



# Relationship of ventricular assist device support duration with pediatric heart transplant outcomes

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## KEYWORDS:

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**BACKGROUND:** There is wide variability in the timing of heart transplant (HTx) after pediatric VAD implant. While some centers wait months before listing for HTx, others accept donor heart offers within days of VAD surgery. We sought to determine if HTx within 30 days versus  $\geq 30$  after VAD impacts post-HTx outcomes.

**METHODS:** Children on VAD pre-HTx were extracted from the Pediatric Heart Transplant Study database. The primary endpoints were post-HTx length of hospital stay (LOS) and one-year survival. Confounding was addressed by propensity score weighting using inverse probability of treatment. Propensity scores were calculated based on age, blood type, primary cardiac diagnosis, decade, VAD type, and allosensitization status.

**RESULTS:** A total of 1064 children underwent VAD prior to HTx between 2000 to 2018. Most underwent HTx  $\geq 30$  days post-VAD (70%). Infants made up 22% of both groups. Patients  $\geq 12$  years old were 42% of the  $< 30$  days group and children 1 to 11 years comprised 47% of the  $\geq 30$  days group ( $p < 0.001$ ). There was no difference in the prevalence of congenital heart disease vs. cardiomyopathy ( $p = 0.8$ ) or high allosensitization status ( $p = 0.9$ ) between groups. Post-HTx LOS was similar between groups ( $p = 0.11$ ). One-year survival was lower in the  $< 30$  days group (adjusted mortality HR 1.76, 95% CI 1.11-2.78,  $p = 0.016$ ).

**CONCLUSIONS:** A longer duration of VAD support prior to HTx is associated with a one-year survival benefit in children, although questions of patient complexity, post-VAD complications and the impact on causality remain. Additional studies using linked databases to understand these factors will be needed to fully assess the optimal timing for post-VAD HTx.

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Ventricular assist devices (VADs) are increasingly used to bridge pediatric patients with both congenital heart disease and cardiomyopathy to transplant.<sup>1,2</sup> There is wide practice variability in the timing of heart transplant (HTx)

listing and consideration of organ offers after VAD implant in children. Some centers prefer to delay HTx listing for several weeks to months, aiming for improvement in heart failure symptoms and end-organ dysfunction prior to HTx.<sup>3,4</sup> By contrast, other centers accept donor offers within hours or days of VAD implant.<sup>5</sup> These centers may wish to avoid complications of mechanical circulatory support, which can lead to waitlist morbidity or mortality.<sup>6-8</sup> Given these risks, it is not known if there is an advantage to delaying HTx after VAD implant in children. We therefore sought to determine if HTx within the first 30 days after VAD implant impacts post-HTx outcomes when compared to HTx after  $\geq 30$  days of VAD support. We hypothesized that patients undergoing HTx  $< 30$  days after VAD implant would have worse post-HTx outcomes than those who were supported for longer durations, as patients supported for  $< 30$  days may not have recovered from VAD surgery and would be unlikely to have recovered from the effects of heart failure. The primary outcomes were post-HTx length of stay (LOS) and one-year survival. Secondary outcomes included post-HTx infections and rejection.

## Methods

### Study design and data source

This study had a longitudinal study design using data from the Pediatric Heart Transplant Study (PHTS). The PHTS is an international, multicenter registry, which collects prospective, event-driven data on children listed for HTx. The registry includes demographic, clinical, and surgical factors for patients prior to and following HTx.<sup>9</sup> Through an agreement with PHTS, a limited data set of patients undergoing HTx after VAD was obtained. All analyses were conducted independently by the authors and not in collaboration with the PHTS.

### Patient selection

The study included patients in the PHTS registry who were  $\leq 18$  years old at the time of HTx listing and who had a VAD in place prior to HTx. We included patients with a primary cardiac diagnosis of myocarditis, cardiomyopathy, and congenital heart disease (CHD). Exclusion criteria included VAD implant prior the year 2000, a primary cardiac diagnosis of cardiac tumor, VAD as a bridge to retransplant, and VAD explant as a separate procedure preceding HTx (Figure 1). Patients were also excluded if they were missing data required for propensity score weighting.

### Measures

We collected demographic characteristics, including patient age at the time of VAD implant, sex, race, as well as primary cardiac diagnosis, and blood type.<sup>10</sup> We compared patients between two transplant eras, identified as early (2000-2009) or late (2010-2018), as the approach toward VAD management has changed at several centers over time. Data collection on VADs included VAD classification (pulsatile vs. continuous flow, CF), along with VAD support type (LVAD, indicating biventricular circulation with systemic VAD; RVAD, biventricular circulation with subpulmonary VAD; SVAD, single ventricular circulation with systemic

VAD; BiVAD, biventricular assist devices; or TAH, total artificial heart). Because the implementation of the term "SVAD" in the registry is more recent, we cross-referenced patients with a diagnosis of "single ventricle CHD" in the database who were identified as either LVAD or RVAD and reclassified them into the SVAD group. High allosensitization status was defined as calculated panel reactive antibodies (cPRA)  $\geq 10\%$ , as documented by entries in the PHTS registry. The primary outcome measures were post-HTx hospital LOS and one-year survival. Secondary outcome measures included post-HTx infection and rejection, defined by entries in the PHTS registry.<sup>11,12</sup>

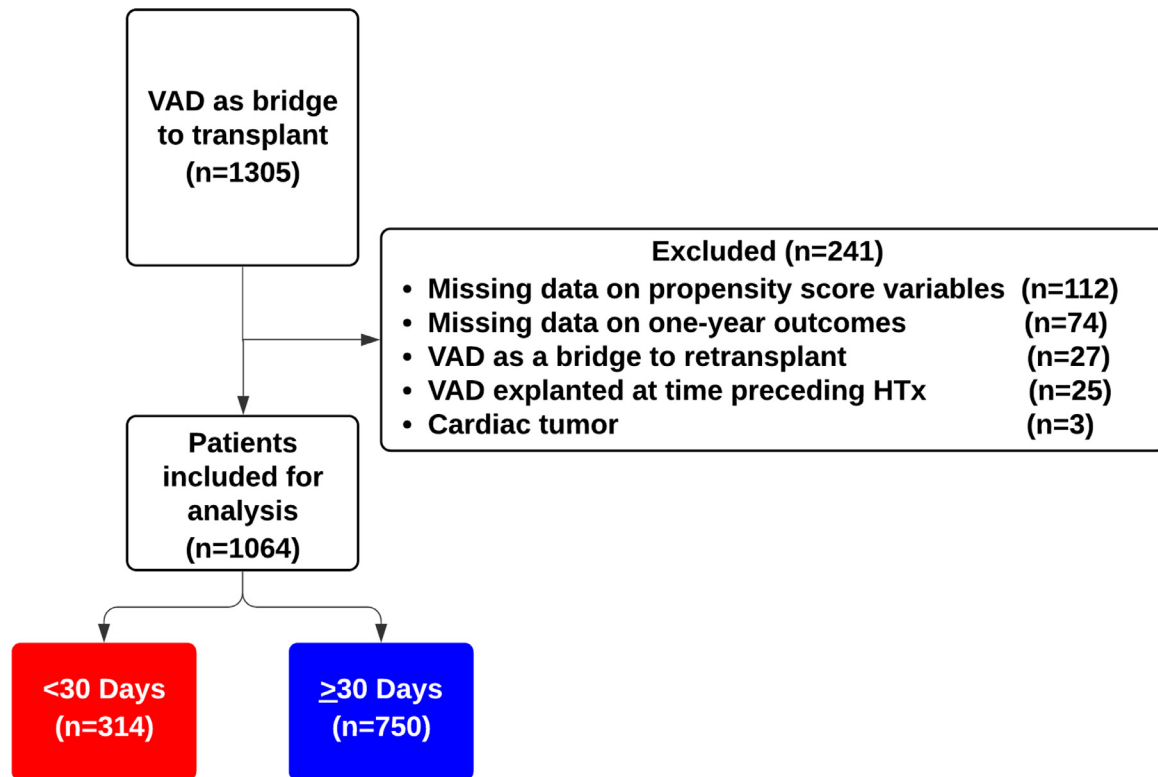
### Statistical analysis

Statistical analyses were performed using SAS v9.4 (SAS Institute, Cary, NC) and statistical significance was assessed at the 0.05 level. Normality of continuous variables was assessed using histogram, normal probability plots, and the Anderson-Darling test for normality. Descriptive statistics are presented as counts and percentages for categorical variables and median (25th percentile – 75th percentile) for continuous data with skewed distributions. Continuous data were compared between VAD duration groups ( $< 30$  days vs  $\geq 30$  days) using Wilcoxon rank-sum tests and comparisons between categorical variables were performed using Chi-square tests, or Fisher's exact test when expected cell counts were  $< 5$ .

Because patient characteristics differed between groups at baseline (Table 1), inverse probability of treatment weighting (IPTW) using propensity scores was used to control for potential confounders and baseline differences between groups.<sup>13</sup> The propensity score was estimated using a logistic regression model in which treatment assignment ( $< 30$  days vs  $\geq 30$  days, with  $\geq 30$  days as the reference group) was regressed on 6 variables chosen *a priori* that were likely to be associated with VAD group and included: age at VAD initiation (treated as categorical), recipient blood type, cardiac diagnosis, transplant decade, VAD support type and allosensitization status. To stabilize the weights, inverted propensity scores were truncated at the 1st and 99th percentiles and were normalized. Normalization consisted of dividing each individual propensity score by the mean propensity score of its respective VAD duration group.<sup>14,15</sup> The standardized mean difference was used to quantify the relative imbalance in a covariate between the two VAD duration groups. All adjusted models included the main effect of VAD duration and were weighted by stabilized propensity score to achieve balance between VAD duration groups (Supplemental Table 1). Elements with standardized mean difference (SMD)  $< 0.20$  after propensity scoring, referred to as "adjusted," achieved satisfactory balance. As sensitivity analyses, various covariates were controlled for as fixed effects in the IPTW adjusted analyses.<sup>13</sup> A separate adjusted model was created for the following covariates: mechanical ventilation, vasoactive support, and outpatient status.

To compare the effect of VAD duration ( $< 30$  days vs  $\geq 30$  days) on the continuous outcome of post-HTx LOS, residual errors were gauged for normality via histograms and quantile-quantile plots. Failing to meet the normality assumption, post-HTx LOS was ranked before analysis and modeling was carried out on the rank-transformed data. Unadjusted and adjusted estimates are presented as unweighted and weighted medians (25th–75th percentile) and adjusted p values were derived from propensity score weighted 2 sample *t*-test on the ranked data.

Time-dependent outcomes (death, rejection, and infection) were analyzed with survival analysis. For the primary outcome



**Figure 1** Study population.

death, Cox-PH regression models were used to estimate the unadjusted and adjusted effect of VAD duration group on survival and the results are reported as HR with 95% confidence intervals. A conditional sub analysis of one-year survival in patients who survived at least one month after HTx was generated using a separate propensity score that consisted of the same variables as the original propensity score. Because death was considered as a competing event for rejection, a competing-risk analysis was performed to model the probability over the first year post-HTx. Hazard ratios were estimated using cause-specific hazard model to account for competing events. A similar competing analysis was carried out for the time-dependent outcome of infection accounting for death.

## Results

### Patient population

A total of 1,305 cases of children with VAD prior to HTx were received from the PHTS registry (Figure 1). The final study population included 1,064 patients (Table 1). The majority of subjects (750, 70%) were on VAD support for  $\geq 30$  days prior to HTx. There were differences based on age between groups. Infants accounted for 22% of both groups, patients  $\geq 12$  years made up 42% of  $< 30$  days group, and children ages 1 to 11 years comprised 47% of the  $\geq 30$  days group ( $p < 0.001$ ). There was also a difference between groups based on race; Black patients made up a greater proportion of the  $< 30$  days group than the  $\geq 30$  days group (27.4% vs 19.9%,  $p = 0.05$ ). While patients with an LVAD accounted for the largest proportion of patients in both groups, the frequency of BiVAD support

was higher in the  $< 30$  days group (31% vs 21% in  $\geq 30$  days,  $p = 0.010$ ). Most patients (82%) were transplanted in the more recent era and accounted for the majority of HTx  $\geq 30$  days after VAD (86%,  $p < 0.001$ ). Two-third of patients in the cohort had pulsatile devices. There were 309 CF devices, 245 (79%) of which were intracorporeal. Intracorporeal CF devices comprised 20% of the  $< 30$  days group and 28% of the  $\geq 30$  days group, while paracorporeal CF devices made up 11% of the  $< 30$  days group and 5% of the  $\geq 30$  days group ( $p = 0.001$ ). There was no difference in the prevalence of CHD (17% vs 18%,  $p = 0.7$ ) or high allosensitization status (24% vs 25%,  $p = 0.9$ ) between groups.

Pre-transplant patient factors are listed in Table 2. Children transplanted  $< 30$  days after VAD were more likely to require mechanical ventilation (38% vs 11%,  $p < 0.001$ ) and to be on vasoactive support (56% vs 27% in  $\geq 30$  days group,  $p < 0.001$ ) prior to HTx. More patients in the  $\geq 30$  days group were outpatients at the time of HTx. While there were statistical differences in laboratory values between groups, many of the median values were similar and likely would not have been distinguishable from a clinical standpoint.

Patients in the  $< 30$  days group were listed for HTx a median of four days prior to VAD implant, compared to 2 days prior to VAD in the  $\geq 30$  days group ( $p < 0.001$ ), although both groups included patients who were listed for HTx after VAD. The median interval between HTx listing and HTx surgery was significantly longer in the  $\geq 30$  days group (88 vs 20 days in  $< 30$  days,  $p < 0.001$ ). HTx listing status (active vs. inactive) was not available in the limited dataset and therefore could not be analyzed.

**Table 1** Baseline Characteristics, VAD Implant

Patient Characteristic	Overall <i>n</i> = 1064	<30 Days <i>n</i> = 314	≥30 Days <i>n</i> = 750	<i>p</i>
Age at VAD Initiation, <i>n</i> (%)				<0.001
< 1 Year	232 (21.8)	68 (21.7)	164 (21.9)	
1-11 Years	465 (43.7)	113 (36.0)	352 (46.9)	
12+ Years	367 (34.5)	133 (42.4)	234 (31.2)	
Male Sex, <i>n</i> (%)	599 (56.3)	176 (56.1)	423 (56.4)	0.92
Race, <i>n</i> (%)				0.05
White	643 (62.4)	184 (59.9)	459 (63.5)	
Black	228 (22.1)	84 (27.4)	144 (19.9)	
Asian	45 (4.4)	11 (3.6)	34 (4.7)	
Other	114 (11.1)	28 (9.1)	86 (11.9)	
Recipient Blood Type, <i>n</i> (%)				0.18
A	333 (31.3)	110 (35.0)	223 (29.7)	
AB	39 (3.7)	14 (4.5)	25 (3.3)	
B	131 (12.3)	40 (12.7)	91 (12.1)	
O	561 (52.7)	150 (47.8)	411 (54.8)	
Cardiac Diagnosis, <i>n</i> (%)				0.89
Cardiomyopathy	808 (75.9)	238 (75.8)	570 (76.0)	
CHD – single ventricle	46 (4.3)	12 (3.8)	34 (4.5)	
CHD – all others	140 (13.2)	41 (13.1)	99 (13.2)	
Myocarditis	70 (6.6)	23 (7.3)	47 (6.3)	
Transplant Decade, <i>n</i> (%)				<0.001
2000-2009	190 (17.9)	81 (25.8)	109 (14.5)	
2010-2018	874 (82.1)	233 (74.2)	641 (85.5)	
VAD Support Type, <i>n</i> (%) <sup>a</sup>				0.010
BiVAD	253 (23.8)	96 (30.5)	157 (20.9)	
LVAD	748 (70.3)	201 (64.0)	547 (72.9)	
RVAD	18 (1.7)	5 (1.6)	13 (1.7)	
Systemic VAD	45 (4.2)	12 (3.8)	33 (4.4)	
VAD Classification, <i>n</i> (%) <sup>b</sup>				0.56
Pulsatile	630 (67.0)	186 (68.6)	444 (66.4)	
Continuous flow	309 (33.0)	85 (31.4)	224 (33.7)	
Allosensitization Status, <i>n</i> (%) <sup>c</sup>				0.89
Highly allosensitized (cPRA ≥10%)	263 (24.7)	75 (23.9)	188 (25.1)	
Not highly sensitized (cPRA <10%)	648 (60.9)	192 (61.1)	456 (60.8)	
No testing available	153 (14.4)	47 (15.0)	106 (14.1)	

<sup>a</sup>BiVAD, biventricular assist device; LVAD, biventricular circulation with systemic VAD; RVAD, biventricular circulation with subpulmonary VAD; Systemic VAD, single ventricular circulation with systemic VAD.

<sup>b</sup>VAD classification, *n* = 939 due to limited data entry.

<sup>c</sup>Highly allosensitized: defined as calculated plasma reactive antibody (cPRA) ≥10% in the Pediatric Heart Transplant Study database.

**Table 2** Pre-Transplant Factors

	Overall <i>n</i> = 1064	<30 Days <i>n</i> = 314	≥30 Days <i>n</i> = 750	<i>p</i>
Mechanical Ventilation, <i>n</i> (%)	200 (18.8)	119 (37.9)	81 (10.8)	<0.001
Vasoactive Support, <i>n</i> (%) <sup>a</sup>	378 (35.5)	175 (55.7)	203 (27.1)	<0.001
Single, low dose	35 (9.7)	15 (8.9)	20 (10.4)	0.64
Multiple or high dose	325 (90.3)	153 (91.1)	172 (89.6)	
Outpatient Status, <i>n</i> (%)	167 (15.7)	7 (2.2)	160 (21.3)	<0.001
Laboratory Data, median (IQR)				
Blood urea nitrogen, mg/dL	15 (10 – 21)	16 (11 – 25)	14 (10 – 20)	0.001
Creatinine, mg/dL	0.44 (0.30 – 0.68)	0.45 (0.30 – 0.70)	0.44 (0.30 – 0.64)	0.17
Albumin, g/dL	3.6 (3.1 – 4.0)	3.1 (2.8 – 3.5)	3.8 (3.3 – 4.1)	<0.001
Total bilirubin, mg/dL	0.50 (0.30 – 1.10)	0.86 (0.40 – 2.00)	0.50 (0.27 – 0.90)	<0.001
Days between VAD and HTx listing, median (IQR)		-4 (-19, -1)	-2 (-14, 6)	<0.001
Days between HTx listing and HTx surgery, median (IQR)		20 (11, 37)	88 (52, 167)	<0.001

<sup>a</sup>Vasoactive support dosages *n* = 360 due to limited data entry

## Primary outcomes

A Kaplan-Meier survival analysis demonstrated a significant difference in one-year survival between the two groups (Figure 2), with 89.8% survival in the < 30 days group and 93.9% survival in the  $\geq 30$  days group (adjusted mortality HR 1.73 in < 30 days group, 95% CI 1.11-2.78,  $p = 0.016$ ). Given the prominent decline in survival among patients within the early post-Htx period, we performed a conditional survival analysis that included only those patients who survived > 30 days after HTx. This conditional analysis demonstrated no significant difference in one-year survival between groups (adjusted mortality HR 1.60 in < 30 days group, 95% CI 0.89-2.87,  $p = 0.11$ ). An additional Kaplan-Meier curve demonstrated no difference in survival between the earlier and later transplant eras (Supplemental Figure 1). As has been shown in prior studies, infants had worse survival than older age groups (Supplemental Figure 2), and children with CHD had worse survival than children with cardiomyopathy or myocarditis (Supplemental Figure 3).

We included the clinical variables of mechanical ventilation, vasoactive support, and outpatient status as fixed effects in the propensity score adjusted model (Supplemental Table 3). When controlling for mechanical ventilation, we found that the survival difference between groups was no longer significant ( $p = 0.32$ ). The difference between the 2 VAD duration groups remained significant when controlling for vasoactive support ( $p = 0.02$ ) and outpatient status ( $p = 0.036$ ).

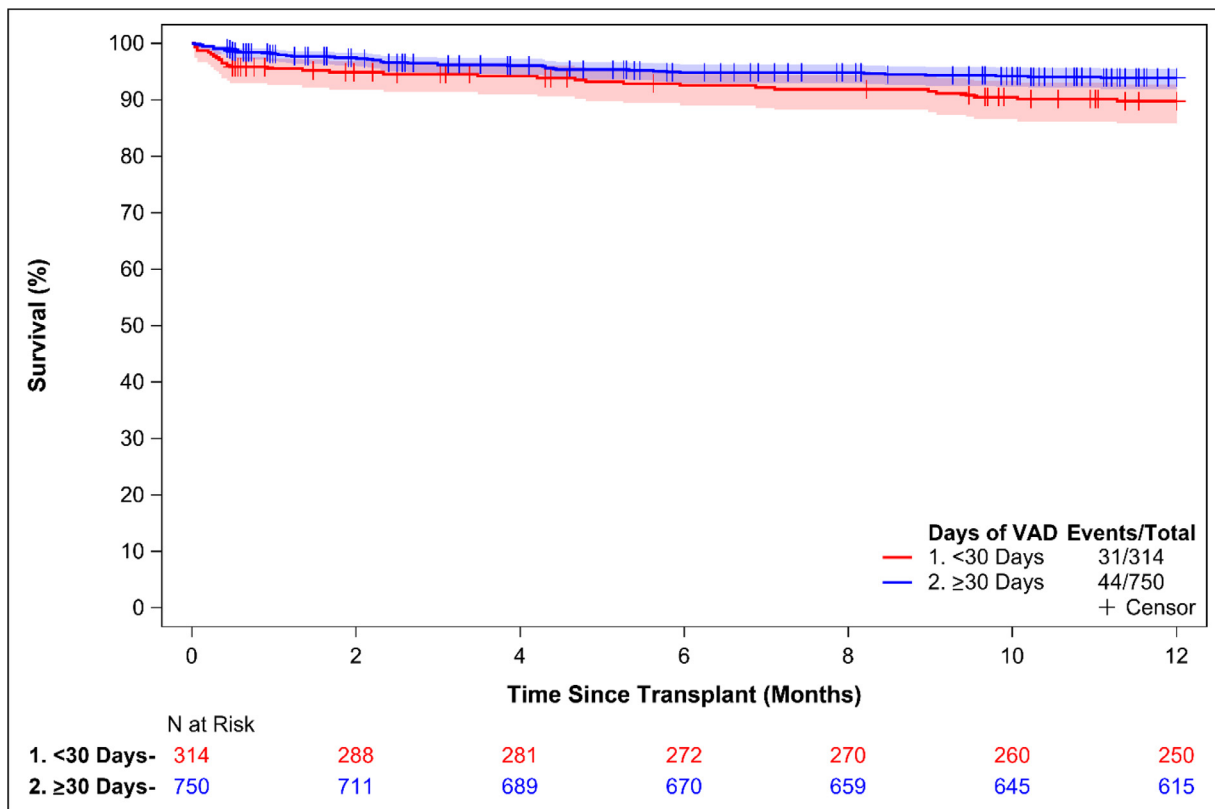
Among the 993 patients who survived to hospital discharge, there was no significant difference in post-HTx LOS between groups with a median LOS of 22 vs 20 days in < 30 vs  $\geq 30$  days of VAD support, adjusted  $p = 0.11$  (Supplemental Figure 4).

## Secondary outcomes

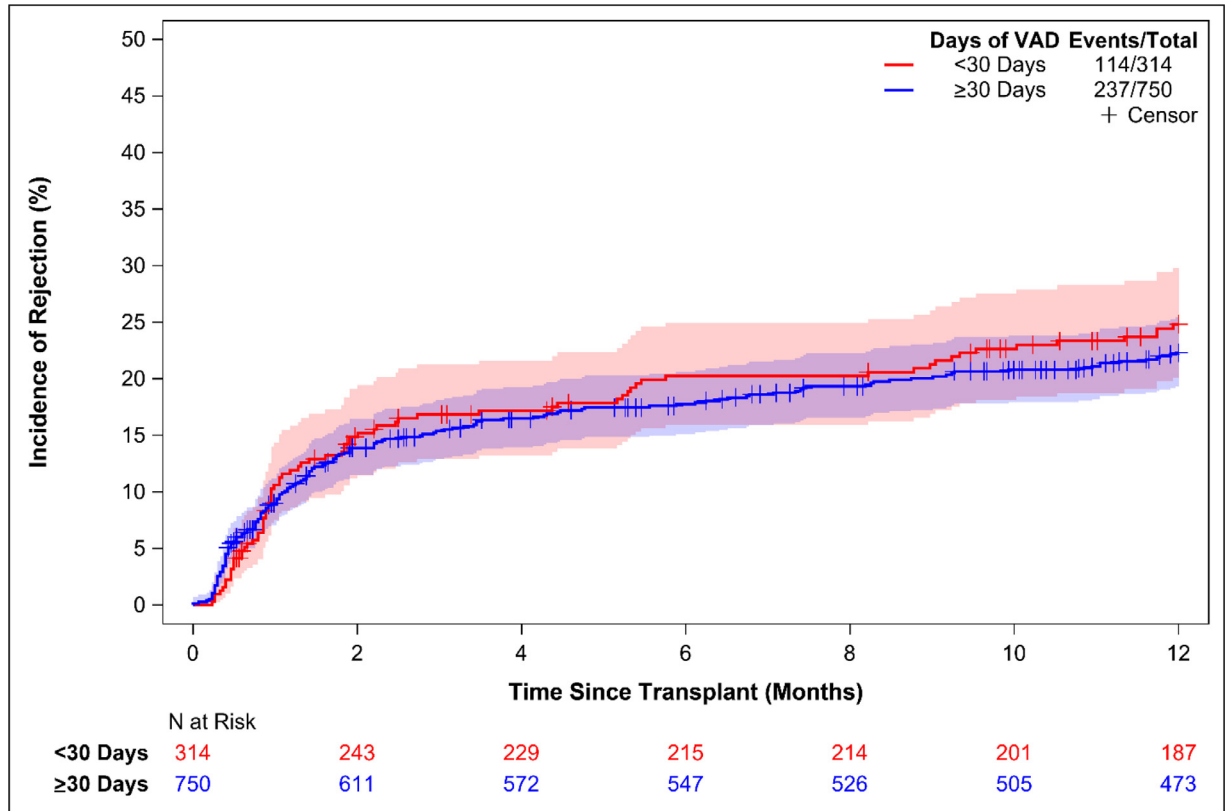
Cumulative incidence curves were generated for the secondary outcomes of rejection and infection, with death treated as a competing risk. There was no significant difference in the incidence of rejection over the first year post-Htx between the two VAD groups (Figure 3). Similarly, there was no difference in the overall incidence of infection (Figure 4).

## Discussion

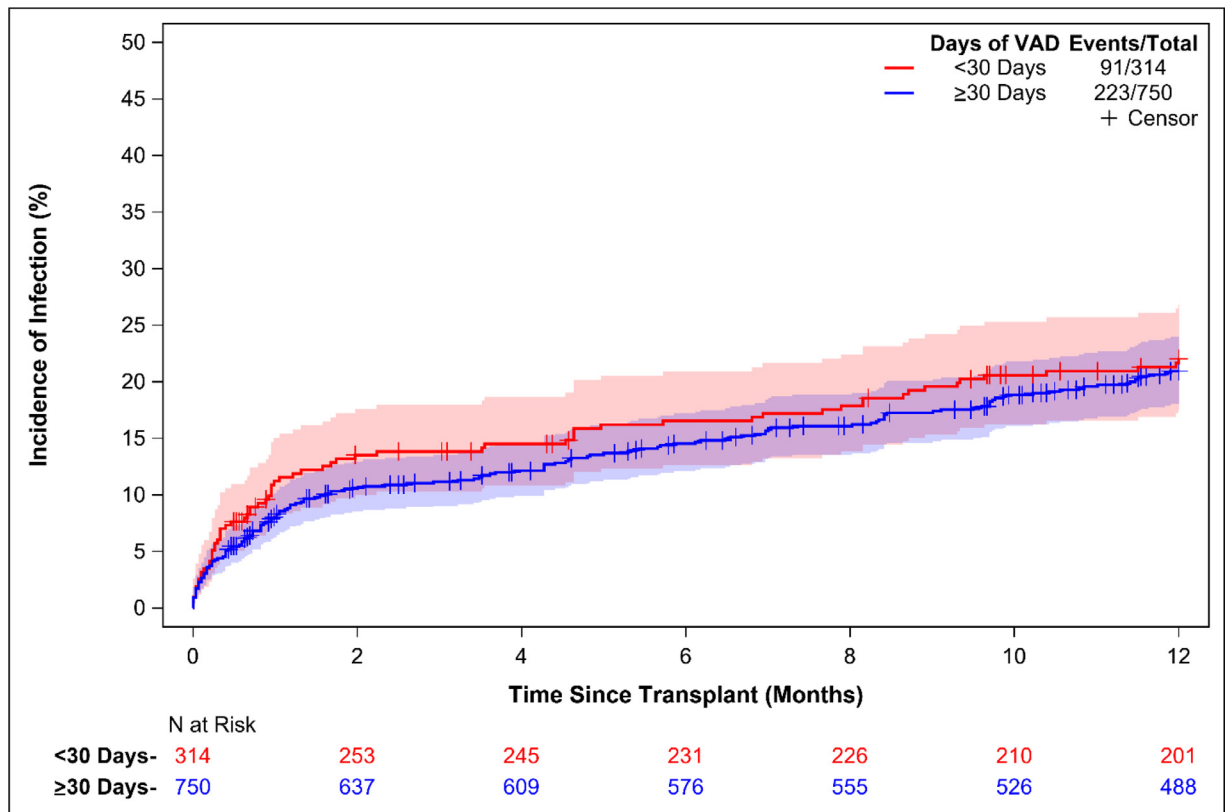
In this large, multicenter registry study of children undergoing HTx after VAD implant, we demonstrate a significant one-year survival advantage in patients who were supported with VADs for  $\geq 30$  days, accounting for several potential confounders with propensity score weighting. Notably, the 1 year survival benefit was not significant after censoring patients who died within a month of HTx, reflecting that the highest risk of mortality is in the early post-Htx period. However, there was no significant difference in rejection or infection in the first year after HTx, with similar post-HTx LOS among survivors to hospital discharge between the 2



**Figure 2** One-year post-transplant survival.  $\geq 30$  Days is the reference group.



**Figure 3** Cumulative incidence of rejection. Death treated as a competing risk. \*>30 Days is the reference group.



**Figure 4** Cumulative incidence of infection. Death treated as a competing risk. \*>30 Days is the reference group.

groups. Notably, patients in the < 30 days group were more likely to be mechanically ventilated and to be on vasoactive support at the time of HTx, potentially reflecting a patient population with greater complexity and illness severity. In the absence of data on VAD-related complications and comorbidities at the time of HTx, it is therefore challenging to determine if patients in the  $\geq 30$  days group truly benefited from more time on VAD support or if they were simply less ill than those in the < 30 days group.

Among pediatric transplant centers, the issue of HTx timing after VAD placement remains highly controversial, related in part to the known complications of VAD support. The most recent report from the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS) demonstrated that 62% of children on VADs experience at least one major adverse event (AE), typically within the first three months of implant.<sup>2</sup> Given the established infectious, thrombotic, and neurologic risks in children, particularly those on paracorporeal devices, centers may choose to accept donor offers soon after VAD implant.<sup>2,6,16,17</sup> However, a recent study linking patients in both the PHTS and PediMACS registries demonstrated that post-HTx survival was not affected by the number of AEs experienced while on VAD support.<sup>17</sup> Our study lacked the granularity to account for potential AEs as an indication to proceed with earlier HTx.

Further, centers may choose to accept early organ offers when the waitlist time is expected to be lengthy, such as among school-age children with limited options for donors due to their size, or in patients who are highly allosensitized. They may also prefer to accept HTx offers in patients who are more challenging to support on VADs, including those with complex or single ventricle CHD. Notably, our study used propensity scores to account for several potential confounders, including patient age and allosensitization, and still found a survival benefit in patients who were supported for longer periods on VADs. However, we lacked data on HTx listing status (active vs inactive), as well as on center-specific listing practices for VAD patients. Without these key data points, it may not be possible to determine the primary driver for these results.

By contrast, other transplant centers have instituted a "waiting policy" for HTx, aiming to improve heart failure symptoms and end-organ dysfunction while on VAD support, often by keeping patients inactive on the HTx waiting list for a specified period.<sup>3-5,18</sup> A recent registry study using the United Network for Organ Sharing (UNOS) database supports the use of this strategy in children, noting that patients on intracorporeal continuous flow (ICF) devices had improved post-HTx survival with longer durations on VAD.<sup>19</sup> They also found a post-HTx survival advantage for patients on pulsatile devices for 2 to 4 months, compared to those of shorter or longer durations. Notably, our dataset found that many patients transplanted within 30 days of VAD implant were older children, with ICF devices accounting for more than 20% of the < 30 days group. These patients may have benefited from a longer duration on VAD support, given the improving stroke profile and low risk of complications on these devices.<sup>4</sup> It is

challenging to know if this practice can be applied to patients on paracorporeal devices, who have historically had a higher risk of stroke, but recent changes in pediatric practice, such as the introduction of bivalirudin, may help mitigate these risks in the future.<sup>6,20</sup>

As has been demonstrated in studies of adult VAD patients, we postulated that children require at least 1 month to recover from the complications of VAD surgery, including postoperative bleeding and weaning of inotropic and ventilatory support, in addition to the initial recovery from the chronic effects of heart failure.<sup>5,21-23</sup> A recent publication using Medicare data demonstrated that both short- and long-term post-HTx survival were lower for adults on VAD support for  $\leq 31$  days, compared to 31-365 days or >365 days.<sup>5</sup> Patients in the  $\leq 31$ -days group had more complications and longer post-HTx LOS, including higher incidences of bleeding, sepsis, and acute kidney injury. Another study found that adults on VADs for >90 days had a significant improvement in functional performance pre-HTx, but found no difference in mortality based on duration of VAD support.<sup>24</sup> While our dataset did not provide this degree of granularity, the recent UNOS study demonstrated improvement in multiple pre-HTx indices of end-organ function and functional status in children supported with all VAD types for longer durations.<sup>19</sup>

Importantly, our study demonstrated that the risk of mortality is high in the first month post-HTx. This finding does not correlate with an increased risk of infection or rejection in the patients supported for < 30 days, suggesting that other factors may contribute. Our fixed effects model found that the difference in survival between the two VAD duration groups persisted when controlling for both the presence of vasoactive support and for outpatient status. However, this difference was no longer significant when we controlled for the presence of mechanical ventilation at the time of transplant. Mechanical ventilation may therefore be a marker of residual end-organ dysfunction as a consequence of heart failure, in whom transplant may have been undertaken before the benefits of the VAD could be reaped.<sup>25</sup> Alternatively, ongoing mechanical ventilation in these patients may reflect a patient population that is more challenging to support on VAD, or those who had incurred AEs in the early postoperative period. Without information on VAD complications and early AEs, we cannot distinguish between patients who may have incurred waitlist mortality, rather than early post-HTx mortality, if a HTx had not been performed. Finally, the similarity of both post-HTx LOS and the incidence of rejection between groups suggests that the clinical courses for these patients have challenges that cannot be overcome by longer duration of VAD support.

## Limitations

As with any registry study, there are important limitations to note. Because this study only captured patients who underwent HTx, we were unable to identify VAD patients who died without receiving HTx. We also lacked the granularity to account for illness severity at the time of HTx,

including nutritional and ambulatory status, VAD complications, or challenges with VAD support. These incomplete data precluded our ability to account for early device complications that may have made earlier HTx more compelling. This dataset also did not identify the centers from which patients were entered into the dataset, making it hard to distinguish center-specific practices that may have influenced outcomes. Finally, due to center-specific variability on listing practices, particularly related to which patients are made active vs. inactive on the HTx waitlist, comparisons to adult practices are limited, particularly because the waitlist time for certain populations can be extremely long.

## Conclusion

Children who are bridged to HTx with a VAD represent a growing population and significant controversy on their treatment strategy exists. Using propensity scores to address potential confounders, our data indicate that a longer duration of VAD support prior to transplant is associated with a survival benefit at one year. However, our dataset did not include key information on VAD complications and center-specific HTx listing practices, which may have influenced our results. In the future, a linkage analysis between PHTS and a registry that collects information on VAD complications, such as PediMACS, UNOS, or ACTION, the Advanced Cardiac Therapies Improving Outcomes Network, is needed to identify additional risk factors for poor outcomes. Ultimately, a prospective study to compare VAD durations pre-HTx is needed to identify optimal timing of HTx surgery, particularly in high-risk populations.

## Author Contributions

Dr. Butto conceptualized and designed the study, analyzed the data, and guided the statistical plan, drafted the initial manuscript, and revised and reviewed the final manuscript.

Drs. Mahle, Mao, and Wright conceptualized and designed the study, aided with analysis, and critically revised and reviewed the manuscript for important intellectual content.

Ms. Wetzel and Mr. Kelleman performed the statistical analyses, created the tables and figures included in the study, and critically reviewed the manuscript for statistical and intellectual content.

Drs. Carboni, Dipchand, Knecht, Reinhardt, Sparks, and Villa critically reviewed the data and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

## Disclosure statement

The authors have no financial conflicts of interest to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.hltun.2021.09.011>.

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