Racial and Ethnic Disparities in Incidence and Prognosis of Perioperative Stroke Among Pediatric Cardiac Transplant Recipients

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BACKGROUND: In the general population, Black children have a higher incidence of stroke and all-cause mortality after stroke than White children. Beginning 6 months following cardiac transplantation, Black children have higher mortality than White children. However, whether there are racial and ethnic disparities in incidence and all-cause mortality following perioperative stroke among pediatric cardiac transplant recipients is unknown.

METHODS AND RESULTS: Using the Scientific Registry of Transplant Recipients, we studied children who underwent their first heart transplant in the United States between January 1994 and September 2019. Using multivariable logistic regression, we assessed the association between race and ethnicity and perioperative stroke. We used multivariable piecewise Cox regression to examine the association between race and ethnicity and mortality among survivors of perioperative stroke. Among 8224 children who had a first cardiac transplant, 255 (3%) had a perioperative stroke. Black children had 32% lower odds of perioperative stroke compared with White children (adjusted odds ratio, 0.68 [95% CI, 0.46–0.996]). Following perioperative stroke, mortality rates were similar for Black and White children in the first 6 months (adjusted hazard ratio [HR], 0.99 [95% CI, 0.44–2.26]). However, Black children had a higher mortality rate than White children beyond 6 months (adjusted HR, 3.36 [95% CI, 1.22–9.22]).

CONCLUSIONS: Among pediatric cardiac transplant recipients, Black children have a lower incidence of perioperative stroke than White children. Among survivors of perioperative stroke, mortality is initially similar by race and ethnicity, but beyond 6 months, Black children have over a 3-fold higher mortality rate than White children. Identifying and intervening on potential differences in care is essential to addressing these disparities.

Key Words: cardiac transplant • pediatric stroke • racial disparities

Pediatric cardiac transplant is performed in children with heart failure, congenital heart disease, and cardiomyopathy for whom medical management has failed. Worldwide, approximately 600 children per year receive cardiac transplants, with 250 to 290 performed annually in the United States. Despite the widespread success of these transplants, 3% of pediatric heart transplant recipients experience a stroke.1 Although posttransplant stroke is rare, it affects the child’s functional outcome, and it is also associated with a higher mortality rate after a cardiac transplant.1,2 Black children experience greater rates of pediatric stroke and stroke mortality compared with White children, even after accounting for differences in the prevalence of sickle cell anemia.3,4 Furthermore, Black and Hispanic pediatric heart, kidney, and lung transplant
CLINICAL PERSPECTIVE

What Is New?
• Black children have a lower incidence of post–cardiac transplant stroke compared with White children.
• Black children have a 3-fold higher long-term mortality rate following post–cardiac transplant stroke compared with White children.

What Are the Clinical Implications?
• The disparities in incidence and long-term mortality demonstrate the need for identifying and intervening on potential differences in care.

Nonstandard Abbreviations and Acronyms

| SRTR | Scientific Registry of Transplant Recipients |

recipients fare worse than White recipients. Black children who receive cardiac transplants have higher rates of death, transplant rejection, and post–cardiac transplant diabetes than White children who receive cardiac transplants. These disparities vary by the time since transplantation. Following cardiac transplant, Black and White children initially have similar mortality rates, but beyond 6 months, the mortality rate is twice as high in Black versus White children.

The disparities seen between Black children and White children in regard to stroke and mortality after cardiac transplantation is most likely multifactorial. Environmental factors including household and school environment, sociodemographic factors including discrimination, and health system factors including insurance coverage, health literacy, and availability of services may all play a part in the disparities. Research into which underlying factors contribute to this association is limited, because most of the studies have used large databases with limited variables for social determinants of health.

There has been limited research on the occurrence of pediatric perioperative stroke and the prognosis of children experiencing these strokes, and no studies to examine whether there are racial and ethnic disparities in the incidence and mortality related to perioperative stroke. Because racial and ethnic disparities exist in pediatric stroke mortality and pediatric cardiac transplant outcomes, we hypothesize that racial and ethnic disparities also exist in the incidence of perioperative stroke as well as the rates of all-cause mortality following perioperative stroke in children who received cardiac transplants.

METHODS

Study Population
The data that support the findings of this study are available from the corresponding author upon reasonable request. We obtained data from the SRTR (Scientific Registry of Transplant Recipients), a national database of all transplants in the United States. The SRTR data system includes data on all donor, wait-listed candidates, and transplant recipients in the United States, submitted by the members of the Organ Procurement and Transplantation Network. The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the Organ Procurement and Transplantation Network and SRTR contractors. We restricted our study to cardiac transplant recipients who received transplants between January 1, 1994 and September 1, 2019, who were <18 years of age at the time of transplant, and for whom this was their first organ transplant. We classified race and ethnicity as reported to the SRTR as Black/African American, White, Hispanic/Latino, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander or Multiracial. Because of the small numbers of Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Multiracial children, these categories were all placed into the category Other for our analysis. We obtained demographic and clinical characteristics of the recipients.

Statistical Analysis
We described the characteristics of the pediatric cardiac transplant recipients according to race and ethnicity. We used logistic regression to calculate odds ratios (ORs) and 95% CIs for the association between race and ethnicity and the occurrence of stroke following a cardiac transplant. We considered the cardiac transplant recipient to have a perioperative stroke if they were positive for stroke in the registry. Because race and ethnicity precede all clinical characteristics, we conducted a crude analysis. To assess whether any disparities would remain even after accounting for other factors, we also conducted analyses adjusting for age and sex, and further adjusting for cognitive difficulties (definite, possible, none, unknown), insurance (Medicaid, private, other), transplant year (1994–1999, 2000–2009, 2010–2019), on extracorporeal membrane oxygenation or ventricular assist device before transplant or after transplant (yes/no), reason for heart transplant (dilated cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, other), congenital heart surgery (yes/no), cardiac surgery not congenital heart surgery (yes/no), reoperation (yes/no), transplant center (135 centers), location before transplant.
Table 1. Characteristics of 8224 Pediatric Cardiac Transplant Recipients by Race and Ethnicity, Scientific Registry of Transplant Recipients, January 1, 1994 to September 1, 2019

|                               | White, n=4682 | Black, n=1618 | Hispanic, n=1389 | Other*, n=535 |
|-------------------------------|---------------|---------------|------------------|---------------|
| **Men**                       |               |               |                  |               |
| Age at transplant median, y (IQR) | 4.25 (0.58–13.08) | 7.38 (1.08–13.75) | 3.50 (0.67–11.83) | 5.25 (1.12–12.71) |
| **Reason for transplant**     |               |               |                  |               |
| Dilated cardiomyopathy        | 1558 (33.3)   | 810 (50.1)    | 547 (39.4)       | 255 (47.7)    |
| Restrictive cardiomyopathy    | 298 (6.4)     | 68 (4.2)      | 93 (6.7)         | 61 (11.4)     |
| Congenital heart disease      | 2358 (50.4)   | 595 (36.8)    | 625 (45.0)       | 167 (31.2)    |
| Other                         | 468 (10.0)    | 145 (9.0)     | 124 (8.9)        | 52 (9.7)      |
| **Location before transplant**|               |               |                  |               |
| ICU                           | 2486 (53.1)   | 922 (57.0)    | 689 (49.6)       | 298 (55.7)    |
| Hospital non-ICU bed          | 731 (15.6)    | 276 (17.1)    | 246 (17.7)       | 96 (17.9)     |
| Not in hospital               | 1465 (31.3)   | 420 (26.0)    | 454 (32.7)       | 141 (26.4)    |
| **Transplant period**         |               |               |                  |               |
| 1994–1999                     | 1029 (22.0)   | 266 (16.4)    | 153 (11.0)       | 60 (11.2)     |
| 2000–2009                     | 1606 (34.3)   | 585 (36.2)    | 478 (34.4)       | 191 (35.7)    |
| 2010–2019                     | 2047 (43.7)   | 767 (47.4)    | 758 (54.6)       | 284 (53.1)    |
| **Bilirubin**                 |               |               |                  |               |
| Normal                        | 3096 (66.1)   | 1082 (66.9)   | 929 (66.9)       | 360 (67.3)    |
| Elevated                      | 1166 (24.9)   | 408 (25.2)    | 358 (25.8)       | 143 (26.7)    |
| Unknown                       | 420 (9.0)     | 128 (7.9)     | 102 (7.3)        | 32 (6.0)      |
| **Creatinine**                |               |               |                  |               |
| Normal                        | 4140 (88.4)   | 1360 (84.1)   | 1255 (90.4)      | 475 (88.8)    |
| Elevated                      | 386 (8.2)     | 209 (12.9)    | 100 (7.2)        | 44 (8.2)      |
| Unknown                       | 156 (3.3)     | 49 (3.0)      | 34 (2.5)         | 16 (3.0)      |
| **Congenital heart surgery**  |               |               |                  |               |
| 148 (3.2)                     | 771 (16.5)    | 211 (13.0)    | 259 (18.6)       | 83 (15.5)     |
| **Cardiac surgery**           |               |               |                  |               |
| 148 (3.2)                     | 148 (3.2)     | 67 (4.1)      | 27 (1.9)         | 14 (2.6)      |
| **Reoperation**               | 285 (6.1)     | 96 (5.9)      | 72 (5.2)         | 28 (5.2)      |
| **Ischemic time**             |               |               |                  |               |
| <120 min                      | 373 (8.0)     | 142 (8.8)     | 123 (8.9)        | 30 (5.6)      |
| 120–240 min                   | 2572 (54.9)   | 956 (59.1)    | 706 (50.8)       | 292 (54.6)    |
| >240 min                      | 1525 (32.6)   | 438 (27.1)    | 494 (35.6)       | 184 (34.4)    |
| Unknown                       | 212 (4.5)     | 82 (5.1)      | 86 (6.8)         | 29 (5.4)      |
| **VAD before transplant**     | 342 (7.3)     | 166 (10.3)    | 124 (8.9)        | 69 (12.9)     |
| **VAD after transplant**      | 712 (15.2)    | 361 (22.3)    | 253 (18.2)       | 124 (23.2)    |
| **ECMO before transplant**    | 285 (6.1)     | 75 (4.6)      | 52 (3.7)         | 21 (3.9)      |
| **ECMO after transplant**     | 279 (6.0)     | 69 (4.3)      | 40 (2.9)         | 34 (6.4)      |
| **Insurance status**          |               |               |                  |               |
| Medicaid                      | 1426 (30.5)   | 995 (61.5)    | 849 (61.1)       | 179 (33.5)    |
| Private                       | 2859 (61.1)   | 499 (30.8)    | 311 (22.4)       | 208 (38.9)    |
| Other                         | 397 (8.5)     | 124 (7.7)     | 229 (16.5)       | 148 (27.7)    |
| **Cognitive difficulties**    |               |               |                  |               |
| Definite                      | 154 (3.3)     | 39 (2.4)      | 50 (3.6)         | 11 (2.1)      |
| Possible                      | 340 (7.3)     | 134 (8.3)     | 168 (12.1)       | 43 (8.0)      |
| None                          | 1271 (27.1)   | 530 (32.8)    | 492 (35.4)       | 212 (39.6)    |
| Unknown                       | 2917 (62.3)   | 915 (56.6)    | 679 (48.9)       | 269 (50.3)    |

Values are presented as n (%) unless otherwise specified. ECMO indicates extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; and VAD, ventricular assist device.

*Other includes Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Multiracial.
(intensive care unit, non-intensive care unit hospital bed, not in hospital), bilirubin (normal, elevated, unknown), and creatinine level (normal, elevated, unknown) at the time of transplant. Because insurance status may mediate the association between race and ethnicity and perioperative stroke, we also conducted an analysis with all covariates except for insurance.

Among pediatric cardiac transplant recipients who experience a perioperative stroke, there may be racial and ethnic disparities in all-cause mortality, and these differences may depend on the amount of time since the stroke. To address these questions, we constructed Kaplan-Meier survival curves comparing rates of all-cause mortality by race and ethnicity within 6 months following perioperative stroke and mortality rates in the time under observation beyond 6 months following perioperative stroke. We used piecewise multivariable Cox proportional hazard model to calculate crude and adjusted hazard ratios (HRs) and 95% CIs for the association between race and ethnicity and all-cause mortality following perioperative stroke for these 2 time periods, adjusting for covariates described above. We examined Schoenfeld residuals to examine the proportional hazard assumption.

The Harvard Chan School of Public Health Institutional Review Board waived need for institutional review board approval for use of this national deidentified registry data. We plotted Kaplan-Meier survival

### Table 2. Perioperative Stroke Comparison of Black and Hispanic Children to White Children, Scientific Registry of Transplant Recipients, January 1, 1994 to September 1, 2019

|                      | White, OR (95% CI) | Black, OR (95% CI) | Hispanic, OR (95% CI) | Other†, OR (95% CI) |
|----------------------|--------------------|--------------------|-----------------------|---------------------|
| Unadjusted           | 1 (Reference)      | 0.87 (0.61–1.22)   | 1.11 (0.80,1.55)      | 1.36 (0.86–2.15)    |
| Adjusted for age and sex | 1 (Reference)   | 0.88 (0.62–1.25)   | 1.10 (0.79–1.54)      | 1.36 (0.86,2.16)    |
| Adjusted for covariates* | 1 (Reference) | 0.68 (0.47–0.996)  | 0.96 (0.65,1.42)      | 1.25 (0.77–2.05)    |
| Adjusted for covariates except insurance | 1 (Reference) | 0.77 (0.54–1.12)   | 1.11 (0.76–1.63)      | 1.31 (0.80–2.13)    |

ECMO indicates extracorporeal membrane oxygenation; OR, odds ratio; and VAD, ventricular assist device.
*Adjusted for sex, age, cognitive difficulties, insurance, transplant year, on ECMO or VAD before transplant or after transplant, type of cardiac surgery and transplant center, hospital status, bilirubin, and creatinine at the time of transplant.
†Other includes Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Multiracial.

### Table 3. Characteristics of 255 Pediatric Cardiac Transplant Recipients With Perioperative Stroke by Race and Ethnicity, Scientific Registry of Transplant Recipients, January 1, 1994 to September 1, 2019

|                      | White, n=143       | Black, n=43        | Hispanic, n=47       | Other*, n=22        |
|----------------------|--------------------|--------------------|----------------------|---------------------|
| Men                  | 79 (55.2)          | 20 (46.5)          | 29 (61.7)            | 11 (50.0)           |
| Age at transplant median, y (IQR) | 3.83 (0.58–10.29) | 6.67 (1.29–11.38)  | 5.42 (1.29–11.17)    | 4.75 (1.46–7.54)    |
| Location before transplant |                    |                    |                      |                     |
| ICU                  | 102 (71.3)         | 27 (62.8)          | 29 (61.7)            | 16 (72.7)           |
| Hospital non-ICU bed | 21 (14.7)          | 8 (18.6)           | 11 (23.4)            | 2 (9.1)             |
| Not in hospital      | 20 (14.0)          | 8 (18.6)           | 7 (14.9)             | 4 (18.2)            |
| Transplant period    |                    |                    |                      |                     |
| 1994–1999            | 27 (18.9)          | 6 (14.0)           | 2 (4.3)              | 3 (13.6)            |
| 2000–2009            | 46 (32.2)          | 10 (23.3)          | 13 (27.7)            | 7 (31.8)            |
| 2010–2019            | 70 (49.0)          | 27 (62.8)          | 32 (68.1)            | 12 (54.5)           |
| VAD after transplant | 38 (26.6)          | 12 (27.9)          | 12 (25.5)            | 8 (36.4)            |
| ECMO after transplant| 22 (15.4)          | 4 (9.3)            | 4 (8.5)              | 3 (13.6)            |
| Insurance status     |                    |                    |                      |                     |
| Medicaid             | 60 (42.0)          | 36 (83.7)          | 34 (72.3)            | 6 (27.3)            |
| Private              | 73 (51.0)          | 6 (14.0)           | 10 (21.3)            | 8 (36.4)            |
| Other                | 10 (7.0)           | 1 (2.3)            | 3 (6.4)              | 8 (36.4)            |
| Cognitive development|                    |                    |                      |                     |
| Definite             | 5 (3.5)            | 1 (2.3)            | 5 (10.6)             | 0 (0)               |
| Possible             | 19 (13.3)          | 6 (14.0)           | 7 (14.9)             | 1 (4.5)             |
| None                 | 37 (25.9)          | 17 (39.5)          | 16 (34.0)            | 11 (50.0)           |
| Unknown              | 82 (57.3)          | 19 (44.2)          | 19 (40.4)            | 20 (45.5)           |

Values are presented as n(%) unless otherwise specified. ECMO indicates extracorporeal membrane oxygenation; ICU, intensive care unit; IQR, interquartile range; and VAD, ventricular assist device.
*Other includes Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Multiracial.
curves using R version 4.1.0, and we conducted all other analyses in SAS version 9.4.

**RESULTS**

Among 8224 children who had their first cardiac transplant in 1994 to 2019, 255 (3%) experienced a stroke during their transplant or before discharge for the hospitalization for the transplant. Black children had a median age of 7.38 years at transplant compared with a median age of 4.25 years and 5.20 years in White and Hispanic children, respectively, which are presented in Table 1. Compared with the incidence of stroke among White children, there was no statistically significant difference in stroke incidence among Hispanic children (adjusted OR, 0.96 [95% CI, 0.65–1.42]) and children...
of Other races (adjusted OR, 1.25 [95% CI, 0.77–2.05]; Table 2). However, there was a suggestion of 32% lower odds of perioperative stroke in Black children (adjusted OR, 0.68 [95% CI, 0.47–0.996]).

The baseline characteristics of the 255 children with perioperative stroke following cardiac transplant are presented by race and ethnicity in Table 3. Most Black and Hispanic children had Medicaid insurance, whereas most White children had private insurance. As seen in the crude Kaplan-Meier survival curves, there was no meaningful racial or ethnic difference in perioperative stroke mortality in the first 6 months following perioperative stroke (log-rank P=0.92; Figure – Panel A). However, beyond 6 months, Black children had a lower survival probability (log-rank P=0.017; Figure – Panel B). In multivariable models accounting for covariates, mortality rates following perioperative stroke were similar for Black children compared with White children within 6 months (adjusted HR, 0.99 [95% CI, 0.44–2.26]). However, Black children had a 3-fold higher mortality rate than White children beyond 6 months (adjusted HR, 3.36 [95% CI, 1.22–9.22]; Table 4). Compared with White children, there was no statistically significant difference in mortality rate among Hispanic children (adjusted HR, 1.71 [95% CI, 0.53–5.55]) and children of Other races (adjusted HR, 2.38 [95% CI, 0.26–22.00]).

**DISCUSSION**

In this national prospective cohort study, Black children had 32% lower odds of perioperative stroke compared with White children. These results were surprising given the previously reported higher rate of pediatric stroke among Black children compared with White children.

This may be because of a selection of healthier Black children receiving transplants, which is not as common among White children. In a recent SRTR study, Black children had a 25% higher mortality rate while on the transplant waitlist compared with White children. This may suggest that Black children at higher risk of perioperative stroke are less likely to survive to receive a heart transplant than White children on the transplant waitlist. Therefore, among waitlist survivors, the (lower risk) Black recipients had a lower rate of perioperative stroke compared with White children.

We found that among pediatric heart transplant recipients who experienced a perioperative stroke, mortality rates were similar for Black children and White children in the first 6 months following perioperative stroke but over a 3-fold higher mortality rate beyond 6 months. These results are similar to findings from a 2011 study including all pediatric primary heart transplant recipients in the Organ Procurement and Transplantation Network database. However, we observed a 3.36-fold higher mortality rate in Black children compared with White children with perioperative stroke following cardiac transplant, which is higher than the prior study that reported a 2.2-fold higher mortality rate in Black children compared with White children following cardiac transplant. This may be because of modeling differences, the children included in the Organ Procurement and Transplantation Network database as compared with the larger SRTR, or it may suggest that long-term structural inequities play a larger role in recent long-term survival among Black children who have experienced a stroke following cardiac transplant.

Because we used an existing database of recipients, we are limited by the data available. For instance, the only marker of socioeconomic position was

### Table 4. Mortality Rates Within 6 Months of a Perioperative Stroke and After 6 Months Following a Perioperative Stroke Among Pediatric Cardiac Transplant Recipients, Scientific Registry of Transplant Recipients, January 1, 1994 to September 1, 2019

| Timeframe          | White, 58/108, HR (95% CI) | Black, 22/108, HR (95% CI) | Hispanic, 19/108, HR (95% CI) | Other*, 9/108, HR (95% CI) |
|-------------------|-----------------------------|-----------------------------|-------------------------------|-----------------------------|
| Within 6mo        |                             |                             |                               |                             |
| Unadjusted        | 1 (Reference)               | 0.96 (0.51–1.84)            | 1.00 (0.54–1.87)              | 1.29 (0.60–2.75)            |
| Adjusted for age  | 1 (Reference)               | 0.96 (0.50–1.83)            | 0.97 (0.52–1.82)              | 1.29 (0.61–2.76)            |
| Adjusted for       | 1 (Reference)               | 0.99 (0.44–2.26)            | 1.08 (0.45–2.55)              | 2.29 (0.84–6.27)            |
| covariates*       | 1 (Reference)               | 1.03 (0.46–2.29)            | 1.07 (0.46–2.47)              | 1.95 (0.71–5.39)            |
| Adjusted for       | 1 (Reference)               | 3.57 (1.55–8.21)            | 1.62 (0.63–4.18)              | 1.07 (0.14–8.18)            |
| covariates except  | 1 (Reference)               | 3.50 (1.51–8.11)            | 1.50 (0.58–3.88)              | 1.06 (0.14–8.07)            |
| insurance*        | 1 (Reference)               | 3.36 (1.22–9.22)            | 1.71 (0.53–5.56)              | 2.38 (0.26–22.00)           |
| Adjusted for       | 1 (Reference)               | 3.38 (1.25–9.15)            | 1.72 (0.54–5.49)              | 1.89 (0.21–17.34)           |
| covariates except  |                             |                             |                               |                             |
| insurance*        |                             |                             |                               |                             |

HR indicates hazard ratio.

*Adjusted for sex, age, transplant period, location before transplant, extracorporeal membrane oxygenation following transplant, ventricular assist device following transplant, transplant center, cognitive development and insurance.

1Other includes Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and Multiracial.
insurance type. We were unable to examine further social determinants of health including environment and health system factors or discrimination, because none of these variables were collected in the SRTR. However, our crude analyses are more likely to reflect actual structural inequities.

We did not have information on whether the strokes were ischemic or hemorrhagic, and some information on covariates and outcomes may be misclassified. However, the strength of using this resource is that we had prospectively collected clinical and demographic information and data on the timing of health outcomes during hospitalization and for several years of follow-up. Because pediatric stroke is rare, the sample size was relatively small, limiting our statistical power and the opportunity to explore potential changes in disparities over time. However, the SRTR includes all transplants in the United States, and to our knowledge, this is the largest cohort study of racial and ethnic differences in perioperative stroke incidence and survival among pediatric cardiac transplant recipients.

In conclusion, the incidence of perioperative stroke is lower in Black children compared with White children even after adjusting for covariates. Black children with perioperative stroke have a similar mortality rate within the first 6 months compared with White children. However, beyond 6 months, Black children have over a 3-fold higher mortality rate compared with White children. This higher mortality rate may be because of sociocultural environment including discrimination, physical environment, and health care system while on a transplant waitlist, during hospitalizations, and during follow-up. Next steps would include examining the selection process for transplant listing. Further interventions are needed to address inequities among cardiac transplant recipients.

ARTICLE INFORMATION

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