# Association Between Rheumatoid Arthritis and Pulmonary Hypertension: A Clinical Investigation

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**Abstract**- Assessment of pulmonary hypertension (PAH) frequency and its association with interstitial lung disease (ILD), left ventricular diastolic dysfunction (LVDD), left ventricular systolic dysfunction (LVSD), and valvular heart diseases (VHD) in adult patients with rheumatoid arthritis (RA). Cross-sectional study. Cardiology and Rheumatology Departments, Ghaem Medical Center, Mashhad University of Medical Sciences, Mashhad, Iran. A total of 40 patients with RA without history or clinical features of cardiac diseases underwent cardiopulmonary and rheumatological assessment, including history taking, physical examination, chest X-ray, chest High-Resolution Computed Tomography (HRCT), and echocardiography. Echocardiographic variables of patients with RA were measured and analyzed. The relationship between rheumatoid arthritis and pulmonary hypertension. The prevalence of PAH was 60% in RA. The tests showed no significant differences in PAH between age and gender groups. The most common valve involvement among patients was tricuspid insufficiency, followed by mitral insufficiency. Grades I and II LVDD were present in 27.5% and 2.5% of patients, respectively. There were significant correlations between systolic velocity (Sm) and ejection fraction, early diastolic velocity and diastolic velocity, as well as Sm and systolic wave velocity. This study revealed a high prevalence of severe LVDD in RA patients with PAH. Early diagnosis and management of cardiovascular risk factors may prevent the development and progression of PAH in RA patients.



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## Introduction

The manifestations of extraarticular in RA patients are reported to be around 50%, in which pulmonary accounts for 10%-67%. With the extraarticular affection comes increased mortality, which is 10%-20% inpulmonary involvement (1). Other accompanied manifestations may include atherosclerosis, pericarditis, congestive heart failure, myocarditis, cardiac bundle block, and valvular abnormalities (2). Pulmonary hypertension (PAH) is a global medical issue that affects all age groups (3).The global prevalence of PAH is 1%, from whichapproximately 80% of patients with PAH live in developing countries (3). PAH is related to increased morbidity and mortality due to cardiovascular disease (3). It is a set of diseases with the property of progressive increase of pulmonary vascular resistance that can lead to right ventricular malfunction, which in turn can lead to premature death. PAH is defined to be a resting mean pulmonary artery pressure (PAP) higher than 30 mmHg. These changesresult in increased pulmonary vascular resistance and may progress to right heart failure and death if remained untreated (4,5). Although the gold standard for diagnosis of pulmonary hypertension is right heart catheterization, electrocardiography is frequently used for its diagnosis as well as progression. This is because it is not invasive, easily available, and relatively less expensive (6,7,8,9). The diagnosis in research is also based on echocardiography.

Rheumatoid arthritis (RA) is a chronic and destructive autoimmune disease and is the most common

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inflammatory musculoskeletal disorder that is linked to physical disability (10,11). Generally speaking, rheumatoid arthritis is triggered through the immune response counter to own proteins, and it leads to high inflammation (12,13,14). The global prevalence of RA is reported to range from 0.3 to 0.6%, and the prevalence of RA among low to middle-income countries ranges from 0.4% to 1.26% based on geographical region (11,15). Extraarticularinvolvement is common in RA, and the most common affected sites are the skin, heart, and lungs (5). Cardiovascular diseasesare more common in RA than in the normal population, and the risk of myocardial infarction (MI) is reported to be twice in women with RA compared to a healthy population (5,16,17,18). RA is also considered to be related to left ventricular diastolic dysfunction (LVD) (5). Endocarditis is another cardiac involvement in RA, which may lead to cardiac valvular dysfunction because of the formation of rheumatoid nodules near the valvular structures of the heart (5). Most of the cardiovascular manifestations of RA may not cause symptomatic presentations and thus may be left undiagnosed (5). PAH is considered as a cardiac complication of RA (5,18). The etiology of PAH in RA is unclear, but it is hypothesized that interstitial lung disease (ILD) due to chronic inflammation might be the reason behind the development of PAH (5,18). The prevalence of PAH among RA patients is reported to range between 11% and 30% in various studies (19,20,21).

The aim of this study is to estimate the prevalence of PAH in adults with RA and to study associations of PAH with ILD,left ventricular diastolic dysfunction (LVDD), left ventricular systolic dysfunction (LVSD), and valvular heart diseases (VHD).

## Materials and Methods

This cross-sectional study was conducted on patients with RA, classified according to the American Rheumatology Association (ARA) criteria, who were referred to the Rheumatology Department of Ghaem Hospital, Mashhad, Iran. Patients were included if they were diagnosed with RA for at least five years and had at least two rheumatologist and cardiologist visits. Patients were excluded if they had a past medical history of cardiovascular disease, including myocardial infarction or cerebrovascular accident (CVA) or had abnormal cardiac findings on physical electrocardiography (ECG) (Suzuken Kenz, Japan) or chest X-ray (CXR) and chest HRCT. Patients with RA who met the inclusion criteria were approached by the researcher and received information regarding the aim and procedure of the study. Patients who were willing to participate in the study were asked to sign a written informed consent form prior to participation in the study. The study protocol was approved by the Ethical Committee of the Mashhad University of Medical Sciences.

A total of 40 patients with RA without a history or clinical manifestations of cardiac diseases were selected during the six months of data collection. During the course of the study, patients underwent thorough physical examination including cardiopulmonary and rheumatologic history taking and physical examination, ECG, CXR, chest HRCT, and the 2D and Doppler Echocardiography (GE, USA) instead of the gold standard invasive method of right heart catheterization (RHC) for the confirmation of the PAH (9,22).The evaluation findings were recorded for all patients.

Echocardiography was performed using the cardiovascular ultrasound (VIVID3, GE, USA) with MHZ 2.5-3.5 probe in left decubitus lateral position based on the European echocardiography guidelines by an experienced cardiologist. The echocardiography indices including left ventricle systolic function, ejection fraction (EF), wall motion abnormality, left ventricle diastolic function parameters including early diastolic velocity (E wave), end-diastolic velocity (A wave). Tissue Doppler (TD) indices were also measured by placing the Doppler course on the lateral and interventricular septum. The indices included systolic velocity (Sm), early diastolic (Em), and end-diastolic (Am) velocity. Furthermore, the flow of the right pulmonary vein indices, including systolic wave velocity (S), diastolic wave velocity (D), and end-diastolic backward flow (Ar), were measured by placing the Doppler course on the right pulmonary vein. Additionally, systolic and diastolic left ventricular volume, presence of stenosis regurgitation of heart valves based on pulmonary pressure, presence of cardiomyopathy, and pericardial effusion or constriction was also simultaneously measured.

LVDD was divided into mild, moderate, and severe as per established criteria based on mitral inflow velocities (MIV) (E and A) and lateral mitral annulus velocity (E) measured by Tissue Doppler Imaging (TDI). LVSD was defined as LVEF <40%. Pulmonary wedge pressure cut off of 30 mmHg was used for the analysis.

### Statistical analysis

Data were analyzed using the Statistical Package for

Social Sciences (SPSS) software (IBM Inc, Chicago, Il, USA) version 20. Continuous data were checked for normality using the Shapiro-Wilk test. Continuous data were presented using mean and standard deviation (SD), while categorical variables were presented using frequency and percentage. The Student's *t*-test was used to compare continuous variables, and *chi*-squared test was used for comparing the distribution pattern of categorical variables between study groups. The *P* of <0.05 was considered significant.

## Results

A total of 40 patients,consisting of 36females (90%) and four males(10%), participated in the study. The mean age of patients was 46.4±15.48 years. The most common valvular comorbidity was tricuspid insufficiency (29, 72.5%) followed by mitral regurgitation (21, 52.5%), aortic insufficiency (6, 15%), pulmonary regurgitation (3, 7.5%), and mitral and tricuspid stenosis (1, 2.5% each). The prevalence of valvular diseases as per gender are presented in Table 1. There was no significant gender difference in the prevalence of valvular diseases in this study (*P*>0.05) (Table 1). There was no significant difference between age groups in terms of the prevalence of valvular diseases either (*P*>0.05). An overview of the echocardiography findings of study subjects is presented in Table 2.

**Table 1. Prevalence of valvular heart diseases among genders in the study**

| Valvular disease | Gender | No involvement | | Mild | | Moderate | | severe | | *p* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Frequency | % | Frequency | % | Frequency | % | Frequency | % | |
| **AI** | Female | 31 | 86.1 | 5 | 13.9 | 0 | 0.0 | 0 | 0.0 | 0.493 |
| | Male | 3 | 75.0 | 1 | 25.0 | 0 | 0.0 | 0 | 0.0 | |
| **MS** | Female | 35 | 97.2 | 0 | 0 | 1 | 2.8 | 0 | 0.0 | 0.736 |
| | Male | 4 | 100.0 | 0 | 0 | 0 | 0.0 | 0 | 0.0 | |
| **MR** | Female | 16 | 44.4 | 19 | 52.8 | 1 | 2.8 | 0 | 0.0 | 0.503 |
| | Male | 3 | 75.0 | 1 | 25.0 | 0 | 0.0 | 0 | 0.0 | |
| **TS** | Female | 35 | 97.2 | 0 | 0 | 1 | 2.8 | 0 | 0.0 | 0.900 |
| | Male | 4 | 100.0 | 0 | 0 | 0 | 0.0 | 0 | 0.0 | |
| **TR** | Female | 10 | 27.8 | 24 | 66.7 | 1 | 2.8 | 1 | 2.8 | 0.862 |
| | Male | 1 | 25.0 | 3 | 75.0 | 0 | 0.0 | 0 | 0.0 | |
| **PI** | Female | 33 | 91.7 | 3 | 8.3 | 0 | 0.0 | 0 | 0.0 | 0.723 |
| | Male | 4 | 100.0 | 0 | 0 | 0 | 0.0 | 0 | 0.0 | |

AI= Aortic insufficiency, MS= Mitral stenosis, MR= Mitral regurgitation, TS= Tricuspid stenosis, TR= Tricuspid regurgitation, PI= Pulmonary insufficiency. The Fisher exact test was used for the comparison

**Table 2. Echocardiographic parameters of studied patients**

| Variable | Mean ± SD |
|---|---|
| **LV end-systolic diameter** | 4.77±0.59 |
| **LV end-diastolic diameter** | 3.18±0.48 |
| **LV end-systolic volume** | 73.75±17.09 |
| **LV end diastolic volume** | 30.87±8.41 |
| **E** | 86.55±24.45 |
| **A** | 78.15±16.56 |
| **DT** | 201.96±47.20 |
| **S** | 51.60±11.02 |
| **D** | 39.67±13.76 |
| **Sm** | 8.1±2.16 |
| **Em** | 9.4±3.44 |

Among the study patients, 28 (70%) had a normal diastolic function, 11 (27.5%) had grade I diastolic dysfunction, and one patient (2.5%) had grade II diastolic dysfunction while none of the patients had grade III diastolic dysfunction. No wall motion dysfunction was observed among study patients.

Considering the cut-off point of 30 mmHg for pulmonary artery pressure, 40% of the patients had PAH. There was a significant difference in EF between patients with normal diastolic function (62.4±4.04) and patients with diastolic dysfunction (58.3±5.64) (*P*=0.047).

## Discussion

The preliminary observation of this study was that 90% of referred patients were female. It is documented that women have a tendency for RA and that the prevalence of RA in women is three times higher than men (16). Although in the current study, the proportion of female to male patients was 9:1, which might be due to the small sample size of the current study.

Based on the findings of this study, the prevalence of PAH among RA patients was 40%. This finding was in line with the findings of the previous study by Gonzalez-Juanatey *et al.,* which reported a higher prevalence of PAH among RA patients compared to the control group (23). The prevalence of PAH among RA patients was previously reported to range from 11% to 30% (19,20,21). In a study in 2000, the prevalence of PAH was reported to be 30% among RA patients (21).

This study revealed a significant difference in EF and Sm between RA patients and control ones. Furthermore, another observation of this study was that the prevalence of grade I and II diastolic dysfunction were 27.5% and 2.5%, respectively. Previous studies have also reported a higher prevalence of diastolic dysfunction among RA patients (19,24). In a systematic review and meta-analysis in 2015, RA was found to be associated with higher myocardial mass and diastolic dysfunction (25,26,27).

The findings of this study further exposed cardiac valvular involvement among RA patients compared to controls, especially in terms of TR (72.5%), MR (52.5%), and AR (15.0%). Similar findings were reported in a study in 2003, which reported a higher prevalence of tricuspid and mitral valve involvements in RA patients (21). In general, the prevalence of cardiac valve involvement is known to be higher among RA patients compared to the healthy population (4). The mechanism of the effect of RA on heart valves includes calcification, fibrosis, or granuloma formation (rheumatoid nodules), among which valvular fibrosis is the most common finding in RA patients (11). Base, mid, and tip of cardiac valves might be affected by focal fibrosis due to valvulitis (11,28).On the other hand, no statistically significant difference in the prevalence of cardiac valvular involvement between genders and age groups wasobserved in our study. This finding was in contrast to the findings of previous studies that reported the prevalence of cardiac valve involvement at higher age (23,29).

The current study revealed cardiac abnormalities, especially in terms of PAH, grade I diastolic dysfunction, and TR, MR, and AR among RA patients compared to healthy control ones.

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