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### ► To cite this version:

Marlene Sousa, Ennio Lubrano, Josef Smolen, Clémence Gorlier, Maarten de Wit, et al.. Patient-defined flares and disease activity worsening in 222 patients with psoriatic arthritis from 14 countries. *Joint Bone Spine*, 2023, 90 (3), pp.105511. 10.1016/j.jbspin.2022.105511 . hal-03957803

**HAL Id: hal-03957803**

**<https://hal.science/hal-03957803>**

Submitted on 26 Jan 2023

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## **Patient-defined flares and disease activity worsening in 222 patients with psoriatic arthritis from 14 countries**

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**Disclosures:**

Laura Coates is funded by a National Institute for Health Research Clinician Scientist award. Her research was supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Ana-Maria Orbai is a Jerome L. Greene Foundation Scholar and is supported in part by a research grant from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the National Institutes of Health (NIH) under award number P30-AR070254 (Core B), a Rheumatology Research Foundation Scientist Development award, and a Staurulakis Family Discovery award. All statements in this report are the opinions of the authors and do not necessarily reflect those of NIH or NIAMS of the Foundation.

Ying-Ying Leung is funded by the National Medical Research Council (NMRC), Singapore. The views in this report are those of author (s) and not necessarily represent those of NMRC.

Other authors: nothing to disclose relevant to this manuscript.

**Highlights:**

1. 27.0% of PsA patients self-reported flares, which was less frequent than DAPSA worsening.
2. Patients reporting flares had more active disease than patients not self-reporting flares.
3. These findings provide preliminary evidence supporting the validity of patient-reported flares in PsA.

## **Abstract**

**Objectives:** To explore patient-defined flares in psoriatic arthritis (PsA), compared to an increase in Disease Activity in Psoriatic Arthritis (DAPSA), and to analyze the validity of a patient-reported flare question.

**Methods:** ReFlap (NCT03119805) was a longitudinal study in 14 countries of consecutive patients with definite PsA. Patients were seen twice in the context of usual care,  $4.5\pm 2.2$  months apart. Flares were reported by patients and physicians at the second visit using a single question. DAPSA worsening was defined as a change to a higher DAPSA category. Agreement between the definitions of worsening was calculated by prevalence adjusted bias adjusted kappa (PABAK). Validity of patient-reported flare was assessed by comparing patients with versus without flare and transition to flares.

**Results:** In 222 patients, mean disease duration  $10.8\pm 8.3$  years, 127 (58.8%) males: disease activity was low (mean DAPSA  $11.5\pm 14.0$ ); 63.3% received a bDMARD. Patient-reported flares between the 2 visits were seen in 27.0% patients (for these patients, mean  $2.2\pm 3.7$  flares per patient, mean duration  $12.6\pm 21.0$  days per flare). Physician-reported flares were seen in 17.6% and worsening in DAPSA in 40.1% of patients. Agreement between definitions was moderate (PABAK=0.32-0.59). Patients in flare had significantly more active disease than patients not in flare for all outcomes (all  $p<0.001$ ). At the patient-level, transition to flare state was associated to a worsening in disease activity and impact outcomes.

**Conclusions:** Patient flares were frequent and were associated with active and symptomatic disease. These findings provide preliminary validation for patient-reported flares in PsA.

**Keywords:** psoriatic arthritis, flare, disease activity, quality of life

**Clinical trial registration number** NCT03119805

## **1. Introduction**

The management of psoriatic arthritis (PsA) rests on tight control of disease activity with a target of remission or low disease activity [1-3].

Patients with PsA experience significant disability and reduced health-related quality of life, resulting from pain, functional impairment and emotional distress [4]. Although flares appear important and have been extensively investigated in rheumatoid arthritis, in PsA, these flares have been little studied [5-7].

Flare represents disease worsening and can be assessed using patient-reported questions, or composite disease activity scores such as the Disease Activity in Psoriatic Arthritis (DAPSA) [8, 9]. Since alignment between patients and health professionals is a key component for shared decision-making, it is of great interest to compare patient-perceived flares with both physicians' perception and composite scores [10]. Furthermore, a single question can be used to assess patient-defined flares but should be validated [11].

The objectives of the present study were to explore flares in PsA when reported by patients, by physicians or by a composite activity score (DAPSA); and to explore the construct validity of a patient-reported flare question.

## **2. Methods**

The ReFlap study (NCT03119805) was a longitudinal observational study in 14 countries (including countries in Europe, North America, Latin America and Asia) of consecutive adult patients with definite PsA and more than 2 years of disease duration [12]. All patients gave written informed consent, and ethical committee approval was obtained at each site. Patients were seen twice in the context of usual care, 1 to 6 months apart.

### **2.1. Definitions of flares**

Patient-defined flares were collected at the second visit according to a patient-reported question: “At this time, are you having a flare of your psoriatic arthritis, if this means the symptoms are worse than usual?”. This question was developed with input from the patient-research partners in the project [12]. Furthermore, the number of flares since the first visit and their duration was collected.

Physician-defined flares were collected using a question developed by the steering committee: “At this time, is the disease in flare (i.e., significantly worsened/more active compared to usual)?” No instructions were given as to which aspects of disease should be considered when answering this question.

A transition to a more active disease level was defined based on DAPSA categories with a change to a higher category: remission ( $\leq 4$ ); Low Disease Activity (LDA) ( $>4$  and  $\leq 14$ ); Moderate Disease Activity (MoDA) ( $>14$  and  $\leq 28$ ); High Disease Activity ( $>28$ ) [8, 9]. Worsening was defined as a transition from low to moderate or high activity or from moderate activity to high activity. As sensitivity analysis, it was checked how many patients increased in DAPSA by 20%, regardless of changing category or not.

### **2.2. Other data collected**

The collected data included demographic variables, clinical and disease characteristics (disease duration, current treatment (conventional disease-modifying anti-rheumatic drugs (csDMARDs) and/or biologic disease-modifying anti-rheumatic

drugs (bDMARDs)) and disease activity variables (C-Reactive Protein (CRP) levels, 66 swollen joint count (SJC), 68 tender joint count (TJC), tender enthesal points (by the Leeds Enthesitis Index), categories of body surface area of psoriasis, pain, global assessment, physician global assessment, HAQ Disability Index and the PsA Impact of Disease (PsAID) score [13].

### **2.3. Statistical Analyses**

Patients were analyzed if they had data available for both visits and were not flaring at first visit, according to the patient single question. A patient-reported flare was defined as a positive answer to the patient flare question at the second visit.

Data were expressed as mean  $\pm$  standard deviations (SDs) for continuous variables and as frequencies (percentages) for categorical variables, with calculation of confidence intervals by bootstrapping. No imputation of missing data was performed.

Agreement between definitions of flares were assessed by % crude agreement and prevalence-adjusted bias-adjusted kappa (PABAK), using Bennett's method and interpreted as  $\leq 0.20$ -poor; 0.21–0.40-fair; 0.41–0.60-moderate; 0.61–0.80-good; 0.81–1.00—very good) was used [14]. The hypothesis was a moderate agreement between the flare definitions.

Known group validity of patient-reported flares question was evaluated by comparing disease status variables at the second visit for patients reporting a flare or not, and between the visits when a flare was reported at the second visit. We hypothesized that all disease status variables worsen in case of flares. Effect sizes were calculated using standardized response mean (SRMs) for continuous variables, with a hypothesis of at least 0.3. p values were based on McNemar test or rank signed test and confidence intervals of the SRMs were calculated by bootstrap.

R software, version 3.4.3, was used for all statistical analyses.

### 3. Results

Of 222 patients, 127 (58.8%) were male, mean age was  $53.5 \pm 12.3$  years, mean disease duration was  $10.8 \pm 8.3$  years; the mean time between the 2 visits was  $4.5 \pm 2.2$  months. Only 23 patients (10.4%) were seen within 2 months after the baseline visit. Most patients were receiving csDMARDs (135, 64.3%) and/or bDMARDs (133, 63.3%). Disease activity was overall moderate and the mean DAPSA at baseline was  $11.5 \pm 14.0$  (table 1); 44 (19.8%) patients were in DAPSA-remission and 94 (42.3%) patients in LDA (table 2).

#### 3.1. Frequency of flares

Patient-reported flares were observed in 27.0% [95% confidence interval, 21.6-33.2] (n=60). For these patients reporting a flare, patients said they had experienced a mean of  $2.2 \pm 3.7$  (median, 1) flares since the previous visit. The mean duration of a flare was  $12.6 \pm 21.0$  days. Thus, for patients reporting a flare, the cumulative time spent in flare was a mean of 27.7. days of reported flares (i.e., 20.4% of the mean duration of observation). At the time of the second visit, patient who self-reported a current flare said they were in flare for less than 1 week (66.0%), or between 1 and 2 weeks (34.0%).

At follow-up physician-reported flares were noted in 17.6% [95% confidence interval, 13.1-23.1] (n=39), and DAPSA worsening (category change) was observed in 40.1% [95% confidence interval, 33.9-46.7] (n=89) patients. Most of the DAPSA worsening corresponded to patients going from remission to LDA (N=24, 27.0% of worsened patients) or from LDA to MoDA (N=24, 27.0%); 8 patients (18.2%) transitioned from MoDA to high disease activity (Table 2 the one you added above). Furthermore, 42 (18.9%) patients had a change in DAPSA of  $\geq 20\%$ .

#### 3.2. Agreements among different definition of flare

The crude agreements between patients question and DAPSA, patients question and physicians and physicians and DAPSA were 69.8% (PABAK=0.40), 79.7% (PABAK=0.59) and 65.8% (PABAK=0.32) respectively (table 3 and 4).

Of 60 patients in self-perceived flare, 41 had DAPSA worsening and 27 had flare according to the physician. Of 162 patients without self-perceived flare, 150 (92.6%) had no physician-reported flare and 114 (70.4%) had no DAPSA worsening (figure 1).

In patients responding positively to the flare question, DAPSA increased from a mean of 11.5 (SD, 2.1) to 25.8 (17.3) at the second visit.

For patients who worsened in DAPSA category, the mean change in DAPSA was higher in 41 patients reporting self-perceived flares (mean change, 22.2±15.0) than in 48 patients with no self-perceived flares (14.3±12.3).

### **3.3. Known group validity of patient-defined flares**

When comparing patients reporting a flare and patients not reporting a flare, patients with a positive response to the flare question had significantly more active disease than patients not in flare for all outcomes, at the group level (all  $p < 0.001$  except skin lesions,  $p = 0.01$ ) though treatment patterns were similar (table 5).

Among patients reporting a flare at the second visit (N=60), all outcomes were worse than at the first visit. Changes from the first visit were most notable for patient global assessment (SRM=1.22), pain assessment (0.92), physician global assessment (0.85), DAPSA (0.83) and PsAID12 (0.80) rather than joint counts (table 5).

#### **4. Discussion**

In the present study, patient-reported flares occurred more often (27.0%) than physician-reported flares (17.6%) but less often than worsening of DAPSA category (40.1%), with a moderate agreement between the three definitions of flares. Furthermore, patients reporting a flare, on average, had significantly more active disease than patients not in flare, regarding all outcomes. A transition to a patient-defined flare state was associated with worsening in disease activity and disease impact outcomes. These findings provide preliminary evidence supporting the construct validity of a single patient-reported flare question in PsA.

This study has strengths and weaknesses. Recruitment took place in tertiary care centers, as reflected by a high intake of biologics, which may limit generalizability of results. However, the international multicentric recruitment increases the representation of PsA cases. It should also be recognized that the study population had limited skin involvement, as is often the case in PsA patients seen in rheumatology clinics [15]. The present study analyzes a simple and single flare question, which may be seen as a weakness; however, in the absence of a validated question, questions were developed for the purpose of this study involving patient research partners to ensure face and content validity. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) proposed a flare instrument derived from the patients' perspective to assess articular, skin, emotional, participation, and fatigue domains in flares, but was not available in the present study [7]. To assess disease worsening, we used a change in DAPSA category; such a change in category is probably too crude for use as a gold standard for disease flare. An analysis of change in DAPSA (e.g. based on clinically relevant changes in DAPSA) would be of interest in this context. Furthermore, DAPSA focuses on peripheral arthritis, however the patient flare question was open to "flare" in any domain of disease e.g. skin, enthesitis, symptoms and impact. This may explain rather low agreement between definitions. However, the DAPSA is a validated and

recognized composite score for peripheral arthritis predominant PsA which was the commonest phenotype in this dataset and most treatment PsA clinical trials [8, 9].

In the ReFlaP study, flares were frequent. Recent studies have indicated similar frequencies of flares (28-30%) when flares were defined as change in treatment or by a patient questionnaire [16]. This indicates the need for better assessments of disease activity fluctuations in PsA as well as their significance, and impact on disease progression and quality of life. The flare question used in the study could be useful in clinical practice as a simple instrument to recognize a global worsening and to detect flares.

Physician flares were less frequent, indicating a discrepancy between patients and physicians' perception of disease activity with a tendency of underestimation from the physicians when compared to patients. This could be explained by areas of disease impact not taken into account by physicians, such as fatigue, sleep and emotional distress [4, 17]. Usually, physicians prioritize inflammatory markers and swollen joints to determine disease activity [18].

The frequency of flares was higher in our study by change in DAPSA category than by patient and physicians question assessments, with only moderate to fair agreements between assessments. It is surprising that patient self-reported flares were less frequent than worsenings in the DAPSA categories. This would go against the idea of 'bad days' (including for example, increases in enthesal pain) [19] being analyzed by patients as flares [20]. DAPSA is a very different outcome compared with a single-item flare question. We can hypothesize that DAPSA worsening was sometimes due to "small fluctuations" around disease activity thresholds, leading to transitions from remission to LDA, or from LDA to MoDA not considered a flare by patients. It is also possible that the discrepancy between patient flares and DAPSA changes reflects profound discordances in assessments. Indeed, PsA patients present with a psychosocial burden related not only to disease activity but also to patient personality, beliefs, and cognition, as well as widespread pain syndrome [21, 22]. Although concomitant FM may influence perception of symptoms, in the present study we analyzed flares though change in status therefore we believe our analyses are valid even for patients with concomitant FM.

Patient-reported flares were associated with more active disease for all PsA outcomes, including CRP, joint counts as well as patient-reported outcomes (HAQ, Patient Global Assessment and PsAID). The latter is an optimal patient-reported instrument to detect the impact of disease on patients and includes both physical and psychological aspects if impact [4, 13].

The study brings important information on self-reported flares' frequency and duration. Among the 27.0% patients flaring, patients experienced a mean of 2.2 flares over the study period and thus spent 20.4% of the time in self-reported flare status. Because most patient-perceived flares are transient (usually less than 2 weeks) and do not necessarily imply a treatment modification, in practice but also in clinical trials, it is difficult to capture these fluctuations of disease [20]. The recognition that flares are frequent is important when considering how such flares should be managed. These findings also reinforce the importance of nuance in assessment of flares in PsA patients for an optimal 'treat-to-target' management of this condition [2].

In conclusion, this study brings new information on the concept of flares in PsA and on the possibility of using a single patient-reported flare question in clinical practice. Further studies are needed to evaluate the importance of measuring flares in PsA.

## **Funding**

Financial support from Pfizer was received through an unrestricted investigator-initiated research grant.

Marlene Sousa received a EULAR Scientific Training Bursary for this work.

Clemence Gorlier received a Société Française de Rhumatologie Master's grant for this work.

## **Data availability statement**

The data that support the findings of this study are available from the senior author, LG, upon reasonable request.

## Acknowledgements

We wish to thank all the patients who participated in the study and medical staff of all participating centers (in particular K. Fedorov, Germany).

We gratefully acknowledge the participation of the following investigators: Déborah Puyraimond-Zemmour (France), Martin Soubrier (France), Sibel Zehra Aydin (Canada), Lihi Eder (Canada), Pascal Richette (France), M Elaine Husni (USA) and the help of our patient research partners: Heidi Bertheussen (Norway), Laurence Carton (France) and Jim Walker (Scotland).

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**Table 1.** Baseline characteristics of 222 patients with PsA, and characteristics according to the presence or absence of patient-defined flares

	Baseline	Follow up	
	All patients n=222	Patients self-reporting flare n=60	Patients not self-reporting flare n=162
Male gender, n (%)	127 (58.8)	30 (50.0)	97 (62.2)
Age, years, mean (SD), median [IQR]	53.5 (12.3) 54.0 [44.5-63.0]	51.6 (13.8) 54.0 [43.0-61.0]	55.1 (11.8) 55.0 [46.0-65.0]
PsA disease duration, years, mean (SD), median [IQR]	10.8 (8.3) 9.0 [4.0-15.0]	10.6 (7.1) 8.0 [5.0-17.0]	11.8 (8.9) 10.0 [5.0-15.0]
Elevated acute phase reactants (CRP > 5mg/L), n (%)	66 (29.7)	24 (40.0)	45 (27.8)
csDMARDs intake, n (%)	135 (64.3)	35 (60.3)	98 (62.4)
bDMARDs intake, n (%)	133 (63.3)	29 (50.9)	96 (59.6)
Tender enthesal points, LEI, mean (SD), Median [IQR]	0.4 (1.1) 0.0 [0.0-0.0]	1.2 (1.6) 0.0 [0.0-2.0]	0.5 (1.2) 0.0 [0.0-0.0]
TJC (0-68), mean (SD), median [IQR]	3.0 (7.5)	8.4 (11.0)	3.2 (7.7)

	1.0 [0.0-3.0]	4.0 [1.0-12.5]	1.0 [0.0-3.0]
SJC (0-66), mean (SD), median [IQR]	1.6 (6.6) 0.0 [0.0-1.0]	2.7 (4.5) 1.0 [0.0-3.0]	0.9 (2.0) 0.0 [0.0-1.0]
Current psoriasis lesions, n (%)	139 (64.0%)	44 (75.9%)	88 (56.0%)
Physician's global assessment of PsA, mean (SD), median [IQR]	2.4 (2.0) 2.0 [1.0-4.0]	4.9 (2.4) 5.0 [3.0-7.0]	2.3 (2.0) 2.0 [1.0-4.0]
Patient's assessment of pain, 0-10 numeric scale, mean (SD), median [IQR]	3.1 (2.4) 3.0 [1.0-5.0]	6.1 (2.5) 6.5 [4.5-8.0]	3.1 (2.4) 3.0 [1.0-5.0]
Patient's global assessment of PsA, mean (SD), median [IQR]	3.2 (2.3) 3.0 [1.0-5.0]	6.3 (2.2) 6.0 [5.0-8.0]	3.4 (2.4) 3.0 [1.0-5.0]
DAPSA, mean (SD), median [IQR]	11.5 (14.0) 8.0 [4.0-14.3]	25.8 (17.3) 22.3 [13.0-34.2]	10.9 (11.6) 8.3 [3.5-14.0]
HAQ (0-3), mean (SD), median [IQR]	0.51 (0.59) 0.25 [0.0-0.88]	0.93 (0.63) 1.0 [0.38-1.44]	0.50 (0.62) 0.25 [0.00-0.88]
PsAID12 (0-10), mean (SD), median [IQR]	2.5 (2.0)	4.8 (2.1)	2.6 (2.2)

	2.0 [0.9-4.1]	5.2 [3.1-6.4]	2.1 [0.9-4.0]
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The first column describes the population at the first visit. The second and third column compare patients by flare status, at the second visit (when flares were assessed).

Percentages were calculated on available data (missing data, <10%).

\*P value comparing patients with versus without flare

P values were all <0.001 except for current psoriasis lesions (P value =0.01) and sex, age, PsA disease duration, CRP, csDMARDs intake, bDMARDs intake (P >0.05)

PsA: psoriatic arthritis; CRP: c-reactive protein; BSA: Body Surface Area; LEI: Leeds enthesitis index; DAPSA: Disease Activity Index for Psoriatic Arthritis; HAQ: Health Assessment Questionnaire; PsAID: PsA Impact of Disease.

**Table 2.** DAPSA status of patients at both visits

	Remission	LDA	MoDA	HDA
Visit 1	57	105	44	16
Visit 2	44	94	53	31

The table shows the number of patients in each DAPSA category at the first and second visit.

**Table 3.** Percentage (%) crude agreement and PABAK between patients and DAPSA

N patients	Patient self-reported flare	No patient self-reported flare	Total
DAPSA worsening	41	48	89
DAPSA not worsening	19	114	133
% Agreement (PABAK)	69.8 (0.40)		

**Table 4.** Percentage (%) crude agreement and PABAK between patients and physicians

N patients	Patient self-reported flare	No patient self-reported flare	Total
Physician flare	27	12	39
Physician not flare	33	150	183
% Agreement (PABAK)	79.7 (0.59)		

The gold standard chosen here was patient flare.

**Table 5.** Change in outcomes between the 2 visits for the 60 patients in self-reported flare at the second visit.

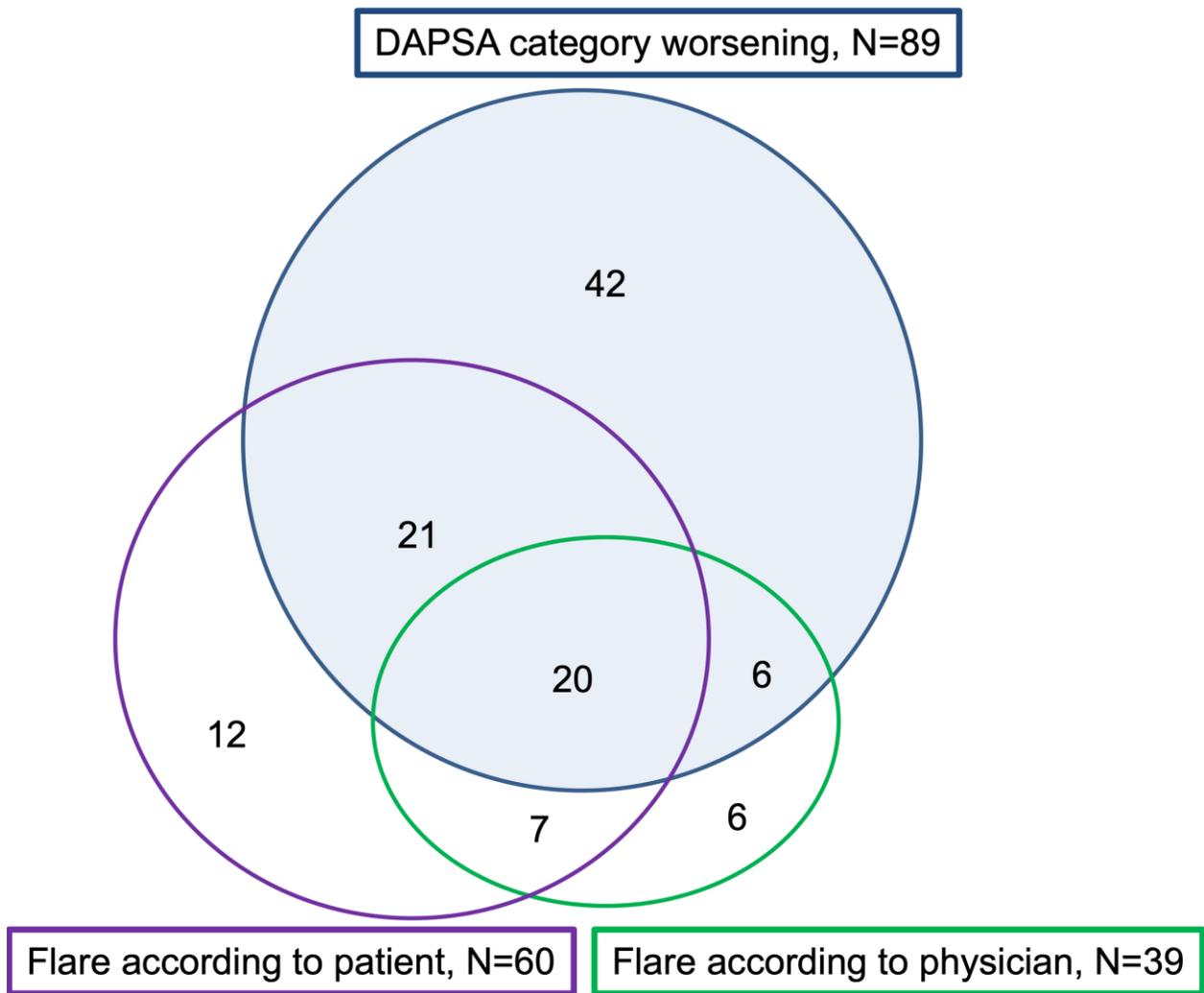
Characteristic	First visit	Second visit	Change between the visits: SRM worsening [95% CI]
Patient global assessment (0-10), mean (SD) median [IQR]	3.2 (2.2) 3.0 [1.0-5.0]	6.3 (2.2) 6.0 [5.0-8.0]	1.22 [0.82; 1.53]
Pain NRS (0-10), mean (SD) median [IQR]	3.3 (2.4) 3.0 [1.0-5.0]	6.1 (2.5) 6.5 [4.5-8.0]	0.92 [0.56; 1.22]
Physician global assessment (0-10), mean (SD) median [IQR]	2.6 (2.0) 2.0 [1.0-4.0]	4.9 (2.4) 5.0 [3.0-7.0]	0.85 [0.60; 1.08]
DAPSA, mean (SD) median [IQR]	11.5 (12.1) 8.9 [4.1-14.6]	25.8 (17.3) 22.3 [13.0-34.2]	0.83 [0.61; 1.06]
PsAID12 (0-10), mean (SD) median [IQR]	2.8 (2.0) 2.5 [1.1-4.2]	4.8 (2.1) 5.2 [3.1-6.4]	0.80 [0.50; 1.12]
HAQ-DI, mean (SD) median [IQR]	0.50 (0.52) 0.38 [0.00-0.88]	0.93 (0.63) 1.0 [0.38-1.44]	0.67 [0.38; 0.96]
Leeds enthesitis index, mean (SD) median [IQR]	0.3 (0.9) 0.0 [0.0-0.0]	1.2 (1.6) 0.0 [0.0-0.2]	0.56 [0.34; 0.73]
TJC (0-68), mean (SD) median [IQR]	3.8 (9.6) 1.0 [0.0-4.0]	8.4 (11.0) 4.0 [1.0-12.5]	0.42 [0.21; 0.62]
SJC (0-66), mean (SD) median [IQR]	0.8 (1.5) 0.0 [0.0-1.0]	2.7 (4.5) 1.0 [0.0-3.0]	0.40 [0.21; 0.56]
Current psoriasis lesions, n (%) *	34 (56.7%)	46 (76.7%)	p value = 0.034

\*For the psoriasis variable, which is analyzed here as binary, no SRM can be calculated.

P values were all <0.001 except SJC (0.002) and skin.

Variables are showed in the order of decreasing SRM.





**Figure 1.** Venn diagram of different definitions of flares in 222 PsA patients

