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ORIGINAL RESEARCH

Longitudinal Instability of Minimal Disease Activity Domains in Psoriatic Arthritis with Fluctuating Response: A Trajectory Analysis of a Real-World Cohort

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ABSTRACT

***Introduction*:** Minimal disease activity (MDA) is a composite tool used to measure disease state in psoriatic arthritis (PsA), but its longitudinal stability across individual domains remains insufficiently understood. We aimed to investigate domain-specific instability of MDA components over time in patients with fluctuating disease states.

***Methods*:** This post hoc analysis of a real-world longitudinal cohort included patients with PsA treated with biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs) who exhibited fluctuating trajectories over 24 months. MDA was assessed at 6-month intervals across seven domains. For each domain, an instability score (IS) was calculated as the number of transitions across the MDA cutoff between consecutive visits. Domains were also grouped into objective, tenderness-based, and subjective categories. Longitudinal instability patterns were analyzed and compared across domains.

***Results*:** Among 289 patients in the parent cohort, 107 (37.0%) exhibited fluctuating MDA trajectories and were included in the analysis. Objective domains showed the lowest instability over time, whereas tenderness-based and subjective domains demonstrated higher and more variable instability patterns. Domain-level analyses revealed marked heterogeneity across individual MDA components.

***Conclusions*:** In patients with PsA and fluctuating disease states, MDA instability is predominantly associated with subjective and tenderness-based domains, whereas objective inflammatory measures remain relatively stable. Domain-level analysis provides additional insight beyond composite MDA and may improve interpretation of longitudinal disease dynamics.

Keywords: Psoriatic arthritis; Minimal disease activity; Disease trajectory; Longitudinal analysis; Disease variability; Treatment response

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Key Summary Points

Why carry out this study?

Minimal disease activity (MDA) is a treat-to-target tool in psoriatic arthritis (PsA) combining physician-assessed and patient-reported domains.

MDA achievement is associated with better outcomes, but longitudinal maintenance is variable in real-world practice.

The longitudinal dynamics of MDA domains remain insufficiently understood.

What was learned from the study?

MDA domains exhibit different degrees of longitudinal instability: objective domains are relatively stable over time, while subjective and tenderness-based domains are more instable and account for most MDA non-achievement.

Instability analysis at domain level reveals heterogeneous temporal dynamics not captured by binary MDA status, supporting a more granular interpretation of disease fluctuation over time.

Longitudinal instability of MDA suggests that composite disease states may hide heterogeneous domain-specific trajectories over time.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory condition characterized by heterogeneous presentation and course [1]. Beyond its clinical manifestations and the broad spectrum of associated comorbidities [2], PsA may profoundly affect multiple aspects of patients' lives, including physical function, fatigue, and psychological well-being [3, 4]. Therefore, within a holistic management, optimal care should also address patient-reported and subjective aspects of disease burden [5]. Reflecting the multidimensional nature of PsA, minimal disease activity (MDA) has become one of the most clinically relevant tools used in treat-to-target strategies, since it combines a set of objective measures with domains directly reflecting patient experience [6, 7]. Real-world studies have shown highly heterogeneous rates of achievement of MDA over time, suggesting substantial variability in disease control among patients with PsA [8, 9].

Although achievement and maintenance of MDA are associated with improved long-term outcomes, growing evidence suggests that MDA may fluctuate over time in a substantial proportion of patients. In this context, in a recent real-world trajectory analysis, nearly one-third of patients failed to maintain a stable longitudinal disease state, instead alternating between achievement and loss of MDA across consecutive visits despite under stable advanced therapy [10]. This observation suggests that disease control in PsA may be far more dynamic and unstable over time than commonly perceived, raising important clinical and conceptual questions. In particular, it remains unclear whether longitudinal variability in MDA reflects true fluctuations in inflammatory activity, patient perception, or treatment-related effects. In fact, the composite nature of MDA implies that its individual domains may exhibit distinct longitudinal dynamics, emphasizing the relevance of disentangling MDA into its constituents to better understand temporal variability. Despite this, current evidence in this regard remains limited.

Trying to address this gap, we aimed to investigate the trajectories of individual MDA domains in fluctuating responders, and to characterize whether longitudinal instability represents a global feature of MDA or a preferentially domain-dependent phenomenon. We also evaluated inter-patient heterogeneity in instability profiles and, in an exploratory analysis, their potential association with treatment modifications during follow-up.

METHODS

Study Design and Participants

This study represents a post hoc analysis of a previously published longitudinal cohort [10]. The original cohort included patients with PsA who initiated their first biologic or targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs or tsDMARDs) between 2020 and 2023 in two Italian tertiary referral centers (Rheumatology Units of University of Molise and University of Rome Tor Vergata). The dataset was originally designed for longitudinal assessment of disease trajectories over a 24-month follow-up period. For the present analysis, we included only patients with a fluctuating response, defined by alternating achievement and non-achievement of MDA during follow-up. Inclusion criteria of this study were (I) age ≥ 18 years; (II) fulfilling the Classification Criteria for Psoriatic Arthritis (CASPAR) [11]; (III) initiation of first bDMARD or tsDMARD between 2020 and 2023; (IV) availability of complete longitudinal clinical assessments at predefined timepoints (T0, T6, T12, T18, T24), allowing reliable reconstruction of MDA status over time. Exclusion criteria included (I) diagnosis of other inflammatory arthritis (e.g., rheumatoid arthritis or other spondyloarthritis); (II) incomplete longitudinal data precluding reliable classification of MDA trajectories; (III) absence of a fluctuating response (i.e., sustained MDA achievement or persistent non-response throughout follow-up). All methodological procedures related to data collection, follow-up schedule, and clinical assessments are consistent with those reported in the parent study (Supplementary Material) [10]. However, for the present post hoc analysis, psoriasis skin involvement was assessed using the Psoriasis Area and Severity Index (PASI) instead of body surface area (BSA), as PASI provides a more sensitive and comprehensive measure of cutaneous disease severity. This modification reflects an analytical refinement and does not affect cohort comparability, as both measures derive from the same standardized dermatological assessment.

Minimal Disease Activity Assessment

MDA status was assessed at each timepoint according to the established seven-domain definition [12]. Patients were considered in MDA when fulfilling at least five of the following seven criteria: (I) tender joint count (TJC) ≤ 1; (II) swollen joint count (SJC) ≤ 1; (III) PASI ≤ 1; (IV) Leeds Enthesitis Index (LEI) ≤ 1; (V) patient pain visual analogue scale (PtPnV 0–10) ≤ 1.5; (VI) Patient Global Assessment (PtGA 0–10) ≤ 2; (VII) Health Assessment Questionnaire (HAQ) ≤ 0.5.

Instability Score, Transition Probability, and Domain Grouping

For each MDA domain, a specific instability score (IS) was calculated as the number of transitions across the predefined MDA cutoff during follow-up. Transitions were defined as any shift across the domain-specific MDA cutoff between consecutive visits, irrespective of the magnitude or direction of change. Transition probability (TP) was calculated by dividing IS by the total number of evaluable consecutive visit intervals, reflecting the mean probability of transition over time for each domain. To explore whether longitudinal instability differed according to the biological nature of MDA components, domains were grouped into three categories: (I) objective domains (OD): SJC, PASI (as they primarily reflect clinically observable inflammatory burden assessed by the physician with limited influence from patient perception); (II) tenderness-based domains (TBD): TJC, LEI (although assessed by the physician, both are strongly influenced by tenderness and pain elicitation, therefore incorporating both inflammatory activity and patient perception); (III) subjective domains (SD): PtPnV, PtGA, HAQ (entirely patient-reported measures reflecting pain perception, global disease experience, and functional impact). Grouped IS were calculated as the mean IS of the domains included within each category, and TP were also calculated for each grouped domain.

Longitudinal Instability Analyses

Sankey plots (created with the free tool SankeyMATIC, publicly available at https://sankeymatic.com) were generated to visualize transitions across MDA cutoffs over time for overall MDA status and for each individual domain. The frequency of domains failing to meet MDA criteria at each study visit was graphically represented using bar plots, while the contribution of each domain to non-achievement of MDA using pie charts. Box plots were employed to display IS of individual and grouped MDA domains. Heatmap visualization was used to explore patient-level longitudinal instability patterns across individual and grouped MDA domains.

Treatment Modification Analysis

For each patient, the total number of bDMARD or tsDMARD treatment changes occurring during follow-up was recorded, irrespective of the mechanism of action, and correlated with IS for both individual and grouped domains. Given the observational design and the bidirectional relationship between treatment changes and disease instability, these analyses were considered exploratory and not intended to establish causal associations.

Statistical Analysis

The Shapiro–Wilk test was used to assess the normality of continuous variables. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), while non-normally distributed variables were reported as median and interquartile range (IQR). Categorical variables were summarized as frequencies and percentages. Since IS were discrete and non-normally distributed, non-parametric statistical methods were used throughout. Differences across the seven individual MDA domains were assessed using Friedman's test for repeated measures. Post hoc pairwise comparisons between domains were performed using Wilcoxon signed-rank tests with Bonferroni correction for multiple comparisons. Comparisons between grouped IS were also performed using Wilcoxon signed-rank tests. Effect sizes for pairwise comparisons were calculated using the correlation coefficient *r*. To assess the relationship between IS and an independent continuous measure of longitudinal disease activity variability, a sensitivity analysis was performed using the mean absolute change of Disease Activity Index for Psoriatic Arthritis (DAPSA-MAC) values over follow-up. DAPSA-MAC was calculated as the average absolute change in DAPSA between consecutive visits across the four follow-up intervals. The cumulative IS was calculated as the sum of domain-specific IS across the seven MDA domains, ranging from 0 to 28. The association between cumulative IS and DAPSA-MAC was assessed using Spearman's rank correlation analysis. Correlations between grouped IS and their associations with treatment modifications were explored using Spearman's rank correlation analysis. All statistical analyses were two-sided, and p values < 0.05 were considered statistically significant unless otherwise specified after correction for multiple testing. All statistical analyses were performed using SPSS version 28 (IBM Corp, Armonk, NY, USA).

The study was approved by the Institutional Review Board of the University of Molise (protocol n. 0001-017-2021) which provided the approval for both centers (the University of Molise and the University of Tor Vergata) and performed according to the Helsinki declaration. Written informed consent to use clinical data of all participants was obtained.

RESULTS

The original parent cohort consisted of 289 patients with PsA initiating their first bDMARD or tsDMARD. During the 24-month follow-up, 107 patients (37.02%) displayed a fluctuating MDA trajectory, and were therefore included in the present analysis. Baseline demographic and clinical characteristics of the study population are summarized in Table 1. Briefly, the 107

Table 1 Baseline demographic, clinical, and treatment characteristics of fluctuating responders included in the study cohort

	Total population (*n* = 107)
Female sex, *n* (%)	58 (54.21%)
Age (years), mean ± SD	53.29 ± 11.93
Disease duration (years), mean ± SD	7.50 ± 5.14
Normal weight, *n* (%)	40 (37.38%)
Overweight, *n* (%)	40 (37.38%)
Obese, *n* (%)	27 (25.23%)
Smoking habit, *n* (%)	45 (42.06%)
Psoriasis, *n* (%)	88 (82.24%)
Nail disease, *n* (%)	43 (40.19%)
Oligoarthritis, *n* (%)	47 (43.93%)
Polyarthritis, *n* (%)	60 (56.07%)
Axial disease, *n* (%)	30 (28.04%)
Enthesitis, *n* (%)	52 (48.60%)
Dactylitis, *n* (%)	30 (28.04%)
Uveitis, *n* (%)	4 (3.74%)
IBD, *n* (%)	2 (1.87%)
Fibromyalgia, *n* (%)	11 (10.28%)
Cardiovascular comorbidities, *n* (%)	51 (47.66%)
Metabolic comorbidities, *n* (%)	47 (43.93%)
Anxiety or depression, *n* (%)	5 (4.67%)
Previous cancer history, *n* (%)	9 (8.41%)
Previous csDMARDs use, *n* (%)	84 (78.50%)
Start with a TNFα inhibitor, *n* (%)	79 (73.83%)
Start with a IL-12/23 inhibitor, *n* (%)	3 (2.80%)
Start with a IL-23 inhibitor, *n* (%)	2 (1.87%)
Start with a IL-17A inhibitor, *n* (%)	19 (17.76%)
Start with a PDE4 inhibitor, *n* (%)	4 (3.74%)
Start with a JAK inhibitor, *n* (%)	0 (0%)
Concomitant csDMARDs use, *n* (%)	53 (49.53%)
TJC, mean ± SD	9.03 ± 7.82
SJC, median (IQR)	1 (0–2.5)
PtPnV, mean ± SD	6.36 ± 1.81
PtGA, mean ± SD	6.08 ± 1.94
PASI, median (IQR)	1 (0.63–2)
LEI, median (IQR)	2 (1–3)
HAQ-DI, median (IQR)	1 (0–3.5)
CRP (mg/dl), median (IQR)	0.30 (0.15–0.7)
DAPSA, mean ± SD	23.99 ± 11.30

SD standard deviation, *IBD* inflammatory bowel disease, *csDMARDs* conventional synthetic disease-modifying antirheumatic drugs, *TNFα* tumor necrosis factor alpha, *IL* interleukin, *PDE4* phosphodiesterase 4, *JAK* Janus kinase, *TJC* tender joint count, *SJC* swollen joint count, *IQR* interquartile range, *PtPnV* patient pain on a visual analog scale, *PtGA* Patient Global Assessment, *PASI* Psoriasis Area Severity Index, *LEI* Leeds Enthesitis Index, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *CRP* C-reactive protein, *DAPSA* Disease Activity Index for Psoriatic Arthritis

patients evaluated (54.2% female) had a mean age of 53.3 ± 11.9 years and a mean disease duration of 7.5 ± 5.1 years. Polyarticular disease was present in 56.1% of patients, while enthesitis, dactylitis, and axial involvement were observed in 48.6%, 28.0%, and 28.0% of cases, respectively. Psoriasis and nail involvement were present in 82.2% and 40.2% of cases, respectively. Most patients had moderate or high disease activity (mean DAPSA 23.99 ± 11.30), and had previously received conventional synthetic DMARDs (csDMARDs, 78.5%). Tumor necrosis factor alpha (TNFα) inhibitors were the most frequently prescribed therapy (73.8%), and nearly half of the cohort (49.5%) continued concomitant csDMARD treatment.

Longitudinal Sankey analyses demonstrated marked fluctuations in overall MDA status across the 24-month follow-up (Fig. 1). At T6,

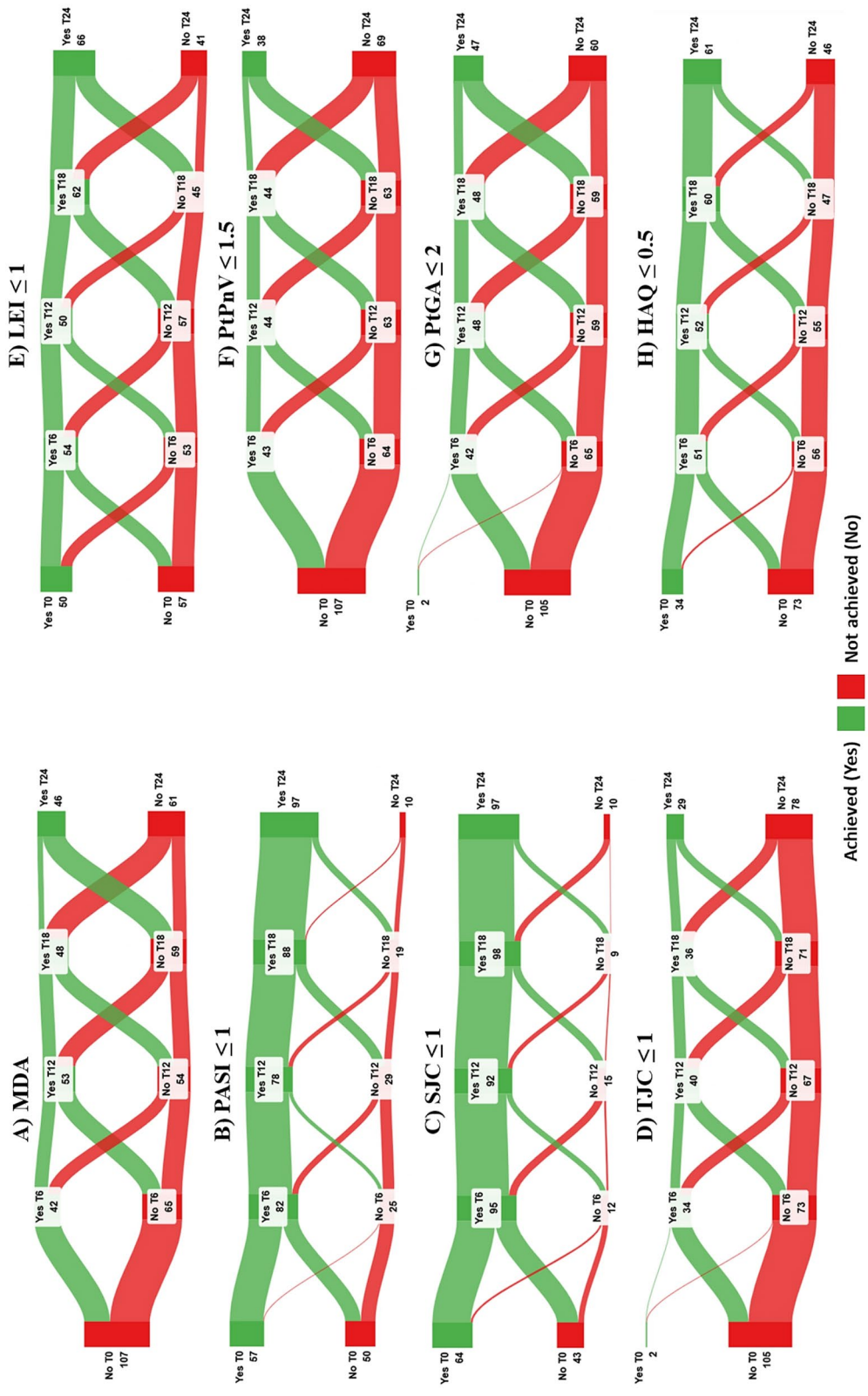

Fig. 1 Longitudinal transitions of overall MDA status and individual MDA domains across the 24-month follow-up. **a** Overall MDA status; **b** PASI ≤ 1; **c** SJC ≤ 1; **d** TJC ≤ 1; **e** LEI ≤ 1; **f** PtPnV ≤ 1.5; **g** PtGA ≤ 2; **h** HAQ ≤ 0.5. Sankey plots illustrate bidirectional transitions across predefined MDA cutoffs between consecutive study visits (T0, T6, T12, T18, T24). Legend: MDA, minimal disease activity; PASI, Psoriasis Area Severity Index; SJC, swollen joint count; TJC, tender joint count; LEI, Leeds Enthesitis Index; PtPnV, patient pain visual analogue scale; PtGA, Patient Global Assessment; HAQ, Health Assessment Questionnaire

42/107 patients (39.3%) achieved MDA; however, maintenance of MDA was limited, as only 22/42 patients (52.4%) who achieved MDA at T6 maintained this state at T12. Similarly, only 22/53 patients (41.5%) maintained MDA from T12 to T18, and only 9/48 patients (18.8%) maintained MDA from T18 to T24. At T24, only 46/107 patients (43.0%) were in MDA. Distinct longitudinal patterns emerged across individual MDA domains. OD showed the greatest longitudinal stability over time. PASI ≤ 1 and SJC ≤ 1 were the most consistently achieved domains throughout follow-up, increasing from 53.3% and 59.8% at baseline to 90.7% for both at T24, with minimal fluctuation across visits. TJC ≤ 1 was infrequently achieved across all timepoints, increasing only from 1.9% at baseline to 27.1% at T24, with most patients persistently remaining above cutoff values during follow-up. LEI ≤ 1 showed recurrent transitions in both directions and achievement rates fluctuating between 46.7% and 57.9% across visits, reaching 61.7% at T24. PtPnV ≤ 1.5 remained poorly sustained over time despite recurrent improvements, with achievement rates ranging from 0% at baseline to 35.5% at T24. Similarly, PtGA ≤ 2 fluctuated markedly across consecutive visits, increasing from 1.9% at baseline to 43.9% at T24. HAQ ≤ 0.5 showed intermediate trajectory, with achievement rates increasing from 31.8% at baseline to 57.0% at T24.

The longitudinal probability of surpassing MDA cutoffs showed marked heterogeneity across individual (Fig. 2a) and grouped domains (Fig. 2b). Domain contribution to MDA non-achievement (Fig. 2c) was mainly driven by TJC, PtPnV, and PtGA (approx. 20% each), followed by LEI and HAQ (approx. 15%), while PASI and SJC contributed < 10%. Consistent with these findings, grouped analysis (Fig. 2d) confirmed that OD contributed modestly to MDA

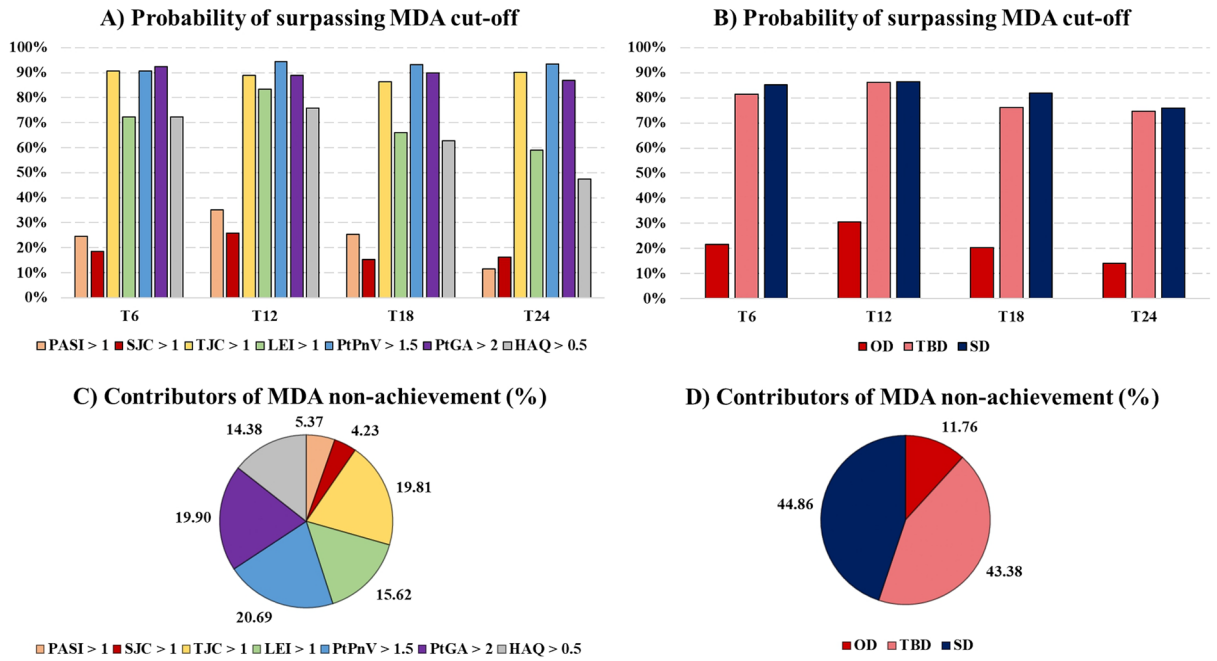

Fig. 2 Longitudinal probability of MDA cutoff achievement and contribution of individual and grouped domains to MDA status over time. **a** Probability of exceeding MDA cutoff for individual domains; **b** Probability of exceeding MDA cutoff for grouped domains; **c** Relative contribution of individual domains to MDA non-achievement; **d** Relative contribution of grouped domains to MDA achievement. Legend: MDA, minimal disease activity; PASI, Psoriasis Area Severity Index; SJC, swollen joint count; TJC, tender joint count; LEI, Leeds Enthesitis Index; PtPnV, patient pain on a visual analog scale; PtGA, Patient Global Assessment; HAQ, Health Assessment Questionnaire; OD, objective domains; TBD, tenderness-based domains; SD, subjective domains

non-achievement (11.76%), while TBD and SD accounted for 43.38% and 44.86%, respectively.

IS and TP showed a clear domain gradient (Table 2), with lowest instability in PASI and SJC and increasing values across other individual domains. A similar pattern was observed at the group level, with lowest instability in OD and higher levels in TBD and SD.

IS differed significantly across MDA domains ($p < 0.001$), indicating heterogeneous longitudinal variability among components. OD showed consistently lower instability than both TBD and SD, while no differences were observed between TBD and SD, as detailed in Table 3 and visualized in Fig. 3.

Consistently, correlation analysis showed no significant association between OD IS and either TBD (Spearman's ρ = 0.02, $p = 0.85$) or SD IS (Spearman's ρ = 0.03, $p = 0.78$). In contrast, TBD and SD IS demonstrated a weak but significant positive correlation (Spearman's ρ = 0.20, $p = 0.04$), further supporting a partial convergence of instability dynamics between them. Moreover, the cumulative IS was positively associated with DAPSA-MAC (Spearman's ρ = 0.19, $p = 0.04$).

At patient-level, these findings are reflected in the heatmap (Fig. 4), which revealed substantial interpatient heterogeneity in IS across MDA domains. The visualization highlights a spectrum of disease expression, with some patients showing globally elevated instability across domains, while others exhibit marked discordance between objective measures and patient-reported outcomes.

Finally, among the 107 patients analyzed, 38 (35.51%) switched their initial bDMARD or tsDMARD during follow-up. Of these, 31 switched once and 7 switched twice; 11 patients underwent a cycling within the same mechanism of action (mainly between different TNFα inhibitors), while 27 changed mechanism at least once, most frequently from TNFα inhibitors to IL-17 inhibitors ($n = 16$). No significant correlations were observed between the number of treatment changes and IS across any individual of grouped MDA domains (Supplementary Table 1).

DISCUSSION

Our study provides a longitudinal disentanglement of MDA instability in PsA, demonstrating

Table 2 IS and TP across individual and grouped MDA domains

	IS median (IQR)	IS mean ± SD	TP (95% CI)
PASI	0 (0–1)	0.77 ± 0.96	19.25% (15.71–23.16)
SJC	0 (0–1)	0.89 ± 0.97	22.25% (21.35–29.56)
TJC	2 (0–2)	1.36 ± 1.11	34.00% (29.78–38.73)
LEI	2 (1–2.75)	1.76 ± 1.01	44.00% (39.53–48.89)
PtPnV	2 (1–2)	1.83 ± 0.95	45.75% (41.13–50.53)
PtGA	2 (1–2)	1.88 ± 0.83	47.00% (42.51–51.93)
HAQ	1 (0.25–2)	1.04 ± 0.99	26.00% (23.58–32.34)
OD (mean PASI + SJC)	0.5 (0.5–1)	0.84 ± 0.71	21.00% (17.22–24.89)
TBD (mean TJC + LEI)	1.5 (1–2)	1.56 ± 0.77	39.00% (34.63–43.84)
SD (mean PtPnV + PtGA + HAQ)	1.67 (1.33–2)	1.60 ± 0.66	40.00% (35.12–44.35)

IS instability score, *IQR* interquartile range, *SD* standard deviation, *TP* transition probability, *CI* confidence interval, *PASI* Psoriasis Area Severity Index, *SJC* swollen joint count, *TJC* tender joint count, *LEI* Leeds Enthesitis Index, *PtPnV* patient pain on a visual analog scale, *PtGA* Patient Global Assessment, *HAQ* Health Assessment Questionnaire, *OD* objective domains, *TBD* tenderness-based domains, *SD* subjective domains

Table 3 Pairwise comparisons of IS across MDA domains

Comparison	Direction	Adjusted *p* value	Effect size (*r*)
PASI vs SJC	n.s.	n.s.	–
PASI vs TJC	TJC > PASI	< 0.001	0.69
PASI vs LEI	LEI > PASI	< 0.001	0.76
PASI vs PtPnV	PtPnV > PASI	< 0.001	0.80
PASI vs PtGA	PtGA > PASI	< 0.001	0.85
PASI vs HAQ	HAQ > PASI	0.002	0.62
SJC vs TJC	n.s.	n.s.	–
SJC vs LEI	n.s.	n.s.	–
SJC vs PtPnV	PtPnV > SJC	< 0.001	0.64
SJC vs PtGA	PtGA > SJC	< 0.001	0.69
SJC vs HAQ	n.s.	n.s.	–
TJC vs LEI	n.s.	n.s.	–
TJC vs PtPnV	n.s.	n.s.	–
TJC vs PtGA	n.s.	n.s.	–
TJC vs HAQ	n.s.	n.s.	–
LEI vs PtPnV	n.s.	n.s.	–
LEI vs PtGA	n.s.	n.s.	–
LEI vs HAQ	n.s.	n.s.	–
PtPnV vs PtGA	n.s.	n.s.	–
PtPnV vs HAQ	n.s.	n.s.	–
PtGA vs HAQ	PtGA > HAQ	0.002	0.18
OD vs TBD	TBD > OD	< 0.001	0.64
OD vs TBD	SD > OD	< 0.001	0.68
TBD vs SD	n.s.	n.s.	–

After Bonferroni correction, statistical significance was set at $p < 0.0024$ for the 21 pairwise comparisons among individual MDA domains and at $p < 0.017$ for the three grouped-domain comparisons

PASI Psoriasis Area Severity Index, *SJC* swollen joint count, *TJC* tender joint count, *LEI* Leeds Enthesitis Index, *PtPnV* patient pain on a visual analog scale, *PtGA* Patient Global Assessment, *HAQ* Health Assessment Questionnaire, *OD* objective domains, *TBD* tenderness-based domains, *SD* subjective domains, *n.s.* Not signifi cant

that fluctuations in disease state are unevenly distributed across its components. A relevant conceptual aspect of our study concerns the grouping of MDA domains into OD, TBD, and SD. This classification was not intended as a rigid methodological subdivision but rather as an exploratory framework reflecting the predominant source of clinical information underlying each domain. While the distinction between OD (PASI, SJC) and SD (PtPnV,

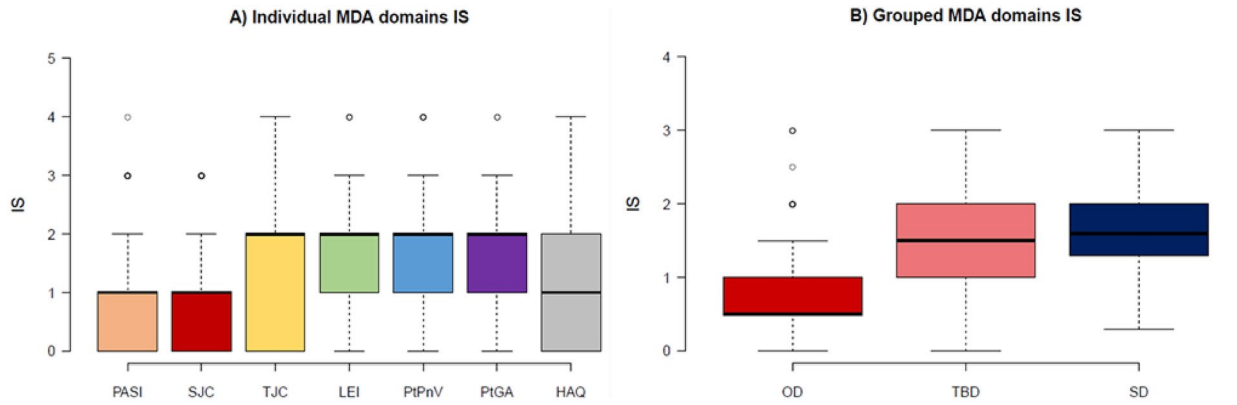

Fig. 3 Boxplots of IS across individual (**a**) and grouped (**b**) MDA domains. Data shown as median (IQR) with outliers. Legend: MDA, minimal disease activity; IS, instability score; PASI, Psoriasis Area Severity Index; SJC, swollen joint count; TJC, tender joint count; LEI, Leeds Enthesitis Index; PtPnV, patient pain on a visual analog scale; PtGA, Patient Global Assessment; HAQ, Health Assessment Questionnaire; OD, objective domains; TBD, tenderness-Based domains; SD, subjective domains

PtGA, HAQ) is intuitive, the categorization of TJC and LEI as TBD deserves some considerations. Although both are formally assessed during physician examination, they fundamentally rely on tenderness elicited by manual pressure and may therefore reflect not only inflammatory activity but also pain perception, central sensitization, and interindividual variability in nociceptive processing [4, 13]. This conceptual distinction was considered particularly relevant in the context of a longitudinal evaluation, as changes in TJC and LEI may reflect fluctuations in the subjective experience of disease in addition to—or even independently from—variations in objectively detectable inflammation [14, 15]. Therefore, although this grouping strategy represents a clinically plausible framework, the proposed classification remains exploratory and requires external validation. Further studies may assess whether these domain-specific instability patterns are reproducible across independent cohorts.

The main finding of our study is that OD remained relatively stable over time and contributed only marginally to MDA non-achievement, consistent with previous literature [16]. In contrast, SD and TBD together accounted for nearly 90% of overall MDA failure and displayed substantially greater longitudinal instability. This pattern suggests that fluctuating MDA trajectories in patients receiving stable bDMARD or tsDMARD therapy may be driven less by recurrent inflammatory reactivation and more by oscillations in pain experience, global disease perception, and functional burden. This observation reflects the complex nature of tenderness and entheseal pain assessment, which likely integrates inflammatory, mechanical, and nociplastic components [17]. The absence of significant differences between TBD and SD instability further supports a convergence in their longitudinal trajectory. This pattern, together with the clear separation from OD, reinforces the presence of a structured gradient of instability across MDA components. However, the lower instability observed in OD may be partly influenced by floor effects, as these domains exhibited low baseline values and limited room for variation below the MDA threshold. This finding may also reflect the high proportion of patients previously exposed to csDMARDs, which could have partially controlled cutaneous and peripheral joint disease prior to b/tsDMARD initiation.

From a pathophysiological perspective, several mechanisms may contribute to these findings. Residual pain despite effective inflammatory suppression is increasingly recognized in PsA and may reflect a combination of central sensitization, structural damage, and

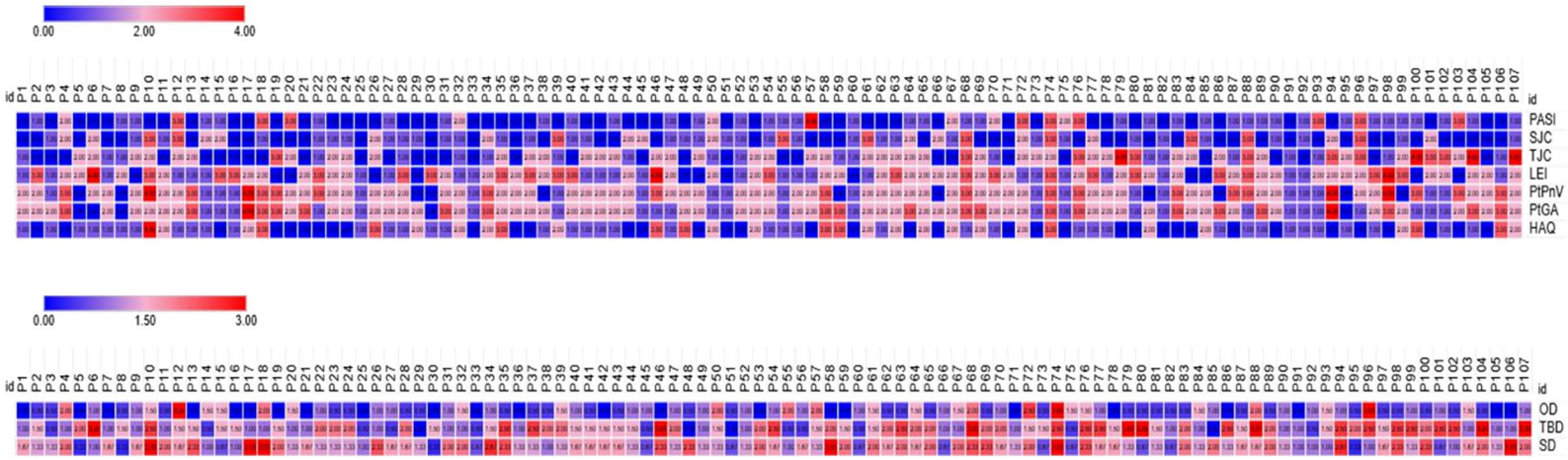

Fig. 4 Patient-level heatmap of IS across individual and grouped MDA domains. Columns represent each domain of MDA and rows represent individual patients. Values are color-coded using a blue-pink-red scale indicating low to high scores. Legend: PASI, Psoriasis Area Severity Index; SJC, swollen joint count; TJC, tender joint count; LEI, Leeds Enthesitis Index; PtPnV, patient pain on a visual analog scale; PtGA, Patient Global Assessment; HAQ, Health Assessment Questionnaire; OD, objective domains; TBD, tenderness-based domains; SD, subjective domains

biomechanical stress [18–20]. In this context, fluctuations in patient-reported outcomes may also be influenced by day-to-day variation in activity, fatigue, and psychosocial factors not captured by standard clinical assessments [21]. This observation is consistent with real-world evidence demonstrating frequent discordance between physician-assessed inflammation and patient-reported disease activity in PsA [22, 23]. This aspect is clinically relevant, as it may directly influence therapeutic decision-making. In routine care, worsening patient-reported domains could lead to treatment escalation or switching, particularly when composite targets such as MDA are lost. However, escalation decisions driven predominantly by isolated worsening of patient-reported domains may not adequately address the underlying determinants of symptom burden and could contribute to potentially unnecessary treatment modifications. Nevertheless, these findings should not be interpreted as diminishing the central role of patient-reported outcomes, which remain important in the assessment of a multidimensional disease that impact patients' physical, psychological, and social well-being [24–26]. Rather, they emphasize the need for a more integrated interpretation of fluctuating MDA trajectories, combining objective inflammatory assessment with careful evaluation of pain mechanisms, psychosocial factors, comorbidities, and other determinants of disease perception. In this context, in patients with well-controlled inflammatory activity, complementary non-pharmacological strategies—such as weight management, physical activity, and psychosocial interventions—may help address residual symptom burden [27, 28]. This supports a more holistic, multidisciplinary approach to treatment adaptation beyond inflammation-targeted therapy alone.

In our cohort, only 38 out of 107 patients with fluctuating response underwent a switch of their initial bDMARD or tsDMARD during follow-up, a proportion that may appear lower than expected. However, diverse factors may explain this finding. First, since the magnitude of longitudinal changes was not specifically assessed, some fluctuations may have been considered clinically manageable by both physicians and patients, and therefore not consistently prompting treatment modification. Second, symptom variability may have been managed through optimization of concomitant treatments, including csDMARD adjustments, non-steroidal anti-inflammatory drugs, analgesics, or local interventions, without necessarily prompting switching. Moreover, treatment decisions in PsA are frequently influenced by additional considerations beyond disease activity alone, including comorbidities, safety concerns, and patient preference [29, 30]. Consistently, IS were not associated with the number of treatment modifications during follow-up. Although exploratory and not intended to establish causality, this finding suggests that longitudinal instability may represent an intrinsic feature of disease expression in some patients, rather than merely reflecting therapeutic failure or insufficient treatment escalation.

Some limitations should be acknowledged. First, the small sample size may limit the robustness and generalizability of the findings; however, the study population consisted of a selected cohort of patients with complete longitudinal assessments. Second, this was a post hoc analysis restricted to fluctuating responders, and findings may not be broadly applicable to patients with sustained remission or persistent non-response, in whom limited longitudinal variability makes such analyses less informative. Third, assessments were performed at 6-month intervals, potentially underestimating shorter-term fluctuations. Fourth, the absence of standardized criteria to contextualize whether observed transitions were clinically meaningful may limit the interpretation of our findings, as the present study cannot determine the number of transitions required to represent a clinically meaningful change. Although repeated transitions may reflect greater longitudinal instability, their clinical relevance may depend on several factors, including the magnitude of change and the specific domain involved. Future studies incorporating patient-reported outcomes, physician judgement, imaging findings, or treatment changes as external anchors will be needed to define clinically

meaningful thresholds for this instability evaluation. Finally, imaging assessments capable of objectively detecting inflammatory activity were not available, and the relatively small group of patients and high number of covariates limited the statistical power of a multivariable analysis, which was not performed [31]. Therefore, fluctuations in MDA cannot be directly linked to objective measures of joint/entheseal inflammation, nor to possible presence of factors such as fibromyalgia, depression, or obesity.

Despite these limitations, this study provides one of the first longitudinal analyses specifically exploring instability patterns across the diverse domains of MDA in patients with PsA exhibiting a fluctuating response to treatment in a real-world setting. Our findings support the concept that longitudinal instability analysis may provide complementary information beyond binary MDA achievement, helping to disentangle persistent inflammatory activity from fluctuating symptom burden and underscoring the need for a careful multidimensional interpretation of disease state in clinical practice.

CONCLUSION

The trajectories of MDA domains appear to be highly heterogeneous in patients with a fluctuating response, with distinct and non-equivalent contributions to overall disease dynamics. In this context, MDA fluctuations in patients with PsA treated with stable bDMARDs or tsDMARDs could be predominantly driven by patient-reported domains, whereas objective inflammatory measures remain relatively stable and contribute only marginally to overall variability.

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Declarations

Conflict of Interest. Mauro Fatica, Noemi Italiano, Eneida Çela, and Maria Sole Chimenti have nothing to disclose. Ennio Lubrano and Fabio Massimo Perrotta are Editorial Board members of *Rheumatology and Therapy*. Ennio Lubrano and Fabio Massimo Perrotta were not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions.

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