Cardiology in the Young

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Outcomes of atrioventricular septal defects with and without down syndrome: analysis of the national inpatient database

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Abstract

Background: Controversial data exist about the impact of Down syndrome on outcomes after surgical repair of atrioventricular septal defect. *Aims:* (A) assess trends and outcomes of atrioventricular septal defect with and without Down syndrome and (B) determine risk factors associated with adverse outcomes after atrioventricular septal defect repair. *Methods:* We queried The National Inpatient Sample using International Classification of Disease codes for patients with atrioventricular septal defect < 1 year of age from 2000 to 2018. Patients' characteristics, co-morbidities, mortality, and healthcare utilisation were evaluated by comparing those with versus without Down syndrome. *Results:* In total, 2,318,706 patients with CHD were examined; of them, 61,101 (2.6%) had atrioventricular septal defect. The incidence of hospitalisation in infants with atrioventricular septal defect ranged from 4.5 to 7.5% of all infants hospitalised with CHD per year. A total of 33,453 (54.7%) patients were associated with Down syndrome. Double outlet right ventricle, coarctation of the aorta, and tetralogy of Fallot were the most commonly associated with CHD in 6.9, 5.7, and 4.3% of patients, respectively. Overall atrioventricular septal defect mortality was 6.3%. Multivariate analysis revealed that prematurity, low birth weight, pulmonary hypertension, and heart block were associated with mortality. Down syndrome was associated with a higher incidence of pulmonary hypertension (4.3 versus 2.8%, $p < 0.001$), less arrhythmia (6.6 versus 11.2%, $p < 0.001$), shorter duration for mechanical ventilation, shorter hospital stay, and less perioperative mortality (2.4 versus 11.1%, $p < 0.001$). *Conclusion:* Trends in atrioventricular septal defect hospitalisation had been stable over time. Perioperative mortality in atrioventricular septal defect was associated with prematurity, low birth weight, pulmonary hypertension, heart block, acute kidney injury, and septicaemia. Down syndrome was present in more than half of atrioventricular septal defect patients and was associated with a higher incidence of pulmonary hypertension but less arrhythmia, lower mortality, shorter hospital stay, and less resource utilisation.

Atrioventricular septal defects represent up to 5% of CHDs with an estimated occurrence of 0.19 in 1,000 live births.[1–4] Approximately 40 to 45% of children with Down syndrome) have CHD, and 45% of those have atrioventricular septal defect. Conversely, up to 50% of patients with atrioventricular septal defect have Down syndrome.[5]

Previous studies have shown clinically relevant differences between atrioventricular septal defect patients with and without Down syndrome. Patients with Down syndrome most often have the complete form of atrioventricular septal defect.[5] Down syndrome patients with atrioventricular septal defect are more likely to have an earlier presentation and worsening evolution of the pulmonary vascular disease and respiratory complications compared to non-Down syndrome Patients.[5–7] However, controversy exists about the impact of Down syndrome on the perioperative outcomes of atrioventricular septal defect patients. Studies have shown that Down syndrome is considered a risk factor for perioperative mortality and is associated with unfavourable outcomes.[7–9] In contrast, other reports demonstrated that the presence of Down syndrome is not a risk factor for adverse outcomes after surgical repair of atrioventricular septal defect.[10–13]

Therefore, in the current study, we aimed to use the National Inpatient Sample database to (a) Examine the trends of atrioventricular septal defect hospitalisation during the study period, (b) Determine the risk factors associated with perioperative mortality after complete surgical repair of atrioventricular septal defect in the first year of life, and (c) Evaluate the impact of Down syndrome on the outcomes after atrioventricular septal defect repair including cardiac

(specifically pulmonary hypertension and arrhythmias), non-cardiac co-morbidities, procedures, length of hospitalisation, and resources utilisation.

Methods

Data source

This is a retrospective observational study using deidentified patient data from the National Inpatient Sample database during the period from 2000 to 2018. The National Inpatient Sample database is part of the Healthcare Cost and Utilization Project, which is collected by the Agency for Healthcare Research and Quality. The National Inpatient Sample database contains approximately 8 million hospital stays each year and randomly samples 20% of the discharges from the participating hospitals.[14] The collection of data is stratified to ensure equal representation of hospitals by geographic region, urban and rural location, teaching status, and hospital bed size. Procedure and diagnostic codes are recorded using the International Classification of Diseases. The International Classification of Disease, Ninth and Tenth Revisions, Clinical Modification were used to identify our patient population. The International Classification of Disease, Ninth Revision was used from January 2000 to September 2015 while the International Classification of Disease, Tenth Revision was used from October 2015 to December 2018.

Patient selection

The study was granted an exempt status from the Institutional Review Board given the use of a deidentified and publicly available database. Patients were included in the study if they were less than one year of age, had the diagnosis of atrioventricular septal defect (International Classification of Disease, Ninth and Tenth Revisions 745.60, 745.69, and Q21.2 and Q21.23, respectively), and had undergone complete surgical repair during the index hospitalisation. Patients were excluded from the study if there were > 1 year of age, had no surgical repair, and/or had any genetic diagnosis other than Down syndrome.

Identification of variables

The National Inpatient Sample database was queried for patients' demographics and clinical characteristics. Demographic data included age, sex, race, primary payer, type of hospital (teaching versus non-teaching, urban versus rural), hospital bed size, and the region of the hospital. The main outcomes of interest included cardiac and non-cardiac co-morbidities, death prior to hospital discharge, length of hospital stay, and hospital charges. The total hospital charges were reported in United States of America dollars. The following ICD codes (758.0, Q90.0, Q90.1, Q90.2, and Q90.9) were used to identify patients with Down syndrome. Patients were divided into two groups: atrioventricular septal defect with versus without Down syndrome. Differences in demographics and clinical characteristics were examined between the two groups including cardiac morbidities (cyanosis, heart failure, pulmonary hypertension, arrhythmia, heart block, and cardiac arrest), respiratory, gastrointestinal, renal co-morbidities, and procedures (mechanical ventilation, extracorporeal membrane oxygenation support, tracheostomy, gastrostomy, and pacemaker implantation).

Statistical analysis

Data were analysed as appropriate, using mean and standard deviation for parametric continuous variables, median and interquartile range for nonparametric continuous variables, and frequencies (percentages) and proportions for categorical variables. We compared the survivors and non-survivors using appropriate statistical analysis; the Mann–Whitney U-test for continuous characteristics and chi-squared or Fisher's exact tests for categorical characteristics. Trends in atrioventricular septal defect admissions and mortality over the study period years were assessed for significance using the Jonckheere–Terpstra test. We used a logistic regression model to examine the factors associated with mortality after atrioventricular septal defect surgical repair. SPSS 25 (SPSS Inc., Chicago, IL) was used for statistical analysis.

In accordance with the Healthcare Cost and Utilization Project data use agreement, cells with values of 1–10 are not published. $P < 0.05$ was considered significant. Data can be weighted such that the results can be extrapolated as representative of the entire inpatient population. Data weighting was developed essentially to obtain trend analysis; however, it can also be utilised for all analyses per the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project. Unweighted counts were used for all statistical analyses except trend assessments, where nationally weighted estimates were used.

Results

During the study period, 86,234,583 infants' records were reviewed from 2000 to 2018. Out of 2,318,706 admissions with CHD diagnosis in the first year of life, 61,101 (2.6%) had atrioventricular septal defect. The incidence of hospitalisations in infants with atrioventricular septal defect ranged from 4.5–7.4/year during the study period. There was a predominance of the female sex in patients with atrioventricular septal defect (53.3 versus 46.7%, $p < 0.001$). The white race was pre-dominant (43%) followed by Hispanic (17%), $p < 0.001$. Medicaid was the primary payer insurance in (47.6%) versus private insurance in (45.8%) $p < 0.001$. Seasonal variations in patients' discharges existed throughout the year (Table 1).

Atrioventricular septal defect with versus without Down syndrome

The diagnosis of Down syndrome was present in 33,453 (54.7%) patients. Trends in atrioventricular septal defect hospitalisation in patients with versus without Down syndrome during the study period are demonstrated in Figure 1. Down syndrome was associated with the female sex (54.9 versus 45.1%, $p < 0.001$). The White and Hispanics were the most associated races with Down syndrome. Regional distribution differences existed between patients with and without Down syndrome. Table 1 illustrates the demographics and patients' characteristics of atrioventricular septal defect patients with versus without Down syndrome.

Association with other CHDs

Isolated atrioventricular septal defects and those associated with simple lesions (secundum atrial septal defects, patent ductus arteriosus, and additional ventricular septal defects) were reported in 35,569 (58.2%) patients. Double outlet right ventricle, coarctation of the aorta, tetralogy of Fallot, and pulmonary atresia were the most common CHDs associated with atrioventricular

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Table 1. Demographics and characteristics of all atrioventricular septal defect patients (n = 61,101).

	Down syndrome (n = 33,453)	Non-Down syndrome (n = 27,648)	*P*-value
Age at admission			<0.001
Neonates	11,784 (35.2)	11,682 (42.3)	
Non-neonates	21,668 (64.8)	15,966 (57.7)	
Sex			<0.001
Male	15,082 (45.1)	13,398 (48.5)	
Female	18,362 (54.9)	14,234 (51.5)	
Gestational Age			
<37 weeks	3697 (11.1)	3385 (12.2)	<0.001
≥37 weeks	29,756 (88.9)	24,263 (87.8)	
Birth weight			
<2500 gram	2237 (6.7)	2419 (8.7)	<0.001
≥2500 gram	31,216 (93.3)	25,229 (91.3)	
Small for gestational age	1308 (3.9)	1052 (3.8)	0.5
Race			<0.001
White	15,077 (45.1)	11,301 (40.9)	
Black	3876 (11.6)	3705 (13.4)	
Hispanic	5652 (16.9)	4936 (17.9)	
Asian or Pacific Islander	752 (2.2)	858 (3.1)	
Native American	120 (0.4)	207 (0.7)	
Other	1614 (4.8)	1523 (5.5)	
Unclassified	6364 (19.0)	5118 (18.5)	
Primary payer			<0.001
Medicaid	14,911 (44.6)	14,186 (51.4)	
Private insurance	16,354 (48.9)	11,653 (42.2)	
Self-pay	634 (1.9)	595 (2.2)	
Other	1555 (4.7)	1175 (4.2)	
Region			<0.001
Northeast	4212 (12.6)	3619 (13.1)	
Midwest	6194 (18.5)	4471 (16.2)	
South	9686 (29.0)	8412 (30.4)	
West	5988 (17.9)	4644 (16.8)	
Unclassified	7372 (22.0)	6503 (23.5)	
Location/teaching status of hospital			<0.001
Rural	232 (0.7)	182 (0.7)	
Urban non-teaching	2424 (7.2)	1539 (5.6)	
Urban teaching	23,362 (69.8)	19,374 (70.1)	
Unclassified	7434 (22.2)	6552 (23.7)	
Bed size of hospital			<0.001
Small	3900 (11.7)	2833 (10.2)	
Medium	5614 (16.8)	4559 (16.5)	
Large	16,504 (49.3)	13,704 (49.6)	
Unclassified	7434 (22.2)	6552 (23.7)	
Disposition of patient			<0.001
Routine	25,623 (76.5)	18,147 (65.6)	

(*Continued*)

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Table 1. (*Continued*)

	Down syndrome (n = 33,453)	Non-Down syndrome (n = 27,648)	*P*-value
Transfer to short-term hospital	2806 (8.4)	2888 (10.4)	
Transfer Other	491 (1.5)	642 (2.3)	
Home Health Care	3709 (11.1)	2898 (10.5)	
Died	808 (2.4)	3074 (11.1)	
Admission day			0.192
Monday–Friday	28,555 (85.4)	23,495 (85.0)	
Saturday–Sunday	4898 (14.6)	4152 (15.0)	
Discharge quarter			<0.001
First quarter (Jan–Mar)	8594 (25.7)	7226 (26.1)	
Second quarter (Apr–Jun)	8402 (25.1)	6632 (24.0)	
Third quarter (Jul–Sep)	8180 (24.5)	7164 (25.9)	
Fourth quarter (Oct–Dec)	8271 (24.7)	6616 (23.9)	

Data are expressed in frequency (%); chi-square or Fisher's exact tests were used for analysis.

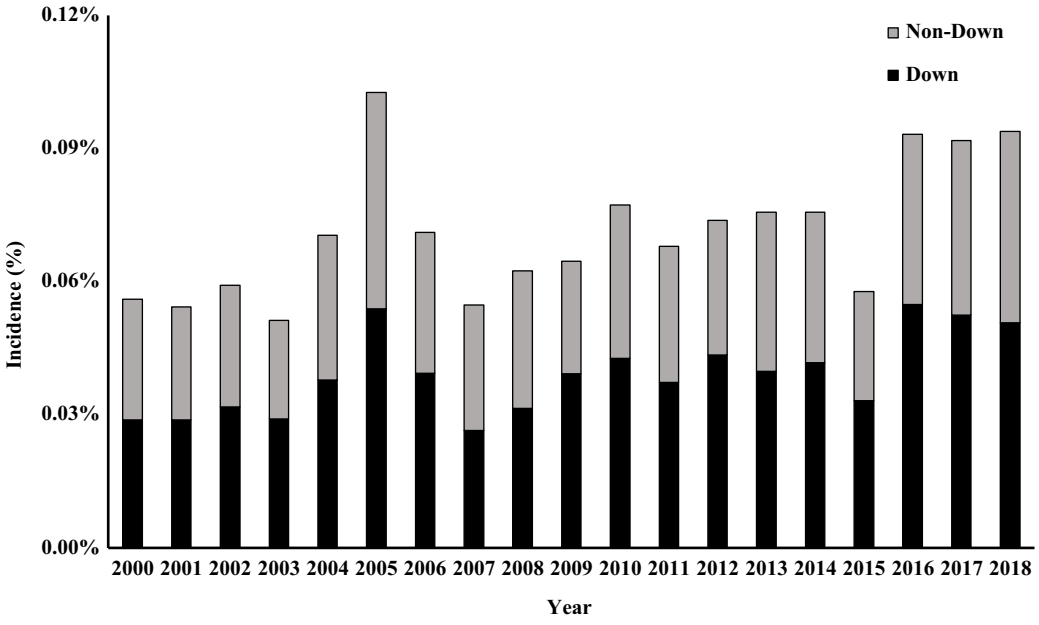

Figure 1. Trends in atrioventricular septal defect hospitalisation during the study period from 2000 to 2018 comparing patients with versus without Down syndrome.

septal defect in 6.9, 5.7, 4.3, and 4.2%, respectively. The association between atrioventricular septal defect and tetralogy of Fallot was more frequent in Down syndrome patients (5 versus 3.4 %, $p < 0.001$) while the association between atrioventricular septal defect and all other forms of CHDs was more frequent in the non-Down syndrome group (Table 2).

Cardiac and non-cardiac co-morbidities and intervention

Atrioventricular septal defect patients with Down syndrome developed more frequent heart failure but less cyanosis, and less respiratory failure compared to non-Down syndrome atrioventricular septal defect patients (28.3 versus 22%, 0.6 versus 0.9%, 14.4 versus 16.9%, $p = 0.01$, < 0.001, and < 0.001, respectively). The development of pulmonary hypertension was more frequent in Down syndrome patients (4.8 versus 2.7%, $p < 0.001$). Cardiac arrhythmias and cardiac arrest tend to occur more frequently in non-Down syndrome patients [11.2 versus 6.6% OR 0.56 (0.53–0.59), $p < 0.001$] and [2.8 versus 1.0%, OR 0.37 (0.32–0.41), $p < 0.001$], respectively Table 3.

Atrioventricular septal defect patients with Down syndrome had less incidence of in-hospital non-cardiac complications including sepsis, acute renal failure, and shock (4.9 versus 8.6%, 2.5 versus 5.1%, and 1.8 versus 3.6%, respectively, with $p < 0.001$ for all). Post-operative pleural effusion was not significantly different in atrioventricular septal defect patients with Down syndrome compared to those without Down syndrome. However, atrioventricular septal defect patients with Down syndrome had a higher frequency of having post-operative chylothorax compared to those without Down syndrome [335 (1%) versus 186 (0.6%), $p < 0.001$)]. Atrioventricular septal defect patients with Down syndrome had a higher incidence of pneumonia compared to

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Table 2. Association of atrioventricular septal defect with other CHDs in patients with versus without Down syndrome.

Associated CHD	AVSD with Down syndrome	AVSD without Down syndrome	*P*-value
Secundum ASD	9782 (29.2)	7627 (27.2)	<0.001
PDA	11,855 (35.4)	8030 (29.0)	<0.001
Pulmonary stenosis	203 (0.6)	1893 (6.8)	<0.001
Tetralogy of Fallot	1683 (5.0)	948 (3.4)	<0.001
Aortic stenosis	29 (0.1)	263 (1.0)	<0.001
Coarctation of the aorta	1163 (3.5)	2373 (8.6)	<0.001
Transposition of great arteries	204 (0.6)	1697 (6.1)	<0.001
Double outlet right ventricle	248 (0.7)	4022 (14.5)	<0.001
Truncus arteriosus	28 (0.1)	247 (0.9)	<0.001
Pulmonary atresia	265 (0.8)	2349 (8.5)	<0.001
Tricuspid atresia	50 (0.1)	313 (1.1)	<0.001
Ebstein's anomaly	10 (0)	58 (0.2)	<0.001
Hypoplastic left heart syndrome	116 (0.3)	2204 (8.0)	<0.001
Common ventricle	166 (0.5)	2695 (9.7)	<0.001
TAPVR	10 (0)	2252 (8.1)	<0.001

TAPVR = total anomalous pulmonary venous return; PDA = patent ductus arteriosus; ASD = atrial septal defects.
Data are expressed in frequency (%); Chi-square or Fisher's exact tests were used for analysis.

non-Down syndrome patients [5.4 versus 4.8%, CI (95%) 1.11 (1.04–1.20), p = 0.004]. While patients with Down syndrome had a lower incidence of respiratory failure [14.4 versus 16.9% CI (95%) 0.83 (0.80–0.87), P < 0.001] and required a shorter duration of mechanical ventilation compared to the non-Down syndrome group. Similarly, atrioventricular septal defect patients with Down syndrome patients received less tracheostomy, and extracorporeal membrane oxygenation support compared to non-Down syndrome atrioventricular septal defect patients, Table 3.

Feeding difficulties were more frequent in atrioventricular septal defect patients with Down syndrome who underwent more gastrostomy tubes compared to those without Down syndrome (8.8 versus 5.9% and 5.6 versus 3.2%, p < 0.001 and 0.03, respectively).

Mortality

In-hospital mortality of atrioventricular septal defect patients during the study period was reported in 3882 (6.3%) patients. Down syndrome patients with atrioventricular septal defect had significantly less mortality incidence than non-Down syndrome patients (2.4 versus 11.1%, p < 0.001). When excluding patients with severely unbalanced atrioventricular septal defect who underwent SV palliative surgeries, mortality continued to be high in non-Down syndrome patients who underwent biventricular repair compared to patients with Down syndrome (7.6 versus 2.2%, p < 0.001). When excluded any associated CHD other than the simple lesions as secundum atrial septal defects and/or PDA, mortality continued to be high in the isolated atrioventricular septal defect non-Down syndrome patients compared to those with Down syndrome (5.9 versus 1.8%, p = 0.01) Trends in the overall mortality in all atrioventricular septal defect patients with versus without Down syndrome are illustrated in Figure 2.

Univariate analysis revealed that the patient's gender was not associated with mortality. White race and elective admission were associated with lower mortality. Higher mortality rates were found in premature (<37 weeks) and low birth weight infants (< 2500 grams) [3.38 (3.14–3.64), p < 0.001 and 3.64 (3.34–3.95), p < 0.001, respectively]. Neonatal repair (less than 28 days) of atrioventricular septal defect was associated with higher mortality rates compared to post-neonatal repair in non-Down syndrome patients (9.1 versus 7.2%, p = 0.02) and in Down syndrome patients (2.6 versus 2.1%, P = 0.04).

The development of pulmonary hypertension, arrhythmias, heart block, acute kidney injury, and sepsis was associated with higher mortality rates. Multivariate regression analysis revealed that the need for extracorporeal membrane oxygenation [15.68 (13.16–18.63)], acute kidney injury [5.21 (4.86–5.92), p < 0.001], mechanical ventilation ≥ 96 hours [2.46 (2.22–2.72), p < 0.001], sepsis [2.21 (1.97–2.48), p < 0.001], and pulmonary hypertension [1.75 (1.46–2.09), p < 0.001] were associated with mortality. Table 4.

Length of stay and charge analysis

Atrioventricular septal defect patients with Down syndrome had shorter hospital stays compared to non-Down syndrome patients [7 (4–16) versus 9 (3–26) days, p < 0.001]. Patients with Down syndrome had lesser cost of hospitalisation compared to non-Down syndrome [$65,725 (19,761–156,253) versus $88,973 (22,981–251,883), p < 0.001). Patients who died had a significantly prolonged median hospital stay and higher cost of hospitalisation.

Discussion

In the current study, we used the largest national multi-centre database for atrioventricular septal defect hospitalisation in the first year of life with 61,101 patients during the period from 2000 to 2018. The primary findings in the current study are as follows: a. atrioventricular septal defect hospitalisation represented 2.6% of CHD admissions during the study period with an overall mortality of 6.3%; b. risk factors associated with perioperative mortality included prematurity, low birth weight, development of pulmonary hypertension, heart block, acute kidney injury, and sepsis; c. Down syndrome was present in 55% of atrioventricular septal defect patients and was associated with a higher incidence of pulmonary hypertension but lower mortality rates, shorter hospital stays, and lesser hospitalisation costs.

Atrioventricular septal defect with versus without Down syndrome

In the current analysis, atrioventricular septal defect represented 2.6% of all CHD hospitalisations in the first year of life. This finding is lower than previously published reports with atrioventricular septal defect representing 4–5% of all CHDs.[5] The numbers presented in the current study probably represent a more reasonable estimate given the large number of patients included over eighteen years.

More than half of atrioventricular septal defect patients had Down syndrome. The association between atrioventricular septal defect and Down syndrome was more prevalent in females, which

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Table 3. Clinical outcomes in AVSD patients with versus without Down syndrome during the study period (2000–2018).

	AVSD with DS (n = 33,453)	AVSD with Non-DS (n = 27,648)	OR (95% CI)	*P*-value
Length of stay, days[a]	7 (4–16)	9 (3–26)		<0.001
Cost of charge, $[a]	65,725 (19,761–156,253)	88,973 (22,981–251,883)		<0.001
Mortality	808 (2.4)	3074 (11.1)	0.20 (0.18–0.21)	<0.001
Cardiac Morbidities: Cyanosis	209 (0.6)	645 (2.3)	0.75 (0.56–0.87)	0.01
Pulmonary hypertension	1437 (4.3)	768 (2.8)	1.57 (1.44–1.73)	<0.001
Heart block	1335 (4.0)	1057 (3.8)	1.05 (0.96–1.14)	0.29
Cardiac dysrhythmias	2200 (6.6)	3100 (11.2)	0.56 (0.53–0.59)	<0.001
Cardiac arrest	343 (1.0)	764 (2.8)	0.37 (0.32–0.41)	<0.001
Systemic hypertension	914 (2.7)	944 (3.4)	0.80 (0.72–0.87)	<0.001
Respiratory Morbidities:				
Pneumonia	1794 (5.4)	1339 (4.8)	1.11 (1.04–1.20)	0.004
Bronchopulmonary dysplasia	370 (1.1)	498 (1.8)	0.61 (0.53–0.70)	<0.001
Respiratory distress syndrome	1240 (3.7)	1507 (5.5)	0.67 (0.62–0.72)	<0.001
Pleural effusion	2339 (7.0)	2020 (7.3)	0.95 (0.90–1.02)	<0.001
Respiratory failure	4825 (14.4)	4662 (16.9)	0.83 (0.80–0.87)	<0.001
Other				
Respiratory anomalies	1296 (3.9)	1375 (5.0)	0.77 (0.71–0.83)	<0.001
Digestive anomalies	2381 (7.1)	3173 (11.5)	0.59 (0.56–0.63)	<0.001
Feeding difficulty	2930 (8.8)	1627 (5.9)	1.54 (1.44–1.64)	<0.001
Necrotising enterocolitis	322 (1.0)	572 (2.1)	0.46 (0.40–0.53)	<0.001
Acute renal failure	828 (2.5)	1423 (5.1)	0.47 (0.43–0.51)	<0.001
Septicaemia	1634 (4.9)	2368 (8.6)	0.55 (0.51–0.59)	<0.001
Shock	594 (1.8)	994 (3.6)	0.49 (0.44–0.54)	<0.001
Procedures:				
Mechanical ventilation				
<96 hours	2996 (9.0)	3309 (12.0)	0.72 (0.69–0.76)	<0.001
≥96 hours	2225 (6.7)	4239 (15.3)	0.39 (0.37–0.42)	<0.001
ECMO support	254 (0.8)	854 (3.1)	0.24 (0.21–0.28)	<0.001
Tracheostomy	132 (0.4)	449 (1.6)	0.24 (0.20–0.29)	<0.001
Gastrostomy	1882 (5.6)	1130 (4.0)	1.22 (1.05–1.49)	0.03
Cardiac catheterisation	1054 (3.2)	3382 (12.2)	0.23 (0.22–0.25)	<0.001
Conversion of cardiac rhythm	310 (0.9)	767 (2.8)	0.33 (0.29–0.37)	<0.001
Pacemaker implantation	295(1.1)	449 (2.0)	0.55(0.47-0.64)	<0.001

AVSD = atrioventricular septal defects; DS = down syndrome, ECMO = extracorporeal membrane oxygenation.
[a]that expressed in median (interquartile range); Mann–Whitney U-test was used for analysis.
Data are expressed in frequency (%); chi-square or Fisher's exact tests were used for analysis except with data.

is consistent with previous reports that suggested a slight female preponderance.[3,5,15] Atrioventricular septal defect was more common in White (43%) followed by Hispanic (17.3%) and Black (12.4%) populations, respectively. Similar to previous reports, racial differences also existed in the association between atrioventricular septal defect and Down syndrome.[5] Black patients with Down syndrome tend to have atrioventricular septal defect more commonly than Whites, while the association between Down syndrome and atrioventricular septal defect was less frequent in Hispanics than in White populations.[3,5]

Isolated atrioventricular septal defect was present in 58.2% of patients in the current analysis. The non-Down syndrome group showed a significantly higher association with CHDs including double outlet right ventricle, coarctation of the aorta, pulmonary atresia, and hypoplastic left heart syndrome. However, tetralogy of Fallot was more pre-dominant in atrioventricular septal defect

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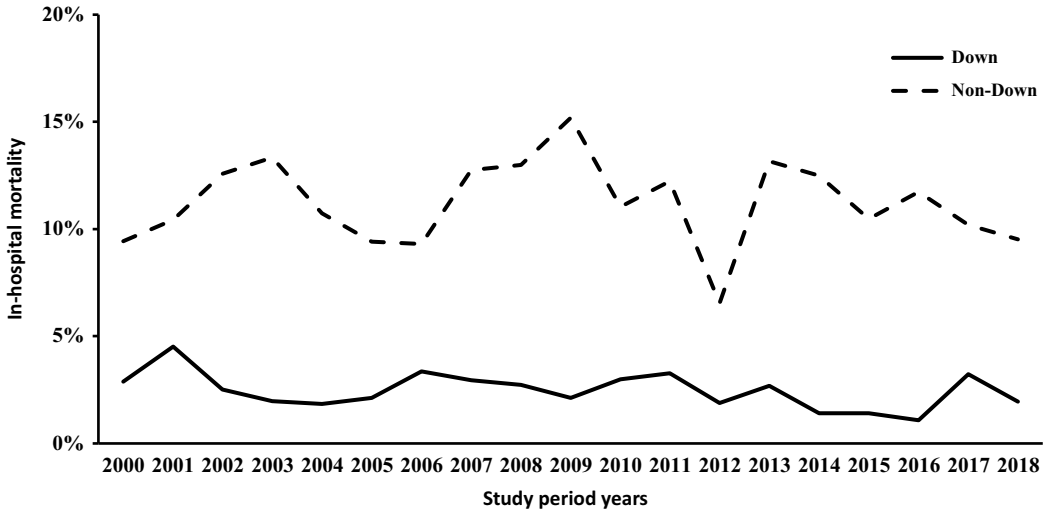

Figure 2. Trends of in-hospital mortality in atrioventricular septal defect patients with versus without Down syndrome. Down syndrome patients had significantly lower mortality compared to non-Down syndrome during the study period.

patients with Down syndrome as previously described.[1,2] Atrioventricular septal defect and tetralogy of Fallot are thought to develop by distinct mechanisms; nonetheless, their co-occurrence in patients with Down syndrome suggests sharing a common developmental basis with multiple hypothetical theories proposed.[5,15,16]

Mortality

The overall atrioventricular septal defect mortality in the current study was 6.3%, consistent with perioperative mortality in previous studies ranging between 3 and 10%. The Pediatric Heart Network study of 120 patients with atrioventricular septal defect from 2002 to 2004 reported 3% mortality rates.[12] Similarly, a multi-centre analysis from the Society of Thoracic Surgeons Congenital Heart Surgery Database revealed a 3% mortality rate.[13] The differences in mortality rates between our 18-year analysis of the national database and these reports might reflect the enormous differences in the sample size and variations in the surgical techniques and intensive care management over the study period.

In the current study, perioperative mortality was associated with prematurity, low birth weight, development of pulmonary hypertension, heart block, acute kidney injury, and septicaemia. Atz et al identified age less than 2.5 months and weight less than 5 kg at the time of surgical repair as risk factors for mortality.[12] Conversely, other studies revealed no difference between neonatal surgical outcomes and surgical repairs performed beyond the neonatal period or based on the weight at the time of surgical repair.[16] While these differences in outcomes might be due to discrepancies in sample size, associated cardiac lesions, and surgical techniques between different institutions, it is worth mentioning that surgical repair at an earlier age was reported to be associated with higher rates of reinterventions.[16–19]

Down syndrome and mortality

In our study, Down syndrome patients with balanced atrioventricular septal defect who underwent biventricular repair had significantly less incidence of mortality compared to non-Down syndrome (2.2 versus 7.6%). This is in alignment with previous reports, St Louis et al reported lower mortality in atrioventricular septal defect patients with Down syndrome.[13,15] A study from Leiden, Netherlands, revealed a dramatic decrease in in-hospital mortality after atrioventricular septal defect repair in Down syndrome patients down to 0%.[16] However, in the Pediatric Heart Network report of 120 patients with atrioventricular septal defect, mortality did not differ based on the presence or absence of Down syndrome despite the higher incidence of in-hospital complications and reinterventions in the non-Down syndrome patients.[12]

In the current report, temporal trends of decreased mortality after atrioventricular septal defect repair existed in the non-Down syndrome patients but not in the Down syndrome group. Dhillon et al recently queried the Texas Inpatient Public Use Data file and reported an improved hospital survival over time after atrioventricular septal defect repair in non-syndromic atrioventricular septal defect patients compared to patients with Down syndrome.[20] The improved survival in non-Down syndrome patients could be secondary to the rising tendency to perform definitive atrioventricular septal defect repair at younger ages, which potentially lowers the risk of developing an advanced pulmonary vascular disease and had been associated with improved survival.[19,20]

Down syndrome and pulmonary hypertension

In our study, pulmonary hypertension was more frequent in atrioventricular septal defect patients with Down syndrome. The link between pulmonary vascular disease and Down syndrome is not clearly understood.[5] Historical and recent histopathological studies failed to show any differences in the extent and progression of pulmonary vascular changes in atrioventricular septal defect patients with versus without Down syndrome despite accounting for the age in the histological findings.[21,22] In contrast, other studies reported earlier development of pulmonary vascular disease in atrioventricular septal defect patients with Down syndrome secondary to pulmonary parenchymal hypoplasia.[8,23] The elevated pulmonary vascular resistance in Down syndrome patients is likely triggered by their higher pre-disposition to having relative hypoxia and carbon dioxide retention secondary to sleep apnoea, hypoventilation, and nasopharyngeal obstruction.[24] On the other side, the association between Down syndrome and pulmonary vascular disease likely plays a role in limiting the net left to right intra-cardiac shunting. The resultant decreased pulmonary blood flow in these patients might explain their less need for mechanical

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Table 4. Univariate and multivariate regression analysis of the risk factors associated with in-hospital mortality after AVSD repair.

	Univariate analysis		Multivariate analysis			
	OR (95% CI)	*P*-value	aOR (95% CI)			*P*-value
Down syndrome	0.20 (0.18–0.21)	<0.001	0.258	0.234	0.285	<0.001
Sex (male)	1.06 (0.99–1.13)	0.083	1.033	0.950	1.124	0.447
Race (White)	0.70 (0.65–0.75)	<0.001	0.786	0.723	0.856	<0.001
Admission (elective)	0.32 (0.29–0.35)	<0.001	0.428	0.375	0.489	<0.001
Gestational age (<37 weeks)	3.38 (3.14–3.64)	<0.001	2.511	2.154	2.927	<0.001
Birth weight (<2500 g)	3.64 (3.34–3.95)	<0.001	1.602	1.353	1.897	<0.001
Pulmonary hypertension	2.54 (2.24–2.88)	<0.001	1.752	1.461	2.099	<0.001
Arrhythmias	1.22 (1.09–1.35)	<0.001	0.780	0.673	0.906	0.001
Heart block	1.31 (1.13–1.52)	<0.001	1.263	1.023	1.560	0.030
Pneumonia	1.73 (1.53–1.95)	<0.001	1.130	0.952	1.341	0.162
Respiratory failure	1.97 (1.83–2.13)	<0.001	1.223	1.086	1.376	0.001
Acute kidney injury	11.55 (10.53–12.66)	<0.001	5.207	4.575	5.926	<0.001
Septicaemia	4.86 (4.46–5.28)	<0.001	2.217	1.977	2.487	<0.001
Mechanical ventilation (≥96 hrs)	5.28 (4.92–5.68)	<0.001	2.460	2.220	2.726	<0.001
Extracorporeal membrane oxygenation	25.78 (22.75–29.22)	<0.001	15.678	13.156	18.683	<0.001

ventilation in comparison to non-Down syndrome patients as demonstrated in the current study.

Down syndrome and arrhythmias

In our study, 8.7% of patients had arrhythmia and 4.4% had heart block. This is consistent with the previously reported post-operative arrhythmia in atrioventricular septal defect patients between 8–9%.[25,26] In atrioventricular septal defect patients, the inferior displacement of the atrioventricular node and bundle of His makes the conduction system more vulnerable to injury during surgical repair.[27] Furthermore, the suboptimal conduction tissue properties pre-dispose these patients to a higher risk of complete heart block.[28] However, there is limited data about the differences in conduction disorders between Down syndrome and non-syndromic patients. In the current study, atrioventricular septal defect patients with Down syndrome had less incidence of arrhythmias with no statistically significant difference in the incidence of heart block between the two groups. This is partially in line with a recent study by Kharbanda et al who found less post-operative arrhythmias and post-operative heart block in atrio-ventricular septal defect patients with Down syndrome compared to those with normal chromosomes.[26]

The impact of Down syndrome on the conduction system and the occurrence of arrhythmia is largely unknown. It is unclear if the extra chromosome in these patients affects the development of cardiac conduction. Blom et al suggested differences in the conduction system between atrioventricular septal defect patients with and without Down syndrome.[29] While there was no statistically significant difference in the incidence of heart block between the two groups, Down syndrome patients needed less pacemaker implantation. The presence of an abnormal left atrioventricular valve often requires reoperation and is considered a risk factor for complete heart block, and the need for pacemaker implantation is less likely to occur in Down syndrome patients.[30,31]

Hospital stay and resource utilisation

In the current study, non-Down syndrome atrioventricular septal defect patients had longer median hospital stay and higher cost of hospitalisation compared to Down syndrome patients. This finding is inconsistent with previous studies that showed longer hospital stay in Down syndrome patients with CHD.[32,33] Our finding could be explained by the significantly higher incidence of cardiac and non-cardiac complications, concomitant cardiac procedures, and longer durations of mechanical circulatory and respiratory support in non-Down syndrome patients.

Feeding difficulties and gastrostomy tube placement were significantly higher in Down syndrome patients. This is not surprising and consistent with studies that demonstrated significant feeding problems, neurologic impairment, and subsequent need for gastrostomy tube in Down syndrome patients.[34,35]

While the feeding difficulties were more common in Down syndrome patients, the pre-operative planning in Down syndrome patients might have led to a shorter duration of hospital stay compared to non-Down syndrome patients. For example, a Down syndrome patient with a G-tube in place before the surgical repair will presumably be discharged earlier than one that had a G-tube during the admission for surgical repair.[36,37]

Limitations

The use of the National Inpatient Sample database has its own limitations including a. Inability to identify the specific details of surgical repair including the exact weight at the time of surgical repair and the presence of any post-operative residual lesions, b. The transition from International Classification of Disease, Ninth Revision to International Classification of Disease, Tenth Revision codes that occurred during the study period might have contributed to coding errors. However, there were no significant differences in the results when we ran an analysis using only International Classification of Disease, Tenth Revision codes to examine the

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difference between atrioventricular septal defect patients with versus without Down syndrome as illustrated in Supplemental Table 1, and c. In the International Classification of Disease, Ninth Revision version, Down syndrome was represented by only one code while in the International Classification of Disease, Tenth Revision version; three different codes were available for the three different Down syndrome subtypes: trisomy 21 (nondisjunction), translocation, and mosaicism. In the current study, we used all available codes for Down syndrome instead of only using trisomy 21code, which represents ~ 95% of Down syndrome patients. This might have limited our ability to examine any differences in outcomes related to the Down syndrome subtype.

Conclusion

Trends in atrioventricular septal defect hospitalisation have been stable over time. Higher mortality after surgical repair was associated with prematurity, low birth weight, pulmonary hypertension, heart block, acute kidney injury, and septicaemia. More than half of atrioventricular septal defect patients had Down syndrome, which was associated with a higher incidence of pulmonary hypertension, less arrhythmia, less mortality, shorter length of hospital stay, and less resource utilisation.

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