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Investigation of the Morphology of the Bicuspid Aortic Valve and Its Association with the Severity of Aortic Stenosis, Aortic Regurgitation, Ascending Aortic Dilation, and Associated Anomalies

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ABSTRACT

Introduction: The bicuspid aortic valve (BAV) is the most common congenital cardiac anomaly. The abnormal bicuspid morphology of the aortic valve leads to valvular dysfunction and aortopathy. However, the clinical presentations of BAV are quite heterogeneous with variable valvular dysfunction and abnormalities. We aim to study the correlations between degrees of aortic stenosis and insufficiency, ascending aorta dilation and associated anomalies in different BAV phenotypes in our local population .

Method: In this cross-sectional study, patients who were referred for echocardiography for any reason and were diagnosed with BAV accidentally, as well as those who were candidates for cardiac surgery due to complications of BAV and referred for echocardiography before surgery, were included. The BAV phenotype was defined as anterior-posterior leaflet orientation (BAV-AP) or right-left leaflet orientation (BAV-RL). Aortic stenosis and insufficiency were assessed. Aortic dimensions were measured at the aortic annulus, sinuses of Valsalva, sinotubular junction (STJ) and ascending aorta. Other cardiac anomalies were also recorded.

Results: A total of 141 patients (mean age 34±12.8 ranging from 11 to 74 years) with BAV were enrolled. The male to female ratio was 3:1. The prevalence of BAV-AP and BAV-RL was 56.7% and 43.3%, respectively. Comparing BAV-AP and BAV-RL, no differences in age or in the prevalence of male sex were identified. The pattern of valvular dysfunction was not statistically different between the two BAV phenotypes, with moderate-to-severe AI being the most common finding (60% in BAV-AP vs. 57.4% in BAV-AP; p= 0.982). Aortic diameter was larger with BAV-AP than BAV-RL at the sinuses (3.49±0.656 cm vs. 3.27±0.507 cm; p= 0.039). Additionally, ascending aorta dilation using the cut off according to sex, age, and body surface area was more common in patients with BAV-AP (60.8% vs. 43.1% in BAVRL; p= 0.043). The most common cardiac anomalies in all patients were patent foramen ovale (8.5%) and aortic coarctation (7.1%).

Conclusion: This study shows that moderate-to-severe AI is the most common valvular dysfunction in BAV patients, which is one of the independent risk factors for cardiac events in these patients; however, the pattern of valvular dysfunction is not different according to BAV phenotype. BAV-AP is associated with larger sinuses of Valsalva and more prevalent ascending aorta dilation, suggesting the possibility of different hemodynamic derangements or etiological entities between the two types of BAV.

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Introduction

Bicuspid aortic valve (BAV) is the most common congenital heart defect, with a prevalence ranging from 0.5% to 2%.(1-3) This condition presents with highly variable manifestations in different individuals; symptoms may emerge in infancy or remain asymptomatic until adulthood (4). Generally, symptoms do not manifest until the valve experiences infection or calcification (5). BAV can be an isolated problem or may coexist with other anomalies such as aortic coarctation, ventricular septal defect (VSD), and others (6, 7). This condition is associated with specific valvular and non-valvular disorders, including aortic regurgitation, aortic stenosis, aortic dissection, aortic aneurysm, and endocarditis (1). In developed countries, with the elimination of risk factors related to endocarditis, BAV has become the most common cause of endocarditis. Additionally, abnormal calcification of the valve can be observed in most BAV patients by the age of 20 and almost universally by the age of 30 (5).

BAV includes different phenotypes that present varying hemodynamic conditions. The most common subgroups of BAV are: BAV with fusion of the left and right coronary cusps (BAV L-R) (60%), BAV with fusion of the right coronary cusp and a non-coronary cusp (BAV N-R) (15-20%), and the form of BAV with fusion of the left coronary cusp and a non-coronary cusp (BAV L-N) (less than 5%) (4). These phenotypes differ significantly in terms of etiology and have their own specific complications, necessitating precise and appropriate screening for each subgroup (8). The incidence and rate of progression of aortic stenosis vary among different types of BAV; for instance, when the cusps are positioned in an anterior-posterior orientation, aortic stenosis tends to progress more rapidly (9). Furthermore, the location of aortic dilation differs among various phenotypes; in the L-N phenotype, isolated dilation of the aortic root is the most common type reported, while in the N-R phenotype, ascending aortic dilation is the most frequently observed type (10).

BAV is the most common congenital heart valve defect, occurring in 0.5 to 1.4 percent of the population, with a male-to-female ratio of 2-4 to 1. Its inheritance pattern appears to be autosomal dominant with variable penetrance; however, some researchers have suggested it may be X-linked due to its increased prevalence among patients with Turner syndrome. In patients with BAV, aortic dilation or medial degeneration frequently occurs, often accompanied by the formation of an ascending aortic aneurysm. Additionally, these patients tend to have larger and more voluminous aortas compared to those with similar conditions involving a trileaflet aortic valve. Aortopathy directly results from the hemodynamic severity of valvular insufficiency and is a risk factor for dissection. BAV can also be part of a more complex congenital heart disease that may or may not be associated with other left heart outflow tract obstructions (11).

The most common anatomy of a bicuspid aortic valve is the left-right (L-R) opening during systole, which occurs due to congenital adhesions of the right and left coronary arteries (BAV L-R) and is observed in 70 to 80 percent of patients. A prominent edge of tissue or a raphe may exist in larger cusps, which can make the closed valve during diastole resemble a trileaflet valve. The diagnosis of the two types of aortic valves is based on images obtained from the opening of the valve during systole with only two aortic connections. Unicuspid valves, having only one aortic connection, are differentiated from bicuspid valves (12). (figure 1/ figure 2)

Bicuspid aortic valve disease is associated with aortopathy, specifically ascending aortic dilation related to rapid degeneration of the aortic media. The presence, location, and severity of aortic dilation are linked to the morphology of the valve and do not appear to have a direct correlation with the severity of valve dysfunction. The risk of aortic dissection in patients with a bicuspid aortic valve is five to nine times higher than in the general population. Some studies have also indicated a connection between bicuspid aortic valve disease (with an anterior-posterior opening pattern) and mitral valve prolapse (12).

Patients with a bicuspid aortic valve may be diagnosed at any age due to the presence of an ejection click or a systolic or diastolic murmur.

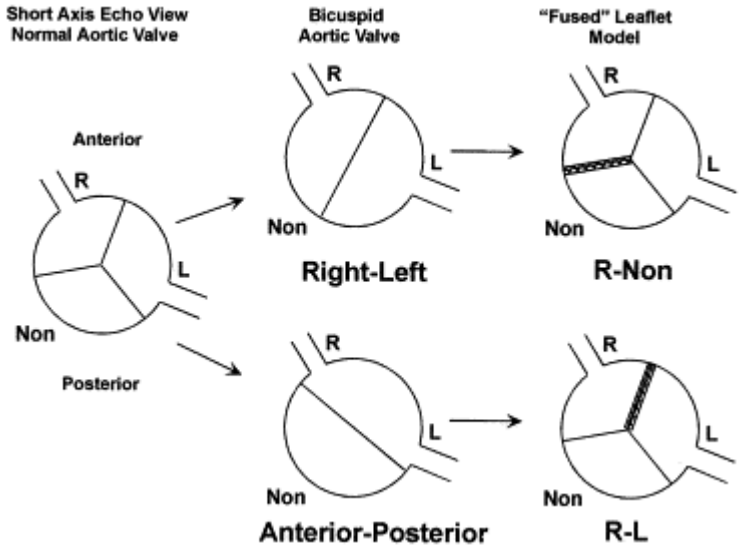

Figure 1. Schematic echocardiographic representation of the two common morphologies of aortic valve with two leaflets and the location of leaflet adhesions.

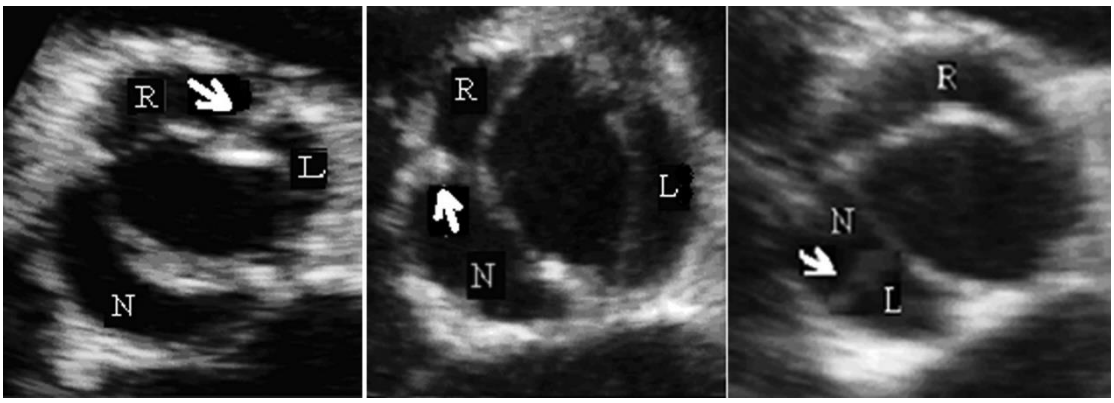

Figure 2. Echocardiographic view of three different phenotypes of Bicuspid Aortic Valve (BAV). R-L form: the right and left cusps are connected by a raphe (arrow). R-N form: the right and non-coronary cusps are connected by a raphe (arrow). N-L form: the non-coronary and left cusps are connected by a raphe (arrow).

However, some patients may be diagnosed during echocardiograms requested for other reasons. In most cases, the diagnosis remains unknown until the patient exhibits valvular dysfunction along with findings on examination and/or clinical symptoms (12).

Most bicuspid valves have normal function until late in life, but some patients may experience dysfunction in their youth. Risk factors include age over 30 years and moderate to severe aortic regurgitation or stenosis. Primary cardiac events have been observed in 25% of patients, and about 20% require surgery. Patients with a bicuspid valve are at greater risk for endocarditis, and aortic stenosis typically manifests after age 50. This condition accounts for more than half of valve replacement surgeries in the United States (12).

Currently, there is no effective treatment to prevent the progressive worsening of a bicuspid valve once it is diagnosed. If aortic valve replacement (AVR) is needed due to stenosis or regurgitation, it is recommended to simultaneously replace the aortic root if the maximal aortic diameter (measured at the end of diastole) is greater than 45 mm. In adults with a bicuspid aortic valve and an aortic diameter greater than 50 mm, even in the absence of valvular disease, aortic root replacement is recommended (12).

Aortic stenosis (AS) is observed in approximately one-quarter of all patients with chronic valvular heart disease; men account for about 80% of adults with symptomatic AS. In adults, AS is primarily

caused by degenerative calcification of the aortic valve and often occurs in the context of congenital conditions ([BAV]), chronic deterioration of the trileaflet valve, or previous rheumatic inflammation. A pathological study on aortic valve samples affected by AS during surgical intervention revealed that 53% of these valves were bicuspid and 4% were unicuspid (11).

Aortic regurgitation (AR) may occur due to primary valve disease or primary aortic root disease. Rheumatic disease causes thickening, deformity, and shortening of the affected aortic valve leaflets. These changes disrupt the opening of the leaflets during systole and their closure during diastole. In patients with isolated AR who do not have associated rheumatic disease, the prevalence of rheumatic disease is significantly lower. Patients with congenital BAV can predominantly develop AR, and approximately 20% of these patients between the ages of 10 and 40 require aortic valve repair. The presence of congenital defects in the aortic valve can occasionally lead to mild AR.

AR may also be primarily due to severe dilation of the aorta, meaning aortic root disease, without any initial involvement of the valve leaflets being observed. Stretching of the aortic valve ring and separation of the valve leaflets from each other is a common cause of AR. Sometimes, AR occurs as a result of retrograde dissection of the aorta, affecting the aortic valve ring and leading to its development (11).

Considering the genetic differences observed in this condition and the varying reports and results from different studies, we aimed to investigate this anomaly in our community. In the present study, given the lack of sufficient research on BAV, particularly in Iran, an effort has been made to provide a precise description of the most common complications of the bicuspid aortic valve in its main phenotypes. This aims to obtain more accurate information regarding the differences present in the phenotypes of the bicuspid aortic valve and the prognosis related to each one, which will help in the management, planning, and closer follow-up of patients with BAV to reduce complications and facilitate earlier diagnosis.

Method

In this study, the population under investigation included all patients referred to the radiology department of Qaem and Razavi hospitals for any reason, in whom a diagnosis of BAV was made. Additionally, patients who underwent cardiac surgery due to complications arising from BAV were also included in this study. The sampling method was non-probabilistic and convenient. Based on minimum comparison assumptions, a sample size of 95 cases for the BAV group was calculated. To enhance the study's power and prevent potential Type II error, it was decided to increase the sample size to at least 100 cases.

All patients referred to Qaem and Razavi hospitals for evaluation, where BAV was diagnosed, or those who were to undergo surgery due to complications from BAV, were included in the study. Patients who met the exclusion criteria were removed from the study. The background information of patients, including age, gender, height, weight, and cardiovascular risk factors such as diabetes, history of ischemic heart disease, hypertension, and smoking status, was recorded for all patients.

To assess valve morphology, insufficiency, stenosis, aortic dilation, and any cardiac abnormalities, transthoracic or transesophageal echocardiography was utilized. After collecting the data and entering it into statistical software, the data were analyzed. All patients diagnosed with BAV who were referred for evaluation or surgery were included in the study. Patients with Marfan syndrome, connective tissue disorders, and inflammatory bowel disease were excluded from the study.

Data collection was conducted in a laboratory setting using a checklist. Descriptive statistics were presented using appropriate charts and tables. For comparing data between two groups, Pearson's Chi-square test was used for qualitative variables; if the necessary conditions for this test were not met, other valid tests such as Fisher's exact test were employed. For quantitative variables, the normality of data distribution was first assessed using the Kolmogorov-Smirnov test. In cases of normally distributed quantitative data, an independent t-test was

used for group comparisons; if normality was not established, the non-parametric Mann-Whitney U test was utilized. A significance level of 5% was set for all tests, and SPSS version 17 was used for data analysis.

Results

In this study, a total of 141 patients with a bicuspid aortic valve were examined. The findings are presented in appropriate tables and graphs. Regarding gender distribution, 105 patients (74.5%) were male and 36 patients (25.5%) were female, resulting in a male-to-female ratio of approximately 3:1. The mean age of the participants was 34 years with a standard deviation of 12.82 years, and their ages ranged from 11 to 74 years. Most individuals (63.9%) were in the age group of 20 to 40 years. Additionally, the mean height, weight, and body surface area of the participants were 169.5 cm (standard deviation of 8.5 cm), 66.2 kg (standard deviation of 2.8 kg), and 1.76 m^2 (standard deviation of 0.76 m^2), respectively. Among the participants, 12 individuals (8.5%) reported tobacco use.

The table below shows the frequency distribution of the medical history of the studied patients concerning four conditions: Ischemic Heart Disease (IHD), Hypertension (HTN), Diabetes Mellitus (DM), and Hyperlipidemia (HLP). Most of the studied individuals had negative medical histories for these conditions, with 1.7% having a history of IHD, 9.2% having a history of HTN, 1.2% having a history of DM, and 6.4% having a history of HLP. (Table 1)

In the studied population, 33 individuals had mild aortic regurgitation (AI), 53 had moderate aortic regurgitation, and 38 had severe aortic regurgitation. Additionally, 17 individuals were normal in this regard (Table 2). Regarding AS, 27 individuals had mild stenosis, 8 had moderate stenosis, and 11 had severe stenosis, while 95 individuals were normal in this aspect. (Table 3)

Finally, by combining these two valvular disorders, 39 individuals (27.7%) were either normal or had mild AS or AI, 11 individuals (7.8%) had moderate to severe AS, 83 individuals (58.9%) had moderate to severe AI, and 8 individuals (5.7%) had moderate to severe AS and AI. (Table 4)

Table 1. Frequency Distribution of the Medical History of the Studied Patients.

Indicator / Medical History		Number	Percentage
Ischemic Heart Disease (IHD)	NO	131	92/9
	YES	10	7/1
	Total	141	100/0
Hyper Tension (HTN)	NO	128	90/8
	YES	13	9/2
	Total	141	100/0
Diabetes Mellitus (DM)	NO	139	98/6
	YES	2	1/4
	Total	141	100/0
Hyperlipidemia (HLP)	NO	132	93/6
	YES	9	6/4
	Total	141	100/0

Table 2. Frequency Distribution of Aortic Insufficiency in the Studied Individuals.

Index / Aortic Insufficiency	Count	Percentage
Normal	17	12/0
Mild	33	23/4
Moderate	53	37/6
Severe	38	27/0
Total	141	100/0

Table 3. Frequency Distribution of Aortic Stenosis in the Study Subjects.

Index / Aortic Stenosis	Count	Percentage
Normal	95	67/4
Mild	27	19/1
Moderate	8	5/7
Severe	11	7/8
Total	141	100/0

Table 4. Frequency Distribution of Valvular Disorders in the Study Subjects.

Index / Valvular Disorder	Count	Percentage
Normal, or Mild AS or AI	39	27/7
Moderate to Severe AS	11	7/8
Moderate to Severe AI	83	58/9
Moderate to Severe AS and AI	8	5/7
Total	141	100/0

Based on the figure below, the valves were classified into five different types. Additionally, according to the valve type, they were divided into two main categories: BAV-AP and BAV-RL. (Figure 3)

The study found that there were 67 cases (47.5%) of type 1 valves, 13 cases (9.2%) of type 2 valves, 45 cases (31.9%) of type 3 valves, 13 cases (9.2%) of type 4 valves, and 3 cases (2.2%) of type 5 valves among the studied individuals.

According to the morphological classification, types 1 and 2 are categorized as BAV-AP, while types 3, 4, and 5 are categorized as BAV-RL. The study showed that among the studied individuals, 80 people (56.7%) had BAV-AP type valves, and 61 people (43.3%) had BAV-RL type valves.

Among the studied individuals, 109 (equivalent to 77.3%) had no cardiac anomalies, while 32 individuals were found to have cardiac anomalies. Among these 32 individuals, 12 had a patent foramen ovale (PFO), 10 had aortic coarctation, 3 had VSD, 5 had mitral valve prolapse (MVP), and 2 had both PFO and aortic coarctation simultaneously.

The analysis revealed that regarding the presence of aortic regurgitation (regardless of severity), 91.3% of individuals in the BAV-AP group and 83.6% in the BAV-RL group had mild to severe aortic regurgitation. Despite the higher prevalence of aortic regurgitation in the BAV-AP group, statistical comparison showed that the difference between the two groups was not significant.

Furthermore, concerning the presence of aortic stenosis (regardless of severity), 30% of individuals in the BAV-AP group and 36.1% in the BAV-RL group had mild to severe aortic stenosis. Although there was a higher prevalence of aortic stenosis in the BAV-RL group, statistical comparison indicated that this difference was also not significant.

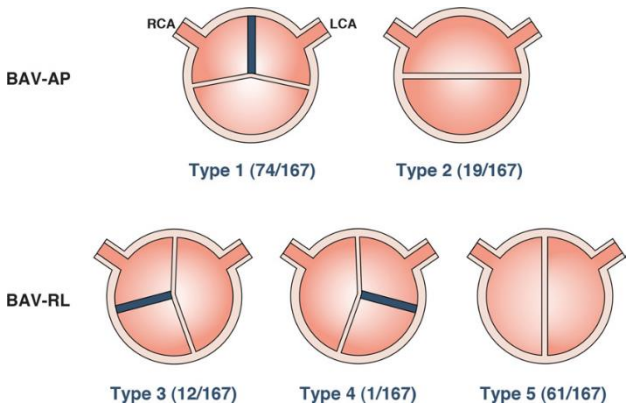

Figure 3. Schematic representation of the morphology of different types of bicuspid valves.

In assessing the diameter of the ascending aorta, the mean diameter in the BAV-AP group was 3.79 ± 0.746 cm, while in the BAV-RL group, it was 3.59 ± 0.605 cm. Statistical comparison demonstrated that there was no significant difference between the two groups in this regard. Additionally, there were no differences in the aortic diameter at the aortic ring and sinotubular junction (STJ) between individuals with the two valve types; however, at the sinuses of Valsalva, the aortic diameter in the BAV-AP group was significantly greater than that in the BAV-RL group (3.49 ± 0.656 cm vs. 3.27 ± 0.507 cm, p = 0.039).

In examining aortic dilation at the ascending aorta (based on sex and body surface area), it was found that 60.8% of individuals in the BAV-AP group had aortic dilation, compared to 43.1% in the BAV-RL group. Statistical comparison indicated that this difference between the two groups was significant.

Comparing the prevalence of cardiac anomalies between the two groups based on valve type revealed that the prevalence of cardiac anomalies in the BAV-AP group was 26.3%, while in the BAV-RL group, it was 18%. The statistical analysis showed no significant difference between the two groups in this regard. Additionally, some anomalies such as aortic coarctation and mitral valve prolapse were more prevalent among individuals with BAV-AP compared to those with BAV-RL; however, due to the small sample size, statistical comparison was not feasible.

The analyses also indicated that regarding the presence of aortic regurgitation (regardless of severity), 92.5% of individuals with type 1 valves, 86.7% with type 3 valves, and 76.9% with type 4 valves exhibited aortic regurgitation. Statistical comparison showed no significant differences among the three groups in this regard.

Regarding aortic stenosis (regardless of severity), 25.4% of individuals with type 1 valves, 42.2% with type 3 valves, and 15.4% with type 4 valves had aortic stenosis. Although there was a higher prevalence of aortic stenosis in type 3 valves, statistical comparison indicated that there was no significant difference among the three groups.

Finally, the assessments showed no significant differences in aortic diameter at various locations such as the ascending aorta, aortic annulus, sinuses of Valsalva, and sinotubular junction among individuals with types 1, 3, and 4 valves. Additionally, concerning aortic dilation at the ascending aorta, it was determined that 61.3% of individuals with type 1 valves, 40.5% with type 3 valves, and 46.2% with type 4 valves experienced aortic dilation. Despite a higher prevalence of aortic dilation among individuals with type 1 valves, statistical comparison indicated no significant differences among the three groups.

Comparing the prevalence of cardiac anomalies across three groups based on valve type revealed that the prevalence of cardiac anomalies was 23.9% for type 1, 17.8% for type 3, and 23.1% for type 4, with no statistically significant differences among the three groups. Additionally, it was noted that the prevalence of aortic coarctation and PFO was higher than other anomalies; however, due to the small sample size, statistical comparison could not be performed.

Discussion

BAV is the most common congenital heart defect, with a prevalence of 0.5% to 2% (13-15). The prevalence of this condition is higher in males, with a male-to-female ratio of approximately 3:1 (16). Complications of this disease are common in adulthood. making BAV the most frequent cause of valve replacement due to stenosis (17-19). Therefore, the burden of this disease is greater than that of other congenital diseases (16). Despite the significance of this condition, our understanding of it is not complete, and there are still unanswered questions regarding this relatively common disease.

It is believed that the morphology of the bicuspid valve in BAV plays a major role in valve insufficiency and the subsequent hemodynamic disturbances. However, the clinical manifestations of this disease are somewhat heterogeneous, with symptoms potentially arising from infancy to late adulthood. These symptoms mainly include aortic stenosis, aortic regurgitation (or both occurring simultaneously), and various associated anomalies such as hypoplastic left

heart syndrome, aortic coarctation, and ascending aortic aneurysm (4). Additionally, the risk of aortic dissection in BAV patients is nine times greater than that in patients with a normal trileaflet valve (14).

The results of a cross-sectional study of 141 patients with BAV showed that the prevalence of this condition was higher in males, with a male-to-female ratio of 3:1. The average age of the patients was 34, and most patients were in the age range of 20 to 40 years.

In terms of valve phenotype, the most common phenotype was Type 1 (fusion of the right and left coronary cusps with a raphe), which accounted for 47.5% of cases. Type 5 (complete two cusps without a raphe with right-left orientation) had the lowest prevalence, with only 3 cases. Ultimately, in terms of anatomical orientation, 57% of individuals had BAV-AP (anterior-posterior) and 43% had BAV-RL (right-left).

Regarding valvular disorders, 88% of individuals had AI, with approximately 65% of all individuals experiencing moderate to severe insufficiency. Additionally, about 33% of individuals had AS, with a prevalence of moderate to severe stenosis at 13.5%. By combining these two valvular disorders, it was found that 59% of individuals had only moderate to severe AI, 8% had only moderate to severe AS, and about 6% had both moderate to severe AI and AS simultaneously; 27% of individuals had normal valve function or mild AI or AS.

The study indicated that the prevalence of aortic insufficiency was higher in the BAV-AP group compared to the BAV-RL group (91% vs. 84%), although the difference between the two groups was not statistically significant. Conversely, the prevalence of aortic stenosis was higher in the BAV-RL group (36% vs. 30%), but this difference was also not statistically significant.

In terms of associated anomalies, 77% of individuals had no other accompanying anomalies; the most common anomalies were PFO and aortic coarctation, observed in 8.5% and 7% of cases, respectively. Other anomalies included VSD, MVP, and the simultaneous presence of PFO and coarctation. A comparison of the prevalence of other associated cardiac anomalies between the two types of valves showed no significant differences between the two groups.

Conclusion

The present study revealed that BAV disease in the northeastern region of Iran differs in some characteristics from other parts of the world. One of the most significant differences is the high prevalence of aortic regurgitation among the individuals studied. Additionally, the prevalence of ascending aortic dilation was also relatively high in this study. This is important to note because aortic dilation is an independent risk factor for life-threatening conditions such as aortic dissection and rupture. The study also highlighted that BAV presents different phenotypes in various communities, and some of its characteristics remain unclear. BVA is not just a valvular issue but is also linked to significant cardiovascular complications. Therefore, that further studies should be conducted in this area, especially in our country, to enhance our understanding the risk factors associated with this disease and to improve patient management.

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