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Outcomes Following Heart Transplantation In A National Cohort: An Analysis Of The Organ Procurement And Transplantation Network's Database

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OUTCOMES FOLLOWING HEART TRANSPLANTATION IN A NATIONAL COHORT: AN ANALYSIS OF THE ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK'S DATABASE. Oliver K. Jawitz, Pramod N. Bonde. Section of Cardiac Surgery, Department of Surgery, Yale University, School of Medicine, New Haven, CT.

Abstract

In this analysis, we examine a large national cohort within the Organ Procurement and Transplantation Network's (OPTN) United Network for Organ Sharing (UNOS) database for the purpose of determining the impact of a recipient history of myocarditis as well as donor/recipient ABO compatibility on outcomes following heart transplantation. We used a nationwide sample with primary stratification between ABO identical and compatible heart transplantations or transplant recipients diagnosed with myocarditis and those diagnosed with ischemic or idiopathic cardiomyopathy. The primary end-point was graft failure from all causes. Post-transplant survival was compared between groups using univariate Kaplan-Meier as well as multivariate Cox proportional hazard and logistic regression models. ABO compatible recipients were generally sicker than ABO identical recipients before transplant as a larger proportion were Status 1A, in the ICU, and on mechanical ventilatory support ($p < 0.05$). Multivariate analysis did not demonstrate adverse outcomes associated with ABO compatible transplants in terms of decreased graft survival (hazard ratio 0.99, $p = 0.87$). Blood type O donor grafts, however, were associated with poorer outcomes compared with all other types ($p < 0.05$), which has important implications for current graft allocation policies. For recipients with a history of myocarditis, survival was comparable with ischemic or idiopathic cardiomyopathy. Patients with myocarditis were more likely to be female, younger, in the ICU before transplant, and on ECMO, ventilatory support, and VAD pre-transplant ($p < 0.05$). Transplant recipients diagnosed with myocarditis were more likely to die from acute ($p < 0.05$) and chronic graft failure ($p < 0.05$). Strategies to safely bridge these patients to transplant such as mechanical circulatory support should be considered earlier in the disease. Furthermore, this analysis suggests that post-transplant outcomes of patients with a history of myocarditis could be improved with more intensive immunosuppression.

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INTRODUCTION

Cardiac transplantation is widely considered the gold-standard therapy for treating patients with end-stage heart failure refractory to medical management. Absolute indications for cardiac transplantation from the ACC/AHA include hemodynamic compromise due to heart failure including refractory cardiogenic shock, dependence on IV inotropes, and peak oxygen consumption less than 10mL per kg per minute with anaerobic metabolism. Other absolute indications include severe debilitating ischemia not amenable to coronary artery bypass surgery or percutaneous coronary intervention as well as recurrent symptomatic ventricular arrhythmias refractory to all other therapies [1].

Outcomes following heart transplantation have improved significantly since Christiaan Barnard performed the first human-to-human heart transplantation in 1967. The most significant scientific breakthrough regarding the management of post-heart transplant recipients was the introduction of cyclosporine-based immunosuppression regimens in the early 1980's [2]. Since this time, post-transplantation survival has continued to improve with further advances in immunosuppression, more careful selection of donors and recipients, as well as the development of more efficacious approaches to preventing and treating infection. Despite the tremendous advances made in the past several decades, of the approximately 2,000 procedures performed in the United States annually, about 10% of patients do not survive the first year post transplant [3]. After one year, annual death rates approach 4% and approximately 50% of heart transplant recipients are alive at 10 years [4].

The purpose of this thesis is to analyze outcomes following heart transplantation using the United Network for Organ Sharing (UNOS) heart transplantation database in

order to identify potential areas of improvement in national organ allocation policies as well as donor and recipient selection strategies. In doing so, the use of the limited supply of donor organs in this country could be made more efficient, thus improving outcomes for potential heart transplant recipients and maximizing the benefit of this limited donor pool. The thesis will be divided into two parts: (1) an analysis of outcomes following heart transplantation for recipients with a history of myocarditis and (2) an analysis of the impact of ABO blood type compatibility on heart transplant outcomes. Both are areas of contention with conflicting evidence presented in the medical literature and both have important implications for optimal organ allocation. This study was deemed exempt by the Yale University's Institutional Review Board.

Part 1

Heart transplantation for myocarditis: outcomes and survival in a national cohort

BACKGROUND

Myocarditis, defined as an inflammatory disease of the myocardium, has a wide range of clinical manifestations and is often the result of infectious and toxic agents as well as hypersensitivity reactions [5]. While the natural history of myocarditis is variable, dilated cardiomyopathy (DCM) is often the result. DCM is the most frequent indication for heart transplantation and is usually considered following the failure of maximal medical management. Between 2006 and 2012, approximately 54% of all heart transplants performed worldwide were for dilated cardiomyopathy [6].

Before considering transplantation, there are a number of medical treatment options available for acute and chronic myocarditis. Pharmacologic treatment focused on the specific etiology of myocarditis is generally considered to be the optimal management strategy. For example, treatment of giant cell myocarditis and cardiac sarcoidosis usually involves immunosuppression. In addition, due to the very high incidence of systolic dysfunction in patients with myocarditis, standard heart failure therapy is also a requirement. This therapy should be administered in accordance with the patient's New York Heart Association (NYHA) functional class and typically involves beta-blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) [7]. In patients with advanced heart failure refractory to maximal pharmacologic therapy, mechanical circulatory support is utilized, including ventricular

assist devices (VAD) or extracorporeal membrane oxygenation (ECMO), as a bridge to recovery or cardiac transplantation [8-11].

Due to the relative paucity of published data investigating post-transplantation outcomes of recipients with a history of myocarditis and chronic inflammatory cardiomyopathy, controversy still exists regarding the optimal use of transplantation in this heterogeneous patient population [12]. Several small, single-center studies published in the early 1990's suggested decreased post-transplant survival as well as increased rates of rejection in these patients compared with the general population [13,14]. Since this time, a number of studies utilizing both single-center and national cohorts have demonstrated varying rates of acute and chronic rejection but equivalent post-transplant survival in patients with myocarditis compared with other recipients [15-17].

The purpose of this study is to characterize the cohort of patients that have undergone heart transplantation for myocarditis in the United States over the past several decades and compare the post-transplant outcomes of these patients to recipients with the most common pre-transplant diagnoses: ischemic and idiopathic dilated cardiomyopathy. It is hypothesized that given the substantial differences between the pathophysiology of these more common conditions with that of end-stage myocarditis requiring orthotopic heart transplantation, the baseline characteristics of these recipients will be quite dissimilar. As a result, post-transplantation outcomes between these two cohorts are likely quite dissimilar as well. The data gleaned from this study will be invaluable for clinical decision-making involving patients with myocarditis who have failed standard pharmacologic heart failure therapy and mechanical circulatory support.

METHODS

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research (STAR) files with de-identified donor and recipient transplant data from October 1987 to March 2013 and recipient follow-up data through December 2012. The database includes prospectively collected demographic, donor, operative, and postoperative information for all thoracic transplant recipients in the United States.

Study Design

We retrospectively reviewed the UNOS database from October 1987 to March 2013. The time-points were chosen to maximize the study period thereby capturing as many patients as possible that fit within the inclusion criteria. All single-organ heart transplants with a primary recipient diagnosis of idiopathic or ischemic dilated cardiomyopathy as well as biopsy-proven myocarditis were included. Transplants were primarily stratified by recipient diagnosis (idiopathic and ischemic DCM vs. myocarditis).

Outcome Measures

Demographic and clinical characteristics of all heart transplant donors and recipients were examined. This includes donor and recipient age, gender, ethnicity, and medical history as well as donor cause of death and recipient waitlist status and location before transplant. The primary end-point was all-cause mortality during the study period. Secondary outcomes of interest included 30-day mortality, length of hospital stay, graft rejection, as well as recipient cause of death.

Statistical Analysis

Baseline demographic and clinical characteristics between the primary study cohorts were compared using Student's *t*-test for continuous variables and the chi-square test for categorical variables. Survival was modeled using the Kaplan-Meier method with statistical differences between survival curves assessed using the log-rank (Mantel-Cox) test. Univariate, unadjusted 30-day, 1-year, 3-year, 5-year, and 10-year graft survival analyses were also conducted using the chi-square test. Multivariate analysis was conducted using the Cox proportional hazards regression model. In order to adjust for potential confounders and accurately determine factors associated with decreased post-transplant survival, variables describing baseline demographic and clinical characteristics that were significantly different ($p < 0.05$) between the two study cohorts on univariate analysis were included in the multivariate model.

Statistical significance was established at $p < 0.05$ (2-tailed) and all hazard ratios are presented with 95% confidence intervals. All statistical analysis was generated using SAS software, Version 9.3 of the SAS System for Windows. (©SAS Institute Inc., Cary, NC, USA). Oliver Jawitz performed all statistical analyses.

RESULTS

The UNOS database contained records of 554 heart transplants for patients with biopsy-proven myocarditis and 32,337 transplants for ischemic and idiopathic dilated cardiomyopathy during the study period that fit the inclusion criteria. The baseline

demographic characteristics of both donors and recipients from these transplant surgeries are summarized in Tables 1 and 2, respectively.

Table 1. Donor Characteristics Stratified by Diagnosis

Variable	Ischemic/Idiopathic DCM N = 32,337[a]	Myocarditis N = 554[a]	p-Value*
Female	9,387 (29.0%)	195 (35.2%)	0.002
Mean (STD) donor age (yr)	29.77 (±13.09)	23.61 (±14.87)	< 0.001
Ethnicity			
White	23,139 (71.7%)	402 (72.8%)	0.55
African American	4,183 (13.0%)	70 (12.7%)	0.85
Hispanic or Latino	4,220 (13.1%)	68 (12.3%)	0.60
Asian	414 (1.3%)	5 (0.9%)	0.43
History of hypertension	3,146 (11.6%)	29 (8.6%)	0.09
History of cancer	427 (1.6%)	2 (0.6%)	0.15
History of diabetes	600 (2.2%)	7 (2.1%)	0.86
History of cigarette use	7,168 (26.5%)	53 (15.8%)	< 0.001
Cause of death			
Anoxia	3,275 (10.2%)	75 (13.6%)	0.008
Cerebrovascular/stroke	8,064 (25.0%)	107 (19.4%)	0.003
Head trauma	18,332 (56.8%)	281 (50.9%)	0.005
CNS tumor	287 (0.9%)	3 (0.5%)	0.39
Mean (STD) LVEF	61.66 (±7.89)	61.19 (±9.14)	0.34

DCM, dilated cardiomyopathy; CNS, central nervous system; LVEF, left ventricular ejection fraction. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

The allograft donors from both cohorts were well matched based on ethnicity, history of hypertension, diabetes, and cancer, as well as mean left ventricular ejection fraction (LVEF). There was a significant difference ($p < 0.05$) between the two groups in terms of donor gender, age, history of cigarette use, and cause of death. Compared with transplants for ischemic/idiopathic dilated cardiomyopathy, donors for patients with myocarditis were more frequently female (35.2% vs. 29.0%), younger (mean age 23.6 vs. 29.8 years), and had a cause of death listed as anoxia (13.6% vs. 10.25). These donors less frequently had a history of cigarette use (15.8% vs. 26.5%) and had a primary cause

of death listed as cerebrovascular/stroke (19.4% vs. 25.0%) or head trauma (50.9% vs. 56.8%).

Table 2. Recipient Characteristics Stratified by Diagnosis

Variable	Ischemic/Idiopathic DCM N = 32,337[a]	Myocarditis N = 554[a]	p-Value*
Gender (female)	7,301 (22.6%)	230 (41.5%)	< 0.001
Mean (STD) recipient age (yr)	50.13 (±15.40)	29.96 (±19.90)	< 0.001
Ethnicity			
White	23,895 (73.9%)	369 (67.0%)	< 0.001
African American	5,276 (16.3%)	118 (21.4%)	0.001
Hispanic or Latino	2,110 (6.5%)	44 (8.0%)	0.17
Asian	727 (2.3%)	11 (2.0%)	0.69
ABO blood group			
A	13,605 (42.1%)	244 (44.0%)	0.35
B	4,411 (13.6%)	87 (15.7%)	0.16
AB	1,657 (5.1%)	21 (3.8%)	0.16
O	12,664 (39.2%)	202 (36.5%)	0.2
Waitlist status at transplant			
Status 1	23,853 (76.1%)	424 (83.8%)	< 0.001
Status 2	7,490 (23.9%)	82 (16.2%)	< 0.001
Location before transplant			
In ICU	12,816 (39.7%)	322 (58.3%)	< 0.001
In hospital (not ICU)	4,743 (14.7%)	88 (15.9%)	0.42
Not in hospital	14,690 (45.6%)	142 (25.7%)	< 0.001
Life support at transplant			
ECMO	153 (0.5%)	37 (6.7%)	< 0.001
IABP	1,660 (5.1%)	35 (6.3%)	0.21
IV Inotropes	13,913 (43.0%)	203 (36.6%)	0.003
Ventilatory support	1,049 (3.2%)	74 (13.4%)	< 0.001
VAD	6,280 (19.4%)	142 (25.6%)	< 0.001
History of dialysis	725 (2.2%)	13 (2.4%)	0.87
History of cardiac surgery	4,320 (13.4%)	29 (5.2%)	< 0.001
History of malignancy	968 (3.0%)	9 (1.7%)	0.06
History of diabetes	6,075 (18.8%)	21 (3.8%)	< 0.001
History of cigarette use	5,806 (18.0%)	30 (5.4%)	< 0.001
History of IV antibiotics in prior two weeks	2,871 (11.0%)	66 (20.1%)	< 0.001
History of chronic steroid use	1,946 (7.5%)	46 (14.0%)	< 0.001
Mean (STD) ischemic time (hr)	3.04 (±1.06)	2.98 (±1.13)	0.2
Mean (STD) serum creatinine at Tx (mg/dL)	1.35 (±1.21)	1.02 (±0.97)	< 0.001
Mean (STD) total bilirubin (mg/dL)	1.28 (±2.97)	1.57 (±3.02)	0.08
CMV IgG positive	11,413 (35.3%)	412 (74.4%)	< 0.001
Most recent PRA > 10%			
Overall	2,315 (11.4%)	43 (12.8%)	0.44
Class I	1,706 (14.1%)	35 (16.1%)	0.41
Class II	889 (7.3%)	18 (8.3%)	0.61

DCM, dilated cardiomyopathy; ICU; intensive care unit; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, intravenous; VAD, ventricular assist device; CMV, cytomegalovirus; IgG, immunoglobulin G; PRA, panel reactive antibody. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

The baseline demographic and clinical characteristics of heart recipients in the myocarditis and ischemic/idiopathic DCM cohorts differed ($p < 0.05$) with respect to gender, age, ethnicity, location before transplant (intensive care unit vs. outside hospital), waitlist status, history of cardiac surgery, diabetes, cigarette use, use of life support, IV antibiotics, chronic steroids, as well as mean serum creatinine and cytomegalovirus (CMV) immunoglobulin G (IgG) status before transplant. Recipients with myocarditis were more often female (41.5% vs 22.6%), younger (mean age 30.0 vs. 50.1 years), African American (21.4% vs. 16.3%), waitlist status 1A and 1B (83.8% vs. 76.1%), in the ICU at transplant (58.3% vs. 39.7%), and on ECMO (6.7% vs. 0.5%), ventilator (13.4% vs. 3.2%), and VAD (25.6% vs. 19.4%) support. They also more frequently had a history of IV antibiotic use in the two weeks prior to transplant (20.1% vs. 11.0%), chronic steroid use (14.0% vs. 7.5%) and were more often CMV IgG positive (74.4% vs. 35.3%). Compared to recipients with ischemic or idiopathic dilated cardiomyopathy, recipients with myocarditis were less frequently white (67.0% vs. 73.9%), on IV inotropes (36.6% vs. 43.0%), had a history of cardiac surgery (5.2% vs. 13.4%), diabetes (3.8% vs. 18.8%), and cigarette use (5.4% vs. 18.0%), and had lower mean serum creatinine at transplant (1.02 vs. 1.35 mg/dL). The two study cohorts were well matched based upon ABO blood type, history of dialysis, mean ischemic time, and pre-transplant overall, class I, and class II panel reactive antibody (PRA).

Table 3 shows unadjusted 30 day, 1 year, 3 year, 5 year, and 10 year post-transplant survival for heart transplant recipients with a history of myocarditis as well as ischemic and idiopathic dilated cardiomyopathy. Survival rates were equivalent ($p > 0.05$) for both cohorts at all time points. In addition, there was no difference in the

incidence of rejection between transplant and discharge (p = 0.16) and mean length of stay, transplant to discharge (p = 0.93).

Table 3. Outcomes Stratified by Diagnosis

Variable	Ischemic/Idiopathic DCM N = 32,337[a]	Myocarditis N = 554[a]	p-Value*
Survival 30 days	30,147 (94.3%)	512 (93.6%)	0.5
Survival 1 yr	26,303 (86.0%)	452 (86.8%)	0.62
Survival 3 yr	21,212 (75.9%)	361 (77.6%)	0.37
Survival 5 yr	16,840 (65.4%)	279 (66.0%)	0.82
Survival 10 yr	7,972 (37.5%)	150 (41.2%)	0.15
Rejection between transplant and discharge	1,823 (5.6%)	39 (7.0%)	0.16
Mean (STD) length of stay, transplant to discharge (days)	19.78 (±24.50)	19.91 (±18.86)	0.93

Survival data based on patient survival time, post-transplant. DCM, dilated cardiomyopathy. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables (p < 0.05 considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

Recipient cause of death differed significantly (p < 0.05) between the two cohorts in terms of death from graft failure as well as infection (Table 4). Recipients with a history of myocarditis more frequently died from graft failure (30.5% vs. 18.3%), including acute rejection (11.7% vs. 6.7%) and chronic rejection (12.7% vs. 3.5%). In addition, compared with recipients with a history of ischemic or idiopathic dilated cardiomyopathy, those diagnosed with myocarditis less frequently died from infection (9.1% vs. 16.0%).

Table 4. Recipient Cause of Death Stratified by Diagnosis

Variable	Ischemic/Idiopathic DCM N = 32,337[a]	Myocarditis N = 554[a]	p-Value*
Graft failure - all causes	2,049 (18.3%)	60 (30.5%)	< 0.001
Primary failure	488 (4.4%)	8 (4.1%)	0.84
Acute rejection	751 (6.7%)	23 (11.7%)	0.006
Chronic rejection	386 (3.5%)	25 (12.7%)	< 0.001
Infection	1,787 (16.0%)	18 (9.1%)	0.009
Cardiovascular	2,495 (22.3%)	46 (23.4%)	0.72
Pulmonary	683 (6.1%)	9 (4.6%)	0.37
Cerebrovascular	519 (4.6%)	11 (5.6%)	0.53
Hemorrhage	212 (1.9%)	5 (2.5%)	0.51
Malignancy	1,588 (14.2%)	26 (13.2%)	0.69
Renal failure	504 (4.5%)	5 (2.5%)	0.19
Multiple organ failure	968 (8.6%)	13 (6.6%)	0.31

DCM, dilated cardiomyopathy. *p-Value based on the chi-square test for categorical variables (p < 0.05 considered statistically significant)

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

When post-transplant survival was compared between the two study cohorts using the Kaplan-Meier method (Figure 1), recipients with a diagnosis of biopsy-proven myocarditis as well as those with ischemic/idiopathic dilated cardiomyopathy were equivalent as demonstrated by the log-rank test ($p = 0.42$).

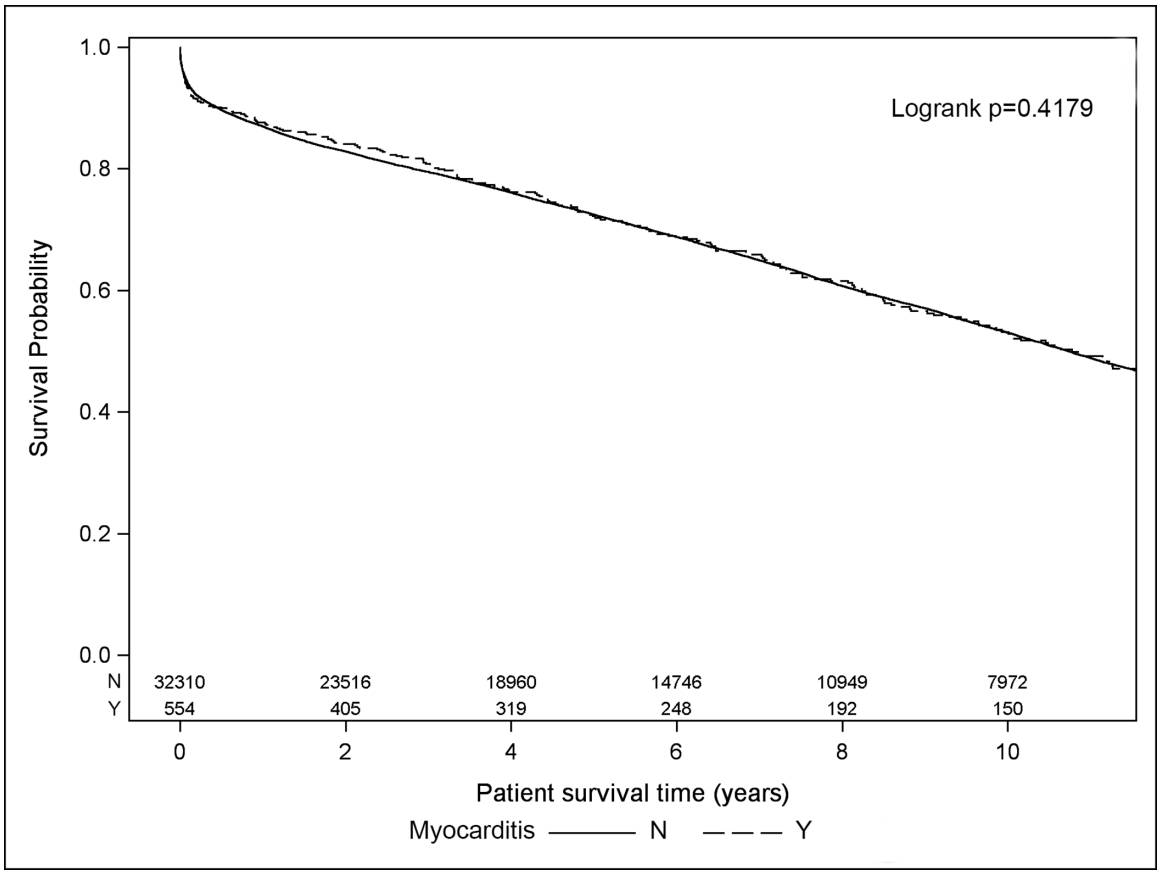

Figure 1. Kaplan-Meier transplant recipient survival analysis, myocarditis vs. ischemic and idiopathic dilated cardiomyopathy (dashed line: myocarditis, solid line: ischemic and idiopathic dilated cardiomyopathy). A table is given with the number of patients at risk at each time point. The p-value corresponds to Mantel-Cox log-rank test results.

The multivariate Cox proportional hazards regression model (Table 5) indicated several variables as independent predictors of increased post-transplant mortality ($p < 0.05$). These include donor and recipient age, recipient ethnicity, use of ECMO, ventilatory support, and VAD at transplant, recipient location before transplant (in the

ICU), recipient serum creatinine, history of prior cardiac surgery, diabetes, and IV antibiotics in the prior two weeks, as well as donor and recipient cigarette use. Importantly, recipient diagnosis of myocarditis, compared with ischemic/idiopathic DCM, was not a significant independent predictor of mortality (hazard ratio [recipient diagnosis – myocarditis] 1.05, p = 0.64).

Table 5. Multivariate Cox Proportional Hazards Regression Model

Variable	Hazard Ratio (95% Confidence Limits)	p-Value*
Diagnosis - myocarditis[a]	1.05 (0.86-1.27)	0.64
Donor age	1.01 (1.01-1.01)	< 0.001
Recipient age	1.00 (1.00-1.01)	< 0.001
Donor gender (male vs. female)	0.97 (0.93-1.01)	0.16
Recipient gender (male vs. female)	0.97 (0.92-1.02)	0.21
Recipient ethnicity[b]		
African American	1.38 (1.31-1.45)	< 0.001
Hispanic	0.99 (0.91-1.08)	0.82
Asian	0.91 (0.78-1.05)	0.2
Life support at transplant[c]		
ECMO	1.45 (1.15-1.84)	0.002
IV inotropes	0.97 (0.92-1.02)	0.19
Ventilatory support	1.47 (1.33-1.63)	< 0.001
VAD	1.07 (1.01-1.13)	0.02
Status before transplant[d]		
In ICU	1.16 (1.10-1.23)	< 0.001
In hospital (not ICU)	1.09 (1.02-1.16)	0.008
Recipient CMV IgG positive	1.05 (0.99-1.12)	0.1
Recipient serum creatinine at transplant	1.02 (1.01-1.03)	< 0.001
History of prior cardiac surgery	1.11 (1.03-1.19)	0.008
History of diabetes	1.23 (1.18-1.29)	< 0.001
History of IV antibiotics in prior two weeks	1.16 (1.09-1.23)	< 0.001
History of chronic steroid use	1.05 (0.97-1.13)	0.23
Recipient history of cigarette use	0.92 (0.86-0.99)	0.02
Donor history of cigarette use	1.08 (1.03-1.12)	< 0.001

ECMO, extracorporeal membrane oxygenation; IV, intravenous; VAD, ventricular assist device; ICU, intensive care unit; CMV cytomegalovirus; IgG, immunoglobulin G. *p-Value based on multivariate Cox proportional hazards regression model, using factors significant on univariate analysis (p < 0.05 considered statistically significant).

[a]vs. ischemic/idiopathic dilated cardiomyopathy

[b]vs. white ethnicity

[c]vs. no life support

[d]vs. not in hospital

DISCUSSION

This study represents the largest investigation of post-heart transplant outcomes in patients with myocarditis to date. A large, diverse cohort of patients was used spanning several decades of heart transplantation in the United States.

Due to the fact that heart transplant donors and recipients are frequently matched based on many factors including age, size, and gender, the differences in baseline characteristics between myocarditis and ischemic/idiopathic DCM transplant donors, especially with regard to age and gender, are likely the direct result of corresponding differences between recipients.

Compared with the most common indications for heart transplant, ischemic and idiopathic dilated cardiomyopathy, organ recipients with a history of myocarditis induced dilated cardiomyopathy had equivalent outcomes in terms of survival, length of hospital stay, and incidence of hyperacute graft rejection. Considering the substantial demographic disparities between the two cohorts pre-transplant, these results are somewhat surprising. The myocarditis patients were more likely to be female, younger, and have less comorbidity than recipients with a history of ischemic or idiopathic dilated cardiomyopathy and might therefore be expected to have increased survival post-transplant.

While actual post-transplant survival was identical between the two cohorts, specific causes of death were quite different. Patients with a history of myocarditis had significantly higher rates of death from primary graft failure including acute and chronic rejection and less frequently died from infection. This is likely the result of significant disparities between the two cohorts in terms of baseline demographic characteristics.

Furthermore, these findings suggest that recipients with a history of myocarditis induced dilated cardiomyopathy might benefit from increased immunosuppression post-transplant. Recent advances in post-transplant immunosuppression regimens have significantly decreased rates of rejection and have therefore certainly helped improve these patients' prognosis [5,18]. It should be noted, however, that analysis of a more recent cohort of patients demonstrated similar findings in terms of recipient survival and cause of death.

CONCLUSIONS

The favorable post-transplant survival rate of patients with a history of myocarditis suggests that those patients with myocarditis induced end-stage heart failure should be aggressively treated and bridged to transplant using mechanical circulatory support modalities IABP and VAD. In addition, the post-transplant survival of these patients could be improved with a more intensive immunosuppression regimen that is specifically tailored to the inflammatory nature of their primary disease.

Part 2

Impact of ABO compatibility on outcomes following heart transplantation in a national cohort over the last decade.

BACKGROUND

There are several risk factors known to be associated with premature death and other complications following cardiac transplantation including donor cardiac function and preexisting disease, toxicity, systemic infection, ischemic time, as well as mismatches between donor and recipient heart size, gender, age, and antigenic phenotypes [19]. Since basic immunological incompatibility is a clear indication for post-transplant complications, it is common practice to avoid antigenic mismatch when pairing donor hearts with recipients. Human leukocyte antigen (HLA) matching is currently applied only to highly sensitized individuals listed for heart transplantation, although many centers are now using a strategy of "virtual" cross-matching [20]. Organ donors and potential recipients are, however, paired based upon ABO blood type matching. There are three categories of ABO matching: ABO identical, ABO compatible, and ABO incompatible. While adult patients typically do not receive organs from ABO incompatible donors, avoiding hyperacute graft rejection, recipients sometimes receive hearts from ABO compatible donors. This is unlike transplant procedures for pediatric recipients, where ABO incompatible grafts are sometimes acceptable due to a delay in the development of natural antibodies to ABO antigens [21].

Morbidity and mortality associated with recent increases in donor shortages for all organ transplantation types has led to a renewed interest in ABO-incompatible matching.

While significant progress has been made on this front in the fields of kidney and pediatric heart transplantation, ABO compatibility is largely still a requirement for adult heart transplantation [22]. Before ABO-incompatible adult heart transplantation can be considered, however, it is important to first solidify our understanding of ABO-identical and ABO-compatible heart transplantation. In the late 1980's and early 1990's, several anecdotal reports suggested unfavorable outcomes among ABO compatible (non-identical) adult heart transplants [23,24]. Since then, however, a number of small, hospital-based retrospective studies have been conducted which have largely determined that there are no significant differences in outcomes of ABO compatible versus ABO identical cardiac transplants [24-26]. The 2012 ISHLT Heart Transplant Report listed non-ABO identical transplants as a borderline significant risk factor for five-year mortality post-transplant [27]. It is hypothesized that ABO compatible and ABO identical transplants are associated with similar post-transplantation survival. We believe that it would be clinically useful to compare the medium and long-term outcomes of ABO compatible and ABO identical heart transplants in a large nationwide modern cohort study. Data gleaned from this study could have significant implications for the maximally efficient usage of the limited donor pool.

METHODS

Data Source

The United Network for Organ Sharing (UNOS) provided Standard Transplant Analysis and Research (STAR) files with de-identified donor and recipient transplant data from October 1987 to March 2012 and recipient follow-up data through December

2011. The database includes prospectively collected demographic, donor, operative, and postoperative information for all thoracic transplant recipients in the United States.

Study Design

We retrospectively reviewed the UNOS database from January 2000 to December 2009. The time-points were chosen to identify a modern cohort of heart transplant patients with adequate time for follow-up. All adult (≥18 years) single-organ heart transplants were included. Transplants were primarily stratified by transplant donor-recipient ABO blood type matching (identical vs. compatible). Transplants without available data on donor and/or recipient ABO types were excluded from the study (n=1).

Outcome Measures

Demographic and clinical characteristics of all heart transplant donors and recipients were examined. This included donor and recipient age, gender, ethnicity, and relevant medical history. Donor cause of death as well as recipient waitlist status, location, and life support at transplant were also analyzed. The primary end-point was all-cause graft failure during the study period. Secondary outcomes of interest included 30-day mortality, length of hospital stay, graft rejection, as well as recipient cause of death.

Statistical Analysis

Baseline demographic and clinical characteristics between the primary study cohorts were compared using Student's *t*-test for continuous variables and the chi-square test for categorical variables. For all Student's *t*-tests conducted, normality was assessed

using skewness and kurtosis. Survival was modeled using the Kaplan-Meier method with statistical differences between survival curves assessed using the log-rank (Mantel-Cox) test. Univariate, unadjusted 30-day, 1-year, 3-year, 5-year, and 10-year graft survival analyses were also conducted using the chi-square test. Multivariate analysis was conducted using both the Cox proportional hazards regression model as well as a logistic regression model. In order to adjust for potential confounders and accurately determine factors associated with decreased graft survival, variables describing baseline demographic and clinical characteristics that were significantly different ($p < 0.05$) between the two study cohorts on univariate analysis were included in the multivariate models. For the logistic regression analysis, variables were removed from the model in a stepwise fashion until all included variables (except ABO compatibility, the variable of interest) were statistically significant ($p < 0.05$).

Statistical significance was established at $p < 0.05$ (2-tailed) and all hazard ratios are presented with 95% confidence intervals. All statistical analysis was generated using SAS software, Version 9.3 of the SAS System for Windows. (©SAS Institute Inc., Cary, NC, USA). Oliver Jawitz performed all statistical analyses.

RESULTS

The UNOS database contained records of 15,267 ABO identical transplants and 2,684 ABO compatible transplants during the study period from January 2000 to December 2009 that fit the study's inclusion criteria (Table 6). Of the transplant recipients with blood types A, B, and AB, the frequency of ABO compatible transplants

was 17.0%, 32.8%, and 61.8%, respectively. Blood type O recipients can only receive ABO identical grafts.

Table 6. ABO Blood Group Distribution

		Donor Blood Type					
		A	**AB**	**B**	**O**	**Total Identical[a]**	**Total Compatible[a]**
Recipient Blood Type	**A**	6340	0	0	1302	6340 (83.0%)	1302 (17.0%)
	AB	274	342	189	90	342 (38.2%)	553 (61.8%)
	B	0	0	1696	829	1696 (67.2%)	829 (32.8%)
	O	0	0	0	6889	6889 (100%)	0 (0%)

[a]Total identical and total compatible measured as proportion of each recipient blood type.

The baseline demographic characteristics of both donors and recipients from these transplant surgeries are summarized in Tables 7 and 8, respectively. The allograft donors from both cohorts were well matched based on gender, age, mean left ventricular ejection fraction (LVEF), cause of death, as well as a history of hypertension, diabetes, and cigarette use. There was a significant difference ($p < 0.05$) between the two groups in terms of donor ethnicity and history of cancer.

Table 7. Donor Characteristics Stratified by ABO Blood Type Matching

Variable	ABO Identical N = 15,267[a]	ABO Compatible N = 2,684[a]	p-Value*
Female	4,306 (28.2%)	787 (29.3%)	0.24
Mean (STD) donor age (yr)	31.54 (±12.35)	31.40 (±12.53)	0.58
Ethnicity			
White	10,687 (70.0%)	1,697 (63.3%)	< 0.001
Black	1,938 (12.7%)	387 (14.4%)	0.01
Hispanic or Latino	2,259 (14.8%)	518 (19.3%)	< 0.001
Asian	213 (1.4%)	46 (1.7%)	0.20
History of hypertension	1,829 (12.0%)	336 (12.6%)	0.42
History of cancer	254 (1.7%)	64 (2.4%)	0.01
History of diabetes	343 (2.3%)	68 (2.5%)	0.35
History of cigarette use	3,903 (25.8%)	698 (26.2%)	0.67
Cause of death			
Anoxia	1,562 (10.2%)	288 (10.7%)	0.44
Cerebrovascular/stroke	3,839 (25.2%)	713 (26.6%)	0.12
Head trauma	9,427 (61.8%)	1,615 (60.2%)	0.12
CNS tumor	158 (1.0%)	25 (0.93%)	0.62
Mean (STD) LVEF	61.57 (±7.83)	61.62 (±8.02)	0.74

CNS, central nervous system. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

The baseline demographic and clinical characteristics of heart recipients in the ABO identical and ABO compatible cohorts differed ($p < 0.05$) with respect to gender, age, ethnicity, waitlist status at transplant, status before transplant (in ICU, in hospital, or not hospitalized), life support before transplant, as well as mean graft ischemic time and total bilirubin. A larger proportion of ABO compatible transplant recipients were waitlist status 1A (50.3%) than ABO identical transplant recipients (28.3%, $p < 0.001$). Additionally, 40.4% of ABO compatible recipients were in the ICU prior to transplant compared to only 28.3% of ABO identical recipients ($p < 0.05$). When compared with ABO identical transplant recipients, ABO compatible transplant recipients were more frequently on life support prior to transplant ($p < 0.05$), including extracorporeal membrane oxygenation (ECMO), intra-aortic balloon pump (IABP), IV inotropes, and ventilator support. There was no statistical difference between the two groups in terms of ventricular assist device (VAD) use ($p = 0.266$). Graft ischemic time and total bilirubin

also differed between the two study cohorts ($p < 0.001$); ABO identical transplant recipients had a longer mean ischemic time and lower total bilirubin (3.23 hours, 1.25 mg/dL) compared to ABO compatible transplant recipients (3.11 hours, 1.48 mg/dL).

Table 8. Recipient Characteristics Stratified by ABO Blood Type Matching

Variable	ABO Identical N = 15,267[a]	ABO Compatible N = 2,684[a]	p-Value*
Female	3,584 (23.5%)	708 (26.4%)	0.001
Mean (STD) recipient age (yr)	51.91 (±12.26)	51.12 (±12.87)	< 0.001
Ethnicity			
White	11,286 (73.9%)	1,882 (70.1%)	< 0.001
Black	2,399 (15.7%)	498 (18.6%)	< 0.001
Hispanic or Latino	1,110 (7.3%)	179 (6.7%)	0.27
Asian	311 (2.0%)	102 (3.8%)	< 0.001
Waitlist status at transplant			
Status 1A	5,771 (37.8%)	1350 (50.3%)	< 0.001
Status 1B	6,040 (39.6%)	928 (34.6%)	< 0.001
Status 2	3,450 (22.6%)	405 (15.1%)	< 0.001
Status before transplant			
In ICU	4,321 (28.3%)	1,083 (40.4%)	< 0.001
In hospital (not ICU)	2,853 (18.7%)	545 (20.3%)	0.05
Not in hospital	8,093 (53.0%)	1,056 (39.3%)	< 0.001
Life support at transplant			
ECMO	67 (0.44%)	25 (0.93%)	0.001
IABP	737 (4.8%)	234 (8.7%)	< 0.001
IV Inotropes	6,786 (44.5%)	1,330 (49.6%)	< 0.001
Inhaled NO	36 (0.24%)	7 (0.26%)	0.81
Ventilatory support	387 (2.5%)	122 (4.5%)	< 0.001
VAD	3,609 (23.6%)	608 (22.7%)	0.27
History of dialysis	368 (2.4%)	76 (2.8%)	0.2
History of cardiac surgery	2,918 (19.1%)	543 (20.2%)	0.18
History of malignancy	739 (4.8%)	137 (5.1%)	0.56
History of diabetes	3,460 (22.7%)	600 (22.4%)	0.73
History of cigarette use	3,848 (25.2%)	700 (26.1%)	0.34
Mean (STD) ischemic time (hr)	3.23 (±1.05)	3.11 (±1.00)	< 0.001
Mean (STD) serum creatinine at Tx (mg/dL)	1.31 (±0.56)	1.33 (±0.63)	0.14
Mean (STD) total bilirubin (mg/dL)	1.23 (±1.94)	1.37 (±2.01)	< 0.001
CMV IgG positive	8,675 (62.6%)	1,567 (63.7%)	0.32
CMV IgM positive	816 (8.8%)	164 (9.6%)	0.24

ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; IV, intravenous; NO, nitric oxide; VAD, ventricular assist device; CMV, cytomegalovirus; IgG, immunoglobulin G; IgM, immunoglobulin M.
*p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

[a]Some patients were excluded from each analysis due to missing data fields or erroneously inputed data in the database

Table 9 shows unadjusted 30 day, 1 year, 3 year, 5 year, and 10 year graft survival for ABO identical and ABO compatible heart transplant recipients. Recipients of ABO identical grafts had increased graft survival ($p < 0.05$) compared to ABO compatible recipients at 30 days (94.4% vs. 93.3%), 1 year (87.0% vs. 84.4%), 3 years (76.3% vs. 73.4%), and 5 years post-transplant (63.1% vs. 60.0%). There was no statistically significant difference in graft survival at 10 years post-transplant ($p = 0.21$). In addition, there was no difference in the incidence of rejection between transplant and discharge ($p = 0.53$) and mean length of stay, transplant to discharge ($p = 0.97$).

Table 9. Outcomes Stratified by ABO Blood Type Matching

Variable	ABO Identical N = 15,267	ABO Compatible N = 2,684	p-Value*
Survival 30 days	14,396 (94.4%)	2,500 (93.3%)	0.02
Survival 1 yr	13,241 (87.0%)	2,258 (84.4%)	< 0.001
Survival 3 yr	10,199 (76.3%)	1,720 (73.4%)	0.003
Survival 5 yr	6,960 (63.1%)	1,140 (59.9%)	0.009
Survival 10 yr	1,147 (17.8%)	187 (16.3%)	0.21
Rejection between transplant and discharge	1,319 (8.6%)	222 (8.3%)	0.53
Mean (STD) length of stay, transplant to discharge (days)	20.04 (±25.86)	20.05 (±22.14)	0.97

Survival data based on graft survival time, post-transplant. *p-Value based on Student's t-test for continuous variables and the chi-square test for categorical variables ($p < 0.05$ considered statistically significant).

Transplant recipient cause of death was similar between ABO identical and compatible recipients except for mortality due to primary graft failure as well as malignancy (Table 10). A greater proportion of ABO compatible heart recipients died from primary graft failure then ABO identical recipients (8.7% vs. 5.8%, $p = 0.003$). Interestingly, ABO identical transplant recipients showed a greater incidence of death due to malignancy than the ABO compatible cohort (9.8% vs. 6.6%, $p = 0.007$).

Table 10. Recipient Cause of Death Stratified by ABO Blood Type Matching

Variable	ABO Identical N = 4,000	ABO Compatible N = 724	p-Value*
Graft failure - all causes	709 (17.7%)	149 (20.6%)	0.07
Primary failure	231 (5.8%)	63 (8.7%)	0.003
Acute rejection	252 (6.3%)	41 (5.7%)	0.51
Chronic rejection	108 (2.7%)	25 (3.5%)	0.26
Infection	615 (15.4%)	119 (16.4%)	0.47
Cardiovascular	773 (19.3%)	144 (19.9%)	0.72
Pulmonary	259 (6.5%)	45 (6.2%)	0.79
Cerebrovascular	180 (4.5%)	23 (3.2%)	0.11
Hemorrhage	98 (2.5%)	17 (2.4%)	0.87
Malignancy	392 (9.8%)	48 (6.6%)	0.007
Renal failure	102 (2.6%)	23 (3.2%)	0.33
Multiple organ failure	417 (10.4%)	78 (10.8%)	0.78

*p-Value based on the chi-square test for categorical variables ($p < 0.05$ considered statistically significant)

When graft survival was compared between the two study cohorts using the Kaplan-Meier method (Figure 2), ABO identical recipients showed a slightly higher degree of graft survival, although the log-rank test showed that this difference was not statistically significant ($p = 0.09$).

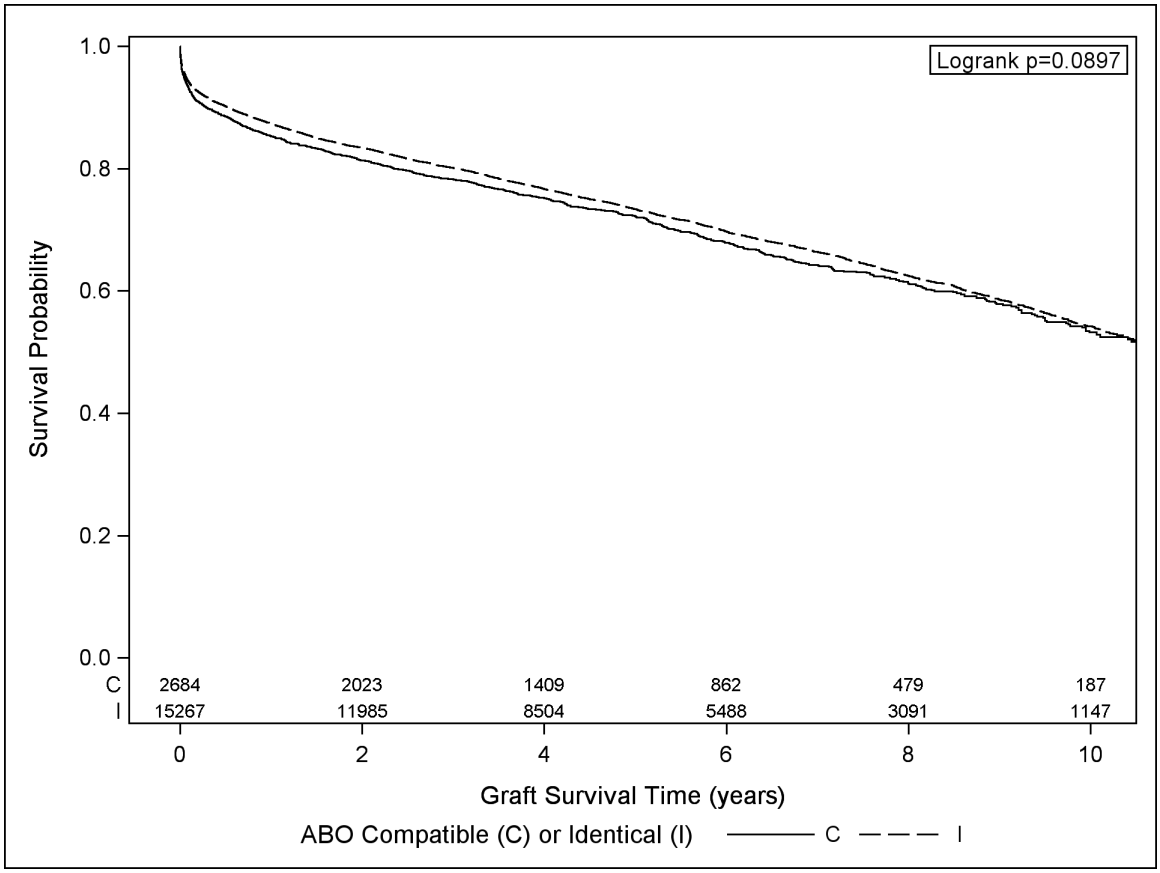

Figure 2. Kaplan-Meier graft survival analysis, ABO compatible vs. ABO identical transplants (solid line: ABO compatible transplants, dashed line: ABO identical transplants). A table is given with the number of patients at risk at each time point. The p-value corresponds to Mantel-Cox log-rank test results.

The multivariate Cox proportional hazards regression model (Table 11) demonstrated six variables of significance ($p < 0.05$) for the outcome measure of graft failure: recipient ethnicity, ventilatory support at transplant, pre transplant ECMO use, graft ischemic time, total bilirubin, as well as patient status before transplant (in ICU, in hospital, or not hospitalized). While univariate analysis showed ABO blood type matching (identical vs. compatible) to have a significant impact on the incidence of graft failure, this effect was eliminated when controlling for potential confounders in the multivariate model (hazard ratio [ABO compatible] 0.991, $p = 0.865$).

Table 11. Multivariate Cox Proportional Hazards Regression Model

Variable	Hazard Ratio (95% Confidence Limits)	p-Value*
ABO compatible[a]	0.99 (0.89-1.10)	0.87
Gender (male vs. female)	0.95 (0.88-1.03)	0.24
Donor ethnicity[b]		
Black	1.08 (0.98-1.20)	0.14
Hispanic	1.00 (0.90-1.10)	0.95
Asian	1.13 (0.87-1.47)	0.37
Recipient ethnicity[b]		
Black	1.42 (1.30-1.56)	< 0.001
Hispanic	1.09 (0.94-1.25)	0.25
Asian	0.92 (0.70-1.19)	0.52
Life support at transplant[c]		
All	1.07 (0.94-1.21)	0.32
IABP	0.98 (0.81-1.20)	0.85
IV Inotropes	0.95 (0.85-1.06)	0.34
Ventilatory support	1.88 (1.50-2.37)	< 0.001
ECMO	2.60 (1.72-3.83)	< 0.001
Ischemic time	1.09 (1.06-1.13)	< 0.001
Waitlist status at transplant[d]		
Status 1B	1.00 (0.90-1.11)	0.95
Status 2	1.08 (0.94-1.23)	0.29
Status before transplant[e]		
In ICU	1.24 (1.10-1.39)	< 0.001
In hospital (not ICU)	1.13 (0.99-1.28)	0.07
Total bilirubin	1.03 (1.02-1.04)	< 0.001

IABP, intra-aortic balloon pump; IV, intravenous; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit. *p-Value based on multivariate Cox proportional hazards regression model, using factors significant on univariate analysis ($p < 0.05$ considered statistically significant).

[a]vs. ABO incompatible

[b]vs. white ethnicity

[c]vs. no life support

[d]vs. UNOS waitlist status 1A

[e]vs. not in hospital

In the multivariate logistic regression model showing risk factors for 30 day graft failure post-transplant, variables of significance ($p < 0.05$) were life support at transplant, including IV inotropes, ventilator support, pre transplant ECMO use; ischemic time, waitlist status at transplant, status before transplant (in ICU, in hospital, or not hospitalized), as well as total bilirubin (Table 12). Once again, when controlling for potential confounding variables, ABO matching (identical vs. compatible) was not statistically significant ($p = 0.08$).

Table 12. Multivariable Logistic Regression Model - 30-Day Graft Failure

Variable	Odds Ratio (95% Confidence Limits)	p-Value*
ABO Compatible	1.23 (0.97-1.56)	0.08
Life support at transplant[a]		
All	1.89 (1.40-2.54)	< 0.001
IV Inotropes	0.58 (0.46-0.74)	< 0.001
Ventilatory support	2.78 (1.87-4.14)	< 0.001
ECMO	7.53 (4.18-13.55)	< 0.001
Ischemic time	1.24 (1.15-1.34)	< 0.001
Waitlist status at transplant[b]		
Status 1B	1.23 (0.97-1.56)	0.09
Status 2	1.68 (1.19-2.36)	0.003
Status before transplant[c]		
In ICU	1.60 (1.23-2.07)	< 0.001
In hospital (not ICU)	1.16 (0.86-1.56)	0.34
Total bilirubin	1.08 (1.05-1.10)	< 0.001

IV, intravenous; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit. *p-Value based on logistic regression model ($p < 0.05$ considered statistically significant).

[a]vs. no life support

[b]vs. UNOS waitlist status 1A

[c]vs. not in hospital

Post-transplant graft survival was also compared among different donor ABO blood groups using the Kaplan-Meier method (Figure 3). This analysis demonstrated decreased graft survival associated with type O donors and increased survival associated with type A donors ($p < 0.05$) when compared to all other blood types. Type B and AB donors were not associated with either increased or decreased graft survival when compared with the other ABO blood types ($p > 0.05$). When looking at post-transplant graft survival in blood type B recipients (Figure 4), blood type O donor hearts were associated with decreased graft survival when compared with type B grafts ($p < 0.05$).

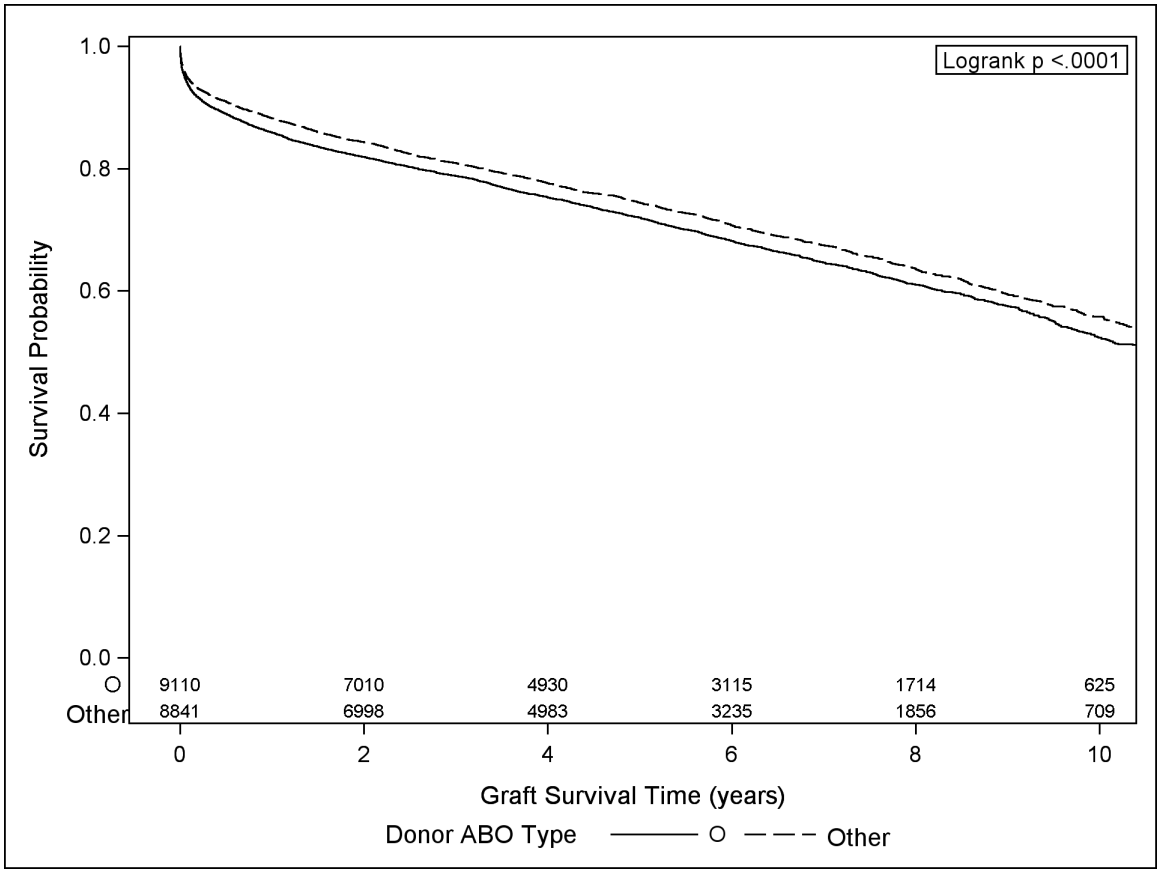

Figure 3. Kaplan-Meier graft survival analysis, donor type O vs. all other heart transplants (solid line: donor ABO type O, dashed line: all other donor types). A table is given with the number of patients at risk at each time point. The p-value corresponds to Mantel-Cox log-rank test results.

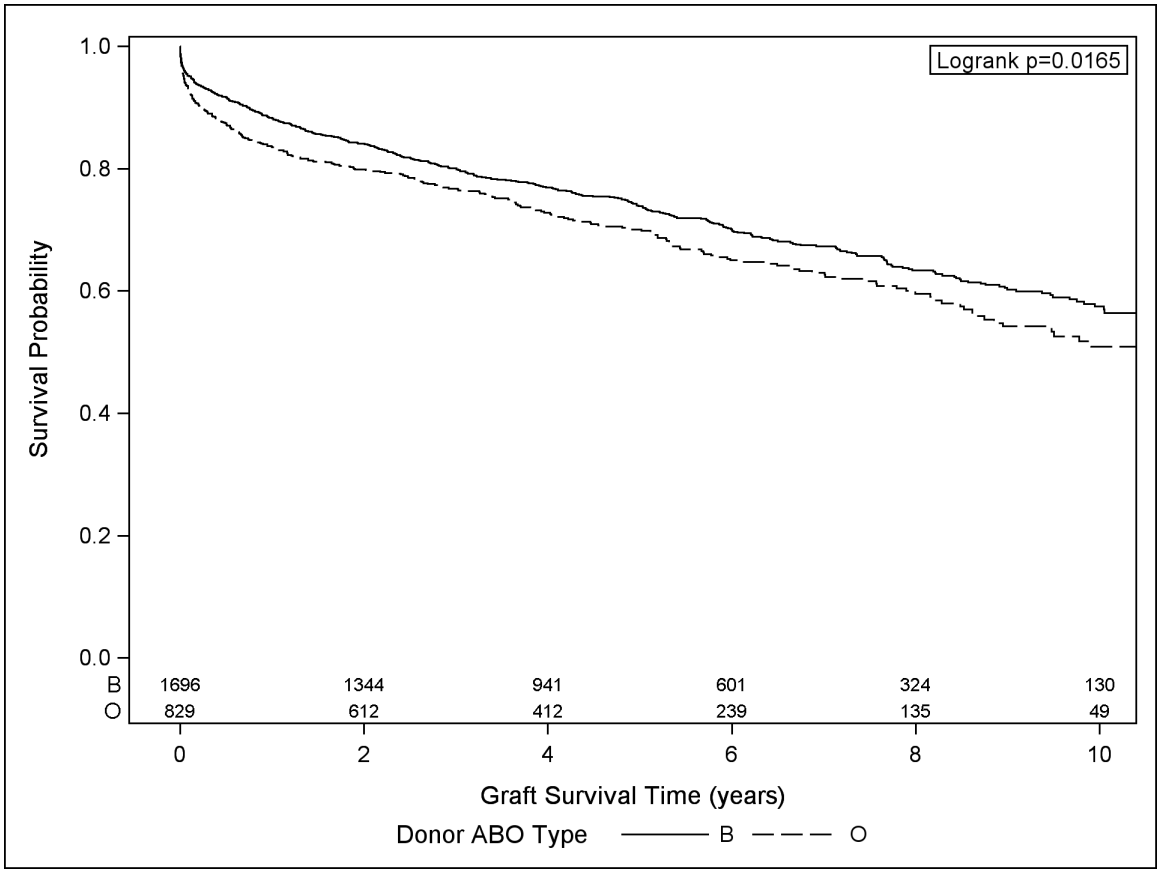

Figure 4. Kaplan-Meier graft survival analysis, donor type B vs. donor type O heart transplants (solid line: donor ABO type B, dashed line: donor ABO type O). A table is given with the number of patients at risk at each time point. The p-value corresponds to Mantel-Cox log-rank test results.

DISCUSSION

Since the advent of cardiac transplantation in the 1960's, physicians have made considerable efforts to improve short and long-term transplant outcomes by investigating the causes of graft rejection and generalized graft failure. Immunologically, as with other transplanted organs, this has involved minimizing antigenic mismatches between graft donors and recipients. Due to the high demand and comparatively low supply of available organs for transplant, emphasis has also been placed on generating graft allocation policies that are fair and effective. Due to the multifactorial nature of graft failure, these

efforts have led to a debate as to the impact of ABO blood type compatibility as well as the importance of HLA-matching on adult heart transplant outcomes.

In terms of HLA-matching, Opelz and colleagues definitively showed a strong relationship between donor-recipient HLA-A, -B, and –DR mismatches on post-transplant graft survival through the collaborative transplant study [28]. More recent studies have demonstrated that the presence of circulating HLA-directed donor-specific alloantibodies is correlated with increased morbidity and mortality, cardiac allograft vasculopathy, and increased rates of graft rejection [29,30].

With regards to ABO blood type matching, initial reports suggested that ABO compatible transplants are less efficacious than ABO identical ones [23,24]. More recently, investigators have disagreed with this conclusion [25,26,31]. A common problem of past studies has been a relatively small sample size precluding strong statistical power. In our analysis, we demonstrated that ABO identical and ABO compatible heart transplants have similar outcomes in terms of graft survival. By analyzing all adult cardiac transplants performed between 2000 and 2010, we were able to utilize a modern cohort of patients with a significantly larger sample size. Although our univariate analysis did show statistically significant differences in survival at 30 days, 1 year, 3 years, and 5 years post-transplant between the two study cohorts, these differences did not hold up after controlling for potential confounding variables in the multivariable models.

One of these possible confounding variables was OPTN waitlist status at transplant. Interestingly, according to our analysis ABO compatible heart recipients were more often status 1A at transplant when compared with ABO identical recipients (50.3%

vs. 37.8%). Additionally, ABO compatible recipients were more likely to be in the ICU as well as on a number of different mechanisms of life support including ECMO, IABP, parenteral inotropes, and ventilator support, than ABO identical heart recipients. This data suggests that ABO compatible recipients are generally sicker than ABO identical recipients, contributing to a worse prognosis. This is further supported by the fact that ABO compatible recipients had a higher pre-transplant mean total bilirubin compared with ABO identical recipients (1.48 vs. 1.25 mg/dL) indicating a greater degree of heart failure.

On analysis of recipient cause of death by ABO blood type matching, ABO compatible recipients died as a result of primary graft failure more frequently than recipients of ABO identical hearts (8.7% vs. 5.8%). Heart transplant recipient mortality due to primary graft failure is frequently associated with "marginal" donors or recipients [32]. This seems to suggest that ABO compatible transplants involve more "marginal" recipients and/or donors than ABO identical transplants.

In multivariate analysis, ABO blood type matching (identical vs. compatible) was not a statistically significant predictor of decreased cumulative or 30-day graft survival. Instead, the Cox proportional hazards model indicated recipient ethnicity (specifically, African American), life support at transplant (ventilator support and ECMO), graft ischemic time, total bilirubin, and recipient status before transplant to be significant predictors of decreased graft survival post-transplant. The multivariate logistic regression model indicated many of these variables – life support at transplant, ischemic time, bilirubin, and status before transplant, as well as waitlist status as statistically significant predictors of graft failure within 30 days of transplant. Other studies have demonstrated

similar results with regards to risk factors for decreased survival and increased graft failure following heart transplants [33-35].

The observed discrepancies in the effect of ABO compatibility on cardiac transplant outcomes between our univariate and multivariate models can be explained by investigating the impact of individual donor ABO blood types on graft survival. As we discovered in both our univariate and multivariate analyses, donor ABO blood type O is associated with decreased graft survival when compared with all other types. Since blood type O donor grafts are transplanted into recipients of all blood types (Table 1), the poorer outcomes associated with type O donor hearts could be skewing the results of our univariate analysis to misleadingly suggest that ABO compatible transplants result in worse outcomes than ABO identical ones. We confirmed this hypothesis by removing all type O donors from our univariate analysis, which demonstrated no statistically significant difference in graft survival at all time points post-transplant between ABO identical and compatible cohorts ($p > 0.05$).

The poor outcomes associated with type O donor grafts do have implications for current organ allocation policies. According to the Organ Procurement and Transplantation Network (OPTN) policy 3.7.8.1 from February 2013, “Blood type O donors shall only be allocated to blood type O or blood type B patients” before being offered to blood type A or AB patients. Given the relatively poorer outcomes associated with blood type O grafts in type B recipients, this policy may need to be reviewed. Any future modification of the current organ allocation scheme must take into account the ABO blood type demographics within the United States, however. Therefore, limiting type B recipients to type B donor grafts for example might do more harm than good.

Interestingly, previous studies have shown that blood type O individuals experience decreased rates of morbidity with regards to conditions such as congestive heart failure [36]. Further research should be conducted to investigate possible explanations for the poor outcomes associated with blood type O donor hearts as well as the best organ allocation scheme for managing these grafts.

CONCLUSION

In the past decade, ABO compatible donor hearts were preferentially given to sicker transplant recipients. As demonstrated in this study, transplantation using ABO compatible adult hearts does not result in adverse outcomes with respect to graft survival and incidence of acute rejection compared with ABO identical grafts. Therefore, ABO compatible and ABO identical heart transplant matches should be viewed equally in clinical decision-making and to maximize efficiency within the available donor pool. This will help optimize the use of donor organs, an extremely important yet scarce resource. In doing so, waiting times could be shortened and overall outcomes could be improved. In addition, since ABO blood type O donor grafts are associated with decreased survival post-transplant, current organ allocation policies should be reviewed; particularly those pertaining to ABO blood type B heart transplant recipients.

OVERALL CONCLUSIONS

Through this retrospective cohort analysis of heart transplantation outcomes, we identified several potential mechanisms through which post-transplant survival could be improved. Before conducting the myocarditis analysis, we hypothesized that post-transplantation survival would be quite dissimilar between recipients with a history of myocarditis and those with ischemic or idiopathic dilated cardiomyopathy. While the baseline characteristics of these two recipient cohorts were indeed quite different, we were surprised to discover that post-transplantation survival was in fact similar, although recipient cause of death varied. With respect to our ABO analysis, we initially hypothesized that ABO identical and ABO compatible transplants would be associated with identical survival curves. We were once again surprised to discover that certain ABO compatible blood type pairings were actually associated with poorer outcomes. While further investigation is certainly warranted, these results suggest that post-heart transplantation survival might be improved with more intensive immunosuppression regimens for myocarditis patients and alterations in the current UNOS organ allocation policy for ABO compatible matches.

LIMITATIONS

Like any other retrospective cohort study, this investigation was limited by the strength of the primary database in terms of completeness, accuracy, quality, and appropriateness of the predictor variables. While the dataset provided by UNOS was extremely comprehensive and included many important variables that described baseline donor and recipient information as well as post-operative outcomes, the study could have been strengthened if additional data were available to us. Furthermore, as it is a large national database compiled over many years, the accuracy of all the patient information coded in the UNOS database cannot be guaranteed. We are confident, however, that given the nature of our investigation, an analysis of a large national cohort of patients, any errors in patient data will not bias our results.

An additional limitation of the study is a result of analyzing many years of data. In order to accumulate enough patient records, in the case of the myocarditis analysis, several decades of patient data was required. During this prolonged period, many advances were made with regard to transplantation techniques, organ allocation policies, and immunosuppression regimens. These advances might have introduced biases into the study, impacting the results.

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