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Functional Status, Time to Transplantation, and Survival Benefit of Kidney Transplantation Among Wait-Listed Candidates

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Background: In the context of an aging end-stage renal disease population with multiple comorbid conditions, transplantation professionals face challenges in evaluating the global health of patients awaiting kidney transplantation. Functional status might be useful for identifying which patients will derive a survival benefit from transplantation versus dialysis.

Study Design: Retrospective cohort study of wait-listed patients using data for functional status from a national dialysis provider linked to United Network for Organ Sharing registry data.

Setting & Participants: Adult kidney transplantation candidates added to the waiting list between 2000 and 2006.

Predictor: Physical Functioning scale of the Medical Outcomes Study 36-Item Short Form Health Survey, analyzed as a time-varying covariate.

Outcomes: Kidney transplantation; survival benefit of transplantation versus remaining wait-listed.

Measurements: We used multivariable Cox regression to assess the association between physical function with study outcomes. In survival benefit analyses, transplantation status was modeled as a time-varying covariate.

Results: The cohort comprised 19,242 kidney transplantation candidates (median age, 51 years; 36% black race) receiving maintenance dialysis. Candidates in the lowest baseline Physical Functioning score quartile were more likely to be inactivated (adjusted HR vs highest quartile, 1.30; 95% CI, 1.21-1.39) and less likely to undergo transplantation (adjusted HR vs highest quartile, 0.64; 95% CI, 0.61-0.68). After transplantation, worse Physical Functioning score was associated with shorter 3-year survival (84% vs 92% for the lowest vs highest function quartiles). However, compared to dialysis, transplantation was associated with a statistically significant survival benefit by 9 months for patients in every function quartile.

Limitations: Functional status is self-reported.

Conclusions: Even patients with low function appear to live longer with kidney transplantation versus dialysis. For wait-listed patients, global health measures such as functional status may be more useful in counseling patients about the probability of transplantation than in identifying who will derive a survival benefit from it.
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INDEX WORDS: End-stage renal disease (ESRD); kidney transplantation; dialysis; renal replacement therapy modality; survival benefit; transplant waiting list; physical function; functional status; 36-Item Short Form Health Survey (SF-36); post-transplantation complications; kidney transplant allocation.

Over the past 2 decades, the population of kidney transplantation candidates in the United States has grown older. While the waiting list for kidney transplantation increased from 30,010 candidates in 1997 to more than 101,000 candidates in 2014, the proportion of candidates 65 years or older increased from 7% to >21%.[1] Additionally, waiting times have lengthened, requiring candidates to receive

several years of maintenance dialysis therapy. Kidney transplantation candidates commonly have multiple comorbid conditions associated with aging and end-stage renal disease (ESRD), including cardiovascular disease, diabetes, and poor nutrition.[2] The relative scarcity of organs and heightened scrutiny of center-specific outcomes[3] have led transplantation professionals to take a strong interest in summary measures of global health that may predict important transplantation outcomes.[4,5] A measure of global health such as functional status might be useful to

select appropriate patients for placement onto the transplant wait-list, counsel patients about the risk of complications, direct resources such as physical therapy to vulnerable patients, or guide centers about which wait-listed patients should be reevaluated frequently, inactivated, or delisted.

Several studies have revealed that global health measures are independent predictors of posttransplantation complications. Using national cohorts, Kutner et al[6] and Reese et al[7] demonstrated that functional status, measured using the Physical Functioning domain of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36), was strongly associated with posttransplantation survival. The SF-36 instrument is usually self-administered and has been implemented in diverse populations, including dialysis patients and individuals without kidney disease.[8-10] Frailty, a syndrome of vulnerability to medical stressors, is also common among kidney transplant recipients and was reported to be associated with delayed graft function, early rehospitalization, and mortality in a single-center cohort.[11-14]

However, little information is available about the utility of measures of global health to predict outcomes for patients awaiting transplantation. While wait-listed, many candidates experience infections, vascular complications, or other illnesses that lead to inactive status, permanent removal from the wait-list, or death. More than a third of the kidney transplant list is inactive and during the past decade, this proportion has grown rapidly. Inactivity is associated with mortality.[15-17] An analysis of Organ Procurement and Transplantation Network (OPTN) data revealed that fewer than half the kidney transplantation candidates older than 60 years ever receive a transplant.[18] These findings suggest that global health measures such as functional status may worsen for transplantation candidates receiving multiple years of dialysis therapy.

The aims of this study were to determine whether functional status is independently associated with the rate of kidney transplantation and whether functional status modifies the survival benefit from transplantation in a national cohort of wait-listed candidates. A secondary aim was to determine whether poorer physical function is associated with inactivation on the wait-list.

METHODS

Study Overview

We performed a retrospective cohort study of US kidney transplantation candidates using a linked data set from the United Network for Organ Sharing (UNOS)/OPTN and Fresenius Medical Care, a provider of maintenance dialysis services.

The OPTN data system includes data for all wait-listed candidates, transplant recipients, and donors in the United States, submitted by OPTN members, and has been described elsewhere.[19] The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN contractor. The University of Pennsylvania Institutional Review Board approved the study.

Inclusion and Exclusion Criteria

Adult ($\geq$18 years at wait-listing) patients who had received 12 or more consecutive months of dialysis therapy provided by Fresenius Medical Care were included if they were added to the kidney transplant wait-list from June 1, 2000, through May 31, 2006. Patients were required to have completed at least one SF-36 form on or after June 1, 2000. We excluded individuals who were never active on the wait-list or were wait-listed for multiorgan transplants other than kidney-pancreas.[7] The observation period was June 1, 2000, until September 3, 2010.

Exposure Assessment

The primary exposure was the Physical Functioning subscale of the SF-36. The protocol at Fresenius dialysis centers was to administer the SF-36 instrument to patients each year as part of routine care. The Physical Functioning scale consists of 10 questions that assess difficulties with common physical activities requiring varying levels of exertion, such as bathing and dressing or walking 100 yards.[20] Physical Functioning scores were transformed into a scale from 0 to 100, by convention.[21] To make results clinically intuitive, we empirically divided the study population into quartiles defined by baseline Physical Functioning scores. We selected the Physical Functioning score collected closest in time to the wait-listing date for the baseline value.

Outcomes Assessment

The primary outcomes were: (1) time to kidney transplantation, and (2) the net survival benefit of kidney transplantation versus remaining wait-listed across strata of Physical Functioning scores. To avoid immortal time bias, follow-up time started at each patient's index date, which was the date of wait-list registration or the date of Physical Functioning measurement, whichever was later (range, June 1, 2000, until November 22, 2008). For the transplantation outcome, we assumed complete follow-up from wait-listing until transplantation, death, or the end of study (September 3, 2010).

Death was ascertained through center reports and linkage to the Social Security Death Master file. For mortality, we assumed complete follow-up from the index date until death or end of study. For the outcome of inactivation, patients were followed up until transplantation, death, inactivation, delisting, or end of study.

Covariate Assessment

We obtained data for the following covariates submitted to the OPTN by transplantation centers at wait-listing: age ($<$35, 35-$<$45, 45-$<$55, 55-$<$65, and $\geq$65 years), sex (male/female), race (white, black, Hispanic, Asian, and other), primary insurance type (private vs Medicare vs other), diabetes (yes/no), prior kidney transplant (yes/no), peripheral vascular disease (yes/no), glomerulonephritis as cause of ESRD (yes/no), polycystic disease as cause of ESRD (yes/no), congenital or reflux disease as cause of ESRD (yes/no), hypertension as cause of ESRD (yes/no), and blood type (AB, A, B, and O). We also estimated waiting time to kidney transplantation in the donor service area in which the candidate was listed. Because $<$50% of candidates undergo transplantation in some areas, we calculated time until 25% of candidates underwent transplantation during 2000 to 2010 (using data for all adult wait-listed candidates, not just this cohort) and used these times to categorize donor service areas into quartiles. We obtained Fresenius Medical Care data for body mass index (kg/m^2), time since dialysis therapy initiation (years), and dialysis modality (hemodialysis vs peritoneal dialysis), measured at each patient's index date.

Statistical Analysis

We conducted analyses using Stata (version 13.0; StataCorp LP) with 2-sided $P < 0.05$ as the criterion for statistical