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The impact of cognitive delay on pediatric heart transplant outcomes

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Abstract

The presence of cognitive delay may be viewed as a relative contraindication to transplantation; however, its impact on pediatric heart transplant (HTx) outcomes is poorly characterized. The aim of this study was to assess the impact of cognitive delay on pediatric HTx outcomes using academic progress as a surrogate measure of cognitive performance. The OPTN database was queried for all pediatric HTx recipients (2004-2014) with reported academic progress. Multivariable analysis assessed the impact of delayed grade level and the need for special education on post-HTx graft survival. A total of 2,245 children were included; 1,707(76%) within grade level, 269(12%) with delayed grade level, and 269(12%) who required special education. The need for special education was not a risk factor for post-HTx mortality; however, delayed grade level was an independent risk factor for worse post-HTx outcomes (AHR 1.4,95%CI 1.02,1.79,p=0.03). Patients who require special education have similar outcomes compared to those without cognitive delay, likely secondary to significant parental involvement. Children with delayed grade level demonstrate inferior post-HTx survival, which could result from less parental oversight in children perceived to maintain compliance. Ensuring adequate social support for patients with evidence of cognitive delay may help to improve outcomes.

Introduction

The impact of cognitive delay (CD) on candidacy for solid organ transplantation has become a topic of much attention in pediatric patients. The presence of CD has previously been listed as a relative contraindication to heart transplant (HTx) (1); however, this has been an

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Disclosures

None.

Author Contributions

Christopher Prendergast: Dr. Prendergast aided in data analysis, drafted the manuscript, and approved the final submission.
Meghann McKane: Dr. McKane reviewed and critically appraised the manuscript, and approved the final submission.
Debra A. Dodd: Dr. Dodd reviewed and critically appraised the manuscript, and approved the final submission.
Justin Godown: Dr. Godown conceptualized the project, aided in data analysis, reviewed and critically appraised the manuscript, and approved the final submission.

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evolving policy with more recent guidelines highlighting the importance of a strong social support system in patients with CD and limiting consideration of transplant only in the setting of severe CD or a persistent vegetative state (2, 3). The use of CD to gauge a patient's transplant candidacy varies considerably among pediatric transplant programs (4). In an effort to standardize the approach to transplant evaluation in patients with CD, Boston Children's Hospital recently developed a transplant center-wide policy using input from across multiple disciplines (3). They concluded that each patient should be evaluated on an individual basis and that the presence of CD should not serve as a relative or absolute contraindication to organ transplantation, except in the most extreme case of a persistent vegetative state with complete unawareness of self and environment.

In considering the appropriateness of listing patients with CD for organ transplantation, it is important to assess transplant outcomes compared to patients without CD as the limited donor pool obliges allocation of organs to candidates who will have the most benefit. Limited data in pediatric renal transplant recipients suggests that patients with CD do not have inferior post-transplant outcomes (5-7). While these findings support the potential benefits of transplantation in patients with CD, this has not been well studied in pediatric HTx. The aim of this study is to assess the impact of CD on outcomes following pediatric HTx using academic progress, as defined by the Organ Procurement and Transplantation Network (OPTN) database, as an objective measure of cognitive performance.

Methods

The OPTN database documents the presence of CD at the time of HTx; however, this is a subjective assessment by a single provider and does not accurately gauge the severity of CD. Academic progress provides a much more quantifiable assessment of CD and therefore is the primary focus of our analysis, with provider documentation of CD incorporated as a secondary analysis. The OPTN database was queried for all pediatric (<18 years of age) patients who underwent HTx between 2004 and 2014. These date ranges were chosen to coincide with the time when academic progress data collection began. For patients >5 years of age, centers report academic progress as within 1 grade level of peers (WGL), delayed grade level (DGL), or special education (SE). These data are collected at the time of HTx and at subsequent follow-up visits. To minimize patients with missing CD data, the lowest recorded academic progress at the time of HTx or at any point during post-HTx follow-up was used in the analysis. Patients were divided into three groups based on their reported academic progress. Key variables were compared across groups. Post-transplant survival curves based on academic progress were constructed using the Kaplan-Meier method and compared using the log-rank test. A multivariable model was constructed using the Cox proportional hazards model. Variables included in the multivariable model were selected a priori and included age, gender, race, blood type, diagnosis (cardiomyopathy, congenital heart disease, re-transplant, or other), listing status, ventricular assist device (VAD) support, extracorporeal membranous oxygenation (ECMO) support, ventilator support, and inotropic support at the time of transplant. To determine potential risk factors for future DGL or the need for SE, logistic regression analysis was performed. The same variables selected a priori for the survival analysis were included in the logistic regression model to assess their

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contribution towards the development of either DGL or the need for SE during post-HTx follow-up.

At the time of transplantation and at post-HTx follow-up visits, centers report cognitive status as definite CD, probable CD, questionable CD, or no CD. Assessment of cognitive status is based on the subjective assessment of a single provider. A secondary analysis was performed substituting CD for academic progress. Patients were divided into 2 groups based on if any concern for CD (questionable, probable, or definite) was ever reported at the time of HTx or in follow-up. Survival curves were generated based on the presence of CD using the Kaplan-Meier method and compared using the log-rank test. A multivariable model was constructed using the Cox proportional hazards model, adjusting for the same variables that were selected a priori for the primary analysis. Provider's assessment of the presence of CD at the time of HTx was also compared to academic progress at post-HTx follow-up to assess the ability of providers to gauge the presence of CD. All analyses were performed in STATA Version 13 IC.

Results

A total of 2,245 children were included in the analysis with documented academic progress at the time of transplantation or during post-HTx follow-up. Missing data was minimal, with only 2.6% of patients eligible for inclusion missing academic progress documentation. Of the patients with complete academic progress data, 1,707 (76%) were WGL, 269 (12%) had DGL, and 269 (12%) required SE.

Baseline patient characteristics are summarized in Table 1. There was no difference between academic progress groups based on gender, listing status, blood type, ethnicity, and the need for inotropes, VAD, ECMO, or ventilator support at the time of transplantation. Patients with DGL were slightly older compared to the other groups and patients with congenital heart disease were more likely to have a DGL or require SE.

There was no significant difference in post-HTx survival between patients WGL and those who required SE (Figure 1). However, patients with DGL demonstrated worse post-HTx survival compared to patients WGL and those who required SE (log rank p-value <0.001). This remained true in the multivariable analysis where the presence of a DGL was an independent predictor of post-HTx graft loss (AHR 1.4, 95% CI 1.02, 1.79. p=0.03) (Table 2a).

Given the possibility that any potential impact of CD may be more prominent in adolescent patients, a repeat analysis was performed examining only patients >11 years of age at the time of HTx. Similar to the primary analysis, patients with DGL demonstrated worse post-HTx graft survival compared to patients WGL and those who required SE (Figure 2). This difference remained in a multivariable analysis and DGL continued to be an independent risk factor for post-transplant graft loss (Table 2a). There was a trend towards improved graft survival in patients who required SE compared to those WGL (AHR 0.6; 95% CI 0.35, 1.02; p=0.058) however, this failed to reach statistical significance at $\alpha = 0.05$.

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Multiple risk factors at the time of HTx were found to be associated with future DGL or the need for SE. Congenital heart disease (AOR 1.8, 95%CI 1.39, 2.33; p < 0.001), retransplants (AOR 1.77, 95%CI 1.17, 2.69; p = 0.007), ventilator use at HTx (AOR 1.54, 95%CI 1.06, 2.23; p = 0.025), and Hispanic race (AOR 1.56, 95%CI 1.15, 2.12; p = 0.005) were all associated with the development of either DGL or the need for SE at any time post-HTx. The need for VAD or ECMO support at the time of HTx did not appear to be risk factors for future delayed academic progress in our analysis.

Due to the potential for missing data to impact results when performing analyses using OPTN data, a missing value analysis was performed. As expected, the majority of patients with missing academic progress data were younger compared to those with complete data, as academic progress is only collected for patients ≥5 years of age. When excluding patients <5 years of age, 2.6% of patients were missing academic progress data. There was no difference between patients with missing and complete academic progress data in terms of diagnosis, gender, listing status, blood type, ethnicity, or the need for ventilator, inotrope, or VAD support. However, patients with missing academic progress data were younger and more likely to have been on ECMO at the time of HTx.

A total of 2,959 children were included in the secondary analysis with complete cognitive status data. Of these patients, 1,783 (60.3%) had no documented CD and 1,176 had definite, probable, or questionable CD documented at the time of HTx or in post-HTx follow-up.

Baseline patient characteristics are summarized in Table 3. Patients with evidence of CD were younger, more likely to be male, have a diagnosis of congenital heart disease, and require ventilator support at the time of HTx. Differences were also noted in ethnicity and blood type between patients with and without CD.

There was no significant difference in post-transplant graft survival based on the presence of CD (Figure 3). This remained true when differences were adjusted for in a multivariable model (Table 2b) (AHR 1.01, 95%CI 0.83, 1.22; p=0.953).

A total of 936 patients had provider assessment of CD at the time of HTx with documented academic progress during post-HTx follow-up, with 67 (7.2%) patients documented to have definite CD at HTx. Of these patients, 64.2% required SE and 11.9% had DGL in post-HTx follow-up. There were 719 (76.8%) patients without documented CD at the time of HTx. In this group, 2.9% required SE and 9.6% had DGL in post-HTx follow-up. There were 52 (5.6%) and 98 (10.5%) patients with documented probable and questionable CD at HTx, respectively. In both of these groups, the majority of patients (60%) were WGL at post-HTx follow-up with 13 to 15% with DGL and 24 to 25% requiring SE.

Discussion

While there may be hesitation to proceed with HTx in the setting of CD due to concerns for poor compliance with a complex medical regimen (8, 9), our analysis demonstrates that pediatric patients with CD can achieve HTx outcomes that are comparable to patients without evidence of CD. This is demonstrated by the fact that patients who required SE did not have inferior graft survival compared to patients WGL. In fact, there was a trend towards

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improved survival in the SE group. However, in our analysis, patients with DGL demonstrated inferior post-HTx graft survival compared to those WGL and those who required SE. We hypothesize that this difference in outcomes may result from less parental oversight in a child perceived to maintain compliance. For patients requiring SE, there is likely to be greater parental control of medication administration due to parents perception that their child is unable to manage their regimen independently. Conversely, for patients WGL and with DGL, parents may believe that their child is able to independently maintain compliance with their medications. This waning of parental oversight over time may contribute to the differences in outcomes observed. This effect appears to be most prominent in older pediatric patients, where there was a trend towards improved graft survival in patients who required SE even compared to those WGL. So while this effect appears to be most significant in patients with DGL, there may also be an impact on patients WGL; suggesting that a strong social support structure may be critical to maintain compliance and improve outcomes. The importance of a strong social support structure is further strengthened by data from the adult population, where patients with mental retardation have significantly benefitted from HTx, provided they had a robust support system in place to assure compliance (10).

The presence of CD is inconsistently used across transplant centers as a criteria to determine transplant candidacy (4). Richards et al recently surveyed a spectrum of pediatric solid organ transplant programs and found that CD was routinely used to assess transplant candidacy in only one-third of programs surveyed, while some programs reported that CD was never used as a criterion to evaluate transplant candidacy. Importantly, in this study the degree of CD impacted the frequency with which centers considered CD in listing, with centers more likely to take CD into consideration with severe or profound delays.

There are limited data available regarding post-transplant outcomes in pediatric patients with CD. However, multiple studies suggest that outcomes in patients with CD after solid organ transplantation are comparable to patients with no CD (5-7, 10). Wightman et al demonstrated that early recipient and graft survival remained equivalent between children with and without CD at three-year follow-up after renal transplantation (7). Similarly, Galante et al demonstrated comparable renal graft survival in patients with and without CD (6). Similar to the findings in renal transplant recipients, our analysis demonstrates that patients with CD can achieve HTx outcomes comparable to those without CD. However, our analysis also highlights the potential impact of varying parental oversight on patient outcomes. While our findings support the current center-wide policy recently published from Boston Children’s Hospital asserting that CD should not serve as a relative or absolute contraindication to organ transplantation (3), ensuring an adequate social support structure is likely a critical step to optimize outcomes for these patients.

Knowledge of the risk factors for delayed academic progress may also aid in identification of patients who warrant careful post-transplant monitoring for compliance and assessment of their social support system in the setting of non-compliance. Not surprisingly, congenital heart disease was found to be a risk factor for delayed academic progress in our analysis. Patients undergoing their second transplant were also found to be at higher risk for future delayed academic progress. This finding may stem from the impact of a chronic illness with

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multiple or prolonged hospitalizations resulting in failure to maintain grade level. Interestingly, the need for VAD or ECMO pre-HTx did not appear to be a risk factor for future delayed academic progress in our analysis; however, the relatively small number of patients in these groups resulted in a low power to detect any potential effect of these factors.

Our secondary analysis utilized provider assessment of cognitive status at the time of HTx or during post-HTx follow-up; however, we found this to be a less useful measure of CD. This measure does not quantify the degree of CD, representing a major limitation to this approach. Additionally, our analysis demonstrates that provider assessment of cognitive status at HTx is reasonably predictive of future academic progress for patients classified as having definite or no CD, but is very poor at predicting future academic outcome when patients are classified as having questionable or probable CD. Developing a more quantifiable measure of CD is needed and may aid in further assessment of the impact of CD on HTx listing practices and post-HTx outcomes.

Limitations

Our study has inherent limitations. Our analysis utilized academic progress as a surrogate marker for the presence of CD. While this is an imperfect measure, the OPTN database does not provide sufficient data granularity to further explore the degree of CD in individual patients. Academic progress may also change over time. To facilitate our analysis, the patient's lowest available grade level at the time of HTx or in post-HTx follow-up was used. This approach has the potential to overestimate the degree of academic progress delay. Additionally, patients with severe CD may be less likely to be listed for HTx, thereby weighting our analysis towards patients with less significant CD. Overall, a more objective measure of cognitive performance may help to better quantify the degree of CD and further elucidate the true impact of CD on pediatric HTx outcomes.

Conclusions

Despite the fact that the presence of CD has previously been considered a relative contraindication to HTx, pediatric patients with CD can achieve similar outcomes after HTx compared to those without CD. These findings support the assertion that CD should not be viewed as a relative or absolute contraindication to HTx in pediatric patients; however, ensuring an adequate social support system is likely a critical step to optimize post-transplant outcomes for these patients.

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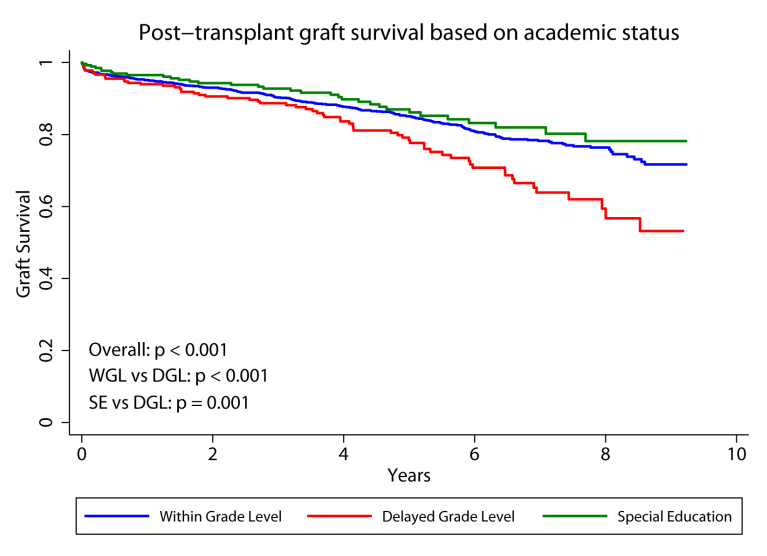

Figure 1.

Post-transplant graft survival based on academic progress. P-values from the log-rank test (60.3%) had no documented CD and 1176 had definite, probable, or questionable CD documented at the time of HTx or in post-HTx follow-up.

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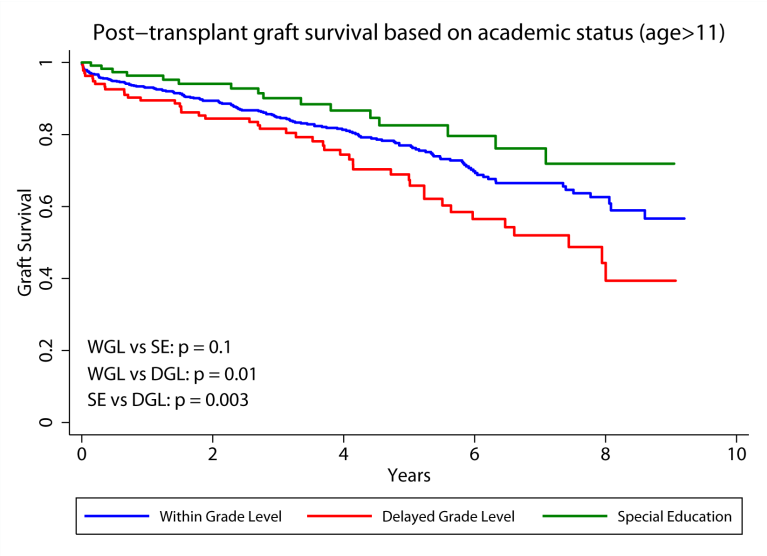

Figure 2.

Post-transplant graft survival based on academic progress for patients aged >11 years of age. P-values from the log-rank test(60%) were WGL at post-HTx follow-up with 13%-15% with DGL and 24%-25% requiring SE.

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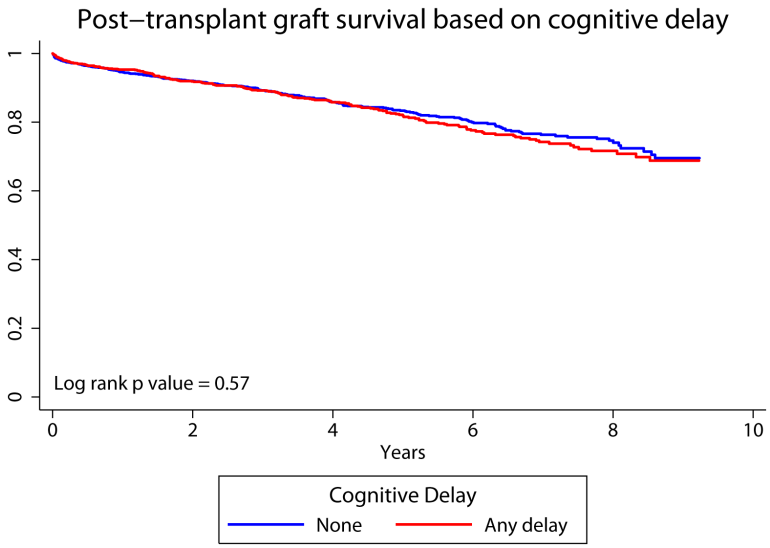

Figure 3.
Post-transplant graft survival based on cognitive delay. P-value from the log-rank test.

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Table 1

Baseline patient characteristics based on academic progress

	Academic Progress								
	Within 1 grade level		Delayed grade level		Special education		Total		p-value
	N= 1707	(76.0%)	269	(12.0%)	269	(12.0%)	2245		
Male gender	918	(53.8%)	142	(52.8%)	165	(61.3%)	1225	(54.6%)	0.057
Status at transplant									
1A	1356	(79.4%)	202	(75.1%)	216	(80.3%)	1774	(79.0%)	
1B	186	(10.9%)	29	(10.8%)	30	(11.2%)	245	(10.9%)	0.205
2	165	(9.7%)	38	(14.1%)	23	(8.6%)	226	(10.1%)	
Diagnosis									
Cardiomyopathy	1027	(60.2%)	133	(49.4%)	119	(44.2%)	1279	(57.0%)	
Congenital Heart Disease	526	(30.8%)	97	(36.1%)	121	(45.0%)	744	(33.1%)	<0.001
Retransplant	130	(7.6%)	35	(13.0%)	22	(8.2%)	187	(8.3%)	
Other	24	(1.4%)	4	(1.5%)	7	(2.6%)	35	(1.6%)	
Age at transplant (years)	10	(4 - 14)	12	(6 - 15)	10	(4 - 14)	11	(4 - 14)	0.032
VAD at transplant	298	(17.5%)	39	(14.5%)	42	(15.6%)	379	(16.9%)	0.401
ECMO at transplant	75	(4.4%)	9	(3.4%)	7	(2.6%)	91	(4.1%)	0.315
Ventilator at transplant	184	(10.8%)	29	(10.8%)	37	(13.8%)	250	(11.1%)	0.347
Inotropes at transplant	796	(46.6%)	121	(45.0%)	120	(44.6%)	1037	(46.2%)	0.755
Blood type									
O	794	(46.5%)	114	(42.4%)	131	(48.7%)	1039	(46.3%)	
A	617	(36.2%)	117	(43.5%)	93	(34.6%)	827	(36.8%)	0.17
B	234	(13.7%)	28	(10.4%)	31	(11.5%)	293	(13.1%)	
AB	62	(3.6%)	10	(3.7%)	14	(5.2%)	86	(3.8%)	
Ethnicity									
Caucasian	927	(54.3%)	133	(49.4%)	143	(53.2%)	1203	(53.6%)	
African American	403	(23.6%)	66	(24.5%)	65	(24.2%)	534	(23.8%)	0.079
Hispanic	260	(15.2%)	52	(19.3%)	53	(19.7%)	365	(16.3%)	
Other	117	(6.9%)	18	(6.7%)	8	(3.0%)	143	(6.4%)	

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Table 2

Cox proportional hazard models assessing the impact of academic progress and the presence of cognitive delay on post-transplant graft survival

			95% Confidence Interval		
		Adjusted Hazard Ratio	Lower	Upper	p-value
A.	Academic Progress (all ages)[a]				
	Delayed grade level	1.4	1.02	1.79	0.03
	Special education	0.79	0.54	1.13	0.196
	Academic Progress (age>11)[a]				
	Delayed grade level	1.43	1.01	2.01	0.04
	Special education	0.6	0.35	1.02	0.058
B.	Cognitive Development				
	Any cognitive delay[b]	1.01	0.83	1.22	0.953

Models adjusted for age, gender, race, blood type, diagnosis, listing status, VAD, ECMO, ventilator, and inotropic support

[a] Reference category: Within grade level

[b] Any delay defined as definite, probable, or questionable cognitive delay

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Table 3

Baseline patient characteristics based on the presence of cognitive delay

	Cognitive Delay						
	None		Any		Total		p-value [a]
	N= 1783	(60.3%)	1176	(39.7%)	2959		
Male gender	912	(51.2%)	666	(56.6%)	1578	(53.3%)	0.003
Status at transplant							
1A	1463	(82.1%)	991	(84.3%)	2454	(82.9%)	
1B	176	(9.9%)	105	(8.9%)	281	(9.5%)	0.272
2	144	(8.1%)	80	(6.8%)	224	(7.6%)	
Diagnosis							
Cardiomyopathy	1039	(58.3%)	543	(46.2%)	1582	(53.5%)	
Congenital Heart Disease	604	(33.9%)	547	(46.5%)	1151	(38.9%)	<0.001
Retransplant	112	(6.3%)	65	(5.5%)	177	(6.0%)	
Other	28	(1.6%)	21	(1.8%)	49	(1.7%)	
Age at transplant (years)	8	(1 - 14)	2	(0 - 10)	5	(0 - 13)	<0.001
VAD at transplant	313	(17.6%)	197	(16.8%)	510	(17.2%)	0.571
ECMO at transplant	73	(4.1%)	59	(5.0%)	132	(4.5%)	0.234
Ventilator at transplant	205	(11.5%)	253	(21.5%)	458	(15.5%)	<0.001
Inotropes at transplant	855	(48.0%)	572	(48.6%)	1427	(48.2%)	0.715
Blood type							
O	800	(44.9%)	568	(48.3%)	1368	(46.2%)	
A	675	(37.9%)	398	(33.8%)	1073	(36.3%)	0.008
B	246	(13.8%)	147	(12.5%)	393	(13.3%)	
AB	62	(3.5%)	63	(5.4%)	125	(4.2%)	
Ethnicity							
Caucasian	994	(55.8%)	616	(52.4%)	1610	(54.4%)	
African American	396	(22.2%)	251	(21.3%)	647	(21.9%)	<0.001
Hispanic	264	(14.8%)	246	(20.9%)	510	(17.2%)	
Other	129	(7.2%)	63	(5.4%)	192	(6.5%)	

[a] p values from the chi square test for categorical and Kruskal Wallis test for continuous variables