Depression and anxiety in a real-world psoriatic arthritis longitudinal study: should we focus more on patients' perception?

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Abstract

Objective

Longitudinal studies using validated tools to evaluate depression and anxiety in psoriatic arthritis (PsA) are lacking. We aimed to estimate their course in PsA and to examine possible associations with disease-related parameters and patient-reported outcomes (PROs).

Methods

PsA patients attending two outpatient rheumatology clinics were consecutively enrolled (January 2019-June 2021, n=128). The hospital anxiety and depression scale (HADS) was used at two sequential visits (mean±SD: 10±6 months) to prospectively assess depression (HADS-Depression) and anxiety (HADS-Anxiety) (cut-off scores ≥11). Associations with demographic, clinical, laboratory features and PROs for quality of life (QoL) (EQ-5D), functional status (HAQ-DI) and nocebo-behaviour (Q-No) were examined. 'Change' was the difference between values at the first and second visit.

Results

Prevalence of depression and anxiety at the first visit was 19.5% and 21.1%, respectively. Depression was associated with EQ-5D [OR (95% CI): 1.70 (1.02-2.59), p=0.019] and anxiety with EQ-5D [1.81 (1.20 to 2.72), p=0.005], nocebo-behaviour [1.19 (1.01-1.40), p=0.04] and current corticosteroid use [6.95 (1.75-27.59), p=0.006].

At the second visit, HADS-Depression and HADS-Anxiety scores were improved in 40.9% and 41.9% of patients, respectively. While no associations were found for HADS-Anxiety score change, changes in HADS-Depression score correlated with changes in subjective (tender joint count, r= 0.204, p=0.049; PtG, r= 0.236, p=0.023; patient pain assessment, r= 0.266, p=0.01) but not objective (swollen joint count, ESR, CRP) parameters of disease activity.

Conclusion

In PsA, depression and anxiety are associated with worse PROs, including QoL. Subjective parameters of disease activity parallel course of depression.

Key words

psoriatic arthritis, depression, anxiety, quality of life

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Introduction

Depression and/or anxiety are commonly encountered in patients with psoriatic arthritis (PsA). Depression is present in about 20% of them (1-3), although prevalence estimates vary depending on the assessment tools used. Of note, higher depression rates have been observed in PsA, compared to the general population and patients with psoriasis alone (3). Anxiety is less studied in PsA with its prevalence ranging from 9% to 61% (2, 3).

A bidirectional relationship between depression/anxiety and PsA has been suggested. Several factors have been hypothesised to affect mental health in the setting of PsA, including demographics (*e.g.* gender), pain/fatigue, physical disability and ensuing social problems, multi-morbidity and received treatments (4, 5). The association between depression/anxiety and disease activity has not been clarified in PsA, while depression has been associated with classic inflammatory markers (*e.g.* CRP) in patients with rheumatoid arthritis (6). Inherent difficulties of measuring disease activity in PsA add another level of complexity (7).

On the other hand, mood disorders may affect patients' perception and thus distort patient-reported outcomes (PROs), which in turn hamper the achievement of minimal disease activity (MDA), as well account for high utility of healthcare services (reviewed in (8)). Besides, it has been found that baseline depression/anxiety reduce the likelihood of treatment response (9) or maintenance of MDA state (10). Additionally, comorbid depression and/or anxiety are expected to further reduce patients' quality of life (QoL) (11). However, this has been ill-assessed so far in PsA. Finally, anxiety has been implicated in nocebo phenomena which are increasingly recognised in rheumatology and beyond (12, 13).

In this study we aimed to:

i) evaluate the course of depression and anxiety in patients with PsA at two sequential visits;

ii) examine their association with disease-related parameters, as well with PROs for pain, QoL, functional status and nocebo-behaviour.

Materials and methods

Patient population and study design

All PsA patients (fulfilling CASPAR criteria(14)) from two tertiary hospitals attending outpatient rheumatology clinics for two sequential visits (between January 2019 and June 2021) and assessed for depression and anxiety, were enrolled in the study.

The following data were recorded:

a) demographic characteristics; age, age at PsA diagnosis, sex, body mass index (BMI), smoking status, HLA-B27, disease duration (time between disease diagnosis and last assessment), time interval between first and second assessment;

b) clinical manifestations present ever and at the time of assessments; peripheral arthritis (66/68 swollen and tender joint count [TJC and SJC] and involvement of distal interphalangeal joints [DIP]), enthesitis, dactylitis, involvement of spine (sacroiliitis and/or spondylitis confirmed by imaging studies), skin involvement (assessed by body surface area [BSA]), nail involvement, uveitis and inflammatory bowel disease (confirmed with colonoscopy);

c) inflammatory markers; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well disease activity indices; Disease Activity in PSoriatic Arthritis (DAPSA) and Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (only for patients with axial disease) at the time of assessments;

d) predefined comorbidities (see below) at any point during the disease course;

e) medications received for PsA ever, as well at the time of clinical assessment;

f) PROs; Patient Global (PtG) and Patient Pain (PtP) Assessment (both on a numerical rating scale from 0 to 10), Health Assessment Questionnaire Disability Index (HAQ-DI) and Bath Ankylosing Functional Index (BASFI, for patients with axial involvement) for assessment of functional status, EuroQol-5 Dimension (EQ-5D) for assessment of QoL, nocebo-behaviour (unfavorable reactions to medical interventions resulting from patients' negative expectations rather than direct pharmacological actions) assessed with Q-No question-

naire (scores: 4–20, higher scores indicate nocebo-prone individuals) (15);
g) Depression and anxiety scores; Hospital Anxiety and Depression Scale (HADS) analysed separately for depression (HADS-Depression) and anxiety (HADS-Anxiety). Each subscale scored from 0 to 21 with ≥11 being used as a cut-off for definite cases (16).

The following definitions were used for comorbidities: dyslipidaemia: total cholesterol >200 mg/dl and/or triglycerides >150 mg/dl and/or receiving lipid-lowering therapy; obesity: BMI ≥30 kg/m^2; hypertension: systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in two measurements and/or when antihypertensive treatment was administered; cerebrovascular accident (CVA): stroke; cardiovascular disease (CVD): myocardial infarction or angina; diabetes mellitus: fasting blood sugar ≥126 mg/dl and/or treatment with anti-diabetic drugs; fibromyalgia: according to ACR 1990 classification criteria (history of chronic widespread pain for ≥3 months and tender points ≥11/16 (17)); antidepressant drugs (Selective serotonin reuptake inhibitors, Serotonin-norepinephrine reuptake inhibitors, Tricyclic antidepressants, Monoamine oxidase inhibitors) prescribed by a psychiatrist for depression diagnosis; anxiolytic drugs (benzodiazepines) prescribed by a psychiatrist for anxiety disorders.

Comparisons were made between PsA patients with depression and/or anxiety (HADS-Depression ≥11 and/or HADS-Anxiety ≥11) and those without depression and/or anxiety to explore associations with demographic, clinical and laboratory characteristics, as well as with PROs. We also examined possible associations between changes in depression/anxiety scores and changes in scores/parameters of disease activity (CRP, ESR TJC, SJC, PtG, PtP, DAPSA). 'Change' was defined as the difference between the values at first and second visit.

Statistical analysis

Two-sided Fisher's and Mann-Whitney tests were used to compare categorical and continuous variables, respectively. Categorical variables were expressed as percentages (%) and continuous as mean ± SD or median (range). Spearman's rank correlation coefficient was used for correlations. Univariate and binomial multivariable logistic regression analyses were conducted. In the latter, the occurrence of depression or anxiety were used as dependent variables (in two different models), while age, sex and features that displayed statistically significant differences (p-value <0.05) in the univariate analyses, served as independent variables. Results were expressed as odds ratios (ORs), 95% confidence intervals (CI). Statistical analyses were performed using GraphPad Prism 5.00 (GraphPad Software, Inc., USA) and SPSS 24.0 (SPSS software, USA).

Ethical approval

The study was approved by the hospitals' Institutional Review Board (Laiko hospital scientific council; number 780-21 and NIMTS hospital scientific council; number 196-19). Written informed consent was acquired from all patients.

Table I. Demographic characteristics, clinical features and comorbidities (ever-present) of PsA patients included in the study.

	PsA patients (n=128)
Demographic characteristics	
Age, years, mean ± SD	53.4 ± 11.7
Age at PsA diagnosis, years, mean ± SD	44.5 ± 12.3
Female gender, n (%)	66 (51.6)
BMI, kg/m^2, mean ± SD	28.3 ± 6.4
Smoking, current, n (%)	52 (40.6)
HLA-B27, n (%)	19/102 (18.6)
Disease duration, months, mean ± SD	93.5 ± 86.1
Clinical features	
Axial disease, n (%)	56 (43.8)
Enthesitis, n (%)	47 (36.7)
Dactylitis, n (%)	40 (3.1)
DIP involvement, n (%)	12 (9.4)
Skin psoriasis[a], n (%)	128 (100)
Nail involvement, n (%)	60 (46.9)
Uveitis, n (%)	5 (3.9)
IBD, n (%)	8 (6.3)
Comorbidities	
Dyslipidaemia, n (%)	67 (52.3)
Obesity, n (%)	38 (29.7)
Hypertension, n (%)	40 (31.3)
Diabetes mellitus, n (%)	22 (17.1)
CVD, n (%)	6 (4.7)
CVA, n (%)	4 (3.1)
Fibromyalgia[b], n (%)	24 (18.8)

[a]Active skin psoriasis disorder(s) ever-present.
[b]Present at the time of clinical assessment.
PsA: psoriatic arthritis; BMI: body mass index; DIP: distal interphalangeal joints; IBD: inflammatory bowel disease; CVD: cardiovascular disease; CVA: cardiovascular accident; n, number; SD: standard deviation.

Results

Cohort characteristics

A total of 128 patients with PsA were included in the study. Of them, 51.6% were females and the mean ± SD age was 53.4 ± 11.7 years. The mean ± SD BMI was 28.3 ± 6.4 kg/m^2. Further demographic and clinical characteristics are displayed in Table I.

Prevalence of depression and associated factors in PsA

The prevalence of depression (HADS-Depression ≥11) in our cohort was 19.5% at the time of first assessment. Only 40% of these patients were on antidepressant medication. In the univariate analyses, we found that patients with depression were more frequently of female gender (80%, p=0.0017), had higher TJC and SJC, higher levels of inflammatory markers (ESR and CRP) and DAPSA score at the time of assessment (Table II and III). Patients with depression displayed higher anxiety score. Depression score was also asso-

Table II. Association of depression and anxiety with clinical manifestations, laboratory and treatment characteristics at the time of first assessment.

	Depression HADS-Depression ≥11 (n=25)	Non-depression HADS-Depression <11 (n=103)	*p*-value	Anxiety HADS-Anxiety ≥11 (n=27)	Non-anxiety HADS-Anxiety <11 (n=101)	*p*-value
Clinical features						
Axial disease, n (%)	6 (24.0)	20 (19.4)	0.590	9 (33.3)	17 (16.8)	0.103
TJC, mean ± SD	5.6 ± 7.4	1.6 ± 2.8	**0.001**	4.7 ± 6.8	1.8 ± 3.2	**0.003**
SJC, mean ± SD	2.6 ± 4.7	0.9 ± 2.3	**0.01**	1.4 ± 2.2	1.2 ± 2.1	0.377
DIP, n (%)	1 (4.0)	2 (1.9)	0.480	1 (3.7)	2 (1.98)	0.520
Enthesitis, n (%)	5 (20.0)	10 (9.7)	0.170	5 (18.5)	10 (9.9)	0.308
Dactylitis, n (%)	0 (0.0)	9 (8.7)	0.204	2 (7.4)	7 (6.9)	1.000
Nail involvement, n (%)	5 (20.0)	22 (21.4)	1.000	7 (25.9)	20 (19.8)	0.595
BSA (%), mean ± SD	2.9 ± 7.2	1.2 ± 2.1	0.149	1.5 ± 2.6	1.5 ± 4.0	0.362
Uveitis, n (%)	0 (0.0)	1 (1.0)	1.000	0 (0.0)	1 (1.0)	1.000
IBD, n (%)	1 (4.0)	0 (0.0)	0.200	0 (0.0)	1 (1.0)	1.000
Inflammatory markers						
ESR, mm/h, mean ± SD	25.7 ± 17.3	19.7 ± 17.0	**0.039**	23.7 ± 16.5	20.0 ± 17.3	0.168
CRP, mg/l, mean ± SD	6.1 ± 5.4	5.1 ± 10.1	**0.037**	6.4 ± 6.6	5.0 ± 10.0	0.310
Treatment[a]						
Corticosteroids, n (%)[b]	7 (28.0)	25 (24.3)	0.780	11 (40.7)	21 (20.8)	**0.045**
cDMARDs, n (%)	14 (56.0)	56 (54.4)	1.000	16 (59.3)	54 (53.5)	0.666
Anti-TNF, n (%)	10 (40.0)	40 (38.8)	1.000	12 (44.4)	38 (37.6)	0.516
Anti-IL-17, n (%)	3 (12.0)	16 (15.5)	1.000	4 (14.8)	15 (14.9)	1.000
Anti-IL-23, n (%)	0 (0.0)	4 (3.9)	1.000	1 (3.7)	3 (3.0)	1.000
Apremilast, n (%)	2 (8.0)	9 (8.7)	1.000	1 (3.7)	10 (9.9)	0.456

[a]Treatment for PsA being received at the time of first clinical assessment.
[b]Current dose of prednisolone <7.5 mg/day.
HADS-Depression/Anxiety: Hospital Anxiety and Depression Scale-Depression/Anxiety; TJC: tender joint count; SJC: swollen joint count; DIP: distal interphalangeal; BSA: body surface area; IBD: inflammatory bowel disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; cDMARDs: conventional disease-modifying anti-rheumatic drugs; TNF: Tumour necrosis factor; IL: interleukin; n: number; SD: standard deviation. Statistically significant values are in bold.

Table III. Association of depression/anxiety with patient-reported outcomes and composite disease activity indices at the time of first assessment.

	Depression HADS-Depression ≥11 (n=25)	Non-depression HADS-Depression <11 (n=103)	*p*-value	Anxiety HADS-Anxiety ≥11 (n=27)	Non-anxiety HADS-Anxiety <11 (n=101)	*p*-value
Patient-reported outcomes						
PtP, mean ± SD	5.8 ± 2.4	3.5 ± 2.4	**<0.0001**	5.3 ± 2.4	3.6 ± 2.5	**0.0026**
PtG, mean ± SD	6.0 ± 2.4	3.4 ± 2.3	**<0.0001**	5.7 ± 2.3	3.4 ± 2.4	**<0.0001**
EQ-5D, mean ± SD	11.1 ± 2.4	7.9 ± 2.1	**<0.0001**	10.5 ± 2.4	8.0 ± 2.2	**<0.0001**
HAQ-DI, mean ± SD	1.7 ± 0.9	0.6 ± 0.8	**<0.0001**	1.5 ± 1.0	0.7 ± 0.8	**<0.0001**
BASDAI, mean ± SD[a]	7.6 ± 1.9 n=6	3.9 ± 2.5 n=14	**0.006**	6.9 ± 2.9 n=7	4.1 ± 2.5 n=13	**0.04**
BASFI, mean ± SD[a]	8.3 ± 1.2 n=8	3.5 ± 2.6 n=15	**0.001**	6.9 ± 2.3 n=7	3.9 ± 3.1 n=14	**0.033**
Q-No, mean ± SD	13.1 ± 3.7	11.5 ± 4.0	0.1	13.7 ± 3.2	11.33 ± 4.0	**0.01**
HADS-Depression, mean ± SD	13.2 ± 0.5	5.6 ± 0.3	**<0.0001**	11.0 ± 3.4	6.1 ± 3.9	**<0.0001**
HADS-Anxiety, mean ± SD	10.4 ± 4.3	6.3 ± 3.6	**<0.0001**	13.3 ± 2.3	5.5 ± 2.6	**<0.0001**
Composite disease activity indices						
DAPSA, mean ± SD	20.3 ± 12.8	9.9 ± 7.6	**<0.0001**	17.7 ± 11.6	10.4 ± 8.6	**0.001**
ASDAS-CRP, mean ± SD[a]	3.9 ± 1.0 n=8	2.2 ± 1.0 n=13	**0.003**	3.5 ± 1.2 n=7	2.3 ± 1.1 n=12	**0.03**

[a]Only for patients with current axial disease, n=26.
HADS-Depression/Anxiety, Hospital Anxiety and Depression Scale-Depression/Anxiety; PtP: patient pain assessment; PtG: patient global assessment; EQD5: EuroQol-5 Dimension; HAQ-DI: Health Assessment Questionnaire-Disability Index; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Functional Index; Q-No: Questionnaire Nocebo; DAPSA: Disease Activity Index for PSoriatic Arthritis; ASDAS-CRP,:Ankylosing Spondylitis Disease Activity Score-CRP; n: number; SD: standard deviation. Statistically significant values are in bold.

ciated with fibromyalgia (Supplementary Table S1), as well with increased pain, poorer QoL and disability, as suggested by worse PROs (PtP, PtG, EQ-5D and HAQ-DI) (all $p<0.0001$). In a sub-analysis examining only patients with axial-PsA, depression associated with disease activity indices and worse physical function as estimated by ASDAS-CRP, BASDAI and BASFI, respectively (Table III). Treatment received for PsA was not associated with depression (Table II).

In the multivariable analysis, after adjusting for age, sex and factors that

indicated statistically significant difference in the univariate analyses, only EQ-5D remained significantly associated with a HAD-Depression score ≥11 [odds ratio (OR) (95% CI): 1.70 (1.02–2.59), p=0.019].

Prevalence of anxiety and associated factors in PsA

The prevalence of anxiety at the time of first assessment was 21.1%. Only 18.5% of these patients reported anxiolytic drug use and 40.7% were on antidepressants. The univariate analyses indicated that anxiety associated with female gender (70.4%, p=0.0317) and comorbid fibromyalgia (Suppl. Table S1). In addition, patients with HADS-Anxiety ≥11 had more tender joints (Table II) and higher DAPSA score at the time of assessment (Table III). PROs, including the HAQ-DI, EQ-5D, PtG and PtP, as well as HADS-Depression score, were higher in PsA patients with anxiety compared to those without (Table III). Also, nocebo-behaviour displayed significant association with anxiety (p=0.01). Among the treatments currently being received, corticosteroid use was associated with HADS-Anxiety ≥11 (p=0.04). For patients with axial involvement, ASDAS-CRP, BASDAI and BASFI scores were significantly higher in those with anxiety (Table III). In the multivariable analysis, anxiety was found to associate with EQ-5D [OR (95% CI): 1.81 (1.20 to 2.72), p=0.005], nocebo-behaviour [OR (95% CI): 1.19 (1.01–1.40), p=0.04] and current corticosteroid use [OR (95% CI): 6.95 (1.75–27.59), p=0.006].

Depression and anxiety at the second assessment

A total of 93 patients (72.7%) completed a questionnaire at the second visit (mean ± SD time interval of 10±6 months). The prevalence of depression at the second assessment was 16.1%. In 38/93 (40.9%) of patients, HADS-Depression score was improved and in 33/93 (35.5%) was deteriorated. Changes in HADS-Depression score were significantly associated with changes in TJC (p=0.049, r=0.204), PtG (p=0.023, r=0.236), PtP (p=0.01, r=0.266) and DAPSA (p=0.005, r=0.286) but not with changes in ESR, CRP and SJC (Table IV).

Table IV. Correlation of changes between values at first and second visit, in depression and anxiety scores with respective changes in disease activity parameters.

Variable	Depression score		Anxiety score	
	r	p-value	r	p-value
ESR	0.18	0.132	0.1	0.42
CRP	0.127	0.225	-0.083	0.34
TJC	0.204	**0.049**	-0.044	0.68
SJC	0.1	0.35	-0.038	0.72
PtG	0.236	**0.023**	-0.006	0.95
PtP	0.266	**0.01**	-0.089	0.34
DAPSA	0.286	**0.005**	-0.035	0.74

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; TJC: tender joint count; SJC: swollen joint count; PtG: patient global assessment; PtP: patient pain assessment; DAPSA: Disease Activity Index for PSoriatic Arthritis. Statistically significant values are in bold.

At this time point, 20.4% of PsA patients had anxiety. HADS-Anxiety score was improved in 39/93 (41.9%) and deteriorated in 36/93 (38.7%) of patients. Changes in HADS-Anxiety score were not associated with any of the parameters tested (Table IV).

Discussion

In this study, collecting prospectively data for depression and anxiety, we found that both conditions were mainly associated with worse QoL. Longitudinal examination of these features showed that changes in depression score were associated with subjective but not objective disease activity parameters.

We found that the prevalence of depression and anxiety was 19.5% and 21.1%, respectively, which is concordant with the pooled prevalence estimates in a recent meta-analysis (17% for depression and 19% for anxiety) (3). Of note, there is a considerable variation of depression and anxiety prevalence in the published literature since investigators have used different tools/thresholds to define cases and, thus, comparisons may be misleading. We used HADS, originally designed to detect mood disorders in patients with non-psychiatric medical conditions attending outpatient clinics (16). The performance of HADS has been validated in several rheumatic diseases (18, 19) and is also a reliable instrument for patients with PsA (20).

In our dataset, depression and anxiety were independently associated with reduced QoL as assessed by EQ-5D, which is an established index of health-related QoL, also validated in patients with spondyloarthritis (21). Similarly, Freire *et al*. in a multicentre study showed that all dimensions of EQ-5D questionnaire were significantly affected in patients with coexisting depressive/anxiety (22). In another smaller study, only anxiety correlated with QoL in terms of its physical aspect (23). However, both aforementioned studies did not control for various PsA facets (such as extra-articular manifestations and inflammatory markers). Other investigators have also showed the relationship between mental health disorders and QoL, but using less robust instruments and/or methods for their detection (24-28). -

Herein, we also showed that PsA patients with anxiety – but not those with depression – were nocebo-prone. Nocebo-behaviour, is an increasingly recognised phenomenon in the general population, present in several rheumatic diseases as well (13), referring to any unfavourable effect of a therapeutic act and high levels of negative expectations, after informing the patient that a negative outcome might occur (29). In our study, nocebo-behaviour was evaluated using the Q-No questionnaire (15), which has been previously employed for patients with systemic rheumatic diseases (30, 31). Anxiety has been suggested to induce nocebo-hyperalgesia (12). One could speculate, therefore, that there is an interplay between pain, anxiety and nocebo phenomenon in PsA, which deserves further study.

An association between anxiety and current treatment with corticosteroids

was also evident in our results. Corticosteroid-induced psychiatric disorders are commonly recognised and mainly pertain to higher dosage and treatment duration (32). Although all our patients were treated with <7.5 mg/day prednisolone, other features of PsA might be accounted for this connection. Also, examining longitudinally depression and anxiety, we found that change in HADS-Depression score associated with TJC, PtG, PtP and DAPSA changes but not with alterations in more objective measurements like SJC, CRP and ESR. In contrast, no associations were observed with HADS-Anxiety score change. In a population-based study including PsA patients (n=5465), both introduction and switching of b-DMARDs were positively associated with antidepressant or anxiolytic drug usage (33). This supports the close relationship between mental health disorders and active disease. However, whether this link owes to inflammation *per se* or more to patients' perception is still an open question. Thus far, studies comparing disease activity in PsA patients with and without comorbid depression/anxiety are scarce. One of them has reported higher pain visual analogue scale in patients with depression or anxiety and higher DAS28 only in those with anxiety (22). To be noted, analyses for DAS28 components and adjustment for confounders were not conducted. Another study noted association between depression/anxiety in PsA and composite disease activity indices but, in concordance with our results, this inferred from differences in subjective outcomes (joint pain, TJC, PtG, physician's global assessment) and not in SJC, CRP and ESR (9). Besides, CRP is commonly not elevated in PsA patients despite active disease (34) and so other markers may contribute better to examine associations. Of note, De Lorenzis *et al*. recently published that depression in PsA associates with high serum IL-6 among other tested markers of systemic inflammation. Also, in line with us, they found association with the subjective components of DAPSA, using however a lower threshold for HADS score (35).

In our study, about 19% of participants had comorbid fibromyalgia, which accords with a recent meta-analysis (36). There is some evidence that fibromyalgia impairs PROs in PsA (37). Interestingly, neuroimaging has demonstrated some shared neurobiological features between fibromyalgia and pain in RA patients with inactive disease (38). Whether this applies also in PsA has not been explored yet. On the other hand, it has been shown that there is an association between fibromyalgia and mood disorders in PsA (36). In our cohort, while fibromyalgia associated with depression/anxiety scores in univariate analyses, this association attenuated after controlling for confounders. It is not irrational to hypothesise that there are common neuronal pathways between depression and fibromyalgia. No matter which is the context, distorted PROs may mislead the assessment of disease activity rising the risk of needless escalation of anti-rheumatic therapy.

PsA patients are undertreated for mental health disorders despite the high comorbidity burden as previously observed (23, 39). In our study, 60% of patients with HADS-Depression ≥11 were not currently taking antidepressants and about 40% of patients with HADS-Anxiety ≥11 were not receiving any drug for mood disorders. One should note, however, that there are non-pharmacological forms of intervention which have not been reported. In any case, these findings should raise awareness among rheumatologists for more comprehensive management. The number of included patients did not allow us to make comparisons using treatment with anti-depressants/anxiolytic drugs as a dependent variable.

Our study has certain strengths. Data about depression, anxiety and PROs were recorded using validated tools in a representative cohort of unselected patients with established PsA. Furthermore, information was recorded longitudinally, allowing comparisons between two different time points. It should be mentioned also that this study is one of the few studies examining anxiety as a separate entity in PsA.

On the other hand, we acknowledge that there are certain limitations in our study. First, the number of participants did not allow us to adjust for all possible confounders, however, the study sample is still one of the largest in the field. Second, study setting precluded drawing of conclusions about a possible causal relationship between mental health disorders and PsA. Inception cohorts enrolling patients with early PsA are needed to answer this question. Third, patients were followed-up by tertiary centres and might have more severe disease. Finally, 35 (27.3%) of our patients did not complete a questionnaire in the second assessment. However, this did not introduce any bias since no differences, in terms of depression/anxiety, were recorded between those who completed both questionnaires and those who did not (data not shown).

In conclusion, depression and anxiety are frequent and often under-treated comorbidities among patients with PsA. Both associate with worse PROs, especially of QoL. Changes in depression (but not anxiety) scores correlated with subjective rather than objective parameters of disease activity. This, implies that the missing link between PsA and depression is not the inflammation *per se*. Instead, other pathways may operate. Furthermore, it can be argued that modification of patients' perceptions via pharmacological or non-pharmacological interventions, could lead to better outcomes. More studies, orientated towards translational research might shed more light on the link between mental health disorders and PsA.

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