# Preterm Birth Is Associated With Adverse Cardiac Remodeling and Worse Outcomes in Patients With a Functional Single Right Ventricle

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**Objective** To assess the effects of preterm birth on cardiac structure and function and transplant-free survival in patients with hypoplastic left heart syndrome and associated anomalies throughout the staged palliation process.

**Study design** Data from the Single Ventricle Reconstruction trial were used to assess the impact of prematurity on echocardiographic measures at birth, Norwood, Stage II, and 14 months in 549 patients with a single functional right ventricle. Medical history was recorded once a year using medical records or telephone interviews. Cox regression models were applied to analyze transplant-free survival to age 6 years. Causal mediation analysis was performed to estimate the mediating effect of birth weight within this relationship.

**Results** Of the 549 participants, 64 (11.7%) were born preterm. Preterm-born participants had lower indexed right ventricle end-diastolic volumes at birth but higher volumes than term-born participants by age 14 months. Preterm-born participants had an increased risk of death or heart transplantation from birth to age 6 years, with an almost linear increase in the observed risk as gestational age decreased below 37 weeks. Of the total effect of preterm birth on transplant-free survival, 27.3% (95% CI 2.5-59.0%) was mediated through birth weight.

**Conclusions** Preterm birth is associated with adverse right ventricle remodeling and worse transplant-free survival throughout the palliation process, in part independently of low birth weight. Further investigation into this vulnerable group may allow development of strategies that mitigate the impact of prematurity on outcomes in patients with hypoplastic left heart syndrome. *(J Pediatr 2022;■:1-9)*.

Approximately 3-5 of every 10 000 neonates are born with hypoplastic left heart syndrome (HLHS) or a related congenital heart defect characterized by hypoplasia of the left heart structures and a functional single right ventricle (FSRV).[1-3] The current standard of care for these patients is a staged surgical palliation that consists of the Norwood procedure (0-2 weeks after birth), Stage II surgery (3-6 months after birth), and the Fontan procedure (2-5 years after birth). This results in a circulation without a subpulmonary pump, with systemic arterial output sustained by the right ventricle (RV) to support the systemic circulation. Although numerous efforts have been undertaken to optimize clinical care for patients with an FSRV, mortality and morbidity remain high throughout the palliation process.[4-6] This is especially true for preterm-born patients, a high-risk group for adverse outcomes that constitutes 15%-20% of all individuals with an FSRV.[7-10] Although preterm birth poses many challenges for the immature cardiovascular system, resulting in a cardiac phenotype of prematurity that persists into adulthood,[11-13] the influence of preterm birth on the univentricular heart remains largely unexplored.

In the Pediatric Heart Network's Single Ventricle Reconstruction (SVR) trial, infants with FSRV undergoing the Norwood procedure were randomly assigned to a modified Blalock-Thomas-Taussig shunt or a RV-to-pulmonary artery shunt at 15 North American centers.[14-16] The extensive data collection in this study has contributed significantly to our understanding of the risk factors

| | |
|---|---|
| BSA | Body surface area |
| EDV | End-diastolic volume |
| EF | Ejection fraction |
| ESV | End-systolic volume |
| FSRV | Functional single right ventricle |
| HLHS | Hypoplastic left heart syndrome |
| -I | Indexed to body surface area |
| MBTS | Modified Blalock-Thomas-Taussig shunt |
| RV | Right ventricle / right ventricular |
| SVR | Single Ventricle Reconstruction |
| TVAA | Tricuspid valve annulus area |

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and outcomes in patients with an FSRV. Previous analyses of the SVR trial have identified preterm birth as an important risk factor for transplant-free mortality but the underlying mechanisms for this association remain unclear.[17-19]

We hypothesize that adverse remodeling of the single RV after premature birth throughout staged palliation may be an important underlying factor for worse transplant-free survival given the added complications associated with disrupted organogenesis that occurs with preterm birth.[20,21] Therefore, in the present study, we aimed to quantify the adaptive response of the single RV after premature birth throughout staged palliation and transplant-free survival in patients with a single RV and to seek out potential mediating effects of birth weight within this relationship.

## Methods

A secondary analysis was performed using data from the National Institutes of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) Pediatric Heart Network's SVR trial and SVR Extension Study (SVR II). Data were downloaded from www.pediatricheartnetwork.org/public-use-data-sets/. Details on the design and results of the SVR and SVR II trials have been reported previously.[14-16] The patient population was derived from 921 neonates with FSRV screened at 15 North American centers between May 2005 and July 2008 (**Figure 1**; available at www.jpeds.com). Neonates were excluded if they had any major congenital or acquired noncardiac anomaly (eg, congenital diaphragmatic hernia, tracheoesophageal fistula, chromosomal disorder, renal failure requiring dialysis, and need for high-frequency ventilation) that could independently affect the likelihood of meeting the primary outcome of transplant-free survival at 12 months post-randomization. Of the original cohort, 555 were enrolled and randomly assigned to receive either an RV-to-pulmonary artery shunt or modified Blalock-Thomas-Taussig shunt during the Norwood procedure. Six patients were excluded from the analysis because they did not undergo a Norwood procedure or withdrew preoperatively, leaving 549 patients in the analytical cohort. Participants had study visits until 6 years of age or until loss to follow-up. The institutional review boards of all participating centers approved the study, and all parents or guardians of the enrolled patients provided informed consent.

Demographic and preoperative data were collected, including gestational age, birth weight, and Apgar scores. Low birth weight was defined as birth weight <2500g, and preterm birth was defined as birth <37 weeks' gestation.[22] Patients were classified with regard to whether they had a genetic syndrome or another anomaly (ie, not associated with a known syndrome) through routine clinical genetic evaluations or an optional research genetic evaluation that was offered to families. Medical status and history were recorded once a year using medical records, telephone interviews with parents or guardians, and the death index.

Enrolled participants at each clinical center underwent echocardiography (1) at baseline (before the Norwood procedure); (2) post-Norwood (at time of discharge or approximately 30 days of age if still hospitalized); (3) pre-Stage II (during the preoperative evaluation for the Stage II procedure); (4) at 14 months of age; (5) pre-Fontan (within 6 months of a planned Fontan procedure); and (6) at 6 years of age (within 1 year of the subject's sixth birth date). Particular attention was placed on RV size, including RV end-diastolic volume (RVEDV), RV end-systolic volume (RVESV), RVEDV indexed to body surface area (BSA) raised to the power of 1.3 (RVEDVI), RVESV indexed to BSA raised to the power of 1.3 (RVESVI), tricuspid valve annulus area (TVAA), and TVAA indexed to BSA (TVAAI).[23-25] RV ejection fraction (RVEF), calculated by the biplane pyramidal method, was assessed as a measure of RV function. All images were analyzed by an echocardiography core laboratory. Additional details of the echocardiography acquisition and analysis have been described previously.[23-25]

Coprimary outcomes were transplant-free survival at 6 years post-randomization and RVEDVI from baseline to 14 months of age. Secondary outcomes included death and heart transplantation separately, RVEDV, RVESV, RVESVI, TVAA, TVAAI, and RVEF. As only 4-6 preterm-born participants had echocardiographic measurements at the pre-Fontan and 6-year time points, we did not analyze echocardiograms obtained at these time points.

The Shapiro-Wilk test was used to verify normality of continuous variables. Subsequently, continuous variables are reported as mean ± SD or median (IQR), as appropriate, while categorical variables are reported as proportion (%). Participants were grouped by gestational age (preterm-born vs term-born) and birth weight (low birth weight vs no low birth weight). Direct group comparisons were performed using parametric (*t* test) or nonparametric (Mann-Whitney U) tests, as appropriate, for continuous variables, and using $X^2$ test or Fisher exact test, as indicated, for categorical variables. Power calculations performed using the "pwr" R package revealed that our current sample size was sufficient to demonstrate small effect sizes (ie, Cohen d ≥ 0.17) on *t* test and small to medium effect sizes (ie, Cohen w ≥ 0.12-0.15 for degrees of freedom 1-4, respectively) on $X^2$ test, with a power of 0.80 and alpha level of 0.05. To investigate the interaction between the grouping variable and the "time" variable on echocardiographic measures, 2-way mixed ANOVA models were additionally performed and visualized using boxplots. In addition, to quantify the extent of potential survivorship bias and as a sensitivity analysis, echocardiographic measurements were compared between those who experienced an event (death or heart transplantation) from birth to 14 months and those who did not, within each group (preterm-born and term-born).

For transplant-free survival, Kaplan-Meier curves were constructed and groups were compared using the log-rank test and Cox regression models (R packages "survival" and "coxph"); results are presented as hazard ratios (HRs) with 95% CIs. In addition, multivariate Cox regression models were used to assess whether the associations between preterm

birth (and low birth weight) and transplant-free survival were independent of genetic syndromes or other genetic anomalies. Incidence rates with 95% CIs were also calculated for each of the outcomes and compared between groups using Poisson regression (R package "rateratio"). Furthermore, a restricted cubic spline analysis with 3 knots was performed to clarify the possible nonlinear association between gestational age and the outcome of death or heart transplantation (R packages "rms," "splines," and "Greg").

Finally, to study the potential mediating effect of birth weight on the relationship between preterm birth and outcomes, 3 methods were used. First, birth weight (as a continuous measure) was introduced as a covariate in the Cox regression model to calculate an adjusted estimate of the effect of preterm birth on death or heart transplantation. Second, results of the Cox regression model were stratified to determine whether they applied in both birth weight groups (low birth weight vs no low birth weight). Third, a causal mediation analysis was performed to estimate the proportion of the total effect of preterm birth on death or heart transplantation that may be mediated by birth weight as a continuous measure (R package "mediation"). Missing data were not imputed and handled with list wise deletion in multivariate models. Statistical analysis was carried out with R, version 4.1.3 (R Foundation for Statistical Computing). *P*-values of <.05 were considered statistically significant, and all tests were 2-sided. Imputation was not performed.

## Results

Of the 549 participants included in the SVR trial (gestational age 38 [37-39] weeks, 61.9% male), 64 (11.7%) were born preterm (**Table I**; available at www.jpeds.com). Preterm-born participants had a lower birth weight (2474 ± 533g vs 3186 ± 486g, $P < .001$) and a lower 1-minute Apgar score (8 [6-9] vs 8 [8-9], $P = .034$). In addition, preterm-born patients were more likely to be diagnosed with a genetic syndrome (6 [9.4%] vs 20 [4.1%], $P = .004$) or another anomaly (19 [29.7%] vs 87 [17.9%], $P = .016$). Shunt types were equally distributed between both groups. There were no significant differences in the number of preterm-born vs term-born patients that used digoxin, angiotensin converting enzyme inhibitors, or diuretics after the Norwood or Stage II procedures, respectively.

The echocardiographic examinations in preterm-born vs term-born participants across the stages of the palliation process are summarized online (**Table II**; available at www.jpeds.com). At baseline and post-Norwood, RVEDV, RVESV, and TVAA were all significantly lower in the preterm-born participants. However, when considering indexed measurements, only RVEDVI at baseline was significantly lower (72.0 [60.1-90.5] vs 85.2 [70.9-100] mL/m$^2$, $P = .019$). Although no differences were observed pre-Stage II, RVEDVI became significantly higher in preterm-born participants at 14 months of age (100 [84.6-126] vs 85.2 [70.6-101] mL/m$^2$, $P = .029$). The proportion of patients with tricuspid valve regurgitation was not significantly different between the preterm and term groups at any of the time points. Two-way ANOVA revealed a significant interaction between prematurity and stage of palliation for RVEDV, RVEDVI, TVAA, and TVAAI, suggesting that preterm-born participants had a different development over time for these variables (**Table III**; available at www.jpeds.com). For each of these variables, as demonstrated in **Figure 2**, preterm-born participants had lower values at baseline but surpassed the term-born participants by the age of 14 months.

To quantify the extent of potential survivorship bias, echocardiographic measurements were compared between those who experienced an event (death or heart transplantation) from birth to 14 months and those who did not, within the preterm-born group (**Figure 3**). Within both groups, RV sizes tended to be greater at the pre-Stage II time point in those who experienced an event. Collectively, these findings suggest that prematurity was associated with larger RV sizes at 14 months of age, even when those with the most severe dilatation had already died or had a heart transplant by that time point.

Because preterm-born participants had lower birth weights compared with term-born participants, we also analyzed the echocardiographic variables in patients who were born with low birth weight (13.8% of all participants). In this group, lower RVEDV, RVESV, and TVAA were observed at baseline (RVEDV: 8.24 [6.59-9.96] vs 11.3 [9.32-13.7] mL, $P < .001$; RVESV: 4.01 [3.34-5.34] vs 6.05 [4.74-7.72] mL, $P < .001$; TVAA: 0.96 [0.84-1.21] vs 1.27 [1.05-1.52] cm$^2$) and post-Norwood (RVEDV: 9.06 [7.62-10.8] vs 12.5 [10.2-14.8] mL, $P < .001$; RVESV: 4.66 [3.92-6.01] vs 6.68 [4.98-8.62] mL, $P < .001$; TVAA: 1.16 [0.94-1.42] vs 1.53 [1.21-1.80] cm$^2$), similar to our findings in the preterm-born group, yet no differences were observed at other time points or between indexed measures at any of the time points. Furthermore, neither comparisons at any time point nor interaction effects for RVEDVI, RVESVI, and TVAAI were significant, suggesting that low birth weight was not a driver of adverse cardiac remodeling.

Outcomes in preterm-born vs term-born participants are summarized in **Table IV**. After a median follow-up of 5.93 [0.34-6.04] years, a total of 212 patients (38.6%) experienced the primary outcome of death (n = 190) or heart transplantation (n = 22). Of these, 81.8% occurred within the first year of life. The Kaplan-Meier survival curve revealed significantly worse transplant-free survival in the preterm-born group (log-rank test: $P < .001$; **Figure 4**, A). The Cox regression model suggested that preterm-born participants had a 114% increased risk of death or heart transplantation (HR 2.14, 95% CI 1.51-3.04, $P < .001$). Preterm-born patients remained at an increased risk for worse transplant-free survival when the models were adjusted for the presence of genetic syndromes (HR 2.01, 95% CI 1.41-2.85, $P < .001$) or other nonsyndromic anomalies (HR 2.13, 95% CI 1.49-3.04, $P < .001$). Correspondingly, the incidence rate of death or heart

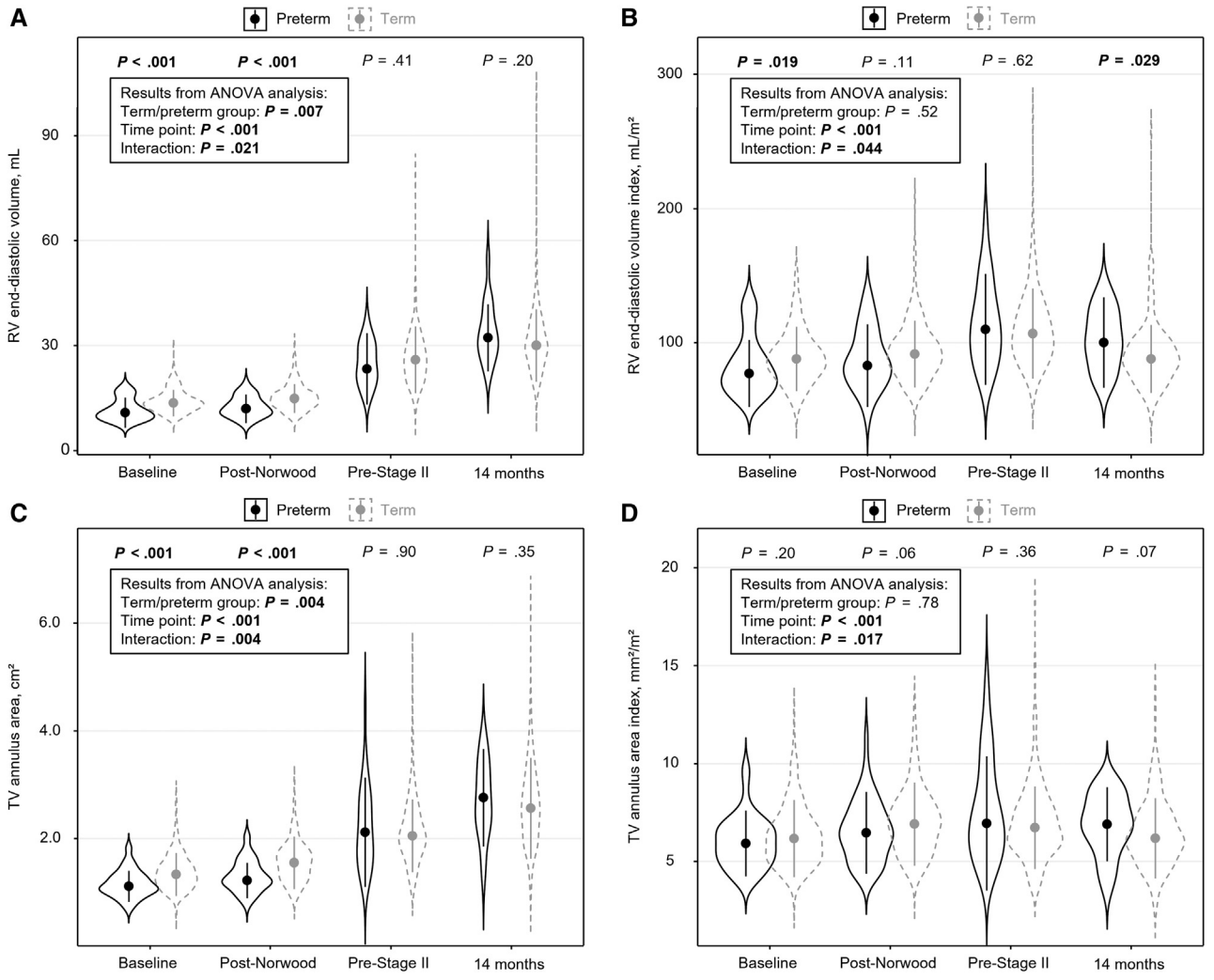


**Figure 2.** RV end-diastolic volume and TV annulus area in preterm-born and term-born patients. The above *P*-values refer to group comparisons of **A,** RV end-diastolic volume, **B,** RV end-diastolic volume index, **C,** TV annulus area, and **D,** RV annulus area index between preterm-born and term-born patients at the indicated time points. The framed *P*-values refer to the overall effects of gestational age group (preterm vs term), time point, and the interaction between these 2. *P*-values in bold indicate statistical significance. The lines inside the violin plots show the interquartile ranges and the dots show the medians. *TV*, tricuspid valve.

transplantation was 23.5 per 100 patient-years in preterm-born participants and 8.9 per 100 patient-years in term-born participants ($P < .001$). These differences were mainly driven by the higher rates of death before 1 year in the preterm-born group (Table IV). Restricted cubic spline analysis showed a U-shaped relationship between gestational age and the HR for death or heart transplantation (Figure 4, C), with an almost linear increase in the observed risk as gestational age decreased below 37 weeks.

Because participants in the preterm-born group had lower birth weights compared with those in the term-born group, we went on to investigate the effect of birth weight on outcomes. The Kaplan-Meier survival curve revealed significantly worse transplant-free survival in the low birth weight group (log-rank test: $P < .001$; Figure 4, B). The Cox regression model suggested that participants with low birth weight had a 96% increased risk of death or heart transplantation (HR 1.96, 95% CI 1.40-2.74, $P < .001$). This increased risk persisted when adjusting for the presence of genetic syndromes (HR 1.74, 95% CI 1.24-2.45, $P = .001$) or other nonsyndromic anomalies (HR 1.80, 95% CI 1.28-2.54, $P < .001$). Correspondingly, the incidence rate of death or heart transplantation was 20.0 per 100 patient-years in participants born low birth weight and 8.9 per 100 patient-years in those with normal or high birth weight ($P < .001$). Restricted cubic spline analysis showed a sigmoid relationship between birth weight and the HR for death or heart transplantation (Figure 4, D), with a sharp increase in the observed risk as birth weight decreased below 2500g.

We subsequently investigated whether birth weight could be a mediator of the effect of preterm birth on outcomes. In our first analysis, the relationship between preterm birth

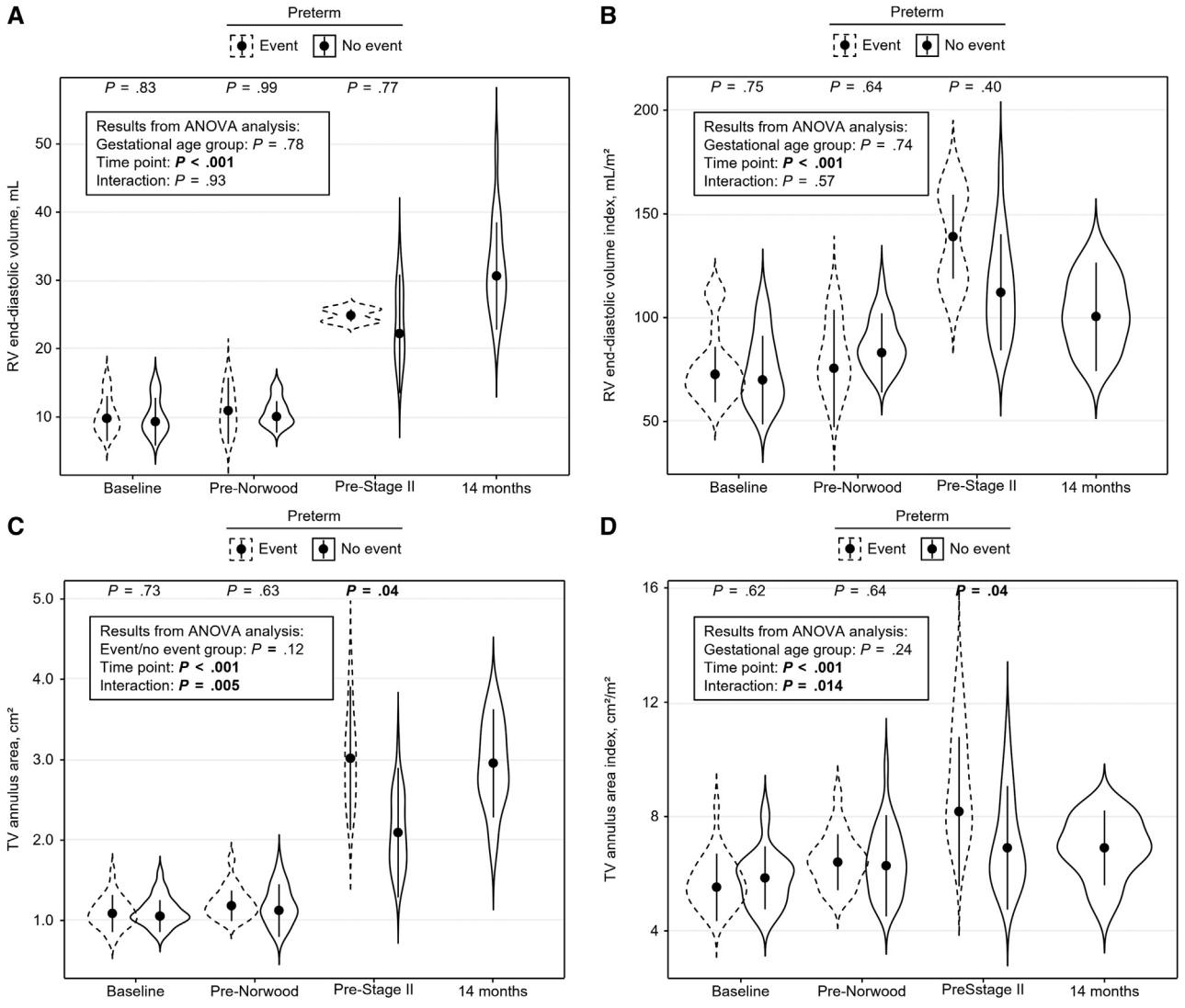


**Figure 3.** RV end-diastolic volume and TV annulus area in preterm-born that did and did not die or undergo heart transplantation. The above *P*-values refer to group comparisons of **A,** RV end-diastolic volume, **B,** RV end-diastolic volume index, **C,** TV annulus area, and **D,** TV annulus area index between preterm-born and term-born patients at the indicated time points. The framed *P*-values refer to the overall effects of event group (death or heart transplantation vs no death or heart transplantation), time point, and the interaction between these 2. *P*-values in bold indicate statistical significance. The lines inside the violin plots show the interquartile ranges and the dots show the medians.

and the primary outcome was slightly attenuated but remained significant after adjusting for birth weight (HR 1.79, 95% CI 1.19-2.69, $P = .005$). Secondly, stratification by birth weight group revealed that the effect of preterm birth on death or heart transplantation was stronger among the 473 participants without low birth weight (HR 2.20, 95% CI 1.31-3.68) than among the 76 participants with low birth weight (HR 1.25, 95% CI 0.68-2.28); however, this analysis revealed no significant interaction effect of the stratifying variable ($P = .168$). Finally, the causal mediation analysis indicated that 27.3% (95% CI 2.5-59.0%) of the total effect of preterm birth on transplant-free survival may be mediated through birth weight.

## Discussion

We found that preterm-born participants had significantly lower absolute and indexed RVEDV and TVAA at birth, but eventually surpassed their term-born counterparts by 14 months of age (between Stage II and Fontan), indicating differences in RV remodeling. Preterm birth was additionally associated with worse transplant-free survival, with an almost linear increase in the risk of death or heart transplantation as gestational age decreased below 37 weeks. Although part of these associations may be mediated by birth weight, prematurity seems to exert an independent effect on cardiac phenotype and outcomes in patients with HLHS and associated anomalies.

**Table IV. Outcomes in preterm-born vs term-born patients**

| Variables | Preterm-born (n = 64) | Term-born (n = 485) | *P*-value |
|---|---|---|---|
| | Median follow-up, years [IQR] | | |
| Follow-up, years | 0.57 [0.09-5.98] | 5.97 [0.48-6.04] | **<.001** |
| Follow-up in event-free patients, years | 6.00 [5.94-6.07] | 6.01 [5.98-6.12] | .296 |
| | Number of patients, n (%) | | |
| Death or heart transplantation | 38 (59.4) | 174 (35.9) | **<.001** |
| Death/transplant ≤1 year | 34 (53.1) | 138 (28.5) | - |
| Death/transplant >1 to ≤3 years | 4 (6.2) | 21 (4.3) | - |
| Death/transplant >3 to ≤6 years | 0 (0) | 15 (3.1) | - |
| Death | 37 (57.8) | 153 (35.9) | **<.001** |
| Heart transplantation | 1 (1.6) | 21 (4.3) | .497 |
| | Incidence rate per 100 patient-years, IR (95% CI) | | |
| Death or heart transplantation | 23.5 (16.6-32.2) | 8.9 (7.7-10.4) | **<.001** |
| Death/transplant ≤1 year | 94.7 (65.6-132.4) | 36.9 (31-43.6) | **<.001** |
| Death/transplant >1 to ≤3 years | 4.9 (1.3-12.5) | 2.1 (1.3-3.2) | .114 |
| Death/transplant >3 to ≤6 years | 0.0 (0.0-2.5) | 0.8 (0.5-1.3) | .621 |
| Death | 22.8 (16.1-31.5) | 7.9 (6.-9.2) | **<.001** |
| Heart transplantation | 0.6 (0.0-3.4) | 1.1 (0.7-1.6) | 1.000 |

*IR*, incidence rate.
Skewed continuous variables were compared using Mann-Whitney U tests. Categorical variables were compared using $X^2$ test or Fisher exact test, as indicated. Incidence rates were compared using Poisson regression. *P*-values in bold indicate statistical significance.

Our study found a large increase in RV size from post-Norwood to pre-Stage II in patients with a single ventricle, suggesting that active remodeling took place in the interstage period. Indeed, RV remodeling has been well-documented in patients with a single ventricle. Although initially an adaptive response of the systemic RV when faced with chronically elevated preload and afterload,[26,27] some patients eventually demonstrate a maladaptive remodeling pattern in which progressive dilatation occurs and ventricular output becomes compromised.[26,28,29] Previous studies of HLHS have associated progressive RV dilatation and dysfunction after the Norwood procedure with worse transplant-free survival.[29]

In the present study, we hypothesized that prematurity would be associated with adverse remodeling when the RV is forced to handle both the systemic and pulmonary circulation in parallel.[12,30,31] Our findings revealed that this was indeed the case; although the RVs from preterm-born participants were smaller at birth, they demonstrated a greater rate of dilatation following the Norwood procedure. In preterm birth, the immature cardiovascular system is abruptly challenged by the hemodynamic changes that come along with the fetal-to-neonatal transition.[32] Prior studies have helped delineate a specific cardiomyopathy of prematurity which is characterized by smaller right and left ventricular sizes, systolic and diastolic dysfunction, myocardial fibrosis, and varying degrees of hypertrophy, all of which persist during childhood into adulthood.[11,12,33] The finding of impaired response to pressure and volume loading in our present study adds to a growing body of evidence associating the cardiomyopathy of prematurity with maladaptive responses to various stressors.[34-36] Altered RV flow dynamics[36] and an impaired ability to augment cardiac output[33,34] during exercise may indicate that the preterm heart is associated with a reduced myocardial reserve, which may in part explain their greater risk of early heart failure.[35,37]

Following Stage II and by 14 months of age, our study found again a decrease in volumes. This is consistent with the fact that the Stage II and Fontan operations sequentially remove the systemic venous return through the superior and inferior vena cava from the RV and redirect it through the pulmonary arteries. The consequence, however, is that the RV suddenly becomes preload deprived and acquires a high ventricular mass-to-volume ratio (due to persistent hypertrophy in the face of decreasing volumes).[38] This state may be mechanically inefficient and contribute to diastolic dysfunction, which is seen in up to 81% of patients with an RV-dominant Fontan circulation.[39-41] Again, our study found a differential response to this stage of palliation according to prematurity. Preterm-born participants seemed to experience a blunted decrease in RV size in response to the volume unloading, potentially due to more pronounced diastolic dysfunction. The Fontan trajectory may represent a "double-hit" injury model for preterm-born participants, predisposing to progressive RV dilatation and dysfunction from volume and pressure overload after the Norwood procedure, followed by diastolic dysfunction from sequential ventricular unloading after the Stage II and Fontan operations. As previous work has shown that digoxin use during the interstage period is associated with better preservation of RV volume and tricuspid valve dimensions and less adverse remodeling of the single ventricle,[42] tailored pharmacological therapies may prove beneficial for preterm-born FSRV patients.

Previous studies have identified preterm-birth and low birth weight as significant risk factors for adverse outcomes in single ventricle patients.[17-19] In a post hoc analysis of the

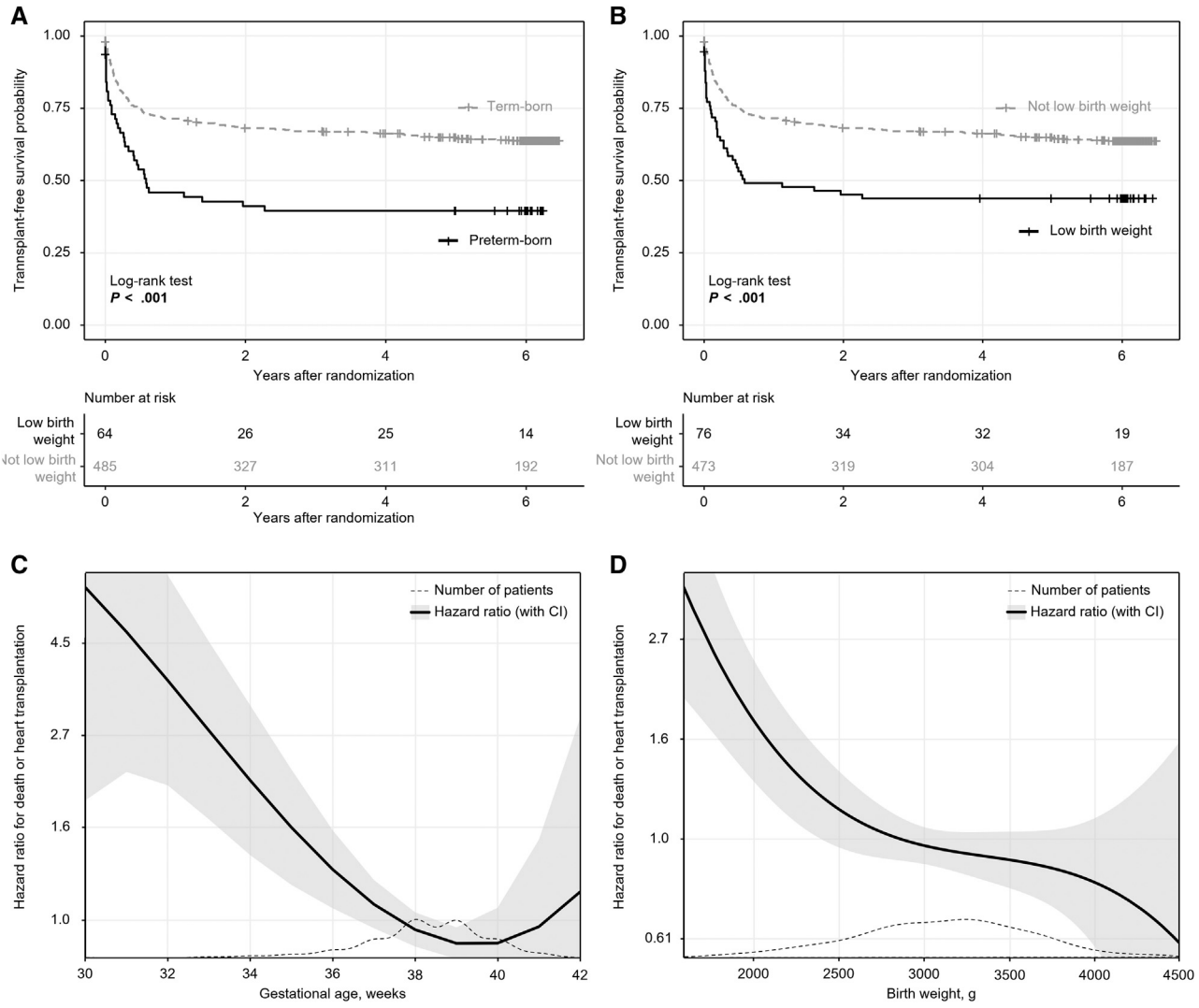


**Figure 4.** Kaplan-Meier curves and hazard ratio splines for transplant-free survival. Transplant-free survival estimates and numbers at risk are shown over time after enrollment to 6 years, stratified by **A,** gestational age (ie, preterm-born vs term-born patients) and **B,** birth weight (ie, low birth weight vs no low birth weight). The vertical stripes in both panels indicate censored data. The splines of the hazard ratios for death or heart transplantation from enrollment to 6 years of age are presented across the different **C,** gestational ages, and **D,** birth weights as the central black lines, with 95% CIs in light gray. The distributions of gestational ages and birth weights, respectively, are demonstrated by the dashed curves.

SVR trial, Miller et al[19] have previously shown that preterm birth and low birth weight were both associated with worse 6-year transplant-free survival on univariate regression, whereas only preterm birth was a significant predictor on multivariate regression. In the present study, we confirmed that preterm-born patients undergoing staged palliation were at a significantly higher risk of mortality or heart transplantation than their term-born counterparts. In addition, we showed that this risk increased linearly as the gestational age decreased below 37 weeks, suggesting a dose-response relationship. As lower birth weight has been linked to the same outcomes as preterm birth has been, a potential mediating effect by birth weight must be considered. We applied 3 methods to assess the potential mediating effect of low birth weight on the association between preterm birth and transplant-free survival and found that only part of the association might have been mediated, but the majority was independent from birth weight.

There are a number of limitations to our study. First, the number of preterm-born patients with available echocardiograms declined significantly at the later time points. In particular, our sample sizes at the pre-Fontan and 6-year time points were not large enough to be included in the main analyses. Additionally, although we were able to perform meaningful comparisons between the preterm and term groups at 14 months, the sample size of the preterm group at this time point was relatively small (n = 16). Second, some of our analyses–in particular those at the later time

points–might be subject to selective attrition and survivorship bias, caused by the high rates of early heart transplantation or death, especially in the preterm group. However, we saw that patients who experienced an event from birth to 14 months did not have smaller RV volumes at any earlier point in time, suggesting that there was no selective attrition of preterm-born patients with the smallest RVs. these analyses demonstrated that prematurity was associated with larger RV size at 14 months of age, even when those with the largest RVs had already died or had a heart transplant. Third, our data on patients born at the earliest gestations (ie, <34 weeks' gestation) was limited. As preterm-born patients born at earlier gestations are characterized by more pronounced cardiac alterations than preterm-born patients born near term gestation,[43] it is plausible that the changes in cardiac phenotype–as well as the rate of adverse outcomes–would be greater in those born more premature. Fourth, we were not able to explore the effects of maternal morbidities or pregnancy complications on offspring cardiac phenotype. As various pregnancy complications such as gestational hypertension, preeclampsia, and gestational hypertension have been linked to adverse cardiac remodeling in the general population,[44-46] this would be of interest to investigate in future studies. Finally, it should be noted that our current study assesses FSRV patients born between 2005 and 2008 and may therefore represent a clinical practice that differs from the enhanced contemporary neonatal and surgical care. However, a recent large register-based cohort study showed that current 1-year survival after Stage I palliation may amount to approximately 75%,[47] which is slightly higher yet similar to the 1-year survival rate of 71% in the SVR trial.[16] As the care for congenital heart disease and preterm patients keeps progressing,[7] it is to be expected that an increasing amount of high-risk premature and FSRV patients will survive into childhood and adulthood, stressing the importance of our findings on long-term cardiac remodeling in FSRV born preterm.

Our results suggest that preterm-born infants with single ventricle physiology would benefit from additional monitoring and follow-up visits compared with their term-born peers, especially in the first year of life. Further investigation of this vulnerable group could allow development of targeted strategies that mitigate the impact of prematurity on outcomes in single ventricle patients. ■

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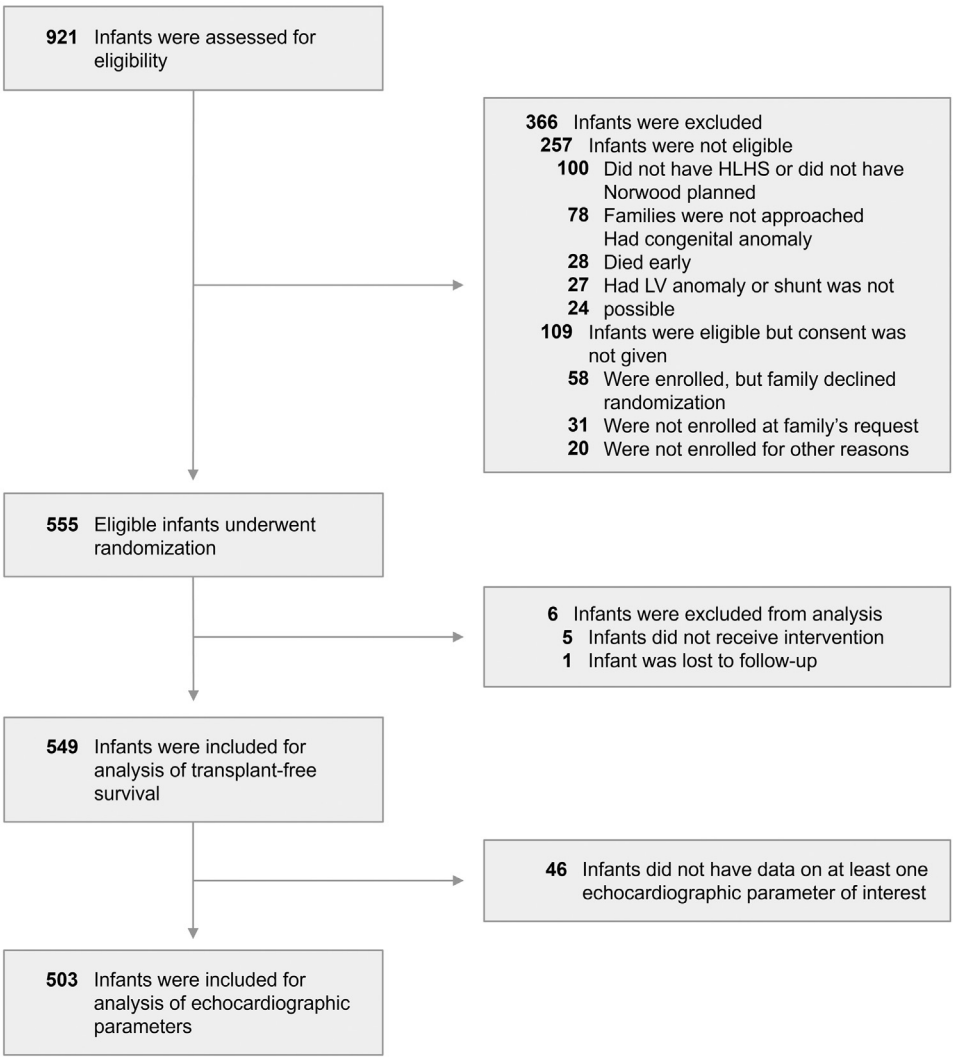


**Figure 1.** Study flow chart. *LV*, left ventricular.

**Table I. Baseline characteristics of preterm-born vs term-born patients**

| Variables | All (n = 549) | Preterm-born (n = 64) | Term-born (n = 485) | *P*-value |
|---|---|---|---|---|
| Male, n (%) | 340 (61.9) | 42 (65.6) | 298 (61.4) | .610 |
| Gestational age, wk | 38 [37-39] | 36 [34-36] | 39 [38-39] | **<.001** |
| < 34 wk, n (%) | 8 (1.5) | 8 (12.5) | - | - |
| 34-36 wk, n (%) | 56 (10.2) | 56 (87.5) | - | - |
| 37-38 wk, n (%) | 234 (42.6) | - | 234 (48.2) | - |
| 39-40 wk, n (%) | 231 (42.1) | - | 231 (47.6) | - |
| > 40 wk, n (%) | 20 (3.6) | - | 20 (4.1) | - |
| Birth weight, g | 3103 ± 541 | 2474 ± 533 | 3186 ± 486 | **<.001** |
| Low birth weight, n (%) | 76 (13.8) | 36 (56.2) | 40 (8.3) | **<.001** |
| 1-m Apgar score | 8 [8-9] | 8 [6-9] | 8 [8-9] | **.034** |
| 5-m Apgar score | 9 [8-9] | 9 [8-9] | 9 [8-9] | .099 |
| Genetic syndrome | - | - | - | **.004** |
| Yes | 26 (4.7) | 6 (9.4) | 20 (4.1) | - |
| No | 347 (63.2) | 31 (48.4) | 316 (65.2) | - |
| Unknown | 176 (32.1) | 27 (42.2) | 149 (30.7) | - |
| Other anomaly | - | - | - | **.016** |
| Yes | 106 (19.3) | 19 (29.7) | 87 (17.9) | - |
| No | 268 (48.8) | 19 (29.7) | 249 (51.3) | - |
| Unknown | 175 (31.9) | 26 (40.6) | 149 (30.7) | - |
| Treatment group | - | - | - | .643 |
| RVPAS | 275 (50.1) | 29 (45.3) | 239 (49.3) | - |
| MBTS | 274 (49.9) | 35 (54.7) | 246 (50.7) | - |

*RVPAS*, right ventricle-to-pulmonary artery shunt.
Group characteristics presented as mean ± SD for normally distributed continuous data, median [IQR] for skewed continuous distributed continuous data, or n (%) for categorical data. Normally distributed continuous variables were compared using unpaired 2-sample t-tests. Skewed continuous variables were compared using Mann-Whitney U tests. Categorical variables were compared using *X2 test* $X^2$ test or Fisher exact test, as indicated. *P*-values in bold indicate statistical significance.

**Table II. Echocardiographic parameters in preterm-born and term-born patients across the stages of the palliation process**

| | Baseline | | | PostNorwood | | | Prestage II | | | 14 Months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Variables** | **Preterm-born** | **Term-born** | ***P*-value** | **Preterm-born** | **Term-born** | ***P*-value** | **Preterm-born** | **Term-born** | ***P*-value** | **Preterm-born** | **Term-born** | ***P*-value** |
| Age at echo, days | 2 [1-5] (n = 55) | 2 [1-4] (n = 448) | .205 | 21 [16-30] (n = 47) | 21 [14-29] (n = 409) | .568 | 148 [128-178] (n = 34) | 139 [116-169] (n = 349) | .259 | 1.15 [1.12-1.21] (n = 25) | 1.18 [1.14-1.23] (n = 302) | .269 |
| RVEDV, mL | 7.99 [6.16-11.0] (n = 35) | 11.1 [9.24-13.5] (n = 323) | **<.001** | 9.26 [7.67-12.2] (n = 36) | 12.5 [10.2-14.7] (n = 331) | **<.001** | 22.0 [18.3-29.8] (n = 21) | 24.9 [19.8-30.5] (n = 259) | .409 | 31.9 [27.5-38.2] (n = 16) | 29.5 [24.3-35.9] (n = 220) | .195 |
| RVESV, mL | 4.33 [3.08-6.20] (n = 35) | 5.88 [4.72-7.63] (n = 322) | **<.001** | 4.56 [3.88-6.71] (n = 36) | 6.60 [5.00-8.56] (n = 331) | **<.001** | 12.8 [8.95-16.8] (n = 21) | 13.7 [10.4-17.6] (n = 259) | .303 | 17.3 [15.5-20.7] (n = 16) | 16.4 [13.4-20.9] (n = 220) | .432 |
| RVEDVI, mL/m$^2$ | 72.0 [60.1-90.5] (n = 35) | 85.2 [70.9-100] (n = 323) | **.019** | 79.1 [65.3-103] (n = 36) | 89.6 [74.9-105] (n = 331) | .110 | 112 [92.0-142] (n = 21) | 108 [88.4-129] (n = 258) | .623 | 100 [84.6-126] (n = 16) | 85.2 [70.6-101] (n = 220) | **.029** |
| RVESVI, mL/m$^2$ | 40.6 [30.9-51.9] (n = 35) | 46.1 [36.2-56.1] (n = 322) | .078 | 39.0 [33.9-56.1] (n = 36) | 48.0 [38.0-60.4] (n = 331) | .079 | 57.9 [42.8-81.2] (n = 21) | 60.6 [47.6-74.8] (n = 258) | .942 | 54.2 [44.0-63.8] (n = 16) | 48.1 [39.1-59.0] (n = 220) | .114 |
| RVEF, % | 45.6 [41.9-50.2] (n = 35) | 46.6 [41.3-52.0] (n = 322) | .997 | 47.1 ± 6.70 (n = 36) | 46.5 ± 8.00 (n = 331) | .644 | 45.9 ± 7.77 (n = 21) | 43.7 ± 8.23 (n = 259) | .234 | 44.1 [41.3-48.6] (n = 16) | 42.1 [37.7-47.5] (n = 220) | .146 |
| TVAA, cm$^2$ | 1.00 [0.88-1.22] (n = 54) | 1.26 [1.04-1.52] (n = 441) | **<.001** | 1.13 [1.04-1.42] (n = 47) | 1.53 [1.21-1.80] (n = 409) | **<.001** | 2.21 [1.68-2.89] (n = 34) | 2.13 [1.78-2.60] (n = 349) | .896 | 2.97 [2.45-3.53] (n = 25) | 2.74 [2.16-3.28] (n = 302) | .352 |
| TVAAI, cm$^2$/m$^2$ | 5.78 [4.74-6.74] (n = 54) | 6.08 [4.88-7.22] (n = 441) | .195 | 6.43 [5.26-7.75] (n = 47) | 6.97 [5.66-8.19] (n = 409) | .060 | 7.00 [5.56-9.64] (n = 34) | 6.76 [5.66-8.17] (n = 348) | .359 | 6.95 [6.11-8.36] (n = 25) | 6.10 [5.03-7.47] (n = 302) | .068 |
| TV regurgitation, n (%) | 15 (24.6) | 154 (32.6) | .266 | 7 (14.0) | 50 (11.6) | .795 | 5 (14.3) | 76 (21.0) | .471 | 6 (24.0) | 45 (14.6) | .244 |

EDVI, end-diastolic volume indexed to body surface area[1,3]; ESVI, end-systolic volume indexed to body surface area[1,3]; TVAAI, tricuspid valve annulus area indexed to body surface area. Group characteristics presented as mean ± SD for normally distributed continuous data, median [IQR] for skewed continuous distributed continuous data, or n (%) for categorical data. Normally distributed continuous variables were compared using unpaired 2-sample *t* tests. Skewed continuous variables were compared using Mann-Whitney U tests. *P*-values in bold indicate statistical significance.

**Table III. Two-way ANOVA results for echocardiographic variables from birth to 14 months**

| | *P*-values for each term in the 2-way ANOVA model | | |
|---|---|---|---|
| **Variables** | **Gestational age group** | **Time point** | **Interaction (prematurity × time point)** |
| RVEDV, mL | **.007** | **<.001** | **.021** |
| RVESV, mL | **.008** | **<.001** | .549 |
| RVEDVI, mL/m$^2$ | .521 | **<.001** | **.044** |
| RVESVI, mL/m$^2$ | .274 | **<.001** | .507 |
| RVEF, % | .127 | **<.001** | .723 |
| TVAA, cm$^2$ | **.004** | **<.001** | **.004** |
| TVAAI, cm$^2$/m$^2$ | .784 | **<.001** | **.017** |

EDVI, end-diastolic volume indexed to body surface area$^{1.3}$; ESVI, end-systolic volume indexed to body surface area$^{1.3}$; TVAAI, tricuspid valve annulus area indexed to body surface area. *P*-values in bold indicate statistical significance ($P < .05$).