



Original Article

Prevalence, risk determinants and consequences of atrial fibrillation in rheumatic heart disease: 6 years hospital based-Himachal Pradesh-Rheumatic Fever/Rheumatic Heart Disease (HP-RF/RHD) Registry



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ABSTRACT

Objective: To report the prevalence, risk factors and consequences of atrial fibrillation (AF) in patients of rheumatic heart disease (RHD).

Methods: The Himachal Pradesh- Rheumatic Fever/Rheumatic Heart Disease (HP-RF/RHD) Registry database of 1918 patients was analyzed. AF was diagnosed with 12-lead ECG recording at entry in to the registry. The association of AF with nature and severity of valvular dysfunction was analyzed, adjusted for age, left atrial (LA) dimension and pulmonary arterial hypertension using multivariable logistic regression model and strength of association was reported as odds ratio (OR) with 95% confidence intervals (C. I.).

Results: The study population consisted of young (40.2 ± 14.3 years), predominantly females (72.3%) from rural area (94.1%). Prevalence of AF was 23.9% (95% C. I. 22.1%–25.8%). The independent determinants AF were age (OR 1.04, 95% C.I. 1.03–1.06), LA size (OR 1.10, 95% C.I. 1.08–1.11). The association of AF with age, New York Heart Association functional class, mitral stenosis severity and tricuspid regurgitation was statistically significant and graded. Mitral regurgitation and aortic valve disease had no significant independent association with AF. The prevalence of heart failure, stroke, peripheral embolism and mortality was significantly higher among patients with AF ($p < .01$).

Conclusion: AF is common in RHD patients and is significantly associated with heart failure and systemic thromboembolism. Age, mitral stenosis severity, tricuspid regurgitation and LA size were independently associated with AF.

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1. Introduction

Rheumatic fever/rheumatic heart disease (RF/RHD) continues to be a major cause of morbidity and mortality in developing countries.^{1,2} Heart failure (HF) and systemic thromboembolism are the primary causes of morbidity and mortality in these patients.^{3,4} Atrial fibrillation (AF) increases the risk of thromboembolism and HF.^{5–8} Prevalence of AF is significantly higher in patients of RHD compared to age matched general population. The contemporary data on risk determinants of AF is scanty. The understanding of factors associated with increased risk of AF in RHD is important for

taking informed preventive interventions to reduce morbidity and mortality.

We aimed to report the prevalence, risk determinants and consequences of AF in patients of RHD by analyzing data of ongoing prospective tertiary care hospital-based HP- RF/RHD registry started since 2011 in Indira Gandhi Medical College (IGMC) and Hospital Shimla, Himachal Pradesh (H.P.) India.

2. Methodology

2.1. Set up and study design

HP-RF/RHD registry is a tertiary care hospital-based registry started since 2011 in the department of cardiology IGMC Shimla. IGMC Shimla is the only tertiary care hospital in the state of H.P.

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India, providing tertiary care services to the patients of RF/RHD. Although the bordering districts seek medical attention in outside state hospitals but majority of the patients of RF/RHD are referred to IGMC hospital Shimla for diagnosis and management of symptomatic patients. Thus, the data captured are fairly representative of symptomatic patients of RF/RHD in the hill state of H.P., India.

2.2. Patient population, sources and selection

All consecutive patients of RF/RHD diagnosed using standard criteria^{9,10} visiting IGMC hospital Shimla were included in the study. Patients of RF/RHD visiting outdoor and or admitted in indoor services of department of cardiology, patients referred for echo evaluation from department of Pediatrics, Internal Medicine were the sources of patients screened for enrollment in the registry. Patients of RHD with replaced valves, and or associated hypertension were excluded from the data analysis that affects the evaluation of nature and severity of valvular dysfunction and non RHD causes of AF. The eligible patients consenting to participate after informed consent were registered.

The study protocol was approved by the ethical committee of IGMC Shimla.

2.3. Outcome

AF as an outcome was diagnosed using 12-lead surface electrocardiogram at registry.

2.4. Risk determinants

Socio-demographics, left atrium (LA) size, left ventricular ejection fraction (LVEF), HF, nature and severity of valvular dysfunction and pulmonary arterial hypertension (PAH) were recorded and evaluated as the potential risk determinants of AF.

2.5. Consequences of AF

HF, stroke and peripheral embolism, endocarditis and death at registry was recorded as the consequences of AF.

3. Data collection and measurements

Self-reported data on socio-demographics, severity of breathlessness using New York Heart Association (NYHA) functional class, present and past history of stroke, peripheral embolism, and endocarditis was recorded systematically using predesigned data recording format at registry. HF was diagnosed based on presence of NYHA functional class 111/1V (marked limitation in physical activity during less than routine exertion/symptomatic at rest). Stroke was labeled based on history of sudden onset of focal neurological deficit with and without computed tomography (CT) of the brain showing evidence of ischemic infarct. Peripheral embolism was diagnosed with history of acute onset of ischemic symptom in affected organ associated with clinical evidence of feeble or absent pulse and Doppler or angiographic evidence of absent or decreased flow. Endocarditis was diagnosed using Duke's criteria- two major, one major and three minor or five minor criteria were required for diagnosing infective endocarditis.

Echocardiography was done using echocardiography machine model I-133 of Philips medical system at registry in left lateral decubitus position. Imaging of cardiac valves were recorded in parasternal long axis, short axis view at aortic valve, mitral valve level, apical four chamber, five chamber and two chamber view to evaluate nature and severity of valvular dysfunction based on morphology, color flow imaging, continuous wave doppler signals

using European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACT) guidelines version 2012.⁸ LA size was measured in parasternal long axis view by recording 2 D guided M mode tracing at the level of aortic root and LA dimension was measured in anterior posterior plane. Three consecutive readings were recorded and average was taken for analysis. LVEF was measured by measuring left ventricular internal diameter (LVID) at end of diastole and systole in reference to simultaneous ECG tracing, recorded in parasternal long axis view from 2 D guided M mode tracing at tip of mitral leaflets. Three readings were recorded and average was taken for analysis. RHD was diagnosed based on the World Heart Federation criteria.⁹

Patients were labeled as having clinically evident RHD when they had auscultatory and echocardiography evidence of RHD. Subclinical RHD was diagnosed when there was no clinical evidence of valvular dysfunction but echocardiography revealed definite RHD. LVEF less than 49% was taken as evidence of depressed LV systolic function. PAH was diagnosed in patients with tricuspid regurgitation (TR) jet velocity equal to and greater than 3.0 m/s recorded in modified four-chamber view in order to obtain near perfect alignment of regurgitant jet with incident ultrasound beam using continuous wave doppler.

3.1. Data analysis

The descriptive statistics of study population was described as absolute counts, percentages and mean \pm standard deviation, respectively for categorical variables and continuous variables with normal distribution. Differences in the distribution characteristics of socio-demographics, NYHA functional class, nature and severity of valvular dysfunction, LA size, PAH and depressed LV systolic function between gender groups were analyzed using Pearson's chi square and unpaired *t*-test respectively for categorical and continuous variables with normal distribution. The association of AF with demographics, NYHA class, LA size, depressed LV systolic function, nature and severity of valvular dysfunction and PAH was analyzed using univariate logistic regression model and odds ratio with 95% CI was reported. The variables found to have significant association in univariate analysis were modeled in multivariate logistic regression. The association of AF with nature and severity of the valvular dysfunction was analyzed using absence of valvular dysfunction as the reference to determine the significance of association with severity of valvular dysfunction adjusted for confounders such as age, LA size, depressed LV systolic function, symptoms of advanced HF and PAH. The association of mitral stenosis (MS) with AF was also adjusted for mitral regurgitation (MR) and TR and vice versa. The strength of independent association between AF with exposure variables were reported as odds ratio with 95% C.I. The consequences of AF were analyzed by comparing the differences in distribution of HF, cerebrovascular accident (CVA), systemic thromboembolism between the group with and without AF using χ^2 test and two-sided *p* value of <0.05 was taken as statistically significant. The data was analyzed using STATA version 13 statistical software.

4. Results

4.1. Population screened and enrolled

Since 2011, a total of 2147 patients of RF/RHD were registered. Fig. 1 describes the patient selection flow chart. Out of 2147 patients registered 229 patients were excluded from analysis due to replaced valves, associated hypertension. Thus, data of 1918 patients were analyzed to determine the prevalence and its risk determinants

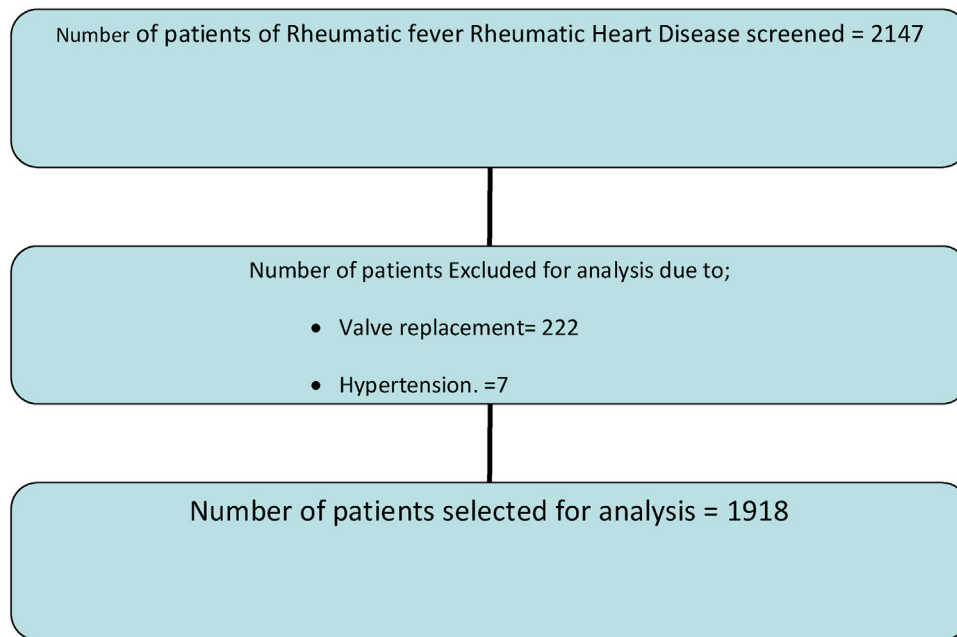


Fig. 1. Flow chart of patient selection.

4.2. Sociodemographic and clinical characteristics

The detailed description of demographic and clinical characteristics of the study population is reported in Table 1. The study population consisted of young population with mean age of 40.2 ± 14.3 years, predominantly females (72.3%) with lower level of education from rural area (94.1%). The patients were mostly symptomatic and had clinically manifest RHD (98.3%) and small percentage had subclinical RHD 14 (0.7%). The number of patients having RF at the time of registry recorded during the 6 years period of registry was very small 16 (0.7%). AF was prevalent in 23.9% (22.1%–25.8%).

Mitral valve was the most commonly affected valve (89.3%) and majority of the patients had multivalvular involvement (94.3%). Patients of RHD were complicated with HF (15.9%), decreased LV systolic function (9.3%), stroke (4.5%), peripheral embolism (3.7%), infective endocarditis in small percentage of patients (0.3%) and 7 (0.36%) patients died.

4.3. Distribution characteristics of AF

The details of the distribution characteristics and its association with AF are reported in Table 2. The prevalence of AF increased significantly with age. It was 2.2% in age group of less than 20 years to 41% in the age group of more than 51 years age group. Thus, the association of AF with age was consistent and graded. AF was equally prevalent among men and women, patients from urban and rural area but was more common in illiterate population. The association of AF with NYHA functional class was consistent and graded and prevalence increases significantly with increasing severity of NYHA functional class. Patients with depressed LV systolic function also had significant association with AF. The distribution characteristics of AF in relation to valve affected, nature and severity of valvular dysfunction revealed it was more prevalent among patients with MS, TR, severe MR and PAH. The aortic valve disease had no association with AF.

4.4. Risk determinants of AF

The details of association between demographic, clinical characteristics, severity and nature of valvular dysfunction with

AF are reported in Table 3. The variables found to have independent and significant associations were- age, MS (moderate and severe), TR, NYHA class and LA size. The association with MR, depressed LV systolic function and PAH when adjusted for age, LA size, MS and NYHA functional class was attenuated.

The patients with combination of mitral and tricuspid valve disease; MS, MR and TR had high prevalence of AF (41%) and association was statistically significant when adjusted for age and LA size.

4.5. Consequences of atrial fibrillation

The prevalence of HF, CVA, peripheral embolism and death was significantly high in patients with AF ($p < 0.01$) (Table 4).

5. Discussion

RHD is the commonest cause of AF in developing countries and is associated with significant morbidity and mortality. Thus, estimation of the burden of AF and its risk determinants in patients with RHD is important for its prevention and control to reduce the morbidity and mortality.

In a large study involving data from 26 countries,⁹ valvular heart disease was observed in 27% of participants with AF. The studies from Africa, Asia, and the Middle East reported RHD as one of the commonest cause of AF accounting for 15–60% of AF.^{11–13}

Diker et al¹⁴ in 1996 retrospectively analyzed data of 1110 patients of RHD and reported prevalence of AF in 439 (39%) patients. Okello et al¹⁵ in 2013 in hospital based cross sectional study analyzed 309 patients of RHD and AF was reported in 13.9% of cases. Sharma et al¹⁶ found 43% of the 94 RHD patients studied had AF.

In present cohort of 1918 patients of RF/RHD, 23.9% (22.1%–25.8%) had AF. The AF was also significantly associated with age, MS and TR and LA size. The association with LA size was significant and was independent of underlying mitral valve dysfunction; MS and MR and age. It is possible that underlying structural remodeling of atrial myocardium independent of hemodynamic stress related to mitral valve dysfunction e.g. chronic rheumatic myocarditis may be responsible for dilatation and altered electrophysiological substrate predisposing to AF.^{17,18}

Table 1
Characteristics of the study population.

Characteristics	Overall N = 1918	Men N = 532 (27.7%)	Women N = 1386 (72.3%)	P value
Age	1918 (40.2 ± 14.3)	532(38.3 ± 15.3)	1386(40.8 ± 13.9)	0.003
Education status				
Illiterate (0)	493(25.7%) (23.7%–27.7%)	77 (14.5%)	416(30.0%)	0.001
Primary (<8th)	292(15.2%) (13.6%–16.9%)	63(11.8%)	229(16.5%)	
Middle (9th–12th)	932(48.6%) 46.3%–50.8%	325(61.1%)	607(43.8%)	
High (graduation and post-graduation)	201(10.5%) 9.1%–11.9%	67(12.6%)	134(9.7%)	
Rural	2021(94.1%) (93.0%–95.2%)	583(94.4%)	1438(93.9%)	0.65
Diagnosis				
Chronic Rheumatic heart disease	1885(98.3%) (97.5–98.7%)	522(98.1%)	1363(98.3%)	0.74
Subclinical Rheumatic heart disease	14(0.7%) (0.4%–1.0%)	3(0.6%)	11(0.8%)	0.63
Acute rheumatic fever	16(0.7%) (0.4%–1.0%)	6(0.97%)	10(0.65%)	0.43
Valve involvement				
Mitral valve disease	1713(89.3%) (87.8%–90.6%)	454(85.3%)	1259(90.8%)	0.001
Aortic valve disease	992(51.7%) 49–5%–53.9%	313(58.9%)	679(49.0%)	0.001
Tricuspid valve disease	1023(53.3%) 51.0%–55.5%	251(47.2%)	772(55.7%)	0.001
Multivalvular disease	1808(94.3%) (93.1%–95.2%)	488(89.7%)	1320(95.2%)	0.03
NYHA functional class				
NYHA class I	458(23.9%) (22.0%–25.8%)	166(31.2%)	292(21.1%)	0.001
NYHA class II	1154(60.2%) 57.9%–62.3%	283(53.2%)	871(62.8%)	
NYHA class III	259(13.5%) 12.0%–15.1%	74(13.9%)	185(13.3%)	
NYHA class IV	47(2.4%) (1.8%–3.2%)	9(1.7%)	38(2.7%)	
Complications				
Heart failure	306 (15.9%) (13.8%–17.7%)	83(15.6%)	223(16.1%)	0.79
Stroke	87(4.5%) (3.0%–5.5%)	19(3.6%)	68(4.9%)	0.21
Peripheral embolism	72(3.7%) 2.9%–4.7%	11(2.1%)	61(4.4%)	0.01
Infective endocarditis	6 (0.3%)	3(0.6%)	3(0.2%)	0.22
Atrial fibrillation	459 (23.9%) (22.1%–25.8%)	122(22.9%)	337(24.3%)	0.57
LVEF < 49%	178(9.3%) (8.0%–10.6%)	63(11.8%)	115(8.3%)	0.01

It is intriguing that although LA size is increased in patients of MR, it was not significantly associated with AF when adjusted for age, MS and LA size. However Moderate and severe MS had significant association with odds for AF of 2.6 (1.7–4.1) and 2.4 (1.4–3.5), respectively adjusted for age, MR and LA size. Thus pressure and volume overload may have role in activating the biological pathways involved in myocardial fibrosis and hypertrophy of atrial myocardium that may predispose to AF. The severity of fibrosis of mitral valve was found to be significantly higher in patients of MS compared to MR by our group (unpublished data).

LA size and severity of MS was also reported as the risk factors of AF in retrospective cohort of patients of RHD with MS and normal sinus rhythm.¹⁹ The independent association of AF with age, LA size, MS and TR was also observed in cross sectional analysis of retrospective database of patients with RHD.¹⁴

The mechanisms of association of AF with TR in a context of lack of association with MR should be the area of future research. Is it the differential size of LA and right atrium important in initiation and perpetuation of AF or is it due to differential expression of factors like hepatocyte growth factors triggered by TR as a result of hepatic congestion²⁰ that needs to be investigated in future studies.

The observed independent association of AF with severity of MS has an important implication for AF prevention. Conventionally, percutaneous transvenous mitral commissurotomy (PTMC) procedure is offered primarily for patients with severe MS. Therefore, this observation may form the basis for future controlled trials to evaluate the role of PTMC in patients with moderate MS in prevention of AF.

HF in RHD is due to either systolic dysfunction as a result of aortic valve disease and or MR or diastolic dysfunction related to

Table 2

Distribution characteristics of atrial fibrillation and its risk factors, unadjusted odds ratio with 95% C.I.

Characteristics	Prevalence of atrial fibrillation	Odds ratio (95% C.I.)
Age group		
<20 years	4(2.2%)	Reference
21–30 years	32(9.6%)	4.7(1.6–13.4)
31–40 years	88(18.1%)	9.7(3.5–27.0)
41–50 years	157(32.4%)	21.1(7.7–57.7)
>51 years	178(41.0%)	30.5(11.1–83.9)
Gender (male)		
Urban area (yes)	122(22.9%)	0.92(0.73–1.17)
Literate (yes)	21(18.9%)	0.72(0.45–1.18)
	309(21.7%)	0.63(0.50–0.79)
NYHA functional class		
NYHA Class I	44(9.6%)	Reference
NYHA class II	293(25.4%)	3.2(2.3–4.5)
NYHA Class III	100(38.6%)	5.9(4.0–8.0)
NYHA Class IV	22(46.8%)	8.3(4.3–15.9)
LVEF <49%	66(37.1%)	2.0(1.5–2.8)
MR status		
No MR		1.00 (reference)
Mild MR	160(23.3%)	1.15(0.88–1.50)
Mod MR	79(22.6%)	1.10(0.80–1.52)
Severe MR	97(33.0%)	1.86(1.36–2.55)
Overall MR (yes)	336(25.3%)	1.28(1.01–1.61)
MS status		
No MS		1.00 (reference)
Mild MS	64(20.6%)	1.89(1.33–2.69)
Mod MS	137(36.0%)	4.11(3.03–5.57)
Severe MS	167(36.0%)	4.06(3.04–5.4)
Overall MS (yes)	368(31.7%)	3.40(2.64–4.37)
AR (yes)	247(25.9%)	1.16(0.94–1.43)
AS (yes)	57(19.8%)	0.75(0.55–1.03)
TR Status		
No TR		1.00(reference)
Mild TR	186(28.1%)	3.0(2.3–3.9)
Mod TR	97(48.5%)	7.2(5.1–10.2)
Severe TR	72(46.5%)	6.6(4.5–9.7)
Overall TR (yes)	355(34.9%)	4.1(3.3–5.2)
MS + MR (yes)	263(33.9%)	2.5(2.0–3.1)
MS + MR + TR (yes)	214(41.1%)	3.3(2.6–4.1)
PAH (Yes)	225(37.1%)	2.8(2.2–3.5)

Abbreviations: MR (Mitral regurgitation), MS (mitral stenosis), AR (aortic regurgitation), AS (aortic stenosis), TR (tricuspid regurgitation), PAH (pulmonary artery hypertension).

MS. AF aggravates symptoms of HF. The AF also increases the risk of thromboembolism by about 5 to 7 folds.

The present study also documented higher prevalence of HF (25.7% vs.12.6%) $p < 0.001$ and systemic thromboembolism (8.6% vs. 5.8%) $p < .02$ in patients with AF. The proportion of patient who died at the time of registry was significantly higher in AF group compared to the group with normal sinus rhythm. Thus AF is a marker of significant stenotic mitral valve disease, TR, HF and systemic thromboembolism and mortality.

6. Limitations

It was a single-centre, tertiary care hospital-based registry having inherent selection biases that may influence the estimation of prevalence and its risk determinants. The prevalence of AF was documented based on ECG done at registry thus paroxysmal AF may have been missed. The echocardiographic evaluation of severity of valvular dysfunction was done by consultant cardiologists in the department of Cardiology and interobserver agreement of assessment of severity of valvular dysfunction was not evaluated. However, all the consultants had experience in performing echocardiographic studies for many years. Thus, the

Table 3

Independent risk determinants of atrial fibrillation, adjusted for age, LA size, functional class, PAH, with Nature and severity of valvular dysfunction.

Characteristics	Adjusted odds ratio (95% C.I.)
Age	1.04(1.03–1.06)
LA size(mm)	1.10(1.08–1.11)
PAH (TR gradient \geq 36 mmHg)	1.1(0.9–1.5)
LVEF (<49%)	1.4(0.67–1.2)
NYHA functional class	
Class I	Reference
Class II	1.7(1.2–2.4)
Class III	2.4(1.6–3.7)
Class IV	2.9(1.4–5.7)
Severity of Mitral stenosis	
No MS	Reference
Mild Mitral stenosis	1.06(0.70–1.61)
Moderate Mitral Stenosis	2.4(1.7–3.4)
Severe Mitral Stenosis	2.1(1.5–3.0)
Severity of Mitral Regurgitation	
No Mitral Regurgitation	Reference
Mild Mitral Regurgitation	1.0(0.7–1.4)
Moderate Mitral Regurgitation	0.7(0.5–1.0)
Severe Mitral regurgitation	0.9(0.6–1.7)
Severity of Tricuspid Regurgitation	
No Tricuspid Regurgitation	Reference
Mild Tricuspid Regurgitation	1.8(1.3–2.5)
Moderate Tricuspid Regurgitation	3.2(2.1–4.9)
Severe Tricuspid Regurgitation	3.0(1.9–4.7)
Mixed valvular dysfunction	
Mitral Stenosis+ Mitral Regurgitation	1.2(0.96–1.61)
Mitral Stenosis+ Mitral Regurgitation + Tricuspid Regurgitation	1.79(1.38–2.32)

Table 4

Consequences of atrial fibrillation.

Characteristics	Atrial fibrillation	Without atrial fibrillation	P value
Heart failure	138(25.75%)	204(12.66%)	0.001
Stroke	36(6.72%)	66(4.10%)	0.01
Systemic thromboembolism	32(5.97%)	54(3.35%)	0.007
Stroke with systemic thromboembolism	46(8.58%)	93(5.77%)	0.02
Infective endocarditis	1(0.19%)	6(0.37%)	0.51
Death	4(0.75%)	3(0.19%)	0.049

conclusions drawn about association of AF with severity of valvular dysfunction should be interpreted in the right context.

6.1. Summary

AF is a frequent chronic atrial tachyarrhythmia in patients with chronic RHD. Prevalence of AF increases with age, increasing LA size, in patients of moderate to severe MS and patients with TR. Patients with MR, aortic valve disease and PAH have no significant independent association with AF. AF increases the risk of HF, systemic thromboembolism and mortality.

7. Scope for future studies

Future studies to investigate mechanistic pathways of pressure and volume overload of atrial chambers, relative contribution of RA and LA chambers sizes in increasing the risk of AF are needed to explore the novel treatment targets to prevent AF. The observed association of severity of MS with AF should form the basis for

exploring role of PTMC in moderate MS in prevention of AF in future trials.

Conflict of interest

There are no conflicts of interest in the paper.

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