

Frailty and Early Hospital Readmission After Kidney Transplantation

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Early hospital readmission (EHR) after kidney transplantation (KT) is associated with increased morbidity and higher costs. Registry-based recipient, transplant and center-level predictors of EHR are limited, and novel predictors are needed. We hypothesized that frailty, a measure of physiologic reserve initially described and validated in geriatrics and recently associated with early KT outcomes, might serve as a novel, independent predictor of EHR in KT recipients of all ages. We measured frailty in 383 KT recipients at Johns Hopkins Hospital. EHR was ascertained from medical records as ≥ 1 hospitalization within 30 days of initial post-KT discharge. Frail KT recipients were much more likely to experience EHR (45.8% vs. 28.0%, $P = 0.005$), regardless of age. After adjusting for previously described registry-based risk factors, frailty independently predicted 61% higher risk of EHR (adjusted RR = 1.61, 95% CI: 1.18–2.19, $P = 0.002$). In addition, frailty improved EHR risk prediction by improving the area under the receiver operating characteristic curve ($P = 0.01$) as well as the net reclassification index ($P = 0.04$). Identifying frail KT recipients for targeted outpatient monitoring and intervention may reduce EHR rates.

Key words: Frailty, readmission, transplantation

Abbreviations: AUC, area under the receiver operating characteristic curve; DGF, delayed graft function; EHR, early hospital readmission; ESRD, end stage renal disease; KT, kidney transplantation; NRI, net reclassification index.

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Introduction

Nearly one-third of kidney transplantation (KT) recipients are readmitted to the hospital within 30 days of discharge (1). Early hospital readmission (EHR) is associated with increased avoidable morbidity, costs, and transition-of-care errors (2–4), and is of great interest in healthcare (5–7). We previously developed a registry-based model to predict EHR in KT recipients and identified recipient and transplant factors as important predictors of EHR in this population (1). However, registry-based prediction, while informative and hypothesis generating, is insufficient for EHR risk prediction (1), so novel predictors are needed.

We hypothesized that frailty, a measure of physiologic reserve initially described and validated in geriatric populations (8), is not only applicable to patients of all ages with end stage renal disease (ESRD) but also may capture the type of risk in this population that leads to EHR. We have previously demonstrated that frailty is an important predictor of mortality and hospitalization in adults of all ages undergoing hemodialysis (9); this supports our hypothesis that ESRD patients experience accelerated aging and thus are similar to older adults. In a cohort of KT recipients of all ages, we have recently identified an association between frailty and delayed graft function (DGF) (10). Furthermore, in general surgery we showed that frailty improved risk prediction for postoperative complications, length of stay and the need for a skilled nursing facility at discharge (11). Others have identified frailty (using alternative definitions of frailty) as a predictor of 30 day EHR in older adults undergoing colorectal surgery (12) as well as 60 day EHR in adults of all ages with chronic diseases or chronic impairment (13).

The goal of this study was to explore frailty, as defined and validated by Fried et al., as a potential risk factor for 30 day EHR in KT recipients of all ages and to test whether frailty could improve EHR risk prediction above and beyond our previously published registry-based model.

Methods

Study design

This was a prospective, longitudinal study of 383 KT recipients at Johns Hopkins Hospital, Baltimore, Maryland, between December 2008 and December 2012. Frailty was measured at the time of KT as described below. EHR was ascertained from medical records and defined as one or more

hospitalizations within 30 days of initial post-KT discharge. Only two participants died within 30 days of KT and both experienced an EHR prior to death, so both were included in the study. Recipient and transplant factors (sex, age, race, BMI, recipient diabetes, recipient heart disease, time on dialysis, donor type, donor age, use of induction therapy, HLA mismatches, and KT length of stay) were ascertained from medical records. The Johns Hopkins Institutional Review Board approved the study.

Frailty

At admission for KT, frailty was measured as defined and validated by Fried et al. (8,14–23) as a phenotype based on five 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) (8). A score of one was given to those with the presence of each measured component. The aggregate frailty score was calculated as the sum of the component scores (range 0–5) and frailty was defined as a score of 3 or higher, as we previously have published (10).

Quantifying the association of frailty and EHR

The association between frailty and EHR was evaluated using modified Poisson regression (24) adjusted for recipient and transplant factors based on our previously published registry-based model (1). For the sake of parsimony, only recipient and transplant factors that were statistically significant predictors of EHR in the original registry-based model were included in this analysis. As a sensitivity analysis, the registry-based model was additionally adjusted for DGF to account for the association between frailty and DGF (10). We tested for effect modification of the association of frailty and EHR by age and race using a Wald test.

Assessing statistical prediction improvement: Nested AUC

Two methods were used to assess and quantify the improvement in risk prediction of EHR by frailty. The overall statistical difference in predictive power of the registry model with and without frailty was measured by the area under the receiver operating characteristic curve (AUC) (25).

Assessing clinically relevant prediction improvement: Net reclassification index

Additionally, we tested the clinically relevant improvement in prediction using the net reclassification index (NRI) (26). In other words, the NRI was

used to quantify the relative ability of the two models (registry-based alone versus registry-based plus frailty) in classifying the patients as low, intermediate, or high risk for EHR as selected *a priori* (<20%, 20–50%, and >50%). First, the participants were classified as above based on predicted probability derived from the model without frailty. Then, participants were reclassified in the same way using the model with frailty, and “movement” from the non-frailty classification to the frailty-based classification was quantified. Finally, the NRI quantified “correct movement” in risk classification: for participants who experienced EHR, correct movement was an *upgrade* in classification (low to intermediate, low to high, or intermediate to high); for participants who did not experience EHR, correct movement was a *downgrade* in classification (high to intermediate, high to low, or intermediate to low). NRI was calculated using the *NRI* package in Stata12, based on methods described by Pencina et al. (26).

Statistical analysis

For all analyses, a *p* value <0.05 was considered significant. All analyses were performed using STATA 12.0 (College Station, TX).

Results

Study population

Among 383 study participants, the mean age was 53.5 years (SD = 13.9), 39.7% were female, 38.9% were African American and 18.8% were frail at KT. Consistent with previous findings of frailty as an independent domain, no recipient factors were associated with frailty except sex (Table 1). Similar to our findings from the national registry, 31.3% of KT recipients at our center were readmitted within 30 days of initial discharge.

Frailty and early hospital readmission

Frail KT recipients were much more likely to experience EHR (45.8% vs. 28.0%, *p* = 0.005), regardless of age (Figure 1). Interestingly, frail younger recipients had the highest EHR rate (46.2%). In an unadjusted regression model, frail KT recipients were 1.64-fold (95% CI: 1.20–2.23, *p* = 0.002) more likely to experience EHR than their non-frail counterparts. After adjusting for sex, age, race, BMI, recipient diabetes, recipient heart disease, time on

Table 1: Study population of kidney transplant recipients, stratified by frailty

	No frailty (n = 311)	Frailty (n = 72)	p value
Recipient factors			
Age (mean [SD])	53.1 (13.8)	54.9 (14.3)	0.3
African American race (%)	39.2	37.5	0.9
Female sex (%)	42.1	29.2	0.046
Body mass index (kg/m ²) (mean [SD])	27.4 [5.4]	27.4 (5.6)	0.9
Diabetes (%)	15.8	23.6	0.1
Heart disease (%)	14.8	13.9	1.0
Time on dialysis (years) (mean [SD])	4.4 (5.7)	4.5 (5.7)	0.9
Transplant factors			
Live donor (%)	48.6	38.9	0.2
Donor age (mean [SD])	41.0 (15.4)	42.7 (14.6)	0.4
Received induction therapy (%)	92.9	90.3	0.5
0 HLA mismatches (%)	4.8	5.6	0.8
Length of stay for the transplant (in days) (median [IQR])	9.0 (7.0)	9.5 (7.5)	0.9

SD, standard deviation; IQR, interquartile range.

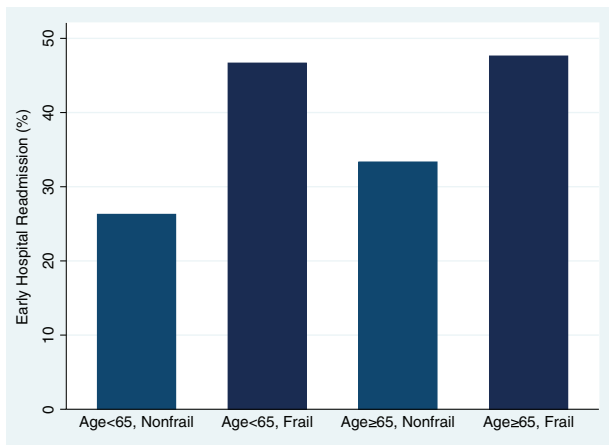


Figure 1: Early hospital readmission, by age and frailty.

dialysis, donor type, donor age, use of induction therapy and HLA mismatches, frailty independently predicted 61% higher risk of EHR (adjusted RR = 1.61, 95% CI: 1.18–2.19, $p = 0.002$) in KT recipients. Adjusting for DGF did not alter the association of frailty and EHR (adjusted RR = 1.59, 95% CI: 1.17–2.17, $p = 0.003$). Consistent with our previous findings in KT, the frailty effect did not differ between older and younger KT recipients (interaction $p = 0.39$) or African American and white KT recipients (interaction $p = 0.81$).

Improved prediction with frailty

Importantly, frailty improved the ability to predict EHR, above and beyond our previously published registry-based model. The area under the ROC curve was statistically higher with the addition of frailty (0.70 vs. 0.63, $p = 0.008$) to the 11 factors in the registry-based model (Figure 2).

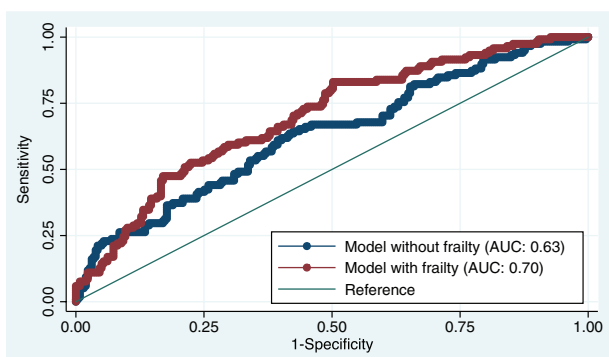


Figure 2: Receiver operating characteristic curve for early hospital readmission prediction models with and without frailty. Note: AUC is the area under the receiver operating characteristic curve. The registry-based model with frailty had statistically significant improvement in EHR prediction ($p = 0.08$). The p value was obtained from a chi-squared test of the difference in the AUC for the registry-based models with and without frailty.

Frailty also improved the classification of KT recipients (Table 2); 10% (13/120) of those with EHR were correctly reclassified as being at higher risk for EHR by frailty and 10% (25/263) of those without EHR were correctly reclassified as being at lower risk of EHR by frailty ($p = 0.04$).

Discussion

In this single-center cohort of 383 patients, frail KT recipients were 1.6-fold more likely to experience EHR than their non-frail counterparts, even after accounting for registry-based risk factors. Furthermore, frailty significantly improved EHR risk prediction when added to the registry-based model.

These results are consistent with previous findings that frailty is an important risk factor in surgical patients, patients undergoing hemodialysis and transplant recipients. First, we previously showed that frailty predicted operative risk in older general surgery patients beyond that which is predicted by the Lee and Eagle or ASA scores (11). Furthermore, we identified frailty as a predictor of mortality and hospitalization in patients undergoing hemodialysis (9). Finally, we found that frailty doubled the risk of DGF in KT recipients (10). Additionally, Englesbe et al. (27) studied sarcopenia as an objective and reproducible measure of frailty in liver transplant recipients, showing an association with 1-year mortality in these patients.

Previous studies have identified an association between frailty and EHR in older adults and patients of all ages with chronic conditions (12,13). However, these studies did not define frailty using the five criteria established and validated by Fried et al.; instead they used a combination of geriatric factors and comorbidities to define frailty. In one study of older adults undergoing elective colorectal surgery, EHR rates were higher for patients who they identified as frail (using an alternative definition) (32%) than for intermediately frail (15%) and non-frail (4%) patients (12). Our study extends the findings that frailty is a predictor of EHR to ESRD patients of all ages who are undergoing KT. Furthermore, our findings demonstrated that frailty is an independent predictor of EHR that improves risk prediction and is not just associated with a higher rate of EHR.

Strengths of this study were the prospective measurement of a validated, objective frailty instrument and granular ascertainment of the recipient and transplant factors that were identified as predictors of EHR in the registry-model using medical records abstraction. Additionally, frailty was ascertained immediately prior to KT and thus prior to EHR, so its predictive value could be assessed. The main limitation was the single-center study design so direct inferences must be interpreted in the context of the demographics of our study population, which is somewhat older and more represented by African Americans. That said, we did not identify any interactions between frailty and

Table 2: Reclassification among kidney transplant recipients who experienced early hospital readmission (EHR) and those who did not

Model without frailty	Model with frailty			Total
	<20%	20–50%	>50%	
Participants who experienced EHR				
<20%	5	3	0	8
20–50%	6	84	10	100
>50%	0	1	11	12
Total	11	88	21	120
Participants who do not experienced EHR				
<20%	33	5	0	60
20–50%	24	187	8	219
>50%	0	1	5	6
Total	57	193	13	263

This reclassification table, stratified by whether or not the participant had the outcome of EHR, was used to calculate the net reclassification index (NRI) (26) for frailty. The table quantifies the correct movement in categories (upward for those with EHR and downward for those without). For those with EHR, 13/120 (10%) were correctly reclassified by including frailty in the model; for those without EHR, 10% (25/263) were correctly reclassified. Overall, the improvement was 10% ($p = 0.04$).

age or race, so the likelihood that this novel association is specific only to our population is low.

Frailty is an independent predictor for EHR following KT; this novel measure of physiologic reserve, originally described in the geriatric literature, is predictive of EHR regardless of recipient age. Risk prediction of EHR is improved by frailty, which will allow high-risk recipients to be identified at the time of transplantation. Identifying frail KT recipients for rehabilitation prior to KT, improved transition-of-care at the time of KT and targeted outpatient monitoring and interventions after KT may reduce the very high EHR rates seen in KT.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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