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Sequelae of Early Hospital Readmission After Kidney Transplantation

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Abstract

We recently elucidated risk factors for early hospital readmission (EHR) following kidney transplantation (KT). We now sought to quantify the independent associations between EHR and post-KT outcomes, including late hospital readmission (LHR: 1 year after EHR window), death-censored graft loss, and mortality, among Medicare-primary KT recipients (2000-2005). Of 32,961 KT recipients, 7.7% had a least one readmission within 3 days of discharge, 14.8% within 7 days, 22.4% within 14 days, and 30.5% within 30 days of discharge after the initial KT hospitalization. KT recipients who experienced EHR within 30 days of discharge after the initial KT hospitalization were more likely to have experienced LHR (29.6% vs. 9.0%, $P<0.001$) and were at 3.02-times higher (95%CI:2.82-3.23, $P<0.001$) risk of LHR. Additionally, EHR was associated with death-censored graft loss (deceased donor recipients HR:1.43, 95%CI: 1.36-1.51, $P<0.001$ and live donor recipients HR:1.54, 95%CI:1.40-1.70, $P<0.001$) and mortality (deceased donor recipients HR:1.50, 95%CI:1.43-1.58, $P<0.001$ and live donor recipients HR:1.45, 95%CI:1.32-1.60, $P<0.001$). 30 days post-transplant represents a high-risk window for KT recipients and the readmissions during this window are strong predictors of adverse sequelae, particularly LHRs. Efforts should be made to implement and improve systems to reduce LHR and subsequent graft loss and mortality among recipients with EHR.

Keywords

Kidney Transplant; Hospital Readmission; Mortality; Death-Censored Graft Loss; Hospitalization

INTRODUCTION

We recently reported, based on national data, that 31% of kidney transplantation (KT) recipients are readmitted within 30 days of discharge from their initial KT hospitalization

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DISCLOSURE

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(1). Factors associated with early hospital readmission (EHR) were older age, African American race, various comorbidities (including obesity, diabetes, heart disease, and chronic obstructive pulmonary disease), and transplant factors (including expanded criteria donor KT, length of stay, and lack of induction therapy) (1) as well as frailty, a geriatric construct measuring physiologic reserve (2). However, the clinical implications of EHR remain unknown.

In other populations, EHR has been identified as a strong predictor of clinically important outcomes. EHR is associated with a nearly 3-fold increased mortality risk for community-dwelling older adults (3) and is associated with 1-year mortality for patients with advanced liver disease and those undergoing colectomy for colon adenocarcinoma (4, 5). EHR is also predictive of mortality after abdominal aortic aneurysm repair (6) and percutaneous coronary interventions (7, 8). Furthermore, previous hospitalizations for those with chronic conditions are associated with readmission (9, 10).

As such, we sought to better understand the relationship between EHR after KT and adverse sequelae including late hospital readmission (LHR), graft loss and mortality. Furthermore, since there is not even a consistent definition of readmission in transplantation (11-15) or specifically in KT (1, 2, 16), we explored various definitions of EHR (including our previous definition of 30-days based on the Medicare standard for reimbursement) for best prediction of adverse sequelae.

MATERIALS AND METHODS

Study population

The study included 32,961 adult first-time kidney-only transplant recipients between January 1, 2000 and December 31, 2005, as reported to the Organ Procurement and Transplantation Network (OPTN) and linked to Medicare claims data by the United States Renal Data System (USRDS), as previously described (1). Donor, recipient, and transplant factors were gleaned from the Scientific Registry of Transplant Recipients (SRTR), a national registry of all solid organ transplants, the CMS 2728 Chronic Renal Disease Medical Evidence form, the OPTN transplant recipient registration form, and CMS claims.

Outcome and exposure ascertainment

EHR was defined as ≥ 1 hospital readmission (to any acute care hospital, based on Medicare claims) within 30 days (or other intervals as below) after discharge from initial KT hospitalization (1). LHR was defined as readmission in the year after the EHR window, and studied as both binary (≥ 1 readmissions) and count (number of readmissions). As is standard with SRTR data, mortality and graft loss were augmented through linkage with the Social Security Death Master File, and data from the Centers for Medicare and Medicaid Services.

Association between EHR and LHR

Differences in the distribution of number of LHRs were tested using a Komogrov Smirnov test. Poisson regression models were used to estimate the association between EHR and the number of LHRs. Additionally, the relative risk (RR) of ≥ 1 LHR by EHR was estimated

using modified Poisson regression, as described previously (17). These models were adjusted for the recipient, donor, and transplant factors that were previously identified as risk factors for EHR (1) and clustered by transplant center. Additionally, we stratified by donor type (live, deceased, SCD, ECD, DCD), occurrence of delayed graft function (DGF), race, and age (<65 or ≥65). For the prediction of subsequent readmission from the modified Poisson regression model, the overall statistical difference in predictive power by EHR was measured by the area under the receiver operating characteristic curve (AUC) (18).

Association between EHR and survival

Kaplan-Meier methods were used to estimate 1, 3, and 5-year patient and death-censored graft survival per stratum. Cox proportional hazards models were used to calculate adjusted hazard rate (HR) of mortality and death-censored graft loss by EHR. To ensure proper risk adjustment, standard factors accounted for in the SRTR program specific reports (19-22) were included in the models, including recipient factors (sex, age, race, BMI, HCV status, previous KT, preemptive KT, cause of ESRD, and peak PRA), transplant factors (HLA mismatches, use of pulsatile perfusion, cold ischemia time, and donor/recipient weight ratio) and donor factors (race, terminal creatinine, hypertension, expanded criteria donor, diabetes, and donation after cardiac death), and the models were all clustered by transplant center. Given that some factors are specific to deceased donor transplantation, survival models were stratified by donor type (living or deceased). We additionally stratified by the occurrence of DGF, race, age (<65 and ≥65) and deceased donor type. For all models, proportional hazards assumptions were confirmed by visual inspection of the complimentary log-log plots and Schoenfeld residuals.

Additionally, we tested whether 30-day EHR was a better predictor of 1 LHR, death-censored graft loss, and mortality than 3-, 7-, and 14-day readmission. All analyses were performed using STATA 12.1/MP for Linux (College Station, Texas).

RESULTS

Early hospital readmission

Of 32,961 KT recipients, 7.7% had a least one readmission within 3 days of discharge, 14.8% within 7 days, 22.4% within 14 days, and 30.5% within 30 days of discharge after the initial KT hospitalization (Figure 1). The mean time to EHR was 10.1 days (SD 7.9; median 8, IQR 3-15).

Late hospital readmission

Incidence of LHR (readmission in the year following the EHR window) was 12.7% for live donor recipients, 15.2% for deceased SCD recipients, 18.1% for deceased DCD recipients, and 11.7% for deceased ECD recipients (15.3% overall). Number of LHRs in this window ranged from 0 to 29. Among those with ≥1 LHR, the median number of readmissions was 4 (IQR: 2-4).

Associations between EHR and LHR

Nearly 30% of KT recipients who experienced EHR within 30 days of discharge after the initial KT hospitalization also experienced LHR in the year thereafter, more than 3 times the incidence among recipients who did not experience EHR (29.6% vs. 9.0%, $P<0.001$); similar patterns were observed for both deceased donor (31.0% vs. 9.5%, $P<0.001$) and live donor (25.1% vs. 7.8%, $P<0.001$) recipients (Table 1). The number of LHRs was also greater for those who experienced EHR ($P<0.001$); among those with 1 LHR, the median number of readmissions was 3 (IQR: 2-6) for those without EHR and 5 (IQR: 3-10) for those with EHR ($P<0.001$) (Figure 2). In adjusted models, EHR was associated with 3.02-fold higher incidence of LHR (95% CI: 2.82-3.23, $P<0.001$) (Table 2). Furthermore, EHR was associated with a 1.59-fold higher number of readmissions (95% CI: 1.50-1.68, $P<0.001$) (Table 2). The effects of EHR and LHR were similar when stratified by donor type, race, and age; however, the association of EHR and LHR as well as the number of LHRs was stronger for live donor recipients with DGF (LHR: 4.56, 95% CI: 2.87-7.25, $P<0.001$; number of LHRs: 2.05, 95% CI: 1.38-2.71, $P<0.001$) (Table 2). EHR improved risk prediction of LHR, raising the AUC from 0.629 (previously described risk factors for readmission) to 0.713 (adding EHR) ($P<0.001$).

Association between EHR and survival

Graft survival was worse for KT recipients who experienced EHR (Figure 3), both in deceased donor (83% vs. 75% at 5 years, $P<0.001$) and live donor (88% vs. 80% at 5 years, $P<0.001$) recipients (Table 1). In adjusted models, death-censored graft loss for deceased donor KT recipients who experienced EHR was 1.43-times higher (95% CI: 1.36-1.51, $P<0.001$) than those without EHR; similarly, death-censored graft loss for live donor KT recipients with EHR was 1.54-times higher (95% CI: 1.40-1.70, $P<0.001$) (Table 2). The effects of EHR and death-censored graft loss were similar when stratified by donor type, DGF, and race; however, the association between EHR and death-censored graft loss was stronger among older recipients of live donor KT (HR: 2.42, 95% CI: 1.68-3.49, $P<0.001$) (Table 2).

Patient survival was worse for KT recipients who experienced EHR (Figure 4), both among deceased donor (83% vs. 72% at 5 years, $P<0.001$) and live donor (89% vs. 80% at 5 years, $P<0.001$) recipients (Table 1). In adjusted models, mortality for deceased donor KT recipients who experienced EHR was 1.50-times higher (95% CI: 1.43-1.58, $P<0.001$) than those without EHR; similarly, mortality for live donor KT recipients with EHR was 1.45-times higher (95% CI: 1.32-1.60, $P<0.001$) (Table 2). The effects of EHR and mortality were similar when stratified by donor type, DGF, race, age (Table 2).

Definition of EHR for KT recipients

EHR occurring in the first 30 days post-KT was overall the best predictor of outcomes after KT (Table 3). There was a statistically significant improvement in predicting LHR, mortality, and death-censored graft loss when EHR defined as 30 days after KT compared to a 3-, 7-, or 14-definition for all but one comparison.

DISCUSSION

In this national study of kidney transplant recipients using longitudinal Medicare claims data, recipients who experienced EHR were at approximately 3.0-times the risk of LHR, 1.5-times the risk of death-censored graft loss, and 1.5-times the risk of mortality. Importantly, EHR substantially improved risk prediction for LHR among KT recipients (from AUC 0.629 to 0.713). EHR defined as readmission occurring in the first 30 days post-KT was the best predictor of these outcomes.

Our findings in KT are consistent within the context of EHR in other surgical specialties. For example, among patients undergoing aneurysm repair, the 1-year mortality in patients who experienced EHR was 23.4% versus 4.5% in those without EHR (6). Similarly, a study of patients undergoing percutaneous coronary intervention found that EHR was independently associated with a 2-fold risk of 1-year mortality (7). Our study extended the previous work on EHR and mortality to KT, and also to other clinically important outcomes including LHR and death-censored graft loss. Additionally, this is the first study to identify a definition of EHR that best predicts these outcomes. While our study clearly identifies a strong association between EHR and LHR, death-censored graft loss, and mortality, it remains unclear whether changes in EHR would improve these outcomes.

Our findings may have implications for how closely a KT recipient should be monitored post-transplant, and how closely linked they should remain to their transplant hospital. In many centers, KT recipients transition their care from the hospital-based transplant team to a community-based general nephrology team at around three months post-KT. It is possible that recipients with EHR might benefit from being cared for by one of the hospital-based transplant teams for longer. These high-risk patients might also benefit from more frequent follow-up visits, bloodwork, phone calls, or other scrutiny. Finally, coordination of care when these patients are transitioned to the nephrologist could be improved through interventions such as a medication compliance phone calls, more appointment reminders, and better follow-up after missed appointments. Although it is unclear whether these interventions will be feasible and effective in KT populations to prevent the sequelae identified in our study, our research suggests that flagging those with EHR as higher-risk, and somehow treating them differently, is likely important.

The possible medical causes of hospital readmission following KT include post-surgical complications, rejection, infection, difficulty achieving adequate drug levels, drug toxicity, and many others (1, 16); in addition, the threshold for readmission (versus outpatient management) might depend on mechanisms such as hospital-level resources and patient-level social support. In many cases, a given cause for readmission may require different intervention depending on the patient. For example, in our own center, we have a relatively high proportion of patients undergoing desensitization therapy prior to and following KT; EHR in these patients is often due to rise in donor-specific antibody requiring plasmapheresis. Interventions to decrease readmission in this group of patients might focus on criteria for sustained absence of donor-specific antibody prior to discharge, and/or better mechanisms for outpatient plasmapheresis and antibody monitoring (23). Another example is readmission due to medication non-compliance. Interventions to decrease readmission in

this group might focus on patient and family education prior to discharge as well as phone call reminders and frequent clinic visits following discharge (24).

This study, like our previous work on EHR (1), has a few notable limitations. In order to detect EHR, we had to limit our population to Medicare-primary patients, a criterion which could differentially affect older and younger patients and thus affect generalizability. However, given that all ESRD patients requiring dialysis therapy are eligible for Medicare, this is a common inclusion criterion in studies of ESRD patients (1, 25-27). Additionally, this national registry does not capture recipient frailty status, which has been identified as an important predictor of EHR (2). Finally, this study was based on observational data and, thus, it remains unclear whether changes in EHR would improve rates of LHR, graft-loss, and mortality.

In conclusion, EHR is a strong, independent risk factor (and improves risk prediction) for sequelae including late readmission, graft loss and mortality after KT. Patients with EHR should be viewed as high risk for other adverse sequelae and efforts should be made to implement and improve systems to minimize risk in these patients.

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Figure 1. Percent of Kidney Transplantation Recipients with Early Hospital Readmission (EHR) by Day Since Discharge for KT
3-, 7-, and 14-day EHR rates are illustrated by red lines.

Figure 2. Number of Late Hospital Readmissions (LHRs) by Early Hospital Readmission (EHR) Status for Kidney Transplant Recipients with 1 LHR

The median number of hospitalizations are illustrated by a red line (No EHR: 3; EHR: 5 hospitalizations). There were 2,066 LHRs for recipients without EHR and 2,974 LHRs for recipients with EHR.

Figure 3. Death-Censored Graft Loss After Kidney Transplantation (KT), by Early Hospital Readmission (EHR)

Figure 4. Mortality After Kidney Transplantation (KT), by Early Hospital Readmission (EHR)

Table 1

Late Hospital Readmission, Death-Censored Graft Loss, and Mortality by Early Hospital Readmission in the first 30 Post-Transplant Days

	Deceased Donor Recipient		Live Donor Recipient	
	No EHR	EHR ¹	No EHR	EHR ¹
Late Hospital Readmission (%)²	9.5	31.0	7.8	25.1
Death-Censored Graft Survival (%)				
3-month	98	94	99	96
6-month	97	92	99	95
1-year	96	89	98	94
3-year	89	82	94	88
5-year	83	75	88	80
Patient Survival (%)				
3-month	99	97	99	98
6-month	98	94	99	97
1-year	97	91	98	95
3-year	91	81	94	88
5-year	83	72	89	80

¹ EHR= Early Hospital Readmission in the first 30 days following kidney transplantation.

² Late Hospital Readmission is 1 hospitalization in the year following EHR.

Table 2

Risk of Late Hospital Readmission, Death-Censored Graft Loss, and Mortality, by Early Hospital Readmission

	RR of Outcomes For Those With EHR			
	Late hospital readmission ¹	Number of LHRs ¹	Death-censored graft loss ²	Mortality ²
All recipients	3.02 2.82-3.23	1.59 1.50-1.68	-	-
Deceased donor recipients	3.03 2.81-3.26	1.59 1.49-1.68	1.43 1.36-1.51	1.50 1.43-1.58
Without DGF	3.07 2.81-3.35	1.59 1.48-1.69	1.36 1.28-1.45	1.48 1.36-1.61
With DGF	2.75 2.46-3.07	1.52 1.37-1.67	1.39 1.27-1.53	1.46 1.38-1.55
Caucasian	3.16 2.91-3.44	1.57 1.46-1.68	1.49 1.39-1.60	1.56 1.48-1.65
African American	2.77 2.49-3.07	1.58 1.45-1.71	1.35 1.25-1.47	1.41 1.29-1.53
Younger adults (<65)	3.06 2.83-3.30	1.60 1.50-1.70	1.40 1.32-1.47	1.50 1.43-1.58
Older Adults (≥ 65)	2.85 2.39-3.40	1.54 1.32-1.76	1.55 1.29-1.85	1.60 1.44-1.77
SCD	3.13 2.92-3.36	1.63 1.59-1.66	1.38 1.29-1.47	1.50 1.43-1.59
DCD	3.25 2.49-4.25	1.46 1.33-1.59	1.72 1.38-2.15	1.30 1.04-1.63*
ECD	2.65 2.33-3.00	1.49 1.43-1.55	1.54 1.39-1.70	1.52 1.37-1.69
Live donor recipients	2.98 2.66-3.33	1.56 1.50-1.61	1.54 1.40-1.70	1.45 1.32-1.60
Without DGF	2.86 2.50-3.27	1.52 1.33-1.71	1.47 1.32-1.65	1.41 1.27-1.56
With DGF	4.56 2.87-7.25	2.05 1.38-2.71	1.53* 1.13-2.06	1.70 1.29-2.25
Caucasian	2.85	1.54	1.67	1.45

	RR of Outcomes For Those With EHR			
	Late hospital readmission ¹	Number of LHRs ¹	Death-censored graft loss ²	Mortality ²
	2.46-3.31	1.34-1.74	1.50-1.88	1.30-1.62
African American	3.35 2.67-4.21	1.63 1.32-1.93	1.27* 1.04-1.54	1.52 1.25-1.84
Younger adults (<65)	2.94 2.56-3.37	1.58 1.37-1.78	1.50 1.35-1.66	1.46 1.31-1.62
Older Adults (≥ 65)	3.30 2.43-4.48	1.50 1.07-1.93	2.42 1.68-3.49	1.51 1.24-1.83

¹ Adjusted for previously published predictors of readmission (1).

² Adjusted for standard factors accounted for in the SRTR program specific reports.

* $P < 0.05$. All other $P < 0.001$. The risk of death-censored graft loss and mortality were not calculated for all recipients because the SRTR models are specific to donor type.

Table 3

Risk Prediction for Late Hospital Readmission, Death-Censored Graft Loss, and Mortality by Varied Definitions of Early Hospital Readmission

	<u>Number of Days Between Kidney Transplantation and Readmission</u>			
	<u>3</u>	<u>7</u>	<u>14</u>	<u>30</u>
Late Hospital Readmission (AUC)	0.637**	0.643**	0.662**	0.713
Death-Censored Graft Loss (C-statistic)				
Deceased Donor Recipients	0.653**	0.654**	0.656*	0.659
Live Donor Recipients	0.663**	0.665**	0.667**	0.672
Mortality (C-statistic)				
Deceased Donor Recipients	0.692**	0.694**	0.696**	0.698
Live Donor Recipients	0.712**	0.715*	0.717	0.718

**
<0.001 compared to EHR defined as 30 days after KT

*
<0.05 compared to EHR defined as 30 days after KT

AUC= Area under the receiver operating characteristic curve

C-statistics= Harrel's C-statistic (28)