Biomarkers in psoriatic arthritis: A meta-analysis and systematic review

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Introduction: Psoriatic arthritis (PsA) is a chronic inflammatory disease that frequently develops in patients with psoriasis (PsO) but can also occur spontaneously. As a result, PsA diagnosis and treatment is commonly delayed, or even missed outright due to the manifold of clinical presentations that patients often experience. This inevitably results in progressive articular damage to axial and peripheral joints and entheses. As such, patients with PsA frequently experience reduced expectancy and quality of life due to disability. More recently, research has aimed to improve PsA diagnosis and prognosis by identifying novel disease biomarkers.

Methods: Here, we conducted a systematic review of the published literature on candidate biomarkers for PsA diagnosis and prognosis in MEDLINE(Pubmed), EMBase and the Cochrane library with the goal to identify clinically applicable PsA biomarkers. Meta-analyses were performed when a diagnostic bone and cartilage turnover biomarker was reported in 2 or more different cohorts of PsA and control.

Results: We identified 1444 publications and 124 studies met eligibility criteria. We highlighted bone and cartilage turnover biomarkers, genetic markers, and autoantibodies used for diagnostic purposes of PsA, as well as acute phase reactant markers and bone and cartilage turnover biomarkers for activity or prognostic severity purposes. Serum cartilage oligomeric metalloproteinase levels were significantly increased in the PsA sera compared to Healthy Control (HC) with a standardized mean difference (SMD) of 2.305 (95%CI 0.795-3.816, p=0.003) and compared to osteoarthritis (OA) with a SMD of 0.783 (95%CI 0.015-1.551, p=0.046). The pooled serum MMP-3 levels were significantly higher in PsA patients than in PsO patients with a SMD of 0.419 (95%CI 0.119-0.719, p=0.006), but no significant difference was highlighted when PsA were compared to HC. While we did not identify any new genetic biomarkers that would be useful in the diagnosis of PsA, recent data with autoantibodies appear to be promising in diagnosis, but no replication studies have been published.

Conclusion: In summary, no specific diagnostic biomarkers for PsA were identified and further studies are needed to assess the performance of potential biomarkers that can distinguish PsA from OA and other chronic inflammatory diseases.

KEYWORDS
psoriatic arthritis, psoriatic biomarker, psoriasis, arthritis, meta-analysis
1 Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory disease that develops in up to 30% of patients with psoriasis (PsO), and can affect up to 0.7% of the general population (1, 2). PsA is characterized as affecting axial and peripheral joints and entheses, which can present clinically with diverse symptoms, often resulting in delayed diagnosis and treatment. PsA can lead to progressive articular damage, thus can be a source of impaired function, permanent disability, quality of life, and an increase in mortality (3, 4).

Through the Biomarkers Project, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) places critical emphasis on the research of biomarkers in its development strategy (5). A biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of pharmacologic responses, or normal or pathogenic biological processes, for a therapeutic intervention (6). Identification of specific biomarkers would improve early diagnosis and management of PsA in patients with joint pain and/or skin psoriasis. Although PsA can develop in up to 30% of PsO patients, the prevalence of undiagnosed PsA in patients with psoriasis is still estimated to be 10-15% (4). Although classification criteria are sometimes used by default, there are currently no diagnostic criteria or specific biomarkers available for PsA (4). Therefore, we sought to identify biomarkers for determining diagnosis and prognosis of PsA by conducting a systematic review and pairwise meta-analysis.

2 Methods

To conduct this research, we followed the guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for reporting on studies evaluating healthcare interventions (7). PRISMA Checklist is provided in supplementary file 1. Ethics approval was not required under local legislation for this study.

2.1 Study selection

A systematic search of English-language literature was conducted in MEDLINE (via PubMed), EMBase, and the Cochrane Library dating from inception to March 1, 2022. We designed the search algorithm according to the Patient-Intervention-Comparison-Outcome-Time (PICOT) format. Search terms corresponded to MeSH or Emtree terms for “psoriatic arthritis” and “biomarkers” or “pharmacological biomarkers”. A manual search was also performed.

After searching with the pre-determined PICOT algorithm, study eligibility was ascertained after reading the title, keywords, and abstract. Once the articles of interest were identified, the full text was read to evaluate it according to the exclusion criteria, and to subsequently extract the necessary data. Inclusion criteria required the following: study must be an observational or interventional clinical trial published in English before March 2022; include an assessment of biomarker(s) in serum (including genetic biomarkers), synovial fluid, urine, or feces as diagnostic or prognostic factors; cohort must include patients with PsA according to a rheumatologist diagnosis, Moll and Wright criteria, or Classification Criteria for Psoriatic Arthritis (CASPAR).

Exclusion criteria were applied in a sequential order, and included an editorial or congress abstract; duplicates (between electronic databases or journals); non-English language full text; non-human, non-PsA, or pediatric (<18 years old) populations; off-topic; not relevant for diagnosis and prognosis in PsA. We focused on prognostic factors of disease severity, regardless of treatment, and did not include prognostic factors of response to treatment, out of the scope.

Study results were highlighted in the main text if select biomarkers were mentioned in at least 2 publications. In addition, all included articles are presented in tabular form (Tables 1, 2).

2.2 Data extraction

All data was extracted into a standardized spreadsheet. For each article, we collected the data according to a pre-specified strategy. Collected information included the year of publication, name of the first author, geographical area, study design, population age and sex, disease duration, how the PsA population was determined (classification criteria used or therapist diagnosis), biomarkers investigated, primary study methodology, proportion of patients using corticosteroid and/or non-steroidal anti-inflammatory drugs (NSAIDs), proportions of patients using conventional disease modifying anti-rheumatic drugs (DMARDs) i.e., methotrexate, salazopyrine or leflunomide), and biological DMARDs. Study objectives (diagnosis or prognosis), primary outcomes, and control groups (i.e. cutaneous psoriasis, rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, undifferentiated arthritis, osteoarthritis or healthy control (HC)) were also recorded. For all extracted data, a central value (mean or median) and variability (standard deviation or interquartile range) was calculated. Study quality and risk of bias was assessed using the Newcastle Ottawa Scale for assessing the quality of non-randomized studies in meta-analysis (131).

2.3 Statistical analysis

Meta-analyses were performed when a diagnostic bone and cartilage turnover biomarker was reported in 2 or more different cohorts of PsA and control. Levels of biomarkers in
PsA and control populations, means differences (MD) and standard deviation (SD) were extracted. If necessary, we converted median and interquartile in MD and SD using previously published methods (132). To perform sensitivity analyses, we applied a random effects models using the “one-study-removed” method as soon as there were more than two publications. Difference effect sizes were ascertained with the standardized mean difference (SMD) and its 95% confidence intervals (CI). A positive SMD confirmed a higher biomarker level in PsA than the control population. Magnitude of SMD was characterized as small (< 0.40), moderate (0.41 to 0.69) or large (> 0.70) (133).

3 Results

We identified 1495 records extracted from the PubMed/MEDLINE (n=514), EMBASE (n=919), and Cochrane Library (n=62) databases. After a manual search, 4 additional publications were included.

After removal of 111 duplicates, 1388 articles were screened and 559 met inclusion criteria. Subsequently, 346 publications were excluded because they did not report specific diagnostic or prognostic data for the biomarkers. Ultimately, a total of 124 studies, published from 1993 to 2022, met the eligibility criteria and were included in the qualitative analysis (Figure 1).
Sixty-eight studies evaluated biomarkers for diagnostic purposes, 48 evaluated biomarkers for activity or prognostic severity purposes, and 8 publications studied both diagnostic and prognostic biomarkers (Tables 1, 2). An assessment of bias risk was performed for each study and is available in Tables 3, 4.

3.1 Diagnostic biomarkers

3.1.1 Bone and cartilage turnover biomarkers

Sixteen articles evaluated biomarkers associated with bone and cartilage turnover for their potential as PsA diagnostic biomarkers. All the studies assessing diagnostic biomarkers in our systematic review, including those assessing biomarkers panels, are listed in chronological order of publication in Table 1. For meta-analyses, we considered only clearly identified individual biomarkers, and not panels of biomarkers. The two mainly assessed biomarkers were Cartilage Oligometrix MetalloProteinase (COMP) and Matrix MetalloProteinase-3 (MMP3).

3.1.1.1 Cartilage oligometrix metalloproteinase (COMP)

Increases of serum COMP levels by one unit resulted in an increased PsO odds ratio (OR) of 1.001 (95% CI=1.000-1.002, p=0.04), but not for PsA (OR=1.00; 95% CI=0.999-1.002, p=0.47) when comparing PsA to both PsO and HC (10). More recently, a cross-sectional study including patients with PsA, osteoarthritis (OA) and HC demonstrated in its primary discovery phase that COMP levels were significantly higher in sera of the PsA population than that of the OA population (OR=1.24; 95% CI=1.06-1.46, p=0.0062) (15). In the validation phase, serum COMP levels were not significantly different between PsA and OA populations (217.3 ng/mL vs 210.3 ng/mL, respectively p=0.344) (15). The diagnostic value of COMP was assessed in two cross-sectional studies. In the first study, serum COMP levels were significantly higher in patients with PsA (2645.3 ± 489.5 ng/mL) than in the HC population (835.9 ± 434.6 ng/mL) and clearly distinguished the 2 populations (Area Under the Curve [AUC]=0.96, 95% CI Not Available [NA]) (17). The second study compared the biomarker in PsA, OA, and HC and reported significantly higher levels in the sera of PsA patients than in the other two populations (18). COMP levels were also reported to be significantly higher in PsA synovial fluid compared to rheumatoid arthritis (RA), even in the presence of joint destruction (8).

The four studies comparing serum COMP levels between PsA and HC were included in a meta-analysis (10, 15, 17, 18). COMP was significantly increased in the serum of the PsA population, and the effect size measured by SMD was 2.305 (95% CI=0.80-3.81, p=0.003; Figure 2). When COMP levels were compared between PsA and OA, the 3-study meta-analysis reported a significant SMD of 0.78 (95% CI=0.02-1.55, p=0.046) (15, 18).

Due to the heterogeneity of the results, sensitivity analyses were also performed. The results remained unchanged after each study was excluded serially. The difference in COMP levels between PsA and PsO was tested in only one study (10).

3.1.1.2 Matrix metalloproteinase-3 (MMP3)

The results are more discordant when considering serum levels of MMP3, also known as stromelysin-1. Five cross-sectional studies revealed that MMP3 levels were significantly higher in patients with PsA than in HC (12–14, 17, 18) or in patients with PsO (13). The accuracy of MMP3 to distinguish PsA from PsO (AUC=0.70, 95% CI=0.65-0.75) and PsA from HC (AUC=0.66, 95% CI=0.59-0.74) was moderate. Other studies did not report any difference in MMP3 levels between PsA and HC (16) or PsO (14). The latter study described an increased concentration of MMP3 in PsA sera compared to PsO, with a significant OR of 1.59 (95% CI=1.21-2.11); however, this disappeared after multivariate regression (14). In a recent study, serum MMP3 levels from PsA compared to PsO and HC were not significantly different. Only one study compared PsA and OA, and did not demonstrate any difference in serum levels of MMP3 (18).

In total, 6 studies compared serum MMP3 levels between PsA and HC (10, 13, 14, 16-18) and 4 studies compared levels between PsA and PsO (10, 13, 14, 16). The pooled results displayed a higher, but not significant, level of MMP3 in sera of PsA patients compared to HC (SMD=0.450, 95% CI=-0.080-0.981, p=0.096; Figure 3). MMP3 was significantly higher in PsA compared to PsO (SMD=0.419, 95% CI=0.119-0.719; p=0.006). Results were confirmed with sensitivity analyses. No significant SMD was found when pooled MMP3 levels of PsO and HC were compared (SMD=-0.118 [95% CI=-0.693-0.457], p=0.689).

3.1.1.3 Receptor activator of nuclear kappa-B ligand (RANK-L)

RANK-L was also assessed as a diagnostic biomarker in three studies. Two studies reported significantly higher serum RANK-L levels in PsA patients compared with HC (59, 134), whereas the remaining study observed the opposite (16). The same three studies also compared RANK-L levels between PsA and PsO, with little or no difference detected between the two populations. The only study reporting significantly higher levels in PsA patients concluded that RANK-L was inaccurate for differentiating PsA from PsO (AUC=0.66 [95% CI NA]) (59). In the meta-analysis of these three publications, comparison of RANKL levels between PsA and HC and between PsA and PsO (10, 16, 59), the SMDs were -0.106 (95% CI=-3.75-3.36, p=0.952) and 0.315 (95% CI=-0.391-
1.021, p=0.382), respectively (Figure 4). Results did not change upon performance of sensitivity analyses.

3.1.1.4 Osteoprotegerin (OPG)

OPG serum levels were significantly increased in a small PsA cohort (n=26 per group) compared with PsO and HC (10). However, levels were not different in a larger PsA cohort (n=200 per group) compared to PsO and HC (13), nor in another smaller PsA cohort (n=50) compared to PsO (n=50) and HC (n=20) (16). In our meta-analysis, we calculated an SMD of 0.405 (95%CI -0.962-1.773, p=0.562) when PsA was compared to HC, and an SMD of 0.644 (95%CI 0.036-1.252, p=0.038) when PsA was compared to PsO (Figure 4).

3.1.1.5 Dickkopf-1 (Dkk-1)

Dkk-1 serum levels were studied in two publications with opposing results (13, 16). After meta-analysis, SMD in Dkk-1 levels between PsA and HC was 3.22 (95% CI=-5.974-12.412, p=0.493; Figure 5). When patients with PsA were compared to patients with PsO, the SMD was 0.992 (95% CI=-0.89-2.87, p=0.301).

3.1.2 Genetic biomarkers

Human Leucocyte Antigen (HLA) was studied in 6 publications (19, 27–29, 35, 36). A family-based study reported an association between PsA and various HLA alleles: HLA-B*27, HLA-B*38, HLA-B*39, and HLA-C*12 (27). HLA-B*27 association with PsA was additionally described in a large cross-sectional study, while HLA-C*06 was found to be associated with skin damage and less prevalent musculoskeletal developmental phenotypes (28). Another study described an association between PsA and HLA-B*27, HLA haplotype C*06/B*57 and HLA-C*06/B*57 (29). Interestingly, HLA-B27 was not associated with PsA in the Jewish Israeli population (19), though HLA-A*01/A*01 and HLA-C*06/C*02 were risk alleles for PsA in the Chinese Han population (35).

Genetic polymorphisms were also explored in 9 different articles (20, 21, 24–26, 30, 31, 33, 41). Polymorphisms of the gene IL-13 were examined in two studies, which reported that rs1800925*C and rs20641*G were significantly associated with skin damage and less prevalent musculoskeletal developmental phenotypes (30). HLA-B27 was not associated with PsA in the Chinese Han population (35). Genetic polymorphisms were also explored in 9 different articles (20, 21, 24–26, 30, 31, 33, 41). Polymorphisms of the gene IL-13 were examined in two studies, which reported that rs1800925*C and rs20641*G were significantly associated with skin damage and less prevalent musculoskeletal developmental phenotypes (30). HLA-B27 was not associated with PsA in the Chinese Han population (35).

3.1.3 Autoantibodies

In our systematic literature review, autoantibodies were explored in 8 articles (43–50). They focused on different autoantibodies, preventing meta-analysis. Among these autoantibodies, those of interest are outlined below. It should be noted that none of these autoantibodies have been evaluated or validated in any additional PsA cohorts beyond those described here.

Anti-Cyclic citrullinated peptides (CCP) were present in some PsA patients (7.9%) (43). Anti-Mutated citrullinated vimentin (MCV) levels were significantly higher in PsA sera (24%) than PsO (8%) (45). The novel autoantibody named anti-PsA peptide was identified after screening of a random synthetic peptide library with pooled immunoglobulins derived from 30 patients with recent onset PsA. Anti-PsA shares a sequence homology with Nebulin Related Anchoring Protein (N-RAP) (46). A peptide corresponding to N-RAP sequence was synthesized and tested by ELISA. Anti-NRP autoantibodies were recognized by 83% of PsA sera, versus 7% of rheumatoid arthritis (RA) anti-CCP positive, 4% of RA anti-CCP negative, 3.3% of PsO, and none of other rheumatic diseases included in this study (46).

Anti-A Disintegrin and MetalloproteinaSe with ThromboSpondin motifs 5 (ADAMST5) and anti-Cathelicidin LL37 (LL37) IgG autoantibodies were assessed for differentiating PsA from PsO. The ROC analysis reported an AUC of 0.84 (95% CI=NA, p<0.01) for anti-ADAMST5 autoantibodies and 0.87 (95% CI=NA, p<0.01) for anti-LL37 autoantibodies (49). Expression of Carbamethylated anti-LL37 was significantly higher in PsA sera (median=0.66, IQR=0.439) than PsO (median=0.43, IQR=0.47, p=0.02) and HC (median=0.158, IQR=0.099, p=0.0001) (48). Finally, higher IgA anti-oxidized collagen type II (oxPTMCII) autoantibodies were detected in PsA (84%, n=33/39) and axial spondyloarthritis (SpA, 47%, n=79/165) sera compared to HC (0%, n=0/28) (50).

3.1.4 Other biomarkers

Two additional biomarkers unrelated to the above categories were also assessed in at least 2 publications.

3.1.4.1 C-X-C motif chemokine ligand 10 (CXCL10)

CXCL10 rates were overexpressed in synovial fluid of PsA versus gout or SpA, but rates were similar to those of RA (61). A prospective follow-up of patients with PsO reported both higher baseline serum CXCL10 levels in patients who subsequently developed PsA as compared with those who did not, and a significant decrease in CXCL10 levels from the year before to the year after PsA onset (70).

3.1.4.2 Calprotectin S100A8/S100A9

A serum calprotectin S100A8/S100A9 with a cut-off of 475 ng/mL was able to discriminate PsA from HC with a 93.3% specificity and 75.0% sensitivity (54). Serum calprotectin levels were increased in PsA but also in other inflammatory arthritis (RA, axial SpA) compared to controls (i.e., OA, fibromyalgia, and undifferentiated arthralgia), with good accuracy for distinguishing inflammatory arthritis from controls (AUC=0.964, 95% CI=NA) (65). Calprotectin levels in each subpopulation were not analysed for a meta-analysis.
| References   | Publication Year | Study Design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|-------------|------------------|--------------|---------|-------------------------|------------|-------------|---------|
| **Bone and cartilage turnover biomarkers** |                 |              |         |                         |            |             |         |
| Mánsson (8) | 2001             | Cross-sectional | 18      | Moll & Wright            | COMP, BSP; Aggrecan | Comparison of COMP, BSP and Aggrecan level by ELISA method in the synovial fluid from 18 PsA and 43 RA. | Increased levels of COMP in PsA synovial fluid compared to RA population. |
| Farouk (9)  | 2010             | Cross-sectional | 30      | CASPAR                  | COMP       | Comparison of COMP level using ELISA with US on 30 PsA and 30 PsO | Moderate diagnosis accuracy of COMP to distinguish PsA of PsO with an AUC of 0.56. |
| Chandran (10)| 2010             | Cross-sectional | 26      | CASPAR                  | hsCRP, IL-12; p40IL12; IL-17; RANK-L; OPG; TNFSF14; MMP3; C2C; C1-2C; CPII; COMP | Comparison between 26 PsA, 26 PsO and 26 HC of several biomarker levels using ELISA methods. | Using of biomarkers panel consisting of hsCRP, OPG, TNFSF14 and CPII:C2C ratio, PsA can be distinguished from PsO with high accuracy (AUC: 0.90). |
| Cretu (11)  | 2014             | Cross-sectional | 10      | CASPAR                  | Protein expression of synovial fluid | Liquid phase chromatography with mass-spectrometry of 10 PsA and 10 OA. | CRP, MMP-3, S100A9, EPO, M2BP, DEFA1, H4, H2AFX, ORM1, CD5L, PFN1 and C4BP were overexpressed in PsA synovial tissues. |
| Dolcino (12)| 2015             | Cross-sectional | 60      | CASPAR                  | Osteopontine; osteoactivin; fibronectin1; MMP3; CathepsinZ; IL-17 | Serum analysis of 60 PsA, 60 HC, 60 RA and 60 SpA after evaluation of genic expression in PBMC from 10 PsA and 10 HC. | Osteoactivin was significantly higher in PsA sera than in RA, SpA and HC sera, with 100% accuracy between PsA and HC. |
| Jadon (13)  | 2017             | Cross-sectional | 200     | CASPAR                  | OPG, MMP3; Dkk-1; M-CSF | ELISA determination of Dkk-1, MMP3, M-CSF and OPG levels in 200 PsA, 200 PsO, 157 SpA and 50 HC. | Biomarkers panel of Dkk-1, M-CSF, MMP3 and OPG was able to distinguish PsA and HC (AUC: 0.84). |
| Cretu (14)  | 2017             | Cross-sectional | 100     | CASPAR                  | M2BP, CD5L; MPO; ITGB, CRP, MMP3 | Level measurement by ELISA of 100 PsA, 100 PsO and 100 HC. | ITGB5, CRP and M2BP levels were increased in PsA patients (Panel of these 3 biomarkers: AUC of 0.85). |
| Chandran (15)| 2019             | Cross-sectional | 73      | CASPAR                  | COMP; hyaluronom; resistin; adiponectin; adipon; HGF; insulin; leptin; CRP; IL-8; IL-6; IL-1ß; TNFα, MCP1; NGF | Serum analysis of 77 PsA, 201 OA and 76 HC by ELISA in a first discovery phase and then comparison of 4 biomarkers in a second validation phase of 73 PsA and 75 OA. | COMP, Resistin, MCP-1 and NGF used as a panel were able to distinguish PsA and OA patients with high accuracy (AUC: 0.99). |
| Diani (16)  | 2019             | Cross-sectional | 50      | CASPAR                  | MMPs; TIMPs; OPG; RANK-L; CTX; Dkk-1; SOST; CTX-I; CTX-II; PINP, Chi3L1 | Serum analysis of osteoimmunologic biomarkers in 50 PsA, 50 PsO and 20 HC. | MMP2, MMP12, MMP13, TIMP2 and TIMP4 was able to distinguish PsA undergoing treatment from PsO. CHI3L1 and MMP10 was able to distinguish PsA not undergoing systemic treatment from PsO. |
| Waszczynski (17)| 2020             | Cross-sectional | 24      | CASPAR                  | IL-18; IL-20; MMP-1; MMP-3; COMP; YKL-40, Aggrecan | ELISA analysis from 24 active PsA sera and 26 HC. | ELISA analysis from 24 active PsA sera and 26 HC. |
| Waszczynski (18)| 2021             | Cross-sectional | 22      | CASPAR                  | IL-6; IL-18; IL-20; MMP-1; MMP-3; COMP; YKL-40, Aggrecan | ELISA analysis from 22 PsA sera, 22 OA and 23 HC. | Age-associated serum COMP and Aggrecan levels discriminate PsA from OA (AUC: 0.94). |
| **Genetic biomarkers** |                 |              |         |                         | HLA        |             |         |
| Elkayam (19)| 2004             | Cross-sectional | 50      | Moll & Wright           | HLA        | HLA class I and II typing on 50 PsA from Israeli Jewish population. | PsA was associated with HLA-A3, HLA-B13, HLA-B38, HLA-DRB101, HLA-DRB0301, and HLA-DRB0401 on Israeli |

(Continued)
| References | Publication Year | Study Design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|------------|-----------------|--------------|--------|------------------------|------------|-------------|---------|
| Alenius (20) | 2004 | Cross-sectional | 120 | Physician diagnosis | CTLA4, TNF, loci 8q24, 16q21 gene polymorphisms | Genotyping of TFN locus 1q21 (PSORS4) and 3q21 (PSORS5), 8q24 loci, 16q21 loci and CTLA4 locus on 120 PsA patients and 90 HC. | Jewish population. HLA-B27 was not associated with PsA in this cohort. |
| Ravindran (21) | 2004 | Cross-sectional | 140 | Moll & Wright | IL-1α, IL-1β, R-IL-1 gene polymorphisms | Genotyping of IL-1α-889; IL-1β +3953 and IL-1R+970 on 140 PsA. | No association reported in this paper. |
| Batliwalla (22) | 2005 | Cross-sectional | 19 | Moll & Wright | Microarray's analysis | Gene expression profiling on peripheral blood cells in 19 PsA patients and 19 age- and sex-matched HC. | Decreased of Nucleoporelin 62KD and MAP3K3 expression was associated with PsA compared to control. |
| Stoeckman (23) | 2006 | Cross-sectional | 16 | Moll & Wright | Microarray's analysis | Whole blood gene expression profiling on 16 PsA and 15 sex- and age-matched HC. | Zinc-finger protein 395, dead box polypeptide 28, pecanex-like 3, and PI3KC2B gene expressions were upregulated in PsA compared to HC. |
| Butt (24) | 2007 | Cross-sectional | 258 | Physician diagnosis | VEGF, FGF1; FGF2; EGF gene polymorphisms | Genotyping with MALDI-TOF spectrophotometry on 258 PsA and 154 HC. | rs3025039*T in VEGF+936 loci was protector of PsA. |
| Bowes (25) | 2011 | Cross-sectional | 1057 | CASPAR | IL-13 gene polymorphism | Genotyping of rs20541 and rs1800925 on 1057 PsA, 778 PsO and 5575 HC. | Double alleles rs1800925*C/C and rs20541*G/G were significantly associated with PsA. |
| Eder (26) | 2011 | Cross-sectional | 555 | Moll & Wright | IL-13 gene polymorphism (Alleles rs20541 and rs1800925) | Genotyping of rs20541, rs843 and rs1800925 single nucleotide polymorphisms on 555 PsA, 342 PsO and 217 HC. | rs20541 and rs843 polymorphism increased the risk of PsA in PsO patients. |
| Eder (27) | 2012 | Cross-sectional | 178 | CASPAR and their family | HLA-B and HLA-C | Family-based association study by HLA-genotyping on 178 PsA, 30 PsO and 561 first degree relatives. | HLA-B27, B-38, B-39 and HLA-C12 were associated to PsA compared to PsO. |
| Winchester (28) | 2012 | Cross-sectional | 359 | CASPAR | HLA-B and HLA-C | Comparison of the HLA-B and HLA-C alleles and haplotypes by HLA-genotyping on 359 PsA, 214 PsO and 1119 HC, divided in two cohort: discovery then validation. | HLA-R27 was associated to PsA. |
| Chandran (29) | 2013 | Cross-sectional | 678 | CASPAR | HLA alleles | HLA-genotyping on 678 PsA and 688 HC. | In comparison of HC, HLA-C12/B38 association, HLA-C*06/B57 association and HLA-B27 were associated to PsA. |
| Chandran (30) | 2014 | Cross-sectional | 678 | CASPAR | KIR2D and KIR3D gene polymorphism | KIR2D and KIR3D genotyping on 678 PsA and 688 HC. | The allele KIR2DS was significantly associated with PsA. |
| Zhang (31) | 2017 | Cross-sectional | 465 | CASPAR | 36 loci, including IL-12B, RUNX5, LCE gene polymorphisms | DNA Genotyping on 465 PsA and 421 HC using MALDI-TOF spectrophotometry. | Polymorphisms in IL-12B, RUNX5 and LCE genes were associated with an increased risk of PsA. |
| Ciancio (32) | 2017 | Cross-sectional | 39 | CASPAR | miR-21-5p | Micro-array expression analysis of 723 miRNA on 39 | miR-21-5p was overexpressed in RA and PsA population. |
| References | Publication Year | Study Design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|------------|------------------|--------------|---------|-------------------------|------------|-------------|---------|
| Cascella (33) | 2017 | Cross-sectional | 500 | CASPAR | KIF3A and IL-4 gene polymorphism | RT-PCR of rs2227282 located in the IL-4 gene and rs2285700, rs10062446 and rs2897442, located in the KIF3A gene from 500 PsA, 426 PsO and 600 HC blood samples. | Except rs2285700 on KIF3A gene, the presence of SNPs increased susceptibility to PsA but not PsO. |
| Abji (34) | 2018 | Cross-sectional | 14 | CASPAR | Genetic expression of Th17 pathway | RT-PCR of 84 genes from synovial fluid samples from 14 PsA, and 9 OA. | MMP3, CCL1, IL-17C, IL-3, CXCL15, IL-6 and CX3CL1 genes were expressed more in samples from PsA compared to OA. |
| Chen (35) | 2019 | Cross-sectional | 111 | CASPAR | HLA class I and HLA DRB1 | HLA Genotyping on 111 PsA and 207 HC from a Chinese Han population. | HLA-A*01/A*01 and HLA-C*06/C*02 were risk alleles for PsA. |
| Smith (36) | 2020 | Cross-sectional | 140 | CASPAR | HLA- C*06:02, B*44:02, B*27:05, B*08:01, TNFRSF9; LCE3C/B, IL-23R, TNFAIP3, CSF2; P4HA2 genes | 11 genes reported to be associated with PsA or PsO were genotyped in 140 PsA, 403 PsO and 181 PsO patients with joint pain. | Low accuracy of this genetic association to PsA diagnosis. |
| Caputo (37) | 2020 | Cross-sectional | 424 | CASPAR | SNPs of COL6A5 (rs12488457 A/C); COL8A1 (rs13081855 G/T); COL10A1 (rs3812111 A/T); miR146A (rs2910164 C/G) | Genotyping of blood sample from 424 PsA, 394 PsO and 600 HC from Italian population. | rs13081855T, rs12488457*C and rs2910164*T were associated with PsA. |
| Lin SH (38) | 2020 | Cross-sectional | 40 | CASPAR | miR-941 and miR-1466-p | Expression of miR941 and miR1466-5p measured in 40 PsA, 40 PsO and 40 HC blood samples. | Higher miR-944 expression in PsA samples than PsO or HC. |
| Pasquali (39) | 2020 | Cross-sectional | 28 | CASPAR | Extra-vesicular micro-RNA | miRCURY™ exosome isolation kit was used to compare 14 PsA and 15 PsO blood samples in the discovery phase and then 24 PsA and 25 PsO in the validation phase. | Plasma extravesicular « let-7b-5p » and « miR-30e-5p » were significantly lower in PsA compared to PsO in validation phase. |
| Wade (40) | 2020 | Cross-sectional | 31 | CASPAR | Micro RNA signature | miRNA panel was assessed using miRNA Fireplex assay in sera of 31 PsA and 20 HC. | miR-221-3p, miR-130a-3p, miR-146a-3p, miR-26a-5p, miR-151a-5p and miR-21-5p were promising candidate biomarkers to distinguish PsA from HC. |
| Iwaszko (41) | 2021 | Cross-sectional | 126 | CASPAR | IL-33 gene polymorphisms (rs16924159; rs10975519; rs7043433) | PCR analysis of 126 PsA sera, 143 SpA, 466 RA and 229 HC. | These SNPs within the IL-33 gene were not useful for PsA diagnosis. |
| Cheleschi (42) | 2022 | Case-control | 50 | CASPAR | Selected mi-RNA, pro-inflammatory cytokines and adipokines | RT-PCR and ELISA analysis in blood samples from 50 PsA, 50 RA and 50 HC. | Increased expression of miR-140 and serum leptin in PsA compared to RA. |

(Continued)
| References          | Publication Year | Study Design | PsA (n) | Classification Criteria      | Biomarkers                          | Methodology                     | Outcome                                                                                                                                 |
|---------------------|------------------|--------------|---------|-----------------------------|-----------------------------------|----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| **Autoantibodies**  |                  |              |         |                             |                                   |                                  |                                                                                                                                       |
| Calzavara-Pinton    | 1999             | Cross-sectional | 76      | Moll & Wright               | Anti-CCP autoantibodies           | Indirect immunofluorescence test  | Anti-CCP autoantibodies were specific of RA but were present in a small number of PsA cases.                                      |
| Chou                | 2010             | Cross-sectional | 13      | CASPAR                      | IgG anti-agalactosyl autoantibodies | ELISA analysis on 13 PsA, 30     | IgG anti-agalactosyl autoantibodies were present in higher quantities in patients with RA, SpA and PsA serum compared to HC.       |
| Dalmady             | 2013             | Cross-sectional | 46      | CASPAR                      | Anti-MCV autoantibodies           | Serum analysis by ELISA on 46     | Anti-MCV autoantibodies were more represented in PsA patients than in those with PsO and HC.                                      |
| Dolcino             | 2014             | Cross-sectional | 100     | CASPAR                      | Anti-PsA peptide (TNRRGSPGAL)     | Serum analysis of 100 PsA, 200     | Anti-NRAP autoantibodies were highly associated with PsA compared to PsO, RA CCP+ or CCP-, HC and the others rheumatic diseases included.|
| Hu                  | 2018             | Cross-sectional | 12      | Physician diagnosis         | AC anti-SIRT1 autoantibodies      | ELISA analysis on 12 PsA, 94      | Anti-SIRT1 autoantibodies were expressed higher in patients with SpA and PsA compared to patients with RA and HC but it seems to be more specific of patients with SpA. |
| Frasca              | 2018             | Cross-sectional | 32      | CASPAR                      | Anti-LL37 carbamylated (carb)     | Serum analysis using ELISA from 32| Anti-LL37 cit were associated to psoriatic disease, while anti-LL37carb were more specific to PsA.                                |
| Yuan                | 2019             | Cross-sectional | 22      | Physician diagnosis         | Anti-ADAMSTS5 and anti-LL37      | ELISA analysis of 22 PsA and 32    | IgG anti-LL37 and anti-ADAMSTS5 autoantibodies distinguished PsA from PsO.                                                          |
| Vinci               | 2020             | Cross-sectional | 69      | CASPAR                      | IgA Anti-oxPTMCII autoantibodies  | ELISA analysis on 69 PsA, 60      | IgG anti-oxPTMCII were associated with RA while IgA anti-oxPTMCII were associated with SpA, PsA and SpA associated with inflammatory bowel disease. |
| **Other biomarkers**|                  |              |         |                             |                                   |                                  |                                                                                                                                       |
| Veale               | 1993             | Cross-sectional | 15      | Benett criteria             | ELAM-1; ICAM-1; VCAM-1            | Immunohistochemistry analysis of  | Increased ELAM-1 expression in RA synovial samples compared to PsA.                                                                   |
| Szodoray            | 2007             | Cross-sectional | 43      | Moll & Wright               | Panel of 23 different biomarkers: | ELISA analysis on 43 PsA and 25    | Overexpression of IFNα and IL-10 in PsA. Under expression of G-CSF, CCL4, CCL11, IL-13, EGF, VEGF and FGF in PsA.                  |
| Firuzi              | 2008             | Cross-sectional | 16      | Moll & Wright               | Carbonyl (CO) and Sulphydryl (SH) | Serum and Synovial analysis using  | Decreased SH-group in RA and PsA synovial samples compared to OA.                                                                   |

(Continued)
| References | Publication Year | Study Design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|------------|------------------|--------------|---------|-------------------------|------------|-------------|---------|
| Hansson (54) | 2014 | Prospective | 65 | CASPAR | Calprotectin S100A8/S100A9 | Serum analysis of 65 PsA and 31 HC. | ROC analysis of calprotectin S100A8/A9 revealed an AUC of 0.87 to distinguish PsA from HC. |
| Bosé (55) | 2014 | Cross-sectional | 30 | CASPAR | IL-2 | Cytokine expression assessed on plasma circulating T-cells of 30 PsA, 21 PsO and 24 HC. | IL-2 expression was significantly associated with PsA. |
| Maejima (56) | 2014 | Cross-sectional | 12 | CASPAR | Moesin, K17, ANXA1, STIP-1. | Level assessment in 12 PsA, 31 PsO and 13 HC sera using dot blot analysis. | Significant increase in K17 and STIP-1 in PsA compared to PsO and HC. |
| Kim (57) | 2015 | Cross-sectional | 25 | CASPAR | Ratio PNN/Ly et PLQ/Ly | Compared between 25 PsA, 111 PsO, and 94 HC. | An increase in the PNN/Ly ratio and PLQ/Ly ratio was predictive of PsA. |
| Armas-González (58) | 2015 | Cross-sectional | 15 | CASPAR | B-cell protein expression profiling | Flow cytometry analysis on 15 PsA and 13 RA. | B-cells in RA synovial samples expressed more MHC class II molecules than those in PsA. |
| Amin (59) | 2016 | Prospective | 20 | Moll & Wright | RANK-L | Level measurement by ELISA of RANK-L from 20 PsA, 40 PsO and 20 HC. | Low accuracy of RANK-L to discriminate PsA from PsO (AUC: 0.66). |
| Gudmann (60) | 2016 | Cross-sectional | 101 | CASPAR | ProC2 and C-coll10 | ELISA analysis on 110 SpA, 101 PsA and 118 HC. | Increased serum ProC2 concentration in PsA and SpA. |
| Muntyanu (61) | 2016 | Cross-sectional | 40 | CASPAR | CXCL10 | Serum analysis of 40 PsA, 14 OA, 11 RA and 8 gouts. | CXCL10 titers were higher in PsA synovial fluid than in gout and OA. No difference from RA. |
| Abji (62) | 2016 | Prospective | 620 | CASPAR | CXCL10 | Monitoring the variation of CXCL10 titres in sera from 620 PsA. | Mean level of CXCL10 was higher in sera from PsA converter compared to non-converter. |
| Reindl (63) | 2016 | Cross-sectional | 33 | CASPAR | 15 serum biomarkers issued in a discovery phase | ELISA analysis of serum from 33 PsA, 100 PsO and 25 HC. | Complement 3, Polymeric Immunoglobulin Receptor, Plasma Kallikrein and Zn-a2-glycoprotein were significantly higher in PsA sera compared to PsO and HC. |
| Alonso (64) | 2016 | Cross-sectional | 200 | Physician diagnosis | Urinary biomarker panel | Urine metabolome of 200 PsA, 200 RA, 200 PsO, 200 SLE, 200 Crohn’s disease, and 200 HC analysed using nuclear magnetic resonance. | Urine metabolome expression was different in PsA compared to RA. |
| Grossi (65) | 2017 | Cross-sectional | 18 | CASPAR | Calprotectin S100A8/S100A9 | Assessment of serum calprotectin mean concentration from 18 PsA, 21 SpA and 73 HC. | High accuracy to Calprotectin S100A8/A9 to distinguish PsA from HC. No difference between PsA and SpA. |
| Ausavarungnirun (66) | 2017 | Cross-sectional | 55 | CASPAR | ESR and hsCRP | Inflammatory markers determination in serum from 55 PsA and 55 PsO. | Increased V5 and hsCRP levels in PsA compared to PsO. |
| Maejima (67) | 2017 | Cross-sectional | 11 | CASPAR | VCP | Serum analysis using Reverse-phase protein array from 11 PsA, 23 PsO and 11HC. | VCP was significantly increased in PsA compared to PsO and HC. |
| Farrag (68) | 2017 | Cross-sectional | 21 | CASPAR | IL-34 | ELISA analysis from 21 PsA, 24 PsO and 20 HC blood samples. | IL-34 concentration was able to distinguish PsA from PsO and HC (AUC: 0.90). |

(Continued)
| References | Year | Study Design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|------------|------|--------------|---------|-------------------------|------------|-------------|---------|
| Sinkeviciute (69) (67) | 2020 | Prospective | 111 | CASPAR | PROM | ELISA analysis of 11 PsA and 55 HC. | PROM was associated with PsA but ROC analysis described low accuracy (AUC: 0.64). Decrease in serum CXCL10 titers in PsA converters before and after conversion to PsA. |
| Abji (70) | 2020 | Prospective | 29 | CASPAR | CXCL10 | Monitoring of serum CXCL10 levels in 644 PsO patients to compare PsA converters (n=29) and matched non-converters (n=52). | Gelsolin was able to discriminate PsA from PsO (AUC: 0.91) and HC (AUC: 0.98). |
| Esawy (71) | 2020 | Cross-sectional | 76 | Moll & Wright | Plasma Gelsolin | Serum analysis by ELISA of 76 PsA, 40 PsO and 40 age and sex-matched HC. | Gelsolin was able to discriminate PsA from PsO (AUC: 0.91) and HC (AUC: 0.98). |
| Souto-carneiro (72) | 2020 | Cross-sectional | 73 | Physician diagnosis | Serum metabolome and lipidome (7 lipid groups and 24 different metabolites) | Proton nuclear magnetic resonance analysis of 73 PsA sera and 49 seronegative RA. | Construction of a predictive model consisting of the lipid ratio and the expression of metabolites made it possible to distinguish RA from PsA (AUC: 0.85). |
| Cuervo (73) | 2021 | Cross-sectional | 35 | CASPAR | Mast-cells CD117 and fibroblasts (hsp47) in synovial fluid | Immunohistochemical analysis of cell types from synovial samples of 35 PsA, 39 RA and 31 UA (19 evolving to RA and 12 evolving to PsA). | Higher mast cell and fibroblastic density were associated with PsA progression. |
| Leijten (74) | 2021 | Cross-sectional | 20 | CASPAR | 951 unique proteins | Serum proteomic analyses from 20 PsA samples, 20 PsO, 19 SpA and 20 HC. | No difference in proteomic expression between PsO and PsA but 68 expressed proteins differ compared to HC. |
| Kishikawa (75) | 2021 | Cross-sectional | 42 | CASPAR | Plasma metabolome | Plasma metabolite profiles investigated in 42 blood samples from PsA, 50 PsO and 38 HC using dual approach by CE-TOFMS and LC-TOFMS. | In PsA compared to PsO: Increased levels of all saturated fatty acid and tyramine level. Decreased levels of mucic acid. |
| Fuentelsaz-Romero (76) | 2021 | Retrospective | 9 | CASPAR | Macrophage polarization | Analysis of GM-CSF expression and macrophage polarization in synovial tissue from 8 UA evolving to RA, 9 UA evolving to PsA, 16 persistent UA, 12 established RA and 10 persistent PsA. | CD163+ CD209+ macrophages were more abundant in synovial tissues from PsA and HC compared to RA and persistent UA. |
| Zhu J (77) | 2021 | Cross-sectional | 4 | CASPAR | Proteome profile of peripheral blood mononuclear cells | Blood samples analysis firstly using mass-spectrometry then using western-blot from 4 PsA, 4 PsO and 4 HC. | Higher SIRT2 expression in PBMC from PsA than PsO and HC. |
| Looby (78) | 2021 | Retrospective | 30 | CASPAR | Metabolomics | Monitoring of metabolite expression by mass spectrometry in 30 PsA, 20 PsO (10 converted to PsA and 10 non-converted to PsA), and 10 HC. | 1,11-undecanedicarboxylic acid expression differed between PsA patients and HC. |
| Leijten (79) | 2021 | Cross-sectional | 21 | CASPAR | CD8+ CCR10+ T-cells | Flow cytometry of PBMC from 21 patients with PsA, 21 with PsO, 16 with SpA and 20 HC. | CD8+CCR10+ T-cells were more represented in PsA sera compared to HC. |
| Ek (80) | 2021 | Cross-sectional | 1025 | NA | 21 inflammatory biomarkers | 21 biomarkers were assessed in 18 different inflammatory | No biomarker measured was associated with PsA diagnosis. |
3.2 Prognostic biomarkers

Prognostic biomarkers, including markers of disease activity, were less frequently assessed than diagnostic biomarkers (Table 2). As such, the data collected were insufficient to perform meta-analyses.

### TABLE 2 Included Prognostic Biomarkers Studies.

| References | Publication year | Study design | PsA (n) | Classification Criteria | Biomarkers | Methodology | Outcome |
|------------|-----------------|--------------|--------|-------------------------|------------|-------------|---------|
| Helliwell (84) | 1991 | Cross-sectional | 36 | Moll & Wright | Cytidine deaminase; ESR; CRP; histidine | Concentration assessment in 36 PsA blood samples. | Better correlation with disease activity was ESR. |
| Mchugh (85) | 2003 | Prospective | 87 | Moll & Wright | ESR | 5-year follow-up of a cohort of 87 PsA patients. | Correlation between high initial ESR level and pejorative disease progression. |
| Bandinelli (86) | 2015 | Cross-sectional | 112 | CASPAR | ESR, CRP; Anti-CCP; HLA | US examination, HLA typing and serum analysis of 112 patients with PsA. | US abnormalities were associated with higher mean serum CRP or ESR levels and expression of HLA-B27, B-35, B38, Cw6 and DR4. |
| References      | Publication year | Study design | PsA (n) | Classification criteria | Biomarkers | Methodology | Outcome                                      |
|-----------------|------------------|--------------|---------|-------------------------|------------|-------------|----------------------------------------------|
| **Bone and cartilage biomarkers** |                   |              |         |                         |            |             |                                              |
| Kane (87)       | 2003             | Retrospective| 22      | Moll & Wright           | MRP8, MRP 14| ELISA analysis of synovial and serum sample from 22 patients with PsA, 11 with RA 15 with SpA. | Serum MRP8 and MRP14 concentrations were markers of disease activity in PsA, RA and SpA. |
| Skoumal (88)    | 2008             | Cross-sectional| 64     | Moll & Wright          | COMP   | ELISA analysis of serum from 64 patients with PsA and 39 with PsO. | COMP concentration was significantly correlated with CRP, ESR, TJC and SJC. |
| Dalbeth (89)    | 2010             | Cross-sectional| 38     | CASPAR                 | Dkk-1; M-CSF; RANK-L; OPG | Serum analysis from 38 PsA, 10 PsO and 12 HC. | RANK-L and M-CSF are correlated with articular radiographic damage in PsA. |
| Van kuijk (90)  | 2010             | Prospective  | 24     | CASPAR                 | CPII; PINP; MIA; MMP-3; C2G; COMP; osteocalcin; NTX-1; CTX-1 | Serum analysis using ELISA for 12 weeks follow-up of 24 PsA in an adalimumab study. | Decreased MMP-3 concentration was associated with DAS28 improvement. |
| Ramonda (91)    | 2013             | Prospective  | 43     | CASPAR                 | MMP3; VEGF; PTX3; hsCRP | ELISA analysis on 43 HC and 43 PsA at inclusion and 24 weeks after anti-TNF introduction. | Decrease in biomarker levels during follow-up. |
| Waszczykowski (18) | 2021             | Cross-sectional| 24     | CASPAR                 | IL-18, IL-20; MMP-1; MMP-3; COMP; YKL-40, Aggrecan | ELISA analysis from 24 patients with active PsA sera and 26 HC. | COMP level was significantly correlated with TJC and SJC. |
| Chung (92)      | 2021             | Cross-sectional| 69     | CASPAR                 | Dkk-1 | ELISA analysis from 69 PsA sera, 39 RA and 21 HC. Radiographic hands erosions and sacroiliitis were assessed. | Bone erosions, sacroiliitis and SJC were correlated with elevated serum levels of Dkk-1. |
| **Genetic biomarkers** |                   |              |         |                         |            |             |                                              |
| Alenius (93)    | 2002             | Cross-sectional| 88     | Moll & Wright          | HLA-A; HLA-B, HLA-Cw*; HLA-DRB1*; HLA-DQB1* | HLA Genotyping of 88 PsA and 1085 HC. | HLA-B37 and HLA-B62 were markers of erosions and deformations in PsA. |
| Iwaszko (41)   | 2021             | Cross-sectional| 126    | CASPAR                 | IL-33 gene polymorphisms (rs16924159; rs10975519; rs7044343) | PCR analysis in 126 PsA, 143 AS, 466 RA and 229 HC. | No correlation between SNPs within IL-33 gene and CRP or BASDA1 in PsA. |
| **Autoantibodies** |                   |              |         |                         |            |             |                                              |
| Korendowych (94)| 2005             | Cross-sectional| 126    | Physician diagnosis    | Anti-CCP | Immunofluorescence analysis from 126 PsA sera. | All PsA CCP+ had radiographic damages and significantly higher SJC. |
| Perez-alamino (95)| 2014            | Prospective  | 81     | CASPAR                 | Anti-CCP | ELISA assessment from 81 PsA sera. | PsA CCP+ had more erosive damage and higher polyarticular forms. |
| Ibrahim (96)    | 2018             | Cross-sectional| 45     | CASPAR                 | Anti-CarP autoantibodies | ELISA analysis of sera from 45 patients with PsA and 45 HC. | Anti-CarP autoantibodies were associated to both clinical and US activity in PsA. |
| Frasca (48)     | 2018             | Cross-sectional| 32     | CASPAR                 | Anti-LL37 carbamylated autoantibodies and Anti-LL37 citrullinated autoantibodies | ELISA analysis from 32 PsA sera, 24 PsO, and 12 HC. | Correlation with DAS44 in PsA. |

(Continued)
### TABLE 2  Continued

| References       | Publication year | Study design       | PsA (n) | Classification criteria | Biomarkers                  | Methodology                              | Outcome                                                                 |
|------------------|------------------|--------------------|---------|-------------------------|------------------------------|------------------------------------------|--------------------------------------------------------------------------|
| **Other biomarkers**                                         |                  |                    |         |                         |                              |                                          |                                                                         |
| Elkayam (97)     | 2000             | Cross-sectional    | 34       | Moll & Wright           | Hyaluronic acid              | Radiometric assay of sera 34 patients with PsA, 34 with RA and 49 with HC. | Hyaluronic acid level was correlated to PASI Score (r: 0.87).            |
| Elkayam (98)     | 2000             | Cross-sectional    | 34       | Moll & Wright           | IL-10, IL-6, IL-1ra, IL-2R   | ELISA analysis of serum samples from 34 patients with PsA and 10 HC.     | Increase in IL-1Ra titers associated with joint activity in PsA.         |
| Foell (87)       | 2003             | Prospective        | 22       | Moll & Wright           | Calprotectin S100A12         | Serum analysis before and after MTX introduction of 22 PsA patients, 9 RA patients, 11 SpA patients and 30 HC. | Calprotectin S100A12 concentration was modestly correlated with ESR and Richie index. |
| Rooney (99)      | 2004             | Prospective        | 5        | Moll & Wright           | IL-18                        | Monitoring expression in synovial tissues from 5 patients with PsA, 11 with RA, 9 with UA and 2 with reactive arthritis before MTX or Salazopyrine introduction, repeated after 12 months delay. | IL-18 expression correlated with CRP circulating levels in all groups before treatment. Decrease expression of IL-18 after treatment correlated with a decrease in CRP levels. |
| Fink (100)       | 2007             | Cross-sectional    | 28       | Moll & Wright           | VEGF                         | ELISA analysis of sera from 28 patients with PsA and 9 HC.               | Higher VEGF titres in the active PsA subgroup.                           |
| Madland (101)    | 2007             | Cross-sectional    | 119      | Physician diagnosis     | ESR, hsCRP; Calprotectin S100A12, Calprotectin S100A9 | Serum analysis from 119 PsA patient blood samples. | Calprotectin S100A9 was inferior to ESR and CRP to assess disease activity but was a better marker of radiographic damage. |
| Szodoray (52)    | 2007             | Cross-sectional    | 43       | Moll & Wright           | Panel of 23 different biomarkers | ELISA analysis from 43 patients with PsA sera and 25 HC.                | EGF, IFNg, VEGF, CCL3 and IL-12 p-40 levels correlated with disease activity. |
| Alenius (102)    | 2009             | Cross-sectional    | 134      | Moll & Wright           | IL-6, IL-2R                  | Serum analysis from 134 patients with PsA and 85 PsO patients using ELISA. | IL-6 is associated to ESR, CRP and TCI.                                    |
| Pongratz (103)   | 2010             | Cross-sectional    | 52       | CASPAR                  | BAFF and testosterone        | Serum analysis from 53 PsA patient blood samples. | In male patients with PsA, the BAFF/testosterone ratio was significantly correlated with DAS28. |
| Cellis (104)     | 2011             | Cross-sectional    | 46       | CASPAR                  | miRNA expression and panel of 21 cytokines. | ELISA analysis associated to quantitative RT-PCR of synovial tissues from 46 PsA. | Association between synovial IL-6 and CCL20 levels and circulating CRP levels. |
| Przepiernybednack (105) | 2013           | Cross-sectional    | 80       | CASPAR                  | VEGF, EGF, FGF, FGFB, FGFr | Serum analysis on 80 PsA patient samples, 18 with SAPHO and 20 HC.     | VEGF and CRP are correlated. VEGF is not associated with several disease activity score. |
| Jensen (106)     | 2011             | Prospective        | 42       | Moll & Wright           | YKL-40 (Chi3l1); hsCRP       | Serum analysis on 42 patients with PsA and 6 with PsO before and after adalimumab introduction. | YKL-40 is decreased in responder PsA patients. |
| Eissa (107)      | 2013             | Cross-sectional    | 50       | CASPAR                  | Kallikreins                  | Serum analysis on 50 patients with PsA, 50 PsO patients and 26 HC.       | Kallikrein 8 and Kallikrein 6 are associated with PASI in PsA patients. |
| Kayikci (108)    | 2013             | Cross-sectional    | 48       | CASPAR                  | IL-17, IL-22, IL-23          | ELISA analysis on 48 patients with PsA, 20 with PsO and 19 HC.           | IL-17 is weakly correlated with TJC.                                      |
| Hansson (54)     | 2014             | Prospective        | 65       | CASPAR                  | Calprotectin S100A8/S100A9   | ELISA analysis in sera from 65 patients with PsA and 31 HC.              | Calprotectin was significantly increased in polyparticular form of PsA. |
| Ahmed (109)      | 2015             | Cross-sectional    | 26       | CASPAR                  | YKL-40 (Chi3l1)              | ELISA analysis of blood samples from 26 patients with PsA, 22 with PsO and 30 HC. | YKL-40 was significantly correlated with CPDAI in PsA patients. |
| Husakova (110)   | 2015             | Cross-sectional    | 40       | Physician diagnosis     | Prolactin                    | Immunoradiometric assay on sera of 70 patients with PsO, 40 with PsA and 27 HC. | No correlation was found with disease activity. |

(Continued)
| Reference     | Publication year | Study design | PsA (n) | Classification criteria | Biomarkers Methodology | Outcome |
|---------------|------------------|--------------|---------|-------------------------|------------------------|---------|
| Matt (111)    | 2015             | Cross-sectional | 23      | CASPAR                  | Fc receptor of Monocyte-cells | Flow cytometry on sera of 23 patients with PsA and 32 HC. | High titer of CD64+ cells was significantly correlated with DAS28. |
| Peled (112)   | 2015             | Cross-sectional | 20      | CASPAR                  | PD1                    | Flow cytometry on 20 patients with PsA and 15 HC. | A low titer of T-cell presenting PD1 is associated with a low DAS28 score. |
| Dikbas (113)  | 2016             | Cross-sectional | 28      | CASPAR                  | Adipocytokines: Visfatin, Resistin, Adiponectin | ELISA analysis on 28 PsA patients and 39 HC. | No correlation found. |
| Munk (114)    | 2016             | Cross-sectional | 101     | CASPAR                  | PIIANP, C2M            | ELISA analysis of 110 patients with SpA, 101 with PsA and 96 HC. | No correlation found. |
| Alonso (64)   | 2016             | Cross-sectional | 200     | Physician diagnosis     | Urinary biomarker panel | Nuclear magnetic resonance analysis of urine samples from 200 patients with PsA, 200 with RA, 200 with PsO, 200 with SLE, 200 with Crohn’s disease, and 200 HC. | Increased urine levels of citrate in active PsA. |
| Inciarte-mundo (115) | 2016 | Cross-sectional | 50      | CASPAR                  | Calprotectin and TNF trough serum levels | Serum analysis from 50 patients with PsA and 42 with RA. | High Calprotectin titers were associated with US activity in both PsA and RA patients. |
| Przepiera (116) | 2016       | Cross-sectional | 76      | CASPAR                  | IL-18, Fetuin A, ICAM-1, ET-1 | ELISA analysis of sera from 76 patients with PsA sera, 81 with SpA and 34 with SAPHO. | ET-1 levels were correlated to DAS28 in PsA. IL-18 levels were associated to BASDAI. |
| Kilic (117)   | 2017             | Cross-sectional | 116     | CASPAR                  | MPV                    | Serum analysis from 116 PsA patients, 41 PsO patients and 90 HC. | Skin disease severity was associated to high MPV concentration in patients with PsA. |
| Farrag (68)   | 2017             | Cross-sectional | 21      | CASPAR                  | IL-34                  | ELISA assessment in sera from 21 patients with PsA, 24 with PsO and 20 HC. | Association between IL-34 and disease articular and PASI, CPDAI and BASDAI. |
| Inciarte-mundo (118) | 2018       | Prospective    | 51      | CASPAR                  | Calprotectin; TNF trough serum levels | Serum analysis at baseline and relapse of 47 PsA patients and 56 with RA treated with anti-TNF. | High Calprotectin concentration at baseline was associated with relapse in both PsA and RA patients. |
| Wade (119)    | 2018             | Cross-sectional | N.A.    | N.A.                    | Polyfunctional T-cells  | Flow cytometry analysis on patients with PsA. | Th1 and Th17 pathways were associated with DAPS. |
| Coras (120)   | 2019             | Cross-sectional | 41      | CASPAR                  | Eicosanoids            | Assessment using liquid phase chromatography and mass spectrometry on 41 patients with PsA. | 9 pro-inflammatory eicosanoids were associated to DAS28 while 18 anti-inflammatory eicosanoids were inversely correlated with it. |
| Colak (121)   | 2019             | Cross-sectional | 50      | CASPAR                  | VASPIN; NGAL, Apolipoprotein | Serum analysis on 50 patients with PsA and 36 HC. | No significant correlation found with disease activity. |
| Sakellariou (122) | 2019    | Cross-sectional | 78      | CASPAR                  | Calprotectin            | ELISA analysis from 78 patients with PsA sera and 78 with RA. | Modest correlation with US activity score. |
| Coras (123)   | 2019             | Cross-sectional | 38      | CASPAR                  | Cholin metabolites     | Liquid phase chromatography and mass spectrometry analysis on 38 PsA. | Trimethylamine-N-oxide was correlated to DAS28, CPDAI and BSA. |
| Ozisler (124) | 2020             | Retrospective  | 47      | CASPAR                  | RDW                    | Blood samples analysed from 47 patients with PsA and 56 HC. | RDW was modestly correlated to DAS28, CRP and ESR in PsA patients. |
| Arias de la rosa (125) | 2020 | Cross-sectional | 80      | CASPAR                  | Complement C3          | Serum analysis on 80 patients with PsA, 200 with RA, 150 with SpA and 100 HC. | Higher C3 concentration in PsA population with DAS28> 5.1. |
| Esawy (71)    | 2020             | Cross-sectional | 76      | CASPAR                  | Plasma Gelsolin        | ELISA analysis of sera from 76 patients with PsA, 40 with PsO and 40 age- and sex-matched HC. | Negative correlation between Gelsolin titers and DAPSA or CPDAI. |

(Continued)
3.2.1 Acute phase reactant biomarkers

One study concluded that erythrocyte sedimentation rate (ESR) was better correlated with Ritchie’s index, tender joint count (TJC) and swollen joint count (SJC) than C-Reactive Protein (CRP) in a 36 patient PsA cohort (84). These potential prognosis markers were explored in a 5-year follow-up prospective study. The 36 patients with PsA demonstrated a disease duration ranging from 1-40 years, and baseline ESR was associated with structural progression (85). Both ESR and CRP were also associated with UltraSonography (US) which are signs of active synovitis (86).

3.2.2 Bone and cartilage turnover biomarkers

Serum COMP levels were correlated with acute phase reactants and disease activity (TJC, r=0.60, p<0.001) and SJC, r=0.75, p<0.0001) (18, 88). A decrease in MMP3 serum levels in PsA patients receiving adalimumab was correlated with Disease Activity Score (DAS)-28 improvement (90).

3.2.3 Autoantibodies

In a cross-sectional study, positivity for anti-CCP antibodies was associated with more radiographic damage and polyarticular phenotypes (95). Anti-LL37 autoantibodies were also described to correlate with disease activity in PsA (48). A strong correlation between Anti-Carbamylated Protein (Protein A) antibodies and both clinical and ultrasonographic activity was described (correlation between anti-CarP and DAS-28 (r=0.96), CRP (r=0.97), ESR (r=0.97) and US power Doppler+synovitis with a Pearson coefficient >0.97) (96).
3.2.4 Other biomarkers

3.2.4.1 Serum calprotectin S100A8/A9

Calprotectin S100A8/A9 plasma levels were not correlated with disease activity (122, 126). Although, one study reported calprotectin S100A8/A9 levels significantly increased in the polyarticular phenotype of PsA, and were correlated with SJC (54). Contradictory results were reported regarding correlation with US synovitis in greyscale and power Doppler analyses (115, 122). High levels of calprotectin were also associated with relapse at 1-year (118).

3.2.4.2 YKL40

Serum concentration of YKL40, also named Chitinase like-3 protein (Chi3L1) was significantly correlated with disease activity (r=0.848, p<0.001) (109). It was also sensitive to changes, with a significant decrease in serum of good responders to TNF inhibitor (106).

TABLE 3 Assessment of bias risk using NOS scale for case-control studies.

| References                  | Selection | Comparability | Exposure | Non-response |
|-----------------------------|-----------|---------------|----------|--------------|
|                            | Is the case definition adequate? | Representatives of the case | Controls selection | Controls definition | Comparability of cases and controls based on the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |
| Abji, 2017 (34)             | A*        | A*            | B        | A*           | D                | A*            | C              |               |
| Ahmed, 2014 (109)           | A*        | B             | A*       | A*           | A*               | D              | A*            | C              |
| Alenius, 2002 (93)          | A*        | B             | B        | A*           | AB**             | D              | A*            | C              |
| Alenius, 2004 (20)          | A*        | B             | A*       | B            | B*               | D              | A*            | C              |
| Alenius, 2009 (102)         | A*        | B             | B        | A*           | D                | A*            | C              |               |
| Alonso, 2016 (64)           | C         | B             | B        | B            | B*               | D              | A*            | C              |
| Amin, 2016 (59)             | A*        | A*            | C        | A*           | A*               | D              | A*            | C              |
| Arias de la rosa, 2020 (125)| A*        | B             | B        | A*           | A*               | D              | A*            | C              |
| Armas-Gonzales, 2015 (58)   | A*        | B             | B        | A*           | D                | A*            | C              |               |
| Ausavarungnirun, 2017 (66)  | A*        | A*            | B        | A*           | AB**             | D              | A*            | C              |
| Bandinelli, 2015 (86)       | A*        | B             | B        | A*           | D                | A*            | C              |               |
| Batliwalla, 2006 (22)       | A*        | B             | A*       | B            | A*               | D              | A*            | C              |
| Bosé, 2014 (55)             | A*        | B             | B        | B            | D                | A*            | C              |               |
| Bowes, 2011 (25)            | A*        | A*            | B        | B*           | D                | A*            | C              |               |
| Boyd, 2020 (129)            | A*        | A*            | A*       | B            | D                | A*            | C              |               |
| Butt, 2007 (24)             | A*        | A*            | A*       | A*           | B*               | D              | A*            | C              |
| Calzavara, 1999 (43)        | A*        | B             | C        | B            | D                | A*            | C              |               |
| Caputo, 2020 (37)           | A*        | A*            | B        | A*           | A*               | D              | A*            | C              |
| Cascella, 2017 (33)         | A*        | A*            | B        | A*           | D                | A*            | C              |               |
| Celia, 2011 (104)           | A*        | B             | A*       | A*           | AB**             | D              | A*            | C              |
| Chandran, 2010 (10)         | A*        | A*            | B        | A*           | A*               | D              | A*            | C              |
| Chandran, 2014 (30)         | A*        | B             | B        | A*           | A*               | D              | A*            | C              |
| Chandran, 2019 (15)         | A*        | B             | B        | A*           | A*               | D              | A*            | C              |
| Cheleschi, 2021 (42)        | A*        | A*            | B        | A*           | A*               | D              | A*            | C              |
| Chen, 2019 (35)             | A*        | B             | C        | A*           | B*               | D              | A*            | C              |

(Continued)
| References | Selection | Comparability | Exposure |
|------------|-----------|---------------|----------|
|            | Is the case definition adequate? | Representatives of the case | Controls selection | Controls definition | Comparability of cases and controls based on the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |
| Chou, 2010 (44) | A* | A* | B | A* | A | D | A* | C |
| Chung, 2021 (92) | A* | A* | C | A* | A* | D | A* | C |
| Ciancio, 2017 (32) | A* | B | C | A* | A* | D | A* | C |
| Colak, 2018 (121) | A* | A* | C | A* | A* | D | A* | C |
| Coras, 2019 (120) | A* | B | D | A* | A* | D | A* | C |
| Coras, 2019 (123) | A* | B | D | A* | A* | D | A* | C |
| Coras, 2021 (130) | A* | A* | A* | B | A* | D | A* | C |
| Cretu, 2014 (11) | A* | B | B | A* | AB** | D | A* | C |
| Cretu, 2018 (24) | A* | B | A* | A* | B* | D | A* | C |
| Cuerve, 2021 (73) | A* | A* | B | A* | B* | D | A* | C |
| Dalbeth, 2010 (89) | A* | B | B | A* | D | A* | C |
| Dalmaidy, 2013 (45) | A* | A* | A* | A* | D | A* | C |
| Diani, 2019 (16) | A* | A* | C | B | A* | D | A* | C |
| Dikbas, 2014 (113) | A* | B | C | B | D | A* | C |
| Dolcino, 2014 (46) | A* | B | C | A* | B* | D | A* | C |
| Dolcino, 2015 (12) | A* | A* | C | A* | AB** | D | A* | C |
| Eder, 2011 (26) | A* | A* | A* | A* | D | A* | C |
| Eder, 2012 (27) | A* | B | B | B | D | A* | C |
| Essa, 2013 (107) | B | B | B | B | AB** | D | A* | C |
| Ek, 2021 (80) | B | A* | B | A* | A* | D | A* | C |
| Elkayam, 2000 (98) | A* | B | B | D | A* | C |
| Elkayam, 2000 (97) | A* | B | C | B | D | A* | C |
| Elkayam, 2004 (19) | A* | A* | C | B | D | A* | C |
| Esawy, 2020 (71) | A* | A* | B | A* | D | A* | C |
| Farouk, 2010 (9) | A* | A* | A* | B | AB** | D | A* | C |
| Farrag, 2017 (68) | A* | A* | C | A* | AB** | D | A* | C |
| Fink, 2007 (100) | A* | B | C | A* | D | A* | C |
| Firuzi, 2008 (53) | A* | B | C | A* | D | A* | C |
| Foell, 2003 (87) | B | B | C | B | D | A* | C |
| Frasca, 2018 (48) | A* | B | B | A* | A* | D | A* | C |
| Grosi, 2017 (65) | A* | A* | C | A* | D | A* | C |
| Gudmann, 2016 (60) | A* | A* | A* | B | B* | D | A* | C |
| Hansson, 2014 (54) | A* | B | C | B | AB** | D | A* | C |
| Hefflewell, 1991 (84) | A* | B | D |
| Hu, 2018 (47) | A* | B | C | A* | A* | D | A* | C |
| Husakova, 2015 (101) | A* | B | C | B | A* | D | A* | C |
TABLE 3 Continued

| References                   | Selection | Comparability | Exposure |
|-----------------------------|-----------|---------------|----------|
|                             |           | Is the case definition adequate? | Representatives of the case | Controls selection | Controls definition | Comparability of cases and controls based on the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |
| Ibrahim, 2017 (96)          | A*        | B             | C        | B       | A*           | D                     | A*         | C                   |                  |
| Inciarte-Mundo, 2016 (115)  | A*        | B             | B        | A       | B*           | D                     | A*         | C                   |                  |
| Jadon, 2017 (13)            | A*        | A*            | A*       | A*      | AB**         | D                     | A*         | C                   |                  |
| Jarborg, 2020 (126)         | B         | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Jensen, 2012v (106)         | A*        | B             | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Kane, 2003 (87)             | A*        | B             | B        | A*      | D            | A*         | C                     |                  |
| Kaykci, 2013 (97)           | A*        | A*            | C        | B       | D            | A*         | C                     |                  |
| Kim, 2015 (57)              | A*        | A*            | B        | A*      | AB**         | D                     | A*         | C                   |                  |
| Kishikawa, 2021 (75)        | A*        | A*            | B        | B       | A*           | C                     | A*         | C                   |                  |
| Korendowych, 2005 (94)     | A*        | B             | D       |         |              |                       |            |                     |                  |
| Leijten E, 2021 (74)       | A*        | A*            | B        | B       | A*           | C                     | A*         | C                   |                  |
| Leijten EF, 2021 (79)      | A*        | A*            | B        | A*      | A*           | C                     | A*         | C                   |                  |
| Lin, 2020 (38)              | A*        | B             | C        | A*      | D            | A*         | C                     |                  |
| Looby, 2021 (78)            | A*        | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Madland, 2007 (101)        | A*        | B             | D       |         |              |                       |            |                     |                  |
| Maejima, 2014 (56)         | A*        | B             | C        | A*      | A*           | A*         | C                     |                  |
| Maejima, 2017 (67)         | B         | A*            | C        | B       | D            | A*         | C                     |                  |
| Maejima, 2017 (118)        | A*        | B             | B        | B       | D            | A*         | C                     |                  |
| Mansson, 2001 (8)          | A*        | A*            | A*       | A*      | D            | A*         | C                     |                  |
| Marzaioli, 2022 (82)       | A*        | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Matt, 2015 (111)           | A*        | B             | C        | B       | A*           | D                     | A*         | C                   |                  |
| Mc Ardle, 2021 (83)        | A*        | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| McHugh, 2003 (85)          | A*        | B             | A*       |         |              |                       |            |                     |                  |
| Medvedeva, 2020 (127)      | A*        | B             | B        | A       | A*           | A*         | C                     |                  |
| Munk, 2015 (114)           | A*        | B             | C        | B       | A*           | D                     | A*         | C                   |                  |
| Muntyanu, 2016 (61)        | A*        | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Ozider, 2019 (124)         | A*        | B             | C        | B       | A*           | D                     | A*         | C                   |                  |
| Pasquali, 2020 (39)        | A*        | A*            | B        | A*      | A*           | D                     | A*         | C                   |                  |
| Pelled, 2015 (112)         | A*        | B             | B        | A*      | B             | D                     | A*         | C                   |                  |
| Perez-Alamino, 2014 (93)   | A*        | B             | D       |         |              |                       |            |                     |                  |
| References | Selection | Comparability | Exposure |
|------------|-----------|---------------|----------|
|            | Is the case definition adequate? | Comparability of cases and controls based on the design or analysis | Same method of ascertainment for cases and controls | Non-response rate |
|            | Representatives of the case | Controls selection | Controls definition | Ascertainment of exposure |
| Pongratz, 2010 (103) | A* | A* | | D |
| Przepiera-Będzak, 2013 (105) | A* | B | C | B | A* | D | A* | C |
| Przepiera-Będzak, 2016 (116) | A* | B | C | B | A* | D | A* | C |
| Ramonda, 2013 (91) | A* | A* | C | B | A* | D | A* | C |
| Ravindran, 2004 (21) | A* | A* | A* | B | | D | A* | C |
| Reinfeld, 2016 (63) | A* | B | C | B | | D | A* | C |
| Rooney, 2004 (99) | A* | B | C | B | | D | A* | C |
| Sakellariou, 2019 (122) | A* | B | B | B | A* | D | A* | C |
| Sinkievicute, 2020 (69) | A* | B | C | B | | D | A* | C |
| Skoumal, 2008 (88) | A* | B | B | A* | | D | A* | C |
| Smith, 2020 (36) | A* | B | A* | A* | | D | A* | C |
| Souto-Carneiro, 2020 (72) | B | B | B | B | A* | D | A* | C |
| Stoelckmann, 2006 | A* | B | C | A* | A* | D | A* | C |
| Szodoray, 2007 (52) | A* | B | C | A* | AB** | D | A* | C |
| van Kuijk, 2010 (90) | A* | A* | | | D | C |
| Veale, 1993 (51) | A* | B | C | A* | AB** | D | A* | C |
| Vinci, 2020 (50) | A* | B | B | B | | D | A* | C |
| Wade, 2018 (119) | A* | B | B | B | | D | A* | C |
| Wang N., 2022 (81) | A* | A* | B | A* | A* | D | A* | C |
| Waszczykowski, 2020 (17) | A* | A* | C | A* | A* | D | A* | C |
| Waszczykowski, 2021 (18) | A* | B | C | A* | A* | D | A* | C |
| Wcisło-Dziadecka, 2020 (128) | B | B | C | A* | | D | A* | C |
| Winchester, 2012 (28) | A* | A* | B | A* | B* | D | A* | C |
| Yuan, 2019 (49) | A* | B | B | B | AB** | D | A* | C |
| Zhang, 2016 (31) | A* | B | A* | A* | B* | D | A* | C |
| Zhu, 2021 (77) | A* | A* | B | B | A* | D | A* | C |

**Selection.** 1) Is the case definition adequate? A: yes, with independent validation*; B: yes, eg record linkage or based on self-reports; C: no description.
2) Representativeness of the cases A) consecutive or obviously representative series of cases*; B) potential for selection biases or not stated.
3) Selection of Controls A: community controls*; B: hospital controls; C: no description.
4) Definition of Controls A: no history of disease (endpoint)*; B: no description of source.

**Comparability.** Comparability of cases and controls on the basis of the design or analysis A: study controls for …*; B: study controls for any additional factor*.

**Exposure.** 1) Ascertainment of exposure A: secure record (eg surgical records)*; B: structured interview where blind to case/control status; C: interview not blinded to case/control status; D: written self-report or medical record only; E: no description.
2) Same method of ascertainment for cases and controls A: yes*; B: no.
3) Non-Response rate A: Same rate for both groups*; B: non respondents described; C: rate different and no designation.
| References                  | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of the study | Comparability of cohorts based on the design or analysis | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts |
|-----------------------------|-----------------------------------------|-------------------------------------|---------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------|----------------------|---------------------------------------------|-------------------------------|
| Abji F, 2020 (70)           | B*                                     | A*                                 | A*                       | A*                                                                             | A*                                              | A*                  | A*                                         | B*                            |
| Abji F, 2020 (BMJ) (70)     | B*                                     | A*                                 | A*                       | A*                                                                             | B*                                              | A*                  | A*                                         | A*                            |
| Chandran, 2013 (29)         | B*                                     | B*                                 | A*                       | A*                                                                             | A*                                              | A*                  | A*                                         | A*                            |
| Fuentelsaz Romero, 2021 (76)| B*                                     | A*                                 | A*                       | A*                                                                             | A*                                              | A*                  | C                                          | D                            |
| Inciarte-Mundo, 2018 (118)  | B*                                     | A*                                 | B*                       | A*                                                                             | B*                                              | A*                  | A*                                         | B*                            |
| Iwaszko, 2021 (41)          | A*                                     | A*                                 | A*                       | A*                                                                             | A*                                              | A*                  | A*                                         | A*                            |
| Wade, 2020 (40)             | A*                                     | A*                                 | B*                       | A*                                                                             | A*                                              | A*                  | B*                                         | A*                            |

1) Representativeness of the exposed cohort: A: truly representative of the average in the community; B: somewhat representative of the average in the community; C: selected group of users eg nurses, volunteers; D: no description of the derivation of the cohort.
2) Selection of the non-exposed cohort: A: drawn from the same community as the exposed cohort; B: drawn from a different source; C: no description of the derivation of the non-exposed cohort.
3) Ascertainment of exposure: A: secure record (eg surgical records); B: structured interview; C: written self report; D: no description.
4) Demonstration that outcome of interest was not present at start of study: A: yes; B: no.
5) Comparability of cohorts on the basis of the design or analysis: A: study controls for …; B: study controls for any additional factor.
6) Assessment of outcome: A: independent blind assessment; B: record linkage; C: self report; D: no description.
7) Was follow-up long enough for outcomes to occur: A: yes (select an adequate follow up period for outcome of interest); B: no.
8) Adequacy of follow up of cohorts: A: complete follow up - all subjects accounted for; B: subjects lost to follow up unlikely to introduce bias; C: follow up rate < ::% (select an adequate %) and no description of those lost; D: no statement.
4 Discussion

Our systematic review of the literature shows that few biomarkers are currently available to guide clinical practice in the diagnosis and prognosis of PsA. This review has highlighted COMP and MMP3 as two potential serum biomarkers for the diagnosis of PsA. However, the discriminative qualities of these bone and cartilage remodeling markers have been revealed as insufficient for clinical use.

The meta-analysis showed that COMP was able to differentiate patients with PsA from those with OA or from healthy subjects. However, serum levels varied widely between studies. One study reported mean COMP rates were 10-fold lower in the PsA, OA, and HC populations compared with those observed in the other studies, while methodologically, only the commercial ELISA kits differed between studies (15). The success of COMP in distinguishing PsA from PsO was different across studies, and the absence of numerical data prevented performance of a meta-analysis and to deduce its efficacy in this application.

The pooled serum MMP-3 levels were significantly higher in PsA patients than in PsO patients. However, the meta-analysis showed that they did not appropriately distinguish patients with PsA from healthy subjects. Similarly, the only publication that studied MMP3 serum levels in PsA and OA reported no difference between the two (134). MMP3 levels were increased in OA when compared to HC, but do not appear to be a reliable biomarker, particularly as their assessment in a multiplex system reported results contrary to those found in this analysis (i.e., lower MMP3 serum levels in patients with PsA and PsO than in healthy subjects) (16). None of the remaining bone remodeling or cartilage markers demonstrated any ability to differentiate patients with PsA from controls. However, all the studies included in the analysis were cross-sectional studies, with patients whose diagnosis was pre-existing and whose disease duration was not considered.

We have not identified any new genetic biomarkers useful in the diagnosis of PsA since the last meta-analyses on the subject, and these analyses on genetic polymorphisms had not identified any useful biomarkers for the practical diagnosis of PsA (135, 136). Our systematic review did not identify all publications on HLA and PsA association, which may be due to the fact that our search algorithm was not specifically focused on genetics. The

![Meta-analysis of COMP levels](image)

**FIGURE 2** Meta-analysis of COMP levels. (A) Forest plot of difference in COMP levels means between PsA and HC in meta-analysis. (B) Forest plot of difference in serum COMP levels means between PsA and OA.
major loci of interest have historically been MHC region and HLA genes, of which certain alleles, primarily HLA-C*06 and HLA-B*27, are carried by about 20-35% of PsA patients (137). Recently, HLA-B27 has been identified as a marker of the axial PsA phenotype, and HLA-C*06 as a marker of the peripheral PsA phenotype (138). Furthermore, both systematic review for PsA biomarkers and a recent meta-analysis examining HLA association in PsA patients confirmed a significant increase in the risk of PsA in HLA-C*02 and C*12 populations (139, 140). Specific non-HLA PsA variants have been identified in GWAS studies, including in the IL12B, NOS2 and IFIH1 regions as reported in a systematic review published in 2015 (141). Several signaling pathways possibly implicated in the pathogenesis of PsA were presented in a recent systematic review published in 2020 (142).

Data concerning autoantibodies in PsA remains sparse in the literature. While some data appears promising, no replication studies have been published. Anti-CCP antibodies are associated with polyarticular phenotypes and structural lesions, and have been shown to be markers of severity rather than diagnosis. Indeed, a recent study reported a correlation between anti-CCP antibodies in PsA and pulmonary manifestations (143).

This systematic review of the literature has several limitations. Only patients with PsA were included while studies involving patients with SpA were excluded, which may have incidentally excluded patients with psoriatic forms of axial disease. The search algorithm also did not include imaging biomarkers, although combining imaging with other biomarkers might help to better define PsA (144). In addition, we choose to focus on diagnosis and prognosis biomarkers unrelated to treatment and did not include predictive biomarkers of treatment response. Finally, our search equation did not allow us to highlight the numerous studies concerning genetics biomarkers in psoriatic arthritis either and should be a focus of a future systemic review.

In summary, this review was broad, with more than 50 studies included since the prior systematic review on diagnostic and prognostic biomarkers in PsA (139). No specific diagnostic biomarkers for PsA were identified, despite the fact that this was the first meta-analyses to assess COMP and MMP3. The search for autoantibodies in PsA appears promising but requires

![Figure 3](https://example.com/figure3.png)
FIGURE 4
Meta-analysis of circulating biomarkers. (A) Forest plot of difference in serum RANK-L levels means between PsA and HC. (B) Forrest plot of difference in mean levels of OPG between PsA and HC. (C) Forrest plot of difference in mean levels of OPG between PsA and PsO.

FIGURE 5
Forest plot of difference in Dkk-1 levels means between PsA and HC in meta-analysis.
additional confirmatory studies. Further studies are also needed to assess the performance of potential biomarkers that can distinguish PsA from OA and other chronic inflammatory diseases.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author/s.

Author contributions

TW: conception and design of the study, acquisition of data, analysis of data, original draft preparation, data curation, reviewing and editing. NB: conception and design of the study, editing LB: analysis of data, stats PL: conception and design of the study, analysis of data, drafting manuscript, supervision, reviewing and editing All authors reviewed and approved the final draft of the manuscript.

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