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The Journal of Heart and Lung Transplantation
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The Registry of the International Society for Heart and Lung Transplantation: Thirtieth Adult Lung and Heart-Lung Transplant Report—2013; Focus Theme: Age

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From the ISHLT Transplant Registry, Dallas, Texas.

This section of the 30th official Registry report of 2013 summarizes data from 43,428 adult lung and 3,703 adult heart-lung transplant recipients and their donors for transplants that occurred through June 30, 2012. This report describes donor and recipient characteristics, transplant type, and recipient outcomes data. The full Registry slide set available online (www.ishlt.org/registries) provides more detail, additional analyses, and other information not included in this printed report. For the first time, the Registry report focuses on an overall theme of recipient and donor age and incorporates new age-related analyses into its annual update.

Data collection and statistical methods

Standard statistical methods were used for analyses and reporting. Where appropriate, a more detailed explanation about the analytical methodology accompanies the Web site slides (in the "Notes Page" view).

The Kaplan-Meier method was used for assessing time-to-event rates (eg, survival). Survival graphs (ie, time-to-event graphs) were truncated when the number of analyzable individuals fell below 10. Censoring occurred at the time a patient was last reported to be alive (eg, most recent annual follow-up) and at the time of retransplantation for analyses that focus on the first transplant. The survival analyses provided patient median survival (where possible) as the estimated time at which 50% of all recipients died. Conditional analyses only included those patients who met the required criterion (eg, survival past 1 year post-transplant). The log-rank test was used to compare survival curves among groups. Cox proportional hazards regression was used for multivariable time-to-event analyses. The Cox models calculated hazard ratios (HR), corresponding 95% confidence intervals (CIs), and p-values. A HR of 1 suggests that the factor (eg, bilateral vs unilateral lung transplantation) is not associated with the event (eg, mortality). A HR $>$ 1.0 suggests that presence of the factor is associated with a higher probability of the event studied (ie, the group exposed to the factor has a higher hazard than the group not exposed), whereas a HR $<$ 1.0 suggests that the factor is associated with a lower probability of the event (ie, the group exposed to the factor has a lower hazard than the group not exposed).

Some analyses incorporated multiple imputations to estimate missing information for continuous data fields, such as ischemic time and donor age.[1] This method produced an estimated value for the missing value based on the other characteristics of the patient, the donor, and/or the transplant. The combining of model fit on each imputed data set produced a final set of estimates and associated HR estimates and p-values. Models may have excluded variables that lacked statistical significance due to small

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1053-2498/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.healun.2013.08.007

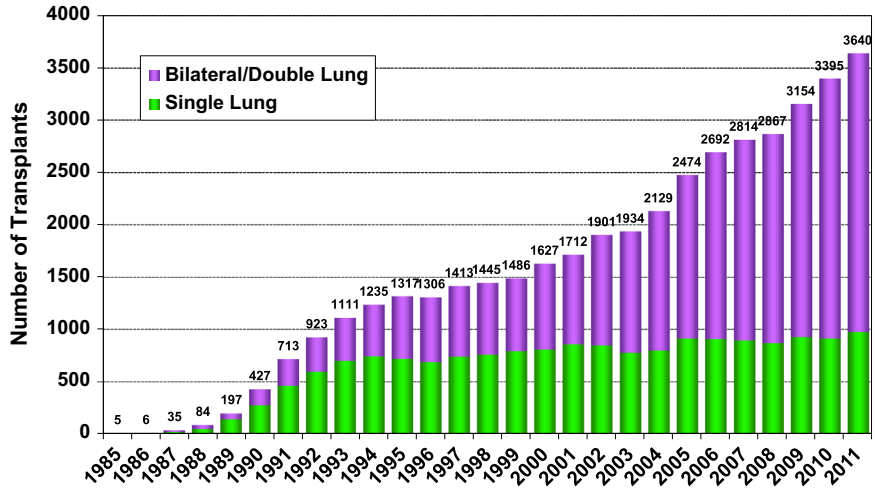

Figure 1 Number of reported adult lung transplants by year and procedure type reported to the International Society for Heart and Lung Transplantation Registry.

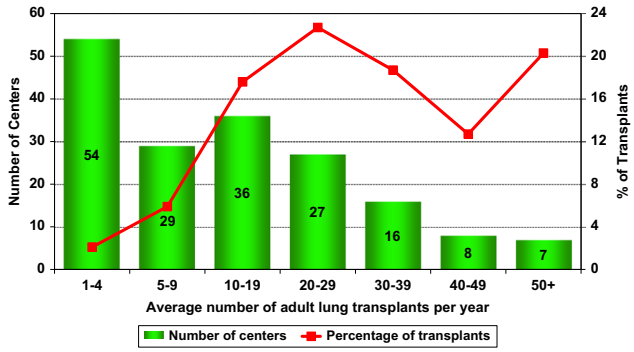

Figure 2 Number of centers and distribution of adult lung transplants by center volume (transplants: January 2000—June 2012). Each bar indicates the number of centers for a given average annual center volume, and each square indicates the percentage of total transplants by average annual center volume.

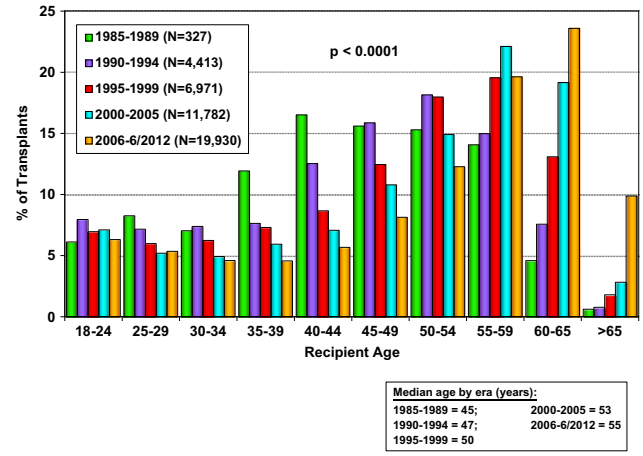

Figure 4 Adult lung transplant recipient age distribution by era. Each bar represents the proportion of lung transplants from a given era within a recipient age category.

sample size, and a type II error may therefore have occurred; that is, a significant association between the variable and the outcome may have escaped detection even though it existed.

Some analyses were adjusted for multiple comparisons (eg, Scheffe, Bonferroni). For unadjusted analyses (eg, survival curves of bilateral vs. unilateral lung transplantation), we

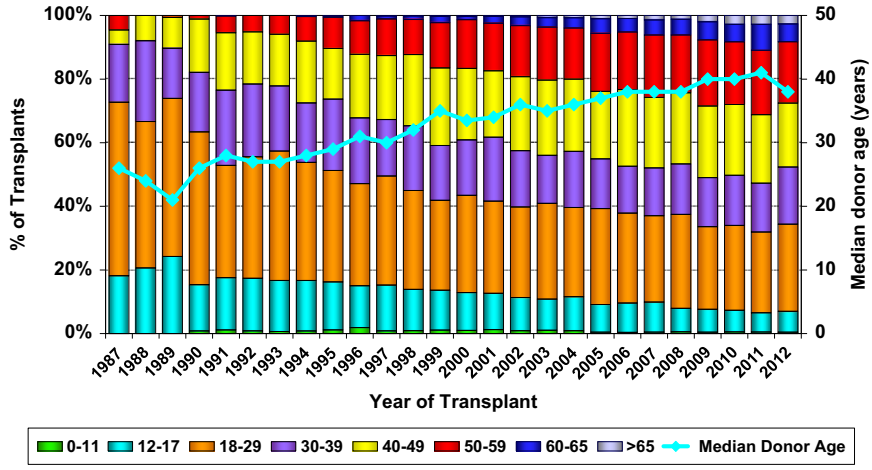

Figure 3 Age distribution of lung donors for adult recipients by year of transplantation (transplants: January 1987–June 2012). Each bar represents the proportion of transplants for donor age categories within a given year, and the diamonds show the median donor age.

recommend cautious interpretation because the different groups of interest may have an uneven distribution of clinical characteristics (eg, recipient age, underlying diagnosis, and comorbidities) and other factors (eg, preference of transplant center and donor lung characteristics) associated with the outcome undergoing assessment (eg, survival). For comparisons of risk among different cohorts (eg, assessment of age relationship to survival in cohorts from different eras), cautious interpretation is recommended for similar reasons. In addition, the models did not adjust for all of the important known and unknown confounders. Also, the models may lack generalizability for specific sub-groups of patients or for specific settings (eg, different organ allocation systems).

Registry data accuracy depended on center reporting accuracy. In addition, some of the reporting procedures may have introduced bias into the data collection process. For example, a 1-year follow-up form was not completed for patients who died before transplantation hospital discharge; thus, events assessed on the 1-year follow-up form were therefore not reported in this scenario even though they might have occurred.

Lung transplantation

Centers and transplant activity

The Registry now contains data from 42,069 adult recipients who underwent lung transplantation (including retransplants) before 2012. From 132 participating transplant centers, the Registry obtained data for 3,640 adult lung transplantation procedures performed in 2011, which represented the highest number reported of any year to date (Figure 1). The increased number of procedures primarily occurred due to the consistent growth in the number of bilateral lung transplants since the mid-1990s; the number of single-lung transplants performed annually during this time has remained relatively stable.

A total of 177 centers reported at least 1 adult lung transplant performed between January 2000 and June 2012 (Figure 2). Fifty-two percent of the transplant procedures were performed at 31 centers (18% of centers) that had an average activity of 30 or more transplants per year. Seven centers (4% of centers) had an average activity of 50 or more transplants per year and performed 20% of the procedures reported during this period. Eighty-three smaller-volume centers (47% of centers) averaged fewer than 10 transplants per year and conducted 8% of the lung transplantations during this period.

Donor age

Young adults (age 18–29 years) comprised 30% of donors in the Registry, whereas only 1% of donors were aged > 65 years (Figure 3). Donors for adult lung recipients during the first 6 months of 2012 had a median age of 38 years. The donor age has trended upward during the past 2 decades. Compared with 2 previous decade eras (1985–1994 and 1995–2004), the latest 7.5-year era (January 2005–June 2012) showed an increase in the proportion of 3 categories of older donors (aged 50–59 years, 60–65 years, and > 65 years), whereas the proportion of 2 categories of younger adult donors (aged 18–29 and 30–39 years) decreased.[2] The proportion of donors aged 40 to 49 years remained stable during over the past 2 eras. Compared with North American and other centers throughout the world for the era of January 2000 to June 2012, European centers used a greater proportion of older donors.[2]

Recipient age

Almost 66% of lung transplant recipients were aged 45 to 65 years.[2] Since 1985, the median age of recipients gradually increased from 45 years to 55 years (Figures 4 and 5). From 2006 through mid-2012, 10% of recipients were > 65 years old and 3% were > 70 years old compared with 3% and 0.3%, respectively, in 2000 to 2005.[2] The increased age of recipients occurred mainly in the diagnostic groups of interstitial lung diseases (ILD) and chronic obstructive pulmonary disease (COPD) exclusive of α_1-antitrypsin deficiency (non-A1ATD COPD).[2] For transplants that occurred January 2000 through June 2012, North American centers had a higher proportion of recipients with aged 60 to 65 years and > 65 years than centers in Europe and other centers throughout the rest of the world.[2]

Donor and recipient age relationships

From January 1985 through June 2012, a very small proportion of adult lung transplant recipients received organs from pre-adolescent (ages 0–11 years) pediatric donors (Figure 6). The proportion of adult recipients that received organs from adolescent (ages 12–17 years) pediatric donors hovered around 10%.

Indications

For adult lung transplantations that occurred between January 1995 and June 2012 (Table 1), the most common primary indications were non-A1ATD COPD (34%), followed by ILD (24%), bronchiectasis associated with cystic fibrosis (CF, 17%), and COPD associated with A1ATD (6%). From 2001 to 2011, the percentage of recipients with non-A1ATD COPD gradually decreased from 40% to 30%, and the percentage of transplants for ILD increased from 17% to 29%.[2]

Centers reported a diagnosis of retransplantation in 2.6% of lung recipients. The most common indication for retransplantation was bronchiolitis obliterans syndrome (BOS; Table 1). The proportion of recipients aged 18 to 65 years who underwent retransplantation was almost twice as high as in recipients older than 65 years.

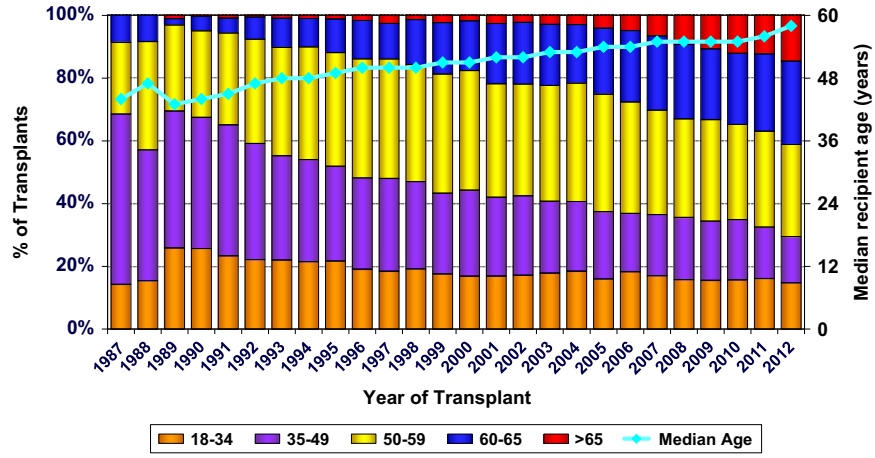

Figure 5 Adult lung transplant recipient age by year (transplants: January 1987–June 2012). Each bar represents the proportion of transplants for recipient age categories within a given year, and the diamonds show the median recipient age.

Procedure types

Although most recipients who had CF or idiopathic pulmonary arterial hypertension (IPAH) underwent bilateral transplantation over the years, a marked change from unilateral to bilateral transplantation occurred for recipients with COPD (non-A1ATD and A1ATD) or ILD (Figure 7).[2]

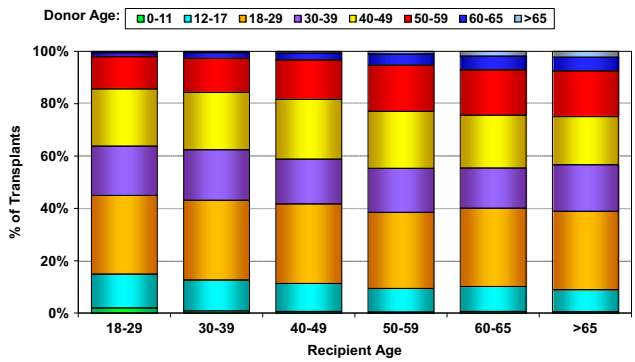

Figure 6 Donor and recipient age for adult lung transplantation (transplants: January 1985–June 2012). Each bar represents the proportion of donors for each donor age category within a given recipient age category.

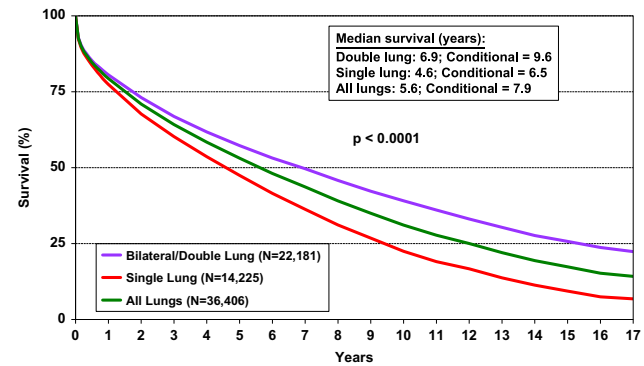

Figure 8 Adult lung transplant recipient Kaplan-Meier survival, stratified by procedure type (transplants: January 1994–June 2011). Conditional median survival for the sub-set of recipients who were alive 1 year after transplantation.

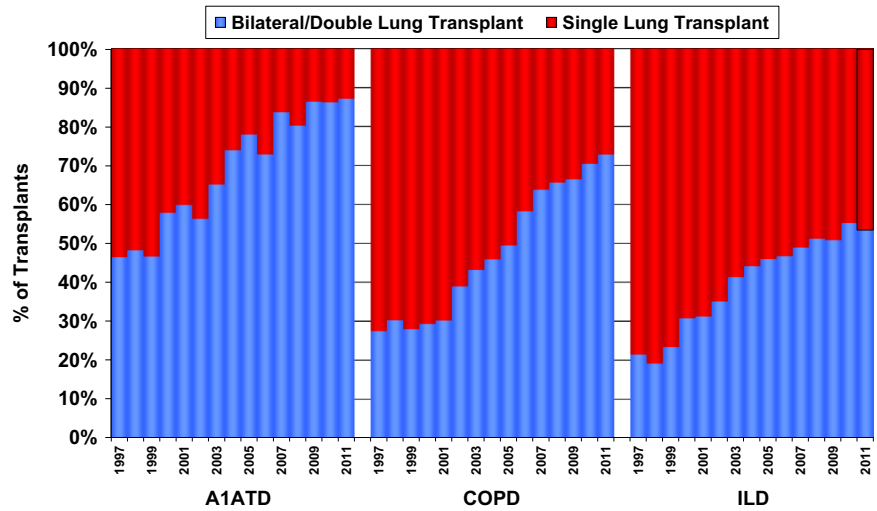

Figure 7 Adult lung transplantation procedure types according to indication and year of transplantation. Each bar represents the proportion of transplants for each procedure type within a given year. A1ATD, α_1-antitrypsin deficiency–associated chronic obstructive pulmonary disease (COPD); COPD, non-A1ATD associated COPD; ILD, interstitial lung disease, which includes idiopathic pulmonary fibrosis (IPF).

Table 1 Indications for Adult Lung Transplants Performed January 1995–June 2012

Diagnosis	Single lung (n = 14,197) No. (%)	Bilateral/double lung (n = 23,384) No. (%)	Total (N = 37,581) No. (%)
COPD			
Without A1ATD	6,312 (44.5)	6,290 (26.9)	12,602 (33.5)
With A1ATD	753 (5.3)	1,429 (6.1)	2,182 (5.8)
Interstitial lung disease[a]	4,872 (34.3)	4,032 (17.2)	8,904 (23.7)
Bronchiectasis associated with CF	229 (1.6)	6,002 (25.7)	6,231 (16.6)
IPAH	87 (0.6)	1,073 (4.6)	1,160 (3.1)
Pulmonary fibrosis, other	563 (4.0)	820 (3.5)	1,383 (3.7)
Bronchiectasis	59 (0.4)	956 (4.1)	1,015 (2.7)
Retransplant[b]			
Obliterative bronchiolitis	276 (1.9)	292 (1.2)	568 (1.5)
Not obliterative bronchiolitis	182 (1.3)	220 (0.9)	402 (1.1)
Sarcoidosis	265 (1.9)	689 (2.9)	954 (2.5)
Connective tissue disease	156 (1.1)	332 (1.4)	488 (1.3)
Obliterative bronchiolitis (not retransplant)	98 (0.7)	298 (1.3)	396 (1.1)
Lymphangioleiomyomatosis	136 (1.0)	255 (1.1)	391 (1.0)
Congenital heart disease	56 (0.4)	269 (1.2)	325 (0.9)
Cancer	7 (0.0)	29 (0.1)	36 (0.1)
Other	146 (1.0)	398 (1.7)	544 (1.4)

A1ATD, α_1-antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension.
[a]Includes idiopathic pulmonary fibrosis.
[b]Combined retransplant data, 970 (2.6%).

In recent years, most recipients in the top 5 indications for lung transplantation underwent bilateral procedures.

Lung transplant outcomes

Survival

Adults who underwent lung transplantation in the era of January 1994 through June 2011 had a median survival of 5.6 years (Figure 8), with unadjusted survival rates of 88% at 3 months, 79% at 1 year, 64% at 3 years, 53% at 5 years, and 31% at 10 years. Recipients who survived to 1 year after transplant had a conditional median survival of 7.9 years. Patients undergoing bilateral lung transplantation had higher overall and conditional unadjusted survival rates than those undergoing unilateral lung transplantation. Survival of adult recipients varied by era (Figure 9). The most recent era showed better survival than the previous 2 eras, and the survival curves separated in the early period after transplant: 3-month survival improved between the earliest era and the most recent era from 81% to 90%, and 1-year survival improved from 70% to 81%.

Survival also varied by indication for transplantation (Figure 10). Those with non-A1ATD COPD had the lowest unadjusted 3-month mortality (9%), whereas those with IPAH had the highest mortality (22%).[2] However, conditional median survival for patients surviving to 1 year was higher for CF (10.5 years), IPAH (10.0 years), sarcoidosis (8.5 years), and A1ATD COPD (8.7 years) compared with those with non-A1ATD COPD (6.9 years) or ILD (7.0 years; Figure 11.

Lung transplant recipient groups stratified by pre-transplantation cytomegalovirus (CMV) serologic status in donors and recipients had different survival rates (Figure 12). Transplant recipients who received lungs from CMV-negative donors had better survival than those who received lungs from CMV-positive donors.

Survival rates for transplants performed between January 1990 and June 2011differed by recipient age (Figure 13). For example, recipients older than 65 years had a median survival of 3.6 years compared with 6.5 years for those aged 35 to 49 years. For the 3 recipient age groups aged older than 49 years, survival rates worsened with increasing age. Interestingly, all of the age groups had similar 3-month survival of 87% to 90%, after which survival rates diverged and favored the younger age groups: 5-year survival was 38% for recipients aged >65 years, 46% for those 60 to 65 years, and 52% to 57% for those younger than 60 years.

Procedure type, era of transplant, age at transplant, primary indication for transplant, and multiple other factors each had a significant association with survival rates, whereas others did not. As noted above, multiple other factors may have affected survival, and these survival figures were not fully adjusted for such factors. Some factors also had significant interactions with others. For example, age-related survival differences became more prominent after adjustment for era. Most of the transplants in older patients occurred in more recent eras, which had better overall reported survival. Also, significant interactions occurred between age group and indication for transplant within the primary lung diagnostic groups of COPD and ILD (Figure 14). Older recipients within each diagnostic group had worse overall and conditional survival. When assessing overall survival, significant interactions also occurred between age groups and type of transplant (bilateral vs unilateral) within primary lung diagnostic groups.[2]

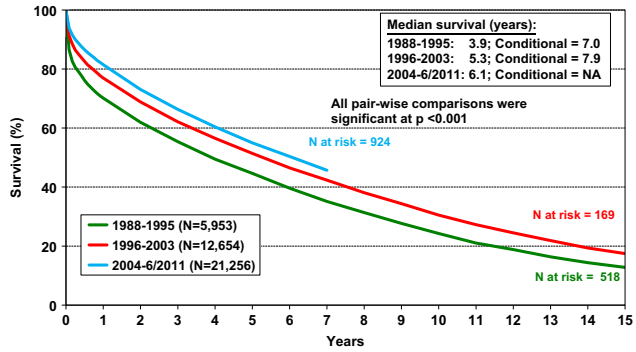

Figure 9 Adult lung transplant recipient Kaplan-Meier survival by era (transplants: January 1988–June 2011). Conditional, median survival for the sub-set of recipients who were alive 1-year after transplantation.

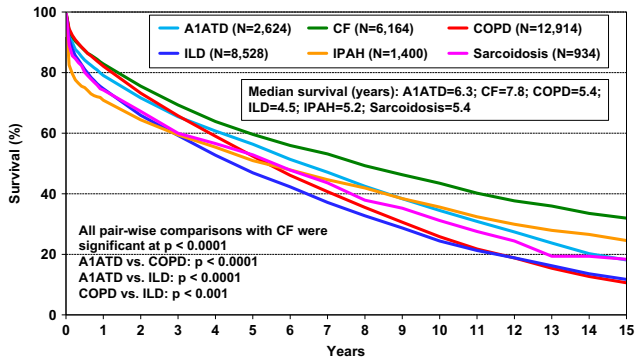

Figure 10 Adult lung transplant recipient Kaplan-Meier survival by diagnosis (transplants: January 1990–June 2011). A1ATD, α_1-antitrypsin deficiency–associated chronic obstructive pulmonary disease (COPD); COPD, non-A1ATD associated COPD; CF, bronchiectasis associated with cystic fibrosis (CF); ILD, interstitial lung disease, which includes idiopathic pulmonary fibrosis (IPF); IPAH, idiopathic pulmonary arterial hypertension.

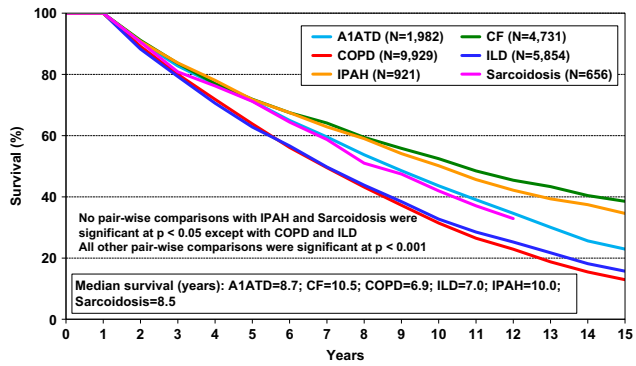

Figure 11 Adult lung transplant recipient Kaplan-Meier survival by diagnosis, conditional on survival to 1 year (transplants: January 1990–June 2011). A1ATD, α_1-antitrypsin deficiency–associated chronic obstructive pulmonary disease (COPD); CF, bronchiectasis associated with cystic fibrosis (CF); COPD, non-A1ATD associated COPD; ILD, interstitial lung disease, which includes idiopathic pulmonary fibrosis; IPAH, idiopathic pulmonary arterial hypertension.

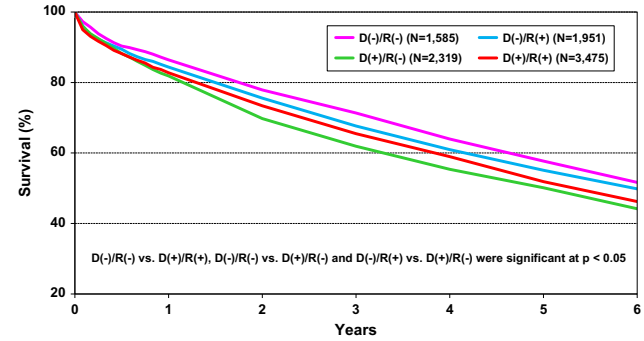

Figure 12 Adult lung transplant recipient Kaplan-Meier survival by donor (D)/recipient (R) pre-transplant cytomegalovirus (CMV) serologic status (transplants: January 2005–June 2011). −, negative; +, positive.

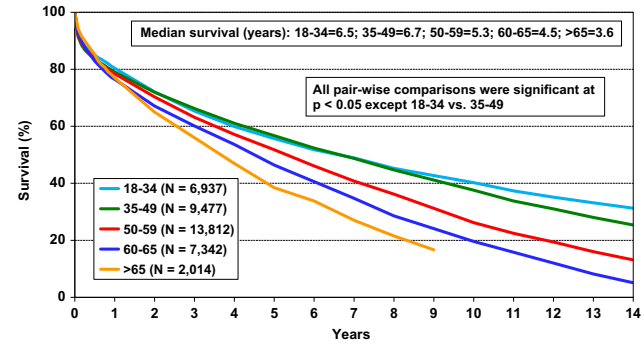

Figure 13 Adult lung transplant recipient Kaplan-Meier survival by age group (transplants: January 1990–June 2011).

Causes of death

The major reported causes of death (January 1992 through June 2012) within the first 30 days after transplantation consisted of graft failure and non-CMV infections (Table 2). During the remainder of the first year, non-CMV infection became the most prominent as a cause of death. After the first post-transplant year, BOS/chronic lung rejection, graft failure (late deaths coded as "graft failure" may represent lung rejection or BOS), and non-CMV infection caused

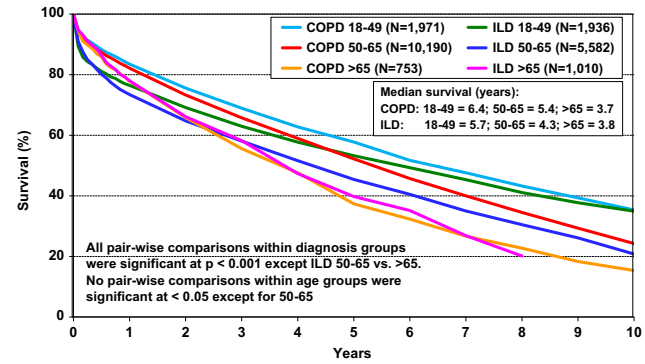

Figure 14 Adult lung transplant recipient Kaplan-Meier survival by diagnosis and age group (transplants: January 1990–June 2011). COPD, chronic obstructive pulmonary disease not associated with α_1-antitrypsin deficiency; ILD, interstitial lung disease, which includes idiopathic pulmonary fibrosis (IPF).

most deaths. Not long after transplant, malignancy became a significant contributor to mortality.

Risk factors for death

Risk factors for death were evaluated using multivariable Cox models. For transplants performed between January 1999 and June 2011, categoric factors that showed an independent association with risk of death during the first post-transplant year, after adjustment for other factors in the model, included era of transplant, type of underlying lung disease of the recipient, retransplantation, the severity of recipient illness at the time of transplantation, recipient age, and transplant center volume (Table 3). Specifically, prior era, more severe illness, advanced age, and low transplant center volume showed an independent association with risk of death. Donor variables played a small role. As described in the statistical methods section, we recommend cautious interpretation of these models.

The increased risk of 1-year mortality with older recipient age began at approximately 55 years and rose exponentially thereafter (Figure 15). An increased risk of 1-year mortality became apparent when transplant center volume fell below 30 transplants per year (Figure 16). Analyses of 1-year mortality performed within models for diagnosis categories of non-A1ATD COPD and ILD yielded mostly similar results.[2] Age remained a significant risk factor in those models. In addition, male gender became a risk factor in the non-A1ATD COPD model.

The 5-year mortality risk factors were similar to those associated with 1-year mortality risk.[2] However, for this analysis, unilateral lung transplantation for ILD (compared with unilateral lung transplantation for non-A1ATD COPD) and extremes of recipient age (Figure 15) conferred an independent risk of death at 5 years after transplant.

Risk factors for 5-year mortality, conditional on survival to 1 year, showed some changes in the diagnostic categories (indications for lung transplant) that were included in the unconditional 5-year survival analysis.[2] For this conditional analysis, compared with the 1-year and 5-year non-conditional survival analyses, the diagnosis of retransplantation was no longer associated with risk of death. The conditional analysis also showed that recipients with BOS or acute rejection in the first year after transplant had a higher risk of death at 5 years. Similar to the non-conditional 5-year mortality risk model, the conditional model demonstrated that extremes of recipient age conferred an independent risk of higher mortality (Figure 15), and the risk in the younger adult recipients became more prominent. Lower transplant center volume again had a negative effect on longer-term survival, even when examining outcomes in the patients who survived to 1 year after transplant. This finding suggests that programmatic differences associated with transplant volume exist beyond those related to the transplant procedure.

Risk factors for 10-year mortality were mostly similar to those identified in the other models. Again, extremes of recipient age conferred an independent risk (Figure 15). Interestingly, for this model, donor age showed an independent association with mortality. The risk of death was increased in recipients of lungs from donors older than 30 years.

Acute and chronic lung rejection

According to data compiled between July 2004 and June 2012, 33% of adult lung recipients experienced at least 1 episode of acute rejection between discharge and the 1-year follow-up (Figure 17). The youngest adult age category (age 18–34 years) had slightly higher incidence of

Table 2 Causes of Deaths for Adult Lung Transplant Recipients (Deaths: January 1992–June 2012)

Cause of Death	0-30 days (n = 2,725) No. (%)[a]	31 days–1 year (n = 4,737) No. (%)[a]	>1–3 years (n = 4,315) No. (%)[a]	>3–5 years (n = 2,449) No. (%)[a]	>5–10 years (n = 2,892) No. (%)[a]	>10 years (n = 899) No. (%)[a]
Bronchiolitis	8 (0.3)	216 (4.6)	1,119 (25.9)	710 (29.0)	734 (25.4)	188 (20.9)
Acute rejection	94 (3.4)	85 (1.8)	63 (1.5)	16 (0.7)	17 (0.6)	2 (0.2)
Malignancy						
Lymphoma	1 (0.0)	110 (2.3)	78 (1.8)	36 (1.5)	56 (1.9)	31 (3.4)
Non-lymphoma	5 (0.2)	134 (2.8)	329 (7.6)	266 (10.9)	379 (13.1)	113 (12.6)
Infection						
CMV	0	112 (2.4)	42 (1.0)	7 (0.3)	4 (0.1)	1 (0.1)
Non-CMV	535 (19.6)	1,687 (35.6)	971 (22.5)	471 (19.2)	523 (18.1)	154 (17.1)
Graft failure[b]	672 (24.7)	790 (16.7)	807 (18.7)	440 (18.0)	515 (17.8)	156 (17.4)
Cardiovascular	298 (10.9)	228 (4.8)	179 (4.1)	120 (4.9)	148 (5.1)	58 (6.5)
Technical	301 (11.0)	162 (3.4)	38 (0.9)	14 (0.6)	24 (0.8)	8 (0.9)
Other	811 (29.8)	1,213 (25.6)	689 (16.0)	369 (15.1)	492 (17.0)	188 (20.9)

[a]Percentages refer to deaths in the respective time period.
[b]Some misclassification may occur among the cause of death terms of bronchiolitis, acute rejection, and graft failure. Graft failure, due to variation in reporting, may represent acute rejection, primary graft dysfunction, or other causes early after transplant, or bronchiolitis obliterans syndrome or other causes late after transplant.

Table 3 Risk Factors From Time of Transplant for 1-Year Mortality in Adult Lung Transplant Recipients (Transplants: January 1999–June 2011; $N = 15,822$)

Category	Variable	No.	HR (95% CI)[a]	*p*-value[a]
Diagnosis[b]	Retransplant	585	1.69 (1.38–2.07)	<.0001
	Connective tissue disease	297	1.36 (1.04–(1.76)	0.0226
	Other	787	1.32 (1.10–1.60)	0.0035
	Lymphangioleiomyomatosis	129	0.47 (0.24–0.93)	0.0289
Transplant characteristics	Transplant year			
	1999/2000 vs 2010/2011	1,655	2.23 (1.92–2.60)	<.0001
	2001/2002 vs. 2010/2011	2,030	1.82 (1.56–2.11)	<.0001
	2003/2004 vs. 2010/2011	2,188	1.39 (1.19–1.62)	<.0001
	2005/2006 vs. 2010/2011	2,753	1.37 (1.19–1.57)	<.0001
	2007/2008 vs. 2010/2011	2,903	1.25 (1.09–1.43)	0.001
	Donor CMV+/ recipient CMV–	3,416	1.17 (1.07–(1.28)	0.0007
Donor characteristics	History of diabetes	764	1.43 (1.21–1.68)	<.0001
Recipient characteristics	Dialysis	79	1.92 (1.34–2.75)	0.0004
	Hospitalized (including ICU)	1,984	1.7 (1.51–1.91)	<.0001
	Ventilator	737	1.53 (1.30–1.79)	<.0001
	Prior transfusion	802	1.18 (1.01–1.38)	0.037
Borderline significant	Pulmonary embolism	135	1.32 (0.95–1.83)	0.0928
	Diagnosis			
	IPAH	375	1.31 (0.99–1.72)	0.0571
	Sarcoidosis, double lung	365	1.27 (0.98–1.64)	0.0673
	COPD with A1ATD	708	1.25 (0.98–1.59)	0.0750
	COPD without A1ATD, single lung	2,867	0.85 (0.71–1.03)	0.0921
	Chronic steroid use	7,562	1.07 (0.99–1.16	0.0765
Continuous characteristics	Recipient age			<.0001
	Transplant center volume			<.0001
	Bilirubin			0.0085
	Recipient oxygen required at rest			0.0001
	Cardiac output			0.0001
	Donor-recipient height difference			0.0032
	Recipient FVC %predicted			0.0018
	Pa_{CO_2}			0.0096

A1ATD, α_1-antitrypsin deficiency; CI, confidence interval; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; HR, hazard ratio; ICU, intensive care unit; ILD, interstitial lung disease; IPAH, idiopathic pulmonary arterial hypertension; Pa_{CO_2}, partial pressure of arterial carbon dioxide.

[a]Calculated using Cox proportional hazard model.

[b]Reference group = ILD. Other = all diagnoses other than COPD without A1ATD, IPAH, ILD, cystic fibrosis, pulmonary fibrosis, bronchiectasis, COPD with A1ATD, retransplant, lymphangioleiomyomatosis, and connective tissue disease.

acute rejection episodes (36%) compared with all other age categories.

BOS, conditioned on surviving to 2 weeks after transplant to avoid biases introduced by early death, remained a common long-term complication, as determined by follow-up assessments performed between April 1994 and June 2012 (Figure 18). Within 5 years of transplantation, 49% of recipients developed BOS, and 76% developed BOS by 10 years post-transplant. Freedom from BOS did not appear to vary much according to age group, indication for transplant, or induction immunosuppression use.[2]

Complications and morbidities

Morbidities commonly caused or exacerbated by immunosuppressive medicines (eg, hypertension, renal dysfunction, diabetes, and hyperlipidemia) occurred frequently after lung transplantation (Table 4). Within the first year after transplantation, recipients aged > 65 years had similar rates of hypertension, diabetes, renal dysfunction, acute rejection, and BOS compared with younger adults.[2] However, the older group had a higher rate of hyperlipidemia.

The complication rates rose significantly over time.[2] Of note, recipients had a high incidence of severe renal dysfunction. Within 5 years after transplantation, 24% of recipients experienced creatinine > 2.5 mg/dl, dialysis, or renal transplant, and 41% experienced any of these complications within 10 years. Older age groups had higher rates of severe renal dysfunction over long-term follow-up than younger age groups.

Cancer rates increased over time after lung transplantation.[2] At least 1 malignancy was reported for 21% of recipients at 5 years post-transplantation and for 40% at 10 years post-transplantation. Skin cancer had the highest incidence of all cancers, although post-transplant lymphoproliferative disease remained an important morbid condition. Recipients aged > 65 years had higher rates of skin cancer over long-term follow-up than younger recipients.

Table 4 Cumulative Morbidity Rates in Adult Lung Transplant Survivors Within 1 and 5 Years After Transplant (Follow-ups: April 1994–June 2012)

Outcome	Within 1 year (%)	Total with known response (No.)	Within 5 years (%)	Total with known response (No.)
Hypertension	51.7	15,267	82.4	4,503
Renal dysfunction	23.3	17,291	55.4	5,571
Abnormal creatinine < 2.5 mg/dl	16.2		36.5	
Creatinine > 2.5 mg/dl	5.2		15.0	
Chronic dialysis	1.7		3.2	
Renal transplant	0.1		0.7	
Hyperlipidemia	25.5	15,975	58.4	4,856
Diabetes	24.6	17,227	40.5	5,498
Bronchiolitis obliterans syndrome	9.5	16,264	39.7	4,701

Heart-lung transplantation

Centers and transplant activity

The Registry now contains data from 3,677 adult recipients who underwent heart-lung transplantation (includes retransplantation) before 2012 (Figure 19). Twenty-nine participating centers reported 63 adult heart-lung transplants performed in 2011. After a rapid rise in the 1980s and a peak at the end of that decade, an overall decline in reported heart-lung transplants occurred throughout the 1990s and into the first few years of the next decade. However, the number of reported adult heart-lung transplant procedures plateaued during the most recent decade and ranged from 63 to 103 transplants per year. As determined from transplants performed between January 2000 and June 2012, 36% of procedures occurred at the 7 centers (7% of centers) that averaged between 4 and 9 procedures per year, whereas 56% of the heart-lung transplant procedures occurred at 87 centers (90% of centers) that averaged only 1 or 2 heart-lung transplants per year (Figure 20).

Donor age

Donors for adult heart-lung transplantation reported to the Registry mainly consisted of adults, although some adolescent and younger children also donated (Figure 21). The Registry recorded a miniscule number of donors aged > 65 years and a limited number aged 60 to 65 years. Donors for adult heart-lung recipients during the first 6 months of 2012 were a median age of 38 years. Compared with North American and European centers for the era of January 2000 through June 2012, other centers located throughout the world used a greater proportion of older and pediatric donors (Figure 22).

Recipient age

Almost 66% of heart-lung transplant recipients are in the group aged 18 to 49 years old (Figure 23). Few recipients were aged 60 years or older. Since 1987, the median age of recipients overall increased from 32 to 42 years (Figures 23 and 24). For transplants that occurred January 2000 through June 2012, North American centers had a higher proportion of recipients aged > 60 years than European and other centers (Figure 25).

Donor and recipient age relationships

From January 1985 through June 2012, adult heart-lung transplant recipients of all defined age groups received organs from pediatric (mainly adolescent, ages 12–17 years) donors (Figure 26). Few donors were aged 60 years or older. As recipient age increased, the proportion with pediatric donors decreased.

Indications

Sixty-three percent of the major indications for adult heart-lung transplantation consisted of congenital heart disease and IPAH (Table 5). For decades, the proportion of adult transplants for diagnoses of congenital heart disease and IPAH remained largely unchanged, while the proportion decreased for CF and increased for acquired heart disease (Figure 27). Significant geographic differences in major

Table 5 Indications for Adult Heart-Lung Transplants Performed January 1982–June 2012

Diagnosis	No. (%) (N = 3,241)
Congenital heart disease	1,154 (35.6)
Idiopathic pulmonary arterial hypertension	890 (27.5)
Cystic fibrosis	453 (14.0)
Acquired heart disease	165 (5.1)
COPD without A1ATD	136 (4.2)
Interstitial lung diseases	119 (3.7)
Retransplant	59 (1.8)[a]
Not obliterative bronchiolitis	37 (1.1)
Obliterative bronchiolitis	22 (0.7)
COPD with A1ATD	61 (1.9)
Sarcoidosis	54 (1.7)
Bronchiectasis	30 (0.9)
Obliterative bronchiolitis (not retransplant)	24 (0.7)
Other	96 (3.0)

A1ATD, α_1-antitrypsin deficiency; COPD, chronic obstructive pulmonary disease

[a]Combined retransplant data.

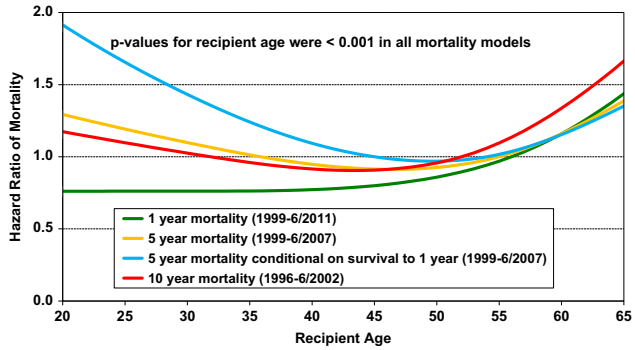

Figure 15 Adult lung transplant recipient age and hazard ratio for mortality. Mortality models used patient cohorts from different eras. The *p*-value is from the Cox proportional hazard multivariate model that included age as an independent predictor, after adjusting for other predictor variables.

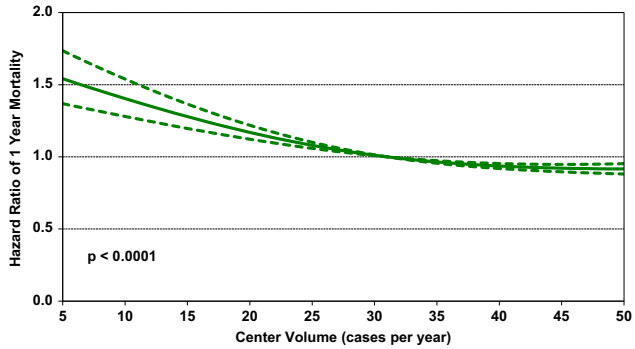

Figure 16 Adult lung transplant recipient center volume and hazard ratio for 1-year mortality (transplants: January 1999–June 2011). The *p*-value is from the Cox proportional hazard multivariate model that included center volume as an independent predictor, after adjusting for other predictor variables. The dashed lines represent the 95% confidence intervals.

indications existed (Figure 28). Between January 2000 and June 2012, congenital heart disease represented the leading diagnosis in all geographic locations (highest in North America). North American centers had a lower frequency of transplant for CF compared with European and other centers.

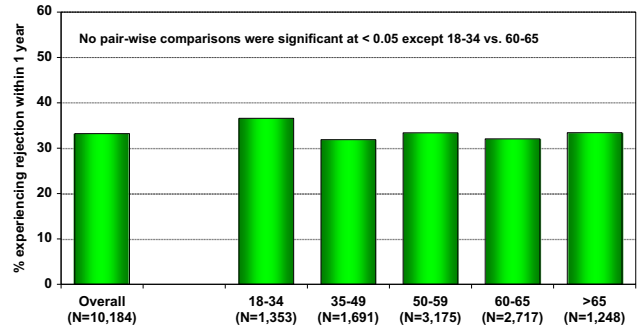

Figure 17 Percentage of adult lung transplant recipient recipients experiencing rejection between transplantation hospitalization discharge and 1-year follow-up, stratified by age (transplant follow-ups: July 2004–June 2012).

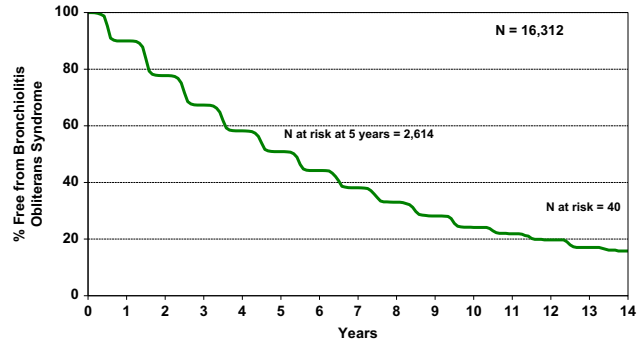

Figure 18 Adult lung transplant recipient freedom from bronchiolitis obliterans syndrome (BOS), conditional on survival to 14 days (transplant follow-ups: April 1994–June 2012). The dashed green line shows the 95% confidence intervals.

Heart-lung transplant outcomes

Survival

Figure 29 presents overall survival for 3,620 heart-lung transplants performed between January 1982 and June 2011. Compared with lung-only transplantation, heart-lung transplantation had a more pronounced early mortality and a

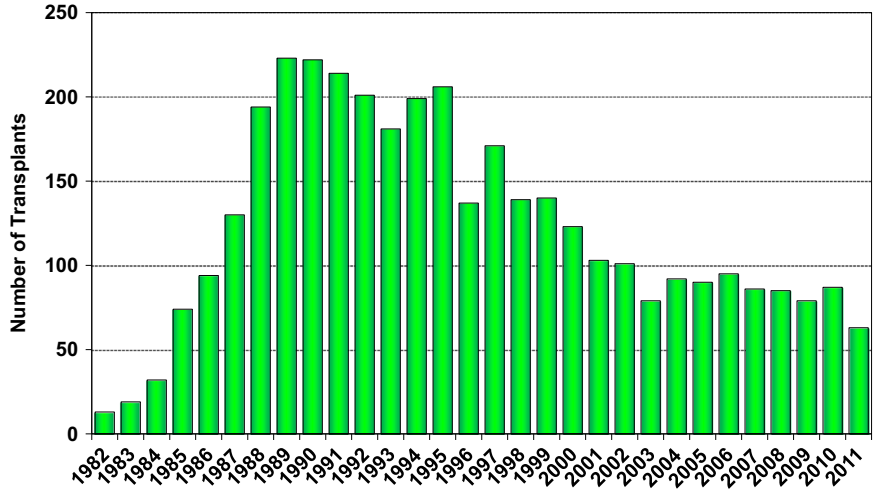

Figure 19 Number of reported adult heart-lung transplants by year reported to the International Society for Heart and Lung Transplantation Registry.

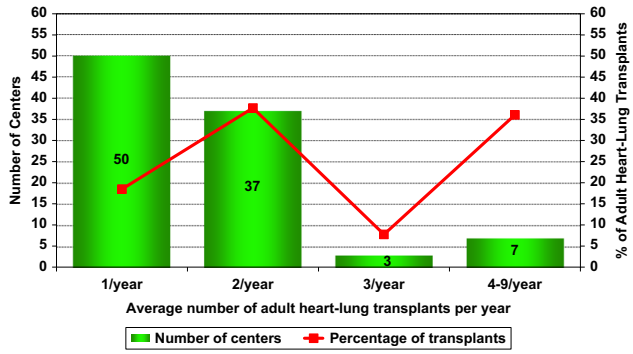

Figure 20 Number of centers and distribution of adult heart-lung transplants by center volume (transplants: January 2000–June 2012). Each bar indicates the number of centers for a given average annual center volume, and each square indicates the percentage of total transplants by average annual center volume.

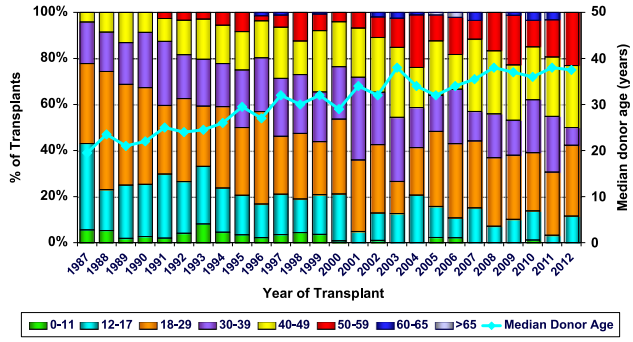

Figure 21 Age distribution of heart-lung donors for adult recipients by year of transplantation (transplants: January 1987–June 2012). Bars represent proportion of transplants for donor age categories within a given year, and the diamonds show the median donor age.

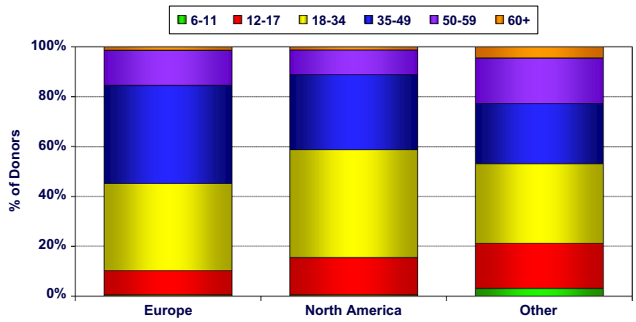

Figure 22 Adult heart-lung transplant donor age distribution by location (transplants: January 2000–June 2012). Each bar represents the proportion of transplants for donor age categories within a given location.

better long-term survival. Heart-lung transplant recipients had survival rates of 71% at 3 months, 63% at 1 year, 51% at 3 years, 44% at 5 years, and 31% at 10 years. Recipients who survived the first year had a median survival of 10.0 years.

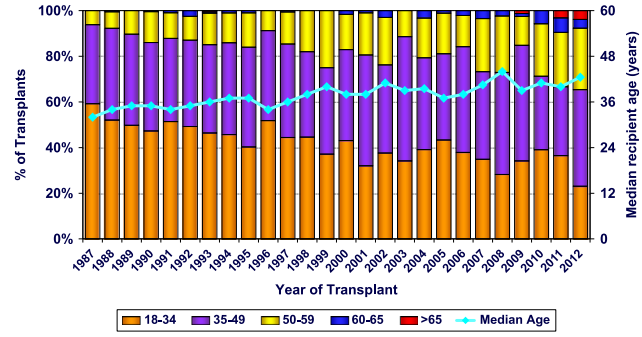

Figure 23 Adult heart-lung recipient age by year (adult heart-lung transplants: January 1987–June 2012). Each bar represents the proportion of transplants for recipient age categories within a given year, and the diamonds show the median recipient age.

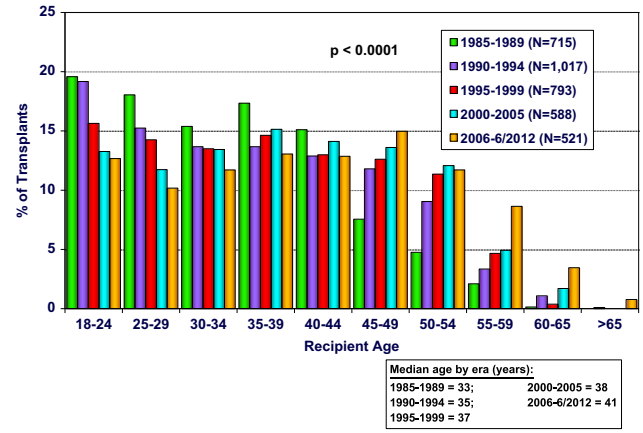

Figure 24 Adult heart-lung transplant recipient age distribution by era. Each bar represents the proportion of transplants from a given era within a recipient age category.

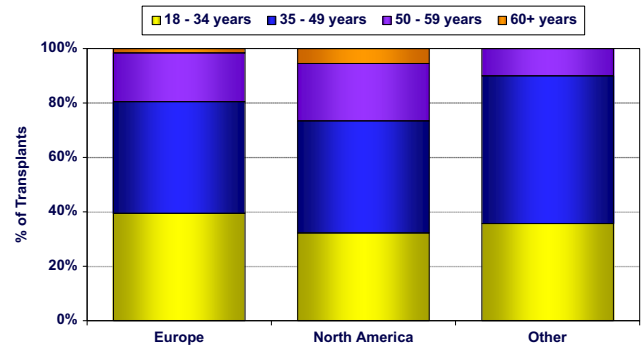

Figure 25 Adult heart-lung transplant recipient age distribution by location (transplants: January 2000–June 2012). Each bar represents the proportion of transplants for recipient age categories within a given location.

Survival showed improvement for successive eras within the time frame of January 1982 through June 2011 (Figure 30). Most of the improvement in survival occurred in the early post-transplant period. Survival and 1-year

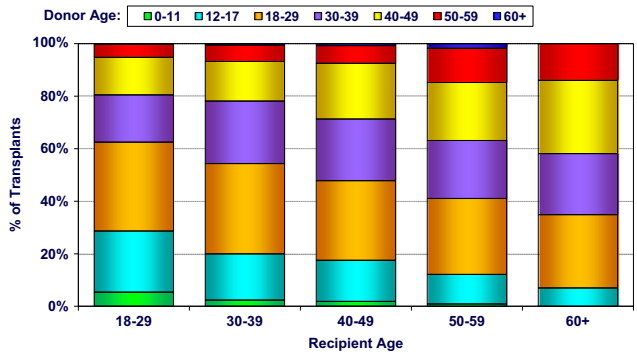

Figure 26 Adult heart-lung transplant donor and recipient age (transplants: January 1985–June 2012). Each bar represents the proportion of donors for each donor age category within a given recipient age category.

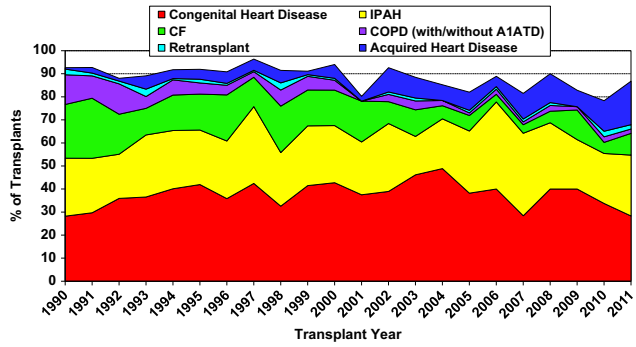

Figure 27 Adult heart-lung transplant major indications by year. Each colored area over each year represents the proportion of transplants reported for each indication. A1ATD, α_1-antitrypsin deficiency; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPAH, idiopathic pulmonary arterial hypertension.

conditional survival did not differ according to pre-transplantation diagnosis.[2] Younger recipient age groups tended to have longer survival than older groups (Figure 31). A multivariable analysis of risk factors for 1-year mortality (Table 6) showed donor age was a significant independent predictor, although it did not demonstrate recipient age as a predictor.

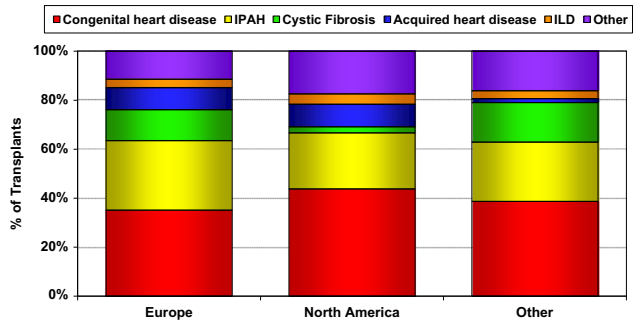

Figure 28 Adult heart-lung transplant diagnosis distribution by location (transplants: January 2000–June 2012). Each bar represents the proportion of transplants for recipient diagnosis (indication for transplantation) categories within a given location.

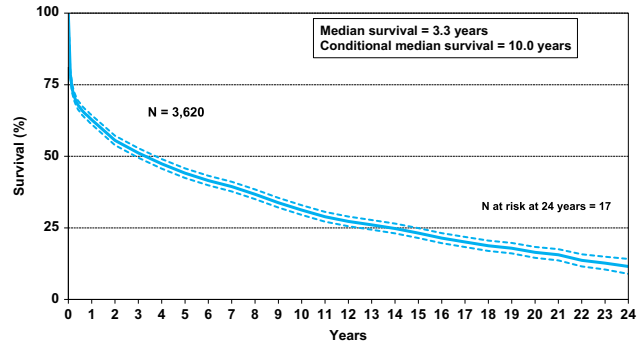

Figure 29 Adult heart-lung transplant Kaplan-Meier survival (transplants: January 1982–June 2011). Conditional, median survival for the sub-set of recipients who were alive 1 year after transplantation. The dashed lines represent the 95% confidence intervals.

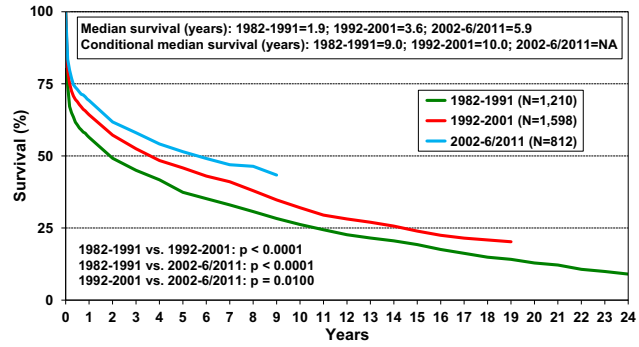

Figure 30 Adult heart-lung transplant Kaplan-Meier survival by era (transplants: January 1982–June 2011). Conditional, median survival for the sub-set of recipients who were alive 1 year after transplantation.

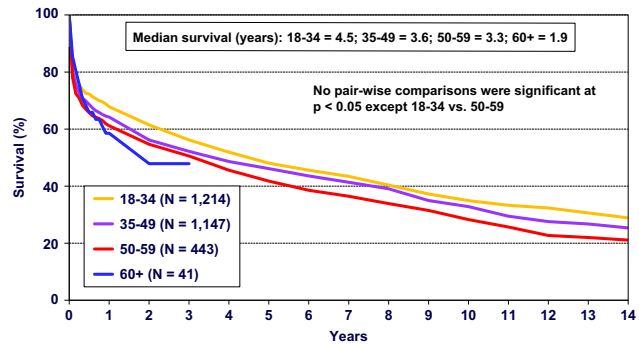

Figure 31 Adult heart-lung transplant Kaplan-Meier survival by age group (transplants: January 1990–June 2011).

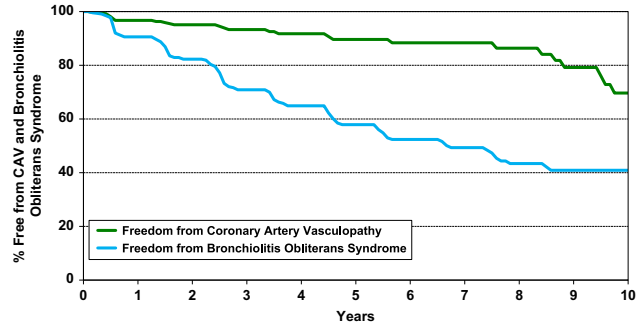

Figure 32 Adult heart-lung transplant freedom from coronary artery vasculopathy (CAV) and bronchiolitis obliterans syndrome (adult heart-lung follow-ups: April 1994–June 2012).

Table 6 Risk Factors From Time of Transplant for 1-Year Mortality in Adult Heart-Lung Transplant Recipients (Transplants: January 1995–June 2011; $N = 1,681$)

Variable	No.	HR (95% CI)[a]	*p*-value[a]
Diagnosis: IPAH vs. other[b]	446	0.78 (0.63– 0.96)	0.0171
Donor age			0.0195
Transplant center volume (borderline significant)			0.0519

CI, confidence interval; HR, hazard ratio; IPAH, idiopathic pulmonary arterial hypertension.
[a]Calculated using Cox proportional hazard model.
[b]All diagnoses other than IPAH and congenital.

Causes of death

For heart-lung transplant recipients, based on reported deaths between January 1992 and June 2012, the most common identifiable causes of death in the first 30 days post-transplant were graft failure, technical complications, and non-CMV infections (Table 7). After the first year, BOS/late graft failure and non-CMV infections became the most common causes of death. Cardiovascular causes of death accounted for a smaller but important proportion of the deaths.

Heart-lung rejection

BOS occurred more commonly than coronary artery vasculopathy (CAV) at all time points, as determined from follow-up data from April 1994 to June 2012 (Figure 32). At 1, 3, 5, and 10 years after heart-lung transplantation, 9%, 29%, 42%, and 59% of recipients developed BOS compared with 3%, 7%, 10%, and 30% who developed CAV, respectively.

Table 7 Causes of Deaths for Adult Heart-Lung Recipients (Deaths: January 1992–June 2012)

Cause of death[a]	0–30 days ($n = 415$) No. (%)[a]	31 days–1 year ($n = 322$) No. (%)[a]	>1–3 years ($n = 263$) No. (%)[a]	>3–5 years ($n = 163$) No. (%)[a]	>5 years ($n = 426$) No. (%)[a]
Bronchiolitis	0	13 (4.0)	64 (24.3)	36 (22.1)	92 (21.6)
Acute rejection	7 (1.7)	9 (2.8)	5 (1.9)	2 (1.2)	3 (0.7)
Malignancy					
Lymphoma	0	8 (2.5)	13 (4.9)	8 (4.9)	9 (2.1)
Other	1 (0.2)	7 (2.2)	12 (4.6)	5 (3.1)	27 (6.3)
Infection					
CMV	0	2 (0.6)	1 (0.4)	1 (0.6)	1 (0.2)
Non-CMV	74 (17.8)	113 (35.1)	75 (28.5)	42 (25.8)	102 (23.9)
Graft failure	112 (27.0)	68 (21.1)	36 (13.7)	29 (17.8)	59 (13.8)
Cardiovascular	32 (7.7)	14 (4.3)	19 (7.2)	16 (9.8)	37 (8.7)
Technical	91 (21.9)	9 (2.8)	3 (1.1)	3 (1.8)	3 (0.7)
Other	98 (23.6)	79 (24.5)	35 (13.3)	21 (12.9)	93 (21.8)

CMV, cytomegalovirus.
[a]Percentages refer to deaths in the respective time period.
[b]Some misclassification may occur among the cause of death terms of bronchiolitis, acute rejection, and graft failure. Graft failure, due to variation in reporting, may represent acute rejection, primary graft dysfunction, or other causes early after transplant, or bronchiolitis obliterans syndrome of the lung or other causes late after transplant.

Table 8 Cumulative Morbidity Rates in Adult Heart-Lung Transplant Survivors Within 1 and 5 Years After Transplant (Follow-ups: April 1994–June 2012)

Outcome	Within 1 Year (%)	Total with known response (No.)	Within 5 Years (%)	Total with known response (No.)
Hypertension	59.1	421	87.8	148
Renal dysfunction	18.2	466	45.3	181
Abnormal creatinine < 2.5 mg/dl	11.2		31.5	
Creatinine > 2.5 mg/dl	2.8		10.5	
Chronic dialysis	4.1		2.2	
Renal transplant	0.2		1.1	
Hyperlipidemia	26.6	443	69.2	156
Diabetes	18.8	469	27.9	179
Coronary artery vasculopathy	3.0	371	7.6	92
Bronchiolitis obliterans syndrome	8.6	441	28.3	152

Complications and morbidities

Morbidities often associated with immunosuppressive therapy commonly occurred at both the 1-year and 5-year time points after heart-lung transplantation, and their rates increased over time (Table 8). Of all malignancies, lymphoma had the highest incidence until about 9 years after transplant, and the highest event rate occurred during the first post-transplant year.[2]

Conclusions

On the basis of Registry reporting, international lung transplantation rates showed continued growth, whereas heart-lung transplantation rates plateaued. Survival for both transplant types improved over time, mainly due to improved survival in the early post-transplant period. Morbidities after lung and heart-lung transplantation frequently occurred, and the main long-term contributors to decreased long-term survival consisted of BOS of the lung and infections. Older donor age showed an association with decreased survival for both transplant types. Recipient age for both transplant types increased over time, and older sub-groups generally had lower long-term survival and higher long-term complication rates than younger sub-groups. However, older recipients had similar short-term survival compared with younger recipients.

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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