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ORIGINAL ARTICLE

Elevated CRP even at the first visit to a rheumatologist is associated with long-term poor outcomes in patients with psoriatic arthritis

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Abstract

Objectives Little is known about the long-term association of CRP levels during psoriatic arthritis (PsA) disease course. In this study, we examined whether raised CRP over the disease course is associated with worse outcome measures in a well-characterised PsA cohort with a long-term follow up.

Methods A cohort of 283 PsA patients (fulfilling CASPAR criteria) was evaluated. All underwent detailed skin and rheumatologic assessments. Moreover, we documented the presence/absence of comorbidities using Charlson Comorbidity Index (CCI). CRP at first visit to a rheumatologist was documented. Cumulative inflammation over time was represented by the cumulative averages of CRP (ca-CRP). Multiple linear regression modelling CRP was used.

Results Two hundred eighty-three PsA patients attended for detailed assessments. A total of 56.5% ($n = 160$) of the cohort had raised CRP at their first visit to our rheumatology department, and this was significantly associated with long-term erosions, sacroiliitis, PsA requiring TNFi, and high comorbidity Index, on logistic regression analysis. Moreover, 24% ($n = 69$) of the cohort never had raised CRP during their long-term follow-up, and on logistic regression analysis, such patients had significantly milder disease with fewer erosions, less sacroiliitis and fewer patients requiring TNFi therapy. The median (IQR) and mean (SD) Ca-CRP was 8.8 (4.6–14.8) and 11.72 (10.52), respectively. On multiple linear regression, erosions, sacroiliitis and CCI were most significantly associated with ca-CRP [($F = 77.6$, $p < 0.001$), 72% (R-square)].

Conclusions Elevated CRP is associated with radiographic damage, disease more resistant to treatment and also having higher number of significant comorbidities. Raised CRP can help stratify patients with a more severe PsA phenotype.

Keywords Comorbidities · CRP · Inflammatory markers · Psoriatic arthritis · Radiographic damage

Key Points
- *Raised CRP can provide important future prognostic information among patients with PsA.*
- *PsA patients with raised CRP at first visit to a rheumatologist had significantly more destructive and refractory disease.*
- *PsA patients with consistently normal CRP had significantly milder disease.*

Introduction

Psoriatic arthritis (PsA) is a progressive immune-mediated inflammatory musculoskeletal disease, which if untreated leads to joint damage and disability. Despite the increasing primary care physician and dermatologist awareness of PsA, the prevalence of undiagnosed PsA remains high [1]. A recent study of psoriasis patients attending a dermatology clinic has shown that 29% of patients had undiagnosed PsA [1]. PsA was formerly considered a milder form of arthritis but an inception cohort study has shown that 47% of the PsA patients who presented within 5 months of onset of symptoms had ≥ 1

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erosion by the second year of follow-up, despite the fact that the majority had been treated with disease-modifying anti-rheumatic drugs (DMARDs) [2]. In another study, 67% of PsA patients demonstrated ≥ 1 radiographic erosion at their initial presentation to a rheumatologist [3]. In PsA, even few months delay from symptom onset to the first visit with a rheumatologist has been shown to contribute to the development of structural damage and worse long-term physical function [4]. Given the propensity for the early occurrence of destructive disease, prompt identification of such patients with poor outcome is an important step towards optimal patient management.

Acute-phase reactants are proteins whose concentrations in blood stream change during inflammation. There are a number of biomarkers of inflammation, such as C-reactive protein (CRP), the erythrocyte sedimentation rate (ESR), serum Amyloid A, fibrinogen, ferritin and serum protein electrophoresis. The acute-phase reactant most commonly used for diagnostic purpose is CRP, since this is simple, cost-effective and widely available. Moreover, CRP is considered a more sensitive and specific marker of the acute-phase reaction and is more responsive to changes in the patient's condition [5]. C-reactive protein is probably the most investigated biomarker, which promotes the interaction between humoral and cellular immunity [6, 7]. It is produced by liver and subsequently binds to pathogens and damaged/apoptotic cells, causing their elimination by activating the complement system and the phagocytes [8].

Since inflammation is the hallmark of inflammatory arthropathies, analysis of inflammatory biomarkers is used in different rheumatologic diseases to monitor disease activity. In contrast to rheumatoid arthritis, however, these markers are raised in less than 50% of people with PsA [9]. Although there is some evidence from randomised controlled trials [10, 11], the real-world evidence is lacking as regards the long-term impact associated with elevation in CRP levels during the course of PsA. In this study, we examined whether raised CRP over the disease course is associated with worse clinical, radiographic, patient-reported outcome measures and the associated clinically important comorbid conditions in a well-characterised PsA cohort with a long-term follow up.

Methods

Patients and comorbidities evaluation

All patients attending rheumatology clinics at St Vincent's University Hospital Dublin with a confirmed diagnosis of PsA, as per the internationally agreed CASPAR criteria (Classification of Psoriatic Arthritis Criteria) [12], were suitable for inclusion in this cross-sectional study. A consecutive cohort of 283 Caucasian patients with an average disease duration of > 10 years was identified, and then invited for evaluation. History of diabetes, hypertension, hypercholesterolaemia, overt cardiovascular disease including myocardial infarction, angina, stroke and transient ischaemic attack and malignant neoplastic disease and the presence/absence of other comorbidities using the Charlson Comorbidity Index (CCI) [13] was documented.

All these patients had periodic CRP [normal value 0-10 mg/L] laboratory values checked along with the other routine laboratory parameters during the disease course. For each patient, we made 3 documentations of CRP values at different time points, which included: first, at the time of the initial diagnosis (first visit with a rheumatologist); second, the highest value of CRP recorded during the disease course and third one at the time of full assessment for this particular clinical study. The long-term impact of CRP values may be better represented by the cumulative average of inflammatory markers than the measurement of these markers at a single time point; hence, cumulative inflammation over time was represented by the cumulative averages of CRP (ca-CRP). Ca-CRP was calculated from the AUC (Area Under the Curve) of 3 documented measurements divided by the total number of months of follow-up.

Evaluation of disease activity and severity

Following informed consent, patients underwent a detailed skin and rheumatologic assessment including disease activity measures. Since the majority of the cohort was in clinical remission at the time of assessment, we made 2 documentations of all reversible clinical features at different time points. These documentations included: firstly, the clinical variables collected at the time of current assessment, e.g. current skin scores and current tender and swollen joints; and secondly, through extensive medical record review, we identified patient's maximum skin and joints disease activity scores ever documented, e.g. maximum skin scores and maximum tender and swollen joints ever raised during a flare of PsA.

For skin psoriasis, the extent and severity of skin psoriasis was assessed by the Psoriasis Area and Severity Index (PASI), which is the most widely used tool for the measurement of severity and extent of psoriasis. For PsA, physical examination included recording the number of tender and swollen joints using the 68 tender/66 swollen joint counts, the presence of dactylitis, the presence of enthesitis and the number of permanently deformed joints. Clinically deformed joints were defined as the presence of fixed deformities, flail joints, fused joints and surgically replaced joints [3, 14]. Laboratory assessments included rheumatoid factor, anti-CCP antibodies and C-reactive protein (CRP). A number of patient-reported outcome measures (PROMs) were also recorded, e.g. Health Assessment Questionnaire (HAQ), Dermatology Life Quality Index (DLQI), Bristol Rheumatoid Arthritis Fatigue

Table 1 Descriptive statistics for numeric variables. Valid $n = 283$

Numerical variables	**Median (IQR)**	**Mean (SD)**
Age, years	55.0 (46.0–63.0)	54.61 (12.22)
PsA duration, years	18.0 (13.0–24.0)	19.41 (9.32)
Smoking, years	13.0 (8.0–21.0)	18.48 (19.63)
BMI	28.2 (25.1–32.5)	29.10 (5.46)
PASI maximum	3.8 (1.8–9.2)	5.72 (5.28)
Surface area of skin affected	6.0 (3.0–12.0)	9.89 (11.29)
Age of PsA onset, years	34.0 (25.0–45.0)	35.04 (12.74)
Number of deformed joints	3.0 (0.0–8.0)	5.88 (7.98)
Number of tender joints	10.0 (8.0–15.0)	11.97 (6.76)
Number of swollen joints	8.0 (5.0–11.0)	8.39 (5.10)
Number of TNFi used	1.0 (1.0–2.0)	1.35 (0.75)
Number of DMARDs failure	1.0 (1.0–2.0)	1.22 (1.00)
Time between PsO and PsA onsets	6.0 (0.0–12.0)	7.30 (10.76)
HAQ	0.5 (0.0–1.0)	0.58 (0.57)
DLQI	1.0 (0.0–3.0)	2.62 (3.98)
PCS-SF36	44.0 (34.0–53.0)	43.05 (10.78)
MCS-SF36	49.0 (38.0–57.0)	47.01 (11.58)
ESR cumulative	13.8 (7.8–20.1)	15.78 (10.46)
CRP cumulative	8.8 (4.6–14.8)	11.72 (10.52)
Charlson Comorbidity Index	5.0 (3.0–8.0)	5.51 (3.12)
Fatigue (BRAF)	14.0 (10.0–18.0)	14.01 (5.08)
Categorical variable—%(*n*)	**Number**	**Percentage**
Gender—male	134	47.3
Smoker	124	43.8
Educated (completed secondary school education)	225	79.5
Nail disease	224	79.2
Severe PsO (PASI score > 10)	70	24.7
Oligoarthritis	25	8.8
Enthesitis	97	34.3
Dactylitis	150	53
Erosion	127	45
Osteolysis	41	14.5
Sacroiliitis	70	25
Deformed joints	183	64.7
Required TNFi	171	60.4
Uveitis	9	3
Arthritis mutilans	23	8
Metabolic syndrome	124	44
History of malignancy	23	8

Valid $n = 171$ for those patients who required TNF therapy. Time between PsO and PsA onsets = time interval between the development of psoriasis and psoriatic arthritis

BMI Body Mass Index, *HAQ* Health assessment questionnaire, *DLQI* Dermatology Life Quality Index, *PCS-SF36* physical component summary score SF-36, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale

Numeric Rating Scale (BRAF-NRS) and quality of life (using SF-36). SF-36 version 2 was used and individual physical and mental component summary scores (PCS-SF36 and MCS-SF36) were recorded. Education status of the cohort was stratified by whether participants completed secondary (high) school education. Finally, radiographs were obtained in all patients of involved joints along with hands, feet and sacroiliac joints at the time of assessment. All of these radiographs were assessed by a consultant musculoskeletal radiologist and 2 trained rheumatologists. This study was approved by the local Medical Research Ethics committee.

Table 2 Clinical characterisation of patients who had raised CRP at first visit with a rheumatologist compared to the rest of the cohort

Numerical variables—%(*n*)	**Cohort with raised CRP at first visit (*n* = 160)**	**Cohort with normal CRP at 1st visit (*n* = 123)**	***p* value**
Age, years	55 ± 12	54 ± 13	0.58
PsA duration, years	20 ± 10	18 ± 8	0.03
Smoking, years	16.7 ± 15	21 ± 24	0.22
BMI	29 ± 6	28 ± 5	0.04
PASI maximum	6 ± 5.7	5 ± 4.5	0.30
Number of deformed joints	7 ± 9	4 ± 6	< 0.001
Number of tender joints	13 ± 7	11 ± 6	0.01
Number of swollen joints	9 ± 5	7 ± 5	0.008
Number of TNFi used	0.98 ± 0.91	0.63 ± 0.79	0.001
Number of DMARDs failure	1.39 ± 1.09	1.01 ± 0.82	0.001
Time between PsO and PsA onsets	6.37 ± 10	8.5 ± 11.6	0.09
HAQ	0.57 ± 0.54	0.58 ± 0.60	0.94
DLQI	2.7 ± 3.9	2.4 ± 4.0	0.54
PCS.SF36	43 ± 10	43 ± 11	0.75
MCS-SF36	45 ± 11	47 ± 11	0.08
Charlson Comorbidity Index	6.2 ± 3.1	4.5 ± 2.8	< 0.001
Fatigue (BRAF)	14.7 ± 5	13 ± 5	0.004
Categorical variables—% (*n*)			***p* value**
Gender—male	49 (79)	45 (55)	0.47
Smoker, active	46 (74)	41 (50)	0.39
Educated	21 (34)	19.5 (24)	0.76
Nail disease	77.5 (124)	81 (100)	0.46
Severe psoriasis	26 (41)	24 (29)	0.78
Oligoarthritis	4 (6)	12 (15)	0.01
Enthesitis	34 (42)	34 (55)	1.0
Dactylitis	56 (89)	50 (61)	0.33
Erosions	57.5 (92)	28.5 (35)	< 0.001
Osteolysis	18 (29)	10 (12)	0.06
Sacroiliitis	34 (54)	14 (17)	< 0.001
Deformed joints	73 (117)	54 (66)	0.001
PsA require TNFi	70 (112)	48 (59)	< 0.001
Uveitis	4.4 (7)	3 (9)	0.30
Arthritis mutilans	9 (14)	7 (9)	0.82
Metabolic syndrome	49 (78)	37 (46)	0.07
History of malignancy	1.4 (4)	7 (9)	0.61

Valid *n* = 171 for those patients who required TNF therapy. Time between PsO and PsA Onsets = Time interval between the development of psoriasis and psoriatic arthritis

BMI Body Mass Index, *HAQ* Health assessment questionnaire, *DLQI* Dermatology Life Quality Index, *PCS-SF36* physical component summary score SF-36, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale

Statistical analysis was performed using the SPSS software, version 21. Significance was defined as $p < 0.05$ (two-tailed). A chi-square (X^2) statistic was used to investigate the distribution of categorical variables, and continuous variables were analysed using Student's *t* test, which were not categorised. We have used the Bonferroni correction because it adjusts probability (*p*) values since there is a risk of type I error when making multiple statistical tests. The association of different clinical variables with CRP was determined using univariate and multivariate regressions. Regarding cumulative averages of CRP (ca-CRP), multiple linear regression was used to investigate clinically important associations.

Results

A total of 283 PsA patients [mean age 54.6 ± 12 years; 52% female; mean PsA duration of 19 ± 9 years; 25% with

Table 3 Univariate and multivariate associations of different clinical variables with the cohort having raised CRP at first visit with a rheumatologist

	Univariate model			Multivariate model		
	OR	95% CI	*p* value	OR	95% CI	*p* value
BMI	1.04	1.00–1.09	0.04	1.06	1.01–1.12	0.01
Time between PsO and PsA onsets	0.98	0.96–1.00	0.09			
Less educated	1.11	0.62–1.99	0.72			
PsA duration	1.02	1.00–1.05	0.03			
Severe PsO (PASI > 10)	1.11	0.64–1.93	0.69			
Erosion	3.40	2.06–5.61	< 0.001	2.50	1.43–4.35	0.001
Sacroiliitis	3.17	1.73–5.83	< 0.001	2.82	1.46–5.47	0.002
PsA requiring TNFi	2.53	1.55–4.12	< 0.001	2.17	1.26–3.72	0.005
Dactylitis	1.27	0.79–2.04	0.31			
Oligoarthritis	0.28	0.10–0.74	0.01			
Number of tender joints	1.05	1.01–1.09	0.01			
Number of swollen joints	1.07	1.01–1.12	0.01			
Number of deformed joints	1.06	1.02–1.09	0.001			
Number of DMARDs failure	1.50	1.16–1.94	0.002			
Charlson Comorbidity index	1.22	1.12–1.32	< 0.001	1.17	1.06–1.28	0.001
Fatigue (BRAF)	1.07	1.02–1.12	0.005			
MCS-SF36	1.01	0.99–1.04	0.08			
Arthritis mutilans	1.21	0.50–2.90	0.66			
Metabolic syndrome	1.59	0.98–2.57	0.057			

A multiple regression was run to model raised CRP at first visit from PsA duration, BMI, number of deformed joints, number of swollen joints, number of tender joints, number of DMARDs failure, PsA requiring TNFi, comorbidity index, oligoarthritis, erosions, sacroiliitis, time interval between the development of psoriasis and psoriatic arthritis, metabolic syndrome, fatigue score, severe PsO (PASI > 10), and smoking. The model is significant (chi square = 70.5, $p < 0.001$). Erosions, sacroiliitis, PSA requiring TNFi, Charlson Comorbidity Index and high BMI were most significantly associated with CRP, when controlled for all other variables in the model. Time between PsO and PsA Onsets = time interval between the development of psoriasis and psoriatic arthritis

BMI Body Mass Index, *HAQ* Health assessment questionnaire, *DLQI* Dermatology Life Quality Index, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale, *OR* odds ratio

sacroiliitis; 44.5% with radiographic peripheral joint erosions; 8% with arthritis mutilans; 60% of patients requiring TNFi for PsA] attended for detailed assessments. Table 1 provides descriptive statistics for numeric and categorical variables in more detail.

We noted that 56.5% ($n = 160$) of the cohort had raised CRP at their first visit to our rheumatology department. It was noteworthy that such patients had high BMI (29 ± 6 vs. 28 ± 5, $p = 0.04$), higher number of deformed joints (7 ± 9 vs. 4 ± 6, $p < 0.001$), higher number of tender joint counts ever (13 ± 7 vs. 11 ± 6, $p = 0.01$), higher number of swollen joint counts ever (9 ± 5 vs. 7 ± 5, $p = 0.008$), higher number of TNFi used (0.98 ± 0.91 vs. 0.63 ± 0.79, $p = 0.01$), higher number of DMARDs failure (1.39 ± 1.09 vs. 1.01 ± 0.82, $p = 0.001$), reduced time interval between the development of PsO and PsA (6.37 ± 10 vs. 8.5 ± 11.6, $p = 0.09$), higher comorbidities (6.2 ± 3.1 vs. 4.5 ± 2.8, $p < 0.001$), and more fatigue (14.7 ± 5 vs. 13 ± 5, $p = 0.004$) (Table 2). A multiple regression was run to model raised CRP at first visit from PsA duration, BMI, number of deformed joints, number of swollen joints ever, number of tender joint counts ever, number of DMARDs failure, PsA requiring TNFi, comorbidity index, oligoarthritis, erosions, sacroiliitis, time interval between the development of PsO and PsA, metabolic syndrome, fatigue score, severe PsO (PASI > 10) and smoking. This model was significant (chi square = 70.5, $p < 0.001$), and it was noted that high CRP at first visit was associated with erosions, sacroiliitis, PsA requiring TNFi, comorbidity index and high BMI, when controlled for all other variables in the model (Table 3).

We also found that 24% ($n = 69$) of patients never had raised inflammatory marker (CRP) during the long-term follow up, even though there were multiple documentations of active inflammatory musculoskeletal disease during clinic visits. It was interesting to note that such patients had low fatigue levels (13 ± 5 vs. 14 ± 5, $p = 0.01$), low comorbidity index (4.3 ± 2.5 vs. 5.8 ± 3.2, $p = < 0.001$), comparable quality of life and functional status (HAQ, SF-36, $p > 0.05$), lower number of DMARDs failure (0.87 ± 0.89 vs. 1.34 ± 1.04, $p \leq 0.001$), lower number of TNFi failures (0.51 ± 0.83 vs.

Table 4 Clinical characterisation of patients who had normal CRP during the disease course compared to the rest of the cohort

Numerical variables	**Cohort with normal CRP**	**Cohort with raised CRP**	***p* value**
Age, years	54 ± 11	54 ± 12	0.94
PsA duration, years	17.7 ± 9.5	20 ± 9	0.08
Smoking, years	21 ± 26	17 ± 6	0.32
BMI	27.7 ± 5	29.5 ± 5	0.03
PASI maximum	5 ± 4	6 ± 5	0.08
Age PsA onset	37 ± 13	34 ± 12	0.14
Number of deformed joints	3 ± 6	7 ± 8	0.001
Number of tender joints	11 ± 7	12 ± 6	0.17
Number of swollen joints	7 ± 5	9 ± 5	0.01
Number of TNFi used	0.51 ± 0.83	0.93 ± 0.86	0.001
Number of DMARDs failure	0.87 ± 0.89	1.34 ± 1.01	0.001
Time between PsO and PsA onsets	11.4 ± 12.8	6 ± 9.6	< 0.001
HAQ	0.54 ± 0.56	0.58 ± 0.57	0.63
DLQI	2.7 ± 4.3	2.6 ± 3.8	0.82
PCS.SF36	43 ± 11	43 ± 10	0.82
MCS-SF36	45 ± 11	47 ± 11	0.07
Charlson Comorbidity Index	4.3 ± 2.5	5.8 ± 3.2	< 0.001
Fatigue (BRAF)	13 ± 5	14 ± 5	0.01
Categorical variables	**mean ± SD**	***p* value**	
Gender—male	42 (29)	49 (105)	0.33
Smoker, active	46 (32)	43 (92)	0.67
Less educated	13 (9)	23 (49)	0.08
Nail disease	83 (57)	78 (167)	0.50
Severe psoriasis	17 (12)	27 (58)	0.11
Oligoarthritis	14.5 (10)	11 (5)	0.01
Enthesitis	35 (24)	34 (73)	1.0
Dactylitis	43.5 (30)	56 (120)	0.07
Erosions	14.5 (10)	55 (117)	<0.001
Osteolysis	7 (5)	17 (36)	0.05
Sacroiliitis	2 (6)	23 (65)	< 0.001
Deformed joints	11 (31)	54 (152)	< 0.001
PsA required TNFi	8.5 (24)	52 (147)	< 0.001
Uveitis	0 (0)	3 (9)	0.08
Arthritis mutilans	0.7 (2)	7 (21)	0.08
Metabolic syndrome	9 (26)	35 (98)	0.26
History of malignancy	1.4 (4)	7 (19)	0.61

Time between PsO and PsA onsets = time interval between the development of psoriasis and psoriatic arthritis

BMI Body Mass Index, *HAQ* Health assessment questionnaire, *DLQI* Dermatology Life Quality Index, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale

0.93 ± 0.86, $p \leq 0.001$), lower number of swollen joint counts (7 ± 5 vs. 9 ± 5, $p = 0.01$), comparable number of tender joint counts ever (11 ± 7 vs. 12 ± 6, $p = 0.17$), lower number of deformed joint counts ever (3 ± 6 vs. 7 ± 8, $p < 0.001$) and lower BMI (27.7 ± 5 vs. 29.5 ± 5, $p = 0.03$). Moreover, such patients had significantly more oligoarthritis than polyarthritis ($p = 0.01$), borderline significance for less dactylitis ($p = 0.07$), significantly fewer erosions (14.5% vs. 55%, $p \leq 0.001$), less osteolysis (7% vs. 17%, $p = 0.005$), less radiographic sacroiliitis (2% vs. 23%, $p \leq 0.001$), less patients requiring TNFi for their PsA (8.5% vs. 52%, $p < 0.001$), but comparable age, gender, smoking and nail disease (Table 4). On logistic regression analysis, such patients had significantly milder disease with fewer erosions, less sacroiliitis and fewer patients requiring TNFi therapy (Table 5). The model was significant with chi square 97.3, $p < 0.001$.

The median (IQR) and mean (SD) Ca-CRP was 8.8 (4.6–14.8) and 11.72 (10.52), respectively. The median (IQR) for CCI was 5.0 (3.0–8.0). The variables were also checked for multicollinearity. As shown in Table 6, longer PsA duration,

Table 5 Univariate and multivariate (adjusted simultaneously for variables shown) associations of different clinical variables with the cohort having normal CRP

	Univariate model			Multivariate model		
	OR	95% CI	*p* value	OR	95% CI	*p* value
BMI	0.94	0.89–0.99	0.03	0.918	0.86–0.97	0.008
Time between PsO and PsA onsets	1.04	1.02–1.07	< 0.001	1.04	1.01–1.07	0.004
Less educated	0.50	0.23–1.09	0.08			
PsA duration	0.97	0.94–1.00	0.08			
Severe PsO (PASI > 10)	0.56	0.28–1.13	0.10			
Erosion	0.14	0.06–0.29	< 0.001	0.16	0.07–0.34	< 0.001
Sacroiliitis	0.21	0.09–0.53	0.001	0.27	0.10–0.72	0.009
PsA requiring TNFi	0.24	0.13–0.43	< 0.001	0.22	0.11–0.43	< 0.001
Dactylitis	0.60	0.35–1.04	0.07			
Oligoarthritis	3.1	1.26–7.72	0.01			
Number of swollen joints	0.92	0.86–0.98	0.01			
Number of deformed joints	0.92	0.86–0.96	0.002			
Number of DMARDs failure	0.58	0.42–0.80	0.001			
Charlson Comorbidity Index	0.84	0.76–0.92	0.001			
Fatigue (BRAF)	0.93	0.88–0.98	0.02			
MCS-SF36	0.98	0.95–1.00	0.07			
Arthritis mutilans	0.27	0.06–1.20	0.08			

A multiple regression was run to model normal CRP during the disease course from PsA duration, BMI, number of deformed joints, number of swollen joints, number of DMARDs failure, PsA requiring TNFi, Charlson Comorbidity Index, oligoarthritis, erosions, sacroiliitis, time interval between the development of psoriasis and psoriatic arthritis, dactylitis, fatigue score, severe PsO (PASI > 10), MCS-SF 36, arthritis mutilans and education status. The model is significant (chi square = 97.3, $p < 0.001$). The cohort with normal CRP during the disease course had significantly less erosions, sacroiliitis, PsA requiring TNFi, greater time interval between the development of PsO and PsA, and low BMI, when controlled for all other variables in the model. Time between PsO and PsA onsets = time interval between the development of psoriasis and psoriatic arthritis

OR odds ratio, *BMI* Body Mass Index, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale

number of deformed joints, number of tender joint counts ever, number of swollen joint counts ever, comorbidity index, extent of joint involvement, erosions and sacroiliitis had significant association with CRP at Bonferroni-corrected *p* value of $p = 0.0023$; however, number of TNFi failures, number of DMARD failures, smoking pack years, younger age of PsA onset, shorter time between the developments of PsO and PsA, osteolysis and insulin resistance were also associated with CRP with *p* value of < 0.05. On multiple linear regression (Table 7), presence of erosions, presence of sacroiliitis and the higher comorbidity index were most significantly associated with CRP (unstandardised coefficient B = 6.4, 2.9, 1.05, respectively, $p < 0.01$), when controlled for all other variables in the model [(F = 77.6, $p < 0.001$), 72% (R-square)]. Borderline associations of number of TNFi failures and number of DMARDs failure were also found in this regression analysis. In this regression model, we also included other significant variables with $p < 0.05$, but the results of linear regression analysis remain unchanged.

Discussion

There has been an overall paucity of research regarding the clinical utility of inflammatory markers in PsA [10, 11]. It is well established that significantly higher number of patients with active PsA has normal or near normal serum inflammatory markers. Our long-term follow-up study clearly shows that patients with raised CRP represent a spectrum of patients with worse radiographic damage, more resistant disease to DMARDs and TNFi and higher significant comorbidities in the long run.

From the clinical standpoint, the results of this study are important in a number of ways. For example, firstly, our study shows that raised inflammatory markers, not only over the disease course, but also at the first visit to a rheumatologist have significant positive association with the number of important comorbidities. This potentially can help stratify patients who will benefit the most from close monitoring to achieve clinical remission. A recent analysis of data from the DANBIO registry of PsA patients treated with TNFi therapy has shown that comorbidities are associated with higher

Table 6 Bivariate correlations of numeric/categorical variables with cumulative CRP

Numerical variables	**Pearson correlation**	***p* value**	**Sig. at 0.0023**
Age, years	0.033	0.58	
PsA duration, years	0.217	< 0.001	*
Smoking, years	− 0.198	0.02	
BMI	0.048	0.42	
PASI maximum	0.030	0.61	
Age PsA onset	− 0.147	0.01	
Number of deformed joints	0.233	< 0.001	*
Number of tender joints	0.197	0.001	*
Number of swollen joints	0.183	0.002	*
Number of TNFi used	0.218	< 0.001	*
Number of DMARDs failure	0.285	< 0.001	*
Time between PsO and PsA onsets	− 0.165	0.005	
HAQ	0.097	0.10	
DLQI	0.026	0.66	
PCS.SF36	− 0.103	0.08	
MCS-SF36	0.019	0.74	
Charlson Comorbidity Index	0.465	< 0.001	*
Fatigue (BRAF)	0.124	0.03	
Categorical variables	**mean ± SD**	***p* value**	
Gender—male	11.9 ± 10 vs. 11.5 ± 10	0.75	
Smoker, active	11.8 ± 10 vs. 11.6 ± 10	0.86	
Less educated	11.9 ± 10 vs. 10.9 ± 8.9	0.53	
Nail disease	11.8 ± 10 vs. 11 ± 8	0.67	
Severe psoriasis	12 ± 10 vs. 11 ± 10	0.52	
Oligoarthritis	5 ± 4 vs. 12 ± 11	< 0.001	*
Enthesitis	12.6 ± 12 vs. 11 ± 9	0.30	
Dactylitis	12 ± 11 vs. 10 ± 10	0.10	
Erosions	17 ± 12 vs. 7 ± 6	< 0.001	*
Osteolysis	16 ± 12 vs. 11 ± 10	0.005	
Sacroiliitis	16 ± 12 vs. 10 ± 9	0.001	*
Deformed joints	13 ± 11 vs. 9 ± 8	< 0.001	*
Require TNFi	13 ± 11 vs. 10 ± 9	0.01	
Uveitis	21 ± 20 vs. 11 ± 10	0.17	
Arthritis mutilans	12 ± 8 vs. 12 ± 10	0.93	
Metabolic syndrome	12 ± 10 vs. 11 ± 10	0.15	
History of malignancy	11 ± 8 vs. 11 ± 10	0.91	

Numeric and categorical variables were tested for correlations with CRP (Pearson correlations and independent sample *t* test). Variables significant under a Bonferroni-corrected *p* value of 0.0023 were included in the multiple regression modelling CRP. These variables were also checked for multicollinearity. There was a strong correlation between the number of tender joints and the number of swollen joints ($r = 0.900$, $p < 0.001$) so only one of these was included in the model. The variables of deformed joints and number of deformed joints were both significant in relation to CRP; however, only the number of deformed joints was included in the model as it is more descriptive. Time between PsO and PsA onsets = time interval between the development of psoriasis and psoriatic arthritis

BMI Body Mass Index, *HAQ* Health assessment questionnaire, *DLQI* Dermatology Life Quality Index, *MCS-SF36* mental component summary score SF-36, *BRAF* Bristol Rheumatoid Arthritis Fatigue scale

* Variables significant under a Bonferroni-corrected *p*-value of 0.0023

baseline disease activity [15], which indirectly support our findings. Link between inflammation and cardiovascular co-morbidities is increasingly recognised, and it has been shown that increased burden of inflammation over time is associated with the extent of atherosclerotic plaques in patients with psoriatic arthritis [16]. We have also recently shown that higher

Table 7 Summary of regression analysis for variables predicting cumulative CRP

Predictor	Unstandardised		Standardized	*p* value	95% CI for B
	B	SE B	Beta		
PsA duration	0.048	0.060	0.066	0.423	(− 0.070, 0.166)
Oligoarthritis	− 0.379	0.560	− 0.070	0.499	(− 1.482, 0.724)
Number of deformed joints	− 0.057	0.079	− 0.036	0.469	(− 0.212, 0.098)
Number of swollen joints	0.084	0.115	0.052	0.467	(− 0.143, 0.310)
Erosions	6.386	1.162	0.272	< 0.001	(4.098, 8.673)
Sacroiliitis	2.918	1.210	0.093	0.017	(0.535, 5.301)
Number of TNFi used	1.128	0.657	0.086	0.087	(− 0.166, 2.422)
Number of DMARDs failure	1.012	0.607	0.101	0.097	(− 0.183, 2.207)
Charlson Comorbidity index	1.055	0.175	0.425	< 0.001	(0.712, 1.399)

A multiple regression was run to model CRP from PsA duration, number of deformed joints, number of swollen joints, number of DMARDs failure, Charlson Comorbidity Index, oligoarthritis, erosions, sacroiliitis and number of TNFi used. The model is significant ($F = 77.598$, $p < 0.001$), and the variables explain 72.0% (R-squared) of the variation in CRP. Erosions, sacroiliitis and the Charlson Comorbidity Index were most significantly associated with CRP, when controlled for all other variables in the model

coronary artery plaque burden in psoriatic arthritis is independent of metabolic syndrome and associated with underlying psoriatic arthritis disease severity [17].

Secondly, this study shows that there is significantly more radiographic damage (both peripheral joint erosions and sacroiliitis) among patients who have raised CRP at their first visit to a rheumatologist, and similar pattern was observed among those patients with repeatedly raised inflammatory markers over the disease course. Since about half of patients with PsA do not mount inflammatory response measurable by serum CRP or ESR [18], this potentially provides an important information about patients destined to have worse radiographic damage. Hence, the positive association between CRP and radiographic changes in patients with PsA indicate the positive prognostic value of these cytokines. Thirdly, PsA patients with raised CRP at first visit to a rheumatologist along with raised cumulative inflammatory markers over time were noted to have the disease which was significantly more refractory to both conventional synthetic csDMARDs and biological agent—TNFi. Even in times of modern therapeutics, a subgroup of patients continues to be refractory to numerous consecutive therapeutic interventions with regard to control of inflammation and joint damage. Definitions of refractory PsA thus far have been arbitrary. Our study shows that raised CRP can help identify such patients, which in turn can help clinicians to provide closer follow up perhaps by providing tight control of synovial inflammation using an intensive management strategy. Furthermore, not surprisingly, we found that inflammatory markers have positive association with BMI, which is in line with the previous findings [19]. Lastly, to our knowledge, this is the first study examining the cohort of such PsA patients who do not have raised inflammatory markers during the disease course. Literature so far describes that around 50% of PsA patients have normal inflammatory markers. This study clearly shows that those PsA patients who do not have raised inflammatory markers have significantly milder disease as regards clinical signs, deformities, radiographic damage, requirement for biologic drugs and comorbidities. Moreover, such patients have longer time interval between the development of PsO and PsA. Our earlier studies have shown that PsA patients with HLA-C0601allele have much greater mean duration of the interval (10 years) between the onset of psoriasis and the development of PsA, and patients with this allele tend to have milder clinical disease which further supports our findings [20].

The strengths of our study include the following: [1] we included a wide range of demographic details, clinical features, PROMs and most of disease activity indices (not only for PsA but also for PsO), and detailed clinical comorbidities, which allowed us to investigate the clinical impact of raised inflammatory markers; [2] to minimize the selection bias, we have attempted to recruit all consecutive patients; [3] to standardise the study procedures, all patients were reviewed by a single, trained rheumatologist; [4] since ethnic variation in CRP concentrations has been described [21, 22], this study was performed in a relatively homogeneous Irish population (both parents of every studied patient were Irish). We acknowledge that there are some limitations to our study. For example, there is a risk of selection bias since this was not a population-based study; selecting the maximal level of inflammatory markers and disease activity measures can also potentially introduce a bias as patients with longer duration of follow-up have more observations recorded and are thus more likely to have higher scores. Nonetheless, this still provides useful information worthy of testing in further prospective studies.

We conclude that raised inflammatory marker (CRP) even at the first visit to a rheumatologist is associated with

significantly more clinically important comorbidities, worse long-term radiographic damage and disease more refractory to conventional DMARDs and TNF inhibitors. Therefore, in a condition in which long-term poor clinical outcome with comorbidities is common, and measuring inflammatory markers is simple and is a part of routine practice, an opportunity to identify such at-risk patients is potentially missed, leading to less than an ideal care for PsA patients. Measuring such routine inflammatory markers can potentially help guide risk assessment and selection of appropriate treatment.

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Author contributions MH, PG, MA, and OF conceived the study, its design, coordination, data interpretation and manuscript drafting and editing.

Data Availability The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest M Haroon: Unrestricted educational grant from Abbvie, Pfizer, and member of advisory boards for Abbvie and Cellgene.

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