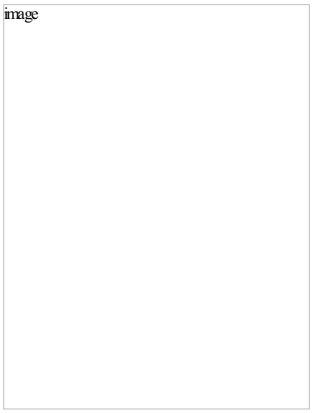


# Post-transplant outcomes in pediatric vad patients: A pedimacs-pediatric heart transplant study linkage analysis

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Title: POST-TRANSPLANT OUTCOMES IN PEDIATRIC VAD PATIENTS: A PEDIMACS-PEDIATRIC HEART TRANSPLANT STUDY LINKAGE ANALYSIS

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## Abstract:

**Background:** Pediatric Ventricular Assist Device (VAD) support as bridge to transplant has improved waitlist survival, but the effects of pre-implant status and VAD-related events on post-transplant outcomes have not been assessed. This study represents the first linkage analysis between Pedimacs and Pediatric Heart Transplant Study databases to determine the effects of VAD course on post-transplant outcomes.

**Methods:** Database linkage between 10/1/12–12/31/15 identified 147 transplanted VAD patients, the primary study group. The comparison cohort was composed of 630 PHTS patients without pre-transplant VAD support. The primary outcome was post-transplant survival, with secondary outcomes post-transplant length of stay, freedom from infection, and freedom from rejection.

**Results:** At implant, the VAD cohort was Intermacs profile 1 in 33 (23%), profile 2 in 89 (63%), and profile 3 in 14 (10%). The VAD cohort was older, larger, and less likely to have congenital heart disease ($p<0.0001$). However, they had greater requirements for inotrope and ventilator support and increased liver and renal dysfunction ($p<0.0001$), both of which normalized at transplant following device support. Importantly, there were no differences in 1-year post-transplant survival (96% vs 93%, $p=0.3$), freedom from infection (81% vs 79%, $p=0.9$), or freedom from rejection (71% vs 74%, $p=0.87$) between cohorts.

**Conclusion:** Pediatric VAD patients have post-transplant outcomes equal to that of medically supported patients despite greater pre-implant illness severity. Post-transplant survival, hospital length of stay, infection, and rejection were not affected by patient acuity at VAD implantation or VAD-related complications. Therefore VAD as bridge to transplant mitigates severity of illness in children.

## Background

From its origin, pediatric mechanical circulatory support has become an integral therapy in the management of pediatric heart failure as a bridge to transplantation (BTT).[1] This development has led to improved patient survival to transplantation; however, the effect of ventricular assist device (VAD) support on post-transplant outcomes has only been reported through small case studies, single device reviews, and limited datasets.[2-5]

Despite improved waitlist survival in VAD-supported patients, this group stands at a significant risk for development of a myriad of complications, most commonly bleeding, neurologic injury, infection, and device malfunction.[6] In adults, VAD-associated complications have been shown to decrease survival to transplant.[7, 8] Although robust analysis of pediatric VAD support has been reported, detailed VAD course as it relates to post-transplant outcomes has not been published.[9] The current study aimed to use a longitudinal cohort of pediatric VAD patients to examine post-transplant outcomes utilizing a linkage analysis of the Pedimacs and Pediatric Heart Transplant Study databases. Linkage of these two registries provides a unique opportunity to assess the relationship between VAD post-implant course and events with transplant outcomes in the first year. The primary outcome was post-transplant survival at one year conditional upon survival to transplant and secondary outcomes included post-transplant length of hospital stay freedom from infection, and freedom from rejection.



## Methods

The Interagency Registry for Mechanical Circulatory Support (Intermacs) is a United States national registry of all patients who undergo support with FDA-approved VADs. Pedimacs is the pediatric specific subgroup of Intermacs initiated on September 19, 2012. Pedimacs prospectively collects data pertaining to patients <19 years of age who undergo VAD implantation at 42 North American sites. Data collection includes events spanning the time from device implantation to

either transplant, recovery, or death. The Pediatric Heart Transplant Study (PHTS) is an event-driven database with participation from 52 international centers. PHTS prospectively collects data for patients <18 years of age who undergo heart transplant listing, and data collection includes events at time of listing, at time of transplant, and triggered events throughout post-transplant follow up.

This longitudinal study linked patients who underwent VAD implantation followed by heart transplantation and were included in both the Pedimacs registry as well as the PHTS database. Linkage was carried out between the dates of October 1, 2012 through December 31, 2015 utilizing indirect patient identifiers including VAD implant and explant dates, VAD and transplant center, and transplant date. The primary study group was composed of the resultant linked VAD-supported patients, and the comparison group was composed of all medically supported patients who underwent transplant in centers enrolled in both Pedimacs and PHTS. Patients were excluded if undergoing re-transplant or requiring ECMO support at transplant, and specifically medically supported patients were excluded if requiring VAD support during waitlist but not transplant. Adverse events in the VAD-supported group were identified using previously defined Intermacs/Pedimacs definitions and included neurologic dysfunction, infection, bleeding, and device malfunction. Post-transplant events of infection and rejection were characterized using PHTS definitions as previously described.[10, 11]

Categorical data were expressed as frequency with percent and were compared using chi-squared statistic or Fischer Exact test, as appropriate. Continuous data including age, BSA, and end-organ laboratory data were expressed as mean with standard deviation or median with interquartile range and were compared using independent t-test or Mann-Whitney U test, as appropriate. Renal function was assessed by calculating estimated glomerular filtration rate (eGFR) using the Schwartz formula with a modified "k" constant to correct for age and gender variations.[12] Waitlist duration and length of stay data were expressed as median with interquartile

range, and cohorts were compared using Mann-Whitney U test. Kaplan-Meier survival analysis using log-rank statistics was used to compare post-transplant outcomes of survival, freedom from infection, and freedom from rejection between groups.

## Results

### Patient Population

Between October 1, 2012 and December 31, 2015, 147 patients were identified in both the Pedimacs and PHTS databases as having undergone VAD implantation followed by transplantation. During this same time period, 630 patients were identified in the PHTS database from Pedimacs centers as having received only medical support followed by transplantation, comprising the comparison cohort. Details of the database linkage, the primary study cohort, and the comparison cohort are shown in Figure 1.

The 147 patients in the linkage cohort were a median age of 10.31 years old [2.37, 15.05] and had a heart disease etiology of CM in 108 (73%) and CHD in 25 (17%). Median duration of VAD support was 2.1 months [1.15, 3.78], and median waitlist time was 2.43 months [1.05, 4.4]. Detailed description of demographics and baseline clinical characteristics of the VAD-supported group at time of device implant (Table 1a) and at time of transplant (Table 1b) compared to the medically supported group at listing and transplant are presented. At the time of initial listing, the vast majority (91%) of VAD patients were listed UNOS Status 1A compared with 71% of medical patients; only 4% were listed Status 2 compared with 14% of medical patients. Using Intermacs profiles as defined by Stevenson et al, VAD patients at time of implant were profile 1 in 23%, profile 2 in 63%, and profile 3 in 10% (Figure 2).[13] Compared to medically supported patients, VAD supported patients were older (10.31 yrs [2.37, 15.05] vs 4.01 yrs [0.69, 12.72]; $p<0.0001$), of larger body surface area ($1.15 \pm 0.65$ m$^2$ v $0.85 \pm 0.54$ m$^2$, $p<0.0001$), and less often carried a

cardiac diagnosis of congenital heart disease (17% v 60%, p<0.0001). Five medically supported patients required ECMO prior to or during listing, however none required support at transplant. Compared to the medically supported group at listing, significantly more patients in the VAD group at time of implant had a requirement for inotropes (94% vs 61%, p=0.0005) and ventilator assistance (44% vs 15%, p<0.0001) with a greater incidence of liver dysfunction as depicted by total bilirubin level (1.43 ± 1.29 mg/dl vs 1.04 ± 1.60 mg/dl, p=0.006) and renal dysfunction as determined by estimated glomerular filtration rate (78.19 ± 39.05 vs 88.76 ± 39.30, p=0.003).

At the time of transplant, median wait list times in VAD patients were 2.43 months [1.05, 4.4] compared with 2.12 months [0.85, 4.73] in medical patients. Despite medical support and end-organ indices consistent with the VAD cohort being more critically ill at device implant, at transplant a smaller number had an inotrope requirement (33% vs 66%, p<0.0001), there were no differences in ventilator requirement (11% vs 14%) or liver function (total bilirubin 0.94 ± 0.89 mg/dl vs 0.92 ± 1.11 mg/dl), and renal function was improved (103.36 ± 5.894 ml/min/1.73m$^2$ vs 93.2 ± 43.03 ml/min/1.73m$^2$, p=0.015) compared with the medically supported cohort.

**Adverse Events During VAD Support**

Serious adverse events (SAEs) including bleeding, neurologic dysfunction, infection, and device malfunction were avoided throughout the duration of device support in 83 (56%) patients, whereas 47 (32%) patients suffered between 1 and 2 SAEs and 17 (12%) between 3 and 6 SAEs. Infection was the most frequently encountered SAE occurring in 24 patients with a cumulative frequency of 44 events and an event rate of 10.4 per 100 patient months. Bleeding occurred in 25 patients with 40 events and an event rate of 9.4 per 100 patient months, while neurologic dysfunction occurred in 20 patients with 37 total occurrences at a rate of 8.7 per 100 patient months. Device malfunction was the least frequently seen SAE occurring in 3 patients with 8 total events and an event rate of 1.9 per 100 patient months.

**Post-Transplant Length of Stay**

Despite high acuity in VAD-supported patients at the time of device implant, post-transplant length of stay was shorter by a median duration of 2 days for the VAD group as compared to the medical group (17 days [13, 28] vs 19 days [13, 33]; p=0.04). Duration of post-transplant length of stay was not significantly affected by pre-implant Intermacs profile (profile 1 – 19 days [15, 49], profile 2 – 16 days [11.5, 26.5], profile 3 – 14 days [11, 19]; p=0.1), however the length of stay was increasingly prolonged with increasing number of SAEs (No SAEs – 16 days [11, 24], 1-2 SAEs – 19 days [14, 31], 3-6 SAEs – 41 days [17.5, 58.5]; p=0.002).

**Post-Transplant Survival**

As shown in Figure 3a, survival at 1 year post-transplant was similar in both groups with 95% in the VAD cohort and 93% in the medical cohort. Of the seven deaths post-transplant in the VAD group, five occurred in 136 durable VAD patients whereas two occurred in 11 temporary VAD patients (p=0.03). There were a similar number of post-transplant deaths in durable VAD patients between those with pulsatile devices (3 deaths in 62 devices) and those with continuous flow devices (2 deaths in 74 devices). Similarly, 1 year post-transplant survival did not differ significantly among VAD patients when stratified by Intermacs profile 1, 2, or 3 as compared to medical patients. As shown in Figure 3b, comparison of survival at 1 year post-transplant between the VAD and medically supported groups when stratified by cardiac diagnosis showed universally worse survival in congenital heart disease (CHD) patients (p<0.01). However, there was no difference between VAD and medically supported patients within common cardiac diagnoses with CHD survival of 84% with VAD support compared to 89% with medical support (p=0.41). When comparing VAD patients to high-risk medical patients subdivided into those with inotrope requirement at transplant and those with inotrope and ventilator requirement, durable VAD

support mitigated the risk of the latter group. However, patients with temporary VAD support had a survival similar to high-risk medically supported patients requiring inotrope and ventilator support. Survival at 1 year in durable VAD patients was 96% as compared with 82% in temporary VAD patients, 95% in medically supported patients on inotropes, and 86% in medically supported patients on both inotropes and a ventilator ($p<0.01$, Figure 3c). Despite the varied occurrence of SAEs, there was no difference in survival at 1 year post-transplant based upon the absence, presence, or number of adverse events suffered (Figure 3d). Similarly, there was no difference in post-transplant survival based upon individual SAEs including major bleeding ($p=0.5$), neurologic dysfunction ($p=0.96$), infection ($p=0.63$), or device malfunction ($p=0.77$).

**Post-Transplant Infection and Rejection**

The frequency of post-transplant infections of the combined cohorts was 20%, a rate that was lower than the 32% determined in a previous era of PHTS patients by Gajarski et al.[14] However, there was no difference in freedom from post-transplant infections within the first year between pulsatile VAD patients, continuous flow VAD patients, temporary VAD patients, or medical patients (Figure 4a). Importantly, there was no difference in freedom from infection in patients who suffered VAD-related infectious adverse events from those who avoided such complications (Figure 4b).

The incidence of rejection within the first year post-transplant was 27% for the total study cohort, a rate which was less than the 40% reported by Gossett and colleagues in a recent era analysis of the PHTS database.[15] As shown in Figure 5a there was no difference in freedom from rejection in the first year post-transplant between the VAD (71%) and the medical (74%, $p=0.93$) groups. Moreover, there was no difference in freedom from rejection based on type of device support (continuous flow 73% vs pulsatile flow 69% vs temporary 73%, $p=0.96$) or incidence of

bleeding adverse events as potential sensitizing events (bleeding SAE 70% vs no bleeding SAE 72%, p=0.76, Figure 5b).

**Discussion**

This study represents the first linkage analysis between two rich and carefully curated datasets: the pre-implant and waitlist data in Pedimacs and the post-transplant data in PHTS. Therefore the analysis represents the largest longitudinal study of post-transplant outcomes of pediatric VAD supported patients to date. In this multicenter experience with enrollment from 38 centers, Pediatric VAD-supported patients were found to be an acutely ill subgroup at the time of implant with a significant degree of hemodynamic instability and end-organ dysfunction exceeding that of medically supported patients at listing. Following VAD support, patients experienced mitigation of the severity of their illness with a decrease in inotropic and ventilator support that resulted in their becoming equivalent to that of less acutely ill, medically supported transplant candidates. The improvement in clinical stability translated to a shortened length of post-transplant hospital stay as compared to medically supported patients, a finding that has never before been reported. However, this benefit was nullified in those with the greatest number of VAD-related adverse events.

As has been appreciated in multiple institutional as well as UNOS database analyses of outcomes in pediatric VAD patients, survival following heart transplant of VAD supported children does not differ from medically supported patients.[4, 5, 16-19] With the great degree of granularity in our study, however, we were additionally able to determine that pre-implant severity of illness did not affect post-transplant survival. Moreover, post-transplant outcomes in congenital heart disease patients regardless of need for mechanical support, as previously shown, are known to be clearly inferior to those of patients with cardiomyopathy.[3, 5, 20, 21] Our study shows that survival by support type within cardiac diagnosis groups led to similar post-transplant outcomes. This finding

is encouraging, given the limited number of options for providing mechanical circulatory support in pediatric congenital heart disease. For the first time in pediatric VAD literature, patients receiving durable device support were shown to experience improved post-transplant survival as compared to medically supported patients requiring ventilator support. What is also clear is that patients requiring temporary device support, as described in the second annual PediMACS report, represent a very high risk population.[22] These findings not only offer direction to clinicians regarding patient selection for device support, but they further support the assertion that durable device support leads to improvement of patient stability. Another finding of major importance is that VAD-related serious adverse events, regardless of number, did not negatively affect post-transplant survival. Coupled with the first Pedimacs analysis of adverse event data by Rosenthal et al, this holds great importance to the field of pediatric heart failure.[6] Though VAD-related adverse events occur with regularity, 53.4 events per 100 patient-months as reported by Rosenthal, improved survival to transplant may in part offset the significance of these complications and, as we have shown, without long-term detrimental effect that carry over post-transplant.

Of additional importance in this study is the correlation of type of device support as well as specific adverse events with post-transplant complications of infection and rejection. Despite pre-transplant infectious risks in the VAD group including externalized cannulae in pulsatile devices, drivelines in continuous flow devices, and even infectious adverse events, critically, there was no difference in post-transplant infection. Whether this represents equal risk of infection with externalized cannulae and drivelines or simply universally effective post-transplant infection prevention strategies was unable to be determined. Institutional reviews have reported a varied rate of VAD-related infectious events ranging from 15-75%, though upwards of 80% of these patients survive to transplantation.[23-25] The significance of infectious events during device support cannot be taken in isolation given the associated secondary complications, including hypercoagulability leading to increased risk of neurologic dysfunction and device malfunction.

However, adequate anti-microbial therapy and vigilance appear to be rewarded with beneficial post-transplant outcomes.

Finally, our study suggests that regardless of VAD implantation and bleeding complications that serve as potential sensitizing events, there was no increased risk of rejection related to VAD support. As reported in the UNOS database analysis by Castleberry et al, VAD patients are at increased risk of sensitization pre-transplant with 42% of device supported patients becoming sensitized as opposed to 30% of medically supported patients.[26] Just as waitlist survival was not shown to suffer in their study, we showed that rates of rejection in this at-risk group were also no different. The current findings provide further cautious support for the hypothesis suggested by Castleberry that VAD-associated sensitization may be less clinically relevant as compared to antibody formation from other etiologies, and that risks of antibody formation with VAD support should be viewed less apprehensively.

**Limitations**

This study should be interpreted in the context of its limitations. Though both Pedimacs and PHTS are prospective, event-driven databases with a great deal of granularity, this study represents a retrospective review and is subject to the biases in such an analysis. Though clinical changes during waitlist follow up were available in the VAD cohort, similar data including waitlist complications were not available in the medically supported cohort. Therefore comparisons to determine relative improvement in the VAD cohort were made to medical patients at the time of transplant and may be overestimated. Moreover, all patients included in this study were from institutions that offered mechanical support and tended to be higher volume transplant center. Therefore the findings in this study may not be generalizable to centers that do not offer such support. Waitlist mortality was not analyzed in the VAD cohort, thus attrition during VAD support cannot be commented on if patients were not transplanted. Despite the fact that this study

represents the largest longitudinal post-transplant analysis of VAD supported patients to date, the VAD cohort was small in number and heterogeneous in age and makeup, therefore limiting the ability to match cohorts or to detect small differences between groups. Finally, as a result of a low mortality rate, multivariate analysis could not be performed, another limitation, but motivation for future studies as additional patients are enrolled in the combined Pedimacs/PHTS registries.

**Conclusions**

Pediatric VAD support has revolutionized the field of pediatric heart failure with improved waitlist outcomes and survival to transplant. Despite greater severity of illness at time of device implant, VAD-supported patients have post-transplant outcomes that are equivalent to that of medically supported patients. In fact, post-transplant outcome for VAD patients was superior to that of patients supported with both inotropes and mechanical ventilation without device support. Therefore in children who undergo VAD as a bridge to transplant, VAD therapy mitigates pre-implant severity of illness and portends excellent post-transplant survival without identifiable detriment. The marriage of these two databases and their rich datasets provides a powerful tool with great granularity of analysis for future study of this important population.

## Author Disclosure

The manuscript above has not been previously published, nor is it under consideration for publication in another journal or electronically distributed source. All authors included in the study are in agreement with the content of the manuscript.

## Financial Conflict of Interest Disclosure

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**Figure Legend**

Figure 1: Cohort selection for the study.

Table 1: Baseline Characteristics for VAD cohort at implant versus Medical cohort at transplant listing.

Figure 2: Pre-implant Intermacs profile in VAD cohort.

Figure 3: Post-transplant survival at 1 year by (a) support type, (b) cardiac diagnosis, (c) high risk medical cohort, and (d) adverse event frequency.

Figure 4: Post-transplant freedom from infection by (a) support type and (b) history of infectious adverse event.

Figure 5: Post-transplant freedom from rejection by (a) support type and (b) history of bleeding adverse event.

## Table 1a Implant/Listing Demographics

| Baseline Characteristics | VAD Linked (n = 147) | Medically Supported n=630 | p-value |
|---|---|---|---|
| Age (years) (median [IQR]) | 10.31 [2.37, 15.05] | 4.01 [0.69, 12.72] | <0.0001 |
| Male | 88 (59.86%) | 355 (56.53%) | 0.5 |
| Non-white Race | 55 (37.41%) | 224 (35.56%) | 0.7 |
| Cardiac Diagnosis | | | <0.0001 |
| Congenital HD | 25 (17.01%) | 359 (59.98%) | |
| Cardiomyopathy | 108 (73.47%) | 263 (41.75%) | |
| Myocarditis | 13 (8.84%) | 5 (0.79%) | |
| Other | 1 (0.68%) | 3 (0.48%) | |
| UNOS Status | | | <0.0001 |
| 1A | 135 (91.84%) | 446 (70.79%) | |
| 1B | 3 (2.04%) | 95 (15.08%) | |
| 2 | 6 (4.08%) | 89 (14.13%) | |
| Inotropes | 138 (93.88%) | 418 (66.35%) | <0.0001 |
| Ventilator | 63 (43.54%) | 88 (13.97%) | <0.0001 |
| Intermacs Profile at Implant | | | |
| 1 – Critical Cardiogenic Shock | 33 (23.24%) | | |
| 2 – Progressive Decline | 89 (62.68%) | | |
| 3 – Stable but Inotrope Dependent | 14 (9.86%) | N/A | - |
| 4 – Resting Symptoms | 1 (0.70%) | | |
| 5 – Exertion Intolerant | 2 (1.41%) | | |
| 6 – Exertion Limited | 2 (1.41%) | | |
| 7 – Advanced NYHA/Ross Class | 1 (0.70%) | | |
| Prior Cardiac Surgery | 39 (26.53%) | 356 (56.61%) | <0.0001 |
| BSA ($m^2$) | 1.15 ± 0.65 | 0.85 ± 0.54 | <0.0001 |
| Selected Laboratory Values | | | |
| Blood urea nitrogen (mg/dl) | 25.97 ± 17.37 | 17.20 ± 9.47 | <0.0001 |
| eGFR (ml/min/1.73$m^2$) | 78.19 ± 39.05 | 88.76 ± 39.30 | 0.003 |
| Total bilirubin (mg/dl) | 1.43 ± 1.29 | 1.04 ± 1.60 | 0.006 |

## Table 1b Transplant Demographics

| Characteristics | VAD Linked (n = 147) | Medically Supported n=630 | p-value |
|---|---|---|---|
| UNOS Status | | | <0.0001 |
| 1A | 147 (100%) | 537 (85.24%) | |
| 1B | 0 | 59 (9.37%) | |
| 2 | 0 | 31 (4.92%) | |
| Inotropes | 48 (32.65%) | 418 (66.35%) | <0.0001 |
| Ventilator | 16 (10.88%) | 88 (13.97%) | 0.3 |
| Selected Laboratory Values | | | |
| Blood urea nitrogen (mg/dl) | 17.11 ± 10.39 | 18.49 ± 11.17 | 0.17 |
| eGFR (ml/min/1.73m$^2$) | 103.36 ± 55.89 | 93.2 ± 43.03 | 0.015 |
| Total bilirubin (mg/dl) | 0.94 ± 0.89 | 0.92 ± 1.11 | 0.8 |
| Waitlist Time (months) (median [IQR]) | 2.43 [1.05, 4.4] | 2.12 [0.85, 4.73] | <0.0001 |
| Device Duration (months) (median [IQR]) | 2.1 [1.15, 3.78] | N/A | - |
| Transplant Length of Stay (days) (median [IQR]) | 17 [13, 28] | 19 [13, 33] | 0.04 |

**Figure 1 Cohort Flow Chart**

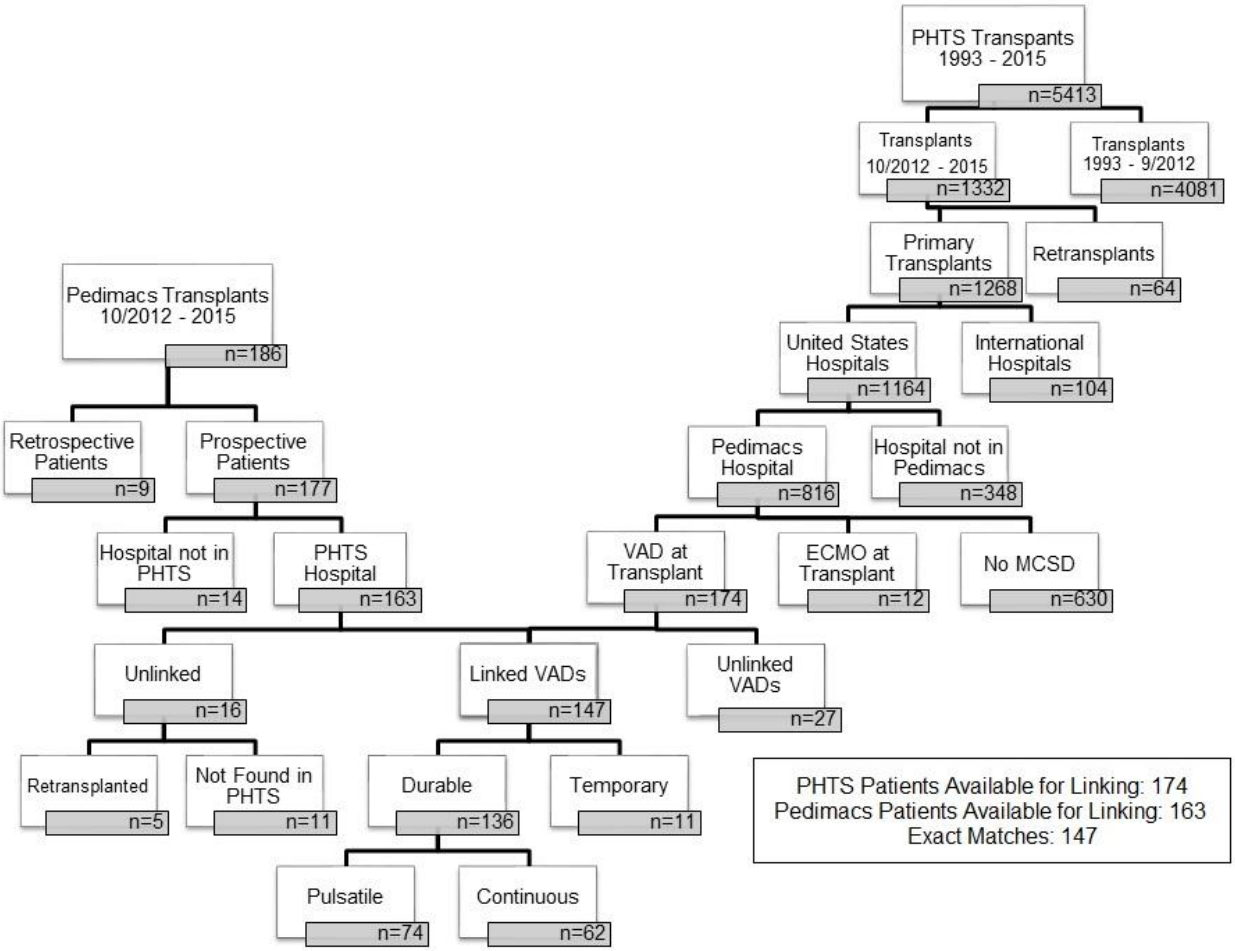


**Figure 2 Pre-Implant Intermacs Level**

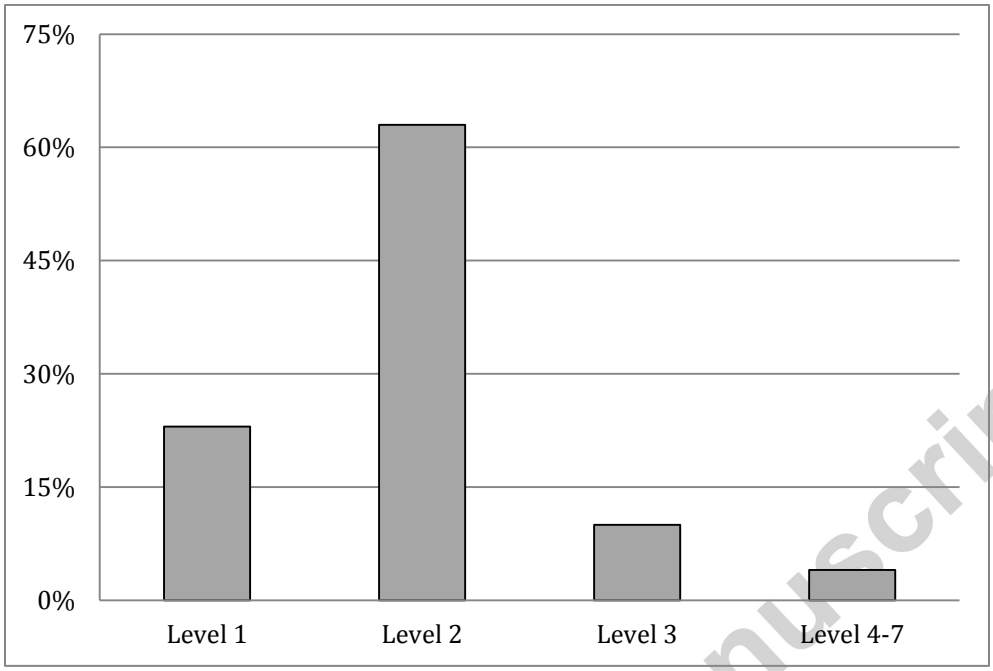
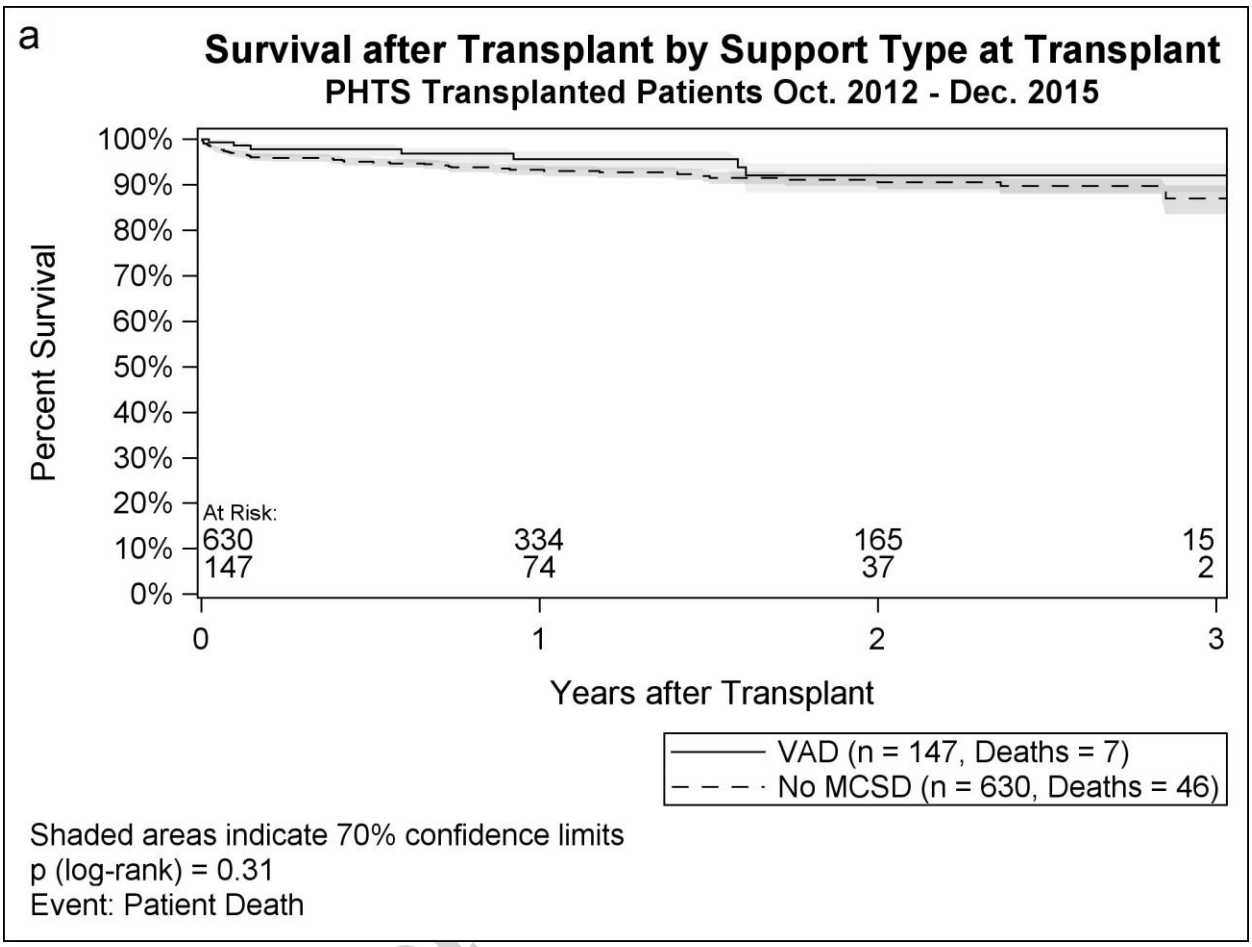
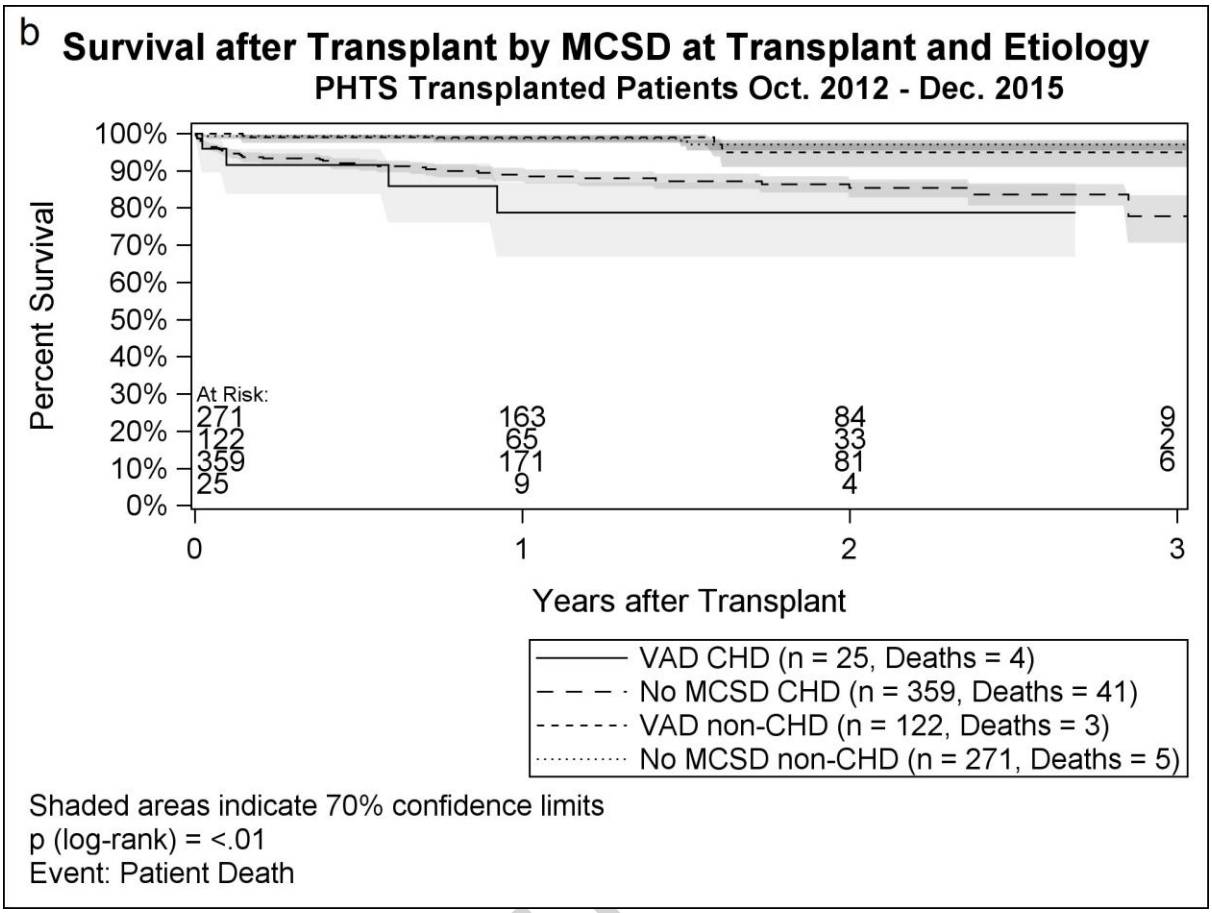
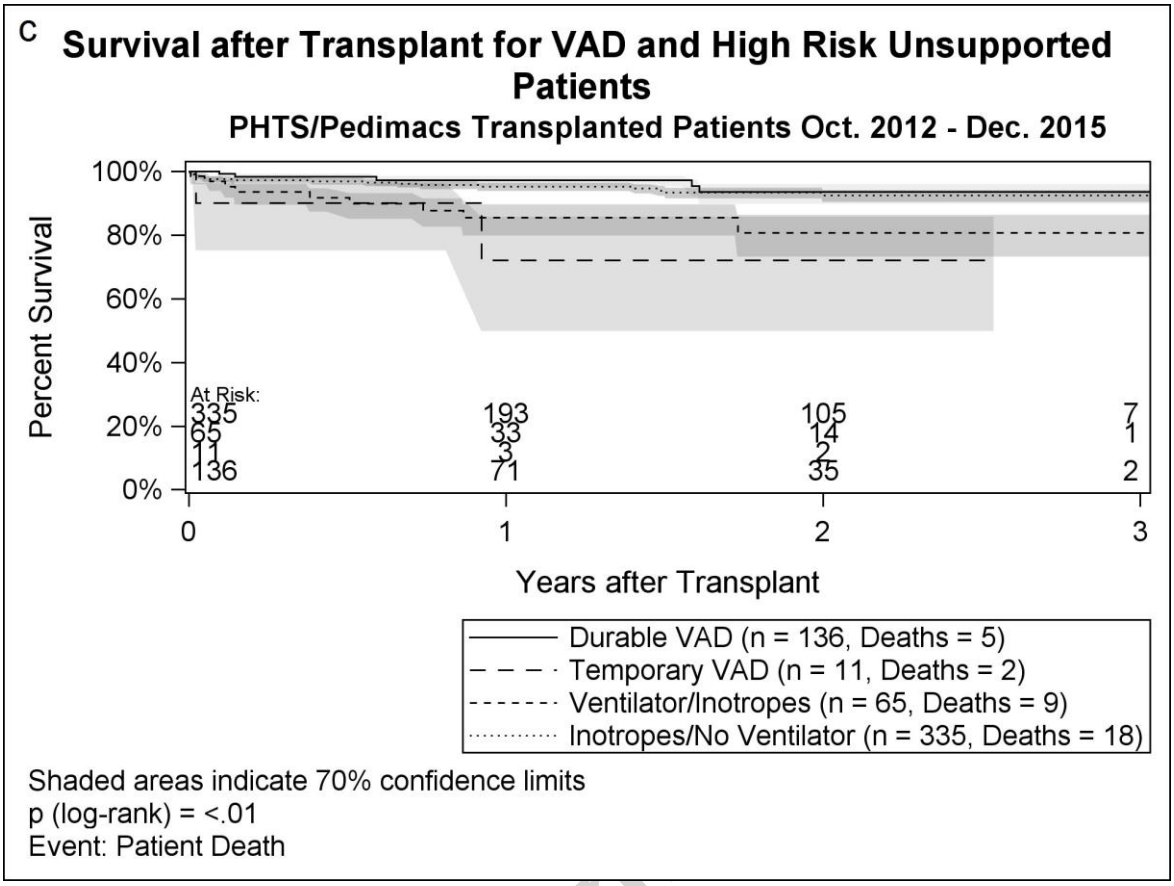


**Figure 3 Post-Transplant Survival**







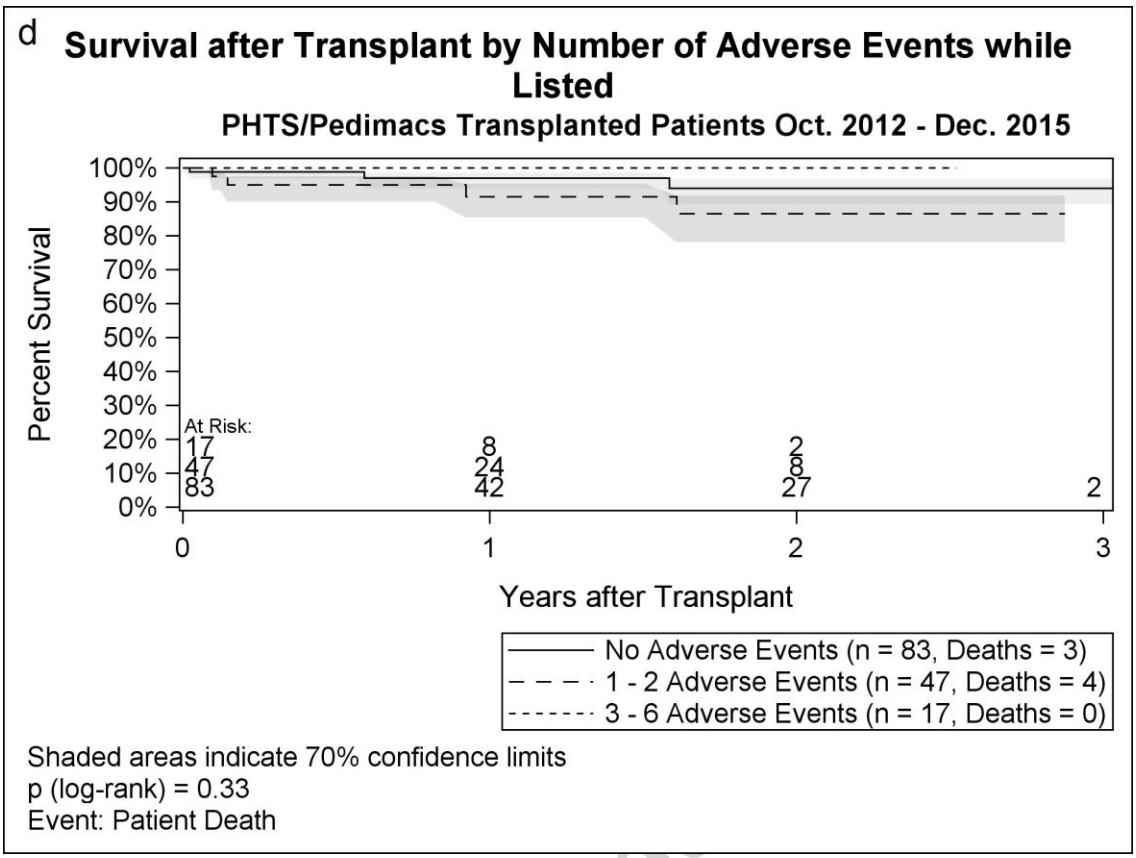
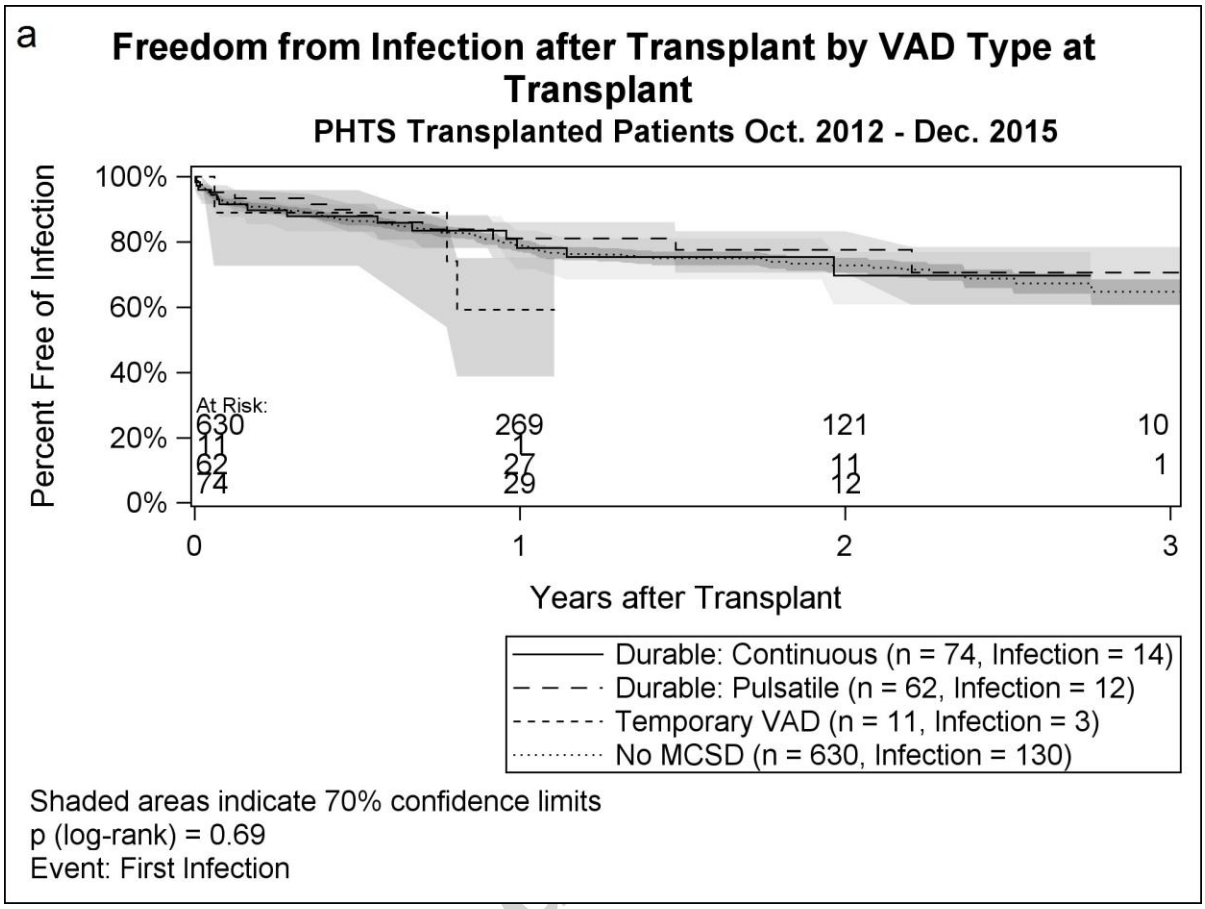


**Figure 4 Post-Transplant Freedom from Infection**



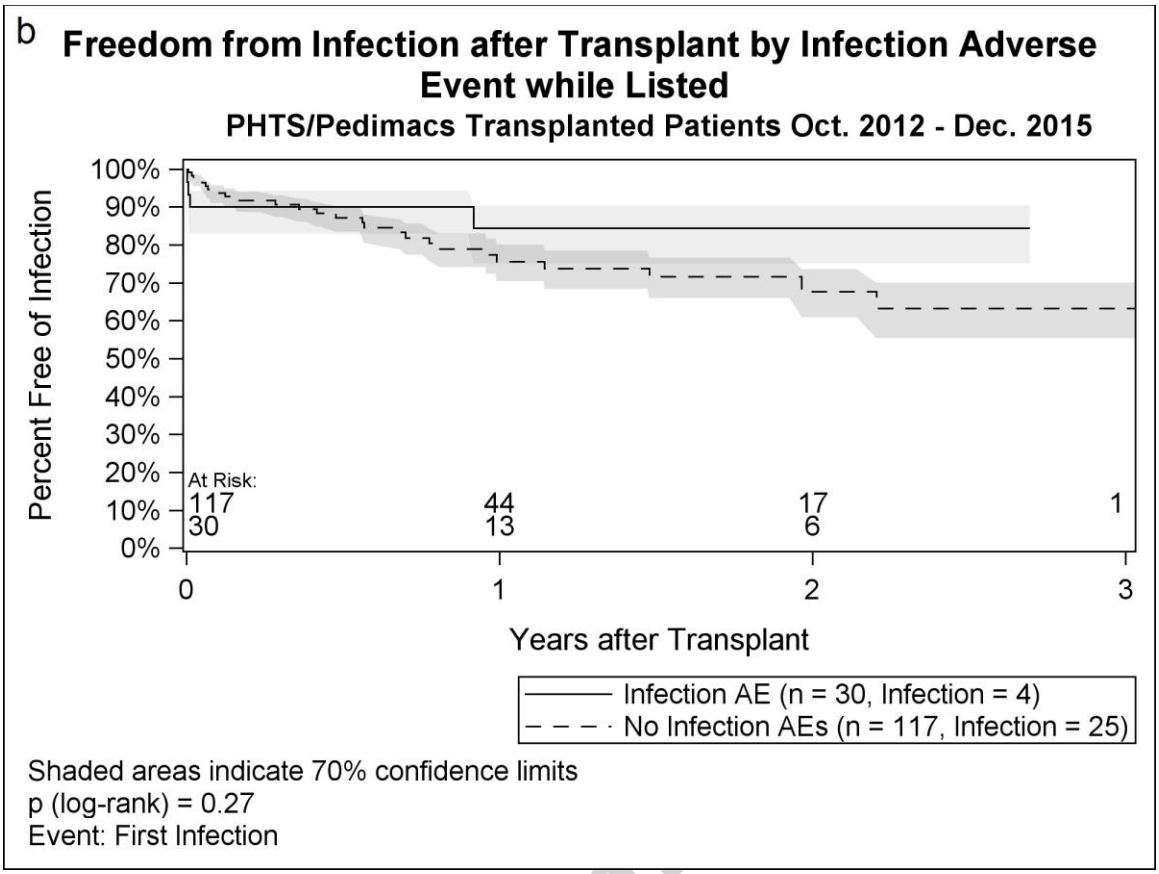
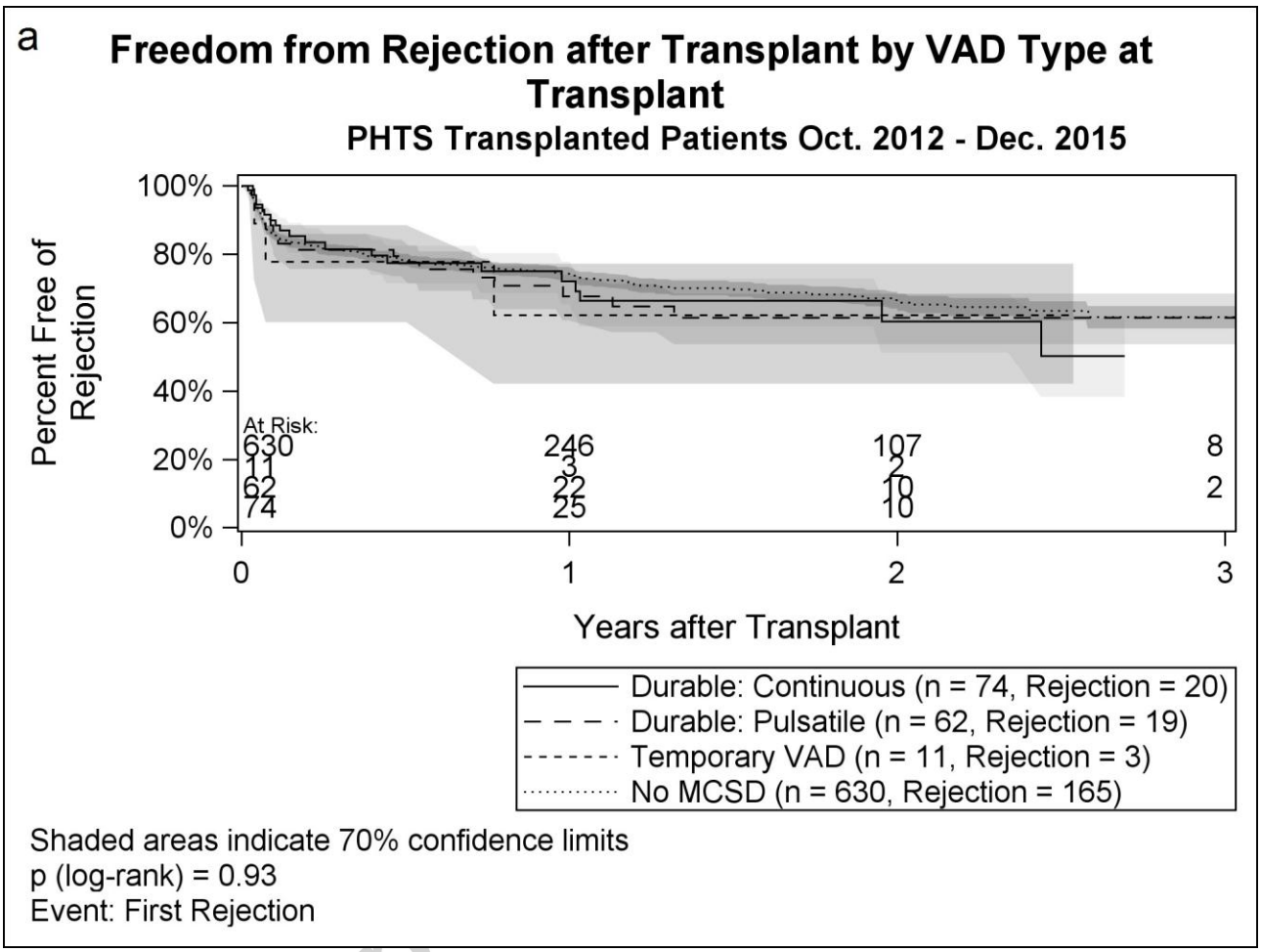
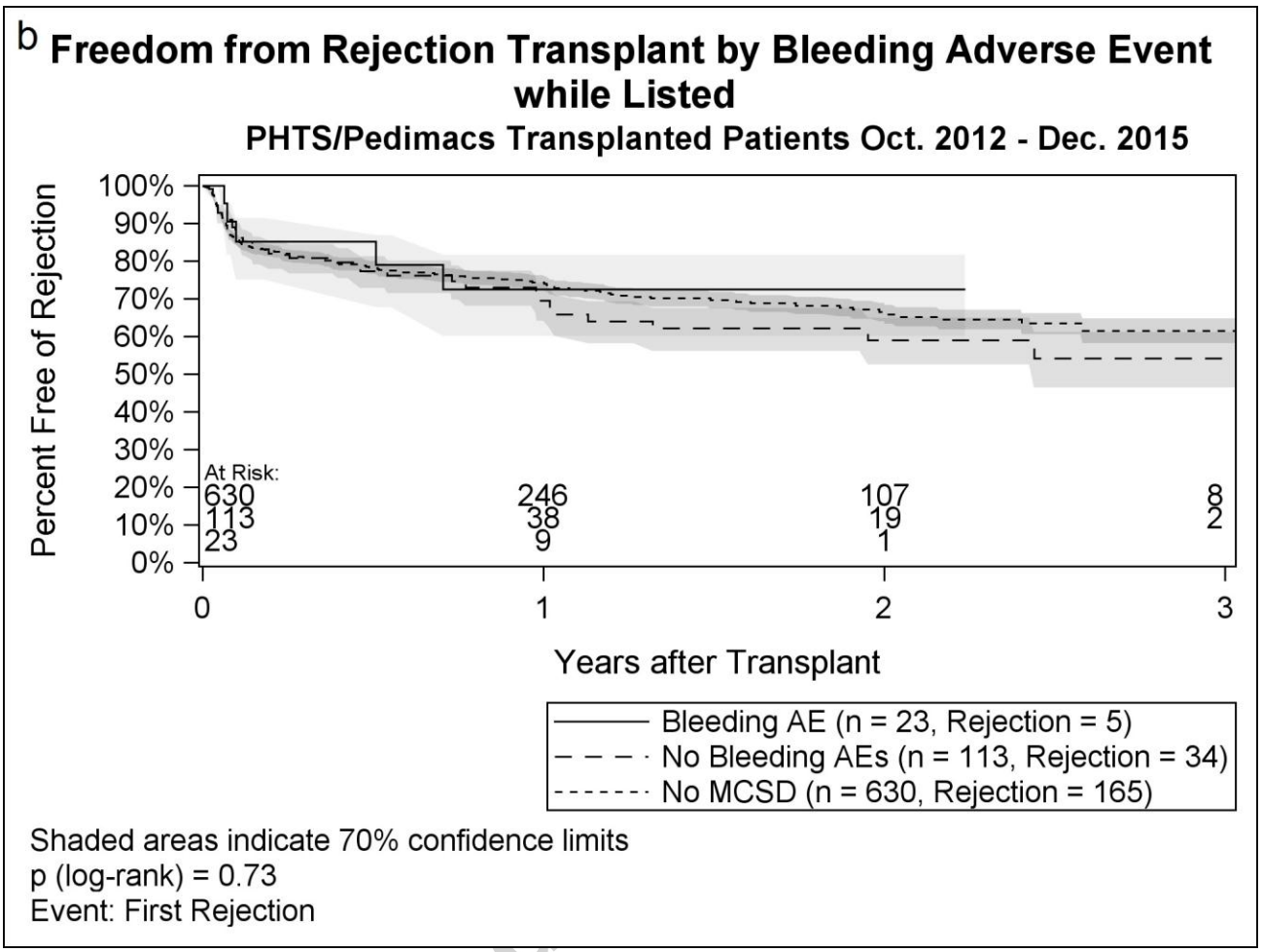

b
Freedom from Infection after Transplant by Infection Adverse Event while Listed
PHTS/Pedimacs Transplanted Patients Oct. 2012 - Dec. 2015
Percent Free of Infection
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
At Risk:
117
30
44
13
17
6
1
0
1
2
3
Years after Transplant
Infection AE (n = 30, Infection = 4)
No Infection AEs (n = 117, Infection = 25)
Shaded areas indicate 70% confidence limits
p (log-rank) = 0.27
Event: First Infection

**Figure 5 Freedom from Rejection**




b Freedom from Rejection Transplant by Bleeding Adverse Event while Listed
PHTS/Pedimacs Transplanted Patients Oct. 2012 - Dec. 2015
Percent Free of Rejection
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
At Risk:
630
113
23
246
38
9
107
19
1
8
2
0
1
2
3
Years after Transplant
Bleeding AE (n = 23, Rejection = 5)
No Bleeding AEs (n = 113, Rejection = 34)
No MCSD (n = 630, Rejection = 165)
Shaded areas indicate 70% confidence limits
p (log-rank) = 0.73
Event: First Rejection