

# Using Acute-phase Reactants to Inform the Development of Instruments for the Updated Psoriatic Arthritis Core Outcome Measurement Set

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**ABSTRACT. Objective.** Systemic inflammation is assessed through measurement of acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). With few exceptions, most randomized controlled trials (RCT) have assessed acute-phase reactants (CRP and ESR) as part of the American College of Rheumatology (ACR) 20 response criteria. As part of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA)–Outcome Measures in Rheumatology (OMERACT) working group, we performed a systematic review of the literature to assess the performance of inflammatory biomarkers in psoriatic arthritis (PsA).

**Methods.** A systematic search of PubMed and Embase was performed. The search included peer-reviewed articles and scientific meeting abstracts about RCT and longitudinal observational studies that assessed systemic inflammation using acute-phase reactants in PsA. Studies were assessed following the components of the OMERACT filter including construct validity, responsiveness, and predictive validity.

**Results.** There were 2764 articles retrieved, and 71 articles were included for this systematic review. Twenty-eight articles reported CRP and/or ESR separately, and the remaining articles reported CRP and/or ESR as part of the ACR response criteria. Studies assessing OMERACT responsiveness provided conflicting reports. Inflammatory biomarkers had construct validity for more active disease. Evidence suggests that an elevation of ESR predicts cardiovascular outcomes.

**Conclusion.** Data regarding assessment of systemic inflammation using acute-phase reactants (CRP and ESR) are limited. There is only weak evidence to support normalization of these biomarkers in predicting good clinical outcomes/remission criteria. The predictive value for cardiovascular outcomes was generally good. Further studies to assess systemic inflammation in PsA using acute-phase reactants and other laboratory biomarkers are needed. (First Release November 1 2018; *J Rheumatol* 2019;46:266–73; doi:10.3899/jrheum.180195)

## Key Indexing Terms:

PSORIATIC ARTHRITIS    INFLAMMATION    OUTCOMES    OUTCOME ASSESSMENT

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Psoriatic arthritis (PsA) is a chronic immune-mediated inflammatory arthritis<sup>1</sup> that occurs in 14–30% of patients with psoriasis and can lead to significant joint damage and disability<sup>2,3,4,5</sup>. PsA is a multifaceted, heterogeneous disease that manifests with the following clinical domains: peripheral arthritis, axial disease, enthesitis, dactylitis, and skin and nail disease. Measuring disease activity accurately can be difficult in PsA, because of the heterogeneity of the clinical features of the disease. Longitudinal studies have consistently demonstrated increased cardiovascular (CV) risk and related metabolic abnormalities in patients with psoriatic

disease<sup>6,7,8,9</sup>. Several studies found an association between the extent of inflammation (both joint inflammation and acute-phase reactants) and poor disease outcomes, including the development of joint damage, cardiometabolic outcomes, and mortality<sup>10–17</sup>.

An updated PsA Core Domain Set was endorsed at Outcome Measures in Rheumatology (OMERACT) 2016 and includes musculoskeletal disease activity, skin disease activity, fatigue, pain, patient's global assessment (PtGA), physical function, health-related quality of life, and systemic inflammation<sup>18</sup>.

Systemic inflammation may be assessed through measurement of acute-phase reactants such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). With few exceptions, most randomized controlled trials (RCT) have assessed acute-phase reactants (CRP/ESR) as part of the American College of Rheumatology (ACR) 20 response criteria primary efficacy endpoints.

The purpose of this paper is to review and summarize the data available for assessment of systemic inflammation using CRP and ESR in PsA RCT, as well as longitudinal observational studies (LOS) and cross-sectional studies. This systematic review will inform selection and/or development of an outcome measurement instrument for the assessment of systemic inflammation in PsA clinical trials.

## MATERIALS AND METHODS

The original search strategy, up to May 2015, has been previously described to identify PsA RCT and observational studies<sup>19</sup>. The search included 2 databases, PubMed and Embase, and had 2 parts: the term for the disease concept "Psoriatic Arthritis" combined with operator "AND" with the validated Cochrane RCT sensitivity filter for each database<sup>20,21</sup>. The literature search was updated from June 2015 to September 2016 using the same methodology; hand searches representing recent interleukin (IL)-17 and IL-6 inhibitors were included from September 2016. We excluded pediatric studies (children age 0–18 yrs) and used the following limits: human studies, English language (Figure 1).

The screening of all titles and abstracts for potential inclusion was performed by 2 investigators (ME and LE). Selected publications were retrieved in full, and 2 reviewers (ME and LE) independently assessed them for eligibility. To be included in the systematic review, original studies in the English language needed to fulfill the following criteria: (1) human studies; (2) adult patients with PsA (> 18 yrs); and (3) RCT, LOS, or cross-sectional studies. Exclusion criteria included animal studies, pediatrics (age 0–18), studies other than RCT, observational studies, and review articles.

Two authors (ME and YYL) independently extracted the data according to a standardized form. Discrepancies were resolved by consensus and involvement of a third author if needed (LE). For each study included, we recorded the following data: population, study design, study drug (if applicable), duration of study, sex, age (weighted mean), PsA disease duration (weighted mean), acute-phase reactant assessed separately, type of acute-phase reactant (ESR and/or CRP), and the extent of change of the acute-phase reactant.

The following components of the OMERACT filter<sup>22</sup> were independently assessed for each study: responsiveness, construct validity, and predictive validity. Responsiveness was evaluated by the ability of the tool to demonstrate change in response to an intervention (e.g., study drug). Construct validity was achieved when the level of acute-phase reactants was concurrently compared with a theoretical concept of inflammation (e.g., clinical disease activity/disease state). Predictive validity was considered when acute-phase

reactant predicted a theoretical concept related to systemic inflammation (e.g., clinical outcomes, radiographic joint damage, CV outcomes). We illustrated the process as recommended in the Preferred Reporting Items for the Systematic reviews and Meta-Analyses (PRISMA) statement<sup>23</sup>.

## RESULTS

An initial literature search for PsA domains and instruments in PsA clinical trials<sup>19</sup> retrieved 2079 entries, of which 60 full-text articles met inclusion criteria. We updated the search in PubMed and Embase and retrieved 685 additional entries. Eleven full-text articles were included, bringing the total number of full-text articles to 71, representing RCT, LOS, and cross-sectional studies (Figure 2).

Following review of full articles and supplementary data, only 28 articles were found to have reported ESR and/or CRP separately. The rest assessed CRP and/or ESR as part of ACR response without separate reporting of their results. The 28 articles represented 12 RCT [tumor necrosis factor inhibitor (2), methotrexate (1), IL-6 inhibitor (1), phosphodiesterase-4 inhibitor (3), IL-17 inhibitor (3), bisphosphonate (1), a panel of 57 protein biomarkers (1)] and 16 observational studies. The total number of patients with PsA included in the studies reviewed was 4761; 40% were female, their mean age was 48.2 years, and mean PsA duration was 8.2 years. The total number of patients in each study varied from 18 to 596.

Eighteen articles assessed OMERACT responsiveness, the ability of CRP/ESR to demonstrate change in response to treatment (11 RCT, 7 observational). Nine studies<sup>24–32</sup> have shown reduction of acute-phase reactants with different treatments. These studies have shown significant reduction of CRP/high-sensitivity CRP (hsCRP), and to a lesser extent, of ESR (Table 1).

Nine other studies<sup>33–41</sup> did report a small change in CRP/ESR; however, they either did not report a p value or the p value was not significant (Table 1).

Ten studies (Table 2) have assessed OMERACT construct validity (level of biomarker correlated with disease state/disease activity measure) representing 3 RCT, 5 LOS, and 1 cross-sectional study. Acute-phase reactants were associated with clinical measures of disease activity. Shen, *et al*<sup>42</sup> demonstrated that patients with PsA had higher CRP/ESR compared to controls, while Sterry, *et al*<sup>39</sup> demonstrated that PsA patients with enthesitis had higher CRP than those without enthesitis.

The association between levels of inflammation at baseline and response to treatment has been assessed in 3 studies with conflicting results. Schett, *et al*<sup>32</sup> reported that elevated CRP (CRP > 8 mg/l) predicted ACR20 response to apremilast. In contrast, Saad, *et al*<sup>43</sup> reported that patients with high ESR (ESR > 28 mm/h) or CRP (CRP > 20 mg/l) are less likely to achieve European League Against Rheumatism response (OR 0.54, 95% CI 0.30–0.96) and remission (OR 0.54, 95% CI 0.31–0.97) at 6 months. Further, Coates, *et al*<sup>44</sup> demonstrated that low ESR predicted minimal disease activity (MDA) in multivariate model with RR 0.62 (p < 0.02).

### Figure 1 - Search parameters and strategies of literature review

**Pubmed:** ("Arthritis, Psoriatic"[Mesh] OR "Psoriatic arthritis" OR "psoriatic arthropathy" OR "arthritis psoriatica" OR "arthropathic psoriasis" OR "psoriasis arthropathica" OR "psoriasis arthropathy" OR "psoriatic polyarthritits" OR "psoriatic rheumatism") AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR "clinical trials as topic"[Mesh] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT ("Animals"[MeSH] NOT ("Animals"[MeSH] AND "Humans"[MeSH])) NOT ("Child"[Mesh] OR "Infant"[Mesh] OR "Infant, Newborn"[MH] OR "Adolescent"[Mesh] OR "Child, Preschool"[MH] OR "child"[all] OR "infant"[all] OR "adolescent"[all] OR "children"[all] OR "infants"[all] OR "adolescents"[all] OR "pediatric patient"[all] OR "pediatric patients"[all] OR "adolescence"[all] OR "youth"[all] OR "youths"[all] OR "juvenile"[all] OR "childhood"[all] OR "teenager"[all] OR "teenagers"[all] OR "teen"[all] OR "teens"[all] OR "preschool child"[all] OR "neonate"[all] OR "newborn"[all] OR "baby"[all]) AND English[lang].

**Embase:** (psoriatic arthritis/exp OR "Psoriatic arthritis" OR "psoriatic arthropathy" OR "arthritis psoriatica" OR "arthropathic psoriasis" OR "psoriasis arthropathica" OR "psoriasis pustulosa arthropathica" OR "psoriasis arthropathy" OR "psoriatic polyarthritits" OR "psoriatic rheumatism") AND (random\* OR factorial\* OR crossover\* OR cross NEXT/1 over\* OR placebo\* OR doubl\* NEXT/1 blind\* OR singl\* NEXT/1 blind\* OR assign\* OR allocate\* OR volunteer\* OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trials'/exp OR 'single-blind procedure'/exp) NOT ('animal'/exp NOT ('animal'/exp AND 'human'/exp)) NOT ('Child'/de OR 'Infant'/de OR 'Adolescent'/de OR 'preschool child'/exp OR 'child':ti,ab OR 'infant':ti,ab OR 'adolescent' OR 'children' OR 'infants' OR 'adolescents' OR 'pediatric patient' OR 'pediatric patients' OR 'adolescence' OR 'youth' OR 'youths' OR 'juvenile'/exp OR 'juvenile' OR 'childhood' OR 'teenager' OR 'teenagers' OR 'teen' OR 'teens' OR 'preschool child' OR 'neonate' OR 'newborn'/de OR 'newborn':ti,ab OR 'baby' OR 'babies' OR 'pediatric':ti,ab OR 'pediatrics':ti,ab OR 'paediatric':ti,ab OR 'paediatrics':ti,ab OR 'toddler'/exp OR 'toddler' OR 'toddlers') AND [english]

Figure 1. A list of the key words and strategies used to conduct the literature review.

One other study assessed other potential inflammatory biomarkers. Ademowo, *et al*<sup>45</sup>, using a proteomic approach in patients with PsA, identified a panel of 57 protein biomarkers in synovial tissue samples of patients with PsA prior to therapy that predicted treatment response to biologic therapy with an area under the curve of 0.76. This novel biomarker panel was developed to be measured at baseline to predict patient response to biologics (adalimumab and abatacept). Some of these proteins on the candidate biomarker panel [fibrinogen, type 11 collagen, serum amyloid A, haptoglobin, and the S100 family proteins (A8, A9, A11, and A12)] have been found previously to play significant roles in inflammation<sup>45</sup>. This study suggests that novel biomarkers may be used in the future to predict PsA response to treatment.

Two LOS<sup>30,46</sup> and a cross-sectional study<sup>47</sup> reported that ESR and CRP do not predict MDA, 28-joint Disease Activity Score remission, PtGA, physician's global assessment, and Assessment of Spondyloarthritis international Society partial remission. No study has evaluated the value of ESR/CRP in predicting radiographic joint damage. Castaneda, *et al*<sup>48</sup> assessed CV morbidity and associated risk factors for CV disease in Spanish patients with chronic inflammatory rheumatic diseases and unexposed individuals attending

rheumatology clinics in a cross-sectional study. They did not establish a statistically significant association between inflammatory markers and CV risk in the PsA group (721 out of 2234 patients); however, most patients generally had mild disease activity at recruitment, were followed periodically by rheumatologists, and over 40% were treated with biologics. Most of the patients had low levels of disability and the acute-phase reactants were within normal range.

Regarding OMERACT predictive validity (predictive validity was considered when acute-phase reactant predicted radiographic damage or clinical outcome), 4 LOS evaluated the predictive validity of ESR and CRP (Table 3). Shen, *et al*<sup>42</sup> demonstrated that cumulative ESR (defined as cumulative averages of ESR over time) was associated with increased arterial stiffness, assessed by pulse wave velocity, independently of traditional CV risk factors (OR 9.455, 95% CI 1.939–46.093;  $p = 0.005$ ). Eder, *et al*<sup>10,15</sup> showed in 2 different studies that elevated levels of ESR were associated with increased CV risk. In the age- and sex-adjusted models, increased adjusted mean ESR (OR 1.41, 95% CI 1.09–1.82) was associated with a more severe degree of carotid atherosclerotic plaques in patients with PsA. In addition, in a longitudinal cohort study of 1091 patients with PsA, Eder, *et al*<sup>10</sup> demonstrated that ESR was an independent predictor of

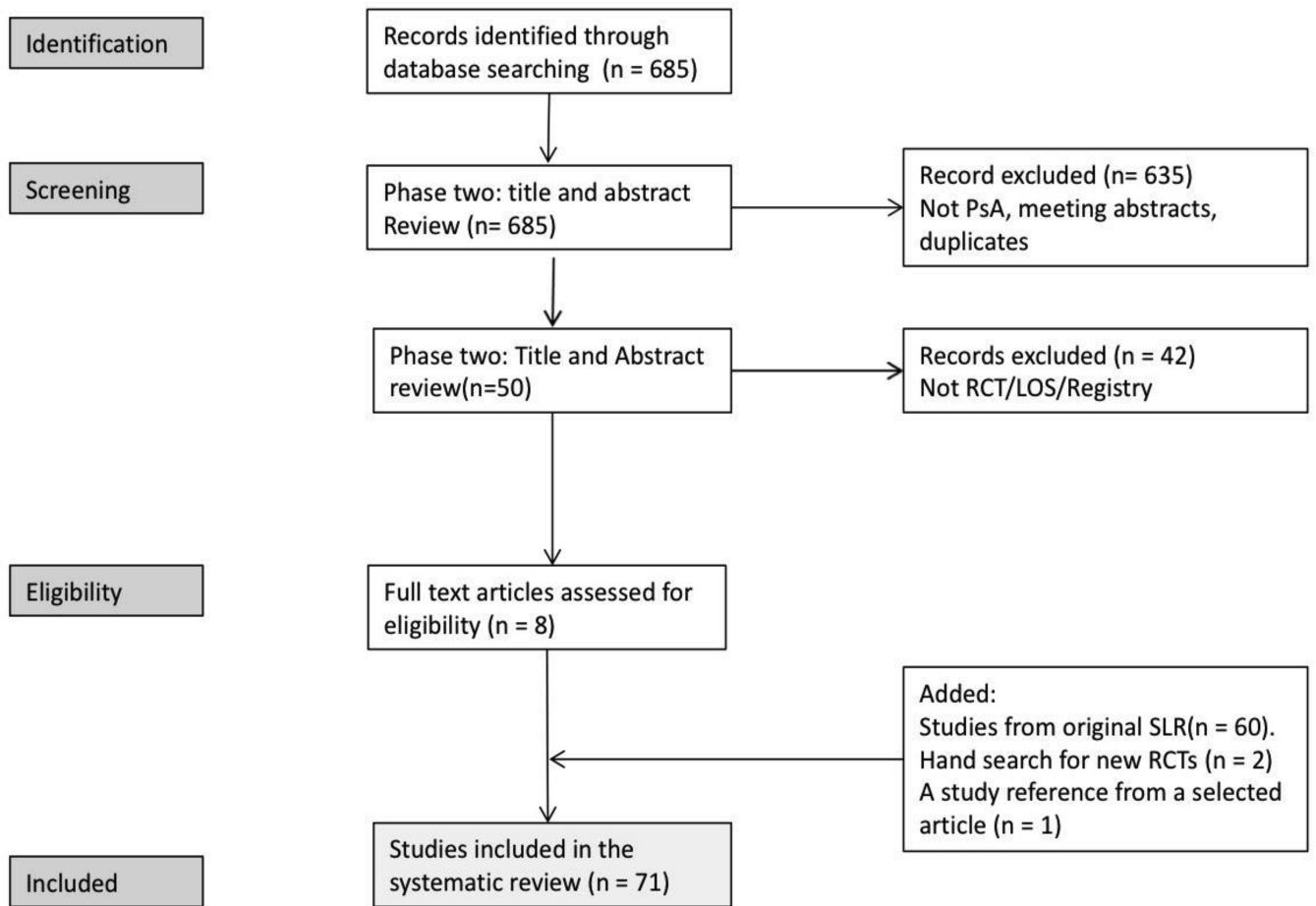


Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram, record identification, screening, eligibility, and inclusion. PsA: psoriatic arthritis; RCT: randomized controlled trial; LOS: longitudinal observational studies; SLR: systematic literature review.

clinical CV events in women after controlling for CV risk factors (RR 1.83,  $p = 0.02$ ). Geijer, *et al*<sup>49</sup> have reported in univariate analysis that baseline ESR correlated with baseline radiographic joint damage as assessed by Wassenberg scores ( $p = 0.027$ ).

## DISCUSSION

Systemic inflammation characterizes psoriatic disease and the assessment of the extent of inflammation using laboratory biomarkers has a potential for improved evaluation of disease activity in patients with PsA. To our knowledge, this is the first study to assess systemic inflammation in PsA using the OMERACT filter. This systematic literature review represents a critical examination of the published data regarding the state of validation of the most commonly used inflammatory biomarkers in PsA.

In this systematic review, all studies have assessed an acute-phase reactant: CRP, hsCRP, or ESR. However, only 40% reported the results of these biomarkers separately, even though all RCT have assessed these biomarkers as part of the

primary endpoint, the ACR20 response. Data available for evidence synthesis were therefore limited.

Studies assessing OMERACT responsiveness provided conflicting reports. Nine of these studies<sup>24–32</sup> demonstrated responsiveness with treatment, while 9 other studies<sup>33–41</sup> did not report significant results. Clearly there is a need for more homogeneous studies to assess this component further with larger RCT or novel biomarkers.

Inflammatory biomarkers had good construct validity, with CRP/ESR being higher in patients with PsA, and patients with enthesitis versus those without enthesitis<sup>39,42</sup>. While the association between ESR/CRP and clinical disease outcomes was conflicting, there was more evidence to suggest that an elevation of ESR predicts CV outcomes. CRP, which was associated with increased CV risk in chronic inflammatory arthritis<sup>50</sup>, was not associated with CV risks in PsA based on a single cross-sectional study. This finding may be explained by the relatively low levels of chronic inflammation found in PsA using only traditional methods (CRP, ESR).

Table 1. Studies that assessed responsiveness of inflammatory markers to treatment.

Author (Year)	Study Type	Study Drug	Biomarker	Responsiveness
Kingsley (2012) <sup>36</sup>	RCT	MTX	CRP, ESR	CRP (mg/dl) 6-month change MTX: -2.0; PBO: -3.6 (not significant); ESR (mm/h) 6-month change MTX: -6.2; PBO: -3.6 (not significant)
Baranauskaite (2012) <sup>24</sup>	RCT	MTX + IFX	CRP, ESR	CRP (mg/l) median change: treatment arm -12.0 vs PBO -5.8 (p = 0.0026); ESR (mm/h) median change: treatment arm -12.0 vs PBO -8.0 (p = 0.0023)
Mease (2014) <sup>26</sup>	RCT	Broda	CRP, ESR	CRP (mg/l) median % change: PBO: 0, Broda 140 mg: -1, 280 mg: -24.6 (p < 0.05); ESR (mm/h) median % change: PBO: -9.1, Broda 140 mg: -14.5, Broda 280: -26.9 (not significant)
McInnes (2014) <sup>25</sup>	RCT	Secukinumab	CRP, ESR, hBD2	Data presented in graphs, no figures available. Significant reduction compared to PBO (from baseline to Week 6): CRP (mg/l) p = 0.039; ESR (mm/h) p = 0.038, hBD -2 (p = 0.009)
Mease (2017) <sup>28</sup>	RCT	IX	hsCRP	hsCRP (mg/l) at Week 12 mean change from baseline: PBO -3.2, IXQ4W -8.8, IXQ2W -9.2 (p < 0.001 vs PBO)
Mease (2016) <sup>27</sup>	RCT	CZK	hsCRP	hsCRP (mg/l) at Week 16 PBO: -0.6 (95% CI -3.24 to 2.03); CZK 25 mg: -13.79 (95% CI -16.42 to -11.16); CZK 100 mg: -14.41 (95% CI -170.2 to -11.79); CZK 200 mg: -14.20 (95% CI -16.86 to -11.54)
Cutolo (2016) <sup>34</sup>	RCT	APM	CRP	CRP (mg/dl) mean change Week 16: PBO -0.10 (1.4), APM 20 mg -0.19 (2.1), APM 30 mg -0.13 (1.7); not significant
Kavanaugh (2014) <sup>41</sup>	RCT	APM	CRP	CRP (mg/dl) mean change PBO: 0.17, APM 20 mg: -0.02 (p = 0.1321), APM 30 mg: -0.05 (p = 0.0713)
Schett (2012) <sup>32</sup>	RCT	APM	CRP	Posthoc analysis: patients with high CRP (> 8 mg/l), significant reduction in CRP. (1) APM 20 mg/BD: change from baseline -49.6%; n = 25; (2) APM 40 mg/om: change from baseline -33.8%, n = 28; (3) PBO change from baseline -18.8%, n = 24.
Sterry (2010) <sup>39</sup>	RCT	ETN	CRP	Mean concentration CRP (mg/l), 50 mg bi-weekly: from 15.3 to 5.5 by Week 24; 50 mg weekly: from 16.2 to 5.7 by Week 24
McQueen (2011) <sup>37</sup>	RCT	ZA	CRP	Not significant, not approved treatment
Theander (2014) <sup>30</sup>	LOS	NA	CRP, ESR	CRP (mg/dl) change: male 12.2-6.3, female 20.7-8.2; ESR (mm/h): male 13.7-8.7, female 22.9-14.7 (p < 0.00)
Virkki (2010) <sup>31</sup>	LOS	ETN, IFX, ADA, anakinra	CRP, ESR	Values not available; p < 0.001. IFX: CRP (mg/l) dropped from around 40 to around 5; ESR (mm/h) dropped from > 40 to around 10. ETN: CRP (mg/l) dropped from around 15 to around 5; ESR (mm/h) dropped from > 20 to < 10.
Vogelzang (2014) <sup>40</sup>	LOS	ADA	CRP, ESR	CRP (mg/l) median: 5, Week 28: 2, Week 52: 1; ESR (mm/h) median: 11, Week 28: 5, Week 52: 5
Paramarta (2013) <sup>38</sup>	LOS	NA	CRP, ESR	Decrease in CRP, ESR not significant (data not shown)
Scarpa (2011) <sup>29</sup>	LOS	Anti-TNF	CRP, ESR	CRP: 1.5, Week 12: 0.6, Week 24: 0.3. p < 0.001; ESR: 24, Week 12: 15, Week 24: 9 (p < 0.001)
Behrens (2013) <sup>33</sup>	LOS	Leflunomide	CRP	German subgroup. CRP (mg/dl) reduction: 25.38 ± 33.62 to 11.48 ± 17.98 at Week 24 (no p value)
Fagerli (2013) <sup>35</sup>	LOS	Anti-TNF	CRP	CRP (mg/l) mean change nonswitcher (switching between anti-TNF) -2; switcher 0 (p = 0.34)

CRP: C-reactive protein; hsCRP: high-sensitivity CRP; ESR: erythrocyte sedimentation rate; hBD2: human β-defensin 2; RCT: randomized controlled trial; LOS: longitudinal observational study; PBO: placebo; MTX: methotrexate; IFX: infliximab; ETN: etanercept; ADA: adalimumab; APM: apremilast; CZK: clazakizumab; TNF: tumor necrosis factor; IX: ixekizumab; IXQ2W: IX every 2 weeks; IXQ4W: IX every 4 weeks; ZA: zolendronic acid; Broda: brodalumab; NA: not applicable; BD: twice daily; om: daily.

One of the limitations of our review is that not all papers reported the results of CRP/ESR separately and therefore only a few studies inform construct and predictive validity. Moreover, some of the studies were observational, raising the issue of selection bias and the uncertainty of the comparability of groups.

Inflammatory biomarkers have good construct validity based on their association with active disease. Inflammatory biomarkers have been incorporated into composite measures

to assess clinical response in clinical trials. However, when used alone they provide inconsistent evidence of responsiveness in clinical trials. There is only weak evidence to support these biomarkers in predicting good clinical outcomes/remission criteria. Derived from 4 studies, the predictive value for CV outcomes was generally good.

Further large RCT to assess systemic inflammation in PsA using acute-phase reactants and high-sensitivity assays are needed. We recommend that all future RCT should assess and

Table 2. Studies that assessed construct validity.

Author (Year)	Study Type	Study Drug	Biomarker	OMERACT/Construct Validity
Ademowo (2016) <sup>45</sup>	RCT	ADA	57 protein biomarkers	Predict treatment response, AUC 0.76.
Sterry (2010) <sup>39</sup>	RCT	ETN	CRP	Patients with enthesitis had higher CRP (mg/l) at baseline than those without enthesitis.
Schett (2012) <sup>32</sup>	RCT	APM	CRP	A greater percentage of APM-treated patients with a baseline CRP level of > 8 mg/l achieved an ACR20 response compared with patients whose baseline CRP level was ≤ 8 mg/l (p ≤ 0.005).
Coates (2010) <sup>44</sup>	LOS	NA	ESR	Low ESR predicted MDA; p < 0.03 in univariate, p < 0.02 in multivariate; RR 0.62, p < 0.02 in Cox proportional hazards model.
Iannone (2013) <sup>46</sup>	LOS	NA	ESR, CRP	Baseline ESR and CRP (mg/dl) do not predict DAS28 remission: (OR 1.03, p = 0.20) and (OR 0.84, p = 0.33), respectively.
Saad (2010) <sup>43</sup>	LOS	Anti-TNF (ETN, ADA, IFX)	ESR, CRP	High CRP or ESR (CRP > 20 mg/l or ESR > 28 mm/h) are less likely to achieve high EULAR response (OR 0.54*, 95% CI 0.30–0.96) and remission (OR 0.54*, 95% CI 0.31–0.97) at 6 months.
Shen (2015) <sup>42</sup>	LOS	NA	ESR, CRP	PsA patients had higher ESR (mm/h) and CRP (mg/dl) compared to healthy controls.
Theander (2014) <sup>30</sup>	LOS	NA	ESR, CRP	ESR (mm/h) and CRP (mg/l) were not predictors of MDA.
Kilic (2015) <sup>47</sup>	Cross-sectional	NA	ESR, CRP	Lowest discriminative capacity. SMD for ESR to predict patient's global 0.38; physician's global 0.44; and ASAS partial remission 0.70. SMD for CRP (mg/l) to predict patient's global 0.38; physician's global -0.12; and ASAS partial remission 0.59.
Castaneda (2015) <sup>48</sup>	Cross-sectional	NA	ESR, CRP	CRP (mg/l): PsA/CVE: 3.6 (IQR 1.5–8.5), PsA no CVE 2.9 (1.3–6.0), p = 0.334. ESR: PsA/CVE: 10 (7–30.2), PsA no CVE 12 (6–20.5), p = 0.491.

OMERACT: Outcome Measures in Rheumatology; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate (mm/h); PsA: psoriatic arthritis; RCT: randomized controlled trial; LOS: longitudinal observational study; ADA: adalimumab; ETN: etanercept; APM: apremilast; AUC: area under the curve; TNF: tumor necrosis factor; SMD: standard mean difference; DAS28: 28-joint count Disease Activity Score; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; ASAS: Assessment of Spondyloarthritis international Society; MDA: minimal disease activity; CVE: cardiovascular event; IQR: interquartile range; NA: not applicable; RR: rate ratio; IFX: infliximab.

Table 3. Studies that assessed predictive validity of inflammatory biomarkers.

Author (Year)	Type of Study	Study Drug	ESR/CRP	OMERACT/Predictive Validity
Eder (2016) <sup>10</sup>	LOS	NA	ESR	In multivariate analysis, ESR was a significant predictor of CVE only among women (RR 1.83, 95% CI 1.12–2.99).
Eder (2015) <sup>15</sup>	LOS	NA	ESR, CRP	Elevated levels of ESR were associated with more severe atherosclerosis. In the age- and sex-adjusted models, increased AM-ESR (OR 1.41, 95% CI 1.09–1.82) were associated with a higher likelihood of being in a more severe atherosclerosis category.
Geijer (2015) <sup>49</sup>	LOS	NA	ESR, CRP	Baseline ESR only correlated with baseline Wassenberg scores (univariate analysis, p = 0.027), not at 5 yrs.
Shen (2015) <sup>42</sup>	LOS	NA	ESR, CRP	High cESR associated with increased arterial stiffness [high cESR was associated with a higher likelihood of being in the high PWV group after adjustment for other clinical and CV risk factors at baseline (OR 9.455, 95% CI 1.939–46.093; p = 0.005) or last visit (OR 9.111, 95% CI 1.875–44.275; p = 0.006)].

CRP: C-reactive protein (mg/dl); ESR: erythrocyte sedimentation rate (mm/h); cESR: cumulative ESR; OMERACT: Outcome Measures in Rheumatology; LOS: longitudinal observational study; CV: cardiovascular; CVE: CV event; PWV: pulse wave velocity; AM: adjusted mean; NA: not applicable.

report the results of acute-phase reactants/systemic inflammation separately. Additional studies are also needed to identify novel laboratory biomarkers for the assessment of systemic inflammation in PsA.

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