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**ORIGINAL PAPER**

# Evaluation of adrenomedullin, growth differentiation factor-15, and atrial natriuretic peptide in patients with rheumatoid arthritis

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**ABSTRACT**

**Introduction and aim.** Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by joint inflammation and systemic complications, including cardiovascular involvement. This study evaluated the diagnostic utility of angiotensinogen (AGT), serum amyloid A-4 protein (SAA4) and C-reactive protein (CRP) in RA, along with new cardiac biomarkers adrenomedullin (ADM), growth differentiation factor-15 (GDF-15), and atrial natriuretic peptide (ANP), to assess cardiac complications.

**Material and methods.** This case-control study included 61 RA patients (divided into newly diagnosed, sDMARD-treated, and sDMARD/bDMARD-treated groups) and 27 healthy controls. Serum levels of AGT, SAA4, CRP, ADM, GDF-15, and ANP were measured using ELISA. Statistical analyses were performed using SPSS software.

**Results.** RA patients exhibited significantly elevated levels of AGT (40.841±17.285 µg/mL), SAA4 (48.128±17.065 ng/mL), CRP (13.097±18.702 mg/L), ADM (96.295±19.424 pg/mL), GDF-15 (1247.049±854.335 pg/mL), and ANP (334.016±40.874 pg/mL) levels compared to controls ($p \leq 0.001$). No significant differences were observed between the treatment groups for AGT, SAA4, or CRP levels. Cardiac biomarkers (ADM, GDF-15, and ANP) remained elevated in all RA groups, with strong inter-parameter correlations (Spearman $r > 0.6$).

**Conclusion.** AGT, SAA4, and CRP demonstrate robust diagnostic value for RA. Persistent elevation of ADM, GDF-15, and ANP in all patient groups confirms significant cardiac involvement in RA.

**Keywords.** adrenomedullin, angiotensinogen, growth differentiation factor-15, rheumatoid arthritis, serum amyloid A-4 protein

## Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily causes symmetric joint inflammation, pain, and swelling. It typically begins in small joints and progresses to larger ones. RA can also affect multiple systems, including the integumentary, ocular, cardiac, renal, and pulmonary.[1,2] Joint involvement leads to erosion of the bone and cartilage, potentially weakening surrounding muscles and ligaments. Its development involves both genetic and environmental factors.[3,4] Recent studies have focused on innovative biochemical markers to diagnose RA, including angiotensinogen (AGT) and serum amyloid A-4 protein (SAA4).[5] AGT is predominantly synthesized in the liver.[6] The conversion of AGT to angiotensin I is catalyzed by the enzyme renin, which is generated by juxtaglomerular cells in the renal cortex. Several components of inflammatory reactions in various tissues are part of the renin-angiotensin system (RAS). The pathophysiology of RA is influenced by several components of this system, including enzymes and peptides.[7] Two opposing but balanced components, classical and protective, regulate blood pressure, body

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fluid, and electrolyte homeostasis in RAS. Pathological inflammatory disorders such as RA can alter this balance and change the plasma concentrations of its components.[8]

SAA4 is an essential acute phase protein in inflammatory rheumatic diseases (IRD). Recent studies have confirmed the role in IRD pathogenesis. Human SAA4 proteins include 104 amino acids and are conserved throughout the mammalian history.[9] Synthesis is performed in the liver and not just in the liver. SAA Insoluble fibrils are formed by solid aggregates, the "amyloid" of "secondary" amyloid disease. Buildups may impair biological activities and cause organ dysfunction. RA is commonly diagnosed by measuring CRP levels to indicate systemic inflammation.[10]

The atrium produces most of the ANP by processing its precursor into prohormones and conserving them in secretory granules within the atrial cardiomyocytes. Elimination separates them into NT-ProANP and ANP.[11] The release of ANP is initiated by distension of the atrial walls, serving two primary functions: promoting vasodilation and improving renal excretion of sodium and water.[12] There is a substantial association occurs between the mechanical and endocrine activities of the heart in individuals with cardiac disease, perhaps indicating the stage and severity of the condition.[13] Natriuretic peptides are essential for heart physiology and pathology. A thorough understanding of their control in both normal and pathological cardiac states may improve diagnostic precision and treatment strategies, particularly for heart failure (HF) and atrial fibrillation (AF), which are intimately interconnected in a cyclical way. The role of ANP in endocrine activity requires a comprehensive examination to clarify the effects of this peptide on mechanical function.[14] Elevated levels of ANP are often seen in individuals with HF and β-thalassemia major, making them significant indicators for the diagnosis and prognosis of this illness.[15]

A divergent member of the transforming growth factor-β superfamily, growth differentiation factor-15 GDF-15, is alternatively referred to as a cytokine that inhibits macrophage (MIC)-1.[16] This superfamily includes several other proteins. When heart myocytes experience ischemia or increased stress on the ventricular wall, their expression of GDF-15 is dramatically increased, in contrast to the usual, low expression of this factor in most tissues. The regulation of GDF-15, a stress-inducible cytokine, appears to be complicated and tissue specific, as it is controlled by many inflammatory or stress-related proteins such as IL-1 β, TNF-α, interleukin-2, and MCSF-1.[17] The precise role of GDF-15 remains unclear; however, it appears to confer protection against cardiac injury through its anti-hypertrophic, anti-apoptotic, and anti-inflammatory properties, which are potentially mediated by its interaction with an unidentified receptor.[18] GDF-15 is an effective prognostic indicator of cardiovascular complications. Experimental murine ischemia/reperfusion injury models demonstrate a rapid increase in circulating and tissue GDF15 levels after cardiac injury, with elevations that persist for several day.[19] GDF-15 levels are also significantly elevated in patients with β-thalassemia major.[20]

Adrenomedullin (ADM), which was initially discovered in pheochromocytoma tissue in 1993, is currently one of the most significant current cardiac indicators.[21] The peptide consists of 52 amino acids. After translation, pro-adrenomedullin (proADM) is produced and converted into biologically active adrenomedullin (bio-ADM).[22] Various body organs, including the kidneys, lungs, endocrine system and cardiovascular system, produce pro-ADM and bio-ADM in response to volume overload, commonly observed in heart failure.[23] Elevated levels of bio-ADM levels in HF suggest a mechanism to mitigate volume overload by stabilizing the function of the endothelial barrier function.[24] There is a critical need for biomarkers that facilitate precise assessment of congestion, as accurately measuring congestion is notoriously challenging due to significant observer variability. Recent studies have demonstrated a significant correlation between elevated bio-ADM levels and systemic congestion as well as negative outcomes, independent of NT-proBNP. Bio-ADM is a useful biomarker for the diagnosis of HF and the assessment of clinical outcomes.[25]

## Aim

This study aimed to evaluate the diagnostic and monitoring efficacy of two novel rheumatoid biomarkers (AGT and SAA4) in patients with RA. Furthermore, we sought to assess cardiac complications associated with RA by quantifying circulating levels of cardiac biomarkers, including ADM, GDF-15, and atrial natriuretic peptide (ANP).

## Material and methods

A case-control study was conducted between November 2023 and June 2024 among RA patients who were subjected to different therapeutic regimens. Participants were recruited from rheumatology clinics at the Al-Basrah Teaching Hospital and Al-Mawanah Teaching Hospital in the Basra Governorate, Iraq. Group 1 (Newly diagnosed): n=10, no previous treatment with disease-modifying anti-rheumatic drugs (DMARD). Group 2 (sDMARD-treated): n=22, receiving conventional synthetic DMARD (csDMARD: methotrexate and sulfasalazine) for 3 months. Group 3 (bDMARD-Treated): n=29, receiving biologic DMARDs (bDMARDs: anti-IL6 agents Tocilizumab or Sarilumab) in addition to csDMARDs. Control group: n=27, healthy volunteers of the same age and sex were included as controls. The

study excluded all participants with preexisting chronic diseases, including cardiovascular disease (for example, hypertension, heart failure), diabetes, liver/kidney dysfunction or active infections, as well as individuals outside the 20–66 age range, to focus on patients with RA diagnosed according to the 2010 ACR/EULAR criteria with 6 months of disease duration, willingness to provide informed consent and no recent corticosteroid use (within 3 months). Disease activity in patients with RA was evaluated using DAS28-ESR. The control group consisted of healthy volunteers from the Basra Governorate, matched with RA patients by age and sex, with no history of autoimmune diseases, chronic inflammation, or recent infections. Samples from both groups were collected in a dedicated laboratory within the same geographic region to ensure consistency. The excluded criteria uniformly applied to both groups included barred pregnant individuals and those with acute or chronic comorbidities.

An agreement was signed to conduct this study before the start of the sample collection process. The study design allowed the evaluation of disease progression and treatment efficacy at different stages of RA management, while the inclusion of a control group allowed the exploration of possible biomarkers and clinical parameters that are specific to patients with RA.

A total of 61 RA patients participated in the study, and the sample size was derived from a combination of statistical and practical considerations. Patient availability, resources, time constraints, ethical considerations, and data from the pilot study contributed to the final sample size. Other factors that have limited patient availability include the prevalence of the disease at the study location. Due to time limitations, the number of patients recruited and followed fell within the specified time frame. In making this decision, ethical dimensions around minimizing the burden on participants while retaining scientific rigor were also important considerations. Data from a pilot study could have adjusted the sample size based on the expectation that 61 patients would be sufficiently motivated to discover clinically meaningful differences. As it is pragmatic in the context of real-life clinical research that involves many investigators, statistical power cannot always be achieved when faced with the practical limitations of the real healthcare environment.

### *Ethical considerations*

The present study was fully approved by the Training and Human Development Unit of the Basrah Health Department, which is part of the Ministry of Health in Iraq. This proposal was authorized by the research committee (number 860/2023) on 23 December 2023, in accordance with the Declaration of Helsinki.

### *Laboratory tests*

A sterile gel tube was used to collect whole blood. As a result, the serum was separated for serological testing and ELISA. All kits used were manufactured by Fine Test Company, China. ANG, Cat: EH0550, SAA4, Cat.: EH1155, ANP, Cat. EH2639; GDF-15, Cat.: EH0150, ADM, Cat: EH0779, and C-Reactive Protein (CRP), REF: ACN 210, levels were measured using a human-adaptable ELISA kit from Shanghai Ideal Medical Technology Co., Ltd., and absorbance was measured at a wavelength of 450 nm using a BioTek (USA) 800TS microplate reader.

### *Statistical analysis*

For tabulation and analysis, SPSS spreadsheet version 26.0 was used. Excel was used to display important facts. For each cardiac and rheumatic parameter, the means and standard deviations were calculated for the control, pretreatment, sDMARDs and bDMARDs groups. The Kolmogorov test determined the normality of the variable, which is a prerequisite for parametric and nonparametric analyses. Tables 1 and 2 show how the Mann-Whitney U test was used to compare the control and patient groups. For each biomarker, the Kruskal-Wallis test and post hoc pairwise comparisons were used to compare the four groups (Tables 3 and 4). Spearman's rank correlation coefficient was used to assess the relationships between the biomarkers.

## Results

This study compared biochemical markers associated with RA in controls (n=27) and patients with RA (n=61). Demographic and clinical characteristics, including age, sex, and body mass index (BMI), were compared between cohorts. No significant differences were observed in age (patients: 46.57±9.65 years; controls: 43.55±8.06 years; p=0.315) or gender distribution (males: 36% vs 33%, females: 64% vs. 67%; p=0.3). However, RA patients exhibited higher BMI values compared to controls (28.6±2.1 kg/m² vs. 23.6±1.9 kg/m²; p=0.02). Different CRP, SAA4 and AGT values were observed. RA patients had significantly higher levels of all indicators than the control group (p <0.001) (Table 1).

**Table 1.** Evaluation of biomarker concentrations in control and patient cohorts*

| | | Patients (n=61) | Control (n= 27) | p |
|---|---|---|---|---|
| Age | | 46.57±9.65 | 43.55±8.06 | 0.315[a] |
| Gender | Male, n (%) | 22 (36 %) | 9 (33 %) | 0.3[b] |
| | Female, n (%) | 39 (64 %) | 18 (67 %) | |
| BMI (kg/m²) | | 28.6±2.1 | 23.6±1.9 | 0.02[a] |
| SAA4 (ng/mL) | | 48.128±17.065 | 2.210±0.647 | <0.0001[a] |
| AGT (µg/mL) | | 40.841±17.285 | 3.573±1.413 | <0.0001[a] |
| CRP (mg/l) | | 13.097±18.702 | 0.756±0.109 | <0.0001[a] |

* [a] – Mann Whitney's test, [b] – Chi-square

Table 2 indicates substantial changes in all cardiac biomarkers between patients and controls. Patients showed significantly higher serum levels of ADM levels (96.295±19.424 pg/mL) than those of the control group (4.191±0.543 pg/mL) (p<0.001). The patient group had substantially higher levels of GDF15 levels (1247.049±854.335 pg/mL) compared to the control group (41.089±14.884 pg/mL) (p<0.00; the sick group exhibited considerably higher levels of ANP levels (334.016±40.874 pg/mL) than the control group (58.200 ±19.592 pg/mL) (p<0.000).

**Table 2.** Patients and controls' cardiac parameters

| | Patients (n=61) | Control (n=27) | p |
|---|---|---|---|
| Age | 46.57±9.65 | 43.55± 8.06 | 0.315 |
| ADM )pg/mL( | 96.295±19.424 | 4.191±0.543 | <0.0001 |
| GDF15 )pg/mL( | 1247.049±854.335 | 41.089±14.884 | <0.0001 |
| ANP )pg/mL( | 334.016±40.874 | 58.200±19.592 | <0.0001 |

Table 3 reveals that the rheumatic parameters indicate that the CRP levels exhibited a significant reduction in the control group (0.756 mg/l) compared to the G1 group (45.600 mg/l), third-month sDMARD therapy group (7.045 mg/l), and the G3 therapy G3 group (bDMARD) (6.479 mg/l. No significant differences were observed between the treatment groups. The control group exhibited significantly lower SAA4 levels (2.21±0.647 ng/mL) compared to the other three groups. The G1 (43.28 ng / mL) G2 (50.4 ng/mL), and G3 (53.7 ng/mL) groups did not exhibit significant differences. The control group exhibited AGT levels of 3.57 μg/mL, which were markedly lower compared to the G1 group at 34.71 μg/mL, the G2 group at 43.5 μg/mL, and the G3 group at 41.23 μg/mL.

**Table 3.** Comparison of rheumatic parameters in patients before and after treatment compared to a control group*

| | Control (n=27) | Pretreatment G1 (n=10) | Third month sDMARDs therapy G2 (n=22) | bDMARDs Therapy G3 (n=29) | p |
|---|---|---|---|---|---|
| Age | 43.55±8.06$^{A}$ | 47.90±11.87$^{A}$ | 47.09±10.84$^{A}$ | 45.72±8.04$^{A}$ | 0.4 |
| SAA4 (ng/mL) | 2.21±0.647$^{A}$ | 43.28±13.46$^{B}$ | 50.4±32.7$^{B}$ | 53.7±30.6$^{B}$ | <0.0001 |
| AGT (μg/mL) | 3.573±1.41$^{A}$ | 38.71±16.41$^{B}$ | 43.5±20.82$^{B}$ | 41.23± 16.74$^{B}$ | <0.0001 |
| CRP (mg/L) | 0.756±0.109$^{A}$ | 45.600±28.733$^{B}$ | 7.045±4.673$^{A}$ | 6.479±4.041$^{A}$ | <0.0001 |

* Capital letters A, B, and C were used to indicate the level of significance following Dunn's multiple comparison test; similar letters indicate no significant difference, whereas different letters indicate significant differences

Table 4 shows that the level of ADM was significantly lower in the control group (4.191 pg/mL) than in the G1 pretreatment G1 group (99.800 pg/mL), the G2 group (95.591 pg/mL), and the bDMARDs) G3 group bDMARDs (95.621 pg/mL), as illustrated in Figure 3. Groups G1, G2 and G3 showed no significant differences. At the GDF15 levels in the control group (41.089 pg/mL) were much lower than in the other three groups. The G1 (2030.1 pg/mL) G2 (1964 pg/mL), and G3 (382.6 pg/mL) groups did not exhibit significant differences. Similarly, ANP levels were markedly reduced in the control group (57.5 pg/mL) compared to those in the other three groups. G1 (305.6 pg/mL), G2 (36.5 pg/mL) and G3 (323.8 pg/mL), with G1 showing a considerable difference from G2.

**Table 4.** Cardiac parameters in patients before and after treatment relative to the control group*

| | Control (n=27) | Pretreatment G1 (n=10) | sDMARDs G2 (n=22) | bDMARDs G3 (n=29) | p |
|---|---|---|---|---|---|
| Age | 43.55±8.06$^{A}$ | 47.90±11.87$^{A}$ | 47.09±10.84$^{A}$ | 45.72±8.04$^{A}$ | 0.4 |
| ADM (pg/mL) | 4.19±0.86$^{A}$ | 100.9±22.48$^{B}$ | 95.6±20.2 $^{B}$ | 92.6±25.6$^{B}$ | <0.0001 |
| GDF15 (pg/mL) | 41.89±14.84$^{A}$ | 2030.1±261$^{B}$ | 1964±470.9$^{B}$ | 382.6±107$^{C}$ | <0.0001 |
| ANP (pg/mL) | 57.5±18.7$^{A}$ | 305.6±29.14$^{B}$ | 360.5 ±40.77$^{C}$ | 323.8±33.4$^{B}$ | <0.0001 |

* Capital letters A, B, and C were used to indicate the level of significance following Dunn's multiple comparison test; similar letters indicate no significant difference, whereas different letters indicate significant differences

ADM had a substantial association with all other cardiac and rheumatic indicators, as shown by a Spearman correlation value over 0.6. GDF15 was significantly correlated with the cardiac parameters of ANP and CRP. Among rheumatic markers, ANP has been shown to correlate with SAA4. Rheumatic CRP, which did not show a connection. The relationship between SAA4 and AGT, as indicated by Spearman's correlation coefficient presented in Table 5.

**Table 5.** Correlation of all parameters

| Parameters | | GDF15 | ANP | CRP | SAA4 | AGT |
|---|---|---|---|---|---|---|
| ADM | r | 0.660 | 0.653 | 0.675 | 0.612 | 0.629 |
| | p | 0.0001 | 0.0001 | 0.0001 | 0.0001 | 0.0001 |
| GDF15 | r | 1.000 | 0.685 | 0.724 | 0.590 | 0.599 |
| | p | | 0.0001 | 0.0001 | 0.0001 | 0.0001 |
| ANP | r | | | 0.561 | 0.600 | 0.590 |
| | p | | | 0.0001 | 0.0001 | 0.0001 |
| CRP | r | | | | 0.589 | 0.591 |
| | p | | | | 0.0001 | 0.0001 |
| SAA4 | r | | | | | 0.755 |
| | p | | | | | 0.0001 |

## Discussion

CRP levels were significantly elevated in patients with RA (Table 1), with the patient group displaying markedly higher values than the control group. Previous research has demonstrated elevated CRP levels in patients with RA compared to healthy controls, since RA is a chronic inflammatory autoimmune disorder and CRP serve as an inflammation marker.28,29

Consistently elevated levels of SAA4 were identified in patients with RA compared to healthy controls, as indicated in Table 1of the current investigation. This finding supports recent research.[30,31] which characterizes increased SAA4 levels to the systemic inflammatory nature of RA. SAA4, an acute phase protein, is classified as a pro-inflammatory cytokines, which stimulates the liver to produce SAA.[32,33] Previous studies have suggested that SAA4 may serve as a more effective marker of disease activity in RA than conventional inflammatory markers such as CRP and ESR, highlighting the importance of SAA4 in the context of RA pathogenesis.[34] Analysis of SAA4 levels between study groups revealed significant differences. The control group showed significantly lower SAA4 concentrations compared to G1, G2, and G3 (Table 3). Furthermore, no statistically significant changes were detected among the three experimental groups. In certain cases, patients with well-managed RA or remission may show lower SAA4 levels, indicating reduced inflammatory activity. Furthermore, specialized treatments, including biological agents that target specific inflammatory pathways, can effectively modulate SAA4 levels. Fragoulis observed that various therapies have varying effects on SAA4 levels in patients with RA, with certain treatments resulting in a significant drop, which differs from the results of the current study.[35]

This study revealed statistically significant differences in AGT values between the patient and control groups (Table 3). This finding aligns with previous studies that have consistently indicated higher AGT levels in patients compared to healthy controls.[36] Unlike SAA4, AGT levels in RA patients are associated with dysregulated function and activity of the renin-angiotensin-aldosterone system (RAAS)under pathological conditions. In patients with chronic inflammation, such as RA, increased activation of the RAAS system leads to elevated production of AGT in the liver and tissues, which subsequently increases angiotensin II levels, which results in hypertension and vascular damage.[37] In RA, cytokine levels are elevated, which promotes the production of AGT.[38] The current study did not reveal significant differences across G1, G2, and G3. Low levels of AGT in RA are rare or nonexistent, but may linked to liver dysfunction, effective inflammation control, or metabolic variables.[39]

In critically ill patients, elevated serum levels of ADM were observed in comparison to controls. Individuals exhibited significantly higher levels of AM compared to healthy controls, as shown in Table (2), corroboration of extensive research that identifies ADM as a potent biomarker closely linked to heart failure, especially in patients with RA.[40,41] Elevated levels of ADM in RA are correlated with chronic inflammation, hypoxia, and vascular dysfunction within synovial tissue.[42] Despite the anti-inflammatory and protective properties of ADM, its overproduction indicates the body's effort to mitigate the pathological processes associated with RA.[43,44] Elevated ADM levels can function as a biomarker for cardiac disease activity and severity; however, direct investigations of ADM levels in RA patients are limited. Its role as a biomarker in other conditions (eg, sepsis and cardiovascular disease) indicates that it could act as a prognostic marker in RA, especially in patients with severe disease or those who did not respond to treatment.[45,46] However, no significant differences in ADM levels were observed between G1, G2 and G3 (Table 4).

The current study demonstrated statistically significant elevations in RA GDF-15 levels in patients compared to healthy controls, as shown in Table (2). These findings correspond to those of a concurrent study that reported similar results.[47] GDF-15 may function as a biomarker for disease activity and could indicate an elevated risk of cardiovascular complications in patients.[48,49] Groups G1 and G2 did not exhibit significant differences, suggesting that these cohorts demonstrate comparable GDF-15 expression. In particular, G3 had significant differences compared to both G1 and G2 (Table 4), indicating that G3 had lower levels of GDF-15, possibly due to the effects of the biologic therapy. The study emphasized the association between GDF-15 and atherosclerosis, demonstrating a gradual elevation of these levels in patients with RA.[50] GDF-15 levels showed a favorable correlation with markers of disease activity. This indicates that GDF-15 can contribute to the pathophysiology of RA and may function as a biomarker for monitoring disease progression.[51]

The study results revealed statistically significant elevations in ANP levels compared to the control group, as shown in Table (2). These findings are consistent with previous studies that demonstrated a correlation between ANP levels and patients with chronic heart failure and RA.[52,53] The observed elevation of ANP in RA patients is probably due to the synergetic effects of chronic inflammation, fluid retention, and cardiovascular stress. ANP regulates fluid balance, vascular tone, and blood pressure, serving as a compensatory mechanism to protect the cardiovascular system from the adverse effects of chronic inflammation in RA.[54] G1, G2, and G3 exhibited equivalent levels of ANP, with no statistically significant differences identified between them. G2 exhibited significantly higher ANP levels compared to G1 and G3. This discrepancy suggests a possible involvement of ANP in the etiology of the disease or as an indicator of the underlying pathological alterations related to RA. The results indicated a significant difference in ANP concentrations between patients with active RA and those in remission; specifically, patients with active RA demonstrated significantly elevated levels of ANP than

their counterparts in remission.[55,56] ADM exhibited a strong correlation with many cardiac and rheumatic parameters, as shown in Table (5); however, GDF15 and ANP exhibited moderate correlations. CRP levels exhibited a modest correlation with SAA4 and AGT levels.

## Conclusion

This study identified notable variations in biomarker levels among RA patients, particularly those with elevated CRP, SAA4, AGT, ADM, GDF-15 and ANP, especially within the pretreatment, chemotherapy and biological treatment groups compared to the control group. SAA4 and GDF-15 are proposed as potential biomarkers of disease activity and progression, with biological treatments linked to a reduction in GDF-15 levels. ADM and ANP levels also exhibited an increase. The findings can help evaluate the severity of the disease, track treatment responses and elucidating the cardiovascular implications of rheumatoid arthritis.

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## Declarations

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***Author contributions***

Conceptualization, A.A.A. and A.M.J.; Methodology, A.A.A.; Software, A.A.A.; Validation, A.A.A., A.M.J.; Formal Analysis, A.A.A.; Investigation, A.A.A.; Resources, A.A.A.; Data Curation, A.A.A.; Writing – Original Draft Preparation, A.A.A.; Writing – Review & Editing, A.A.A.; Visualization, A.A.A.; Supervision, A.M.J.; Project Administration, A.M.J.; Funding Acquisition, A.A.A.

***Conflicts of interest***

The authors confirm that there are no conflicts of interest to disclose.

***Data availability***

The data sets used and analyzed during the current study are available from the corresponding author upon reasonable request.

***Ethics approval***

This study proposal was authorized by the research committee (number 860/2023) on December 23, 2023, in accordance with the Declaration of Helsinki.

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