Early Hospital Readmission in Older and Younger Kidney Transplant Recipients

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Keywords

Kidney transplantation · Older adults · Hospital readmission

Abstract

Background: Up to 31% of kidney transplant (KT) recipients experience early hospital readmission (EHR). We hypothesized that EHR among older KT recipients is higher than younger recipients due to increased comorbidities and higher prevalence of frailty. **Methods:** We identified 22,458 older (age ≥ 65) and 86,372 younger (18 to < 65) first-time KT recipients (December 1, 1999 – December 31, 2014) using United States Renal Data System data. We estimated the association between patient-level characteristics and EHR (30 days post-KT discharge) with modified Poisson regression among older and younger KT recipients, separately. We estimated the association between graft loss and mortality and EHR using Cox proportional hazards. **Results:** EHR was more common in older KT recipients (30.1 vs. 27.6%; $p < 0.001$). Risk factors for EHR that differed by recipient age included female sex, African American race, diabetes, smoking, dialysis vintage, donor age, and length of stay. Risk of graft loss associated with EHR was greater among older KT recipients (adjusted hazard ratio [aHR] 1.64, 95% CI 1.51–1.77, $p < 0.001$)

than younger KT recipients (aHR 1.43, 95% CI 1.38–1.48, $p < 0.001$; interaction $p < 0.01$). However, the risk of mortality associated with EHR was greater among younger recipients (aHR 1.52, 95% CI 1.47–1.57, $p < 0.001$) than that in older recipients (aHR 1.40, 95% CI 1.34–1.47, $p < 0.001$; interaction $p < 0.01$). **Conclusions:** Older KT recipients are more likely to experience EHR and are at a higher risk of graft loss after EHR than younger recipients. Targeted interventions to prevent EHR and subsequent graft loss in this population should be identified.

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Introduction

Approximately one-third of all kidney transplant (KT) recipients experience early hospital readmission (EHR) within 30 days of discharge after transplantation [1, 2]; known risk factors include age, frailty, race, obesity, comorbidities, post-operative complications, extended criteria donors, and lack of induction immunosuppression

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[1–3]. EHR in KT recipients is associated with adverse outcomes such as graft loss and mortality along with an increased risk for subsequent hospital readmissions [4–6]. However, EHR may be preventable in many KT recipients [3]. While older age is associated with EHR [1], we hypothesized that specific risk factors for EHR in older KT recipients would differ from risk factors in younger recipients due to a comorbidity burden, a higher prevalence of frailty, and a senescent immune system [7–10], and that the impact of EHR on post-transplant outcomes such as graft loss and mortality might also be augmented in older recipients who have less physiologic reserve.

Risk factors for EHR have been investigated in older surgical patients in other specialties (trauma, breast, surgical oncology, and orthopedic) and include age-specific factors such as higher number of comorbidities, increasing age, and postoperative complications [11–15]; however, inferences from surgical patients in these populations may not be generalizable to older KT recipients because of immunosuppressive regimens, rejection, and transplant-specific infectious complications, which often require readmission. Additionally, over the past decade, graft and overall survival in older KT recipients have significantly improved [16], but EHR after KT may modify and attenuate the improvement in outcomes. As the proportion of older adults undergoing KT increases, it is important to understand the risk factors for EHR and its impact on post-transplant outcomes in order to inform targeted EHR prevention strategies in this unique population [16].

Understanding the burden, risk factors, and sequelae of EHR in older KT recipients is imperative for the care of this population. In this study, we used national registry data to (1) quantify the burden of EHR in older versus younger recipients, (2) identify recipient and transplant factors for EHR in older versus younger recipients, (3) quantify the effect of EHR on graft loss and mortality in older versus younger KT recipients, and (4) identify center-level variation in EHR for older recipients.

Methods

Data Source

This study used data from the Organ Procurement and Transplantation Network (OPTN) and linked to Medicare claims data by the United States Renal Data System (USRDS). USRDS release data were available through December 31, 2014; therefore, this was the censoring date for death and graft loss analyses. Donor, recipient, and transplant factors were obtained from the 2728 Chronic Renal Disease Medical Evidence form, the OPTN registrant form

and Center for Medicare and Medicaid Services claims. Mortality and graft loss were augmented through linkage with the Social Security Master Death File, Center for Medicare and Medicaid Services data, and waitlist data.

Study Population

The study population included 108,830 adult (age ≥ 18) first-time kidney-only transplant recipients between December 1, 1999 and December 31, 2014, of whom 22,458 were older (age ≥ 65). EHR was defined as at least 1 hospital readmission (to any acute hospital, based on Medicare claims) within 30 days of discharge from initial KT hospitalization. To allow for appropriate longitudinal follow-up, the population was limited to recipients with Medicare as their continuous primary insurer over the 30-day period post-KT and recipients who did not die within 30 days of KT. We included recipients who died after EHR. Because of mechanistic differences, we excluded recipients who were initially discharged to a skilled nursing facility or nursing home to examine specific characteristics that lead to EHR from home. Also, we excluded patients with initial length of stay (LOS) >30 days after initial KT hospitalization.

EHR Factors Specific to Older KT Recipients

Recipient and transplant factors considered to be potential factors of EHR are listed in Table 1. Body mass index (BMI) was classified by WHO classification. All other comorbidities were categorized as reported on 2728 or as reported by OPTN. Recipients with missing HCV serostatus were considered to be HCV negative. Use of an induction agent was categorized as interleukin-2 receptor antagonists (Zenapax or Simulect), anti-CD3 or anti-CD52 agents (OKT3, OKT4, Thymoglobulin, ALG, ATG, Alemtuzumab), or no induction. Donor type was classified into 3 categories (live donor, deceased donor after brain death, deceased donor after cardiac death).

Relative risk (RR) of EHR by recipient and transplant factors was estimated using modified Poisson regression, as described previously [17]. Modified Poisson regression allows reporting of more interpretable RRs instead of odds ratios with logistic regression. To test whether the risk of EHR associated with each factor differed between older and younger KT recipients, interactions between recipient age (older and younger) and each factor were explored. We ascertained the stratified associations from the modified Poisson models and estimated the stratified associations using the *lincom* command in Stata. Functional forms of continuous variables were based on the exploratory data analysis. The final multivariate model was selected for optimal parsimony by minimizing the Akaike Information Criteria.

Death-Censored Graft Loss and Mortality after EHR

Kaplan-Meier methods were used to evaluate 1-, 3-, and 5-year death-censored graft loss and mortality in older KT recipients with EHR compared to those without EHR. Cox proportional hazards models were used to calculate adjusted hazard ratio (aHR) of death-censored graft loss and mortality associated with EHR. For risk adjustment, recipient factors (sex, race, diabetes, BMI, dialysis vintage, history of cancer, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), smoking, LOS, and panel reactive antibody [PRA; 0, 1–79, 80–97, 98–100]), donor factors (age, donor type [live donor, deceased donor after brain death, deceased donor after cardiac death], and extended criteria donor),

Table 1. Characteristics of older KT recipient study population stratified by EHR

	No EHR (<i>n</i> = 15,696)	EHR (<i>n</i> = 6,762)	<i>p</i> value
<i>Recipient Factors</i>			
Age, years [‡]	68 (66–71)	69 (66–72)	<0.01
Female, %	37.3	35.9	0.04
African American, %	17.6	21.7	<0.001
BMI, %			<0.001
Underweight	1.5	1.3	
Normal	29.1	26.0	
Overweight	40.0	39.0	
Obese	29.5	33.8	
Hypertension, %	86.3	87.2	0.07
Diabetes, %	40.9	48.4	<0.001
Cancer, %	5.0	5.7	0.04
Congestive heart failure, %	13.1	16.8	<0.001
Chronic obstructive pulmonary disease, %	2.6	3.3	0.02
Hepatitis C virus positive, %	2.4	2.7	0.2
Dialysis vintage, years ⁺	2.5±2.5	2.9±2.6	<0.001
Smoker, %	2.2	2.0	0.3
Panel reactive antibody, %			0.1
0	57.9	57.4	
1–79	32.2	31.7	
80–97	3.3	3.5	
98–100	6.6	7.4	
<i>Transplant factors</i>			
Donor age, years ⁺	44.8±15.7	46.6±15.9	<0.001
Donor diabetes (%)	6.2	7.8	<0.001
Donor hepatitis C virus (%)	1.2	1.2	0.8
African American donor (%)	10.4	13.1	<0.001
Donor type (%)			<0.001
Deceased after brain death	63.6	68.5	
Live donor	28.8	22.8	
Donation after cardiac death	7.6	8.7	
Extended criteria donor (%)	22.8	30.3	<0.001
Received induction therapy (%)	77.5	75.5	<0.001
0 HLA mismatches (%)	9.0	8.2	0.03
Length of stay, days [‡]	5 (4–7)	7 (5–10)	<0.001
⁺ Reported as (mean ± SD). [‡] Reported as median (interquartile range). KT, kidney transplant; EHR, early hospital readmission.			

and transplant factors (year of KT) were included in the models. Additionally, we stratified survival models by age of KT recipient (younger or older). To test whether the risk of EHR associated with graft loss and mortality differed between older and younger KT recipients, interactions between recipient age (older and younger) and EHR were explored. For all models, proportional hazards assumptions were confirmed by visual complementary log-log plots and Schoenfeld residuals.

Center Level Variation in EHR in Older KT Recipients

To determine whether EHR in older recipients varied significantly across transplant centers, we used a multi-level model with a random intercept framework and reported the intraclass correlation

coefficient (ICC). In the context of this study, the ICC quantifies the variance in EHR explained by transplant center. This model was adjusted for recipient (sex, age, BMI, race, history of cancer, diabetes, smoking, COPD, CHF, LOS, dialysis vintage, PRA, LOS) and transplant factors (donor age, donor type, extended criteria donor, HCV donor status, donor diabetes, and donor race) and used to test the association of center-level factors and baseline rates of admission.

Statistical Analysis

All analyses were two-tailed and α was set at 0.05. Analyses were performed using STATA 14.2/MP (College Station, TX, USA).

Table 2. RR of early hospital readmission for older ($n = 22,458$) and younger ($n = 86,372$) KT recipients

	Younger KT recipients RR (95% CI)	Older KT recipients RR (95% CI)	Interaction p value
Female	1.05 (1.02–1.07)	0.96 (0.92–1.00)	<0.001
African American	1.13 (1.10–1.16)	1.02 (0.97–1.07)	<0.001
Body mass index			
Underweight	1.07 (0.99–1.15)	0.94 (0.77–1.14)	0.3
Normal	Ref.	Ref.	
Overweight	1.00 (0.97–1.03)	1.04 (0.99–1.10)	0.2
Obese	1.06 (1.03–1.09)	1.12 (1.06–1.18)	0.07
Diabetes	1.23 (1.20–1.26)	1.17 (1.12–1.21)	0.03
Smoker	1.09 (1.03–1.15)	0.92 (0.78–1.07)	0.04
Prior cancer	1.10 (1.00–1.20)	1.18 (1.08–1.28)	0.3
COPD	1.13 (1.03–1.23)	1.14 (1.02–1.28)	0.9
Congestive heart failure	1.09 (1.06–1.14)	1.10 (1.04–1.16)	0.9
Dialysis vintage, per year	1.04 (1.04–1.05)	1.03 (1.02–1.04)	<0.01
Panel reactive antibody			
0	Ref.	Ref.	
1–79	1.04 (1.02–1.07)	0.98 (0.94–1.03)	0.02
80–97	1.12 (1.06–1.18)	1.05 (0.93–1.17)	0.3
98–100	1.07 (1.02–1.12)	1.11 (1.03–1.21)	0.3
Donor age, per 10 years	1.00 (1.00–1.00)	1.01 (1.00–1.01)	0.047
Donor diabetes	1.06 (1.01–1.12)	1.08 (1.00–1.16)	0.7
Donor hepatitis C virus	1.26 (1.18–1.35)	1.04 (0.86–1.25)	0.06
African American donor	1.10 (1.07–1.14)	1.10 (1.03–1.16)	0.9
Donor type			
Deceased after brain death	Ref.	Ref.	
Live donor	0.97 (0.94–1.00)	1.00 (0.95–1.06)	0.3
Donation after cardiac death	1.07 (1.03–1.12)	1.04 (0.96–1.12)	0.4
Extended criteria donor	1.14 (1.09–1.18)	1.15 (1.10–1.21)	0.7
Transplant length of stay, per 5 days	1.20 (1.18–1.21)	1.24 (1.22–1.27)	<0.001

RR, relative risk; KT, kidney transplant.

Results

Study Population

Among the 22,458 older KT recipients, the median (interquartile range [IQR]) at KT was 69 (66–71) years, 36.8% were female, and 18.9% were African American (Table 1). There were 6,762 (30.1%) older recipients with EHR. Of older recipients with EHR, 17.5% had readmission within 2 days of discharge, 45.2% within 7 days, and 70.0% within 14 days. The median (IQR) length of readmission after initial KT was 9 (4–16) days. The median (IQR) length of follow-up in our study was 1,471 (642–2,521) days for older KT recipients.

Factors Associated with EHR

Risk factors for EHR that differed between younger and older recipients included female sex, African American race, diabetes, smoking, PRA 1–79, dialysis vintage,

donor age, and LOS (Table 2). Almost all risk factors were equally associated or more strongly associated with EHR in younger KT recipients. For example, younger female recipients had a higher risk of EHR than younger male recipients, but older female recipients had a lower risk of EHR than older male recipients (interaction $p < 0.001$); younger female recipients had a 5% increased risk of EHR (adjusted RR [aRR] 1.05, 95% CI 1.02–1.07, $p < 0.001$), whereas older female recipients had similar risk of EHR compared to older males (aRR 0.96, 95% CI 0.92–1.00, $p = 0.07$). Both older and younger recipients with diabetes had a higher risk of EHR, but this association was stronger in younger recipients (interaction $p = 0.03$). Younger recipients with diabetes had a 23% higher risk of EHR (aRR 1.23, 95% CI 1.20–1.26, $p < 0.001$), whereas older recipients with diabetes had a 17% higher risk of EHR (aRR 1.17, 95% CI 1.12–1.21, $p < 0.001$) compared to older recipients without diabetes. LOS at transplantation was

Fig. 1. **a** Death-censored graft loss and early hospital readmission (EHR) by age of kidney transplant (KT) recipient. **b** Mortality and EHR by age of KT recipient. Older KT recipients were age ≥ 65 .

more strongly associated with EHR in older recipients (interaction $p < 0.001$): older recipients had a 24% higher risk of EHR for each 5-day increase in LOS (aRR 1.24, 95% CI 1.22–1.27, $p < 0.001$), whereas younger recipients had a 20% higher risk of EHR for each 5-day increase in LOS (aRR 1.20, 95% CI 1.18–1.21, $p < 0.001$). Prior cancer, obesity, COPD, CHF, PRA 98–100, African American donor, donor diabetes, extended criteria donors, and DCDs were associated with increased risk of EHR that did not differ between older and younger KT recipients (Table 2).

Death-Censored Graft Loss after EHR

Death-censored graft loss in older KT recipients with EHR was higher than no EHR (Fig. 1a). In older KT recipients, 1-, 3-, and 5-year death-censored graft loss was 5, 8, and 12% respectively. For older KT recipients, 1-, 3-, and 5-year death-censored graft loss for EHR versus no EHR was 9 vs. 3, 14 vs. 6, and 18 vs. 10% respectively. The risk of graft loss associated with EHR varied by recipient age (interaction $p < 0.01$): Older KT recipients with EHR were at a 1.64-fold increased risk of graft loss compared to older recipients without EHR (aHR 1.64, 95% CI 1.51–1.77, $p < 0.001$). However, among younger KT, the strength of this association was diminished; younger recipients with EHR were at a 1.43-fold (aHR 1.43, 95% CI 1.38–1.48, $p < 0.001$) increased risk of graft loss compared to younger recipients without EHR.

Mortality after EHR

Mortality in older KT recipients with EHR was higher than in those with no EHR (Fig. 1b). In older KT recipients, 1-, 3-, and 5-year patient mortality was 5, 15, and

28% respectively. For older KT recipients, 1-, 3-, and 5-year patient mortality for EHR versus no EHR was 10 vs. 4, 22 vs. 12, and 37 vs. 23% respectively. The risk of mortality associated with EHR varied by recipient age (interaction $p < 0.01$): Older KT recipient with EHR were at a 1.40-fold increased risk of mortality compared to older recipients without EHR (aHR 1.40, 95% CI 1.34–1.47, $p < 0.001$). However, among younger KT recipients, the strength of this association was stronger; younger KT recipients were at a 1.52-fold (aHR 1.52, 95% CI 1.47–1.57, $p < 0.001$) increased risk of mortality compared to younger recipients without EHR.

Center-Level Factors Associated with EHR among Older KT Recipients

Including transplant center in a multilevel model improved the fit (likelihood ratio test $p < 0.001$). However, the ICC was 0.036, meaning that only 3.6% of the variation in EHR for older adults was explained by the transplant center. However, 57 (21.0%) of 271 transplant centers had a statistically significantly higher odds of EHR as compared to the national average, and 37 (13.7%) had statistically significantly lower odds of EHR as compared to the national average (Fig. 2). Center-specific odds ratios of EHR ranged from 0.22 (95% CI 0.14–0.33) to 1.96 (1.68–2.30).

Discussion

In this national study of 108,830 KT recipients, of which 22,458 were older KT recipients, 30.1% of older KT recipients experienced EHR. Risk factors for EHR that

Fig. 2. Relative odds of early hospital readmission (EHR) after kidney transplantation in older recipients by transplant center compared to national average. Each dot represents the relative risk of EHR for each transplant center in the United States with 95% CI.

differed between younger and older recipients included female sex, African American race, diabetes, smoking, PRA 1–79, dialysis vintage, donor age, and LOS. Younger recipients who were female, were African American, and had diabetes were at increased risk of EHR compared to younger male, non-African American, non-diabetic recipients; these associations were weaker in older recipients. Older recipients with a longer LOS after KT were at an increased risk of EHR compared to younger recipients with longer LOS after KT. EHR is associated with an increased risk of mortality, and the association of mortality and EHR was stronger in younger recipients compared to older recipients (aHR 1.52 vs. 1.40, $p < 0.01$). However, the association of EHR and graft loss was significantly higher for older recipients compared to younger recipients (aHR 1.64 vs. 1.43 $p < 0.01$). Importantly, there was little variation in EHR of older KT recipients across transplant centers.

Our findings of an association between EHR and obesity, African American race, dialysis vintage, and longer LOS after KT are consistent with previous reports in KT recipients of all ages [1]. However, our study identified differences EHR in risk factors between older and younger KT recipients, such as sex, race, diabetes, and time on dialysis, and LOS. These associations are more strongly associated with risk of EHR in younger recipients compared to older recipients, except longer LOS, which is more strongly associated with EHR in older recipients. Furthermore, diabetes and smoking are associated with

EHR in older and younger recipients, but more strongly in younger recipients, likely given that comorbidities play a larger role in EHR for younger patients.

Additionally, our group previously demonstrated that intermediate center-level volume and average LOS after KT were center-level factors associated with EHR [1]. Although, in this study, we found no center-level variation in EHR for older KT recipients; this is consistent with findings in simultaneous pancreas-KT recipients that demonstrated no variation between centers [18]. The lack of center-level variation in EHR for older KT recipients may be due to the higher medical complexity of older recipients or longer LOS compared to younger recipients rather than poor quality of care.

Furthermore, EHR is associated with increased mortality and graft loss after KT, and the 30-day readmission window represents a high-risk window for KT recipients of all ages [4, 6, 19]. These previous studies are consistent with our findings that EHR is associated with mortality in older and younger KT recipients, and not surprisingly, we demonstrated that risk of graft loss associated with EHR is greater in older KT recipients than younger KT recipients [20]. However, risk of mortality associated with EHR is greater in younger KT recipients compared to older KT recipients. The weaker association of mortality, but stronger association of graft loss among older KT recipients may be due to the fact that older recipients are at increased risk due to a number of other causes and EHR may be a marker of overall health in this population.

The greatest strength of this study is the use of a national population with a large sample size. The most notable limitation is a potential selection bias: in order to assess the prevalence and risk factors for EHR, we limited our inclusion criteria to Medicare-primary patients. However, over three-fourths of older (age ≥ 65) KT recipients are primarily covered by Medicare and, given that all ESRD patients requiring dialysis and KT are eligible for Medicare, this is a common inclusion criterion in studies of ESRD patients including our own previously published studies [1, 18]. Also, we excluded patients who were discharged to non-home facility. However, the mechanism for EHR from a non-home facility is quite different than from home, so we focused on EHR that occurs for patients at home. Another limitation is the lack of granular cause of death data available in USRDS and SRTR databases.

In conclusion, 30.1% of older KT recipients are readmitted within 30 days of transplantation, and older KT recipients have a greater risk of EHR than younger recipients. Risk factors for readmission are weaker among

older recipients than younger recipients. However, the risk of graft loss associated with EHR is greater in older KT recipients, so strategies to prevent EHR in older KT recipients would decrease costs of readmission and potentially improve patient outcomes. As an important first step, we have identified risk factors in for EHR than differ between older and younger KT recipients; further work is needed to explore interventions, which could decrease potentially preventable readmissions.

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Disclosure Statement

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

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