RESEARCH PAPER

# Association of serum uric acid with markers of inflammations And disease severity in ankylosing spondylitis patients

**Mustafa E. Omran[1], Faiq I. Gorial[2]**

1. MBChB, CABM, FIBMS (Rheum. & Med. Rehab.), Instructor, Al-Zahraa College of Medicine, University of Basrah
2. CABM, FIBMS (Rheum. & Med. Rehab.), Consultant Rheumatologist, College of Medicine University Baghdad

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## Abstract

***Objective:*** To clarify the relationships between Serum uric acid with inflammatory laboratory markers and Ankylosing Spondylitis Disease Activity Score (ASDAS-ESR) in patients with ankylosing spondylitis.

***Method:*** A total of 73 ankylosing spondylitis patients with age ≥ 16 years with AS fulfilling ASAS criteria were included in a cross-sectional study. The laboratory measures included values of uric acid, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) obtained.

Disease activity is calculated by Ankylosing Spondylitis Disease Activity Score (ASDAS-ESR). Demographic and laboratory investigations were recorded.

***Results:*** The mean age of the studied sample was 35.04 ± 7.99 years with a range of (17-52 years) & the mean Body Mass Index was 27.91 ± 5.78 with a range (18-46).

The majority of them were married (80.8%), working (94.5%), and non-smokers (52.1%) and (94.5%) on biological therapy. Comparing serum uric acid with ESR value revealed no statically significant association (P = 0.47). Again, this is observed when comparing serum uric acid with CRP Value (P = 0.27).

Finally, there was no association between Serum uric acid with any level of disease activity measured through ASDAS-ESR score (P = 0.52).

***Conclusion*:** The study concludes that there is no association between Serum uric acid and the routine inflammatory markers and Ankylosing Spondylitis disease activity score (ASDAS-ESR).

**Keywords:** Uric acid, Ankylosing Spondylitis, Inflammatory Markers, Disease activity scores

**Corresponding author: Mustafa E. Omran, Instructor, Al-Zahraa College of Medicine, University of Basrah**

✉ **E-mail**: **mustafaomran1978@gmail.com**

## Introduction

Ankylosing spondylitis is a chronic, inflammatory disease characterized by inflammation and new bone formation in the axial skeleton, and that often results in progressive, irreversible structural damage, disability, deterioration of functioning, and reduced quality of life.[1] Several tools for assessing disease activity and outcome in ankylosing spondylitis have become widely used, most notably:

1. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).
2. Bath Ankylosing Spondylitis Functional Index (BASFI), which are self-administered patient questionnaire.



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3. Bath Ankylosing Spondylitis Metrology Index (BASMI), which is used to assess spinal mobility.Modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS), which is used to assess radiographic damage.
4. Ankylosing Spondylitis Disease Activity Score (ASDAS).[2]

Inflammatory parameters such as CRP and ESR should be determined in all patients with suspected axial spondyloarthropathy since CRP also represents a parameter in the ASAS classification criteria. It is a note that increased ESR and/or CRP can only be found in 38%–63% of the patients. However, increased CRP is linked to a more rapid radiographic progression.[3]Uric acid (UA) is the end product of the metabolic pathway for purines, the main constituents of nucleotides. The pathway of UA generation is derived from de novo purine synthesis and purine salvage.[4] In experimental studies, UA stimulates the release of chemokine monocyte chemoattractant protein-1 and interleukin-1b (IL-1b), interleukin-6 (IL-6), and tumor necrosis factor-a (TNF-a) synthesis.[5] To our best knowledge and in the scanning literature, this is the only study that investigated SUA levels with routine inflammatory laboratory markers and AS disease activity in AS patients in Iraq.

## Method

It's a Cross-sectional study conducted in the rheumatology outpatient department in Basrah teaching hospital, Basrah, Iraq, and at outpatient clinics in Baghdad Teaching Hospital/Medical City Complex during a period from the 1st of January to the 30th of November 2020**.** A total of 73 adults (67 males and 6 females) consecutive Iraqi patients with AS were diagnosed according to the ASAS criteria included in this study. Patients with hypertension, diabetes mellitus, and those who had used drugs such as Aspirin, Oral antidiabetic agents (Metformin), lipid-lowering drugs (Fenofibrate, Simvastatin, Atorvastatin), CCBs (Amlodipine), ACE Inhibitor (Captopril, Enalapril, Ramipril), ARBs (Losartan), estrogens, corticosteroids, and the dietary supplements and those with any condition that may influence serum uric acid levels were excluded from the study. The laboratory measures included values of uric acid, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) obtained. Disease activity Ankylosing Spondylitis Disease Activity Score (ASDAS- ESR), was calculated (Inactive < 1.3, Low 1.3-2.1, High 2.2-3.5. Very high > 3.5). ESR (normal range: Female 0-20 mm/h male 15 mm/h) is analysed by Westergren method. CRP (normal range: 0-6 mg/L) is analysed by turbidimetry test in a private lab. The social and demographic features of the sample patients were presented in (Table-1).

**Table 1.** The Baseline patient's characteristics

| Variables | | No. | % |
|---|---|---|---|
| **ASDAS-ESR No. (%)** | Inactive <1.3 | 7 | 9.6 |
| | Moderate 1.3-2.1 | 18 | 24.7 |
| | High 2.2-3.5 | 40 | 54.8 |
| | Very High >3.5 | 8 | 11.0 |
| **Uric acid** | Mean ± SD | 4.95±1.32 | |
| | Range | 2.9-9.2 | |
| **ESR mm/h** | Mean ± SD | 17.27±1.93 | |
| | Range | 2-80 | |
| **CRP ng\dl** | Mean ± SD | 0.85 ± 0.63 | |
| | Range | 0-48 | |



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Verbal permission was obtained from each before collecting data, and all information was anonymous. The data were analyzed using a statistical package for social science (SPSS) version 22. The data were present as means, Standard deviations, and ranges. Categorical data are presented by frequencies and percentages. The Chi-square was used to assess the statistical significance between patients' serum uric acid level, and inflammatory markers (ESR, CRP) with the indicator of disease Activity (ASDAS-ESR). P-values less than 0.5 considered statically significant.

***Administrate approval were granted from the following:***

1. The Council of Iraqi board of Medical Specialization.
2. Approval of the department of internal medicine of Basrah Teaching Hospital.
3. The ethical approval from rheumatology Unit, Department of Medicine, College of medicine, University of Baghdad number 469 in 30-1-2020.

## Results

The current study included 73 ankylosing spondylitis patients; most of them were males (91.8%). The mean age of the studied sample was (35.04 ± 7.99) years with a range of (17-52 years). The mean BMI was (27.91 ± 5.78) and ranged (17.5-46.4). The majority of them were married (80.8%), working (94.5%), and non-smokers in (52.1%) and (94.5%) on biological therapy. When comparing serum uric acid in patients with normal ESR (*N* =60) & the patients with elevated ESR (*N*=13), this was associated with a higher level of Serum uric acid value in the second group as shown in (Table-2).

**Table 2.** The distribution of SUA according to ESR categories.

| | ESR | No. | Mean | SD | P Value |
|---|---|---|---|---|---|
| SUA | Normal ESR | 60 | 4.84 | 1.19 | 0.47 |
| | Elevated ESR | 13 | 5.12 | 1.42 | |

**SUA=Serum Uric acid, ESR= Erythrocyte sedimentation rate**

To test the hypothesis of whether there was a statistically significant difference in means between these two groups; an independent sample t-test was performed which disclosed no statistical difference between them P= 0.47. Similarly, comparing Serum Uric acid in CRP negative group (N=57) with Serum Uric acid of with CRP positive group (N=16) yielding no statistically significant results, P = 0.27 as shown in (Table 3).

**Table 3.** The distribution of SUA according to CRP categories.

| | CRP | No. | Mean | SD | P - Value |
|---|---|---|---|---|---|
| SUA | Negative | 57 | 4.80 | 1.16 | 0.27 |
| | Positive | 16 | 5.20 | 1.49 | |

**SUA=Serum Uric acid, CRP=C - reactive protein**

When comparing serum uric acid with ESR value. Pearson's analysis revealed a positive association but still not statistically significant since P = 0.21 as shown in (Table- 4).

**Table 4.** The correlation between SUA and ESR value

| | | ESR |
|---|---|---|
| SUA | Pearson Correlation | 0.15 |
| | P Value | 0.21 |

**SUA=Serum Uric acid, ESR= Erythrocyte sedimentation rate**



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On the other hand, Pearson's correlation failed to identify a statistically significant association P = 0.28 between the serum uric acid with CRP Value as shown in (Table-5).

**Table 5.** The correlation between SUA and CRP value

| | CRP | |
|---|---|---|
| **SUA** | Pearson Correlation | 0.13 |
| | P Value | 0.28 |

**SUA=Serum Uric acid**

To test whether the ASDAD-ESR Classes influenced Serum uric acid levels, an ANOVA test was performed. The ANOVA failed to exhibit any statistically significant *P*=0.052. Thus, the null hypothesis of no difference between the means was accepted. Shown in Table 6.

**Table 6.** The distribution of SUA according to ASDAS-ESR activity classes

| SUA | No. | Mean | SD | P Value |
|---|---|---|---|---|
| **Inactive <1.3** | 7 | 5.30 | 1.01 | 0.052 |
| **Moderate 1.3-2.1** | 18 | 5.19 | 1.04 | |
| **High 2.2-3.5** | 39 | 4.53 | 1.17 | |
| **Very High >3.5** | 8 | 5.56 | 1.67 | |
| **Total** | 72 | 4.89 | 1.23 | |

**SUA=Serum Uric acid**

Table-(7,8), represent the association between ASDAS-ESR activity classes and CRP and ESR. Both had a significant association since p-value = 0.042 and 0.001 for both groups, respectively.

**Table 7.** The distribution of CRP according to ASDAS-ESR activity classes

| CRP | No. | Mean | SD | P Value |
|---|---|---|---|---|
| **Inactive <1.3** | 7 | 0 | 0 | 0.042 |
| **Moderate 1.3-2.1** | 18 | 0.06 | 0.02 | |
| **High 2.2-3.5** | 39 | 0.3 | 0.03 | |
| **Very High >3.5** | 8 | 6.38 | 5.80 | |
| **Total** | 72 | 0.85 | 0.64 | |

**Table 8.** The distribution of ESR according to ASDAS-ESR activity classes

| ESR | No. | Mean | SD | P Value |
|---|---|---|---|---|
| **Inactive <1.3** | 7 | 11.86 | 8.71 | 0.001 |
| **Moderate 1.3-2.1** | 18 | 10.72 | 5.37 | |
| **High 2.2-3.5** | 39 | 15.30 | 12.71 | |
| **Very High >3.5** | 8 | 46.63 | 24.57 | |
| **Total** | 72 | 17.27 | 1.93 | |

## Discussion

This study was designed to establish the relationship between Serum uric acid values with the routine laboratory inflammatory markers on one hand and Ankylosing spondylitis disease activity reflected by ASDAS-ESR score on the other hand in a sample of Iraqi Ankylosing spondylitis patients. The purpose of this research was to test the implication of serum uric acid as an independent inflammatory marker and as a tool to measure disease activity in AS patients. Despite the expected significant correlation between the inflammatory markers and ASDAS-ESR that was most prominent with ASDAS-ESR and CRP, unfortunately, the study failed to demonstrate any association between SUA and Inflammatory markers



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(with ESR *P* = 0.47 & with CRP P = 0.27). Once more, the study was incapable to found any association between serum uric acid level and disease activity measured by ASDAS-ESR on the other side (P = 0.28). A potential clarification for this outcome is that most of the patients enrolled in the study were utilizing biologics which appears to influence the level of serum uric acid in ankylosing spondylitis patients. This finding can be illuminated by Sargın *et al* 2018 which found a low level of SUA levels in patients treated with TNF alpha inhibitors compared with those treated with NSAIDs.[6] Choe *et al* 2015 studied SUA levels in rheumatoid Arthritis patients and their association with inflammatory markers. Comparing two groups of patients the first used methotrexate (MTX) alone, and the other group of patients were treated with MTX and leflunomide. This study recognized a significant reduction in SUA in MTX with Leflunomide group-treated patients but failed to approve any correlation with the inflammatory markers.[7] Sheikh, et al, 2016 noticed that elevated uric acid levels in SLE patients were associated with a higher incidence of stroke, peripheral neuropathy, hypertension, hyperlipidemia, and a history of arterial thrombosis.[8] The study of Isha et al , 2011 compare psoriatic patients with active skin disease with a group of patients with skin diseases other than psoriatic lesions and concluded that the mean SUA concentration was significantly higher in patients with psoriasis but then after 12 weeks of treatment, the mean value for SUA meaningfully decline. Another observation in the former study is that the Mean value for CRP was initially high (> 20 folds) in patients with psoriasis, which was successively reduced to nearly 50% of the initial value after 12 weeks of treatment.[9] What intentioned but not reached in this study was to find a correlation between serum uric acid and disease activity similar to that agreed by Zhao et al, 2016 which found that uric acid decreased considerably with a decrease in the inflammatory burden in patients with Takayasu's arteritis. [10] Reviewing the medical literature and to our knowledge, this research is the first study that tried to find a linkage between serum uric acid with the routine laboratory inflammatory markers namely ESR and CRP, and with ankylosing g spondylitis disease activity score ASDAS-ESR in Iraqi patients.

**Limitations of the study**

1. Small sample size thus a further study is required with a larger patient sample size to establish the different aspects of correlation between serum uric acid and AS disease activity indices and treatment modalities.
2. The majority of patients enrolled in the study were treated with different types of TNF-alpha inhibitors. Hence including the patients who are treated with NSAIDs and physiotherapy may modify the final result steered by this study.

**In conclusion & recommendations, a**ccording to the results of this study, there was no statistically significant relationship between SUA with the Laboratory inflammatory markers namely ESR and CRP. There was no statistically significant



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relationship between SUA and AS disease activity measured with ASDAS-ESR score. Larger and longer prospective studies are needed to validate the results of this study. Emphasizing the cornerstone role of traditional routine laboratory inflammatory markers especially high sensitivity C-reactive protein and the standardized clinical tools (AS disease activity scores) in assessing AS patient's disease activity.

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# ارتباط حمض اليوريك في الدم مع علامات الالتهاب وفعالية المرض في مرضى التهاب الفقار المقسط

***الخلفية المرضية:*** التهاب الفقار المقسط هو مرض مزمن يتسم بالتهاب يصيب في الغالب الهيكل العظمي المحوري مما يؤدي إلى تلف هيكلي متقدم لا رجعة فيه وإعاقة دائمة. يتغير حمض اليوريك "المنتج النهائي لاستقلاب البيورين" بشكل ملحوظ ويرتبط بمضاعفات خطيرة في بعض أمراض المناعة الذاتية الروماتيزمية.

***الهدف من الدراسة:*** تم تنفيذ هذه الدراسة لاستقصاء العلاقة بين معدلات تراكيز حمض اليوريك ومعدلات ترسيب كرات الدم الحمراء وقيم البروتين التفاعلي ولتقييم العلاقة بين حمض اليوريك ونشاط المرض باستخدام درجة نشاط مرض التهاب الفقار المقسط.(ASDAS-ESR)

***طرائقَ العمل:*** هي دراسة مقطعية ، أجريت هذه الدراسة في مستشفيي البصرة وبغداد التعليمين في وحدتي أمراض الروماتيزم فيهما في الفترة من ١ يناير إلى ٣٠ نوفمبر ٢٠٢٠. المرضى البالغون بعمر أكثر من ١٧ عامًا و المصابون بمرض التهاب الفقار المقسط والذين تم تشخيصهم وفقًا لمعايير ASAS أُدرجوا في هذه الدراسة. تم الحصول على القياسات المختبرية بما في ذلك قيم حمض اليوريك ومعدل ترسيب كرات الدم الحمراء والبروتين التفاعلي.تم احتساب نشاط المرض من خلال نتيجة نشاط مرض التهاب الفقار المقسط(ASDAS- ESR)

***النتائج:*** بعد تحليل النتائج الديموغرافية و المخبرية تبين التالي :

من بين ٧٣ مريضا عراقيا (٦٧ ذكور و ٦ اناث) مسجلين في الدراسة ,كان متوسط عمر العينة المدروسة ٣٥,٠٤ ± ٧,٩٩ سنة بمدى (١٧-٥٢ ) سنة و كان الغالبية من المرضى متزوجون (٨٠,٨٪) ، يعملون (٩٤,٥٪) ، غير مدخنين في (٥٢,١٪) و كان (٩٤,٥٪) يستخدمون العلاج البيولوجي.

أظهرت مقارنة حمض اليوريك في الدم مع قيمة معدل ترسيب كرات الدم الحمراء عدم وجود علاقة ذات دلالة إحصائية (P=0.47).مرة أخرى ، لوحظ هذا عند مقارنة حمض اليوريك في الدم مع قيمة البروتين لتفاعلي.(P=0.27) في النهاية ، لم تنجح الدراسة في إثبات أي ارتباط بين حمض اليوريك في الدم مع أي مستوى من نشاط المرض المقاس من خلال درجة ASDAS-ESR ((P=0.10 .

***الاستنتاج:*** لم تنجح الدراسة في ايجاد أي ارتباط بين حمض اليوريك في الدم وعلامات الالتهاب المخبرية الروتينية ودرجة نشاط مرض التهاب الفقار المقسط.(ASDAS-ESR)

***الكلمات المفتاحية:*** *حمض اليوريك ، التهاب الفقار اللاصق، علامات الالتهاب، درجات نشاط المرض*



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