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The Registry of the International Society for Heart and Lung Transplantation: Sixteenth Official Pediatric Heart Transplantation Report—2013; Focus Theme: Age

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From the The ISHLT Transplant Registry, Dallas, Texas.

Pediatric heart transplantation has grown worldwide since the first procedure in 1967. With more than 11,000 transplants in children reported, the Registry of the International Society for Heart and Lung Transplantation (ISHLT) is well poised to examine the evolving management of pediatric heart transplant recipients and their outcomes.

Registry data sources and statistical methods

ISHLT Registry data are provided by individual centers and national or regional Organ Procurement and Organ Exchange Organizations; these are listed in the introduction to the Annual Reports.

This 16th pediatric heart transplant report from the ISHLT Registry is centered on age as the central theme, focusing on the year 2000 onwards. Key topics include geographic trends, diagnosis, survival, and the conventional post-transplant morbidities. A number of these characteristics and outcomes were analyzed for age-related differences between the newly defined age groups of 0 to <1 year, 1 to 5 years, 6 to 10 years, and 11 to 17 years. In follow-up of last year's reported regional variation, we explored interactions among age, diagnosis, and geography and their respective effect on transplant survival. The Tables and Figures published in this report, as well as the slides describing additional analyses, are available for download from www.ishlt.org/registries.[1] Source data can be accessed by clicking the graphs and selecting "edit data." Data for the previous 12 ISHLT Registry reports can also be accessed through the ISHLT Web site.[1,2]

Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Adjustments for multiple comparisons were done using Scheffe's method. Multivariable analyses were performed using Cox proportional hazard regression analysis. Results of the multivariable analyses are reported as the hazard ratio (HR) with a corresponding 95% confidence interval (CIs) and/or p-value. Factors with a HR significantly >1 indicate that the factor is associated with an increased likelihood of the event occurring. Conversely, a HR of <1 indicates that the event is less likely to occur when that factor is present. Multiple imputations were used to handle missing information for continuous data fields, such as ischemia time and donor age.[3] This method produces an estimated value for the missing value based on the other characteristics of the patient, donor, and/or transplant. The algorithm is performed multiple times, producing new estimates for the missing information. Models are fit on each imputed data set and then combined to produce a final set of estimates from which the relative risk estimates and p-values are obtained.

Centers and activity

There were 565 heart transplants in children (aged <18 years) reported to the Registry in 2011 (Figure 1), a slight increase from previous years. These comprise 14% of all

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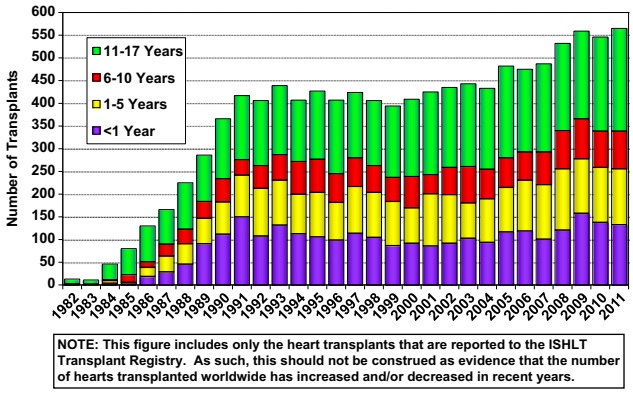

Figure 1 Recipient age distribution by year of transplant. ISHLT, International Society for Heart and Lung Transplantation.

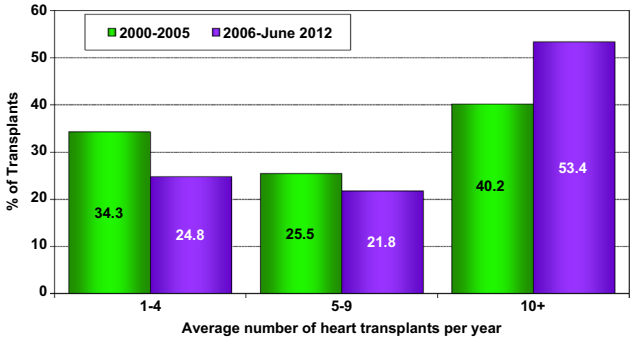

Figure 2 Distribution of transplants by center volume (Transplants: January 2000–June 2012).

cardiac transplants. The proportion of pediatric transplants by recipient age has remained relatively stable for the last decade. Of the centers reporting pediatric heart transplants in 2011, 54 were from North America, 40 from Europe, and 12 from the other parts of the world, with the most notable change being the slow increase over time in the number of centers reporting to the Registry other than from Europe or North America.[1]

For the most recent era, 53% of the transplants in the Registry were undertaken in larger centers ($\geq$ 10 pediatric heart transplants performed per year) compared with 40% in 2000 to 2005 (Figure 2). Between 2006 and June 2012, 25% of all transplants were still performed in centers undertaking $<$ 4 transplants per year. These smaller centers were less likely to transplant the younger groups of pediatric

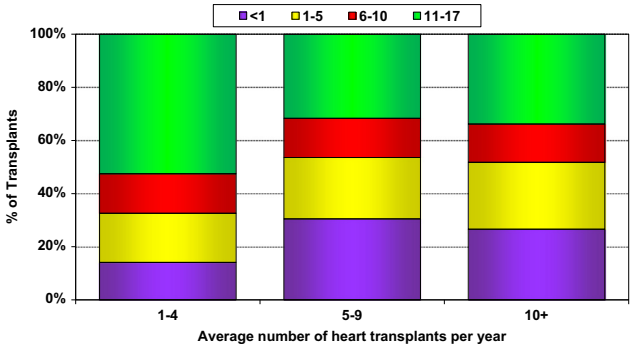

Figure 3 Age distribution by center volume (Transplants: January 2000–June 2012).

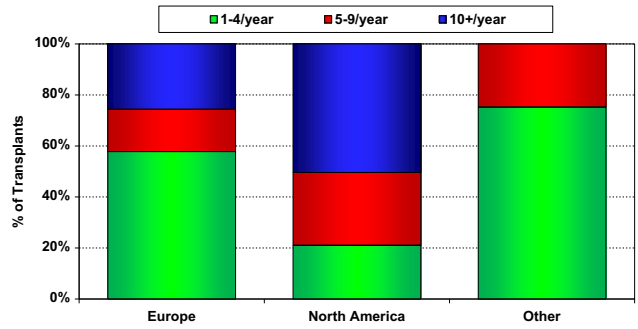

Figure 4 Distribution of transplants by location and average center volume (Transplants: January 2000–June 2012).

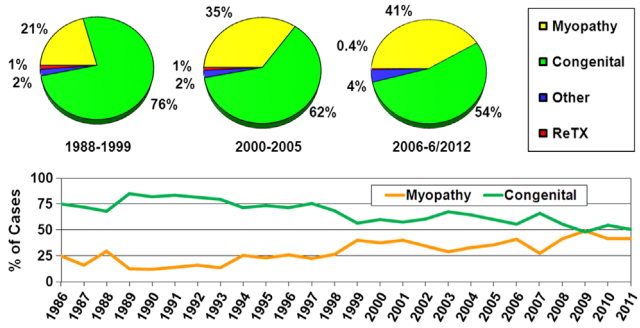

Figure 5 Recipient diagnosis in recipients aged $<$ 1 year. ReTX, retransplant.

recipients: between 2000 and 2012, $>$ 50% of transplants were in the group aged 11 to 17 years, and only 14% were in recipients aged $<$ 1 year (Figure 3). Small but statistically significant differences were noted in age distribution by center volume for centers doing $>$ 5 transplants per year. In addition, there were significant geographic differences: only 25% of European centers undertook $>$ 10 transplants a year compared with 50% of North American centers and none of the centers in other regions (Figure 4).

Indications for transplantation

Congenital heart disease remains the most common indication for heart transplant in the infant age group (54%) but has significantly decreased over time, while cardiomyopathy increased from 35% in the period 2000 to 2005 to 41% in the most recent era (Figure 5). For the other

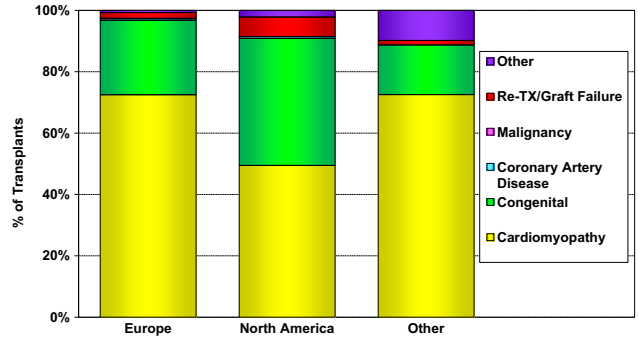

Figure 6 Diagnosis distribution by location (Transplants: January 2000–June 2012). Re-TX, retransplant.

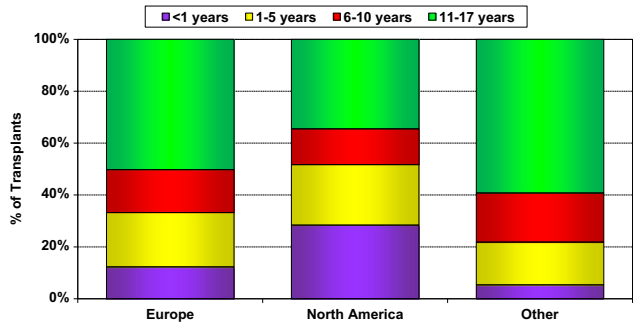

Figure 7 Recipient age distribution by location (Transplants: January 2000-June 2012).

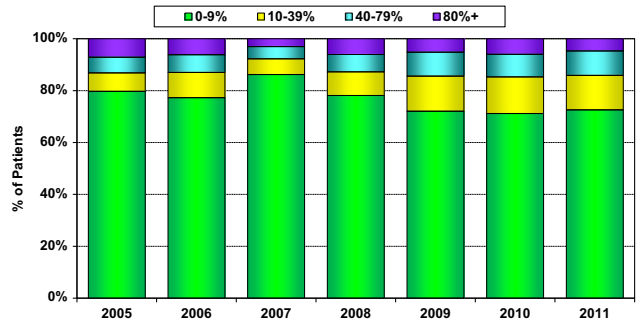

Figure 9 Panel reactive antibody distribution by year (Transplants: January 2005–December 2011).

age groups, the indications for pediatric heart transplantation have remained remarkably stable over time: approximately 65% and 25% of the 11-to 17-year-olds and 55% and 38% of the 1- to 10-year olds had a transplant for cardiomyopathy and congenital heart disease, respectively. There are geographic differences, with congenital heart disease remaining a more common indication in North America.

Recipient characteristics

Approximately 25% of transplant recipients in 2011 were infants (age < 1 year), 22% were aged between 1 and 5 years, 15% were between 6 and 10 years, and 40% were between 11 and 17 years (Figure 1). Infants comprised 28% of North American transplants compared with 12% in Europe and 5% in the rest of the world, where the group aged 11 to 17 years predominated (59%; Figure 7).

The proportion of children bridged to transplantation with mechanical circulatory support (MCS) remained stable at 26% in 2011, comprising a ventricular assist device (VAD) or total artificial heart (TAH) in 20%, extracorporeal membrane oxygenation (ECMO) in 4%, and ECMO and VAD in 2%. Of infants bridged with MCS, ECMO was used in 60%, a proportion that decreased with increasing age down to 18% for the group aged 11 to 17 years (Figure 8).

The proportion of sensitized patients with a panel reactive antibody (PRA) of ≥ 10% remained stable at 27% (Figure 9). Looking at age, the infant group had the lowest proportion of sensitized recipients (18%), with the highest being age 1 to 5 years and 6 to 10 years, at 28% to 29% (Figure 10). Adult recipients were less likely to be sensitized, with 19% having a PRA of 10% or more.[4]

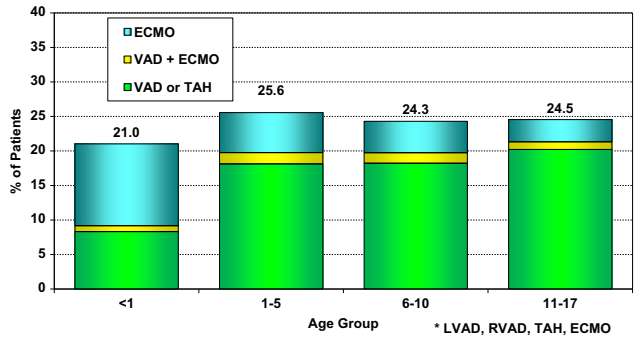

Figure 8 Percentage of patients bridged with mechanical circulatory support by age group (Transplants: July 2004–June 2012). ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

Donor characteristics

Twenty-five percent of pediatric recipients receive a heart from an adult donor (> 18 years). Similarly to what was reported last year, a significant geographic variation exists in the proportion of adult donors allocated to pediatric recipients: 18% in North America, 43% in Europe, and 48% in the rest of the world. Not surprisingly, the groups aged 6 to 10 years and 11 to 17 years used the broadest spectrum of donors by age (Figure 11). Sixty-eight percent of recipients received a size-matched donor heart (weight ratio, 1.0–1.9), and no substantial changes have occurred during the last decade.

Immunosuppression

Induction

As noted last year and still in contrast to the adult population,[3] the use of induction therapy continues to trend upwards. Most pediatric heart transplant recipients (71%) receive induction therapy, comprising 47% anti-thymocyte globulin and 25% interleukin-2 receptor (IL2-R) antagonists. In a univariate analysis examining survival out to 9 years after transplant, patients who received polyclonal induction therapy had a better survival than those who

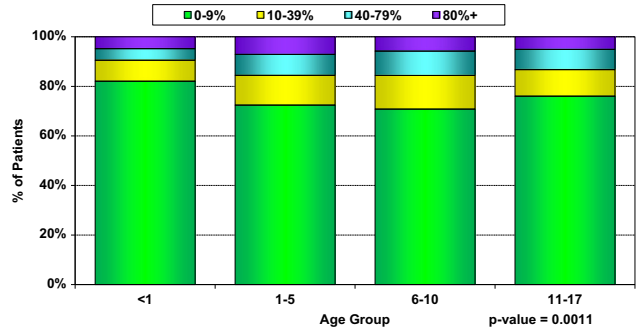

Figure 10 Panel reactive antibody distribution by age group (Transplants: July 2004–June 2012).

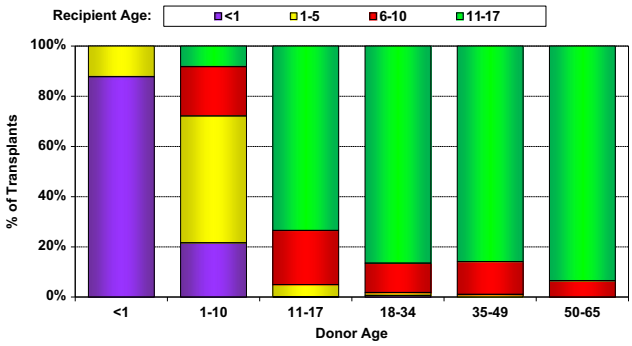

Figure 11 Donor and recipient age (Transplants: January 2000–June 2012).

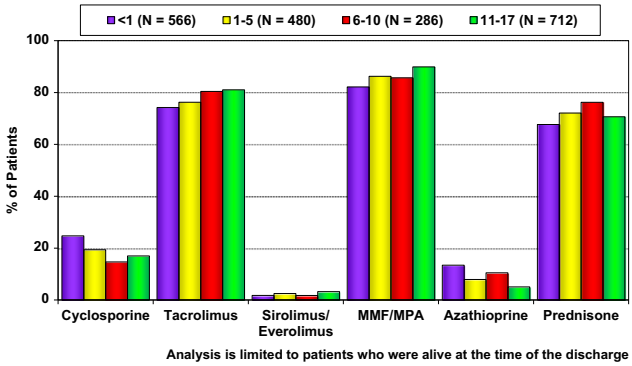

Figure 12 Maintenance immunosuppression at time of transplant discharge by age (Follow-up: January 2007–June 2012). MMF, mycophenolate mofetil; MPA, mycophenolic acid.

received IL2-R antagonists ($p = 0.014$). In a number of subgroup analyses, we were not able to identify patient characteristics that would suggest survival benefit with the use of induction. Specifically, there was no survival benefit of induction therapy in relationship to recipient age or presence or absence of treated rejection. Induction therapy did not appear to influence the proportion of patients experiencing rejection between discharge and 1 year after transplant (regardless of recipient age), freedom from coronary allograft vasculopathy (CAV), or freedom from lymphoma.

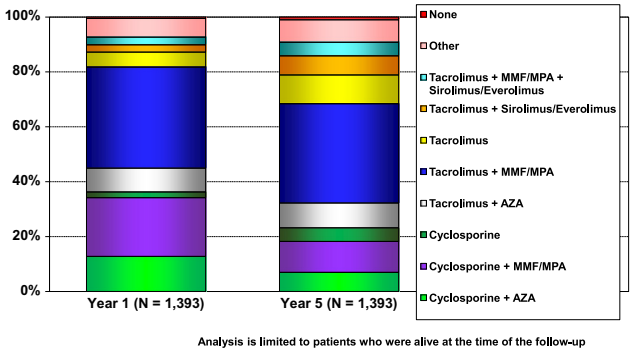

Figure 13 Maintenance immunosuppression at time of follow-up for the same patients at each time point (Follow-up: January 2001–June 2012). AZA, azathioprine; MMF, mycophenolate mofetil; MPA, mycophenolic acid.

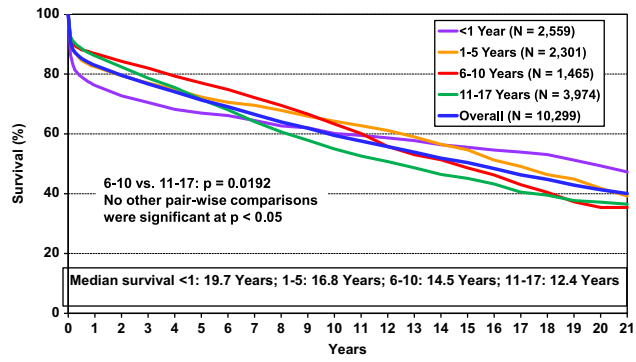

Figure 14 Kaplan-Meier survival for pediatric heart transplant recipients (Transplants: January 1982–June 2011).

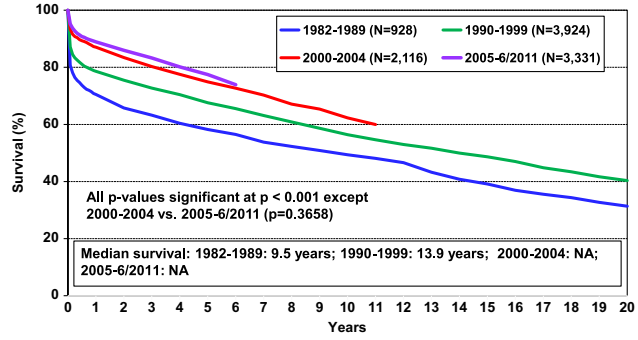

Figure 15 Kaplan-Meier survival by era (Transplants: January 1982–June 2011).

Maintenance

At the time of discharge from the transplant hospitalization, the use of tacrolimus as the calcineurin inhibitor (CNI) increased from 52% (between 2001 and 2006) to 78% (from 2007 onwards). Similarly, mycophenolate mofetil (MMF) or mycophenolic acid (MPA) use increased from 64% to 86%, with a concomitant drop in azathioprine use to 9% in the most recent era. Prednisone use at the time of hospital discharge decreased marginally to 71%. These proportions did not vary significantly by recipient age (Figure 12). Adjusting for multiple comparisons, there were no significant differences in the use of CNIs or prednisone according

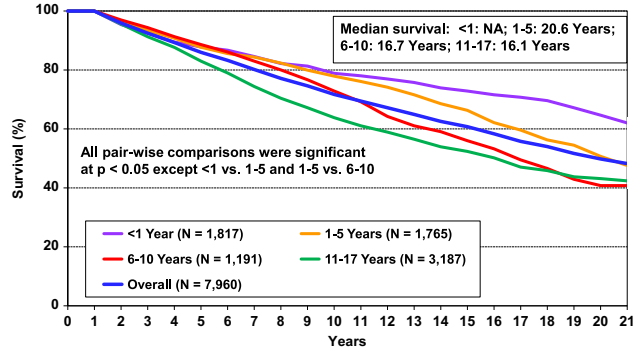

Figure 16 Kaplan-Meier survival conditional on survival to 1 year (Transplants: January 1982–June 2011).

to age group; however, the use of MMF/MPA and azathioprine differed significantly by age group.

At a 1-year follow-up (visits from 2007 onwards), 80% of patients received tacrolimus and 18% received cyclosporine. MMF/MPA, azathioprine, and prednisone use was 77%, 13%, and 56%, respectively. Mammalian target of rapamycin (mTOR) inhibitor (sirolimus or everolimus) use was 10%. At 5 years after transplant, 95% of patients remained on a CNI (tacrolimus use was 71% and cyclosporine was 24%), 74% of patients remained on an antimetabolite (MMF/MPA use was 57% and azathioprine was 17%), mTOR inhibitor use was 20%, and steroid use was 34%. In a cohort of 1,393 patients monitored from 1 to 5 years post-transplant, the most common combination of agents was tacrolimus and MMF/MPA (37% at 1 year and 36% at 5 years). Use of cyclosporine combined with an antimetabolite (MMF/MPA or azathioprine) dropped from 34% to 18%. Monotherapy was used in 15% at 5 years after transplant (Figure 13).

Survival

Differences remain in survival by age, diagnosis, and clinical characteristics that impact long-term survival, now reported out to 15 years post-transplant. Regional differences play a role in survival as well and are examined in an exploratory manner later in this year's report.

Age at transplant

The youngest recipients continue to experience the longest median survival (the time at which 50% of recipients remain alive). Median survival was 19.7 years for infant transplant recipients, 16.8 years for children who received transplants between the ages of 1 and 5 years, 14.5 years for recipients between the ages of 6 and 10 years, and 12.4 years for adolescents (Figure 14). The infant survival curve continues to show an increased early mortality within the first few months but then a reduced rate of attrition.

Era of transplant

Survival curves continue to show improvement over time—primarily in relation to reduced early post-transplant mortality (Figure 15). For the cohort from 1982 to 1989, median survival was 9.5 years, and in the subsequent decade, 13.9 years. Owing to the favorable survival in the more recent eras, the median survival is not calculable. This era trend is evident across all recipient age groups, with the most marked improvement within the 0- to $<$ 1-year recipient age category (1982–1989 median survival was 10.8 years and 1990–1999 median survival was 18.3 years).

Conditional survival

For recipients surviving the first year post-transplant, the median conditional survival was $>$ 21 years for those who received a transplant in the first year of life, 20.6 years for those whose transplant occurred between 1 and 5 years of age, 16.7 years for recipients between 6 and 10 years of age, and 16.1 years for adolescents (Figure 16). These survival outcomes are sustained and remain significantly different between the younger age groups and the adolescents in the most recent era (out to 9 years post-transplant).[1]

Pre-transplant diagnosis

Age-related differences in survival based on the pre-transplant diagnosis were observed. For infant recipients, a diagnosis of cardiomyopathy portended a 10 percentage points survival advantage at 11 years after transplant compared with congenital heart disease, mostly due to a lower early mortality in the cardiomyopathy group.[1] For the group aged 1 to 5 years, a similar significant survival difference was seen between cardiomyopathy and congenital heart disease. In addition, patients receiving retransplant had a lower survival than those with cardiomyopathy (Figure 17). There was no significant survival difference between congenital heart disease and retransplant. Similar observations also applied to the 2 older age groups.[1]

Mechanical circulatory support

ECMO use as a bridge to transplantation resulted in a markedly poorer post-transplant survival, predominantly due to early post-transplant mortality (Figure 18). However, survival after support with a VAD or TAH was equivalent to survival with no MCS in the most recent era.

Immunosuppression

As noted, no difference was found in survival related to induction usage for pediatric recipients as a group or stratified by age[1] or in survival based on type of CNI or on the combination of immunosuppressive agents at the time of hospital discharge.[1] Interestingly, there was a difference in survival at 11 years conditional on survival to 5 years between patients who were receiving cyclosporine at discharge and at 5 years and those receiving cyclosporine at discharge and tacrolimus at 5 years (88% vs 71%, $p = 0.0017$).[1] One hypothesis for this observation relates to the reason for the switch from cyclosporine to tacrolimus (which is not available within the Registry): if the switch was done because of rejection or a comorbidity, this could possibly account for the increased mortality. Prednisone use at 1 year post-transplant remains significantly associated with reduced 10-year survival conditional on survival to 1 year post-transplant. This was most apparent in the group aged 1 to 5 years.[1]

Interaction between age, era, and geography

Last year, some regional differences for 7-year survival were observed in survival rates by age and diagnosis; this analysis did not include any interactions between these

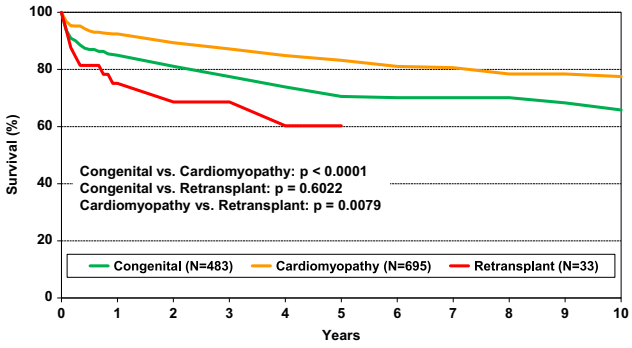

Figure 17 Kaplan-Meier survival by diagnosis for patients aged 1 to 5 years (Transplants: January 2000–June 2011)

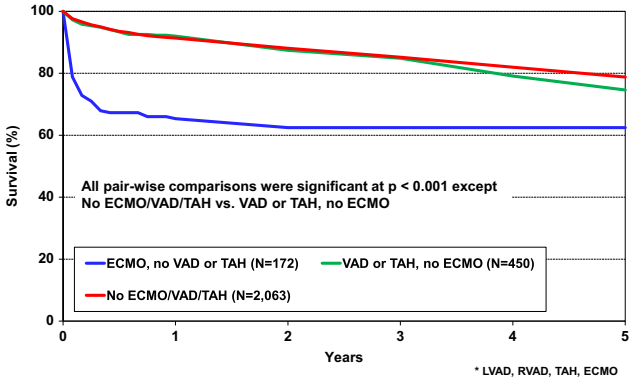

Figure 18 Kaplan-Meier survival by use of mechanical circulatory support (Transplants: January 2000–June 2011). ECMO, extracorporeal membrane oxygenation; LVAD, left ventricular assist device; RVAD, right ventricular assist device; TAH, total artificial heart; VAD, ventricular assist device.

parameters.[2] This year, these relationships were explored for 1-year survival.

For patients with a diagnosis of cardiomyopathy, the HR varied according to recipient age, with the greatest HR at the age extremes (eg, the young child or older teenager). In addition, the risk varied according to geographic location (Figure 19). These differences remained after adjustment in a multivariate analysis.

For patients with a diagnosis of congenital heart disease, there was a statistically significant interaction between

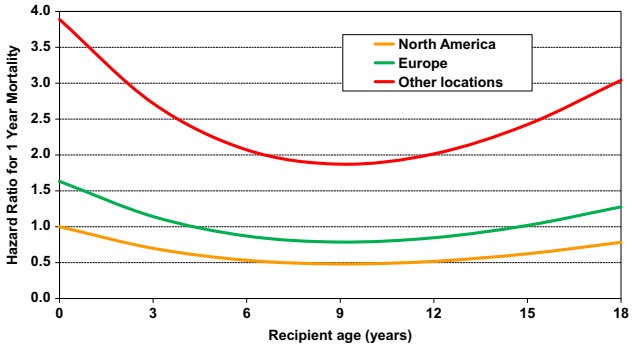

Figure 19 Regional variation in 1-year mortality by recipient age in patients with a diagnosis of cardiomyopathy (Transplants: January 2000–June 2010).

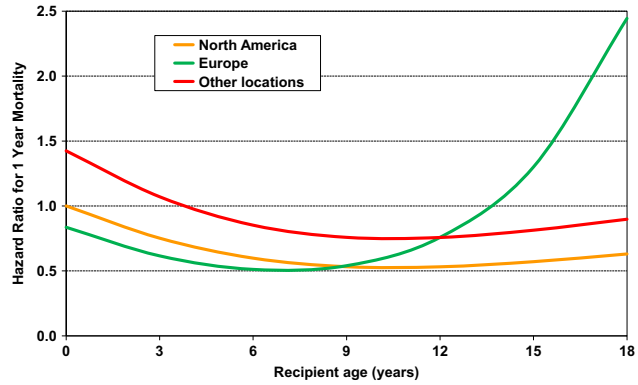

Figure 20 Regional variation in 1-year mortality by recipient age in patients with a diagnosis of congenital heart disease (Transplants: January 2000–June 2010)

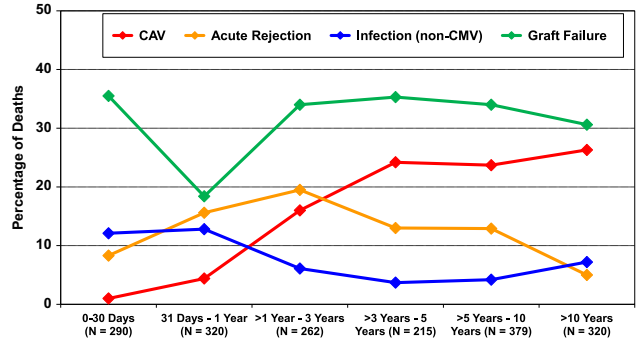

Figure 21 Relative incidence of leading causes of death (Deaths: January 2000–June 2012). CMV, cytomegalovirus.

recipient age and location for transplants performed in Europe compared with those performed in North America and other parts of the world (Figure 20). The HR for mortality within 1 year was similar for Europe and North America through approximately 9 to 10 years of age, when the curves start to diverge. There was a steep increase in the HR for transplants in teenaged recipients in Europe compared with North America. However, the Registry data do not provide us with detailed information on the types of congenital heart disease in the individual groups. These results vary some compared with the observations from last

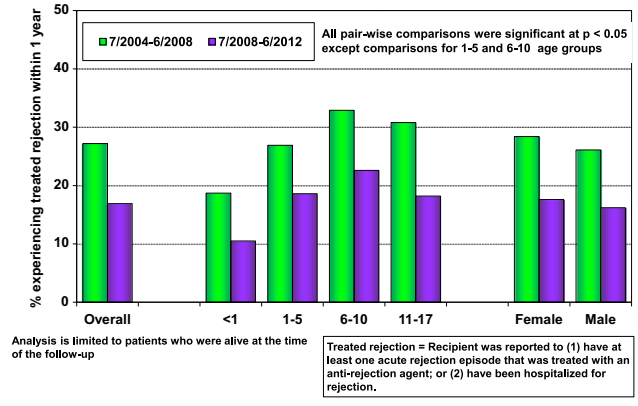

Figure 22 Percentage of patients experiencing *treated* rejection between discharge and 1-year follow-up by era (Follow-up: July 2004–June 2012).

Table 1 Cause of Death for Pediatric Heart Transplant Recipients (Deaths: January 2000–June 2012)

Cause of death	0-30 days ($n = 290$) No. (%)	31 days–1 year ($n = 320$) No. (%)	>1–3 years ($n = 262$) No. (%)	>3–5 years ($n = 215$) No. (%)	>5–10 years ($n = 379$) No. (%)	>10 years ($n = 320$) No. (%)
Coronary artery vasculopathy	3 (1.0)	14 (4.4)	42 (16.0)	52 (24.2)	90 (23.7)	84 (26.3)
Acute rejection	24 (8.3)	50 (15.6)	51 (19.5)	28 (13.0)	49 (12.9)	16 (5.0)
Lymphoma	…	5 (1.6)	6 (2.3)	7 (3.3)	26 (6.9)	20 (6.3)
Malignancy, other	…	4 (1.3)	4 (1.5)	2 (0.9)	8 (2.1)	13 (4.1)
CMV	…	7 (2.2)	1 (0.4)	…	…	…
Non-CMV infection	35 (12.1)	41 (12.8)	16 (6.1)	8 (3.7)	16 (4.2)	23 (7.2)
Graft failure	103 (35.5)	59 (18.4)	89 (34.0)	76 (35.3)	129 (34.0)	98 (30.6)
Technical	21 (7.2)	3 (0.9)	1 (0.4)	1 (0.5)	4 (1.1)	6 (1.9)
Other	22 (7.6)	25 (7.8)	23 (8.8)	16 (7.4)	26 (6.9)	18 (5.6)
Multiple organ failure	38 (13.1)	59 (18.4)	12 (4.6)	9 (4.2)	10 (2.6)	17 (5.3)
Renal failure	…	7 (2.2)	1 (0.4)	1 (0.5)	2 (0.5)	9 (2.8)
Pulmonary	14 (4.8)	31 (9.7)	10 (3.8)	8 (3.7)	11 (2.9)	7 (2.2)
Cerebrovascular	30 (10.3)	15 (4.7)	6 (2.3)	7 (3.3)	8 (2.1)	9 (2.8)

CMV, cytomegalovirus.

year for cardiomyopathy and congenital heart disease patients and point to the importance of further study to understand the interplay of the factors that contribute to post-transplant outcomes. Although this year's analysis focuses on 1-year survival in more depth in addition to differences in patient and donor characteristics and center volumes between the geographic regions, these observations could also relate to differences in the organization of post-transplant follow-up care and behavioral factors, including non-adherence.

Mortality

The first year after transplant remains the period with the highest mortality (Figure 14), although there has been improvement over time (Figure 15). Graft failure and technical issues accounted for 30% of deaths in this time period, followed by multisystem organ failure (16%), infection, including cytomegalovirus (14%), and rejection (12%; Table 1). These causes were among the top causes of death in all 4 age groups.[1]

Overall, graft failure was the most common cause of death throughout the entire post-transplant period. Rejection remained amongst the leading causes of death up to 10 years after transplant, whereas deaths from infection decreased significantly after the first year and remained low thereafter (Figure 21). CAV as a cause of death steadily increased with time, and beyond 3 years post-transplant, combined with graft failure, was responsible for almost 60% of deaths across all of the age groups.[1]

Risk factors for 1-year mortality

There are no surprises in the risk factor analysis for the years 2001 to 2010 for 1-year mortality (Table 2). Higher pre-transplant clinical acuity was reflected by ECMO support (HR, 2.65), dialysis (HR, 2.03), and mechanical ventilation (HR, 1.35). Retransplant as a diagnosis remains a significant risk factor (HR, 2.16), probably a reflection of worse outcome in acute retransplants (see below). Transplant for congenital heart disease also remains a significant risk factor (HR, 2.04). Increasing recipient body mass index, examined as a continuous variable, negatively affected 1-year survival ($p = 0.03$). Results of an expanded analysis that examined risk factors for 1-year mortality within the different age groups are summarized in Table 3.

Risk factors for 5-, 10-, and 15-year mortality

MCS (in its different forms over the years) remains a significant risk factor for mortality out to 15 years post-transplant, as does a diagnosis of congenital heart disease (Table 3). Dialysis, mechanical ventilation, and hospitalization at the time of transplantation also have a prolonged impact on mortality, perhaps related to comorbidities. Finally, retransplantation remains in the multivariate analysis as a risk factor for mortality out to 15 years post-transplant.

Post-transplant morbidity

Functional status

Functional status data, reported in the Registry since 2005, are predominantly from the United States, where submission is mandatory, and assessed with the Lansky score. A score of 100 represents full activity, 90 indicates minor restrictions to strenuous activity, and 80 indicates that the patient tires more quickly but is capable of participating in physical activity. At 1 year post-transplant, 93% of recipients have a score of $\geq$ 80.[1]

Re-hospitalization rates remain high during the first year after transplant for the cohort followed up between 2000 and June 2012, with 49% requiring readmission: 18% for infection, 11% for rejection, 6% for infection and rejection,

Table 2 Risk Factors for Mortality at 1 Year, $N = 3,516$ (Pediatric Heart Transplants: January 1, 2001–December 31, 2010)

Variable	No.	HR (95% CI)	*p*-value
Extracorporeal membrane oxygenation	280	2.65 (2.00–3.50)	<0.0001
Retransplant	206	2.16 (1.42–3.27)	0.0003
Congenital diagnosis	1426	2.04 (1.58–2.64)	<0.0001
On dialysis	123	2.03 (1.42–2.90)	<0.0001
Donor cause of death =			
Cerebrovascular/stroke vs head trauma	327	1.53 (1.11–2.11)	0.0090
Other than (head trauma, cerebrovascular/stroke, anoxia, and CNS tumor) vs head trauma	289	1.49 (1.05–2.12)	0.0270
Anoxia vs head trauma	902	0.75 (0.58–0.97)	0.0260
Male donor/female recipient vs male donor/male recipient	913	1.44 (1.11–1.88)	0.0060
Prior sternotomy	830	1.42 (1.10–1.83)	0.0070
On ventilator	700	1.35 (1.06–1.73)	0.0170
Panel reactive antibody > 10%	311	1.35 (1.00–1.81)	0.0500
Infection requiring intravenous drug therapy (≤ 2 weeks of transplant)	610	1.32 (1.03–1.69)	0.0270
Previous transfusions (borderline significant)	1265	1.25 (0.98–1.58)	0.0669
Transplant year: 2009-2010 vs. 2001-2002 (borderline significant)	779	0.75 (0.54–1.04)	0.0826
Cerebrovascular event before transplant (borderline significant)	198	0.65 (0.41–1.03)	0.0688
Donor height			<0.0001
Recipient body mass index			0.0295
Ischemia time			0.0035
Recipient pre-transplant creatinine			0.0009

CI, confidence interval; CNS, central nervous system; HR, hazard ratio.
Reference group = cardiomyopathy, no devices

and 14% for other reasons. By 5 years post-transplant, hospital admissions were reduced to 28%.

Rejection

For this year's analysis, rejection was separated into *treated rejection* (at least 1 acute rejection episode that was treated with an anti-rejection agent or hospitalization for rejection) and *any rejection.* A significant decrease occurred in treated rejection between July 2004 and June 2008 and July 2008 and June 2012 among all patients and in most age subgroups (Figure 22). This decrease also applied to any rejection, which was reported in a greater proportion of patients (compared with treated rejection) and was true across all 4 age groups. As noted above, there was no significant difference in rejection episodes based on use of induction therapy. Tacrolimus use at the time of discharge was associated with a significantly lower percentage of recipients with treated rejection episodes between discharge and 1 year post-transplant (30% reduction). Maintenance immunosuppression of tacrolimus and MMF/MPA was associated with significantly less treated rejection between discharge and 1 year post-transplant compared with cyclosporine and MMF/MPA.

In patients surviving past 1 year after transplant, treated rejection within the first year after transplant was associated with a 7 percentage points lower survival at 6 years, a greater difference than the 5% reported in 2012.[2] This decrement in survival was significant in the group aged 11 to 17 years but did not reach statistical significance in younger children.[1]

Coronary allograft vasculopathy

Freedom from CAV declined inexorably with time post-transplant, with 53% of patients free of CAV 14 years after transplant. Infant and young child (1–5 and 6–10 years) recipients had slower progression of CAV: 31% of infants had developed CAV by 10 years post-transplant, 29% of 1- to 5-year-olds, 36% of 6- to 10-year-olds, and 48% of 11- to 17-year-olds. After a diagnosis of CAV, graft survival drops precipitously, regardless of recipient age, and was approximately 50% after 5 years.[1]

Renal dysfunction

Infant and young child (1–5 years) recipients experienced significantly less severe renal dysfunction than adolescent recipients—7%, 5% and 14%, respectively—at 11 years after transplant ($p = 0.0008$ and $p = 0.0005$). Overall, 5% of patients required renal replacement therapy in the form of dialysis or renal transplant by 11 years post-transplant. As has been shown previously, the type of CNI had no effect on late renal function.

Malignancy

Overall, 18% of patients developed a malignancy by 15 years post-transplant, the vast majority being lymphoma. There was no effect based on induction therapy, but the choice of CNI showed statistical significance in the younger age groups, where the incidence of malignancy with tacrolimus was higher.[1] The nature of the Registry data

Table 3 Categoric Risk Factors for 1-Year, 10-Year, and 15-year Mortality for Pediatric Heart Recipients[a]

	Model						
	1 year by recipient age group						
Time post-transplant	<1 year[b]	1–5 years[c]	6–10 years[c]	11–17 years[c]	5-year[c]	10-year[c]	15-year[c]
ECMO, diagnosis = congenital	3.91	…	…	…	…	3.91[d]	…
ECMO or VAD, diagnosis = congenital	…	3.79	…	…	…	…	…
ECMO, diagnosis = not congenital	2.37	…	…	…	…	…	…
ECMO	…	…	2.56	2.17	2.68[d]	…	…
Balloon pump	…	…	…	…	…	1.78	1.59
On dialysis	2.12	2.28[e]	…	2.47	1.67	…	…
On ventilator	1.78	…	…	…	1.26	1.19	1.28
Panel reactive antibody > 10%	1.77	1.72[e]	…	…	1.48	1.22[e]	…
Prior sternotomy	1.67	…	…	…	…	…	…
Infection requiring intravenous drug therapy (≤2 weeks of transplant)	1.64	…	…	…	1.24	…	…
Previous transfusion	…	2.01	…	1.53	…	…	…
Diagnosis							
Cardiomyopathy	0.59[e]	…	…	…	…	…	…
Congenital	…	…	2.30[e]	2.17	1.62	1.95[e]	1.18
Congenital, no ECMO or VAD	…	1.89	…	…	…	…	…
Congenital, no PGE or ECMO	…	…	…	…	…	1.60[d]	…
Congenital, age = 2–17 years	…	…	…	…	…	1.27	…
Retransplant	…	…	…	2.75	1.75	2.05	1.84
Donor cause of death =							
Cerebrovascular/stroke vs head trauma	2.25	…	…	…	1.28	…	…
Other than (head trauma, cerebrovascular or stroke, anoxia, and CNS tumor) vs head trauma	…	…	…	1.88	…	…	…
Anoxia vs head trauma	…	…	…	0.41	…	…	…
Donor clinical infection	…	…	…	0.68[e]	…	…	…
Transplant year							
2003–2004 vs 2001–2002	…	…	…	0.59[b]	…	…	…
2005–2006 vs 2001–2002	1.73[e]	…	0.27	…	…	…	…
2007–2008 vs 2001–2002	1.85	0.50	…	0.58[e]	…	…	…
2009–2010 vs 2001–2002	…	0.49	…	…	…	…	…
1998/1999 vs 1992/1993	…	…	…	…	…	0.72	…
1996/1997 vs 1992/1993	…	…	…	…	…	0.72	…
2000/2001 vs 1992/1993	…	…	…	…	…	0.65	…
1995–1996 vs 1988–1989	…	…	…	…	…	…	0.82
Female recipient	…	1.43[e]	…	…	…	1.17	1.10[e]
Male donor/female recipient vs male donor/male recipient	…	…	…	…	1.38	…	…
Not ABO identical	…	…	…	…	0.77	…	…
Hospitalized at time of transplant	…	…	…	…	…	1.19	…
Donor CMV+/recipient CMV–	…	…	…	…	…	1.14	…
Recipient history of malignancy	…	…	…	…	…	…	1.41[e]
Cerebrovascular event before transplant	…	0.30	…	…	…	…	…
0–3 vs. 4–6 total HLA mismatches	…	…	…	…	…	0.80	
2 mismatches at DR locus	…	…	…	…	…	…	0.78

CMV, Cytomegalovirus; CNS, central nervous system; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; PGE, prostaglandin E; VAD, ventricular assist device.

[e]Age = 1 year.

[e]Borderline significant.

[a]1 year: January 1, 2001–December 31, 2010; 5 years: January 1, 1997–December 31, 2006; 10-years: January 1992–December 2001; 15 years: January 1988–December 31, 1996 transplants.

[b]Reference group = congenital, no devices.

[c]Reference group = cardiomyopathy, no devices.

[d]Age = 0 years.

limit further analysis that could elucidate the reasons for these differences, including the possible role of overall intensity of immunosuppression and viral status.

Retransplantation

In 2011, 32 retransplants were reported to the Registry (5.6% of total transplants). Retransplantation remains most common in North America (6%) compared with the rest of the world (2%; Figure 6). Age differences in retransplantation as an indication for transplantation were in line with previous reports, with $< 1\%$ in infancy and rising to 9% in the group aged 11 to 17 years. Most retransplants (72%) occurred beyond 3 years after the primary transplant, and when done within that interval, had similar survival to a primary transplant. Survival for retransplants done earlier, especially within 1 year from the primary transplant, was much poorer. Survival after retransplantation is reduced in all recipients aged >1 year compared with cardiomyopathy but is not significantly different from patients with congenital heart disease (early survival curves for congenital heart disease and retransplantation are almost superimposable for older recipients).

Conclusions

The field of pediatric heart transplantation continues to evolve. With an increasing number of patients reported to the Registry, the trend toward larger-volume centers continues but with different patient profiles based on region. Although indications for transplantation have remained essentially unchanged during the last decade, immunosuppressant combinations continue to change with an effect on incidence of rejection, which continues to decrease. Survival continues to improve, and Registry data demonstrate that some factors from very early post-transplant continue to affect 10- and 15-year survival. Finally, exploratory analyses continue to point toward the importance of regional variations in practice on outcomes. The Registry continues to be a valuable international resource documenting changes in pediatric transplant practice.

Disclosure statement

All relevant disclosures for the Registry Director, Executive Committee Members, and authors are on file with the ISHLT and can be made available for review by contacting the Executive Director of the ISHLT.

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