Functional status and survival after kidney transplantation[1–,12]

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Abstract

Background—Older patients constitute a growing proportion of U.S. kidney transplant recipients and often have a high burden of comorbidities. A summary measure of health such as functional status might enable transplant professionals to better evaluate and counsel these patients about their prognosis after transplant.

Methods—We linked UNOS registry data about post-transplant survival with pre-transplant functional status data (physical function [PF] scale of the Medical Outcomes Study Short Form-36) among individuals undergoing kidney transplant from 6/1/2000 – 5/31/2006. We examined the relationship between survival and functional status with multivariable Cox regression, adjusted for age. Using logistic regression models for three-year survival, we also estimated the reduction in deaths in the hypothetical scenario that recipients with poor functional status in this cohort experienced modest improvements in function.

Results—The cohort comprised 10,875 kidney transplant recipients (KTRs) with a mean age of 50 years; 14% were ≥65. Differences in three-year mortality between highest and lowest PF groups ranged from 3% among recipients <35 years to 14% among recipients ≥65 years. In multivariable Cox regression, worse PF was associated with higher mortality (HR 1.66 for lowest versus highest PF quartiles; p<0.001). Interactions between PF and age were non-significant. We estimated that 11% fewer deaths would occur if KTRs with the lowest functional status experienced modest improvements in function.

Conclusions—Across a wide age range, functional status was an independent predictor of post-transplant survival. Functional status assessment may be a useful tool with which to counsel patients about post-transplant outcomes.

Keywords

Older age; functional status; kidney transplant; survival

Background

The kidney transplant population is aging rapidly.(1) During the decade from 1999 – 2008, the proportion of incident kidney transplant recipients (KTRs) in the U.S. who are elderly (>65 years) more than doubled from 7% to 16%.(2) Additionally, waiting times have lengthened and transplant candidates commonly carry a heavy burden of comorbidities that worsen with chronic dialysis.(3) Transplant professionals therefore face challenges in evaluating a population of older and increasingly complicated patients about kidney transplantation.

Functional status has potential advantages as a tool to evaluate and counsel patients about transplantation. Adequate functional status depends on physical fitness, sensory function, and the ability to negotiate the external environment.(4) Functional status usually worsens with advanced age, particularly among elderly individuals with chronic disease.(5)

Functional status can capture the cumulative impact of chronic health conditions that have a high prevalence in the end-stage renal disease (ESRD) population, such as diabetes, cardiovascular disease, and hepatitis C. Independent of age and comorbidities, ESRD is associated with loss of functional status as well as poor physical performance and the syndrome of frailty.(6–8) This loss of function may be driven by the systemic inflammation, cachexia, and sarcopenia associated with the uremic state.(9–12)

Limited high-quality data are available about functional status among KTRs, particularly elderly recipients.(13–15) Given the extensive medical work-up required to be accepted for transplantation,(16) it is unclear whether substantial variation in function exists across transplant candidates. It is also unknown whether functional status assessments while patients are on the transplant waiting list are associated with survival after transplant for different age groups. Therefore, the aims of this study were to determine 1) whether a self-reported measure of functional status predicts survival after kidney transplantation, and 2) whether this predictive ability differs by age at transplantation.

Results

Study Cohort

We identified 150,843 adults who had received ≥12 consecutive months of hemodialysis or peritoneal dialysis through Fresenius Medical Care (FMC), a provider of chronic dialysis services. Among these, 114,133 (76%) had completed at least one Medical Outcomes Study Short Form-36 questionnaire (SF-36). Using patient identifiers, we linked this file of dialysis patients to a file from the United Network for Organ Sharing (UNOS) and identified 10,994 individuals who had undergone kidney transplantation after SF-36 measurement. 119 (1%) had missing PF responses, leaving 10,875 KTRs at 212 transplant centers.

The cohort had a wide age range and substantial racial/ethnic diversity. We compared our cohort to all adults on dialysis who underwent kidney transplantation in the U.S. during the same period (n=113,675). Compared to KTRs outside the cohort, this cohort had a similar mean age (50 years versus 49 years outside the cohort), a similar proportion of elderly (≥65 years) recipients (14% versus 13% outside the cohort), and similar proportions of male (63% versus 61% outside the cohort), and diabetic patients (36% in both groups). The study cohort had a higher proportion of Black (34% versus 26% outside the cohort) and Hispanic participants (17% versus 14% outside the cohort).

Physical Function Scores and Subject Characteristics

We empirically divided physical function (PF) subscores of the SF-36 into quartiles. The median PF score was 60 (interquartile range [IQR] 40, 85). The median interval between SF-36 completion and transplantation was 228 days (IQR 113, 563) and did not differ between PF quartiles (p=0.58). As in Figure 1, PF scores were highest among patients <45 years and showed a general trend of decline among older age groups.

Table 1 presents subject characteristics. Compared to recipients in the lowest PF quartile, recipients in the highest quartile were younger (median 47 versus 55 years), more likely to be male (69% versus 57%), and less likely to be CMV positive (60% versus 67%) or have diabetes (26% versus 49%).

Overall Mortality

2,089 KTRs (19%) died. Median follow-up time after transplant was 1,631 days (IQR 997, 2218). Figure 2 shows post-transplant survival. Recipients with the highest function had the best survival, and recipients with the lowest function had the worst survival. Survival curves

for KTRs in the second and third PF quartiles did not separate consistently until 5 years after transplantation.

Stratified analyses showed that lowest versus highest PF quartile was significantly associated with worse survival for every age group (p<0.01) except KTRs <35 years (p=0.10). A global test for interaction between age and PF quartiles, however, was not significant.

As in Table 3, multivariable Cox regression confirmed that lower functional status was independently associated with higher mortality (hazard ratio [HR] 1.66 for lowest versus highest PF quartiles; 95% CI 1.45, 1.89; p<0.001). SDC Table 1 shows the full model.

Three Year Mortality

Among recipients with at least three years of follow-up (n=9,307), 12% of the KTRs died (1,089). Figure 3 shows the absolute difference in risk between the highest and lowest PF quartiles, which ranged from 3% among recipients <35 years, to 14% among recipients over 65 years. Notably, younger recipients with poor function had lower survival than recipients with good functional status in the adjacent older age category.

We fit a multivariable logistic regression model for the outcome of three-year mortality. The logistic model predicted 1,065 deaths by three years, similar to the number observed. To estimate the deaths that would occur if KTRs in this cohort experienced modest improvements in function, we increased the PF quartile of recipients in the lower half of functional status by one quartile. With this new PF distribution, the model predicted 946 deaths, an 11% decrease in mortality.

Secondary analyses of mortality

In multivariable logistic regression models, KTRs in the highest PF quartile experienced lower death rates than KTRs in the lowest quartile at six months (HR 1.70; p=0.001) and one year (HR 1.74; p<0.001) after transplant.

Delayed graft function and allograft failure

A total of 2,604 (24%) KTRs experienced delayed graft function, while 2,975 (27%) experienced allograft failure. In multivariable logistic regression, only KTRs in the lowest PF quartile had a higher odds of delayed graft function (OR 1.18; CI 1.04, 1.35; p=0.01).

In multivariable Cox regression, the lowest PF quartile was associated with a higher rate of allograft failure (HR 1.35; CI 1.21, 1.50; p<0.001). The association of near-lowest PF quartile with allograft failure did not reach statistical significance (HR 1.11; CI 1.00, 1.23; p=0.057).

Discussion

In a diverse cohort of KTRs across 212 centers, pre-transplant functional status was an independent predictor of post-transplant survival. Differences in three-year mortality across PF quartiles were substantial in all age strata except individuals <35 years. These findings provide evidence that measures of function could prove useful during the evaluation of ESRD patients considering kidney transplantation.

Wide variation in functional status was evident. Despite the multidisciplinary evaluation required for kidney transplantation, a process that commonly includes cardiovascular testing and age-appropriate cancer screening(17), the cohort showed variation in PF scores within all age strata. As shown in Figure 1, PF scores were lower in the older age groups but

appeared to level off after age 55 years. Given that function usually decreases with advancing age, and certainly after age 55, this finding could be explained if older patients with worse function were not selected by centers for wait-listing. This finding could also be explained by the self-reported nature of the PF score.(18) Studies in non-transplant populations suggest that after adjustment for comorbidities, older individuals rate their health as better than younger individuals.(5, 19) If the older individuals in this cohort rated their health more highly than younger patients, this would lead our models to underestimate the magnitude of the hazard associated with worse functional status. Thus, it is possible that if the PF scale were compared to observed physical performance, a physical performance measure might show a more consistent pattern of decline with older age than functional status would.

Although functional status had a strong association with mortality in patients across a wide age spectrum, a functional measure may be particularly useful in evaluating older candidates who have the highest rate of death after transplant. As shown in Figure 3, the oldest patients in our cohort had the largest risk difference between low and high PF quartiles at three years. Notably, despite multiple studies showing that the elderly derive a survival benefit from kidney transplant compared to dialysis, elderly patients with ESRD have much lower access to kidney transplantation.(20–22) Alexander et al. studied 7,125 incident dialysis patients and reported that older patients were far less likely to be referred to transplant centers, to complete evaluation, and to receive a kidney transplant.(23) More recently, using United States Renal Data Systems data that allowed limited adjustment for comorbidities, Kucirka et al. reported that older patients were less likely to receive information about kidney transplant options.(24) This diminished transplant access extends to live donor kidney transplant (LDKT). A single center study by Weng et al. showed that older patients were less likely to attract potential donors and undergo LDKT, such that transplant candidates >60 years had an odds ratio of 0.21 for LDKT compared to candidates <40 years. (20) These troubling findings are not easily explained. It is possible that providers, using the "eyeball test" in a clinical evaluation, overestimate the frailty or comorbidities of older patients.(25, 26) Another explanation is that older patients are less willing to accept the short-term risks of peri-operative events and infection with transplant in order to enjoy the long-term benefits of quality of life and survival. In any case, the use of a validated functional status measure may enable providers to assess the global health of an elderly transplant candidate in a more standardized and just way than relying solely on age or a subjective evaluation of physical fitness.

These results complement a growing literature about the relationships of functional status, frailty, and physical performance to transplant outcomes. Our finding that functional status is an independent predictor of post-transplant survival confirms the work of Kutner et al. in a larger, more contemporary cohort that permitted examination of function across multiple age strata.(13) The distribution of PF scores in our cohort was similar to the distribution in the Kutner study. In a single-center study, Garonzik-Wang reported that 24% of KTRs met frailty criteria when evaluated immediately prior to transplant surgery; frailty predicted a higher odds of delayed graft function.(27) Although the relationship of pre-transplant physical performance to survival after kidney transplant has not been reported, Hartmann et al. examined physical performance among 26 renal transplant candidates over 60 years of age using the Short Physical Performance Battery (SPPB), which comprises observed tests of walking speed, standing balance, and chair raises. SPPB scores among these renal transplant candidates were lower than among older individuals with heart failure and chronic obstructive pulmonary disease.(7) Taken together, these findings suggest that KTRs commonly have poor functional status or other evidence of physical deterioration, and that assessing function may help transplant professionals characterize the survival opportunities of these patients. Additionally, it is possible that assessments of functional status could

identify wait-listed patients who would benefit from physical therapy or other interventions with the goal of helping these individuals survive to transplant.

The SF-36 and its method of collection in this study offered advantages. The SF-36 has been validated in elderly patients and dialysis patients.(28–30) Individuals in the cohort completed the SF-36 as part of routine data collection in dialysis units. Thus, we have no basis for concern that responses would be affected by patient expectations about transplant candidacy. Because dialysis providers are required by regulation to collect quality of life data (encompassing questions about function), nephrologists already have access to information about functional status for many patients who they might consider for transplant referral or other services.(31) In contrast to binary clinical attributes such as diabetes or hepatitis C (HCV), a continuous measure such as the PF scale may have advantages in that it classifies patients over a spectrum of severity. Our results reveal that differences in functional status as measured by the SF-36 are associated with a large and clinically meaningful difference in mortality. We estimated that 11% fewer deaths would occur in the scenario that the KTRs in our cohort with the lowest functional status experienced modest improvements in function.

These findings should be evaluated in the context of the study's limitations. The PF scale is a subjective, self-reported measure. An observed measure of function, such as gait speed evaluation or the full SPPB, might better distinguish differences in global health between subgroups, such as those defined by age. Also, functional status can change over time, and the utility of functional status as a tool may depend on regular assessments of it. The study population was also limited to individuals receiving chronic dialysis. Given known associations between ESRD, poor nutrition, and loss of muscle,(9, 10, 32, 33) functional status in our population might be worse than among individuals undergoing pre-emptive transplantation. In this retrospective study, residual confounding is also plausible. Finally, UNOS registry data lack detailed information about important comorbidities such as cardiovascular disease and about the severity of known comorbidities such as diabetes.

Conclusion

Independent of age, pre-transplant functional status predicted mortality after kidney transplantation. Future studies should prospectively examine a range of related measures including functional status, frailty, and physical performance to determine their utility in predicting transplant outcomes. Functional status assessment might also identify individuals on the waiting list who would benefit from physical therapy or more frequent evaluation by the transplant center.

Methods

We performed a retrospective cohort study of adult (age ≥18 years) KTRs in the United States using a linked dataset from the UNOS/Organ Procurement and Transplantation Network and the Fresenius Medical Care Corporation, a provider of chronic dialysis services. The primary outcome was patient survival after transplantation and the primary exposure was the PF subscale of the SF-36. The study was approved by the University of Pennsylvania Institutional Review Board.

Participants had received >12 months of chronic dialysis through Fresenius, were wait-listed for kidney transplantation from 6/1/2000 – 5/31/2006, and had completed the SF-36 at least once before transplantation. Patients wait-listed for multi-organ transplants other than kidney-pancreas, and patients without responses to all 10 PF scale questions were excluded.

FMC administered the SF-36 to patients approximately every year. The PF scale is generated from 10 items that address activities of daily living and more strenuous tasks such as carrying groceries and walking a mile.(18) The PF score collected closest to the transplantation date was used and transformed into a scale from 10 – 100.(34) We empirically divided the population into quartiles of PF scores. The rationale was that these four ordered categories would be more clinically intuitive than a PF variable transformed to a normal distribution and that these four categories would be amenable to graphical representation.

The UNOS dataset provided detailed information about every KTR.(35) Death was ascertained through center reports and linkage to the Social Security Death Master File (SSDMF). Because of the high level of death ascertainment, we performed analyses assuming complete follow-up from transplant until the date of merger of the UNOS file with the SSDMF.

Statistical analysis

We conducted analyses using Stata (version 11.0, Stata Corporation, College Station, TX). We used the t-test to compare PF scores between patients with and without diabetes. We used ANOVA to compare the means of normally distributed variables and Chi-square tests to compare categorical variables across PF quartiles.

We fit multivariable Cox regression models for mortality. Our selection of independent variables was guided by prior studies.(36–38) Recipient variables included age (<35, ≥ 35 & <45, ≥ 45 & <55, ≥ 55 & <65, and ≥ 65 years), sex, race, prior organ transplant, dialysis vintage (<3, ≥ 3 and <5, ≥ 5 years), high peak panel reactive antibody (PRA, defined by UNOS convention as $\geq 80\%$ versus $<80\%$)(39), cytomegalovirus (CMV) serostatus, glomerulonephritis, polycystic kidney disease, congenital/reflux renal disease, hypertensive renal disease, diabetes, and HCV seropositivity. Donor variables included age, sex, race (black or non-black), CMV, and donor type (live, deceased, expanded criteria deceased donor).(40) Allograft variables included human leukocyte antigen mismatch (zero or nonzero). We performed stratified analyses and tests for interaction between PF quartile and age.(39) We examined Schoenfeld residuals and log-log plots to confirm the proportional hazards assumption.

Outcome of three-year mortality and estimation of mortality reduction in a hypothetical scenario that transplant recipients experienced improvements in function

To express our results in a transparent way to clinicians and policymakers, we examined three-year survival. Pre-transplant characteristics would be expected to influence mortality within this time-frame, and three-year survival is a metric of quality for transplant institutions.(41) To have sufficient follow-up, this analysis was restricted to recipients transplanted before the year 2008 (n=9,307, 86% of total). We fit a multivariable logistic model for the outcome of three-year survival, using the same covariates used in the Cox model for mortality. The hypothesis of good fit using the Hosmer-Lemeshow test was not rejected (p=0.91).

To estimate the expected deaths if kidney allografts were distributed to a hypothetical population that had experienced improvements in function, we increased the PF quartile of recipients in the lower half of functional status by one quartile. Specifically, we raised the PF quartile for those in the third quartile to the second quartile, and we raised those in the fourth quartile to the third, leaving other recipient attributes unchanged. We applied our logistic regression model to this hypothetical population and summed the predicted probabilities of death by three years.

Secondary outcomes

We fit multivariable logistic regression models for the outcomes of delayed graft function (defined as dialysis in the first week after kidney transplantation), as well as six month and one year survival. We also fit a multivariable Cox regression model for all-cause allograft failure. These models included the same covariates used in the Cox model for mortality.

Missing Data

A minority of recipients had missing data on variables relevant to the primary analysis, including PRA (n=588, 5%). In primary analyses, for categorical values with >1% missing data, we created a separate category for missingness. In addition, we performed sensitivity analyses in which extreme values for missing data were assigned to individuals with missing data. The associations between PF quartile and the outcomes were unchanged and not shown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Abbreviations

AUC	Area-Under-the-Curve
CMV	Cytomegalovirus
ESRD	End-Stage Renal Disease
FMC	Fresenius Medical Care
HCV	Hepatitis C Virus
KTR	Kidney Transplant Recipient
PF	Physical Function
SSDMF	Social Security Death Master File
UNOS	United Network for Organ Sharing

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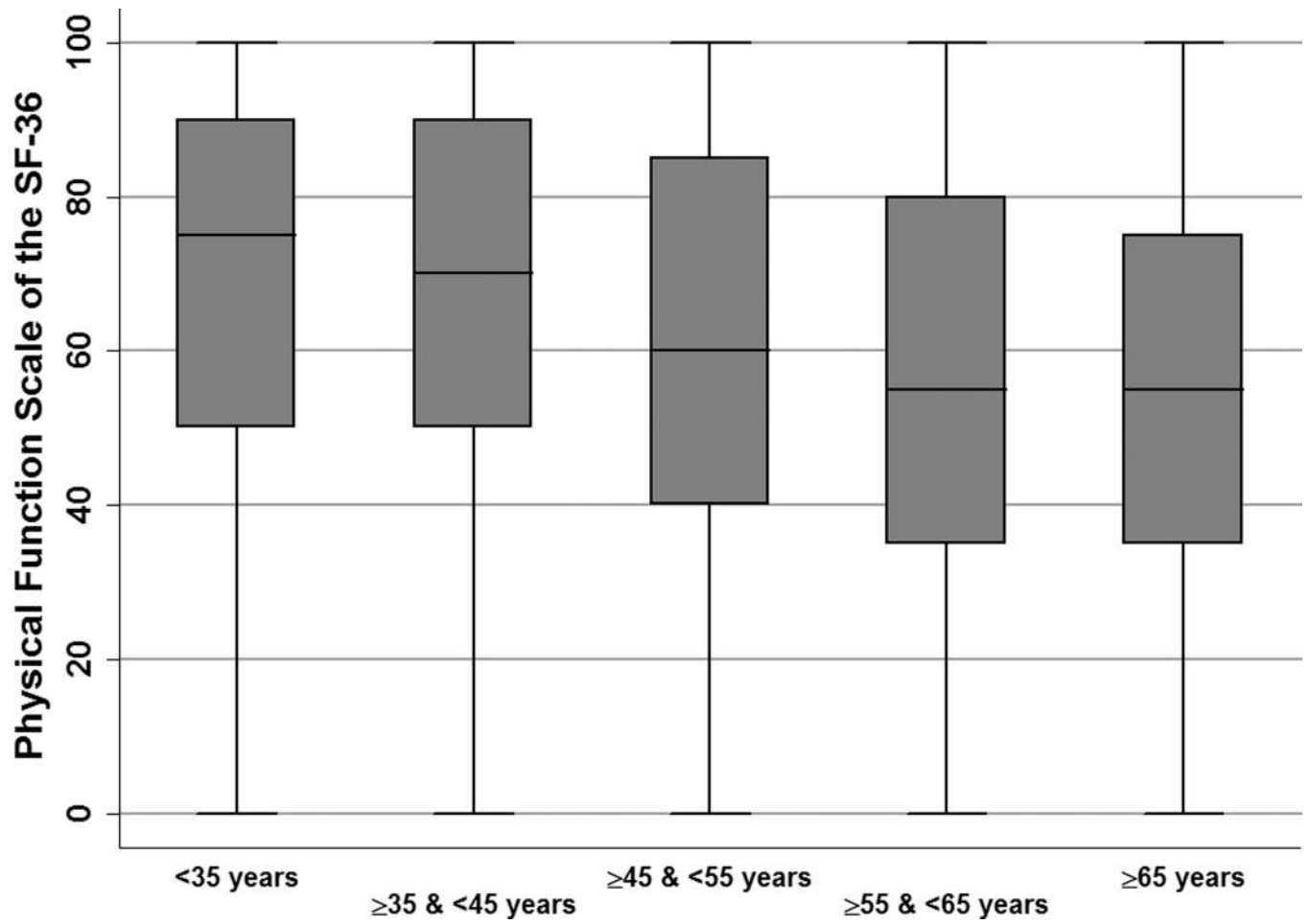
Figure 1.
Distribution of Physical Function Scores, by Recipient Age
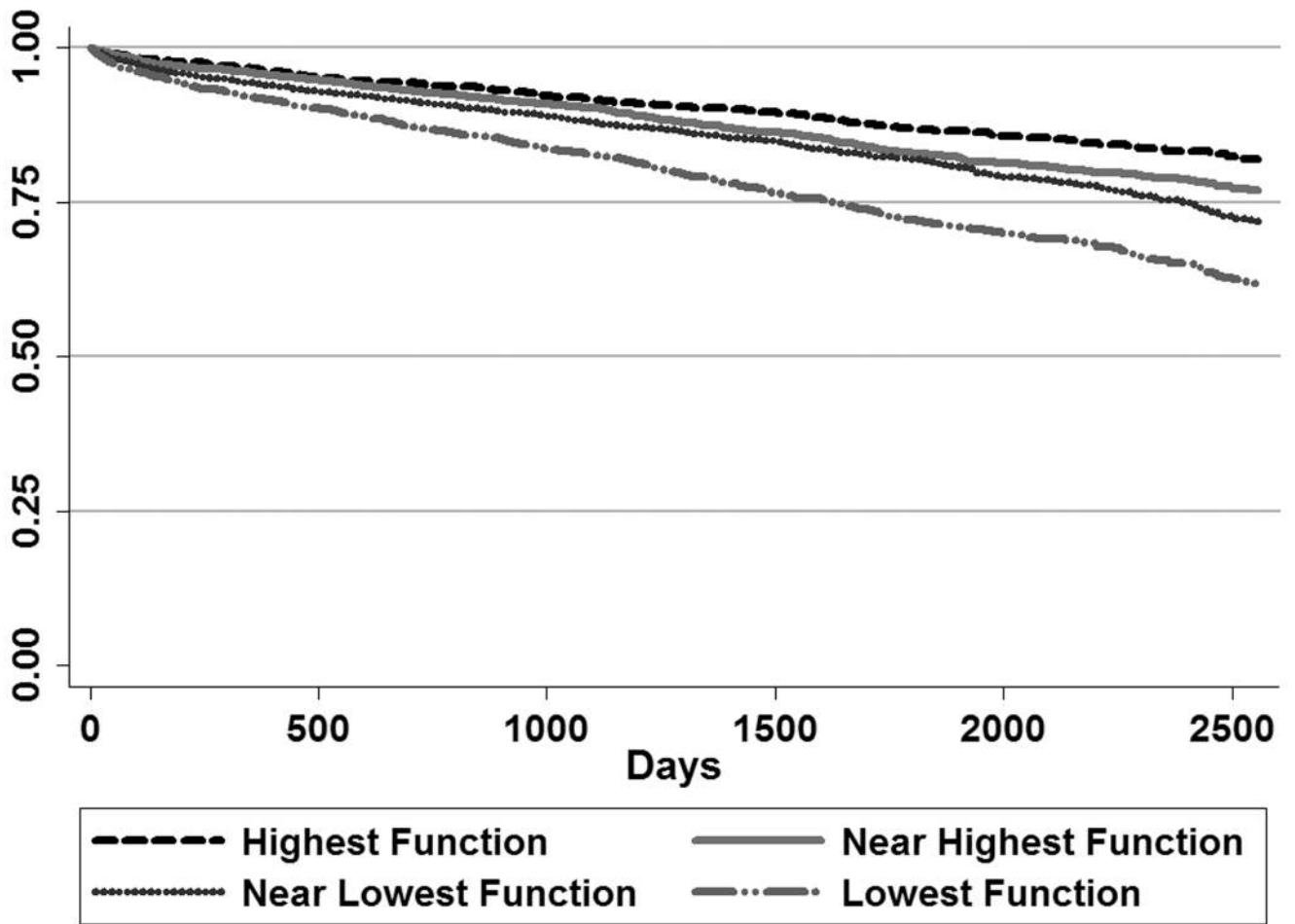
Figure 2.
Survival after Kidney Transplantation, by Quartile of Physical Function Scale of the SF-36
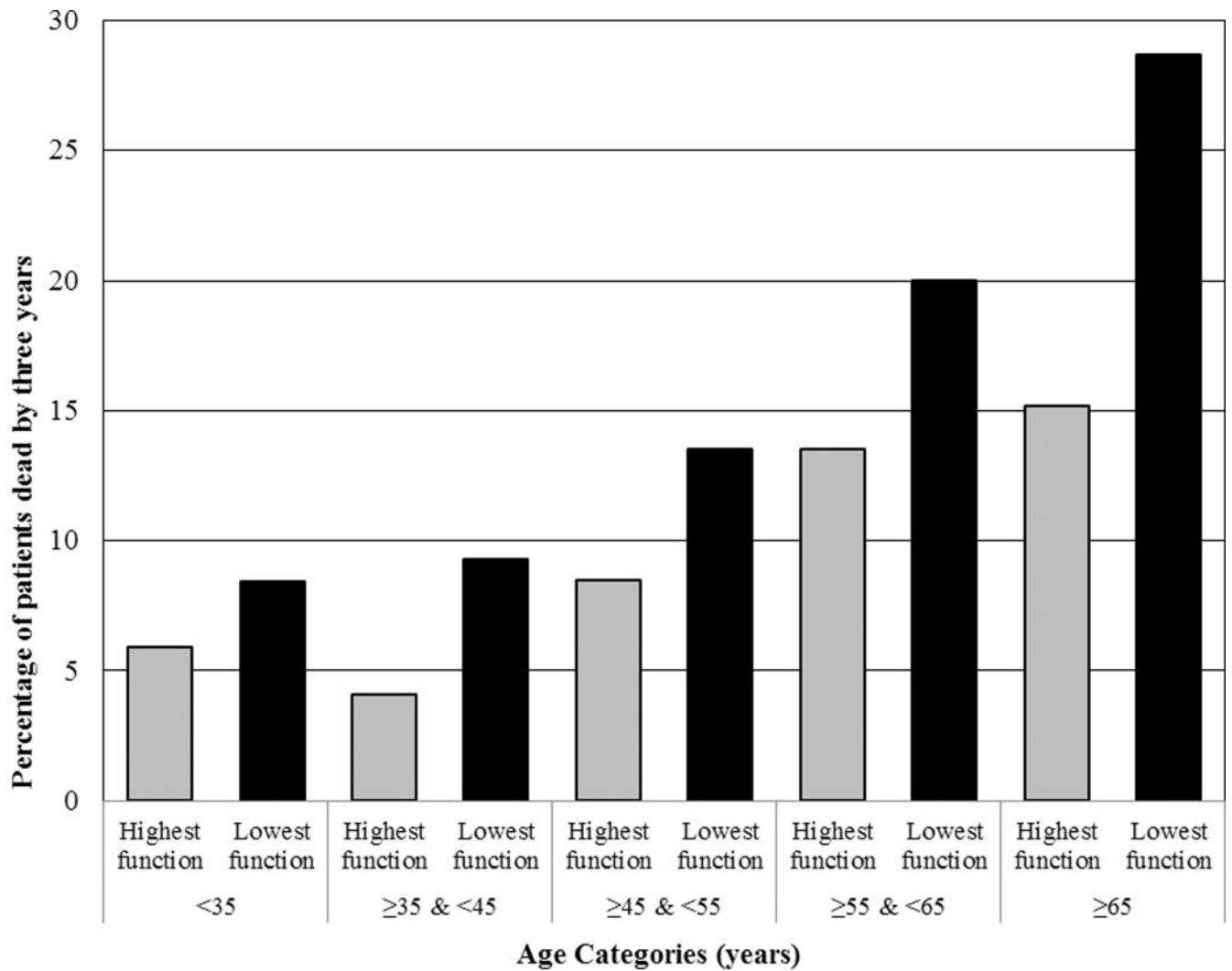
*Analysis restricted to recipients with at least three years of follow-up by final study date
P<0.01 for comparisons in each age stratum except those <35 years (p=0.10)

Figure 3.
Three-Year Mortality after Kidney Transplantation Contrasted between Recipients in
Highest versus Lowest Physical Function Quartiles, by Recipient Age Strata

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Table 1

Demographic and Clinical Characteristics of Kidney Transplant Recipients and Donors, by Recipient Physical Function Quartile

RECIPIENT CHARACTERISTICS	Highest Physical Function (n=2,843)	Near-highest Physical Function (n=2,543)	Near-lowest Physical Function (n=2,957)	Lowest Physical Function (n=2,532)	p-value
MEAN AGE (standard deviation)	47 (13)	51 (13)	52 (13)	55 (12)	<0.001
<35 years (%)	300 (11)	170 (7)	183 (6)	92 (4)	<0.001
≥35 & <45 years (%)	957 (34)	665 (26)	714 (24)	460 (18)	
≥45 & <55 years (%)	736 (26)	681 (27)	832 (28)	686 (27)	
≥55 & <65 years (%)	558 (20)	687 (27)	818 (28)	853 (34)	
≥65 years (%)	292 (10)	340 (13)	410 (14)	441 (17)	
MALE (%)	1,970 (69%)	1,645 (65)	1,746 (59)	1,442 (57)	<0.001
RACE (%)					0.001
White	1,200 (42)	1,100 (43)	1,202 (41)	1,183 (47)	
Black	1,006 (35)	865 (34)	1,033 (35)	769 (30)	
Hispanic	488 (17)	412 (16)	524 (18)	448 (18)	
Asian	98 (3)	113 (4)	135 (4)	91 (4)	
Other	51 (2)	53 (2)	63 (2)	41 (2)	
CAUSE OF ESRD (%)					<0.001
Diabetes	588 (21)	626 (25)	887 (30)	964 (38)	
Hypertension	778 (27)	622 (24)	735 (25)	571 (23)	
Glomerulonephritis	637 (22)	542 (21)	519 (18)	352 (14)	
Polycystic Kidney Disease	210 (7)	177 (7)	195 (7)	138 (5)	
Congenital/Reflux	56 (20)	40 (2)	35 (1)	31 (1)	
Other	574 (20)	536 (21)	586 (20)	476 (19)	
DIABETES (%)	742 (26)	827 (33)	1,125 (38)	1,229 (49)	<0.001
HEPATITIS C SEROPOSITIVE (%)	151 (5.3)	143 (5.6)	150 (5.1)	158 (6.3)	0.20
PEAK PANEL REACTIVE ANTIBODY >80 (%)	214 (7.5)	233 (9.2)	245 (8.3)	213 (8.4)	0.22
YEARS ON DIALYSIS (%)					0.24
≥1 & <5	1,171 (41)	983 (39)	1,155 (39)	970 (38)	
≥3 & <5	831 (29)	768 (30)	900 (30)	811 (32)	

	Highest Physical Function (n=2,843)	Near-highest Physical Function (n=2,543)	Near-lowest Physical Function (n=2,957)	Lowest Physical Function (n=2,532)	p-value
≥5	813 (29)	758 (30)	877 (30)	725 (29)	<0.001
CYTOMEGALOVIRUS SEROPOSITIVE	1,708 (60)	1,610 (63)	1,890 (64)	1,686 (67)	<0.001
PRIOR ORGAN TRANSPLANT	304 (11)	278 (11)	303 (10)	254 (10)	0.70
DONOR CHARACTERISTICS					
MEAN AGE (standard deviation)	37 (16)	38 (16)	37 (16)	38 (16)	0.01
<40 years (%)	1,491 (52)	1,260 (50)	1,520 (51)	1,252 (49)	<0.001
≥40 & <50 years (%)	650 (23)	590 (23)	662 (22)	543 (21)	
≥50 & <60 years (%)	535 (19)	483 (19)	551 (19)	484 (19)	
≥60 years (%)	167 (6)	210 (8)	224 (8)	253 (10)	
MALE	1,588 (56)	1,427 (56)	1,670 (56)	1,483 (59)	0.18
BLACK (vs. NON-BLACK)	430 (15)	396 (16)	469 (16)	404 (16)	0.83
DONOR TYPE[*]					<0.001
Live donor	510 (18)	420 (17)	501 (17)	410 (16)	
Deceased, non-ECD	2,032 (71)	1,729 (68)	2,050 (69)	1,721 (68)	
ECD deceased donor	301 (11)	394 (15)	406 (14)	401 (16)	
CYTOMEGALOVIRUS SEROPOSITIVE	1,476 (52)	1,352 (53)	1,547 (52)	1,335 (53)	0.82

[*] Abbreviations: ECD – Extended criteria donor

Table 2

Multivariable Cox regression analysis of patient survival after kidney transplantation[*]

	Recipient Functional Status alone		Recipient Age alone		Recipient Age and Functional Status		Full Model: All Recipient and Donor Attributes	
	HR (CI)	p-value	HR (CI)	p-value	HR (CI)	p-value	HR (CI)	p-value
FUNCTIONAL STATUS								
Highest	*Reference*				*Reference*		*Reference*	
Near-highest	1.28 (1.12, 1.47)	<0.001			1.15 (1.01, 1.33)	0.04	1.09 (0.94, 1.77)	0.25
Near-lowest	1.54 (1.36, 1.76)	<0.001			1.36 (1.20, 1.55)	<0.001	1.28 (1.12, 1.46)	<0.001
Lowest	2.30 (2.03, 2.61)	<0.001			1.88 (1.66, 2.14)	<0.001	1.66 (1.45, 1.89)	<0.001
AGE								
<35 years			*Reference*		*Reference*		*Reference*	
≥35 & <45 years			1.54 (1.17, 2.04)	0.002	1.49 (1.13, 1.96)	0.005	1.25 (0.94, 1.67)	<0.001
≥45 & <55 years			2.47 (1.89, 3.23)	<0.001	2.26 (1.73, 2.96)	<0.001	1.75 (1.32, 2.32)	<0.001
≥55 & <65 years			3.84 (2.95, 5.00)	<0.001	3.40 (2.61, 4.43)	<0.001	2.55 (1.92, 3.38)	<0.001
≥65 years			5.71 (4.37, 7.47)	<0.001	5.10 (3.90, 6.68)	<0.001	3.79 (2.84, 5.05)	<0.001

[*] Full model also adjusted for: recipient attributes of race, sex, diabetes status, prior solid organ transplant, dialysis time, panel reactive antibody, hepatitis C serostatus, glomerulonephritis, polycystic kidney disease, congenital/reflex kidney disease, hypertensive kidney disease, and cytomegalovirus status; donor attributes of type (live, deceased versus extended criteria deceased), age, race (black versus other), and cytomegalovirus status; and allograft attributes of human leukocyte antigen mismatch.