



Original Article

Gender differences in the epidemiology of Rheumatic Fever/ Rheumatic heart disease (RF/RHD) patient population of hill state of northern India; 9 years prospective hospital based, HP-RHD registry



Prakash Chand Negi*, Arvind Kandoria, Sanjeev Asotra, Neeraj kumar Ganju,
Rajeev Merwaha, Rajesh Sharma, Kunal Mahajan, Shivani Rao

Indira Gandhi Medical College, Shimla, HP, India

ARTICLE INFO

Article history:

Received 28 February 2020

Accepted 10 September 2020

Available online 18 September 2020

Keywords:

Gender

Epidemiology

Rheumatic fever

Rheumatic heart diseases

Prevalence

Adverse cardiovascular events

ABSTRACT

Objectives: We report the gender-based differences in the prevalence, severity, pattern of valvular involvement, and complications in patients with Rheumatic Fever/Rheumatic heart disease (RF/RHD).

Methods: The 2475 consecutive patients with RF/RHD diagnosed using clinical and echocardiographic criteria were registered prospectively from January 2011 till December 2019. The association of gender with the pattern of valvular involvement, nature, and severity of valvular dysfunction and cardiovascular complications was analyzed using a logistic regression model, and odds ratios with 95% CI were estimated.

Results: The mitral and tricuspid valve involvement was significantly lower in the male gender, odds ratio with 95% CI of 0.55 (0.44–0.61), and 0.69 (0.58–0.83) respectively, while the aortic valve was affected more frequently than females, odds ratio 1.36 (1.14–1.62). The severity of valvular disease had no significant association with gender, 0.99 (0.82–1.20). The association between gender and cardiovascular complications, heart failure, stroke, and atrial fibrillations were not statistically significant. The prevalence of RF/RHD was more than two-fold higher in female gender than male (71.4% vs. 29.6%, $p < 0.0001$).

Conclusions: RF/RHD is more prevalent in females. Gender has a significant association with the pattern of valvular involvement. The severity of valvular dysfunction and cardiovascular complications had no significant association with gender.

© 2020 Cardiological Society of India. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Rheumatic fever (RF)/Rheumatic heart disease (RHD) is a leading cardiac cause of morbidity and mortality in children, adolescents, and young adults in low and middle-income countries.^{1,2} Gender is an important biological determinant of susceptibility to diseases and their outcomes. The sex hormones are known to regulate both adaptive and innate immune responses. It is a well-established fact that autoimmune diseases have gender predilections.^{3–5} RHD is an autoimmune-mediated valvular injury triggered by group A beta-hemolytic streptococcus pharyngitis. Therefore, the autoimmune response may differ between genders, leading to differences in valvular damage and severity. The epidemiological studies of RF and

RHD report no gender predilection for the incidence of RF; however, RHD is more prevalent in females.^{5,6}

Thus gender-based differences in the severity and pattern of valvular involvement and associated complications need to be explored. There is limited data available in the literature on gender-based differences in the epidemiological characteristics of RF/RHD and the prevalence of associated cardiovascular complications.⁶ We analyzed data of the Himachal Pradesh RHD (HP-RHD) registry to examine the gender differences in the clinical characteristics, severity, and pattern of valvular involvement, and treatment practices among patients of RF/RHD in the hill state of northern India.

2. Methodology

2.1. Study design and area and setup

HP-RHD registry is a tertiary care hospital-based prospective registry of the patients with RF/RHD, who are the native residents of Himachal Pradesh. The state has a population of about 6.8 million

* Corresponding author. Indira Gandhi Medical College, Department of Cardiology, Shimla, 171001, HP, India.

E-mail address: negiprakash59@gmail.com (P.C. Negi).

as per the 2011 census and has twelve districts with one secondary level hospital in each district manned by physicians in most districts and two teaching hospitals with cardiologists. The registry center hospital is the only teaching hospital providing catheter and surgical based treatment of RHD in the state. Thus, patients with advanced RHD are referred to the registry hospital for tertiary care from all over the state. Some of the patients with mild to moderate diseases not requiring intervention are managed at district level hospitals and the other teaching hospital of the state. The registry of patients started in January 2011, and the present report is based on the data recorded until December 2019.

All consecutive patients visiting outdoor services and/or admitted in the registry center were screened clinically and, if suspected to have RF/RHD, were subjected to echocardiography and other relevant laboratory investigations. Patients were diagnosed as RF-based on world health organization criteria and RHD with the World Heart Federation's echocardiographic criteria.^{7,8} The severity of valvular dysfunction was evaluated using the American society of echocardiography and the European association of echocardiography guidelines.^{9,10} The patients with prosthetic valve replacement and/or those with a history of balloon valvuloplasty for stenotic valves were excluded from assessing the severity of valvular dysfunction. All patients of RF/RHD were registered after obtaining informed consent in the HP-RHD register. The institutional ethical committee of the registry center approved the study protocol.

2.2. Data collection

The details of the methodology and data collection as a part of the HP-RHD registry have been published previously.^{11,12} In brief, the data of socio-demographics, clinical characteristics, treatment practices were recorded systematically. The history of complications in the past and/or at registry was recorded using predefined criteria. The New York Heart Association (NYHA) functional class III/IV was used as the criteria for advanced heart failure symptoms. The patient records and history were carefully screened for systemic thromboembolism or stroke, or infective endocarditis in the past. The events that occurred at the time of registry were also recorded using predefined criteria.¹³ The detailed echocardiography study was done at the registry to record valvular dysfunction's nature and severity using predefined criteria.^{9,10} The left ventricular ejection fraction (LVEF) was estimated using the biplane Simpson's method. The LVEF of $\leq 54\%$ were diagnosed as LV systolic dysfunction. The 12-lead surface electrocardiogram was recorded at the registry to document the presence of atrial fibrillation.

The patients were labeled as a high-risk group for systemic thromboembolism if had any one of the following;

- Patients with mechanical prosthetic valves
- Patients with atrial fibrillation
- Patients with a history of systemic thromboembolism
- Patients with Left atrial (LA) and or left atrial appendage (LAA) clot.

Patients were followed annually to record adverse cardiovascular outcomes and for monitoring of echocardiographic changes in the severity of valvular dysfunction, LV systolic function, LA/LAA clot, and assessment of tricuspid regurgitation (TR) jet velocity derived pulmonary artery pressure (PAP). The present report aimed to identify the gender-based differences in clinical characteristics, nature, the severity of valvular dysfunction, the presence of LV systolic dysfunction, complications, and treatment practices at the registry time.

2.3. Data Analysis

The data of 2475 patients registered till Dec 2019 were analyzed to compare the gender-based differences in severity of valvular dysfunction, the pattern of valvular involvement, and associated complications. The categorical variables were reported as frequency and percentages and mean \pm SD for continuous variables with a normal distribution. The statistical significance of gender-based differences in the distribution of categorical variables was tested using the chi square test and unpaired *t*-test for continuous variables with a normal distribution. The significance of the association of gender with the nature and severity of valvular dysfunction, presence of pulmonary artery hypertension (PAH), heart failure, atrial fibrillation, and systemic thromboembolism was assessed using logistic regression modeling. The strength of the association between gender with the severity of valvular dysfunction and adverse events was expressed as an odds ratio of 95% CI. A two-sided *p*-value of <0.05 was taken as statistical significance. The statistical analysis was done using STATA version 13 statistical software.

3. Results

The details of the differences in the distribution of socio-demographic, clinical characteristics, treatment practices, nature, and severity of the valvular dysfunctions between genders are described in Table 1. The mean age of the female RHD population was significantly higher (41.3 ± 14.3 vs. 38.3 ± 14.1 , $p < 0.001$) and the level of education (below primary education) (47.1% vs. 26.1%, $p < 0.0001$) was significantly lower compared to the male counterpart. The urban and rural distribution of the patient population was not significantly different. The distribution of the nature of occupation was significantly different between the genders. The males were more frequently engaged in the farming and employment sector while females were in housekeeping. Although the prevalence of left ventricular (LV) systolic dysfunction was significantly high in males, there was no significant difference in the prevalence of cardiovascular complications; heart failure, PAH, atrial fibrillation, and systemic thromboembolism. The mitral and tricuspid valve involvement was more frequently observed in females, while aortic valve involvement was more frequent in the males, and the difference was statistically significant. Multi valvular involvement was equally prevalent in both the genders. The severe valvular dysfunction affecting mitral and tricuspid valve was equally prevalent in both the genders; however, severe aortic regurgitation (AR) was significantly more frequent in males.

3.1. Distribution of valvular dysfunctions across the age groups

The detailed graphical depiction of trends of distribution of mitral and aortic valvular dysfunction across the age groups in male and female gender is reported in Figs. 1 and 2, respectively. The prevalence of mitral regurgitation (MR) declined significantly with age in females, while the mitral stenosis (MS) increased in both the genders. The trends of increase in the prevalence of aortic stenosis (AS) were statistically significant in the male gender, while no significant change in the prevalence of aortic regurgitation was observed in either gender.

3.2. Treatment practices

(Table 1) The use of oral anticoagulants among high-risk populations was low in both the genders, and the difference was not statistically significant. The history of balloon mitral valvuloplasty procedures done in the past was significantly higher among

Table 1
Gender based differences in the clinical characteristics of the study population.

Characteristics	Overall study population = 2475 Number (%)	Male 708 (28.6%) Number (%)	Female 1767 (71.4%) Number (%)	p value
Age groups				
<10 years	14 (0.57)	8 (1.13)	6 (0.34)	0.0001
11–20 years	197 (7.9)	86 (12.1)	111 (6.3)	(trends)
21–29 years	363 (14.7)	94 (13.3)	269 (15.2)	
30–39 years	582 (23.5)	165 (23.3)	417 (23.6)	
40–49 years	638 (25.8)	190 (26.8)	448 (25.3)	
50–59 years	492 (19.9)	122 (17.2)	370 (20.9)	
60–69 years	140 (5.7)	33 (4.7)	107 (6.1)	
>70 years	49 (2.0)	10 (1.4)	39 (2.2)	
Age, in years (mean ± SD)	40.6 ± 14.3	38.9 ± 14.3	41.3 ± 14.1	0.0001
Education status below Primary	1018 (41.1)	185 (26.1)	833 (47.1)	0.0001
Rural background	2346 (94.8)	677 (95.6)	1669 (94.5)	0.23
Occupation status				
Unemployed	95 (3.8)	24 (3.4)	79 (4.2)	0.001
Students	186 (7.5)	85 (12.0)	101 (5.7)	(trends)
Retired	16 (0.65)	10 (1.4)	6 (0.34)	
Farming	966 (36.0)	417 (58.9)	549 (31.1)	
Employed	275 (11.1)	164 (23.2)	111 (6.3)	
House keeping	937 (37.7)	8 (1.1)	929 (52.6)	
Clinical characteristics				
	Male	Female	Odds ratio (95% C.I.)	
Acute rheumatic Fever	6 (0.85)	7 (0.40)	2.1 (0.72–6.4)	0.31
NYHA class III/IV	106 (14.9)	272 (15.4)	0.96 (0.75–1.23)	0.76
Atrial fibrillation	184 (26.1)	500 (28.3)	0.88 (0.73–1.08)	0.52
History of stroke and/or peripheral embolism	33 (4.6)	105 (5.9)	0.75 (0.50–1.13)	0.20
History of Infective endocarditis	2 (0.28)	1 (0.06)	5.0 (0.91–27.4)	0.06
High-risk for thromboembolism	216 (30.5)	655 (37.1)	0.86 (0.72–1.04)	0.12
High-risk population on oral anticoagulation	127 (58.5)	383 (58.7)	0.92 (0.75–1.13)	0.81
LV systolic dysfunction (LVEF ≤54%) (yes) %	82 (12.5)	140 (8.7)	1.5 (1.12–2.0)	0.003
PAH (TR velocity >3.0 m/s)	203 (62.5)	557 (58.6)	1.15 (0.89–1.49)	0.27
Valvular involvement				
Mitral valve disease	446 (76.1)	1234 (85.5)	0.55 (0.44–0.61)	0.0001
Aortic valve disease	331 (56.4)	685 (47.5)	1.36 (1.14–1.62)	0.001
Tricuspid valve disease	263 (44.8)	792 (54.9)	0.69 (0.58–0.83)	0.001
Multi valvular disease	376 (64.4)	986 (68.3)	0.84 (0.72–1.01)	0.06
Severity of valvular dysfunction				
Severe valvular heart disease	261 (44.5)	643 (44.6)	0.99 (0.82–1.20)	0.96
Severe mitral valve disease	201 (34.2)	526 (36.4)	0.90 (0.74–1.11)	0.13
Severe aortic valve disease	72 (12.3)	89 (6.2)	2.12 (1.53–2.94)	0.001
Severe tricuspid valve disease	39 (6.6)	133 (9.7)	0.70 (0.48–1.01)	0.59
Type of valvular dysfunction				
Mitral stenosis	278 (47.4)	888 (56.0)	0.70 (0.58–0.85)	0.001
Mitral regurgitation	355 (60.5)	988 (68.5)	0.70 (0.57–0.86)	0.001
Aortic regurgitation	321 (54.7)	661 (45.8)	1.42 (1.17–1.73)	0.001
Aortic stenosis	100 (17.0)	193 (13.4)	1.32 (1.02–1.73)	0.03
Tricuspid stenosis	4 (1.4)	21 (2.7)	0.49 (0.16–1.46)	0.19
Tricuspid regurgitation	262 (44.6)	789 (54.7)	0.66 (0.55–0.81)	0.0001
Treatment				
History of prosthetic valve implantation	66 (9.3)	126 (7.1)	1.33 (0.98–1.82)	0.06
History of balloon valvuloplasty	56 (7.9)	201 (11.4)	0.66 (0.49–0.91)	0.01
Proportion of high-risk patients on oral anticoagulants	169 (68.7)	611 (66.6)	1.14 (0.83–1.56)	0.40
Secondary prophylaxis in eligible patients (age <35 years)	120 (42.8)	315 (49.5)	0.76 (0.57–1.01)	0.06
Digoxin	118 (16.7)	324 (18.3)	0.89 (0.70–1.12)	0.32
Beta blockers	362 (51.1)	999 (56.5)	0.80 (0.67–0.95)	0.01
Diuretics	326 (46.0)	961 (54.4)	0.71 (0.60–0.85)	0.001
MRA	406 (57.3)	1052 (59.5)	0.91 (0.76–1.09)	0.31
Ace/ARBs	228 (32.2)	484 (27.4)	1.25 (1.04–1.51)	0.018

Abbreviations: Ace inhibitor/ARB; Angiotensin converting enzyme inhibitors/Angiotensin receptor blockers, LV; left ventricle, LVEF; left ventricular ejection fraction, MRA; Mineralocorticoid receptor antagonist, NYHA class; New York Heart association, PAH; pulmonary artery hypertension, TR; tricuspid regurgitation.

females. The use of beta-blockers and diuretics was significantly higher in females than the use of renin angiotensin system (RAS) inhibitors, which was more common in males.

4. Discussion

The significant gender-based differences were observed in the demographics, prevalence, nature of valvular dysfunction, and the valves affected. However, the severity of valvular dysfunction and

complication rates were not significantly different. The female preponderance of RHD is also well documented in other registries and survey studies.^{14–18} The present registry data did not show any gender predilection in the prevalence of RHD up to the age of 20 years. However, after 20 years of age, the prevalence of RHD increased by about two-fold in female genders. The age-related increase in the female gender prevalence has also been reported consistently in other registries.^{6,15,19,20} The higher proportion of the RHD population from the female gender in the age group above 20

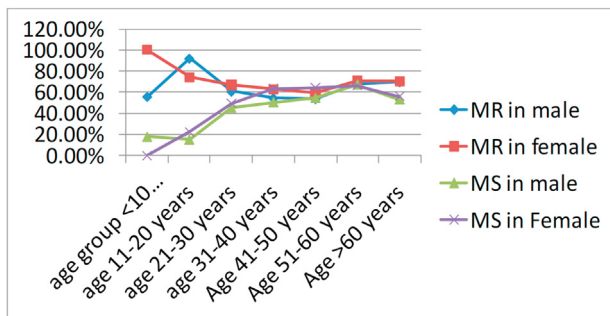


Fig. 1. Trends of distribution of Mitral regurgitation (MR), mitral stenosis (MS), across the age groups in male and female genders.

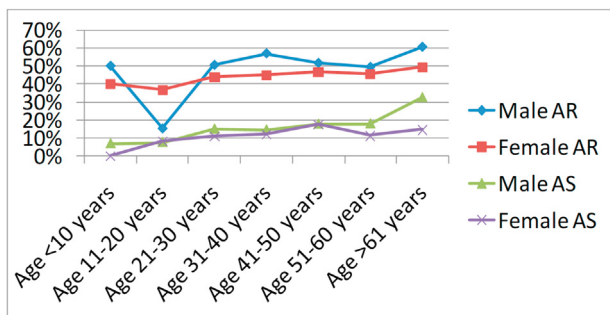


Fig. 2. Trends of distribution of aortic regurgitation (AR), aortic stenosis (AS), across the age groups in male and female genders.

years may be related to increased detection rate among females during the reproductive age group as part of antenatal care. However, the community-based survey studies in the adult population confirm that the higher prevalence of RHD in females may not be the result of selection bias in registries.^{15–18}

The incidence of RF is not significantly different between the genders; however, RHD’s progression is significantly higher in females.⁵ The echo-based screening for RF/RHD in school children revealed a higher prevalence of RHD in female children.^{21,22} However, the survey studies of RF/RHD in school children screened clinically, followed by echocardiography in suspected cases, revealed no significant gender difference in the prevalence of RF/RHD.¹³ Thus, it suggests that RHD following RF is more common in females, which is initially subclinical and later progresses to clinically evident RHD.

The gender-based differences in the mitral valve and aortic valve involvement have also been reported in other registries.^{6,23,24} In the present registry, both stenotic and incompetent mitral valve dysfunction was significantly higher in females. The severity of the mitral valvular dysfunction was not gender-dependent, although severe aortic valve dysfunction was more prevalent in males. The lack of association of severity of valvular dysfunction with gender was also reported in the RHD population of Northern territory of Australia.⁵ A hospital-based data of valvular heart disease of rheumatic etiology reported a significantly higher prevalence of mitral stenosis of varying severity in females than male gender.²⁴

The age-related changes in the prevalence of stenotic and incompetent mitral and aortic valves have been reported by other investigators.^{6,19} However, trends of change in the prevalence of stenotic and incompetent valvular dysfunction with increasing age in males and females have not been reported earlier.

Rheumatic heart disease following rheumatic carditis begins with incompetent valvular dysfunction. In some patients, the

incompetent valves progress to develop stenosis, and severity increases with age. There are significant gender-based differences in the evolution of stenosis and incompetence of mitral and aortic valves with age. The present registry data revealed that the stenotic mitral and aortic valvular dysfunction increased with age in both the genders; however, MR declined with age, while the prevalence of AR did not change significantly in either of the genders.

Although the gender formed the vital determinant of valvular predilection, there were no significant differences in the complications of RHD, symptoms of advanced heart failure, PAH, atrial fibrillation, stroke between the genders. The significant gender-based differences in the pharmacological treatment of heart failure were observed in the present registry. The use of beta-blockers, diuretics, and the catheter-based intervention for mitral stenosis was significantly more frequent in the female gender, while RAS inhibitors’ use was significantly higher in males. The differences in the use of pharmacological and catheter-based intervention between the genders result from differences in the valves affected and the nature of valvular dysfunction. There was no gender-based difference in the use of oral anticoagulants among patients at high risk of stroke and/or systemic thromboembolism, and similarly, no significant difference was observed in the use of secondary prophylaxis for RF. Before the present study, there were hardly any reported data addressing the gender-based differences in the treatment of patients with RHD.

4.1. Limitations

The observations reported in this study were based on the single-center tertiary care hospital registry data. Thus, an inherent element of selection bias is likely to be present. Asymptomatic RHD patients and patients with mild symptoms were likely to be underrepresented in the present study. Thus, the gender-based differences in the prevalence and severity of valvular heart disease and clinical complications should be viewed in this context. Furthermore, the present registry center is a tertiary care center in the government set up, and the services are accessible to all patients irrespective of their socioeconomic status and gender. Thus, the gender-based differences observed are less likely to be influenced by the study design.

4.2. Future scope of Research

Future appropriately designed studies are required to evaluate the role of genetic factors in gender-based differences in RHD prevalence, the pattern of valvular involvement, and incident adverse outcomes. Such studies are needed to undertake evidence-based quality initiatives to improve outcomes.

4.3. Conclusions

A definite gender predilection towards females among patients with RHD was noted in the present study. The mitral and tricuspid valve involvement was more frequently observed in females, while aortic valve involvement was more common in males. The stenotic mitral and aortic valve dysfunction increased, while mitral incompetence declined significantly with age among both the genders. Gender was not a significant determinant of the severity of valvular dysfunction and cardiovascular complications.

Funding source

Nil.

Declaration of competing interest

All authors have none to declare.

Acknowledgments

We acknowledge the contribution of Mr. Chaman Thakur, a data entry operator working for the global-CHF registry, to record and upload the data of patients with RF/RHD with utmost dedication and sincerity without any remuneration.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ihj.2020.09.011>.

References

- Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010 [published correction appears in *Lancet*. 2013 Feb 23;381(9867):628. AlMazroa, Mohammad A [added]; Memish, Ziad A [added]] *Lancet*. 2012;380(9859):2095–2128. [https://doi.org/10.1016/S0140-6736\(12\)61728-0](https://doi.org/10.1016/S0140-6736(12)61728-0).
- Carapetis JR, Steer AC, Mulholland EK, Weber M. The global burden of group A streptococcal diseases. *Lancet Infect Dis*. 2005;5(11):685–694. [https://doi.org/10.1016/S1473-3099\(05\)70267-X](https://doi.org/10.1016/S1473-3099(05)70267-X).
- Eaton WW, Rose NR, Kalaydjian A, Pedersen MG, Mortensen PB. Epidemiology of autoimmune diseases in Denmark. *J Autoimmun*. 2007;29(1):1–9. <https://doi.org/10.1016/j.jaut.2007.05.002>.
- Biver E, Beague V, Verloop D, et al. Low and stable prevalence of rheumatoid arthritis in northern France. *Joint Bone Spine*. 2009;76(5):497–500. <https://doi.org/10.1016/j.jbspin.2009.03.013>.
- Lawrence JG, Carapetis JR, Griffiths K, et al. Acute rheumatic fever and rheumatic heart disease: incidence and progression in the Northern Territory of Australia, 1997 to 2010. *Circulation*. 2013;128(5):492–501. <https://doi.org/10.1161/CIRCULATIONAHA.113.001477>.
- Shrestha NR, Pilgrim T, Karki P, et al. Rheumatic heart disease revisited: patterns of valvular involvement from a consecutive cohort in eastern Nepal. *J Cardiovasc Med*. 2012;13(11):755–759. <https://doi.org/10.2459/JCM.0b013e32835854b6>.
- Oct 29–November 1, 2001. WHO Technical Report Series WHO Expert Consultation Geneva. vol. 923. Geneva: WHO; 2004.
- Reményi B, Wilson N, Steer A, et al. World Heart Federation criteria for echocardiographic diagnosis of rheumatic heart disease—an evidence-based guideline. *Nat Rev Cardiol*. 2012;9(5):297–309. <https://doi.org/10.1038/nrcardio.2012.7>. Published 2012 Feb 28.
- Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr*. 2003;16(7):777–802. [https://doi.org/10.1016/S0894-7317\(03\)00335-3](https://doi.org/10.1016/S0894-7317(03)00335-3).
- Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice [published correction appears in *Eur J Echocardiogr*. 2009 May;10(3):479]. *Eur J Echocardiogr*. 2009;10(1):1–25. <https://doi.org/10.1093/ejechocard/jen303>.
- Negi PC, Sondhi S, Rana V, et al. 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. *Indian Heart J*. 2018;70(Suppl 3):S68–S73. Suppl 3.
- Negi PC, Mahajan K, Rana V, et al. Clinical characteristics, complications, and treatment practices in patients with RHD: 6-year results from HP-RHD registry. *Glob Heart*. 2018;13(4):267–274. <https://doi.org/10.1016/j.ghart.2018.06.001.e2>.
- Li JS, Sexton DJ, Mick N, et al. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis*. 2000;30(4):633–638. <https://doi.org/10.1086/313753>.
- He VY, Condon JR, Ralph AP, et al. Long-term outcomes from acute rheumatic fever and rheumatic heart disease: a data-linkage and survival analysis approach. *Circulation*. 2016;134(3):222–232. <https://doi.org/10.1161/CIRCULATIONAHA.115.020966>.
- Berry JN. Prevalence survey for chronic rheumatic heart disease and rheumatic fever in northern India. *Br Heart J*. 1972;34(2):143–149. <https://doi.org/10.1136/hrt.34.2.143>.
- Marijon E, Ou P, Celermajer DS, et al. Prevalence of rheumatic heart disease detected by echocardiographic screening. *N Engl J Med*. 2007;357(5):470–476. <https://doi.org/10.1056/NEJMoa065085>.
- Paar JA, Berrios NM, Rose JD, et al. Prevalence of rheumatic heart disease in children and young adults in Nicaragua. *Am J Cardiol*. 2010;105(12):1809–1814. <https://doi.org/10.1016/j.amjcard.2010.01.364>.
- Reeves BM, Kado J, Brook M. High prevalence of rheumatic heart disease in Fiji detected by echocardiography screening. *J Paediatr Child Health*. 2011;47(7):473–478. <https://doi.org/10.1111/j.1440-1754.2010.01997.x>.
- Zühlke L, Engel ME, Karthikeyan G, et al. Characteristics, complications, and gaps in evidence-based interventions in rheumatic heart disease: the Global Rheumatic Heart Disease Registry (the REMEDY study). *Eur Heart J*. 2015;36(18). <https://doi.org/10.1093/eurheartj/ehu449>, 1115–22a.
- Sliwa K, Carrington M, Mayosi BM, Zigiriadis E, Mvungi R, Stewart S. Incidence and characteristics of newly diagnosed rheumatic heart disease in urban African adults: insights from the heart of Soweto study. *Eur Heart J*. 2010;31(6):719–727. <https://doi.org/10.1093/eurheartj/ehp530>.
- Nascimento BR, Beaton AZ, Nunes MC, et al. Echocardiographic prevalence of rheumatic heart disease in Brazilian schoolchildren: data from the PROVAR study. *Int J Cardiol*. 2016;219:439–445. <https://doi.org/10.1016/j.ijcard.2016.06.088>.
- Saxena A, Desai A, Narvencar K, et al. Echocardiographic prevalence of rheumatic heart disease in Indian school children using World Heart Federation criteria – a multi site extension of RHEUMATIC study (the e-RHEUMATIC study). *Int J Cardiol*. 2017;249:438–442.
- Grover A, Dhawan A, Iyengar SD, et al. Epidemiology of rheumatic fever and rheumatic heart disease in a rural community in northern India. *Bull World Health Organ*. 1993;71(1):59–66.
- Manjunath CN, Srinivas P, Ravindranath KS, et al. Incidence and patterns of valvular heart disease in a tertiary care high-volume cardiac center: a single center experience. *Indian Heart J*. 2014;66(3):320–326. <https://doi.org/10.1016/j.ihj.2014.03.010>.