

# Serum Level of Calprotectin and High Sensitive C-Reactive Protein in Patients with Psoriatic Arthritis and Their Relation to The Severity of the Disease

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## Abstract

**Background:** Psoriatic arthritis (PsA) is defined as an inflammatory arthropathy correlated with psoriasis and is a member of the spondyloarthropathy family. Laboratory assessments for PSA, which involve C-reactive protein and erythrocyte sedimentation rate, often fail to provide accurate indicators of illness activity.

**Aim:** To assess the serum calprotectin and hs-CRP concentrations in PsA cases and to explore their potential relations to disease activity, skin affection and musculoskeletal US findings.

**Patients and methods:** The present research involved 55 PsA cases and 30 healthy subjects as a control. All subjects underwent medical history, musculoskeletal examination, ultrasound of hand and wrist joints, lower limb entheses, and laboratory assessment.

**Results:** Serum CALP and hs-CRP concentrations were significantly elevated in PsA cases compared to the control group ( $p$ -value<0.05). Both markers were positively associated with PASI, DAPSA-28 and US scores, demonstrating their association with disease activity. Receiver Operating characteristic analysis identified optimal cut-off values (>144 ng/ml for CALP and >1.63 milligram per liter for hs-CRP with high specificity and sensitivity).

**Conclusion:** Serum calprotectin and hs-CRP are promising biomarkers for assessing PsA disease activity, particularly in musculoskeletal and skin involvement. Their integration into routine clinical assessments may enhance disease monitoring and therapeutic decision-making.

**Keywords:** PsA; Calprotectin; hs-CRP; disease activity; US

## 1. Introduction

Psoriatic arthritis (PsA) is classified within the spondyloarthropathy family and is characterized as an inflammatory arthropathy correlated with psoriasis, often testing negative for rheumatoid factor.<sup>1</sup> Joint /tendon inflammation, enthesitis, severe osteolysis, new bone formation, and an overlap of these conditions are all present in PsA cases.<sup>2</sup>

Peripheral arthritis is a characteristic of other inflammatory arthritis, such as crystal arthritis, and a less inflammatory type of arthritis, including osteoarthritis. In a case with peripheral inflammatory arthritis, the pattern of

joint involvement and the involvement of specific joints, including the distal interphalangeal joints, could offer clues to the diagnosis.<sup>3</sup> Enthesitis can be the initial location of musculoskeletal inflammation in psoriatic arthritis, which describes a significant number of clinical characteristics of the illness, and approximately one-third of cases with PsA develop it at some stage throughout the course of their illness. The severity of clinical enthesitis is correlated with worse disease results. Consequently, it is advised to evaluate enthesitis in all cases with PsA.<sup>6</sup>

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The quantification of the burden of systemic inflammation in PsA is difficult to do because acute phase reactants, involved C-reactive protein and ESR, are usually within the normal range, regardless of the presence of active illness. Consequently, they are variable indicators of inflammation. Consequently, it is essential to identify a promising biomarker that can be used to evaluate the inflammatory process. One of the most promising is highly sensitive C-reactive protein (hs-CRP).<sup>4</sup>

It has been proposed that the determination of hs-CRP is more sensitive compared to the conventional measurement of CRP and offers greater sensitivity in the confirmation of inflammation. Additionally, its expression in inflammatory dermatoses has made it a potential indication of inflammation.<sup>5</sup>

Calprotectin is a heterodimer composed of 2 proteins, S100A9 and S100A8, that are primarily produced by activated neutrophils and monocytes in inflamed tissues and in the circulation. It's a member of the S-100 protein family that binds zinc and calcium and accounts for fifty to sixty percent of the cytosolic proteins in neutrophils.<sup>7</sup>

Serum calprotectin may be used as an inflammatory indicator in rheumatological illnesses such as RA and axial spondylarthritis, and was found to be associated with the presence and severity of the illness.<sup>16</sup>

This research aimed to assess serum calprotectin and hs-CRP protein levels within psoriatic arthritis cases and to examine their probable correlation with disease activity, skin lesions and US findings in PsA.

## 2. Patients and methods

The current research has been performed on 85 participants, 55 Psoriatic arthritis patients (PsA) and 30 healthy subjects as a control selected from Rheumatology and Rehabilitation outpatient's clinics at AL-Zahraa University Hospital.

**Ethical approval:** The Ethical Committee of Al-Azhar University accepted the design of the study and consent was taken from each patient. The cases have been exposed to complete history taking with confirmation of inclusion and exclusion criteria, clinical examination, laboratory evaluation, and ultrasound with power doppler examination of bilateral wrist, hands joints and lower limb entheses.

**Inclusion criteria:** Age between 18 and 50 years and fulfilling the classification criteria for Psoriatic arthritis.<sup>8</sup>

**Exclusion criteria:** Patients with dermatological illness other than psoriasis, other rheumatic diseases, other causes of inflammation

like infection, inflammatory bowel diseases, any patient with a BMI of more than 30 and patients with a recent history of hand or foot trauma.

### Methods:

A complete medical history has been obtained, and a full clinical assessment has been conducted. The Disease Activity Index for Psoriatic Arthritis (DAPSA-28) has been evaluated and classified as follows: equal or less than four remissions, more than four and equal or less than fourteen mild illness activity, more than fourteen and equal or less than twenty-eight moderate illness activity, and >28 high illness activity.<sup>14</sup>

Dermatological examination and the psoriasis area and severity index (PASI) score have been used to measure the severity of psoriasis. Psoriasis is classified as mild when the psoriasis area and severity index score is lower than ten, as moderate when the score is between ten and twenty, and as severe when it exceeds twenty.<sup>15</sup>

Laboratory examinations, which involved the erythrocyte sedimentation rate (ESR), complete blood count (CBC), and C-reactive protein, were conducted on every participant in accordance with the established protocols of the university hospital. Serum calprotectin was measured utilizing a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Bioassay Technology Laboratory; Cat. No. E4010Hu). Quantification of highly sensitive C-reactive protein was conducted using the Hs-CRP ELISA test system reagent (Bioassay Technology Laboratory; Cat. No. EL1-1049). The manufacturer's instructions were followed for measuring the two serum CALP and hs-CRP.

Musculoskeletal ultrasound has been done for hand and wrist joints using semiquantitative Power Doppler (PD) and Gray Scale (GS) scoring using an ultrasound machine (Xario 200, Toshiba ultrasound machine, utilizing a multi-frequency linear probe with frequency (7-11 MHz) within B-mode and power Doppler, Tochigi, Japan). GS synovial and PD signal scores and any other findings were also recorded. Separate grayscale and Power Doppler scores have been recorded for every joint. The scores were utilized to produce the composite US measurements of synovial pathology, the following: Grayscale Joint Score (GSJS): the sum of gray scores for every examined joint. II: Power Doppler Joint Score (PDJS): the sum of Power Doppler scores for every examined joint.<sup>16</sup>

Additionally, the Glasgow Ultrasound Enthesitis Scoring System (GUESS) has been utilized to conduct sonographic evaluations and scoring of the lower limb entheses. This system evaluated the quadriceps tendon, Achilles tendon, patellar ligament, enthesophytes, plantar fascia thickness, and erosions at the origin and attachment sites of the previously mentioned

tendons. The same scanner was used for these assessments. Suprapatellar, infrapatellar, and retrocalcaneal bursae were additionally assessed.<sup>17</sup>

**Statistical Analysis:** Data analysis was conducted using IBM SPSS version 27. The data were examined utilizing the following tests: Chi-square, independent t, Mann-Whitney, Kruskal-Wallis, Spearman correlation coefficient, receiver operating characteristic curve (ROC), and logistic regression. They were expressed as numbers (%), means  $\pm$  standard deviations (SD), or medians (range). A p-value of  $\leq 0.05$  has been considered to be statistically significant.

### 3. Results

The mean age of the 55 PsA cases was  $33.36 \pm 5.79$  years, they were (13) men (23.6%) and (42) women (76.4%), and the mean of their BMI was  $(23.81 \pm 2.23 \text{ kg/m}^2)$ . The mean age of the 30 control subjects was  $32.82 \pm 5.43$ , they were (eight) men (26.7%) and (twenty-two) women (73.3%) and the mean of their BMI was  $23.56 \pm 2.33 \text{ kg/m}^2$ . A statistically insignificant variances were found among PsA cases and the control group according to age, sex and BMI. In comparison to the control group, cases with PsA showed significantly elevated levels of serum

calprotectin, hs-CRP, CRP, and ESR ([table 1 & figure 1](#)). Serum calprotectin concentrations were significantly greater in PsA cases with polyarthritis than patients with oligoarthritis ([table 2](#)). Clinical manifestations, used medications, PASI score, disease activity and MSUS findings are presented in ([table 3](#)).

The Receiver Operating Characteristic curve has been utilized to determine the optimal cut-off value for serum calprotectin and hs-CRP. The ROC curve identified more than 144 nanogram per milliliter as the best cut-off value for serum calprotectin, with an area under the curve of 1.000, a specificity and sensitivity of 100%, and a positive predictive value of 100%. The examination of hs-CRP revealed that the ROC curve identified  $>1.63$  milligram per liter as the best cut-off, with an AUC of 0.998, a specificity and sensitivity of 100%, and a positive predictive value of 100% as demonstrated within [table 4](#).

A significant association was discovered among concentrations of serum calprotectin and high-sensitivity C-reactive protein and (DAPSA-28 with its components and PASI score), [table 5](#). Also, A high significant correlation was discovered among concentrations of serum calprotectin and high sensitivity C-reactive protein and musculoskeletal US scores ([table 6](#)).

*Table 1. Comparison of general characteristic and laboratory parameters among psoriatic patients and control group:*

STUDIED VARIABLES		CONTROL GROUP (NUMBER = 30)	PSA PATIENTS (NUMBER = 55)	TEST VALUE	P VALUE	SIG .
AGE (YEARS)	Mean $\pm$ Standard Deviation	$32.82 \pm 5.43$	$33.36 \pm 5.79$	-0.425•	0.672	NS
	Range	25 – 42	23 – 47			
GENDER	Female	22 (73.3%)	42 (76.4%)	0.096*	0.757	NS
	Male	8 (26.7%)	13 (23.6%)			
BMI (KG/ M <sup>2</sup> )	Mean $\pm$ Standard Deviation	$23.56 \pm 2.33$	$23.81 \pm 2.23$	-0.485•	0.629	NS
	Range	18 – 27.2	18 – 28			
HEMOGLOBIN (GRAM PER DECILITERS)	Mean $\pm$ SD	$11.6 \pm 1.4$	$11.12 \pm 1.1$	1.730•	0.087	NS
	Range	10 – 15	9 – 13.5			
PLATELET (X10 <sup>3</sup> /MM <sup>3</sup> )	Mean $\pm$ SD	$224.2 \pm 63.4$	$233.27 \pm 70.41$	-0.587•	0.558	NS
	Range	150 – 396	140 – 455			
TLC (X10 <sup>3</sup> /MM <sup>3</sup> )	Mean $\pm$ SD	$7.16 \pm 2.15$	$6.55 \pm 2.02$	1.307•	0.195	NS
	Range	4 – 11	3.1 – 11			
ESR (MM/ 1ST HR.)	Mean $\pm$ SD	$11.13 \pm 2.4$	$27.56 \pm 11.75$	-7.555•	0.000	HS
	Range	6 – 15	15 – 49.6			
CRP (MG/L)	Mean $\pm$ SD	$1.92 \pm 0.81$	$6.05 \pm 2.73$	-8.066•	0.000	HS
	Range	0 – 3	1.2 – 12			
HS-CRP (MG/L)	Mean $\pm$ SD	$0.89 \pm 0.4$	$5.35 \pm 1.94$	-12.397•	0.000	HS
	Range	0.43 – 1.63	1.54 – 9.5			
SERUM-CALP (NG/ML)	Mean $\pm$ SD	$119.77 \pm 15.07$	$441.98 \pm 138.62$	-12.657•	0.000	HS
	Range	93 – 144	250 – 720			

TLC: total leucocytic count

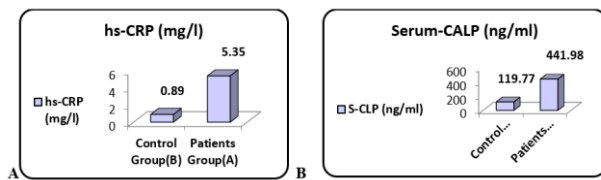


Figure (1): Comparison between the control group and the PsA patients regarding hs-CRP level and serum calprotectin level.

Table 2. Comparison between polyarthritis and oligoarthritis regarding Serum-CALP in PsA patients

PATTERN OF AFFECTION	SERUM-CALP (NG/ML)		TEST VALUE	P-VALUE	SIG.
	Mean $\pm$ SD	Range			
OLIGOARTICULAR	325.5 $\pm$ 45.56	250 – 400	-8.160*	0.000	HS
POLYARTICULAR	532.16 $\pm$ 117.21	290 – 720			

Table 3. Characteristics of psoriatic arthritis patients.

STUDIED VARIABLES			PSA PATIENTS (N=55)
DISEASE DURATION (YEARS) {MEDIAN (IQR)}			4 (2.5 – 5.5)
POLYARTICULAR %			56.4%
OLIGOARTICULAR %			43.6%
SKIN AFFECTION %			43.6%
NAIL AFFECTION %			14.5%
ENTHESITIS (CLINICAL) %			34.5%
TREATMENT	DMARDs %		69.1%
	Biological treatment %		30.9%
	Mean $\pm$ SD		17.11 $\pm$ 8.21
	Range		4.03 – 35.52
	Low disease activity (n)		29
	Moderate disease activity (n)		16
	High disease activity (n)		10
	Median (IQR)		0 (0 -10)
PASI SCORE	Range		0-30
	Mild (n)		9
	Moderate (n)		10
	Severe (n)		5
	MUSCLOSKELETAL US		
	Synovial hypertrophy (n)		55
WRIST & HAND US	Power Doppler (n)		15
	Erosion (n)		8
	Extensor tenosynovitis (n)		4
US OF LOWER LIMB	Quadriceps (n)		25
ENTHESIS	Distal patellar tendon (n)		21
	Proximal patellar tendon (n)		15
	Achilles tendon (n)		18
	Planter fascia (n)		13
US SCORES	GSJS	Median (IQR)	9 (5 - 13)
		Range	1 – 21
	PDJS	Median (IQR)	0 (0 - 4)
		Range	0 – 9
	GUESS	Median (IQR)	0 (0 - 10)
		Range	0 – 16

DMARDs: disease-modifying anti-rheumatic drugs

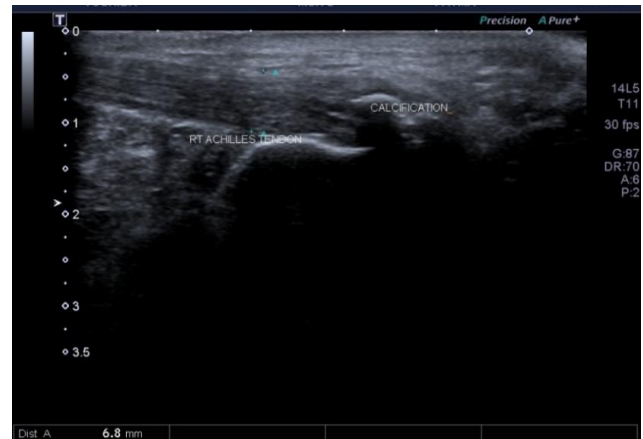


Figure 2. US of Rt. Achilles tendon (longitudinal scan) showing increased thickness and calcification.



Figure 3. US of Lt. wrist joint (dorsal longitudinal scan) showing synovial hypertrophy with PD signals.

Table 4. Receiver operating characteristic curve (ROC) for hs-CRP and Serum-CALP

	CUT OFF POINT	AUC	SENSITIVITY	SPECIFICITY	PPV	NPV
HS-CRP (MG/L)	>1.63	0.998	98.18	100	100	96.8
SERUM-CALP (NG/ML)	>144	1.000	100	100	100	100

Table 5. Correlation between serum CALP, hs-CRP and DAPSA-28 & PASi scores in PsA patients.

STUDIED VARIABLES	HS-CRP		SERUM-CALP	
	r	P- value	r	P- value
TJC	0.652**	.000	0.840**	0.000
SJC	0.394**	.003	0.695**	0.000
VAS	0.437**	.001	0.675**	0.000
PTGA	0.384**	.004	0.663**	0.000
DAPSA-28	0.565**	.000	0.870**	0.000
PASI	0.358**	0.007	0.660**	0.000



Table 6. Correlation between serum CALP, hs-CRP and US scores in PsA patients.

STUDIED VARIABLES	SERUM-CALP		HS-CRP	
	r	P-value	r	P-value
PDJS	0.717**	0.000	0.527**	.000
GSJS	0.960**	0.000	0.552**	.000
GUESS	0.869**	0.000	0.648**	.000

#### 4. Discussion

Psoriatic arthritis is a progressive, chronic musculoskeletal disorder defined by the absence of reliable biomarkers for diagnosis and follow-up. PsA impacts approximately 0.1-1% of the overall population and occurs in 20-30% of individuals diagnosed with psoriasis worldwide. The present study revealed that serum calprotectin and hs-CRP concentrations were markedly elevated in PsA cases compared to controls and could effectively differentiate between the two at threshold values of >144 nanograms per milliliter and >1.63 milligrams per liter, respectively.

Serum CALP concentrations in the polyarticular group exceeded those in cases with oligoarticular illness. This agrees with prior research by Hanson C et al.,<sup>10</sup> which demonstrated that serum concentrations of calprotectin and hs-CRP were markedly elevated in cases with mono-/oligoarthritis and polyarticular illness compared to healthy controls, with the polyarticular group showing higher concentrations compared to those with mono/oligoarticular illness. This comes in agreement with findings of the research by Li et al.,<sup>12</sup> who found that serum calprotectin concentrations were significantly greater within PsA and psoriasis cases. Furthermore, the study by Jarlborg et al.,<sup>13</sup> found high levels of serum calprotectin in patients with RA, ax-SpA and PsA disease. Similarly, the study by Elwan et al.,<sup>4</sup> determined an optimum cutoff value of  $111.1 \pm 15$  ng/ml for serum calprotectin in PsA cases. A past prospective cohort Study by Eder L et al.,<sup>9</sup> concluded that, cases with psoriasis who are at an increased risk of developing arthritis in the future may be identified by elevated concentrations of systemic inflammation, as measured by hs-CRP.

In the current study, DAPSA-28 score and its components were correlated with serum calprotectin and hs-CRP levels. This comes in line with findings of a research by Li et al.,<sup>12</sup> which found that serum calprotectin level was correlated with illness activity in PsA, and the study by Cheng et al.,<sup>11</sup> considered serum calprotectin as a beneficial biomarker correlated with a high inflammatory problem. Another research by Gaballah A, et al,<sup>26</sup> concluded that within PsA cases, serum calprotectin levels can act as a prospective proinflammatory indicator

for illness activity, enthesitis involvement, and severity.

In contrast, a past study by Sakellariou et al.,<sup>19</sup> and the research by Madland et al.,<sup>20</sup> reported that in the evaluation of PsA activity, serum calprotectin was not superior to traditional biomarkers for illness activity.

In this study, the hs-CRP and serum calprotectin concentrations were significantly correlated with PASI score, while no correlation was found between PASI score and CRP or ESR. In agreement with this findings Hamza et al.,<sup>21</sup> and Qian et al.,<sup>22</sup> reported a significant positive correlation between serum calprotectin and PASI score. Also, Uaratanawong et al.,<sup>23</sup> found that, hs-CRP level was significantly correlated with PASI score.

Within the current research, hs-CRP and serum calprotectin were significantly associated with US findings. This comes in accordance with findings of a research by Sakellariou et al.,<sup>19</sup> who discovered that serum calprotectin has been associated with ultrasound measures of illness activity in early PsA disease. Additionally confirmed in polyarticular PsA was a significant association among calprotectin and GS and PD scores, while CRP failed to demonstrate a significant association with US parameters. This comes in line with findings of a study by Elwan et al.,<sup>4</sup> who discovered that serum calprotectin was significantly greater in psoriatic cases with synovial inflammation, both clinical and subclinical, compared to those without synovial involvement and to the control group. Another study performed by Badr FM et al.,<sup>24</sup> discovered that serum calprotectin was significantly correlated with MSUS changes, especially synovial hypertrophy in the small hand joints.

#### 4. Conclusion

This study highlights the significance of serum calprotectin and hs-CRP as a biomarkers for PsA activity. Elevated levels of serum CALP and hs-CRP correlate with clinical, ultrasound and disease activity indices, offer a comprehensive approach to monitor PsA. Their integration into clinical practice could enhance diagnostic accuracy and treatment efficacy.

#### Disclosure

The authors have no financial interest to declare in relation to the content of this article.

#### Authorship

All authors have a substantial contribution to the article

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