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Research Article

Impact of Elevated Uric Acid on the Recurrence of Atrial Fibrillation after Pharmacological Cardioversion in Patients with Metabolic Syndrome

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Abstract

***Background*:** Approximately 50% of patients undergoing cardioversion usually present with recurrence of Atrial Fibrillation (AF) within 3–6 months of cardioversion despite ongoing treatment[3]. Uric acid (UA) is known to promote inflammation, and inflammation has been suggested to be essential in the pathophysiological mechanisms of AF[6,7]. However, robust evidence on the association between the UA and recurrent AF after pharmacological cardioversion (PCV) in patients with Metabolic Syndrome (MS), is unclear. Therefore, identifying patients at high risk of AF recurrence remains challenging.

***Objective*:** We tested hypothesis: increased serum uric acid (SUA) levels are associated with greater risk of AF recurrence after PCV, in patients with MS.

***Methods*:** We conducted a multicenter observational cross-sectional study.204 consecutive adult participants(≥18 and <65years of age) were recruited with MS and symptomatic AF{paroxysmal(PAF) and persistent(PsAF)},admitted at 6 general cardiology Health Care Clinics ,who underwent PCV, during 1 calendar year follow-up period, stratified in two group according to SUA levels:(101 with SUA levels level of > 7.0 mg/dL in men or > 6.0 mg/dL in women , and 103 with SUA level of <7.0 mg/dL in men or < 6.0 mg/dL in women). Recurrence of AF, during follow-up period was defined as the study end-point.

***Results*:** After the follow-up of 1.0 years, the recurrence rate of AF in participants with SUA levels above (> 7.0 mg/dl in men or >6.0 mg/dl in women) was higher when compared with participants with SUA levels below <7.0 mg/dl in men or below 6.0 mg/dl in women {58(57.4.1%) vs. 31(30.6%) p=0.009}. There was observed significant association of SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl in women) with: rate of AF recurrence (OR=3.938, 95%CI:2.234-6.942), PsAF(OR=3.808 ,95% CI:2,116-6.852;Females(OR= 1.278; CI:0.989-1.544),LAVI(OR=1.74;95%CI:1.549-1.975),LVMI (OR=1.041,95% CI: 1.022-1.061).

***Conclusions*:** The findings of this study suggest that hyperuricemia is a risk factor of AF-reccurence and could be useful for predicting recurrence of AF after successful pharmacologic cardioversion in clinical practice.

Keywords: Hyperuricemia and reccurence of Atrial Fibrillation.

Introduction

Atrial fibrillation (AF) is a common cardiac arrhythmia, with its incidence and related mortality increased significantly[1]. Despite the effective prediction of AF using ECG and its treatment with rhythm control strategies, high recurrence and mortality rates persist[2]. Approximately 50% of patients undergoing cardiove rsion usually present with recurrence of AF within 3–6 months of cardioversion despite ongoing treatment[3]. Several studies reported that Metabolic Sydrome (MS) a cluster of atherogenic risk factors, could influence the development of atrial fibrillation. An association between atrial fibrillation and the metabolic syndrome has been suggested [4].

The precise mechanisms of AF recurrence have not been fully elucidated.

Many evidences indicated that inflammatory changes and oxidative stress is essential for recurrence of AF[5].

Uric acid (UA) is known to promote inflammation, and inflammation has been suggested to be essential in the pathophysiological mechanisms of AF[6,7]. However, robust evidence on the association between the UA and recurrent AF after pharmacological cardioversion (PCV) in patients with MS, is unclear. It is also not known whether increased uric acid contributes to a higher risk of AF recurency or if it is just a marker for overall cardiometabolic burden in patients with MS, which brings certain limitations to clinical application and reference. Elucidating the association between increased levels of serum uric acid (SUA) and recurrence of AF after PCV in patients with MS, may help to gain a better understanding of AF risk factors and thus lend support to better preventive strategies.

We tested hypothesis: increased serum uric acid (SUA) levels are associated with greater risk of AF recurrence after PCV,in patients with MS.

Methods

Study design

The total of 204 consecutive adult participans (≥18 and <65years of age),with MS and symptomatic AF,{(paroxysmal(PAF) and persistent (PsAF)} defined on the basis of the classification guidelines of ESC[8], were enrolled in a multicenter observational cross-sectional study at 6 general cardiology Health Care Clinics ,who underwent pharmacologic cardioversion during 1 calendar year (from November 2023, through November 2024.), and were stratified in two group:101 participants with SUA level of > 7.0 mg/dL in men or > 6.0 mg/dL in women , and 103 with level of SUA < 7.0 mg/dL in men or < 6.0 mg/dL in women. Exclusion criteria were as follows: Hemodynamically unstable patients, a previous cardioversion (CV) within 1 year, previous AF ablation, moderate-to-severe valvular heart disease, hypertrophic cardiomyopathy, cardiac implantable electrical devices, congenital heart disease, poor left ventricular function n (EF<35%).previous cardiac surgery, thyroid disease, impaired renal function patients with estimated glomerular filtration rate(eGFR)<60 mL/(min·1.73m^2), patients who received uric acid lowering drugs and pregnant or lactating women.

Health screening included a physical examination, standard 12-lead ECG anthropometrics and echocardiographic examination. Patients with AF were identified as having a prolonged duration of arrhythmia, with a 12-lead ECG recorded or lasting at least 30 seconds[9].

Metabolic Syndrome

MS,was defined according to the harmonized definition of the International Diabetes Federation and other organizations [10].On the basis of the baseline examination, the metabolic syndrome was diagnosed when at least 3 of the following criteria were met.(1) central adiposity {Waist circumference (WC)} >102 cm in men and >88cm in women); (2) serum HDL-C < 50 mg/dL in women or < 40 mg/dL in men; (3) serum triglyceride levels > 150 mg/dL; (4) SBP ≥ 140mm Hg or DBP ≥ 90mm Hg or use of antihypertensive drugs;(5) the presence of diabetes mellitus(DM) or use of anti-diabetic drugs.

Blood pressure (BP) obtained after 10 min of rest in the sitting position, expressed as the average of 3 consecutive measurements. Hypertension, was defined as a systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg and/or current anti-hypertensive therapy[11]. Diabetes mellitus (DM), was defined as a fasting serum glucose level ≥126 mg/dL and/or current medical therapy with an oral hypoglycemic agent and/or insulin[12].

Blood sample collection

Blood samples were collected and analyzed pre-cardiovesion.The SUA concentration were measured using standard laboratory procedures. Hyperuricemia was diagnosed if SUA level > 7.0 mg/dL in men or > 6.0 mg/dL in women in this study[13]. SUA reported in μmol/L, converted to 1 mg/dL = 59.45 μmol/L.

Conventional Echocardiography

Prior to the procedure, all patients underwent a comprehensive transthoracic echocardiographic examination, compliant with the recommendation of the American Society of Echocardiography and the European Association of Cardiovascular Imaging [14]. The transthoracic echocardiography was always performed together with transesophageal echocardiography before PCV.

Pharmacological cardioversion

Was performed as previously described elsewhere[15]. In brief, according to our hospital protocol: intravenous (IV) Propafenon (at a rate of 2 mg/kg over 15 minutes), Flekainide (at rate of 2mg/kg over 10minutes), Amiodarone (at rate of 5mg/kg over 1h) and metoprolol 5 mg,or oral medications (pill-in-the-pocket" single doses of propafenone 450–600mg,Flecainide 200–300 mg**)** have been administered**.**

The follow-up period was 1 year. Heart rate, PQ, QRS and QT intervals were measured in the 12-lead ECG, 1 day,1 month after successful cardioversion and at 3 monthly intervals thereafter.

Recurrence of AF, was defined as the study end-point. In cases when experiencing palpitations, patients were asked to visit our outpatient department or nearby hospital as soon as symptoms occur, for ECG documentation of heart rhythm, and in cases of sinus rhythm a Holter ECG was conducted to preclude atrial fibrillation. Diagnosis of AF recurrence was made when AF was confirmed on 12-lead ECG, or AF lasting at least 30 s was documented on Holter monitoring. Time to AF recurrence was calculated from successful PCV to the first AF rhythm documentation on ECG or Holter monitoring.

Statistical Analysis

Statistical analyses were performed with the SPSS software package (SPSS 19.0). For evaluation of the data obtained from the study, descriptive statistical methods of mean ± standard deviation, frequency and ratio values were used**.**The distribution of variables was tested for normality using the Kolmogorov-Smirnov test, and the heterogeneity of variances was evaluated by Levene's test.Analysis of quantitative variables with normal distribution was performed using the Student- *t* test and analysis of variance (ANOVA).Continuous variables with abnormal distribution and qualitative variables were analyzed using the Fisher –test, χ^2 test.The association between variables were analyzed using logistic regression,odds ration (OR) and 95% confidence interval(CI) were estimated. A,p value <0.05,was considered statistically significant for a confidence interval of 95%. Statistical analyses were performed using the MedCalc software package, version 23.1.3 (MedCalc Software, Mariakerke, Belgium).

Results

A total of 204 patients with MS and AF, stratified in two groups:103 participants with SUA level < 7.0 mg/dL in men or < 6.0 mg/dL in women and 101 participants with SUA level > 7.0 mg/dL in men or > 6.0 mg/dL in women befor pharmacologic cardioversion (Pre-PCV), completed the survey. The baseline demographic, clinical, electrocardigraphic, echocardographic and laboratoric characteristics of each study group are summarized in (Table.1).

Table 1: Baseline characteristics of patients with AF and MS (n.204), according to SUA levels.

Variables	Patient with **AF (N.204)**						P - value
	Gr. with SUA levels > 7mg/dl (n-101)			**Gr.with SUA levels < 7mg/dl (n.103)**			
	N. (%)	**Mean**	**±SD**	**N. (%)**	**Mean**	**±SD**	
Gender. F/M	50(49.5) 53(52.4)			45(43.6) 58(56.3)	60		0.47
Age (year)	59.6	58.8	±5.2		56.9	±5.4	0.39
BMI(kg/m^2)		29.5	±4.2		26.1	±4.1	**0.0001**
AF(paroxysmal)	57(56.4)			61 (59.2)			0.46
AF(persistens)	44(43.6)			42 (40.7)			0.44
SUA(mg/dl)		8.87	±1.39		6.0	±0.4	**0.00**
CAD-pres. n(%)	7 (6.9)			9(8.7)			0.42
HF - pres. n(%)	12(11.8)			11(10.6)			0.49
RD - pres. n(%)	5 (4.9)			7(6.7)			0.40
STROK-pres. n(%)	12(11.8)			10(9.7)			0.41
MS(3- risk factors)	37(36.6)			57(55.3)			**0.02**
MS(4-risk factors)	36(35.6)			29(28.1)			0.49
MS(5-risk Facrors)	28(27.7)			17(16.5)			**0.04**
LAd(cm/m^2)		4.2	±0.2		3.9	±0.2	**0.001**
LAVI(mL/m^2)		31.1	±4.5		27.9	±4.2	**0.001**
LVMI(g/m^2)		97.4	±1.0		68.4	±1.9	**0.000**

F: females; M: males; BMI:body mass index; AF: Atrial Fibrilation; SUA: serum uric acid; CAD: coronary disease; HF: heart failure; RD: renal disease; LAD: left atrial dimension; LAVI: left atrial vollum index; LVMI: left ventricular mass index. MS: Metabolic Syndrome.

There were no statistically significant differences between the participants with SUA level of (> 7.0 mg/dL in men or > 6.0 mg/dL in women) and participants with SUA level of (< 7.0 mg/dL in men or < 6.0 mg/dL in women) in: gender (p=0.47), ages (p= 0.39), systolic(p=0.59);diastolic blood pressure(p=0.08); Number of risk factors of MS: three risk factors of MS(p=0.07),four risk factors of MS(p=0.33) and five risk factors of MS(p=0.12);type of AF(paroxysmal p=0.28;persistens p=0.50);presence of disease:{(coronary disease p=0.39,heart failure p=0.48;kidey disease p=0.40,stroke p=0.41);AADs used for Pharma-cological cardioversion: (Amiodarone p=0.49, Flecainide p=0.45,Propaphenone p=0.47; Metoprolol p=0.26, oral medications (pill-in-the-pocket") Propaphenone p=0.53, Flecainide p= 0.37); antiarrhythmic drugs(AADs) used after pharma-cological cardioversion:(Amiodarone p=0,57,Flecainide p=0.35, Propaphenone p=0.37,Metoprolol p=0.23).

Of all participans included in the study,67(65%) partaicipants had no evidence of organic heart disease in group with SUA level < 7.0 mg/dL in men or < 6.0 mg/dL in women and 54(63.3%) participants in group with leve SUA > 7.0 mg/dL in men or > 6.0 mg/dL in women(p=0.49).In the remaining participants , the underlying heart disease was: coronary artery disease in 16(7.8%) participants, 7(6.9%) in group with SUA level < 7.0 mg/dL in men or < 6.0 mg/dL in women and 9(8.1%) in group with SUA level > 7.0 mg/dL in men or > 6.0 mg/dL in women ,p=0.39); Heart failure in 12(11.5%) participnts with SUA level < 7.0 mg/dL in men or <6.0 mg/dL in women and 11(9.9%)} in group with SUA level > 7.0 mg/dL in men or > 6.0 mg/dL in women p=0.48);Kidney disease in 7(6.7%) participants with SUA level < 7.0 mg/dL in men or < 6.0 mg/dL in women ,and 5(4.5) in group with SUA level > 7.0 mg/dL in men or >6.0 mg/dL in women , p=0.40);Strok, in 10(9.6%) participants with SUA level < 7.0 mg/dL in men or < 6.0 mg/dL in women and 12(10.9%) in participants with SUA level of > 7.0 mg/dL in men or >6.0 mg/dL in women p=0.41).

Significant differences between groups were observed in relation to BMI.There was significantly higher BMI in participants with SUA level of > 7.0 mg/dL in men or >6.0 mg/dL in women than participants with SUA level of < 7.0 mg/dL in men or <6.0 mg/dL in women (29.5±4.1 vs.26.1±4.1; p=0.001).

Echocardiographic data of cardiac structure and function according SUA levels, are presented in Table 1. There were not significant changes between groups in relation to left ventricular dimensions and ejection fraction, but in relation to LVMI there was significant difference. Patients who had SUA level of > 7.0 mg/dL in men or >6.0 mg/dL in women ad higher LVMI than patients with SUA levels <7.0 mg/dL in men or <6.0 mg/dL in women (97.4±1.0 vs. 68.3±1.9;p=0.00). There were significant changes between groups in relation to dimension and function of LA. Patients who had SUA level of > 7.0 mg/dL in men or >6.0 mg/dL in women had increased dimension of LA (4.2±0.2

vs. 3.9±0.1, p=0.001); higher prevalence of enlargement of LA{LAVI(31.1±4.5 vs.27.9±4.2; p=0.001)}.

After the follow-up of 1.0 years,the recurrence rate of AF in participants with MS and SUA levels above (> 7.0 mg/dl in men or >6.0 mg/dl in women) was higher when compared with participants with MS and SUA levels below <7.0 mg/dl in men or below 6.0 mg/dl in women { 58(57.4.1%) vs. 31(30.6%),Fisher exact p=0.009}. (Table.1 and Fig.1).

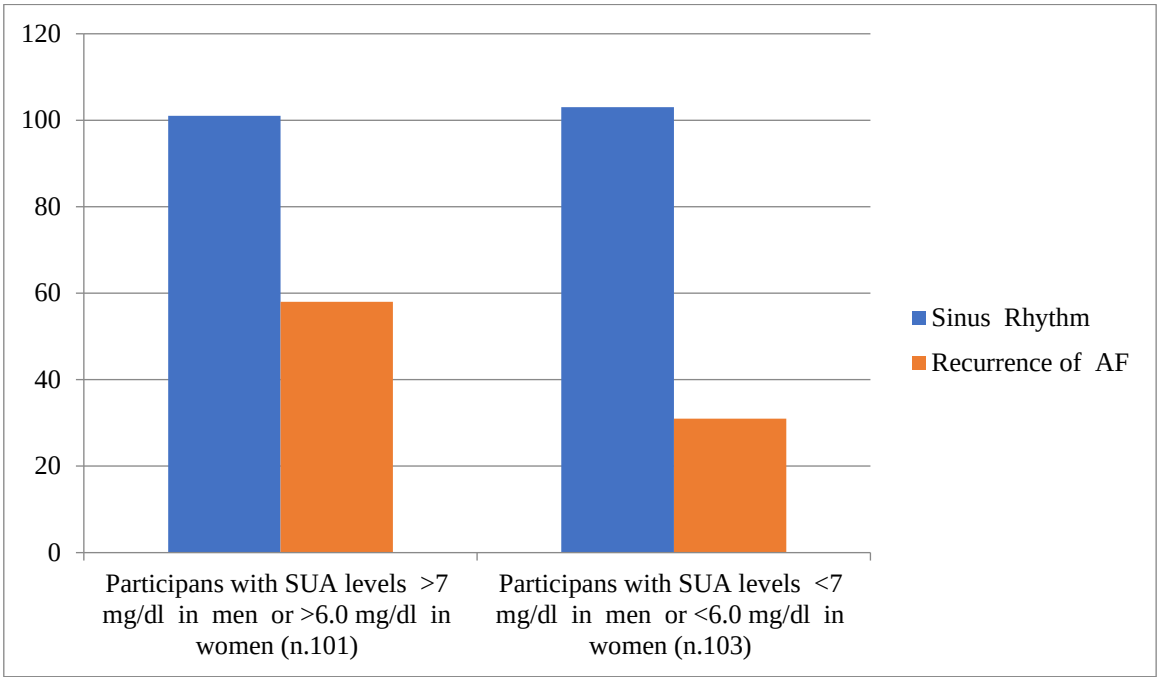

Figure 1: Atrial Fibrillation Recurrence according to SUA levels.

Of all recurrences of atrial fibrillationin in all participans, 89{70(78.6%)} occurred within the 6-month. With significant difference between the two groups {45(44.5% in patients with MS and SUA levels above (> 7.0 mg/dl in men or >6.0 mg/dl in women), vs 25(24.2%) in the patients with MS and SUA levels below (< 7.0 mg/dl in men or <6.0 mg/dl) in women (Fisher exact p=0.02)}.

Table 2: Results of Atrial Fibrillation Recurrence according to SUA levels.

Atrial Fibrillation Recurrence according to SUA levels. **Study Participans (n-204).**					
Participants with SUA levels >7 mg/dl in men or >6.0 mg/dl in women (n.101)			Participants with SUA levels <7.0 mg/dl in men or >6.0 mg/dl in women (n.103)		Total (n.204)
AF-Recurrence		Sinus Rhythm	AF-Recurrence	Sinus Rhythm	P
(No)	58	43	31	72	0.009
(%)	57.4	42.6	30.1	69.9	
SUA: serum uric acid; AF: Atrial Fibrilation; No: number of participans; %: perecnt of participans; p-significance.					

There was not significant difference between groups in used ADDs after PCV durig follow up period. Amiodarone was used in (38.7% of patients with SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl), vs. 37.5% patients with SUA levels {(< 7.0 mg/dl in men or <6.0 mg/dl in women); p=0.48)}, Propaphenon (23.3% vs. 25.2%, p=0.38), Flekainide (16.2% vs.18%;p=0.46),Metoprolol(1.9 % vs.2.3%,p= 0.51). There was not significant difference between participants those which did not use any of AADs during follow up period (18.5% vs.16.7%; p=0.42).

In a logistic regression(Table.3), there was observed significant association of SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl in women) with: rate of AF recurrence (OR=3.938, 95%CI:2.234-6.942), PsAF(OR=3.808 ,95% CI:2,116-6.852;Females(OR= 1.278; 95%CI: 1.723-2.322, BMI(OR=2.072, 95%CI: 1.203-3.571),LAd(OR=3.817,95%CI:0.989-1.544),LAVI(OR=1.74; 95%CI:1.549-1.975), LVMI (OR=1.041,95% CI :1.022-1.061).

Table 3: Logistic Rgression Model: Association of SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl in women) with: AF-recurrence, Gender (Females), PsAF (AF-type), LAd, LAVI, LVMI.

	OR*	95% CI for Exp (B)	
		Lower	Upper
AF recurrence	3.282	1.837	5.861
Gender (Females)	1.723	1.278	2.322
PsAF (AF-type)	3.808	2.116	6.852
LAd	1.404	0.538	3.664
LAVI	0.552	0.315	0.969
LVMI	1.041	1.022	1.061
AF:Atrial Fibrilation; PsAF: persistens atrial fibrilation; MS: Metabolic Syndrome; LAD: Left Atrial dimension; LAVI: Left Atrial Vollum Index; LVMI: Left Ventricuar mass Index; BMI: Body mas Index.			

Discussion

In the present study we observed that, frequency of AF recurrence after the follow-up of 1.0 years of pharmacologic cardioversion, in participants with MS and SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl in women),was significantly higher than AF recurrence among participants with MS and SUA levels (< 7.0 mg/dl in men or <6.0 mg/dl in women), indicating that increased SUA levels are associated with greater risk of AF recurrence after pharmacologic cardioversion in patients with MS. Results that confirmed our hypothesis.

Many previous cross-sectional, prospective cohort studies and meta-analyses reported the association between increased SUA levels and the incidence of AF[16,17], however, conflicting results have also been reported[18-19]. The precise mechanisms are not fully understood. Is well-established that inflammation is independently associated with the development of AF[20,21]. Experimental and clinical data indicate that inflammation have been involved in the pathogenesis of both, metabolic syndrome and atrial fibrillation [21], this makes inflammation one of many possible cofactors of AF. Based on basic research, SUA is the end product of purine degradation catalyzed by xanthine oxidase, which has been reported to induce endothelial dysfunction, oxidative stress, and systemic inflammatory responses[22]. Thus, increased SUA level is thought to be a marker of tissue oxidative stress and inflammation, which leads to the generation of atrial remodeling as an AF substrate[22,23]. Several previous studies have shown that high pre-SUA level is a predictor of AF recurrence after rhythm control[24], however, conflicting results have also been reported [25].Several cohort studies could not prove the significant association between high SUA levels and the increased risk of recurrence of AF after rhythm control strategies [25].The designs of these studies were defferent rhythm control strategies, thus it is difficult to draw a conclusion.

LA remodeling is a key process in AF generation and is a consequence of structural and functional maladaptation against external stress. LA remodeling, in turn, promotes electrical disturbance that can increase incident AF [26]. In the present study, we found significant association of increased rate of AF recurrence in participants with SUA levels (> 7.0 mg/dl in men or >6.0 mg/dl in women) and LA remodeling (increased LA dimensions and LAVI). Similar results have been found in others studies [27]. Based on previous research demonstrating a positive correlation between the LAD and SUA levels [28], irreversible atrial structural remodeling or remaining triggers after rhythm cardioversion strategies, might promote sources of arrhythmia for the recurrence of AF. In fact, a previous study demonstrated that the presence of reverse remodeling in the LA volume after rhythm cardioversion strategies, was one of the predictors of a successful outcome [29]. In the present study, the association between increased SUA levels and LA enlargement remained independent in women suggesting that increased SUA levels, is specifically associated with an increased risk of LA enlargement in women and could be an independent risk factor for LA enlargement. Therefore, our results may explain the gender differences in the association of elevated SUA with risk of AF-reccurence. Further study is warranted to explain this connection and explore the potential mechanisms.

In addition, our study also found a significant association between SUA levels and types of AF. Specifically, compared with PAF, persistent PsAF were more likely to have high levels of SUA. This observation may be attributed to higher levels of inflammation and oxidative stress damage in patients with persistent PsAF. However, few studies with large sample sizes have investigated the association between SUA and AF subtypes. Studies with larger sample sizes may uncover more interesting situations among AF types.

Finally, further prospective studies are needed to determine whether the treatment of increased SUA levels can improve atrial remodeling and then reduce AF-reccurence. Pharmacologic cardiovesion is a widely conducted procedure that restores the AF to SR in a patients with AF, despite AADs in clinical practice. The clinical significance of this study is that SUA levels is an easily determined marker in everyday clinical practice worldwide that may be helpful for predicting early AF recurrence after successful pharmacologic cardiovesion.

Future Directions: Understanding the pathogenesis of AF and the relationships between increased SUA levels and AF-reccurence is of both academic and clinical interest, because insights might lead to better prevention and treatment of this common but dangerous dysrhythmia in patients with MS.

Several limitations deserve mention. Firstly, the present study comprised a relatively small group of patients. Therefore, the present findings need to be validated in a larger group of patients. Secondly, the cross-sectional design precludes the assessment of causal relationships between: increased SUA levels and AF-reccurence. Thirdly, detection of AF recurrence,

was based on ECG recordings acquired on a systematic basis and/or 24 h Holter registration. Importantly, patients were encouraged to obtain an ECG registration when experiencing palpitations in order to confirm AF as the cause of these complaints. Nevertheless, asymptomatic episodes may have been missed.

Conclusions

The findings of this study suggest that hyperuricemia is a risk factor of AF-reccurence and could be useful for predicting recurrence of AF after successful pharmacologic cardioversion in clinical practice. Therapeutic strategies of targeting hyperuricemia might become a potential strategy to reduce the risk of hyperuricemia-induced reccurence of atrial fibrillation.

Author Contributions

Ylber Jani, involved in conceptualization and supervision; Valbona Aliu, Entela Neziri, Bekim Pocesta, Atila Rexhepi, Fatmir Ferati, Sotiraq Xhunga,Artur Serani,Agim Zeqiri, investigated the study; Kastriot Haxhirexha, formally analyzed the study; Valbona Aliu involved in original draft preparation;Ylber Jani,Kastriot Haxhirexha,reviewed and edited the study; Bekim Pocesta visualized the study;Petrit Bara, involved in supervision.

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Declarations:

Conflict of interest. Authors declare no conflict of interests for this article.

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Consent to participate. All patient was written informed, consent was obtained from all participating patients before they were enrolled into the study. A local ethics committee ruled that no formal ethics approval was required in this particular case.

Ethics approval. 'Not applicable' for that section.

Consent for publication. 'Not applicable' for that section.

Availability of data and materials. 'Not applicable' for that section.

Competing interests. 'Not applicable' for that section.

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