ORIGINAL CLINICAL SCIENCE

Evidence supports severe renal insufficiency as a relative contraindication to heart transplantation

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BACKGROUND: This study was conducted to determine whether survival after orthotopic heart transplant (OHT) is associated with pre-transplant estimated glomerular filtration rate (eGFR) and to define ranges of pre-OHT eGFR associated with differences in post-transplant survival. The 2006 International Society for Heart and Lung Transplantation revised listing criteria for OHT stated that chronic kidney disease, defined by an eGFR < 40 ml/min is a relative contraindication for OHT alone. The committee noted that this recommendation was supported by consensus opinion of experts and not data derived from a randomized trial or non-randomized studies.
METHODS: The United Network for Organ Sharing provided deidentified patient-level data. The study population included 17,459 OHT recipients aged ≥ 18 years who received allografts between January 1, 2001, and December 31, 2009. Logistic regression was used to assess the effect of multiple variables on survival after OHT. Receiver operating characteristic curves and stratum-specific likelihood ratios were generated to compare 1-year survival at eGFR thresholds. The primary outcomes measure was actuarial post-transplant survival expressed in years.
RESULTS: Regression analysis showed that a lower pre-transplant eGFR is associated with worse post-transplant survival. Threshold analysis demonstrated 3 distinct survival strata: eGFR ≤ 34 ml/min, eGFR 35 to 49 ml/min, and eGFR > 49 ml/min. Graft survival at all times is decreased for patients with eGFR ≤ 34 ml/min. They are also more likely to have in-hospital and long-term complications.
CONCLUSIONS: eGFR is a strong predictor of post-transplant survival and should be considered when assessing patients for OHT. This analysis supports current International Society for Heart and Lung Transplantation guidelines and suggests that end-stage heart failure patients with an eGFR ≤ 34 ml/min is a relative contraindication for heart transplantation alone.
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End-stage heart failure is a significant problem in the United States. Currently, more than 60,000 deaths per year are directly attributed to end-stage disease, and an additional 250,000 patients with advanced stages of heart failure die from related causes.[1] Orthotopic heart transplantation

(OHT) remains the gold standard in the treatment of end-stage heart failure. Unfortunately, due to a critical scarcity of available organs for transplantation, in any given year, fewer than 2,500 potential beneficiaries undergo OHT.[2] Therefore, achieving maximal benefit from this therapy is predicated on improved patient selection.

To this end, revised listing criteria for OHT were published by the International Society for Heart and Lung Transplantation (ISHLT) in 2006.[3] The current guidelines state that chronic kidney disease (CKD), defined by an estimated glomerular filtration rate (eGFR) < 40 ml/min, is a relative contraindication for OHT alone. CKD has a strong association with end-stage heart failure, and is therefore commonly seen in OHT candidates. However, this recommendation related to severity of kidney disease and a candidate's appropriateness for transplantation was supported only by consensus opinion (Level C Evidence) and not by objective data (Level A or B Evidence). A better body of evidence is clearly needed to refine future guidelines.

We therefore, we chose to analyze the United Network for Organ Sharing (UNOS) database in an attempt to objectively define risks facing OHT recipients with various degrees of kidney disease. The purposes of this study were to (1) define ranges of eGFR before OHT associated with differences in post-transplant survival and (2) to describe post-transplant outcomes within eGFR strata.

Methods

Data collection

Use of these data is consistent with the regulations of the University of Chicago's Institutional Review Board. UNOS provided deidentified patient-level data from the Thoracic Registry (data source 01052011–6). These data include all OHT recipients and donors in the United States and reported to the Organ Procurement and Transplantation Network between January 1, 2001, and December 31, 2009. Data entry by all United States transplant centers is mandated by the 1984 National Transplantation Act. The eGFR was calculated from pre-OHT serum creatinine using the Modification of Diet in Renal Disease (MDRD) Study Equation. Chronic dialysis patients were assigned an eGFR of 10 ml/min.

Study population

The study population included 17,459 first-time OHT patients aged 18 years and older between January 1, 2001, and December 31, 2009. The analysis excluded 980 patients because of lack of data (n = 484) or because they were multiorgan transplant recipients (n = 496). Patients were monitored from the date of transplantation to January 3, 2011, which was the last day of follow-up provided by UNOS.

Outcome measures

The primary outcomes measure was actuarial post-transplant graft survival. Other outcomes of interest included primary graft failure at 1 year, transplant hospitalization morbidity, and long-term complications. Measures of transplant hospitalization morbidity included incidence of stroke, infection, and need for hemodialysis (HD) during the transplant hospitalization. Long-term complications were assessed by time-to-event analysis where the events of interest include transplant coronary artery disease (TCAD), chronic HD, severe infection, and severe rejection. HD-dependent recipients at transplant were dropped from the chronic HD–free survival analysis.

Data analysis

Continuous variables are reported as means ± standard deviation and were compared by using the Student's t-test. Categoric variables were compared with the chi-square test. The conventional p-value value of 0.05 was used to determine statistical significance. All reported p-values are 2 sided.

Survival and other time-to-event analysis

Kaplan-Meier analysis was used to calculate actuarial event-free survival. For survival analysis, the outcome of interest was death (4,771 [27.0%]) or re-transplantation (198 [1.1%]). Other patients, including those lost to follow-up (526 [3.0%]) or alive at last follow-up (11,964 [69.0%]), were censored on the day of last known follow-up. To assess the simultaneous effect of multiple variables on the graft survival after OHT, multivariable logistic regression analysis (backward, p < 0.15) was used to determine the relationship between groups and 1-year graft survival. Long-term complications, excluding renal failure, were reported as event-free survival, where the outcome of interest was the specified complication. A composite end point that included death, HD, or renal transplantation was used to evaluate time to CKD stage 5 requiring HD.

Threshold analysis

Receiver operating characteristic (ROC) curves and stratum-specific likelihood ratios (SSLR) were used in the threshold analysis to define eGFR strata. Receiver-operating characteristic curves were generated (Figure 1) by plotting sensitivity on the ordinate and 1–specificity on the abscissa with eGFR as a
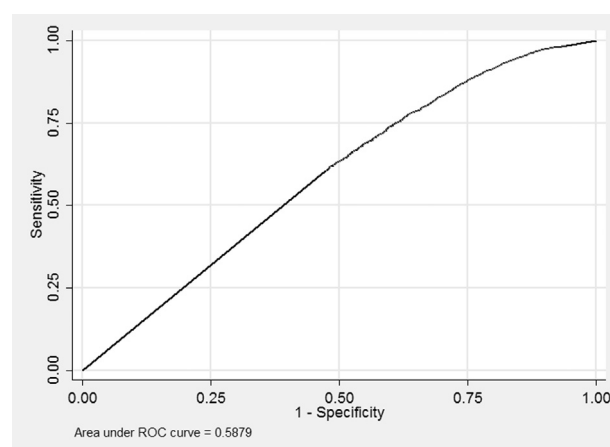

Area under ROC curve = 0.5879

Figure 1   Receiver operating characteristic (ROC) curve shows the estimated glomerular filtration rate as a predictor of 1-year mortality.