

## Research Article

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### Study of Serum Uric Acid Level in Non-Valvular Atrial Fibrillation

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#### ABSTRACT

**Background:** Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with high morbidity and mortality, mainly due to stroke. Non-valvular atrial fibrillation (NVAF) is its most frequent form. Serum uric acid, a marker of oxidative stress and inflammation, has been suggested as a risk factor for cardiovascular disease, but its association with NVAF remains uncertain.

**Methods:** A hospital-based, case-control study was conducted at a tertiary care centre, including 80 patients with NVAF and 80 age- and gender-matched controls. Serum uric acid was estimated using the Uricase method. Clinical characteristics, comorbidities, and complications were assessed. Statistical analysis was performed using Student's t-test and Chi-square test.

**Results**: The mean serum uric acid level was significantly higher in NVAF cases compared to controls ( $6.44 \pm 1.3$  mg/dl vs.  $5.54 \pm 1.4$  mg/dl; p=0.001). Hyperuricemia was observed in 56.25% of cases versus 32.5% of controls (p=0.002). Significant associations were found between hyperuricemia and age >65 years (OR 3.7; p=0.013), hypertension (OR 3.46; p=0.014), type 2 diabetes mellitus (OR 2.72; p=0.031), left atrial size >40 mm (OR 4.75; p=0.001), and hypertriglyceridemia (OR 10.66; p=0.001). No significant association was found with mortality, stroke, or COPD.

**Conclusion**: Hyperuricemia is common in NVAF and significantly associated with important risk factors and comorbidities, including advanced age, hypertension, diabetes, left atrial enlargement, and hypertriglyceridemia. Serum uric acid estimation, being simple and inexpensive, may serve as a useful adjunct marker in the evaluation of NVAF patients. Larger multicentric studies are needed to validate these findings.

**Keywords**: Non-valvular atrial fibrillation, serum uric acid, hyperuricemia, comorbidities, risk factors.

#### INTRODUCTION

Atrial fibrillation (AF) is the most commonly encountered supraventricular arrhythmia, accounting for about 1/3rd of hospitalizations for cardiac rhythm disturbances reported in clinical practice. Uncoordinated electrical activation of the atria along with an irregular, and often quick, ventricular response that causes hemodynamic compromise are characteristics of AF. As the atria fibrillate, blood pools in the atria, and a clot may form in the atrial appendage, increasing the risk of embolic stroke. This is the commonest arrhythmia carrying a high morbidity and mortality risk, primarily due to the elevated risk of ischemic stroke. Tremendous evolution in the past few years has resulted in significant advancements in AF management. Evidence from literature shows that the electrophysiological and structural remodelling of the atria impacts the development of AF. Atrial fibrillation may result from several disease processes, each having distinctive prognoses. Non-valvular atrial fibrillation (NVAF), occurring in the absence of rheumatic valve disease, a mechanical or bio prosthetic valve, or mitral valve abnormalities, is the commonest AF type. Obesity and diabetes are among the major hypothesized contributing factors for AF pathogenesis. Moreover, inflammation has been shown to play a part in the pathophysiological mechanism of AF. Moreover, inflammation through the activation of pro-inflammatory cytokines. Several studies have been published to assess the association between serum

uric acid levels and the risk of AF, with inconsistent results.<sup>13, 14</sup> The prevalence of hyperuricaemia (HUA) ranges between 13.3% and 21.6% and has been observed to vary with gender and among countries or regions.<sup>15</sup> This study was thus performed to evaluate the evidence of the association between serum uric acid levels and AF risk.

#### AIM AND OBJECTIVES

Aim To assess the relationship between raised serum uric acid level and non-valvular AF & its comorbidities Objectives

- 1. To estimate serum uric acid in cases of non-valvular atrial fibrillation and to compare it with age group and gender matched controls.
- 2. To study clinical characteristics and etiological profile in cases of non-valvular atrial fibrillation.
- 3. To find out association of serum uric acid with risk factors/comorbidities for atrial fibrillation viz .in cases of non-valvular atrial fibrillation (Old Age/ Male/ Sex/ Hypertension/ DM/Heart Failure/Coronary Artery Disease/ LA size/ Thyrotoxicosis/ COPD//Obesity).
- 4. To find out association of serum uric acid with complications of atrial fibrillation (heart failure, thromboembolism, stroke, death)

#### METHODOLOGY AND MATERIAL

Type of study: -

1. Case-control study

2. Observational, Hospital-based

Study setting: Tertiary Care Centre

Study factors: - Serum uric acid, Atrial fibrillation

Study variables: - Uric acid /HTN/DM/Male gender/Age> 65 Years

Outcome variable: - Uric acid/stroke/peripheral embolism/CHF/cardiogenic shock/death

Sample size: - Calculated as 75

Method: - Serum uric acid is estimated by Uricase method (available kit at biochemistry department) Normal values: - • Males up to 3.1 to 7 mg/dl • Females up to 2.5 to 5.6 mg/dl Abnormal Values: - Uric acid levels in males >7mg/dl and in females >5.6 are labeled as hyperuricemia

Inclusion Criteria for Cases: - Cases of Atrial fibrillation (persistent/permanent) admitted in ICU/Medicine wards of a tertiary care center with Age >18 Years and willing to participate in the study.

Exclusion Criteria for Cases: - 1. Malignancy (myeloproliferative/lymphoproliferative disorders) 2. Cases with renal failure (serum creatinine >1.5 mg%)/evidence of CKD 3. Known cases of gout. 4. Subjects taking medications for hyperuricemia (allopurinol, febuxostat/others) 5. Cases of psoriasis 6. End-stage liver disease (cirrhosis liver/hepatic encephalopathy.) 7. HIV-positive patients. 8. Subjects not willing to participate in the study 9. Age < 18 years 10. Rheumatic heart disease 11. Paroxysmal AF

Inclusion criteria for controls: - Age group and gender-matched controls with no evidence of atrial fibrillation

Exclusion Criteria for Controls: - 1. Malignancy (myeloproliferative/lymphoproliferative disorders) 2. Cases with renal failure (serum creatinine >1.5 mg%)/evidence of CKD 3. Known cases of gout. 4. Subjects taking medications for hyperuricemia (allopurinol, febuxostat/others) 5. Cases of psoriasis 6. End-stage liver disease (cirrhosis liver/hepatic encephalopathy 7. HIV positive patients 8. Subjects not willing to participate in the study 9. Age < 18 years 10. Rheumatic heart disease 11. Paroxysmal AF Source of Controls: - Relatives of the admitted patients or social visitors of the admitted patients. Statistical analysis: - • Data is collected and entered in Microsoft excel -10 • Statistical analysis is done by using Epi info and SPSS version 20. • Continuous variables are compared by student t test • Categorical variables are compared by chi square test • Analysis is performed to find out the independent association of serum uric acid with comorbidities /risk factors viz. HTN/DM/LVEF/LA size/Male gender. An attempt is made to find out the association of hyperuricemia with poor prognostic factors in cases of NON-VALVULAR AF (CHF/CARDIOGENIC SHOCK/STROKE/DEATH)

#### **OBSERVATION & RESULTS**

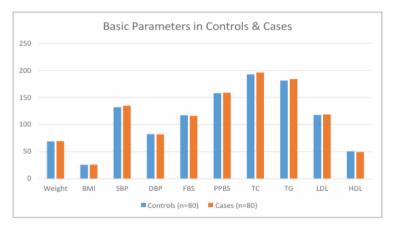
The present study has been conducted in a tertiary care setting centre to study the correlation of serum uric acid levels in patients with non-valvular AF (persistent/permanent). We have included 80 diagnosed cases with non-valvular AF (referred to as "Cases"), along with age- and gender-matched 80 patients, i.e. "Controls", for the purpose of comparison. The demographic and baseline characteristics between the two groups were compared. The study estimates serum uric acid in "cases" and "control" groups.

Age distribution in cases & controls

No cases of non-valvular AF found in the age group 19-29 years and 30-39 years. In the age group 40-49 years, there were 7 (8.75%) patients in cases and 10 (12.5%) in controls. In the age group 50-59 years, there were 10 (12.5%) patients in cases and 13 (16.25%) in controls. In the age group 60-69 years, there were 17 (21.25%) patients in cases and 17 (21.5%) in controls. In the age group 70 years and above, there were 46 (57.5%) patients in cases and 40 (50%) in controls.

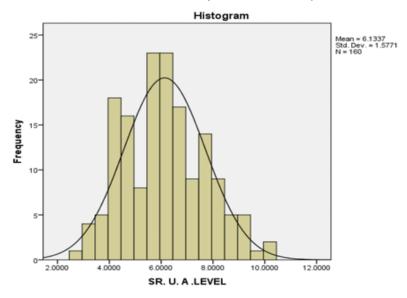
the mean age in cases was 69.07 years with standard deviation of 12.18 years whereas the mean age in controls was 67.26 years with standard deviation of 12.20 years. The p value of the parameters is 0.349 which indicates that there is no significant difference between the groups with respect to the age and gender.

Clinical and Biochemical parameters were studied in the study population. In cases mean weight was observed as 69.19 (10.5) kg and in control 68.94 (8.7) kg. In cases mean BMI was observed as 25.94 (3.7) and in controls 25.71 (8.7) kg/m2. The mean systolic blood pressure is 134.59(18.8) mmhg in cases and 131.85(17.03) mmhg in controls. The mean diastolic blood pressure is cases is 81.85 (12.3) mmhg and in controls it is 82.05 (11.8) mmhg. The mean fasting blood sugar is 116.04 (27.5) mg% in cases and 117.25 (22.5) mg% in controls. The mean post prandial blood sugar is 158.71(42.7) mg% in cases and 157.74 (33.1) mg% in controls. The mean total cholesterol is 196.01 (37.6) mg/dl in cases and 192.56 (32.11) mg/dl in controls. The mean triglycerides is 198.63 (56.4) mg/dl and 181.11 (26.9) mg/dl in controls. The mean low-density lipoprotein is 118.46 (32.6) mg/dl and 117.75 (28.8) mg/dl in controls. The mean high-density lipoprotein is 49.43 (10.7) mg/dl and 50.41 (11.9) mg/dl in controls. The clinical and biochemical parameters in cases and controls were compared using ANOVA test to avoid any confounding factor. There was no significant difference among any of the factors



Distribution of Uric acid among the study population

Figure below the serum acid levels in the study population which have formed a normal distribution curve. Hence Mean can be a good parameter to use in our statistical purpose. Secondly, it implies that one standard deviation (both sides of mean) will cover about 68% values and 2 standard deviation (both sides of mean) will cover about 95% values.



Comparison of Serum Uric Acid Level in cases and controls

Present study revealed that the mean serum uric acid is 6.44 (1.3) mg/dl and 5.54 (1.4) mg/dl in cases and controls respectively. The ANOVA test for Serum Uric Acid levels in study populations shows that there is a significant difference between the population with p value 0.001.

Present study demonstrates that hyperuricemia present in 45 patients in cases and 26 patients in control. The p value is 0.002 which is significant. The table demonstrates that hyperuricemia is present in the cases of AF.

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	Cases (n=80)	Controls (n=80)	
Male (UA>7 mg/dl)	18 (22.5%)	10 (15%)	
Female (UA> 5.6 mg/dl)	27(33.75%)	16 (22.5%)	
Total	45	26	

Sr. Uric acid level in male = 3.1 - 7.0 mg/dl

Sr. Uric Acid level in Female =2.1- 5.6 mg/dl

#### Clinical Characteristics in cases of AF

Palpitation was the main presenting complaint in 41 patients (51.25%). Oedema Feet was noted in 28 patients (35%). Patients with complaint of fatigue were 23 (28.75%). Raised JVP has been seen in 21 patients (26.25%). 16 patients had presented with chest pain (20%). Orthopnea was complained by 15 patients (18.75%). Dizziness was reported by 14 patients (17.5%). 12 patients had presented with complaint of syncope (15%). Patient presented with paroxysmal nocturnal dyspnea were 9 (11.25). Convulsions were reported by 4 patients (5%). Ecchymosis was seen 4 patients (5%). Motor weakness was found in 4 patients (5%). Loss of consciousness were reported in 3 patients (3.75%).

#### CHA2DS2VASc Score in Cases of AF

CHA <sub>2</sub> DS <sub>2</sub> VASC	Cases (n=80)	Percentage
0	4	5
1	9	11.25
2 and above	67	83.75

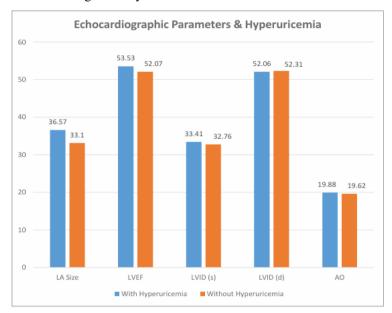
CHA <sub>2</sub> DS <sub>2</sub> VASC	Mean Uric Acid	p value
0	5.9	0.606
1	6.1	
2 and above	6.5	

The study shows that patients with CHA2DS2VASc score of 0 had mean serum uric acid 5.9 mg/dl. Patients with CHA2DS2VASc score 1 had mean serum uric acid 6.1 mg/dl. Patients with CHA2DS2VASc score more than 2 had mean serum uric acid had uric acid 6.5 mg/dl. The difference in mean values of the three groups was compared using ANOVA. It was not significant (0.606).

	With Without Hyperuricemia	
	Hyperuricemia	Mean (SD)
	(n=45) Mean	
	(SD)	
LA Size	41.36(4.04)	34.94 (6.6)
LVEF	51.0 (12.1)	55.57 (9.6)
LVID (s)	33.47 (6.9)	32.80 (8.2)
LVID (d)	51.51 (8.0)	52.97 (7.0)
AO	19.42 (3.2)	20.26 (3.0)

	ANOVA F Value	Significance
LA Size	28.16	0.001
LVEF	3.33	0.072
LVID (s)	0.154	0.695
LVID (d)	0.723	0.398
AO	1.356	0.248

Echocardiography in cases of AF shows mean LA size of 41.36(4.04) mm in cases with hyperuricemia. The study population shows that A significant difference was seen in LA size among patients with and without hyperuricemia (p=0.001). Other parameters were not significantly different.



Association of Sr. Uric Acid with risk factor /comorbidities /complications of AF

	Hyperuricemia (n=45)		Without Hyperuricemia (n=35)	
	Male (n=18)	Female	Male	Female (n=17)
		(n=27)	(n=18)	
Age >65 years	14	20	9	8
Age < 65 years	4	7	9	9
Hypertension	14	23	8	12
No Hypertension	4	4	10	5
Diabetes	12	13	5	6
No Diabetes	6	14	13	11
IHD	7	12	6	6
No IHD	11	15	12	11
LA size > 40 mm	12	16	4	5
LA size up to 40 mm	6	11	14	12
Thyrotoxicosis	1	0	1	2
No Thyrotoxicosis	17	27	17	15
COPD	2	1	3	4
No COPD	16	26	15	13
Triglyceride>150	16	24	8	7
Triglyceride Up to 150	2	3	10	10
Stroke	2	2	2	1
No Stroke	16	25	16	16
HF	6	6	2	2
No HF	12	21	16	15
Death – Yes	2	4	1	2
No	16	23	17	15

Table represents the association of serum uric acid with risk factors, comorbidities, and complications of AF. In the age group more than 65 years, there were 34 cases with hyperuricemia and 17 without hyperuricemia. In the age group less than 65 years, there were 11 cases with hyperuricemia and 18 without hyperuricemia. In the cases with hyperuricemia and 20 cases were without hyperuricemia. In cases with diabetes, 25 cases were with hyperuricemia and 11 were without hyperuricemia. Cases those had ischemic heart disease hyperuricemia was seen in 19 cases and 12 cases were without hyperuricemia. In cases with LA size more than 40 mm, 28 cases were with hyperuricemia and 9 cases were without hyperuricemia. For the cases with thyrotoxicosis, 1 cases was hyperuricemic and 3 cases were without hyperuricemia. In cases with COPD, 3 cases were with hyperuricemia and 7 cases were without hyperuricemia. In cases with Triglyceride more than 150 mg/dl, 40 cases were with hyperuricemia and 15 were without hyperuricemia. In cases with strokes 4 were with hyperuricemia and 3 were without hyperuricemia. Heart failure was seen in 12 patients with hyperuricemia and 4 were without hyperuricemia. 6 cases with hyperuricemia and 3 cases of without hyperuricemia died.

	p value	Odds	Confidence Interval	
		Ratio		
Age ( 65 years)	0.013	3.7	1.41	9.73
HTN (No/Yes)	0.014	3.46	1.25	9.58
DM (No/Yes)	0.031	2.72	1.08	6.87
IHD (No/Yes)	0.470	1.4	0.56	3.49
Thyrotoxicosis (No/Yes)	0.196	0.24	0.024	2.43
COPD (No/Yes)	0.074	0.28	0.068	1.19
LA size (40)	0.001	4.75	1.8	12.53
Hypertriglyceridemia (	0.001	10.66	3.39	33.54
150mg/dL)				
Stroke (No/Yes)	0.960	1.04	0.217	4.98
HF (No/Yes)	0.091	2.81	0.82	9.67
Death (No/Yes)	0.504	1.64	0.38	7.08

Association of hyperuricemia in cases of non-valvular AF with 1. Age (>65 years) 2. Hypertension 3. Type 2 DM 4. LA size (>40 mm) 5. Hypertriglyceridemia (>150 mg/dl) Statistical analysis by Pearson Chi Square Test revealed that there is that there is a significant association of hyperuricemia in cases of non-valvular AF with age more than 65 years with p value of 0. 0.013. The risk of having hyperuricemia for the age group is 3.7 times higher as per the Odds Ratio. Hypertension and hyperuricemia in cases of non-valvular AF also shows strong association with p value of 0.014. The odds of ratio of 3.46 shows the times higher risk of having hyperuricemia in hypertension. Type 2 DM also has a strong association with hyperuricemia with p value 0.031 and shows 2.72 times higher risk of having hyperuricemia in cases of non-valvular AF. The cases with LA size more than 140 mm and hyperuricemia also shows a strong association with p value 0.001 with odds ratio 4.75. Hypertriglyceridemia and hyperuricemia in cases with non-valvular AF shows a strong association. The p value for the same is 0.001 with 10.66 times higher risk of having hyperuricemia in the cases.

#### DISCUSSION

An observational case-control study has been conducted in a hospital-setting with a total of 160 participants. In this study, 80 people with AF (persistent/permanent) were included, while 80 participants of the same age and gender served as controls. The two groups had comparable basic characteristics (p>0.05).

Association of Serum Uric Acid with AF in Cases and Controls Serum uric acid showed normal distribution among the study population with a mean value of 5.99 (SD=1.4) mg/dl. Mean uric acid levels in cases and controls were 6.44 and 5.54 mg/dl, respectively. There was a significant difference between the two groups (p=0.001). A meta-analysis of total 6 studies showed that hyperuricemia was significantly associated with an increased risk of atrial fibrillation. ATHANASIOS J. MANOLIS concluded in a study that SUA may be considered an emerging risk factor for AF, and suggesting that urate-lowering therapy may have a role in the prevention and treatment of AF. In a study, hyperuricaemia was correlated with AF after adjustment for various cardiovascular risk factors in all participants. Greater serum uric acid level is associated with higher AF incidence is shown by SHANSHAN LI in a prospective study. S MARUHASHI et al. have suggested an association between elevated SUA levels and AF, but the pathophysiological mechanism behind this effect is not known. However, SUA biology may be a potential mechanism. Uric acid is the final product of purine metabolism catalysed by xanthine oxidase, which plays an important role in the formation of free radical superoxide anion and oxidative stress. Resulting in calcium overload, decreasing sodium

channels, and aggravating cellular damage. These pathological processes promote electrical remodelling of the left atria. 19,20 In addition, SUA promotes inflammation via releasing pro inflammatory cytokines (e.g., interleukin-6, interleukin-8, tumour necrosis factor, and monocyte chemoattractant protein or local activation of the renin—angiotensin system (RAS)). It is well known that chronic inflammation leads to endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation, and elevated 56 expression of fibrinogen. Inflammation also upregulates the RAS and increases angiotensin II (Ang II) levels, which activate the Janus kinase (JAK)/signal transducers and activators of the transcription (STAT) pathway. It has been shown that the Ang II/Rac1/STAT3 pathway is an important signalling pathway that can promote AF. Both JAK/STAT and RAS signalling play a role in left atrial structural remodelling, and both electrical and structural remodelling contribute to the occurrence and development of AF. Another potential epidemiological explanation for the relationship between SUA and AF could be that SUA is an independent predictor of various cardiovascular diseases, including stroke, hypertension, coronary heart disease, and congestive heart failure. Thus, elevated SUA levels may lead to increased AF prevalence via increasing the risk of cardiovascular diseases. Moreover, the use of allopurinol, a medication that lowers urate through inhibition of xanthine oxidase, is associated with a lower risk of AF. Elevated SUA levels may lead to increased AF prevalence via increasing the risk of cardiovascular diseases. Moreover, the use of allopurinol, a medication that lowers urate through inhibition of xanthine oxidase, is associated with a lower risk of AF.

Etiology (or Risk Factors) and Complications in AF Cases Diseases that can be the etiological factor (risk factor) for AF in cases were hypertension (17.5%), DM & COPD (3.75% each), IHD, and Thyrotoxicosis (2.5% each). However, many had more than one cause for AF (63%). Hypertension was present in 57 out of 80 patients. WEI-DONG LIN observed hypertension as a common cause of AF in their study (p0.05). Other studies also noted that the positive relation of hyperuricemia to stroke was weakened when additionally adjusted for possible confounding variables<sup>27</sup>

Hyperuricemia and AF Associated Factors This study compared the aetiology, comorbidities, and complications of AF patients with and without hyperuricemia. Based on the observations the differences are as follows: age above 65 (75.55% Vs 48.57%), hypertension (82.22% vs 57.14%), diabetes (55.56% vs 31.42%), IHD (42.22% vs 34.28%), LA size > 40mm (62.22% vs 25.71%), Thyrotoxicosis (2.22% vs 8.57%), COPD (6.66% vs 20%), Hypertriglyceridemia (88.8% vs 42.8%), stroke (8.88% vs 8.57%), heart failure (26.67% vs 11.42%) and mortality (13.33% vs 8.57%). Based on the chi square test, the prevalence of only hypertension, diabetes, age (above or below 65), LA size (greater or smaller than 40 mm), and hypertriglyceridemia was significantly different between the groups (p< 0.001) was markedly larger in patients with LA-SEC. In multivariate regression analysis, SUA level was an independent risk factor for LA-SEC (OR: 1.008, p < 0.001). Hence, they concluded that SUA level is an independent risk factor and has a moderate predictive value for LA-SEC (LA size) among non-valvular AF patients.64 RI-BO TANG et al. tried to investigate SUA and the risk of left atrial (LA) thrombus in patients with non-valvular atrial fibrillation (AF).<sup>28</sup> LA thrombus is a complication of LA dilatation. The incidence of LA thrombus was significantly greater in patients with hyperuricemia than in those with a normal SUA level. The author has noted that SUA levels in patients with LA thrombus were significantly greater (413.5  $\pm$  98.8  $\mu$ mol/L vs.  $366.7 \pm 94.3 \,\mu\text{mol/L}$ ; p < 0.001). Hyperuricemia had a negative predictive value of 98.1% in women and 97.1% in men for identifying LA thrombus. In multivariable analysis, SUA was an independent risk factor of LA thrombus (odds ratio, 1.004; 95% confidence interval, 1.000-1.008; p = 0.028). <sup>28</sup>

Association of Hyperuricemia and AF with Mortality This study could not find any significant difference in mortality related to hyperuricemia in AF. This contradicted a recent meta-analysis that found uric acid to be an independent predictor of cardiovascular mortality.66 In contrast to many previous studies, this study found no significant correlation between hyperuricemia in AF and gender, IHD, heart failure, stroke, COPD, or mortality. The reason for this discrepancy can be: (1) the small sample size in study. Most of the studies have included more than a thousand patients. (2) Many of 61 them are prospective cohort study while this is a cross-sectional study. Some of them have even used serial measurements of uric acid levels. (3) Most of the studies are conducted in the Chinese population. There can be some ethnic and environmental variations in the parameters. Even studies from north China and south China differ in their findings regarding the prevalence of hyperuricemia and other factors. It is probably due to changes in lifestyle and diet customs (e.g., meat, seafood and milk).67 (4) Inferences were limited by the fact that most of the studies have only 1-time measurement of serum urate. Serum urate is time-varying by nature. One measurement at baseline may be subject to measurement errors and may lead to biased results.

Implications Atrial Fibrillation is one of the important clinical morbidities in the community as well as in patients with risk. Hyperuricemia has recently been found as one of the causes for Non valvular atrial fibrillation and it is also associated with risk factors causing Non-valvular atrial fibrillation e.g., Age >65 years, HTN, DM etc. Estimation of serum uric acid is easy, simple, cheap, and doesn't require high tech machine and can be used in a case of Non-valvular AF. Whether Hyperuricemia in non-valvular AF needs to be treated or it can interfere with course of disease needs to be studied in a large sample size community study.

#### Limitations

- Small sample size
- · Cardiac catherization /EPS studies and ablation /CVTS surgeons /cardiologists are not available
- Rate control strategy followed in most of the cases
- · All cases may not receive oral anticoagulants because of financial constraints and difficulties faced for follow up INR

- Short term study
- Unicentric, hospital-based

#### **CONCLUSION**

The study concludes that:

- 1. Hyperuricemia is prevalent in the cases of non-valvular atrial fibrillation.
- 2. Cases with AF had higher mean SUA level as compared to controls.
- 3. In cases of AF, hyperuricemia is associate with
  - a. Hypertension
  - b. Age more than 65 years
  - c. Type II Diabetes Mellitus
  - d. Hypertriglyceridemia
  - e. Enlarged left atrium

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