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ORIGINAL RESEARCH

Risk of developing psoriatic arthritis in psoriasis cohorts with arthralgia: exploring the subclinical psoriatic arthritis stage

Alen Zabotti ,[1] Filippo Fagni ,[2] Laure Gossec ,[3,4] Ivan Giovannini,[1] Michael Sticherling,[5,6] Annarita Tullio,[1] Xenofon Baraliakos ,[7] Gabriele De Marco ,[8] Salvatore De Vita,[1] Enzo Errichetti,[9] Luca Quartuccio,[1] Ettore Silvagni,[10] Josef S Smolen,[11] Ilaria Tinazzi,[12] Abdulla Watad,[13] Georg Schett,[2] Dennis G McGonagle,[8] David Simon[2]

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For numbered affiliations see end of article.

Correspondence to
Dr Alen Zabotti;
zabottialen@gmail.com

ABSTRACT

Objective Subjects with subclinical psoriatic arthritis (PsA), defined as the presence of arthralgia in psoriasis (PsO), are at higher risk of PsA but scant real-world data exist. Our aims were to (1) estimate the probability of PsA development in subclinical PsA, (2) characterise subclinical PsA symptoms and (3) determine the clinical patterns at PsA diagnosis.

Methods Patients with PsO, mainly subclinical PsA, were evaluated longitudinally in two European cohorts. The key outcome was new-onset PsA. Musculoskeletal symptoms including inflammatory and non-inflammatory symptoms before PsA diagnosis were collected. Occurrence of PsA was analysed with survival analysis and cumulative incidence functions (CIFs).

Results 384 patients with PsO were included with a mean follow-up of 33.0 (±20.9) months. 311 of 384 (80.9%) had subclinical PsA with a PsA incidence rate of 7.7 per 100 patient-years. Subclinical PsA displayed a higher risk of PsA development compared with PsO (HR=11.7 (95% CI 1.57 to 86.7), p=0.016). The probability of new-onset PsA estimated by the CIF was 9.4% (95% CI 4.7% to 10.6%) at month 12 and 22.7% (95% CI 17.2% to 28.6%) at month 36. 58.9% of cases reported inflammatory symptoms in the months immediately prior to PsA diagnosis but prior non-inflammatory symptoms were evident in 83.9% prior to PsA diagnosis. Peripheral joint swelling was the predominant PsA presentation pattern (82.1%).

Conclusions The probability of PsA development among subclinical PsA was relatively high, emphasising the importance of emergent musculoskeletal symptoms when aiming for PsA prevention. Joint swelling was the dominant feature in new-onset PsA, likely reflecting clinical confidence in recognising joint swelling.

INTRODUCTION

Psoriatic arthritis (PsA) affects up to one-third of people with psoriasis (PsO) and in about 70% of these cases, skin and/or nail

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Limited and controversial information has been made available concerning the progression from psoriasis (PsO) to psoriatic arthritis (PsA). A more comprehensive grasp of the phases occurring prior to the onset of PsA could streamline the early detection of PsA and the development of novel preventive treatment approaches. Recently, a European Alliance of Associations for Rheumatology task force has proposed a nomenclature that represents a temporal continuum of psoriatic disease. This continuum comprises: (a) a stage of being at higher risk in patients with PsO (eg, nail involvement); (b) the 'subclinical stage', encompassing clinical attributes like arthralgia and/or imaging findings; and (c) the 'clinical' stage, which is defined by the presence of clinical synovitis in individuals with PsO.

WHAT THIS STUDY ADDS

⇒ In patients with PsO identified as having subclinical PsA due to the presence of arthralgia, we determined a 9.4% probability of developing PsA within the initial 12 months of follow-up, increasing to 22.7% after 36 months. Peripheral arthritis was the predominant presentation pattern (82.1%), with oligoarthritis being particularly common. Remarkably, musculoskeletal symptoms often persisted for an extended period and, in many cases, exhibited a 'non-inflammatory' nature in the months leading up to the diagnosis of PsA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study emphasises the necessity to enhance the identification of symptoms in the subclinical PsA. Such improvement can significantly bolster our capability to spot PsA in its early stages, allowing for a swifter diagnosis and the possibility of preventative or interceptive actions.

involvement precedes the onset of PsA.[1–3] The lack of a biomarker similar to anticitrullinated protein antibodies in preclinical rheumatoid arthritis (RA) complicates the study of PsO to PsA transition.[4 5] Thus far, limited and controversial data have been published regarding the transition from PsO to PsA.[6 7] A better understanding of the phases before PsA onset could facilitate early PsA detection and designing new preventative treatment strategies.[8]

It has been suggested that the development of PsA within clinically meaningful time frames can be predicted using readily available clinical variables, including prodromal symptoms of PsA and phenotypical features of PsO.[9 10] However, these prediction tools are preliminary and need further validation. Recently, a European Alliance of Associations for Rheumatology (EULAR) task force developed *points to consider* for the definition of clinical and imaging features suspicious for progression to PsA.[11] A nomenclature reflecting a temporal, although non-linear continuum, of psoriatic disease was proposed: (a) a stage of being 'at higher risk' in patients with PsO (eg, severe skin involvement, nail involvement); (b) the 'subclinical stage', including clinical features, namely arthralgia and/or imaging features typically linked to more imminent progression to PsA; and (c) the'clinical' stage defined by the presence of clinical synovitis in an individual with PsO.[11]

A recent systematic literature review[6] informing this EULAR project highlighted the fragmentary knowledge on the transition from PsO to PsA. Thus, it appeared there is a major unmet need for the characterisation of the symptoms before the clinical onset of PsA, as well as the clinical features at the moment of diagnosis of PsA.[12–14] These could help to better define outcomes for PsA prevention studies in the context of prevention/interception of PsA and early diagnosis.[9] Therefore, this study investigated the subclinical stage of PsA in terms of risk of progression and clinical symptoms, and to describe the clinical features of new-onset PsA in PsO cases.

Patients and methods

Data from two European prospective cohorts of patients with PsO were analysed. The Italian cohort, RAPSODI (*UltRasonographic risk fActors to develoP pSOriatic arthritis in psoriatic patients with anD without clinIcal arthralgia*),[15] and the German PACE cohort (*Psoriasis and Psoriatic Arthritis Cohort Erlangen*) are both ongoing longitudinal studies.[16 17] Subjects had definite PsO of skin or nails diagnosed by a dermatologist. The two cohorts were enriched for risk of PsA, with a high proportion of patients with significant short-term risks of PsA development due to the presence of arthralgia.[16]

The patients were defined as subclinical PsA solely based on the presence of arthralgia. Imaging was not used to identify subclinical forms, and it was beyond the scope of the study to assess whether the presence of musculoskeletal (MSK) inflammation detected by imaging was a predictor of PsA development.

The patients analysed did not have PsA at entry in the cohort and no patient had visible joint swelling at the time of inclusion in the cohorts.[15] Indeed, in both cohorts, all subjects with PsO were evaluated by a rheumatologist and patients with joint swelling, dactylitis, clinical signs of enthesitis or inflammatory back pain and, in general, those fulfilling the Classification of Psoriatic Arthritis (CASPAR) criteria,[18] were excluded before enrolment.

To exclude past MSK involvement, medical history and patient records were also reviewed. Identification of a history of synovitis, enthesitis, dactylitis and/or inflammatory back pain in the past or evidence of meeting the CASPAR criteria at any time also led to exclusion. In both cohorts during the study follow-up, patients with PsO were reassessed every 6 months and patients were instructed to contact the rheumatologist prior to their scheduled assessment if they developed inflammatory symptoms (eg, worsening of joint pain or onset of joint swelling).

Patients with PsO from the RAPSODI cohort

Between January 2017 and 31 December 2022, 215 patients with PsO attending the Dermatology Department of three Italian hospitals (Udine, Negrar-Verona and Ferrara) were enrolled into the RAPSODI cohort.[15] 142 of 215 patients with PsO (66.0%) described arthralgia not explained by other diagnoses at baseline and are analysed, for the purpose of this study, as subclinical PsA. The remaining 73 of 215 (34%) patients with PsO did not report arthralgia and/or other symptoms potentially associated with PsA. The mean follow-up of the 215 patients with PsO was 35.9 (±16.9) months and the median was 41 (IQR 21–59) months.

Patients with PsO from the PACE cohort

Between January 2011 and July 2018, 169 patients with PsO attending the Dermatology Department of the University of Erlangen-Nuremberg (Germany) were enrolled into the PACE cohort, as detailed elsewhere.[16] Briefly, patients had definite PsO and had to answer positively to at least one of the questions of the GErman Psoriatic Arthritis Diagnostic Questionnaire, that is, all subjects presented with arthralgia and/or low back pain not explained by other diagnoses[19 20]; therefore, all are considered here as subclinical PsA. The mean follow-up was 25.3 (±15.2) months, while the median was 20 (IQR 12–33) months.

Case definition and characteristics of new-onset clinical PsA

During the follow-up, incident new-onset clinical PsA was defined by the diagnosis of an experienced rheumatologist and with the fulfilment of CASPAR criteria (score ≥3 points).[18]

The predominant manifestations of new-onset clinical PsA were described and to this end, at the visit where PsA was established, we characterised the type of PsA involvement. Peripheral manifestations were defined clinically: peripheral arthritis was defined by joint swelling, and

dactylitis (a manifestation of digit swelling clinically including tenosynovitis and synovitis) was determined by clinical examination. With respect to peripheral arthritis, polyarticular disease was defined as five or more active (ie, swollen) joints, while oligoarthritis was defined as four or less active (swollen) joints according to Gossec *et al*.[12]

Enthesitis was defined by entheseal pain confirmed by ultrasound in the lateral humeral epicondyle, proximal and distal patellar insertion, plantar fascia (only in the RAPSODI cohort) and Achilles tendon insertion. Active enthesitis was ultrasonographically defined according to the OMERACT definition.[21] Axial involvement was determined by a combination of inflammatory back pain and imaging evidence of sacroiliitis or spondylitis on X-rays or MRI.[22 23] At PsA diagnosis, the clinical features were collected, including gender, age, body mass index, 66 swollen and 68 tender joint count, Leeds Enthesitis Index (LEI),[24 25] and presence of dactylitis in hands and feet.

Definition of MSK symptoms before PsA onset

The precise characterisation of the MSK symptoms before the onset of clinical PsA was retrospectively collected from the medical clinical charts of patients who developed PsA during the follow-up.

The MSK patterns before clinical PsA onset were defined as:

1. Inflammatory—when at least two of the following features were present: (a) duration of morning stiffness >30 min; (b) most severe symptoms present in the morning; (c) improvement of symptoms during the day.
2. Non-inflammatory—defined as arthralgia without inflammatory features.
3. Mixed—defined by a combination of non-inflammatory symptoms initially and inflammatory symptom development thereafter.

Statistical analysis

Continuous variables were expressed as mean±SD or median and IQR according to data distribution after performing the Kolmogorov-Smirnov test for normality. Categorical variables were expressed as absolute and relative frequencies and percentages.

Occurrence of arthritis over time was analysed using survival analysis, censoring patients at last follow-up. We calculated the cumulative incidence function (CIF) to estimate the probability of arthritis development,[26–29] Gray's homogeneity test to compare the CIF estimates between groups, and Fine and Gray regression models.[30] The significance level was set at 0.05. All statistical analyses were performed using R software, V.3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Across both cohorts, a total of 384 patients were included and the mean follow-up was 33.0 (±20.9) months. 56 out of the 384 patients with PsO (14.6%) developed new-onset PsA. The flow chart of the incident cases of PsA among the cohorts is reported in figure 1.

Frequency of new-onset clinical PsA among subclinical PsA

311 of 384 (80.9%) fitted within the subclinical PsA category, and the incidence rate of new-onset PsA was 7.7 per 100 patient-years in this group. The overall probability of new-onset PsA in subclinical PsA, estimated by the CIF, was 2.6% (95% CI 1.2% to 4.8%) at month 3, 4.9% (95% CI 2.9% to 7.7%) at month 6, 9.4% (95% CI 6.4% to 13.0%) at month 12, 18% (95% CI 13.6% to 23.0%) at

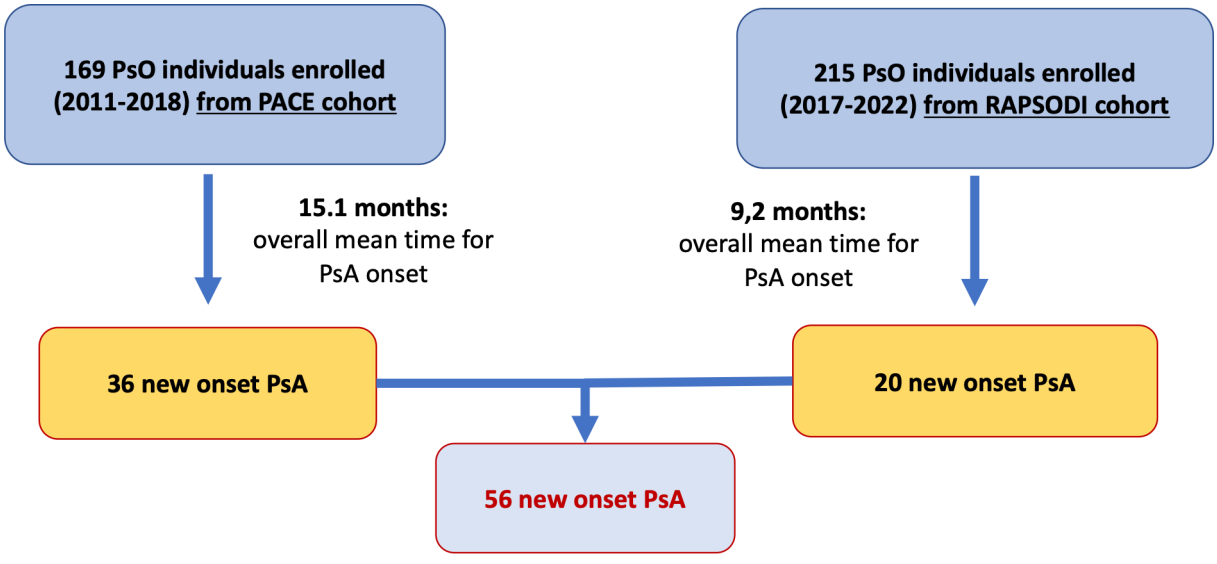
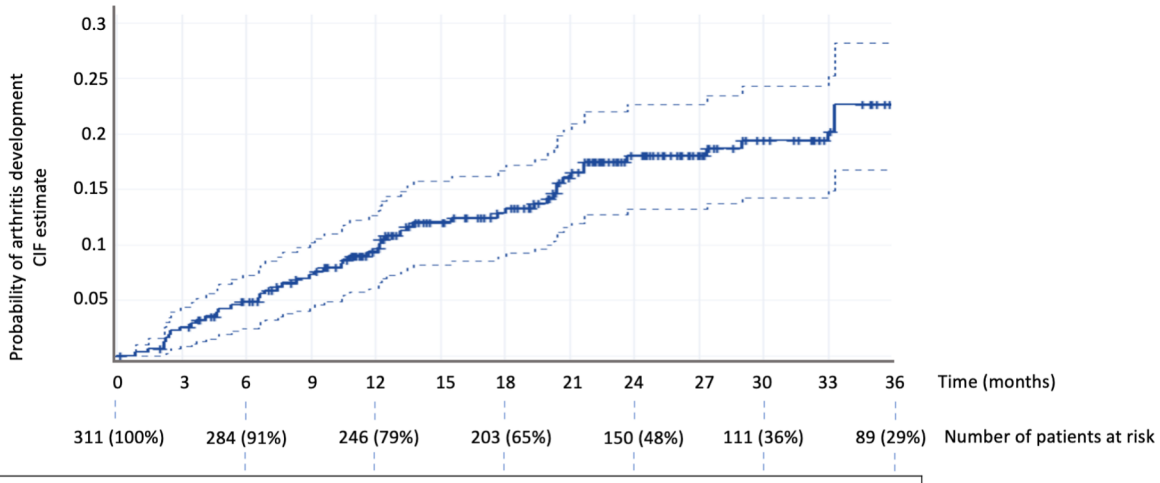


Figure 1 Flow chart of the selection of patients among the cohorts. PACE, Psoriasis and Psoriatic Arthritis Cohort Erlangen; PsA, psoriatic arthritis; PsO, psoriasis; RAPSODI, UltRasonographic risk fActors to develoP pSOriatic arthritis in psoriatic patients with anD without clinIcal arthralgia study.



Time (months)	3	6	9	12	15	18	21	24	27	30	33	36
CIF estimate (%)	2,6	4,9	7,3	9,4	12,1	12,9	16,1	18,0	18,0	19,4	19,4	22,7
Standard error	0,9	1,2	1,5	1,7	1,9	2,0	2,3	2,4	2,4	2,6	2,6	2,9
Lower confidence limit	1,2	2,9	4,7	6,4	8,6	9,3	11,9	13,6	13,6	14,7	14,7	17,2
Upper confidence limit	4,8	7,7	10,6	13,0	16,1	17,1	20,8	23,0	23,0	24,7	24,7	28,6

Figure 2 The arthritis development probability in subclinical PsA. CIF, cumulative incidence function; PsA, psoriatic arthritis.

month 24 and 22.7% (95% CI 17.2% to 28.6%) at month 36 (figure 2). The probability of new-onset PsA for each cohort of subclinical PsA is provided in online supplemental figure 1. Among the RAPSODI cohort, subclinical PsA displayed an 11.7-fold increased risk of PsA development compared with PsO (HR=11.7 (95% CI 1.57 to 86.7), p=0.016) and the comparison of CIF estimation between subclinical PsA and PsO is provided in figure 3.

Clinical features and phenotypes of new-onset clinical PsA

Regarding the prevalent patterns of presentation of new-onset PsA, peripheral arthritis was the predominant pattern in 46 of 56 (82.1%) patients followed by enthesitis in 7 of 56 (12.5%), axial in 2 of 56 (3.6%) and dactylitic pattern in 1 of 56 (1.8%) (figure 4). Within patients with peripheral arthritis as the predominant pattern, 43 of 56 (76.8%) had oligoarthritis and 3 of 56 (5.3%) polyarthritis. Among the 56 new-onset PsA, the median swollen joint count was 1 (IQR 1–2), the median tender joint count was 2 (IQR 0–4) and the median LEI score was 1 (IQR 0–2) (table 1). The clinical presentation of new-onset PsA is represented in figure 5.

At PsA onset, patients had a median duration of morning stiffness of 15 (IQR 0–45) min and the mean pain Visual Analogue Scale was 49.2 (±24.4) mm.

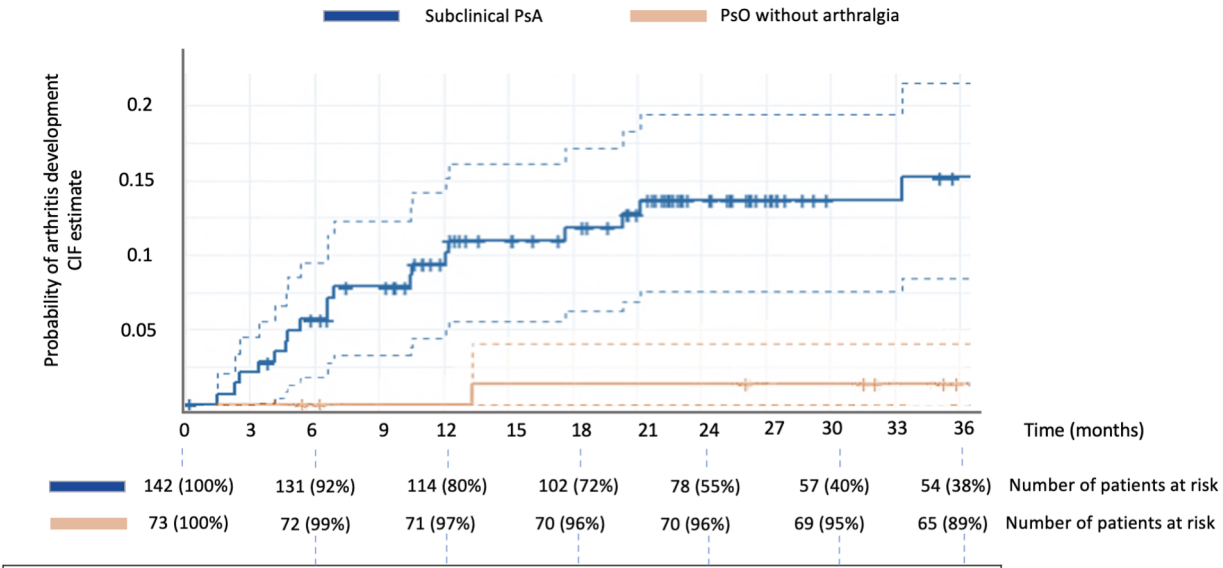
Clinical characterisation of MSK symptoms before PsA onset

The pattern of MSK involvement prior to a diagnosis of PsA, during the follow-up was as follows (figure 6):

1. 16.1% (9 of 56) of patients with future-onset PsA had an inflammatory pattern before the PsA development with a mean duration before PsA diagnosis of 1.9 (±2.0) months (median 1 (IQR 1–1) months).
2. 41.1% (23 of 56) had non-inflammatory pattern and for these patients, we noted a long duration of symptoms before PsA diagnosis, with a mean of 57.2 (±92.6) months (median 27 (IQR 4.5–37) months).
3. 42.8% (24 of 56) had mixed pattern characterised by first non-inflammatory symptoms with a mean duration before PsA diagnosis of 22.8 (±64.5) months (median 9.5 (IQR 4–14.75) months) followed by inflammatory symptoms (mean 3.9±3.6 months; median 3 (IQR 1.75–5.25) months).

DISCUSSION

Prior studies in subjects with PsO, not enriched for arthralgia, showed that the development of arthralgia was associated with later PsA development.[9 10 15] Therefore, we evaluated two PsO cohorts enriched for arthralgia to shed light on the transition from PsO to PsA. In patients with PsO regarded as subclinical PsA, we estimated a probability of PsA development of 9.4% after 12 months of follow-up and 22.7% after 36 months. The annual incidence rate of PsA development from population-based and psoriasis registry has been reported between 0.3% and 3.7% and so our findings suggest a substantial enrichment.[7] We found peripheral arthritis as the major pattern of presentation (82.1%) and in particular, oligoarthritis was very frequent. Finally, MSK symptoms were usually of long duration and 'non-inflammatory' in nature in many cases in the months preceding PsA diagnosis.



Subclinical PsA	Time (months)	3	6	9	12	15	18	21	24	27	30	33	36
	CIF estimate (%)	2,1	5,6	7,9	9,4	11	11,9	12,8	13,7	13,7	13,7	13,7	15,2
	Standard error	1,2	2,0	2,3	2,5	2,7	2,8	2,9	3,0	3,0	3,0	3,0	3,3
	Lower confidence limit	0,6	2,7	4,2	5,3	6,4	7,1	7,7	8,4	8,4	8,4	8,4	9,4
	Upper confidence limit	5,6	10,4	13,1	15,0	16,9	18,0	19,1	20,2	20,2	20,2	20,2	22,3
PsO without arthralgia	Time (months)	3	6	9	12	15	18	21	24	27	30	33	36
	CIF estimate (%)	0	0	0	0	0	1,4	1,4	1,4	1,4	1,4	1,4	1,4
	Standard error	0	0	0	0	0	1,4	1,4	1,4	1,4	1,4	1,4	1,4
	Lower confidence limit	NA	NA	NA	NA	NA	0,1	0,1	0,1	0,1	0,1	0,1	0,1
	Upper confidence limit	NA	NA	NA	NA	NA	6,8	6,8	6,8	6,8	6,8	6,8	6,8

Figure 3 The comparison of arthritis development probability in subclinical PsA versus PsO without arthralgia in the RAPSODI cohort. CIF, cumulative incidence function; PsA, psoriatic arthritis; PsO, psoriasis; RAPSODI, UltRasonographic risk fActors to develoP pSOriatic arthritis in psoriatic patients with anD without clinIcal arthralgia study.

The low incidence rate of PsA development in patients with PsO is the major determinant for limited data on the clinical characterisation of new-onset PsA, since prospective cohorts including a large number of patients with PsO followed for many years are needed to achieve an adequate number of cases of PsA development to allow early disease characterisation.[6] To overcome these limitations, studies focusing on the transition to PsA, enrolling patients with PsO at higher risk of short-term/imminent PsA development, have been analysed here.

We noted that peripheral arthritis was the main phenotype of new-onset of PsA with the majority of patients showing at least one swollen joint/digit, with a median swollen joint count of 1 and tender joint count of 2 indicating an oligoarthritis pattern as the typical presentation of new-onset PsA. These findings are in coherence with other reports focusing on the transition from PsO to PsA, reporting a mean number of active joints between 1 and 3.[6 31 32] Studies examining inception cohorts of early PsA cases have also documented oligoarthritis and polyarthritis as frequently observed clinical presentations.[33–35] Furthermore, the frequency of dactylitis at the PsA diagnosis (3.6%) reported in this study is notably lower compared with what is noted in early PsA inception cohorts with approximately 40–50% of patients presenting dactylitis at the time of diagnosis.[35 36] However, our data about the frequency of dactylitis align with the low disease activity observed in our patients with new-onset PsA, as the presence of dactylitis appears to be associated with a polyarticular pattern and higher disease activity. The development of polyarthritis and dactylitis likely reflects disease spread or evolution.

Our results confirm the need of characterisation of arthralgia in terms of pain (eg, non-inflammatory vs

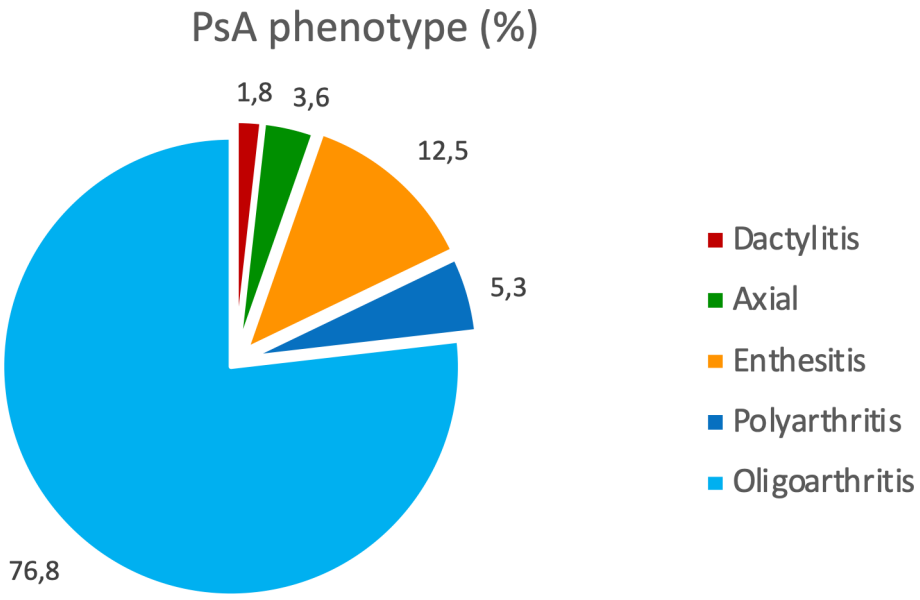


Figure 4 Clinical phenotype of new-onset psoriatic arthritis (PsA).

Table 1 Baseline features of new-onset PsA

Baseline features of new-onset PsA (N=56)	
Demographic features	
Age, years, mean (±SD)	50.2 (±13.1)
Gender, male, n/N (%)	34/56 (60,1)
BMI, mean (±SD)	32.0 (±8.1)
Conventional synthetic and/or biological treatment before PsA diagnosis, n/N (%)	8/56 (14.3)
Clinical examination	
VAS pain, mean (±SD)	49.2 (24.2)
Morning stiffness, median (IQR)	15 (0–45)
Swollen joint count (66), median (IQR)	1 (1–2)
Tender joint count (68), median (IQR)	2 (0–4)
Dactylitis, median (IQR)	0 (0–0)
Dactylitis at the onset, n/N (%)	2/56 (3.6)
LEI, median (IQR)	1 (0–2)
Laboratory and imaging features	
CRP (mg/dL), mean (±SD)	0.8 (1.4)
RF, n (%)	1 (1.8)
ACPA, n	0
Sacroiliitis at X-ray or MRI, n (%)*	6 (13.6)
Radiographic juxta-articular bone proliferation, n (%)†	14 (35)
Radiographic bone erosion, n (%)†	5 (12.5)

*Imaging of the sacroiliac joints was performed according to clinical practice in 44 patients.
†Hands and feet X-rays were performed in 40 patients.
ACPA, anticitrullinated peptide antibody; BMI, body mass index; CRP, C reactive protein; LEI, Leeds Enthesitis Index; PsA, psoriatic arthritis; RF, rheumatoid factor; VAS, Visual Analogue Scale.

inflammatory pain), sites involved and duration of symptoms in order to optimise the therapeutic targeting of subclinical PsA. Differently from RA, a substantial number of patients reported non-inflammatory MSK pain before the PsA onset, highlighting the importance and difficulty in understanding symptomatology in the subclinical PsA arena but it is noteworthy that the non-inflammatory groups had a much longer duration to PsA onset, that is very relevant for duration of prevention trial design.[37] Conversely, the 'pure' inflammatory pattern seemed to be a subacute onset with a short duration of inflammatory symptoms prior to PsA diagnosis.

This study has some limitations. First, we included two cohorts that had different inclusion criteria but still showed a similar expression of subclinical PsA due to the presence of arthralgia. Moreover, the heterogeneity of imaging data (in terms of imaging used and sites evaluated) did not allow us to analyse these data collectively. Furthermore, the objective assessment of synovitis (ie, swelling) is easier than enthesitis or axial disease which may have facilitated the higher rate of synovitis as the main recognised feature of new-onset disease. Moreover, our sample size is not very large; however, it is the first study focusing on subclinical PsA and our results are in coherence with other studies in terms of patient characteristics at the PsA onset, indicating the validity of our results.[6 31 32] Finally, the description of symptoms before PsA onset was retrospectively collected leading to a low level of granularity.

In conclusion, the present study provides new insights into the subclinical phases of PsA. We have confirmed that patients with PsO experiencing unexplained arthralgia, also reporting non-inflammatory symptoms, are at a significantly elevated risk of developing PsA. Additionally, peripheral arthritis, mainly oligoarthritis, is the most common PsA presentation in cohorts with PsO enriched for arthralgia.

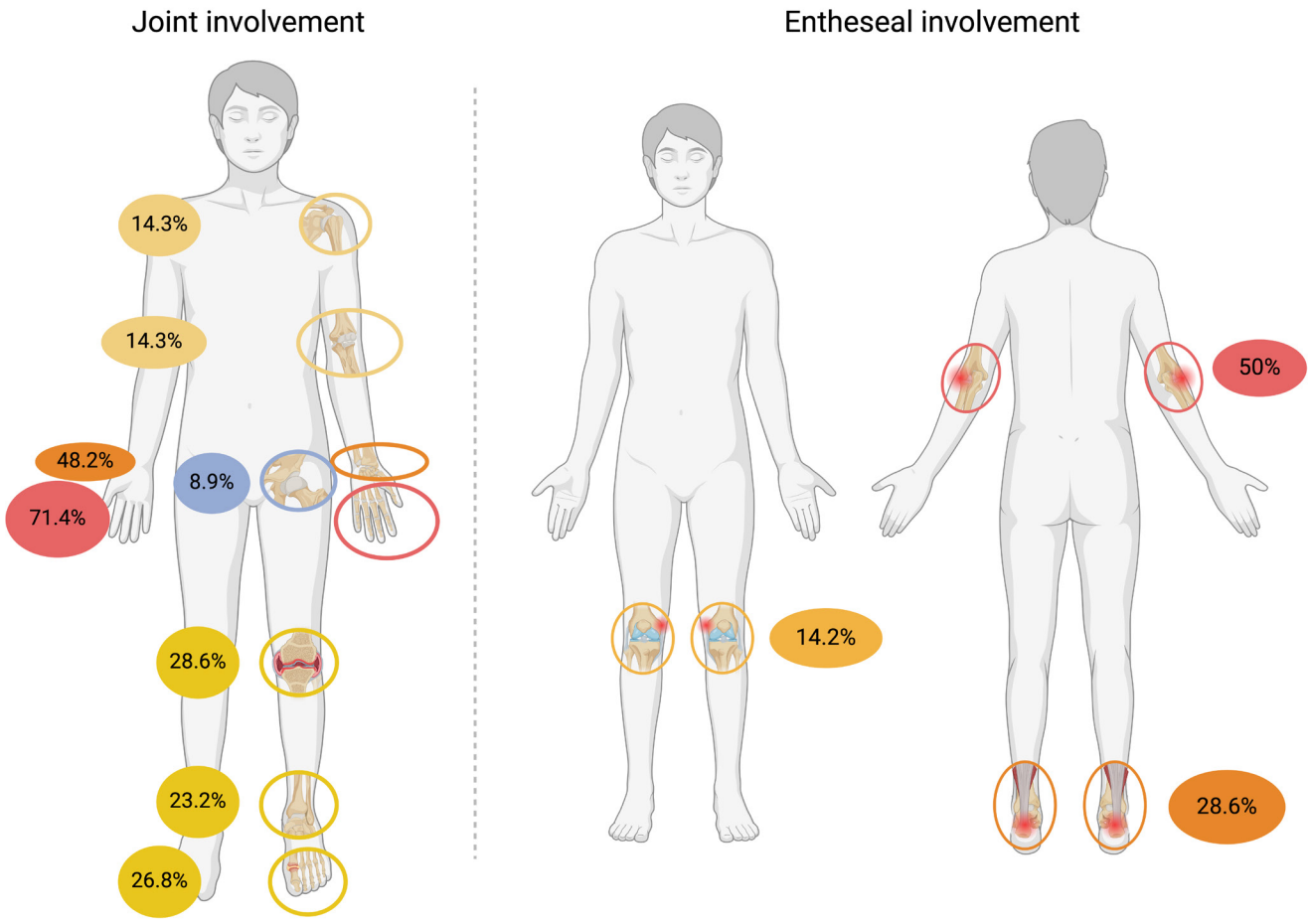


Figure 5 Graphic description of clinical manifestation at psoriatic arthritis onset. Joint involvement (according to tender and/or swollen joints) and entheseal involvement (according to Leeds Enthesitis Index).

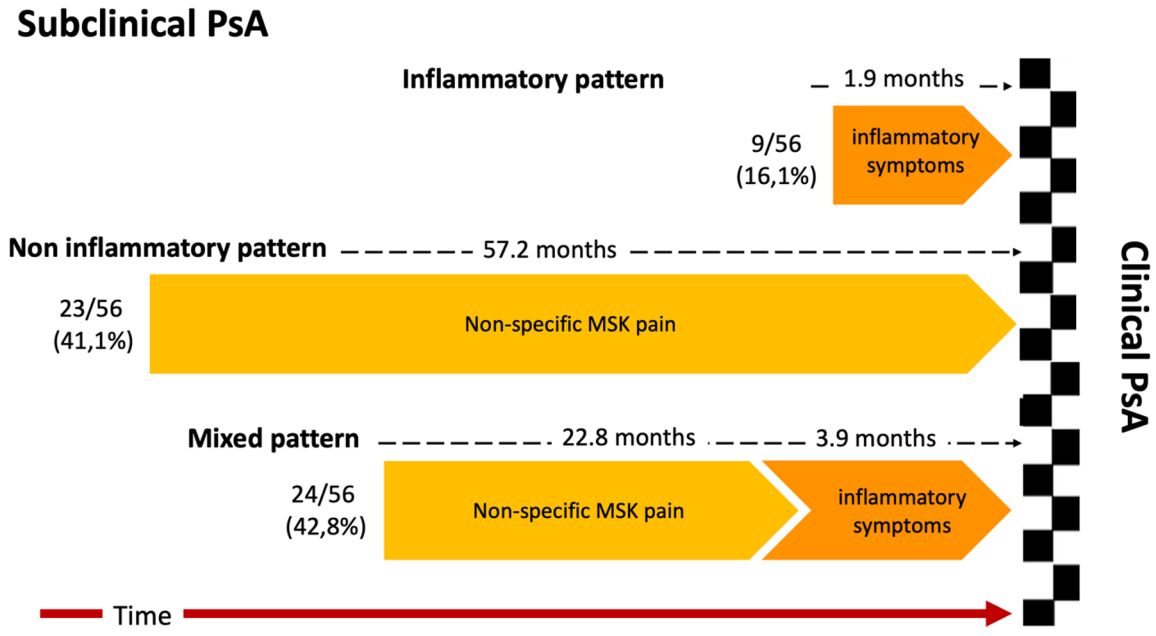


Figure 6 Patterns of musculoskeletal (MSK) symptoms before psoriatic arthritis (PsA) onset.

This study underscores the need to improve the characterisation of symptoms during the subclinical phase, as it can greatly enhance our ability to identify PsA at an early stage and facilitate prompt diagnosis and prevention/interception of PsA.

Author affiliations
[1]Department of Medical and Biological Sciences, Rheumatology Clinic, University Hospital Santa Maria della Misericordia, Udine, Italy
[2]Department of Internal Medicine, Rheumatology and Immunology, University of Erlangen, Erlangen, Germany
[3]INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Sorbonne Universite, Paris, France
[4]APHP, Department of Rheumatology, Hopital Universitaire Pitie Salpetriere, Paris, France
[5]Department of Dermatology, University of Leipzig, Leipzig, Germany
[6]Department of Dermatology, University Hospital Erlangen, Erlangen, Germany
[7]Rheumazentrum Ruhrgebiet, Ruhr University Bochum, Herne, Germany
[8]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK
[9]Department of Medical and Biological Sciences University Hospital 'Santa Maria della Misericordia', Institute of Dermatology, Udine, Italy
[10]Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliero-Universitaria S Anna, Ferrara, Italy
[11]Medical University of Vienna, Vienna, Austria
[12]Unit of Rheumatology, 'Sacro Cuore' Hospital, Negrar, Italy
[13]Internal Medicine, Sheba Medical Center at Tel Hashomer, Tel Hashomer, Israel

Contributors AZ—1a, 1b, 1c, 2, 3. FF—1b, 2, 3. LG—1a, 1c, 2, 3. IG—1b, 2, 3. MS—1b, 2, 3. AT—1c, 2, 3. XB—1a, 2, 3. GDM—1a, 2, 3. SDV—1a, 2, 3. EE—1a, 1b, 2, 3. LQ—1a, 2, 3. ES—1b, 2, 3. JSS—1a, 1c, 2, 3. IT—1b, 2, 3. AW—1a, 2, 3. GS—1a, 2, 3. DGM—1a, 1c, 2, 3. DS—1a, 1b, 1c, 2, 3. (1) Substantial contributions to study conception and design; and/or b) Substantial contributions to acquisition of data; and/or c) Substantial contributions to analysis and interpretation of data. (2) Drafting the article or revising it critically for important intellectual content. (3) Final approval of the version of the article to be published. AZ acts as responsible author for the overall content.

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ORCID iDs
Alen Zabotti http://orcid.org/0000-0002-0573-464X
Filippo Fagni http://orcid.org/0000-0002-6122-0774
Laure Gossec http://orcid.org/0000-0002-4528-310X
Xenofon Baraliakos http://orcid.org/0000-0002-9475-9362
Gabriele De Marco http://orcid.org/0000-0003-2406-161X

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