0.82	0.008
Psoriasis	1.88	1.04 - 3.33	0.02
NSAIDs	0.44	0.25- 0.79	0.006
TJ	0.86	0.81-0.93	<0.001
PP	0.69	0.61-0.78	<0.001
PtGA	0.67	0.59-0.77	<0.001
LEI	0.73	0 .55-0.99	0.040
HAQ	0.22	0.14-0.38	<0.001
PSAID	0.61	0.52-0.72	<0.001
DAPSA	0.91	0.88-0.95	<0.001
MDA	6.22	2.66-14.57	<0.001

NSAIDs: non-steroidal anti-inflammatory drugs; TJ: tender joints; PP: patient pain; PtGA: patient global assessment; LEI: Leeds enthesitis Index; HAQ: Health Assessment Questionnaire; PSAID: psoriatic arthritis impact of disease; DAPSA: Disease Activity in PSoriatic Arthritis; MDA: minimal disease activity.

Results

221 participants were included in the study. The main demographic, anthropometric, and clinical characteristics of the study population are reported in Table I.

All the participants were Caucasian, with a large preponderance of females (63.96%) and a median age of 56 (48-63) years. Concomitant fibromyalgia was present in 36.53% out of the participants. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) were used by 49.32% out of the participants, whilst biologic DMARDs (bDMARDs) or the phosphodiesterase-4 (PDE-4) inhibitor were used by 30.63% out of our participants. As far as the disease activity scores, at the enrolment, were concerned, the observed median DAPSA value was 14.29 (7.04–20.87). 26% of the participants achieved MDA criteria.

63% of the participants reported an acceptable PASS-yes. All the participants accepted to answer the question, confirming the PASS' feasibility and intelligibility.

Overall, the 139 PsA participants who reported an acceptable PASS-yes showed a significantly better mean DAPSA score than the 82 participants reporting PASS-no. Furthermore, PASS-yes participants showed lower LEI, significantly lower impact of disease (PsAID), lower pain and a better function when compared to the PASS-no participants. On the other hand, a greater proportion of female participants (78.05 %), as well as the majority of participants with concomitant fibromyalgia (67.50%) reported a PASS-no.

The univariable regressions show a positive association between PASS and i) female gender; ii) fibromyalgia; iii) axial involvement; iv) psoriasis; v) NSAIDs; vi) TJ; vii) PP; viii) LEI; ix) HAQ; x) DAPSA; xi. MDA; xii) PtGA; all these results are summarised in Table II.

Successively, the multivariable logistic regression (Table III) showed a significant association between PASS and disease activity only in those participants in DAPSA remission (namely, DAPSA<4) (OR 11.82863, 95% CI 1.386086-100.9436, p=0.024), and in MDA (OR 4.239422, 95% CI 1.666865-10.78233, p=0.002).

Multivariable logistic regressions (Table III), adjusted for the presence of fibromyalgia, using PASS and DAPSA low disease activity (namely, DAPSA14) as dichotomic values, did not show any significant association between these two variables (OR 0.5138862, 95% CI 0.215316–1.226472, p=0.134). Similarly, considering PASS as dichotomic variable and DAPSA as nominal variable (remission, low disease activity, moderate disease activity, high disease activity), we did not observe significant differences (OR 0.6491727, 95% CI 0.3865742–1.090154, p=0.102). Finally, no differences were observed when DAPSA was analysed as continuous variable (OR 0.9867319, 95% CI 0.9409574–1.034733, p=0.582).

Discussion

PASS is a patient-reported measure evaluating the acceptable and/or satisfactory level of symptoms in rheumatic diseases (19), which has been proposed as a disease activity index, in patients with PsA. The association between PASS and different disease activity indices has been studied in different rheumatic disorders, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus erythematosus, osteoarthritis, and PsA as well. As far as the latter is concerned, it has been reported that PASS might be an useful instrument to assess PsA disease activity in rheumatologic clinical practice, mostly in DAPSA low disease activity patients (17). The disease activity assessment, that has a pivotal role for choosing b/tsDMARDs therapy and/or identifying refractory patients, may be conditioned by the wide range of signs and symptoms that partly overlap with PsA, including chronic pain conditions. Among these, fibromyalgia (20), a complex chronic pain condition affecting at least 2-3% of adult population in Italy and worldwide (21), and the most common cause of generalised musculoskeletal pain in women aged

Table III. Multivariable logistic regressions.

PASS Multivariable model 1	OR	Std. Err.	*p*	95% CI
Age	1.043	0.018	0.017	1.007782-1.080814
Sex	1.241	0.605	0.657	0.4774767-3.229528
DAPSA	0.986	0.023	0.582	0.9409574-1.034733
Fibromyalgia	0.400	0.174	0.036	0.1703211-0.9421625
Psoriasis	1.038	0.445	0.929	0.4485188-2.405815
Axial involvement	0.289	0.127	0.005	0.1221999-0.6853655
NSAIDs	0.582	0.235	0.181	0.2633828-1.286786
HAQ	0.195	0.069	0.000	0.0972771-0.392384
PASS Multivariable model 2	**OR**	**Std. Err.**	***p***	**95% CI**
Age	1.044	0.018	0.016	1.00807-1.082137
Sex	1.317	0.653	0.578	0.498609-3.480694
DAPSA nominal	0.649	0.171	0.102	0.3865742-1.090154
Fibromyalgia	0.421	0.183	0.047	0.1793073-0.9890925
Psoriasis	1.078	0.464	0.860	0.4643545-2.506731
Axial involvement	0.307	0.134	0.007	0.1300607-0.7259793
NSAIDs	0.548	0.224	0.142	0.2461564-1.222007
HAQ	0.210	0.073	0.000	0.10601-0.416452
PASS Multivariable model 3	**OR**	**Std. Err.**	***p***	**95% CI**
Age	1.043	0.018	0.020	1.006744-1.080694
Sex	1.452	0.740	0.464	0.53459-3.944827
DAPSA<14	0.513	0.228	0.134	0.215316-1.226472
Fibromyalgia	0.399	0.172	0.034	0.1707605-0.932545
Psoriasis	1.074	0.462	0.867	0.4624017-2.498591
Axial involvement	0.299	0.131	0.006	0.126833-0.7081203
NSAIDs	0.527	0.218	0.122	0.2344992-1.18637
HAQ	0.202	0.070	0.000	0.1028133-.3988593
PASS Multivariable model 4	**OR**	**Std. Err.**	***p***	**95% CI**
Age	1.046	0.019	0.016	1.008348-1.085168
Sex	1.208	0.607	0.706	0.4510106-3.238921
DAPSA<4	11.828	12.939	0.024	1.386086-100.9436
Fibromyalgia	0.444	0.193	0.063	0.1892773-1.043548
Psoriasis	1.048	0.458	0.913	0.4456963-2.468877
Axial involvement	0.309	0.135	0.007	0.131273-0.7313922
NSAIDs	0.543	0.224	0.140	0.2416403-1.222601
HAQ	0.201	0.070	0.000	0.1015042-.4018381
PASS Multivariable model 5	**OR**	**Std. Err.**	***p***	**95% CI**
Age	1.013	0.015	0.363	0.984562-1.043408
Sex	0.879	0.349	0.746	0.4032396-1.916965
MDA	4.239	2.019	0.002	f
Fibromyalgia	0.164	0.058	0.000	0.081723-0.3318059
Psoriasis	1.162	0.416	0.675	0.5752973-2.347949
Axial involvement	0.539	0.186	0.074	0.2743662-1.061187
NSAIDs	0.538	0.185	0.073	0.2738947-1.059528

DAPSA: Disease Activity in PSoriatic Arthritis; NSAIDs: non-steroidal anti-inflammatory drugs; HAQ: Health Assessment Questionnaire.

20–55 years, makes PsA diagnosis and management challenging (22-24).

Our study suggests that during PsA, the relationship between PASS and disease activity is deeply influenced by concomitant fibromyalgia, thus biasing its reliability in real world clinical practice (18, 25). In fact, fibromyalgia dramatically impacts on pain perception and discomfort in the affected patients, thus significantly influencing PROs, including PASS, independently from the disease activity.

We observed higher tender joint count, VAS patient pain, VAS patient global assessment, VAS evaluator global assessment, as well as higher levels of HAQ and PsAID in PASS-no participants. On the other hand, we did not find any significant correlations between the number of swollen joint count and the levels of CRP and the PASS positivity/negativity. These results confirm that PASS explores subjective perception of symptoms more than objective biologic parameters. This is further supported by the highest levels of DAPSA-patient, in PASS-no participants, compared to PASS-yes participants. DAPSA-patient is an index showing the ratio between the sum of subjective DAPSA components (*i.e.*, tender joint count, patient pain, and patient global assessment) divided by the whole DAPSA (namely, the sum of tender joint count, swollen joint count, patient pain, patient global assessment, and CRP in mg/dl) (9). Moreover, in our cohort, the large majority of participants, which did not reach a positive PASS were affected by comorbid fibromyalgia (67.5 *vs*. 32.5%). As consequence, considering different independent variables including fibromyalgia, we did not find any significant association between PASS and DAPSA, DAPSA low disease activity state, and DAPSA categories (remission, low disease activity, moderate disease activity, and high disease activity).

The association between disease activity and PASS was observed only by univariable analysis, but not by multivariable analysis, showing that comorbid fibromyalgia significantly biases the feasibility of PASS in real-world clinical practice.

A significant association between PASS and both MDA and DAPSA remission was shown, although a limited sensitivity of this index, with regard to MDA and DAPSA remission has been already reported (17). In this setting further studies should be done to better define the relationship between MDA, DAPSA remission and PASS.

We are aware of some possible limitations of our study, such as the cross-sectional design, not allowing us to recognise the possible modification of both PASS and disease activity over time. Moreover patients enrolled in this study showed a relatively long disease duration; of note recent studies have suggested that subjective and semi-objective measures of disease activity, such as the PGA and tender joints, could be

more strictly correlated with inflammation in the early phases of rheumatoid arthritis (26, 27). Indeed, patients' perception of their disease activity may vary according to disease duration and general improvement or worsening of their symptoms (25, 28). Furthermore, a significant number of patients did not achieve a strict definition of remission (for instance, MDA state or DAPSA remission) predominantly for PROs rather than objective components of the disease activity indexes.

On the other hand, despite the reported limitations, the screening for any psychiatric disease in our participants clearly select a well-defined cohort.

Our data suggest that different variables, including fibromyalgia, influence the patient's perception of the disease and has a negative impact on PASS status independently of disease activity, thus limiting the utility of this PROs in real world clinical practice and in assessing the results of clinical trials.

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