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Individual Frailty Components and Mortality In Kidney Transplant Recipients

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Abstract

Background—Frailty increases early hospital readmission and mortality risk among kidney transplant (KT) recipients. While frailty represents a high-risk state for this population, the

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Disclosure

The authors have no conflict of interest to disclose.

correlates of frailty, the patterns of the 5 frailty components, and the risk associated with these patterns are unclear.

Methods—663 KT recipients were enrolled in a cohort study of frailty in transplantation (12/2008-8/2015). Frailty, ADL/IADL disability, CESD depression, education, and HRQOL were measured. We used multinomial regression to identify frailty correlates. We identified which patterns of the 5 components were associated with mortality using adjusted Cox proportional hazards models.

Results—Frailty prevalence was 19.5%. Older recipients (adjusted prevalence ratio [PR]=2.22, 95%CI:1.21-4.07) were more likely to be frail. The only other factors that were independently associated with frailty were IADL disability (3.22, 95%CI:1.72-6.06), depressive symptoms (11.31, 95%CI:3.02-31.82), less than a high school education (3.10, 95% CI:1.30-7.36) and low HRQOL (Fair/Poor:3.71, 95%CI:1.48-9.31). The most common pattern was poor grip strength, low physical activity and slowed walk speed (19.4%). Only 2 patterns of the 5 components emerged as having an association with post-KT mortality. KT recipients with exhaustion and slowed walking speed (HR=2.43, 95%CI:1.17-5.03) and poor grip strength, exhaustion, and slowed walking speed (HR=2.61, 95%CI:1.14-5.97) were at increased mortality risk.

Conclusion—Age was the only conventional factor associated with frailty among KT recipients; however, factors rarely measured as part of clinical practice, namely HRQOL, IADL disability and depressive symptoms, were significant correlates of frailty. Redefining the frailty phenotype may be needed to improve risk stratification for KT recipients.

INTRODUCTION

The Fried physical frailty phenotype, a measure of physiologic reserve and increased vulnerability to stressors, was originally characterized in populations of community-dwelling older adults (1) and recently associated with poor outcomes in adults of all ages with end stage renal disease (ESRD) (2-8). Among adults of all ages with ESRD treated by kidney transplantation (KT), frailty increases the risk of delayed graft function, early hospital readmission after KT, MMF intolerance and mortality (3-5, 7, 8). The association between frailty and these poor outcomes does not seem to differ for older and younger KT recipients.

In gerontology, there is substantial evidence that the Fried physical frailty phenotype is separate but related to functional disability and comorbidity (1). However, the relationship among these three conditions is not well understood in ESRD. In fact, ESRD patients are younger and experience distinct physiologic changes as the result of this chronic condition; therefore, the clinical and non-clinical correlates of frailty in this population, other than perhaps age, likely differ from older adults. Better understanding frailty in ESRD patients is particularly important in those undergoing the major surgical stressor of KT.

Among older adults in whom the Fried physical frailty phenotype was described, the prevalence of the 5 individual components ranges from 15.0% for weight loss to 29.8% for low physical activity (9). It is unknown whether these 5 components, and their relative weights in the existing gerontologic frailty phenotype, represent the best measure of physiologic reserve among ESRD patients, as some components may be playing a larger role

in the manifestation of frailty in this unique population. Finally, it is unclear which patterns of the components most strongly increase the risk of mortality in this population.

Frailty may help improve pre-operative planning, pre-operative risk prediction and post-operative decision-making in ESRD patients undergoing KT. However, a better understanding of which recipients are most likely to be frail and how frailty manifests in adults with ESRD is needed before frailty can be incorporated into clinical practice for this population. The goals of this study were to 1) identify characteristics of frail KT recipients, 2) identify the most common components of frailty among KT recipients and 3) explore which patterns of the frailty components are most strongly associated with mortality risk among KT recipients.

MATERIALS AND METHODS

Study Design

We studied 663 KT recipients who were enrolled in a cohort study of frailty and ESRD (December 2008-August 2015) at Johns Hopkins Hospital. In this study, we measured the physical frailty phenotype (as described below), Activities of Daily Living (ADL), Instrumental Activities of Daily Living (IADL), Centers for Epidemiologic Studies Depression (CESD), and Health-related Quality of Life (HRQOL) at the time of admission for KT. In addition, recipient factors (sex, age, race, education, body mass index [BMI], history of CVD, history of diabetes, Charlson Comorbidity Index (10), cause of ESRD, previous transplant, time on dialysis, and type of dialysis) and transplant factors (donor type and induction therapy) as well as mortality were ascertained from medical records. The Johns Hopkins Institutional Review Board approved the study.

Frailty Measurement

We studied the physical frailty phenotype using the Fried frailty score (1). Frailty was measured as defined and validated by Fried in older adults (1, 8, 9, 11-20) and by our group in ESRD and KT populations (2-8). The phenotype was based on 5 components: shrinking (self-report of unintentional weight loss of more than 10 lbs in the past year based on dry weight); weakness (grip-strength below an established cutoff based on gender and BMI); exhaustion (self-report); low activity (Kcals/week below an established cutoff); and slowed walking speed (walking time of 15 feet below an established cutoff by gender and height) (1). Each of the 5 components was scored as 0 or 1 representing the absence or presence of that component. The aggregate frailty score was calculated as the sum of the component scores (range 0-5); nonfrail was defined as a score of 0 or 1, intermediate frailty was defined as a score of 2, and frailty was defined as a score of ≥3 as we previously have reported in this specialized population (2, 3, 5-7). The cut points for nonfrail and intermediately frail differed from the standard calculation of the Fried physical frailty phenotype because there are too few adults with ESRD who had none of the frailty components.

Statistical Analysis of Frailty Correlates and Components

We plotted the prevalence of frailty status and the individual components for all KT recipients. Additionally, among those who were frail, we estimated the prevalence of each component pattern.

We estimated the prevalence of frailty in various subgroups. Then we used adjusted multinomial regression to identify correlates of frailty. Multinomial regression was used because frailty has three categories (nonfrail, intermediately frail and frail). This model allowed us to compare frail to nonfrail and intermediately frail to nonfrail in the same model and to estimate a different association between each correlate and each level of frailty status. Therefore, the associations were not constrained to be the same between each level of the outcome of frailty as they would be in ordinal logistic regression.

Statistical Analysis of Frailty Components and Mortality

Additionally, among all KT recipients, regardless of whether they were defined as frail by the Fried physical frailty phenotype, we explored the role of the 5 components and tested to see which patterns were associated with mortality. We tested whether a specified subset of the 5 frailty components was associated with post-KT mortality using a Cox proportional hazards model adjusted for age, sex, race, donor type and Charlson Comorbidity Index (10); the mean follow-up time for mortality was 3.1 years (SD=2.1 years) with a maximum of 6.8 years.

For all analyses, a P value <0.05 was considered significant. All analyses were performed using STATA 13.0 (College Station, Texas).

RESULTS

Study Population

The study population mean age was 53.0 years old (SD= 13.9, range 18.7 - 83.0), 38.0% were female and 41.4% were African American. When compared to KT recipients at Johns Hopkins who were not enrolled in our prospective study, there were no differences in age (P=0.16), sex (P=0.05), race (P=0.28), or donor type (P=0.23).

Frailty Prevalence

Among KT recipients, 19.5% were frail and 31.7% were intermediately frail (Table 1). Although frailty prevalence increased with age (Figure 1; P=0.007), the increase was not monotonic. The prevalence was 13.6% among recipients aged less than 35 years, 15.5% among those aged 35-44 years, 15.5% among those aged 45-54 years, 24.5% among those aged 55-64 years, 23.7% among those aged 65-74 years, and 22.7% for those recipients aged ≥75 years. Older (age ≥ 65 years) KT recipients were 2.11-fold (95% CI: 1.16-3.85; P=0.015) more likely to be frail, independent of all other factors (Table 2).

Association Between Recipient Characteristics and Frailty

Frailty prevalence was higher among KT recipients with ADL (66.7 vs. 18.6%; P=0.009) and IADL (37.8 vs. 15.9% %; P<0.001) disability, CESD depression (53.2 vs. 16.0%;

P<0.001), less than a high school education (32.5 vs. 17.6%; P=0.045), no residual kidney function (25.0 vs. 14.0%; P=0.003) and those who reported fair or poor HRQOL (excellent/very good: 8.6%, good: 18.6% and fair/poor: 26.9%; P<0.001) (Table 1).

KT recipients with an IADL disability (PR=3.22, 95%CI: 1.72-6.06; P=0.001), CESD depression (PR=11.31, 95%CI: 4.02-31.82; P<0.001), or less than a high school education (PR=3.10, 95%CI: 1.30-7.36; P=0.01) were more likely to be frail after adjustment for clinical characteristics (Table 2). Compared to those who reported excellent/very good HRQOL, fair/poor HRQOL was independently associated with a 3.71-fold increased prevalence of frailty (95%CI: 1.48-9.31; P=0.007) after adjustment for clinical characteristics. Older KT recipients, those with CESD depression and those undergoing hemodialysis for 0-2 years were also independently associated with increased prevalence of intermediate frailty (Table 2).

Distribution of Frailty Components and Mortality Risk

Among all KT recipients, the two most frequent frailty components were poor grip strength (50.1%) and low physical activity (49.0%) (Figure 2). The most common pattern among the frail KT recipients was poor grip strength, low physical activity and slowed walk speed (19.4%) (Figure 3). KT recipients with exhaustion and slowed walking speed (HR=2.43, 95%CI:1.17-5.03) and poor grip strength, exhaustion and slowed walking speed (HR=2.61, 95%CI:1.14-5.97) were at increased mortality risk.

DISCUSSION

In this single-center cohort study of frailty in ESRD patients treated by KT, 19.5% were frail, including 13.6% of those younger than 35 years old. While older recipients were twice as likely to be frail as younger recipients, other factors like fair or poor HRQOL, ADL as well as IADL disability, less than a high school education and CESD depression were strong correlates of frailty. This finding is important, as these factors are commonly studied in gerontology but not conventionally measured as part of clinical care of ESRD or KT patients. Additionally, we found that poor grip strength occurred in over half of all KT recipients, regardless of whether they were ultimately classified as frail or nonfrail after considering the other 4 components. Poor grip strength, low physical activity and slowed walk speed was the most common pattern of the components among KT recipients classified as frail. However, exhaustion and slowed walking speed as well as poor grip strength, exhaustion and slowed walking speed were patterns that were both associated with more than 2-fold increased mortality risk among all KT recipients.

Similar to studies of older adults (9), we found a higher prevalence of frailty with age. However, the frailty prevalence did not increase monotonically after age 55. 24.5% of recipients aged 55-64 years old were frail and 23.7% of those 65-74 years old and 22.7% of those aged 75 years or older were frail. This plateauing of the frailty prevalence for older adults may be due to the selection bias that only the healthiest older adults are selected as KT candidates.

In our study population, those who had CESD depressive symptoms, IADL/ADL disability, less than a high school education and poor HRQOL were most likely to be frail. As with community-dwelling older adults, we found frailty to be separate than comorbidity (1). These findings are consistent with what is reported in the gerontology literature (1). However, unlike the studies of community-dwelling older adults (1, 9), we did not observe significant differences in frailty prevalence by sex or race.

Our previous study has suggested that frailty changes with transplantation; in the first month, KT recipients are on average more frail, by two months their frailty status has returned to where it was immediately prior to KT on average, and by 3 months their frailty status has improved (21). Our current research builds upon this study of post-KT frailty by identifying which KT recipients are most likely to be frail prior to KT. Other retrospective registry and cross-sectional analyses have studied a modified the Fried frailty phenotype among hemodialysis patients (16, 22-26); our study adds to this literature by focusing on the Fried frailty phenotype among KT recipients. However, many of these studies, looked at proxies of the Fried frailty phenotype without measuring physical function (13, 15, 22). Measuring physical function as part of the frailty definition is important among ESRD patients (24) and has implications for risk prediction (27).

Strengths of this study were the prospective measurement of a validated, objective frailty instrument, the granular ascertainment of the recipient and transplant factors that were identified as predictors of frailty, and the long-term linkage-augmented outcomes of the cohort participants. The main limitation was the single-center study design, so direct inferences must be interpreted in the context of our study population.

In conclusion, we found that none of the conventionally measured dialysis, ESRD or transplant factors except age are correlated with frailty status among KT recipients. Importantly, we were able to identify two high-risk patterns of the 5 components that increased the risk of mortality among KT recipients. It is likely that, although the physical frailty phenotype is associated with poor outcomes among KT recipients, a measure of frailty built for patients with ESRD would greatly improve our ability to identify the latent biological construct of frailty in this population.

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ABBREVIATIONS

ADL	activities of daily living
BMI	body mass index

CESD	centers for epidemiologic studies depression scale
ESRD	end stage renal disease
HRQOL	health related quality of life
IADL	instrumental activities of daily living
KT	kidney transplantation
PR	prevalence ratio

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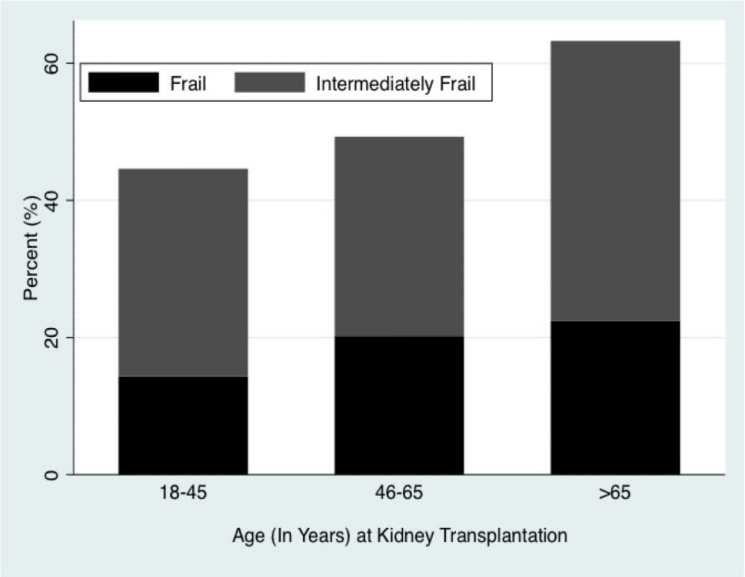

Figure 1. Prevalence of Intermediate Frailty and Frailty Among Kidney Transplant Recipients (KT), by Age (n=663)

The frailty score is calculated using the cutpoints from the Fried Frailty Phenotype (1). Frailty is defined as a score of 3 or more and intermediate frailty as a score of 2.

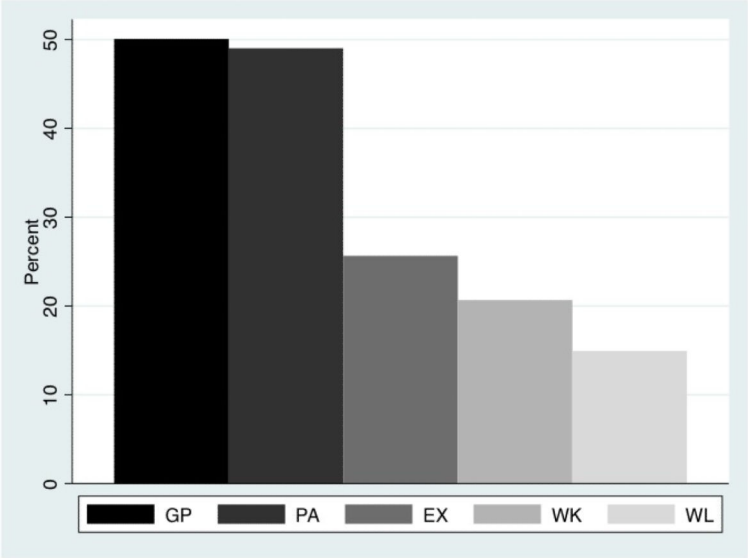

Figure 2. Prevalence of the Frailty Components Among Kidney Transplant (KT) Recipients (n=663)

GP=Poor grip strength; PA=Low physical activity; EX=Exhaustion; WK=Slowed walk speed; WL=Unintentional weight loss.

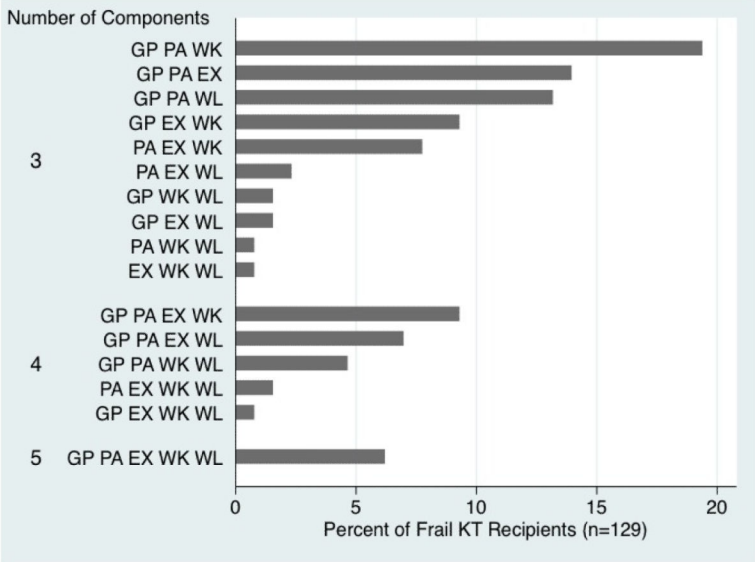

Figure 3. Frailty Components Patterns Among Frail Kidney Transplant (KT) Recipients (n=129)
GP=Poor grip strength; PA=Low physical activity; EX=Exhaustion; WK=Slowed walk speed; WL=Unintentional weight loss.

Table 1

Frailty Prevalence in Subgroups of KT Recipients (n=663). The frailty score is calculated using the cutpoints from the Fried Frailty Phenotype (1). Frailty is defined as a score of 3 or more and intermediate frailty as a score of 2. The row percentages are provided to give the prevalence of frailty for each subgroup of KT recipients.

Characteristics	Not frail (n=324, 48.9%)	Intermediately frail (n=210, 31.7%)	Frail (n=129, 19.5%)	P-Value
Age (years)				
<35	59.1	27.3	13.6	0.002
35-44	53.6	30.9	15.5	
45-54	60.3	24.7	15.5	
55-64	42.2	33.3	24.5	
65-74	38.1	38.1	23.7	
≥75	27.3	50.0	22.7	
Sex				
Male	50.6	30.8	18.6	0.51
Female	46.0	33.2	20.8	
Race				
African American	49.6	28 .2	22.2	0.18
Not African American	48.4	34.0	17.6	
Obesity				
Normal weight (<25)	50.2	31 .7	18.1	0.75
Overweight (25-29)	50.9	29.7	19.4	
Obesity (≥30)	45.1	33.7	21.1	
ADL disability				
Yes	33.3	0.0	66.7	0.009
No	49.3	32.1	18.6	
IADL disability				
Yes	31.7	30 .5	37.8	<0.001
No	52.2	31.9	15.9	
CESD depression				
Yes	14.9	31 .9	53.2	<0.001
No	52.3	31.7	16.0	
Education				
Less than a high school	35.0	32 .5	32.5	0.045
High school or higher	50.5	31.9	17.6	
Current smoker				
Yes	56.8	29 .7	13.5	0.57
No	48.6	32.1	19.3	
Residual kidney function				
No	48.6	26.4	25.0	0.003
Yes	50.3	35.7	14.0	

Characteristics	Not frail (n=324, 48.9%)	Intermediately frail (n=210, 31.7%)	Frail (n=129, 19.5%)	P-Value
Time on dialysis (years)				
0	52.3	30 .0	17.7	0.21
0-2	44.5	38.0	17.5	
>2	50.4	28.7	20.9	
Type of dialysis				
Hemodialysis	48.0	31.5	20.5	0.87
Peritoneal	52.9	29.9	17.2	
Not on dialysis	52.3	30.0	17.7	
Cause of ESRD				
Hypertension	48.5	32 .5	18.9	0.45
Diabetes	42.3	35.8	22.0	
Glomerulonephritis	60.0	16.0	24.0	
Other	51.0	31.3	17.8	
History of CVD				
Yes	51.2	25.6	23.3	0.68
No	49.7	31.2	19.1	
History of Diabetes				
Yes	40.4	34.7	24.9	0.01
No	52.2	30.5	17.3	
Charlson Comorbidity Index				0.14
0	51.2	30.6	18.3	
1-2	45.1	27.5	27.5	
≥3	44.4	44.4	11.1	
Self-rated HRQOL				
Excellent/Very good	61.9	29 .5	8.6	<0.001
Good	49.8	31.7	18.6	
Fair/Poor	39.1	34.0	26.9	
Donor type				
Live	53.2	28 .8	18.0	0.22
Deceased	46.3	33.4	20.3	
Induction				
ATG	46.9	34.1	19.0	0.43
IL-2RA	58.7	21.7	19.6	
Other	51.2	26.2	22.6	
No induction agent	55.8	25.6	18.6	

ATG= anti-thymocyte globulin; IL-2RA= interleukin-2 receptor blockers.

Table 2

Correlates of Frailty Status Among Kidney Transplant (KT) Recipients (n=663). The frailty score is calculated using the cutpoints from the Fried Frailty Phenotype (1). Frailty is defined as a score of 3 or more and intermediate frailty as a score of 2.

Correlate	Intermediately frail		Frail	
	PR (95% CI)	P value	PR (95% CI)	P value
Age ≥ 65 years	1.82 (1.11, 2.96)	0.02	2.22 (1.21, 4.07)	0.01
Female sex	1.17 (0.79, 1.73)	0.43	0.92 (0.56, 1.53)	0.76
Black race	0.68 (0.44, 1.06)	0.09	0.97 (0.55, 1.69)	0.90
Obesity				
Normal weight (BMI<25)	Ref		Ref	
Overweight (BMI 25-29)	0.85 (0.54, 1.36)	0.51	1.11 (0.62, 1.96)	0.73
Obesity (BMI ≥30)	1.12 (0.69, 1.81)	0.65	1.11 (0.61, 2.01)	0.74
IADL disability	1.41 (0.74, 2.67)	0.29	3.22 (1.72, 6.06)	<0.001
CESD depression	3.52 (1.34, 9.26)	0.01	11.31 (4.02, 31.82)	<0.001
< High school education	1.68 (0.75, 3.75)	0.21	3.10 (1.30, 7.36)	0.01
Current smoker	0.71 (0.31, 1.64)	0.42	0.45 (0.12, 1.62)	0.22
No residual kidney function	0.76 (0.47, 1.21)	0.25	1.56 (0.69, 3.52)	0.27
Time and type of dialysis				
Not on dialysis	Ref		Ref	
Hemodialysis; 0-2 y	2.35 (1.17, 4.69)	0.02	1.43 (0.51, 4.06)	0.49
Hemodialysis; >2 y	1.19 (0.63, 2.25)	0.58	1.08 (0.38, 3.07)	0.89
Peritoneal dialysis; 0-2 y	1.08 (0.46, 2.54)	0.86	0.67 (0.20, 2.25)	0.51
Peritoneal dialysis; >2 y	1.37 (0.49, 3.83)	0.54	1.25 (0.38, 4.09)	0.70
Charlson Comorbidity Index				
0 points	Ref		Ref	
1-2 points	0.82 (0.48, 1.41)	0.48	1.31 (0.66, 2.58)	0.43
≥3 points	1.58 (0.62, 3.99)	0.33	0.61 (0.12, 3.12)	0.55
Cause of ESRD				
Hypertension	Ref		Ref	
Diabetes	1.11 (0.64, 1.92)	0.71	1.06 (0.53, 2.12)	0.86
Glomerulonephritis	0.47 (0.14, 1.58)	0.22	1.27 (0.39, 4.10)	0.69
Other	0.98 (0.62, 1.57)	0.95	0.88 (0.49, 9.31)	0.67
Self-rated HRQOL				
Excellent/Very good	Ref		Ref	
Good	1.37 (0.83,2.25)	0.22	2.80 (2.29, 6.07)	0.01
Fair/Poor	1.80 (1.07, 3.05)	0.03	3.71 (1.48, 9.31)	0.01
Donor type				
Live	Ref		Ref	
Deceased	1.51 (0.98, 2.32)	0.06	1.16 (0.67, 2.00)	0.59

ADL disability was excluded from the model for KT recipients because there were no participants with an ADL disability and intermediate frailty.