Clinical Characteristics, Complications, and Treatment Practices in Patients With RHD

6-Year Results From HP-RHD Registry

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ABSTRACT

Background: Despite the high prevalence of rheumatic heart disease (RHD) in developing countries such as India, data on characteristics, complications, and treatment practices are lacking. The HP-RHD (Himachal Pradesh Rheumatic Heart Disease) registry aimed at reporting these parameters in patients with RHD from a northern state of India.

Methods: A total of 2,005 consecutive patients of RHD were enrolled over a period of 6 years (2011 to 2016) in the present study. The clinical characteristics, complications, and treatment practices were systematically recorded.

Results: The mean age for patients with RHD was 40.3 ± 14.3 (range 5 to 83 years). RHD predominantly affected females (72.3%) and population from rural background (92%). Multivalvular involvement was frequent (43.2%), mitral valve was the commonest affected valve (83.3%). The majority of the patients had moderate-to-severe valvular dysfunction (69.3%). Mitral and tricuspid valve involvement was more frequent in female subjects compared with more frequent aortic valve involvement in male subjects ($p < 0.001$). The major adverse cardiovascular events were recorded in 23.4% patients at the time of registry and comprised mainly advanced heart failure (15.6%), peripheral embolism (4.1%), and stroke (3.9%). The independent risk determinants of major adverse cardiovascular events (were advanced age (odds ratio [OR]: 1.01; 95% confidence interval [CI]: 1.00—1.02), severe mitral stenosis (OR: 1.73; 95% CI: 1.34—2.20), severe tricuspid regurgitation (OR: 2.11; 95% CI: 1.48—3.02), presence of pulmonary artery hypertension (OR: 1.33; 95% CI: 1.04—1.69), and atrial fibrillation (OR: 1.64; 95% CI: 1.28—2.11). Evidence-based use of oral anticoagulant therapy was documented in 77.7% of high-risk patients. Only 28.5% of study population was receiving secondary prophylaxis.

Conclusions: Complications in patients with RHD increase with age and worsening valvular dysfunction. Programs focused on early detection and evidence-based management will assist in improving outcomes.

Contemporary information on rheumatic fever/rheumatic heart disease (RF/RHD), the commonest valvular disorder in developing countries, barring a few small studies [1-7] is lacking. An updated understanding of comorbidities as well as downstream outcomes such as heart failure and stroke is necessary for timely interventions to prevent and treat these complications [8-10]. We describe clinical characteristics and management of a contemporary cohort of patients with RF/RHD at enrollment using the HP-RHD (Himachal Pradesh Rheumatic Heart Disease) registry from January 2011 to December 2016.

METHODS

Study design

The HP-RHD registry is a single-center, tertiary care hospital—based prospective registry. In the present study, we have analyzed the baseline 6 years' data from the registry. The study protocol was approved by the Institutional Review Board of Indira Gandhi Medical College, Shimla, India.

Study population

All consecutive patients with valvular heart disease visiting Indira Gandhi Medical College hospital between 2011 and

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2016 were screened for enrollment in the HP-RHD registry irrespective of their age and other comorbidities. Patients with RF/RHD were diagnosed using standard clinical and echocardiographic criteria [11,12]. Informed consent was obtained from each eligible patient of RF/RHD before recording the data.

Data collection

The data related to sociodemographic profile, medical history, and treatment practices and complications were collected systematically at the time of enrollment in the registry using predesigned structured data recording format.

Diagnosis of RF/RHD

The diagnosis of RF was based on the updated Jones criteria [13]. RHD was diagnosed using World Heart Federation and American Heart Association guidelines [11,12], based on clinical and echocardiographic examination. The nature and severity of valvular dysfunction and left ventricular (LV) systolic function was assessed using standard criteria [10] at the time of enrollment in the registry, in all the consecutive patients of RF/RHD whether diagnosed newly or in the past. Mitral valve area (MVA) was calculated by using planimetry and/or pressure half time. Planimetry of mitral valve was done at the level of the leaflets tips in parasternal short-axis view and was considered as the gold standard for calculating MVA in the present study [10-12]. Calculation of MVA by pressure half time was done in the apical 4-chamber view using continuous wave Doppler. Transmitral gradients were also calculated. We relied more on MVA instead of transmitral gradients for severity estimation as the latter get easily affected by the heart rate and flow conditions across the valve. The severity of mitral stenosis (MS) was defined as mild if MVA was >1.5 cm^2, moderate if MVA was >1.0 and ≤ 1.5 cm^2, and severe if MVA was ≤ 1.0 cm^2 [10-12]. Patients of RHD were classified into clinically evident RHD and clinically silent or subclinical RHD. The clinically evident RHD was diagnosed based on clinical evidence of valvular heart disease confirmed on echocardiography. The clinically silent or subclinical RHD was diagnosed in patients without any clinical evidence of valvular heart disease (no audible murmur) but with definite evidence of RHD on echocardiography, irrespective of the past history of documented rheumatic carditis. The pulmonary arterial hypertension was diagnosed using tricuspid regurgitation velocity and gradient using standard criteria [10]. LV systolic dysfunction was defined as LV ejection fraction $<50\%$ assessed using 2-dimensional–guided M-mode tracing of LV in parasternal long-axis view at the tip of mitral valve leaflet using Teichholtz formula [14].

Cardiovascular complications

Complications were recorded at the time of registry, including those that had already occurred in the past and those that developed during the index hospital admission at the time of registry. The principal complications of interest were advanced heart failure, stroke, peripheral embolism, infective endocarditis, major bleeding, and death. Advanced heart failure was defined as breathlessness at rest and/or less than routine physical activity, that is, New York Heart Association (NYHA) functional classes III and IV, respectively. Stroke was defined as sudden onset of the focal neurological deficit with computed tomographic brain evidence of ischemic infarct. Peripheral embolism was diagnosed in the presence of end-organ ischemia with a feeble or absent pulse and/or Doppler evidence of decreased/occluded flow in the affected vessel. Infective endocarditis was diagnosed using modified Duke criteria [15]. Major bleeding was labeled if it was intracranial or fatal or if it required blood transfusion. Death due to the cardiovascular cause was labeled if it was related to heart failure, stroke, or sudden death. Composite major adverse cardiovascular event (MACE) was defined as the composite of heart failure, stroke, peripheral embolism, infective endocarditis, major bleeding, and/or cardiovascular death. Prosthetic valve thrombosis was diagnosed based on clinical suspicion and echocardiographic demonstration of prosthetic valve dysfunction with or without thrombus. Fluoroscopic demonstration of restricted leaflet mobility was further used to confirm the diagnosis in doubtful cases.

Statistical analysis

The descriptive statistics of the study population were reported as counts and percentages for categorical variables and mean $\pm$ SD for continuous variables with normal distribution. The sex-based distribution of sociodemographic parameters, clinical characteristics, and complications of RHD was compared using chi-square test. The significance of the difference in the distribution of nature and severity of valvular dysfunction across the age groups was also analyzed using chi-square test. The association of sociodemographic characteristics, nature, and severity of valvular dysfunction with each component and composite of MACE was analyzed using the multivariate logistic regression modeling to identify the independent determinants of complications. The strength of association between independent variables with outcome variables was reported as odds ratios (ORs) with 95% confidence intervals (CIs). The data analysis was done using STATA 13 statistical software (StataCorp, College Station, TX, USA). Statistical significance was defined as 2-sided p values < 0.05.

Contribution of authors

Drs. Negi and K. Mahajan were involved in the conception and design of the study. Drs. Rana, Sondhi, Rathour, Verma, Dhiman, Dev, Rao, N. Mahajan, Asotra, Bhardwaj, Ganju, Kandoria, Merwaha, Sharma, Kolte, Kumar V, Paul, and Singh helped in acquisition of data. Drs. Negi and K. Mahajan analyzed the data, reviewed the published data,

and wrote the manuscript. Dr. N Mahajan gave conceptual advice. All the authors read and approved the final manuscript.

RESULTS

Clinical characteristics

A total of 2,005 patients of RF/RHD were enrolled over a period of 6 years from 2011 to 2016. The study population comprised mainly young and middle-age population with mean age of 40.3 ± 14.3 years (age range 5 to 83 years; median age: 40 years) affecting predominantly female subjects (1,450, 72.3%) and patients from the rural background (1,845, 92%) (Table 1). A large number of patients had not completed even primary level schooling (810, 40.4%). Clinically evident chronic RHD was the predominant presentation (1,955, 97.5%) while a small percentage (2.1%) had subclinical RHD. Since 2011, only 8 patients (0.4%) were diagnosed to have acute rheumatic fever. Past history suggestive of acute rheumatic fever was recalled by 25.1% of patients (501). Symptoms of advanced heart failure (NYHA functional classes III and IV) were recorded in 15.7% of patients (314) at the time of registry. Although female subjects outnumbered male subjects in the study population, no sex difference in prevalence of moderate-to-severe valvular heart disease was noted (Table 2). Atrial fibrillation was observed in almost one-fourth of the total study population (489, 24.4%). The complications of stroke and peripheral thromboembolism were reported in 3.9% (80) and 4.1% (83) of patients, respectively (Table 1). Presence of clot in the left atrium (LA) and/or left atrial appendage (LAA) was seen in 62 patients (3.1%). Infective endocarditis and major bleeding were reported in 18 patients (0.9%) and 8 (0.4%), respectively. Pulmonary artery hypertension (PAH) was seen in one-third (612, 30.5%) of patients while LV systolic dysfunction was found in 10 patients (0.5%) (Table 2).

Distribution and severity of valvular dysfunction

The data of patients without valvular replacement and catheter or surgical valvotomy were analyzed for severity of valvular involvement. Involvement of ≥2valves was seen in 43.2% of patients (866). Moderate-to-severe valvular dysfunction was seen in 69.3% of patients (1,390). The mitral valve was the most frequently affected valve (83.3%). Overall mitral regurgitation (MR) (1,284, 64%) was the most common valvular lesion followed by MS (1,118, 55.8%), tricuspid regurgitation (TR) (1,012, 50.5%), aortic regurgitation (AR) (936, 46.7%), aortic stenosis (AS) (280, 14%), and tricuspid stenosis (29, 1.4%). Involvement of mitral and tricuspid valves was significantly more frequent in female than male subjects, while aortic valve involvement was more common in male subjects (54.6% vs. 47.6%, $p < 0.01$) (Table 2). Isolated involvement of aortic valve was recorded in only 6.3% of the patients as compared to 40.2% for the mitral valve. The prevalence of MR decreased significantly with age while the prevalence of MS, TR, and AS increased. No significant change in the prevalence of AR was noted with age (See Online Figure 1). On analysis of the progression of severity of valvular dysfunction with age, MS, AS, and TR progressed in severity with age in contrast to MR and AR, which decreased in % CI: severity with age (See Online Figure 2).

Interventions and therapy

At the time of registry, valvotomy (closed or balloon) had already been performed in 16.1% of patients (323) with mitral stenosis while 9.7% of patients with RHD (194) had already undergone mitral and/or aortic valve replacement (mechanical/bioprosthetic). Overall, 26.4% (529 of 680) were on oral anticoagulants (OAC) (Table 3). Among patients at high risk for stroke and peripheral embolism (characterized by the presence of ≥1 of the following 4 risk factors: prosthetic valve; atrial fibrillation; LA/LAA clot; and past history of thromboembolism), 77.8% (529) were using OAC. All the patients who had undergone mechanical prosthetic valve implantation (149) were using OAC, while only 65.5% (321 of 489) of patients with atrial fibrillation, 74.2% (46 of 62) with LA/LAA clot, and 54.8% (57 of 104) with history of cerebrovascular accident (CVA) and/or peripheral embolism were using OAC at the time of registry (Table 3).

Determinants of cardiovascular complications and MACE

Multivariable logistic regression analysis was used to determine the independent risk determinants of individual and composite MACE (Table 4). The independent predictors of development of heart failure were advanced age (OR: 1.01; 95% CI: 1.00−1.02), severe MR (OR: 1.77; 95% CI: 1.27−2.46), severe MS (OR: 1.82; 95% CI: 1.36−2.44), severe AS (OR: 1.96; 95% CI: 1.02−3.75), severe TR (OR: 2.27; 95% CI; 1.55−3.32), presence of PAH (OR: 1.35; 95% CI: 1.02−1.77), and atrial fibrillation (OR: 1.60; 95% CI: 1.25−2.20). The variables having independent association with stroke and/or peripheral embolism were advanced age (OR: 1.02; 95% CI: 1.00−1.85), severe MS (OR: 2.13; 95% CI: 1.36−3.33), and atrial fibrillation (OR: 1.62; 95% CI: 1.03−2.54). Severe MR was associated with significantly lower risk of stroke and/or peripheral embolism (OR: 0.43; 95% CI: 0.19−0.95). The clinical variables associated with composite MACE were advanced age (OR: 1.01; 95% CI: 1.00−1.02), severe MS (OR: 1.73; 95% CI: 1.34−2.20), severe TR (OR: 2.11; 95% CI: 1.48−3.02), PAH (OR: 1.33; 95% CI: 1.04−1.69), and atrial fibrillation (OR: 1.64; 95% CI: 1.28−2.11) (Table 4).

DISCUSSION

Though India contributes to nearly 25% to 50% of the global burden of RHD [5,6], very few studies have addressed the pattern of disease involvement among patients with RHD in India [4,7]. In a study published in 2003, Chockalingam et al. [7] described their 20 years'

TABLE 1. Sociodemographic and clinical characteristics and complications in the study population

	Counts (N = 2,005)	Percentage	Male (n = 555 [27.7%])	Female (n = 1,450 [72.3%])	p Value*
Age, yrs	40.3 ± 14.3		38.8 ± 15.1	40.9 ± 13.9	0.003
Patients according to age					
<20 yrs	186	9.3	83 (14.9)	103 (7.1)	0.001
21–30 yrs	342	17.0	89 (16.1)	253 (17.5)	
31–40 yrs	498	24.8	120 (21.6)	378 (26.1)	
41–50 yrs	520	25.9	141 (25.4)	379 (26.1)	
>51 yrs	459	23.0	122 (22.0)	337 (23.2)	
Women in reproductive age	877	60.5		877 (60.5)	
Rural background	1,845	92.0	514 (92.6)	1,331 (91.7)	0.34
Education					
Less than primary	810	40.4	147 (26.5)	663 (45.7)	0.01
Middle	305	15.2	92 (16.6)	213 (14.7)	
High school	676	33.7	241 (43.4)	435 (30.0)	
Graduation and higher	214	10.7	75 (13.5)	139 (9.6)	
Medical history					
Chronic RHD	1,955	97.5	530 (95.5)	1,425 (98.3)	0.003
Subclinical RHD	42	2.1	20 (3.6)	22 (1.5)	0.003
ARF	8	0.4	5 (0.9)	3 (0.2)	0.02
Past history suggestive of ARF	501	25.1	148 (26.9)	353 (24.5)	0.24
Breathlessness NYHA functional class					
I	498	24.8	182 (32.8)	316 (21.8)	0.001
II	1,193	59.5	291 (52.4)	902 (62.2)	
III	267	13.3	71 (12.8)	196 (13.5)	
IV	47	2.4	11 (2.0)	36 (2.5)	
Stroke	80	3.9	21 (3.8)	59 (4.0)	0.78
Peripheral thromboembolism	83	4.1	17 (3.1)	66 (4.5)	0.13
Infective endocarditis	18	0.9	6 (1.1)	12 (0.83)	0.58
Major bleeding	8	0.4	1 (0.2)	7 (0.48)	0.12
Death	11	0.55	3 (0.53)	8 (0.55)	0.98
Composite MACE	470	23.4	121 (21.9)	349 (24.5)	0.35
Prosthetic valve thrombosis	31	1.5	13 (2.3)	18 (1.2)	0.07
Atrial fibrillation	489	24.4	133 (24.0)	356 (24.5)	0.82

Values are n, mean ± SD, or n (%).
ARF, acute rheumatic fever; MACE, major adverse cardiovascular event(s); NYHA, New York Heart Association; RHD, rheumatic heart disease.
*Comparing male and female subjects.

experience regarding the clinical spectrum of chronic rheumatic heart disease in the setting of a tertiary care institute in southern India. More recently, a multinational REMEDY (Global Rheumatic Heart Disease Registry) registry with 3,343 participants enrolled from 25 sites in 12 African countries, Yemen, and India discussed the characteristics, complications, and treatment gaps in patients of RHD, but the registry had a small Indian cohort [4]. Barring the REMEDY registry, we could not find any contemporary data addressing the prevalence and determinants of RHD complications and gaps in RHD treatment in an Indian cohort.

The present study highlights multiple findings. First, the patients with RHD were middle-aged (median age: 40 years), largely female (72.3%), with rural background (92%), and 40.4% of patients had not completed even primary level schooling. Second, differential patterns of valvular involvement were seen across sex and age categories and the majority of the patients had moderate-to-severe valvular dysfunction (69.3%) with high rates of composite MACE (23.4%), advanced heart failure (15.7%), pulmonary hypertension (30.5%), and atrial fibrillation (24.4%) at the time of registry. Third, stroke and peripheral embolism were reported in 3.9% and 4.1%, respectively, despite a high overall use of OAC in patients with appropriate indications. Fourth, the use of secondary antibiotic prophylaxis was suboptimal. Finally, the study has identified certain determinants of RHD complications that would be of importance in planning timely interventions to reduce these complications.

RHD is a squeal of rheumatic carditis resulting from immune-inflammatory injury to cardiac valves triggered by

TABLE 2. Echocardiographic characteristics of study population

	Counts (N = 2,005)	Percentage	Male (n = 555 [27.7%])	Female (n = 1,450 [72.3%])	p Value*
Moderate-to-severe valvular heart disease	1,390	69.3	371 (66.9)	1,019 (70.3)	0.18
Multivalvular heart disease	866	43.2	258 (46.5)	608 (41.9)	0.05
Mitral valve disease (MS + MR)	1,671	83.3	429 (77.3)	1,242 (85.7)	0.001
Aortic valve disease (AR + AS)	993	49.5	303 (54.6)	690 (47.6)	0.004
Tricuspid valve disease (TR + TS)	1,058	52.8	252 (45.4)	806 (55.6)	0.001
Isolated mitral valve disease (MS + MR)	806	40.2	171 (30.8)	635 (43.8)	0.001
Isolated aortic valve disease (AR + AS)	127	6.3	45 (8.1)	82 (5.7)	0.04
MR	1,284	64.0	333 (60.0)	951 (65.6)	0.04
Isolated MR	272	13.6	52 (9.4)	220 (15.2)	0.001
MS	1,118	55.8	268 (48.3)	850 (58.6)	0.001
Isolated MS	206	10.3	40 (7.2)	166 (11.5)	0.01
TR	1,012	50.5	241 (43.4)	771 (53.2)	0.01
TS	29	1.4	7 (1.3)	22 (1.5)	0.69
AR	936	46.7	290 (52.3)	646 (44.6)	0.001
AS	280	14.0	92 (16.8)	188 (13.0)	0.03
Pulmonary hypertension	612	30.5	165 (29.7)	447 (30.8)	0.68
LV systolic dysfunction	10	0.5	6 (1.1)	4 (0.3)	0.02
LA/LAA clot	62	3.1	11 (2.0)	51 (3.5)	0.07

Values are n or n (%).

AR, aortic regurgitation; AS, aortic stenosis; LA, left atrium; LAA, left atrial appendage; LV, left ventricle; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis.

*Comparing male and female subjects.

group A beta hemolytic streptococcal acute pharyngitis [1]. It contributes significantly to the cardiovascular-related loss of disability-adjusted life years in children [4]. In the present registry data, the median age of patients was 12 years more than reported in the REMEDY registry [4] and only 186 patients (9.3%) were < 20 years of age (Table 1). This could be an indicator of declining prevalence of RF/RHD in our part of the world [6,16], however, more studies are required before we reach to any conclusion.

Female predominance has been hypothesized in RHD due to greater exposure to group A beta hemolytic streptococcal, greater involvement of women in child-rearing, increased innate susceptibility, and reduced access to medical care [17]. The present study reinforces the female preponderance of RHD (72.3% female subjects). However, 60.5% of these female subjects were in their reproductive age group (Table 1), which might have serious implications on their reproductive health. In a study involving 50 pregnant African female subjects [18], RHD was identified as among the major nonobstetric causes of maternal death. It is therefore essential to educate the patients and their families about the importance of family planning and multidisciplinary antenatal care.

Our results demonstrate a high prevalence of MS and MR in female subjects compared with an increased prevalence of AS and AR in male subjects (Table 2). Similarly, a retrospective study published in 2009, involving 1,900 Turkish patients also documented sex differences in the nature of valvular lesions [19]. This sex predilection is a matter of clinical curiosity and requires further research to identify the responsible mechanisms. We observed that the combination of MR and MS was the most frequently observed combination of lesions (Table 2). In accordance with the finding observed in the REMEDY registry [4], our results also show that MR was the predominant lesion in the first 2 decades of life, while patients with MS outnumbered patients with MR in the third and fourth decades (Online Figure 1). This could be explained by the fact that a long latent period generally exists between the acute attack of rheumatic fever and the development of mitral stenosis [5,7]. Prevalence of AS and TR was also shown to increase with age in our study. A similar pattern of differential prevalence of valvular lesions with age has also been reported in a Nepalese cohort of 1,713 patients with RHD [17]. It is hypothesized that this is probably related to the differences in the pathological mechanisms behind the progression of various valvular lesions with age. Our study results also demonstrate that the severity of MR and AR decreases with age while that of MS, AS, and TR increases with age (Online Figure 2). However, these observations remain speculative because of the cross-sectional design of the study; therefore, longitudinal studies would be required to draw any conclusions.

We observed the majority of the patients had moderate-to-severe valvular dysfunction (69.3%) at the time of enrollment in the registry (Table 2). Probably this reflects the referral bias as our institute is the only tertiary care center in the region that has the infrastructure to diagnose and manage

TABLE 3. Distribution by sex of medical and interventional therapeutics

	Counts (N = 2,005)	Percentage	Male (n = 555 [27.7%])	Female (n = 1,450 [72.3%])	p Value*
Prosthetic valve replacement	194	9.7	75 (13.5)	118 (8.1)	0.003
BMV	210	10.5	49 (8.8)	161 (11.1)	0.28
CMV	113	5.6	17 (3.1)	96 (6.6)	0.002
Secondary prophylaxis	572	28.5	177 (32.0)	394 (27.2)	0.09
Patients on OAC	529	26.4	145 (26.1)	384 (26.5)	0.9
High-risk patients on OAC†	529/680	77.8	145/188 (77)	384/492 (78.1)	0.7
Atrial fibrillation patients on OAC	321/489	65.6	86 (64.7)	235 (66)	0.75
Patients with stroke/peripheral embolism on OAC	57/104	54.8	14 (56)	43 (54.4)	0.8
LA/LAA clot receiving OAC	46/62	74.2	9 (81.8)	37 (72.5)	0.001
Patients with mechanical prosthetic valves on OAC	149/149	100			
Diuretics	773	38.6	194 (35.2)	579 (39.9)	0.02
Beta-blockers	691	34.5	190 (34.6)	501 (34.5)	0.37
ACE-I/ARB	80	4.0	26 (4.7)	54 (3.7)	0.34
Digoxin	384	19.2	100 (18.5)	284 (19.6)	0.23

Values are n, n (%), or n/n.

ACE-I, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; BMV, balloon mitral valvotomy; CMV, closed mitral valvotomy; OAC, oral anticoagulant; other abbreviations as in Table 2.

*Comparing male and female subjects.

†High-risk patients refer to patients with increased risk of stroke and peripheral embolism and characterized by presence of ≥1 of the following risk factors: prosthetic valve; atrial fibrillation; LA/LAA clot; and past history of thromboembolism.

such patients with advanced disease. In addition, milder forms of the disease are probably under diagnosed in the peripheral centers and are therefore not referred. The higher severity of lesions also explains a high prevalence of advanced heart failure (15.7%), pulmonary hypertension (30.5%), and atrial fibrillation (24.4%) in the present study (Table 1). The similar pattern of disease severity at time of registry was observed in the REMEDY registry, which had >60% of patients presenting with moderate-to-severe valvular dysfunction, resulting in a high prevalence of patients with NYHA functional classes III and IV symptoms (13.9%–27.6%), pulmonary hypertension (19%–29.9%), and atrial fibrillation (17.9%–22.7%) [4].

TABLE 4. Independent determinants of heart failure, stroke/peripheral embolism, and composite of MACE, using multivariate logistic regression analysis

Characteristic	Heart Failure	Stroke/Peripheral Embolism	Composite MACE
Age	1.01 (1.00–1.02)	1.02 (1.00–1.85)	1.01 (1.00–1.02)
Severe MR	1.77 (1.27–2.46)	0.43 (0.19–0.95)	1.34 (0.99–1.81)
Severe MS	1.82 (1.36–2.44)	2.13 (1.36–3.33)	1.73 (1.34–2.20)
Severe AR	1.46 (0.82–2.58)	0.91 (0.27–3.04)	1.35 (0.81–2.24)
Severe AS	1.96 (1.02–3.75)	0.59 (0.13–2.52)	1.64 (0.90–2.90)
Severe TR	2.27 (1.55–3.32)	1.09 (0.74–1.83)	2.11 (1.48–3.02)
Multivalvular disease	0.95 (0.73–1.24)	1.12 (0.74–1.71)	0.95 (0.75–1.19)
Pulmonary hypertension	1.35 (1.02–1.77)	1.17 (0.56–2.10)	1.33 (1.04–1.69)
Atrial fibrillation	1.60 (1.25–2.20)	1.62 (1.03–2.54)	1.64 (1.28–2.11)

Values are OR (95% CI).

CI, confidence interval; OR, odd ratio; other abbreviations as in Tables 1 and 2.

It is well recognized that heart failure is a common cause of disability among patients with RHD [4]. The results of the present study demonstrated 75.2% of the patients had breathlessness NYHA functional class II and above at the time of enrollment (Table 1). Increasing age, severe mitral valve disease (both incompetent and stenotic), severe TR, severe AS, the presence of associated PAH, and atrial fibrillation were identified as independent determinants of symptoms of advanced heart failure (Table 4). The severity of both MS and AS increased with age while that of MR decreased (Online Figure 2). The association of increased heart failure with age can be attributed to age-related increment in the severity of stenotic lesions and atrial fibrillation.

Current therapeutic modalities to address heart failure due to stenotic/regurgitate lesions include balloon valvuloplasty and valve replacement. In the present study, 194 subjects (9.7%) had prosthetic heart valves implanted before enrollment in the registry, whereas 323 (16.1%) had undergone surgical or catheter-based valvuloplasty of the stenotic mitral valve to relieve the symptoms of heart failure (Table 3). This probably seems to have resulted in the very low prevalence (0.5%) of LV systolic dysfunction in the study population recorded at the time of registry (Table 2). Preservation of LV systolic function was observed more frequently than those reported from other developing countries [4]. This probably reflects closer follow-up, optimal medical therapy, and timely interventions in patients with RHD predisposed to develop LV systolic dysfunction.

The prevalence of cardioembolic stroke and peripheral embolization are not uncommon and are well-documented

causes of morbidity and mortality in patients of RHD [8]. Stroke and peripheral embolism were reported in the range from 3.8% to 14.5% and 0.2% to 2.2%, respectively, across different income groups of developing countries in the REMEDY registry [4]. Our observation is in tune with these numbers, 3.9% and 4.1% patients, respectively, had stroke and peripheral embolism (Table 1). Age, the presence of atrial fibrillation, and MS were identified as the independent determinants of stroke and peripheral embolism in the present study. Interestingly risk of stroke and peripheral embolization was significantly low with severe MR (OR: 0.43; 95% CI: 0.19—0.95) (Table 4). It is possible that in patients with severe MR, the large regurgitant blood volume jet prevents stasis in the LA, thus preventing the formation of LA/LAA clot [20].

OAC have proven efficacy in preventing systemic thromboembolism and stroke, thus the incidence of stroke and peripheral embolism in patients of RHD reflects the adequacy of use of evidence-based OAC in the population at risk [4]. In the present registry, 77.8% of eligible patients were receiving OAC, which was higher when compared with the REMEDY registry (70%) and a worldwide registry of nonrheumatic atrial fibrillation (58%) [4,21]. Unfortunately, the percentage of patients on OAC with the international normalized ratio in therapeutic range was not recorded in the present registry.

Secondary prevention with benzathine penicillin G is the most cost-effective measure for RHD control [2,9]. However its implementation is difficult and underuse has been documented in many prior registries [4]. In the present registry, 28.5% patients were receiving secondary prophylaxis with benzathine penicillin G injections. In patients of RHD, the secondary prophylaxis with benzathine penicillin G is generally recommended until the age of 40 years or 10 years after the last attack of RF, whichever is later [22]. In the present registry, almost 51% patients were $\leq$40 years of age. Thus, only one-half of the eligible patients were receiving secondary prophylaxis. This reflects the practice of stopping secondary prophylaxis around 10 years after the last attack of RF in our region [6,16]. The efficacy of such a practice might indirectly be supported by the fact that the number of patients with recurrence of RF was negligible (<0.4%) in the present cohort. This also implies that the guidelines cannot generalize the duration of secondary prophylaxis for all populations and should rather be formulated according to the endemicity of RF in different populations. However, our observation remains speculative in the absence of longitudinal follow-up and because the data regarding adherence to secondary prophylaxis were not systematically recorded.

Limitations of the registry

First, this is a hospital-based single-center registry study and has inherent selection and referral bias, and thus the characteristics, complications, and treatment practices may not be the representative of the patient population in the community. However, our institute is the only tertiary care center in the state providing tertiary care services to cardiac patients. Thus, it is a general practice of the peripheral health care hospitals across the state to refer all suspected cases of RF/RHD for echocardiographic confirmations to our institute, thereby providing a fair representation of disease characteristics of the patients in the state. Second, another important limitation of the study was its cross-sectional design, recording only the baseline characteristics of study population. Longitudinal follow-up data were not analyzed. This attenuates the reliability of observed associations between the baseline characteristics and the outcome complications. Third, transesophageal echocardiography was not routinely used to detect LAA clot, which probably resulted in underestimation of its true incidence. Fourth, the adherence to the secondary prophylaxis was not documented and recorded. Lastly, the adequacy of OAC therapy was not systematically recorded using international normalized ratio monitoring.

Future scope of research

There is a need of focused research exploring the understanding of the mechanistic pathways involved in progressive fibrosis leading to commissural fusion that will provide potential targets for the medical management of patients with stenotic RHD. It is high time to conduct population-based registry studies similar to ours in India and other developing countries with a joint aim to formulate informed policies and programs for prevention and control of RF/RHD.

CONCLUSIONS

RHD is a disease of young and middle-aged population affecting predominantly female subjects and is associated with substantial morbidity due to heart failure, stroke, and peripheral thromboembolism. Early detection is important to identify high-risk patients for evidence-based management and to ensure control of heart failure and prevention of stroke. There is a treatment gap in the use of OAC in high-risk patients for prevention of cardioembolic complications, which needs to be addressed.

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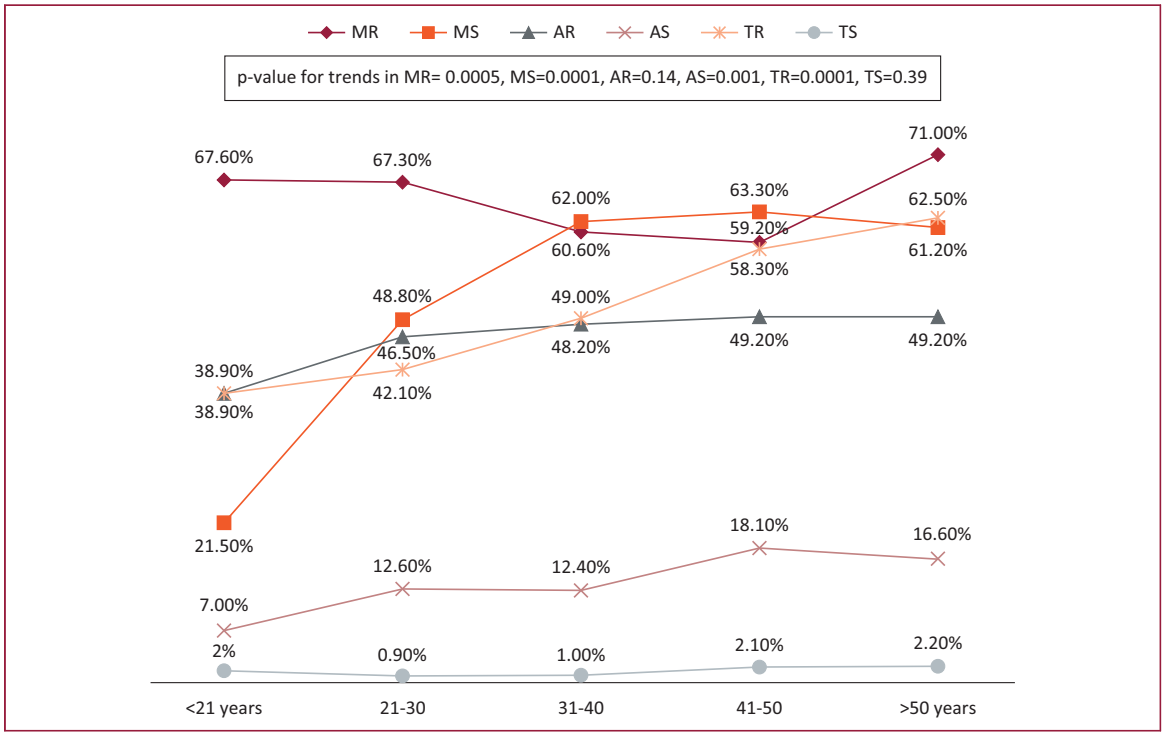
APPENDIX



ONLINE FIGURE 1. Age-wise distribution of valvular involvement. AR, aortic regurgitation; AS, aortic stenosis; MR, mitral regurgitation; MS, mitral stenosis; TR, tricuspid regurgitation; TS, tricuspid stenosis.

ONLINE FIGURE 2. Distribution of various valvular lesions according to age and severity of lesions. **(A)** Mitral regurgitation (MR), **(B)** mitral stenosis (MS), **(C)** aortic regurgitation (AR), **(D)** aortic stenosis (AS), **(E)** tricuspid regurgitation (TR).