Comparison of Clinical and Echocardiographic Features of Asymptomatic Patients With Stenotic Bicuspid Versus Tricuspid Aortic Valves

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The clinical and imaging differences between bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) patients with medically managed asymptomatic moderate-to-severe aortic stenosis (AS) have not been studied previously. We aim to characterize these differences and their clinical outcomes in this study. A retrospective observational study was conducted on 836 consecutive cases of isolated asymptomatic moderate-to-severe AS, with median follow-up of 3.4 years. Clinical and echocardiographic characteristics were compared between BAV and TAV patients. Subgroup analysis stratified by AS severity were performed. Survival analysis of all-cause mortality was performed using Kaplan-Meier curves and Cox proportional hazards model. Compared to BAV patients, TAV patients were older (76 ± 11 vs 55 ± 16 years, p <0.001) and had more co-morbidities including hypertension (78% vs 56%; p <0.001), diabetes (41% vs 24%; p <0.001), and chronic kidney disease (20% vs 3%; p = 0.001). TAV patients had less severe aortic valve disease than BAV patients, with a higher aortic valve area index (0.71 ± 0.20 cm^2/m^2 vs 0.61 ± 0.18 cm^2/m^2, p <0.001) and less aortic dilation (sinotubular junction: 23.7 ± 4.0 mm vs 26.9 ± 4.8 mm, p <0.001; mid-ascending aorta: 31.4 ± 4.7 mm vs 36.3 ± 6.3 mm, p <0.001). TAV patients were more likely to have eccentric left ventricular hypertrophy and less likely to have a normal geometry (p = 0.003). Competing risk analysis identified increased age (hazard ratio 1.03, 95% confidence interval 1.02 to 1.05, p <0.001) and LVEF (hazard ratio 0.98, 95% confidence interval 0.97 to 0.99, p <0.001) as independent risk factors of all-cause mortality. Valve morphology was not a significant independent risk factor for aortic valve replacement or mortality. In conclusion, asymptomatic TAV patients had more cardiovascular risk factors, less severe aortic valve disease, less sinotubular and mid-ascending aortic dilation, more severe LV remodeling. **(Am J Cardiol 2020;128:210−215)**

Previous studies have focused on clinical and imaging differences between bicuspid aortic valve (BAV) and tricuspid aortic valve (TAV) patients with severe aortic stenosis (AS) planned for aortic valve replacement (AVR) and the subsequent outcomes post-AVR.[1−6] The differences between BAV and TAV patients with asymptomatic moderate-to-severe AS who are medically managed are unclear. We aim to study the clinical and echocardiographic differences and outcomes between these 2 groups of patients.

Methods

A retrospective observational study was conducted. A cohort of 836 consecutive cases of isolated medically-managed asymptomatic moderate-to-severe AS from September 7, 2011 to December 31, 2015 was identified from a database of patients diagnosed with AS on transthoracic echocardiography at a tertiary academic center in Singapore. Baseline demographics, AS severity, valve morphology, and parameters on left ventricular (LV) geometry and function were collected and analyzed from the electronic medical records. Echocardiographic data was collected and analyzed according to the American Society of Echocardiography and European Association for Cardiovascular Imaging guidelines[7] by experienced certified cardiologists. AS severity was defined using aortic valve area (AVA), mean gradient and maximum

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Doppler velocity (Vmax), and categorized into moderate AS (AVA 1 to 1.5cm,[2] Vmax 3.0 to 3.9m/s, mean gradient 20 to 39 mm Hg) and severe AS (AVA <1 cm,[2] Vmax ≥4.0 m/s, mean gradient ≥40 mm Hg). Where discordant grading were identified, moderate or severe AS were classified based on fulfilment of at least 2 criteria. Outcomes including AVR and all-cause mortality were collected until December 31, 2017.

The study was approved by the institutional review board. Continuous variables were presented as mean ± standard deviation and categorical variables as frequency and percentages. Continuous variables were analysed with independent samples *t* test and categorical variables with the Chi-sqaure test with intergroup analyses. Survival analysis was performed using multivariate Cox model for AVR and all-cause mortality, as well as with AVR as the time-dependent co-variate in a competing analysis. All p-values of <0.05 were considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics 25 (IBM Corp., Armonk, New York).

Results

The baseline clinical characteristics according to valve morphology of the 836 patients are shown in Table 1. There were 168 (20%) patients with BAV and 668 (80%) patients with TAV. The median follow-up duration was 3.4 years (interquartile range 2.2 to 4.7). In this cohort, 691 (83%) patients had moderate AS, 138 (17%) patients had severe AS and 134 (16%) had left ventricular ejection fraction (LVEF) of <50%. Patients with TAV were about 20 years older. Those with TAV were more likely to have hypertension, dyslipidemia, stroke or transient ischemic attack (TIA), diabetes, and chronic kidney disease (CKD) compared with BAV, and the mean Charlson comorbidity index was significantly higher.

Subgroup analysis was then performed with patients stratified by the severity of AS. In the moderate AS subgroup, hypertension (80% vs 56%, p <0.001), diabetes (43% vs 21%, p <0.001), dyslipidemia (64% vs 49%, p = 0.002), and CKD (22% vs 2%, p = 0.003) were found to be more common in TAV compared with BAV patients. However, there were no significant differences in co-morbidities in the severe AS subgroup. Interestingly, patients with moderate AS were significantly older (72% vs 68%, p = 0.002), had more hypertension (76% vs 60%, p <0.001), stroke or TIA (19% vs 8%, p = 0.005), CKD (21% vs 10%, p = 0.009), and peripheral vascular disease (PVD) (7% vs 1%, p = 0.016). The death rate was not significantly higher in the moderate AS group (32% vs 27%, p = 0.268) but AVR rate was much lower (8% vs 52%, p <0.001). The proportion of BAV was significant lower in moderate versus severe AS (18% vs 31%, p <0.001). Together with the finding that BAV patients had fewer co-morbidities, the higher prevalence of hypertension, stroke or TIA, CKD and PVD, and increased age may be confounded by a higher proportion of TAV patients.

Echocardiographic characteristics of the BAV and TAV groups are shown in Tables 2 and 3. TAV patients had less severe aortic valve disease as compared to BAV patients, with a higher AVA index, energy loss index, and aortic valve velocity dimensionless index. TAV patients had a lower mean gradient, peak velocity, and aortic valve resistance. There was less sinotubular and mid-ascending aortic dilation in TAV compared with BAV patients. There was no significant difference in Doppler stroke volume index between TAV and BAV patients.

Table 1
Baseline demographics

Variable	Overall(n = 836)	Bicuspid aortic valve(n = 168)	Tricuspid aortic valve(n = 668)	p Value
Age (years)	72 ± 15	55 ± 16	76 ± 11	**<0.001**
Women	457 (55%)	67 (40%)	390 (58%)	**<0.001**
Ethnicity				0.429
Chinese	447 (62%)	36 (61%)	411 (62%)	
Malay	113 (16%)	5 (9%)	108 (16%)	
Indian	67 (9%)	7 (12%)	60 (9%)	
Others	93 (13%)	11 (19%)	82 (12%)	
Height (cm)	157 ± 10	161 ± 9	156 ± 9	**<0.001**
Body mass index (kg/m^2)	24.8 ± 5.3	25.0 ± 4.3	24.8 ± 5.5	0.635
BSA (m^2)	1.6 ± 0.2	1.7 ± 0.2	1.6 ± 0.2	**<0.001**
Systolic blood pressure* (mm Hg)	136 ± 24	129 ± 19	137 ± 25	**0.017**
Hypertension	609 (73%)	94 (56%)	515 (78%)	**<0.001**
Dyslipidemia*	506 (62%)	88 (54%)	418 (63%)	**0.037**
Diabetes mellitus	310 (38%)	38 (24%)	272 (41%)	**<0.001**
Ischemic heart disease	276 (38%)	16 (27%)	260 (39%)	0.064
Stroke or TIA	127 (18%)	4 (7%)	123 (19%)	**0.023**
Atrial fibrillation	121 (17%)	5 (9%)	116 (18%)	0.074
Heart failure	83 (11%)	6 (10%)	77 (12%)	0.753
Chronic kidney disease	136 (19%)	2 (3%)	134 (20%)	**0.001**
Peripheral vascular disease	42 (6%)	2 (3%)	40 (6%)	0.402
Charlson Comorbidity Index	5.0 ± 2.8	2.2 ± 1.8	5.7 ± 2.6	**<0.001**

BMI, body mass index; BSA, body surface area; TIA, transient ischemic attack; Values are expressed as mean ± SD or n (%).

*Systolic blood pressure recorded at visit closest to index echocardiogram. Dyslipidemia was defined as total cholesterol ≥240mg/dL, LDL cholesterol ≥160 mg/dl, HDL cholesterol <40 mg/dl or triglyceride ≥200 mg/dl.

Table 2
Aortic stenosis severity and transvalvular flow

Variable	Overall(n = 836)	Bicuspid aortic valve(n = 168)	Tricuspid aortic valve(n = 668)	p Value
AVA (cm^2)	1.10 ± 0.29	1.03 ± 0.29	1.12 ± 0.29	**<0.001**
AVA index (cm^2/m^2)	0.69 ± 0.20	0.61 ± 0.18	0.71 ± 0.20	**<0.001**
Energy loss index (cm^2/m^2)	0.72 ± 0.22	0.63 ± 0.19	0.75 ± 0.22	**<0.001**
Mean gradient (mm Hg)	25 ± 22	31 ± 18	24 ± 22	**<0.001**
Mean gradient >40 mm Hg	134 (17%)	40 (24%)	94 (15%)	**0.004**
Peak velocity (m/s)	3.0 ± 0.9	3.4 ± 1.0	2.9 ± 0.9	**<0.001**
Peak velocity >4.0 m/s	132 (17%)	45 (27%)	87 (14%)	**<0.001**
Velocity index	0.36 ± 0.17	0.26 ± 0.07	0.36 ± 0.18	**<0.001**
Aortic valve resistance (dyn × s × cm-5)	134 ± 110	177 ± 117	129 ± 109	**0.006**
Doppler SVi (ml/m^2)	40 ± 13	40 ± 11	40 ± 13	0.790
Doppler SVi <35 ml/m^2	265 (34%)	38 (33%)	227 (35%)	0.692
LVOT velocity (m/s)	97 ± 23	91 ± 19	97 ± 23	**0.014**
Aortic dimensions				
Sinus	31.3 ± 4.4	31.8 ± 5.2	31.2 ± 4.2	0.147
Sinotubular junction	24.4 ± 4.4	26.9 ± 4.8	23.7 ± 4.0	**<0.001**
Ascending aorta	32.5 ± 5.5	36.3 ± 6.3	31.4 ± 4.7	**<0.001**

Values are expressed as mean ± SD or n (%).
AVA = aortic valve area; LVOT = left ventricular outflow tract; SVi = stroke volume index.

There was no significant difference in LVEF and LV mass index between TAV and BAV patients. TAV patients had higher degrees of diastolic dysfunction with a higher LV filling pressure as documented by septal *E/e′* and left atrial diameter, and higher average e' and average E/e' which almost reached statistical significance (Table 3). There was a significant difference in LV geometric patterns between BAV and TAV patients (p = 0.003). TAV patients were more likely to have eccentric LV hypertrophy and less likely to have a normal geometry despite less severe AS. This remained significantly different in the moderate AS subgroup (p <0.001) but not severe AS subgroup (p = 0.833).

On follow up of 5 years, 126 (15%) of the overall cohort had AVR, of whom 37 (22%) had BAV while 89 (13%)

Table 3
Left ventricular geometry and function

Variable	Overall(n = 836)	Bicuspid aortic valve(n = 168)	Tricuspid aortic valve(n = 668)	p Value
LV geometry				
End-diastolic volume index (ml/m^2)	67 ± 23	63 ± 21	68 ± 24	**0.01**
End-systolic volume index (ml/m^2)	27 ± 19	24 ± 17	28 ± 19	**0.04**
Interventricular septum (mm)	10.9 ± 2.5	11.0 ± 2.6	10.9 ± 2.5	0.64
Posterior wall thickness (mm)	10.4 ± 2.1	10.4 ± 2.3	10.4 ± 2.0	0.89
Relative wall thickness (%)	45 ± 12	45 ± 11	45 ± 12	0.79
Relative wall thickness >42%	376 (72%)	94 (56%)	400 (61%)	0.27
LV mass index (g/m^2)	115 ± 39	111 ± 42	116 ± 39	0.10
LV mass to end-diastolic volume ratio (g/ml)	1.8 ± 0.6	1.8 ± 0.6	1.8 ± 0.6	0.95
LV hypertrophy	478 (58%)	90 (54%)	388 (59%)	0.22
Geometric patterns				**0.003**
Normal	179 (22%)	53 (32%)	126 (19%)	
Concentric LV remodeling	182 (22%)	146 (22%)	36 (22%)	
Concentric LV hypertrophy	296 (36%)	54 (32%)	242 (37%)	
Eccentric LV hypertrophy	166 (20%)	24 (14%)	142 (22%)	
LV systolic and diastolic functions				
Ejection fraction (%)	62 ± 14	64 ± 12	62 ± 14	0.10
Ejection fraction <50%	134 (16%)	20 (12%)	114 (17%)	0.10
Fractional shortening (%)	34.4 ± 9.4	35.3 ± 8.5	34.2 ± 9.6	0.16
E velocity (cm/s)	94 ± 36	84 ± 29	96 ± 38	**<0.001**
E/A ratio	1.1 ± 1.7	1.3 ± 0.6	1.0 ± 1.9	0.19
Septal E/e'	20.2 ± 12.9	15.5 ± 12.1	20.6 ± 12.9	**0.006**
Lateral E/e'	12.3 ± 9.3	10.4 ± 10.0	12.5 ± 9.2	0.10
Average e' (cm/s)	5.9 ± 2.5	6.5 ± 2.2	5.9 ± 2.5	0.07
Average E/e'	18.2 ± 11.5	15.5 ± 11.7	18.4 ± 11.5	0.08
LA diameter (mm)	42.3 ± 9.1	39.0 ± 7.5	42.5 ± 9.2	**0.005**

Values are expressed as mean±SD or n (%).
A = late diastolic transmitral inflow velocity; AVA = aortic valve area; E = early diastolic transmitral inflow velocity; e' = early diastolic mitral annular velocity; LA = left atrial; LV = left ventricular.

had TAV. Of the 257 (31%) patients who died, 18 (11%) had BAV and 239 (36%) had TAV. Decreasing age, ischemic heart disease and AVA index are independent predictors of AVR. It was also associated with stroke and TIA. For all-cause mortality, competing risk analysis with Cox regression and AVR as a time-dependent co-variate identified increased age (hazard ratio 1.03, 95% confidence interval 1.02 to 1.05, p <0.001) and LV ejection fraction (LVEF) (hazard ratio 0.98, 95% confidence interval 0.97 to 0.99, p <0.001) as independent risk factors. Valve morphology was not a significant independent risk factor for AVR or mortality. The results are summarized in Table 4.

Discussion

This study compared clinical and echocardiographic parameters of asymptomatic BAV and TAV patients and the outcomes of AVR and all-cause mortality which is understudied but nevertheless has an important role in advancing the knowledge in surveillance and management of this group of patients. The major findings of our study were that asymptomatic TAV patients compared with BAV patients had (1) more cardiovascular risk factors; (2) significantly less severe aortic valve disease; (3) less sinotubular and mid-ascending aortic dilation; (4)increased diastolic dysfunction and eccentric hypertrophy, and (5) increased risk of all-cause mortality.

Previous studies on AS patients who underwent AVR found that patients with TAV were more likely to have multiple comorbidities compared BAV, namely hypertension, dyslipidemia, diabetes, coronary artery disease, PVD, and dialysis use,[2] and were more likely to be older and female.[4] This larger cohort of patients with asymptomatic AS was consistent with these findings and hence precedes the worsening of the AS. BAV and TAV patients differ in terms of cardiac, valvular, and aortic parameters on imaging.[8–11] TAV patients compared to BAV patients has similar indexed AVA and LVEF but higher septal E/e'^2, but on CT pretranscatheter aortic valve implantation, BAV patients had higher indexed AVA than TAV patients.[12] In this cohort of asymptomatic AS patients, TAV patients have less severe AS than BAV patients. BAV is associated with mid-ascending aortic dilation on echocardiography[13] and MRI,[14] which is also observed in this cohort. Although there is still a lack of evidence on the optimal treatment modality for the medical management of BAV patients with aortic enlargement, it has been suggested that β-blocker or losartan therapy may be considered.[15] If medical therapy can delay the progression of the aortopathy, this may slow down the progression toward surgery.

TAV patients had more significant LV geometric changes, with reduced normal geometry and increased eccentric hypertrophy, despite having significantly less severe AS. In AS, LV remodeling occurs to compensate for the increased wall stress and maintenance of systolic function. It is associated with poorer clinical outcomes and increased LV mass is associated with a composite outcome of death, AVR, and congestive heart failure.[16] Many studies demonstrated LV reverse remodeling after AVR likely due to reduced afterload and improved active myocardial relaxation, leading to reduced LV mass and normalization of geometry. Medical treatment of AS with renin-angiotensin blockers (RAB) is also found to reduce LV pathological remodeling and decrease LV mass.[17,18] Further research is needed to establish if RAB may be beneficial at an asymptomatic stage of moderate-to-severe AS and delay the need for AVR. It would be of interest to study the response to RAB in TAV versus BAV patients, given their differences in baseline LV geometric changes. Other pharmacologic attempts to slow the progression of AS, include statins, nitrate derivatives and anticalcific therapy,[19] and increasing understanding of asymptomatic AS may help identification of potential targets.

Risk factors for progression of asymptomatic AS is an important clinical question in deciding the optimum timing of AVR and delaying symptom onset. Asymptomatic AS has low mortality risk but its natural history consist of a gradual increase in AS severity.[20] We found that moderate TAV AS patients had more co-morbidities, less severe AS and higher LV remodeling compared to BAV patients, but there were no differences in co-morbidities, AS severity and LV remodeling in the severe AS. Previous studies have reported that co-morbidities such as diabetes, CAD, dyslipidemia, dialysis and hypertension[21–23] have little to no influence on AS progression. Instead, these co-morbidities are shown in animal and human studies to lead to myocardial stiffening and LV diastolic dysfunction progression.[24,25] Pathological remodeling may occur earlier in disease progression in TAV than BAV due to higher prevalence of co-morbidities, and as severity of AS increases, BAV patients also develop co-morbidities, therefore, mitigating the differences in LV remodeling in severe AS. The increased diastolic dysfunction in TAV patients supports this relationship. As AS is both a valve disease and a ventricular disease,[26] controlling co-morbidities may attenuate the effects on LV

Table 4
Cox proportional hazards model covariates in the survival analysis of AVR, and Cox proportional hazards model with AVR as time-dependent co-variate in the analysis of all-cause mortality

Variable	AVR		Mortality	
	Hazard ratio (95% CI)	p Value	Hazard ratio (95% CI)	p Value
Age (years)	0.97 (0.95–0.98)	**<0.001**	1.03 (1.02–1.05)	**<0.001**
Ischemic heart disease	0.48 (0.31–0.73)	**0.001**	1.01 (0.77–1.33)	0.93
Stroke or TIA	3.93 (1.44–10.73)	**0.008**	1.30 (0.95–1.79)	0.10
AVA index (cm^2/m^2)	0.002 (0.001–0.008)	**<0.001**	0.87 (0.43–1.73)	0.69
Ejection fraction (%)	1.01 (1.00–1.02)	0.16	0.98 (0.97–0.99)	**<0.001**
Valve morphology	0.83 (0.44–1.57)	0.57	1.61 (0.73–3.53)	0.24

AVA = aortic valve area; TIA = transient ischemic attack.

remodeling and slow down progression to valve replacement, highlighting the need for good control of co-morbidities in asymptomatic AS.

Much is known about outcomes after AVR in BAV and TAV patients,[1–6] but no studies compared the outcomes of asymptomatic BAV and TAV patients. Asymptomatic TAV patients showed increased all-cause mortality, consistent with previous literature on post-AVR TAV and BAV patients.[2] Increasing age and reduced LVEF were independent predictors of mortality, taking into account AVR, but valve morphology alone did not predict all-cause mortality, suggesting that the increased LV remodeling in TAV patients may explain the higher all-cause mortality.

Our study consisted of a moderately sized cohort of aortic stenosis patients. Nevertheless, we acknowledge that our study is inherently limited by its retrospective design. The number of BAV patients compared to TAV patients in our cohort is relatively low and thus may have restricted the power of our study.

In conclusion, asymptomatic BAV and TAV patients exhibit many differences. When AS severity is moderate, TAV patients tend to have more cardiovascular comorbidities than BAV patients; this difference disappears when AS is severe. TAV patients also had more severe LV remodeling despite less severe AS, possibly associated with the higher prevalence of co-morbidities. Therefore, underlying valve morphology should be considered when managing co-morbidities and planning surveillance for valvulopathy, aortopathy, and LV dysfunction.

Author Contributions

Ching-Hui Sia: Conceptualization, Methodology, Validation, Investigation, Writing – Original Draft, Supervision, Project administration. **Jamie Ho:** Methodology, Formal analysis, Investigation, Data curation, Writing – Original Draft. **Joe Chua:** Methodology, Formal analysis, Investigation, Data curation, Writing – Original Draft, Visualization. **Benjamin Tan:** Conceptualization, Writing – Review & Editing, Supervision. **Nicholas Ngiam:** Investigation, Writing – Review & Editing, Supervision. **Nicholas Chew:** Validation, Writing – Review & Editing, Data Curation, Supervision. **Hui-Wen Sim:** Investigation, Writing – Review & Editing, Supervision. **Ruth Chen:** Formal analysis, Investigation, Resource, Writing – Review & Editing. **Chi-Hang Lee:** Investigation, Writing – Review & Editing, Supervision. **Tiong-Cheng Yeo:** Investigation, Writing – Review & Editing, Supervision. **William Kong:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration. **Kian-Keong Poh:** Conceptualization, Methodology, Resources, Writing – Review & Editing, Supervision, Project administration.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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