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# Independent relationship between uveitis and increased left atrial volume index in ankylosing spondylitis patients

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## Abstract

**Aim:** The aim of this study was to evaluate the relationship between uveitis and left atrial volume index (LAVI) in patients with ankylosing spondylitis (AS).

**Materials and Methods:** Demographic, clinical, echocardiographic and brachial artery flow-mediated dilation measurement data of patients diagnosed with AS were recorded prospectively between January 2019 and June 2023. The patients were categorized into two groups: increased (Group 2) and normal (Group 1) based on a cut-off value of 34 ml/m2 for increased LAVI and the data were compared.

**Results:** Of the 89 patients with AS, 54 were male and 35 were female, with a mean age of 42.8±11.8 years. There were N=67 patients in the group with normal LAVI levels, and N=22 patients in the group with high LAVI levels. Mean age, uveitis and comorbid conditions were higher in Group 2. Among the basic echocardiographic parameters that may affect LAVI, only the left ventricular mass index was different in Group 2. In Group 2, flow-dependent dilatation in the vessel decreased. When we evaluated all parameters by multivariate logistic regression analysis, we found that age (odds ratio:1.097; 95% confidence interval:1.017-1.183; P=0.016) and the presence of uveitis (odds ratio:21.3; 95% confidence interval:2.476-182.1; P=0.005) independently predicted Group 2.

**Conclusion:** Evaluation of LAVI in AS patients with uveitis may be a guide in predicting the risk of cardiovascular events and early treatment.



## Introduction

Ankylosing spondylitis (AS) is a rheumatological illness that creates a significant health problem in society as a result of pain in axial and peripheral joints, limitation of movement and spinal deformity [1]. Uncontrolled inflammation in AS causes systemic organ involvement similar to uveal inflammation in the eye, heart involvement, apical pulmonary fibrosis in the lung, and nonspecific colitis in the intestine. Iridocyclitis is seen in 45% of AS cases. Uveitis is the most frequent systemic finding of AS [2,3]. In cases with uveal inflammation, an increase in inflammation-related proteins and peptides was observed in the examination of serum, teardrop, aqueous and vitreous materials. Therefore, uveitis in patients with AS may be indicative of active systemic inflammation (SI) [4].

Left atrial volume index (LAVI) varies consistent with sex, age and body dimension LAVI is measured by dividing LAV by body surface area. Increased LAV is associated with serious cardiovascular (CV) events such as myocardial infarction [5]. Therefore, LAVI is a simple and easily applicable parameter used to predict mortality from cardiovascular disease. Inflammatory changes can affect atrial myocardial and vascular structures, increasing LAV and triggering mechanical dysfunction. In addition, researches have shown that autoimmune illnesses causes inflammation-related impairment of LA function, leading to an increased incidence of cardiac events. It has also been reported that LA functions decrease as the duration of inflammation increases [6].

Based on this inflammatory process, we aimed to detect the relationship between LAVI and uveitis seen in AS cases.

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## Materials and Methods

### *Patients*

Our study is a prospective study conducted on a total of 89 patients diagnosed with AS based on the international task team evaluation rules of the International Spondyloarthritis Society (ASAS) who applied to rheumatology between January 2019 and June 2023 [7]. The research was carried out with the permission of the Recep Tayyip Erdoğan University Non-invasive Clinical Research Ethics Committee, numbered 2023/223.

### *Exclusion criteria*

Persons under the age of 18, patients with rheumatological diseases other than AS, patients with heart valve disease and surgery, patients with renal failure and hematological diseases were not included in the resarch.

### *Data collection*

The study recorded patients' gender, age, height, weight, smoking status, duration of ankylosing spondylitis, comorbidities, and medications used. AS patients with active uveitis or previous sequelae of uveitis confirmed by ophthalmologists were included in the study. Laboratory analyses were conducted on venous blood samples obtained after a 12-hour fast. Diabetes Mellitus (DM), hypertension and hyperlipidemia (HL) were diagnosed based on guidelines [8,9]. Cigarette use was calculated as packs per year. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were measured at diagnosis and follow-up [10].

### *Echocardiography*

Detailed two-dimensional (2D) transthoracic echocardiography (TTE) was performed on all patients. Left atrial left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD), pulse and continuous Doppler measurements, E and A wave velocities, and deceleration time (DT) were measured using standard two-dimensional M-mode echocardiographic images. Left ventricular ejection fraction (LV EF) was measured by the modified Simpson method. Left ventricular septal (LVS) and posterior wall (PW) thicknesses were calculated at the end of diastole in the parasternal long-axis view. Devereux et al.'s formula was applied to calculate left ventricular mass (LVM), and LV mass index (LVMI) was defined as LV mass/BSA (body weight × 0.425 × height × 0.725 × 0.007184) [11-13].

Left atrial (LA) volume was assessed by the area-length method on both A4C and A2C views. LA maximum volume and LA minimum volume measurements were obtained, and LAVI was determined by dividing LA volume by body surface area.

### *Brachial artery flow-mediated dilation*

Flow-dependent dilatation (FMD) of the brachial artery (BA) was assessed from the right brachial artery after ensuring that participants refrained from exercising, smoking, or consuming beverages that would affect the result for at least 8 hours before measurement. Brachial artery width was measured during the end-diastolic phase, and the maximum diameter was recorded at the 15th second, 1st, 3rd, and 5th minutes during the hyperemia phase using an ultrasonic 5 to 13 MHz linear transducer. FMD% was measured as [(mean brachial artery diameter after reactive hyperemia – initial brachial artery diameter) x 100/initial brachial artery diameter] [14].

### *Statistical analysis*

The statistical analysis was performed with the use of SPSS (ver. 26) software. Data distribution normality was assessed through visual (histograms, probability plots) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk's test). Participants were categorized into two groups: increased (Group 2) and normal (Group 1) based on a cut-off value of 34 ml/m$^2$ for increased LAVI. The study compared parameters between groups using one-way ANOVA for continuous variables with normal distribution. Results were presented as mean ± standard deviation. Categorical variables were expressed as percentages and compared using the chi-square test or Fisher's exact chi-square test. Cross-tabulations were used to compare proportions of patients with categorical variables. Initially, we conducted univariate logistic regression analysis to identify factors predicting group two. We utilized parameters with statistically significant differences, as shown in Table 2. Subsequently, we performed multivariate logistic regression analysis using all significant parameters, employing the backward method. We considered a p-value of $<0.05$ to be statistically significant in all analyses.

## Results

An analysis was made of 89 patients diagnosed with AS, 54 males and 35 females, with an average age of 42.811.8. The patients were divided into two groups according to the LAVI level. There were N=67 patients in the group with normal LAVI levels (Group 1), and N=22 patients in the group with increased LAVI levels (Group 2). Fifty-five patients (61%) were receiving anti-tumor necrosis factor (TNF) treatment, and 2 patients (2.2%) were receiving anti-interleukin (IL)-17 treatment. When we compared the demographic features of the patients (Table 1), the average age, BMI level, and rates of DM, hypertension, and uveitis were higher in Group 2. There were no differences between other demographic features. Basic laboratory parameters, except glucose level, were also similar. Fasting glucose level was higher in Group 2. Similarly, patients in Group 2 were more likely to use statins. Among the basic echo parameters that may affect LAVI, only the left ventricular mass (LV MASS) index was different in Group 2. There was no difference reaching statistical significance in parameters related to diastolic dysfunction. In addition, flow-dependent dilatation (FMD) in the vessel decreased in Group 2.

We first evaluated the parameters that differed between the two groups with univariate logistic regression analysis, and then all the parameters that remained significant with multivariate logistic regression analysis (Table 2). As a result, we found that age (OR:1.097 95%CI 1.017-1.183; P=0.016) and the presence of uveitis (OR:21.3, 95%CI 2.476-182.1; P=0.005) independently predicted Group 2.

**Table 1.** Demographic, medical, laboratory and echocardiographic data of the patients.

| Variables, meanSD, % | Group 1(N=67) | Group 2 (N=22) | p |
|---|---|---|---|
| Demographic Data | | | |
| Sex (male) | 41 (60.3) | 13 (59.1) | 0.556 |
| Age (years) | 41.1±11.2 | 49±13.2 | **0.008** |
| BMI (kg/m$^2$) | 26.9±4.7 | 30.3±5 | **0.004** |
| Diabetes mellitus | 4 (5.9) | 38 (13.6) | 0.226 |
| Hypertension | 12 (17.6) | 9 (40.9) | **0.029** |
| Hyperlipidemia | 29 (42.6) | 13 (59.1) | 0.136 |
| Smoking | 30 (44.1) | 8 (36.4) | 0.350 |
| HLA-B27 (+) | 35 (52.2) | 13 (59.1) | 0.379 |
| BASDAI Scr. | 4.22±2.14 | 3.65±2.3 | 0.291 |
| BASFI Scr. | 2.7±2.1 | 2.9±2.6 | 0.827 |
| Uveit | 4 (5.9) | 6 (27.3) | **0.012** |
| Peripheral Arthritis | 12 (17.6) | 3 (13.6) | 0.472 |
| Waist-Hip Pain | 66 (97.1) | 21 (95.5) | 0.573 |
| Enthesitis | 12 (17.6) | 4 (18.2) | 0.590 |
| Dactylitis | 3 (4.5) | 0(0) | 0.422 |
| Sacroiliitis | 64 (94.1) | 22 (100) | 0.319 |
| Medical Treatment | | | |
| CCB | 6 (8.8) | 6 (27.3) | 0.037 |
| ACEI | 4 (5.9) | 5 (22.7) | 0.036 |
| ARB | 6 (8.8) | 3 (13.6) | 0.383 |
| Diuretic | 9 (13.2) | 6 (27.3) | 0.116 |
| Statin | 1 (1.5) | 5 (22.7) | 0.003 |
| OAD | 2 (2.9) | 2 (9.1) | 0.250 |
| NSAID | 24 (35.3) | 9 (40.9) | 0.409 |
| Anti TNF alpha | 42 (61.8) | 13 (59.1) | 0.507 |
| Secukinumab | 2 (2.9) | 0 (0) | 0.569 |
| Laboratory Data | | | |
| WBC ($10^3$/µl) | 7.6±2.1 | 8.6±2.7 | 0.065 |
| Hemoglobin (g/dl) | 14.1±1.5 | 13.6±1.9 | 0.387 |
| Fasting glucose (mg/dl) | 94.1±12.2 | 110.2±28 | **<0.001** |
| Serum creatinine (mg/dl) | 0.79±0.16 | 0.77±0.17 | 0.802 |
| eGFR (ml/min/1.73 m$^2$) | 106.2±15.3 | 100.6±17.7 | 0.154 |
| Echocardiography Data | | | |
| LVEF (%) | 62.1±4.3 | 60.7±4.1 | 0.243 |
| EA Ratio | 1.2±0.4 | 1.15±0.30 | 0.554 |
| EE Ratio | 9.1±4.05 | 8.82±2.7 | 0.839 |
| Deceleration time (L/dk) | 198.9±53 | 202±44.1 | 0.813 |
| LV mass index (g/m$^2$) | 77.1±22 | 96.1±29.6 | **0.002** |
| FMD (%) | 11.9±5.3 | 8.2±3.2 | **0.016** |

BMI, body mass index; HLA-B27, human leukocyte antijen; BASDAI, bath ankylosing spondylitis disease activity index; BASFI, bath ankylosing spondylitis functional index; CCB, calcium channel blocker; ACEI, angiotensin-converting-enzyme inhibitors: ARB, angiotensin receptor blocker; OAD, oral antidiabetic drugs;NSAID, nonsteroidal anti-inflammatory drugs; WBC-White Blood Cell; eGFR, estimated glomerular filtration rate LVEF, left ventricular ejection fraction; LV mass index, left ventricular mass index; FMD, flow-mediated dilation; Em: early diastolic peak, Am:late diastolic peak.

## Discussion

It is known that the risk of developing cardiovascular disease is higher in ankylosing spondylitis patients than in the normal population [15]. The uvea is heterogeneous, pigmented and highly vascular. Uveitis has been reported to be a marker of atherosclerosis-associated CVD in newly diagnosed AS patients, even after correction for known risk factors [16]. In AS patients, eye inflammation is mostly in the anterior segment. Similar inflammatory cytokines such as TNF alpha, IL-17A and IL-23 were observed to be increased in the aqueous humor of the eye in the patient with acute anterior uveitis, similar to the synovial fluid of a patient with arthritis. Uveitis is more frequent and severe in human leucocyte antigen (HLA)-B27 positive patients. Berg IJ et al. found a significant relationship between uveal inflammation and hypertension and atherosclerosis in AS patients. This indicates that patients with uveitis or active uveitis may be at risk for developing CV illnes [17,18]. Uveitis may indicate the intensity of SI in AS. Uveitis may be a potential risk for CV illnes in AS, as inflammation can lead to cardiovascular endothelial damage [16]. One study found an increase in carotid artery intima-media thickness in children with long-term uveitis. HLA-B27, which may act through the IL-23 axis, is associated with uveitis in spondyloarthritis [20,21]. LA is a dynamic structure in which cardiac muscle cells, located beneath the innermost layer of endothelium, are in charge of contraction and relaxation [22,23]. LA myopathy often accompanies many chronic systemic inflammatory diseases [24]. Cardiac imaging studies confirm that the systemic inflammatory process has spread to the atrium wall, resulting in abnormalities, particularly in left atrium geometry and filling characteristics [25]. Impaired atrial mechanical function in patients with AS may also result from SI, aortic regurgitation, conduction abnormalities, and fibrosis of the atrial myocardium [26,27]. Long-term presence of uveitis as a chronic systemic inflammatory condition may increase the risk of atherosclerosis as a result of further endothelial damage by promoting the inflammatory cytokine cascade that activates circulating cytokines and secondary adhesion molecules [28]. This plays an important role in LA mechanical function and modeling. In addition, the in-

**Table 2.** Logistic regression analyzes of the parameters differing between Groups 1 and 2.

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| Variables | OR | 95%CI Lower-Upper | p | OR | 95%CI Lower-Upper | p |
| Age | 1.055 | 1.012-1.100 | 0.013 | 1.097 | 1.017-1.183 | **0.016** |
| BMI | 1.161 | 1.040-1.296 | 0.008 | | | |
| Hypertension | 3.231 | 1.126-9.270 | 0.029 | | | |
| Uveitis | 6.001 | 1.511-23.83 | 0.011 | 21.3 | 2.476-182.1 | **0.005** |
| Fasting glucose | 1.048 | 1.015-1.081 | 0.004 | | | |
| LV mass index | 1.029 | 1.009-1.050 | 0.005 | | | |
| CCB | 3.875 | 1.101-13.634 | 0.035 | | | |
| ACEIs | 4.706 | 1.138-19.457 | 0.032 | | | |
| FMD | 0.755 | 0.608-0.937 | 0.011 | | | |
| Statin | 19.706 | 2.157-179.9 | 0.008 | 9.486 | 0.742-121.3 | 0.084 |
| Constant | | | | | | 0.002 |

BMI, body mass index; LV mass index, left ventricular mass index, CCB, calcium channel blocker; ACEIs, angiotensin-converting-enzyme inhibitors; FMD, flow-mediated dilation; CI, confidence interval; OR: odds ratio.

flammatory state associated with uveitis may explain the increase in LA diameter and myopathy, and therefore cardiac screening can be performed for the early detection of cardiovascular diseases in AS patients with uveitis.

An increase in LA pressure and LA remodeling results in an increase in LAVI [29,30]. In addition to predicting events such as heart failure, atrial fibrillation, and cerebral stroke, LAVI is recommended as a marker for the duration and severity of diastolic dysfunction. In one study, increased LAVI was determined to be an independent predictor in patients with acute coronary syndrome [31,32]. In our study, we found higher rates of hypertension and iridocyclitis in AS patients with increased LAVI. We also found that age and iridocyclitis independently predicted the parameters of AS patients with increased LAVI.

In our study, we can attribute this to the high LV MASS index and other comorbid conditions in AS patients with increased LAVI. In addition to, in AS patients with increased LAVI, prolongation of the disease duration with increasing average age and exposure to chronic inflammation may increase the risk of cardiac complications in AS. Although LV MASS Index and diastolic dysfunction are known to be independent predictors of LAVI, the situation was different in patients with AS. We think that the characteristics of the patient group and the relatively lower average age for CV diseases may be decisive in this. Another possible factor may be that the inflammatory process that is effective in the development of uveitis strongly affects left atrial myocytes.

It is well known from previous studies that AS, like many systemic inflammatory diseases, has high CV mortality and morbidity [33,34]. Vascular endothelial damage due to long-term inflammation may result in atherosclerosis and thrombosis, causing CV events [35]. In the cohort study of Erikson et al., acute coronary, cerebral and thromboembolic events that could not be explained by traditional risk factors were increased by 30-50% in AS patients compared to the general population [36]. In atherosclerosis, similar to inflammatory diseases such as AS, C reactive protein is associated with systemic inflammatory markers such as fibrinogen and, more recently, cytokines, chemokines, adhesion molecules and proteases [37,38]. Deterioration in FMD and increase in carotid intima thickness, which indicate endothelial dysfunction and increased atherosclerosis, have been detected [39]. In our study, we found a decrease in FMD in Group 2 AS patients with increased LAVI compared to Group 1. In these patients, the presence of traditional risk factors in addition to inflammation and their older average age carried a higher risk of endothelial damage and accelerated atherosclerosis, which was consistent with the literature.

### *Limitations*

The study was conducted at a single center and had a relatively limited number of patients. The relatively small sample size and the fact that the study was conducted in a single center may limit the generalizability of the findings. Echocardiographic evaluations were only performed using 2D echocardiography. The use of invasive or advanced imaging methods may provide more accurate results.

## Conclusion

This study demonstrates that uveitis is independently associated with elevated LAVI in patients with AS. Therefore, evaluation of the LAVI in patients diagnosed with AS and detected with uveitis may be a guide in predicting the risk of cardiovascular events and early treatment. In our literature review, to the best of our knowledge, we did not find any other study on the relationship between LAVI and uveitis in AS patients. Prospective and multicenter studies are needed to confirm these results.

### *Ethical approval*

This research was carried out with the permission of the Recep Tayyip Erdoğan University Non-invasive Clinical Research Ethics Committee, numbered 2023/223.

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