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Prime Time: Is there an Optimal VAD Duration Prior to Heart Transplant in Children?

By

Arene Butto
M.D., University of Michigan Medical School, 2011

Advisor: Jordan Kempker, MD, MSc

An Abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science in Clinical Research
2023

Abstract

Prime Time: Is there an Optimal VAD Duration Prior to Heart Transplant in Children?
By Arene Butto

Purpose: Early pediatric ventricular assist device (VAD) studies showed high adverse event (AE) rates within one month after VAD implant, prompting heart transplant (Tx) soon after VAD surgery. However, recent data indicate that shorter VAD durations are associated with worse post-Tx outcomes. We compared outcomes of patients bridged to Tx with <30 vs. ≥30 days of VAD support by assessing both VAD and Tx risk factors.

Methods: We merged data from children in the PediMACS and Pediatric Heart Transplant Study registries. Inverse probability of treatment weighting using propensity scores (PS) was used to control for potential confounders, including age at VAD implant, recipient blood type, cardiac diagnosis (cardiomyopathy, congenital heart disease, myocarditis), VAD support type (left, right, single, and biventricular VAD), allosensitization, and pre-Tx mechanical ventilation and vasoactive support. The primary endpoint was one-year post Tx mortality.

Results: Among 271 patients, there were 60 in the <30 days and 211 in the ≥30 days groups. Baseline and VAD characteristics were similar. The ≥30 days group had higher prevalence of blood type O and allosensitization. At Tx, the <30 days group had more mechanical ventilation (34% vs. 7%, $p<0.001$) and vasoactive use (60% vs. 24%, $p<0.001$ vs. ≥30 days). There were 187 VAD AEs in the first 30 days after implant. The overall weighted AE rate per patient was lower in the <30 days group than in the ≥30 days group (0.42 vs. 0.78, $p=0.02$). There were 2 deaths in the <30 days group and 13 in the ≥30 days group (log-rank $p=0.38$). A PS-weighted Cox proportional hazards model, adjusted for 30-day AE rate while on VAD support, demonstrated a non-significant mortality hazard ratio of 0.43 for the <30 days vs. ≥30 days group (95% CI 0.07-2.70, $p=0.37$).

Conclusion: VAD support durations <30 days were associated with a non-significant lower post-Tx mortality after accounting for illness severity and VAD AEs in children bridged to Tx with VAD. The effect size must be interpreted with caution due to the small event number but raises important questions regarding the need for a mandatory waiting period prior to Tx in VAD patients.

Prime Time: Is there an Optimal VAD Duration Prior to Heart Transplant in Children?

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Advisor: Jordan Kempker, MD, MSc

A thesis submitted to the Faculty of the
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Table of Contents

Introduction:

Children with refractory heart failure face a high risk of mortality as they await heart transplantation (HTx), which may be mitigated by the use of ventricular assist devices (VADs).[1-4] These mechanical devices, typically implanted surgically, have revolutionized the care of some children by taking over the pump function of the failing heart. The indications for pediatric VAD implantation vary widely, from growth failure to end-stage disease requiring mechanical ventilation and inotropes. The goal of VAD use is to improve a child's candidacy for a HTx, either by preventing death, in cases of cardiogenic shock, or by reducing end-organ dysfunction that can preclude HTx candidacy. In addition, VAD support may allow for optimized nutrition and physical rehabilitation prior to HTx, which could improve their post-HTx course.

However, there is controversy regarding the optimal duration of VAD support prior to HTx, with some centers choosing to proceed with HTx immediately after VAD surgery and others setting a mandatory waiting period before accepting a HTx offer. This study aims to investigate the issue of VAD duration prior to HTx by performing a linkage analysis using the Pediatric Heart Transplant Study (PHTS) and Pediatric Interagency Registry for Mechanically Assisted Circulatory Support (PediMACS), the largest available pediatric HTx and VAD registries, respectively. A prior linkage analysis of PHTS and PediMACS found similar rates of one-year post-HTx survival, infection, and rejection in children who underwent VAD prior to HTx, compared to those transplanted without VADs.[5] These findings, as well as growing comfort with pediatric VAD use, have led to the increasing use of VADs as a bridge to HTx in select pediatric populations.[6] Recent data show that more than 30% of pediatric HTx recipients undergo VAD implant prior to HTx, with higher prevalence among older children and those with cardiomyopathy.[7-9]

In some cases, center preference or strategy may determine VAD duration prior to HTx. Some programs accept donor offers within hours or days of VAD implant, preferring to proceed with HTx soon after VAD surgery rather than risk VAD complications.[10, 11] In the early era of pediatric VAD, for instance, undertaking HTx soon after VAD surgery was preferred given the high prevalence of VAD

adverse events (AEs) like stroke, bleeding, and infection. One study of 200 children using early PediMACS data reported only 46% freedom from AEs in the first month after VAD.[10, 12] Because these AEs can negatively affect HTx candidacy, centers may be compelled to proceed with HTx soon after VAD surgery. Alternatively, centers may choose to accept donor offers soon after VAD in those patients otherwise anticipated to have a long waitlist time.

In contrast, some centers now programmatically delay HTx listing for months after VAD implantation, anticipating progressive improvement in the non-cardiac organ systems affected by heart failure with longer VAD support durations, including the kidneys, liver, and gastrointestinal tracts, known as the "end-organs."[13, 14] Rather than using VAD as "salvage" therapy for children in cardiogenic shock or protracted heart failure, these centers have shifted to use VADs as a means of strengthening HTx candidacy by allowing additional time on VAD support to permit recovery from VAD surgery and from end-organ dysfunction.

This approach is supported by a study using data from the United Network for Organ Sharing (UNOS). UNOS is a non-profit group that manages the data for listed patients and potential donors for all solid organ transplants, providing potential matches for patients awaiting transplant, which are ultimately acted upon by the transplant center. UNOS collects demographic, laboratory, and clinical data at the time of HTx listing, as well as details related to the donor, HTx surgery, and post-HTx course. The authors assessed data from 685 children with VAD as a bridge to HTx and found that VAD duration for more than two months prior to HTx decreased the use of inotropes and mechanical ventilation prior to HTx, compared to those supported for shorter durations.[15] This strategy coincides with recent changes in pediatric VAD management strategies that have also improved VAD outcomes. The use of bivalirudin as the primary anticoagulant for paracorporeal pulsatile devices, for instance, has reduced the risk of stroke, as has the widespread collaboration facilitated by the Advanced Cardiac Therapies Improving Outcomes Network (ACTION), a multicenter quality improvement initiative.[16-18]

Importantly, pediatric heart failure is a heterogeneous condition, affecting children of all ages, sizes, and cardiac anatomy, including congenital heart disease (CHD).[19] As a result, several different

VAD classifications exist to describe the types of VADs that may be implanted. VADs may be considered temporary or durable, with pumps that are either intracorporeal or paracorporeal.[11, 14] Pediatric VADs may function with continuous flow or with pulsatile flow. The most common devices currently implanted in children are the Berlin Heart EXCOR, a paracorporeal pulsatile device and, more recently, the HeartMate III, an intracorporeal continuous flow device. Prior to the advent of the HeartMate III, the HeartWare HVAD was the most commonly used intracorporeal continuous flow device. VADs are typically implanted in the left ventricle (LVAD), which is usually the ventricle supplying the systemic circulation. However, VADs can also be implanted in the right sub-pulmonary ventricle (RVAD), in both ventricles (BiVAD) or, in cases of single ventricle CHD, can be placed in whichever ventricle is considered systemic (SVAD). Each type of device comes with its own set of risk factors, which have variable impacts on patients of different sizes.[11, 20] Given the complex array of risk profiles for each device type in different pediatric heart failure populations, there is wide practice variation with regard to the optimal duration of VAD support prior to pediatric HTx.

Several factors outside of the control of the transplant center affect the timing of HTx after VAD, including donor availability, recipient blood type, patient size, and pediatric listing status as established by UNOS. For example, older school-age children and adolescents may receive HTx offers relatively soon after listing owing to the UNOS listing protocol. Conversely, the scarcity of donor hearts in smaller children can lead to lengthy HTx waitlist times in infants and young children, or in those with significant allosensitization; a donor offer may therefore be strongly desired at any time after VAD.[21] Centers may also consider donor offers soon after VAD surgery due to issues unique to pediatrics. For instance, there may be anatomical challenges that complicate VAD implantation in children with non-dilated cardiomyopathy or CHD, leading to inability to provide full cardiac support.[22] In such scenarios, centers may accept a donor offer in the early post-VAD period, despite incomplete surgical recovery from VAD implantation.

Data from adults bridged to HTx with VAD support are mixed with regard to optimal duration of HTx timing after VAD implant. An early study of adults on pulsatile VADs used UNOS data to

demonstrate lower post-HTx survival for patients bridged to HTx with less than two weeks of support, while another study examining both pulsatile and continuous flow VADs using data from the Nationwide Inpatient Sample demonstrated worse outcomes for patients transplanted within one week of VAD implant.[23, 24] A subsequent multicenter study evaluating outcomes of patients on a continuous flow VAD, the HeartMate II, found no difference in post-HTx survival based on duration of VAD therapy.[25] More recently, a large study using Medicare data demonstrated that a short interval (≤31 days) from VAD implant to HTx was associated with worse post-HTx survival and longer post-HTx length of stay (LOS), compared to patients who remained on VAD support between one month and one year.[26] Importantly, VAD implantation has also been associated with improved quality of life in some adults, both before and after HTx.[27, 28]

Our prior work in the area of pediatric VAD duration prior to HTx, which examined data from the PHTS registry, showed a post-HTx survival benefit in children with longer durations of VAD support. Among 1,064 patients who underwent VAD as a bridge to HTx, we found higher one-year post-HTx mortality for patients transplanted <30 vs. ≥30 days after VAD (hazard ratio 1.73, 95% CI 1.11-2.78, p=0.016), accounting for confounders including age, blood type, and cardiac diagnosis using propensity score methods.[29] We postulated that children benefit from having a minimum of 30 days to recover from postoperative bleeding, wean vasoactive and respiratory support, and improve end-organ dysfunction caused by heart failure, as shown in studies of adult VAD patients. However, VAD-specific complications were not available in the PHTS registry, which could have affected results.

It is critical to evaluate both VAD and HTx-specific risk factors that can affect post-HTx outcomes in heterogeneous pediatric population. While PHTS provides granular data on the pre- and post-HTx course for patients, a dedicated VAD registry, such as PediMACS, is needed identify important details on VAD-related complications, such as stroke or device malfunction, which may also influence the decision to accept a donor offer soon after VAD. PHTS is a pediatric HTx registry that provides event-driven data from the time of HTx listing, including post-HTx infection and rejection. This high-quality database has been utilized for ~100 publications; data is available for >8,000 heart transplants.[21, 30-33]

PediMACS is a pediatric VAD registry that prospectively collects data on children from the time of VAD implant through an outcome of HTx, death, or recovery/explant. PediMACS accounts for >1000 devices in 856 children between 2012 and 2020 and is the primary source for multicenter VAD research in North America.[6, 11, 14, 19, 34-36] Prior linkage studies of these two registries have compared outcomes of children bridged to HTx with and without VAD support, as described above, in addition to assessing risk factors for persistent renal dysfunction after HTx in VAD patients and the effect of VAD-related infections on post-HTx outcomes.[5, 37, 38] However, there has not been a linkage analysis that evaluates the effect of VAD duration on post-HTx outcomes.

The purpose of this study was to investigate the optimal timing of HTx after VAD implant in children by integrating the PHTS registry with PediMACS, allowing us to account for VAD-specific issues that may affect outcomes. We hypothesized that children who have at least one month of VAD support prior to HTx will have improved post-HTx outcomes, including better survival, shorter hospital LOS, and lower incidences of infection, rejection, and renal failure.

Methods:

Study Design and Data Source

We conducted a retrospective cohort study by linking data from the two largest HTx and VAD databases dedicated to children, PHTS and PediMACS. PHTS is an international registry of children undergoing HTx that began data collection in 1993 and includes 62 participating centers, primarily in North America. PHTS provides granular data on pre-HTx factors, HTx surgery, and post-HTx outcomes, including episodes of rejection, infection, renal failure, coronary artery graft vasculopathy, and death. It collects prospective, event-driven data and follows patients longitudinally from the time of HTx listing via standardized forms (available at https://pediatricheartransplantsociety.org/2015-forms/), until death or their transition to an adult HTx center. It does not include data on children who were listed but never underwent HTx.

PediMACS is a registry that is a key data source for pediatric VAD research in North America, with increasing annual enrollment of patients and devices since it began collecting data in 2012.[6] It includes detailed pre-VAD patient characteristics, device-specific information, and VAD-related AEs, which are not available in PHTS. PediMACS enrolls children who are <19 years at the time of implant; otherwise, they are entered into its adult corollary, the INTERMACS database. Patients are followed until they reach an outcome of death, HTx, or recovery/explant.

The Data Coordinating Center (DCC) at the University of Alabama linked the PHTS dataset with the publicly available NHLBI PediMACS datasets through 12/13/2017. Through an agreement with PHTS, a limited data set of cross-linked patients was obtained. All analyses were conducted independently by the authors and not in collaboration with the PHTS. Because of the retrospective nature of the study, analyzing deidentified data from a publicly available dataset, Institutional Review Board approval was waived.

Study Population

We included all patients <19 years old who underwent VAD implant at centers enrolled in both PediMACS and PHTS, between 9/1/2012 and 12/31/2017. Patients were excluded if they were not enrolled in both registries, if they did not undergo VAD implantation prior to HTx, or if they died prior to HTx. Patients were followed until death or through the duration that they were in the PHTS database.

Patients were divided into two groups based on the duration of VAD support prior to HTx, <30 days (shorter duration) or ≥30 days (longer duration). The time point of 30 days was selected because of the known center practice variation regarding immediate vs. delayed acceptance of HTx donor offers after VAD. Among centers that have a set waiting period, we anticipated that the shortest waiting time would be 30 days.

Study Variables and Outcomes

Baseline information was obtained from PHTS, including demographics, underlying cardiac diagnosis (cardiomyopathy vs. single or biventricular CHD vs. myocarditis), recipient allosensitization status (highly allosensitized, defined as calculated panel reactive antibodies ≥10%) and UNOS listing

status (1A, 1B, 2, or 7) at the time of both HTx listing and HTx surgery. PHTS also provided detailed information on the HTx hospitalization, including mechanical ventilation and vasoactive support prior to HTx, renal and hepatic function at the time of HTx surgery and duration of hospitalization after HTx.

VAD data were obtained from PediMACS, including patient size and renal and hepatic function at the time of VAD implant, as well as VAD support type (LVAD, referring to biventricular circulation with VAD in the systemic ventricle; RVAD, biventricular circulation with VAD in the subpulmonary position; SVAD, single ventricle circulation with VAD in the systemic ventricle; and BiVAD or TAH, biventricular assist devices or total artificial heart, respectively). VAD classification was defined as intracorporeal continuous flow (ICF), paracorporeal continuous flow (PCF) and paracorporeal pulsatile flow (PPF). Additional VAD data included serious AEs on VAD support, specifically bleeding, device malfunction/pump thrombosis, infection, and neurologic dysfunction.

The primary outcomes were one-year post-HTx mortality and post-HTx hospital LOS. The secondary outcomes were post-HTx rejection, infections, and renal failure in the first year after HTx, as defined by PHTS.

Statistical Analysis

Statistical analyses were performed using SAS v9.4 (Cary, North Carolina, USA), and significance was evaluated two-sided 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. ≥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, inverse probability of treatment weighting (IPTW) using propensity scores was used to control for potential confounders and baseline differences between groups.[39] The propensity score was estimated using a logistic regression

model in which treatment assignment (<30 days vs. ≥30 days, with ≥30 days as the reference group) was regressed on 7 variables, chosen *a priori*, which were thought to be associated with VAD group and included: age at VAD initiation (treated as categorical), recipient blood type, cardiac diagnosis, VAD support type, allosensitization status, mechanical ventilation, and vasoactive support pre-HTx.

To stabilize the weights, IPTW scores were divided by the mean propensity score of its respective VAD duration group and were truncated at the 1st and 99th percentile. The standardized mean difference (SMD) 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 SMD <0.20 after propensity scoring, referred to as "weighted," achieved satisfactory balance.

For the primary outcome of one-year post-HTx mortality, weighted Cox proportional hazards 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. The Cox models were adjusted for adverse event rate in each group, calculated as the number of AEs in the first occurring within the first 30 days of VAD implant.

To compare the effect of VAD duration 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 two-sample t-test on the ranked data.

Cumulative incidence curves were generated for the secondary outcomes of infection, rejection, and renal failure, with death treated as a competing risk.

Results:

A total of 271 linked patients from PHTS and PediMACS met criteria to be included in the linkage analysis, in whom a total of 333 devices were implanted prior to HTx. Among this group, 60 patients (22%) had a VAD for <30 days before HTx and 211 patients (88%) had a VAD for ≥30 days prior to HTx. The median VAD duration was 76 days (IQR 34-146).

Baseline Characteristics

At the time of VAD implant, several demographic variables were similar between the <30 and ≥30 days VAD groups, including age distribution, sex, and race, but there were also important differences (Table 1). There was a higher prevalence of blood type O in the ≥30 days group (54% vs. 33% in the <30 days group, p=0.02). Allosensitization was more prevalent in the ≥30 days group (25% vs. 22% in the <30 days group, p=0.02). There was no difference based on underlying cardiac diagnosis (p=0.9), VAD support type (p=0.9), VAD classification (p=0.5), or UNOS status at time of listing (p=0.1) between groups. Baseline renal and hepatic function were similar between groups, while the heart failure markers of brain natriuretic peptide (BNP) and N-terminal (NT) pro-hormone BNP were significantly higher in the <30 days group (Supplemental Table 2).

A total of 187 AEs occurred in the first 30 days after VAD implant among 111 patients and a total of 116 devices (Table 2). The overall weighted AE rate per patient within the first 30 days after VAD implant was lower in the <30 days group than in the ≥30 days group (0.42 vs. 0.78, p=0.02). There were no statistical differences in the individual AEs of bleeding, device malfunction infection, or neurological dysfunction, though all rates were lower in the <30 days group.

At the time of HTx, there were additional differences between groups. The <30 days group had a median waitlist time of 20 days (IQR 11-45 days), while the ≥30 days group had a median waitlist time of 89 days (IQR 52-170 days), p<0.001. Patients in the <30 days group were sicker, with a higher prevalence of mechanical ventilation (33% vs. 7% in ≥30 days, p<0.001), vasoactive support (60% vs. 24%, p<0.001), and ICU status (76% vs. 52%, p<0.001). There were few outpatients at the time of HTx across the entire cohort; all patients in the <30 days group remained hospitalized at the time of HTx, while 86% of the ≥30 days group was hospitalized at HTx (p=0.002). Both unweighted and propensity score-

weighted laboratory values were similar at the time of HTx, in the <30 days group, or at 30 days post-VAD implant in the ≥30 days group (Table 3).

Primary Outcomes

There were 15 deaths in the first year post-HTx, with two deaths (3.3%) in the <30 days group and 13 deaths (6.2%) in the ≥30 days group. A weighted Kaplan-Meier curve, which accounted for baseline differences between groups, as well as mechanical ventilation and vasoactive support at the time of HTx, demonstrated no significant difference in one-year post-HTx mortality (log-rank p=0.38, Figure 1). A Cox proportional hazards model, adjusted for 30-day AE rate while on VAD support, demonstrated a non-significant mortality hazard ratio of 0.43 for the <30 days vs. ≥30 days group (95% CI 0.07-2.70, p=0.37).

There was no significant difference in post-HTx LOS between groups, with a median LOS of 21 vs. 18 days in the <30 vs. ≥30 days groups, p=0.54 (Supplemental Table 3).

Secondary Outcomes

By the end of the first year post-HTx, there was a 20.6% incidence of infection in the <30 days group and 19.6% incidence in the ≥30 days group (p=0.9, Supplemental Table 4). The incidence of rejection was also similar between groups (24.2% in <30 days vs. 22.8% in ≥30 days, p=0.8), as was the incidence of renal failure (1.7% <30 days vs. 3.4% ≥30 days, p=0.5, Figures 2-4).

Discussion:

In this analysis, we linked patients between the two largest pediatric HTx and VAD registries in North America, PHTS and PediMACS, to examine the effect of VAD duration on post-HTx outcomes. By using propensity score methods to account for baseline demographic differences, AEs while on VAD support, and markers of illness severity at the time of HTx, we found a lower hazard ratio of one-year post-HTx mortality among patients on VAD support for <30 days, which was not statistically significant, and no significant difference in the post-HTx hospital LOS between patients on VAD support for <30

days vs. ≥30 days. We further found no difference in the secondary outcomes of infection, rejection, or renal failure in the first year after HTx between the two VAD duration groups.

These findings differ from those seen in prior studies, including a prior analysis from PHTS alone that demonstrated a one-year survival benefit for patients who remained on VAD support for ≥30 days prior to HTx.[29] The difference in findings between the PHTS study and this linkage analysis may be related to sample size as well as a difference in eras examined, with the PHTS study examining more than 1,000 patients between 1993-2018, as opposed to 271 patients between 2012-2018 in the current study. The current study thus may not have been adequately powered to detect significant differences. Further, changes to VAD management, including patient selection and device availability, may be reflected in the differences seen between the two studies. Finally, the PHTS study did not include data on the VAD course and complications for each patient. In this PHTS-PediMACS linkage study, we expected that patients in the <30 days group would be more likely to have had VAD AEs, potentially prompting centers to accept earlier donor offers.[10] However, the AE rate in the <30 days group was approximately half of the AE rate seen in the ≥30 days group, suggesting that AEs were not the primary driver for HTx after a shorter duration of VAD support.

We were also able to account for markers of illness severity that can affect outcomes. Despite a higher prevalence of both mechanical ventilation and vasoactive support at the time of HTx in the <30 days group compared to the ≥30 days group, one-year post-HTx mortality was not significantly different between the two VAD duration groups. These result contrasts with the findings of the Medicare study that showed improved outcomes for adults who remain on VAD support for 31 days to one year before HTx.[26] It is key to note that the incidence of post-HTx mortality in our study was infrequent, occurring in only 15 patients out of the total cohort, and only two of the 60 patients in the <30 days group. The rarity of this event potentially limits interpretation of our findings. However, it is also notable that laboratory markers of renal and hepatic function at approximately 30 days post-VAD implant were similar between the two groups, suggesting that at least some organ recovery had taken place within this short duration of time. These findings differ from those seen in the UNOS study that demonstrated superior renal function in

children that had been on VAD support for longer durations.[15] While the current study provides more granular data than the Medicare and UNOS datasets, it is limited by a markedly smaller sample size, which constrains the ability to draw conclusions.

We had also hypothesized that patients who were on VAD support for longer durations would be healthier at the time of HTx, potentially reducing the risk of post-HTx complications. Renal failure after HTx, for instance, is likely influenced by the severity of renal dysfunction prior to HTx, as well as the effects of cardiopulmonary bypass and nephrotoxic medications used after HTx.[37] In this study, we demonstrated similar degrees of renal recovery in the first 30 days after VAD implant for the two VAD duration groups, which likely explains the low incidence of renal failure post-HTx in both groups. Further, the cumulative incidences of post-HTx infection and rejection, two of the most common reasons for graft failure within the first year after HTx, were similar between the two VAD duration groups.[7, 30] Given the lack of difference in one-year post-HTx survival based on VAD duration, it is not surprising that the two groups faced similar incidences of all secondary outcomes that we examined.

The similarity of post-HTx mortality, hospital LOS, and complications in patients with VAD durations less than and greater than 30 days therefore questions the need for set waiting times on VAD support prior to HTx. While prior studies have shown improved outcomes, including better survival, in patients who remain on VAD support for longer durations before HTx, this study was able to account for AEs that may attenuate that benefit.[10, 11, 40] It is not clear if those in the <30 days group simply had fewer complications while on VAD support, or if centers chose to wait for AE resolution prior to HTx, leading to a higher AE rate in the ≥30 days group. Additionally, our data show that patients can achieve renal and hepatic recovery, based on laboratory results, within one month of VAD support. Of note, these findings are influenced by the high prevalence of mechanical ventilation and vasoactive support in patients who are on VAD support for <30 days prior to HTx. It may therefore be prudent to look at markers of heart failure recovery other than VAD duration, such as end-organ recovery and functional status, which may not always correlate with time from VAD, to help determine HTx timing. With careful patient selection,

centers may therefore choose to proceed with a strategy of listing for HTx soon after VAD, as an obligatory waiting period may not have significant benefit in the overall patient outcome.

Limitations:

This registry study has inherent limitations secondary to its retrospective nature, limiting the ability to identify causation, which we addressed with the use of propensity score methods. Because of the inclusion criteria that patients needed to be enrolled in both PHTS and PediMACS, the sample size is smaller than in similar studies, although it is the largest of the linkage analyses between these two registries to date. It therefore may not have been adequately powered to detect a difference. Further, data entry for this study was completed at the end of 2017. The number of VAD implants, as well as centers enrolled into PediMACS, has increased during the last five years, as has center comfort with VADs in more complex patient populations.[20] More recent data would both increase the sample size and potentially change results. Finally, this study is unable to account for patients who died prior to receiving a HTx; their degree of end-organ recovery and VAD AEs are not included in either of the VAD duration groups, which may also have affected results.

Conclusions:

In this linkage analysis between PHTS and PediMACS, there was no significant difference in post-HTx mortality, hospital LOS, and post-HTx infection, rejection, and renal failure between patients on VAD support for <30 and ≥30 days. This study accounted for VAD-specific complications, such as AEs, which can affect outcomes, and demonstrated a lower AE rate in the <30 days group. Centers may therefore reconsider the need to set a mandatory waiting period before listing select VAD patients for HTx, and identify markers of surgical and end-organ recovery that suggest readiness for HTx.

References:

1. Denfield SW, Azeka E, Das B, Garcia-Guereta L, Irving C, Kemna M, Reinhardt Z, Thul J, Dipchand AI, Kirk R, Davies RR and Miera O. Pediatric cardiac waitlist mortality-Still too high. *Pediatr Transplant*. 2020;24:e13671.
2. Mah D, Singh TP, Thiagarajan RR, Gauvreau K, Piercey GE, Blume ED, Fynn-Thompson F and Almond CS. Incidence and risk factors for mortality in infants awaiting heart transplantation in the USA. *J Heart Lung Transplant*. 2009;28:1292-8.
3. Almond CSD, Thiagarajan RR, Piercey GE, Gauvreau K, Blume ED, Bastardi HJ, Fynn-Thompson F and Singh TP. Waiting list mortality among children listed for heart transplantation in the United States. *Circulation*. 2009;119:717-727.
4. Singh TP, Almond CS, Piercey G and Gauvreau K. Trends in wait-list mortality in children listed for heart transplantation in the United States: era effect across racial/ethnic groups. *Am J Transplant*. 2011;11:2692-9.
5. Sutcliffe DL, Pruitt E, Cantor RS, Godown J, Lane J, Turrentine MW, Law SP, Lantz JL, Kirklin JK, Bernstein D and Blume ED. Post-transplant outcomes in pediatric ventricular assist device patients: A PediMACS-Pediatric Heart Transplant Study linkage analysis. *J Heart Lung Transplant*. 2018;37:715-722.
6. Adachi I, Peng DM, Hollander SA, Simpson KE, Davies RR, Jacobs JP, VanderPluym CJ, Fynn-Thompson F, Wells DA, Law SP, Amdani S, Cantor R, Koehl D, Kirklin JK, Morales DLS, Rossano JW and Pedimacs I. Sixth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report. *Ann Thorac Surg*. 2022.
7. Rossano JW, Cherikh WS, Chambers DC, Goldfarb S, Khush K, Kucheryavaya AY, Levvey BJ, Lund LH, Meiser B, Yusen RD, Stehlik J, International Society for H and Lung T. The Registry of the International Society for Heart and Lung Transplantation: Twentieth Pediatric Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant*. 2017;36:1060-1069.
8. Morales DLS, Rossano JW, VanderPluym C, Lorts A, Cantor R, St Louis JD, Koeh D, Sutcliffe DL, Adachi I, Kirklin JK, Rosenthal DN, Blume ED and Pedimacs I. Third Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report: Preimplant Characteristics and Outcomes. *Ann Thorac Surg*. 2019;107:993-1004.
9. Blume ED, VanderPluym C, Lorts A, Baldwin JT, Rossano JW, Morales DLS, Cantor RS, Miller MA, St Louis JD, Koehl D, Sutcliffe DL, Eghtesady P, Kirklin JK, Rosenthal DN and Pedimacs I. Second annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) report: Pre-implant characteristics and outcomes. *J Heart Lung Transplant*. 2018;37:38-45.
10. Rosenthal DN, Almond CS, Jaquiss RD, Peyton CE, Auerbach SR, Morales DR, Epstein DJ, Cantor RS, Kormos RL, Naftel DC, Butts RJ, Ghanayem NS, Kirklin JK and Blume ED. Adverse events in children implanted with ventricular assist devices in the United States: Data from the Pediatric Interagency Registry for Mechanical Circulatory Support (PediMACS). *J Heart Lung Transplant*. 2016;35:569-77.
11. Lorts A, Eghtesady P, Mehegan M, Adachi I, Villa C, Davies R, Gossett JG, Kanter K, Alejos J, Koehl D, Cantor RS and Morales DLS. Outcomes of children supported with devices labeled as "temporary" or short term: A report from the Pediatric Interagency Registry for Mechanical Circulatory Support. *J Heart Lung Transplant*. 2018;37:54-60.
12. Almond CS, Morales DL, Blackstone EH, Turrentine MW, Imamura M, Massicotte MP, Jordan LC, Devaney EJ, Ravishankar C, Kanter KR, Holman W, Kroslowitz R, Tjossem C, Thuita L, Cohen GA, Buchholz H, St Louis JD, Nguyen K, Niebler RA, Walters HL, 3rd, Reemtsen B, Wearden PD, Reinhartz O, Guleserian KJ, Mitchell MB, Bleiweis MS, Canter CE and Humpl T. Berlin Heart EXCOR pediatric ventricular assist device for bridge to heart transplantation in US children. *Circulation*. 2013;127:1702-11.

13. Adachi I, Zea-Vera R, Tunuguntla H, Denfield SW, Elias B, John R, Teruya J and Fraser CD, Jr. Centrifugal-flow ventricular assist device support in children: A single-center experience. *J Thorac Cardiovasc Surg*. 2019;157:1609-1617 e2.
14. VanderPluym CJ, Adachi I, Niebler R, Griffiths E, Fynn-Thompson F, Chen S, O'Connor MJ, Machado D, Hawkins B, Bleiweis MS, Koehl DA, Cantor RS, Morales D and Lorts A. Outcomes of children supported with an intracorporeal continuous-flow left ventricular assist system. *J Heart Lung Transplant*. 2019;38:385-393.
15. Riggs KW, Zafar F, Lorts A, Villa CR, Bryant R, 3rd and Morales DLS. Optimizing Postcardiac Transplantation Outcomes in Children with Ventricular Assist Devices: How Long Should the Bridge Be? *ASAIO J*. 2020;66:787-795.
16. Bates A, Buchholz H, Freed D, MacArthur R, Pi DT and Conway J. Bivalirudin Experience in a Heterogeneous Ventricular Assist Device Population. *ASAIO J*. 2020;66:677-682.
17. Bearl DW, Feingold B, Lorts A, Rosenthal D, Zafar F, Conway J, Elias B, Tunuguntla H, Thurm C, Amdani S, Jaworski N and Godown J. Discharge and Readmissions After Ventricular Assist Device Placement in the US Pediatric Hospitals: A Collaboration in ACTION. *ASAIO J*. 2020.
18. Peng DM, Rosenthal DN, Zafar F, Smyth L, VanderPluym CJ and Lorts A. Collaboration and new data in ACTION: a learning health care system to improve pediatric heart failure and ventricular assist device outcomes. *Transl Pediatr*. 2019;8:349-355.
19. Peng DM, Koehl DA, Cantor RS, McMillan KN, Barnes AP, McConnell PI, Jordan J, Andersen ND, St Louis JD, Maeda K, Kirklin JK and Kindel SJ. Outcomes of children with congenital heart disease implanted with ventricular assist devices: An analysis of the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs). *J Heart Lung Transplant*. 2019;38:420-430.
20. Adachi I, Peng DM, Hollander SA, Simpson KE, Davies RR, Jacobs JP, VanderPluym CJ, Fynn-Thompson F, Wells DA, Law SP, Amdani S, Cantor R, Koehl D, Kirklin JK, Morales DLS, Rossano JW and Pedimacs I. Sixth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report: The Society Of Thoracic Surgeons Pedimacs Annual Report. *Ann Thorac Surg*. 2022.
21. Thrush PT, Pahl E, Naftel DC, Pruitt E, Everitt MD, Missler H, Zangwill S, Burch M, Hoffman TM, Butts R and Mahle WT. A multi-institutional evaluation of antibody-mediated rejection utilizing the Pediatric Heart Transplant Study database: Incidence, therapies and outcomes. *J Heart Lung Transplant*. 2016;35:1497-1504.
22. Amdani S, Boyle G, Saarel EV, Godown J, Liu W, Worley S and Karamlou T. Waitlist and Post-Heart Transplant Outcomes for Children With Nondilated Cardiomyopathy. *Ann Thorac Surg*. 2021;112:188-196.
23. Gammie JS, Edwards LB, Griffith BP, Pierson RN, 3rd and Tsao L. Optimal timing of cardiac transplantation after ventricular assist device implantation. *J Thorac Cardiovasc Surg*. 2004;127:1789-99.
24. Gulati G, Ouyang D, Ha R and Banerjee D. Optimal timing of same-admission orthotopic heart transplantation after left ventricular assist device implantation. *World J Cardiol*. 2017;9:154-161.
25. John R, Pagani FD, Naka Y, Boyle A, Conte JV, Russell SD, Klodell CT, Milano CA, Rogers J, Farrar DJ and Frazier OH. Post-cardiac transplant survival after support with a continuous-flow left ventricular assist device: impact of duration of left ventricular assist device support and other variables. *J Thorac Cardiovasc Surg*. 2010;140:174-81.
26. Brown CR, Khurshan F, Chen Z, Groeneveld PW, McCarthy F, Acker M, Rame JE and Desai N. Optimal timing for heart transplantation in patients bridged with left ventricular assist devices: Is timing of the essence? *J Thorac Cardiovasc Surg*. 2019;157:2315-2324 e4.
27. Grady KL, Naftel D, Stevenson L, Dew MA, Weidner G, Pagani FD, Kirklin JK, Myers S, Baldwin T and Young J. Overall quality of life improves to similar levels after mechanical circulatory support regardless of severity of heart failure before implantation. *J Heart Lung Transplant*. 2014;33:412-21.
28. Grady KL, Fazeli PL, Kirklin JK, Pamboukian SV and White-Williams C. Factors Associated With Health-Related Quality of Life 2 Years After Left Ventricular Assist Device Implantation: Insights From INTERMACS. *J Am Heart Assoc*. 2021;10:e021196.

29. Butto A, Mao CY, Wright L, Wetzel M, Kelleman MS, Carboni MP, Dipchand AI, Knecht KR, Reinhardt Z, Sparks JD, Villa C and Mahle WT. Relationship of ventricular assist device support duration with pediatric heart transplant outcomes. *J Heart Lung Transplant*. 2022;41:61-69.
30. Dipchand AI, Kirk R, Mahle WT, Tresler MA, Naftel DC, Pahl E, Miyamoto SD, Blume E, Guleserian KJ, White-Williams C and Kirklin JK. Ten yr of pediatric heart transplantation: a report from the Pediatric Heart Transplant Study. *Pediatr Transplant*. 2013;17:99-111.
31. Bock MJ, Pahl E, Rusconi PG, Boyle GJ, Parent JJ, Twist CJ, Kirklin JK, Pruitt E and Bernstein D. Cancer recurrence and mortality after pediatric heart transplantation for anthracycline cardiomyopathy: A report from the Pediatric Heart Transplant Study (PHTS) group. *Pediatr Transplant*. 2017;21.
32. Schumacher KR, Almond C, Singh TP, Kirk R, Spicer R, Hoffman TM, Hsu D, Naftel DC, Pruitt E, Zamberlan M, Canter CE, Gajarski RJ and Investigators PSG. Predicting graft loss by 1 year in pediatric heart transplantation candidates: an analysis of the Pediatric Heart Transplant Study database. *Circulation*. 2015;131:890-8.
33. Sparks JD, Cantor RS, Pruitt E, Kirklin JK, Carboni M, Dreyer W, Kindel S, Ryan TD and Morrow WR. New-onset diabetes after pediatric heart transplantation: A review of the Pediatric Heart Transplant Study. *Pediatr Transplant*. 2019;23:e13476.
34. Morales DLS, Adachi I, Peng DM, Sinha P, Lorts A, Fields K, Conway J, St Louis JD, Cantor R, Koehl D, Jacobs JP, Kirklin JK, Blume ED, Rossano JW and Pedimacs I. Fourth Annual Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs) Report. *Ann Thorac Surg*. 2020;110:1819-1831.
35. Baez Hernandez N, Kirk R, Sutcliffe D, Davies R, Jaquiss R, Gao A, Zhang S and Butts RJ. Utilization and outcomes in biventricular assist device support in pediatrics. *J Thorac Cardiovasc Surg*. 2019.
36. Butto A, Teele SA, Sleeper LA, Thrush PT, Philip J, Lu M, Cantor RS and Rossano JW. The impact of pre-implant illness severity on the outcomes of pediatric patients undergoing durable ventricular assist device. *J Heart Lung Transplant*. 2020;39:666-674.
37. Hollander SA, Cantor RS, Sutherland SM, Koehl DA, Pruitt E, McDonald N, Kirklin JK, Ravekes WJ, Ameduri R, Chrisant M, Hoffman TM, Lytrivi ID and Conway J. Renal injury and recovery in pediatric patients after ventricular assist device implantation and cardiac transplant. *Pediatr Transplant*. 2019;23:e13477.
38. Auerbach SR, Cantor RS, Bradford TT, Bock MJ, Skipper ER, Koehl DA, Butler K, Alejos JC, Edens RE and Kirklin JK. The Effect of Infectious Complications During Ventricular Assist Device Use on Outcomes of Pediatric Heart Transplantation. *ASAIO J*. 2022;68:287-296.
39. Austin PC and Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661-79.
40. Auerbach SR, Richmond ME, Schumacher KR, Lopez-Colon D, Mitchell MB, Turrentine MW, Cantor RS, Niebler RA and Eghtesady P. Infectious complications of ventricular assist device use in children in the United States: Data from the Pediatric Interagency Registry for Mechanical Circulatory Support (Pedimacs). *J Heart Lung Transplant*. 2018;37:46-53.

Tables and Figures

Table 1. Baseline Characteristics Between VAD Duration Groups.

Variable	Overall n=271	< 30 days n=60	≥ 30 days n=211	p value
Age at VAD initiation, n (%)				
<1 year	52 (19.2)	14 (23.3)	38 (18.0)	
1-12 years	104 (38.4)	20 (33.3)	84 (39.8)	0.545
>12 years	115 (42.4)	26 (43.3)	89 (42.2)	
Female Sex, n (%)	111 (41.0)	26 (43.3)	85 (40.3)	0.672
Race, n (%)				
White	159 (58.7)	33 (55.0)	126 (59.7)	
Black	64 (23.6)	21 (35.0)	43 (20.4)	0.067
Asian	5 (1.8)	1 (1.7)	4 (1.9)	
Other	43 (15.9)	5 (8.3)	38 (18.0)	
Recipient Blood Type, n (%)				
O	133 (49.1)	20 (33.3)	113 (53.6)	
A	99 (36.5)	26 (43.3)	73 (34.6)	0.019
B	28 (10.3)	9 (15.0)	19 (9.0)	
AB	11 (4.1)	5 (8.3)	6 (2.8)	
Cardiac diagnosis, n (%)				
Cardiomyopathy*	203 (74.9)	46 (76.7)	157 (74.4)	0.919
Congenital heart disease†	52 (19.2)	11 (18.3)	41 (19.4)	
Myocarditis	16 (5.9)	3 (5.0)	13 (6.2)	
VAD support type, n (%)‡				
LVAD	202 (74.5)	46 (76.7)	156 (73.9)	
RVAD	4 (1.5)	1 (1.7)	3 (1.4)	0.926
BiVAD/TAH§	36 (13.3)	8 (13.3)	28 (13.3)	
SVAD	29 (10.7)	5 (8.3)	24 (11.4)	

Variable	Overall n=271	< 30 days n=60	≥ 30 days n=211	p value
VAD classification, n (%)				
Intracorporeal continuous	151 (55.7)	32 (53.3)	119 (56.4)	
Paracorporeal continuous	30 (11.1)	9 (15.0)	21 (10.0)	0.532
Paracorporeal pulsatile	88 (32.5)	18 (30.0)	70 (33.2)	
Other	2 (0.7)	1 (1.7)	1 (0.5)	
Allosensitization status, n (%)				
Allosensitized	66 (24.4)	13 (21.7)	53 (25.1)	0.021
Not allosensitized	176 (64.9)	46 (76.7)	130 (61.6)	
Data unavailable	29 (10.7)	1 (1.7)	28 (13.3)	
UNOS Status at HTx listing, n (%)				
1A	229 (84.5)	52 (86.7)	177 (83.9)	
1B	18 (6.6)	6 (10.0)	12 (5.7)	0.195
2	14 (5.2)	2 (3.3)	12 (5.7)	
7	10 (3.7)	0 (0)	10 (4.7)	
Pre-HTx Factors, n (%)				
Mechanical Ventilation	35 (12.9)	20 (33.3)	15 (7.1)	<0.001
Vasoactive Support	87 (32.1)	36 (60.0)	51 (24.2)	<0.001
Hospitalized at Time of HTx	241 (89.3)	60 (100.0)	181 (86.2)	0.002
ICU at Time of HTx	131 (58.0)	45 (76.3)	86 (51.5)	<0.001
Days from VAD to HTx, median (IQR)‖	74 (34-141)	12 (8-21)	93.5 (58-161)	<0.001
Days from listing to HTx, median (IQR)	75.0 (37-144)	20 (11.5-45)	89 (52-170)	<0.001

* Dilated cardiomyopathy, n=177. Restrictive cardiomyopathy, n=6. Hypertrophic cardiomyopathy, n=7.

† Single ventricle CHD, n=29.

‡LVAD, biventricular circulation with VAD in systemic ventricle. RVAD, biventricular circulation with VAD in subpulmonary ventricle. BiVAD, biventricular VAD. TAH, total artificial heart. SVAD, single ventricular circulation with VAD in systemic ventricle.

§ BiVAD, n=34. TAH, n=2.

‖ n=258

Table 2. Adverse Event Rate in First 30 Days of VAD Support

30-Day Adverse Events per patient	Overall LS-Mean (95% CI)	< 30 days LS-Mean (95% CI)	≥ 30 days LS-Mean (95% CI)	p-value
Unweighted				
All	0.69 (0.56-0.82)	0.40 (0.25-0.64)	0.77 (0.63-0.94)	**0.011**
Bleeding	0.26 (0.19-0.33)	0.18 (0.10-0.35)	0.28 (0.21-0.38)	0.229
Device Malfunction and/or Pump Thrombosis	0.20 (0.13-0.27)	0.10 (0.04-0.26)	0.22 (0.15-0.33)	0.131
Infection	0.10 (0.06-0.15)	0.03 (0.01-0.14)	0.12 (0.08-0.19)	0.086
Neurological Dysfunction	0.13 (0.08-0.18)	0.08 (0.03-0.22)	0.14 (0.09-0.21)	0.310
Weighted				
All	0.75 (0.61-0.88)	0.42 (0.25 – 0.68)	0.78 (0.64 – 0.95)	**0.018**
Bleeding	0.29 (0.21-0.36)	0.19 (0.10-0.38)	0.29 (0.21-0.38)	0.286
Device Malfunction and/or Pump Thrombosis	0.21 (0.14-0.29)	0.10 (0.04-0.30)	0.23 (0.15-0.34)	0.174
Infection	0.11 (0.07-0.16)	0.03 (0.01-0.15)	0.13 (0.08-0.19)	0.097
Neurological Dysfunction	0.13 (0.09-0.18)	0.08 (0.03-0.22)	0.14 (0.10-0.21)	0.295

*Adverse events occurred in 116 devices in 111 patients in the first 30 days after VAD implant.

Table 3. Laboratory Studies Between Groups at Time of HTx or 30 Days Post-VAD.

Laboratory Value	N	Overall	<30 days*	≥30 days†	p-value
Unweighted, Median (IQR)					
BUN mg/dL	258	13 (9 – 21)	17 (10 – 23)	12 (9 – 20)	0.173
Creatinine mg/dL	258	0.45 (0.3-0.6)	0.49 (0.23-0.7)	0.41 (0.3-0.6)	0.367
ALT U/L	223	31 (21-48)	30.5 (20-54.5)	31 (21-47)	0.782
AST U/L	223	35 (26-60)	58.5 (34.5-98.5)	34 (25-53)	<0.001
Total Bilirubin mg/dL	202	0.6 (0.4-1)	0.9 (0.5-1.7)	0.6 (0.4-0.9)	0.002
BNP pg/mL or ng/L	75	352 (151-891)	1011 (611-2662)	301.5 (121-672)	0.004
NT-ProBNP	48	3455 (1279-7300)	8172 (2088-19748)	2329 (980-4722)	0.011
Weighted, Median (IQR)					
BUN mg/dL	258	12 (9-20)	13 (9-22)	12 (9-19)	0.173
Creatinine mg/dL	258	0.41 (0.27-0.6)	0 (0-1)	0 (0, 1)	0.718
ALT U/L	223	33 (21-48)	35 (23-77)	31 (21-47)	0.077
AST U/L	223	35 (26-57)	57 (36-105)	34 (25-52)	<0.001
Total Bilirubin mg/dL	202	0.6 (0.4-1)	1 (0-2)	1 (0-1)	0.190
BNP pg/mL or ng/L	75	348 (161.3-819)	753 (161-1077)	340 (151-672)	0.098
NT-ProBNP	48	2088 (914-5387)	2088 (756-6562)	2383 (980-5387)	0.790

BUN, blood urea nitrogen. ALT, alanine aminotransferase. AST, aspartate aminotransferase. BNP, brain natriuretic peptide. NT-ProBNP, N-terminal (NT)-pro hormone BNP.

* Labs from time of HTx in <30 days group

† Labs from 30 days post-VAD implant in ≥30 days group

Table 4. Weighted Cox Proportional Hazards Model for One-Year Post-HTx Mortality.

	Unadjusted HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
VAD Duration				
<30 days	0.38 (0.06 – 2.36)	0.298	0.43 (0.07 – 2.70)	0.368
≥30 days	Ref		Ref	
30-Day Adverse Event Rate[1]	1.39 (1.02 – 1.89)	0.037	1.37 (0.99 – 1.87)	0.051

[1]Rate of adverse events occurring in first 30 days of VAD implant.

Supplemental Table 1. Baseline Characteristics with Unadjusted and Adjusted SMD

Variable	Level	Overall n=271	<30 days n=60	≥30 days n=211	p-Value	Unadjusted SMD*	Adjusted SMD†
Age at VAD initiation	Less than 1 year	52 (19.2)	14 (23.3)	38 (18.0)	0.545	0.163	0.127
	1-12 years	104 (38.4)	20 (33.3)	84 (39.8)			
	Greater than 12 years	115 (42.4)	26 (43.3)	89 (42.2)			
Recipient Blood type	O	133 (49.1)	20 (33.3)	113 (53.6)	**0.019**	0.502	0.152
	A	99 (36.5)	26 (43.3)	73 (34.6)			
	B	28 (10.3)	9 (15.0)	19 (9.0)			
	AB	11 (4.1)	5 (8.3)	6 (2.8)			
Cardiac diagnosis	Cardiomyopathy	203 (74.9)	46 (76.7)	157 (74.4)	0.919	0.092	0.048
	Congenital Heart Disease	52 (19.2)	11 (18.3)	41 (19.4)			
	Myocarditis	16 (5.9)	3 (5.0)	13 (6.2)			
VAD support type	LVAD	202 (74.5)	46 (76.7)	156 (73.9)	0.926	0.155	0.115
	RVAD	4 (1.5)	1 (1.7)	3 (1.4)			
	BiVAD/TAH	36 (13.3)	8 (13.3)	28 (13.3)			
	SVAD	29 (10.7)	5 (8.3)	24 (11.4)			
Allosensitization status	Sensitized	66 (24.4)	13 (21.7)	53 (25.1)	**0.021**	0.507	0.140
	Not Sensitized	176 (64.9)	46 (76.7)	130 (61.6)			
	Data unavailable	29 (10.7)	1 (1.7)	28 (13.3)			
Mechanical ventilation		35 (12.9)	20 (33.3)	15 (7.1)	**<0.001**	0.082	-0.004
Vasoactive support		87 (32.1)	36 (60.0)	51 (24.2)	**<0.001**	0.082	-0.004

*Unadjusted Standardized Mean Difference (SMD) indicates difference between groups prior to propensity scoring.

†Adjusted SMD indicates difference between groups after propensity scoring; <0.20 indicates adequate balance.

Supplemental Table 2. Laboratory Values Prior to VAD Implant

Laboratory Value	N	Overall	<30 days	≥30 days	p-value
Unweighted, Median (IQR)*					
BUN (mg/dL)	271	20 (14-28)	20 (14-28.5)	20 (14-27)	0.828
Creatinine (mg/dL)	270	0.61 (0.40-0.90)	0.60 (0.40-0.90)	0.62 (0.40-0.90)	0.893
Total Bilirubin (mg/dL)	247	1.10 (0.70-1.80)	1.40 (0.77-2.30)	1.10 (0.70-1.70)	0.079
AST (u/L)	266	41 (28-93)	46 (22-124)	41 (28-91)	0.945
ALT (u/L)	266	43 (26-103)	52 (23-145)	42 (26-100)	0.522
Weighted, Median (IQR)*					
BUN (mg/dL)	271	20 (15-28)	21 (16-33)	20 (14-27)	0.563
Creatinine (mg/dL)	270	0.60 (0.40-0.90)	0.60 (0.43-0.9)	0.60 (0.39-0.9)	0.840
Total Bilirubin (mg/dL)	247	1.10 (0.70-1.80)	1.50 (0.90-2.10)	1.10 (0.70-1.70)	0.024
AST (u/L)	266	42 (28-109)	51 (27-125)	41 (28-94)	0.629
ALT (u/L)	266	43 (26-117)	58 (32-155)	42 (26-100)	0.117

BUN, blood urea nitrogen. ALT, alanine aminotransferase. AST, aspartate aminotransferase. *Missing n: Creatinine n=1; ALT n=5; AST U/L=5; Total Bilirubin n=24.

Supplemental Table 3. Post-Transplant Length of Stay.

	Median Days (IQR)	p value
Unweighted		0.223
<30 days on VAD	22 (14.5 – 42)	
≥ 30 days on VAD	18 (13 – 32)	
Weighted		0.535
<30 days on VAD	21 (14 – 46)	
≥ 30 days on VAD	18 (13 – 37)	

Supplemental Table 4. Cumulative Incidence of Infection, Rejection, and Renal Failure in First Year Post-Transplant.

	Events	Competing Events	Censored	Endpoint (95% CI)	p value*
Infection					
<30 VAD days	12	1	47	20.6% (11.26-31.77)	0.854
≥30 VAD days	40	9	162	19.6% (14.42-25.27)	
Rejection					
<30 VAD days	14	2	44	24.2% (14.04-35.92)	0.816
≥30 VAD days	47	11	153	22.8% (17.33-28.78)	
Renal Failure					0.508
<30 VAD days	1	2	57	1.7% (0.14-8.16)	
≥30 VAD days	7	10	194	3.4% (1.49-6.47)	

* Gray's k-sample test for equality of cumulative incidence functions

Figure 1. Weighted Kaplan-Meier Plot of One-Year Post-HTx Mortality by VAD Duration.

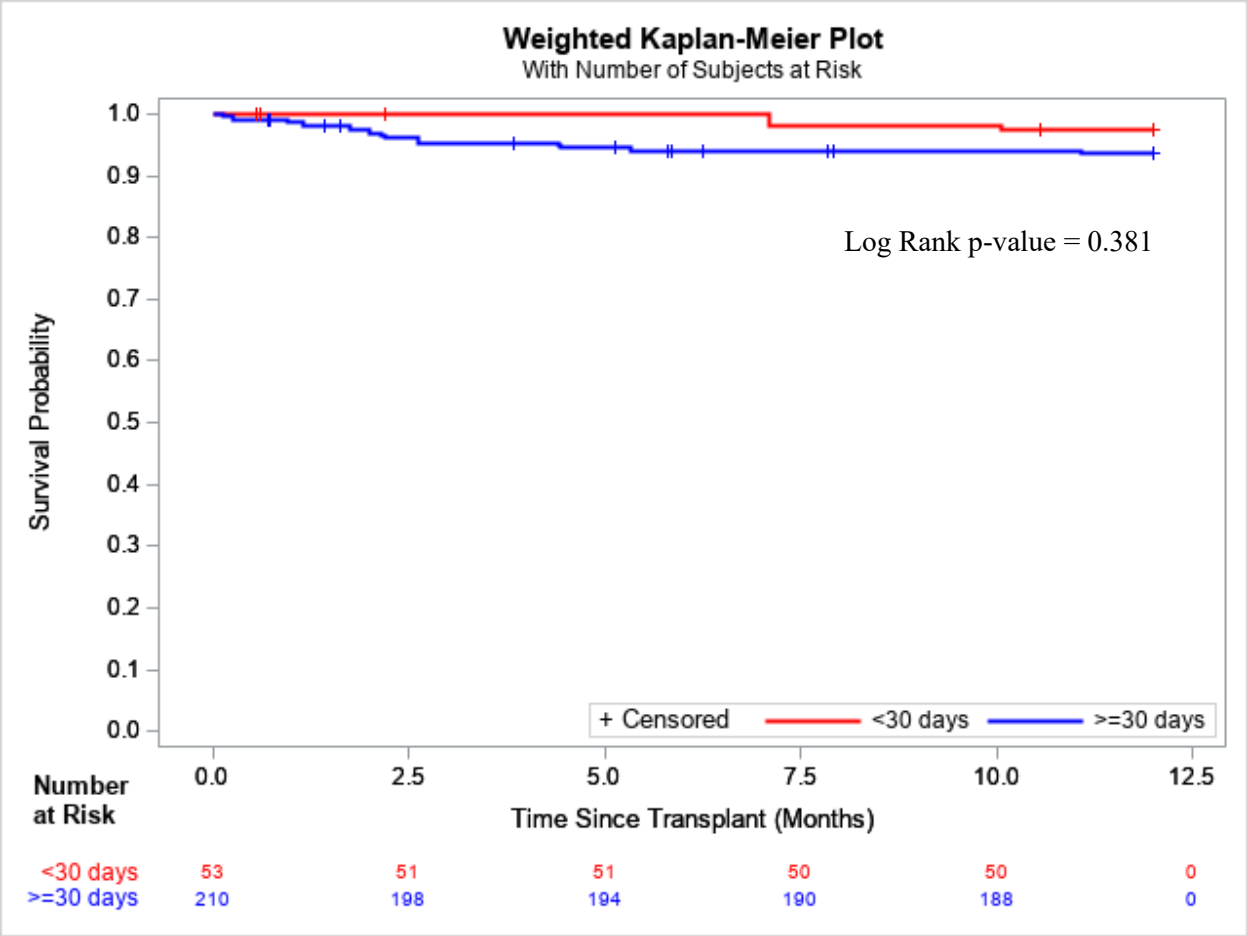
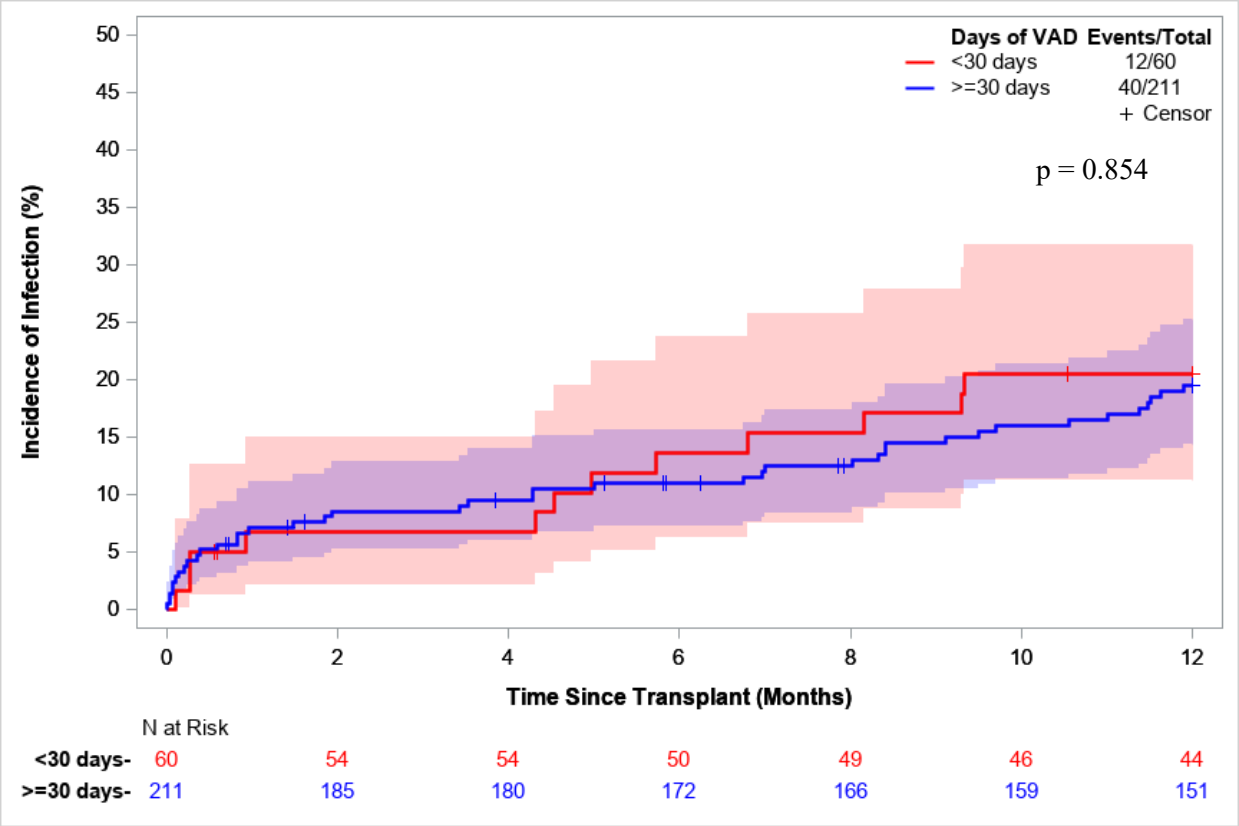
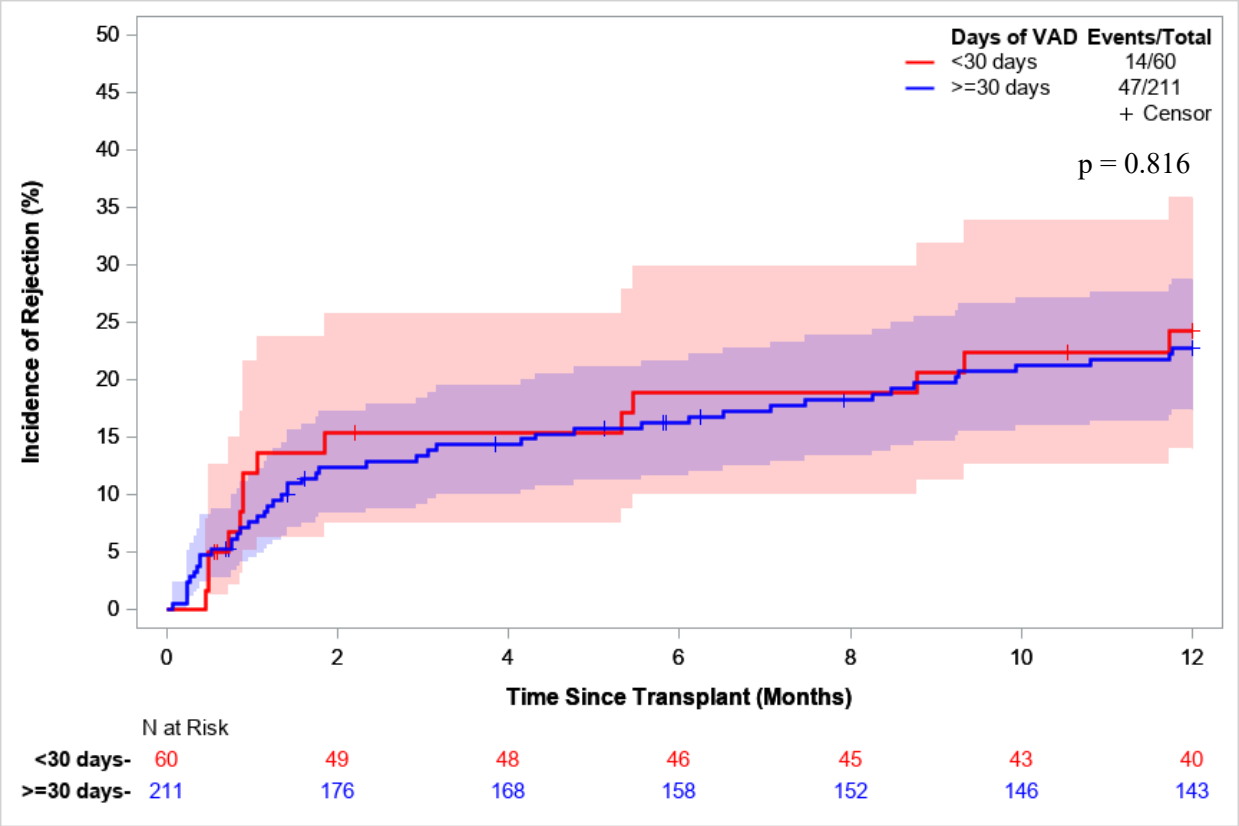


Figure 2. Cumulative Incidence of Infection in First Year Post-Transplant.



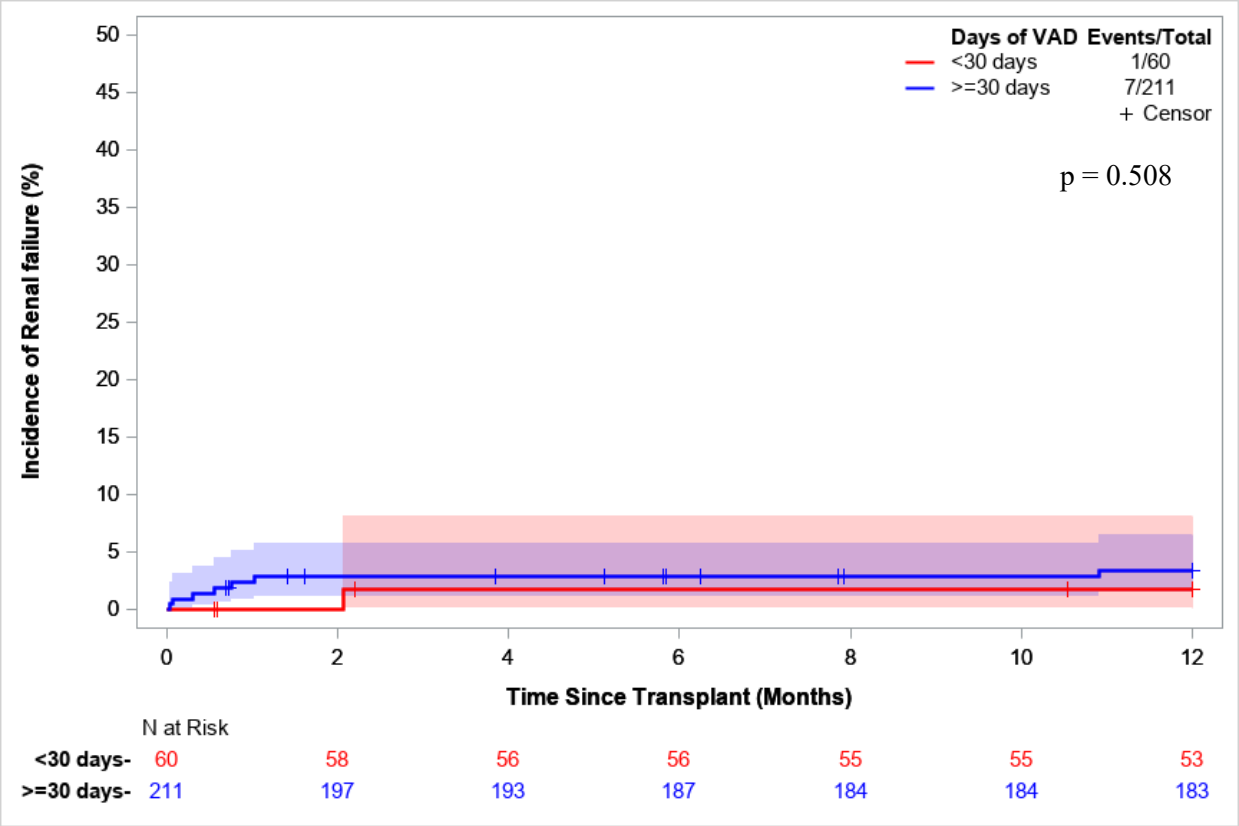
≥30 Days is the reference group. Death treated as a competing risk.

Figure 3. Cumulative Incidence of Rejection in First Year Post-Transplant.



≥30 Days is the reference group. Death treated as a competing risk.

Figure 4. Cumulative Incidence of Renal Failure in First Year Post-Transplant.



≥30 Days is the reference group. Death treated as a competing risk.