The effect of ischemic time on survival after heart transplantation varies by donor age: An analysis of the United Network for Organ Sharing database

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Objectives: (1) To examine the interaction of donor age with ischemic time and their effect on survival and (2) to define ranges of ischemic time associated with differences in survival.

Methods: The United Network for Organ Sharing provided de-identified patient-level data. The study population included 33,640 recipients undergoing heart transplantation between October 1, 1987, and December 31, 2004. Recipients were divided by donor age into terciles: 0 to 19 years (n = 10,814; 32.1%), 20 to 33 years (11,410, 33.9%), and 34 years or more (11,416, 33.9%). Kaplan-Meier survival functions and Cox regression were used for time-to-event analysis. Receiver operating characteristic curves and stratum-specific likelihood ratios were generated to compare 5-year survival at various thresholds for ischemic time.

Results: In univariate Cox proportional hazards regression, the effect of ischemic time on survival varied by donor age tercile: 0 to 19 years ($P = .141$), 20 to 33 years ($P < .001$), and 34 years or more ($P < .001$). These relationships persisted in multivariable regression. Threshold analysis generated a single stratum (0.37-12.00 hours) in the 0- to 19-year-old group with a median survival of 11.4 years. However, in the 20- to 33-year-old-group, 3 strata were generated: 0.00 to 3.49 hours (*limited*), 3.50 to 6.24 hours (*prolonged*), and 6.25 hours or more (*extended*), with median survivals of 10.6, 9.9, and 7.3 years, respectively. Likewise, 3 strata were generated in the group aged 34 years or more: 0.00 to 3.49 (*limited*), 3.50 to 5.49 (*prolonged*), and 5.50 or more (*extended*), with median survivals of 9.1, 8.5, and 6.3 years, respectively.

Conclusions: The effect of ischemic time on survival after heart transplantation is dependent on donor age, with greater tolerance for prolonged ischemic times among grafts from younger donors. Both donor age and anticipated ischemic time must be considered when assessing a potential donor.

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During the past 30 years of heart transplantation, it has become common practice to procure hearts from younger donors even when extended ischemic times are required. However, among older donors, convention dictates that ischemic time should be limited to 4 hours or less.

To test these practices, this study examined the effect of ischemic time on recipient survival within various donor age ranges. In addition, it sought to define thresholds for ischemic time associated with worse survival within these donor age groups. To achieve sufficient power to detect differences in survival across a broad range of ischemic times, we analyzed the United Network for Organ Sharing (UNOS) registry, which includes all heart transplants from US centers since 1987.

Abbreviations and Acronyms
CI = confidence interval
ROC = receiver operating characteristic
SSLR = stratum-specific likelihood ratio
UNOS = United Network for Organ Sharing

Materials and Methods

Data Collection and Study Population

UNOS provided de-identified patient-level data from the Thoracic Registry (data source No. 092005-7). The registry includes all heart transplant recipients and donors in the United States since October 1, 1987. This study included 34,556 heart transplants performed from October 1, 1987, to December 31, 2004. Patients with a previous heart transplant were excluded from the study population (n = 916, 2.5%). Recipients were divided by donor age into terciles: 0 to 19 years (n = 10,814; 32.2%), 20 to 33 years (11,410, 33.9%), and 34 years or more (11,416, 33.9%).

Data Analysis

All data were analyzed with a standard statistical software package, Stata 9 (Stata Corp, College Station, Tex). Continuous variables were reported as means ± standard deviation and compared using the Student's *t* test. The chi-square test was used to compare categoric variables. All reported *P* values were 2-sided.

The primary outcome measure was survival reported as median survival and incidence rate of death per 100 patient-years with 95% confidence intervals (CIs). Kaplan–Meier analysis with Cox proportional hazards regression was used for time-to-event analysis. Outcome of interest was death (n = 13,478, 40.1%) or retransplant (n = 840, 2.5%), whichever came first. Patients lost to follow-up (n = 2,168, 6.44%) or alive on September 15, 2005 (17,154, 51.0%) were censored at the date of last known follow-up. A multivariate Cox regression was performed (backward, remove $P > .10$) in which the dependent variable was survival and the independent variables were donor age, recipient age, ischemic cause of disease, intensive care unit immediately before transplant, UNOS status 1/1A/1B at transplant, waiting time, year of transplant, and ischemic time. To assess the impact of ischemic time on early and late mortality, the incidence rate of death per 100 patient-years was calculated at multiple time intervals (<30 days, 30 days to 1 year, 1-5 years, 5-10 years, and ≥10 years). Receiver operating characteristic (ROC) curves and stratum-specific likelihood ratios (SSLRs) were used in threshold analysis. ROC curves were generated by plotting *sensitivity* on the ordinate and *1-specificity* on the abscissa with ischemic time as a continuous variable and mortality (at 5 years) as a binary outcome.[1,2] SSLRs and 95% CIs were generated using data cut-points at regular intervals as previously described.[3,4] Cut-points, or threshold values, for ischemic time were determined by combining adjacent ischemic time strata in 15-minute (0.25 hours) intervals with other statistically indistinct strata based on the presence of SSLRs with overlapping 95% CIs. Cut-points occurred when 2 statistically distinct strata could be formed. This process was repeated until no additional cut-points were found.

Results

Study Population

Analysis included 178,031.1 at-risk years with a median survival of 10.3 years. The mean ischemic time for the 0- to 19-year-old, 20- to 33-year-old, and ≥34-year-old donor terciles was 3.1 ± 1.2 hours, 2.8 ± 1.0 hours, and 2.9 ± 1.0 hours, respectively. Table 1 summarizes recipient and donor characteristics by donor age terciles and ischemic time strata.

Survival Analysis

In univariate Cox proportional hazards regression, the effect of ischemic time on survival varied by donor age terciles: 0 to 19 years ($P = .141$), 20 to 33 years ($P < .001$), and 34 years or more ($P < .001$). In multivariate analysis, increasing donor age ($P = .006$), increasing recipient age ($P < .001$), and earlier year of transplant ($P < .001$) were associated with worse survival in the ≤19-year-old donor age tercile; increasing donor age ($P < .001$), increasing recipient age ($P < .001$), ischemic cause ($P < .001$), intensive care unit pretransplant ($P = .004$), earlier year of transplant ($P < .001$), and increasing ischemic time ($P < .001$) were associated with worse survival in the 20- to 33-year-old donor age tercile; and increasing donor age ($P < .001$), increasing recipient age ($P = .014$), ischemic cause ($P < .001$), intensive care unit pretransplant ($P = .004$), earlier year of transplant ($P < .001$), and increasing ischemic time ($P < .001$) were associated with worse survival in the ≥34-year-old donor age tercile. Table 2 demonstrates a trend toward an increase in the incidence rate of death at nearly every time point.

Receiver Operating Characteristic

ROC curves and the corresponding area under the curve were 0.53 (0.52-0.55), 0.52 (0.51-0.53), and 0.53 (0.52-0.55) for the 0- to 19-year-old, 20- to 33-year-old, and ≥34-year-old donor groups, respectively. The results of threshold analysis are presented in Table 2. SSLR analysis generated only a single stratum (0.37-12.00 hours) in the 0- to 19-year-old group with a median survival of 11.4 years; however, in the 20- to 33-year-old group, 3 strata were generated: 0.00 to 3.49 hours (*limited*) with an SSLR of 0.97 (0.94-0.99) and median survival of 10.6 years; 3.50 to 6.24 hours (*prolonged*) with an SSLR of 1.11 (1.01-1.23) and median survival of 9.9 years; and 6.25 hours or more (*extended*) with an SSLR of 2.87 (1.29-6.40) and median survival of 7.3 years. Likewise, 3 strata for ischemic time were generated in the ≥34-year-old group: 0.00 to 3.49 hours (*limited*) with an SSLR of 0.94 (0.92-0.97) and median survival of 9.1 years; 3.50 to 5.49 hours (*prolonged*) with an SSLR of 1.15 (1.06-1.27) and median survival of 8.5 years; and 5.50 hours or more