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The Registry of the International Society for Heart and Lung Transplantation: Thirty-first Official Adult Heart Transplant Report—2014; Focus Theme: Retransplantation

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Since the first heart transplant was performed in 1967, heart transplantation has grown worldwide. This 31st adult heart transplant report is based on data submitted on 116,104 heart transplants in recipients of all ages (including 104,027 adult heart transplants) through June 30, 2013.

Data collection and statistical methods

Data are submitted to the International Society for Heart and Lung Transplantation (ISHLT) Registry by national and multinational organ and data exchange organizations or by participating individual centers. Since the Registry inception, 416 heart transplant centers, 241 lung transplant centers, and 168 heart-lung transplant centers have reported data to the registry. We estimate that data submission to the Registry represents approximately 66% of worldwide thoracic transplant activity.

This report used standard statistical methodology for analyses and reporting. Where appropriate, a more detailed explanation about the analytic methodology accompanies the Web site slides (in the "Notes Page" view). To assess time-to-event rates (e.g., survival), this report used the Kaplan-Meier method. Survival graphs (i.e., time-to-event graphs) underwent truncation when the number of analyzable individuals fell below 10. Within the era undergoing assessment, the analyses censored the follow-up of the surviving recipients (1) at the time last reported to be alive (e.g., most recent annual follow-up), or (2) at the time of retransplantation. The median time to event (e.g., survival) estimated the time point at which 50% of all recipients experienced the event (e.g., death). Conditional analyses only included those patients who met the required criterion (e.g., survival past 1 year post-transplant). The log-rank test was used to compare survival curves among groups. To prevent spuriously statistically significant findings, we adjusted all pair-wise tests for multiple comparisons (Scheffe or Bonferroni).

For multivariable time-to-event analyses, this report used Cox proportional hazards regression. The analyses used the censoring approaches described above. Cox models only included transplant recipients for whom data were available for most of the risk factors in the final model. We used restricted cubic splines to fit continuous data variables. Model assumptions were tested, and regression diagnostics were performed.

The Cox models calculated hazard ratios (HRs), their corresponding 95% confidence intervals (CIs), and p-values. A HR = 1 suggests that the presence of the factor (e.g., donor gender) is not associated with the event (e.g., mortality). A HR $>$ 1.0 suggests that presence of the factor is

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associated with a higher probability of the event studied (i.e., 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 (i.e., the group exposed to the factor has a lower hazard than the group not exposed). A 95% CI of a HR that includes a HR of 1.0 does not show statistical significance for that factor as a risk factor for the outcome, whereas a 95% CI of a HR that does not include 1.0 shows statistical significance. Forest plots and Tables show HRs and 95% CIs for categoric variables in final models.

Some analyses incorporated multiple imputation to estimate missing information for continuous data fields such as ischemic time and donor age. This method produced an estimated value for the missing value based on the other characteristics of the patient, the donor, and/or the transplant. Models fit on each imputed data set were combined to produce a final set of estimates and associated HR estimates and *p*-values.

Registry data quality depends on center reporting accuracy and completeness. The Registry uses various quality control measures to ensure acceptable data quality and completeness before including data in the main data set and using data for analyses. Insufficient variable data completeness leads to variable exclusion from analyses. For patients who died, some secondary outcomes may have been under-reported in the final follow-up year before the death. The Registry did not capture the exact occurrence date for most secondary outcomes, such as renal dysfunction and cardiac allograft vasculopathy (CAV), but it did capture the window of occurrence (i.e., the event occurred between the first and the second year annual follow-up visits).

For this report that has retransplantation as the theme, a heart retransplant occurred when a heart or heart-lung transplant recipient received a subsequent heart transplant. For transplant recipients undergoing retransplantation, we addressed certain methodologic limitations. Retransplant events were identified by a prior transplant reported to the Registry. Because identification of all transplants for an individual may not be complete, the number of retransplant events may be slightly underestimated.

We recommend cautious interpretation of unadjusted analyses and predictive and comparative risk models. For unadjusted analyses (e.g., survival curves stratified by gender), the different groups of interest may have an uneven distribution of clinical characteristics (e.g., recipient age, underlying diagnosis, comorbidities) and other factors (e.g., donor characteristics) associated with the outcome undergoing assessment (e.g., survival). Multivariable models may have excluded variables that lacked statistical significance due to small 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. In addition, predictive models only included data captured in the Registry and did not adjust for all important known and unknown confounders. The models may lack generalizability for specific sub-groups of patients or for specific settings (e.g., different organ allocation systems).

The focus theme of this 2014 report is retransplantation, where outcomes are thought to be worse than for primary transplants,[1] but little is known about recipient characteristics and predictors of outcomes. The standard overview of donor and recipient characteristics and outcomes is presented throughout the report, along with an in-depth analysis of retransplantation characteristics and outcomes. These data are paralleled with additional and extended analyses presented in the online slide sets (3 separate slide sets, named "Introduction," "Heart overall," and "Heart adult"). New in this year's report is continuous referral to specific online eSlides when particular data are discussed but not shown due to space limitations. The eSlide numbers refer to the online "Heart adult" slides, unless otherwise specified. The Tables and Figures published in this report and the eSlides describing additional analyses are available for download from the ISHLT Web site (www.ishlt.org/registries).

Heart transplant donor and recipient demographics and characteristics

Transplant volumes

A total of 4,196 adult and pediatric heart transplants were reported to the ISHLT Registry in 2012 (Figure 1). After a decline between 1993 and 2004, the number of reported heart transplants remained stable for several years and now appears to be slowly increasing, particularly in North America and "other" regions (Figure 1).

The volume of transplants performed at different centers varies considerably (Figure 2). Of 297 centers reporting heart transplants in 2006 to 2013, 235 perform fewer than 20 heart transplants per year and are responsible for 50% of all transplant volume.

Donor demographics

Donor demographics for adult recipients since 1992 are presented in Table 1 and Figure 3. Median donor age since 1992 increased from 31 to 35 years. Age matching is similar in primary transplants and in retransplants (Figure 3). The proportion of male donors has consistently been 68% to 69%. Donor diabetes mellitus (3%) and hypertension (14%) are rare but increasing, whereas donor history of cigarette use has decreased to 19%. The leading cause of donor death is head trauma (45%).

Recipient demographics and characteristics

As addressed in detail in the 2013 report,[2] the median adult recipient age increased from 42 years in 1982 to 54 years in the 1990s and has been constant during the last 20 years (Table 2). However, the proportion of patients transplanted at the extremes of age (for recipients of all ages) continues to increase (Figure 4).

Cardiomyopathy and coronary artery disease (CAD) are overwhelmingly the leading underlying heart disease