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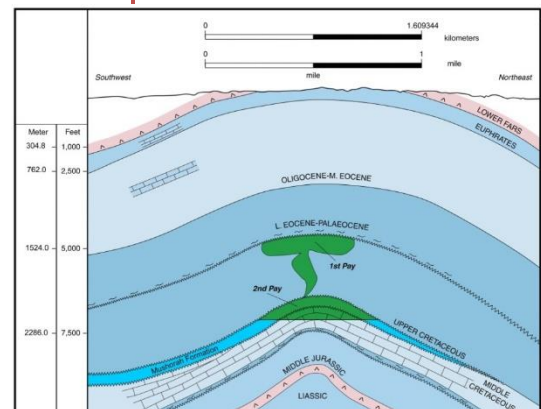
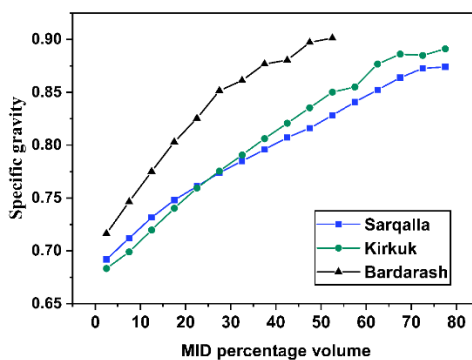
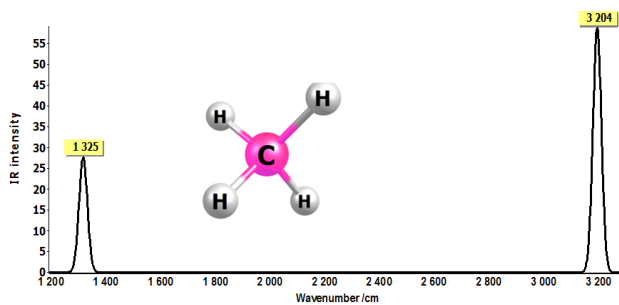
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## Cardiac Valve Involvement in Rheumatoid Arthritis: A Case-Control Study Among Adult Patients in Sulaimaniyah Province

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### Abstract

**Background:** The frequency of valvular heart disease (VHD) among rheumatoid arthritis (RA) patients varies in the literature ranging between 3-70%. This considerable variability might be attributed to the examined population's varied genetic backgrounds and the different methodologies utilized to identify valvular disease. VHD resulting in severe symptomatic aortic insufficiency is an uncommon RA consequence. **Objectives:** This study aimed to look for cardiac valve involvement in RA patients and determine whether it is linked with disease activity and duration. **Methods:** Fifty RA patients were recruited consecutively, 5 were males, and 45 were females, aged 27 to 65 years, with a mean of  $49.86 \pm 9.98$ . All patients were free from cardiac diseases and underwent entire history, physical examination, laboratory test, and transthoracic echocardiography. The findings were compared to those of age and gender-matched controls, who had no rheumatic and cardiac diseases. **Results:** Valvular lesions were found in 18 (36%) RA patients, whereas only 2 (4%) of the controls had valvular lesions ( $p=0.000063$ ). The most frequently affected valve was the mitral valve 11(61%). There was no relationship between VHD and the duration of the disease, clinical disease activity index (CDAI) score, body mass index (BMI), and smoking. **Conclusions:** This study has confirmed that VHD (specific to the mitral valve) is significantly higher in RA patients compared with the control sample. There was no correlation between VHD and RA's disease duration, clinical, laboratory, or treatment characteristics.

## Introduction

Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disease distinguished by polyarticular inflammatory arthritis in addition to diverse Extra-articular symptoms, affecting between 0.5 and 1% of the general adult population worldwide, with women affected two to three times more commonly than men (1, 2 and 3). Regardless of geographic area or race, the prevalence is relatively consistent over the globe (4). The synovial membrane is the primary site of RA expression and is clinically distinguished by symmetrical polyarthritis, which can result in gradual joint destruction (5). RA can cause significant functional impairment, morbidity, and accelerated mortality, which imposes a significant societal burden (2, 6 and 7). The exact cause of RA remains unknown; however, in recent years, it has been evident that RA is connected with genetic and epigenetic factors, but also the environment, including cigarette smoke, dust exposure, and notably, the microbiome also plays an essential impact (8, 9).

Extra-articular RA symptoms occur in around 40% of individuals, either at the onset or throughout their disease (1, 7). In RA, cardiovascular disease continues to be a leading cause of higher mortality; in a review of 50 studies that comprised 91 618 patients and 33 250 deaths, 39.6% of deaths were attributed to cardiac diseases (1, 10). Among RA patients, pericarditis is the most recognized cardiac manifestation; however, it is also possible to see myocardial disease, coronary vasculitis, accelerated atherosclerotic disease, diastolic dysfunction, and valvular abnormalities (11, 12). Inflammatory cells, cytokines, chemokines, proteolytic enzymes, and autoantibodies are all implicated in these complications, which directly influence all parts of the cardiovascular system, including the pericardium, myocardium, cardiac valves, conduction system, and vasculature (13, 12).

Patients with RA have an increased risk of developing valvular heart disease compared to the general population (VHD) (14). The ideal method for identifying VHD is transthoracic echocardiography (15). VHD can be found in approximately 30% of people with RA; however, it is usually clinically silent (16). The most frequent valvular condition among RA patients is mitral regurgitation (17). In addition, aortitis and valvular incompetency can develop from the granulomatous disease of the endocardium spreading to the base of the aorta in patients with severe RA, which, in rare cases, might require an urgent valve replacement (2, 18).

The frequency of VHD among RA patients is variable in the literature ranging from 3% to 70% (19). This considerable variability might be attributed to the examined population's varied genetic backgrounds and the different methodologies utilized to identify valvular disease. In some studies, VHD has been linked to the male gender, age, rheumatoid nodules, and disease duration. However, other studies could not find such associations (13, 14). Roldan et al. reported valvular lesions in 59% of RA individuals as opposed to 15% of the general population (20). Pathologic investigations characterize VHD associated with RA as valve nodules and leaflet fibrosis, which may spread and affect valve rings and the subvalvular apparatus, causing valve regurgitation (20, 21). VHD in RA patients can be associated with various complications, such as severe valve regurgitation, thromboembolism, rupture of a valve nodule, infective endocarditis, or the need for high-risk valve surgery (1). In addition, no clinical or laboratory predictors of RA-associated VHD have been established (22). Furthermore, there has been a shortage of new information about this subject in the local area. This study aims to look for VHD in RA patients and determine whether or not it is associated with the duration and activity of the disease.

## **Materials and Methods**

### *Sample size and study setting*

This case-control study was conducted at the Rheumatology and Rehabilitation center in Sulaimaniyah, Iraq, from 15<sup>th</sup> October 2021 to 1<sup>st</sup> June 2022 on 50 consecutive RA patients (5 males and 45 females) aged >18 to ≤65 years. In addition, as controls, we included 50 individuals who visited the same health center for musculoskeletal conditions other than rheumatological diseases.

### *Inclusion criteria*

Who met the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) classification criteria for RA were enrolled in the study.

### *Exclusion criteria*

Patients with any rheumatic conditions besides RA, prior cardiologic problems and congenital cardiac lesions, arterial hypertension, or diabetes mellitus were eliminated from the study.

### Study procedure

Demographic and clinical data such as sex, age, smoking habit, drug history and disease duration, detailed clinical history, including any previous rheumatic and cardiologic conditions, physical examination, CIDA score, BMI, blood pressure, and blood sugar were gathered. The controls had no history of arterial hypertension, diabetes mellitus, or rheumatic diseases, including RA, prior cardiologic problems, or congenital cardiac lesions. The controls were age and gender-matched to the RA patients and were subjected to the same procedures as RA patients.

An individual was considered to have hypertension if their systolic or diastolic blood pressure was 140/90 mm Hg or above on two separate occasions or if they were prescribed antihypertensive medication. Diabetes was identified as having a fasting blood glucose level of 126 mg/dL or being prescribed oral hypoglycemic medication. Smoking status was reported as either a previous or present smoker or nonsmoker. CIDA score was used to measure the disease activity, and patients were grouped as remission, low, moderate, and high disease activity.

All participants were examined through bidimensional transthoracic echocardiography using a Philips ClearVue-550 Ultrasound Apparatus with color Doppler. The same physician did the echocardiography according to a standardized protocol. The cardiac valves were observed for thickening and hyperechoic characteristics. In addition, transvalvular gradients were assessed, and valvular regurgitation was measured using color flow Doppler.

### Ethical approval and patient consent

The Ethical Committee of the College of Medicine, University of Sulaimani, Sulaimaniyah, Iraq, approved the study protocol, and the enrolled patients were given written consent.

### Statistical analysis

The data was analyzed using IBM SPSS version 26.0. Mean, and standard deviation was calculated for continuous parameters. To compare quantitative variables, the T-test was used. Pearson Chi-square test and Fisher's Exact test were used to comparing qualitative variables. P-value <0.05 was counted to be statistically significant.

## Results

Among 50 RA patients investigated, 5 were males, and 45 were females, aged 27 to 65 (49.86±9.98) years. The controls included the same number of males and females aged between 28 to 64 years (47.10±9.53, p=0.161). The mean age of patients with VHD was 48.40±8.51, while the mean age of the non-VHD population was 48.50±10.16 (p=0.97). A 26.1% of RF-positive patients had VHD (p=0.66). In terms of treatment options, thirty patients were on methotrexate (MTX), 10 (33.3%) had VHD (p=0.630) while 7 patients were on triple (MTX+PDL+HCQ) therapy, 2 (28.6%) had VHD (p=1.00) (Table 1). Eighteen (36%) RA patients had VHD, 28 valvular lesions were detected in total, and two patients had valvular lesions in two different valves. The mitral valve was most commonly affected in 11(61%) patients, while the most prevalent lesion type was regurgitation, found in 13 different valves. Also, trivial valvular regurgitation was considered normal.

**Table 1.** Associations between VHD and clinical and demographic factors.

RA Patients (n= 50)	VHD		p-value
	Yes n=18	No n=32	
Sex (%)			1.00
Female (n=45)	16 (35.6%)	29 (64.4%)	
Male (n=5)	2 (40%)	3 (60%)	

<b>Age (mean ± SD)</b>	48.5 ± 8.86	46.31 ± 9.94	0.44
<b>RF +ve (%)</b>	(26.1%)	(73.9%)	0.66
<b>Smoking (n= 3)</b>	2 (66.7%)	1 (33.3%)	0.29
<b>Disease Duration (Year)</b>			
Mean ± SD	4.05 ± 3.6	5.4 ± 4.5	0.26
≤ 5	15 (39.5%)	23 (60.5%)	
6 to 10	2 (25%)	6 (75%)	0.66
> 10	1 (25%)	3 (75%)	
<b>BMI Class (%)</b>			
Underweight	0	0	
Normal	6 (50%)	6 (50%)	0.28
Overweight	7(41.2%)	10 (58.8%)	
Obese	5 (23.8%)	16 (76.2%)	
<b>Medication (%)</b>			
MTX	10 (33.3%)	20 (66.7%)	0.63
Prednisolone	12 (34.3%)	23 (65.7%)	0.7
HCQ	7 (33.3%)	14 (66.7%)	0.74
TNF-Inhibitors	2 (25%)	6 (75%)	0.69

VHD= valvular heart disease; RA= rheumatoid arthritis; SD= standard deviation; RF= rheumatoid factor; BMI= body mass index; MTX= methotrexate; HCQ= hydroxychloroquine; TNF= tumor necrosis factor

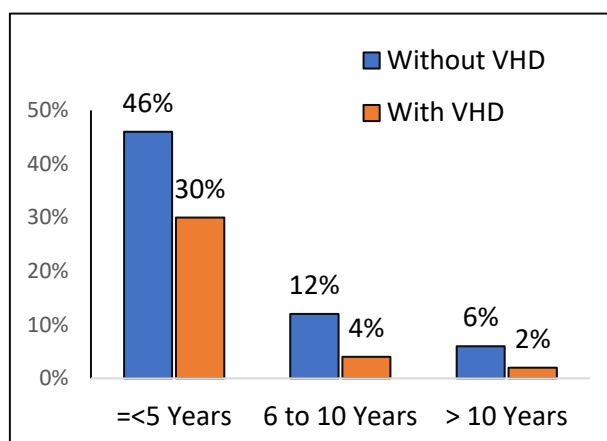
However, among the 50 controls, 3 valvular lesions were detected in 2 (4%) patients, including 2 mild mitral valve regurgitation and 1 mitral valve prolapse (Table 2). In general, comparing both RA and controls, valvular lesions were found in 18 (36%) RA patients, whereas only 2 (4%) of the controls had valvular; this result shows that RA significantly increased the risk of developing VHD (OR=13.5; 95% CI: 2.9-62.2). To find out the association between VHD and disease duration of RA, we categorized RA patients into 3 groups, the majority of patients had a disease duration of ≤5 years, and only 4 individuals had a disease duration of >10 years. However, no association between the development of VHD and the chronicity of RA was found (p=0.661).

**Table 2.** Frequency of valve lesions in RA patients and controls.

Valve Lesion	RA n = 50	Control n = 50	p-value
<b>Mitral valve (n= 11)</b>			
Thickening	6 (12%)	0	0.03
Sclerosis	5(10%)	0	0.06
Prolapse	1 (2%)	1 (2%)	1.00
Regurgitation	6 (12%)	2 (4%)	0.27
<b>Aortic valve (n=6)</b>			
Thickening	2 (4%)	0	0.49
Sclerosis	3 (6%)	0	0.24
Prolapse	0	0	
Regurgitation	2 (4%)	0	0.49
<b>Tricuspid valve (n=3)</b>			
Thickening	0	0	
Sclerosis	0	0	
Prolapse	0	0	
Regurgitation	3 (6%)	0	0.24
<b>Pulmonic valve (n=0)</b>	0	0	
<b>Sum of lesions</b>	28	3	
<b>Positive VHD</b>	18 (36%)	2 (4%)	< 0.001*

RA= rheumatoid arthritis; VHD= valvular heart disease, \*OR=13.5 (95% CI: 2.9-62.2)

Figure 1 illustrates the distribution of VHD among RA patients based on disease duration.



**Figure 1.** Involvement of valvular heart disease (in percent) according to disease duration (p= 0.661).

Among 50 RA patients, only 3 were smokers; 2 had VHD, and the association between smoking and VHD was insignificant (p= 0.25). CDAI score was used to measure disease activity for RA patients; the score has 4 levels; remission, low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA). The majority of the patients (23) had MDA; among them, 7 (30.4%) had VHD, while only 3 were counted to be in remission, and 2 (66.7%) of them had VHD. The result shows no association between the development of VHD and the disease activity scores of RA patients (p=0.663) (Table 3). To assess the correlation between VHD and BMI, the RA population was classified into 3 BMI classes, 12 RA patients had normal BMI, 6 (50%) of them had VHD, while 5 (23.8%) out of 21 obese patients had VHD. No significant differences were found as regards all the considered BMI classes (p=0.276).

**Table 3.** Frequency of VHD among RA patients according to their CIDAI score (p=0.663).

RA patients	CIDAI score				Total
	Remission	LDA	MDA	HDA	
<b>With VHD (%)</b>	2.0 (11.1)	8.0 (44.4)	7.0 (38.9)	1.0 (5.6)	18
<b>Without VHD (%)</b>	1.0 (3.1)	13 (40.6)	16 (50)	2.0 (6.3)	32
<b>Total</b>	3.0	21	23	3	50

VHD= valvular heart disease; CIDAI= clinical disease activity index; LDA= low disease activity; MDA= moderate disease activity; HDA= high disease activity

## Discussion

The result of this study shows various valvular lesions among 50 RA patients, in which 18 (36%) patients had at least one valvular lesion while within the controls; only 2 (4%) patients had valvular lesions (OR= 13.5; 95% CI: 2.9-62.2). The most frequently affected valve was the mitral valve 11(61%). These results are consistent with other studies (13, 14). Mitral valve thickening and regurgitation were the most frequent lesions; each was found six times. Including participants with no cardiac symptoms was a key element of the current study, and patients >65 were excluded. This was done to determine the prevalence of cardiac valve lesions without apparent heart illness, avoiding confounding factors. This might clarify why no severe valvular lesions were detected in this study.

Cardiac valve involvement in 184 RA patients was evaluated in a case-control study by Beckhauser et al., and 15.2% were found to have VHD (19). Valve lesions were more frequent in RA patients whose disease duration was more than 15 years, and indifferent to the current study, the aortic valve was most

commonly involved. They found no association between VHD and sex, age, smoking, rheumatoid nodules, positive rheumatoid factor (RF), antinuclear antibody (ANA), or anti-cardiolipin antibodies. The current study revealed a higher rate of valvular involvement at 36% when compared to the results found by Beckhauser et al. Using transesophageal echocardiography, Roldan et al. studied 34 RA patients with an average age of  $50 \pm 10$  years. The results were compared to 34 gender-matched controls with an average age of  $42 \pm 6$  years. Twenty (59%) patients had VHD; they classified the findings according to the type of lesions instead of the involved valves. The result showed 18 (53%) valve thickening, 11 (32%) valve nodules, 7 (21%) valve regurgitation, and 1 (3%) valve stenosis, whereas only 5 controls (15%) had VHD (20). The use of the transesophageal method, which has more sensitivity than the transthoracic technique, may explain the greater frequency of VHD in this study; furthermore, individuals experiencing cardiovascular symptoms were not excluded from the study.

Guedes et al. prospectively studied 30 RA individuals between the ages of 27-84 ( $57.8 \pm 15.1$ ) who completed laboratory, transesophageal and transthoracic echocardiographic examinations. The outcomes were compared with those of a control group with age and sex matching who underwent transesophageal echocardiography for a cardiac or neurologic problem. VHD was more prevalent in RA patients compared to controls (83% vs. 53%,  $p=0.02$ ). A total of 24 patients (80%) and 11 controls (37%) had mitral regurgitation ( $p 0.001$ ). However, only 3 (10%) patients had valve nodules (26). Including patients  $>65$  may explain the increased prevalence of VHD in RA patients. The overall prevalence of valvular abnormalities detected in a study conducted by Ibrahim-Sayo et al. was 30.8%; in contrast to this study, the valvular lesion reported by Guedes et al. was mostly tricuspid valve regurgitation at 15.4%. Mitral regurgitation was observed in 5.8% of individuals, while mitral stenosis was found in 1.9% (23).

No valve nodules were detected among the 50 studied RA patients; the same result was found by other researchers (19, 24). However, different numbers of valve nodules were founded in some other studies; for instance, Roldan et al. detected 11(32%) valve nodules by transesophageal echocardiography, whereas 5 (11%) nodules were found among 47 RA patients in a study by Gonzalez-Juanatey et al. (25, 20). This could be clarified by the fact that echocardiography is an operator-dependent examination and that the transthoracic and transesophageal methods have different levels of accuracy. Furthermore, this study was not powered to detect any relationships between VHD and smoking as a few numbers of the participants were smokers. Also, no association between VHD and obesity was found.

The results of this study, like those of previous research, found no correlation between VHD and disease duration, clinical, laboratory results, or therapeutic elements of RA (19, 20, 23, 26). Different factors could account for this lack of association, including the cross-sectional nature of the research, in addition to the fact that cardiac imaging is often not conducted at the time of the onset of clinical symptoms of RA. In addition, RA's clinical and serologic activity varies significantly throughout time, and VHD develops independently from other organ disorders. Therefore, to better identify clinical correlations and the impact of therapy on VHD caused by RA, more considerable cross-sectional and longitudinal research with cardiac imaging conducted at the time of emergence of clinical characteristics and change in RA therapy is required.

## **Conclusions**

This study confirmed that valvular heart disease (particularly of the mitral valve) is significantly higher in RA patients than in the control group. The study assumes that diagnosing undetected heart valve problems in asymptomatic individuals is critical for proper RA therapy. Therefore, a regular cardiological examination (especially echocardiographic) for RA patients is recommended so cardiac involvement may be discovered and treated early and more severe illnesses can be avoided. However, more long-term research is needed to understand the possible link between the findings of this study and the increased cardiovascular mortality in these patients. In addition, this study was limited by using

a small number of patients; hence, it was not powered to make associations between VHD in RA and some clinical variables.

### Conflict of interest

The authors confirm that they are not affiliated with or involved in any organization or entity with financial interests.

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