Assessment of Serum S100A8 Levels in Rheumatoid Arthritis Patients on Infliximab

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Abstract:

Background: Rheumatoid arthritis is a chronic, damaging autoimmune disease identified by systemic inflammation; it initially impacts the joints. S100A8 is a calcium-binding protein and one of the S100 protein family, which is crucial for developing multiple inflammatory diseases, especially rheumatoid arthritis.

Objective: This study aims to estimate serum S100A8 levels in rheumatoid arthritis patients receiving infliximab therapy and its effect on disease activity.

Methods: A case-controlled study was conducted on 65 rheumatoid arthritis patients receiving infliximab infusion therapy and 25 healthy individuals as control. The enzyme-linked immunosorbent assay (ELISA) was applied to determine S100A8 levels. In addition, Clinical Disease Activity Index (CDAI) scores and erythrocyte sedimentation rate (ESR) were also assessed.

Results: The current study demonstrated that the levels of S100A8 in patients with rheumatoid arthritis were significantly higher than in healthy controls, with a p-value less than 0.0001. Also, it was useful for distinguishing individuals with rheumatoid arthritis from a healthy subject, with excellent Area Under the Curve (AUC) and very high sensitivity and specificity (95.38% and 100%, respectively). Furthermore, this study shows a weak positive correlation between S100A8 and the Clinical Disease Activity Index (CDAI) in rheumatoid arthritis patients ($R = 0.087$, $p = 0.491$).

Conclusion: This study concluded that, despite taking infliximab therapy, the levels of S100A8 remained higher in rheumatoid arthritis patients when compared with controls, indicating that it could be a marker for rheumatoid arthritis disease.

Keywords: Rheumatoid arthritis, S100A8, CDAI, Infliximab, ESR

تقييم مستويات S100A8 في مصل مرضى التهاب المفاصل الروماتويدي الذين يتلقون علاج انفلكسيماب

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****قسم التقنيات الاحيائية /كلية العلوم المساندة وتقنيات المتقدمة في علوم الحياة / جامعة العلوم والثقافة طهران-إيران***

الخلاصة

الخلفية:التهاب المفاصل الروماتويدي (RA) هو اضطراب المناعة الذاتية المزمنة الضارة يتم التعرف عليه من خلال الالتهاب الجهازي، ويؤثر بشكل أساسي على المفاصل، ويمكن أن يؤثر على العديد من الأعضاء الداخلية. S100A8 هو بروتين رابط للكالسيوم، وهو عضو في عائلة بروتين S100، يلعب دورًا مهمًا في تطوير العديد من الأمراض الالتهابية، مثل التهاب المفاصل الروماتويدي.

الهدف من الدراسة: تهدف هذه الدراسة إلى تقدير مستويات S100A8 في مصل الدم لمرضى التهاب المفاصل الروماتويدي الذين يتلقون انفلكسيماب وتأثيره على نشاط المرض.

طريقة العمل: تم اجراء الدراسة على المرضى والناس الاصحاء ل 65 مريضًا بالتهاب المفاصل الروماتويدي يتلقون علاج انفلكسيماب بالتسريب الوريدي و25 فردًا سليمًا كمجموعة مسيطرة. تم استخدام اختبار الممتز المناعي المرتبط بالإنزيم (ELISA) لتحديد مستويات S100A8. كما تم تقييم كل من درجات مؤشر نشاط المرض السريري (CDAI) ومعدل ترسيب كرات الدم الحمراء (ESR).

النتائج: وجدت هذه الدراسة أن مستويات S100A8 في المرضى المصابين بالتهاب المفاصل الروماتويدي كانت أعلى بشكل ملحوظ من تلك الموجودة في الناس الاصحاء بقيمة p اقل من0.0001. كما أنها مفيدة لتشخيص الأفراد المصابين بالتهاب المفاصل الروماتويدي مقارنة بالناس الاصحاء مع AUC ممتازة وحساسية عالية جدًا وخصوصية (95.38٪ و100٪ على التوالي). تظهر الدراسة الحالية ارتباطًا إيجابيًا ضعيفًا بين S100A8 وCDAI في مرضى التهاب المفاصل الروماتويدي (R = 0.087، p = 0.491).

الاستنتاج: لخصت هذه الدراسة إلى وجود فرق كبير في مستويات S100A8 في مصل الدم بين مجموعتي المرضى والناس الاصحاءعلى الرغم من تناول علاج انفلكسيماب ، مما يشير إلى أنه يمكن أن يكون علامة على مرض التهاب المفاصل الروماتويدي.

الكلمات المفتاحية: التهاب المفاصل الروماتويدي, S100A8 ,درجات مؤشر نشاط المرض السريري، معدل ترسيب كريات الدم الحمراء

Introduction

Rheumatoid arthritis is a chronic, damaging autoimmune disease identified by systemic inflammation; it first impacts the joints, causing pain, swelling, and stiffness. In severe cases, disability can occur; additionally, other internal organs can be affected. The disease's difficulty originates from its complex etiologic, involving genetic, environmental, and immunological components (1). This condition may manifest even at a young age, but it increases during the third and fifth years of life (2), and it is two to three times higher in females than in males. The prevalence of rheumatoid arthritis globally ranges from 0.5 to 1.0%, but in Babylon- Iraq, the prevalence of RA is around 3% (3). Biological therapy infliximab, a chimeric (human and animal) monoclonal antibody that attaches to tumor necrosis factor-α (TNF-α), thereby inhibiting its biological function, is utilized to treat moderate to severe conditions in RA patients (4).

S100 proteins are a group of calcium-binding proteins that received this name because of their solubility in a 100% saturated solution of ammonium sulphate at neutral ph. S100 proteins have many intracellular roles through their interaction with several effector proteins within cells and their binding with Ca^{2+}, and Zn^{2+} Therefore, they are involved in the regulation of multiple cellular processes such as contraction, motility, cell growth, division and differentiation, transcription, enzyme activation, and also in the structure of membranes, In addition, they have a role in protection from oxidative cell damage and protein phosphorylation and

secretion (5). S100A8, also known as calgranulin A, is a calcium-binding protein and one of the S100 protein family, which is crucial in developing multiple inflammatory diseases, especially rheumatoid arthritis (6). It is highly expressed and produced by neutrophils, monocytes, and activated macrophages (7). Macrophages that produce S100A8 are located at the sites of joint degradation within the synovial membrane and the cartilage-pannus junction, leading to the destruction of the bone (8). S100A8 induces inflammation in RA by interacting with Toll-like receptors (TLR) or receptors for advanced glycation end products (RAGE), activating innate immune pathways. This elevates the levels of tumor necrosis factor (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). The elevated concentrations of these inflammatory mediators can then activate neutrophils and macrophages, generating a harmful inflammatory cycle (9).

Several composite measurements are available for evaluating the activity of rheumatoid arthritis; one of them is the Clinical Disease Activity Index (CDAI), which is an efficient and uncomplicated score for monitoring the disease activity of RA (10). The current study aims to estimate the serum level of S100A8 in RA patients taking infliximab therapy and assess their effectiveness as a biomarker for RA diagnosis, and its impact on the activity and severity of the disease.

Methods

Study design

The present study was designed as a case-controlled study, involving 65 patients (9 male and 56 female) diagnosed with rheumatoid arthritis taking infliximab biological therapy and 25 healthy individuals as a control group (5 male and 20 female). After getting approval from the scientific committee at the College of Pharmacy-Mustansiriyah University, blood samples were taken from volunteers at the al-Yarmouk Teaching Hospital in Baghdad.

Patients Criteria

Inclusion Criteria

Adult patients aged between 18 and 60 diagnosed with rheumatoid arthritis who have been undergoing infliximab therapy for a minimum of 6 months.

Exclusion Criteria

Patients receiving infliximab infusion therapy for less than 6 months, pregnant women, rheumatoid arthritis patients with chronic diseases such as diabetes, other autoimmune diseases like Crohn's disease, heart disease, chronic liver or kidney disease, and patients with cancer.

Blood Samples Collection

About 5 mL of blood was withdrawn from the patients and the control group, then divided into two parts. The first 3 mL of blood was placed in a sterile gel tube and allowed to settle for about 1 hour before being centrifuged at 3000 rpm for approximately 15 minutes, The resulting serum was isolated using a micropipette, transferred to Eppendorf tubes, labelled, and frozen at -40 °C until a quantitative assay of S100A8 was performed using the sandwich enzyme-linked immunosorbent assay (ELISA) technique. The remaining 2 mL of whole blood was kept in the EDTA tube for immediate erythrocyte sedimentation rate (ESR) measurement.

Assessment of Clinical Disease Activity Index (CDAI)

The measurement of disease activity in rheumatoid arthritis (RA) using (CDAI) can be obtained by a simple summation of the number of tender joints (0–28), the number of swollen joints (0–28), patient's global assessment of disease activity and physician

global assessment of the disease activity by VAS (Visual Analogue Scale) ranging from 0 to 10 cm (11).Disease activity can be classified as remission (CDAI ≤2.8), low (CDAI >2.8 but ≤10), moderate (CDAI >10 but ≤22), or high (CDAI >22) (12).

Statistical Analysis

Statistical analyses were performed utilizing IBM® SPSS® Statistics version 26 (IBM, NY, USA) and GraphPad Prism version 10 (GraphPad Software, CA, USA). Continuous variables that were not normally distributed were described as median (interquartile range). The Shapiro-Wilk test was used to assess normality. For non-normally distributed variables, the Kruskal-Wallis test followed by Dunn's post hoc test was employed. Fisher's exact test was used for comparisons between categorical variables.

The optimal cutoff points for S100A8 in predicting RA were determined through receiver operating characteristic (ROC) analysis, which computed the area under the curve (AUC) to maximize the sum of sensitivity and specificity. Spearman rank correlation was utilized to assess associations between continuous variables. Statistical significance was established at $p < 0.05$.

Results

Serum levels of S100A8

The result found that there was a highly significant difference in the median serum levels of S100A8 between patients and controls with a p-value less than 0.0001 (in patients median 165.2 pg/mL; IQR 144.2-182 pg/mL) and (in controls median 80.75 pg/mL; IQR 67.33-91.04 pg/mL). **Table 1.** displays the S100A8 median in patients and controls, and **Figure 1.** describes the comparison in levels of S100A8 between patients and controls.

Table 1. The serum S100A8 levels in patients and controls.

Biomarker	Patients (n=65) median (IQR)	Controls (n=25) median (IQR)	p-value
S100A8 (pg/mL)	165.2 (144.2-182)	80.75 (67.33-91.04)	<0.0001*

IQR: Interquartile Range, n: Frequency, pg/mL: Picograms Per Milliliter
*Statistical significance is indicated by (p<0.05), Man Whitney test

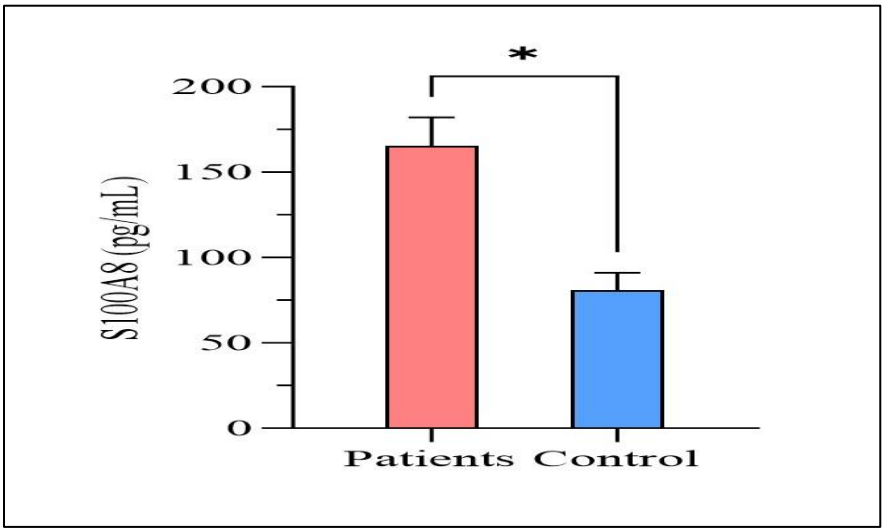

Figure 1. The comparison in levels of S100A8 between patients and controls.
*Statistical significance is indicated by (p<0.05).

Estimation of ESR levels

The present study demonstrated that the median (IQR) of ESR levels in the patient group was 38 (22.5-58) mm/h, while in the healthy control group, it was 11 (7-15) mm/h. The median of ESR levels demonstrates a very high significant difference in ESR patients compared with the control group (p <0.0001). **Table 2** and **Figure 2** show the levels of ESR in patients and controls.

Table 2 The median levels of ESR in patients and control group.

parameter	Patients (n=65) median (IQR)	Controls (n=25) median (IQR)	p-value
ESR (mm/h)	38 (22.5-58)	11 (7-15)	<0.0001*

IQR: Interquartile Range, n: Frequency, ESR; Erythrocyte Sedimentation Rate, mm/h; Millimeters per hour
*Statistical significance is indicated by (p<0.05), Man Whitney test

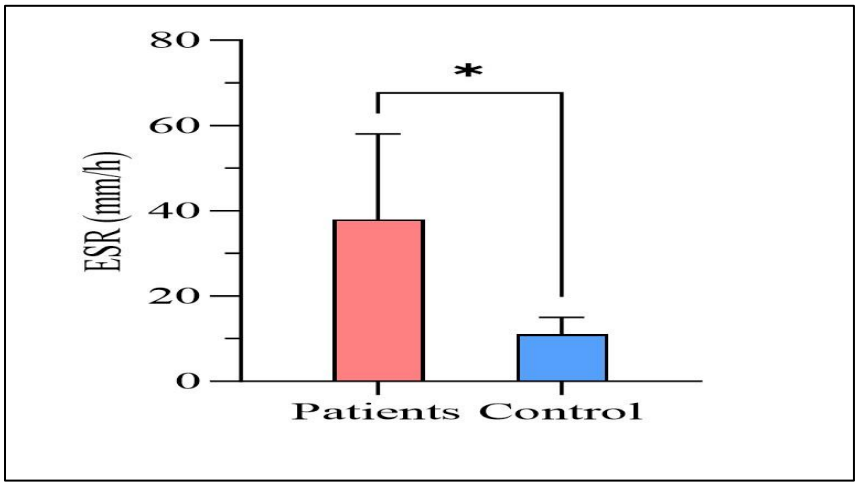

Figure 2 The levels of ESR in patients and control.

*Statistical significance is indicated by (p<0.05).

Receiver Operating Characteristic (Roc) for S100A8

In the purpose to assess the specificity and sensitivity of S100A8 in the diagnosis of patients, ROC analysis was applied, the result found that S100A8 had an excellent AUC=0.9785, SE=0.01490, 95% CI ranging from 0.9493 to 1.000, P-value<0.0001 Cut-off value > 99.08 with sensitivity 95.38 and specificity100. As shown in **Table 3** and **Figure 3**.

Table 3. ROC analysis for S100A8 to predict RA.

Biomarker	AUC	SE	95% CI	P-value	Sensitivity	Specificity	Cut-off value
S100A8 (pg/mL)	0.9785	0.01490	0.9493 to 1.000	<0.0001*	95.38	100	> 99.08

AUC: Area Under the Curve, SE: Standard Error, 95% CI: 95% Confidence Interval, pg/mL: Picograms Per Milliliter
*Statistical significance is indicated by (p<0.05).

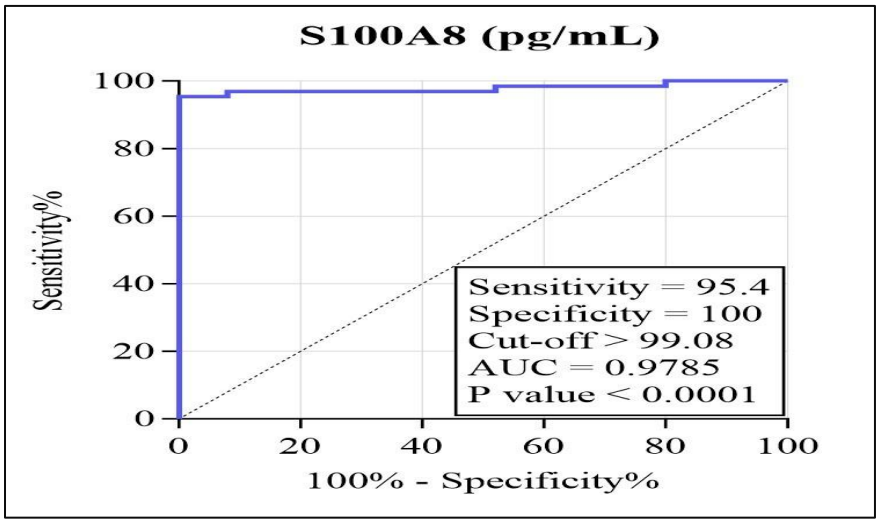

Figure 3. ROC analysis for S100A8 to predict RA.

Serum of S100A8 and ESR levels across CDAI categories

In this study, patients were divided into three groups (low, moderate, and high disease activity) according to the clinical disease activity index (CDAI).

As shown in **Table 4**, the median (IQR) of S100A8 for low disease activity was 147.4 (128.1-165.6), while the median (IQR) of S100A8 for moderate disease activity was 167.5 (144.7-182.9), and the median (IQR) of S100A8 for high disease activity was 164.6 (147.6-184.5). The median serum levels of S100A8 in CDAI categories showed no significant difference with a p-value of 0.106, although there was a numerical difference in the median of S100A8 between low and moderate disease activity.

The result observed a highly significant difference in the median of the ESR according to disease activity with a p-value <0.0001. The median (IQR) for low disease activity was 19.5 (14.25-22.25), while the median (IQR) for moderate disease activity was 38 (22-47), and the median (IQR) for high disease activity was 62 (35.25-87.5).

Table 4. The median of S100A8 and ESR across disease activity categories based on CDAI.

Parameters	**Low-disease activity**	**Moderate-disease activity**	**High-disease activity**	**p-value**
	CDAI >2.8 ≤ 10	**CDAI > 10 and ≤ 22**	**CDAI > 22**	
	n = 10	**n = 33**	**n = 22**	
S100A8 (pg/mL), median (IQR)	147.4 (128.1-165.6)	167.5 (144.7-182.9)	164.6 (147.6-184.5)	0.106
ESR (mm/h), median (IQR)	19.5 (14.25-22.25)	38 (22-47)	62 (35.25-87.5)	<0.0001*

CDAI; Clinical Disease Activity Index, ESR; Erythrocyte Sedimentation Rate, mm/h; Millimeters per hour, pg/mL: Picograms Per Milliliter, IQR: Interquartile Range, n: Frequency.

*Statistical significance is indicated by ($p<0.05$), Kruskal-Wallis test followed by Dunn's post hoc test

Spearman Correlation of S100A8

Spearman correlation was used to estimate the association of S100A8 with other continuous variables in patients and control groups. As shown in **Table 5,** there was a weak positive correlation between S100A8 and CDAI with R = 0.087, p = 0.491; also, there was a weak positive correlation between S100A8 and ESR (R = 0.066, p = 0.604 in patients), (in control R =0.301, p = 0.276).

Table 5. Spearman correlation of S100A8 with other continuous variables in patients and control groups.

Variables	Patients (n=65)		Controls (n=25)	
	R	P	R	P
S100A8	1		1	
Age	−0.069	0.585	0.015	0.943
BMI	0.028	0.827	0.215	0.301
CDAI	0.087	0.491		
ESR	0.066	0.604	0.301	0.276

R: spearman correlation, P: P value, BMI: body mass index, CDAI: clinical disease activity index, ESR: Erythrocyte Sedimentation Rate

Discussion

S100A8 regulates proliferation and inflammation in rheumatoid arthritis. Raised S100A8 protein levels have been identified in the serum of rheumatoid arthritis patients and may function as effective biomarkers to determine disease activity (6).

This study displays a significantly elevated S100A8 level in patients compared with the controls, and this agrees with L. Roszkowski *et al*. (2023), who suggest a strong increase in protein concentration of S100A8 in RA patients compared with sera of healthy individuals (13). Previous studies by Yuling Xiang *et al*. (2022), Michael Gernert *et al*. (2022), and Jiashun Zeng *et al*. (2023) demonstrated that S100A8/S100A9 levels increased in patients compared with healthy controls (14-16).

The findings of the present study demonstrate a significant difference in ESR in patients compared with controls, supporting the results of Nader A. Salman *et al*. (2024), Zahraa Jabbar Diwan *et al*. (2024), Tamara Salman Mohammed *et al*. (2022), and Jung-Yoon Choe *et al*. (2023), which suggest that ESR is markedly elevated in RA patients compared to healthy individuals (17-20).

In rheumatoid arthritis, the inflammatory parameters ESR along with various clinical scores such as Clinical Disease Activity Index (CDAI) and Disease Activity Score-28 (DAS-28) were employed to assess the activity of the disease and if the disease was in remission or active state (10). In the current study, the CDAI score revealed that from 65 patients there was no remission state, only ten had low disease activity, thirty- three patients had moderate activity, and twenty-two had severe disease activity. Furthermore, a p-value of 0.106 indicates no significant difference in serum levels of the S100A8 and CDAI categories. A recent study conducted by Michael Gernert *et al*. (2022) revealed no significant difference in S100A8/S100A9 levels between patients with a CDAI-remission and patients with CDAI-low activity. Additionally, patients with CDAI-moderate disease activity show a non-significant but numerical difference in

S100A8/S100A9 levels compared to patients with CDAI-high activity (15).

Furthermore, this study observed there was a high significant difference in ESR related to disease activity with a p-value <0.0001. This matches with Nurten Seringec Akkececi *et al*. (2024), Mohammad Movahedi *et al*. (2022), Rusul H.Ahmad *et al*. (2021), and Abd Elatif Ahmed Gaballah *et al*. (2022), but opposed to Tamara Salman Mohammed *et al*. (2022) and Michael Gernert *et al*. (2022), who proposed that ESR values did not display a significantly different towards the CDAI categories (15, 19, 21-24).

The AUC of S100A8 to discriminate individuals with RA from healthy controls was 0.9785, indicating an excellent discriminatory power of S100A8 between RA patients and controls. S100A8 demonstrated a very high sensitivity and specificity of 95.38% and 100%, respectively. With significant differences (P-value<0.0001), this result indicates that S100A8 could be used as a biomarker to differentiate between RA patients and controls. Research conducted by L. Roszkowski *et al*. (2023) observed that the AUC of S100A8 in early RA patients was 0.71 with a p-value of 0.122 and the AUC of S100A8 in advanced RA patients was 0.83 with a p-value of 0.073 (13). A study by Athan Baillet *et al*. (2010) shows that S100A8 displayed a sensitivity of 82% and a specificity of 69% in distinguishing RA patients from other inflammatory arthritis but not healthy individuals (25). Xu Huang *et al*. (2023) concluded that S100A8 had a high diagnosis value for osteoarthritis and metabolic syndrome (26).

Spearman correlation was employed in this study and was found a weak positive correlation between S100A8 with CDAI and S100A8 with ESR. A study by L. Roszkowski *et al*. (2023) demonstrates a positive correlation of S100A8 with ESR and DAS28-ESR (13). Another study by Michael Gernert *et al*. (2022) suggests that S100A8/S100A9 values correlated with CDAI (r = 0.401; P = 0.001) in RA treated with TNF-inhibitor (15).

Limitations of the study

This study possesses a few limitations that need acknowledgment. The limited study size of 65 rheumatoid arthritis patients and 25 healthy controls may restrict the applicability of the findings to wider groups, especially beyond the Iraqi context. Moreover, although S100A8 was recognized as a potential biomarker for RA, other complicating factors, including comorbidities, fluctuations in disease duration, and treatment protocols, were not adequately controlled, potentially affecting S100A8 levels and disease activity. Furthermore, dependence on self-reported demographic data may result in bias or mistakes during data collection. These limitations highlight the need for larger, multicenter studies to validate these findings and explore the role of S100A8 in diverse patient populations.

Conclusion

This study concluded that there was a significant difference in serum S100A8 levels between the patient and control groups, indicating that it could be a marker for RA disease. A weak positive correlation was observed between the elevation of S100A8 and disease activity. S100A8 accurately differentiates RA patients from healthy individuals, displaying excellent AUC with significant sensitivity and specificity values.

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