Risk factors for psoriatic arthritis development in psoriasis patients: myths, pitfalls, and pearls

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ABSTRACT

Psoriatic arthritis (PsA) predominantly emerges in individuals previously diagnosed with psoriasis (PsO), offering a unique opportunity to study the transition from PsO to PsA. This progression provides a window to identify characteristics of PsO patients who may develop PsA, facilitating early intervention and potentially informing prevention and treatment strategies. This review evaluates a wide array of research focusing on various risk factors for PsA development. These factors span demographic characteristics, concomitant diseases and habits, characteristics of skin and nail psoriatic disease, and symptoms and imaging abnormalities associated with PsA. By summarising the existing literature, this review critically examines each risk factor, highlighting the strengths and limitations inherent in the studies. Each section of the review not only summarises the current state of knowledge but also includes an expert opinion, culminating in a final concluding remark. This integration allows physicians to utilise the confluence of established literature and ongoing clinical experience, facilitating a rationalised decision-making process that is deeply informed by both empirical evidence and practical insights.

Introduction

Psoriatic arthritis (PsA) typically emerges in individual who have already been diagnosed with psoriasis (PsO) (1, 2). Evidence suggests that the likelihood of developing PsA following the onset of PsO increases over time (3). Recent studies have also suggested that the early intervention of PsO with biologic therapies may delay or even prevent the onset of PsA (4, 5). Therefore, it becomes clear that the identification of risk factors for the development of arthritis in PsO individuals can promote early diagnosis of PsA and potentially favor its prevention/interception (6, 7). Traditionally, factors such as nail, scalp, inverse psoriasis and the severity of PsO involvement have all been associated with heightened risk of subsequently developing PsA (8). However, follow up of these PsO patterns is necessary over many decades since the mere presence of PsO is not linked with imminent PsA development. This challenge means that large number of PsO patients followed up for many years is needed when planning prospective studies that focus on PsA development out of patients affected by PsO. How to deal with this limitation deserves careful consideration and thorough discussion to be properly interpreted.

Recently, a EULAR task force has proposed a distinction between long-term and short-term risk factors for PsA development and in the case of the presence of the former, the PsO patient is defined as "at higher risk of PsA", while when the latter are present, an instance of "subclinical PsA" occurs (9).

As already alluded, the task force included severe skin involvement and nail involvement as long-term risk factors for PsA development. Obesity and familial history of PsA were also recognised as long term risk factors. The potential short-term risk factors that were highlighted included development of new and otherwise unexplained arthralgia and imaging abnormalities or both. The aim of this review is to provide a detailed overview of risk factors of PsA development by presenting its "pros" and "cons", followed by a final concluding remark. Moreover, this review extends its discussion to encompass additional manuscripts that shed light

on the underlying explanations and pathophysiology of these risk factors. This expanded focus aims to enhance our understanding of the significance of these risk factors, offering insights into their roles in the progression from PsO to PsA.

Methods

The evaluated studies were selected from the recently published systematic literature reviews (SLR) focusing on the transition from PsO to PsA (10). Cohort studies and case-control studies were both included for the evaluation, instead results from cross-sectional studies were not considered.

In case-control studies the cases were incident PsA OR prevalent PsA with skin PsO with an onset before arthritis development. Compared to the published systematic reviews, this review provides a detailed analysis with commentary for each potential risk factor associated with the transition from PsO to PsA. Furthermore, as recently recommended (10), risk factors are categorised into long-term and short-term risk factors (*i.e.* indicators of potential subclinical disease).

Results

Long-term risk factors

Age

The role of age as a potential risk factor for PsA development has been examined in seven cohort studies (PsO=86,282, incident PsA=2,082) (8, 11-16) and one case-control study (PsO=401, PsA =654) (17). Among the selected studies, only the study by Gisondi *et al*. (12) identified older age as being independently associated with a heightened risk of PsA development, presenting a Hazard Ratio (HR) of 1.04 (95% CI, 1.02–1.07). Conversely, the study by Lewinson *et al*. (11), although not explicitly making a statement within their manuscript, seemed to suggest a decreased risk in groups aged above 45, with an HR of 0.72 (95% CI 0.63–0.83, $p<0.0001$). Additionally, in the case-control study by Eder *et al*. (17), when each age group was compared to the reference group aged 30 years and younger, the odds ratio (OR) exhibited a significant and gradual decrease with advancing age (31–40 years, OR 0.49; 41–50 years, OR 0.43; 51–60 years, OR 0.18; over 60 years, OR 0.06). Wilson *et al*. (8) found that a younger age at PsO onset corresponded with a slightly diminished risk of PsA (HR 0.91, 95%CI 0.77–1.07), however, such finding did not achieve statistical significance ($p=0.25$).

Comment: The reviewed studies manifested heterogeneity in the definition of age, with some focusing on the age at PsO onset, while others considered the age at enrolment in the study. The authors conclude that, given the evidence available, age should not be considered a risk factor for the development of PsA.

The complexity of the situation is further compounded by the correlation between age and various degenerative tendinopathies and enthesopathies, potentially leading to diagnostic challenges. Moreover, the association between obesity and PsA risk, as well as the link between obesity and biomechanical and degenerative pains contribute to additional complications in this context.

Gender

A total of six cohort studies (PsO=85,818, incident PsA=2,031) (8, 11, 13-16) and one case-control study (PsO=401, PsA=654) (17) delved into the influence of gender on PsA development. The outcomes, however, have been varied. Acosta-Felquer *et al*. (13) observed that the male gender was associated with a higher risk, displaying an HR of 1.7 (95% CI 1.1–2.6). Similarly, there is a discernible trend across several studies suggesting that the male gender might act as a risk factor for PsA, albeit without achieving statistical significance. For instance, Wilson *et al*. (8) found an HR of 1.35 (95% CI 0.78–2.33), and Eder *et al*. (14) reported an HR of 1.46 (95% confidence interval (CI) 0.59–3.63).

Conversely, data from Lewinson *et al*. (11) point to a different perspective. Their results indicated an HR of 1.21 (1.06–1.38) for PsA development, likely suggesting the female gender as risk factor, even though the specific gender was not explicitly mentioned in their study.

Comment: Specific considerations related to gender are essential in PsA due to the clinical prevalence of peripheral arthritis in female patients, while male patients tend to experience more axial disease, severe PsO, and significant radiographic damage (14). Despite these differences in clinical presentation reflecting possible genetic dissimilarities, there is not a conclusive difference between genders concerning the risk of PsA development.

Family history of PsA

The influence of family history on the development of PsA in patients with PsO has been the subject of 4 cohort studies (PsO=1356, PsA=130) (12, 14, 16, 18) and a single case-control study (PsO=58, PsA=40) (19). These studies varied in their definitions of "family history", with some considering a history of PsO in either first- or second-degree relatives, others focusing solely on first-degree relatives, and yet others factoring in a history of PsA or even ankylosing spondylitis (AS). While most of these studies did not find a statistically significant influence of familial predisposition on PsA development, certain findings deserve particular attention. Gisondi *et al*. (12) showed that, in a univariate Cox regression model, recorded family history of PsA increased the risk of PsA onset in PsO patients, with an HR of 2.3 (95%CI 1.04–5.12). However, this correlation diminished and lost statistical significance in a multivariate model, producing an HR of 1.36 (95%CI 0.58–3.18). Eder *et al*. (20) further suggested that a family history of PsO, as well as a history of PsA or AS, could elevate the risk for PsA development, although their results were not statistically significant, with HRs of 1.42 (95%CI 0.82–2.45) and 1.96 (95%CI 0.57–6.71), respectively.

Comment: The literature regarding the significance of family history as a risk factor for the development of PsA is primarily based on cross-sectional studies and hence not specifically selected in this review. Furthermore, it is worth noting that in the two international consensuses on the topic, expert judgment has highlighted the importance of familial history (*i.e.* mainly

having a first-degree relative with PsA) as a risk factor for the development of PsA, albeit with limited evidence (6, 21). Similar to the approach taken in rheumatoid arthritis (RA), the authors recommend considering familiar history as a potential risk factor in PsA.

Psoriatic disease-related conditions

The interplay between various psoriatic disease related conditions in PsO patients and the risk of transitioning to PsA has been the focus of five cohort studies (PsO=10,204, PsA=442) (12, 15, 16, 20, 22) and one case-control study (PsO =120, PsA=60) (19). These studies have encompassed a wide range of comorbidities, including but not limited to hypertension, dyslipidaemia, diabetes, thyroid disorders, and inflammatory bowel disease (IBD).

Although the association between these comorbidities and the development of PsA was not consistently established across the studies, specific conditions have been identified as potential risk factors. Eder *et al*. (20) investigated the time-varying nature of certain comorbidities and identified a significant association between uveitis and an increased risk of developing PsA, with a risk ratio (RR) of 25.3 (95%CI 4.93–130.2). Thyroid disease was also associated with a heightened risk, with an RR of 2.27 (95%CI 1.04–4.95), although this link was not observed when thyroid disease was considered a baseline variable. Furthermore, an increased likelihood of developing PsA was noted in PsO patients with IBD in the study by Belman *et al*. (22), who reported a HR of 3.51 (95%CI 1.4–8.78).

Comment: The inflammatory involvement of extra-cutaneous domains, as in the case of uveitis and IBD, is clinically relevant, both in terms of therapeutic implications but also in terms of possible more aggressive and systemic disease. The evidence suggesting that a previous diagnosis of IBD or uveitis may be predictors of PsA is limited; only one study highlighted an association between acute anterior uveitis and later PsA development. Furthermore, uveitis was included as a possible predictor of PsA development in one expert consensus review (21). Focusing on uveitis, the literature shows that patients with PsO had a higher risk of both development and recurrence of uveitis, especially with severe PsO and PsA, and that the uveitis preceded the diagnosis of PsA in 62.5% of the patients, however the incidence rate in PsO is very low (*e.g*. 1.18 per 1000 person-years) (23, 24). Therefore, we believe that the presence of uveitis in a patient with PsO should be considered a sign of systemic disease and valued in individual patient management, even from a therapeutic standpoint. However, given its low frequency in PsO and what emerged from the studies, it is the authors' opinion that it could not be included among the major predictors of PsA development.

Depression

Major depressive disorder and its role in PsA development has been described in 4 cohort studies (PsO=82,861, PsA=9,968) (11, 15, 20, 22) and one case control study (PsO=159, PsA=159) (25).

Lewinson *et al*. (11) described a statistically significant association between PsA development and the diagnosis of depression in psoriatic patients (HR 1.37; 95%CI 1.05–1.8). Belman *et al*. (22) and Ogdie *et al*. (15) have also described a similar association (HR of 1.78 [95%CI 1.22–2.59], 1.68 [95%CI 1.21–2.33], respectively). These findings support the hypothesis that depression may be associated with systemic inflammation, which could be itself a risk factor for PsA development. Eder *et al*. (25) have specifically studied the association with previously treated depression or anxiety, but they did not report a statistically significant association (OR 0.8 [0.39–1.45]).

Comment: The risk of depression was significantly increased in patients with PsO, PsA and in general among spondylarthritis, when compared to the general population. Furthermore, depression in PsA seems to be associated to lower response to therapy and higher discontinuation rates of biologics (26, 27). Regarding the role of depression in the transition from PsO to PsA, its potential as predictor is not definitely ascertained. This topic deserves attention, particularly for the identification of the pathogenetic mechanisms linking depression with disease activity in the psoriatic disease.

Two decades ago, it was believed that stress associated with the presence of skin symptoms in PsO causes depression and it was seen as a consequence of the cutaneous disease, but not as part of it. Recently, it was found that depression can be regarded as an inflammatory condition and the neuroinflammatory events had a similar signature as in the major domains of psoriatic disease, also involving the IL17/23 axis. In this regard, in PsA patients, serum interleukin-23 levels were found to be correlated with depression, anxiety, and disease activity (28). Reinforcing this hypothesis, Bandinelli *et al*. (29) observed that patients with early PsA exhibited higher scores on the Hospital Anxiety and Depression Scale (HADS) compared to healthy controls. Notably, the presence of anxiety and depression was not associated with functional impairment or demographic factors, suggesting the influence of underlying mechanisms, potentially of an inflammatory nature.

Furthermore, the best effect on depressive symptoms was consistently seen with IL-6 inhibitors used to treat RA, followed by the IL-23 inhibitors for PsO (30). It is the opinion of the authors that such findings reinforce the emerging concept that depression has an inflammatory mechanism and that biologics used for skin and joint may bring benefits also to depressive aspects.

The existence of a continuum between PsO, depression, and joint involvement will undoubtedly pose a challenge for the rheumatologist in the context of transitioning from PsO to PsA, as well as in the context of "difficult to treat" PsA.

Obesity

The relationship between obesity, as measured by body mass index (BMI), and the risk of developing PsA has been substantiated in nine cohort studies (11, 13, 15, 16, 20, 22, 31-33) (PsO=250,490, PsA=4,627). The evidence predominantly supports a dose-response effect, with an increased risk of PsA corresponding to higher BMI categories.

In this regard, Li *et al*. (32) reported

that individuals with BMI ranges of 25–29.9, 30–34.9, and >35 were at a progressively higher risk of developing PsA, with RR of 1.83, 3.12, and 6.60, respectively. Their study also assessed other obesity metrics, such as weight change since age 18, waist and hip circumferences, and waist-to-hip ratio, which were all positively associated with a greater risk of PsA onset. Love *et al*. (31) and Green *et al*. (33) have corroborated these findings, noting a similar escalation in PsA incidence alongside increasing BMI.

However, not all research aligns with these conclusions. Some studies have not found a statistically significant link between obesity and PsA. Belman *et al*. (22) did not observe a notable risk increase with BMI measured at age 18, presenting an HR of 1 (95% CI 0.96–1.05). Similarly, while examining BMI at age 18, Li *et al*. found no significant association (p=0.10).

Comment: Among modifiable risk factors, obesity is the most significant for the development of PsA. Recently, Green *et al*. (33) showed that reducing BMI gradually over a span of 10 years was linked to a decreased likelihood of developing PsA compared to maintaining a consistent BMI over the same duration. The role of obesity as predictor of PsA development is expected, given that obesity represents a condition characterised by a mild, ongoing systemic inflammation, and elevated protein (CRP) levels and have been consistently observed across various demographics, irrespective of sex or age. Adipokines, which are released by adipose tissue, are increasingly acknowledged for their role in regulating diverse immune responses. Notably, the most extensively studied adipokine, leptin, fosters the propagation of pro-inflammatory signals such as interleukin IL-17, and tumour necrosis factor (TNF)-α - both key cytokines in the psoriatic disease spectrum (34). Future algorithms aimed at preventing PsA should involve weight reduction in obese PsO patients and highlight that a disease that was considered to be preventable with immumodulatory drugs might actually respond to metabolic or endrocrine hormone manipulation.

Smoking

The association between smoking and the risk of developing PsA has been extensively studied, as evident from nine cohort studies (PsO=399,022, PsA=8,043) (11, 12, 15, 16, 20, 22, 33, 35, 36) and three case-control studies (PsO=618, PsA=853) (17, 19, 25). However, the results across these studies have been inconsistent.

Li *et al*. (36) observed that the risk of developing PsA among patients with confirmed PsO escalates with both the intensity and duration of smoking. The risk was notably significant in current heavy smokers, defined as those smoking 15 or more cigarettes daily (RR 1.93, 95% CI 1.09–3.40), for individuals with a smoking history of 25 years or longer (RR 1.90, 95% CI 1.09–3.33), and among those with a 20 or more pack-years history (RR 2.02, 95% CI 1.24–3.29).

Conversely, data from other researchers point towards an inverse relationship, where smoking appears to serve as a protective factor against the development of PsA. Lewinson *et al*. (11) and Eder *et al*. (17, 25) reported lower risks of PsA among current smokers when compared to non-smokers (HR 0.87 [95% CI 0.80–0.94] and OR 0.57 [95% CI 0.41–0.81], respectively). Nguyen *et al*. (35) suggested that while smoking increases the risk of PsA in the general population, its effect among PsO patients is inversely related to PsA development (HR 0.91; 95% CI 0.84–0.99). This observation led to the hypothesis that PsO may act as an intermediate factor, potentially reversing the smoking-PsA association and elucidating the so-called "smoking paradox" in PsO patients. Yet, there remains a subset of studies that have not established a clear link between smoking and PsA risk.

Comment: Smoking generally heightens vulnerability to inflammatory diseases, exacerbates the severity of such conditions, and diminishes responsiveness to treatment. Among the umbrella of spondyloarthropathy diseases, smoking offers a protective effect against ulcerative colitis but does not provide the same against the development of Crohn's disease (37). Similarly, there might be an association between smoking and PsO; however, studies conducted through case-control and cohort methods have demonstrated a potential protective effect against the development of PsA.

Considering the relatively low blood supply to the enthesis and the occurrence of changes in blood flow around this area in approximately 10% of individuals with PsO, it is plausible that the vasoconstrictive and anti-angiogenic effects of cigarette smoke could mitigate symptoms associated with PsA onset. Further research is necessary, but these findings could potentially guide innovative approaches using anti-angiogenic therapies to prevent PsA in individuals with PsO.

Alcohol

The potential association between alcohol consumption and PsA development has been explored in four cohort studies (PsO=64,426, incident PsA=2,948) (11, 16, 20, 33), and two case-control studies (PsO 59, PsA=694) (17, 19).

Of all these studies, only Green *et al*. (33) observed a heightened risk of PsA in PsO patients who were categorised as moderate drinkers (intake of 0.1–3 units per day). Their findings suggested an OR of 1.57 (95% CI 1.16–2.11) when compared to non-drinkers. Interestingly, upon examination of heavy drinkers (those consuming over 3 units per day) or former drinkers relative to non-drinkers, no statistically significant difference in risk was discerned. The remaining studies did not find an association between alcohol consumption and the likelihood of PsA onset.

It is noteworthy that there existed considerable heterogeneity across the studies regarding the criteria set for alcohol consumption. Definitions ranged from "any level of consumption" to "social drinking" (defined as one or more alcoholic beverages per week), to daily and weekly intake, and further distinctions were made between heavy and moderate drinking.

Comment: The reviewed studies showed no association between alcohol consumption and PsA development in PsO patients. More research is needed to address this matter.

Psoriasis onset and duration

The influence of the age at onset and the duration of PsO on the progression to PsA has been examined in two cohort studies (PsO=10,475, incident PsA=1,320) (12, 38).

Gisondi *et al*. (12) identified a notable association between a PsO duration exceeding 10 years and an increased risk of PsA development, with an HR of 2.02 (95% CI 1.09–3.76). Egeberg *et al*. (38) explored both the duration of PsO and age at PsO onset in relation to the risk of developing PsA. They found that the incidence and prevalence of PsA were correlated with the amount of time passed since PsO diagnosis, but this was significant only in cases of severe PsO (p=0.0002), with no marked trend observed in mild PsO cases (p=0.4936). However, when considering the time passed since the first cutaneous symptoms, a significant trend was evident across all classes of severities (p<0.0001).

In terms of the onset age of PsO, Egeberg *et al*. observed that patients with early onset of cutaneous symptoms (before age 30 years) were more likely to develop PsA compared to those with late onset (after age 50 years), as indicated by an OR of 1.22 (95% CI 1.03–1.45). Notably, this increased risk was significant exclusively in patients with severe PsO who had an early onset, evidenced by an OR of 1.28 (95% CI 1.02–1.61). However, the trend reverses when considering the age of PsO diagnosis; thus, early diagnosis was associated with a lower risk of developing PsA (OR 0.52; 95% CI 0.39–0.69). This association was significantly pronounced only in cases of mild PsO, with an OR of 0.38 (95% CI 0.25–0.57).

Comment: Recent studies suggest that the duration of psoriasis, particularly when exceeding 10 years, appears to be a significant risk factor for the development of PsA. However, the evidence relating to the age of psoriasis onset as a risk factor remains less definitive.

Type and localisation of psoriasis

The relationship between the type of PsO or its localisation on the human body surface and the risk of developing PsA has been explored in four cohort studies (PsO = 3,010, incident PsA = 258) (8, 12, 16, 22). Types of PsO considered in these studies included plaque, guttate, pustular, and erythrodermic psoriasis, while sites of involvement encompassed scalp, folds, palmoplantar, extremities, among others.

Wilson *et al*. (8) identified a statistically significant association between PsA development and PsO affecting the scalp and intergluteal area (a localisation of PsO affecting the folds), with HRs of 3.75 (95% CI 2.09–6.71) and 1.95 (95% CI 1.07–3.56), respectively. However, they did not find a similar association for PsO involving the extremities, trunk, face, axilla, or other types of PsO (plaque, guttate and sebopsoriasis).

Belman *et al*. (22) reported that pustular PsO, both palmoplantar and generalised, as well as the Koebner phenomenon, were significant predictors of PsA development, with HRs of 3.32 (95% CI 1.91–5.77) and 1.90 (95% CI 1.31–2.76), respectively. However, for other PsO types like Guttate, Erythrodermic, and Inverse psoriasis, no increased risk for PsA was noted.

Conversely, Balato *et al*. (16) did not observe any association between plaque and palmoplantar pustulosis PsO and the risk of PsA. Similarly, when examining specific sites of PsO such as folds, scalp, arms, legs, trunk, head, hands, and feet, both Balato *et al*. and Gisondi *et al*. (12) found no significant association with PsA development.

Comment: The reviewed studies did not select the type (*e.g*. plaque, guttate) and the site of PsO (*e.g*. scalp and inverse psoriasis) as risk factors for PsA development.

Psoriasis severity

The predictive value of PsO severity in the development of PsA has been investigated in eight cohort studies (PsO=95,339, incident PsA=3,269) (8, 11, 12, 14, 15, 20, 22, 38) and two case-control studies (PsO=521, PsA=714) (17, 19). These studies employed varied methods to define and measure PsO severity. Some distinguished mild from moderate-severe PsO based on the type of treatment (systemic or topical), others quantified the number of affected areas, while the majority utilised scoring systems like the Psoriasis Area Severity Index (PASI) and body surface area (BSA).

Lewinson *et al*. (11) and Egeberg *et al*. (38) used systemic therapy as an indicator of severity, but only Lewinson *et al*. established a significant association with an HR of 5.02 (95% CI 4.18–6.04). Wilson *et al*. (8) assessed severity by counting the number of affected sites, finding that while two sites did not indicate an increased risk, three or more sites showed a notable risk with an HR of 2.24 (95% CI 1.23–4.08). Conversely, Thumboo *et al*. (19), categorising skin severity as limited (≤2 sites) or generalised (>2 sites), did not find an increased risk for PsA development.

The use of PASI or BSA generally indicated a clear correlation between severity and the risk of developing PsA. Belman *et al*. (22) demonstrated that patient self-assessment of the severity of their typical untreated lesions (by BSA) correlated more closely with the risk of PsA development than investigator reports at enrolment. Eder *et al*. (20) established that only severe PsO, characterised by a PASI score greater than 20 *versus* mild PsO, was associated with a significantly higher risk of developing PsA with RR 5.39 (95% CI 1.64–17.7). This association was not observed when comparing moderate to mild PsO. However, Ogdie *et al*. (15) also highlighted an increased risk in moderate PsO cases (HR 1.44, 95% CI 1.02–2.03), employing BSA categories (<3%, 3–10%, and >10%, representing mild, moderate, and severe psoriasis, respectively).

In a study conducted by Bandinelli *et al*. (39), ultrasonographic examination of over a thousand joints in early PsA patients revealed that wrist and hand abnormalities, including active synovitis and erosions, showed no correlation with the severity of psoriasis as indicated by the PASI score. Interestingly, these ultrasonographic abnormalities were significantly associated with systemic inflammation markers, such as elevated CRP and ESR.

Comment: The data concerning the role of PsO severity as a risk factor for the development of PsA are undoubtedly limited by the heterogeneity of the skin

assessment. When expressed as units, the PASI score showed a weak predictive value for the development of PsA, instead, a clear predictive value emerged when the classes of severity were compared. The severity of PsO is included among the four major long term risk factors for PsA development from the EULAR Point to consider on pre-PsA (6). From the CORRONA PsA registry data, it should be noted that moderate-severe skin involvement (>3% BSA PsO) is present in a minority of patients with PsA seen in the rheumatology setting (40).

This should not cast doubt on the importance of PsO severity as a predictor. Rather, it should be clarified that the data presented here likely stem mainly from rheumatological cohorts. There is a need for validation of current predictive studies, by including patients with minimal PsO or those in hidden areas typically handled by general practitioners (41).

Nail involvement

The relationship between psoriatic nail involvement and the development of PsA has been explored in six cohort studies (PsO=5,277, incident PsA=583) (8, 12-14, 20, 22) and one nested case-control study (PsO=120, PsA=60) (19). These studies primarily focused on nail dystrophy manifestations such as onycholysis, pitting, or hyperkeratosis. A majority of the studies established a clear link between nail involvement and an increased risk of developing PsA. Specifically, Wilson *et al*. (8) reported that nail dystrophy was associated with a HR of 2.24 (95% CI 1.26–3.98). In contrast, Eder *et al*. (20) found no overall association between "any psoriatic nail lesions" and PsA (RR 1.36; 95% CI 0.76–2.45), although nail pitting alone was associated with an increased risk (RR 2.21; 95% CI 1.24–3.92).

Furthermore, Belman *et al*. (22) demonstrated that both the history of nail involvement as recorded by investigators at enrolment and patient self-assessments were linked to a higher risk of PsA (HR 2.38 [95% CI 1.64–3.45] and HR 2.04 [95% CI 1.40–2.95], respectively). However, other studies, including those by Thumboo *et al*. (19) and Eder *et al*. (14), did not identify a significant association between nail involvement and the development of PsA.

Comment: Anatomically, a strong connection exists between PsA and nail inflammation, underlining the importance of psoriatic nail involvement as a potential predictor of PsA.

Studies using MRI and histology have demonstrated that the extensor tendon traversing the Distal Interphalangeal joint (DIP) becomes fused with the nail root and matrix. This fusion involves the envelopment of the nail root by tendon fibres (42).

Furthermore, the fibres of the extensor tendon divide and merge with the periosteum surrounding the terminal phalanx, establishing an indirect anchoring of the enthesis to the bone of the phalanx, which is linked to the nail bed. Additionally, the nail plate combines with the collateral ligaments of the DIP enthesis, thus reinforcing the sides of the nail. Despite the nail's developmental origin from the skin and its common perception as a specialised modification of skin, it is functionally integrated into the musculoskeletal system.

Due to this intricate interconnection between the enthesis and the nail, inflammation of the extensor tendon enthesis often affects the nail bed. This prompts a discussion about the possible correlation between the enthesis and nail pathology in PsA.

Focusing on the elementary lesions that characterise nail involvement in PsO, nail pitting is undoubtedly the most evident lesion selected as a possible risk factor of PsA. However, most studies only include whether nail involvement was present, without reporting the severity of nail involvement or the specific lesions that characterised it.

Trauma

The potential link between physical trauma and the subsequent development of PsA has been the subject of investigation in two cohort studies (PsO=71,110, incident PsA=1,061) (20, 43) and two case-control studies (PsO=279, PsA=219) (19, 25).

Thorarensen *et al*. (43) reported that PsO patients who had experienced physical trauma exhibited an increased risk of developing PsA, with a HR of 1.32 (95% CI 1.13–1.54). When analysing specific types and sites of trauma, bone and joint trauma showed a notably higher association, with HRs of 1.46 (95% CI 1.04–2.04) and 1.50 (95% CI 1.19–1.90), respectively. However, trauma to nerves and skin did not demonstrate a statistically significant increase in PsA risk compared to controls.

In a different approach, Eder *et al*. (25) stratified trauma types into categories: road traffic accidents requiring medical treatment, fractures, and "other injuries". Their findings indicated no significant association between road traffic accidents or fractures and the risk of PsA development. Nevertheless, an increased risk was observed in relation to "other injuries", presenting an OR of 2.1 (95% CI 1.11–4.01) for the development of PsA.

Conversely, other studies in this area did not find a significant relationship between trauma, inclusive of its subtypes, and the risk of PsA.

Comment: Experiments involving the unloading of entheseal areas in mice, prone to develop SpA, have demonstrated the need for mechanical activation in the development of arthritis, particularly through the production of cytokines by stromal cells (44). Understanding how mechanical stress triggers the immune system at the enthesis is an active area of investigation. It appears that factors influencing entheseal loading and age-related microdamage in typical conditions could significantly influence the development of SpA. From a clinical perspective, recognising the role of mechanical stress in PsA offers a mechanistic connection to skin and nail Koebner responses. Moreover, this concept could be corroborated by epidemiological insights into why PsA tends to manifest in individuals with higher BMI, particularly during their fourth and fifth decades of life. However, the literature data are inconclusive regarding the role of trauma (namely, the type of trauma and the effect of cumulative injuries/microtraumas) as a predictor of PsA. Yet among rheumatologists, a connection between trauma/repetitive activity type and the onset of PsA, as well as the potential

clinical phenotype at onset, is clear from clinical experience.

Infection

The relationship between prior infections and the onset of PsA has been evaluated in two cohort studies (PsO=1,091, PsA=179) (20, 22) and two case-control studies (PsO=279, PsA=219) (19, 25). These studies employed varying definitions of 'infection', encompassing criteria such as any infection within the previous year, infections requiring antibiotic therapy, a history of infectious diarrhoea, HIV, and throat Streptococcal infection.

The majority of these studies did not find a significant association between these definitions of infection and an increased risk of developing PsA. However, Eder *et al*. (25) observed an association in cases of infections requiring antibiotics, reporting an OR of 1.7 (95% CI 1.00–2.77).

Comment: Although the published evidence is limited, it is common clinical experience that infections can be possible triggers of PsA. Even if not associated with potential subclinical PsA, they can be considered short-term risk factors for PsA in predisposed individuals, as they may promote an acute onset of joint disease in a manner similar to what we observe in reactive arthritis.

Biomarkers

In a case-control study that involved psoriatic patients who later developed PsA (termed 'converters') and those who did not (termed 'non-converters'), the potential of chemokine (C-X-C motif) ligand 10 (CXCL10) serum levels as a predictor for PsA development was explored (PsO non-converters = 52, PsO converters = 29) (45).

Both groups, converters and nonconverters, were matched based on the duration of their PsO and the interval between their follow-up visits. Using linear mixed-effects models, the study aimed to compare CXCL10 levels between these two groups over time.

The findings revealed that among converters, there was a marked decrease in CXCL10 levels both before (slope –53.87, 95% CI 83.74–23.99; $p<0.001$) and after (slope –39.18, 95% CI 58.58 t–19.77; $p<0.001$) the onset of PsA. In contrast, nonconverters showed no significant shift in CXCL10 levels either before or after what is termed 'pseudoconversion' – the first visit post the diagnosis of PsA in converters. Notably, among the converters, there was no statistically significant difference in CXCL10 levels when comparing the post and pre-conversion periods.

Comment: The study on biomarkers like CXCL10 in PsA highlights their potential in disease prediction and treatment. However, despite these promising developments, the practical application of such biomarkers in daily clinical practice is still some distance away, requiring further research and validation.

Short-term risk factors

Arthralgia and other preclinical PsA symptoms

Four cohort studies (PsO=667, incident PsA=99), investigated the influence of musculoskeletal symptoms, notably arthralgia, on PsA progression (14, 18, 46, 47). The majority of these studies reported an elevated risk of PsA onset in PsO patients presenting with arthralgia or similar symptoms.

For instance, Zabotti *et al*. (18) compared pain symptoms in PsO patients with and without subsequent PsA progression. They employed measures such as the visual analogue scale (VAS) for pain, Health Assessment Questionnaires (HAQ), and tender joint count (TJC). Patients progressing to PsA exhibited significantly higher VAS pain scores (5.92 *vs*. 2.63, $p<0.01$), HAQ scores (0.44 *vs*. 0.26, $p=0.03$), and TJC (6.8 *vs*. 1.74, $p=0.03$) compared to those who remained PsA-free. Further, Faustini *et al*. (46), in a comparison between PsO subgroups, those with MRI-documented synovitis and positive TJC had a 55.5% risk of PsA development, in contrast to the 15.3% risk observed in those without any MRI findings and TJC=0.

Eder *et al*. (14) showed that the presence of arthralgia in women (HR 2.59, $p=0.02$), heel pain (HR 4.18, $p=0.02$), elevated fatigue scores (HR 2.36, $p=0.007$), and pronounced stiffness scores (HR 2.03, $p=0.045$) were significant predictors of subsequent PsA onset. When these factors were assessed as time-dependent predictors, an even stronger association with PsA development was evident. Moreover, they corroborated their hypothesis about the association between the magnitude of change from baseline in fatigue, pain, stiffness, psychological distress, and physical function and the subsequent diagnosis of PsA.

Conversely, Simon *et al*. (47) did not identify a statistically significant HR linking arthralgia to PsA (HR 1.84, $p=0.344$). However, their Kaplan-Meier plots of PsA-free survival across various groups revealed that individuals without structural entheseal lesions and arthralgia had a lesser propensity for PsA progression compared to those with arthralgia (3.4% *vs*. 15.2%, respectively).

Comment: Arthralgia of otherwise unexplained origin should be regarded as the primary symptom that precedes the onset of clinical PsA, representing the major risk factor for the short-term development of PsA (6). The incidence rate of PsA development in people with PsO with arthralgia is significantly higher compared with PsO without such symptom (ranging from 11 to 34 per 100 patient-years). However, any precise definition of arthralgia specifically predictive of progression to PsA is still lacking at present. The characterisation of arthralgia in terms of type of pain (*e.g*. non-specific musculoskeletal pain vs inflammatory pain), sites involved (*e.g*. knee, Achilles tendon) and duration of symptoms will certainly be a matter of future studies focusing on the field of transition from PsO to PsA.

Imaging

Four cohort studies (PsO=366, incident PsA=51) sought to determine if subclinical changes identified through different imaging modalities could predict PsA development (18, 46-48). Across all modalities, whether MRI, US, or CT, the studies consistently indicated that inflammatory changes visible on imaging could foreshadow the onset of PsA. However, it is noteworthy that most studies also considered the presence of arthralgia in tandem with these radiological findings.

Faustini *et al*. (46) reported that when patients exhibited subclinical synovi-

Table I. Overview of risk factors for PsA in psoriasis patients.

Risk factors	
Age	The relationship between age and the risk of developing PsA has shown inconsistent results across studies. Gisondi *et al*. (12) and Wilson *et al*. (8) indicated a higher risk of PsA development with increasing age, while other observed a decreased risk in individuals older than 45 years (11).
Gender	Most studies suggest that male PsO patients have a higher risk of developing PsA (13). Conversely, Lewinson *et al*. (11) present findings that indicate a higher risk in female patients.
Family history	International consensus statements on PsA emphasise the importance of family history, particularly having a first-degree family member with PsA, as a significant risk factor for developing PsA (6, 21). However, empirical studies present a mixed picture. Gisondi *et al*. (12) identified a significant association in a univariate Cox regression model, however, this association, was not maintained in a multivariate model. Eder *et al*. (20) also suggested a potential elevated risk linked to a family history of psoriasis, PsA, or ankylosing spondylitis, but these results did not achieve statistical significance.
Psoriatic disease related conditions	Eder *et al*. (20) found a significant association between uveitis and an increased risk of PsA development. Similarly, Belman *et al*. (22) identified a higher likelihood of PsA in PsO patients with IBD. These associations suggest that the inflammatory involvement of extra-cutaneous domains, such as in uveitis and IBD, should be recognised as indicators of systemic disease.
Depression	Multiple studies have identified a significant relationship between major depressive disorder and the development of PsA (11, 15, 22). The prevailing hypothesis is that depression could contribute to systemic inflammation and correlated with reduced therapeutic response with higher discontinuation rates of biologic treatments.
Obesity	Several studies have consistently demonstrated a strong association between higher BMI and an increased risk of developing PsA. Li *et al*. (32) provided compelling evidence of this relationship, showing that individuals within higher BMI categories (25-29.9, 30-34.9, and >35) face a progressively greater risk of PsA development. Among various modifiable risk factors, obesity stands out as one of the most significant for PsA development, indicating a clear potential for intervention strategies.
Smoking	The relationship between smoking and the risk of developing PsA presents a unique paradox. Li *et al*. (36) reported that both the intensity and duration of smoking increase the risk of PsA development. However, most studies have intriguingly indicated that smoking may act as a protective factor against PsA (11, 17). Nguyen *et al*. (35) further proposed that this protective effect might be specific to individuals with psoriasis, contrasting with the increased risk in the general population. This phenomenon has led to the hypothesis that psoriasis could serve as an intermediary factor, potentially reversing the typical association between smoking and PsA.
Alcohol	Most studies have not established a significant association between alcohol consumption and PsA onset. However, Green *et al*. (33)observed an increased risk of PsA among moderate drinkers, defined as those with an alcohol intake of 0.1-3 units per day.
Psoriasis onset and duration	Gisondi *et al*. (12) highlighted an increased risk of PsA with psoriasis duration exceeding 10 years. Egeberg *et al*. (38) reported that PsA incidence and prevalence were correlated with the time since psoriasis diagnosis, particularly in severe cases, but a significant trend was observed across all severities when considering the time since the first cutaneous symptoms. Moreover, they noted a higher likelihood of PsA in patients with early onset of cutaneous symptoms (before age 30 years) in severe PsO cases, while early diagnosis in mild psoriasis was associated with a lower PsA risk.
Type and site of psoriasis	Wilson *et al*. (8) found a significant association between the development of PsA and psoriasis involving the scalp and intergluteal areas. Additionally, Belman *et al*. (22) observed that pustular psoriasis, encompassing both palmoplantar and generalised types, along with the Koebner phenomenon, were significant predictors of PsA. However, they did not note an increased PsA risk with other psoriasis types such as guttate, erythrodermic, and inverse psoriasis.
Psoriasis severity	Various studies have explored the severity of psoriasis as a risk factor for the development of PsA, utilising different methods to categorise severity, including the need for systemic therapy (11), Body Surface Area (BSA) assessment (15, 22), and the Psoriasis Area Severity Index (PASI) score (20). These investigations consistently found a clear association between greater severity of psoriasis and an increased risk for PsA development.
Nail involvement	Several studies have drawn attention to the association between nail involvement and PsA development. Wilson *et al*. (8) observed that nail dystrophy was linked to an increased risk of developing PsA. Eder *et al*. (20) while not finding a significant association with "any psoriatic nail lesions" in general, noted that nail pitting specifically was associated with PsA.
Trauma	The association between physical trauma and PsA development presents inconclusive results. Thorarensen *et al*. (43) reported an increased risk of PsA in psoriasis patients who experienced trauma, particularly with bone and joint trauma. In contrast, they found no significant association between PsA and trauma to nerves or skin. Eder et al. (25) did not observe a link between PsA development and road traffic accidents or fractures. However, they identified an increased risk of PsA associated with "other injuries."
Infection	While the majority of studies did not establish a significant association between infection and an increased risk of developing PsA, Eder *et al*. (25) identified that cases of infections necessitating antibiotic treatment were linked with an elevated risk of PsA development.
Biomarkers	A case-control study focusing on biomarkers in PsO patients who developed PsA compared to those who did not, revealed significant findings regarding CXCL10 levels. The study showed that serum levels of CXCL10 were decreased in PsO patients both before and after the onset of PsA (45).
Arthralgia and other preclinical PsA symptoms	Several studies have established a clear association between arthralgia, other preclinical symptoms, and the development of PsA. Zabotti *et al*. (18) conducted a comparative analysis of pain symptoms in psoriasis patients who either progressed to PsA or did not. They observed that those who developed PsA had significantly higher scores in various pain assessments, including the visual analogue scale (VAS) for pain, Health Assessment Questionnaires (HAQ), and tender joint count (TJC). Similarly, Eder *et al*. (14) identified the presence of arthralgia, especially in women, heel pain, high fatigue scores, and increased stiffness as significant predictors for the onset of PsA.
Imaging	Studies utilising various imaging modalities, including MRI, US, and CT, have consistently shown that visible inflammatory changes can predict the development of PsA. Faustini *et al*. (46) reported that psoriasis patients with MRI-documented synovitis and symptoms of arthralgia had a significantly higher risk (55.5%) of developing PsA compared to those without MRI findings or arthralgia (15.3%). Zabotti *et al*. (18) observed that baseline US markers of enthesitis were associated with the development of clinical PsA, whereas tenosynovitis was not. Simon *et al*. (47) employed high-resolution peripheral quantitative CT to demonstrate that the presence of structural entheseal lesions significantly increased the risk of PsA in psoriasis patients.

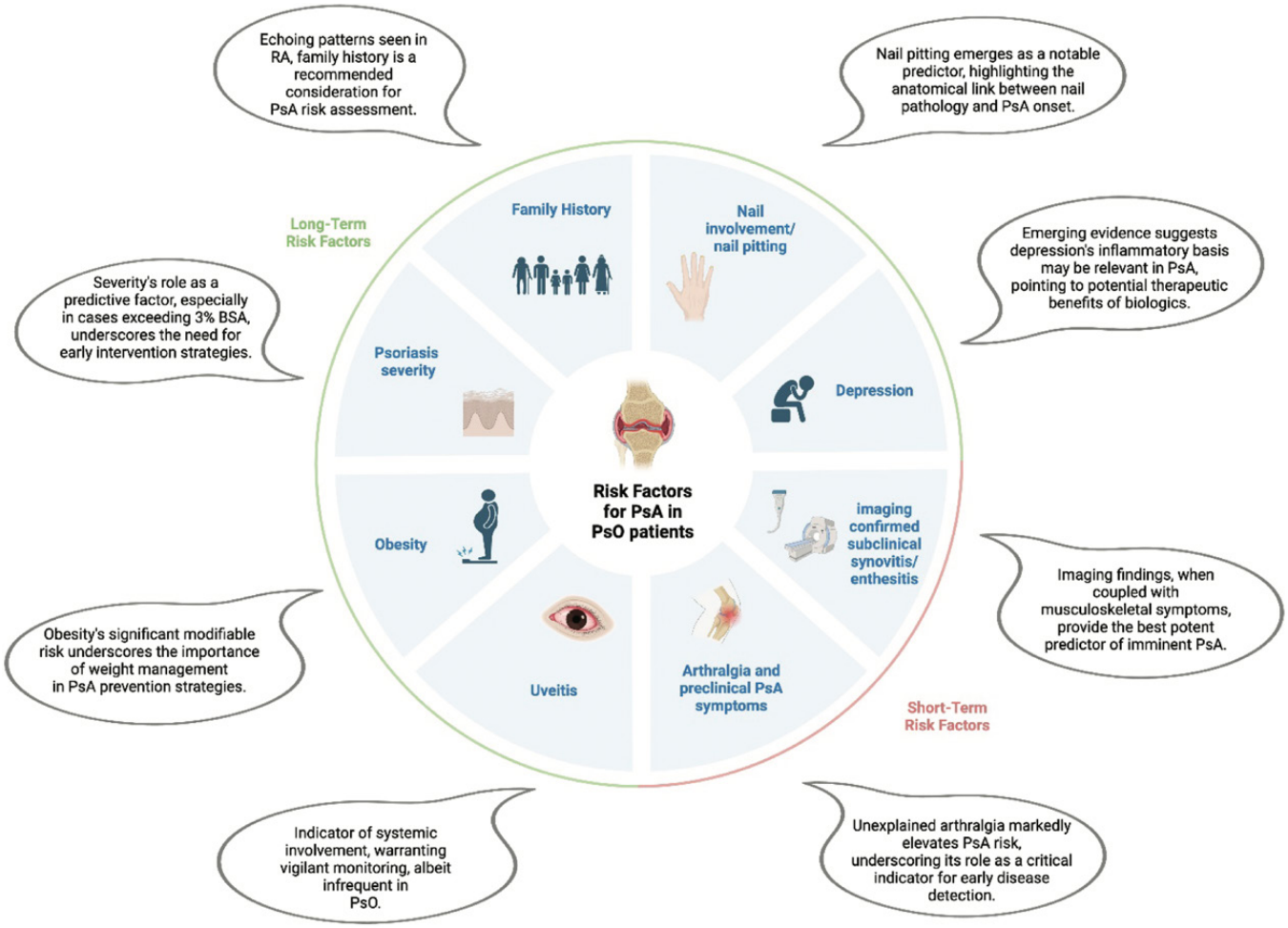

Fig. 1. Risk factors for transition from psoriasis to psoriatic arthritis with authorial insights.

tis in MRI combined with arthralgia symptoms, the risk of developing PsA surged to 60%. Conversely, those without MRI abnormalities or arthralgia symptoms had a lower 15% risk. Interestingly, when MRI synovitis was evaluated in isolation, it didn't display any significant difference between the groups (p=0.32). Elnady *et al*. (48) employed musculoskeletal ultrasound (MSUS), utilising both grayscale ultrasound (GSUS) and power Doppler ultrasound (PDUS). Their research emphasised that signs of subclinical enthesitis and synovitis could predict the emergence of PsA (p<0.001).

Zabotti *et al*. (18) found in their study that baseline US markers of enthesitis were associated with clinical PsA development in longitudinal analysis (p=0.03). Interestingly, tenosynovitis, on the other hand, failed to be a reliable predictor.

Lastly, Simon *et al*. (47) made use of high-resolution peripheral quantitative computed tomography and identified that the presence of structural entheseal lesions significantly increased the risk of PsA in PsO patients (HR 5.10, 95% CI 1.53–16.99). They also highlighted that a lower cortical volumetric bone mineral density (vBMD) at entheseal segments influenced PsA development risk. A 1-SD increase in vBMD was linked with around a 30% reduction in the likelihood of PsA onset.

Comment: PsO patients with imaging-detected MSK inflammation (*e.g*. synovitis, enthesitis) or imaging-detected structural damage (*e.g*. erosions) were almost four times more likely to develop PsA (10). Interestingly, two studies by Bandinelli *et al*. (39, 49) have collectively demonstrated that US could reveal abnormalities such as thickness, bursitis, enthesophytes, and erosions, independent of the clinical examination and symptoms. Remarkably, US abnormalities were detected even in asymptomatic patients, underscoring the sensitivity of the technique to early disease processes not yet evident through clinical assessment or symptom reporting.

Nevertheless, as recommended in the recently published EULAR points to consider, imaging abnormalities should be carefully regarded when in the absence of musculoskeletal symptoms. This is in order to avoid the risk of inappropriate treatment since the detection of subclinical synovio-entheseal inflammation in people with PsO is a common finding, even in patients without musculoskeletal complaints (6). We suggest that the combination of musculoskeletal symptoms and imaging abnormalities characterise the subclinical PsA spectrum and this combination should be considered as the best short term predictor of PsA development in people with PsO.

A summarised view of the risk factors for PsA in Psoriasis patients identified in this review is provided in Table I.

Conclusion

This review aimed to elucidate the current literature on risk factors for PsA development in patients with PsO, promoting studies on the transition field from PsO to PsA and emphasising the importance of early identification and potential prevention strategies.

While several meta-analyses and systematic reviews have delineated the progression from PsO to PsA, this review augments these foundational works by embracing a wider array of studies, including those that do not meet the stringent inclusion criteria of meta-analyses. In doing so, it delves into the pathophysiology behind these risk factors and provides a comprehensive overview that integrates both established knowledge and emerging research findings. Furthermore, our analysis extends into domains less commonly addressed in previous syntheses, exploring the impact of age, gender, duration of psoriasis, infections, and psoriatic disease-related conditions on the development of PsA.

Importantly, this review uniquely integrates the authors' expert opinions, which are grounded in extensive clinical practice and a comprehensive examination of the literature. This approach aims to equip physicians with a more nuanced understanding, enabling them to identify and prioritise risk factors through a synthesis of empirical evidence and real-world clinical judgment. We explored a variety of risk factors, from modifiable elements like high BMI, which presents an opportunity for preventive intervention, to more intrinsic factors such as prolonged PsO duration, severe disease manifestation, and nail involvement (Fig. 1). These insights are crucial for identifying patients who would more likely benefit from more vigilant follow-up and management.

Depression emerged as a notable risk factor, potentially facilitating the development of PsA and posing challenges in patient management due to the possibility of lower treatment compliance. We also discussed promising developments such as biomarkers and imaging techniques. The integration of these advanced tools into patient management could significantly aid in the early detection of PsA.

However, it is important to acknowledge the heterogeneity present in the numerous studies examining these risk factors. Such variability often poses challenges in drawing definitive conclusions about the impact of candidate risk factors and underscores the need for continued research in this field.

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