Residual disease activity and associated factors in Psoriatic Arthritis.

by

Ennio Lubrano[1], MD, PhD; Silvia Scriffignano[1], MD; Fabio Massimo Perrotta[1], MD, PhD

Ennio Lubrano, MD, PhD, Associate Professor of Rheumatology, ORCID ID: 0000-0001-6189-5328

Silvia Scriffignano, MD, Specialist Registrar in Rheumatology

Fabio Massimo Perrotta, MD, PhD, Lecturer in Physical Medicine and Rehabilitation, ORCID ID: 0000-0003-3771-5205

Institution:

[1] Dipartimento di Medicina e Scienze della Salute "Vincenzo Tiberio", Università degli Studi del Molise, Campobasso, Italy.

Corresponding Author:

Ennio Lubrano, MD, PhD

Associate Professor of Rheumatology

Head of Academic Rheumatology Unit and MoRhe Project

Dipartimento di Medicina e Scienze della Salute "Vincenzo Tiberio"

Università degli Studi del Molise,

Via Giovanni Paolo II, C/da Tappino,

86100 Campobasso, Italy

tel: +39 0874 404745

fax: +39 0874 404745

email: enniolubrano@hotmail.com

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Short title: residual disease activity in PsA

Abstract

Objective. Remission or low disease activity should be the treatment target of Psoriatic Arthritis (PsA). However, residual disease activity (RDA) in some domains could persist. The aim of this study was to assess RDA and its associated factors in a group of PsA patients.

Methods: PsA patients satisfying CASPAR criteria, with >6 months follow up and achieved a status of low disease activity (LDA), MDA or remission (DAPSA remission or VLDA) were enrolled. RDA was assessed by the percentage of patients who had, although in LDA or remission, tender and/or swollen joints>1, LEI>1, HAQ>0.5, PASI>1, PtGA>20, physician VAS>20 and VAS pain>15. Associated factors of RDA were also assessed.

Results: Of 113 enrolled patients, 78 (69%) were in MDA. Moreover, DAPSA remission was observed in 46 (40.7%) while VLDA only in 32 (28.3%) of PsA patients. VLDA seems to be the most stringent criteria with a minimal RDA only in the VAS physician in one patient (3.1%) and none in the different domains, while patients in MDA had RDA in tender joints (14.1%), VAS pain (29.4%) and PASI>1 or BSA>3% (17.9%). Of note, although patients in DAPSA remission show a very low rate of RDA in almost all domains, 12 (26%) of them show a PASI>1 or BSA>3%. Finally, LDA shows RDA in higher percentage, mainly in PROs, tender joints and skin domain.

Conclusion: RDA is possible to be recognized in PsA patients. VLDA seems to be the most stringent composite index to identify patients in absence of RDA.

Introduction

Psoriatic arthritis (PsA) is a multifaceted chronic inflammatory disease characterized by an association of psoriasis and arthritis (1). It can be recognised as a "syndrome" in which different manifestations (arthritis, skin involvement, enthesitis, extra-articular involvement and comorbidities) "run together". In the context of the disease, there are still some unmet needs that should be addressed, mainly on treatment strategies (2). The achievement of the best possible disease control such as disease remission or low disease activity (LDA) have been proposed as treatment targets and may be an achievable goal for PsA patients (3-5). The recent treat-to-target recommendation stated that remission or LDA should be the target of treatment (6). However, due to the complexity of the disease, unidimensional and multidimensional disease activity indices that encompass different disease domains were developed. Of these, the Disease Activity score for PSoriatic Arthritis (DAPSA) and the Minimal Disease Activity criteria (MDA) have been included as treatment targets in the recent recommendation (6-8). The DAPSA is based on the assessment of tender and swollen joints, pain, patient's global assessment of disease activity and C reactive protein-CRP (mg/dl). A DAPSA ≤ 4 defines a status of remission while a DAPSA ≤ 14 a status of LDA (7). Patients are considered in MDA when they satisfy 5/7 of previously published criteria (8,9). The importance of disease control with the lowest grade of disease activity is justified by the fact that achieving sustained MDA (defined as MDA for over 12 months at consecutive clinic visits) reduced radiographic joint damage progression over a 3-year period (10). In a more recent study, the same authors proposed a more stringent definition of remission (very low disease activity – VLDA) in which all 7/7 criteria had to be satisfied (11). However, due to the construction of these indices, residual disease activity (RDA) could persist, mainly in PsA patients that achieved less stringent criteria such us LDA or MDA. At present, a few reports are available on RDA in PsA patients when they achieve a status of remission or LDA (12). Moreover, it is possible that the impact of RDA on PsA and its consequences on the

management of this condition might be an important issue for physicians but, mainly, for patients. The aim of this study was to investigate RDA in the different PsA domains (articular, skin, enthesis), systemic inflammation (C-Reactive Protein, CRP) and patient reported outcomes (PROs), in patients in DAPSA LDA, MDA or remission (VLDA, DAPSA≤4). Secondary endpoint was to analyse the differences between PsA patients with or without RDA in each single domain, in order to evaluate associated factors to RDA.

Patients and methods

Patient selection

In this cross-sectional analysis of a longitudinal cohort, patients were enrolled at the Rheumatology Unit, Department of Medicine and Health Science - University of Molise. During the period of time **(**1st January 2017 - 31st December 2018**)**, all patients with PsA, who were on at least 6-month follow-up treatment with conventional (cs) and biologic (b) disease modifying anti-rheumatic drugs (DMARDs) were considered potentially eligible for the study.

Inclusion criteria were:

1) PsA classified with the ClASsification criteria for Psoriatic ARthritis (CASPAR) criteria (23),
2) age > 18 years,
3) at least 6 months follow-up at the study visit,
4) stable treatment with a csDMARDs or bDMARDs for at least 6 months.
5) Patients in a condition of LDA or remission by using: DAPSA score ≤14, MDA, VLDA, DAPSA≤ 4.

The study protocol was in compliance with the declaration of Helsinki and written consent was obtained from each participant. The study was approved by the Institutional Review Board of the University of Molise (protocol n. 0001-09-2017)

Data collection

Patient data collection included a medical history, physical examination, current use of medications and laboratory assessment. Demographics and disease characteristics including age, gender, disease duration and pattern of articular manifestation were taken into account. The clinical assessment encompassed the number of tender joints (of the 68 assessed joints) and swollen joints (total of 66 joints), enthesitis and dactylitis. Enthesitis was measured using the Leeds Enthesitis Index (LEI) (13), and dactylitis as present/absent. Skin assessment included the Psoriasis Area Severity Index (PASI) score and the body surface area (BSA) (14). The Health Assessment Questionnaire (HAQ) (15) was used to assess function. Patient Global Assessment (PtGA) and pain assessment on Visual Analogic Scale (VAS) were performed by all patients. Physician's global evaluation of disease activity on a VAS scale was also recorded (16). CRP was also collected.

MDA, VLDA, DAPSA remission and DAPSA LDA.

MDA was defined according to Coates et al (8). Patients were considered in MDA when they satisfied 5/7 of the following criteria: tender joint count ≤ 1; swollen joint count ≤ 1; psoriasis activity and severity index ≤ 1 or body surface area ≤ 3; patient pain visual analogue scale (VAS) score of ≤15; patient global disease activity VAS score of ≤ 20; HAQ score ≤ 0.5; and tender entheseal points ≤ 1 (17). Moreover, MDA 6/7, MDA joints, MDA joint/skin and MDA skin were also analysed (12).

VLDA was satisfied when all 7 criteria were met (11). DAPSA score was identified according to Nell-Duxneur et al. and was calculated by adding the number of tender and swollen joints, VAS pain, PtGA and CRP (mg/dl) (29). DAPSA score ≤ 4 identified remission while DAPSA ≤ 14 a condition of LDA.

RDA

RDA was assessed by the percentage of patients who had, although in DAPSA LDA, MDA, VLDA or DAPSA remission, tender and / or swollen joints> 1, LEI> 1, HAQ> 0.5, PASI> 1, PtGA> 20 mm and VAS pain > 15 mm (17). PsA patients with RDA in the different domains were compared to

patients without RDA in order to identify factors associated with RDA. HAQ is considered a measure of function and, therefore, we evaluated the rate of patients with an HAQ>0.5 as it is part of the MDA criteria.

Finally, the global assessment of disease activity by the physicians was also performed, in the same fashion of a previous study and expresses as VAS ≤20, meaning a status of good control of the disease or remission/low disease activity. This was considered as the external anchor for the assessment of remission (16). Therefore, we aimed to evaluate any concordance with MDA, VLDA, DAPSA remission and LDA with the external anchor.

Statistical Analysis

Proportions of patients achieving each definition of low disease activity and remission were calculated. The proportion of RDA was established for clinical domains of PsA (articular, enthesitis, psoriasis), HAQ, VAS pain, PtGA and Physician's global assessment of disease activity, and levels of CRP. Normal distribution was assessed by using the D'Agostino-Pearson's test. Categorical variables were analysed by χ-square test with Yates' correction or Fisher's exact test. The significance of the differences was determined using the Mann–Whitney test for unpaired samples. Factors associated with RDA in each domain were explored by evaluating the differences between PsA patients with or without RDA in each single domain using Mann-Whitney for categorical variables or Fisher's exact test for non-categorical ones. Results were expressed as median (25^{th}-75^{th} percentile). Concordance was assessed using Cohen's kappa coefficient and was considered as follows: < 0.20: poor; 0.21-0.40: fair; 0.41-0.60: moderate; 0.61-0.80: good; 0.81-1.00: very good. All statistical procedures were two-sided; a significance level was accepted at $p< 0.05$.

Results

Patient characteristics and overall disease activity

In the study period, 113 PsA satisfied the inclusion criteria and were enrolled. All PsA patients were in stable treatment with conventional or biologic DMARDs (32 with etanercept, 23 with adalimumab, 13 with golimumab, 5 with ustekinumab, 16 with secukinumab, 2 with ixekizumab, and 22 with cDMARDs monotherapy). All patients were in LDA according to DAPSA≤14.

In table 1 the main clinical characteristics of enrolled patients are shown.

Achievement of MDA, MDA 6/7, MDA joints, MDA joint/skin, MDA skin, DAPSA remission and VLDA

Figure 1 describes the achievement of all targets of PsA patients enrolled, as well as the percentage of global disease activity assessed by physicians (VAS physician ≤20). In particular, 76 PsA patients (67.2%) were deemed as VAS≤20 by the physicians.

Residual Disease Activity and associated factors

Overall, 81 (71.7%) of patients showed RDA in at least one domain. Furthermore, the rate of patients with RDA was significantly higher among csDMARDs treated patients in respect to bDMARDs treated patients (86.3% vs 63.7% p=0.04). Figure 2 shows the rate of RDA in the different disease domains observed in the group of patients enrolled. According to these results, VLDA seems to be the most stringent criteria with a minimal RDA only in the VAS physician in one patient (3.1%) and none in the different domains, while patients in MDA had RDA in tender joints (11 patients, 14.1%), VAS pain (23 patients, 29.4%) and skin (14 patients,17.9%) . Of note, although patients in DAPSA remission show a very low rate of RDA in almost all domains, 12 (26%) of them show a PASI >1. Finally, DAPSA LDA patients show RDA with a higher percentage, mainly in PROs, tender joints and skin domain (see figure 2). When evaluated the RDA in those patients with Physician's VAS ≤20, tender joints, PROs and skin were the main domains involved (see figure 2).

Table 2a shows the comparison of different features between PsA patients (all in DAPSA LDA as per protocol) with and without RDA in three different domains (articular, PROs and skin). A more detailed comparison of patients with and without RDA in each domain is showed in supplementary tables 4a and 4b.

PsA patients with RDA in articular domain (tender joints>1) had significantly higher number of swollen joints, higher HAQ score, and higher values of VAS pain, PtGA and VAS Physician. Patients with RDA in PROs had significantly higher CRP values, HAQ, tender joints and LEI. No factors were associated with RDA in skin domain, while reduced function (HAQ>0.5) was seen in patients with higher disease duration, CRP values, PASI values, higher pain and PtGA values, when compared to non-categorical variables (see table 2a and supplementary table 4a).

Furthermore, HAQ>0.5 was associated with female sex and presence of axial involvement when compared to categorical variables (see supplementary table 4b).

Concordance between Physician's global assessment and MDA, DAPSA remission and VLDA

When evaluated the agreement between the physician's assessment (≤20), a good agreement was found with MDA, while a fair agreement was found with DAPSA. Poor agreement was found with VLDA (see table 3).

Discussion

The assessment of a complex disease such as PsA could be a difficult task most of the time. In fact, the development of composite indices in the last 10 years has tried to identify those domains which are important for physicians and patients in order to set up a treat to target strategy in PsA patients.

The emerging factors associated with these indices are the identification of a primary target to be adopted in a treat-to-target strategy (18) and, secondary, if they are capable or not to reflect the control of all domains. The latter has as a consequence, the possibility that some RDA could persist even when patients are identified in a condition of LDA, MDA, VLDA and remission. Potentially, it is

implicit that a condition of LDA or MDA could show RDA since the intrinsic concept of low disease activity that, per se, is not considered as a full control of the disease (19). Therefore, the assessment of RDA could be an important aspect for the management of PsA, given the fact that LDA and MDA are widely used in routine clinic as main treatment targets.

The present study showed that RDA is detectable in PsA patients in a status of LDA, MDA and even DAPSA remission, while VLDA seems to be the only index capable to identify a condition of remission without RDA. To support this result, all patients in VLDA, but one, were deemed by the physician to have a VAS≤ 20 even if VLDA does not encompass the VAS physicians. In particular, our results showed that PsA patients achieving a VLDA status did not have any residual raised CRP, demonstrating that no systemic inflammation was still present in those patients. Coates et al showed in a recent study that, in their group of PsA patients, a residual CRP was numerically lower in patients in remission, and concluded that the inclusion of CRP may be not necessary since the absence of any impact on the achievement of remission or LDA or an HAQ score (18). When RDA was evaluated as residual functional impairment (HAQ>0.5), this was observed in a small percentage of MDA and DAPSA remission PsA patients, while it was higher in those in LDA. These results are in keeping with a study performed in 2018 in Turkey (20), showing that the disease burden could still persist in some patients.

When assessed the RDA to a condition of MDA and LDA, our results showed that all domains were involved, while the residual skin component was pretty high in those achieving DAPSA remission, confirming its unidimensional capacity to assess mainly joint disease activity. This latter result could be potentially deemed as good when patients attending rheumatology clinics are mainly "joint focused" and skin is not an "important" aspect of the disease (21). On the other hand, the median BSA was 1%, showing a minimal skin involvement in our patients.

Moreover, when evaluating the associated factors to a potential RDA, our results showed that PsA patients in LDA with tender joints as RDA had a significantly higher number of swollen joints, higher

values of VAS pain, PtGA and VAS Physician, as well as higher HAQ score. This result implies that these patients are potentially more severe and the physicians should pay more attention in the treatment strategy (22). In fact, the RDA in tender joints could be deemed by patients as the trigger for a treatment change.

The discordance observed between the physician's judgment and the possibility of any RDA, mainly on tender and swollen joints is in keeping with other previous studies (23) and confirms, to a certain extent, that a true agreement between patients and physician's assessment is still an unmet need (2).

Patients with RDA in PROs had significantly higher CRP values, higher HAQ, tender joints and LEI. This result could suggest that persistence of systemic inflammation, loss of function and some clinical manifestations are definitely perceived as persistence of disease activity by the patients and deemed as not a complete disease control.

No factors were associated with RDA in skin domain, while reduced function (HAQ>0.5) was associated with female sex and presence of axial involvement. Finally, patients with residual systemic inflammation (CRP>0.5) had significantly higher median tender joints higher LEI, pain and PtGA as well as higher PASI.

Another interesting result is the higher rate of RDA in patients treated with csDMARDs in respect to bDMARDs. This could be potentially due to a better effectiveness of these drugs in all disease domains.

Our study has strengths as well as limitations. We decided to perform an assessment in a group of patients in a stable treatment and in LDA only with a cross-sectional design, aiming to overview the RDA. At the same time, we did not perform any analysis on potential treatment implications in those patients in RDA (such as change therapy) due to the study design and this aspect could be of some interest for practical issues. However, our study tried to identify potential factors associated -with a RDA condition and, as far as we know, this is a novelty in this intriguing topic. The results of our

study could be useful to identify patients in which some RDA are potential factors driving to a possible change of treatment strategy, even if the same patients achieved a condition like LDA or MDA.

In conclusion, a residual disease activity could be recognized in PsA patients and this seems more present when some targets are identified for the assessment of disease activity. VLDA seems to be the most stringent composite index to identify patients in absence of RDA.

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Table 1. Demographic and clinical disease activity characteristics of PsA patients in LDA

Female / male	49/64
Mean age (SD), years	53.7 (12.4)
Disease duration, mean (SD), years	8 (8.8)
Axial involvement, n (%)	42 (37.1)
Tender joints, median (25th-75th percentile)	1 (0-2)
Swollen Joints, median (25th-75th percentile)	0 (0-1)
BSA % (25th-75th percentile)	1 (1-3)
PASI, median (25th-75th percentile)	0.3 (0-1)
Enthesitis (LEI), median (25th-75th percentile)	0 (0-0)
CRP, mg/dl, median (25th-75th percentile)	0.3 (0.2-0.4)
MDA 5/7, n (%)	78 (69)
VLDA, n (%)	32 (28.3)
DAPSA remission	46 (40.7)
HAQ, median (25th-75th percentile)	0.25 (0.125-0.5)
VAS pain, median (25th-75th percentile)	16.5 (10-30)
PtGA, median (25th-75th percentile)	20 (10-30)
VAS Physician, median (25th-75th percentile)	15 (10-23.5)
Treatment	
- **csDMARDs monotherapy**	22 (19.4)
- **ETANERCEPT, n (%)**	32 (28.3)
- **ADALIMUMAB, n (%)**	23 (20.3)
- **GOLIMUMAB, n (%)**	13 (11.5)
- **USTEKINUMAB, n (%)**	5 (4.4)
- **SECUKINUMAB, n (%)**	16 (14.1)
- **IXEKIZUMAB, n (%)**	2 (1.7)

Table 2a: Comparison of different features between PsA patients in DAPSA LDA with and without RDA in the articular domain (tender joint), PROs (VAS pain and PtGA) and skin domain (PASI) (t-test or Mann–Whitney test for unpaired samples) (non-categorical variables).

	Disease domains (articular, PROs and skin)											
	Tender Joints			VAS pain (mm)			PtGA (mm)			PASI		
	RDA+[§]	RDA-	P	RDA+[#]	RDA-	P	RDA+[°]	RDA-	P	RDA+[$]	RDA-	p
CRP mg/dl (median/IQR)	0.3 (0.2-0.48)	0.2 (0.2-0.39)	ns	0.3 (0.2-0.5)	0.2 (0.2-0.3)	<0.01	0.3 (0.17-0.5)	0.2 (0.2-0.4)	ns	0.2 (0.2-0.4)	0.3 (0.2-0.4)	ns
Tender Joints (median/IQR)	-	-	-	1 (0-2)	0 (0-1)	<0.01	1 (0-3)	1 (0-1)	0.05	0 (0-2)	1 (0-2)	ns
Swollen Joints (median/IQR)	1 (0-1.5)	0 (0-0)	<0.01	0 (0-1)	0 (0-0)	ns	0 (0-1)	1 (0-1)	ns	0 (0-0)	0 (0-1)	ns
HAQ (median/IQR)	0.5 (0.25-0.75)	0.25 (0-0.5)	<0.01	0.5 (0.25-0.75)	0.12 (0-0.31)	<0.01	0.68 (0.5-0.96)	0.25 (0-0.43)	<0.01	0.25 (0-0.5)	0.25 (0.12-0.53)	ns
LEI (median/IQR)	0 (0-1)	0 (0-0)	ns	0 (0-1)	0 (0-0)	<0.01	0 (0-1)	0 (0-0)	<0.01	0 (0-1)	0 (0-0)	ns
VAS pain	20 (15-36)	15 (2.7-30)	<0.01	-	-	-	35 (30-50)	10 (0-20)	<0.01	10 (0-25)	10 (0-20)	ns
PtGA	25 (20-32)	15 (10-29)	<0.01	28 (20-40)	10 (0-10)	<0.01	-	-	-	17.5 (0-25)	20 (10-30)	ns
PASI	0.3 (0-1.4)	0.3 (0-1)	ns	0.3 (0-0.8)	0.3 (0-1.2)	ns	0.15 (0-0.92)	0.3 (0-1)	ns	-	-	-

RDA: residual disease activity

§ Tender Joints RDA+: >1, # VAS pain RDA+: >15 mm, ° PtGA RDA+: > 20 mm, $ PASI RDA+: >1.

Note: residual disease activity in articular domain (swollen joints) and enthesitis (LEI) was not evaluated due to small number of patients with RDA in these domains.

Table 2b: Comparison of different clinical features between PsA patients (number) in DAPSA LDA with and without RDA in the articular domain (tender joint), PROs (VAS pain and PtGA) and skin domain (PASI) (Fisher exact test). (categorical variables)

	Tender Joints			VAS pain (mm)			PtGA (mm)			PASI		
	RDA+§	RDA-	P	RDA+#	RDA-	P	RDA+°	RDA-	P	RDA+$	RDA-	p
Male	16	46	ns	28	34	ns	16	46	0.04	21	40	0.01
Female	13	31		27	17		20	24		3	39	
Axial involvement	2	39	ns	25	16	ns	16	25	ns	6	33	ns
No axial involvement	6	56		20	42		19	43		17	44	

RDA: residual disease activity

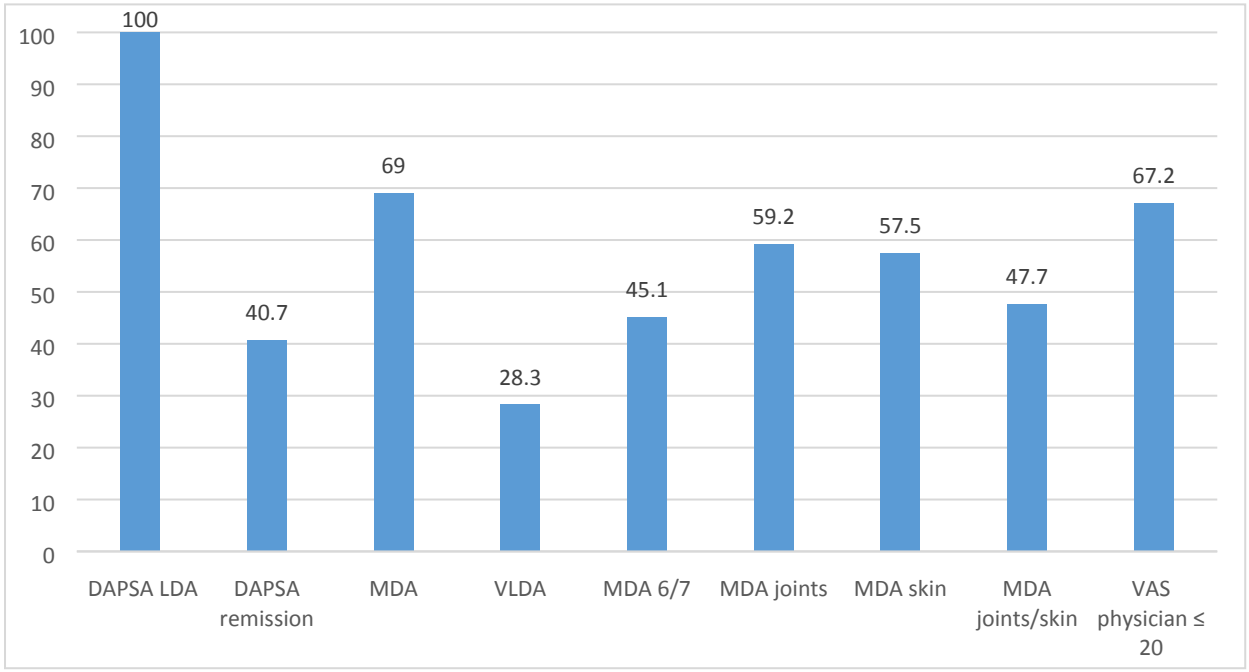
§ Tender Joints RDA+: >1, # VAS pain RDA+: >15 mm, ° PtGA RDA+: > 20 mm, $ PASI RDA+: >1.

Table 3. Concordance (Cohen's Kappa) between Physician's global assessment and the three definitions of remission and minimal disease activity indices evaluated.

	VAS physician ≤20	DAPSA remission	MDA	VLDA
VAS physician ≤20	-	0.24	0.64	0.15
DAPSA remission	0.24	-	0.35	0.57
MDA	0.64	0.35	-	0.31
VLDA	0.15	0.57	0.31	-

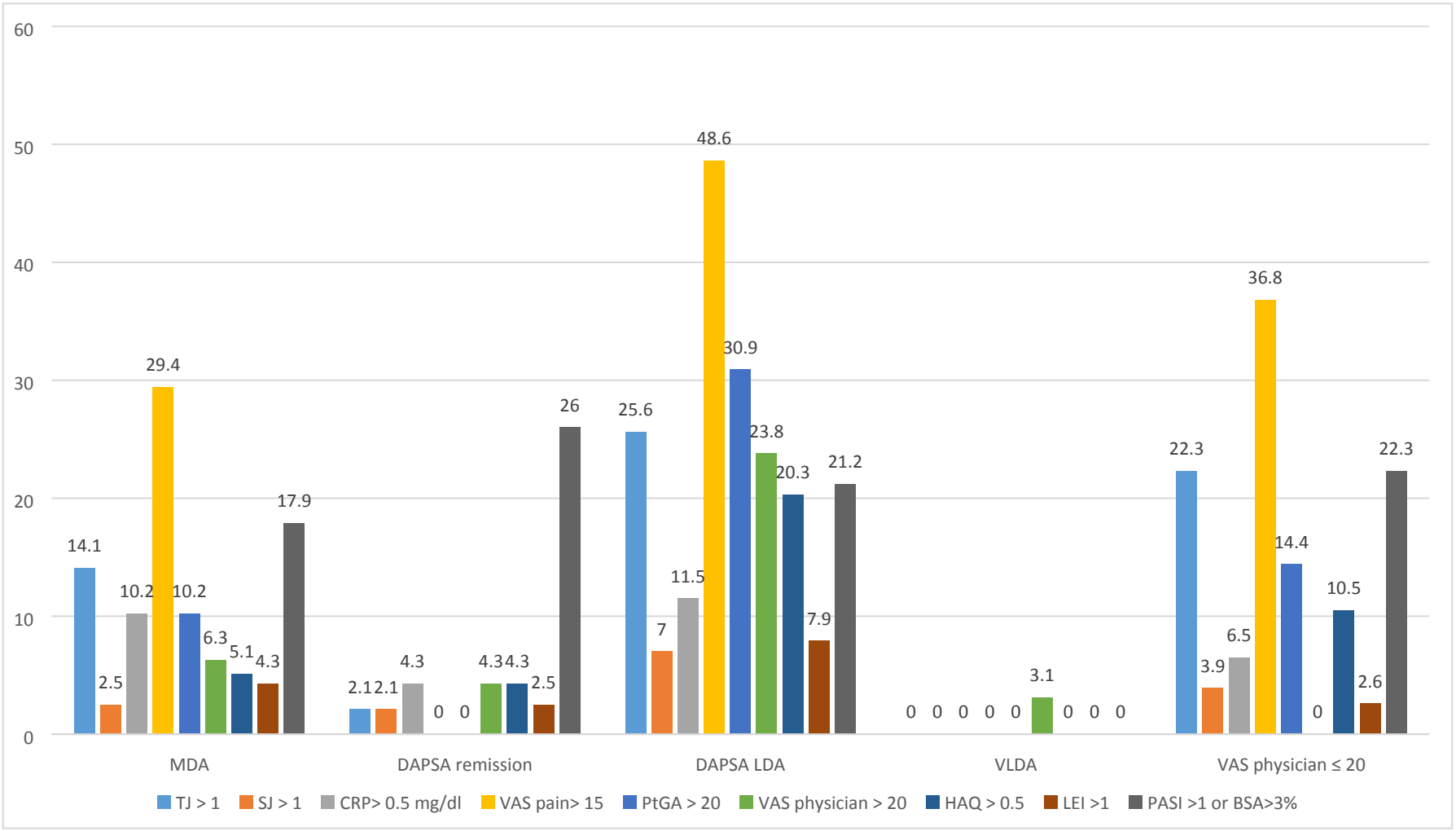
DAPSA: Disease Activity score for PSoriatic Arthritis; MDA: Minimal Disease Activity; VLDA: Very Low Disease Activity; VAS: Visual Analogue Scale.

Figure 1. Percentage of PsA patients (n=113) in remission or low disease activity according to various indices.



DAPSA: Disease Activity score for PSoriatic Arthritis; LDA: Low Disease Activity; MDA: Minimal Disease Activity; VLDA: Very Low Disease Activity; VAS: Visual Analogue Scale.

Figure 2. Residual disease activity in different domains according to the various indices used.



MDA: Minimal Disease Activity; DAPSA: Disease Activity score for PSoriatic Arthritis; LDA: Low Disease Activity; VLDA: Very Low Disease Activity; VAS: Visual Analouge Scale; TJ: Tender Joints; SJ: Swollen Joints; CRP: C Reactive Protein; PtGA: Patient's Global Assessment; HAQ: Health Assessment Questionnaire; LEI: Leeds Enthesitis Index; PASI: Psoriasis Area Severity Index; BSA: Body Surface Area