INTRODUCTION

A congenitally bicuspid aortic valve has two functional leaflets rather than the normal three. Bicuspid aortic valve may be diagnosed in about 1%–2% of the pediatric congenital heart disease population. In one study, the median age of pediatric patients being diagnosed with bicuspid aortic valve was 4 years. However, because the bicuspid aortic valve may be entirely silent and undiagnosed birth through adolescence, these prevalence figures may be underestimated, and children with bicuspid aortic valve may be older at diagnosis. A majority of patients with bicuspid aortic valve may have relatively normal valve function until they develop stenosis in late adulthood. Other reports have suggested a much lower than expected prevalence in African-Americans, whereas the male-to-female
ratio may be > 2:1, with males constituting 70%-80% of bicuspid aortic valve cases.[3,8-10]

Patients with isolated bicuspid aortic valve are generally asymptomatic and follow a rather benign course, but one recent investigation found that the severity of aortic regurgitation increased with age.[11] However, patients with bicuspid aortic valve and coexisting congenital heart diseases, such as an interrupted aortic arch, coarctation of the aorta, or ventricular septal defect may be more susceptible to complications than in the general population.[12-14] Bicuspid aortic valve morphology is a common risk factor for valve-related complications, for example, dilation of the aorta, which may be present at birth and could progress over time irrespective of the functional state of the valve.[5,15-19] Furthermore, bicuspid aortic valve has been identified as the root cause of aortic stenosis in 70%-85% of pediatric cases and is associated with a higher risk of infective endocarditis and acute thoracic aortic emergencies, such as aneurysm and dissection and valve-related re-intervention.[2,14,20] Despite advances in disease management, children with congenital heart disease who survive into adulthood are at increased risk of sudden death, with a relatively high percentage of these patients having bicuspid aortic valve.[21]

Conventional aortic valve repair has been used for bicuspid aortic valve patients with coexisting aortic pathology such as dilation, aneurysm, coarctation, and other structural pathologies including ventricular septal defect, with acceptable outcomes.[2,14] Spaziani et al. retrospectively investigated the medium-term clinical outcomes associated with conventional aortic valve repair, exploring the risk of progression of aortic valve disease and aortic dilation in pediatric patients with isolated bicuspid aortic valve, and focusing on the clinical outcomes of cardiac death, infective endocarditis, and other aortic complications.[22] Across several investigations, clinical outcomes in pediatric patients with isolated or complicated bicuspid aortic valve were generally favorable to excellent, and the progression of aortic valve dysfunction and aortic dilation was relatively slow, except for those with comorbid hypertension.[10,14,22-24]

Bicuspid aortic valve is not a “traditionally-defined” congenital heart disease and is frequently omitted from pediatric congenital heart disease studies.[25,26] Furthermore, some previous epidemiologic bicuspid aortic valve studies are also over a decade old and cover relatively brief periods of time,[1-3] whereas clinic-based studies are somewhat less generalizable to practice settings in other geographic areas. An updated, pediatric population-based investigation, using a heterogeneous bicuspid aortic valve cohort that includes both isolated and complicated patients from a large, routine health-care system is, therefore, warranted. That is the aim of this investigation.

MATERIALS AND METHODS

Access to healthcare in South Carolina USA is funded predominantly by public (for low-income families) or private insurance payers, which cover about 90% and 10%, respectively, of the children and adolescents residing in the state. Once a child is diagnosed with a serious or persistent condition, including a congenital heart disease, the family can apply for Medicaid coverage of his/her special medical needs regardless of income. There are three subspecialty outpatient clinics in each major region of SC, and these pediatric cardiologists work closely with primary care center physicians throughout the state. When intensive, medical intervention is warranted, the patient is referred to the Medical University of South Carolina or to Duke Medical Center for care. All inpatient and outpatient medical services are covered under Medicaid, as long as the child remains eligible.

Data for this study were obtained retrospectively from the South Carolina Medicaid database during a 15-year-period from January 1, 1996, to December 31, 2010. Annually, about 375,000 children are covered by Medicaid; over the 15-year period examined in this study, about 500,000 were included in the Medicaid dataset. Medical claims were used to identify a service encounter, date of service, and the International Classification of Diseases, 9th Clinical Modification diagnosis codes (ICD-9) related to that visit. Inclusion criteria were age ≤ 17 years, continuous enrollment in Medicaid for a minimum of 9 months in each calendar year and at least one initial service encounter with an ICD-9 diagnosis of 746.4 (bicuspid aortic valve or congenital aortic insufficiency). Diagnoses of bicuspid aortic valve were confirmed by clinical examination or consultation to the treating pediatrician by a pediatric cardiologist plus echocardiography with or without cardiac catheterization, or cardiac surgery, and diagnostic codes were assigned when the service contact/visit was billed. However, since the ICD-9 code is the same for bicuspid aortic valve and congenital aortic insufficiency, we assumed that bicuspid aortic valve was the root cause of the insufficiency in these pediatric patients.

The following categories of concomitant, intracardiac conditions, and interventional procedures indicating the presence of coexisting congenital heart lesions or development of complications affecting prognosis in bicuspid aortic valve cases were also coded and controlled for in the regression analysis: ventricular septal defect (ICD-9 code: 745.4), aortic arch anomaly (747.21), coarctation of the aorta (747.10), coronary artery...
anomaly (746.85), interrupted aortic arch (747.11), and aortic stenosis (746.3). Complications and end-points such as aortic dilation (441.9), primary or secondary hypertension (401; 405), heart failure (428xx), infective endocarditis (421.0), aneurysm/dissection (414.1), or supraventricular tachycardia (427.0) leading to sudden cardiac death were also coded. The Current Procedural Terminology codes for surgical or transcatheter aortic valve repair/replacement and the patient’s age in months when the repair/replacement was performed were also coded and used in the multivariate analysis. Furthermore, since this is an epidemiologic investigation, using a secondary database relying on available ICD-9 diagnostic codes and American Medical Association Current Procedural Terminology codes, we do not have echocardiograph results (e.g., functional/pure bicuspid aortic valves), specific valve morphology (e.g., orientation), or definition of complications (e.g., “dilated” ascending aorta cutoff percentages), which would allow us to address specific pathophysiology in more detail. These Medicaid data files are routinely cleaned to eliminate duplicate visit records, frequently updated before being made available for analysis, and have been used in the previous investigations of particular congenital heart lesions.[27-29] The methods involved in this study were approved by the University of South Carolina Institutional Review Board as exempt from human subject research guidelines (45 Code of Federal Regulations part 46) because deidentified, existing medical database records were used for the secondary analysis.

Descriptive statistical analyses (frequencies and means) were performed to better characterize the bicuspid aortic valve cases. One multivariable logistic regression model was then created using receipt of aortic valve repair/replacement/not as the dependent variable, and the following independent predictor variables indicating type of coexisting congenital heart disease or complication: ventricular septal defect, aortic arch anomaly, coarctation of the aorta, coronary artery anomaly, interrupted aortic arch, and aortic stenosis (dichotomized as yes/no), controlling for individual risk factors of gender and race (dichotomized as African-American/all else and male/female), and age at bicuspid aortic valve diagnosis. The measure of association reported from these regression analyses is the adjusted odds ratio (aOR) with a corresponding 95% confidence interval. $P < 0.05$ (two-sided tests) were considered statistically significant, and all statistical analyses were performed in SAS software, version 9.2 (SAS Institute, Cary, North Carolina).

RESULTS

After applying the inclusion criteria, the final Medicaid cohort included 14,496 unduplicated pediatric patients diagnosed with congenital heart disease. Out of this group, a total of 378 patients with bicuspid aortic valve were identified; 22% were African-American, and 61.1% were male. As indicated in Table 1, 20.6% of the bicuspid aortic valve cohort also had coarctation of the aorta, 20.6% ventricular septal defect, 28% developed aortic stenosis, and 8.5% had diagnosed hypertension, but <1%-2% of the cohort had any of the diagnosed coexisting congenital heart diseases. Mean age at diagnosis of bicuspid aortic valve was 56.8 months (4.7 years of age) including neonates diagnosed at birth, and the mean length of individual patient follow-up in the Medicaid database was 1–2 years. The 15-year-treated prevalence rate of bicuspid aortic valve was 2.0% of the congenital heart disease population or 20/1000 pediatric cases of congenital heart disease. Of the bicuspid aortic valve cases examined, 10.3% received an aortic valve repair/replacement at a mean age of 82.4 months (6.9 years of age). Complications were present in <1% of the cases for infective endocarditis, aneurysm or dissection, or supraventricular tachycardia during the study observation period. However, 9.5% had heart failure, which was most frequently related to diagnosed cardiomegaly (likelihood ratio Chi-square $[LR] = 10.98; \, P = 0.0009$) or cardiomyopathy ($LR = 15.99; \, P \leq 0.0001$) rather than the presence of a specific coexisting congenital heart disease. None of the bicuspid aortic valve patients died during the study [Table 1].

Table 2 presents a statistical comparison of the cohort subgroup which did receive an aortic valve repair/replacement procedure and those that did not, controlling for individual risk factors (i.e., age, gender, and race), the presence of coexisting congenital heart diseases or complicating medical conditions. Those patients who developed aortic stenosis (aOR = 12.90), had a concomitant ventricular septal defect (aOR = 2.68) or had diagnosed hypertension (aOR = 5.00) were significantly more likely to have a bicuspid aortic valve repair/replacement procedure.

DISCUSSION

Compared to the previous studies of bicuspid aortic valve and its management, our results confirm some previous findings while augmenting the extant literature with new or updated findings which may be useful to providers treating pediatric bicuspid aortic valve cases in routine health-care systems. Regarding treated prevalence, bicuspid aortic valve was the diagnosed anomaly in 2% (20/1000) children with congenital heart disease before or at 4–5 years of age, which comports with previous findings that were limited to the pediatric congenital heart disease population.[1-3] As children age into adulthood, bicuspid aortic valve and its management occur more frequently.
Table 1: Characteristics of the bicuspid aortic valve (n=378) cohort

| Indicator                                | n (%)            |
|------------------------------------------|------------------|
| Gender (male)                            | 231 (61.1)       |
| Race (African American)                  | 83 (22.0)        |
| Median age in months at first bicuspid aortic valve diagnosis | 0-1              |
| Mean length of time (years) in the Medicaid dataset (SD) | 1.2 (2.3)       |
| Comorbid medical conditions              |                  |
| Diagnosed with diabetes                  | 8 (2.1)          |
| Diagnosed with dyslipidemia              | 8 (2.1)          |
| Diagnosed with hypertension              | 32 (8.5)         |
| Coexisting congenital heart diseases     |                  |
| Diagnosed with aortic arch anomaly       | 5 (1.3)          |
| Diagnosed with aortic dilation           | 2 (0.5)          |
| Diagnosed with aortic stenosis           | 106 (28.0)       |
| Diagnosed with coarctation of the aorta  | 78 (20.6)        |
| Diagnosed with coronary artery anomaly   | 3 (0.8)          |
| Diagnosed with interrupted aortic arch   | 8 (2.1)          |
| Diagnosed with ventricular septal defect | 78 (20.6)        |
| Medical intervention                     |                  |
| Had aortic valve repair                  | 39 (10.3)        |
| Mean age in months at aortic valve repair/replacement (SD) | 82.4 (53.0)     |
| Outcomes/complications                   |                  |
| Diagnosed with heart failure             | 36 (9.5)         |
| Diagnosed with infective endocarditis    | 1 (0.3)          |
| Diagnosed with supraventricular tachycardia | 1 (0.3)     |
| Diagnosed with aneurysm or dissection    | 1 (0.3)          |
| Died                                      | 0.0              |

SD: Standard deviation

Table 2: Adjusted odds ratios for having aortic valve repair/replacement

| Parameter                  | OR    | 95% CI   |
|----------------------------|-------|----------|
| Ventricular septal defect  | 2.68**| 1.20-5.99|
| Aortic stenosis            | 12.90**| 5.66-29.44|
| Hypertension               | 5.00**| 1.74-14.38|

**Significant at P<0.0001. CI: Confidence interval, OR: Odds ratio

Furthermore, non-African-Americans were more likely to have bicuspid aortic valve (3.5:1 ratio) whereas males demonstrated the higher rates of bicuspid aortic valve (1.6:1 ratio), as consistently noted for predominantly isolated bicuspid aortic valves in the extant literature, but our cohort also included those with associated congenital heart disease abnormalities yielding updated, population-based estimates for the congenital heart disease subgroup.[1,7-10]

Most isolated bicuspid aortic valve patients are usually asymptomatic, which comports with our finding that 80% of pediatric patients with bicuspid aortic valve had no complications or the coexisting congenital heart diseases noted in the previous studies. However, some patients may have mild exercise intolerance and fatigability through young adulthood. In a small percentage of patients, significant symptoms (e.g., chest pain with exercise, dizziness, and syncope) manifest in the first decade. Murmur or abnormal heart sound (specifically a systolic ejection click) on physical examination is the most common initial sign, which probably triggered an echocardiogram in the preschool years for this cohort. Progression to aortic stenosis has been associated with advancing age in children with isolated bicuspid aortic valve, similar to our results.[11]

Unlike previous reports that 10% of bicuspid aortic valve patients have aortic coarctation,[12] our cohort displayed 20.6% aortic coarctation; however, this coexisting condition was not associated directly with surgical intervention or outcome. Early heart failure occasionally occurs when a critical obstruction is present at birth, or coarctation of the aorta or coexisting congenital heart diseases are detected. Heart failure was diagnosed in 9.5% of this bicuspid aortic valve cohort, probably representing the more complicated coexisting aortic arch obstructions or isolated bicuspid aortic valve which progressed to aortic stenosis. These treated prevalence rates of coexisting congenital heart diseases and incidental complications comport with some previous reports focused exclusively on pediatric patients.[4,12-20] Diagnosed hypertension was also present in 8.5% of these bicuspid aortic valve cases, which has also been associated with faster progression of aortic valve disease.[24] as we also found.

The use of an aortic valve repair/replacement procedure in children and adolescents[14] does appear to be relatively rare, being reserved for the most progressed or complicated cases, primarily those with aortic stenosis, coexisting ventricular septal defect, and hypertension in this cohort. Consistent with previous studies, clinical outcomes over time in these pediatric patients were favorable compared to existing findings regarding heart failure, infective endocarditis, aneurysm and dissection, and death.[10,12-20,22-24]

The perspective provided by this observational, longitudinal study has several strengths, and there are several ways in which this research cohort differs from those of previous epidemiologic investigations. We followed this bicuspid aortic valve cohort longitudinally for an average of 1–3 years in the 15-year Medicaid data setup to the age of 17 years, so we were more likely to identify those cases which presented several years after birth, and were then treated in primary care, specialty clinics, and inpatient units across the state system. The size of the congenital heart disease cohort and the bicuspid aortic valve cohort entail sufficient power to detect relationships among relatively low-incidence cardiovascular conditions, medical interventions, and outcomes. Major barriers to conducting prospective clinical studies of such conditions relate to cost and the ability to identify the large numbers of representative subjects; however, longitudinal observational datasets are representative, readily available, and complement results from prospective, intensive (but small-scale) clinical studies. Our research cohort included a higher...
percentage of African-Americans than the previous studies, except those conducted in Atlanta, Georgia USA, so our racial/ethnic estimate appears to be more precise but not significantly higher than other studies.\cite{25,26}

Finally, our pediatric bicuspid aortic valve cohort best represents a heterogeneous group of children in routine care settings in the Southeastern USA states in terms of age, sex, racial demographics, and Medicaid eligibility;\cite{30-32} however, the results might also be informative to pediatric cardiologists in countries with predominantly small urban and rural populations.

At the same time, some limitations of the study, include children and adolescents who dropped out of treatment, were periodically ineligible, or for patients who died before they were registered in Medicaid coverage are not represented in this data set; and a reliance on physician-assigned ICD-9 codes to categorize patients may have contributed some degree of ascertainment bias or coding invalidity which we cannot quantify; the results that may not be generalizable to patients with referral limitations or other constraints on access to care or no coverage, and we had no access to family history of cardiac anomalies or comorbid medical conditions from the Medicaid data set, which might be pertinent to exploring care for bicuspid aortic valve and interpreting these findings. Although Medicaid covers about 100% of diagnosed congenital heart disease patients including patients who are covered by private insurance, we acknowledge that there may be pediatric patients with bicuspid valves who were not diagnosed or included in the pediatric Medicaid data set, which we cannot quantify. Finally, due to the overlapping ICD-9 code for both bicuspid aortic valve and aortic insufficiency, we cannot precisely distinguish these conditions.

**CONCLUSIONS**

With increased cardiac surveillance through echocardiograms, especially for those with suspected congenital heart disease, more bicuspid aortic valves are being detected and diagnosed. The majority of isolated bicuspid aortic valve cases do not require surgical intervention. Our findings demonstrate, however, several quantitative ways in which the prevalence of complicated bicuspid aortic valve and coexisting congenital heart disease differ from those noted in the existing literature and update the knowledge base of pediatric practitioners to anticipate the clinical care needs of young patients with coexisting conditions and to provide them more effective care.

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**Conflicts of interest**

There are no conflicts of interest.

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