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Original Article

Etiology and distribution of isolated aortic stenosis in Indian patients – A study from a large tertiary care hospital in north India

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ABSTRACT

Background: Isolated aortic valve disease (IAVD) has traditionally been a disease of elderly, etiology being either senile degeneration of a tricuspid aortic valve or calcification of a bicuspid aortic valve. However, there is scarcity of Indian data regarding demographic distribution and etiological patterns of IAVD in context of emerging therapies like transcatheter aortic valve implantation (TAVR).

Methods & results: A retrospective observational analysis of 60,560 echocardiograms over three years revealed 3728 newly diagnosed cases of valvular heart disease (VHD). Isolated mitral valve disease (IMVD) constituted 48.7% (n = 1815) of all VHD, including 1104 (29.6%) cases of pure mitral stenosis (MS) which was the commonest single lesion followed by combined mitral and aortic valve disease (CMAVD) (n = 1320, 34.5%), mixed aortic valve disease (MAVD) (n = 349, 9.4%), isolated aortic stenosis (IAS) (n = 179, 4.8%) and isolated aortic regurgitation (IAR) (n = 75, 2.0%). IAS patients had bimodal age distribution with peaks in first and sixth decade, contributed by congenital and acquired IAS respectively. Acquired IAS comprised of degenerative tricuspid aortic valve (n = 79, 58.1%; mean age: 63.2 ± 8.8 years), bicuspid aortic valve (BAV) (n = 34, 25.0%; mean age: 36.0 ± 8.3 years), rheumatic (n = 4, 2.9%; mean age: 55.3 ± 3.4 years) and non-rheumatic IAS with unclear morphology (n = 19, 14%; mean age: 48.5 ± 9.3 years). 65.6% patients with acquired non-rheumatic isolated aortic stenosis were less than 60 years of age.

Conclusion: In Indian population, senile valvular degeneration is the commonest cause of acquired IAS with majority of them presenting before 60 years of age, thereby bereaving them with the option of TAVR as a treatment modality.

1. Introduction

Rheumatic heart disease (RHD) remains the predominant contributor to valvular heart disease (VHD) usually affecting the younger population, especially in the developing world. Mitral valve involvement is the commonest in this setting.[1] Being uncommon, isolated aortic valve involvement comprises less than 8% of the total RHD burden; with isolated aortic stenosis contributing only 2% to the overall RHD cases.[2] Isolated aortic stenosis however contributes an ever-increasing proportion of VHD in the elderly, with majority of cases being non-rheumatic.[3–6] With the advent of transcatheter aortic valve replacement (TAVR) as standard of care for isolated aortic stenosis and especially in light of its approval in low risk patients it may appear that a majority of patients with isolated aortic stenosis could then call for TAVR with a major decrease in numbers of surgical aortic valve replacement (SAVR).[7] However, this assumption pre-supposes that majority of isolated aortic stenosis would also be in the elderly age group only. There is however, no data on age distribution of isolated aortic stenosis from the Indian subcontinent. We therefore planned this study to look at the age and etiological distribution pattern of isolated aortic stenosis amongst our patients from the Indian subcontinent.

1.1. Objective

To evaluate the demographic and etiological distribution pattern of various valvular heart disease, with special focus on isolated aortic valve stenosis and its age and aetiology specific

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distribution pattern in consecutive patients from a high volume, tertiary care hospital in north India.

2. Methodology

In this retrospective, observational, single centre study all consecutive patients of VHD undergoing echocardiography examination from January 2014 to December 2016 were analysed.

2.1. Inclusion criteria

All the newly diagnosed cases of valvular heart disease having hemodynamically significant lesions (anything more than mild valvular involvement) were included in the study.

2.2. Exclusion criteria

1. Clinically insignificant regurgitant lesions for e.g. any isolated trivial to mild mitral regurgitation (MR), trivial to mild aortic regurgitation (AR), trivial to mild tricuspid regurgitation (TR) and trivial to mild pulmonary regurgitation (PR).
2. Valvular abnormality without stenosis or regurgitation e.g. bicuspid aortic valve without aortic stenosis (AS) or aortic regurgitation (AR), calcified or thickened aortic valve without aortic stenosis and mitral annular calcification without MR.
3. Prior percutaneous valve intervention or cardiac valve surgery (for e.g. post balloon mitral valvotomy, post aortic valve replacement or post mitral valve replacement.)
4. Idiopathic hypertrophic obstructive cardiomyopathy causing subvalvular aortic stenosis was excluded.

2.3. Methods

All cases with clinical diagnosis of valvular heart disease were included in accordance with the inclusion and exclusion criteria shown above. Manual verification of data was done to screen out any incomplete data or data duplication. All index echocardiograms were done by in-hospital cardiology fellows on Vivid^{TM}E9 cardiovascular ultrasound system (GE healthcare, Chicago, IL, USA) using standard ASE (American society of echocardiography) protocols. All echocardiograms included in the study were reviewed by in-hospital consultant cardiologists. Only the index echocardiography report of any given patient was included for the study. Demographic and echocardiographic data of each patient including age, sex, echocardiography parameters, type and severity of valve lesion, aetiology, chamber dimensions, left ventricular ejection fraction (LVEF) and presence of atrial fibrillation were obtained. Clinical parameters were obtained from the digital records available in hospital information system (HIS).

2.4. Definitions

Valvular lesions and their echocardiographic severity were defined based on 2017 ACC/AHA guidelines on valvular heart disease.[7] The valvular diseases were stratified into groups based on following definitions:-

1. Pure mitral stenosis (MS) defined as moderate to severe degree of MS with none or less than or equal to mild regurgitation. Mild MS without any regurgitation was also included in this group.
2. Isolated aortic stenosis (IAS) was defined as AS without AR, or AR of less than mild grade. Mild to moderate grade functional mitral regurgitation was included in IAS. Less than or equal to mild MS or MR, were also included in IAS when AS was severe.
3. Isolated aortic regurgitation (IAR) was defined as AR without any degree of AS. Mild to moderate grade functional mitral regurgitation was included in IAR. Less than or equal to mild MS or MR, were also included in IAR when AR was severe.

Accordingly cases were further grouped into isolated mitral valve disease (IMVD), isolated aortic valve disease (IAVD) and combined mitral and aortic valve disease (CMAVD) as following:-

1. Isolated mitral valve disease (IMVD) was defined as mitral valve involvement in any form, including pure MS group. Pure mitral regurgitation was also included in this group.
2. Mixed aortic valve disease (MAVD) was defined as presence of both AS and AR of any severity. Functional mitral regurgitation was included in MAVD. Less than or equal to mild MS or MR, were also included in MAVD when AS or AR was severe.
3. Combined mitral and aortic valve disease (CMAVD) was defined as presence of both aortic and mitral valve stenosis or regurgitation and not included in any of the categories described above.

Etiological diagnosis of each patient with isolated aortic valve disease was made based on standard clinical criteria for non-rheumatic aetiology including a mandatory absence of rheumatic mitral valve involvement. Aetiology of mitral valve disease was based on standard echocardiographic criteria described to diagnose or exclude rheumatic aetiology. Isolated aortic stenosis was further classified into congenital or acquired based on a clinical presentation of <18 years versus >18 years of age along with etiological correlation.

2.5. Statistical analysis

The distribution of categorical data and its relation to gender and clinical characteristics were expressed in frequency and percentage. The continuous variables related to clinical characteristics like age, chamber dimensions were expressed in mean±SD or median with inter-quartile range (IQR). The data was entered in an excel chart and analysed using SPSS® statistical analysis software (IBM SPSS statistics for windows (2011), version 20.0, IBM corps, Armonk, NY, USA).

3. Results

A total of 60,560 echocardiograms were done in 3 years, from January 1, 2014 to December 31, 2016. Among them 16,783 cases were valvular heart diseases. After excluding the redundant echocardiograms based on the exclusion criteria, a total of 3728 new cases of significant valvular heart disease were included in the study. The flow chart of the study methodology has been shown in Supplementary Fig. 1.

3.1. Distribution pattern of valvular heart disease

Among all the valvular heart diseases, the most common valvular lesion was IMVD constituting 48.7% (n = 1815) of all VHD including 29.6% cases of pure MS (n = 1104) followed by CMAVD (n = 1320, 34.5%) and predominant aortic valve involvement (n = 604, 16.2%). Among the patients with predominant aortic valve involvement IAS, IAR and MAVD constituted 4.8% (n = 179), 2.0% (n = 75) and 9.4% (n = 349) respectively. Pulmonary stenosis and isolated tricuspid valve disease constituted only a handful of cases (0.9%, n = 34). The distribution of different VHD has been shown in Supplementary Fig. 2.

3.2. Age and gender distribution of VHD

The entire population of VHD in the study was stratified by age into 2 groups: <60 years and ≥60 years. The distribution of VHD based on age group is shown in Supplementary Fig. 3. Most of the patients were younger than 60 years of age constituting 92.6% of patients. Only 7.3% of entire population belonged to ≥60 years age group. The age distribution of IAS patients is shown in Fig. 1. Isolated aortic stenosis patients had a bimodal distribution pattern with two peaks, first at <10 years of age (congenital origin) and second at 50–59 years of age (acquired origin). The mean age of VHD cases included in the study was 36.9 ± 15.5 years (Table 1). The etiological pattern of distribution of IAS with respect to age is shown in Fig. 2. Amongst 136 acquired IAS patients, 60.3% (n = 82) were less than 60 years of age.

Males predominated in all the varieties of aortic valve disease. In IAS, IAR and MAVD males constituted 68.7%, 77.3% and 72.2% of cases respectively (Table 1). Females were most commonly affected in IMS (63.6%) and MMVD (65.7%). Overall, out of 179 isolated aortic stenosis patients 123 (68.7%) were male and 56 (31.3%) were female (Table 3). The gender distribution of isolated aortic stenosis patients stratified according to various aetiologies is shown in Supplementary Fig. 4.

3.3. Aetiology wise distribution of isolated aortic valve disease

The etiological distribution of all VHD included rheumatic in (83.1%), congenital in (7.9%) and degenerative (6.6%). Out of 179 IAS patients, 24.1% (n = 43) cases had aortic stenosis of congenital origin. Amongst acquired IAS (n = 136 [75.9%]), the most common etiological cause was degenerative (senile) tricuspid aortic valve disease constituting 58.1% (n = 79) of cases followed by calcification of congenitally bicuspid aortic valve (25.0%, n = 34). Isolated involvement of aortic valve was rarely of rheumatic in origin seen only in 2.9% of cases. In about 14.0% (n = 19) of cases, the valve morphology could not be discerned due to valve deformation caused by heavy calcification (Table 2). Sub aortic membrane was found only in 0.56% (n = 1) of IAS patients.

Among patients with IAR, the most common cause was congenital i.e. BAV (n = 32, 42.7%), followed by RHD (n = 27, 36.0%). Aortic root disease constituted 10.7% (n = 8) of cases. Subaortic membrane (n = 2, 2.7%) and native valve infective endocarditis (n = 2, 2.7%) constituted a few cases. Among patients with MAVD, the distribution was equipoised between the three aetiologies - congenital (n = 130, 37.2%), degenerative (n = 116, 33.2%) and rheumatic (n = 103, 23.5%).

3.4. Pulmonary hypertension in VHD

Severe pulmonary hypertension was present in 21% of all patients with VHD, out of which 60% of cases had predominant mitral valve involvement. Severe pulmonary hypertension was rarely seen in isolated aortic valve disease, present in only 1.1% and 6% of IAS and MAVD respectively. None of the patients with isolated AR had severe PAH. The presence and severity of pulmonary hypertension in various valvular lesions is shown in Supplementary Fig. 5.

3.5. Atrial fibrillation in VHD

Overall, AF was present in 24.6% (n = 912) of all echocardiograms and was commonly seen in VHD with predominant mitral valve involvement (n = 518). AF was rarely seen in patients with isolated aortic valve disease, being present only in 0.6%, 2.7% and 0.6% of IAS, IAR and MAVD respectively. The distribution of AF in various types of VHD is shown in Supplementary Fig. 6.

4. Discussion

In our study, more than 90% of the patients with significant VHD were less than 60 years of age and isolated AVD constituted 16.2% of the overall study population with IAS constituting 4.8% of total valvular heart disease. This is much less when compared to western population as shown by Nkomo et al[8] from USA where in IAS constituted 16.5% of VHD. In a Swedish study, aortic stenosis constituted 55% of VHD.[9] However in Indian studies, proportion of AS is relatively less as seen in a study by Manjunath et al where isolated AS was found in 7.3% of cases and was the third most

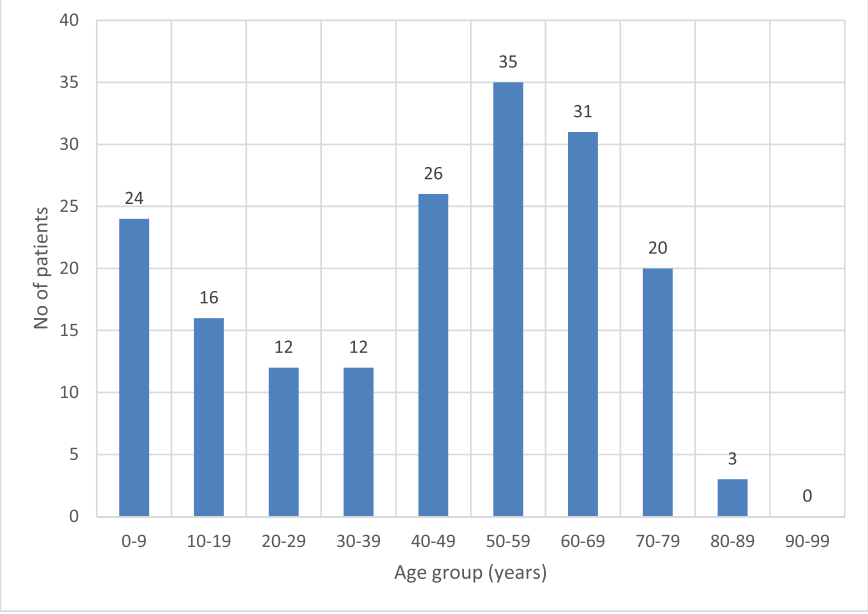

Fig. 1. Age-wise group distribution of patients with isolated aortic stenosis.

Table 1
Demographic characteristics in various valvular heart disease (VHD).

VALVULAR LESION (N = 3705)	N (%)	Age (yrs)	Sex	
			M (%) n = 1947 (52.5)	F (%) n = 1758 (47.5)
PURE MS	1104 (29.8)	35.2 ± 12.8	402 (36.4)	702 (63.6)
ISOLATED MVD	1815 (48.9)	35.0 ± 15.6	244 (34.3)	467 (65.7)
COMBINED MVD & AVD	1287 (34.7)	36.8 ± 14.4	678 (52.7)	609 (47.3)
ISOLATED AS	179 (4.8)	43.5 ± 23.2	123 (68.7)	56 (31.3)
ISOLATED AR	75 (2.0)	35.5 ± 13.6	58 (77.3)	17 (22.7)
MIXED AVD	349 (9.4)	44.9 ± 17.7	252 (72.5)	96 (27.5)

Values expressed in mean ± SD. MS = mitral stenosis, MVD = mitral valve disease, AVD = aortic valve disease, AS = aortic stenosis, AR = aortic regurgitation, AVD = aortic valve disease.

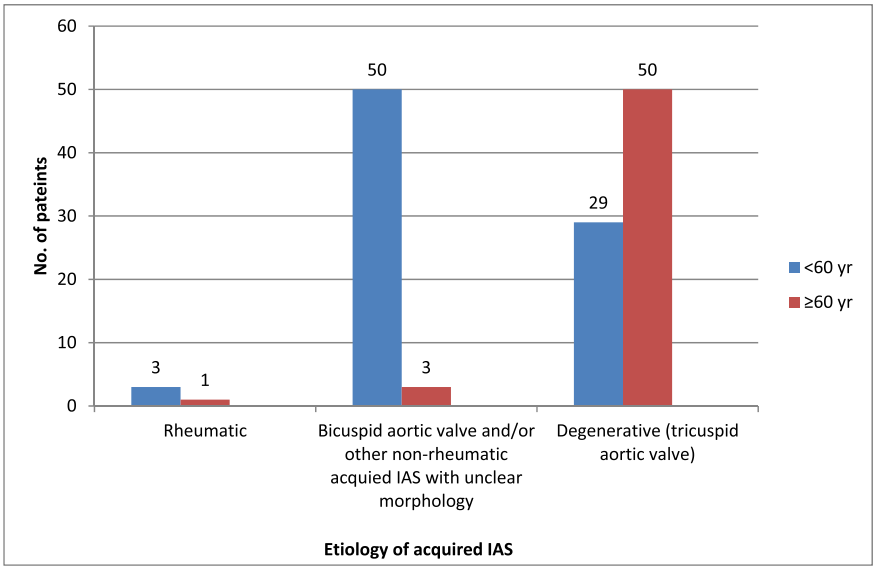

Fig. 2. Etiology based distribution of acquired isolated aortic stenosis with age groups <60 years versus ≥60 years.

Table 2
Etiology-wise distribution of acquired isolated aortic stenosis (IAS).

Etiology of acquired IAS (N = 136)	No of cases	%	Age, yrs (Mean ± SD)
Rheumatic	4	2.9	55.25 ± 3.4
Bicuspid	34	25.0	36.0 ± 8.3
Degenerative	79	58.1	63.2 ± 8.8
Non-rheumatic *(morphology not clear)*	19	14.0	48.47 ± 9.3

SD = standard deviation.

Table 3
Gender distribution of etiology specific isolated aortic stenosis (IAS).

Etiology of Isolated AS *(n = 179)*	Male (n = 123) *n, %*	Female (n = 56) *n, %*
Congenital *(n = 43)*	29 (23.6)	14 (25)
Acquired *(n = 136)*	94 (76.4)	42 (75)
Rheumatic *(n = 4)*	0 (0)	4 (9.5)
Bicuspid *(n = 34)*	22 (23.4)	12 (28.6)
Degenerative *(n = 79)*	57 (60.6)	22 (52.4)
Non-rheumatic *(morphology not clear) (n = 19)*	15 (16)	4 (9.5)

AS = aortic stenosis.

common type of VHD.[10] In our study, IAS constituted only 4.8% of VHD. This was not only less when compared to western studies but also slightly compared to the only available Indian study.

In our study, IAR constituted only 2.0% of VHD which is also less when compared to western studies. In the study by Nkomo et al, AR constituted 14.6% of VHD.[8] In the Swedish study, aortic regurgitation constituted 21% of VHD.[9]

Degenerative aortic valve stenosis was the commonest aetiology (58.1%) followed by bicuspid aortic valve (25%) and rarely rheumatic (2.9%) for acquired IAS which was similar to a study by

Manjunath et al,[10] where degenerative calcification constituted 65% of AS, followed by bicuspid aortic valve (33.9%) and RHD (2.2%). A unique observation in our study was that patients with acquired IAS, more often (65.6% of IAS) were younger (<60 years of age) contrary to majority being beyond 60 years of age in the western world. Our patients of isolated AS showed a bimodal age distribution pattern with peak prevalence at two age groups:- one at younger age (0–9 years) and second at an older age (50–59 years) which was related to the etiological pattern: congenital versus acquired aortic stenosis. Pondering over the aetiology of isolated acquired AS, one needs to keep in mind that it sometimes become difficult on echocardiography alone in degenerated and calcified valves to decipher if the actual valve was bicuspid or tricuspid and therefore there could be an overlap in our analysis which is a limitation of our study. However, an important point to note is that with 60% of acquired non-rheumatic aortic stenosis patients being less than 60 years of age, this observation could have important clinical implications on the penetration of TAVR in the Indian subcontinent. Firstly, with a lower prevalence of acquired isolated AS, the volumes of TAVR in our society would be less and secondly, with 60% of these patients being less than 60 years of age they may not call for TAVR, age being an important determinant for TAVR irrespective of the risk category of the patient. Hence, 'TAVR being approved for low risk category' sending a message to interventionists that now all AS patients could call for TAVR, may not be true in the Indian scenario because age would still be a limiting factor in patients with isolated acquired aortic stenosis.

Trying to figure out as to why degenerative AS was observed at a relatively younger age in our patient subgroup, we could only surmise that this could be akin to CAD being seen 10 years younger in Indian patients than the western population as shown in the INTERHEART study by Yusuf Set al[11] with median age of presentation with myocardial infarction in south-Asian region being 53 years as compared to 59–63 years in Caucasian people of western Europe and north America. The degenerative process of acquiring AS at least in the tricuspid isolated degenerative AS subgroup is not much different to atherosclerosis otherwise. This is because degenerative aortic stenosis and coronary artery disease have a possible common inflammatory and atherogenic etiology.[12] The above statement however is only hypothesis generating as we have not shown any proof of the same with the observation made in this study of ours. In addition, another important fact to be considered is that the overall life expectancy of Indians is 69.5 years as compared to 78.8 years in United States according to world population review done by UNICEF[13] in 2019. The age threshold of TAVR could be put at least 10 years lower as compared to the western standards, which will lead to enhanced population coverage and optimal penetration of the interventional procedure.

Males were most commonly affected by aortic valve disease. Male constituted more than two third of cases. The prevalence of BAV in general population is estimated to be higher in males (0.6–0.8%) than in females (0.2%).[14–16] In the pathological study on surgically explanted valves, BAV was the most common valve morphology found in males.

In our study, isolated aortic valve involvement was rarely associated with AF (1%) and/or severe PAH (1.3%). On the other hand, AF and PAH were found in higher proportion of patients with associated mitral valve disease while being rare in patients with predominant aortic valve involvement. This is mainly due to lack of underlying left atrial enlargement and absence of passive, reactive or obliterative changes of pulmonary vasculature in patients with aortic valve disease. This also supports the classical teaching that presence of AF and PAH in a case of aortic valve disease, points towards a hemodynamically significant associated mitral valve disease with RHD as the possible aetiology. Since AF is less prevalent in AVD, most of them have no indication for long term anticoagulation and could be candidates for bioprosthetic valves or TAVR.

4.1. Limitation

This being a retrospective echocardiographic data analysis only, the morphology of aortic valve determined in the study may not be as accurate in all the cases. Also, because echocardiographic examination is more operator dependent and no compulsory CT/CMR imaging was considered for confirmation, therefore, diagnostic bias cannot be completely eliminated. Since this is a hospital-based registry data analysis, prevalence in general population cannot be determined but only extrapolated. The limitations inherent to any retrospective study also holds good for this study.

5. Conclusion

We conclude that firstly, the prevalence of isolated aortic valve disease including isolated aortic stenosis is lesser in Indian population and secondly, that patients with isolated acquired aortic valve disease present at a relatively younger age with more than 60% of cases presenting at less than 60 years of age.

5.1. Clinical implication

In spite of TAVR becoming standard of care with benefit shown even in low surgical risk patients with aortic stenosis, its penetration into the Indian patients could be limited because of the lower mean age of presentation of patients with acquired IAS and this may act as a major deterrent in advocating TAVI in several patients with intermediate and low surgical risk who would otherwise call for the same as per current indications.

Statement of authorship

Ankit Kumar Sahu: Did advance statistical analysis, refined the results and prepared the draft of this manuscript. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Pramod Sagar: Collected the data, did preliminary statistical analysis and generated crude results.

Roopali Khanna, Sudeep Kumar, Satyendra Tewari, Aditya Kapoor: These authors gave consent and contributed their individual patient data for inclusion in the study.

Pravin K Goel: Conceived the basic idea for the study and actively participated in the interpretation and editing of the manuscript. This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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None.

Declaration of Competing Interest

All authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ihj.2020.06.013.

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