

Pretransplantation Patient Characteristics and Survival Following Combined Heart and Kidney Transplantation

An Analysis of the United Network for Organ Sharing Database

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Hypothesis: Pretransplantation patient characteristics determine survival following combined heart and kidney transplantation (HKT).

Design: Time-to-event analysis.

Setting: Academic research.

Patients: The United Network for Organ Sharing provided deidentified patient-level data. Analysis included 19 373 heart transplant recipients from January 1, 1995, to December 31, 2005.

Main Outcome Measures: Multivariate Cox proportional hazards regression analysis was performed to identify pretransplantation recipient characteristics associated with improved long-term survival following HKT. Kaplan-Meier survival functions and Cox proportional hazards regression were used for time-to-event analysis. Using the relative risks calculated in regression analysis, weights were assigned for each risk factor, allowing for the construction of a risk score.

Results: Among heart transplant recipients, 264 (1.4%) underwent HKT. Factors associated with diminished survival included peripheral vascular disease, recipient age

older than 65 years, nonischemic etiology of heart failure, dialysis dependence at the time of transplantation, and bridge to transplantation using a ventricular assist device. After stratification by risk score, 1-year survival was 93.2% and 61.9% in the lowest- and highest-risk HKT groups, respectively. Further stratification by estimated glomerular filtration rate (eGFR) was performed based on a previous study showing decreased survival of patients undergoing orthotopic heart transplantation with a preoperative eGFR of less than 33 mL/min. Low-risk patients with an eGFR of less than 33 mL/min undergoing HKT constituted the only group that had significantly better survival compared with isolated patients undergoing orthotopic heart transplantation with eGFRs and risk scores in the same range ($P = .006$).

Conclusions: When patients were stratified by risk score and by diminished eGFR (<33 mL/min), low-risk HKT recipients with a diminished eGFR had improved survival following HKT over isolated heart transplant recipients. Only low-risk patients with combined kidney failure (eGFR, <33 mL/min) and heart failure seem to gain a survival benefit from HKT.

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IN THE PAST, PATIENTS WITH END-stage heart failure having concurrent renal disease were not considered candidates for heart transplantation. More than 30% of recipients of heart transplantation alone (HTA) have estimated glomerular filtration rates (eGFRs) of less than 45 mL/min (unpublished data, United Network for Organ Sharing [UNOS] Standard Transplant Analysis Research [STAR] Database, data source 022706-3; date of run: February 27, 2006). With advances in operative techniques and perioperative management, combined heart and kidney transplantation (HKT) is offered to select patients in this population.

A 1997 landmark article demonstrated that HKT recipients achieved the same survival as HTA recipients.¹ More than a decade later, there are still no standardized guidelines for HKT, despite the growing number of HKTs being performed.

The objective of this study was to define pretransplantation patient characteristics that predict posttransplantation survival following HKT. By analyzing all heart transplantations (including all HKT cases) performed in the United States during an 11-year period, this study is the first (to our knowledge) with sufficient power to define preoperative patient characteristics that predict post-HKT survival. This study is im-

Table 1. Characteristics of the Study Patients

Characteristic	Non-HKT (n=19 109)	HKT (n=274)	Total (N=19 383)	P Value
Age, mean (SD), y	52.0 (11.6)	50.6 (11.8)	52.0 (11.6)	.10
Male sex, No. (%)	14 651 (76.7)	208 (75.9)	14 859 (76.7)	.77
Estimated glomerular filtration rate, mean (SD), mL/min	79.9 (38.4)	33.4 (18.2)	79.6 (38.4)	<.001
Dialysis dependence at the time of transplantation, No. (%)	420 (2.2)	156 (56.9)	576 (3.0)	<.001
Body mass index, mean (SD) ^a	26.0 (4.8)	25.6 (5.4)	26.0 (4.8)	.23
History of peripheral vascular disease, No. (%)	651 (3.4)	12 (4.4)	663 (3.4)	.38
Diabetes mellitus, No. (%)	3395 (17.8)	73 (26.6)	3468 (17.9)	<.001
Etiology of heart failure, No. (%)				
Ischemic	9294 (48.6)	117 (42.7)	9411 (48.6)	.05
Dilated	7820 (40.9)	99 (36.1)	7919 (40.9)	.11
Other	1995 (10.4)	58 (21.2)	2053 (10.6)	<.001
UNOS status at the time of transplantation, No. (%)				
1	13 637 (71.4)	207 (75.5)	13 844 (71.4)	.13
2	5472 (28.6)	67 (24.5)	5539 (28.6)	.16
Life support at the time of transplantation, No. (%)				
Ventricular assist device	3516 (18.4)	34 (12.4)	3550 (18.3)	.07
Intubation	579 (3.0)	12 (4.4)	591 (3.0)	.20
Donor characteristics, mean (SD)				
Ischemic time, h	3.03 (1.02)	3.13 (0.93)	3.04 (1.02)	.23
Donor age, y	31.3 (12.8)	30.8 (12.5)	31.3 (12.8)	.37

Abbreviations: HKT, combined heart and kidney transplantation; UNOS, United Network for Organ Sharing.

^aCalculated as weight in kilograms divided by height in meters squared.

portant because, given the critical scarcity of donor organs, achieving maximal benefit from transplantation is predicated on understanding the risks and benefits associated with allocating organs to various populations of transplant candidates, especially for those who are candidates for simultaneous multiorgan transplantation in which 2 or more organs are allocated to a single recipient.

100 patient-years). Kaplan-Meier analysis with log-rank test and Cox proportional hazards regression were used for time-to-event analysis. The end points of outcome measures were patient death (5840 patients [30.1%]) or heart retransplantation (212 patients [1.1%]), whichever came first. Patients lost to follow-up (836 patients [4.3%]) or alive at the last follow-up (12 495 patients [64.5%]) were censored at the date of the last known follow-up.

METHODS

STUDY POPULATION

UNOS provided deidentified patient-level data from the thoracic registry (data source 022706-3). The registry includes all heart transplant recipients in the United States since October 1, 1987. Because of changes in data entry by UNOS in 1995, the present study included only all orthotopic heart transplant recipients, 18 years or older, who underwent transplantation between January 1, 1995, and December 31, 2005. The data provided by UNOS included follow-up through February 10, 2006. Exclusion criteria included all patients undergoing simultaneous transplantation of liver, pancreas, or small intestine (n=50). All patients were followed up from the date of transplantation until death, retransplantation (heart), or the date of the last known follow-up. Using the Modification of Diet in Renal Disease Study² equation, the eGFR was calculated based on pretransplantation serum creatinine level.

DATA ANALYSIS

All data were analyzed using commercially available software (STATA 9; StataCorp LP, College Station, Texas). Continuous variables (mean [SD]) were compared using the *t* test. The χ^2 test was used to compare categorical variables. Results were considered statistically significant at *P* < .05. All reported *P* values were 2-sided.

The primary outcome measures were (1) median patient survival and (2) incidence (95% confidence interval of death per

RISK SCORE

In constructing the risk score, multivariate regression analysis was performed to determine the predictors of survival after transplantation, where 1-year survival was the dependent variable. Independent variables included the following: (1) UNOS status 1 (before 1999, high-priority candidates with a life expectancy of less than 6 months in the absence of transplantation) or status 1A (after 1999, status 1A referring to candidates with a life expectancy of less than 6 weeks) or 1B (after 1999, with a life expectancy between 6 weeks and 6 months) at transplantation, (2) pretransplantation patient demographics (male sex, recipient age >65 years, and African American race), and (3) medical history (ongoing dialysis, diabetes mellitus, previous organ transplant, peripheral vascular disease, nonischemic etiology of heart failure, bridge to transplantation with a ventricular assist device, and body mass index [calculated as weight in kilograms divided by height in meters squared] >35). Using the relative risks calculated in regression analysis, weights were assigned for each risk factor. Factors with *P* > .20 were not included in the model. Model discrimination between survivors at 1 year and nonsurvivors was assessed by calculating the area under the receiver operating characteristic curve.^{3,4}

Risk score strata (low, medium, or high) were determined using threshold analysis. Receiver operating characteristic curves were generated by plotting sensitivity on the ordinate and 1 minus specificity on the abscissa, with the use of risk score as a continuous variable and 1-year survival.⁵⁻⁷ Threshold analysis was then performed using stratum-specific likelihood ratios and 95% confidence intervals as previously described.^{7,8} In this study,

Table 2. Variables Included and Excluded in the Risk Score

Variable	No.	Weight	Relative Risk (95% Confidence Interval)	P Value
Included				
History of peripheral vascular disease	14	4	4.07 (1.71-9.70)	<.001
Recipient age >65 y	21	3.5	3.68 (1.51-8.99)	<.001
Nonischemic etiology of heart failure	188	2	2.08 (1.09-3.96)	.03
Bridge to transplantation with a ventricular assist device	39	2	2.16 (1.05-4.42)	.04
Dialysis dependence at the time of transplantation	146	2.5	2.35 (1.16-4.74)	.02
Total	...	14
Excluded				
Diabetes mellitus	1.09 (0.52-2.30)	.81
Previous transplant	0.82 (0.30-2.25)	.70
African American race/ethnicity	1.11 (0.52-2.32)	.78
Donor age >40, y	1.34 (0.70-2.56)	.38
Body mass index >35 ^a	0.51 (0.16-1.63)	.26

Abbreviation: Ellipsis, not applicable.

^aCalculated as weight in kilograms divided by height in meters squared.

stratum-specific likelihood ratios represent the proportion of recipients within a given risk score stratum who were dead at 1 year, divided by the proportion within the same stratum alive at 1 year. Cut points, or threshold values, for the risk score were determined by combining adjacent donor score strata in 0.1-point intervals with other statistically indistinct strata based on the presence of stratum-specific likelihood ratios with overlapping 95% confidence intervals. Cut points occurred when 2 statistically distinct strata could be formed. This process was repeated until no additional cut points were found. Based on this method, low risk was defined as a score of less than 4, medium risk as a score of 4 to 6, and high risk as a score of 7 or higher.

RESULTS

STUDY POPULATION

The study population included 19 373 heart transplant recipients, of which 19 109 were HTA (98.6%) and 274 were HKT (1.4%). One-year follow-up data were available on 264 of 274 patients (96.4%) undergoing HKT. Analysis included 78 338 years at risk for all heart transplant recipients; the median survival for all recipients was 10.1 years. The mean follow-up was 4.04 (2.98) years. Demographic and clinical characteristics of the study patients are given in **Table 1**.

SURVIVAL ANALYSIS

As summarized in **Table 2**, factors associated with worse survival following HKT included the following: (1) history of peripheral vascular disease, (2) recipient age older than 65 years, (3) nonischemic etiology of heart failure, (4) bridge to transplantation with a ventricular assist device, and (5) dialysis dependence at the time of transplantation. The variable risk factors that were excluded because they were unassociated with worse survival following HKT are also listed in Table 2. The excluded variables were (1) diabetes mellitus, (2) heart retransplantation, (3) African American race, (4) donor age older than 40 years, and (5) recipient obesity.

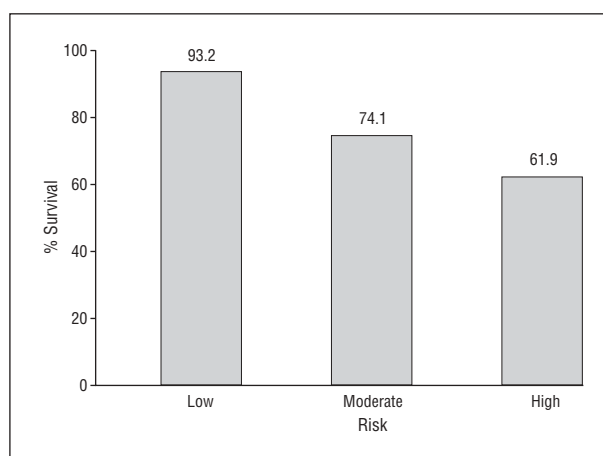


Figure 1. Percentage patient survival at 1 year by risk group. A risk score of less than 4 indicates low risk; 4 to 6, moderate risk; and 7 or higher, high risk.

Risk factors were assigned the following weights based on relative risk: 4 for history of peripheral vascular disease, 3.5 for recipient age older than 65 years, 2.5 for dialysis dependence at the time of transplantation, 2 for nonischemic etiology of heart failure, and 2 for bridge to transplantation with a ventricular assist device. The weights were rounded off. The risk score was the total of the weights of the individual risk factors present.

RISK SCORE

Figure 1 shows the 1-year survival by risk group. One-year survival was 93.2% in the lowest-risk HKT group and 61.9% in the highest-risk HKT group. **Figure 2** shows the area under the receiver operating characteristic curve that assesses model discrimination, confirming that the model has good ability to discriminate between survivors and nonsurvivors based on an area under the curve of 0.77 (95% confidence interval, 0.69-0.84). **Figure 3** shows Kaplan-Meier patient survival curves for low-, moderate-, and high-risk HKT groups and for control subjects undergoing HTA. Survival is signifi-

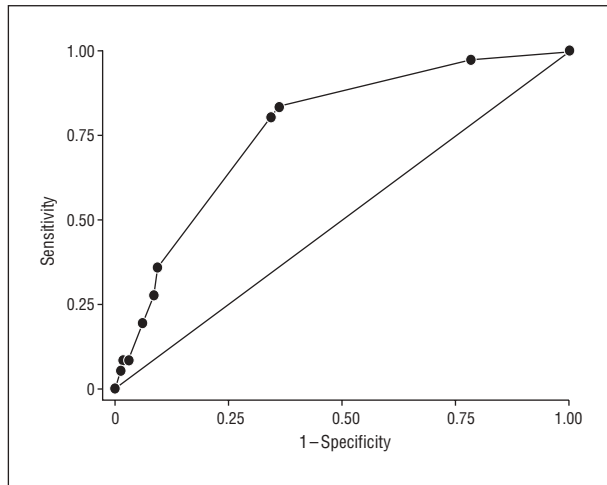


Figure 2. The area under the receiver operating characteristic curve that assesses model discrimination. The area under the curve is 0.77. Sensitivity is the number of true-positive results, divided by the number of true-positive results plus false-negative results. Specificity is the number of true-negative results, divided by the number of true negative results plus false-positive results.

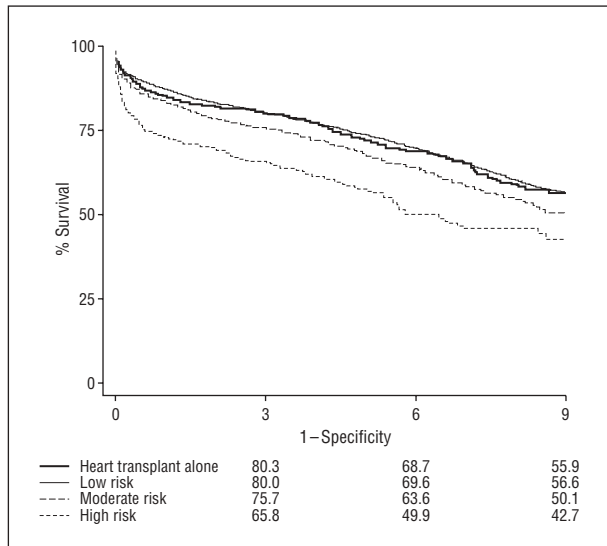


Figure 3. Kaplan-Meier survival curves by risk score and by transplant type.

cantly worse in the moderate- and high-risk HKT groups compared with the low-risk HKT group and the control subjects.

We compared controls undergoing HTA vs patients undergoing HKT who had an eGFR of less than 33 mL/min at the time of heart transplantation in each risk group. In the low-risk group, patients undergoing HKT had significantly better survival than the patients undergoing HTA ($P = .006$). In the moderate-risk group, there was a trend toward better survival in the HKT group, but the difference was not significant ($P = .13$). In the high-risk group, there was no benefit to HKT ($P = .43$). Few patients with eGFRs of 33 mL/min or higher underwent HKT ($n = 60$). When outcomes of HKT and HTA were compared among patients with eGFRs of 33 or higher, there were no statistical differences in survival between the low-risk ($P = .31$), moderate-risk ($P = .61$), and high-risk ($P = .72$) groups.

CAUSE OF DEATH

In the highest-risk HKT group, nearly one quarter of patients ultimately died of infection. This was twice the proportion of deaths in the intermediate-risk group and 4 times higher than the rate of death in the lowest-risk group.

COMMENT

With graft survival exceeding 10 years for heart-alone or kidney-alone transplantation, single-donor organ transplantation offers substantial benefits to patients with isolated end-stage heart disease or renal failure. Because of a critical scarcity of available organs for transplantation, achieving maximal benefit from transplantation is predicated on improved patient selection. This is especially important when considering patients for simultaneous multiorgan transplantation (including HKT), where 2 organs are allocated to a single recipient (and 1 organ is “taken away” from another potential recipient).

RISK FACTORS

In an effort to improve patient selection for HKT, this study sought to identify objective pretransplantation patient characteristics associated with superior post-HKT survival. Analysis was intentionally limited to characteristics that were static and unlikely to change during the waiting period. Therefore, this model did not consider several more dynamic variables shown to be associated with success or failure seen in other models such as prothrombin time, albumin level, and liver function test results. Consideration of these variables may offer further opportunity to increase the predictive value of the model. However, if this tool is heavily weighted to these more dynamic characteristics, it may be less clinically useful at the time of initial assessment for determining who might most benefit from multiorgan transplantation.

Among the variables considered in multivariate analysis, the following were each associated with worse survival following HKT: recipient age older than 65 years, nonischemic etiology of heart failure, history of peripheral vascular disease, dialysis dependence at the time of transplantation, and bridge to transplantation with a ventricular assist device. Previous investigations have demonstrated that patients who have peripheral vascular disease and chronic renal failure have worse survival even after HTA.⁹ Those findings are consistent with our analysis and likely reflect the extensive comorbidities associated with these conditions. The increased mortality among the recipients having a bridge to transplantation with a ventricular assist device seems to be explained by an increased risk of infection, similar to HTA recipients with peripheral vascular disease and recipients older than 65 years, which leads to death in the first year after transplantation in a large percentage of patients in each group. Ischemic cardiomyopathy is the leading etiology of heart failure in heart transplant recipients. In HTA recipients, there is no clinically significant difference in 1-year survival between those with or without an ischemic etiol-

ogy. The increased risk of death related to a nonischemic etiology of heart failure remains unclear in HKT recipients, with the excess mortality in the first year not clearly attributable to any specific cause.

RENAL FUNCTION AND RISK SCORE

Individual institutional criteria have thus far dictated patient selection criteria in patients who require heart transplantation and who have decreased renal function at the time of or before transplantation. For example, Temple University Hospital, Philadelphia, Pennsylvania, selected patients for HKT requiring dialysis or having creatinine clearance of less than 30 mL/min/1.73 m² (to convert creatinine clearance to milliliters per second per meter squared, multiply by 0.0167).¹⁰ At the National Taiwan University Hospital, Taipei, HKT is limited to patients with creatinine clearance of less than 20 mL/min/1.73 m² or a serum creatinine level exceeding 3.0 mg/dL (to convert creatinine level to micromoles per liter, multiply by 88.4).¹¹ So far, selection at these and other institutions has been based on criteria derived from limited experience with few patients.

In this analysis, we sought to establish better defined criteria based on a study with sufficient power for analysis to arrive at conclusive recommendations. Previous work examined the effect of pretransplantation renal function on posttransplantation survival in isolated HTA recipients using the Modification of Diet in Renal Disease Study² equation (eGFR) to calculate pretransplantation renal function.^{12,13} Using threshold analysis herein to define ranges of pre-HTA eGFRs associated with differences in post-HTA survival, we were able to stratify heart transplant recipients into 2 groups, namely, those with an eGFR of less than 33 mL/min and those with an eGFR of 33 mL/min or higher. Recipients who had an eGFR of less than 33 mL/min, including those requiring dialysis, had the worst survival, reaching statistical significance. This finding is similar to the revised listing criteria for heart transplantation (to our knowledge) by the International Society for Heart and Lung Transplantation, which considered an eGFR of less than 40 mL/min to be a relative contraindication to transplantation.¹⁴

When the analysis was limited to patients with an eGFR of less than 33 mL/min, patients in the low-risk group achieved better survival when undergoing HKT than HTA. In the moderate-risk group, there was a trend toward better survival, but no statistical difference was demonstrated. In the high-risk group, there was no difference in survival between the HKT and HTA groups. Few patients with an eGFR of 33 mL/min or higher underwent HKT, and there were no statistical differences in survival among the low-risk, intermediate-risk, and high-risk groups.

In summary, this suggests that, in the low-risk group, with an eGFR of less than 33 mL/min, HKT provides a survival benefit over HTA; while benefits in the moderate-risk group seem likely, the findings are not definitive. Conversely, even with a severely decreased eGFR, there seems to be no benefit in the high-risk group for HKT. Therefore, we believe that pretransplantation patient characteristics determine survival following HKT. The use of

the eGFR and our risk profile can guide the allocation of heart and kidney organs.

LIMITATIONS

Creatinine clearance and eGFR are imperfect measures of kidney disease. While other investigators^{2,15} have applied similar approaches to characterize severity of renal dysfunction, a complex multidimensional construct such as severity of disease may not be fully characterized by any single measure or group of measures. For example, it was impossible to determine reversibility of kidney disease from available data.

Since passage of the National Transplantation Act of 1984, data entry has been mandatory for all US transplant centers. Fields contained within the UNOS database were generally well populated, with a 95% to 99% data entry rate for most variables. Findings from this study using large cohorts of patients are unlikely to be affected by missing data. Furthermore, all patient registries often contain variability in data entry. The UNOS reporting system provides guidelines for defining conditions such as cerebrovascular accident, peripheral vascular disease, and organ rejection, but definitions may vary by center.

Finally, there are other outcome issues that must be considered. In clinical decision making, these include quality of life, functionality, and return to work.

In conclusion, the following variables were each associated in multivariate analysis with worse survival following HKT: recipient age older than 65 years, previous organ transplant (any type), history of peripheral vascular disease, nonischemic etiology of heart failure, and bridge to transplantation with a ventricular assist device. Among patients with combined kidney failure (eGFR, <33 mL/min) and heart failure, those classified by this risk stratification scheme as low risk should undergo HKT, while there is no demonstrable benefit for HKT over HTA in patients classified as high risk.

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Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data in the study and the accuracy of the data analysis. *Study concept and design:* Russo, Rana, Chen, Naka, and Hardy. *Acquisition of data:* Russo. *Analysis and interpretation of data:* Russo, Rana, Ratner, and Hardy. *Drafting of the manuscript:* Russo, Rana, Widmann, and Hardy. *Critical revision of the manuscript for important intellectual content:* Russo, Rana, Widmann, Ratner, and Hardy. *Statistical analysis:* Russo, Hong, Gelijns, and Moskowitz. *Obtained funding:* Hardy.

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