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Original article

Role of Symmetric Dimethylarginine as a Marker of Myocardial Function and Atherosclerosis in Patients with Rheumatoid Arthritis

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Abstract:

Background: The primary etiology of morbidity and death in rheumatoid arthritis (RA) is cardiovascular disease. The burden of cardiovascular disease remains an unmet requirement in the treatment of RA, even with the introduction of novel medications that target the articular symptoms. There are currently no accurate and precise indicators of early cardiovascular involvement, and the biology of accelerated atherosclerosis linked to RA is not well understood. Symmetric dimethylarginine (SDMA) is becoming more well-known due to its potential role as a biomarker of subclinical atherosclerosis and in the pathophysiology of endothelial dysfunction. **Aim:** To detect the relation between SDMA and myocardial function, subclinical atherosclerotic changes, and relation with disease activity in rheumatoid arthritis. **Methods:** The rheumatology, physical medicine, and rehabilitation departments at Benha University Hospitals served as the sites for this comparative case control research. Cases have been separated into 35 adult RA patients made up Group (I), and Group (II): 25 apparently healthy personnels served as a control group. SDMA, echocardiography and CIMT were utilized as assessment tools in all subjects. **Results:** There was a highly statistically significant increase in the mean serum SDMA level in RA group in comparison with control group. SDMA had a positive correlation with CIMT while there was no correlation with ejection fraction. **Conclusion:** Symmetric dimethylarginine (SDMA) emerges as a powerful biomarker in rheumatoid arthritis (RA), reflecting both disease activity and cardiovascular risk.

Keywords: symmetric dimethylarginine; myocardial function; atherosclerosis; rheumatoid arthritis.

Introduction

Rheumatoid arthritis (RA), a chronic and systemic inflammatory illness that can lead to permanent disability, is marked by persistent synovitis in the joints and systemic inflammatory reactions [(1)].

It is a long-term inflammatory disorder that mostly affects synovial joints and is frequently caused by a combination of environmental factors, involving tobacco use, and genetics. Joint inflammation eventually results in cartilage loss and bone erosion, which destroys the joint [(2)].

Cardiovascular disease (CVD), a prevalent comorbidity, is known to increase the illness burden in cases with RA. Cases with RA were 1.5 times more likely to have CVD in comparison with the general population [(3)].

When peripheral vascular disease and coronary artery disease occur in rheumatoid arthritis cases, the primary cause of morbidity and death (CAD) is accelerated atherosclerosis (ATS) [(4)].

Both vascular alterations and compromised myocardial function appear to be significantly influenced by the chronic inflammatory state of RA itself [(5)].

An essential component of fundamental cellular metabolism, symmetric dimethyl arginine (SDMA) is a stable chemical derived from intracellular proteins. Every cell's nucleus produces SDMA and related substances [(6)]. Methylated arginine residues undergo proteolysis during intracellular protein degradation to produce SDMA [(7)].

By blocking the renal and cellular uptake of arginine, SDMA may have a distinct function in the pathogenesis of endothelial dysfunction and cardiovascular disease, in addition to the cellular transport of l-arginine and other amino acids. This might potentially reduce the bioavailability of NO. Furthermore, SDMA has been characterized as a pro-inflammatory agent and causes monocyte-mediated reactive oxygen species generation [(8)].

Methods:

This comparative case control research has been performed at the rheumatology, rehabilitation, and physical medicine departments at Benha University Hospitals between October 2022 and March 2023. Cases have been divided into: **Group (I):** included 35 adult RA patients, 30 of whom were female and 5 of whom were male, who had been clinically diagnosed and categorized using the American College of Rheumatology/European League Against Rheumatism (ACR/EULAR)-recommended criteria for RA diagnosis [(9)] and **Group (II):** As a control group, 25 employees—23 females and 2 males—who have been matched for sex and age have been selected from the hospital.

The Benha Faculty of Medicine's local ethical committee gave its approval to the project number {M.D.3.9.2022. Written informed permission was obtained from each participant.

Inclusion criteria:

- Adult patients of any age.
- Both sexes.

Exclusion criteria:

Cases have been excluded from this research if they had:

- Hypertension.
- Diabetes mellitus.
- Hyperlipidemia.
- Other rheumatic or auto-immune disease.

Every RA patient had a complete medical history taken, which included a general and local examination as well as information about the disease's past, current, and family history.

Assessment of rheumatoid arthritis patients:

A. Clinical assessment of disease activity:

The modified disease activity score of joint count (DAS-28) was utilized to measure the severity of RA illness (10). DAS is a statistically calculated indicator that includes the patient's global health evaluation, ESR, and the number of

swollen and sore joints. DAS 28 = 0.14 (GH) + 0.70 Ln (ESR) + 0.56 (TEN 28) + 0.28 (SW 28). The final score is determined and assigned a grade of:

- DAS 28 < 2.6 indicates remission; DAS 28 ≥2.6 ≤ 3.2 indicates low disease activity; DAS 28 > 3.2 and < 5.1 indicates moderate disease activity; and DAS 28 > 5.1 indicates high disease activity [10].

B. Ultrasonographic Studies:

1. Echocardiography: To quantify cardiac function.

2. Sonographic evaluation of intima media thickness:

The carotid intima media thickness (IMT) on each side of the patients and controls, who underwent GE P6 scanning with a 7.5 MHs probe was measured. Carotid intima-media thickness (CIMT) is an important marker to quantify atherosclerotic burden in the common carotid artery (CCA) [11]. Carotid ultrasound provides quantitative measurements of CIMT that can be used to assess cardiovascular disease (CVD) risk.

C. Laboratory investigations:

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Rheumatoid factor (RF), Antibodies against cyclic citrullinated peptide (anti-CCP), lipid profile, fast blood sugar levels.

Analysis of Serum symmetric dimethylarginine (SDMA)

All study participants had their SDMA tested by enzyme linked immune sorbent assay (ELISA) technique. The kit was supplied by (AB SCIEX, Framingham, MA, U SA). Assay range was (6.5nmol/L-1800 nmol/L).

Statistical Analysis:

Version 25.0 of the SPSS application (Statistical Package for Social Science) was used to computerize and statistically analyze the gathered data. The collected data were revised, coded, and tabulated using the software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp.). Descriptive statistics were summarized using the mean ± SD. The data were sorted in either ascending or descending order to determine the median, with the mildest observation recorded. The chi-square test was used to determine the variance between qualitative parameters. The unpaired t-test was applied to compare the mean differences between two groups, while one-way analysis of variance (ANOVA) was utilized for comparisons involving more than two groups. Additionally, Spearman's correlation coefficient was calculated. A P-value was considered significant if it was less than 0.05 [12].

Results

According to the results, the comparison of the RA and control groups regarding age and BMI. The results show statistically insignificant differences between the two groups in terms of age (p=0.125) and BMI (p=0.231). The mean age was 37.66 ± 2.79 years in the RA group and 36.08 ± 4.48 years in the control group, indicating a similar age distribution. The mean BMI was also similar between the two groups, with 26.35 ± 1.91 kg/m2 in the RA group and 26.86 ± 1.37 kg/m2 in the control group **(Table 1)**.

The comparison of SDMA levels among rheumatoid arthritis and control groups. Cases with RA had significantly greater SDMA levels in comparison with the control group (median=870.1 vs. 192.6; p-value below 0.001) **(Table 2).**

The Control group had significantly greater EF in comparison with patients with RA (p<0.001 for both) while CIMT values are greater in RA cases in comparison with control group (p-value below 0.001 for both) **(Table 3).**

Cases with high illness activity had the highest SDMA levels, followed by those with moderate and low disease activity, respectively. The SDMA levels of the DAS28 disease activity groups varied statistically significantly (p-value below 0.001). **(Table 3, Figure 1).**

The outcomes demonstrated that compared to individuals with high disease activity, those with moderate and low disease activity had lower CIMTs. There were statistically significant variations in CIMT thickness among the DAS28 disease activity grades. (p=0.009) **(Table3).**

Area under the curve (AUC) values of 0.985 and 0.994, correspondingly, demonstrate the high diagnostic accuracy of both SDMA and CIMT. For SDMA and CIMT, the cutoff values are >510.4 and >0.6, respectively. When it came to differentiating RA patients from controls, both markers had high sensitivity (97.14%) and specificity (92% for SDMA and 96% for CIMT), with overall accuracy of 95% for SDMA and 96.7% for CIMT.

In contrast, EF's accuracy AUC (0.828) at differentiating between the RA and control groups was moderate. ≤70 is the cutoff value. It had an overall accuracy of 80.3%, a sensitivity of 88.6%, and a specificity of 72%. **(Table 4, Figure 2).**

Number of NTJ, NSJ, ESR, CRP, CIMT, and SDMA were significant predictors in both the univariate and multivariate analyses, with p-values below 0.05, according to the linear regression analysis utilized to predict DAS28 among RA patients. In both the univariate and multivariate analyses, the other variables—such as age, BMI, duration of the disease, Hb, WBC, platelets, lipid profile, RF, anti-CCP, and EF—were not significant predictors. **(Table 5).**

Table 1 Comparison of RA and control groups regarding personal history.

	RA **n = 35**	**Control** **n = 25**	**Test**	**p**
Age (years)				
Mean ± SD.	**37.66 ± 2.79**	**36.08 ± 4.48**	**t=**	**0.125**
Median	**38.0**	**38.0**	**1.571**	
Min. – Max.	**26.0 – 40.0**	**25.0 – 40.0**		
BMI (kg/m2)				
Mean ± SD.	**26.35 ± 1.91**	**26.86 ± 1.37**	**t=**	**0.231**
Median	**26.30**	**26.80**	**1.210**	
Min. – Max.	**22.40 – 29.20**	**24.0 – 29.20**		

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, t: Student t test, BMI, Body Mass Index.

Table 2: Comparison of ejection fraction (EF), SDMA and carotid intima media thickness (CIMT) among RA and control groups.

	RA **n = 35**	**Control** **n = 25**	**Test**	**p**
EF (%)				
Mean ± SD.	65.14 ± 5.29	74.08 ± 7.56	t=	<0.001*
Median	66.0	77.0	5.394*	
Min. – Max.	55.0 – 76.0	58.0 – 87.0		
CIMT (mm)				
Mean ± SD.	0.85 ± 0.13	0.47 ± 0.10	U=	<0.001*
Median	0.80	0.50	5.50*	
Min. – Max.	0.60 – 1.20	0.30 – 0.70		
SDMA (µmol/L)				
Mean ± SD.	1069.5 ± 526.0	282.3 ± 182.6	U=	<0.001*
Median	870.1	192.6	13.0*	
Min. – Max.	472.2 – 2929.0	62.50 – 783.4		

SD.: Standard deviation, Min.: Minimum, Max.: Maximum, t: Student t test, U: Mann Whitney.
χ^2: Chi Square test, *: Significant when p value <0.05. EF.: Ejection Fraction, CIMT.: Carotid Intima Media Thickness, SDMA.: Symmetric Dimethylarginine.

Table 3: Association between CIMT, SDMA and DAS28 grades among patients with RA.

	SDMA (µmol/L) Mean ± SD.	**Median**	**Min. – Max.**	**Test**	**p1**	**Pairwise comparison**
DAS28 grades						
Remission, n=1[#]	754.5					
Low disease activity, n=7	727.1 ± 126.3	771.3	472.2 – 875.8	H= 24.365*	<0.001*	p2=0.401 p3<0.001* p4<0.001*
Moderate disease activity, n=13	792.9 ± 109.6	815.1	531.3 – 929.9			
High disease activity, n=14	1520.0 ± 582.6	1392.5	929.4 – 2929.0			
	CIMT (mm) Mean ± SD.	**Median**	**Min. – Max.**	**Test**	**p1**	**Pairwise**
DAS28 grades						
Remission, n=1[#]	0.90					
Low disease activity, n=7	0.79 ± 0.07	0.80	0.70 – 0.90	H= 9.425*	0.009*	P2=0.886 p3=0.016* p4=0.007*
Moderate disease activity, n=13	0.79 ± 0.06	0.80	0.70 – 0.90			
High disease activity, n=14	0.93 ± 0.17	0.90	0.60 – 1.20			

SD. Standard deviation, Min.: Minimum, Max.: Maximum, H: Kruskal Wallis test, U: Mann Whitney test. DAS.: Disease Activity Score.
p1: Comparing different grades, p2: Comparing low versus moderate disease,
p3: Comparing low versus high disease, p4: Comparing moderate versus high disease,
#: Exclude from association due to small size n=1, *: Significant when p value <0.05.

Table 4: Validity of SDMA and CIMT for discrimination between patients with RA and the control group.

AUC	**95% CI**	**p**	**Cut off**	**Sensitivity (%)**	**Specificity (%)**	**PPV (%)**	**NPV (%)**	**Accuracy (%)**
SDMA								
0.985	0.960-1.000	<0.001*	>510.4	97.14	92.0	94.44	95.83	95.0
CIMT								
0.994	0.981-1.000	<0.001*	>0.6	97.14	96.0	97.14	96.0	96.67
EF								
0.828	0.713-0.943	<0.001*	≤70	88.6	72	76.0	86.3	80.3

*P value Significant <0.05; CI: Confidence interval; PPV: Positive Predictive Value; NPV: Negative Predictive Value; AUC: Area under the ROC curve.

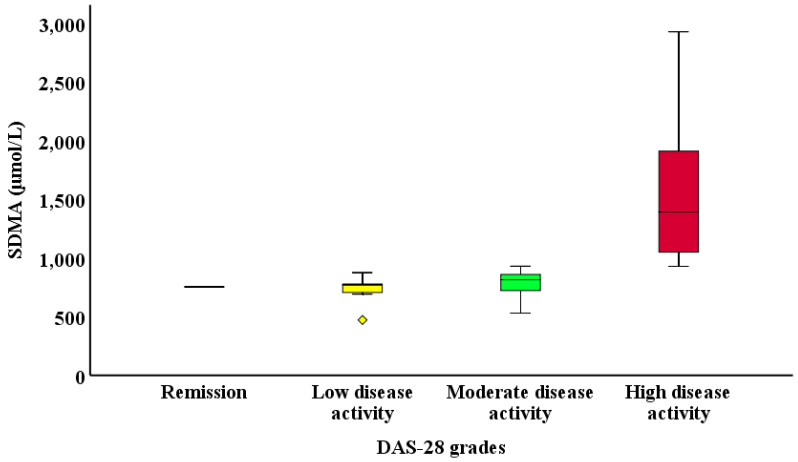

Figure (1): Boxplot chart for association between SDMA and DAS28 grades among patients with RA.

Table 5: Linear regression analysis for prediction of DAS28 among patients with RA.

	Univariate		Multivariate	
	β	*p*	*β*	*p*
Age	0.044	0.612		
BMI	0.159	0.200		
Duration of disease		0.425		
NTJ	0.360	<0.001*	0.125	0.002*
NSJ	0.363	<0.001*	0.060	0.003*
TC	-0.009	0.399		
TG	-0.014	0.120		
LDL	-0.020	0.129		
HDL	0.016	0.661		
ESR	0.074	<0.001*	0.055	<0.001*
CRP	0.080	<0.001*	0.016	0.048*
RF	0.006	0.084		
Anti-CCP	0.247	0.602		
EF	0.053	0.241		
CIMT	4.277	0.013*	1.034	0.007*
SDMA	0.002	<0.001*	0.022	0.016*

CI, or confidence interval; OR, or odd ratio; *: Significant when p value is less than 0.05. Body Mass Index, or BMI. NTJ.: Tender Joint Number, Number of Swollen Joints (NSJ) Disease Activity Score, or DAS. Hemoglobin, or Hb. White blood cells, or WBCs TG.: Triglycerides, HDL stands for high density lipoprotein, and LDL for low density lipoproteins. CRP stands for C-Reactive Protein, and ESR for Erythrocyte Sedimentation Rate. Anti-CCP: Anti Cyclic Citrullinated Peptide; RF: Rheumatoid Factor. Ejection Fraction (EF.) Carotid Intima Media Thickness (CIMT). Symmetric dimethylarginine, or SDMA.

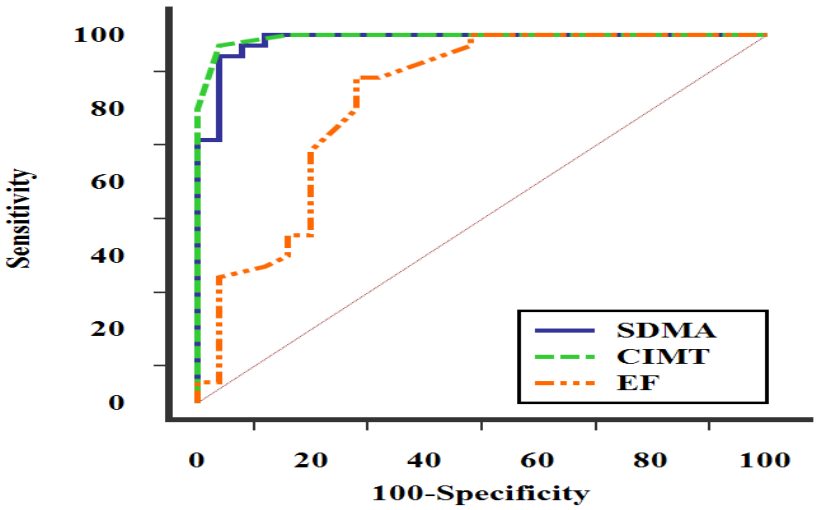

Figure (2): ROC Curve of SDMA, CIMT and EF for discrimination between patients with RA and the control group.

Discussion

The current study found that there is a comparison of the RA and control groups regarding age and BMI. The results show statistically insignificant differences between the two groups in terms of age (p=0.125) and BMI (p=0.231) respectively. Most RA patients (85.7%) were female, with a mean age of 37.66 ± 2.79 years. These outcomes are consistent with Tidblad et al. [13] who found that 68% of RA patients were female. Similarly, Chen et al. [14] discovered that RA was more common in women (63%) in a

population-based study. Furthermore, Jiang et al. [15] pointed out that reproductive and hormonal factors can raise the chance of having RA, which would help to explain why the condition is more common in women.

Our results demonstrated that the ejection fraction (EF) was lower in the RA group (p-value below 0.001) compared to healthy controls. This research strengthens the connection between systemic inflammation and subclinical cardiac dysfunction by indicating that RA patients may have early myocardial function deficits even in the absence of overt cardiovascular symptoms.

Since persistent inflammation in RA can change the structure and function of HDL particles, compromising their anti-atherosclerotic characteristics, the decrease in HDL levels in RA cases is clinically relevant, according to Yan et al. [16]. In addition to losing its capacity to encourage cholesterol reverse, dysfunctional HDL can also turn pro-oxidative, increasing LDL oxidation and hastening the development of plaque. Even in the absence of obvious hyperlipidemia, this inflammatory change in lipid metabolism raises the risk of which may be a contributing factor to subclinical atherosclerosis, endothelial dysfunction, and cardiovascular disease (CVD) in RA cases.

Our outcomes are consistent with earlier research. The left ventricular ejection fraction (LVEF) of RA cases was lower than that of healthy controls (60.1% vs. 65.7%, $p < 0.001$), Dijkshoorn et al. [17]. Similarly, EF was significantly lower in RA cases (p-value below 0.01), according to Setouhi et al. [18]. Additionally, Pan& Wang [19] found that RA patients had significantly worse EF than controls ($p < 0.05$).

While Alexandre et al. [20] demonstrated no significant association between RA activity and EF, indicating that EF changes may appear more gradually or in later stages of the disease, this finding partially agrees with Ibrahiem et al. [21], who documented poorer LV function with increased disease activity.

Our study showed that Carotid intima-media thickness (CIMT) measurements were greater in RA cases compared to the control group (p-value below 0.001). So, RA cases were more likely to develop subclinical atherosclerosis even in the absence of clinically apparent cardiovascular disease.

Our research demonstrated a significant relationship ($p = 0.009$) between RA patients' carotid intima-media thickness (CIMT) and DAS28 disease activity grades. Cases with high disease activity had the highest CIMT values, followed by those with moderate and low disease activity, in that order.

These findings are in line with earlier studies. These findings are consistent with Rajabzadeh et al. [22] and Bahls et al. [23]; they discovered that the CIMT readings of RA cases were greater in comparison with those of healthy controls (p-value below 0.001).

Rajabzadeh et al. [22] showed that in RA patients, CIMT dramatically rose as disease severity increased. Furthermore, a high association between mean CIMT and DAS28 scores was discovered by Maldar & Suhas [24] as well. Our results further confirmed the idea that systemic inflammation speeds up vascular remodeling is further supported, the usefulness of CIMT as a non-invasive technique for identifying people at higher risk of RA and associated cardiovascular issues.

Amer et al. [25] revealed that RA patients had significantly greater right (RT) and left (LT) CIMTs than controls ($p < 0.001$). Which is consistent with our findings and supports the connection between RA-associated inflammation and early vascular remodeling.

Rojas-Giménez et al. [26] found that the CIMT values of RA patients and controls did not differ significantly (0.64 vs. 0.61, $p = 0.444$). This discrepancy is explained by

differences in the duration of the disease, the kind of medicine taken, or the patient demographics.

The SDMA levels of RA cases were higher compared to those of the control group in the current study (median = 870.1 vs. 192.6; $p < 0.001$). This significant increase in SDMA points to a close connection between endothelial dysfunction and systemic inflammation linked to RA, which can be a factor in the increased cardiovascular risk seen in RA cases.

Our results support the idea that SDMA buildup may be a key factor in vascular dysfunction, as described by Chandrasekharan et al. [27], They discovered that RA patients' SDMA levels were much greater than those of healthy controls. Kwaśny-Krochin et al. [28] further reinforced the association among increasing SDMA and RA disease activity by finding that RA cases had significantly greater SDMA levels (0.45 ± 0.07 vs. 0.36 ± 0.046 μmol/L, p-value below 0.0001).

In contrast to our study, Zafari et al. [29] explained that SDMA levels of RA patients and controls did not differ significantly, according to a comprehensive review and meta-analysis. Also, Erre et al. [30] found no discernible variations in the two groups' plasma SDMA concentrations. These disparities may be explained by variations in sample numbers, variations in the severity of RA, or variations in the analytical techniques employed to quantify SDMA.

The assessment of disease activity and its relationship to SDMA levels in the current study revealed that cases with greater DAS28 scores had significantly greater SDMA levels than those with moderate or low disease activity ($p < 0.001$). Given the systemic inflammatory burden and its role in vascular dysfunction, our research suggests that SDMA may serve as a biomarker of disease severity in RA.

These results are consistent with Dimitroulas et al. [31], SDMA levels and DAS28 had a positive association (p-value equal to 0.007). The association between SDMA and the burden of inflammatory diseases in RA was further supported by Kwaśny-Krochin et al. [28] who found that SDMA was significantly positively related to DAS28 ($r = 0.40$, $p = 0.005$), ESR ($r = 0.57$, $p = 0.00003$), and CRP ($r = 0.82$, p-value below 0.00001).

Conversely, the lack of a significant association among RA disease activity (DAS28) and SDMA levels was documented by Chandrasekharan et al. [27] and may be the result of variations in patient characteristics, the length of the disease, or treatment approaches.

Variability in disease phenotypes, methodological variations in SDMA measurement, or heterogeneity in study populations could all account for the disparity between studies.

The outcomes of the recent research demonstrated a substantial positive association between SDMA levels and DAS28 score ($r = 0.907$, p-value below 0.001), erythrocyte sedimentation rate (ESR) ($r = 0.859$, p-value below 0.001), number of swollen joints (NSJ) ($r = 0.751$, $p < 0.001$), number of tender joints (NTJ) ($r = 0.751$, p-value below 0.001), and C-reactive protein ($r = 0.749$, p-value below 0.001) were all significantly positively related to SDMA levels.

Additionally, a significant association ($r = 0.456$, p-value equal to 0.006) was discovered between SDMA and carotid intima-media thickness (CIMT). Which lends more credence to SDMA's involvement in vascular pathology and endothelial dysfunction in RA patients. According to Kumar et al. [32] Proinflammatory cytokines (including TNF-α and IL-6) thicken the artery wall, encourage vascular injury, and help create foam cells, all of which accelerate the development of CIMT.

Likewise, Riddell et al. [33] and Bahls et al. [23] both found a favorable correlation between CIMT and elevated levels of circulating SDMA, which lends further credence to this finding.

Ejection fraction (EF) and DAS28 disease activity grades among RA patients did not significantly correlate in the current research. Cases with high disease activity had an average EF of 66.00 ± 5.52, whereas those with moderate disease activity had an EF of 65.62 ± 5.66, and those with low disease activity had an EF of 62.71 ± 4.35. These variations were not statistically significant, though.

The difficulties of using these conventional biomarkers for early cardiac disease detection in RA patients were highlighted by Alexandre et al. [20], They discovered no connection between RA activity features (RA duration, DAS28-ESR score), subclinical left ventricular impairment, and inflammatory markers (e.g., ESR and CRP).

Even in the absence of clinically evident heart failure, Ibrahiem et al. [21] discovered that elevated disease activity as determined by the DAS28 was significantly correlated with declining left ventricular function. This implies that cardiac dysfunction may eventually result from chronically elevated disease activity.

With high AUC values of 0.985 and 0.994, respectively, the current study showed that both SDMA and CIMT had outstanding diagnostic accuracy for differentiating RA patients from healthy controls. Both indicators demonstrated 97.14% sensitivity, 92% specificity for SDMA, and 96% specificity for CIMT at cutoff values of >510.4 for SDMA and >0.6 for CIMT. On the other hand, at a threshold of ≤70, EF demonstrated moderate accuracy (AUC = 0.828), with 88.6% sensitivity and 72% specificity. SDMA and CIMT seem to be more dependable in identifying vascular and endothelial alterations associated with RA, whereas EF might suggest subclinical cardiac dysfunction.

According to the aforementioned research, SDMA and CIMT may be useful, non-invasive biomarkers for RA patients' early cardiovascular risk assessment, which could lead to better patient outcomes through earlier intervention and focused treatment. To validate these results and determine clinical value, larger, multicenter investigations are required.

The findings of the linear regression analysis demonstrated that NTJ, NSJ, ESR, CRP, CIMT, and SDMA were significant independent predictors of DAS28, but age, BMI, disease duration, RF, anti-CCP, and EF was not significant. While indicating that conventional cardiovascular risk factors and autoantibody status may have a less direct impact on clinical disease severity, our findings demonstrate the direct impact of joint inflammation, systemic inflammation, and vascular dysfunction on disease activity.

Conclusion

In rheumatoid arthritis (RA), symmetric dimethylarginine (SDMA) becomes a potent biomarker that reflects both cardiovascular risk and disease activity. It is strong associations with systemic inflammatory markers, DAS28, and CIMT highlight its capacity to capture the effects of long-term inflammation on vascular disease and endothelial dysfunction, and detection of subclinical atherosclerosis in patients with normal BMI or lipid profiles. However, EF stayed mostly unchanged across disease activity stages, indicating that in RA, subclinical myocardial dysfunction might occur before overtly systolic impairment. These results emphasize how crucial it is to monitor vascular health, especially in patients who do not have overt cardiac failure.

Conflict of interest:

None declared any conflict of interest.

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