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Candidacy for Kidney Transplantation of Older Adults

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Abstract

OBJECTIVES—To develop a prediction model for kidney transplantation (KT) outcomes specific to older adults with end-stage renal disease (ESRD) and to use this model to estimate the number of excellent older KT candidates who lack access to KT.

DESIGN—Secondary analysis of data collected by the United Network for Organ Sharing and U.S. Renal Disease System.

SETTING—Retrospective analysis of national registry data.

PARTICIPANTS—Model development: Medicare-primary older recipients (aged ≥ 65) of a first KT between 1999 and 2006 (N = 6,988). Model application: incident Medicare-primary older adults with ESRD between 1999 and 2006 without an absolute or relative contraindication to transplantation (N = 128,850).

MEASUREMENTS—Comorbid conditions were extracted from U.S. Renal Disease System Form 2728 data and Medicare claims.

RESULTS—The prediction model used 19 variables to estimate post-KT outcome and showed good calibration (Hosmer–Lemeshow $P = .44$) and better prediction than previous population-average models ($P < .001$). Application of the model to the population with incident ESRD identified 11,756 excellent older transplant candidates (defined as >87% predicted 3-year post-KT survival, corresponding to the top 20% of transplanted older adults used in model development), of whom 76.3% ($n = 8,966$) lacked access. It was estimated that 11% of these candidates would have identified a suitable live donor had they been referred for KT.

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CONCLUSION—A risk-prediction model specific to older adults can identify excellent KT candidates. Appropriate referral could result in significantly greater rates of KT in older adults.

Keywords

kidney transplantation; older adults; risk prediction; transplant outcomes

Adults aged 65 and older account for nearly half of the population with incident end-stage renal disease (ESRD).¹ Like their younger counterparts, appropriately selected older adults with ESRD derive a substantial survival benefit from kidney transplantation (KT) over remaining on dialysis,^{2,3} but older adults have less access to transplantation (ATT).⁴ In 2007, only 10.4% of individuals undergoing dialysis aged 65 to 74 were listed for KT, versus 33.5% and 21.9% of those aged 18 to 44 and 45 to 64, respectively.¹ Similarly, older adults made up only 15.9% of the active waiting list and 14.0% of the KT recipients.⁵

Lower ATT in older adults is probably in part a consequence of good clinical practice. Some older adults undergoing dialysis are simply not appropriate transplantation candidates, given age-related comorbid conditions such as delirium and dementia; however, some inappropriate barriers for older yet excellent candidates may exist. Patients and healthcare providers may harbor regressive attitudes toward KT in older adults, perhaps based on historical outcomes, viewing it as a riskier or less-valuable option in older adults than in younger candidates. In addition, identification of appropriate older candidates is complex, with few resources available to aid in KT risk-benefit calculations and none specific to older adults.

Existing transplantation risk-prediction models may be ill suited for guiding transplantation referral practice, particularly in older KT candidates. First, most existing models of transplantation outcomes incorporate donor characteristics, which are often unavailable at the time of transplantation referral and evaluation. Second, current models rely on the limited comorbidity data supplied at ESRD onset, information that may be outdated by the time of transplantation. Outdated information may disproportionately affect prediction accuracy in older adults, who have a greater burden of comorbid conditions.⁶ Third, despite the substantial heterogeneity in the transplantation recipient population, most KT risk prediction models are population based.^{7–10} “Average” population-based models may miss interactions between age and predictors. For example, given the small percentage of older adults among transplantation recipients, only a very strong predictor that is unique to older adults would sway population-average estimates.

Misperception of the risks and benefits of KT in older adults, combined with the complexity inherent in multi-morbidity and organ availability, may result in overly restrictive referral, listing, and transplantation practices in older adults. Predictors of adverse post-KT outcomes in older adults may be distinct from those in younger recipients. For example, a relative contraindication in younger patients, such as coronary artery disease, may unduly exclude a majority of older adults undergoing dialysis. In addition, a far greater proportion of older KT recipients accept extended criteria donor organs, or kidneys from older donors, resulting in a relative benefit of KT that varies according to age.^{5,11} With the ultimate goal of improving ATT in older adults by aiding the identification of older yet potentially excellent transplantation candidates, the primary objectives of the current study were to develop an accurate KT risk-prediction model specific to older adults and to use this model to estimate the number of excellent older candidates who lack ATT. Because live-donor KT (LDKT) recipients do not contribute to the organ shortage, the number of excellent older candidates who would have undergone LDKT if they had ATT also was estimated.

METHODS

Study Population and Data Sources

Using U.S. Renal Data System (USRDS) data from January 1, 1999, to December 31, 2006, all first-time KT recipients aged 65 and older at the time of transplantation were identified (N = 12,282). Because of the use of Medicare claims data to longitudinally ascertain comorbidity information beyond that directly reported to USRDS, the study population was limited to individuals with Medicare as the primary payer during the 3 months before transplantation (N = 9,327, 75.9%), as previously reported.⁷ The population was further limited to recipients who had at least one Medicare claim (either Part A or B, and including claims for dialysis) issued in the 6 months before transplantation (N = 6,988, 56.9%).

Comorbid conditions were derived from Medical Evidence Health Care Financing Administration Form 2728 and augmented with Medicare claims data in the 6 months before transplantation. Medicare claims corresponding to the 30 Elixhauser categories¹² were abstracted, and a comorbid condition was assigned to a recipient if found in at least one inpatient Medicare Part A claim or at least two Medicare Part B claims during the 6-month pretrans-plantation period.⁷ For a comorbid condition that was reported on Form 2728 and represented by an Elixhauser category, composite variables reflected the identification of the comorbidity in either data source. In addition, composite versions were constructed for complicated diabetes mellitus (defined as the presence of at least one of the following: Form 2728 diabetes mellitus as a primary or contributing cause, Form 2728 diabetes mellitus listed as the cause of ESRD, Form 2728 diabetes mellitus requiring insulin, or Medicare claims corresponding to the complicated diabetes mellitus Elixhauser category), cancer (defined as Medicare claims corresponding to Elixhauser solid tumor without metastasis or Form 2728 mention of malignant neoplasm), and coronary artery disease (defined according to any of the three Form 2728 categories ischemic heart disease, myocardial infarction, and atherosclerotic heart disease).

A candidate was considered to have ATT if he or she had ever been listed for or received KT. Mortality information was gleaned from USRDS and augmented using center-reported data from the United Network for Organ Sharing (UNOS) and linkage to the Social Security Death Master File, current through February 25, 2010.

Prediction Model Development and Validation

The prediction model for posttransplantation survival was developed within the specified study population. Using 3-year posttransplantation survival (irrespective of graft function) as the primary outcome, multivariate logistic regression models were fit on demographic and comorbidity data, constructing models in tandem using a step-down and step-up strategy based on minimization of the Akaike Information Criterion (AIC) for the purpose of parsimony. Donor characteristics were purposely omitted from the model building process because they are not available at the time of KT candidate referral. Because transplantation outcomes have improved over the years, year of transplantation was also included, as was pretransplantation time on dialysis. Functional form of continuous predictors was based on exploratory data analysis using Lowess-smoothed nonparametric regressions. Models were compared using area under the receiver operating characteristic curve (AUC). Model fit was tested using the Hosmer–Lemeshow statistic. For sensitivity analysis, the model building process was repeated using 1-, 2-, and 5-year posttransplantation survival as the outcome, as well as including and excluding race, time on dialysis, and year of transplantation.

The model was validated in several ways. First, the final model's AUC was recalculated using fivefold cross-validation, verifying that a small number of outliers did not drive the results. Second, it was confirmed that all significant interactions were identified by using

random forest methodology, a machine learning-based classification tree system that can be efficiently implemented on large data sets with large numbers of potential covariates. Generating 500 trees and using all continuous and dichotomous covariates as potential predictors, the relative estimates of importance of each predictor were evaluated, comparing percentage of cases correctly classified using random forests with that generated using logistic regression. Third, the calculated AUC was compared with a prediction model using only Form 2728 information and with the standard Scientific Registry of Transplant Recipients (SRTR) transplantation outcome model used to evaluate transplantation center performance.

Application and Inferences from Prediction Model

The pool of potential older KT candidates was drawn from older adults with incident ESRD who initiated renal replacement therapy between 1999 and 2006 (n = 304,902). Only those who used Medicare as their primary insurance payer (n = 244,879) and had at least one Medicare claim (including dialysis) during a 6-month coverage period after ESRD onset were included (n = 240,471). An additional 112,250 individuals with ESRD were excluded because of the presence of an absolute or relative contraindication to KT: human immunodeficiency virus (HIV), acquired immunodeficiency syndrome, recent acute myocardial infarction, recent tuberculosis, systemic lupus erythematosus, active malignancy, hepatitis B or C, cirrhosis, semivegetative state, antiphospholipid syndrome, dementia, paralysis, obesity, psychosis, recent transient ischemic attack, amputation, or poor functional status with inability to ambulate or transfer. The prediction model was applied to the selected population; individuals with ESRD falling into the upper quintile of predicted survival were labeled excellent candidates, and those with predicted survival probabilities in the second and third quintiles were labeled good candidates.

Development of a Model for LDKT

Given the dramatic shift in LDKT in older adults in recent years, the probability of undergoing LDKT was estimated using KT candidates aged 65 and older from 2005 until 2008. A logistic regression model of LDKT was fit on age, sex, race, cause of ESRD, and blood type. Coefficients from this model were applied to individuals undergoing incident dialysis without ATT who were predicted to be excellent and good KT candidates.

Statistical Analysis

Analyses were performed using Stata 11.0/MP (StataCorp, College Station, TX), except for the random forest generation, which was implemented using R 2.7.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Prediction Model Study Population

Between 1999 and 2006, 6,988 older adults (≥ 65) underwent KT and met eligibility for use in the transplantation outcomes prediction model. Overall, 79% of the transplanted older adults survived 3 years (Table 1). Survivors were more often female (38.1% vs 33.3%) and white (77.9% vs 76.2%), had a shorter dialysis vintage (mean 2.3 vs 2.8 years), and had fewer comorbid conditions (mean 1.9 vs 2.3). They were much more likely to have received an organ from a live donor (31.7% vs 18.4%) and less likely to have received an extended criteria donor organ (22.2% vs 29.7%).

Prediction Model Development

All comorbid conditions reported on Form 2728 and all Elixhauser comorbidities abstracted from claims were considered potential predictors and were tested using univariate logistic regression (Table 2). Thirteen comorbidities reported on Form 2728 were significantly associated with 3-year mortality: alcohol dependence, congestive heart failure, two categories of diabetes mellitus, drug dependence, cardiac arrhythmia, ischemic heart disease, myocardial infarction, pericarditis, chronic obstructive pulmonary disease (COPD), peripheral vascular disease, current smoking, and HIV. Sixteen Elixhauser comorbidities were also associated with 3-year mortality: congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disease, other neurological disorders, COPD, complicated and uncomplicated diabetes mellitus, renal failure, liver disease, peptic ulcer disease, coagulation disorders, fluid and electrolyte disorders, iron-deficiency anemia, and depression. The resulting empirically constructed optimal multivariate model included 15 of these comorbidities in addition to age, dialysis vintage, and sex. Transplantation year was also included to account for secular trends (Table 3). Although highly correlated with transplantation outcomes, donor characteristics were omitted from the model, because they are generally not available at the time of KT candidate evaluation or referral.

Prediction Model Performance

The Hosmer-Lemeshow test indicated appropriate goodness of fit ($P = .44$). Model prediction accuracy was evaluated using quintiles of predicted survival. The ratio of observed to expected 3-year survival in each quintile ranged from 0.99 to 1.01. The AUC revealed reasonable discrimination in the original cohort (0.66, 95% confidence interval (CI) = 0.65–0.68) and by cross-validation (0.68, 95% CI = 0.67–0.70). The prediction model outperformed one using comorbidities from Form 2728 only, as well as a recipient factor-only adaptation of the standard SRTR model of center-level performance ($P < .001$ for both comparisons of AUC). Multilevel interactions did not appear to influence post-KT prediction; the logistic-based model performed similarly to one using random forest machine learning.

Models developed using alternate outcomes (1-, 2-, and 5-year posttransplantation survival) were also similar in covariates and performance.

Categorizing KT Candidate Appropriateness Using the Prediction Model

Older KT recipients were stratified into quintiles of predicted post-KT survival. In the top quintile, predicted 3-year post-KT survival ranged from 87.6% to 96.6%; those with predictions in this range were considered excellent candidates. The second and third quintiles of older KT recipients had a predicted 3-year survival between 78.3% and 87.6%; these patients were considered good candidates. The bottom two quintiles had a predicted survival between 14.5% and 78.3%. Actual 3-year post-KT survival rates were 89.6%, 83.7%, and 69.3% in the excellent, good, and remaining transplantation recipients (Figure 1, $P < .001$).

Application of Prediction Model to Incident Dialysis Population

Of 128,850 older individuals undergoing dialysis without contraindications to KT (e.g., dementia and HIV), 11,756 and 43,291 were classified as excellent and good candidates, respectively. ATT for even the most-robust older adults with ESRD was poor; 76.3% of excellent candidates and 91.3% of good candidates were never placed on the waiting list or referred for LDKT (Table 4). Only 13.2% of excellent candidates and 4.2% of good candidates were eventually transplanted. If all excellent candidates lacking ATT had been

referred for KT and found living donors at the same rate as older adults who actually were referred for KT, 996 would be predicted to have undergone LDKT. For good candidates, another 3,979 would be predicted to have undergone LDKT.

DISCUSSION

This study presents a novel prediction model for KT outcomes specific to older adults, the age group with the largest proportion of individuals undergoing dialysis and the lowest rate of access to transplantation. By design, the model lacks donor characteristics and posttransplantation interventions, which although significant predictors of risk, are generally not known at the time of transplant referral. Using this methodology, it was possible to develop an accurate model of 3-year post-KT survival in older adults with good calibration and discrimination. More than 75% of older ESRD population predicted to have excellent outcomes after KT. Were these patients appropriately referred for transplantation, an estimated 11% would have undergone LDKT, resulting in better individual patient survival without exacerbating the national organ shortage.

Much has been published regarding the poor predictive performance of KT outcome models.^{13–15} There are several reasons for this. First, outcomes are somewhat dependent on choices made after the transplantation (and thereby not available at the time of the transplantation), such as choice of immunosuppressive regimen and patient adherence to medical therapy.¹⁶ Second, transplantation recipients represent a heterogeneous population with a wide range of ages and comorbid conditions.¹ Third, short-term mortality in transplantation recipients is relatively low, and the length of time between baseline predictors (especially if captured at the time of ESRD onset rather than transplantation) and death can result in low accuracy of prediction.

By using a population of older transplantation recipients and longitudinal claims data through the time of KT, two of these difficulties were addressed. Despite the exclusion of donor and posttransplantation characteristics, which are powerful predictors of mortality and graft survival,⁹ the model developed has discriminative power similar to that of commonly used clinical risk scores in other diseases, such as contrast nephropathy and coronary heart disease.^{17,18} The proposed model offers substantial improvement over the existing outcome studies, which are population based and thus miss subgroup-specific effects unique to older adults.^{7,9,10,15,16,19–21} In addition, Form 2728 comorbidities filed at the time of ESRD onset were augmented with claims comorbidities through the time of transplantation, capturing a more-recent and comprehensive list of comorbid conditions. As a result, the model's predictive accuracy was similar to that of existing models that rely on posttransplantation and donor characteristics;⁹ yet the model is more relevant to what would be used in clinical practice.

The empirical findings are biologically plausible and consistent with previous evidence. A previous study found congestive heart failure, cardiac arrhythmias, and other neurological disorders to be predictive of graft failure; hypertension was protective.⁷ Another study determined that diabetes mellitus and number of comorbid cardiovascular conditions were associated with posttransplantation coronary events (defined as fatal or nonfatal myocardial infarction, coronary revascularization, or sudden death).¹⁹ A third study found that congestive heart failure, diabetes mellitus, smoking history, valvular disorders, peripheral vascular disease, and cardiac arrhythmias were significantly associated with posttransplantation death.⁹ Finally, pretransplantation gastroesophageal reflux disease (GERD) was identified as a predictor of posttransplantation GERD, and posttransplantation GERD was identified as an independent predictor of graft loss and death.⁸ The current study

combined these comorbid conditions with age, dialysis vintage, and transplantation year and estimated the effects of these factors specifically in older adults.

There are some notable limitations to the methods used. The prediction model was developed on a highly specific study population: Medicare-primary KT recipients ages 65 and older. The requirement of Medicare-primary insurance is probably not overly restrictive given the older ESRD population; however, few older adults are referred for transplantation, and fewer still are actually transplanted.^{1,22} Comorbid conditions are typically fewer in transplanted individuals,²³ and in the model, they were identified according to claims data, which may have somewhat low sensitivity.^{24,25} The Elixhauser Comorbidity Index,¹² although used in previous studies of transplantation recipients,⁷ has not been validated for predicting mortality in transplantation populations; however, the model significantly improves upon a model using only Form 2728 information. In addition, when applied to the incident ESRD population, the model identified candidates with excellent 3-year survival despite low rates of KT, indicating good discrimination.

CONCLUSIONS

Transplantation remains the optimal mode of renal replacement therapy for many older adults. Access to transplantation is poor in this population, in part because of the difficulty in selecting appropriate candidates. The present study proposes a simple yet accurate subgroup-specific risk prediction model by which older transplantation candidates may be identified, demonstrating that thousands of older adults with ESRD lack access to a modality that is predicted to offer them excellent outcomes.

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Number at risk						
Excellent candidates:	1,349	1,252	1,168	626	258	49
Good candidates:	2,698	2,388	2,079	1,161	457	103
Remaining candidates:	2,693	2,080	1,647	888	317	54

Figure 1.

Older kidney transplantation recipients: proportion surviving, stratified according to quintile of predicted 3-year posttransplantation survival. Top quintile, excellent candidates; quintiles 2 and 3, good candidates; quintiles 4 and 5, remaining candidates.

Table 1

Characteristics of Older Transplant Recipients and Allografts, Stratified According to 3-Year Survival

Characteristic	Died within 3 Years of Transplantation, n = 1,451	Survived 3 Years After Transplantation, n = 5,537	P-value
Female, %	33.3	38.1	<.001
Age, mean	70.0	69.6	<.001
Race, %			
White	76.2	77.9	.03
Black	19.3	16.6	–
Other	4.5	5.5	–
Body mass index, kg/m ² , mean	27.2	26.9	.1
Years on dialysis before transplantation, mean	2.8	2.3	<.001
Total number of Form 2728 comorbidities, mean	2.3	1.9	<.001
Live donor kidney, %	18.4	31.7	<.001
Extended criteria donor kidney, %	29.7	22.2	<.001

Table 2**Baseline Comorbidities Associated with 3-Year Survival in Univariate Analysis**

Comorbid Condition	Incidence	3-Year Survival, %	Odds Ratio (95% Confidence Interval)	P-Value
Form 2728				
Congestive heart failure	16.3	71.7	0.61 (0.53–0.71)	<.001
Diabetes mellitus, on insulin	15.8	74.4	0.73 (0.62–0.85)	<.001
Diabetes mellitus (primary or contributing)	40.5	75.3	0.69 (0.61–0.78)	<.001
Drug dependence	0.1	25.0	0.09 (0.01–0.84)	.035
Cardiac arrhythmias	3.8	68.1	0.55 (0.42–0.73)	<.001
Ischemic heart disease	18.4	74.7	0.73 (0.63–0.84)	<.001
Myocardial infarction	5.2	71.9	0.67 (0.52–0.85)	<.001
Pericarditis	0.6	65.0	0.49 (0.26–0.95)	.03
Chronic pulmonary disease	2.9	66.3	0.51 (0.38–0.68)	<.001
Peripheral vascular disease	7.1	72.3	0.67 (0.54–0.82)	<.001
Current smoker	2.1	69.1	0.58 (0.40–0.84)	.004
Human immunodeficiency virus	1.2	68.5	0.56 (0.31–0.99)	.048
Medicare claims				
Congestive heart failure	13.2	68.2	0.51 (0.43–0.59)	<.001
Cardiac arrhythmias	12.4	69.0	0.53 (0.45–0.62)	<.001
Valvular disease	15.1	73.8	0.69 (0.60–0.81)	<.001
Pulmonary circulation disease	1.1	64.9	0.48 (0.30–0.77)	.002
Peripheral vascular disease	12.3	69.4	0.55 (0.47–0.64)	<.001
Other neurological disorder	1.2	58.3	0.36 (0.23–0.56)	<.001
Chronic pulmonary disease	8.6	70.6	0.60 (0.50–0.72)	<.001
Diabetes mellitus, uncomplicated	31.1	75.3	0.71 (0.63–0.81)	<.001
Diabetes mellitus, complicated	27.6	74.4	0.68 (0.60–0.77)	<.001
Renal failure	98.0	79.1	0.58 (0.36–0.95)	.03
Liver disease	4.2	68.2	0.54 (0.42–0.70)	<.001
Peptic ulcer disease	1.2	67.4	0.54 (0.34–0.85)	.008
Coagulation disorder	4.8	74.9	0.77 (0.60–0.99)	.042
Fluid and electrolyte disorder	27.3	76.9	0.83 (0.73–0.94)	.003
Iron-deficiency anemia	82.3	78.2	0.68 (0.58–0.81)	<.001
Depression	2.4	67.3	0.53 (0.38–0.74)	<.001
Combined categories				
Congestive heart failure	24.9	71.2	0.55 (0.48–0.62)	<.001
Cardiac arrhythmias	14.6	69.5	0.54 (0.46–0.63)	<.001
Diabetes mellitus, complicated	42.3	75.1	0.65 (0.58–0.73)	<.001
Chronic pulmonary disease	10.2	70.3	0.58 (0.49–0.69)	<.001
Coronary artery disease	19.9	74.2	0.70 (0.61–0.81)	<.001

Comorbid Condition	Incidence	3-Year Survival, %	Odds Ratio (95% Confidence Interval)	P-Value
Drug abuse	0.1	42.9	0.20 (0.04–0.88)	.033
Peripheral vascular disease	17.2	71.5	0.60 (0.52–0.69)	<.001

Table 3**Multivariate Model of 3-Year Transplant Survival in Older Adults**

Characteristic	Adjusted Odds Ratio (95% Confidence Interval)	P-Value
Age (per year, centered at 70)	0.96 (0.94–0.97)	<.001
Dialysis time before 3 years (spline) *	0.78 (0.73–0.84)	<.001
Dialysis time after 3 years (spline) *	0.93 (0.88–0.99)	.03
Female	1.12 (0.98–1.27)	.09
Congestive heart failure	0.74 (0.65–0.85)	<.001
Cardiac arrhythmia	0.64 (0.55–0.75)	<.001
Complicated diabetes mellitus	0.71 (0.62–0.80)	<.001
Chronic pulmonary disease	0.71 (0.59–0.85)	<.001
Coronary artery disease	0.84 (0.72–0.98)	.03
Hypertension	1.24 (1.03–1.51)	.02
Drug dependence	0.16 (0.03–0.78)	.02
Peripheral vascular disease	0.74 (0.63–0.86)	<.001
Polycystic kidney disease	1.59 (1.20–2.11)	.001
Deficiency anemia	0.85 (0.71–1.02)	.08
Other neurological disorder	0.52 (0.32–0.83)	.007
Liver disease	0.61 (0.46–0.80)	<.001
Depression	0.66 (0.46–0.95)	.02
Peptic ulcer disease	0.66 (0.41–1.06)	.08
Current smoking	0.69 (0.47–1.02)	.06
Year of transplantation after 1999	1.05 (1.01–1.08)	.007

* Dialysis time spline term has knot at 3 years. First term set as time on dialysis if less than 3 years and 3 if longer than 3 years. Second term set as 0 if time on dialysis less than 3 years and time on dialysis minus 3 if longer than 3 years.

Table 4

Characteristics of Kidney Transplant-Eligible Older Dialysis Patients, Stratified by 3-Year Predicted Survival

Characteristic	Excellent Candidates* (Predicted 3-Year Survival > 87.6%) n = 11,756 (9.1%)	Good Candidates* (Predicted 3-Year Survival 78.3–87.6%) n = 43,291 (33.6%)	Remaining Candidates (Predicted 3-Year Survival < 78.3%) n = 72,913 (56.6%)
Female, %	56.7	50.6	45.4
Age, mean	69.5	73.0	77.3
Race, %			
White	64.6	66.8	77.9
Black	29.1	26.8	17.6
Other	6.3	6.4	4.5
Form 2728 comorbidities, n	1.7	2.5	3.5
With access, %	23.7	8.7	2.5
Transplanted, %	13.2	4.2	1.1

* Excellent candidates represent the top quintile of posttransplantation survival among older adults; good candidates represent quintiles 2 and 3.