*Heart Surgery Forum* 2024; 27(4): E397–E405
doi: 10.59958/hsf.7289
https://journal.hsforum.com/

*Article*

# The Effect of Neurodevelopmental Disorders on the Prognosis of Children Undergoing Heart Transplantation: A Retrospective Analysis of the National Inpatient Sample 2011–2019

Ian Ergui[1,*], Fatima Lakhani[2], Rahul Sheth[2], Bertrand Ebner[2], Michael Dangl[1], Karla Inestroza[3], Louis Vincent[2], Rosario Colombo[2,4], George Marzouka[2,5], Luanda Grazette[2]

[1]Division of Internal Medicine, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[2]Division of Cardiology, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL 33136, USA
[3]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN 55905, USA
[4]Department of Cardiology, Jackson Memorial Hospital, Miami, FL 33136, USA
[5]Department of Cardiology, Miami Veteran Affairs Healthcare System, Miami, FL 33136, USA
*Correspondence: Ian.Ergui@jhsmiami.org (Ian Ergui)

Submitted: 29 January 2024 Revised: 4 March 2024 Accepted: 13 March 2024 Published: 15 April 2024

## Abstract

**Background**: Many international governing bodies recommend against heart transplantation in patients with severe cognitive-behavioral disabilities, however no clear criteria are offered to define severity. Patients with neurodevelopmental disorders may face systematic discrimination when being evaluated for transplant. We set out to investigate whether children with neurodevelopmental disorders that undergo heart transplantation have poorer in-hospital outcomes compared to neurotypical children. **Methods**: A retrospective analysis of the National Inpatient Sample database was conducted to identify pediatric patients with neurodevelopmental disorders who underwent heart transplantation from 2011–2019. Baseline characteristics and in-hospital outcomes between patients were compared. Binary logistic regression was used to investigate the association between the documented presence of a neurodevelopmental disorder and in-hospital outcomes in children undergoing heart transplantation. **Results**: We identified a weighted sample of 3770 pediatric cardiac transplant patients, of whom 245 (6.5%) had a documented diagnosis of neurodevelopmental disorder. There was no significant difference in the odds of major adverse cardiovascular events (all-cause mortality, stroke complications or myocardial infarction), surgical complications, infection, venous thromboembolic events, delirium/restraint use, or cardiac dysrhythmia. Patients with neurodevelopmental disorders had lower overall length of stay (44.0 days interquartile range (IQR): 16.0–90.0 *vs*. 57.08 days IQR: 22.0–112.0, $p < 0.050$), and cost of stay ($956,031 IQR: 548,559.0–1,801,412.0 *vs*. $1,074,793 IQR: 599,089.8–2,129,086.0, $p < 0.050$). Patients with neurodevelopmental disorders had significantly lower odds of acute transplant complications (adjusted odds ratio (aOR): 0.39, 95% confidence interval (CI): 0.21–0.74, $p < 0.050$) vascular complications (aOR: 0.36, 95% CI: 0.19–0.66, $p < 0.050$) and acute kidney injury (AKI) (aOR: 0.52, 95% CI: 0.33–0.83, $p < 0.050$). **Conclusions**: These data suggest that patients with neurodevelopmental disorders have overall similar if not potentially improved post-transplant outcomes in the acute setting compared to neurotypical patients, possibly secondary to selection bias in the patient selection process.

## Keywords

neurodevelopmental disorder; heart failure; heart transplant; transplant rejection

## Introduction

For children with end-stage heart failure refractory to medical management, heart transplantation is the standard of care [1]. The most common indication for transplantation in patients under 1 year of age is congenital heart disease [1]. For older children, conversely, the commonest indication is cardiomyopathy [1]. In-hospital and short-term outcomes after transplant have improved consistently over the past 30 years, and patients that live to 1-year post-transplant have a 60% survival into adulthood [2]. Despite these advances, limited donor availability remains challenging for transplant teams. Patients with 1A status often experience wait times of up to 80–108 days and wait-list mortality of up to 19.7–21.4% [3]. Most children on the wait-list are aged 12–17 years (28.4%), followed by patients aged 1–5 years (26.4%) and patients younger than 1 year (21.3%) [4]. The majority of children listed for transplant are White (51.3%), followed by Hispanic (21.0%) and African-American children (19.6%) [4]. While the total number of pediatric transplants has risen in recent times (a 36.1% increase from 2010–2021), there are significant concerns regarding mor-

bidity and mortality in various pediatric transplant candidate subgroups [4–6]. Pediatric patients with neurodevelopmental disorders (NDDs) represent a subgroup that is undergoing transplant at increased frequency, yet studies regarding post-transplant prognosis in this group are lacking [7]. The Diagnostic and Statistical Manual of Mental Disorders 5 (DSM-5) defines NDDs as a group of conditions that begin early in childhood and result in developmental deficits that impair personal, social, academic or occupational functioning [8]. Specific NDDs include autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID), specific learning disorder (SLD), motor disorders (MD) and communication disorders (CD) [8,9].

Epidemiological data from the National Health Interview Survey indicate that 18% of children have some form of NDD as of 2017, a 9.5% increase over the prior 9 years [10]. In terms of specific NDDs, approximately 1 in 36 children aged 8 years have ASD, with male children being 3.8 times more likely to carry the diagnosis [11]. The global prevalence of ADHD is estimated to be anywhere between 4.8% and 9.4% of children and teenagers [12]. Intellectual disabilities are estimated to affect up to 3% of the population [13]. Specific learning disorders, which encompass neurocognitive deficits in verbal and mathematical perception, afflict up to 5–15% of children [8,14]. Similar to IDs, MDs are thought to impact 2–3% of children [15]. Communication disorders are diagnosed more frequently, with an estimated prevalence of 5–10% [16]. NDDs may be associated with an increased risk of developing atherosclerotic heart disease, dyslipidemia, stroke, heart failure and cardiometabolic disease [17–21]. It is unclear what factors contribute to this increased risk of heart disease, but effects of atypical antipsychotics, food selectivity, sedentary lifestyle, disturbed sleep patterns, disparities in the use of guideline directed medical therapy, prematurity, genetic and epigenetic variation, intrauterine growth restriction, autonomic nervous system dysfunction, prenatal infections, maternal obesity and maternal diabetes have all been offered as potential etiologies [17,20–22]. Children with congenital heart disease (CHD) have increased odds of being diagnosed with NDDs [23–28]. Up to 30% of children with CHD have concomitant NDDs [29]. The American Heart Association and American Academy of Pediatrics recommend that clinicians consider enhanced screening for NDDs in children with CHD [23]. While data regarding the prevalence of specific acquired cardiac abnormalities in patients with NDDs is sparse, genetic mouse models of NDDs show altered anterior and posterior wall thickness, differential myocardial fractional shortening and increased left ventricular chamber diameter when compared to wild-type mice [30]. Genetic variants implicated in the pathogenesis of some NDDs, have also been tied to pathologic cardiac morphologic abnormalities [29,31–47]. Although models demonstrating the relationship of these shared neurological and cardiovascular allelic variants with heart disease in higher mammals have not yet been developed, children with NDDs have been shown to have higher rates of atrial septal defects, ventricular septal defects, and left heart obstructive lesions [24]. Conversely, magnetic resonance imaging (MRI) studies in fetuses with isolated CHD show decreased brain volumes and maturation when compared to controls [48,49].

Many international societies and governing bodies recommend against heart transplantation in patients with severe cognitive/behavioral disabilities, yet criteria to define severity are not offered [50]. Patients with NDDs and end-stage heart failure may face systematic discrimination during evaluation for ventricular assist device (VAD) or transplant. We sought to investigate in-hospital outcomes in pediatric patients with NDDs undergoing heart transplantation. We hypothesized that in-hospital outcomes after transplant would be similar between groups.

## Methods

### *Study Design*

A retrospective cohort analysis was performed using the National Inpatient Sample (NIS) database. The NIS is the largest public all-payer inpatient dataset, encompassing an approximate 20% sample of hospitalizations from US hospitals participating in the Healthcare Cost and Utilization Project. Information on all hospital stays is offered, irrespective of payer. Rehabilitation hospitals and long-term acute care facilities are excluded from the NIS. Patient, hospital, and state identifiers are universally excluded from the NIS, and all information is de-identified. Institutional Review Board oversight and approval was not necessary since patient-level information is de-identified within the database. Data was weighted as recommended by the NIS. Weights are attached to each case by the NIS to approximate a nationwide sampling of patients, and these weights are applied to the sample prior to the application of statistical tests.

The NIS was queried from 1 January 2011 through 31 December 2019, resulting in 324,130,692 weighted cases. Patients undergoing cardiac transplantation were identified based on ICD-9 or ICD-10 procedure codes corresponding to heart transplant (**Supplementary Table 1**). A total of 25,456 transplant patients were identified, of whom 340 had concomitant documented NDDs (**Supplementary Table 2**). Patients with individual and mixed NDDs were included in the analysis. To capture all codes used for NDDs, publicly available spreadsheets consisting of all ICD 9/10 codes from the Healthcare Cost and Utilization Project (HCUP) Distributor were cross-referenced against the Diagnostic and Statistical Manual of Mental Disorders-V (DSM-V) [8,51]. Notably, only 95 (27.94%) of the total

NDD coded patients who underwent transplant were adults. Patients older than 18 years of age were excluded from the analysis, as were patients with a medical diagnosis of heart transplant history. After exclusion of transplant recipients aged >18 years, a total of 3770 pediatric cardiac transplant admissions were identified, of whom 245 (6.5%) were coded as having an NDD (Fig. 1).

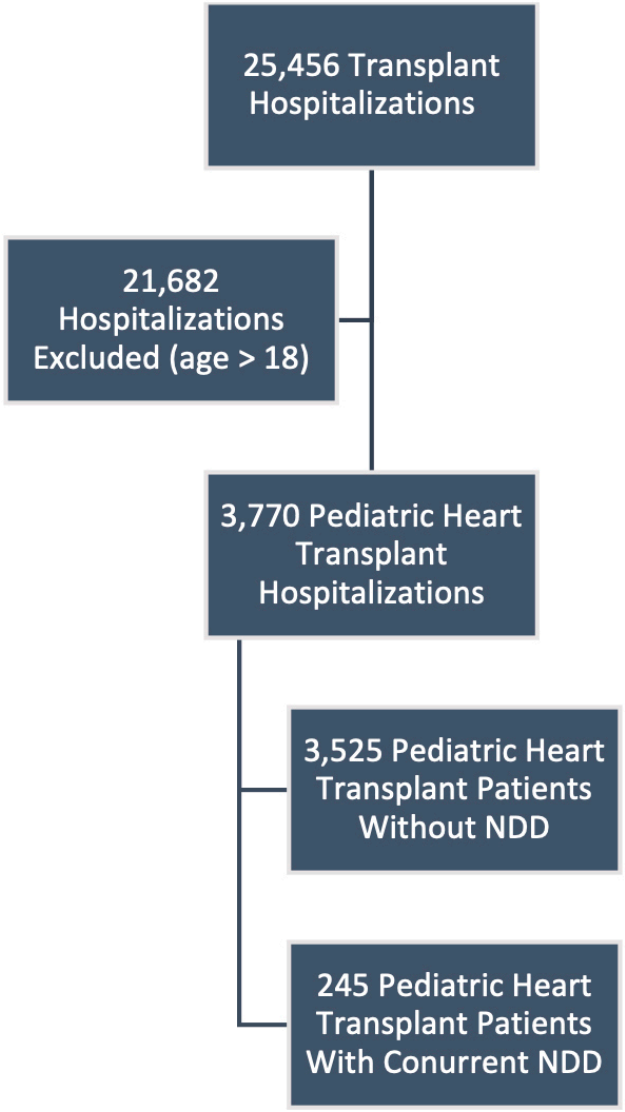


**Fig. 1. Flow chart detailing the selection of patients who underwent heart transplantation between 2011 and 2019 with and without neurodevelopmental disorder (NDD).**

Baseline characteristics were evaluated, including age, sex, race, elective admission status, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, obstructive sleep apnea, asthma, pulmonary hypertension, history of stroke, anemia, obesity, major depressive disorder, history of malignancy, hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis (**Supplementary Table 3**). Groups were also analyzed at baseline for the presence of congenital heart disease, including atrial septal defect, ventricular septal defect, hypoplastic left heart syndrome, Tetralogy of Fallot, patent ductus arteriosus and a history of prior surgical correction of congenital heart defects.

The primary outcome was a composite of mortality, stroke complications or myocardial infarction (major adverse cardiovascular events, MACE). Secondary outcomes included length of stay, cost of stay, transplant-associated rejection/complications, intraoperative complications/pericardial complications, bleeding, transfusions, infection, postoperative deep vein thrombosis/pulmonary embolism (DVT/PE), delirium/restraint use, ventricular dysrhythmia, atrial fibrillation/flutter, vascular complications, cardiac arrest, cardioversion, acute kidney injury, post procedural cardiogenic shock, post-transplant lymphoproliferative disorders and pneumothorax.

### *Statistical Analysis*

Descriptive statistics were used to express continuous and categorical variables. Missing values for race were handled using multiple imputation as recommended by the Healthcare Cost and Utilization Project [51]. Mean and standard deviations were given for parametric continuous variables, median and interquartile range for non-parametric continuous variables, and percentages for categorical variables. Independent samples *t*-tests were used for parametric continuous variables, and Pearson's chi-square for categorical variables. The Mann-Whitney U test was used for non-parametric continuous variables. A $p$ value of $<0.05$ was considered statistically significant. Multivariate logistic regression was utilized to develop adjusted odds ratios (aORs) and 95% confidence intervals to estimate the association between NDD and in-hospital outcomes after heart transplant. Models were adjusted for prespecified covariates including age, infant status, race, sex, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, stroke history, anemia, obesity, obstructive sleep apnea, asthma, congenital heart disease, dilated cardiomyopathy, and history of surgically corrected congenital malformations. Statistical analyses were performed using SPSS (IBM SPSS statistics for MAC, Version 26.0; IBM Corporation, Armonk, NY, USA).

## Results

Baseline characteristics of patients with and without coded NDDs are shown in Table 1.

In patients with NDDs undergoing transplant, 20.4% (N = 50) had mixed or overlapping syndromes. The predominant NDD was ADHD (36.7%, N = 90) followed by ASD (28.6%, N = 70) and then CD (22.4%, N = 55). Intellectual disability was less common in transplant recipi-

**Table 1. Baseline characteristics of patients undergoing heart transplant.**

| Variable | No NDD (n = 3525) | NDD (n = 245) | *p*-value |
|---|---|---|---|
| Age | 7.2 ± 6.5 | 8.9 ± 6.0 | <0.001* |
| Female | 42.0% (1481) | 32.7% (80) | 0.004* |
| Non-white Race | 48.6% (1713) | 47.3% (116) | 0.170 |
| Elective Admission | 16.3% (571) | 16.3% (40) | 0.990 |
| Hypertension | 28.1% (992) | 40.8% (100) | <0.001* |
| Diabetes Mellitus | 1.4% (45) | 9.8% (20) | <0.001* |
| Chronic Kidney Disease | 4.4% (155) | 10.2% (25) | <0.001* |
| Chronic Liver Disease | 7.5% (265) | 14.3% (35) | <0.001* |
| Obstructive Sleep Apnea | 2.8% (100) | 8.2% (20) | <0.001* |
| On Hemodialysis | N ≤ 10 | N ≤ 10 | |
| Asthma | 6.1% (214) | 20.4% (50) | <0.001* |
| Pulmonary Hypertension | 18.4% (647) | 20.4% (50) | 0.430 |
| Prior Stroke | 5.4% (190) | N ≤ 10 | |
| Anemia | 6.4% (149) | N ≤ 10 | |
| Obesity | 3.1% (110) | 10.2% (25) | <0.001* |
| Major Depressive Disorder | 7.1% (251) | 6.1% (15) | 0.560 |
| Congenital Heart Disease | 18.9% (666) | 6.1% (15) | <0.001* |
| Personal History of Malignancy | 0.7% (25) | N ≤ 10 | |
| Hypertrophic Cardiomyopathy | 4.0% (140) | 6.1% (15) | 0.100 |
| Dilated Cardiomyopathy | 40.8% (1439) | 53.1% (130) | <0.001* |
| Myocarditis | 3.0% (105) | N ≤ 10 | |
| History of Myocardial Infarction | 0.6% (20) | N ≤ 10 | |
| History of Surgically Corrected Congenital Heart Lesion | 6.2% (220) | 10.2% (25) | <0.015* |

Values are reported as mean ± standard deviation for continuous variables and percentage (number) for categorical variables. $p$-value $< 0.05$ is considered significant (asterisk). Cells with values ≤10 are not reported as recommended by the National Inpatient Sample (NIS) and denoted as N ≤ 10.

ents with diagnosed NDDs (16.3%, N = 40). Patients with SLDs and MDs each made up less than 10% of the NDD cohort. Patients with NDDs were more likely to have hypertension (40.8% *vs*. 28.1%), diabetes mellitus (9.8% *vs*. 1.4%), chronic kidney disease (10.2% *vs*. 4.4%), chronic liver disease (14.3% *vs*. 7.5%), obstructive sleep apnea (8.2% *vs*. 2.8%), asthma (20.4% *vs*. 6.1%), obesity (10.2% *vs*. 3.1%), dilated cardiomyopathy (53.1% *vs*. 40.8%) and a history of a prior surgically corrected congenital heart lesion (10.2% *vs*. 6.2%) with $p < 0.05$ for all. Unexpectedly, for pediatric patients selected for transplantation, patients without NDDs had a higher frequency of congenital heart disease compared to patients with NDDs (18.9% *vs*. 6.1%). Patients with NDDs were older than the non-NDD cohort (8.94 ± 6.02 years *vs*. 7.23 ± 6.46 years, $p < 0.05$).

The NDD group had a lower rate of females than the non-NDD group (32.7% *vs*. 42.0%). There was a lower rate of non-white race in the NDD group (45.2% *vs*. 48.8%). There were no significant differences in the incidence of elective admissions. The frequency of prior stroke, dialysis, anemia, malignancy history, myocarditis and prior myocardial infarction were too low to calculate differences between groups.

Unadjusted in-hospital outcomes after heart transplant are shown in Table 2.

Patients with NDDs who underwent cardiac transplant had lower rates of MACE, defined as a composite of mortality, stroke complications or myocardial infarction (6.1% *vs*. 13.7%), acute transplant complications (12.2% *vs*. 21.4%), intraoperative/pericardial complications (8.2% *vs*. 13.8%), bleeding complications (10.2% *vs*. 22.6%), vascular complications (14.3% *vs*. 26.0%) and acute kidney injury (AKI) (18.4% *vs*. 33.4%). The average length of stay was shorter in the NDD group as was the average cost of stay. There was no significant difference in blood product transfusions (26.5% *vs*. 23.7%), postoperative deep venous thrombosis (14.3% *vs*. 14.9%), ventricular dysrhythmias (28.6% *vs*. 29.3%), cardioversion (6.1% *vs*. 4.2%) or pneumothorax (6.1% *vs*. 8.0%) between groups.

A binary logistic regression model was used to adjust for the prespecified covariates of age, infant status, race, sex, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, stroke history, anemia, obesity, obstructive sleep apnea, asthma, congenital heart disease, dilated cardiomyopathy, and history of surgically corrected congenital malformations. The age variable was dichotomized into patients ≤7 years old *vs*. those >7 for the binary logistic regression model. Infant status was defined as patients <1 year old. The non NDD group contained 972 infants (27.6%) while the NDD group contained 35

**Table 2. Outcomes following heart transplant.**

| Outcome | No NDD (n = 3525) | NDD (n = 245) | *p*-value |
|---|---|---|---|
| MACE [A] | 13.7% (483) | 6.1% (15) | <0.001* |
| Length of Stay [B] | 57 IQR (22–112) | 44 IQR (16–90) | <0.001* |
| Cost of Stay [C] | 1,074,793 IQR (599,090–2,129,086) | 956,031 IQR (548,559–1,801,412) | <0.030* |
| Acute Transplant Complications [D] | 21.4% (755) | 12.2% (30) | <0.001* |
| Iatrogenic or Pericardial Complications of Cardiac Surgery | 13.8% (488) | 8.2% (20) | 0.012* |
| All Major Bleeding | 22.6% (798) | 10.2% (25) | <0.001* |
| Blood Product Transfusion | 23.7% (837) | 26.5% (65) | 0.323 |
| Infectious Complications [E] | 12.0% (423) | N $\leq$ 10 | |
| Postoperative Deep Venous Thrombosis or Pulmonary Embolism | 14.9% (526) | 14.3% (35) | 0.787 |
| Delirium or Restraint use | 4.4% (156) | N $\leq$ 10 | |
| Ventricular Dysrhythmia | 29.3% (1032) | 28.6% (70) | 0.814 |
| Atrial Fibrillation/Flutter | 6.2% (217) | N $\leq$ 10 | |
| Vascular Complications | 26.0% (916) | 14.3% (35) | <0.001* |
| Cardiac Arrest | 9.3% (326) | N $\leq$ 10 | |
| Cardioversion | 4.2% (149) | 6.1% (15) | 0.160 |
| Acute Kidney Injury | 33.4% (1178) | 18.4% (45) | <0.001* |
| Post Procedural Cardiogenic Shock | 1.3% (45) | N $\leq$ 10 | |
| Post Transplant Lymphoproliferative Disorder | N $\leq$ 10 | N $\leq$ 10 | |
| Pneumothorax | 8.0% (283) | 6.1% (15) | 0.285 |

Outcomes reported as median (interquartile range) for continuous variables and percentage (number) for categorical variables. [A] MACE: combined primary endpoint including mortality, all stroke complications, and all acute myocardial infarctions. [B] Length of stay reported in days. [C] Cost of stay reported in USD. [D] Acute transplant complications include rejection, graft dysfunction and allograft vasculopathy. [E] Infectious complications include postoperative infection, sepsis, or septic shock. *p*-value considered significant <0.05 (asterisk). Cells with values $\leq$10 are not reported as recommended by the NIS and denoted as N $\leq$ 10. MACE, major adverse cardiovascular events; IQR, interquartile range.

(14.3%). After adjustment, there was no significant difference in the odds of MACE (aOR: 0.69, 95% confidence interval (CI): 0.34–1.44, $p = 0.333$), intraoperative/pericardial complications (aOR: 0.79, 95% CI: 0.42–1.49, $p = 0.469$), or bleeding complications (aOR: 0.64, 95% CI: 0.35–1.16, $p = 0.137$), between NDD and non-NDD patients. Patient with NDDs had significantly lower odds of acute transplant complications (0.39, 95% CI: 0.21–0.74, $p < 0.001$) vascular complications (aOR: 0.36, 95% CI: 0.19–0.66, $p = 0.003$) and AKI (aOR: 0.52, 95% CI: 0.33–0.83, $p = 0.004$) compared to non-NDD patients during the index admission (Fig. 2). A comorbidity adjusted Brown-Mood median test was conducted to compare the median cost and length of stay between NDD and non NDD groups given the non-parametric distribution of those variables. The median length of stay was shorter in the NDD group (44.0 days interquartile range (IQR): 16.0–90.0 *vs.* 57.08 days IQR: 22.0–112.0, $p = 0.004$), and there was no significant comorbidity adjusted difference in the median cost of stay between NDD and non NDD groups ($956,031 IQR: 548,559.0–1,801,412.0 *vs.* $1,074,793 IQR: 599,089.8–2,129,086.0, $p = 0.098$).

## Discussion

We present the only multi-center retrospective cohort study of heart transplantation outcomes in patients with NDDs to date. In this cohort we demonstrate that overall, the presence of NDDs was not associated with increased odds of major adverse cardiovascular events, intraoperative complications, or graft dysfunction. Patients with NDDs, interestingly, had decreased odds of acute transplant complications, vascular complications, and acute kidney injury. This is despite the fact that patients with NDDs had higher rates of comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, and asthma. This may be because a higher proportion of the neurotypical patients had concomitant CHD as compared to the NDD patients, whereas the NDD patients had a higher degree of dilated cardiomyopathy. The likely shortened time to transplant for children with dilated cardiomyopathy may explain fewer overall complications being seen in this group [52]. Selection bias in the organ allocation process may also be partly responsible for the improved outcomes in the NDD group in this study. Patients with NDDs may be viewed as sicker than their neurotypical counterparts and

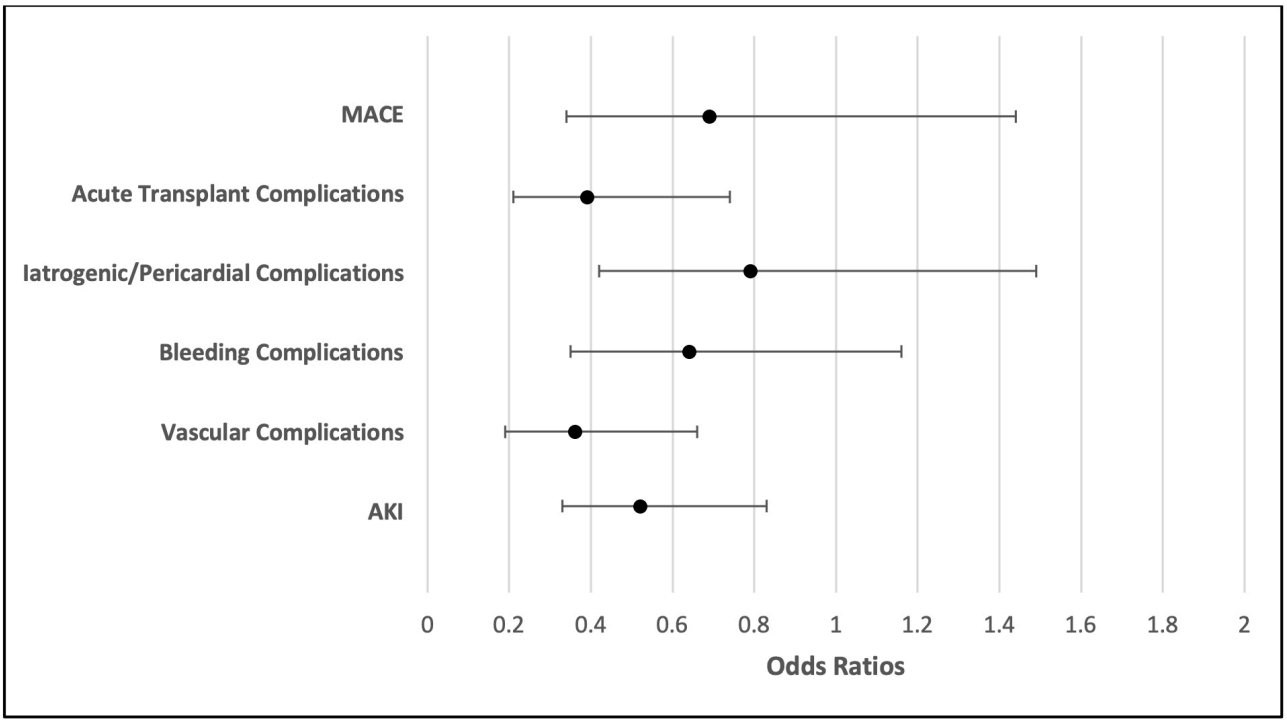


**Fig. 2. Adjusted in-hospital outcomes following heart transplant in patients with NDDs. Values <1 favor patients with NDDs.** AKI, acute kidney injury.

may be excluded from the transplant conversation. While the phenomenon of over-diagnosis and under-treatment has been shown in racial minorities [53], there have not been similar studies in patients with NDDs.

Despite the increasing prevalence of NDDs, heart transplantation in neurodivergent populations remains an area of controversy. Several state legislatures in the US have recently passed legislation to protect the rights of patients with NDDs being evaluated for transplant [54]. Up to 43% of pediatric transplant centers consider NDDs when evaluating a patient for transplant, with 14% of centers regarding even mild NDDs a relative contraindication to transplant [55]. Data from the Organ Sharing Network has shown that children with NDDs have longer wait times prior to transplant, but similar survival and graft function after surgery [56]. There is a distinct lack of guidance and standardization regarding the inclusion of neurodevelopmental delay in the transplant evaluation [55]. The low frequency of CHD in the NDD group in this study despite the numerous genetic associations between the conditions raises the question of whether patients with CHD are not being transplanted because of their NDDs. Epidemiological data suggest that up to 18% of US children may have some form of NDD, however patients with NDDs only made of 6.5% of the population of this study [10]. Patient and institution level analyses are needed to assess whether patients with IDs are being excluded from consideration for transplant based on their neurodivergent status [57,58].

Patients with NDDs suffer from persistent difficulties with social interaction, communication, and learning [8,59]. For NDD patients with concomitant heart failure who are *in extremis* and require transplant for a chance at survival, the pre, peri and post-operative periods can be especially challenging. Overstimulation in the inpatient and intensive care units, higher doses of sedating medications, difficulties communicating symptoms, "picking" at lines or surgical wounds, concerns regarding long term immunosuppressant adherence and problems with dietary and fluid restrictions are all valid concerns for NDD patients facing the possibility of transplant surgery. The results from this retrospective study support the notion that patients with NDDs can benefit from similar in-hospital outcomes to patients without NDDs after cardiac transplant.

Some pediatric transplant centers have had success with limiting the number of patient visitors, minimizing the number of distracting stimuli, decreasing the frequency of vital sign monitoring, and emphasizing the importance of open and empathetic communication with NDD patients [60]. Physicians, case managers, family members, nurses and mental health practitioners are equally important and all play vital roles in serving this vulnerable population. Up to 24% of neurotypical children may suffer from psychological distress after heart transplant, and an individualized approach is needed for all children facing the prospect of such major intervention [61]. One survey of a large pediatric tertiary center showed that nurses with frequent interactions with patients with NDDs have significantly higher

self-reported effectiveness at communicating with and caring for these populations compared to staff with less frequent interactions [62]. Successful strategies reported in that study included partnering with families to understand what techniques were effective to communicate with and calm children with NDDs, as well as better understand what stimuli upset them [62]. Studies in older adults with neurocognitive disorders indicate that one to one specialling and close observation in this population may result in higher quality care, however data regarding specialling and closer observation in pediatric patients with NDDs is not available at this time [63]. Increased supervision, more frequent contact with clinical staff and access to nurses specialized in these behavioral interventions may bely the improved outcomes for the NDD group in this study.

The current study has several limitations. The low sample size of NDD patients reduces the generalizability of this study. A weighted population of 245 NDD patients undergoing transplant ensures that any observations drawn from this study are mainly descriptive and causation cannot be inferred. The accuracy of coding for NDDs is likely heterogenous between centers. We were unable to evaluate patients with or without NDDs who were considered for transplant and ultimately not listed and therefore cannot estimate the possible role of selection bias on these outcomes. Patients with NDDs being considered for transplant may, for instance, have fewer overall comorbidities and greater performance status at baseline. The former, however, is belied by the higher baseline rates of diabetes mellitus, chronic kidney disease and pulmonary hypertension in the NDD group.

Despite the above-mentioned limitations, in this cohort NDD patients who underwent heart transplant had similar to improved posttransplant outcomes compared to neurotypical patients. Efforts are underway in various governmental bodies to protect the rights of intellectually divergent patients in need of solid organ transplants. The exclusion of patients with NDDs from some transplant programs represents a major disparity in healthcare and transplant teams should consider a multidisciplinary approach to evaluating NDD patients for transplant.

## Conclusions

Pediatric patients with neurodevelopmental disorders have similar or potentially improved outcomes post-cardiac transplant when compared to neurotypical patients, however they are transplanted at a lower frequency then would be expected based on epidemiological data.

## Availability of Data and Materials

The datasets analyzed in the current study are available from the Healthcare Cost and Utilization Project Central Distributor (https://hcup-us.ahrq.gov/tech_assist/centdist.jsp).

## Author Contributions

IE: conceptualization, methodology, software, formal analysis, data curation, writing- original draft, visualization. FL: methodology, formal analysis, data curation, writing- review and editing. RS: formal analysis, writing- review and editing. BE: methodology, software, validation, formal analysis, resources, data curation, writing- review and editing. MD: methodology, software, validation, formal analysis, resources, data curation, writing- review and editing. KI: validation, writing- review and editing. LV: methodology, software, validation, formal analysis, resources, data curation, writing- review and editing. RC: writing- review and editing, project administration, resources, supervision. GM: writing- review and editing, project administration, resources, supervision. LG: conceptualization, methodology, validation, resources, writing- review and editing, supervision, project administration. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspect of the work.

## Ethics Approval and Consent to Participate

Oversight and approval from the University of Miami institutional review board was not necessary since patient-level information was de-identified within the database.


## Acknowledgment

Not applicable.

## Funding

This research received no external funding.


## Conflict of Interest

The authors declare no conflict of interest.

## Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.59958/hsf.7289.

## References


[1] Dipchand AI. Current state of pediatric cardiac transplantation. Annals of Cardiothoracic Surgery. 2018; 7: 31–55.

[2] Dipchand AI, Webber SA. Pediatric heart transplantation: Looking forward after five decades of learning. Pediatric Transplantation. 2024; 28: e14675.

[3] Williams RJ, Lu M, Sleeper LA, Blume ED, Esteso P, Fynn-Thompson F, *et al*. Pediatric heart transplant waiting times in the United States since the 2016 allocation policy change. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2022; 22: 833–842.

[4] Colvin MM, Smith JM, Ahn YS, Messick E, Lindblad K, Israni AK, *et al*. OPTN/SRTR 2021 Annual Data Report: Heart. American Journal of Transplantation: Official Journal of the American Society of Transplantation and the American Society of Transplant Surgeons. 2023; 23: S300–S378.

[5] Amdani S, Bhimani SA, Boyle G, Liu W, Worley S, Saarel E, *et al*. Racial and Ethnic Disparities Persist in the Current Era of Pediatric Heart Transplantation. Journal of Cardiac Failure. 2021; 27: 957–964.

[6] Zubair MM, Chen Q, Rowe G, Gill G, Thomas J, Timbalia SA, *et al*. Evolving Trends and Widening Racial Disparities in Children Listed for Heart Transplantation in the United States. Circulation. 2022; 146: 262–264.

[7] Adebiyi E, Jennifer Christine MP. Temporal trends and regional variation of heart transplantation in children with intellectual and developmental disabilities. Pediatric Transplantation. 2023; 27: e14620.

[8] Association AP. Diagnostic and Statistical Manual of Mental Disorders. American Psychiatric Association: San Francisco, CA. 2013.

[9] Francés L, Quintero J, Fernández A, Ruiz A, Caules J, Fillon G, *et al*. Current state of knowledge on the prevalence of neurodevelopmental disorders in childhood according to the DSM-5: a systematic review in accordance with the PRISMA criteria. Child and Adolescent Psychiatry and Mental Health. 2022; 16: 27.

[10] Durkin MS. Increasing Prevalence of Developmental Disabilities Among Children in the US: A Sign of Progress? Pediatrics. 2019; 144: e20192005.

[11] Maenner MJ, Warren Z, Williams AR, Amoakohene E, Bakian AV, Bilder DA, *et al*. Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years - Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002). 2023; 72: 1–14.

[12] Ayano G, Demelash S, Gizachew Y, Tsegay L, Alati R. The global prevalence of attention deficit hyperactivity disorder in children and adolescents: An umbrella review of meta-analyses. Journal of Affective Disorders. 2023; 339: 860–866.

[13] Patel DR, Cabral MD, Ho A, Merrick J. A clinical primer on intellectual disability. Translational Pediatrics. 2020; 9: S23–S35.

[14] Moll K, Kunze S, Neuhoff N, Bruder J, Schulte-Körne G. Specific learning disorder: prevalence and gender differences. PLoS ONE. 2014; 9: e103537.

[15] Chouksey A, Pandey S. Functional Movement Disorders in Children. Frontiers in Neurology. 2020; 11: 570151.

[16] Ruben RJ. Redefining the survival of the fittest: communication disorders in the 21st century. The Laryngoscope. 2000; 110: 241–245.

[17] Dhanasekara CS, Ancona D, Cortes L, Hu A, Rimu AH, Robohm-Leavitt C, *et al*. Association Between Autism Spectrum Disorders and Cardiometabolic Diseases: A Systematic Review and Meta-analysis. JAMA Pediatrics. 2023; 177: 248–257.

[18] Li L, Chang Z, Sun J, Garcia-Argibay M, Du Rietz E, Dobrosavljevic M, *et al*. Attention-deficit/hyperactivity disorder as a risk factor for cardiovascular diseases: a nationwide population-based cohort study. World Psychiatry: Official Journal of the World Psychiatric Association (WPA). 2022; 21: 452–459.

[19] Wang H, Lee PMY, Zhang J, Svendsen K, Li F, Li J. Association of intellectual disability with overall and type-specific cardiovascular diseases: a population-based cohort study in Denmark. BMC Medicine. 2023; 21: 41.

[20] Zwack CC, McDonald R, Tursunalieva A, Cooray A, Lambert GW, Lambert EA. Does autonomic nervous system dysfunction influence cardiovascular disease risk in young adults with intellectual disability? American Journal of Physiology. Heart and Circulatory Physiology. 2021; 320: H891–H900.

[21] Rossi M, Wainsztein N, Merello M. Cardiac Involvement in Movement Disorders. Movement Disorders Clinical Practice. 2021; 8: 651–668.

[22] Erickson SR, Basu T, Dorsch MP, Kamdar N. Disparities in the Use of Guideline-Based Pharmacotherapy Exist for Atherosclerotic Cardiovascular Disease and Heart Failure Patients Who Have Intellectual/Developmental Disabilities in a Commercially Insured Database. The Annals of Pharmacotherapy. 2020; 54: 958–966.

[23] Marino BS, Lipkin PH, Newburger JW, Peacock G, Gerdes M, Gaynor JW, *et al*. Neurodevelopmental outcomes in children with congenital heart disease: evaluation and management: a scientific statement from the American Heart Association. Circulation. 2012; 126: 1143–1172.

[24] Sigmon ER, Kelleman M, Susi A, Nylund CM, Oster ME. Congenital Heart Disease and Autism: A Case-Control Study. Pediatrics. 2019; 144: e20184114.

[25] Radoeva PD, Coman IL, Salazar CA, Gentile KL, Higgins AM, Middleton FA, *et al*. Association between autism spectrum disorder in individuals with velocardiofacial (22q11.2 deletion) syndrome and PRODH and COMT genotypes. Psychiatric Genetics. 2014; 24: 269–272.

[26] Wier ML, Yoshida CK, Odouli R, Grether JK, Croen LA. Congenital anomalies associated with autism spectrum disorders. Developmental Medicine and Child Neurology. 2006; 48: 500–507.

[27] Hultman CM, Sparén P, Cnattingius S. Perinatal risk factors for infantile autism. Epidemiology (Cambridge, Mass.). 2002; 13: 417–423.

[28] Fourdain S, St-Denis A, Harvey J, Birca A, Carmant L, Gallagher A, *et al*. Language development in children with congenital heart disease aged 12-24 months. European Journal of Paediatric Neurology: EJPN: Official Journal of the European Paediatric Neurology Society. 2019; 23: 491–499.

[29] Ji W, Ferdman D, Copel J, Scheinost D, Shabanova V, Brueckner M, *et al*. De novo damaging variants associated with congenital heart diseases contribute to the connectome. Scientific Reports. 2020; 10: 7046.

[30] Assimopoulos S, Hammill C, Fernandes DJ, Spencer Noakes TL, Zhou YQ, Nutter LMJ, *et al*. Genetic mouse models of autism spectrum disorder present subtle heterogenous cardiac

abnormalities. Autism Research: Official Journal of the International Society for Autism Research. 2022; 15: 1189–1208.
[31] Cusmano-Ozog K, Manning MA, Hoyme HE. 22q13.3 deletion syndrome: a recognizable malformation syndrome associated with marked speech and language delay. American Journal of Medical Genetics. Part C, Seminars in Medical Genetics. 2007; 145C: 393–398.
[32] Ornoy A, Weinstein-Fudim L, Ergaz Z. Genetic Syndromes, Maternal Diseases and Antenatal Factors Associated with Autism Spectrum Disorders (ASD). Frontiers in Neuroscience. 2016; 10: 316.
[33] Pierpont ME, Brueckner M, Chung WK, Garg V, Lacro RV, McGuire AL, *et al*. Genetic Basis for Congenital Heart Disease: Revisited: A Scientific Statement From the American Heart Association. Circulation. 2018; 138: e653–e711.
[34] Batsukh T, Pieper L, Koszucka AM, von Velsen N, Hoyer-Fender S, Elbracht M, *et al*. CHD8 interacts with CHD7, a protein which is mutated in CHARGE syndrome. Human Molecular Genetics. 2010; 19: 2858–2866.
[35] Cohen ED, Tian Y, Morrisey EE. Wnt signaling: an essential regulator of cardiovascular differentiation, morphogenesis and progenitor self-renewal. Development (Cambridge, England). 2008; 135: 789–798.
[36] Cotney J, Muhle RA, Sanders SJ, Liu L, Willsey AJ, Niu W, *et al*. The autism-associated chromatin modifier CHD8 regulates other autism risk genes during human neurodevelopment. Nature Communications. 2015; 6: 6404.
[37] Hubert F, Payan SM, Rochais F. FGF10 Signaling in Heart Development, Homeostasis, Disease and Repair. Frontiers in Genetics. 2018; 9: 599.
[38] Shanks MO, Lund LM, Manni S, Russell M, Mauban JRH, Bond M. Chromodomain helicase binding protein 8 (Chd8) is a novel A-kinase anchoring protein expressed during rat cardiac development. PLoS ONE. 2012; 7: e46316.
[39] Ko JM. Genetic Syndromes associated with Congenital Heart Disease. Korean Circulation Journal. 2015; 45: 357–361.
[40] Lim S, Naisbitt S, Yoon J, Hwang JI, Suh PG, Sheng M, *et al*. Characterization of the Shank family of synaptic proteins. Multiple genes, alternative splicing, and differential expression in brain and development. The Journal of Biological Chemistry. 1999; 274: 29510–29518.
[41] Man W, Gu J, Wang B, Zhang M, Hu J, Lin J, *et al*. SHANK3 Coordinately Regulates Autophagy and Apoptosis in Myocardial Infarction. Frontiers in Physiology. 2020; 11: 1082.
[42] Ghebranious N, Giampietro PF, Wesbrook FP, Rezkalla SH. A novel microdeletion at 16p11.2 harbors candidate genes for aortic valve development, seizure disorder, and mild mental retardation. American Journal of Medical Genetics. Part a. 2007; 143A: 1462–1471.
[43] Sun H, Wang Y. Branched chain amino acid metabolic reprogramming in heart failure. Biochimica et Biophysica Acta. 2016; 1862: 2270–2275.
[44] Wang Y. Mitogen-activated protein kinases in heart development and diseases. Circulation. 2007; 116: 1413–1423.
[45] Xie H, Hong N, Zhang E, Li F, Sun K, Yu Y. Identification of Rare Copy Number Variants Associated With Pulmonary Atresia With Ventricular Septal Defect. Frontiers in Genetics. 2019; 10: 15.
[46] Xu M, Yao J, Shi Y, Yi H, Zhao W, Lin X, *et al*. The SRCAP chromatin remodeling complex promotes oxidative metabolism during prenatal heart development. Development (Cambridge, England). 2021; 148: dev199026.
[47] Hunter JE, Berry-Kravis E, Hipp H, Todd PK. FMR1 Disorders. GeneReviews® [Internet]. 2019. Available at: https://www.ncbi.nlm.nih.gov/books/NBK1384/ (Accessed: 1 October 2023).
[48] Mlczoch E, Brugger P, Ulm B, Novak A, Frantal S, Prayer D, *et al*. Structural congenital brain disease in congenital heart disease: results from a fetal MRI program. European Journal of Paediatric Neurology: EJPN: Official Journal of the European Paediatric Neurology Society. 2013; 17: 153–160.
[49] Schellen C, Ernst S, Gruber GM, Mlczoch E, Weber M, Brugger PC, *et al*. Fetal MRI detects early alterations of brain development in Tetralogy of Fallot. American Journal of Obstetrics and Gynecology. 2015; 213: 392.e1–392.e7.
[50] Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, *et al*. The 2016 International Society for Heart Lung Transplantation listing criteria for heart transplantation: A 10-year update. The Journal of Heart and Lung Transplantation: the Official Publication of the International Society for Heart Transplantation. 2016; 35: 1–23.
[51] Houchens R, Elixhauser A. Using the HCUP Nationwide Inpatient Sample to Estimate Trends. US Agency for Healthcare and Research Quality. Rockville, MD. 2005.
[52] Hsich EM, Rogers JG, McNamara DM, Taylor DO, Starling RC, Blackstone EH, *et al*. Does Survival on the Heart Transplant Waiting List Depend on the Underlying Heart Disease? JACC. Heart Failure. 2016; 4: 689–697.
[53] Breathett K, Yee E, Pool N, Hebdon M, Crist JD, Knapp S, *et al*. Does Race Influence Decision Making for Advanced Heart Failure Therapies? Journal of the American Heart Association. 2019; 8: e013592.
[54] Pendo E. Equal Access to Organ Transplantation for People with Disabilities. The Hastings Center Report. 2021; 51: 4–6.
[55] Richards CT, Crawley LM, Magnus D. Use of neurodevelopmental delay in pediatric solid organ transplant listing decisions: inconsistencies in standards across major pediatric transplant centers. Pediatric Transplantation. 2009; 13: 843–850.
[56] Goel AN, Iyengar A, Schowengerdt K, Fiore AC, Huddleston CB. Heart transplantation in children with intellectual disability: An analysis of the UNOS database. Pediatric Transplantation. 2017; 21: e12858.
[57] Bircan E, Politis MD, Gokun Y, Luo C, Leonard H, Bourke J, *et al*. Intellectual disabilities and autism among children with congenital heart defects, Western Australia, 1983-2010. BMC Pediatrics. 2023; 23: 106.
[58] Downing KF, Oster ME, Klewer SE, Rose CE, Nembhard WN, Andrews JG, *et al*. Disability Among Young Adults With Congenital Heart Defects: Congenital Heart Survey to Recognize Outcomes, Needs, and Well-Being 2016-2019. Journal of the American Heart Association. 2021; 10: e022440.
[59] Hirota T, King BH. Autism Spectrum Disorder: A Review. JAMA. 2023; 329: 157–168.
[60] Bailey D, Schneider L, Maeda K, Hollander S, Shaw R, Rosenthal D. Orthotopic Heart Transplant in a Child with Nonverbal Autism. Austin Journal of Autism and Related Disabilities. 2016; 2: 1017.
[61] Todaro JF, Fennell EB, Sears SF, Rodrigue JR, Roche AK. Review: cognitive and psychological outcomes in pediatric heart transplantation. Journal of Pediatric Psychology. 2000; 25: 567–576.
[62] Mahoney WJ, Villacrusis M, Sompolski M, Iwanski B, Charman A, Hammond C, *et al*. Nursing care for pediatric patients with autism spectrum disorders: A cross-sectional survey of perceptions and strategies. Journal for Specialists in Pediatric Nursing: JSPN. 2021; 26: e12332.
[63] Gilmore-Bykovskyi AL, Fuhr H, Jin Y, Benson C. Use of Direct In-Person Observation in the Care of Hospitalized Older Adults with Cognitive Impairment: A Systematic Review. Journal of Gerontological Nursing. 2020; 46: 23–30.