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Original Scientific Paper

DIFFERENCES IN THE PREVALENCE OF ATRIAL FIBRILLATION IN RHEUMATOID ARTHRITIS AND OSTEOARTHRITIS PATIENTS: A MULTICENTER STUDY

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SUMMARY – We conducted a cross-sectional, multicenter study on two groups of patients: one with rheumatoid arthritis (RA) and the other with osteoarthritis (OA). Both diseases affect the joints, cause disability and require chronic treatment. The purpose of this study was to evaluate the prevalence of atrial fibrillation (AF) in these two diseases that primarily affect the joints, and whether chronic systemic inflammation influences the prevalence of AF, along with other previously validated risk factors. Data were collected at University Hospital Dubrava and collaborating rheumatology centers across Croatia.

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This study included 627 patients with RA and 352 patients with OA. Demographic data, comorbidities (including a previous diagnosis of AF), medication use and electrocardiograms were recorded for each patient. We analyzed serum concentrations of C-reactive protein (CRP), sedimentation rate, glucose, creatinine, lipid parameters and calculated the body mass index (BMI) and cardiovascular risk using the Framingham Risk Score calculator.

In the analysis, we found no difference in the prevalence of AF between RA and OA patients (4.2% vs. 4.3%, $P > 0.999$). Almost all the analyzed risk factors for AF were more prevalent in the OA group, such as age, arterial hypertension, diabetes, history of cardiovascular diseases, signs and symptoms of heart failure, metabolic syndrome, chronic kidney disease, and use of diuretic and non-steroidal anti-inflammatory drugs, except tobacco usage, which was more prevalent in the RA group ($P < 0.001$). In addition, RA patients had higher CRP levels, sedimentation rates and a longer disease duration ($P < 0.001$). In conclusion, because the risk factors for AF were more prevalent in the OA group, but we found no difference in the prevalence of AF between the groups, we assume that chronic systemic inflammation likely contributes to the development of AF.

Keywords: *rheumatoid arthritis; atrial fibrillation; C-reactive protein; osteoarthritis*

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice and it is strongly correlated with cardiovascular diseases (CVD)[1–3]. It is a worldwide health care problem due to the increasing prevalence and lifetime risk of AF development because of aging, increased detection rates and an increased survival of patients with AF. In 2021, 52.55 million individuals worldwide were estimated to have AF or atrial flutter, with a higher prevalence in men compared to women[4,5].

Patients with AF have an increased risk of stroke and heart failure, and increased overall mortality[6]. Age and arterial hypertension are the strongest risk factors for AF[7,8], along with other comorbidities such as valvular and ischemic heart disease[9–11], heart failure[12], diabetes mellitus[13], obesity[14], sleep apnea, hyperthyroidism and chronic kidney disease[15–17]. Lifestyle risk factors for AF development include alcohol abuse, smoking and a sedentary lifestyle[18–20]. In approximately 15% of cases, AF occurs in younger patients without the abovementioned classical risk factors, suggesting an inheritable genetic predisposition[21].

Previous research also suggests an important role of systemic inflammation in the development and maintenance of AF[22–25]. There is a significant correlation between the concentrations of proinflammatory cytokines, such as interleukin (IL)-6, tumor necrosis factor (TNF)-α, IL-2, IL-8, markers of acute inflammation, such as CRP, and the risk for the development and maintenance of AF[26–32]. This has also been confirmed by findings of inflammation and increased fibrosis in biopsies of atrial tissues in patients with AF, which provides evidence of the role of inflammation in structural and electrical atrial remodeling[33,34].

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic systemic and joint inflammation, which causes progressive joint damage and disability. The estimated worldwide prevalence of RA in The Global Burden of Disease Study 2021 was 0.21%, with the highest prevalence being in Australia, Western Europe and North America[35]; in those regions, some studies estimated a higher prevalence of 0.5 to 1%[36,37]. In women, RA is more than twice as prevalent as it is in men[35].

The pathogenesis of RA is complex and involves interactions of genetic and environmental risk factors in patients with immune system dysregulation. In RA patients, cardiovascular morbidity and mortality are significantly increased, and it is now known that RA is an independent risk factor for the development of CVD[38–40]. Lifestyle risk factors that increase the risk of RA development are cigarette smoking, poor diet,

obesity, alcohol consumption and physical inactivity, with cigarette smoking being the strongest risk factor[41].

Autocrine and paracrine communication through proinflammatory cytokines, such as the previously mentioned IL-6, TNF-α, IL-2 and many others, play a key role in the initiation and maintenance of RA, and the production of these proinflammatory cytokines precedes the clinical onset of RA for years[42]. CRP is a marker of systemic inflammation, which is routinely assessed in patients with RA and correlates with disease activity, severity and progression, and also serves as a marker of treatment response[43,44].

Osteoarthritis (OA) is a chronic degenerative joint disease that also causes progressive joint damage and disability. Its prevalence increases with age and women are more affected than men. The Global Burden of Disease Study estimated that, in 2020, approximately 595 million individuals (7.6% of the global population) were affected by OA[45], and women accounted for 60% of OA cases, with the most prominent differences observed in knee and hand OA, especially in women after menopause[46,47].

Obesity and joint injuries are the predominant risk factors for the disease, with the destruction and loss of articular cartilage as the central event.

The main goal of this study was to evaluate whether patients with RA have an increased prevalence of AF compared to patients with OA.

Metods and patients

We conducted a multicenter, cross-sectional study of two groups of patients: one with RA and another with OA. The data were collected between 2009 and 2010 at University Hospital Dubrava and collaborative rheumatology centers across Croatia. All patients provided an informed consent before data collection. The survey was conducted during one visit and included data and blood collection, with an electrocardiogram (ECG) recorded for each patient. The data were entered into previously defined questionnaires for RA and OA, alongside the set of demographic data, comorbidities and medication usage for each patient. We collected data from 627 patients with RA and 352 patients with OA; both men and women ≥ 18 years of age residing in Croatia. RA was diagnosed by a rheumatology specialist according to the 1987 American College of Rheumatology (ACR) classification criteria, whereas hand, hip and knee OA were diagnosed according to the ACR criteria for OA[48–51]. Patients were excluded from the study if they had an OA diagnosis according to the ACR criteria, but had a positive rheumatoid factor.

Ethics

This study was approved by the Ethical Committee of University Hospital Dubrava in Zagreb, which was the coordinating center of this study.

Data

Several predefined variables associated with the development of AF were identified. These variables included demographic data, such as age, sex, height, weight, and waist and hip circumference, with a calculation of the body mass index (BMI) and waist-to-hip ratio. We documented the presence of arterial hypertension, dyslipidemia, diabetes mellitus, metabolic syndrome, known arrhythmias, smoking status and a history of previously known CVD. This group included patients with previously diagnosed and well-documented heart failure, significant valvular heart disease (defined as moderate or severe stenosis and/or insufficiency based on echocardiography), a prior diagnosis of angina pectoris and confirmed coronary artery disease. In addition, current signs and symptoms of heart failure and ischemic heart disease were recorded through the presence of peripheral edema, dyspnea, angina pectoris and the use of diuretics. We recorded all medication used for hypertension, dyslipidemia, diabetes mellitus and pain relief, such as non-steroidal anti-inflammatory drugs (NSAIDs) and other analgesics, and all disease-modifying antirheumatic drugs used for RA treatment. Blood pressure was measured three times after resting for five minutes in a sitting position and its mean value was calculated.

Patients with AF were identified if they had previously well-documented episodes of AF (episodes of paroxysmal, persistent, or permanent AF), or if AF was diagnosed on the ECG recorded on the day of the visit. A cardiology specialist evaluated the ECG findings.

The following blood tests were done in the laboratories of all the collaborating centers: erythrocyte sedimentation rates (ESR), CRP, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), plasma glucose levels and creatinine levels with a calculation of estimated glomerular filtration rates (eGFR).

General health (GH) is a patient's assessment of general health on a visual analog scale from 0 to 100 mm.

To define arterial hypertension, we used guidelines from the European Society of Hypertension and the European Society of Cardiology; arterial hypertension was diagnosed if the patients had systolic blood pressure ≥ 140 mmHg, and/or diastolic blood pressure ≥ 90 mmHg, or if they had previously well-documented hypertension and/or were taking antihypertensive medication.

Diabetes mellitus was diagnosed if the patients had fasting glucose levels ≥ 7 mmol/L, if the levels were ≥ 11.1 mmol/l after an oral glucose tolerance test, or if the patients had previously defined diabetes mellitus and were taking medication[52].

Dyslipidemia was diagnosed if the values of LDL cholesterol were ≥ 4.1 mmol/l and/or the levels of total cholesterol were ≥ 6.2 mmol/L, if the values of triglycerides were ≥ 1.69 mmol/l, or if the patients had previously documented dyslipidemia and if they were taking statins[53].

We used the third report of the National Cholesterol Education Program – Adult Treatment Panel (NCEP-ATP) criteria to evaluate the presence of metabolic syndrome. Patients were diagnosed with metabolic syndrome if they had at least three out of the five following criteria: waist circumference > 102 cm in men and > 88 cm in women; triglyceride levels ≥ 1.69 mmol/l or intake of medication for elevated triglycerides; HDL cholesterol levels < 1.03 mmol/l in men and < 1.29 mmol/l in women; elevated systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg, or intake of medication for arterial hypertension; and elevated concentrations of fasting glucose ≥ 5.6 mmol/l or intake of medication for diabetes[54].

For both groups, 10-year cardiovascular (CV) risk was estimated using the Framingham Risk Score calculator[55].

The Health Assessment Questionnaire Disability Index (HAQ-DI) was calculated for all patients with OA and RA. The questionnaire evaluates difficulties in performing daily activities (such as dressing oneself, rising, eating, walking, tending to personal hygiene, etc.), with higher scores indicating that patients are less active[56].

OA was selected as the control group because it is also a chronic, debilitating joint disease that requires long-term treatment, similar to RA, but lacks the pronounced chronic systemic inflammation typical of RA. Both patient groups frequently use NSAIDs for pain relief, and NSAID use is a recognized risk factor for atrial fibrillation[57].

Statistics

The normality of continuous data distribution was analyzed using the Shapiro-Wilk test. Data are reported as frequencies and percentages, medians with interquartile ranges, or means with standard deviations (± SD). Group comparisons for continuous variables were performed using the t-test for parametric data and the Mann–Whitney test for nonparametric data. Intergroup relationships between categorical variables were assessed using Pearson's $\chi 2$ test or Fisher's exact test. Associations between demographic and clinical factors and the occurrence of AF were investigated using univariate binary logistic regression, with results presented as odds ratios (ORs) and 95% confidence intervals (CIs). All statistical tests were two-sided. Intergroup differences with $P < 0.05$ were considered statistically significant. Statistical analyses were performed using SPSS, Version 29 (IBM Corp., Armonk, NY, USA).

Results

The basic stratification data and cardiovascular comorbidities of patients with RA and OA are presented in Table 1. CVD symptoms, intake of medication and basic laboratory findings are presented in Table 2.

There was no difference in the prevalence of AF between RA and OA patients (4.2% vs. 4.3%, $P > 0.999$), as presented in Table 1.

Table 1. Basic stratification data and cardiovascular comorbidities between RA and OA patients.

Variable		**Rheumatoid arthritis N=627**	**Osteoarthritis N=352**	***P*-value**
Age in years		59.0 (52.0-68.0)	67.0 (58.0-73.0)	**<0.001**
Sex	*Male*	104 (16.6)	57 (16.2)	0.928
	Female	523 (83.4)	295 (83.8)	
BMI (kg/m^2)		26.5 (23.8-29.3)	29.5 (26.1-32.1)	**<0.001**
SBP (mmHg)		131 (120.0-145.0)	135 (126.0-145.0)	**0.017**
DBP (mmHg)		80.0 (76.5-88.0)	82.0 (79.3-90.0)	**0.032**
Waist-to-hip ratio		0.88 (0.82-0.94)	0.90 (0.83-0.96)	**0.006**
Smoking history	*No*	353 (56.3)	247 (70.2)	**<0.001**
	Yes	274 (43.7)	105 (29.8)	
Hypertension	*No*	380 (60.7)	186 (52.8)	**0.018**
	Yes	246 (39.3)	166 (47.2)	
Dyslipidemia	*No*	241 (38.5)	75 (21.3)	**<0.001**
	Yes	385 (61.5)	277 (78.7)	
Diabetes	*No*	554 (88.4)	278 (79.0)	**<0.001**
	Yes	73 (11.6)	74 (21.0)	
Metabolic syndrome	*No*	325 (55.7)	124 (36.2)	**<0.001**
	Yes	259 (44.3)	219 (63.8)	
History of cardiovascular diseases	*No*	516 (82.3)	241 (68.5)	**<0.001**
	Yes	111 (17.7)	111 (31.5)	
Disease duration in years		7.0 (3.0-15.0)	5.0 (2.0-10.0)	**<0.001**
Atrial fibrillation	*No*	573 (95.8)	330 (95.7)	>0.999
	Yes	25 (4.2)	15 (4.3)	

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure.

RA patients were significantly younger (median 59 years, IQR 52-68 years vs. median 67 years, IQR 58-73 years, $P < 0.001$), had a longer duration of the disease (median 7 years, IQR 3-15 years vs. median 5 years, IQR 2-10 years, $P < 0.001$), had lower BMI values (median 26.5 kg/m^2, IQR 23.8-29.3 kg/m^2 vs. 29.5 kg/m^2, IQR 26.1-32.1 kg/m^2, $P < 0.001$), a lower waist-to-hip ratio (median 0.88, IQR 0.82-0.94 vs. 0.90, IQR 0.83-0.96, $P = 0.006$), and a lower prevalence of arterial hypertension (39.3% vs. 47.2%, $P = 0.018$), dyslipidemia (61.5% vs. 78.7%, $P < 0.001$), diabetes (11.6% vs. 21%, $P < 0.001$) and metabolic syndrome (44.3% vs. 63.8%, $P < 0.001$).

There were no differences in sex distribution between RA and OA patients (104 men (16.6%) in the RA group vs. 57 men (16.2%) in the OA group, and 523 women (83.4%) in the RA group vs. 295 (83.8%) in the OA group $P = 0.928$).

RA patients had higher levels of tobacco consumption (43.7% vs. 29.8%, $P < 0.001$) and a lower prevalence of previously known CVD (17.7% vs. 31.5%, $P < 0.001$), dyspnea (7.5% vs. 20.5%, $P < 0.001$), peripheral edema (5.4% vs. 13.6%, $P < 0.001$), symptoms of angina pectoris (9.5% vs. 21%, $P < 0.001$) and less frequent use of diuretics (19.6 % vs. 31.3 %, $P < 0.001$) for congestive heart failure. Also, patients with RA had lower levels of NSAIDs usage (49.8% vs. 65.3%, $P < 0.001$).

With regards to laboratory parameters, RA patients had higher ESR levels (median 25.5 mm/h, IQR

Table 2: Symptoms of cardiovascular disease, medication use and basic laboratory findings.

Variable		**Rheumatoid arthritis N=627**	**Osteoarthritis N=352**	***P*-value**
Dyspnea	*No*	579 (92.5)	280 (79.5)	**<0.001**
	Yes	47 (7.5)	72 (20.5)	
Edema	*No*	592 (94.6)	304 (86.4)	**<0.001**
	Yes	34 (5.4)	48 (13.6)	
Angina	*No*	565 (90.5)	278 (79.0)	**<0.001**
	Yes	59 (9.5)	74 (21.0)	
Statins	*No*	540 (86.3)	265 (75.5)	**<0.001**
	Yes	86 (13.7)	86 (24.5)	
Antirheumatic drugs	*No*	7 (1.1)	46 (13.1)	**<0.001**
	Yes	620 (98.9)	306 (86.9)	
Beta blockers	*No*	514 (82.0)	273 (77.6)	0.111
	Yes	113 (18.0)	79 (22.4)	
ACE inhibitors	*No*	478 (76.2)	215 (61.1)	**<0.001**
	Yes	149 (23.8)	137 (38.9)	
Diuretics	*No*	504 (80.4)	242 (68.8)	**<0.001**
	Yes	123 (19.6)	110 (31.3)	
Number of antihypertensive drugs in therapy		0.0 (0.0-2.0)	1.0 (0.0-2.0)	**<0.001**
Opioids	*No*	627 (100.0)	229 (65.1)	**<0.001**
	Yes	0 (0.0)	123 (34.9)	
Analgesics	*No*	438 (69.9)	233 (66.2)	0.252
	Yes	189 (30.1)	119 (33.8)	
NSAID	*No*	315 (50.2)	122 (34.7)	**<0.001**
	Yes	312 (49.8)	230 (65.3)	
CRP (mg/L)		8.1 (3.1-20.1)	2.1 (1.2-3.8)	**<0.001**
ESR (mm/h)		25.5 (13.0-42.0)	14.0 (9.0-23.0)	**<0.001**
Cholesterol (mmol/L)		5.5 (4.8-6.3)	5.7 (4.8-8.5)	**0.024**
Creatinine (umol/L)		76.0 (67.0-86.2)	79.0 (68.0-89.0)	0.151
eGFR (ml/min/1.73 m^2)		79.0 (65.0-91.0)	73.0 (61.0-86.0)	**<0.001**
GUP (mmol/L)		4.9 (4.5-5.4)	5.5 (4.9-6.0)	**<0.001**
HAQ		1.8 (0.7-2.1)	1.3 (0.6-1.8)	**<0.001**
VAS		50.0 (30.0-70.0)	50.0 (32.0-70.0)	0.958
CVR		0.06 (0.03-0.11)	0.09 (0.05-0.16)	**<0.001**

ACE = angiotensin-converting enzyme; NSAID = nonsteroidal anti-inflammatory drug; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; eGFR = estimated glomerular filtration rate; GUP = glucose plasma; HAQ = Health Assessment Questionnaire; VAS = Visual Analog Scale; CVR = cardiovascular risk

13.0-42.0 mm/h vs. median 14.0 mm/h, IQR 9.0-23.0 mm/h, $P < 0.001$), higher CRP levels (median 8.1 mg/L, IQR 3.1-20.1 mg/L vs. median 2.1 mg/L, IQR 1.2-3.8 mg/L, $P < 0.001$) and a higher eGFR (median 79 ml/min/1.73 m^2, IQR 65-91 vs. 73 ml/min/1.73 m^2, IQR 61-86, $P < 0.001$), while OA patients had higher cholesterol levels (median 5.7 mmol/L, IQR 4.8-8.5 mmol/L vs. median 5.5 mmol/L, IQR 4.8-6.3 mmol/L, $P = 0.024$) and triglyceride levels (median 1.7 mmol/L, IQR 1.2-2.2 mmol/L vs. median 1.3 mmol/L, IQR 1-1.8 mmol/L, $P < 0.001$) (see Table 1 and 2).

The groups also differed in CV risk estimated by the Framingham Risk Score calculator, with the RA group exhibiting a significantly lower calculated risk compared to OA (RA group median 6%, IQR 3-11%; OA group median 9%, IQR 5-16%; $P < 0.001$).

In this study, we identified the following as significant risk factors for AF development: age ($P < 0.001$), disease duration ($P = 0.035$), waist-to-hip ratio ($P = 0.016$), arterial hypertension ($P < 0.001$), history of CVD ($P < 0.001$), dyspnea ($P < 0.001$), peripheral edema ($P < 0.001$), anginal complaints ($P = 0.01$), the use of diuretics and beta blockers ($P < 0.001$), creatinine levels ($P = 0.011$) and eGFR ($P = 0.008$).

In the RA group, AF was recorded in 25 patients, whereas 573 had sinus rhythm (SR). Patients who developed AF were older (median 68 years, IQR 63-74.5 years vs. median 59 years, IQR 51-68 years, $P < 0.001$), had a longer disease duration (median 13 years, IQR 7-19 years vs. median 6 years, IQR 2-14 years, $P = 0.002$), a higher waist-to-hip ratio (median 0.92, IQR 0.88-0.98 vs. median 0.88, IQR 0.82-0.94, $P = 0.016$), a higher prevalence of CVD history (21 patients (pt) (84%) vs. 85 pt (14.8%), $P < 0.001$), arterial hypertension (22 pt (92%) vs. 337 pt (59%), $P < 0.001$), angina (7 pt (28%), vs. 50 pt (8.8%), $P = 0.006$) edema (10 pt (40%) vs. 23 pt (4%), $P < 0.001$) and dyspnea (12 pt (48%) vs. 33 pt (5.8%), $P < 0.001$). Also, patients with RA who developed AF had lower values of eGFR (70 ml/min/1.73m^2, IQR 49-86 ml/min/1.73m^2 vs. 79 ml/min/1.73m^2, IQR 65.8-91 ml/min/ 1.73 m^2, $P = 0.04$) and significantly higher usage of beta blockers (11 pt (44%) vs. 98 pt (17.1%), $P = 0.002$) and diuretics (14 pt (56%) vs. 108 pt (18.8%), $P < 0.001$).

There were no significant differences in sex between patients in SR and those with AF (2 men (8%) in the AF group vs. 95 men (16.6%) in the non-AF group, $P = 0.404$) nor in BMI (median 27.63 kg/m^2, IQR 25.04-30.82 kg/m^2 in the AF group, vs. 26.47 kg/m^2, IQR 23.81-29.3 kg/m^2 in the non-AF group, $P = 0.282$).

Also, no differences were found in the frequency of dyslipidemia (19 pt (76%) in the AF group vs. 348 (60.8%) in the non-AF group, $P = 0.146$), the presence of metabolic syndrome (56.5% in the AF group vs. 43.9% in the non-AF group, $P = 0.285$), tobacco consumption (56% in the AF group vs. 42.2% in the non-AF group, $P = 0.216$) and diabetes (6 pt (24%) in the AF group vs. 65 pt (11.3%) in the non-AF group, $P = 0.103$).

In the OA group, AF was recorded in 15 patients, whereas 329 patients had SR. Within the OA group, there were no significant differences between the subgroups in age (median 71 years, IQR 63-74 years in the AF group vs. median 67 years, IQR 57.5-73 years in the non-AF group, $P = 0.246$), sex (11 women (73.3%) in the AF group vs. 277 women (83.9%) in the non-AF group, $P = 0.286$) and BMI (median 31 kg/m^2, IQR 27.5-33 kg/m^2 in the AF group vs. median 29.29 kg/m^2, IQR 26-32.15 kg/m^2 in the non-AF group, $P = 0.256$) between patients who developed AF compared to patients in SR.

There was also no difference in the prevalence of dyslipidemia (11 pt (73.3%) in the AF group vs. 259 pt (78.5%) in non-AF group, $P = 0.748$), diabetes (3 pt (20%) in AF group vs. 69 pt (20.9%) in the non-AF group, $P = 1$), the duration of OA (median 4 years, IQR 1-15 years in the AF group vs median 5 years, IQR 2-10 years in the non-AF group, $P = 0.998$) and tobacco consumption (4 pt (26.7%) in the AF group vs. 101 pt (30.6%) in the non-AF group, $P = 1$)

In terms of the comorbidities, patients in the OA group who developed AF had a significantly higher prevalence of CVD (13 pt (86.7%) vs. 94 pt (28.5%), $P < 0.001$), arterial hypertension (15 pt (100%) vs. 238 pt (72.1%), $P = 0.008$) and peripheral edema (5 pt (33.3%) vs. 41 pt (12.4%), $P = 0.036$), while the prevalence of dyspnea was similar between groups (4 pt (26.7%) in the AF group vs. 65 pt (19.7%) in the non-AF group, $P = 0.512$). Patients who developed AF more frequently used diuretics for congestive heart failure (9 pt (60%) vs 98 pt (29.7%), $P = 0.02$) and beta blockers (7 pt (46.7%) vs. 69 pt (20.9%), $P = 0.027$).

Discussion

This study showed that there was no difference in the prevalence of AF between patients with RA and OA. The overall prevalence of AF in RA and OA was low in both groups, possibly due to a female predominance (~83%) in both cohorts, while in the general population the prevalence of AF is higher in men — a difference seen in every age group[4,5].

In both groups, patients who developed AF had a higher prevalence of previously known and validated risk factors for AF. In the OA group, patients with AF had a significantly higher prevalence of arterial hypertension and history of previous CVDs, and a higher frequency of peripheral edema and use of diuretics for heart failure than patients with SR. In addition to the abovementioned risk factors, in the RA group, patients with AF were older, had a longer duration of their underlying disease, and had a higher prevalence of dyspnea and angina pectoris than RA patients in SR.

AF risk factors that were more prevalent in the RA group were tobacco consumption and elevated CRP and ESR values as a sign of chronic inflammation, whereas all other risk factors for the development of AF, such as age, arterial hypertension, diabetes, history of CVD, metabolic syndrome, dyslipidemia, chronic kidney disease measured by eGFR, and the use of diuretics, NSAIDs and other medication, were more pronounced in the OA group (Table 1 and 2).

Given that age is one of the main risk factors for AF development[58], the prevalence of AF should have been higher in our group of OA patients, who were older. In addition, all other strong risk factors for the development of AF (except tobacco consumption) were more prevalent in the OA group.

Research on AF in patients with RA and its impact on AF incidence and prevalence remains inconclusive. The two largest surveys yielded opposite results. In a Danish study conducted by Lindhardsen et al., which included more than 18,000 patients with RA, there was a 40% increased risk of AF in patients with RA compared to the general population[59]. The study did not adjust for all cardiovascular risk factors and failed to include information on several strong risk factors for AF, such as smoking, dyslipidemia, chronic kidney disease and NSAIDs use[17,19,60], which could change the risk estimates. In another large study conducted by Kim et al., patients with RA did not have an increased risk for the development of AF compared to the general population and a cohort of patients with OA after a multivariable adjustment for the number of risk factors, such as medication, comorbidities and healthcare use. This study evaluated over 20,000 patients with RA[61].

Previous research has suggested a significant role of systemic inflammation, such as in patients with sepsis, evaluated through levels of inflammatory markers such as CRP and proinflammatory cytokines, in the development and persistence of AF[62]. CRP is an inflammatory marker most commonly used in daily clinical practice to assess the presence and severity of inflammation, and the main trigger for CRP production in the liver is IL-6[63]. Many studies have associated AF with elevated CRP levels. Patients with AF tend to have higher CRP levels than those in SR, and higher CRP levels were observed in patients with persistent AF than in those with paroxysmal AF[64]. Patients with elevated pre-cardioversion CRP levels were more likely to develop AF recurrence after cardioversion than patients with lower CRP levels[65]. Furthermore, in the Atorvastatin for Reduction of Myocardial Dysrhythmia After cardiac surgery (ARMYDA-3) study, patients with elevated postoperative CRP levels following cardiac surgery or catheter ablation experienced a higher incidence of postoperative AF[66].

In addition, there is a connection between AF and several proinflammatory cytokines, which are also key cytokines in the pathogenesis and maintenance of RA, such as IL-6 — the main driver of CRP synthesis[67] — and TNF-α. Levels of IL-6 were significantly higher in patients with coronary artery disease who developed AF than in those in SR[27]. Preoperative CRP and IL-6 levels were significantly higher in patients who subsequently developed postoperative AF than in those who maintained SR[68].

Serum TNF-α levels were significantly higher in patients with AF than in those in SR, with higher levels observed in patients with persistent or long-standing forms of AF compared to individuals with paroxysmal AF[28].

There is also evidence of structural and electrical atrial remodeling under the influence of proinflammatory cytokines. IL-6 modulates the expression of gap junction channels, such as connexins on cardiomyocytes,

thereby facilitating AF development and maintenance. TNF-α contributes to abnormal calcium handling, while IL-6, TNF-α and interleukin-1β promote the proliferation and activation of cardiac fibroblasts, enhancing fibrogenesis and atrial fibrosis[25,69].

The main characteristic of RA is chronic systemic inflammation, predominantly driven by previously mentioned proinflammatory cytokines IL-6 and TNF-α, which play central roles in both the initiation and maintenance of RA, along with many other cytokines (IL-2, IL-7, IL-17, IL-21, IL-23, etc.)[70]. Moreover, IL-6 plays a pivotal role in the transition from acute to chronic inflammation. It is found in high concentrations in both the synovial fluid (SF) and serum of patients with RA[71,72], and its levels are closely correlated with disease activity and the extent of joint destruction[73,74].

TNF-α expression is upregulated in patients with RA, with significantly higher TNF-α concentrations detected in both SF and serum compared to healthy controls[75,76], and its concentrations also correlate with disease activity[77].

There is some evidence of local inflammation in the pathogenesis of joint OA, but without the chronic systemic inflammation typical for RA. In a study assessing the discriminatory capacity of serum IL-6 levels to differentiate between inflammatory and non-inflammatory arthritis, IL-6 emerged as a robust predictor of disease activity and severity in both RA and psoriatic arthritis (PsA), but not in OA. Furthermore, inflammatory markers, such as ESR and CRP, were significantly elevated in RA and PsA patients compared to OA patients and healthy controls[78].

With evidence that inflammation drives atrial remodeling[68,79–82] and that proinflammatory cytokines and inflammatory markers are positively correlated with the onset and maintenance of AF[27,65,66,83], patients with RA may be at increased risk for AF development. If chronic systemic inflammation is an independent risk factor for the development of AF with the involvement of the same proinflammatory cytokines and inflammatory markers, patients with chronic inflammatory diseases, such as RA, might have an increased risk for the development of AF regardless of CVD and the risk could be positively correlated with disease activity and duration. The development of AF in patients with RA could be a consequence of the increased prevalence of CVDs, which has been proven in patients with RA[84–87], but also a consequence of the direct pathogenic effects of chronic inflammation on atrial tissue, further contributing to AF risk through inflammation-mediated atrial remodeling and electrophysiological changes[88–90].

Since almost all the risk factors for AF development in our study were more prevalent in the group of OA patients, with no difference in the prevalence of AF between the two groups, it can be assumed that the risk factors that were more prevalent in the RA group (tobacco consumption and systemic inflammation) were sufficient to equalize the overall risk for the onset and maintenance of AF, and that chronic inflammation plays a significant role in the pathogenesis of AF.

Additionally, our study demonstrated that patients with RA who developed AF had a longer disease duration, suggesting prolonged exposure to systemic inflammation, which could directly influence atrial remodeling.

Regarding the two previously mentioned large studies, our results are more aligned with the Danish study done by Lindhardsen et al., where a 40% increased risk of AF was found in RA patients[59]. A limitation of their study is the lack of information on several risk factors for AF, which could change the risk estimates. In a study conducted by Kim et al., where there was no increased risk of AF in RA[61], patients in nursing homes were excluded and the overall study population was younger compared to the Danish study (the mean age was 52 years vs. 59.2 years in the Danish study) — and we know that age is the strongest AF risk factor. Moreover, the median follow-up was shorter (2 years vs 4.8 years), and one of the inclusion criteria for the RA cohort was at least one disease-modifying antirheumatic drug used for RA administered at the time of inclusion. Both factors could have influenced the level and duration of systemic inflammation, which is hypothesized to be a risk factor for AF. In addition, some other factors might have influenced AF risk between these two studies, such as the percentage of seropositive vs. seronegative RA — which is not known in these two studies — with some new evidence showing that seropositive RA confers a greater risk for the development of CVD and AF[91,92].

The main limitation of our study is its cross-sectional design, which establishes an association, but not

causality. In addition, some patients with paroxysmal AF might not have been included in either group because we relied on previous medical documentation and current ECG taken on the day of the visit to diagnose patients with AF. CRP and ESR measured during a single visit may not reflect the overall inflammation to which patients with RA have been exposed for years. Future research should include other key inflammatory markers, such as IL-6 and TNF-α, and disease activity scores to more accurately assess the impact of systemic inflammation on the prevalence of AF in this group of patients, along with prospective patient follow-ups to better evaluate the effect of chronic inflammation on AF.

Conclusion

In this study, the prevalence of AF did not differ between patients with RA and OA. Given that almost all of the classical AF risk factors were more prevalent in the OA group, we can assume that chronic systemic inflammation associated with RA may play a significant role in the development and maintenance of AF in patients with RA.

Consent to participate: All patients provided a written informed consent, including the publication of the analyzed data.

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Sažetak

RAZLIKA U PREVALENCIJI FIBRILACIJE ATRIJA U BOLESNIKA S REUMATOIDNIM ARTRITISOM I OSTEOARTRITISOM: MULTICENTRIČNA STUDIJA

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Cilj ovog presječnog, multicentričnog istraživanja bila je usporedba prevalencije fibrilacije atrija (AF) u dvije skupine bolesnika: bolesnika s reumatoidnim artritisom (RA) i osteoartritisom (OA). Također, istražili smo utječe li kronična sistemska upala uz ostale poznate i validirane čimbenike rizika na pojavnost AF. Obje bolesti primarno zahvaćaju zglobove, uzrokuju fizičku onesposobljenost te zahtijevaju kronično liječenje, a razlikuje ih prisustvo kronične sistemske upale koja je karakteristična za bolesnike s RA. U istraživanje smo uključili 627 bolesnika s RA te 352 bolesnika s OA, a podaci su prikupljeni u Kliničkoj bolnici Dubrava i suradnim ustanovama Republike Hrvatske. Prikupljeni su demografski podaci i podaci o komorbiditetima, lijekovima te postojanju ranije dijagnosticirane AF. Snimljen je elektrokardiogram na dan vizite te su uzeti uzorci krvi za analizu koncentracije parametara akutne faze (CRP-a i sedimentacije eritrocita), glukoze, kreatinina, lipidograma te je izračunat indeks tjelesne mase i ukupni kardiovaskularni rizik za obje skupine bolesnika koristeći Framingham risk score model. U našem istraživanju nismo ustanovili razliku prevalencije AF između bolesnika s RA i OA (4,2 % naspram 4,3 %, $P > 0,999$). Gotovo svi analizirani čimbenici rizika za razvoj AF bili su češći u grupi bolesnika s OA, kao što su starija životna dob, prevalencija arterijske hipertenzije, dijabetesa, kardiovaskularnih bolesti, znakova i simptoma srčanog popuštanja, metaboličkog sindroma, kronične bubrežne bolesti, upotrebe diuretika i nesteroidnih protuupalnih lijekova, osim konzumacije cigareta koja je bila češća u bolesnika s RA ($P < 0,001$), koji su također imali više vrijednosti CRP-a i sedimentacije eritrocita te duže trajanje bolesti ($P < 0,001$). Zaključno, s obzirom na prisutnu veću prevalenciju rizičnih čimbenika za AF u grupi bolesnika s OA i činjenicu da nije nađena razlika u prevalenciji AF između ispitivanih grupa, pretpostavljamo da kronična sistemska upala pridonosi razvoju AF u bolesnika s RA.

Ključne riječi: *reumatoidni artritis; fibrilacija atrija; C-reaktivni protein; osteoartritis*