Do Patients with Psoriatic Arthritis Have More Severe Skin Disease than Patients with Psoriasis Only? A Systematic Review and Meta-Analysis

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Keywords
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Abstract

Background: Early identification of patients at risk of psoriatic arthritis (PsA) is essential to facilitate early diagnosis and improve clinical outcomes. Severe cutaneous psoriasis has been proposed to be associated with PsA, but a recent assessment of the evidence is lacking. Therefore, in this systematic review, we address the association of psoriasis skin severity with the presence and development of PsA. Summary: We included articles from a review published in 2014 and supplemented these with recent literature by performing an additional systematic search to identify studies published between 1 January 2013 and 11 February 2021. A meta-analysis was performed when sufficient comparable evidence was available. Of 2,000 screened articles, we included 29 in the analysis, of which 16 were identified by our updated search. Nineteen studies reported psoriasis severity as psoriasis area and severity index (PASI), ten studies as body surface area (BSA), and two studies as “number of affected sites.” Most studies show that more extensive skin disease is associated with the presence of PsA. The quantitative pooled analyses demonstrate higher PASI (mean difference $\Delta$ 1.59; 95% confidence interval [CI] 0.29–2.89) and higher BSA ($\Delta$ 5.31; 95% CI 1.78–8.83) in patients with PsA as compared to psoriasis patients without PsA. Results from prospective studies – that assess the risk of future development of PsA in psoriasis patients – were inconclusive. Key Messages: In patients with psoriasis, more severe skin involvement is associated with the presence of PsA, underpinning the importance of optimal dermatology-rheumatology collaboration in clinical care. There are insufficient data to support the use of psoriasis skin severity to predict the future development of PsA in psoriasis patients.

Introduction

Psoriatic arthritis (PsA) is a musculoskeletal disorder characterized by inflammation of the skin, nail deformities, arthritis, axial spondyloarthritis, enthesitis, and dactylitis [1]. PsA develops in 6–41% of psoriasis patients, but it

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is unknown why only a subset of patients transits to PsA [1–3]. Psoriatic skin disease precedes PsA in 85% of the cases (on average, 10 years), which opens a window of opportunity for early recognition, treatment initiation, and possibly delaying or even prevention of the onset of PsA [1, 4]. Early diagnosis and treatment of PsA are essential because irreversible joint damage can develop within 6 months and delayed diagnosis is associated with long-term adverse outcomes [5–8]. Therefore, defining patients at risk of PsA transition has been a topic of interest [9, 10].

Multiple clinical predictors for PsA in psoriasis patients have been suggested, including obesity, trauma, nail dystrophy, and psoriasis localization [9, 10]. Moreover, a meta-analysis published in 2014 reported a trend for an association between the extent of psoriasis and the presence of PsA [9]. The extent of cutaneous disease—commonly expressed as psoriasis area and severity index (PASI; range 0–72) or body surface area (BSA; range 0–100)—is a relatively quick and noninvasive clinical outcome and could therefore function as a useful predictor for transition to PsA in psoriasis patients that can readily be applied in clinical practice [11]. However, a meta-analysis investigating this potential predictor for PsA development is lacking [10]. We aimed to update and complement the prior meta-analysis by Rouzaud et al. [9] with current knowledge of the association of psoriatic skin disease severity with PsA by assessing not only the association of psoriasis severity with the presence of PsA but also the association with later development of PsA. Furthermore, we postulate that defining the association between the skin disease severity and the development of PsA may support our understanding of shared pathogenic features within the psoriatic spectrum of disease [12].

**Methods**

**Search**

We conducted a systematic literature search in PubMed and Embase on 11 February 2021 (PICO question: “Is psoriasis skin severity predictive of transition to PsA in psoriasis patients?”). We used a combination of synonym terms in the title/abstract and MeSH/Emtree terms for “psoriasis,” “psoriatic arthritis,” "severity," “PASI,” and “BSA” (online suppl. Table S1; for all online suppl. material, see ). We screened studies using predefined eligibility criteria in line with Rouzaud et al. [9] (online suppl. Table S2). We included original studies published after 1 January 2013, that studied human subjects aged >18 years old and compared psoriasis severity between psoriasis patients without PsA (Pso-PsA), patients with PsA (PsA), and/or psoriasis patients that developed PsA. We focused on publications after 2012 to supplement the comprehensive meta-analysis by Rouzaud et al. [9] (search period 1980 to January 2013).

**Data Extraction**

Eligibility of selected studies for qualitative and quantitative analysis was discussed by two authors (M.E.J. and J.N.P.) and a quality assessment was reported. After study selection, we identified estimators for the association of PsA and psoriasis severity (PASI, BSA, affected sites): mean and standard deviation (±) in (sub)groups, mean difference between groups (Δ), median and interquartile range in (sub)groups, odds ratio (OR), risk ratio, and hazard ratio (HR) for the association of psoriasis severity and PsA (development) with confidence intervals (95% CI). We calculated missing OR and CI and requested the corresponding authors to provide additional data if information to perform quantitative analyses was lacking.

**Differentiation by Research Question**

We differentiated between studies that report the association of cutaneous psoriasis severity with the presence of PsA and studies that report the association with later development of PsA in patients with psoriasis because these studies answer different clinical questions. Articles that report the extent of skin disease at a certain baseline and subsequently study conversion to PsA (prospective design) are important to support the potential use of psoriasis severity as a biomarker to identify psoriasis patients at risk for PsA transition. On the other hand, studies that compare skin disease severity between Pso-PsA and PsA (cross-sectional design) enable us to study the association of psoriasis severity and the present risk of PsA. Although these studies do not address our PICO, we reckon that they do answer a clinically relevant question and therefore we included them in our analyses.

**Meta-Analysis**

We performed quantitative meta-analyses if ≥3 studies used a homogenous study design, reported similar psoriasis severity measures, and used the same association measures. For quantitative analyses, we used random effects models and evaluated heterogeneity with the I² statistic. Meta-analyses were performed using review manager (Version 5.4) and meta-regression with comprehensive meta-analysis (Version 3). We considered a p value <0.05 to be statistically significant.

**Results**

**Search Results**

The search yielded 2,000 unique studies. One author performed title/abstract screening and thereafter screening of 90 studies in full-text (M.E.J.). Selection of 14 studies was discussed by three authors (M.E.J., J.N.P., and E.F.A.L.) (Fig. 1). Two articles were retrieved via reference and related citations in PubMed and supplemented with 13 studies selected by Rouzaud et al. [9]. Of the 29 articles included in our final analysis, three studies assessed the extent of skin disease in Pso-PsA patients and the later development of PsA (PASI n = 2, affected sites n = 1). The other 26 studies reported psoriasis severity and the presence of PsA in Pso-PsA and PsA patients: either
the highest value from repeated measures over a period of time (PASI $n = 1$, BSA $n = 2$) or a single measurement (PASI $n = 14$, BSA $n = 6$, PASI and BSA $n = 2$, affected sites $n = 1$) (Table 1).

**Study Quality**

Concerning studies that investigated psoriasis severity and the presence of PsA, the overall quality was low. In seven studies, selection bias could have been introduced by patient selection (Choi et al. [13]; Cinar et al. [14]; Haroon et al. [15]; Henes et al. [16]; Jamshidi et al. [17]; Leijten et al. [18]; Truong et al. [19]), as they assessed previously undiagnosed PsA in cohorts of psoriasis patients (online suppl. Table S3: detailed study characteristics). The majority of studies recruited patients at dermatology departments of hospitals or dedicated dermatology cli-
Table 1. Studies that report the association of cutaneous psoriasis severity and PsA

| Psoriasis measure | Studiesa | Severity assessmentb | Patients Pso-PsA/PsA | Severity stratification | Results (Pso-PsA vs. PsA unless otherwise specified) |
|-------------------|----------|----------------------|----------------------|-------------------------|--------------------------------------------------|
| PASI Present PsA  |          |                      |                      |                         |                                                  |
| Choi et al. 2017 [13] | Cross   | 173/27               | <10: mild 10–20: moderate >20: severe | (I) Mean 6.8±4.3 versus 9.5±6.3; p = 0.014* (II) Stratified Mild: 78.5% versus 61.9%; p NR Moderate: 21.5% versus 33.3%; p NR Severe: 0.0% versus 4.8%; p NR (III) ORc PASI > 10: 2.24 (CI 0.86–5.86); p = 0.099 |
| Cinar et al. 2015 [14] | Cross   | 94/32                | <3: mild 3–15: moderate >15: severe | (I) Median 2.8 (0.3–30.0) versus 3.6 (0.8–37.7); p = 0.032* (II) Stratified Mild: 59.6% versus 40.6%; NS Moderate: 33.0% versus 53.1%; NS Severe: 7.4% versus 6.3%; NS (III) ORc PASI > 15: 0.83 (95% CI 0.16–4.21); p = 0.821 |
| Dağdelen et al. 2020 [33] | Cross   | 80/40                | na                   | Mean 10.2±9.9 versus 4.9±4.8; p NR |
| Eder et al. 2011 [30] | Cross   | 159/159              | Highest during first 3 yr FU <10: non-severe ≥10: severe | (I) Mean 7.1±7.2 versus 7.3±9.6 (II) Multivariable logistic regression Severe: OR 0.89 (95% CI 0.49–1.61); NS |
| El Miedany et al. 2015 [43] | Cross   | 112/126              | na                   | Mean 11.7±11.8 versus 12.4±10.4; NS |
| Gladman and Chandran 2011 [44] | Cross   | 438/1,066            | na                   | Mean 5.7±5.8 versus 7.0±8.9; p NR |
| Haroon et al. 2013 [15] | Cross   | 71/29                | na                   | (I) Mean 1.89±1.14 versus 2.40±1.13; p = 0.04* (II) Multivariable logistic regression PASI: OR 1.61 (95% CI 1.06–2.44); p = 0.02* |
| Henes et al. 2013 [16] | Cross   | 48/50                | 0–1: not active 2–10: mild 11–15: moderate >15: severe | (I) Median 1 (0–3) versus 1 (0–3); NS (II) Stratified Not active: 26.2% versus 23.9%; NS Mild: 42.9% versus 45.7%; NS Moderate: 21.4% versus 28.3%; NS Severe: 10.4% versus 10.0%; p NR (III) ORc PASI > 10: 0.86 (95% CI 0.38–1.94); p = 0.715 PASI > 15: 0.42 (95% CI 0.13–1.34); p = 0.144 |
| Jamshidi et al. 2008 [17] | Cross   | 291/29               | na                   | Mean 10.70±8.44 versus 24.3±10.36; p < 0.05* |
Psoriasis

Studies<br>

Psoriasis Severity Assessment Patients Pso-PsA/PsA Severity Stratification Results (Pso-PsA vs. PsA unless otherwise specified)

| Study                  | Design | Patients | Pso-PsA/PsA | Severity Stratification | Results (Pso-PsA vs. PsA unless otherwise specified) |
|------------------------|--------|----------|-------------|-------------------------|-----------------------------------------------------|
| Leijten et al. 2017 [18] | Cross  | 68/18    | na          | Mean 5.69±4.84 versus 4.65±5.75; p = 0.478 |
| Maejima et al. 2010 [45] | Cross  | 23/23    | na          | Mean 9.5±9.4 versus 9.5±13.3; NS |
| Pietrzak et al. 2019 [34] | Cross  | 62/31    | na          | Mean 26.00±6.54 versus 28.07±5.87; p = <0.05* |
| Reich 2009 [46]        | Cross  | 1,055/312| na          | Mean 11.5 versus 14.3; p = <0.0001* |
| Salvarini et al. 1995 [20] | Cross  | 130/75   | na          | Mean 4.7±3.5 versus 5.4±5.1; NS |
| Schons et al. 2015 [47] | Cross  | 49/16    | na          | Mean 8.3±7.4 versus 11.3±9.6; NS |
| Soy et al. 2008 [48]   | Cross  | 40/49    | na          | Mean 6.2±8.2 versus 8.6±12.2; NS |
| Yang et al. 2011 [49]  | Cross  | 1,816/112| na          | Mean 6.0±5.6 versus 9.7±10.4; p = <0.001* |

Later development of PsA

| Study                  | Design | Baseline: | Stratified | Multivariable Logistic Regression |
|------------------------|--------|-----------|------------|----------------------------------|
| Eder et al. 2016 [31]  | Pro    | Baseline: 464/0 | Mild: 88.1% versus 78.3%; p NR | Moderate: 10.1% versus 15.0%; p NR | Severe: 1.7% versus 6.7%; p NR | Stratified: Moderate versus mild: RR 1.16 (95% CI 0.50–2.64); NS | Severe versus mild: RR 5.39 (95% CI 1.64–17.7); p = 0.006* |
| Zenke et al. 2017 [21] | Pro    | At first, visit dermatology clinic | Mild: 4.5±7.5 versus 9.3±10.2; p = <0.01* | Moderate: 1.55 (95% CI 0.89–2.71); NS |

Present PsA

| Study                  | Design | Patients | Stratified | Multivariable Logistic Regression |
|------------------------|--------|----------|------------|----------------------------------|
| Choi et al. 2017 [13]  | Cross  | 173/27   | <3: mild 3–10: moderate >10: severe | Mean 6.7±6.6 versus 11.0±16.4; p = 0.029* | Stratified: Mild: 27.8% versus 14.3%; p NR | Moderate: 55.7% versus 66.7%; p NR | Severe: 16.5% versus 19.0%; p NR | OR 1.19 (95% CI 0.37–3.84); p = 0.765 |
| Christophers et al. 2010 [23] | Cross  | 1,434/126| na         | Mean 17.2±16.9 versus 26.6±19.9; p = <0.0005* | Multivariable logistic regression: BSA: OR 1.020 (95% CI 1.012–1.029); p = <0.0005* |
Table 1 (continued)

| Psoriasis measure | Studies\(^a\) | Severity assessment\(^b\) | Patients Pso-PsA/PsA | Severity stratification | Results (Pso-PsA vs. PsA unless otherwise specified) |
|-------------------|--------------|---------------------------|----------------------|------------------------|-----------------------------------------------------|
| BSA               | Gelfand et al. 2005 [24] | Cross | 530/71 | <1: no or little 1–2: mild 3–10: moderate >10: severe | (I) Stratified  
No or little: 75.7% versus 30.8%; p NR  
Mild: 14.5% versus 30.8%; p NR  
Moderate: 8.0% versus 21.5%; p NR  
Severe: 1.8% versus 16.9%; p NR  
(II) OR\(^c\)  
BSA > 10: 11.06 (95% CI 4.11–29.75); p < 0.001* |
|                   | Ogdie et al. 2013 [25]    | Cross | 3,699/365 | ≤2: mild 3–10: moderate >10: severe | Multivariable logistic regression  
Moderate versus mild: OR 1.49 (95% CI 1.1–1.99); p < 0.001*  
Severe versus mild: OR 3.34 (95% CI 2.40–4.65); p < 0.001* |
|                   | Pietrzak et al. 2019 [34] | Cross | 62/31 | na | Mean 35.83±15.59 versus 38.64±13.95; p = 0.2438 |
|                   | Soltani-Arabshahi et al. 2010 [26] | Cross | 693/250 | Highest ever <5: mild 5–10: moderate >10: severe | Cox regression  
Worst BSA ever: OR 1.01 (95% CI 1.00–1.01); p < 0.05 |
|                   | Stern 1985 [27] | Cross | 1,019/266 | na | Mean 31% versus 37%; p <0.01* |
|                   | Tey et al. 2010 [22]    | Cross | 266/134 | Max. in 1 yr FU 0–25%: I 26–50%: II 51–75%: III 76–100%: IV | Multivariable logistic regression  
II versus I: OR 1.53 (95% CI 0.86–2.71); NS  
III versus I: OR 1.64 (95% CI 0.85–3.19); NS  
IV versus I: OR 2.52 (95% CI 1.33–4.75); p = 0.004* |
|                   | Truong et al. 2015 [19] | Cross | 399/169 | na | Mean 13.4±17.4 versus 16.7±21.3; p = 0.05 |
|                   | Yan et al. 2018 [28]    | Cross | 497/175 | Mild to moderate Moderate to severe Severe\(^c\) | (I) Stratified  
Mild: 6.0% versus 3.6%; NS  
Moderate to moderate: 21.5% versus 13.1%; p = 0.021*  
Moderate to severe: 37.2% versus 30.9%; NS  
Severe: 32.0% versus 50.3%; p = 2.39−5*  
(II) OR\(^c\)  
BSA “severe”: OR 2.15 (95% CI 1.51–3.06); p < 0.001*  
(III) Univariate logistic regression  
Severe: OR 2.15 (95% CI 1.51–3.05); p NR  
(IV) Multivariable logistic regression  
Severe: OR 1.92 (95% CI 0.88–4.21); NS |
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Psoriasis (15 studies). Five studies were performed in combined dermatology/rheumatology clinics, two in rheumatology departments, and of the remaining studies, the setting was unknown or of another category. Concerning the classification of PsA, one third of the studies applied validated criteria (CASPAR, Moll & Wright, ESSG), while 11 studies used either a clinical or self-reported diagnosis (Salvarani et al. [20]; Zenke et al. [21]; Tey et al. [22]; Christophers et al. [23]; Gelfand et al. [24]; Ogdie et al. [25]; Soltani-Arabshahi et al. [26]; Stern [27]; Truong et al. [19]; Yan et al. [28]; Thumboo et al. [29]). Whether psoriasis severity was determined by an experienced dermatologist was not described in more than half of the studies. All studies assessed psoriasis severity at a single time point, except for three studies that measured repeatedly over a period of time and reported the highest value during follow-up (Eder et al. [30], Soltani-Arabshahi et al. [26]; Tey et al. [22]). Most studies reported psoriasis duration. As expected, because psoriasis precedes PsA in most cases, psoriasis duration was longer in PsA patients compared to PsO patients (range 0.2–9.5 years) [1, 4]. Details of therapies were not well described in most studies and varied greatly between studies. With regards to confounding, only two studies (Haroon et al. [15] and Eder et al. [31]) corrected for the use of (topical or systemic) psoriasis therapy. After selection based on our criteria of homogeneity, we included 15 studies in two meta-analyses to compare ΔPASI (n = 13) and ΔBSA (n = 4) between PsO-PsA and PsA patients (Fig. 2).

With regards to the three studies that reported psoriasis severity and later development of PsA, the overall risk of bias was low. However, heterogeneity with regards to the reported psoriasis severity measures and estimators impeded pooling of results in quantitative analyses (Eder et al. [31]; Zenke et al. [21]; Wilson et al. [32]).

### Psoriasis Severity and Presence of PsA

Sixteen cross-sectional studies reported PASI from one single measurement, of which 12 studies observed a higher mean or median PASI in PsA compared to PsO-PsA. We included 13 studies in our meta-analysis, that showed a significantly higher PASI in PsA (Δ 1.59 [95% CI 0.29–2.89]) with a high level of heterogeneity (I² 85%) (Fig. 2a). Given the high heterogeneity and possible publication bias (online suppl. Fig. S1), we performed a sensitivity analysis by removing the studies by Dağdelen et al. [33] and Jamshidi et al. [17]. The result of the adjusted meta-analysis showed a smaller but still significant differ-

| Psoriasis measure | Studies † | Severity assessment ‡ | Patients | Severity stratification | Results (PsO-PsA vs. PsA unless otherwise specified) |
|-------------------|----------|------------------------|---------|-------------------------|--------------------------------------------------|
| Affected sites    | Present PsA | Cross | 120/60 | ≤2: limited >2: generalized | (I) Generalized 38.3% versus 41.7%; p NR (II) Univariate logistic regression Generalized: OR 1.18 (95% CI 0.59–2.34); NS |
| Later development of PsA | Wilson et al. 2009 [32] | Pro | Baseline: 1,633/0 End of 20.936 person years FU: 1,593/57 | At baseline Unknown 1 site 2 sites ≥3 | (I) Cox regression univariate 2 versus 1 sites: HR 0.77 (95% CI 0.37–1.64); p NR ≥3 versus 1 sites: HR 2.24 (95% CI 1.23–4.08); p NR* (II) Cox regression multivariate NR (NS) |

BSA, body surface area (1% is equivalent to the size of the palm of the patient’s hand); CI, confidence interval; FU, follow-up; na, not applicable; NR, not reported; NS, not significant (p value not reported); OR, odds ratio; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsO-PsA, psoriasis without psoriatic arthritis; SD, standard deviation; RR, risk ratio. * Significant (p value <0.05). † Differentiation between studies that report the association of cutaneous psoriasis severity with the presence of PsA and studies that report the association with future development of PsA. ‡ Assessment of psoriasis severity in a either a cross sectional (Cross) or prospective (Pro) design. § ORs calculated as follows: (a × d)/(b × d), with the standard error (SE) of the log OR being SE[ln(OR)] = √[(1/a) + (1/b) + (1/c) + (1/d)], and 95% CI = exp[ln(OR) − 1.96 × SE[ln(OR)]] to exp[ln(OR) + 1.96 × SE[ln(OR)]].
Skin Disease Severity in Psoriasis versus Psoriatic Arthritis

Heterogeneity ($\tau^2$ = 3.68, $\chi^2$ = 79.55, df = 12 ($p < 0.00001$); $I^2$ = 85%)

Test for overall effect: $Z = 2.95$ ($p = 0.003$)

| Study or subgroup | PsA mean | PsO-PsA mean | Weight, % | Mean difference IV, random, 95% CI | Mean difference IV, random, 95% CI |
|------------------|----------|--------------|----------|------------------------------------|-----------------------------------|
| Choi, 2017       | 9.5      | 6.3          | 27       | 6.8                                | 4.3                               | 173                               | 8.4 | 2.70 [0.24, 5.16] |
| Dağdelen, 2020   | 4.9      | 4.8          | 40       | 10.2                               | 9.9                               | 80                                | 8.0 | –5.30 [–7.93, –2.67] |
| El Miedany, 2014 | 12.4     | 10.4         | 126      | 11.7                               | 11.8                              | 112                               | 7.6 | 0.70 [–2.14, 3.54] |
| Gladman, 2011    | 7        | 8.9          | 1,066    | 5.7                                | 5.8                               | 438                               | 11.5 | 1.30 [0.54, 2.06] |
| Haroon, 2013     | 2.4      | 1.13         | 29       | 1.89                               | 1.14                              | 71                                | 11.8 | 0.51 [0.02, 1.00] |
| Jamshidi, 2008   | 24.33    | 10.36        | 29       | 10.7                               | 8.44                              | 291                               | 5.8 | 13.63 [9.74, 17.52] |
| Leijten, 2017    | 4.65     | 5.73         | 18       | 5.69                               | 4.84                              | 68                                | 7.5 | –1.04 [–3.93, 1.85] |
| Mäeijima, 2010   | 9.5      | 13.3         | 23       | 9.5                                | 9.4                               | 23                                | 2.9 | 0.00 [–6.66, 6.66] |
| Pietrzak, 2019   | 28.07    | 5.87         | 31       | 26.54                              | 6.54                              | 62                                | 8.0 | 2.07 [–0.56, 4.70] |
| Salvarini, 1995  | 5.4      | 5.1          | 75       | 4.7                                | 3.5                               | 75                                | 10.5 | 0.70 [–0.70, 2.10] |
| Schons, 2015     | 11.3     | 9.6          | 16       | 8.3                                | 7.44                              | 16                                | 3.4 | 3.00 [–2.95, 8.95] |
| Soy, 2008        | 8.6      | 12.2         | 49       | 6.2                                | 8.2                               | 40                                | 5.2 | 2.40 [–1.86, 6.66] |
| Yang, 2011       | 9.7      | 10.4         | 112      | 6                                  | 5.6                               | 1,816                              | 9.4 | 3.70 [1.76, 5.64] |

Total (95% CI): 1,641

Heterogeneity: $\tau^2 = 7.00$, $\chi^2 = 6.78$, df = 3 ($p = 0.08$); $I^2$ = 56%

Test for overall effect: $Z = 2.95$ ($p = 0.003$)

| Study or subgroup | PsA mean | PsO-PsA mean | Weight, % | Mean difference IV, random, 95% CI | Mean difference IV, random, 95% CI |
|------------------|----------|--------------|----------|------------------------------------|-----------------------------------|
| Choi, 2017       | 11       | 16.4         | 27       | 6.7                                | 6.6                               | 173                               | 18.8 | 4.30 [–1.96, 10.56] |
| Christophers, 2020 | 26.6     | 19.9         | 126      | 17.2                               | 16.9                              | 1,434                              | 31.3 | 9.40 [5.82, 12.98] |
| Pietrzak, 2019   | 38.64    | 13.95        | 31       | 35.83                              | 15.59                             | 62                                | 18.8 | 2.81 [–3.45, 9.07] |
| Truong, 2015     | 16.7     | 21.3         | 169      | 13.4                               | 17.4                              | 399                               | 31.0 | 3.30 [–0.34, 6.94] |

Total (95% CI): 353

Heterogeneity: $\tau^2 = 7.00$, $\chi^2 = 6.78$, df = 3 ($p = 0.08$); $I^2$ = 56%

Test for overall effect: $Z = 2.95$ ($p = 0.003$)

Fig. 2. Meta-analysis: psoriasis severity in PsO-PsA and PsA patients Forrest plots of studies that measure psoriasis severity as PASI (a) or BSA (b) and compare mean values between PsO-PsA and PsA patients. BSA, body surface area; CI, confidence interval; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; Pso-PsA, psoriasis without psoriatic arthritis; SD, standard deviation.

e (Δ 1.25 [95% CI 0.55–1.95]) and with acceptable heterogeneity ($I^2$ 42%) (online suppl. Fig. S2). Further, three studies (Choi et al. [13]; Cinar et al. [14]; Henes et al. [16]) compared PASI between PsO-PsA and PsA by stratification into mild, moderate, or severe psoriasis. Although two studies found that moderate-severe psoriasis was more prevalent amongst PsA patients, these results were not statistically significant. One study assessed psoriasis severity repeatedly over time and compared the highest PASI (dichotomized <10 vs. ≥10) during 3 years of follow-up (Eder et al. [30]), but these results too were not significantly different.

Eight cross-sectional studies reported BSA, of which five studies reported mean or median BSA. All studies (Choi et al. [13]; Christophers et al. [23]; Pietrzak et al. [34]; Stern [27]; Truong et al. [19]) showed that PsA patients have higher BSA compared to psoriasis patients. Our meta-analysis confirms that BSA is significantly higher in PsA patients (Δ 5.31 [95% CI 1.78–8.83]) with an intermediate level of heterogeneity ($I^2$ 56%) (Fig. 2b).

Furthermore, three studies that stratified patients into mild, moderate, and severe psoriasis showed that patients with severe skin disease (BSA > 10) were more likely to have PsA than those with non-severe psoriasis. This association was significant in two studies (Gelfand et al. [24] OR 11.06 < 0.001; Yan et al. [28] OR 2.15 $p < 0.001$). Moreover, severe psoriasis was a predictor of present PsA in two studies that performed multivariable regression analysis (Ogdie et al. [25] OR 3.34 $p < 0.001$; Yan et al. [28] OR 1.92 $p = NS$). Furthermore, two studies measured BSA...
Psoriasis Severity and Future Development of PsA

We identified three prospective studies that reported psoriasis severity in PsO-PsA patients and assessed later development of PsA (Eder et al. [31]; Zenke et al. [21]; Wilson et al. [32]). One study showed with multivariable logistic regression that severe psoriasis (PASI ≥ 10) at psoriasis onset is not a statistically significant predictor for PsA transition (OR 1.55, p value not reported), after correction for young age, sex, scalp psoriasis, and nail dystrophy [21]. The second study reported that severe psoriasis (PASI ≥ 20) is significantly associated with PsA transition within 8 years (risk ratio 5.39; p = 0.006) [31]. Finally, one study indicated using univariate Cox regression that patients with ≥3 affected sites were significantly more at risk to develop PsA (HR 2.24 [95% CI 1.23–4.08]), but this effect was not sustained in multivariate analysis after correction for age, sex, calendar year, scalp psoriasis, intergluteal psoriasis, and nail dystrophy (HR not reported) [32].

Discussion

To our knowledge, this is the first systematic review and meta-analysis in 8 years to provide both qualitative and quantitative answers as to whether psoriasis severity is associated with the presence and development of PsA. This is a clinically relevant question because skin severity measurement could aid in identifying those psoriasis patients at risk for PsA transition and thus serve as an easily implementable clinical measurement to facilitate early PsA diagnosis and improve clinical outcomes. Our results confirm that in patients with psoriasis, the presence of slightly more extensive skin disease, as measured by higher PASI and BSA, is associated with concurrent PsA. We were unable to draw a definite conclusion about the association of psoriasis severity with later development of PsA.

The majority of the cross-sectional studies found a positive association between severe psoriasis and the presence of PsA. Moreover, our meta-analyses revealed a statistically significant mean difference of both PASI and BSA between PsO-PsA and PsA patients, although the differences were relatively small. We speculate these results may be an underestimation because most studies included psoriasis patients that were treated in a hospital and patients with only mild psoriasis are typically less prone to visit a dermatologist. Unfortunately, we were unable to accurately assess the association of psoriasis severity with transition to PsA, as prospective studies were limited and heterogeneous. Although all point estimates were in the direction of a higher risk of developing PsA, the results were not always significant. Therefore, there is currently insufficient evidence to recommend dermatologists using psoriasis severity as a reliable biomarker for PsA development.

In the past, specific psoriasis localizations have been suggested to associate with PsA, including scalp and intergluteal psoriasis [9]. PASI and BSA capture all anatomically affected sites of psoriasis and therefore may not be the most suitable outcome measures to assess risk for PsA transition. Moreover, a PASI score of severe scalp psoriasis can be numerically comparable with that of only moderate psoriasis on the knees. Therefore, we recommend future studies to include an in-depth topographic assessment of psoriasis localization and report individual PASI components.

The difference in psoriasis severity between PsA and psoriasis patients could improve our understanding of the pathogenic link between skin and joint disease. From a pathophysiologic perspective, the association between severe psoriasis and PsA may be explained by the important role of the interleukin (IL)-23, IL-17, and tumor necrosis factor alpha (TNF) pathways in inflammation of both the skin and musculoskeletal apparatus [1]. Overlapping cytokines – including IL-17, IL-22, IL-23, and tumor necrosis factor alpha – play a role in immune-mediated inflammation of skin and synovium that involves infiltration of pathogenic CD8+ T cells, macrophages, dendritic cells, monocytes, and B cells [35]. It is hypothesized that local proinflammatory cytokine production and activated immune cells in psoriatic skin create a self-perpetuating inflammatory response that results in systemic inflammation and PsA [35]. However, this does not explain why in 15% of the patients, arthritis precedes skin lesions [1]. Moreover, cutaneous psoriasis severity has...
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shown only a modest correlation with joint disease [36]. Thus, the exact relation between inflammation of the skin, joints, and other domains remains incompletely understood [35].

This review has several limitations. First, we have not repeated the systematic search performed by Rouzaud et al. [9], but as they employed validated methodology and even broader search methods, we assume to have included all relevant publications. Second, our meta-analyses were limited by heterogeneity and a relatively small number of included studies. Third, most studies were conducted in dermatology clinics, which may have resulted in an overestimation of psoriasis severity in PsA, since patients with “PsA sine psoriasis” and limited psoriasis – typically seen by rheumatologists – could have been missed. Fourth, it needs to be taken into account that the meta-analysis did not include high-quality studies. Most importantly, the use of therapies could have confounded the results. However, those studies do represent daily clinical practice, as psoriatic patients are frequently treated with topical and/or systemic treatment. Furthermore, we examined the effects of two potential confounders that are associated with PsA in psoriasis patients, i.e., the presence of nail psoriasis and psoriasis disease duration. Meta-regression analysis suggested that our results were not explained by confounding by nail psoriasis or psoriasis duration, although we could only analyze the effects in six and eight studies, respectively (online suppl. Table S4). Additional subgroup analyses to investigate potential confounders – including psoriasis localization, family history of PsA, obesity, history of trauma of fracture, and smoking status – could unfortunately not be performed in consequence of limited reporting of data [10, 37]. Overall, we deem that these results are the currently best available answer to a clinically relevant question.

**Concluding Remarks**

Our results demonstrate that psoriasis severity is associated with increased likelihood of concurrent PsA. The high extent of psoriasis skin activity in PsA patients reinforces the necessity of multidisciplinary collaboration between rheumatologists and dermatologists in PsA care.

Defining psoriasis patients at risk for PsA transition remains an important topic to facilitate early recognition and prevent irreversible joint damage. Long lasting follow-up studies are necessary to study predictors for the development of PsA in psoriasis patients. Given the complexity of PsA pathogenesis, we deem that prediction models that combine genotypic and phenotypic predictors are the most promising to identify psoriasis patients at risk for PsA transition [38–42].

**Key Message**

In patients with psoriasis, more severe skin involvement is associated with the presence of psoriatic arthritis.

**Statement of Ethics**

The paper is exempt from ethical committee approval because data were collected from published trials in which informed consent had been obtained by the trial investigators.

**Conflict of Interest Statement**

J.M.L. has received honoraria from Abbvie, Arxx Tx, Boehringer Ingelheim, Galapagos, Gesyntha, Leadiant, Magenta, Roche, and Sanofi-Genzyme and research grants from Astra Zeneca, Boehringer Ingelheim, MSD, Pfizer, and Roche. All other authors have no conflicts of interest to declare.

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**Author Contributions**

M.E.J., J.N.P., and E.F.A.L. were responsible for conceptualization. J.N.P. and M.E.J. extracted the data and performed the analyses. All the authors contributed substantially to reviewing and editing the manuscript before submission.

**Data Availability Statement**

All data generated or analyzed during this study are included in this published article and its online supplemental information files.

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