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Assessment of Bicuspid Aortic Valve in Children

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ABSTRACT

Background: Bicuspid aortic valve (BAV) is the most common congenital heart defect and is frequently associated with aortic dilation (aortopathy) and other cardiovascular malformations. In pediatric patients, the relationship between BAV morphology and associated valvular and structural anomalies remains an important area of investigation. **Aim:** To assess the characteristics of BAV in the pediatric population and to analyze its association with other cardiac lesions, including valvulopathies. **Methods:** This retrospective study included 62 children diagnosed with BAV. We evaluated BAV morphology and analyzed associated valvulopathies and congenital heart defects using clinical and echocardiographic data. **Results:** BAV was more common in men, accounting for 80.6% of cases. Type 1 BAV was the predominant phenotype. Aortic dilation was present in 69.3% of patients, aortic regurgitation (AR) in 64.5%, and aortic stenosis (AS) in 48.3%. Other congenital anomalies, such as atrial septal defect, ventricular septal defect, and mitral valve malformations, were observed in 59.5% of cases. No significant associations were found between gender and valvulopathies or between valve morphology and coarctation of the aorta (CoA). However, the R/L phenotype was strongly associated with AR, while the R/N phenotype was more frequently associated with AS. **Conclusion:** Aortopathy was identified in two-thirds of patients, primarily involving the sinotubular junction and ascending aorta. CoA was significantly associated with a lower prevalence of AS, while AR was notably more frequent in patients with aortopathy.

Keywords: bicuspid aortic valve, children, echocardiography, pediatric cardiology

INTRODUCTION

Bicuspid aortic valve (BAV) is a common congenital heart condition that warrants careful monitoring and management due to its association with aortic dilation (AD), also referred to as aortopathy.[1,2] In daily clinical practice, we often ask: Is this the initial reason for presentation, or is it more frequently identified during follow-up? How does it evolve over time? And is it an independent risk marker?

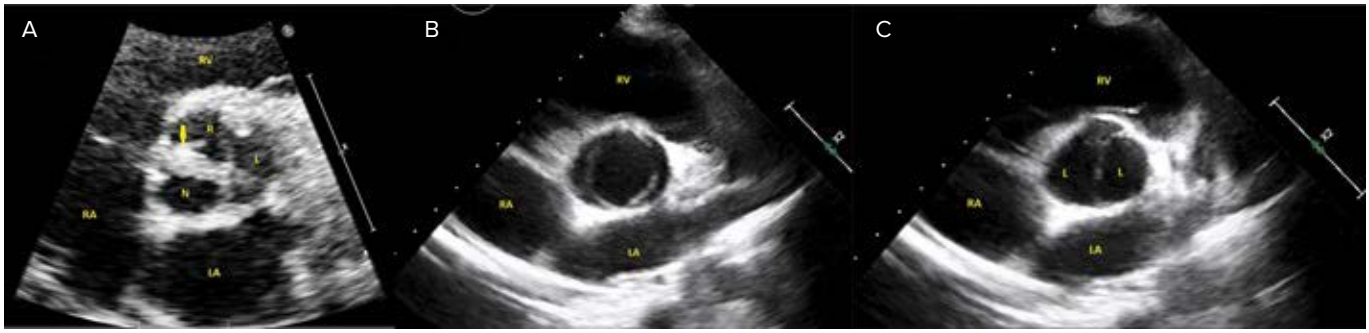

FIGURE 1. Transthoracic echocardiogram parasternal short axis view. **A.** Diastolic view of BAV with raphe (arrow), phenotype 1B (right–noncoronary cusp fusion). L, left coronary cusp; LA, left atrium; N, noncoronary cusp; R, right coronary cusp; RA; right atrium; RV, right ventricle. **B.** Systolic view of phenotype 0 (no raphe) BAV. **C.** Diastolic view of phenotype 0 (no raphe) BAV. L, leaflet.

Addressing these questions is essential for improving patient outcomes and informing therapeutic strategies.

Aortopathy is a complex condition with multiple underlying mechanisms. One key feature is medial degeneration, characterized by fragmentation of elastic fibers and apoptosis of smooth muscle cells, a process that appears to be accelerated in patients with both aortic stenosis (AS) and BAV.[3,4] Studies have shown that the silent, gradual progression of AD can lead to severe complications in up to 30% of affected individuals, including aneurism formation, aortic dissection, or rupture, typically in adulthood.[2,5,6] In the adult population, the incidence of aortic dissection has been reported at 6–7.2 cases per 100,000 people. However, these figures may underestimate the true incidence, as many cases result in sudden death before hospital admission.[7–9]

Over the past decade, two main hypotheses have emerged regarding the pathophysiological mechanisms underlying aortopathy. One supports a genetic etiology, often associated with a high prevalence of aortic root dilation, while the other highlights the hemodynamic effects of the altered transvalvular flow on the aortic wall.[10,11] It is important to emphasize that the pattern and rate of aortic dilation differ significantly between pediatric and adult populations.[12,13]

BAV is frequently associated with other cardiovascular malformations, most notably left ventricular outflow tract obstructions, coarctation of the aorta (CoA), and Shone syndrome. CoA is present in 7–10% of adults with BAV, while BAV is identified in over half of patients with CoA. This association greatly increases the risk of adverse outcomes.[13–17]

Enhanced surveillance aimed at preventing BAV-related complications can improve patient outcomes and reduce morbidity and mortality.[18,19] With this in mind, the present study was designed to assess BAV in the pediatric population. As a secondary objective, we also examined the relationship between BAV and other structural cardiac anomalies, including valvular defects.

MATERIAL AND METHOD

This retrospective study was conducted at a tertiary pediatric cardiology center between 2019 and 2023. We used the following inclusion criteria: patients aged 1 month to 17 years (median age 10 years) diagnosed with BAV of any type. Subjects with unicuspid, tricuspid, and quadricuspid aortic valves, associated extracardiac malformations, underlying genetic syndromes, or incomplete echocardiographic evaluations were excluded from the study.

We analyzed the association of BAV with other congenital heart defects, particularly AD, aortic regurgitation (AR), aortic stenosis (AS), and CoA, as well as other malformations such as atrial septal defect (ASD), ventricular septal defect (VSD), and mitral valve abnormalities. CoA was defined as narrowing of the aorta, including isthmic stenosis,

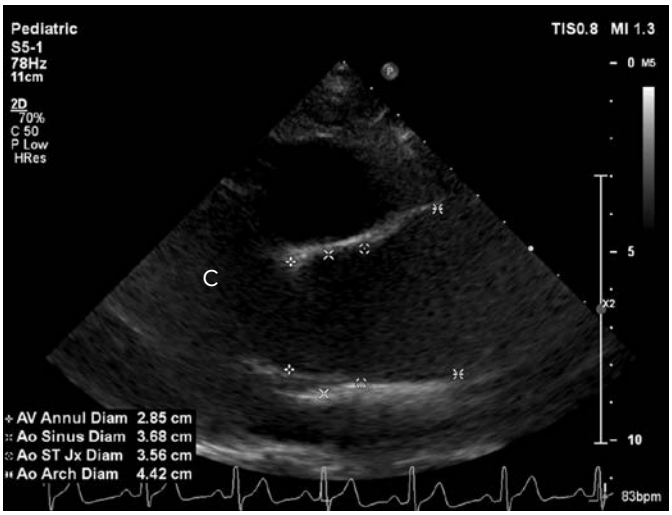

FIGURE 2. Aortic measurement, transthoracic echocardiogram parasternal long axis view. Ao Arch Diam, aortic arch diameter; Ao Sinus Diam, aortic sinuses diameter; Ao ST Jx Diam, aortic sinotubular junction diameter; AV Annul Diam, aortic valve annular diameter.

TABLE 1. Demographic characteristics of the study population

Characteristics	n = 62
Sex	
Male	50 (80.6%)
Female	12 (19.4%)
Age at diagnosis (years)	
0–1	29 (46.8%)
1–3	5 (8%)
3–10	13 (11%)
10–17	15 (24.2%)
Weight (kg)	38.25 ± 22.75
Height (cm)	148 (108–166)
BSA (m^2)	1.17 ± 0.52
BMI (kg/m^2)	18.21 ± 4.06

Data expressed as number (frequency), mean ± s.d., or median (interquartile range), as appropriate.

transverse aortic arch hypoplasia, or abdominal aorta stenosis, as diagnosed by transthoracic echocardiography.

Demographic data collected included age, sex, weight, height, and the date of BAV diagnosis. The anatomical and developmental characteristics of the aortic valve, aorta, and associated cardiovascular anomalies were assessed based on serial echocardiographic measurements, including valve morphology and aortic diameters. BAV morphology was classified using the Sievers and Schmidtke system: type 0 (no raphe), type 1 (one raphe), and type 2 (two raphes).[20] Type 1 BAV was further categorized according to the location of the fused cusps: right–left (R/L), right–non-coronary (R/N), and left–non-coronary (L/N) (Figure 1).

Aortic measurements were obtained using 2D transthoracic echocardiography, in accordance with European guidelines. The aortic annular diameter was measured from inner edge to inner edge between the hinge points of the aortic valve leaflets, in the left parasternal long-axis view during systole, which reveals the largest aortic annular diameter. Diameters at the level of the sinuses of Valsalva, the sinotubular junction and the ascending aorta were also measured inner edge to inner edge in the left parasternal long-axis view, during systole. The ascending aorta was measured at its widest visible diameter (Figure 2).[21] CoA was defined as hemodynamically significant when the systolic pressure gradient at the isthmic level, as measured by echocardiography, exceeded 20 mmHg.

Given the heterogeneity of the studied parameters in our pediatric study population, standardization of measurements was necessary. Therefore, echocardiographic Z scores were calculated using the Cantinotti formula, following prior estimation of body surface area (BSA) using the Haycock formula: BSA [m^2] = Weight [kg] × 0.5378 × Height [cm] × 0.3964 × 0.024265).[22] Aortopathy was defined as pathological enlargement of the aorta. We considered enlargement at the level of the aortic annulus, aortic root, sinotubular junction, and ascending aorta as indicative of global aortic dilation. Segmental dilation was defined as enlargement of at least one of these segments. To diagnosis of aortopathy was established using Z scores derived from the Cantinotti reference values, with a Z score greater than 2 s.d. indicating

TABLE 2. BAV phenotype distribution in the study population

Phenotype	n = 62
Type 0	12 (19%)
Type 1	49 (79%)
R/L	18%
R/N	25%
L/N	6%
Type 2	1

Data expressed as number (frequency).

TABLE 3. Cardiovascular malformations associated to BAV

Characteristics	n	%
AD	43	69.3
Moderate	25	40.3
Severe	14	22.6
AR	40	64.5
Mild	20	32.3
Moderate	18	29
Severe	2	3.2
AS	30	48.3
Mild	5	3.2
Moderate	20	32.3
Severe	5	3.2
CoA	21	33.8
Hemodynamically significant	15	24.2
Hemodynamically insignificant	6	9.7
Other cardiovascular pathologies	37	59.7

Data expressed as number (frequency).

TABLE 4. Relationship between BAV phenotype and associated pathologies

Characteristics	CoA p value	AR p value	AS p value	AD p value
Type 0	0.51	0.51	0.75	0.08
Type 1				
R/L	0.37	0.009	0.05	0.06
R/N	0.09	0.05	0.004	0.40
L/N	>0.99	0.65	0.67	0.35

Data expressed as number (frequency). All p values calculated using Fisher's exact test.

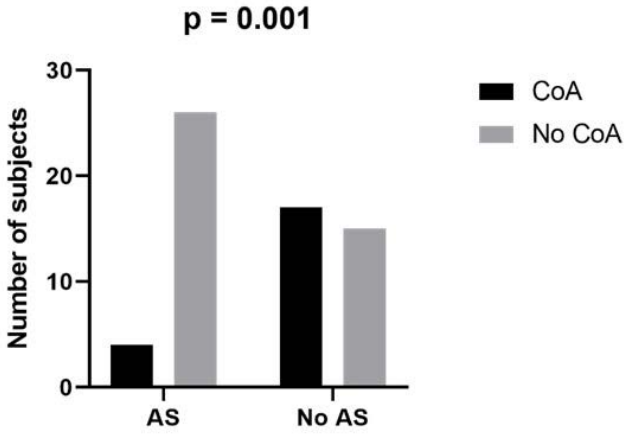

FIGURE 3. The relationship between CoA and AS. Calculated using Fisher's exact test.

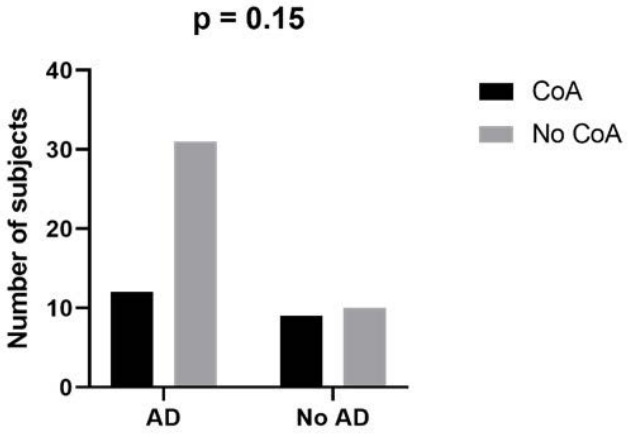

FIGURE 4. The relationship between CoA and AD. Calculated using Fisher's exact test.

aortopathy. For further stratification, moderate aortopathy was defined as a Z score between 2 and 3.9 s.d., and severe aortopathy as a Z score ≥ 4 s.d.[23]

Statistical analysis

Echocardiographic data and patient information were collected from medical charts and entered into a Microsoft Excel database. Statistical analysis was performed using GraphPad Prism v.9.3.1 for Windows (GraphPad Software).

The Kolmogorov–Smirnov normality test was used to assess data distribution. We used the unpaired t test to evaluate differences between two groups with normally distributed data, with results reported as mean ± s.d. The Mann–Whitney U test was used to investigate differences between two groups with non-normally distributed data, with results reported as median (interquartile range). Pearson or Spearman correlation coefficients were calculated to determine the relationship between continuous parameters or between continuous and semiquantitative variables. Fisher's exact test was used to identify associations between categorical variables. All statistical tests were two-sided, and a p value of <0.05 was considered statistically significant.

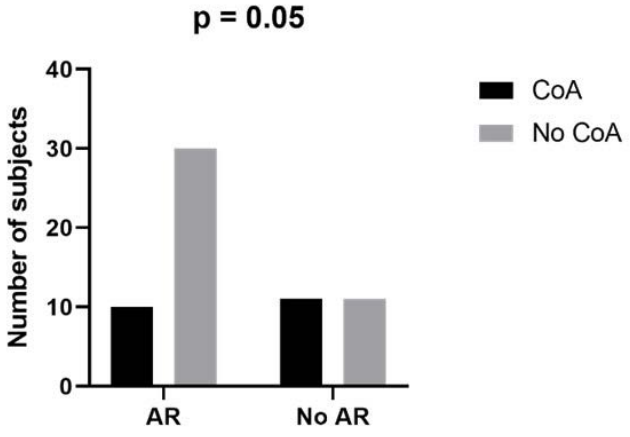

FIGURE 5. The relationship between CoA and AR. Calculated using Fisher's exact test.

RESULTS

The demographic characteristics of the study population are summarized in Table 1. We observed a higher prevalence of BAV in male patients, accounting for 80.6% of cases. The age at diagnosis was similar between male and female subjects, and no significant association was found between sex and phenotype ($p > 0.05$). The distribution of BAV phenotypes is presented in Table 2. Type 1 BAV was the predominant morphology, identified in over two-thirds of patients, followed by types 0 and 2.

TABLE 5. General characteristics and associated diseases of patients with and without AD

Characteristics	AD (n = 43)	No AD (n = 19)	p value
Sex, male	36 (83.7%)	14 (73.7%)	0.48*
Age at diagnosis (years)	1 (0–10)	2 (0–7)	0.93#
AR	34 (79.1%)	6 (31.6%)	0.0005*
AS	23 (53.5%)	7 (36.8%)	0.27*
CoA	12 (27.9%)	9 (47.4%)	0.15*

Data expressed as number (frequency) or median (interquartile range), as appropriate.
*Calculated using Fisher's exact test; # Calculated using the Mann–Whitney U test

TABLE 6. Distribution of severity grades in associated cardiovascular diseases

Characteristics	AD (n = 43)	No AD (n = 19)
AR		
Mild	16 (37.2%)	4 (21%)
Moderate	16 (37.2%)	2 (10.5%)
Severe	2 (4.6%)	-
AS		
Mild	4 (9.3%)	1 (5.26%)
Moderate	15 (34.9%)	5 (26.3%)
Severe	4 (9.3%)	1 (5.26%)
CoA	12 (27.9%)	9 (47.4%)
Hemodynamically significant	8 (18.6%)	7 (38.8%)
Hemodynamically insignificant	4 (9.3%)	2 (10.5%)

Data expressed as number (frequency).

Associated cardiovascular malformations are listed in Table 3. In terms of vascular involvement, 69.3% of patients exhibited AD, 64.5% had AR, and 48.3% presented with AS. Additionally, 59.5% had other structural anomalies, such as ASD, VSD, or mitral valve malformations. No significant association was found between sex and the presence of valvopathies ($p > 0.05$). However, the R/L and R/N phenotypes were associated with valvular abnormalities, particularly AR and AS, as shown in Table 4.

Regarding the association between BAV and other congenital heart defects, CoA was the most frequently identified lesion. Patients with CoA were significantly less likely to present AS compared to patients without CoA (Figure 3). Although the association between CoA and AD was not statistically significant (Figure 4), CoA showed a tendency to co-occur with AR (Figure 5). No significant relationship was found between BAV morphology and the presence of CoA (Table 4).

The general characteristics of the study population, stratified by the presence or absence of AD, are summarized in Table 5. AD was identified in 69.3% of patients, with a predominance among males, who accounted for 83.7% of this group. Nearly 80% of patients with AD also exhibited AR. Among patients with AD, and 53.5% had AS, compared to only 36.6% of patients without AD. Additionally, one-third of children with AD had CoA, a condition observed in only half of the patients without AD.

AR and AS were common findings among patients with BAV. The distribution of severity is detailed in Table 6. Although mild to moderate forms were present, no statistically significant differences were found between severity grades ($p > 0.05$ for all comparisons).

The associations between segmental AD and factors such as sex, valve morphology, AR, AS, and CoA are outlined in Table 7. Of note, dilation of the aortic annulus and ascending aorta was significantly associated with AR, while ascending aortic dilation was also linked to AS.

To assess the progression of AD, we analyzed serial echocardiographic measurements obtained from the same patients at different time points. Z score values remained relatively stable over time, with comparable measurements observed across the study population, as illustrated in Figures 6–9.

TABLE 7. The relationship between sex, phenotype, AR, AS, CoA, and AD at different aortic levels

Characteristics	Annulus			Valsalva sinuses			Sinotubular junction			Ascending aorta		
	AD	No AD	p value*	AD	No AD	p value*	AD	No AD	p value*	AD	No AD	p value*
Sex, male	17 (85%)	32 (78.05%)	0.73	9 (81.82%)	34 (82.93%)	0.99	19 (79.17%)	30 (81.8%)	0.99	28 (87.5%)	20 (76.92%)	0.31
0	5 (41.67%)	7 (58.33%)	0.50	3 (25%)	9 (75%)	0.67	5 (45.45%)	6 (54.55%)	0.99	7 (58.33%)	5 (41.67%)	0.99
R/L	5 (27.78%)	13 (72.22%)	0.76	2 (13.33%)	13 (86.67%)	0.47	7 (50%)	7 (50%)	0.75	6 (35.29%)	11 (64.71%)	0.08
R/N	8 (33.33%)	16 (66.67%)	0.99	4 (21.05%)	15 (78.95%)	0.99	10 (41.67%)	14 (58.33%)	0.78	16 (69.57%)	7 (30.43%)	0.10
L/N	1 (16.67%)	5 (83.33%)	0.65	1 (20%)	4 (80%)	0.99	2 (40%)	3 (60%)	0.99	3 (50%)	3 (50%)	0.99
AR	19 (95%)	20 (48.78%)	0.0004	26 (63.41%)	9 (81.82%)	0.3	19 (79.17%)	18 (60%)	0.15	26 (81.25%)	12 (46.15%)	0.006
AS	8 (40%)	21 (51.22%)	0.43	4 (36.36%)	21 (51.22%)	0.5	9 (37.5%)	17 (56.67%)	0.18	21 (65.63%)	8 (30.77%)	0.01
CoA	6 (30%)	15 (36.59%)	0.77	4 (36.36%)	12 (29.27%)	0.71	5 (20.83%)	12 (40%)	0.15	8 (25%)	12 (46.15%)	0.1

Data expressed as number (frequency). * Calculated using Fisher's exact test.

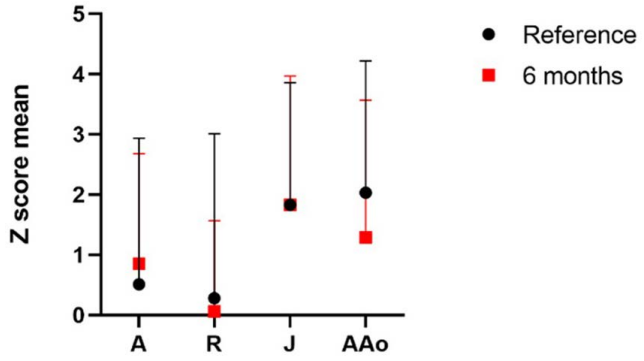

FIGURE 6. The relationship between Z score values at 6 months. A, aortic annulus; Aao, ascending aorta; J, sinotubular junction; R, aortic root.

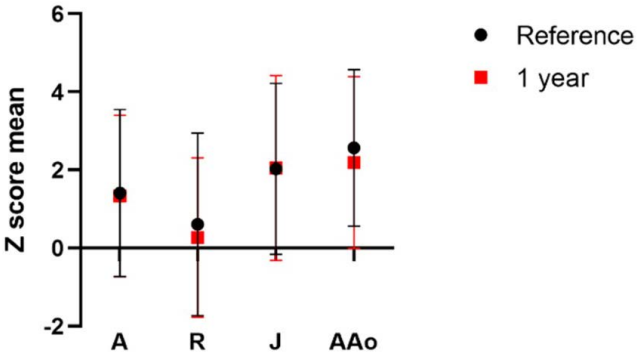

FIGURE 7. The relationship between Z score values at 1 year

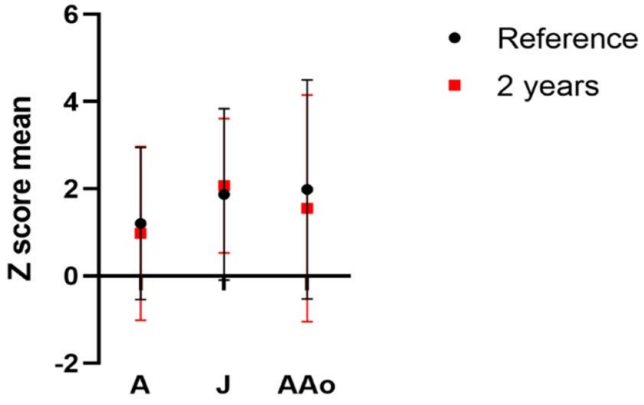

FIGURE 8. The relationship between Z score values at 2 years

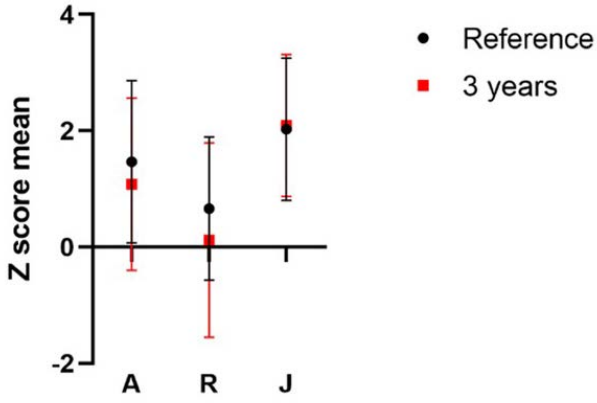

FIGURE 9. The relationship between Z score values at 3 years

DISCUSSION

Bicuspid aortic valve (BAV) is relatively common among male patients, as supported by existing literature and confirmed by our findings: 80.6% of patients with BAV in our study were male. BAV is frequently associated with aortic dilation (AD), occurring in approximately two-thirds of cases.[24,25] Despite this association, severe complications such as aortic dissection or thoracic aortic aneurysm (potential consequences of progressive AD) are rare during childhood and more likely to emerge in adulthood. Although AD can occur at any age and may be accompanied by histopathological changes such as fibrotic degeneration,[26] these complications highlight the importance of close monitoring and timely intervention. In particular, determining the optimal timing for preventative surgical procedures, such as aortic valve replacement, remains a clinical challenge.[27,28]

Supporting the hypothesis that aortic wall changes in BAV originate during embryogenesis, studies have found intimal abnormalities and a significantly thinner medial layer in the ascending aorta of premature infants with BAV, compared to older age groups.[29,30]

Consistent with the findings of Spaziani *et al.*,[31] our study included only patients with non-syndromic aortopathy. We acknowledge that syndromic forms of aortopathy, such as those seen in Marfan, Turner, or Loeys-Dietz syndromes, have distinct clinical courses and management considerations, due to their multifactorial nature.[32–37] As a result, BAV associated with significant AD is extensively discussed in the literature, with well-established treatment strategies.

The analysis of BAV morphology in relation to valvular and aortic wall modifications has been a subject of ongoing interest among researchers. Several studies have reported associations between R/L and R/N phenotypes and conditions such as CoA and valvopathies.[31,38,39] In our study, the R/N phenotype was the most common and tended to be associated with the presence of CoA. Although the association between phenotype and aortopathy was not statistically significant, AD tended to be more common in patients with the R/L phenotype. We also found that the R/N phenotype was significantly more common in pa-

tients with valvopathies, especially AS, whereas the R/L phenotype was more frequently associated with AR.[39] Data concerning the relationship between R/N and L/N phenotypes and AR is inconsistent. Some studies support our findings, while others report opposing results.[40,41] These discrepancies may reflect population-specific variations in the predominant phenotype associated with valvopathies.

In the context of BAV and aortopathy, certain features require close monitoring, particularly the potential correlations between BAV phenotypes and the development of AD, AR, or AS. Previous studies, including those on pediatric and young adult populations, have documented similar trends.[38,42–47] Data from the literature suggest that the presence of AR in conjunction with aortic root or ascending aorta dilation does not necessarily result in significant progression of these lesions during childhood, regardless of severity.[30,38,48,49] In our analysis, AR was significantly more frequent among patients with aortopathy compared to those without (OR 8.18; 95% CI 2.40–24.33; p = 0.0005). However, there was no significant association between AD and the severity of the AR (p > 0.05).

Similarly, ascending aorta dilation was associated with AS, consistent with previous studies linking moderate-to-severe AS to dilation of the ascending aorta.[38,49–55] Our findings support this association. However, as with AR, AD was not significantly associated with the severity of AS (p = 0.27).

Limitations

Several limitations of the present study should be acknowledged. First, its retrospective design inherently limits the ability to establish causal relationships. Second, the relatively small sample size reflects the fact that data were collected from a single tertiary pediatric cardiology center, which may limit the generalizability of the findings. Additionally, the use of Z scores to assess aortic dimensions in the pediatric population has known limitations, including variability based on the chosen reference model and body size calculations.

CONCLUSIONS

The predominant BAV phenotype observed in our cohort was characterized by the fusion of two commissures and the presence of a raphe (type 1 morphology). Aortopathy was identified in approximately two-thirds of patients, with a notable tendency for dilation at the level of the sinotubular junction and ascending aorta. Patients with CoA were significantly less likely to present with AS, while AR was significantly more frequent among those with aortopathy. Regarding valve morphology, the R/L subtype was strongly associated with AR, whereas the R/N subtype showed a stronger association with AS.

CONFLICT OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

The study was approved by the ethics committee of the Emergency Institute for Cardiovascular Diseases and Transplantation of Târgu Mureș, Romania (approval no. 8094/03.11.2023).

CONSENT TO PARTICIPATE

The research complied with the ethical principles outlined in the Declaration of Helsinki. Informed consent was not required due to the retrospective and anonymized nature of the data.

DATA AVAILABILITY

Further data are available from the corresponding author upon reasonable request.

FUNDING

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