



Rheumatic heart disease revisited: patterns of valvular involvement from a consecutive cohort in eastern Nepal

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Background The burden of rheumatic heart disease (RHD) continues to be a major contributor to morbidity and premature death in poor and developing countries. We investigated patterns of valvular involvement in patients with RHD as observed in a large tertiary care hospital in eastern Nepal.

Methods We retrospectively reviewed transthoracic echocardiography reports from patients diagnosed with RHD between June 1999 and February 2011.

Results Among 10 860 transthoracic echocardiography studies, 1055 female and 658 male patients were diagnosed with RHD, 25.7% of the patients being below 20 years of age. Mitral regurgitation was the most common valvular lesion across all age groups irrespective of sex ($n = 1321$, 77.1%). Female patients were significantly older as compared to male patients at the time of presentation (32.8 ± 15.2 versus 28.5 ± 15.4 years; $P < 0.001$) and more commonly presented with mitral stenosis as compared to male patients (62.8 versus 51.5% ; $P < 0.001$), with a peak between the age of 30 and 49 years. Conversely, aortic regurgitation was

more common in men as compared to women (55.6 versus 48.9%; $P = 0.007$). Involvement of both the mitral and the aortic valve was observed in 49.8% of the patients and was more common in men as compared to women (52.7 versus 47.8%; $P = 0.047$).

Conclusion In this consecutive cohort of patients with RHD in Nepal differential patterns of valvular involvement are observed across sex and age categories.

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Background

Although there has been a decline in the incidence of rheumatic heart disease (RHD) in industrialized nations, the burden of RHD in poor and developing countries has remained a major contributor to the morbidity and premature death in the working age population. RHD is estimated to affect at least 15.6 million people worldwide and causes 233 000 deaths each year.¹

Acute rheumatic fever (ARF) is precipitated by pharyngitis with group A β -haemolytic streptococci (GABHS), and results from an autoimmune response due to molecular mimicry between the M-protein on the GABHS cell membrane and cardiac myosin. Recurrent or sustained inflammation entertained by cross-reactivity may eventually lead to RHD.² Major determinants of ARF and RHD comprise environmental factors such as poverty, overcrowding and malnutrition, a potential genetic susceptibility related to human leukocyte antigen (HLA) alleles, and possibly particularly virulent strains of GABHS.^{3,4}

Several observational studies have reported the prevalence of RHD among various populations in different parts of the world.^{3,5–8} A particularly high prevalence of

ARF and RHD has been reported in South-East Asia, the Western Pacific and Africa.² Moreover, systemic screening with echocardiography revealed a 10 times higher prevalence of RHD among schoolchildren in Cambodia and Mozambique as compared to clinical screening, amounting to rates of 21.5 cases to 30.4 cases per 1000 persons.⁹ Primary prevention with timely antibiotic treatment of GABHS pharyngitis and secondary antibiotic prophylaxis in patients who have undergone ARF are often inappropriate in developing countries due to ineffective health resources and lack of awareness of the disease.

The objective of this study was to investigate patterns of left-sided valvular involvement as assessed by echocardiography in a large consecutive cohort from a tertiary care referral hospital in eastern Nepal.

Methods

B.P. Koirala Institute of Health Sciences (BPKIHS) is a university hospital in Dharan, eastern Nepal, established in 1993, with undergraduate and postgraduate medical and paramedical programmes. The hospital has 750 beds and hosts over 30 000 patients per year. About

180 000 patients consult the outpatient department yearly. The town of Dharan has a population of 118 000, and the hospital is the only referral centre outside Kathmandu for the inhabitants in eastern Nepal, and also serves parts of the neighbouring states of West Bengal and Bihar in India.

Patient population and data collection

We retrospectively reviewed all consecutive transthoracic echocardiography (TTE) reports from patients diagnosed with RHD collected from the echocardiography laboratory from June 1999 to February 2011. The data collected included age, sex, clinical diagnosis and findings on TTE. As we collected the data retrospectively, consent was waived by the Ethics Committee of our institute.

Echocardiographic criteria

Echocardiographic studies were performed with Hewlett Packard Sonos 1500 using a 5 MHz transducer. All patients underwent a standard echocardiographic examination, including M-mode, two-dimensional and Doppler echocardiography. Since no central external memory system for the storage of echocardiographic clips existed, pertinent findings were temporarily stored on the echocardiography machine and printed for inclusion into the paper-based charts.

Pathological valvular lesions were systematically recorded, whereas trivial mitral regurgitation or tricuspid regurgitation was not reported. Since we were interested in patterns of valvular involvement rather than severity of the disease, we refrained from grading of valvular lesions for the purpose of this analysis. Mitral stenosis was diagnosed on the presence of valve thickening, diastolic doming, restriction of leaflet motions, and was quantified by pressure half-time and planimetry. Presence of calcification, fibrosis, and limited leaflet excursion and fusion of commissures and chordate tendinae were also identified. Mitral regurgitation was diagnosed in the presence of thickened valves, dilated mitral valve annuli, and left atrial and left ventricular dilatation, and lack of coaptation of the mitral valve leaflets in systole. Doppler echocardiographic analyses identified the presence and severity of regurgitation of the aortic, mitral and tricuspid valves. Thickened and calcified aortic valve leaflets with reduced leaflet motion (aortic cusp separation less than 9 mm) suggested aortic stenosis along with a peak gradient of more than 15 mmHg in continuous-wave Doppler. Aortic regurgitation was diagnosed when echocardiography with Doppler interrogation of the aortic valve showed the spatial extent of the colour Doppler aliasing in the outflow tract and was used as a rough guide of the severity of aortic insufficiency.

Echocardiographic findings associated with pulmonary hypertension included a dilated pulmonary artery and dilation and hypertrophy of the right ventricle (RV), diastolic flattening of the interventricular septum, and Doppler evidence of pulmonary hypertension.

Statistical analysis

SPSS Statistics version 17.0 (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. Continuous variables are expressed as mean \pm SD, whereas categorical data are presented as frequency (percentages). Two-sided *t*-tests were used to compare continuous variables; categorical variables were compared by using the chi-square test. A *P* value less than 0.05 was considered statistically significant.

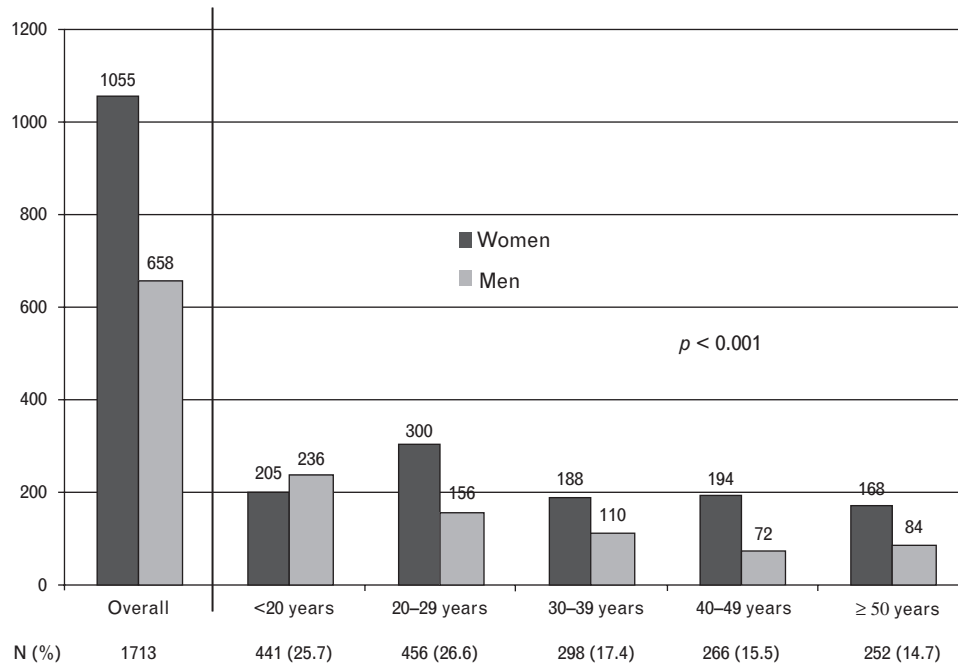
Results

Among 10 860 transthoracic echocardiography studies performed between June 1999 and February 2011, a diagnosis of RHD was made in 1713 patients (15.8%), of which 1055 women and 658 men were diagnosed to have RHD (sex ratio 1.6:1). Patients presented for TTE at an average age of 31.1 ± 15.4 years, women being significantly older than men at the time of presentation (32.8 ± 15.2 versus 28.5 ± 15.4 years; $P < 0.001$). One in four patients presenting with RHD was younger than 20 years of age (Fig. 1). Frequencies of isolated and combined left-sided valvular involvement stratified by sex are summarized in Table 1. Mitral stenosis was more common in women as compared to men (62.8 versus 51.5%; $P < 0.001$), whereas aortic regurgitation was more common in men as compared to women (55.6 versus 48.9%; $P = 0.007$). Patterns of valvular involvement are illustrated in Fig. 2. Involvement of both the mitral and the aortic valve was observed in 49.8% of the patients and was more common in men as compared to women (52.7 versus 47.8%; $P = 0.047$); there was no significant difference with regard to age at presentation between patients with single-valve involvement versus patients with combined valvular involvement. A combination of mitral regurgitation with mitral stenosis (19.3%) or with aortic regurgitation (17.9%) was the most common finding (Fig. 3). Mitral regurgitation was the most common valvular pathology across all age groups ($n = 1321$, 77.1%), followed by mitral stenosis, with the exception of patients below 20 years of age, who presented more frequently with aortic regurgitation than with mitral stenosis. Aortic stenosis was the least common valvular lesion found in this cohort, but was increasingly observed with advancing age. The prevalence of pulmonary hypertension amounted to 34.9% in our cohort and increased with advancing age, from 27.0% in patients below 20 years of age to 43.7% in patients aged at least 50 years. Echocardiographic evidence of infective endocarditis was documented in 212 (12.4%) patients.

Discussion

The major findings of our retrospective analysis can be summarized as follows: the prevalence of RHD among patients referred for transthoracic echocardiography in this single-centre experience from eastern Nepal was high; one in four patients diagnosed with RHD was younger than 20 years; more than 60% of the patients

Fig. 1



Distribution of age and sex among patients presenting with rheumatic heart disease.

diagnosed with RHD were women; and differential patterns of valvular involvement were observed across sex and age categories.

Among patients referred for echocardiography at this university hospital in eastern Nepal, left-sided rheumatic valvular heart disease was diagnosed in 15.8% of patients. Prevalence rates of RHD among the general population from neighbouring India and Bhutan range from 4 to 10 cases per 1000 persons² and may be translated to eastern Nepal. RHD substantially contributes to morbidity and mortality in the working-age population and continues to be a challenging burden to the healthcare system of Nepal.

Consistent with cohorts from rural Pakistan and India,^{5,10} patients younger than 20 years constituted over a quarter of all patients in our series. Juvenile RHD was first

reported in India in 1963.¹¹ The underlying reasons may relate to recurrent, unrecognized or untreated streptococcal infections, lack of secondary prophylaxis, unusual strains of streptococci, malnutrition, or to genetic and ethnic differences in patients from this part of the world.^{12,13}

The female-to-male ratio amounted to 1.6:1 in our cohort and was consistent with previous studies observing a higher prevalence of RHD in women.^{5,6,14-16} It has been hypothesized that the female predominance might be explained by a greater exposure to GABHS because of greater involvement of women in child rearing, increased innate susceptibility or reduced access to medical care.⁶ At the same time, women presented at an older age as compared to men in our cohort (32.8 ± 15.2 versus 28.5 ± 15.4 years; $P < 0.001$). In contrast, among urban

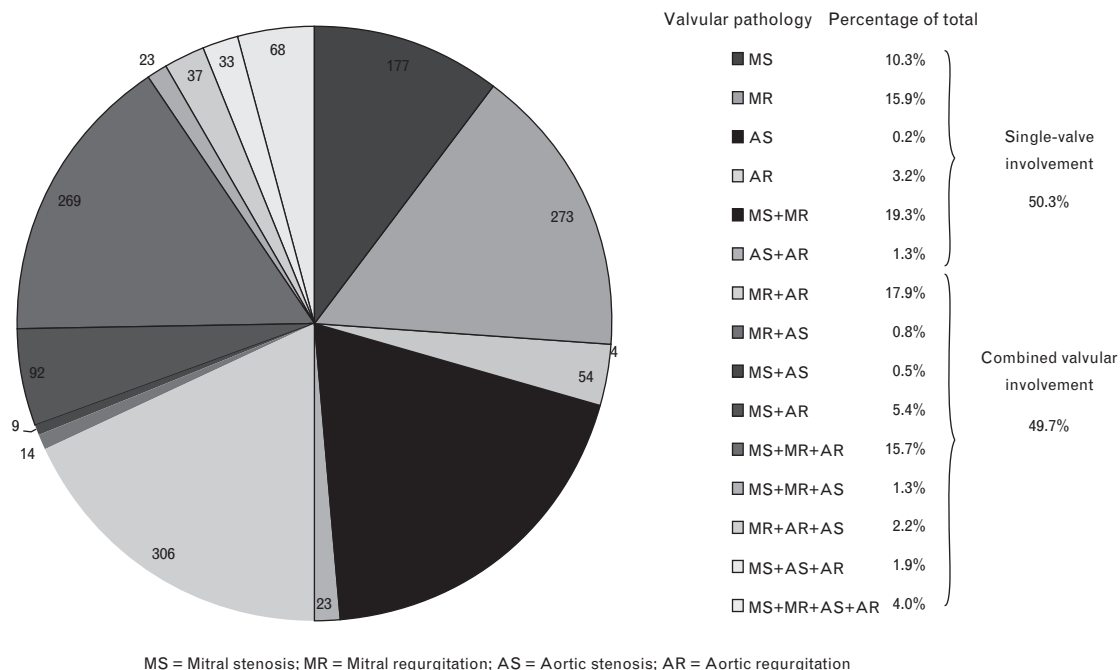
Table 1 Patterns of valvular involvement

	Overall (n/%)	Women (n/%)	Men (n/%)	P value
Single-valve disease	1713 (100)	1055 (61.6)	658 (38.4)	
Isolated valvular disease ^a	862 (50.3)	551 (52.2)	311 (47.3)	0.047
Mixed valvular disease ^b	508 (29.7)	316 (30.0)	192 (29.2)	0.22
Combined valvular disease ^c	354 (20.7)	235 (22.3)	119 (18.1)	0.22
Combined valvular disease ^c	851 (49.7)	504 (47.8)	347 (52.7)	0.047
Mitral regurgitation	1321 (77.1)	820 (77.7)	501 (76.1)	0.48
Mitral stenosis	1002 (58.5)	663 (62.8)	339 (51.5)	<0.001
Aortic regurgitation	882 (51.5)	516 (48.9)	366 (55.6)	0.007
Aortic stenosis	211 (12.3)	120 (11.4)	91 (13.8)	0.15

^a Mitral regurgitation or mitral stenosis or aortic regurgitation or aortic stenosis. ^b Mitral regurgitation and mitral stenosis or aortic regurgitation and aortic stenosis.

^c Involvement of both the mitral valve and the aortic valve.

Fig. 2



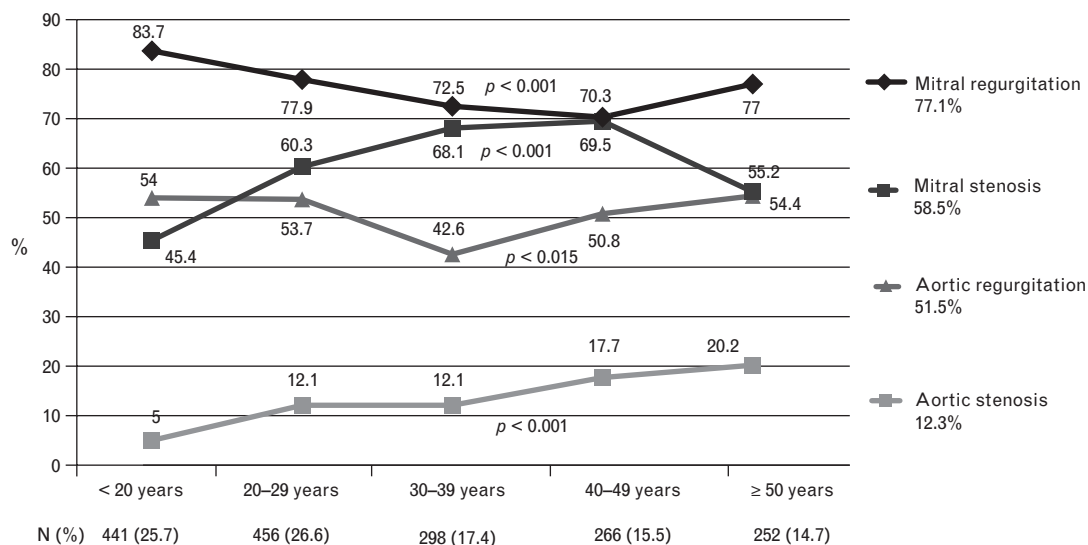
Numbers and percentages of left-sided valvular involvement.

African adults in the Soweto study the age of presentation was older [median age 43 years, interquartile range (IQR) 32–56 years] without differences between sex. Whether our observation might be explained by earlier or more severe occurrence of the disease in men, as suggested by a study from south-eastern Anatolia,¹⁵ remains speculative

due to the cross-sectional design of our study, without longitudinal follow-up.

Combined involvement of both the mitral and the aortic valve was observed in approximately half of the patients and was more common among men as compared to

Fig. 3



Patterns of valvular involvement stratified by age groups.

women (52.7 versus 47.8%; $P=0.047$). In agreement with previous studies, mitral regurgitation was the most common valvular lesion across all age groups irrespective of sex.^{6,16–21} Patients below 20 years of age presented more commonly with mitral regurgitation and aortic regurgitation, whereas a peak of mitral stenosis was observed in middle-aged patients aged from 30 to 49 years. These findings are consistent with observations from the Soveto study, in which younger patients (10–29 years) presented predominantly with pure mitral regurgitation, whereas middle-aged adult patients (age range 20–39 years) developed mitral stenosis.¹⁶ Mitral stenosis was more frequently documented in women as compared to men (62.8 versus 51.5%; $P < 0.001$) confirming previous observations.²² Conversely, aortic regurgitation was more frequently reported in male as compared to female patients (55.6 versus 48.9%; $P=0.007$), in accordance with findings from a retrospective study from Turkey.¹⁵ The correlation between a higher rate of aortic regurgitation in patients below 20 years and a relatively higher proportion of males among this age group remains to be explained. Moreover, longitudinal studies are needed to investigate whether different valvular involvements among age categories reflect progression of disease.

The data from this consecutive cohort demonstrate the spectrum of RHD as encountered in a tertiary care centre in eastern Nepal. A combination of poverty, lack of awareness, limited access to primary prevention and secondary prophylaxis ensure the high prevalence of ARF and make RHD an unresolved problem in this part of the world. Once significant valvular disease has developed, medical options are limited; cardiac surgery for valve replacement is available in the capital city of Kathmandu 500 km west of Dharan, and percutaneous mitral valvotomy has only recently been introduced in our centre.

The observational study has several limitations. First, the analysed cohort reflects a selected patient population that was referred for echocardiography. The reasons for referral to echocardiography and symptom status have not been documented in the echocardiography database and could not be assessed retrospectively. Second, the retrospective analysis was based on review of the charts; no core-lab evaluation of the echocardiographic clips was performed. Third, no longitudinal follow-up was performed, hence echocardiographic findings could not be correlated with clinical outcome. Finally, this analysis reflects a single-centre, hospital-based retrospective observation.

In conclusion, in this retrospective, single-centre cohort study, one in four patients diagnosed with RHD was aged

below 20 years, the female-to-male ratio amounted to 1.6:1, and women presented at an older age than men. Whereas mitral regurgitation was the most common valvular lesion across all age groups irrespective of sex, mitral stenosis was more frequently observed in women, with a peak between 30 and 49 years of age, and aortic regurgitation was more common in male patients.

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