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# Association of recipient age and causes of heart transplant mortality: Implications for personalization of post-transplant management—An analysis of the International Society for Heart and Lung Transplantation Registry

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**BACKGROUND:** Survival beyond 1 year after heart transplantation has remained without significant improvement for the last 2 decades. A more individualized approach to post-transplant care could result in a reduction of long-term mortality. Although recipient age has been associated with an increased incidence of certain post-transplant morbidities, its effect on cause-specific mortality has not been established.

**METHODS:** We analyzed overall and cause-specific mortality of heart transplant recipients registered in the International Society for Heart and Lung Transplantation Registry between 1995 and 2011. Patients were grouped by recipient age: 18 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, and ≥ 70 years. Multivariable regression models were used to examine the association between recipient age and leading causes of post-transplant mortality. We also compared immunosuppression (IS) use among the different recipient age groups.

**RESULTS:** There were 52,995 recipients (78% male; median age [5th, 95th percentile]: 54 [27, 66] years). Survival through 10 years after transplant was lower in heart transplant recipients in the 2 more advanced age groups: 49% for 60 to 69 years and 36% for ≥ 70 years ($p < 0.01$ for pairwise comparisons with remaining groups). The risk of death caused by acute rejection (hazard ratio [HR], 4.11; $p < 0.01$), cardiac allograft vasculopathy (HR, 2.85; $p < 0.01$), and graft failure (HR, 2.29; $p < 0.01$) was highest in the youngest recipients (18–29 years) compared with the reference group (50–59 years). However, the risk of death caused by infection (HR, 2.10; $p < 0.01$) and malignancy (HR, 2.23; $p < 0.01$) was highest in older recipients (≥ 70 years). Similarly, the risk of death caused by renal failure was lower in younger recipients than in the reference group (HR, 0.53; $p < 0.01$ for 18–49 years vs 50–59 years). The use of induction IS was similar among the different recipient age groups, and differences in maintenance IS were not clinically important.

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**CONCLUSIONS:** Causes of death in this large cohort of heart transplant recipients varied significantly with recipient age at the time of transplant, with cause-specific mortality profiles suggesting a possible effect of inadequate IS in younger recipients and over-IS in older recipients. Thus, a more personalized approach, possibly including different IS strategies according to recipient age, might result in improved post-transplant survival.
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Heart transplantation has become standard therapy for patients with advanced heart failure refractory to medical therapy. Median survival after transplantation has steadily improved, from 8 years in the 1980s to nearly 11 years in the 1990s and further improvement in the last decade.[1] However, most of all the improvement in survival has been the result of lower mortality during the early post-transplant period, specifically the first year, which is likely related to improvements in operative technique, perioperative management, and immunosuppressive (IS) therapies directed at acute graft rejection most prevalent early after transplant.

After the first year, mortality rates have remained constant at 3% to 4% per year for the last 20 years [1] and are considerably higher than the rates observed in the general population. New and individualized strategies targeted at reducing long-term mortality will likely be needed to further improve post-transplant survival. This fact has motivated in-depth investigation of donor-specific and recipient-specific characteristics that influence long-term post-transplant outcomes.[2–5]

Age is a recipient characteristic that has consistently been shown to be a predictor of early and late mortality after heart transplantation.[6–10] Observed median survival steadily declines from 12.4 years in recipients aged 18 to 29 years to 7.6 years in recipients aged 70 to 74 years.[1] Although the survival disparity observed in recipients of different age groups could be influenced by differences in the prevalence of comorbidities and baseline risk, age remains a strong independent predictor of mortality, even after adjusting for baseline variables.[1]

Furthermore, findings from prior clinical studies suggest that age-related alterations in the immune system and differences in susceptibility to IS regimens likely have a major influence on transplant outcomes.[11–14] Several single-center studies reported a higher incidence of morbidities, such as acute rejection, in younger recipients, whereas the incidence of infection and malignancy was higher in older recipients, suggesting an attenuation of the immune response with increasing recipient age.[12,13] More recently, a multi-institutional analysis of the Pediatric Heart Transplant Study and the Cardiac Transplant Research Database examined the association of recipient age with rejection-related and infection-related death and demonstrated that death from rejection affects preferentially young adults, whereas death from infection affects predominantly recipients aged $>$ 60 years.[15]

Prior studies evaluating the effect of recipient age on post-transplant outcomes have focused on morbidity outcomes or evaluated mortality in a limited number of recipients, particularly in the older patient groups. In view of these limitations, we examined the influence of recipient age on overall and cause-specific mortality (acute rejection, cardiac allograft vasculopathy [CAV], graft failure, infection, renal failure, and malignancy related) by using a comprehensive approach in a large, contemporary cohort of heart transplant recipients.

## Methods

### Data source and study population

The International Society for Heart and Lung Transplantation (ISHLT) Registry collects data on thoracic organ transplantation performed worldwide. The Registry provided deidentified patient-level data on all heart transplant recipients. Because no patient or center identifiers were included in the ISHLT data set, our center did not require Institutional Review Board approval. We retrospectively examined data for all heart transplants performed in adult ($\geq$18 years) recipients between January 1995 and August 2011. The analysis excluded recipients of multi-organ transplants, retransplants, domino transplants, and unknown status at 1 year of follow-up. The study cohort was divided according to recipient age at the time of transplant. Our analysis focused on 6 age groups: 18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, and $\geq$ 70 years.

### Study variables and outcomes

Recipient, donor, and transplant variables were selected by their clinical relevance and results from previously published research (Table 1). The outcomes examined in our study were all-cause mortality and cause-specific mortality, which included mortality related to acute rejection, CAV, graft failure, infection, renal failure, and malignancy. Because these outcomes may also be affected by the choice of IS agents, we also compared the use of induction therapy and maintenance IS regimens among the different recipient age groups.

### Statistical analysis

Continuous variables are summarized as median [5th percentile, 95th percentile] and were compared by means of Mann-Whitney *U* test. Categoric variables are summarized as frequencies and percentages and were compared by the Pearson chi-square test or, when $<$ 5 outcomes were expected per cell, by the Fisher exact test. Survival rates were estimated with the Kaplan-Meier method and compared between groups by the log-rank test.[16,17]

Time to event was the time from transplantation until death or retransplantation. Survival was censored at the last follow-up