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Journal
Pediatric Transplantation, 19(1)

ISSN
1397-3142

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Publication Date
2015-02-01

DOI
10.1111/petr.12382

Peer reviewed

Pediatr Transplantation 2015: 19: 68–75

Pediatric Transplantation
DOI: 10.1111/petr.12382

Extracorporeal membrane oxygenation support after pediatric orthotopic heart transplantation

Su JA, Kelly RB, Grogan T, Elashoff D, Alejos JC. (2015) Extracorporeal membrane oxygenation support after pediatric orthotopic heart transplantation. *Pediatr Transplant*, 19: 68–75. DOI: 10.1111/petr.12382.

Abstract: Mechanical circulatory support has been used for more than 30 yr to allow the heart to recover from ischemia and injury. There are limited pediatric data, however, on the efficacy of ECMO in the setting of post-transplantation support for primary graft dysfunction or rejection. Data from all patients at our university-affiliated, tertiary care children's hospital who underwent OHT between 1998 and 2010 and required subsequent ECMO support were analyzed. The primary outcome measure was survival to hospital discharge. Two hundred and three pediatric patients underwent OHT between 1998 and 2010 at our institution. Twenty-nine of these patients experienced post-transplantation cardiac failure requiring ECMO support, 18 of whom survived to hospital discharge (62%). Survival in the rejection and allograft vasculopathy group was 75%, and survival in patients with primary graft failure was 53% after ECMO support ($p = 0.273$). Patient survival to hospital discharge was not associated with ischemic time or duration of ECMO. ECMO provides hemodynamic support in the setting of cardiac failure and can be used successfully after pediatric OHT for primary graft dysfunction or rejection.

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Key words: extracorporeal membrane oxygenation – mechanical circulatory support – orthotopic heart transplantation – pediatric

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Accepted for publication 3 October 2014

In an era of rapid technological and surgical advancement, an increasing number of children with complex cardiac disease are surviving to adulthood. In severe cases that are not amenable to surgical correction or palliation, heart transplantation remains a final option (1). Pediatric cardiac transplantation has evolved substantially over the past four decades, with improving long-term outcomes (2). Postoperatively, OHT requires close monitoring, cardiac intensivist management, and pharmacologic support. If a graft is unable to maintain adequate cardiac output despite conventional postoperative management, mechanical circulatory support may be considered as a bridge to recovery of cardiac function.

There has been much advancement in the field of mechanical circulatory support in the past decade, which has broadened its application as well as improved survival and outcomes. In the setting of post-cardiac transplantation, ECMO remains the most feasible form of mechanical circulatory support because of its ability for rapid initiation as well as portability. ECMO may be applied in many clinical situations, for both cardiac and respiratory support. ECMO has been used successfully in cardiac disease in cases of inadequate cardiac output, extracorporeal cardiopulmonary resuscitation, bridging to heart

Abbreviations: ATG, antithymocyte globulin; CAV, cardiac allograft vasculopathy; CHD, congenital heart disease; CPB, cardiopulmonary bypass; ECMO, extracorporeal membrane oxygenation; OHT, orthotopic heart transplantation; VAD, ventricular assist device.

transplantation or retransplantation, and postoperatively in cases of post-cardiotomy cardiogenic shock (3–7). In our experience, ECMO can also be effectively implemented in pediatric patients in cases of primary graft failure as a bridge to recovery after heart transplantation as well as in cases of rejection months later. The primary objective of our study is to report our institution's survival to hospital discharge for pediatric patients receiving ECMO support after OHT. Our secondary objective is to analyze whether our center's survival was associated with any particular demographic or clinical variables. We hypothesized that longer graft ischemic time and longer duration of ECMO would be associated with worse survival among pediatric patients receiving ECMO support.

Methods

Our university's institutional review board approved this study and waived the need for informed consent.

Patient population

Records of all pediatric heart transplantation recipients <21 yr of age at the time of OHT at our tertiary care children's hospital between January 1, 1998 and December 31, 2010 were reviewed. We identified and evaluated all patients who required ECMO support after cardiac transplantation. Variables examined included demographic data, pre-OHT diagnosis, indication for ECMO, donor ischemic time, total CPB time, past cardiac surgical history, ECMO initiation location, time between OHT and ECMO initiation, ECMO duration, and survival to hospital discharge.

We separated our cohort into two groups based on their underlying reason for requiring ECMO support: (1) patients with primary graft dysfunction and (2) patients with transplant rejection. Patients experiencing hemodynamic compromise occurring within 24 h of OHT without evidence of elevated panel-reactive antibodies were considered to experience primary graft dysfunction. Patients were presumed to have transplant rejection if they had normalized cardiac function after transplantation that subsequently deteriorated by quantitative measurement of shortening fraction via echocardiogram, and one of the following: (1) a biopsy demonstrating cellular or antibody-mediated rejection >1R based on the International Society for Heart and Lung Transplantation classification; (2) evidence of clinical improvement with empiric antirejection therapy; or (3) autopsy-demonstrated cellular or antibody-mediated rejection. Also included in this late ECMO support group was any patient with CAV who required mechanical circulatory support. CAV is considered to be a manifestation of transplant rejection. None of the patients who experienced transplant rejection or CAV had previously been on ECMO support following their transplantation.

Immunosuppression

During our study period, routine immunosuppression consisted of a combination of tacrolimus (Astellas, Chuo, Japan), mycophenolate mofetil (Roche, Basel, Switzerland), and corticosteroids. Mycophenolate mofetil dose was initiated at 1500 mg/m^2 divided twice a day and was titrated to maintain mycophenolic acid levels between 2 and 4 μg/dL. Tacrolimus dose was titrated to achieve levels of 12 to 15 ng/mL in the first month after transplant, then 8 to 10 ng/mL from one to six months post-OHT, 6 to 10 ng/mL from six months to five yr post-OHT, and finally 4 to 8 ng/mL for patients who were more than five yr post-OHT. After the immediate post-transplantation period, intravenous methylprednisolone was converted to prednisone, which was tapered off over 12 months as clinically appropriate. Sirolimus (Pfizer, New York, NY, USA) was in certain cases utilized to replace mycophenolate mofetil for high-risk patients such as those demonstrating presensitization with donor-specific antibodies, and in patients with evidence of CAV. These high-risk patients and patients with renal compromise received induction therapy with ATG (Sanofi-Aventis, Paris, France) for the first five days postoperatively. These patients were then transitioned to standard immunosuppression protocol at our institution. Patients who experienced episodes of biopsy-proven rejection or suspected rejection (based on history, physical examination and echocardiography) were treated with intravenous pulse methylprednisolone, or an advanced protocol including plasmapheresis, rituximab (Genentech, South San Francisco, CA, USA), and/or ATG.

ECMO

A standardized ECMO circuit was implemented with appropriate cannulas according to patient size. Cannulation sites for ECMO depended on the adequacy of vessels. All patients were cannulated for venoarterial ECMO, either via a transthoracic approach or via peripheral arteries and veins. Standard anticoagulation at our institution is achieved with heparin. Our institutional preference for initial cardiac support is a centrifugal pump due to the ease of deployment and smaller size. A common indication for changing to a roller pump at our institution is hemolysis.

Statistical analysis

The distribution of patient demographics and transplantation variables were compared between survivors and nonsurvivors to hospital discharge. For categorical variables, differences between the two groups were examined using Fisher's exact test. Wilcoxon rank sum tests were utilized to compare continuous variables between groups. Kaplan–Meier curves were constructed to visualize overall survival rates between the late rejection and graft dysfunction subgroups. The differences in overall survival were formally tested using the log-rank test. A p-value < 0.05 was considered significant. All statistical analyses were performed using SAS (version 9.2; SAS Institute, Cary, NC, USA) and R (version 2.15.0; www.rproject.org).

Results

Transplantation demographics

There were 203 pediatric patients who underwent heart transplantation between 1998 and 2010 at our institution. Twenty-nine of these patients experienced cardiac failure following OHT requiring ECMO support. Patients ranged in age

from two months to 21 yr (mean, 8.8 yr; median, 9.9 yr). Nineteen patients were male, and 10 were female. Patient weight ranged from 2.5 to 94 kg (mean 37.3 kg; median 35.2 kg). Of these patients, indications for transplantation were cardiomyopathy in 18, CHD in seven, and graft failure (re-transplantation) in four. The cardiomyopathy group included 13 patients with dilated cardiomyopathy, three with restrictive cardiomyopathy, one with non-compaction, and one with hypertrophic cardiomyopathy. The CHD group was heterogeneous, and all patients in this group had previous failed corrective or palliative heart surgery (two hypoplastic left heart syndrome, two pulmonary atresia with intact ventricular septum, one total anomalous pulmonary venous return, one truncus arteriosus, and one double-outlet right ventricle).

Indications for ECMO

ECMO was initiated because of primary graft dysfunction in 17 patients (59%). These patients were either cannulated in the operating room, intensive care unit, or post-anesthesia care unit. They were all cannulated within 24 h of cardiac transplantation (Table 1). The remaining patients required ECMO support after transplantation because of transplant rejection (11 patients), or CAV established by coronary angiography (one patient). All patients who were deemed to have rejection or CAV requiring ECMO support had recovered during the initial postoperative period and were re-hospitalized remote from their heart transplantation (Table 1).

Outcomes

The length of ECMO support ranged from 1 to 34 days (mean 8.4 days, median six days). There was not a significant difference in length of ECMO support between the patients with primary graft dysfunction and patients with transplantation rejection/CAV (interquartile range 2–9 days vs. 4–15 days; $p = 0.244$). Of these 29 patients, 18 survived to hospital discharge (62%). Survival was similar among patients with transplantation rejection/CAV compared to those who required ECMO due to primary graft dysfunction (75% vs. 53%; $p = 0.14$; Fig. 1). Of those patients who died prior to discharge, four patients experienced multiorgan system failure, two experienced cardiac failure, one experienced central nervous system failure, and two died of septic shock. In five cases, ECMO was withdrawn upon the family's request (Table 1). In both groups, patient survival to hospital discharge was not associated with gender, age, indication for OHT, past surgical history, ischemic time, CPB time, intra-operative or postoperative ECMO cannulation, time between OHT and ECMO, or duration of ECMO (Tables 2 and 3). Patient weight was not associated with survival in patients who required ECMO for support of primary graft dysfunction, but increased weight was inversely associated with survival in patients suffering from late rejection ($p = 0.009$; Tables 2 and 3).

Table 1. Early outcome of post-transplantation ECMO

Initial diagnosis	Post-operative day to ECMO	Days on ECMO	Survival to hospital discharge
ECMO for graft dysfunction			
Cardiomyopathy	0	2	Survived
Cardiomyopathy	0	8	Survived
Cardiomyopathy	0	5	Survived
Cardiomyopathy	0	4	Survived
Cardiomyopathy	0	31	Survived
Cardiomyopathy	0	2	Survived
Cardiomyopathy	0	2	Survived
CHD	1	6	Survived
CHD	1	3	Survived
Cardiomyopathy	1	12	Died
Cardiomyopathy	0	2	Died
Cardiomyopathy	1	6	Died
CHD	0	2	Died
CHD	0	7	Died
CHD	0	4	Died
Retransplantation	0	24	Died
Retransplantation	0	10	Died
ECMO for late rejection			
Cardiomyopathy	23	5	Survived
Cardiomyopathy	304	1	Survived
Cardiomyopathy	214	3	Survived
Cardiomyopathy	1147	8	Survived
Retransplantation	2763	34	Survived
Cardiomyopathy	326	16	Survived
CHD	711	8	Survived
CHD	203	4	Survived
Cardiomyopathy	68	6	Survived
Retransplantation	649	4	Died
Cardiomyopathy	145	15	Died
ECMO for CAV			
Cardiomyopathy	677	11	Died

POD, postoperative day.

Discussion

There has been much advancement in the field of mechanical circulatory support since ECMO was first introduced in the early 1970s (8). From 2000 to 2013, implementation of ECMO for cardiac indications in the pediatric population has grown (9). ECMO is now widely used for maintenance of cardiac output in pediatric patients with cardiogenic shock or cardiopulmonary resuscitation failure as a bridge to recovery, VAD implantation or cardiac transplantation (6, 7, 10). ECMO has also been implemented postoperatively in

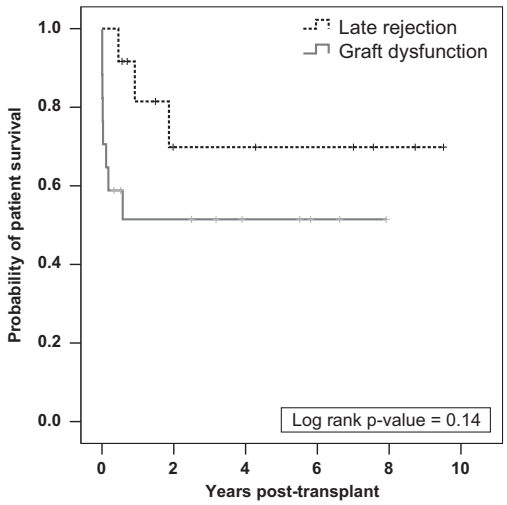

Fig. 1. Survival trends for post-OHT patients requiring ECMO for primary graft dysfunction versus rejection.

patients who are unable to wean from CPB or who develop post-cardiotomy low cardiac output syndrome (11). Similarly, ECMO is a practical option for pediatric OHT patients with depressed postoperative cardiac output, allowing time for graft recovery from stress of organ recovery and surgery, as well as gradual adaptation to a new hemodynamic environment (12–14).

Our recent data over a 12-yr period confirm that ECMO can be lifesaving in the pediatric post-cardiac transplantation population, as both a bridge to graft recovery or re-transplantation. Currently, overall survival after heart transplantation in the pediatric population is approximately 90% at one yr and 78% at five yr (15). Primary graft failure and rejection are complications that significantly affect morbidity and mortality, with primary graft failure accounting for 35% of deaths within the first 30 days after transplantation, and the combination of primary graft failure and rejection accounting for more than half of all deaths in the first three yr following transplantation (15). Of our 203 pediatric patients who received OHT, we found that 29 required ECMO for cardiac support after their transplantation (14%), either in the immediate postoperative period for primary graft failure (17 patients), or remotely due to clinical findings of rejection and CAV (12 patients; Table 1). Our cohort included young patients and those with CHD. In one report, 17% of patients <1 yr of age required ECMO for primary graft failure (16). In another report, primary graft failure as the cause of death among pediatric and adult patients with CHD dying within 30 days of transplantation has been reported to be 9% (17). We speculate that the relatively high incidence of

Table 2. Pediatric heart transplantation recipients who required ECMO support postoperatively for primary graft dysfunction (n = 17)

Data	All patients (n = 17) Mean ± s.d. Frequency	Survivors (n = 9) Mean ± s.d. Frequency	Nonsurvivors (n = 8) Mean ± s.d. Frequency	p-Value
Demographics				
Recipient weight (kg)	24.9 ± 22.9	17.1 ± 18.9	33.6 ± 25.0	0.277
Age at OHT (yr)	6.7 ± 7.5	4.3 ± 6.9	8.9 ± 7.8	0.2
Gender				
Male	9	4	5	0.637
Female	8	5	3	
Indications for OHT				
Cardiomyopathy	10	7	3	0.205
CHD	5	2	3	
Retransplantation	2	0	2	
Past surgical history				
Previous OHT	1	1	0	0.185
Previous palliative surgery	5	1	4	
No past surgeries	8	6	2	
Both	3	1	2	
Transplantation				
Ischemic time (min)	239.3 ± 87.1	245.2 ± 77.9	233.3 ± 102.6	>0.99
Total CPB time (min)	202.7 ± 90.2	191.2 ± 87.9	214.2 ± 99.3	0.699
ECMO cannulation				
Intra-operative	6	1	5	>0.99
Postoperative	11	8	3	
Days b/w OHT and ECMO	0.3 ± 0.4	0.2 ± 0.4	0.3 ± 0.5	>.99
ECMO duration (days)	7.6 ± 8.1	7.0 ± 9.2	8.4 ± 7.2	0.423

Table 3. Pediatric heart transplantation recipients who required ECMO support postoperatively for clinical evidence of rejection (n = 12)

Data	All patients (n = 12) Mean ± s.d. Frequency	Survivors (n = 9) Mean ± s.d. Frequency	Non-survivors (n = 3) Mean ± s.d. Frequency	p-Value
Demographics				
Recipient weight (kg)	46.5 ± 20.9	38.19 ± 13.90	71.33 ± 19.63	0.009
Age at OHT (yr)	12.0 ± 4.1	12.65 ± 4.08	9.97 ± 4.46	0.373
Gender				
Male	10	8	2	
Female	2	1	1	
Indications for OHT				
Cardiomyopathy	7	5	2	0.714
CHD	3	3	0	
Retransplantation	2	1	1	
Past surgical history				
Previous OHT	3	2	1	0.755
Previous palliative surgery	3	3	0	
No past surgeries	6	4	2	
Both				
Transplantation				
Ischemic time (min)	189.4 ± 58.3	199.4 ± 55.9	166.0 ± 68.4	0.517
Total CPB time (min)	138.4 ± 57.3	135.3 ± 64.2	145.7 ± 47.7	0.833
ECMO cannulation				
Intra-operative	1	1	0	>0.99
Postoperative	11	8	3	
Days b/w OHT and ECMO	602.6 ± 756.3	691.4 ± 855.7	336.0 ± 273.3	0.600
ECMO duration (days)	9.6 ± 9.0	10.3 ± 9.9	7.3 ± 6.7	0.482

post-OHT requirement for ECMO encountered at our institution is in part due to our large CHD population, as well as our acceptance of high-risk transplantation patients from referring centers. CHD patients are known to experience significantly increased early post-OHT complications and mortality (18). Our center also transplants young patients. We, therefore, believe that our experience is similar to other centers with regard to the incidence of primary graft dysfunction and not related to a specific institutional factor at our center (such as a surgical technique or medical practice). In our post-transplantation population who experienced these life-threatening complications, nine of 12 patients with rejection survived to hospital discharge after ECMO (75%), and nine of 17 patients with primary graft dysfunction survived to hospital discharge after ECMO (53%). Although we did not randomize our patients to ECMO, leading to possible selection bias, the utilization of ECMO at our institution for this patient population may have improved the survival of this high-risk group.

Primary graft dysfunction versus late rejection

We recognize that our cohort of patients who required ECMO for post-transplantation hemodynamic support represents two distinct populations requiring mechanical circulatory support under different circumstances. Among our 29 patients, 17 required ECMO soon after transplantation for primary graft failure. All of these patients were cannulated for ECMO within 24 h of their heart transplantation. In contrast, the remainder of our cohort required mechanical circulatory support for clinical evidence of rejection and CAV. These patients did not require ECMO support until months to years after their initial heart transplantation. These two groups were thus analyzed separately because of their inherent differences. Although we did not find that survival was significantly impacted by any of our examined clinical or demographic variables, we made several observations.

First, we found that in patients who required ECMO for graft dysfunction, there was a trend toward improved survival in patients who had no past surgical history (Table 2). Specifically, patients who had previously undergone surgical palliation prior to heart transplantation appeared to have a lower survival rate when cannulated for ECMO. While this finding did not reach statistical significance in our study, we speculate that this possible association may be related to increased technical difficulty in transplanting a patient who has had previous surgery, including previous anatomic manipulation and associated comorbidities such as end-organ injury and pulmonary vascular disease. Our observation is consistent with the knowledge that

CHD, for which previous palliation may have been attempted, is an individual risk factor for post-heart transplantation mortality (19, 20).

Second, we found that survival may be improved in patients who required ECMO support for rejection compared with those who were cannulated for ECMO for primary graft failure, although we were not able to reach statistical significance in our limited cohort (Fig. 1). A similar observation was noted in 2011 by Chen and colleagues, who found that 70% of patients requiring ECMO for support of cardiac rejection survived to wean off of mechanical circulatory support or re-transplantation, compared with only 50% of patients requiring ECMO for primary graft dysfunction (20).

We speculate that this is partially reflective of the inherently fragile hemodynamic state of patients who are immediately post-cardiac transplantation. Not only have these patients failed medical management to require heart transplantation, they have also undergone CPB. In addition, primary graft failure may occur due to recipient and donor risk factors. Recipient risk factors may include the need for mechanical support prior to transplantation, a history of CHD, increased pulmonary vascular resistance, and renal dysfunction. Donor risk factors may include increased donor–recipient size discrepancy, prolonged graft ischemic time, and administration of cardiopulmonary resuscitation and/or anoxic damage to the donor prior to organ recovery (19, 20). Beyond implementation of ECMO to support a graft that may have impaired function postoperatively, many of these risk factors are not amenable to specific treatment. In contrast, patients who experience rejection profound enough to require mechanical circulatory support will undergo aggressive and protocolized antirejection therapy. The ability to direct treatment while concurrently supporting cardiac output with ECMO allows for improved recovery in patients who experience graft failure from rejection.

Length of support

An extended requirement for mechanical circulatory support is reflective of poor clinical status, and such an extension exposes patients to a continual risk of secondary complications (12, 21). There have been conflicting findings as to whether prolonged support with ECMO affects survival outcome. Several studies have found that a requirement for mechanical circulatory support >4 days was associated with a significantly decreased survival outcome, while others have found no such correlation (12, 14, 21, 22). We did not find patient survival to be associated with duration of ECMO (Tables 2 and 3), but our sample size was small. A larger multicenter study would be required to confirm this. Patients with primary graft dysfunction who were started on ECMO intra-operatively did not have a significantly higher mortality compared to those who were cannulated postoperatively. We speculate that ECMO complications and individual patient precannulation end-organ condition may play a role in ultimate survival to discharge. Future studies would be required to confirm these hypotheses.

Patient age and size

We did not find any significant association between patient age and survival to discharge (Tables 2 and 3). Although smaller and younger patients may be technically difficult surgical patients, our findings show that weight and age are not associated with survival in post-transplantation patients requiring ECMO for support of primary graft dysfunction. Our observations are consistent with recent pediatric post-transplantation data among patients >1 yr of age showing no significant association between age and early survival (15). In our transplant patients who required ECMO support for late rejection, however, we found an unexpected and unexplained association between weight and mortality ($p = 0.009$; Table 3). Further investigation of this population is required to identify potential causality.

Although VAD support in this population is conceptually possible (including the use of a centrifugal pump without an oxygenator), only certain children may benefit from such devices. Three limitations to VAD support in this population are the small size of pediatric patients, the potential for urgent deployment need, and the frequent need for an oxygenator. Until the recent approval of the EXCOR Pediatric VAD (Berlin Heart GmbH, Berlin, Germany), no known pulsatile VAD small enough for young children was available. In addition, deployment of a pulsatile VAD, such as the EXCOR device, is impractical in emergent situations such as cardiac failure or resuscitation.

Limitations

Limitations of our study include our small sample size as well as a lack of clearly defined criteria for the use of ECMO after OHT at our center. Furthermore, our patients were not randomized to receive ECMO, therefore introducing likely

selection bias. In addition, institutional differences in graft preservation after recovery as well as immunosuppressant regimens may affect the ability to generalize our results to other institutions, providers, and patients. Also, institutional ECMO familiarity and expertise likely varies. A larger sample size may be required to see larger or additional differences between survivors to hospital discharge and non-survivors. Our study is retrospective and observational in nature, potentially affecting the ability to generalize our findings to other institutions, providers, and patients. Although both groups of - patients required ECMO support for different reasons, our results highlight the utility of ECMO following transplantation, whether employed in the early postoperative period or months later. Given these two indications for ECMO, statistical analysis to assess for similarity was conducted.

Conclusion

To date, this is the largest single-center pediatric series examining the impact of ECMO in post-heart transplantation patients over a 12-yr period. In our experience, ECMO provides hemodynamic support in the setting of cardiac failure and can be used successfully after pediatric OHT for primary graft dysfunction or rejection. Our study serves to help inform pediatric cardiothoracic surgery, cardiology, and critical care providers that ECMO can be used successfully after pediatric OHT for primary graft dysfunction or rejection/CAV with acceptable survival. While describing and distinguishing two distinct patients that may require ECMO support following transplantation, namely, those with primary graft dysfunction and those with rejection/CAV, our experience may help to preserve scarce cardiac grafts. We believe that a large, multicenter, prospective cohort study will be useful to clearly define criteria for the use of ECMO after OHT to maximize survival.

Acknowledgments

Statistical analyses for this research were supported by NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124.

Authors' contributions

Jennifer Su: Primary researcher and principal investigator of this project, helped developed the research question, reviewed the available databases, organized the information for analysis, and drafted the manuscript; Robert Kelly: Faculty sponsor and primary advisor of this project, supervised the development of the project, provided research mentorship and advice throughout the project, and closely reviewed and revised the manuscript; Tristan Grogan: Primary statistician involved with the project; Tristan Grogan and David Elashoff: Drafted the statistics section of the manuscript and provided the statistical analyses of the data; David Elashoff: Overseeing statistician involved with the project; Juan Alejos: Faculty advisor from the Division of Cardiology, provided access to the heart transplantation, and ECMO databases at UCLA, contributed to the development of the project, detailed the immunosuppression and transplantation protocols, and revised the manuscript.

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