参考資料 6

EXECUTIVE SUMMARY
OF THE MINUTES
OPTN/UNOS BOARD OF DIRECTORS MEETING

June 19-20, 2008

Richmond, Virginia

Dr. Pruett called the meeting to order at 3:00 p.m. on June 19, 2008. A quorum was present, and 33 of the Board members were in attendance during the meeting.

The Board appointed Dolph Chianchiano, J.D. to fill the vacancy created by the passing of Flora Solarz, M.P.S., ATR, representing the General Public category on the Board of Directors.

The Board approved several resolutions contained in the Consent Agenda in a single vote. The subject of the various individual resolutions follows here:

1. The Board approved modifications to the Bylaws Appendix B, Attachment I, Section XIII (Transplant Programs), D (2) and (4) (Designated Transplant Program Criteria), to require written notification (or disclosures) to living kidney and liver donors from recipient transplant programs.

2. The Board approved the minutes of the February 20-21, 2008, Meeting of the Board of Directors in Orlando, Florida.

3. The Board approved modifications to Policy 3.6.4.1 (Adult Candidate Status) to clarify that CVVHD (continuous veno-venous hemofiltration) is a "form of dialysis" for the purpose of calculating MELD score.

4. The Board approved modifications to the Bylaws, Appendix B, Attachment I, Section XIII, D, (4) (Liver Transplant Programs that Perform Living Donor Liver Transplants) to clarify that a center is expected to inactivate or stop performing living donor transplants if the applicable Bylaw requirements are not met by the end of the conditional approval period.

5. The Board approved modifications to Policy 5.5 (Standard Organ Packaging Specifications) to define "a plastic bag" as "a red plastic biohazard bag" and to promote consistency within the policies.

Following passage of the Consent Agenda, the Board approved the OPTN 2009 Operating Budget and an increase in the Registration Fee to $547 based upon the projected level of operational activities.

The Board approved the 2007 audited financial statements for OPTN Operations and the related OMB Circular A-133 compliance audit for the year ended September 30, 2007.

The Board approved modifications to Policy 3.5.3 (Mandatory Sharing of Zero Antigen Mismatch Kidneys) that will eliminate mandatory sharing of kidneys at the regional and national levels for adult candidates who have a sensitization level (PRA or CPRA) less than 20%.

The Board approved modifications to Policies 3.5.3.5 (Time Limit); 3.8.1.7.1 (Organ Offer Limit); and 7.6.1.2 (Validation of Offers) to clarify the time limits for offering zero antigen mismatched kidneys, with additional amendments to specify that the Host OPO must, rather than may, either allocate the organ according to the standard geographic sequence of kidney and pancreas allocation or allocate the organ(s) for the remaining zero antigen mismatched potential recipients.

The Board approved modifications to Policy 3.8.8 (Waiting Time Reinstatement for Pancreas Recipients) to allow the Organ Center to reinstate a pancreas recipient's waiting time after the recipient's graft had failed but before a pancreatectomy was performed.

The Board of Directors approved modifications to the Bylaws Appendix A, Sections 3.01A and 5.05A, and new Section 5.07A, regarding restoration of full membership privileges following an adverse action, with additional amendments to Section 5.07A to clarify the section further. The purpose of the proposal is two-fold: to better define how a Member may be considered for restoration of full membership privileges, and to clarify the way to move from "Member Not in Good Standing" to a lesser action, such as Probation.

The Board approved modifications to Policies 3.6 (Allocation of Livers) and 3.11.4.2 (Combined Liver-Intestinal Organs from Donors 0-10 Years of Age), which will extend offers nationally to all 0-11 year old Status 1A pediatric liver and combined liver-intestine candidates before making local adult Status 1A offers for the 0-10 donor age group in order to reduce pediatric waiting list mortality.

The Board approved modifications to Policies 3.7.6.2 (Candidates Age 0-11), 3.7.11 (Sequence of Adult Donor Lung Allocation), and 3.7.11.1 (Sequence of Pediatric Donor Lung Allocation), which will allow the creation of a stratified allocation system for 0-11year-old lung candidates to improve access to organs for the sickest candidates by more broadly sharing young pediatric donor lungs to reduce pediatric waiting list mortality.

The Board approved modifications to Policies 3.7.5 (Allocation of Adolescent Donor Hearts to Pediatric Heart Candidates) and 3.7.10.1 (Sequence of Adolescent Donor Heart Allocation), which incorporate all pediatric donor hearts into the current adolescent algorithm and share these hearts more broadly to the sickest candidates to reduce pediatric waiting list mortality.

The Board tabled a proposed statement acknowledging that living-related organ donation from persons currently incarcerated is ethical and should be permissible under certain circumstances pending review by the Living Donor Committee.

The Board approved non-substantive modifications to the OPTN Charter to remove language that unnecessarily referenced expired OPTN contracts.

The Board ratified Executive Committee-approved modifications to Policies 4.6 (Screening Potential Organ Donors for Transmission of Diseases or Medical Conditions, Including Malignancies) and 2.2 (Evaluation of Potential Donors) to specify that donors may be tested for transmissible diseases using FDA-licensed, approved, or cleared serological tests capable of determining whether the donor is or has been infected with these specific diseases.

The Board ratified Executive Committee-approved modifications to Policy 3.2.1.2 (Prohibition of Access by Non Members) to clarify appropriate access to UNet^{sm}, including the requirement to have a data use agreement with third parties to whom the member has granted access to UNet^{sm}.

The Board resolved to support efforts by the Association of Organ Procurement Organizations (AOPO) to encourage the Centers for Disease Control and Prevention (CDC) to develop an updated and comprehensive definition of "high risk donor" for organs recovered for transplantation.

The Board approved modifications the Bylaws Article I (Members), Article II (Board of Directors), and Article VI (Officers) that would permit each Histocompatibility Laboratory and Medical/Scientific Member to receive one vote in the OPTN/UNOS matters and remove the need for separate national elections for both the Histocompatibility Member and Medical/Scientific Member electors. The MPSC will consider whether to retain the elector system that remains for Public Organization Members and Individual Members.

The Board approved a pilot program for a national Kidney Paired Donation System (KPD).

The Board approved modifications to Policies 3.11.4 (Combined Intestine-Liver Candidates); 3.9.3 (Organ Allocation to Multiple Organ Transplant Candidates); and 3.6.4.8 (Combined Liver-Intestine Allocation) to eliminate potential confusion about which match run to use for the allocation of combined liver-intestine grafts.

The Board referred a proposed Statement on Organ Trafficking back to the Ethics Committee for further review in light of the recent Istanbul conference on organ transplantation.

Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Heart Transplantation Report—2009

Richard Kirk, MA, FRCP, FRCPCH, Leah B. Edwards, PhD, Paul Aurora, MRCP, PhD, David O. Taylor, MD, Jason D. Christie, MD, MS, Fabienne Dobbels, PhD, Anna Y. Kucheryavaya, MS, Axel O. Rahmel, MD, Josef Stehlik, MD, and Marshall I. Hertz, MD

The first pediatric heart transplantation reported to the International Society of Heart and Lung Transplantation (ISHLT) Registry was in 1982; since then, more than 8,000 children have been registered. Many have survived into adult life, and some have had their own children. This 12th Report continues to document the evolving management of pediatric transplant recipients and their outcomes.

REGISTRY DATA SOURCE AND STATISTICAL METHODS

The ISHLT Registry data are provided by individual centers or a data-sharing arrangement with a national or regional organ procurement or exchange organization. Approximately 450 pediatric heart transplants are reported to the Registry each year. Most the data are provided from North American centers, but significant contributions come from centers in Europe and the rest of the world (Figure 1). The Registry Committee is actively seeking participation from all centers performing pediatric heart transplants.

The tables and figures in this report and additional slides are all available from the ISHLT Web site.[1] Contributing centers are recognized in the Introduction to the 2009 Annual Reports.

Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Multivariable analyses were performed using Cox proportional hazard regression analysis. Results of the multivariable analyses are reported as relative risks (RR) with a corresponding p-value or 95% confidence interval, or both. A RR significantly > 1 indicate that the factor is associated with an increased likelihood of the event occurring, such as death, development of coronary allograft vasculopathy, or others. Conversely, a RR < 1 indicates that the event is less likely to occur when that factor is present.

CENTERS AND ACTIVITY

The total of 8,058 pediatric (age < 18 years) heart transplants were reported to the Registry between 1982 and 2007, with an annual transplant rate of 450 during the last 3 years. This represents about 12.5% of the 3,300 adult heart transplants per annum.[2] The number of centers reporting transplant activity increased rapidly in the 1980s and early 1990s to a peak of 106 in 1994. It has decreased slightly since then and has now plateaued at 80 centers.

A gradual trend has developed during the last 10 years toward centers undertaking larger volumes of transplants. For the 1997 to 2000 cohort, 82% of centers undertook 4 or fewer transplants per year, accounting for 34% of all transplants reported to the Registry. Only 6% of centers undertook more than 10 transplants per year, accounting for 31% of total transplants. Since the year 2001, there has been a trend toward slightly fewer centers (79%) undertaking a small number of transplants (1 to 4 per annum), accounting for 28% of all transplants. There has been a corresponding increase in centers (9%) undertaking more than 10 transplants per year, accounting for 44% of all pediatric heart transplants reported to the Registry (Figure 2). In general, European centers had smaller annual volumes, with 44% of centers undertaking 4 or fewer transplants per year compared with 23% in North America (Figure 3).

The annual center volume is one of the factors influencing survival; the RR of 1-year mortality is less than 0.9 for those centers undertaking 15 or more transplants per year compared with 1.06 for those undertaking 4 or less (Figure 4).

DONOR CHARACTERISTICS

There was a significant difference in donor demographics between transplant centers in North America and other centers. In North America, only 20% are adult donors (Figure 5), whereas in the rest of the world,

International Society for Heart and Lung Transplantation, Addison, Texas.

Submitted July 8, 2008; revised August 5, 2009; accepted August 5, 2009.

All of the figures and tables from this report, and a more comprehensive set of Registry slides, are available at www.ishlt.org/registries/.

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 1053-2498/09/$-see front matter. doi:10.1016/j.healun.2009.08.008

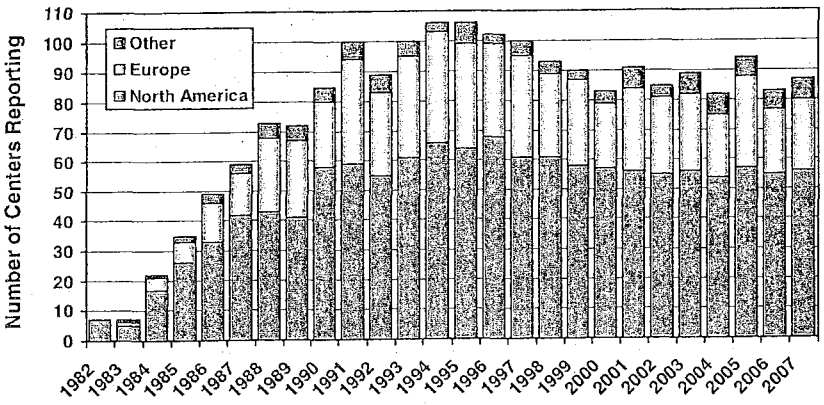

Figure 1. Number of centers reporting pediatric heart transplants by location.

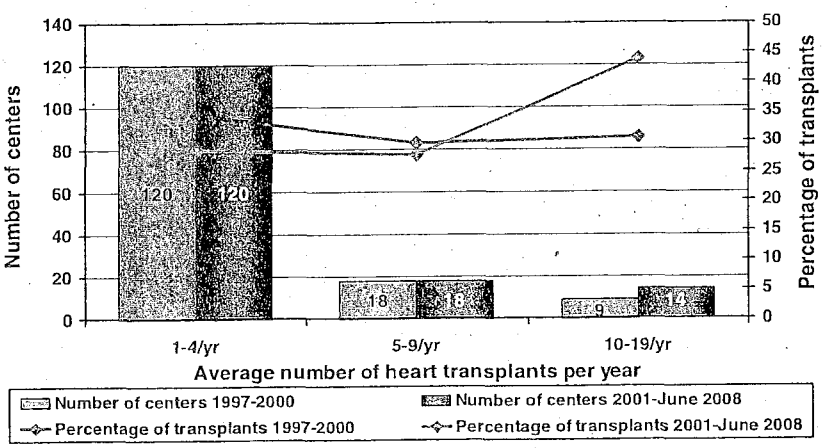

Figure 2. Average center volume for transplants from January 1997 through June 2008.

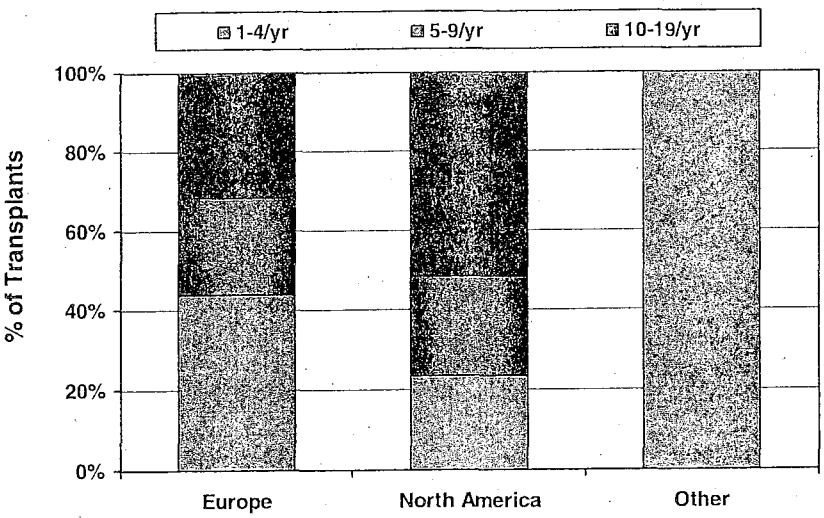

Figure 3. Average center volume distribution by location for transplants from January 2000 through June 2008.

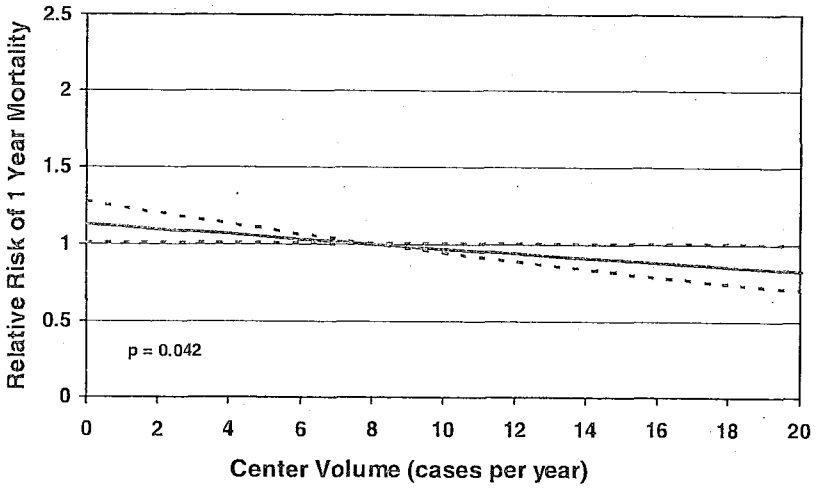

Figure 4. Center volume risk factor for 1-year mortality for transplants from January 1995 to 2007. The dotted lines show the 95% confidence interval for the relative risk.

more than 40% of heart transplant donors for pediatric recipients were from the adult pool. This is of significance, because increasing donor age is associated with reduced 1-year survival (Figure 6).

TRANSPLANT DEMOGRAPHICS

Very few infants (age < 1 year) received an allograft in the early years of transplantation; however, since the early 1990s, approximately 25% of all pediatric heart transplants are undertaken in infancy, with the remainder split amongst other ages (Figure 7). In North America, the proportion transplants performed in infants is 27%, compared with 11% in the rest of the world (Figure 8). The commonest indication for transplant during infancy is congenital heart disease (63%), followed by cardiomyopathy (31%). In older patients the reverse is true, and cardiomyopathy predominates (64%) over congenital heart disease (24%). This contrasts with the adult population,[2] where cardiomyopathy accounts for 50% of transplants, congenital heart disease for 3%, and coronary disease for 34%.

There are also geographic differences in the diagnoses leading to transplant (Figure 9). For all age groups, cardiomyopathy is the reason for transplant in 69% in Europe compared with 49% in North America, where a much higher number of transplants have been for congenital heart disease.

Retransplants (considered as a diagnostic category) occur in 1% infant recipients but now account for 5% of pediatric recipients. This compares with 3% in the adult population.[2] The sudden increase from about 20 retransplants yearly to 35 retransplants in 2005 fell back to 21 reported in 2006, but increased again in 2007 to 36. Retransplants are now being reported in Europe (1.6%), in contrast to previous years. Fifty percent of all retransplants occur more than 5 years after the initial transplant.

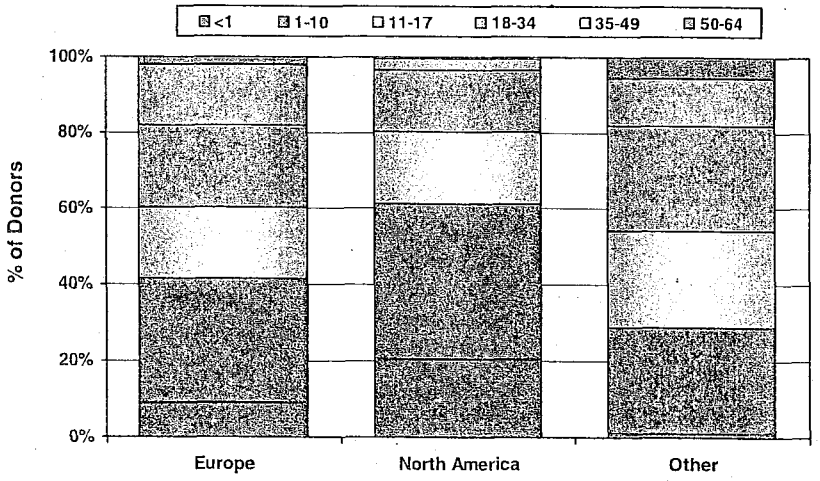

Figure 5. Donor age distribution by location for transplants from January 2000 through June 2008.

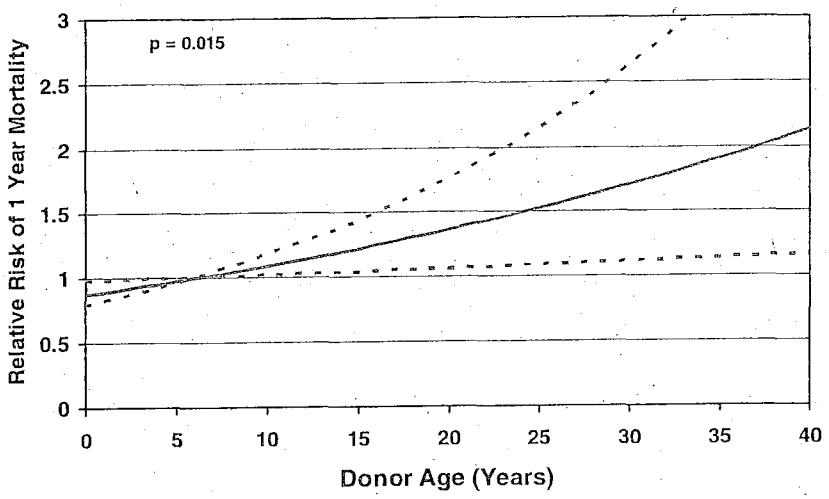

Figure 6. Donor age risk factor for 1-year mortality for transplants from January 1995 through June 2007. The dotted lines show the 95% confidence interval for the relative risk.

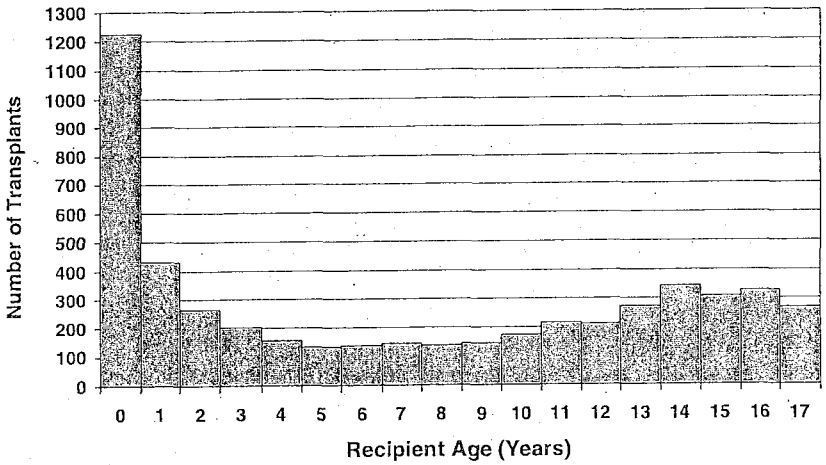

Figure 7. Age distribution of pediatric heart recipients for transplants from January 1996 through June 2008.

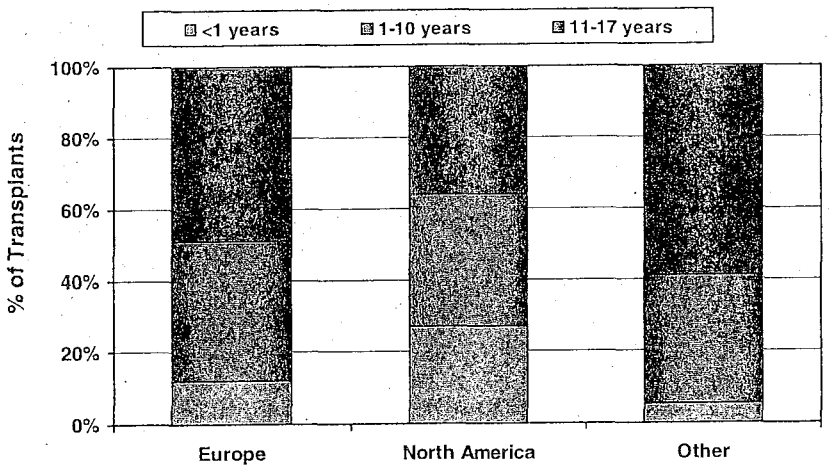

Figure 8. Age distribution by location for transplants from January 2000 through June 2008.

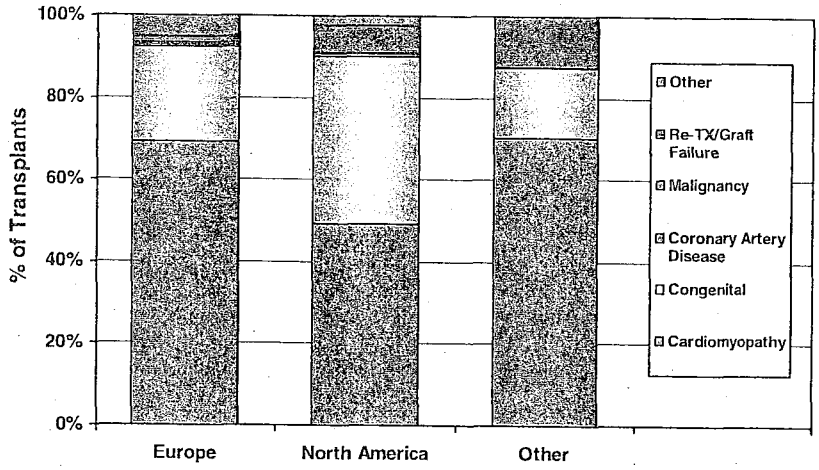

Figure 9. Diagnosis distribution by location for transplants from January 2000 through June 2008.

IMMUNOSUPPRESSION

Induction

Induction therapy is designed to reduce the incidence of early rejection and allow a delay, if necessary, of the introduction of maintenance immunosuppression. The tendency for induction has increased during the past 6 years, with 37% receiving induction in 2001 and 60% in 2008 (Figure 10). This can mainly be accounted for by an increase in polyclonal anti-lymphocyte antibody use from 23% to 39%, although the use of interleukin-2 receptor (IL-2R) antagonists has also increased from 12% to 22%. The overall use of induction agents in the adult population is similar, although the use of IL-2R antagonists is greater. Rejection episodes between transplant discharge and 1 year were not reduced by induction therapy (Figure 11). Neither did the induction strategy (none, polyclonal anti-lymphocyte antibodies, or IL-2R antagonists) influence survival regardless of age at transplant (Figure 12).

There has been some concern that induction therapy might increase the risk of cytomegalovirus (CMV) disease or the development of post-transplant lymphoproliferative disease, driven by Epstein-Barr virus (EBV). However, no relationship has been found between the reported rate of CMV disease according to donor/recipient status combinations and the use or otherwise of induction therapy. Likewise, the use of induction therapy did not increase the likelihood of developing post-transplant lymphoproliferative disease (Figure 13).

Maintenance

Most immune suppressive regimens include a combination of a calcineurin inhibitor (CNI) and cell cycle inhibitor, with a significant number of patients also

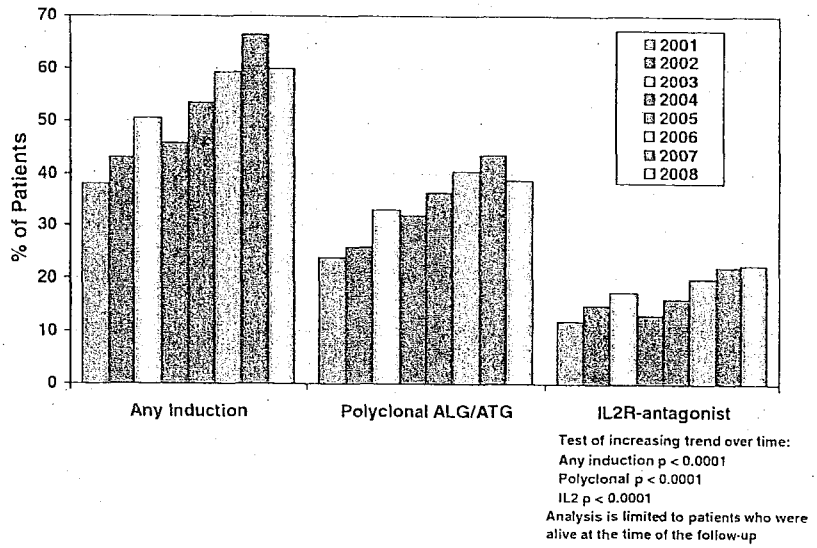

Figure 10. Induction immunosuppression for transplants from January 2001 through June 2008. ALG, anti-lymphocyte globulin; ATG, anti-thymocyte globulin; IL2R, interleukin 2 receptor.

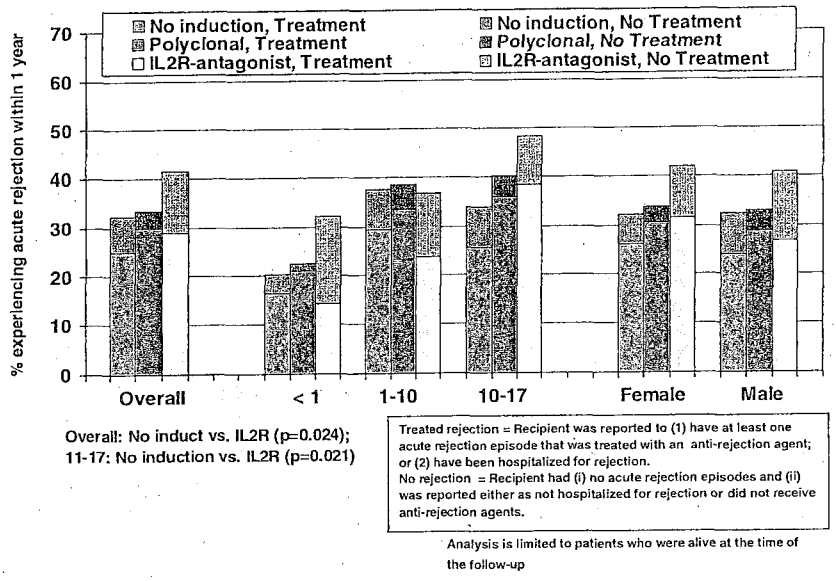

Figure 11. Percentage of pediatric heart transplant recipients experiencing acute rejection between transplant discharge and 1-year follow-up stratified by type of induction for follow-up occurring from July 2004 through June 2008. IL2R, interleukin 2 receptor.

receiving corticosteroids. With regard to the choice of CNI, 38% of patients at the 1-year follow-up received cyclosporine, and 58% received tacrolimus. Cell cycle inhibitors were used by 80% of patients (20% azathioprine, 59% mycophenolate mofetil [MMF]). Prednisone was given to 55%, and 8% received a target of rapamycin inhibitor (Figure 14). These figures broadly reflect the adult practice.[2] A total of 631 patients were tracked for Years 1 to 5 to see how their immunosuppression regimens changed (Figure 15). There were many combinations of therapies, and some uncommon combinations were therefore categorized as "other," accounting for 8% of combinations at 1 year and 19% at 5 years. The percentage change of the more common regimens has been calculated after this "other" category was removed. At Year 1, 15% were receiving cyclosporine and azathioprine, and this decreased to 9% by Year 5. The percentage of patients in this cohort who were receiving a combination of cyclosporine and MMF halved, from 23% to 13%. Overall, the proportion of these 631 patients receiving cyclosporine regimens reduced from 45% to 28%, whereas the proportion with tacrolimus-based regimens rose from 46% to 52%. The proportion taking azathioprine fell from 24% to 16%, and those taking MMF fell from 51% to 43%.

SURVIVAL

The average survival—the time at which 50% of recipients remain alive—varies with the age of the recipient at transplant. The average survival is 11 years for those who receive an allograft as teenagers and 18 years for infants. The highest risk of dying is in the first 6 months after transplant (Figure 16). By estimating survival for those who have exceeded this high-risk period and

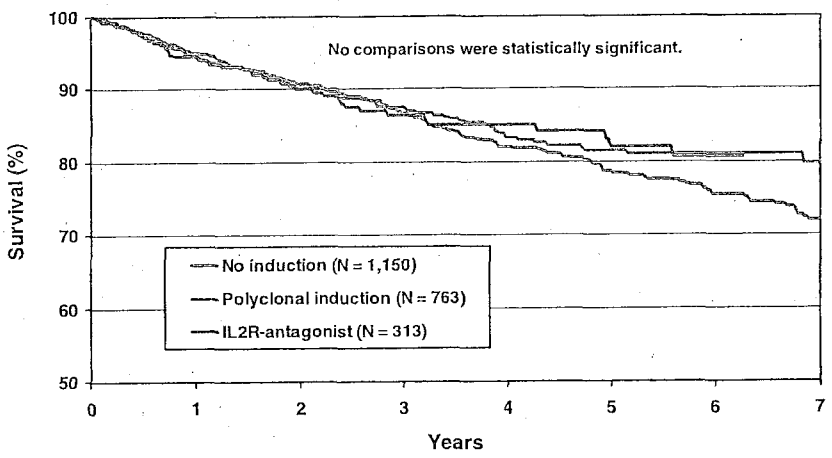

Figure 12. Kaplan-Meier survival by induction group conditional on survival to 14 days for transplants from January 2000 through June 2007.

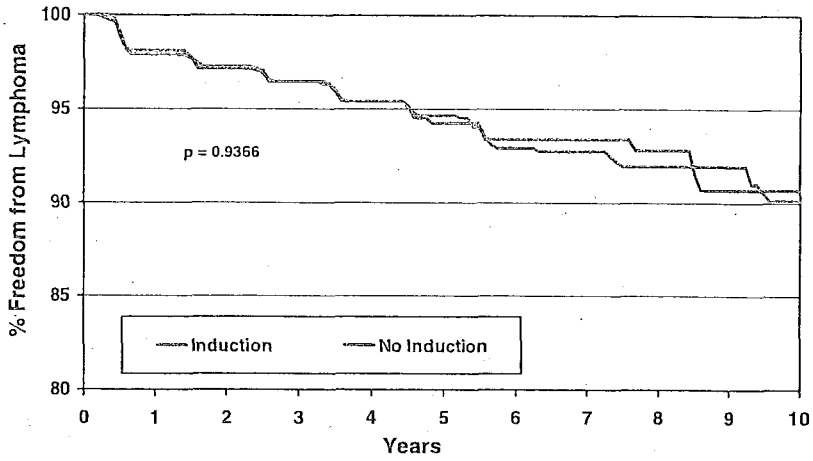

Figure 13. Freedom from lymphoma stratified by induction for follow-up from April 1994 through June 2008.

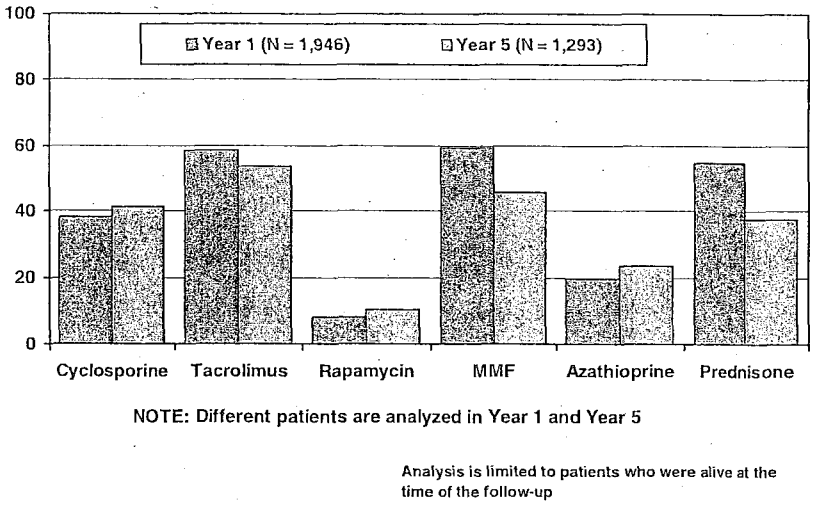

Figure 14. Maintenance immunosuppression at time of follow-up from January 2001 through June 2008. MMF, mycophenolate mofetil.

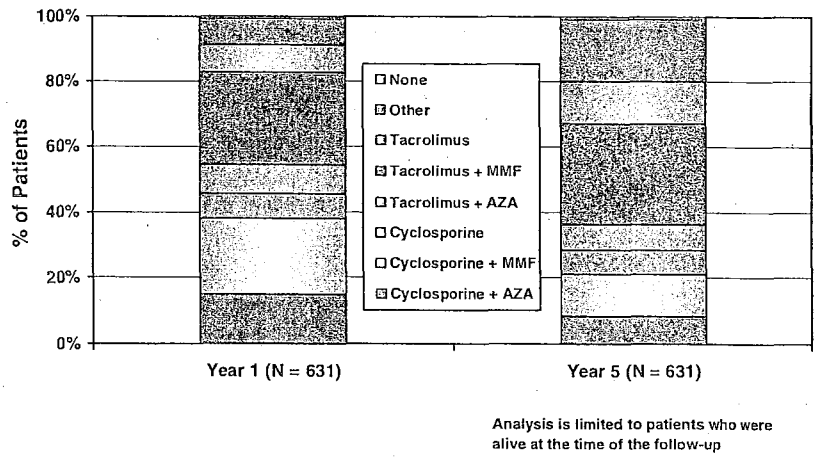

Figure 15. Maintenance immunosuppression at time of follow-up for same patients at each time point from January 2001 through June 2008. AZA, azathioprine; MMF, mycophenolate mofetil.

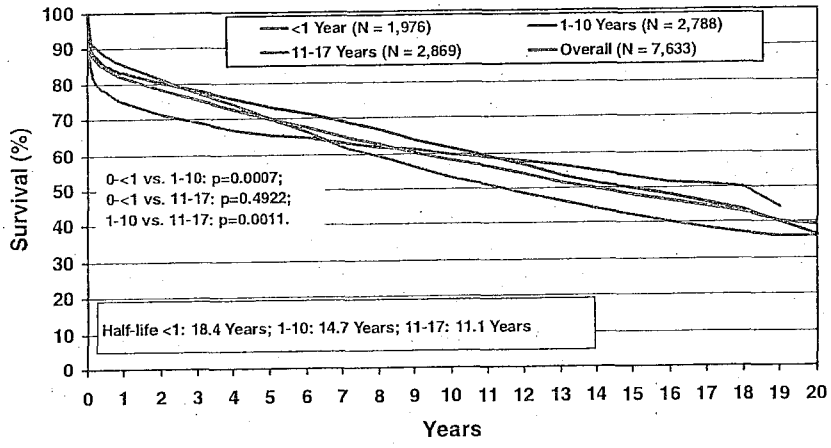

Figure 16. Kaplan-Meier survival for transplants from January 1982 through June 2007.

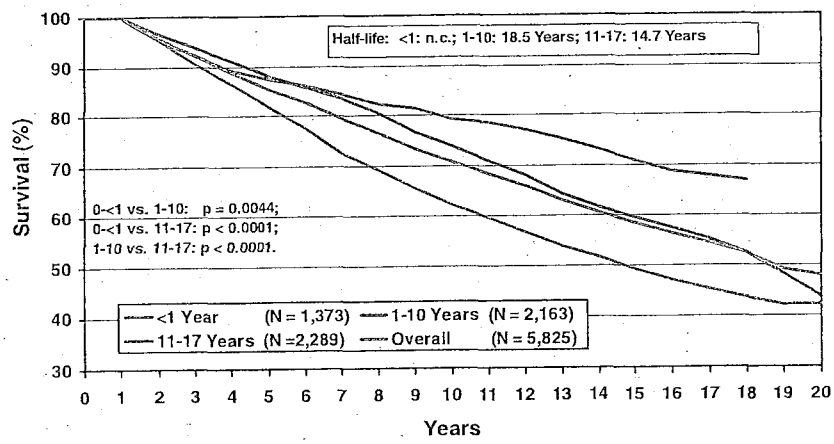

Figure 17. Kaplan-Meier survival conditional on survival to 1 year for transplants from January 1982 through June 2007.

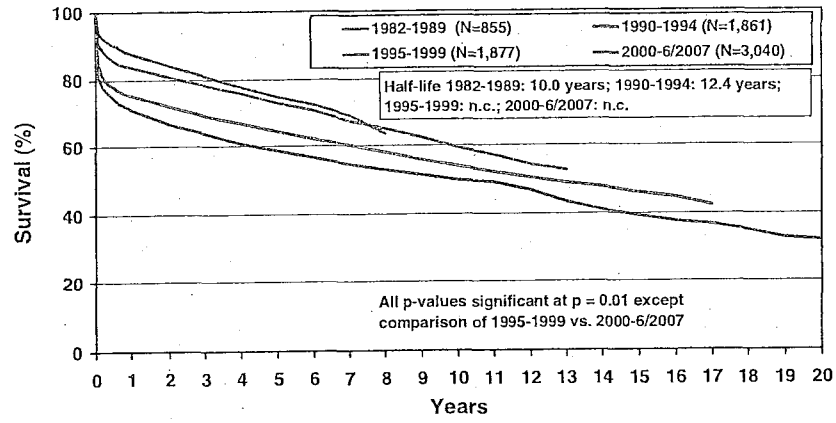

Figure 18. Kaplan-Meier survival by era for transplants from January 1982 through June 2007.

Table 1. Risk Factors for Mortality Within 1 Year for 3,756 Transplants Performed January 1995 Through June 2007

Variable	No.	RR	95% CI	*p*-value
Congenital diagnosis, age = 0, on ECMO	74	2.70	1.57–4.63	0.0003
Congenital diagnosis, age > 0	893	2.17	1.67–2.83	<0.0001
Retransplant	225	2.09	1.42–3.07	0.0002
On ventilator	706	1.80	1.45–2.23	<0.0001
On dialysis	91	1.62	1.08–2.43	0.0210
Year of transplant: 1995–1996 vs 2001–2002	506	1.55	1.14–2.09	0.0049
Panel reactive antibody ≥ 10%	344	1.37	1.04–1.79	0.0228
IV drug therapy for infection ≤2 wk HTx	565	1.29	1.03–1.62	0.0267
Donor cause of death = anoxia vs head trauma	863	0.80	0.64–1.00	0.0468
Not ABO identical	843	0.79	0.63–0.99	0.0384
Diagnosis other than congenital, no ECMO, age = 0	295	0.46	0.27–0.78	0.0042
Recipient age	...	...	...	0.0230
Donor age	...	...	...	0.0150
Creatinine	...	...	...	0.0230
Pediatric transplant volume	...	...	...	0.0420
Recipient height	...	...	...	0.00013
Donor height	...	...	...	0.0470

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation; IV, intravenous; RR, relative risk.

NOTE: Reference diagnosis = cardiomyopathy.

including only those who survived at least 1 year after transplant (conditional survival), the average conditional survival is 15 years for teenagers and nearly 19 years for those who undergo transplantation between age 1 and 10 years. The infant average survival is not calculable, because 50% have not yet died (Figure 17). The average survival in the adult population is approximately 1 year less, and conditional average survival is 2 years less than the teenager group.

Survival can also be shown to be improving in relation to the date of transplantation (Figure 18), with the transplant average survival improving from 9.9 years for the period 1982 to 1989 to 12.4 years for the period 1990 to 1994. The transplant average survival is not calculable for more recent eras because the 50% failure rate has not yet been reached. This improvement has occurred primarily due to a decrease in early death (within the first 3 months).

Post-transplant care after the first few months of life appears not to have significantly improved medium to late outcomes. This is also borne out by a recent detailed analysis of pediatrics recipients using the ISHLT Registry. Although data showed the risk-adjusted 5-year survival after transplant has improved by 30% in the recent era, all of this effect appears to be due to improved survival during the first 6 months after transplantation.[3]

Risk factors predictive of 1-year mortality are listed in Table 1. In general, these risk factors follow common sense, with patients requiring the most pre-transplant support (eg, mechanical support and ventilation) having the greatest risk of dying in the first year. Similarly, factors reflecting recipient illness, such as pre-transplant creatinine levels, influenced the 1-year survival (Figure 19). However, other recipient markers of severity of illness (eg, hospitalization and intravenous inotrope use) had no influence on 1-year mortality. Transplant center volume had an influence: busier centers had better survival (Figure 4).

Congenital diagnosis predicts a worse outcome. Donor gender had no effect, but increased donor age did adversely affect survival (Figure 6). Transplant factors

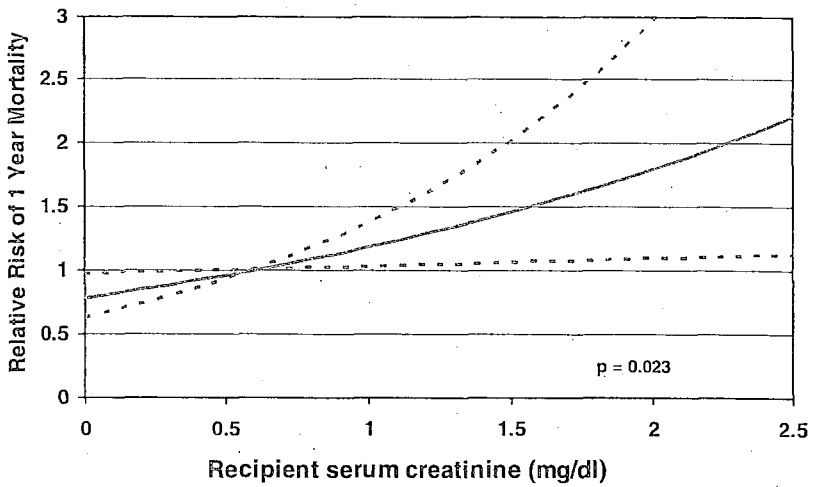

Figure 19. Pre-transplant creatinine risk factor for 1-year mortality is shown with the 95% confidence interval (dotted lines) for transplants January 1995 through June 2007.

Table 2. Risk Factors for Mortality Within 5 Years for 2,364 Transplants Performed January 1995 Through June 2003

Variable	No.	RR	95% CI	*p*-value
Congenital diagnosis, age = 0, on ECMO	36	2.12	1.23–3.67	0.0072
Retransplant, age > 0	131	1.86	1.34–2.59	0.0002
On dialysis	49	1.59	1.04–2.43	0.0337
Panel reactive antibody ≥ 10%	240	1.45	1.15–1.83	0.0019
Congenital diagnosis, age > 0	586	1.38	1.11–1.71	0.0039
On ventilator	445	1.30	1.05–1.61	0.0169
Female recipient	1,006	1.25	1.06–1.47	0.0081
Diagnosis other than congenital, no ECMO, age = 0	185	0.53	0.34–0.83	0.0050
Recipient age	...	...	...	<0.0001
Donor age	...	...	...	0.0230
Pediatric transplant volume	...	...	...	0.0078

CI, confidence interval; ECMO, extracorporeal membrane oxygenation; RR, relative risk.

NOTE: Reference diagnosis = cardiomyopathy.

that had no influence included CMV mismatch, ischemia time, and human leukocyte antigen mismatch.

Risk factors for 5-year mortality include congenital diagnosis with extracorporeal membrane oxygenation (RR, 2.1), dialysis (RR, 1.59), ventilation (RR, 1.3), or female recipient (RR, 1.25; Table 2). Donor age influenced survival, with adult donors leading to poorer survival. The RR of death using a 40-year-old donor was 1.8 compared with that of a 6-year-old donor. Risk factors for 10-year mortality were detailed in last year's report.[4]

Rejection during the first year after transplant appears not to affect short- to medium-term survival (Figure 20). Survival for those discharged with cyclosporine therapy was 69% compared with 63% for tacrolimus at 9 years. This effect persisted for those who continued taking cyclosporine at 1 year, demonstrating 5-year survival of 87% compared with 81% for those maintained on tacrolimus at discharge through to 1 year. This effect also persisted at 9 years, with 73% survival in the cyclosporine group compared with 68% in the tacrolimus group (Figure 21). Patients who changed from one CNI to the other had worse survival times. At the 1-year follow-up, patients who were still receiving corticosteroids as part of their immunosuppression regimen had a worse survival of 69% at 9 years with compared with 81% for those who were not receiving corticosteroids. This may well reflect the occurrence of rejection managed with the inclusion of corticosteroids in the first year, which is known to be associated with a worse outcome rather than a direct effect of corticosteroids.

TRANSPLANT MORBIDITY

Functional status in the Registry is available for 557 transplant recipients who survived at least 10 years. Although the Registry measures of functional status are limited, they do show that 92% of recipients have no limitations on physical activity, and only 1% require total assistance. There is little change in functional status of patients with time, with those having little or no limitations initially continuing to have few limitations later. Rehospitalization during the first year after transplantation is significant, with 50% of the patients requiring readmission for infection (35%), rejection (25%), and for both infection and rejection (15%; Figure 22). By 10 years, hospitalization is much less frequent, with 36% hospitalized for infection, 15% for rejection, and 4% for both infection and rejection. These figures are very similar to the adult data.

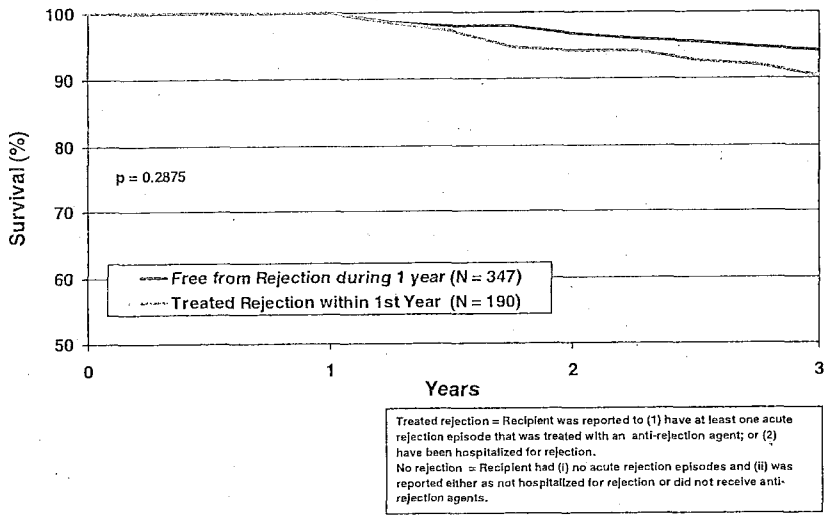

Figure 20. Kaplan-Meier survival based on treated rejection within 1st year conditional on survival to 1 year for 1-year follow-up from July 2004 through June 2007.

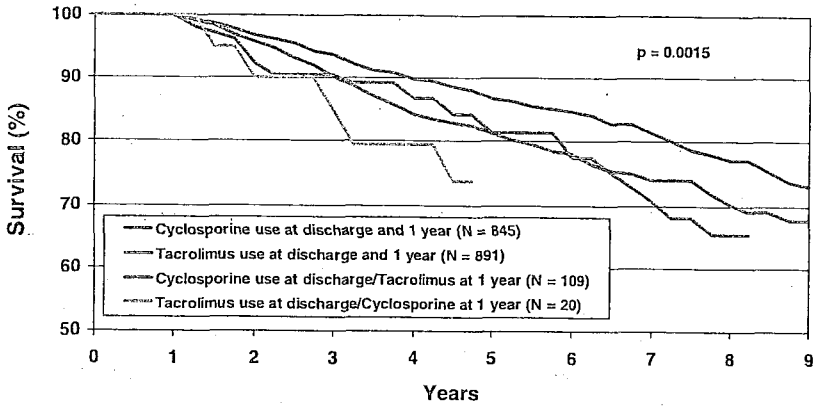

Figure 21. Kaplan-Meier survival stratified by tacrolimus vs cyclosporine use conditional on survival to 1 year for transplants from January 1998 through June 2007.

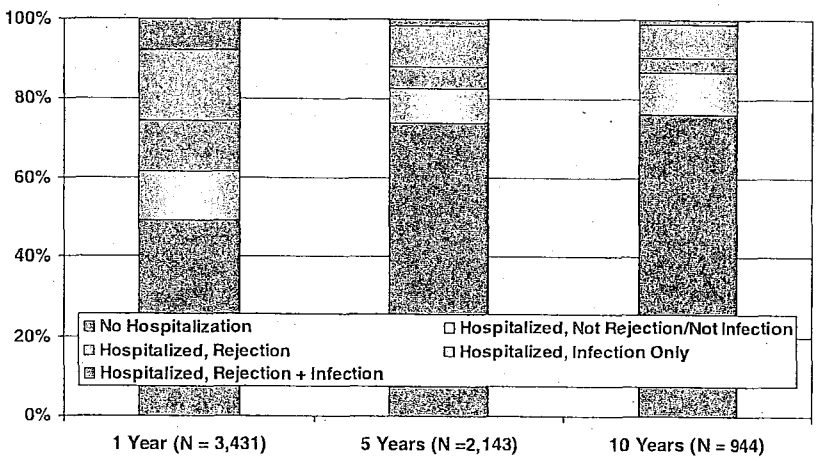

Figure 22. Rehospitalization after transplantation of surviving recipients from April 1994 through June 2008.

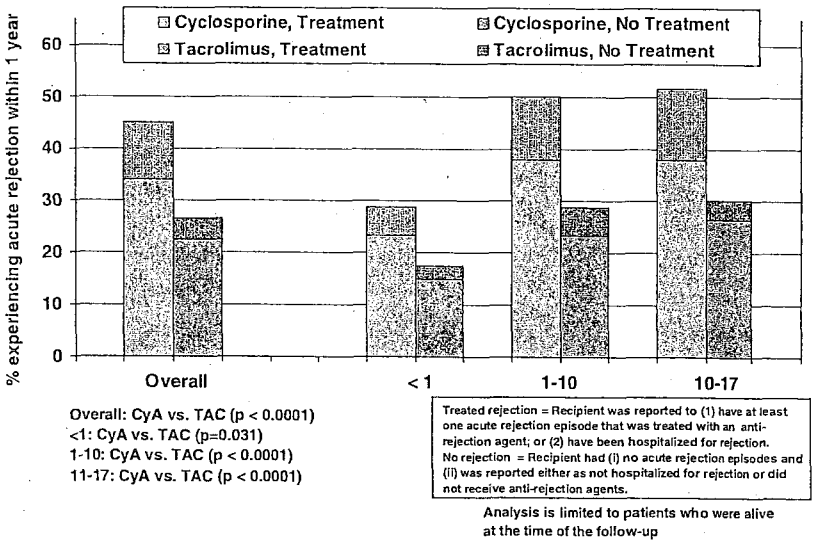

Figure 23. Percentage of pediatric heart transplant recipients experiencing acute rejection between transplant discharge and 1-year follow-up stratified by calcineurin inhibitor use at discharge for follow-up from July 2004 through June 2008.

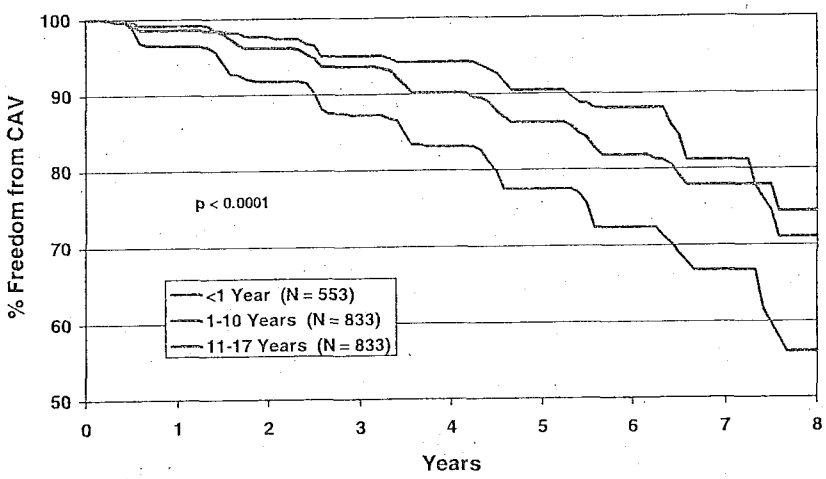

Figure 24. Freedom from cardiac allograft vasculopathy (CAV) stratified by age group for follow-up from January 1999 through June 2008.

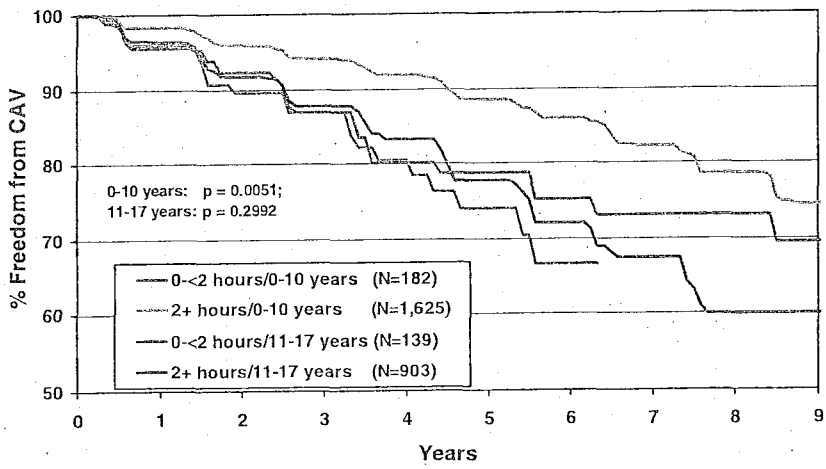

Figure 25. Freedom from cardiac allograft vasculopathy (CAV) stratified by ischemia time and recipient age for follow-up from April 1994 through June 2008.

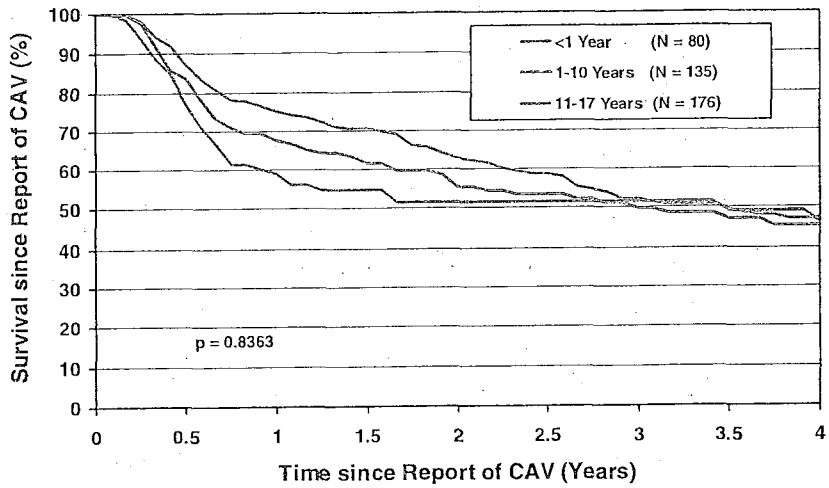

Figure 26. Graft survival after a report of cardiac allograft vasculopathy (CAV) stratified by age group for follow-up from April 1994 through June 2008.

Table 3. Malignancy After Heart Transplantation for Pediatric Recipients, Cumulative Prevalence in Survivors for Follow-up From April 1994 through June 2008

Malignancy and type[a]	1-year survivors No. (%)	5-year survivors No. (%)	10-year survivors No. (%)
No malignancy	3,361 (98.1)	1,343 (95.2)	332 (92.2)
Malignancy (all types)	64 (1.9)	68 (4.8)	28 (7.8)
Lymph	59	64	26
Other	4	5	2
Skin	...	1	...
Type not reported	1	...	...

[a]Patients may have more than one type, thus, sum of types may be greater than total number with malignancy.

Rejection

Despite the increasing use of induction agents, rejection episodes do not appear to have been reduced, at least as recorded after discharge. In fact, 36% of patients rejected after receiving induction therapy compared with 32% of those who received no induction therapy (Figure 11). The increase in rejection episodes with induction therapy was, however, only true for IL-2R antagonists (41% vs 32%), because only a small difference in rejection episodes if a polyclonal anti-lymphocytic antibody was used (35% vs 32%). This effect was noted across all age groups. The adult data are comparable to the pediatric data. Patients receiving cyclosporine at discharge have a 45% incidence of rejection in the first year compared with 27% for those discharged with tacrolimus therapy (Figure 23).

Cardiac Allograft Vasculopathy

Overall, 66% of patients are still free of cardiac allograft vasculopathy (CAV) 10 years after transplant. Age at the time of transplant (Figure 24) has an influence. Patients who undergo transplantation in infancy or early childhood have a reduced incidence of CAV at 8 years after transplant (freedom from CAV of 71% and 74%, respectively) compared with those aged older than 11 years (freedom from CAV 56%).

A short ischemic time of less than 2 hours in children undergoing transplantation when aged younger than 10 years (but not older than 10 years) reduced the freedom from CAV (Figure 25); the explanation for this phenomenon is unclear. Once CAV has occurred, the 3-year graft survival is only 45% for all age groups but then appears to plateau (Figure 26).

Renal Dysfunction

Severe renal dysfunction, defined as a patient requiring renal dialysis, transplant, or with a serum creatinine level more than 2.5 mg/dl (221 μmol/liter), analyzed by the Kaplan-Meier method, shows a linear increase after transplantation, occurring in 11% of pediatric recipients 10 years after transplant. This contrasts with the adult group, in which 60% have severe renal dysfunction by 10 years. The type of CNI selected had no influence on late renal function.

Malignancy

A malignancy had occurred in 8% of patients by 10 years after transplant using the cumulative prevalence in survivor's method (Table 3). In the pediatric age range, almost all malignancies are lymphomas. This contrasts with adults, in whom malignancy is more common (32% by 10 years after transplant) and in which most are skin and other non-lymphoma tumors.

Table 4. Cause of Death in Pediatric Heart Recipients From January 1998 through June 2008

Cause of death	0–30 days (n = 213) No. (%)	31 days–1 year (n = 241) No. (%)	1–3 years (n = 192) No. (%)	3–5 years (n = 153) No. (%)	5–10 years (n = 286) No. (%)	>10 years (n = 165) No. (%)
CAV	2 (0.9)	14 (5.8)	33 (17.2)	43 (28.1)	77 (26.9)	47 (28.5)
Acute rejection	22 (10.3)	45 (18.7)	36 (18.8)	23 (15.0)	36 (12.6)	10 (6.1)
Lymphoma	...	6 (2.5)	7 (3.6)	4 (2.6)	28 (9.8)	11 (6.7)
Malignancy, other	...	1 (0.4)	1 (0.5)	...	4 (1.4)	10 (6.1)
CMV	...	7 (2.9)	1 (0.5)	...	...	...
Infection, Non-CMV	26 (12.2)	31 (12.9)	11 (5.7)	3 (2.0)	13 (4.5)	11 (6.7)
Primary failure	44 (20.7)	9 (3.7)	4 (2.1)	6 (3.9)	10 (3.5)	5 (3.0)
Graft failure	31 (14.6)	25 (10.4)	48 (25.0)	44 (28.8)	66 (23.1)	42 (25.5)
Technical	14 (6.6)	...	2 (1.0)	...	4 (1.4)	1 (0.6)
Other	19 (8.9)	20 (8.3)	24 (12.5)	17 (11.1)	26 (9.1)	10 (6.1)
Multiple organ failure	27 (12.7)	40 (16.6)	10 (5.2)	5 (3.3)	8 (2.8)	8 (4.8)
Renal failure		4 (1.7)	1 (0.5)	1 (0.7)	1 (0.3)	3 (1.8)
Pulmonary	11 (5.2)	27 (11.2)	10 (5.2)	6 (3.9)	7 (2.4)	5 (3.0)
Cerebrovascular	17 (8.0)	12 (5.0)	4 (2.1)	1 (0.7)	6 (2.1)	2 (1.2)

CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus.

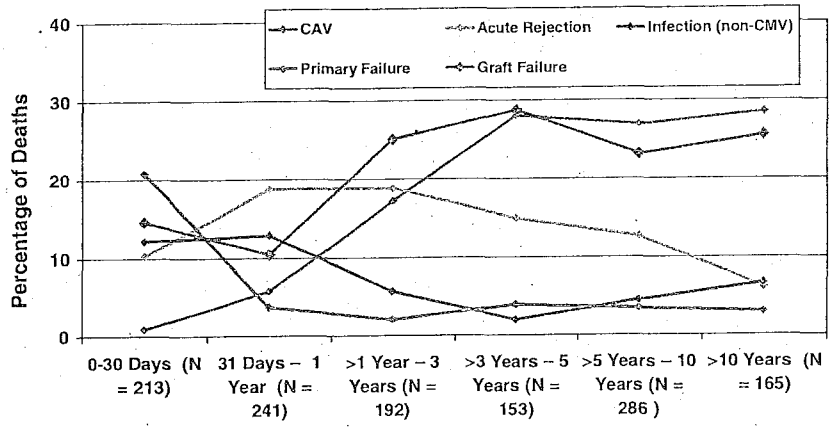

Figure 27. Relative incidence of leading causes of death from January 1998 to June 2008. CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus.

Hypertension

Approximately 69% of patients surviving to 8 years after transplant were documented to have hypertension. By comparison, hypertension had developed in 94% of the adult population 94% by 5 years after transplant.

CAUSE OF DEATH

Nearly 50% of all deaths in the first 30 days after transplant occurred due to graft failure, either primary or secondary to rejection, and technical factors, among others (Table 4); with acute rejection, infection, and multiple organ failure each accounting for about 10% of deaths. Trends in causes of death are shown in Figure 27. Acute rejection remains an ever-present threat, accounting for about 20% of all deaths through 3 years after transplant, with a gradual decline thereafter. CAV and graft failure may well reflect the same pathologic process, that is, individual centers may classify graft failure as CAV and vice versa, but these have traditionally been identified separately in the database. Infection and CAV/graft failure mirror each other, with the risk of infection leading to death declining rapidly after the first year and an increasing number of deaths from CAV/graft failure, which become the leading cause of death (approximately 60% between them) more than 3 years after transplant.

A recent report from Loma Linda University and Children's Hospital[5] similarly identified acute graft dysfunction and technical issues as being implicated in 66% of deaths in the first 30 days after transplant. Their late cause of death was somewhat different, however, with 30% due to acute rejection and 24% to CAV. These differences are likely to relate to ascertainment—the ISHLT Registry data are from many centers, whereas the Loma Linda data were from a detailed retrospective review of all deaths at a single institution with a 75% postmortem rate. This discrepancy highlights the different information from registry and single-center data, with pros and cons of each approach.

In conclusion, this Registry report continues to document the outcome in pediatric heart transplant recipients. It is a registry report, and not a double-blind randomized trial of treatment options and outcomes. The information is therefore imperfect and often poses more questions than answers. The Report will have achieved its objective if it stimulates discussion and suggests areas fruitful for research.

DISCLOSURE STATEMENT

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

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参考資料8

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Waiting List Mortality Among Children Listed for Heart Transplantation in the United States

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Waiting List Mortality Among Children Listed for Heart Transplantation in the United States

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Background—Children listed for heart transplantation face the highest waiting list mortality in solid-organ transplantation medicine. We examined waiting list mortality since the pediatric heart allocation system was revised in 1999 to determine whether the revised allocation system is prioritizing patients optimally and to identify specific high-risk populations that may benefit from emerging pediatric cardiac assist devices.

Methods and Results—We conducted a multicenter cohort study using the US Scientific Registry of Transplant Recipients. All children <18 years of age who were listed for a heart transplant between 1999 and 2006 were included. Among 3098 children, the median age was 2 years (interquartile range 0.3 to 12 years), and median weight was 12.3 kg (interquartile range 5 to 38 kg); 1294 (42%) were nonwhite; and 1874 (60%) were listed as status 1A (of whom 30% were ventilated and 18% were on extracorporeal membrane oxygenation). Overall, 533 (17%) died, 1943 (63%) received transplants, and 252 (8%) recovered; 370 (12%) remained listed. Multivariate predictors of waiting list mortality include extracorporeal membrane oxygenation support (hazard ratio [HR] 3.1, 95% confidence interval [CI] 2.4 to 3.9), ventilator support (HR 1.9, 95% CI 1.6 to 2.4), listing status 1A (HR 2.2, 95% CI 1.7 to 2.7), congenital heart disease (HR 2.2, 95% CI 1.8 to 2.6), dialysis support (HR 1.9, 95% CI 1.2 to 3.0), and nonwhite race/ethnicity (HR 1.7, 95% CI 1.4 to 2.0).

Conclusions—US waiting list mortality for pediatric heart transplantation remains unacceptably high in the current era. Specific high-risk subgroups can be identified that may benefit from emerging pediatric cardiac assist technologies. The current pediatric heart-allocation system captures medical urgency poorly. Further research is needed to define the optimal organ-allocation system for pediatric heart transplantation. (***Circulation.* 2009;119:717-727.**)

Key Words: pediatrics ■ transplantation, heart ■ heart failure ■ survival ■ heart-assist devices

Of all patients wait-listed for solid-organ transplantation in the United Sates, children listed for heart transplantation face the highest waiting list mortality regardless of age.[1] To address this problem, in 1999, the United Network for Organ Sharing (UNOS) implemented a major change in the way donor hearts were allocated by assigning higher priority to sicker status 1 patients[2] (ie, status 1A patients as determined by circulatory support requirements) who were less likely to survive a prolonged wait period. Over the same timeframe, after the landmark study by West and colleagues in 2001,[3] the practice of listing infants across all blood types has increased steadily, a development that has the potential to shorten wait times for infant candidates considerably.[3,4]

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The collective impact of these changes on present-day waiting list mortality is unknown, in large part because earlier studies were conducted primarily in the 1990s, before changes in organ-allocation practice occurred.[5–12] In addition, earlier studies were limited by smaller sample sizes or single-institution experiences,[9,10,12,13] the findings of which may not be generalizable owing to regional differences in practice or may be underpowered to detect important national trends. A contemporary analysis of the primary risk factors associated with waiting list mortality that included all US patients would be useful for 3 specific reasons: (1) To help policy makers determine whether the current organ-allocation

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*The first 2 authors contributed equally to this report.

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The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as an official policy of or interpretation by the Scientific Registry of Transplant Recipients or the US government.

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Table 1. Characteristics of Patients by Cardiac Diagnosis

Variables	CHD (n=1494)	Myocarditis (n=178)	Cardiomyopathy (n=1186)	Other (n=240)	Total (n=3098)	P*
Age, y	1 (0–7)	4 (1–12)	6 (0.8–13)	8 (0.9–14)	2 (0.3–12)	<0.001
Weight, kg	8.2 (3.5–22.3)	16 (9.1–44.9)	18.8 (7.6–49.5)	28.2 (8.2–50.4)	12.3 (5.1–37.6)	<0.001
Body surface area, m^2	0.42 (0.23–0.87)	0.72 (0.44–1.4)	0.78 (0.39–1.5)	1.0 (0.41–1.5)	0.57 (0.3–1.26)	<0.001
Female, %	39	49	49	42	44	<0.001
Nonwhite race, %	37	50	47	38	42	<0.001
UNOS listing status, %						<0.001
1A	63	77	56	59	60	
1B	12	11	15	15	13	
2	25	12	29	26	26	
Blood type, %						0.80
A	37	38	33	34	35	
AB	4	5	4	4	4	
B	11	10	12	11	11	
O	49	47	50	51	49	
Prostaglandin support, %	12	0	<1	2	6	<0.001
Invasive hemodynamic support, %						<0.001
ECMO support	23	28	11	16	18	
Ventilator support	31	31	29	33	30	
Other support (1A)	46	41	60	51	51	
Inotropic support	46	69	54	53	51	<0.001
Dialysis	2	2	1	2	2	0.46
Creatinine, mg/dL	0.6 (0.4 to 0.8)	0.6 (0.4 to 0.9)	0.6 (0.4 to 0.8)	0.7 (0.4 to 1.0)	0.6 (0.4 to 0.8)	<0.001

Values represent median (IQR) or percentage.
*χ^2 Test or Kruskal-Wallis test.

system is serving children with end-stage heart disease optimally, (2) to better define specific high-risk populations that may benefit from emerging mechanical circulatory support technologies, and (3) to determine more precisely where the national organ shortage for pediatric donor hearts is most critical (especially with respect to age and size) as part of a nationwide effort to establish pediatric-specific organ-donation goals.

Methods

Study Population and Data Source

All pediatric subjects less than 18 years of age who were listed for first orthotopic heart transplantation in the United States between January 20, 1999, and July 12, 2006, were identified retrospectively through the US Scientific Registry of Transplant Recipients. The Scientific Registry of Transplant Recipients is an internally audited, mandatory, government-sponsored, solid-organ transplant registry that collects information on all solid-organ transplants in the United States. Demographic and clinical information is reported by transplanting centers to the Organ Procurement and Transplantation Network, supplemented by data from the Social Security Administration and the Center for Medicare and Medicaid Services. January 20, 1999, marks the point in time at which status 1 patients were subdivided into status 1A and status 1B patients. July 12, 2006, marks the point in time at which older status 1A children within 500 miles were given priority over status 1B children within the region. Patients listed for heart retransplantation or multivisceral transplants were excluded. All patients were followed up from the time of listing for heart transplantation until death or the day of last observation on August 3, 2007.

Study Definitions and Outcome Measures

The primary study hypothesis was that among children listed for orthotopic heart transplantation, mechanical ventilation is associated with reduced waiting list survival after adjustment for other patient factors. Time on the waiting list was defined as time from initial listing for heart transplantation to the time of waiting list removal due to transplant, death, or recovery. Subjects who died were considered to have reached the primary end point (ie, had an event). Subjects were censored at the time of transplantation or recovery. All other subjects who remained on the waiting list were censored on August 3, 2007. All clinical and demographic variables were defined at the time of listing for heart transplant unless otherwise specified. Race/ethnicity data (categories included black, white, Hispanic, Asian, American Indian/Alaska Native, Native Hawaiian/Pacific Islander, multiracial, and other) were analyzed as reported by the transplanting center. Glomerular filtration rate was estimated with the Schwartz formula.[14]

Statistical Analysis

Summary statistics are presented as median (interquartile range [IQR]) or number (percent). Patient characteristics were compared across cardiac diagnostic subgroups with the χ^2 test for categorical variables and the Kruskal-Wallis test for continuous variables. Survival time on the waiting list was estimated by the Kaplan-Meier method. Univariate relationships between patient characteristics and waiting list mortality were evaluated with the log-rank test. Multivariable analysis was performed with the Cox proportional hazards model and a stepwise selection technique. Only risk factors that were statistically significant at the 0.05 level were retained in the final multivariable models. These models were then reevaluated with control for UNOS region. Analyses were performed with SAS version 9.1 and Stata version 10.0.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Study Cohort

Of 3416 pediatric patients listed for heart transplant during the study period, 3098 met the inclusion criteria (308 were excluded owing to heart retransplantation and 10 owing to multivisceral transplantation). The baseline characteristics of the study cohort are summarized in Table 1. Of 3098 children listed for first orthotopic heart transplant, the median age was 2 years (IQR 0.3 to 12 years), and the median weight was 12.3 kg (IQR 5 to 38 kg); 1359 (44%) were female, and 1294 (42%) were nonwhite. The primary cardiac diagnosis that led to heart transplant listing was congenital heart disease (CHD) in 1494 (48%), cardiomyopathy in 1186 (38%), and myocarditis in 178 (6%).

Overall, 1874 children (60%) were listed as status 1A, 418 (13%) as status 1B, and 806 (26%) as status 2. Among children listed as status 1A, 570 (30%) were supported with mechanical ventilation, 346 (18%) were supported by extracorporeal membrane oxygenation (ECMO), and 958 (51%) did not receive either type of support. Overall, children listed because of CHD were younger ($P<0.001$) and smaller ($P<0.001$ for both weight and body surface area) than children listed because of cardiomyopathy or myocarditis. Children with cardiomyopathy were less likely to be supported with ECMO or mechanical ventilation than children with CHD or myocarditis ($P<0.001$).

Survival

Among 3098 children listed for heart transplants, 533 (17%) died, 1943 (63%) received a transplant, 252 (8%) were removed from the waiting list because of recovery, and 370 (12%) remained alive on the waiting list on August 3, 2007. Table 2 summarizes the univariate predictors of waiting list mortality.

Table 3 summarizes the multivariable predictors of waiting list mortality. Among all children listed, independent predictors of waiting list mortality included ECMO support, ventilator support, CHD, listing status 1A, dialysis support, and nonwhite race. A glomerular filtration rate <50 mL · min^{-1} · 1.73 m^{-2} was also found to be an independent predictor of mortality but was collinear with dialysis and thus was not included in the final model. Age, weight, and body surface area were not statistically significant predictors of waiting list mortality after adjustment for other covariates in the model. All of the variables in the final model remained statistically significant after adjustment for region and year of transplantation.

Because a large majority of the 533 deaths occurred among children listed as status 1A, we performed a secondary analysis to determine the risk factors associated with mortality among children listed as status 1A (Table 3). Except for listing year (1999 to 2002 versus 2003 to 2006), which became significant in the 1A subgroup analysis, the multivariate predictors, hazard ratios, and 95% confidence intervals were essentially unchanged compared with the overall analysis.

Table 2. Univariate Predictors of Waiting List Mortality

	Univariate Predictors		
Variable	Survived (n=2565)	Died (n=533)	P*
Age, y	3 (0.3–12)	1 (0.1–8)	
Weight, kg	13.4 (5.5–39.5)	8.8 (3.7–24.8)	
Weight categories			<0.001
<10 kg	42	54	
10–19 kg	17	17	
20–39 kg	16	12	
40–59 kg	14	8	
≥60 kg	11	9	
Female	44	44	0.74
Nonwhite race	40	51	<0.001
UNOS listing status			<0.001
1A	58	74	
1B	15	8	
2	28	18	
Cardiac diagnosis, %			<0.001
CHD	45	64	
Cardiomyopathy	41	23	
Myocarditis	6	5	
Other	8	8	
Blood type			0.10
A	37	27	
O	48	57	
B	11	11	
AB	4	4	
Prostaglandin support	6	9	<0.001
Invasive hemodynamic support			<0.001
ECMO support	16	28	
Ventilator support	29	37	
Other support (1A)	55	36	
Inotropic support	50	57	<0.001
Dialysis	1	4	<0.001
Creatinine, mg/dL	0.6 (0.4–0.8)	0.6 [0.4–0.9]	
GFR <50 mL · min^{-1}1.73 m^{-2}	17	33	<0.001
Year of listing			0.24
1999–2002	52	58	
2003–2006	48	42	

Values represent median (IQR) or percentage. GFR indicates glomerular filtration rate.
*Log-rank test.

Figure 1 shows the estimated survival for all children listed for heart transplant according to UNOS listing status (Figure 1A) and for all children listed as status 1A according to the level of invasive hemodynamic support (Figure 1B). No appreciable difference was found in overall waiting list mortality for patients listed as status 2 versus status 1B (11.7% versus 10.5%). By contrast, among patients listed as

Table 3. Multivariate Predictors of Waiting List Mortality*

	Adjusted HRs			
	All Patients		Status 1A Only	
Variable	HR (95% CI)	P	HR (95% CI)	P
ECMO	3.1 (2.4–3.9)	<0.001	3.0 (2.3–3.8)	<0.001
Ventilator support	1.9 (1.6–2.4)	<0.001	1.9 (1.5–2.4)	<0.001
Cardiac diagnosis of CHD	2.2 (1.8–2.6)	<0.001	2.1 (1.7–2.6)	<0.001
Dialysis	1.9 (1.2–3.0)	0.006	2.0 (1.3–3.2)	0.004
UNOS listing status 1A	2.2 (1.7–2.7)	<0.001	...	
Nonwhite race, %	1.7 (1.4–2.0)	<0.001	1.7 (1.4–2.0)	<0.001
Year of listing 1999–2002			1.2 (1.0–1.5)	0.040

*Cox proportional hazards model.

status 1A, a substantial difference was found in risk of waiting list mortality based on the level of invasive hemodynamic support (ie, required ECMO, mechanical ventilation, or neither).

Status 1A Risk Stratification

Table 4 summarizes the observed waiting list mortality of status 1A patients with risk stratification by subgroup. Among children listed as UNOS status 1A, a 7-fold difference was found in the 90-day risk of death on the waiting list on the basis of patient characteristics, with a range from 5% to 39%. The 14- and 30-day waiting list mortality variation for patients listed as status 1A was even more striking. For example, a child weighing <10 kg who was supported on ECMO for CHD (n=155) had a 12-fold higher risk of death by 14 days without transplantation (20.7% versus 1.5%) and an 8-fold higher risk of death by 30 days without transplantation (32% versus 4%) than a child weighing >10 kg with cardiomyopathy who was supported with inotropes alone (n=263). Figure 2 shows the competing outcomes for waitlisted children based on UNOS status at the time of listing and competing outcomes for children listed as status 1A according to their level of invasive hemodynamic support.

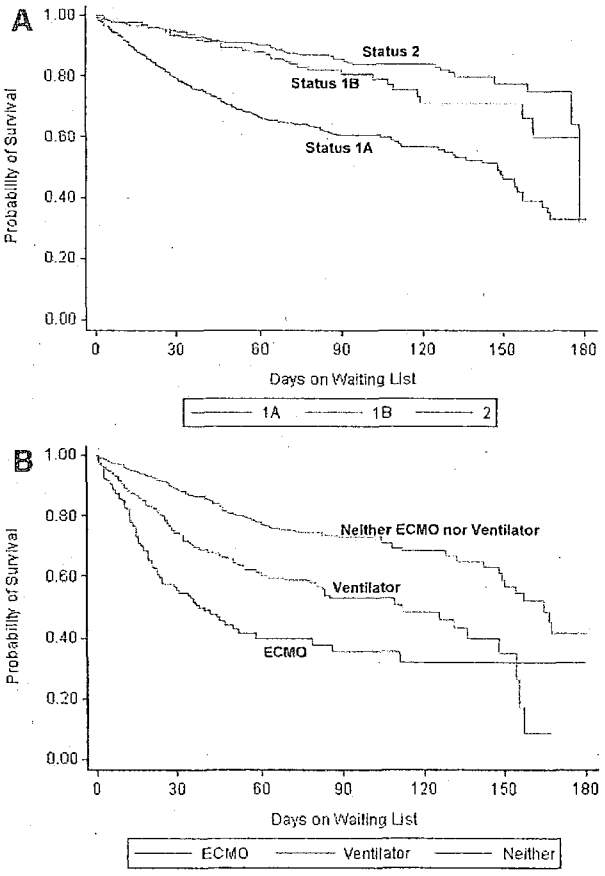

Figure 1. Kaplan-Meier survival for all children listed for heart transplant according to listing status (A) and for those children listed as status 1A according to invasive hemodynamic support (B).

Among those listed as status 1A, the following subgroups of children were found to be at 30% or greater risk of waiting list mortality based on observed mortality (Table 4): (1) Children weighing <10 kg who were listed because of CHD and who required mechanical ventilation (mortality 32%, n=231), and (2) children weighing <10 kg who were listed because of CHD and who required ECMO (mortality 36.1%, n=155). Children with a predicted risk of waiting list mortality of ≥20% included most children listed as status 1A for CHD and most children who required either mechanical ventilation (waiting list mortality 25%, n=570) or ECMO (waiting list mortality 31.5%, n=346).

Figure 3 summarizes the weight distribution of children who died while on the waiting list in the current era. Overall, 10% of patients weighed <3 kg, 34% weighed <5 kg, 54% weighed <10 kg, 64% weighed <15 kg, and 71% weighed <20 kg.

Discussion

In this study, we found that over a 6-year period, 533 US children with severe heart failure died while on the heart transplant waiting list before a suitable donor heart could be identified. Expressed as a rate, children awaiting heart transplantation experience the single highest waiting list mortality compared with all other age groups and all other solid organs in transplant medicine.[1] Although the average status 1A pediatric patient is at higher risk of waiting list mortality statistically, status 1A patients as a group represent a large and heterogeneous population whose risk of waiting list

Table 4. Risk Stratification of Status 1A Candidates Based on Observed Waiting List Mortality for Patient Subgroups

	7 Days	14 Days*	30 Days	60 Days	90 Days	6 Months	Overall
All status 1A candidates (n=1874)	4.9	8.5	13.7	18.0	18.9	20.3	21.1
ECMO (n=346)	10.1	17.9	25.7	29.8	30.4	30.6	31.5
Cardiomyopathy	5.7	11.4	15.7	21.4	21.4	21.4	24.3
Weight ≥10 kg (n=34)	0	8.8	14.7	23.5	23.5	23.5	26.5
Weight <10 kg (n=36)	11.1	13.9	16.7	19.4	19.4	19.4	22.2
Myocarditis	7.7	12.8	20.5	23.1	23.1	25.6	25.6
Weight ≥10 kg (n=26)	3.9	7.7	15.4	15.4	15.4	19.2	19.2
Weight <10 kg (n=13)	15.4	23.1	30.8	38.5	38.5	38.5	38.5
CHD	11.2	19.6	28.5	32.7	33.6	33.6	33.6
Weight ≥10 kg (n=56)	5.4	14.3	17.9	21.4	25.0	25.0	25.0
Weight <10 kg (n=155)	13.6	20.7	31.6	36.1	36.1	36.1	36.1
Mechanical ventilation (n=570)	6.0	10.4	17.0	22.1	23.5	25.1	25.4
Cardiomyopathy	4.6	8.3	16.0	17.0	18.0	19.6	19.6
Weight ≥10 kg (n=69)	10.1	17.4	27.5	29.0	29.0	29.0	29.0
<10 kg (n=122)	1.6	3.3	9.0	9.8	11.5	13.9	13.9
Myocarditis	2.4	7.1	7.1	9.5	9.5	9.5	11.5
Weight ≥10 kg (n=20)	5.0	15.0	15.0	15.0	15.0	15.0	20.0
<10 kg (n=22)	0	0	0	4.6	4.6	4.6	4.6
CHD	7.3	12.5	19.8	27.4	29.2	30.9	31.3
Weight ≥10 kg (n=55)	9.1	14.6	16.4	25.5	27.3	27.3	27.3
Weight <10 kg (n=231)	6.9	12.1	20.4	27.7	29.4	31.6	32.0
No ventilation or ECMO (n=958)	2.3	4.1	7.4	11.3	12.1	13.8	14.7
Cardiomyopathy	1.3	2.3	4.3	6.3	6.8	7.1	7.6
Weight ≥10 kg (n=263)	0.8	1.5	3.8	4.9	5.7	5.7	6.1
Weight <10 kg (n=127)	2.4	3.9	5.5	9.5	9.5	10.2	11.0
Myocarditis	1.8	3.6	7.1	10.7	10.7	12.5	14.3
Weight ≥10 kg (n=45)	2.2	4.4	6.7	11.1	11.1	13.3	15.6
Weight <10 kg (n=10)	0	0	10.0	10.0	10.0	10.0	10.0
CHD	3.5	5.8	10.8	16.6	18.0	21.0	22.1
Weight <10 kg, *no* PGE (n=159)	1.9	4.4	8.2	12.6	14.5	16.4	17.0
Weight ≥10 kg (n=161)	4.4	6.8	13.0	18.6	19.9	24.2	24.8
Weight <10 kg, PGE (n=107)	3.7	5.6	11.2	19.6	20.6	23.4	26.2

Values represent percentage of eligible patients who were removed from the waiting list due to death during the specified time frame. PGE indicates prostaglandin E infusion.

*14 Days is the standardized time interval for status 1A justification by UNOS.

mortality varies by as much as 10-fold or more based on patient-specific factors. The single most important patient factor predictive of waiting list mortality is the level of invasive hemodynamic support, as defined by ECMO versus mechanical ventilation versus inotropic support alone. Other patient factors associated with waiting list mortality include cardiac diagnosis, dialysis, and nonwhite race/ethnicity.

These findings are consistent with earlier reports from the 1990s that found that ECMO, former listing as status 1 (predecessor of the 1A/1B classification system), and CHD were associated with waiting list mortality in children[5–7,9,10,13]; however, no studies have analyzed waiting list outcomes since the pediatric heart-allocation system was revised in 1999. Consequently, the present report has 2 advantages over earlier reports in that (1) it analyzes outcomes since 1999, which permits a focused look at waiting list mortality under the present allocation system and practice conditions, and (2) it captures all children officially listed for a heart transplant in the United States, which provides the necessary statistical power to identify several important national trends for the first time. Specifically, this is the first published report (1) to identify nonwhite race and mechanical ventilation as powerful independent risk factors for waiting list mortality across the pediatric age spectrum, (2) to describe the striking variability in waiting list mortality observed among children listed as status 1A, and (3) to exclude blood type as an independent factor associated with waiting list mortality in the current era.

Our finding that the level of invasive hemodynamic support (ie, ECMO support versus mechanical ventilation

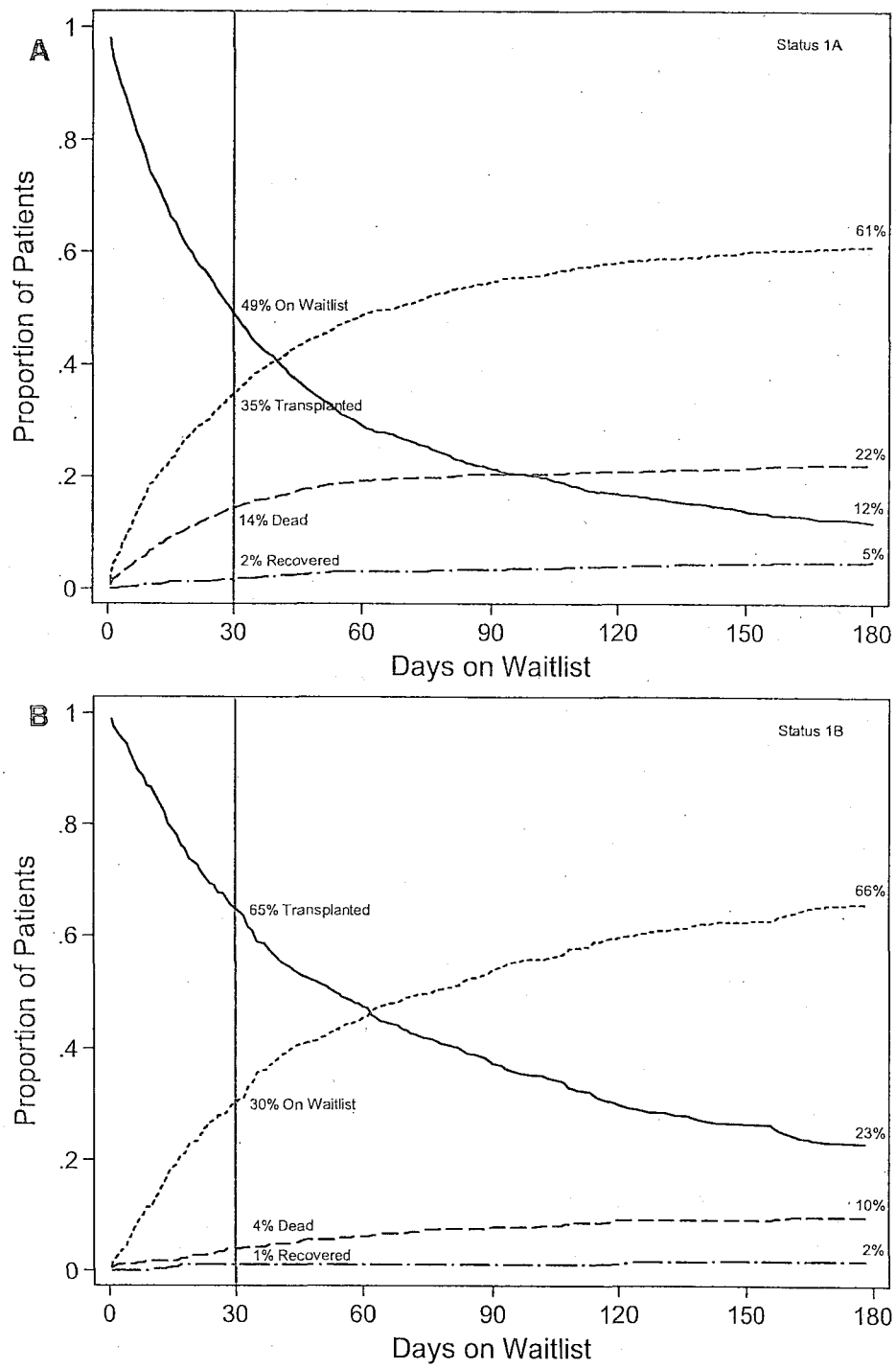

Figure 2. Competing outcomes for wait-listed children according to UNOS status at the time of listing (A, B, and C), and for children listed as status 1A according to their level of invasive hemodynamic support: ECMO (D), mechanical ventilation (E), and neither ECMO nor mechanical ventilation (F).

versus inotropic support alone) is associated with waiting list survival is reasonably intuitive; however, we were surprised at the magnitude of effect, specifically, that the level of invasive hemodynamic support appears to be a much stronger predictor of waiting list mortality and therefore a more accurate reflection of medical urgency than UNOS listing status itself, the current system used to categorize children according to medical urgency.[2,15] We believe the relatively poor correlation between UNOS listing status and medical urgency in pediatrics stems largely from the heterogeneity of the status 1A patient cohort resulting in greater waiting list mortality variability within UNOS listing groups than between listing groups. This heterogeneity is likely driven by 2 factors: (1) Greater numbers of high-risk children are listed as status 1A because of more widespread use of technologies like

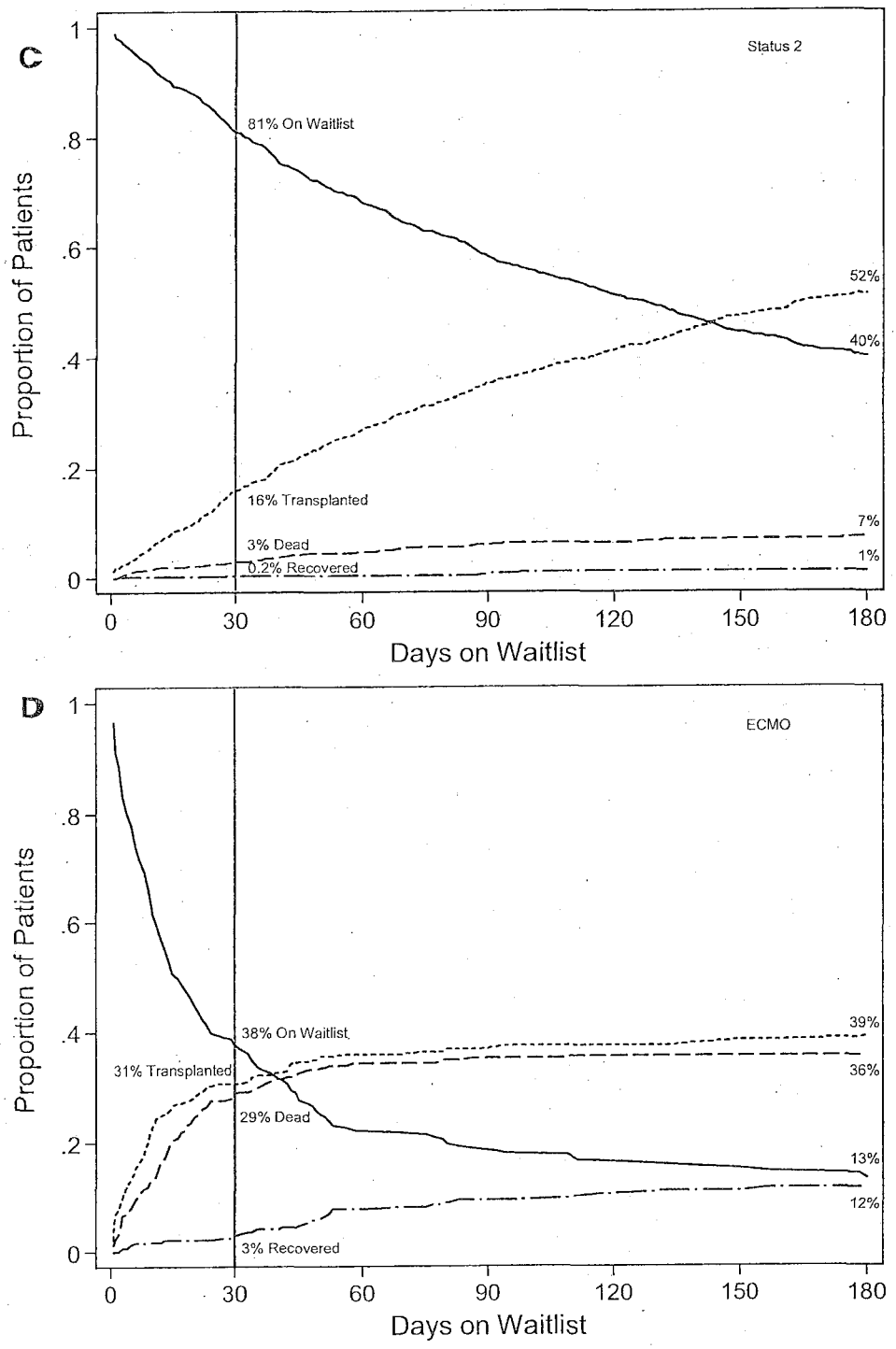

Figure 2 (Continued).

ECMO[16] in pediatrics, combined with fewer absolute contraindications to transplant,[17] and (2) greater numbers of low-risk patients are listed as status 1A because of less stringent status 1A criteria for children. (*NB*: Adult status 1A criteria generally necessitate pulmonary artery catheter placement, whereas pediatric status 1A criteria can be met with as little as minor dosing adjustments in intravenous medications.) It is likely that the less stringent status 1A criteria in pediatrics are largely responsible for the disproportionately large number of children who qualify for the highest tier of medical urgency (>60% of children at the time of listing and nearly three quarters [72%] by the time of transplantation).

The findings of the present study have several implications. First, our findings raise questions about whether the current allocation system is structured optimally to reduce pediatric transplant mortality. Because the current system captures medical urgency poorly, children facing markedly

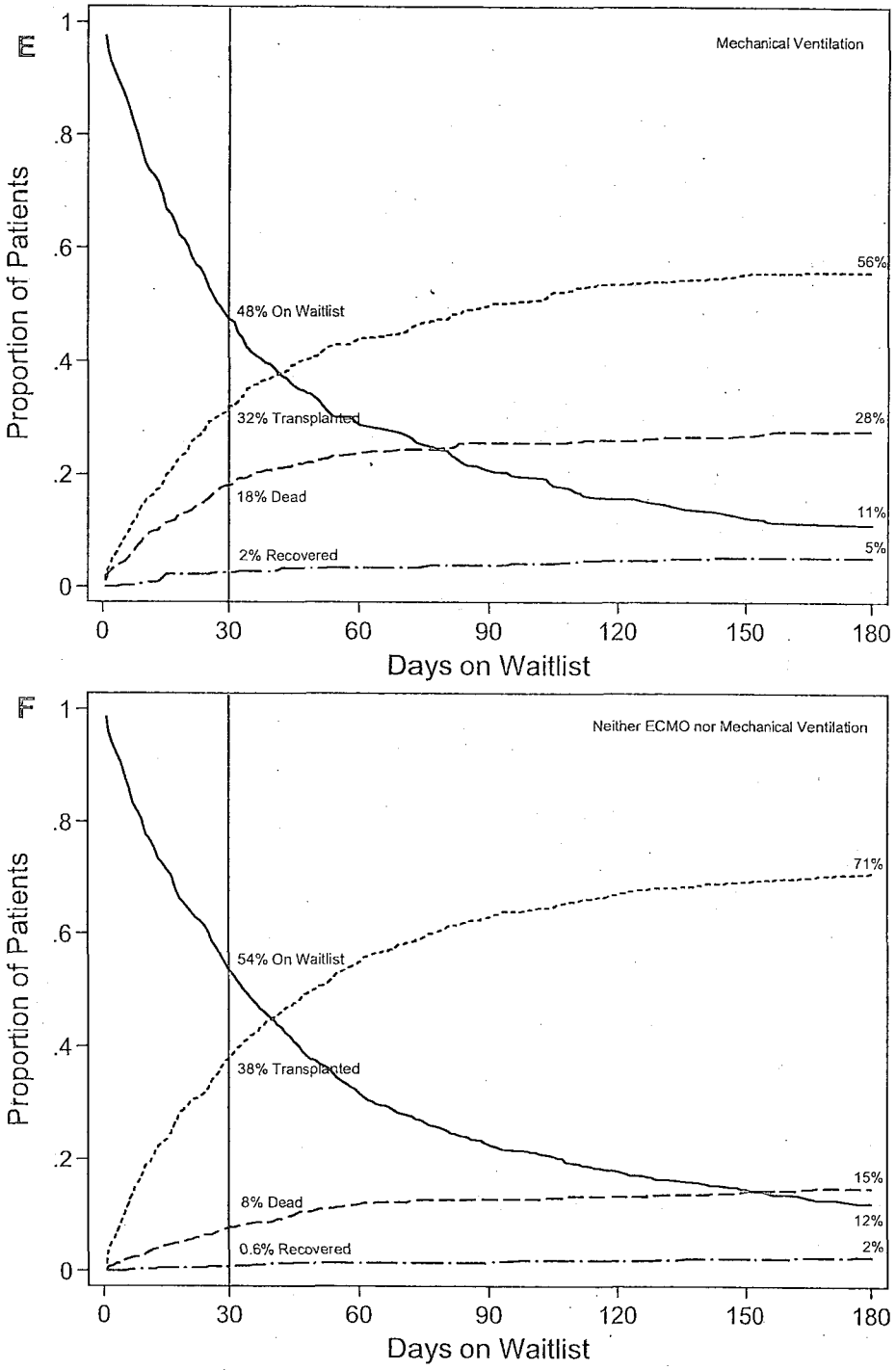

Figure 2 (Continued).

different short-term mortality risks are forced to compete directly for the same scarce donor organs. For example, under the current system, a child actively listed for heart transplant who is on ECMO support with days to live must compete directly with a child being supported by inotropes alone, who, according to our data, has a relatively low imminent risk of death. Consequently, an available heart is offered first to the child who has accumulated more status 1A wait time, rather than to the child who is likely to die without transplant. Ultimately, because the majority of pediatric patients and virtually all at-risk pediatric patients are listed as status 1A, "first come, first served" has functionally supplanted medical urgency as the primary determinant of pediatric donor heart allocation for the majority of children awaiting heart transplantation.

The discrepancy between medical urgency and waiting list seniority, a major problem in solid-organ transplantation historically, raises the possibility that some pediatric deaths

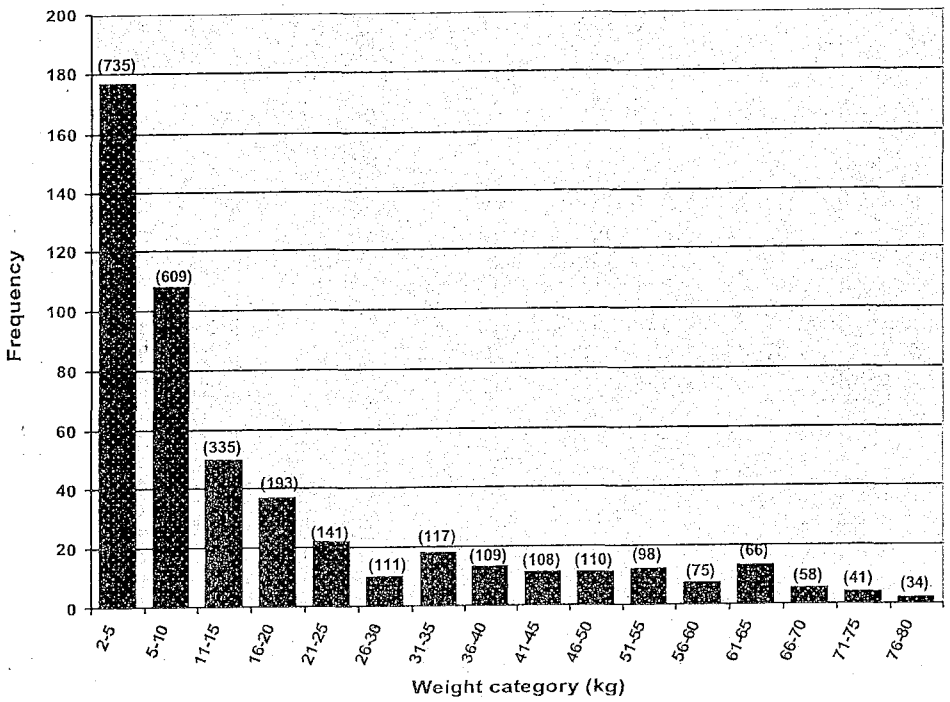

Figure 3. Number of children who died while on the waiting list according to weight at listing (n=533). The numbers above each bar denote the total number of children who were listed for heart transplant within each weight category.

could be prevented by moving away from an allocation system that relies heavily on waiting time toward an allocation system that better reflects medical urgency while also incorporating potential transplant benefit. Such a shift would be consistent with the Final Rule on Organ Allocation published by the US Department of Health and Human Services,[15] which discourages the use of waiting time as a criterion for organ allocation and encourages organ sharing based on medical urgency (while avoiding futile transplantations) with the use of objective medical criteria that cannot be manipulated by patients or physicians. Accordingly, the US allocation systems for liver and lung allografts[18–23] have undergone major revisions recently to bring them into compliance with contemporary standards. We believe a similar reappraisal is warranted for pediatric hearts, not only because of the excessively high waiting list mortality[1] but also because of better data on the factors that drive pretransplantation and posttransplantation attrition.[24,25] Because some factors such as ECMO may be associated with both pretransplantation[5–7,9,10] and posttransplantation[24,25] mortality, revising the current system will require complex simulation analyses to balance competing risks, as has been done successfully with the lung-allocation score recently.[26]

Second, the present findings suggest that specific high-risk subgroups of patients can be identified who may be suitable candidates for emerging pediatric mechanical support devices. By the same token, our findings suggest that low-risk subgroups can also be identified for whom investigational devices should generally not be used at the present time. Because of this heterogeneity, clinicians and investigators will need to use caution in selecting patients for evolving mechanical circulatory support devices[26,27] and in developing selection criteria for clinical trials to obtain regulatory approval.[28,29] For example, patients with an estimated waiting list mortality of less than 10% (eg, stable children with cardiomyopathy who are on inotropes) are unlikely to benefit from device therapy if the device itself carries a risk that could be higher. The use of such devices in such patients could not only expose children to unnecessary risks but could also undermine the interpretability of data in support of a regulatory claim of efficacy or probable benefit, the legal threshold for Food and Drug Administration approval in the United States.

Third, although age and size were not independently associated with waiting list mortality, the present findings indicate that the vast majority of children dying while on the waiting list weigh <10 to 15 kg (Figure 3). The skewed weight distribution draws needed attention to precisely where the national organ shortage for pediatric donor hearts is most critical: among infants and toddlers. Creating greater public awareness is a key first step for organ-donation advocates who are looking for high-impact strategies to reduce pediatric waiting list mortality.[30] Although it would be beneficial to improve organ donation among children of all ages and sizes, the present findings suggest that the greatest benefit would come from a successful campaign to increase organ donation among infants and toddlers. The disproportionate number of deaths among infants and toddlers further underscores the need to develop reliable miniaturized mechanical circulatory support devices for infants and smaller children,[26,27] similar to the approved ventricular assist devices that are widely available for larger children and adults.[31–34]

We were surprised to find that nonwhite race/ethnicity was associated with waiting list mortality, particularly among

children listed as status 1A, a group that is uniformly hospitalized and usually under the watchful eye of intensivists. Contributing factors may include differences in timing of presentation, access to care, delivery of medical treatment, disease progression, regional heterogeneity, misclassification of race/ethnicity by centers, or some combination thereof. Adult studies of waiting list mortality have reported mixed findings on the relationship between race/ethnicity and waiting list mortality.[13,35] Further research is needed to explore the effect of race/ethnicity on waiting list mortality in transplant candidates across all ages.

The findings of the present study should be interpreted within the context of the study design. First, the analysis did not account for changes in listing status while patients were on the waiting list; however, changes in status would be expected to result in misclassification of risk factor assignment, which would lead to an underestimate of the true effects of a given risk factor, which in this analysis were all highly significant. Second, the primary analysis did not account for patients who were removed from the waiting list because of clinical deterioration rather than death; however, secondary analyses using the combined outcome of death or delisting due to clinical deterioration yielded similar results. Lastly, all retrospective studies are inherently susceptible to selection bias that could skew findings if a nonrandom population of patients were selected for analysis; however, because the Scientific Registry of Transplant Recipients captures all patients officially listed for transplant in the United States, it is unlikely that patient selection bias would play a major role in the findings of this retrospective analysis.

In summary, despite improvements in pediatric heart allocation over the past decade, pediatric heart transplant waiting list mortality remains unacceptably high in the current era and is an outlier in transplant medicine. The current pediatric heart-allocation system captures medical urgency poorly, which raises the possibility that the current allocation system may not be prioritizing scarce donor hearts optimally. Although status 1A patients are at higher risk of waiting list mortality statistically, status 1A patients as a group represent a large and heterogeneous population. Independent risk factors for waiting list mortality can be used to risk-stratify children, which can help facilitate patient selection of emerging pediatric cardiac assist devices and guide pediatric donor allocation in a manner that is consistent with contemporary organ-allocation standards. Lastly, most children who die while on the waiting list are those who weigh <10 kg, which underscores the tremendous need for reliable pediatric mechanical support devices for the smallest children. Targeted efforts to expand infant donation through expanded neonatal intensive care unit donation or more widespread acceptance of donation after cardiac death[36] are urgently needed.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Despite improvements in pediatric heart allocation over the past decade, children listed for heart transplantation face the highest waiting list mortality in solid-organ transplant medicine. Data on waiting list outcomes since the pediatric heart-allocation system was revised in 1999 are limited. This study examines waiting list outcomes from all 3098 children <18 years of age listed in the United States for primary heart transplant during the period from 1999 to 2006. Overall, 533 children (17%) died, whereas 63% received transplants and 8% recovered. Although status 1A patients were at higher risk of waiting list mortality than status 1B or status 2 patients, waiting list mortality varied by a greater degree within status 1A and was best predicted by the level of invasive hemodynamic support (defined as extracorporeal membrane oxygenation versus ventilator versus neither). The study thus demonstrates that the current pediatric heart-allocation system captures medical urgency among those waiting for a heart poorly. Because patients on a higher level of invasive support at listing may also be at higher risk of posttransplantation death, further research is needed to determine what changes in the current pediatric allocation system will reduce overall (pretransplantation and posttransplantation) mortality in children listed for a heart transplant. Lastly, the study demonstrates that the vast majority of children who die on the waiting list weigh <10 to 15 kg, which underscores the need to develop and refine new technologies to support the smallest children with advanced heart failure and to expand opportunities for infant organ donation.

参考資料９

HEART TRANSPLANTATION

Pediatric Recipients

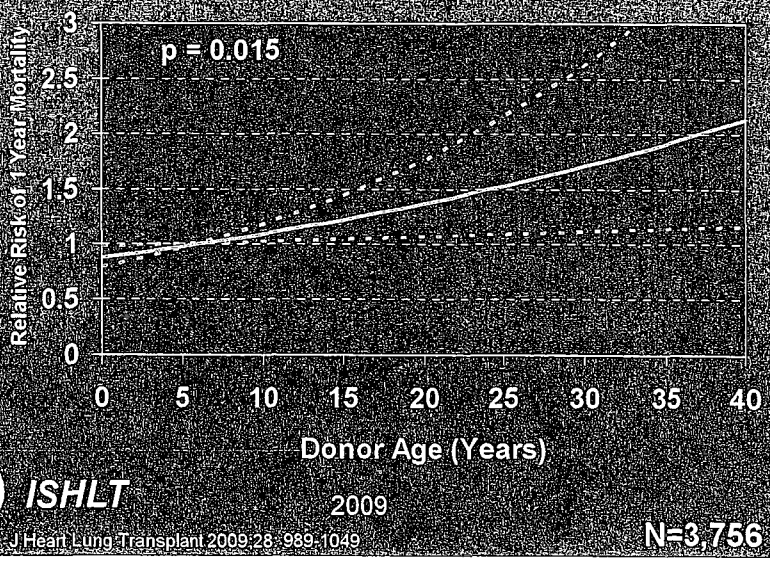
ISHLT 2009

J Heart Lung Transplant 2009;28:989-1049

PEDIATRIC HEART TRANSPLANTS (1/1995-6/2007)

Risk Factors for 1 Year Mortality

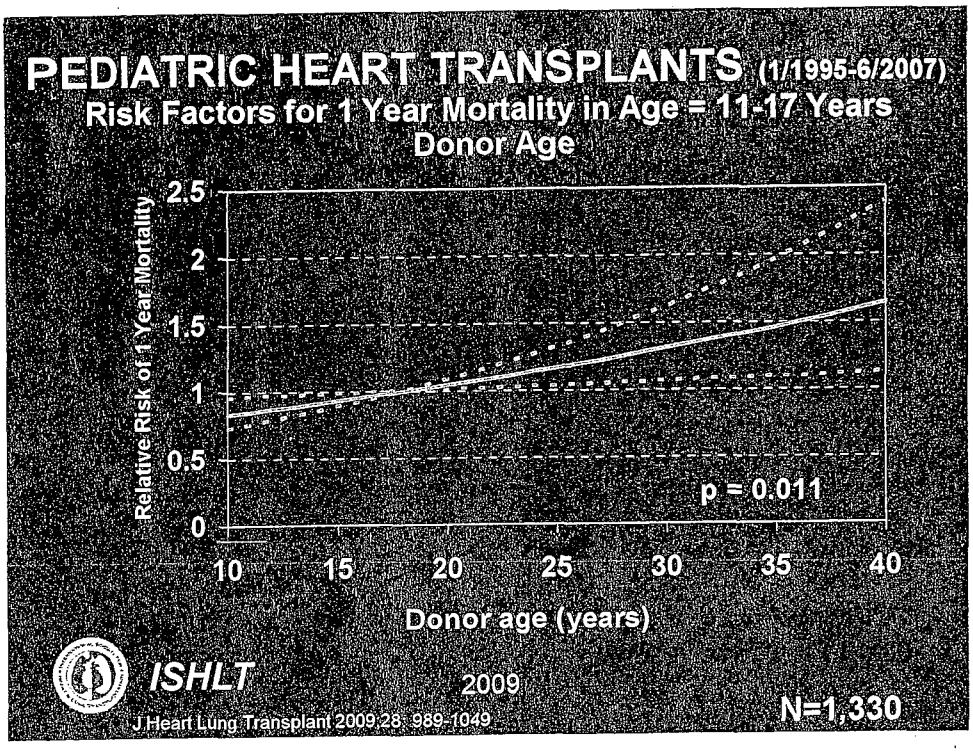
Donor Age

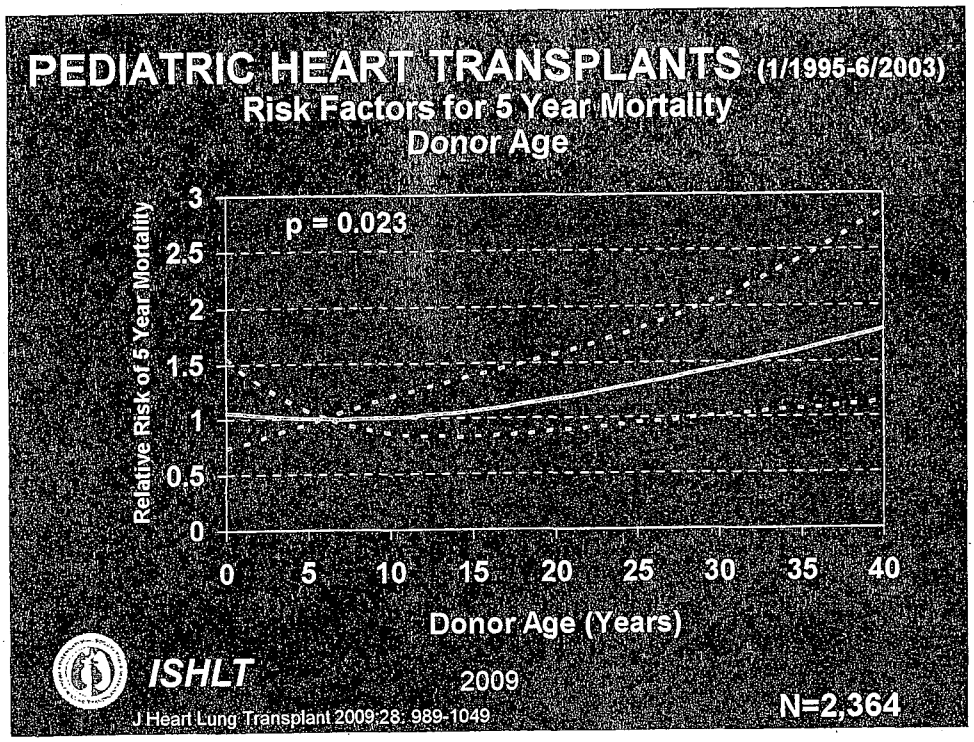


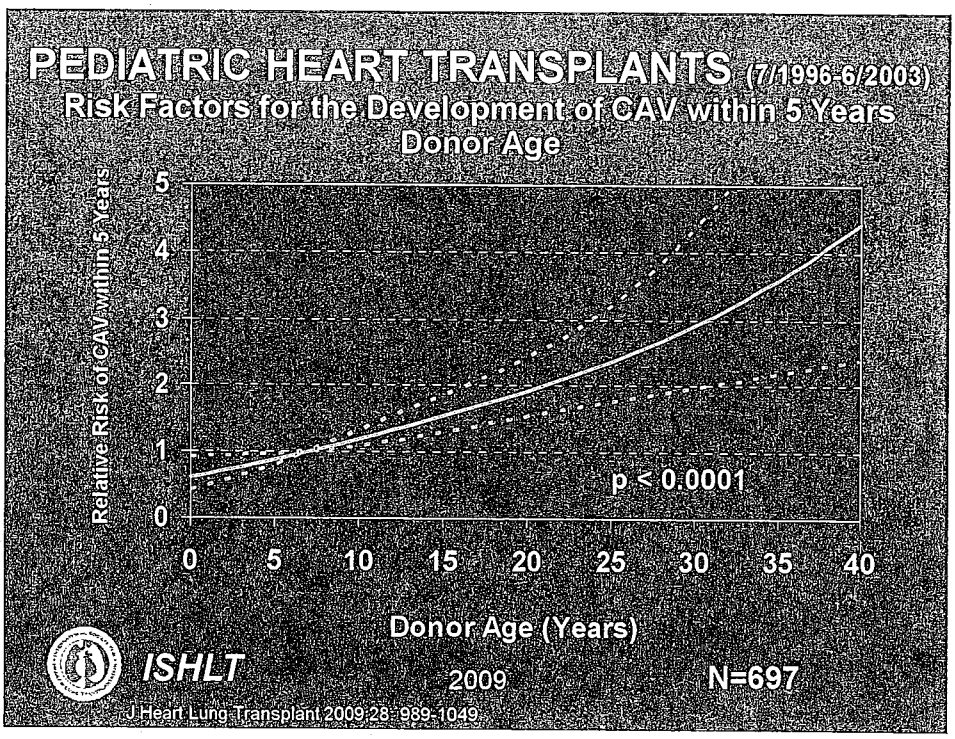
ISHLT 2009

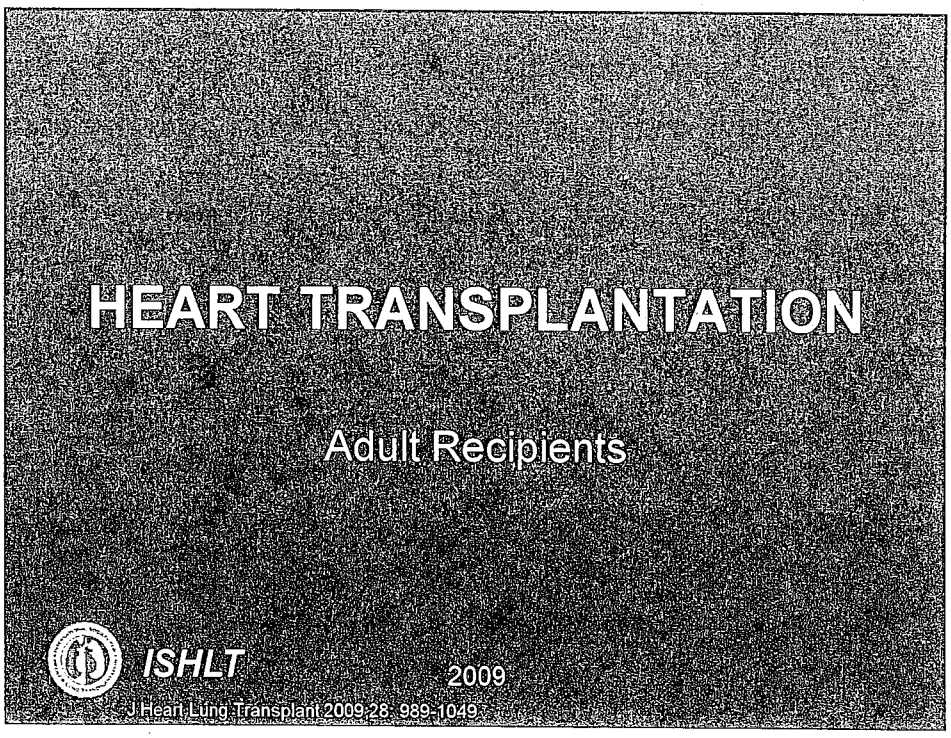
J Heart Lung Transplant 2009;28:989-1049

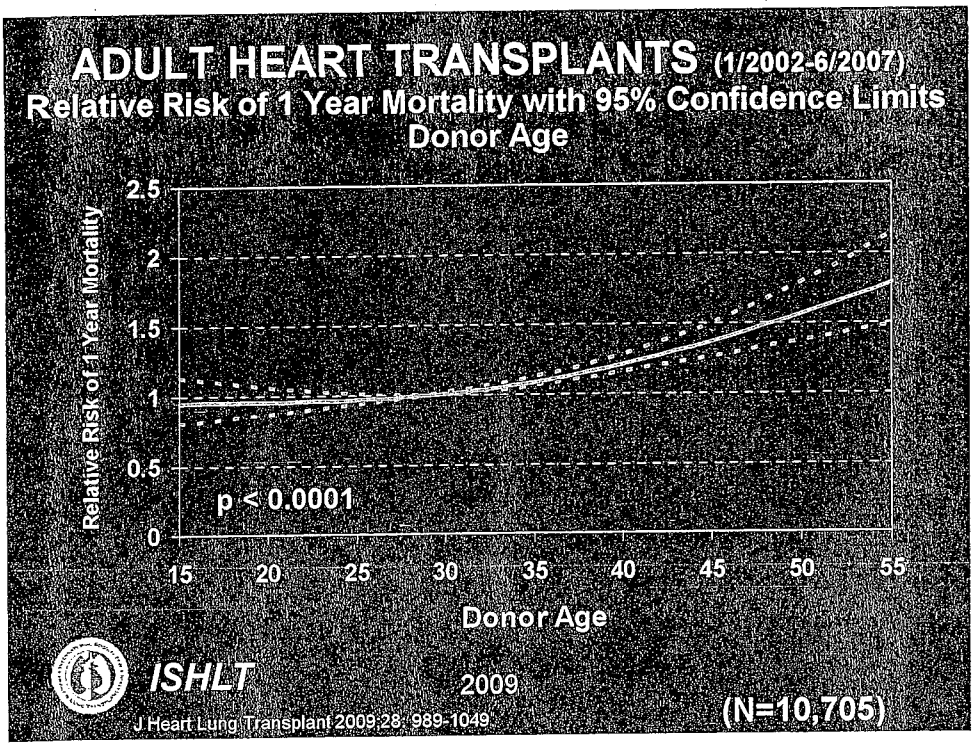
N=3,756

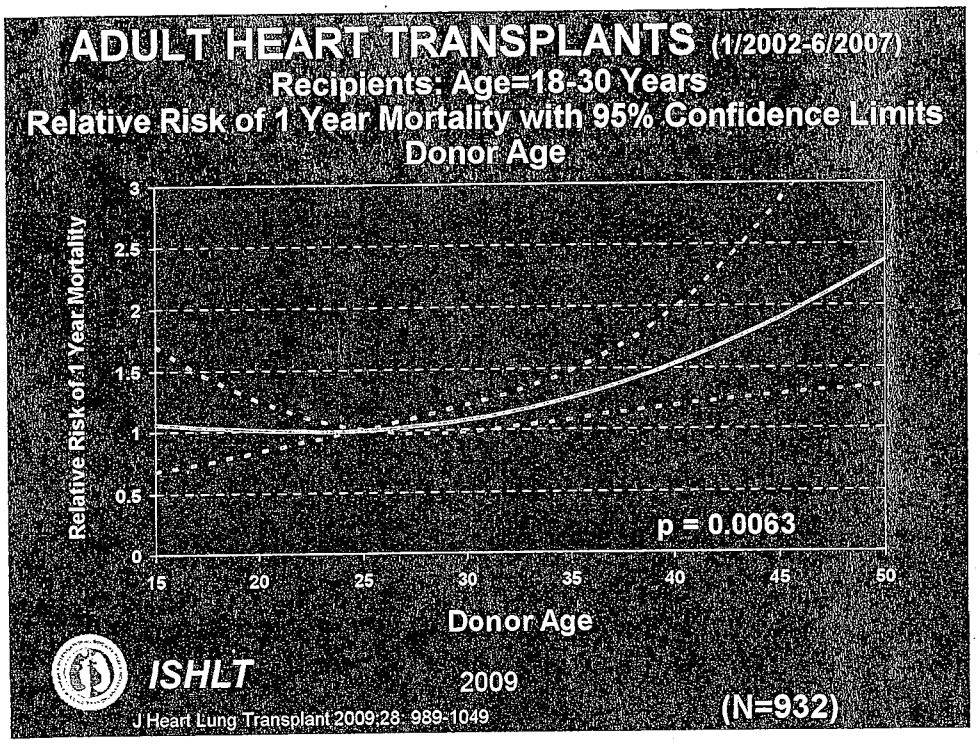

PEDIATRIC HEART TRANSPLANTS (1/1995-6/2007)
Risk Factors for 1 Year Mortality in Age = 11-17 Years
Donor Age
Relative Risk of 1 Year Mortality
2.5
2
1.5
1
0.5
0
p = 0.011
10
15
20
25
30
35
40
Donor age (years)
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
N=1,330

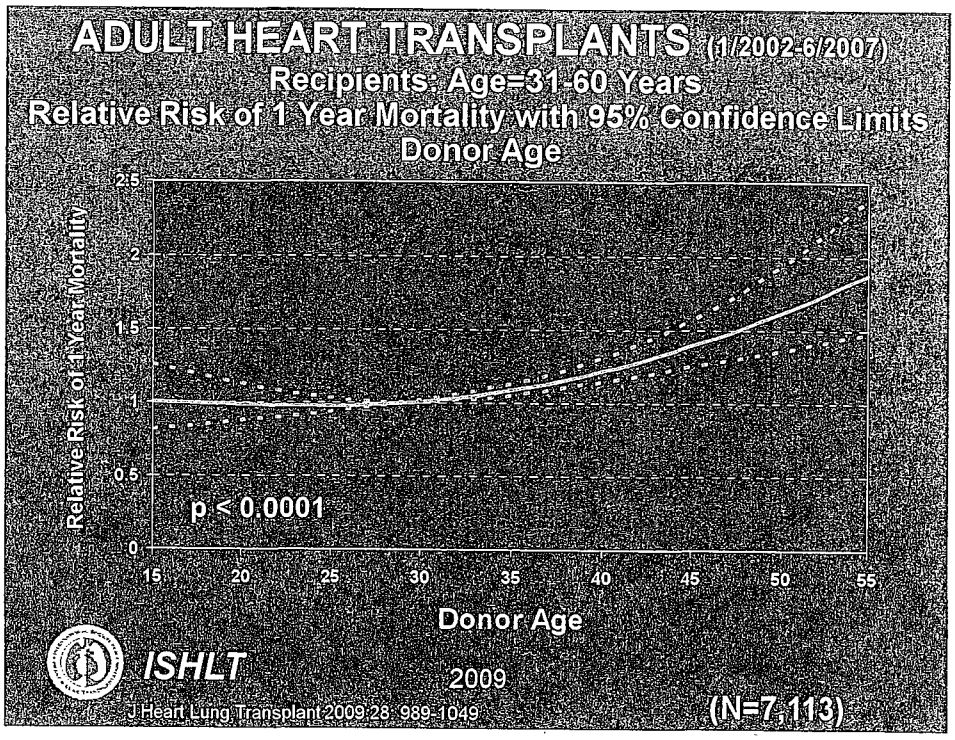

PEDIATRIC HEART TRANSPLANTS (1/1995-6/2003)
Risk Factors for 5 Year Mortality
Donor Age
Relative Risk of 5 Year Mortality
3
2.5
2
1.5
1
0.5
0
p = 0.023
0
5
10
15
20
25
30
35
40
Donor Age (Years)
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
N=2,364

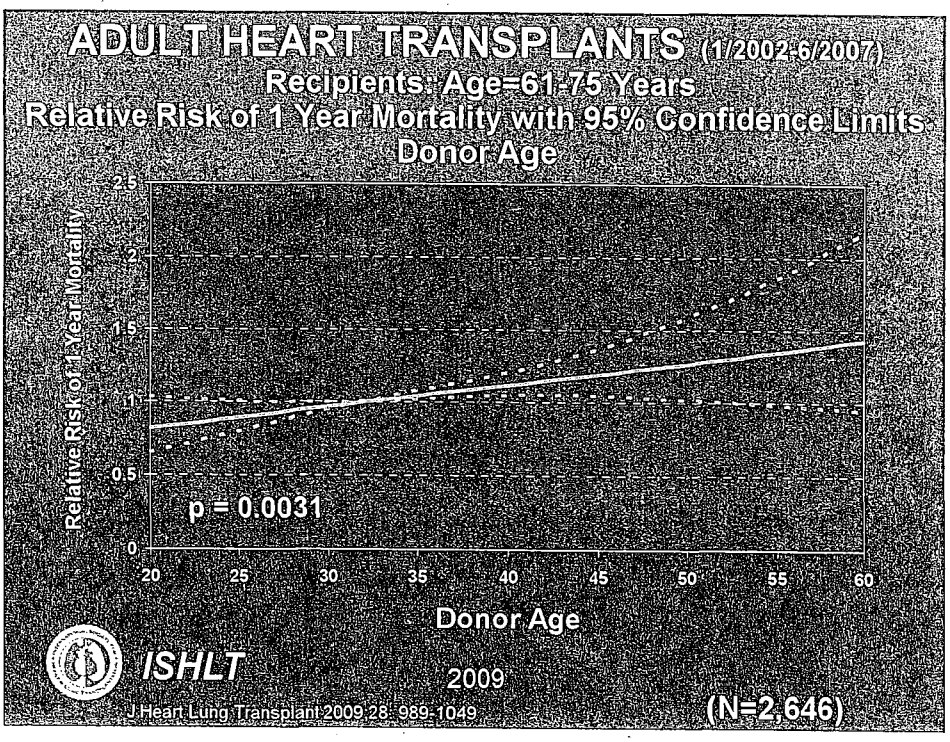

PEDIATRIC HEART TRANSPLANTS (7/1996-6/2003)
Risk Factors for the Development of CAV within 5 Years
Donor Age
Relative Risk of CAV within 5 Years
5
4
3
2
1
0
p < 0.0001
0
5
10
15
20
25
30
35
40
Donor Age (Years)
ISHLT
2009
N=697
J Heart Lung Transplant 2009;28:989-1049

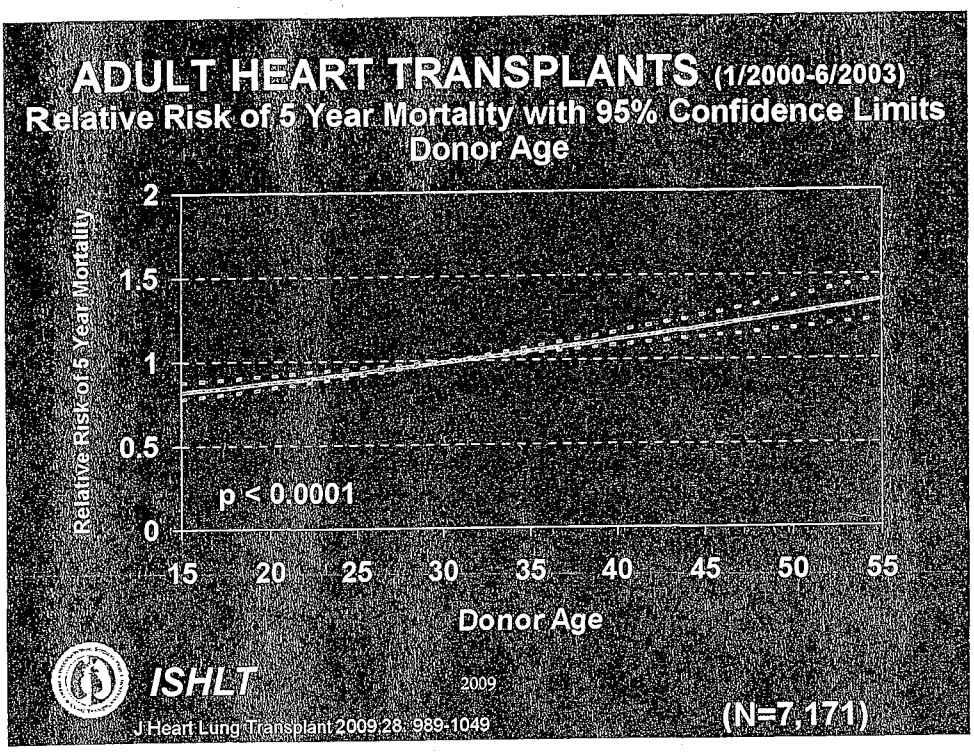

HEART TRANSPLANTATION
Adult Recipients
ISHLT
2009
J Heart Lung Transplant 2009;28:989-1049

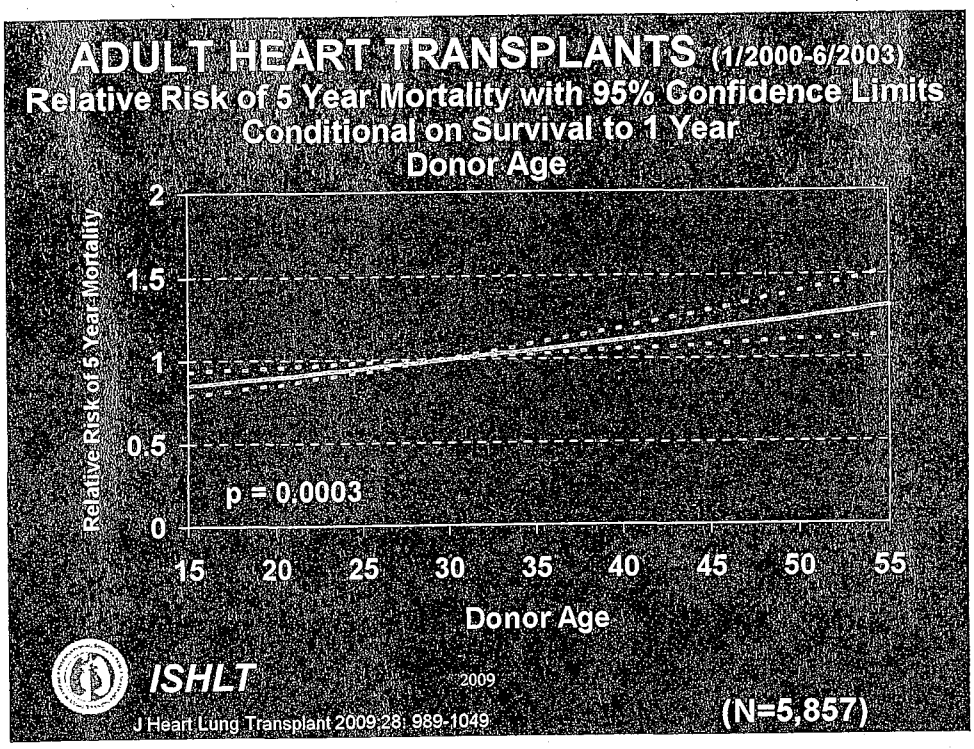

ADULT HEART TRANSPLANTS (1/2002-6/2007)
Relative Risk of 1 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 1 Year Mortality
2.5
2
1.5
1
0.5
0
p < 0.0001
15
20
25
30
35
40
45
50
55
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
(N=10,705)

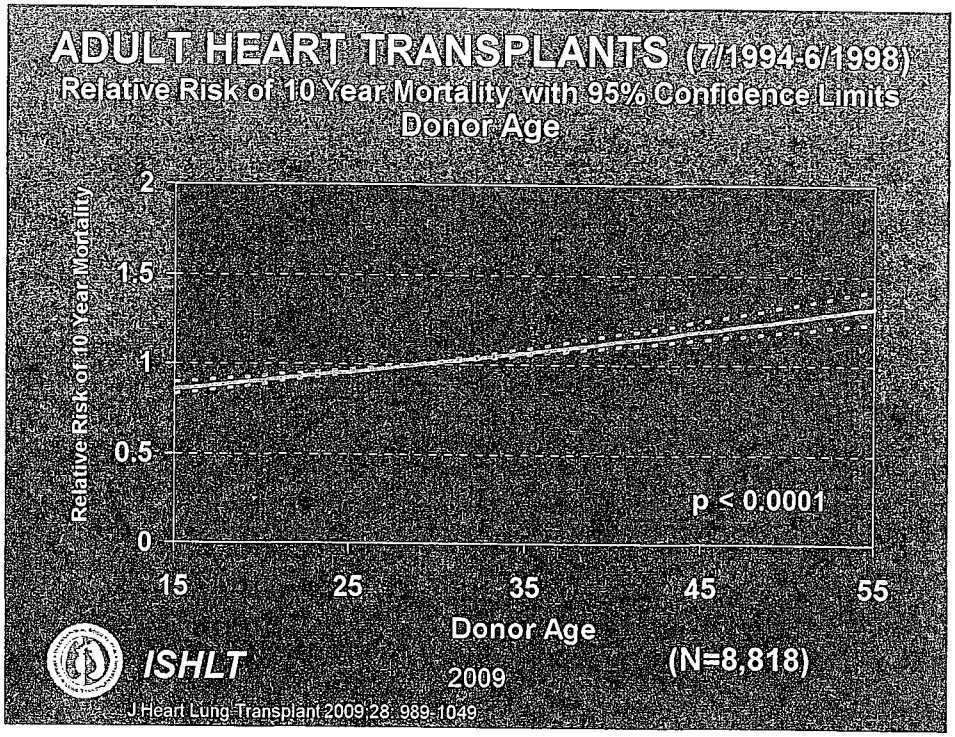

ADULT HEART TRANSPLANTS (1/2002-6/2007)
Recipients: Age=18-30 Years
Relative Risk of 1 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 1 Year Mortality
3
2.5
2
1.5
1
0.5
0
p = 0.0063
15
20
25
30
35
40
45
50
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
(N=932)

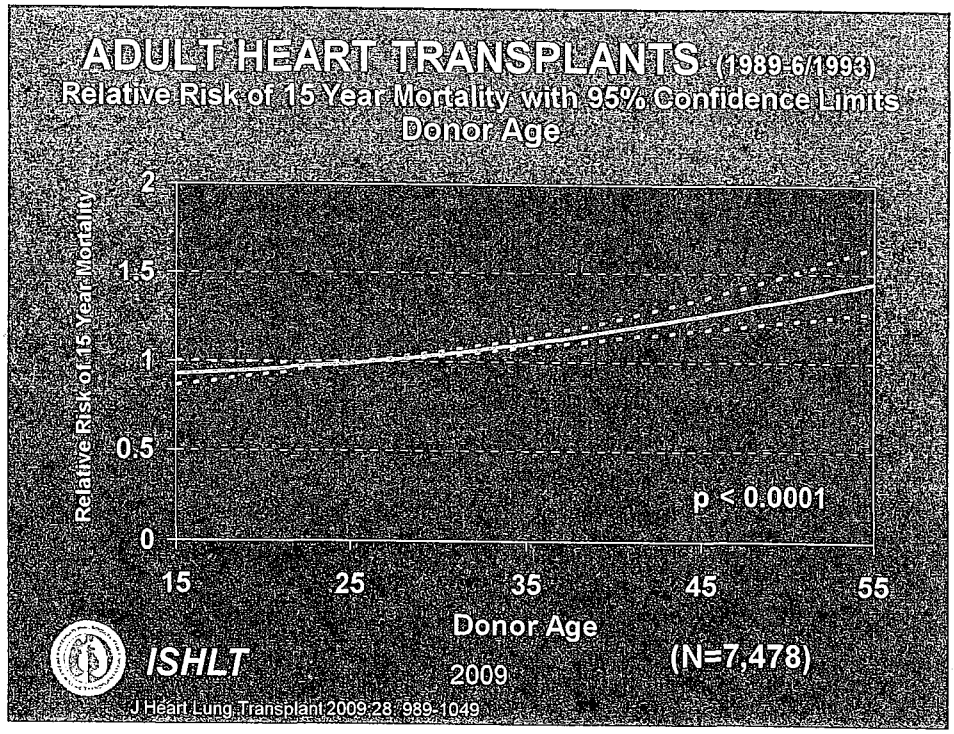

ADULT HEART TRANSPLANTS (1/2002-6/2007)
Recipients: Age=31-60 Years
Relative Risk of 1 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 1 Year Mortality
2.5
2
1.5
1
0.5
0
p < 0.0001
15
20
25
30
35
40
45
50
55
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28:989-1049
(N=7,113)

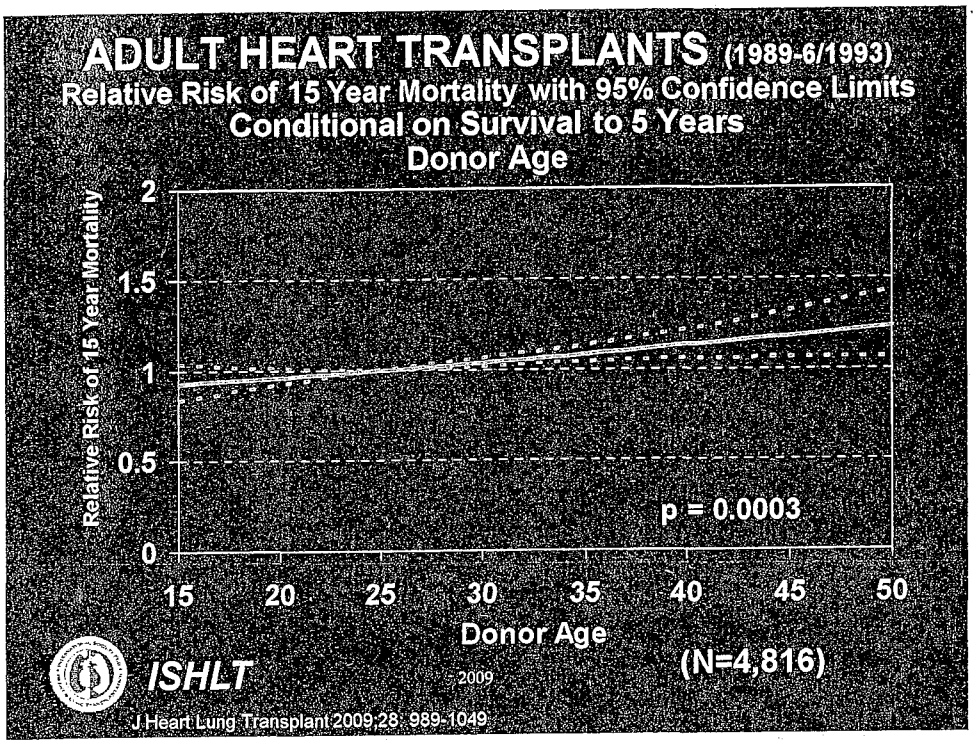

ADULT HEART TRANSPLANTS (1/2002-6/2007)
Recipients: Age=61-75 Years
Relative Risk of 1 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 1 Year Mortality
2.5
2
1.5
1
0.5
0
p = 0.0031
20
25
30
35
40
45
50
55
60
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28:989-1049
(N=2,646)


ADULT HEART TRANSPLANTS (1/2000-6/2003)
Relative Risk of 5 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 5 Year Mortality
2
1.5
1
0.5
0
p < 0.0001
15 20 25 30 35 40 45 50 55
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
(N=7,171)


ADULT HEART TRANSPLANTS (1/2000-6/2003)
Relative Risk of 5 Year Mortality with 95% Confidence Limits
Conditional on Survival to 1 Year
Donor Age
Relative Risk of 5 Year Mortality
2
1.5
1
0.5
0
p = 0.0003
15 20 25 30 35 40 45 50 55
Donor Age
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049
(N=5,857)


ADULT HEART TRANSPLANTS (7/1994-6/1998)
Relative Risk of 10 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 10 Year Mortality
2
1.5
1
0.5
0
p < 0.0001
15
25
35
45
55
Donor Age
ISHLT
2009
(N=8,818)
J Heart Lung Transplant 2009;28: 989-1049


ADULT HEART TRANSPLANTS (1989-6/1993)
Relative Risk of 15 Year Mortality with 95% Confidence Limits
Donor Age
Relative Risk of 15 Year Mortality
2
1.5
1
0.5
0
p < 0.0001
15
25
35
45
55
Donor Age
ISHLT
2009
(N=7,478)
J Heart Lung Transplant 2009;28: 989-1049


ADULT HEART TRANSPLANTS (1989-6/1993)
Relative Risk of 15 Year Mortality with 95% Confidence Limits
Conditional on Survival to 5 Years
Donor Age
Relative Risk of 15 Year Mortality
2
1.5
1
0.5
0
p = 0.0003
15
20
25
30
35
40
45
50
Donor Age
(N=4,816)
ISHLT
2009
J Heart Lung Transplant 2009;28: 989-1049