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Early hospital readmissions post-kidney transplantation are associated with inferior clinical outcomes

Luan FL, Barrantes F, Roth RS, Samaniego M. Early hospital readmissions post-kidney transplantation are associated with inferior clinical outcomes.

Abstract: Unplanned hospital readmissions are common early post-kidney transplantation. We investigated the relationship between early hospital readmissions and clinical outcomes in a single-center retrospective study that included all adult kidney transplant patients between 2004 and 2008 with follow-up to December 2012. The early hospital readmissions within the first 30 d were numbered and the diagnosis ascertained. Patients were grouped as none, once, and twice or more readmissions. Predictors of early readmissions were assessed, and clinical outcomes and patient and death-censored kidney survival were compared. Among 1064 patients, 203 (19.1%) patients had once and 83 (7.8%) patients had twice or more readmissions within 30 d. Surgical complications, infections, and acute kidney injuries/acute rejection were three most common diagnoses. The length of initial hospital stay and African American race were among the variables associated significantly with readmissions. Patients with early readmissions had lower baseline renal function ($p < 0.01$) and more early acute rejection ($p < 0.01$). During follow-up, only frequent readmissions, twice or more, within 30 d were associated with increased risk of death (AHR 1.75, $p = 0.01$) and death-censored kidney failure (AHR 2.20, $p < 0.01$). Frequent early hospital readmissions post-transplantation identify patients at risk for poor long-term outcomes, and more studies are needed to understand the mechanisms.

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Unplanned hospital readmissions following index medical and/or surgical events are common and costly (1). Readmissions increase the burden to patients and their care providers, place patients at high risk for errors related to transition-of-care, and likely reflect suboptimal patient care (2, 3). Reducing readmissions through specific interventions has the potential to both lower the cost associated with readmissions and improve clinical outcomes (4). While researchers have investigated hospital readmissions following index medical and/or surgical admissions and/or procedures among general population, there are relatively few publications that examined hospital readmissions among patients undergoing kidney transplantation (5–7). Early studies have generally focused on the incidence and the causes of hospital readmissions, either at 30 d or within the first year (5, 8, 9). There have been only two reports exploring the association between hospital readmissions with subsequent clinical outcomes among kidney transplant patients (5, 10).

The need for hospital readmissions early after kidney transplantation is likely multifactorial and related, in part, to the transplant procedure itself. Demographic factors, pre-existent medical and psychological comorbidities, and pre-transplant physical conditioning may each interfere with the recovery process post-transplantation and may result in the need for early readmission (8, 11–13). In addition, the requirement for long-term use of immunosuppressive medications adds to the uniqueness of this patient population as adverse effects of immunosuppressants can also lead to hospital readmissions (12, 14). Further, the frequency of readmissions early post-transplantation could reflect deficits in post-transplant medical management and thus may be useful in scrutinizing

standard practice patterns for patients who undergo kidney transplantation. To this end, we conducted a single-center retrospective study to investigate the causes and clinical predictors of early hospital readmissions within 30 d following kidney transplantation and to explore the relationship between early hospital readmissions and long-term clinical outcomes.

Patients and methods

This is a retrospective and single-center observational study that included all adult kidney transplant recipients engrafted between January 1, 2004 and December 31, 2008 with follow-up to December 31, 2012. The institutional review board approved the study.

Patients who received simultaneous multi-organ transplants, who died or lost the kidney graft during the initial hospital stay, or who experienced primary non-function of the graft were excluded. Demographic and baseline characteristics of the study population including recipient, donor, and transplant-related parameters were obtained from the institutional electronic medical record database. In particular, we identified the pre-transplant history of illicit drug and alcohol abuse, chronic opioid usage, and self-reported psychiatric conditions such as depression, anxiety, etc. among others during the transplant evaluation process. Baseline renal function was expressed as estimated glomerular filtration rate (eGFR) calculated by the Modification of Diet in Renal Disease (MDRD) four-variable formula using stably achieved lowest serum creatinine levels (at least three readings in a two-wk period) within the first month after transplantation (15). The occurrence of acute rejection during the first month was documented through clinically indicated biopsy according to Banff classification (16). Finally, the information on death and graft loss beyond the first 30 d was collected during the follow-up and the causes documented.

The unplanned early readmissions within 30 d following the transplant surgery were documented from the institutional electronic medical records with admission diagnosis verified using related discharge summaries. The causes of hospital readmissions were grouped into the following categories: cardiovascular events (CVE), infectious events, surgical complications, acute kidney injuries/acute rejection (AKI/AR), fluid and electrolytes (FE) issues, gastrointestinal (GI) disorders, deep vein thrombosis (DVT), and others.

We separated the study population into three groups according to the number of hospital readmissions within 30 d post-transplantation: none, once (isolated), and twice or more readmissions (frequent). We included all baseline patient, donor, and transplant-related characteristics to assess their potential association with unplanned readmissions.

We compared the baseline renal function achieved and the incidence of biopsy-proven acute rejection among the three groups during the first 30 d. We then performed conditional survival analysis beyond 30 d and considered separately patient and death-censored kidney survival as long-term clinical outcomes among the three groups. We further compared the cause of death and/or kidney graft loss among the three groups.

The distribution of categorical variables was expressed as proportions and compared using chi-square (χ^2) test, and the measurements of continuous variables were summarized as a mean and standard deviation and compared using the analysis of variance (ANOVA) test. Multinomial logistical regression analyses were used to assess predictors as adjusted odds ratios (AOR) of hospital readmission: once and twice or more readmissions. All recipient, donor, and transplant-related characteristics were assessed individually and included in the multivariate models via a backward selection. Kaplan–Meier survival curves with log-rank testing were performed to compare patient and death-censored graft survival beyond 30 d among the three groups. Cox regression analyses were performed to calculate adjusted hazard ratios (AHR) for the entire cohort groups: all recipient, donor, and transplant characteristics, as well as achieved baseline renal function and occurrence of acute rejection were individually assessed and considered for inclusion in the multivariate models if the individual p-value was 0.10 or less. Alternatively, we included all baseline variables in the models to obtain statistically significant association. We assessed the potential for multicollinearity among the baseline variables by visually inspecting the correlation coefficiency between each and individual pair of variables. Backward selection method was employed. A cutoff of 0.05 was used to individually and independently determine the contribution of such variables to the outcomes.

All statistical tests were two sided, and a p-value equal to or less than 0.05 was considered significant. Statistical analyses were conducted using SAS 9.3. (Cary, NC, USA).

Results

Study population

During the study period, 1064 kidney transplant patients met the criteria to be included in the

analyses. The mean length of follow-up was 64.0 ± 26.8 months and the median 66.1 (50.0, 83.7) months. Overall, 286 (26.9%) patients had a total of 383 (36.0%) hospital readmissions within 30 d post-transplantation. Among them, 204 (19.2%) patients had one and 82 (7.7%) patients had twice or more readmissions. The demographic and baseline characteristics of study population are shown in Table 1. Mean age of entire study population was 49.3 (±13.2) years old. Median length of initial hospital stay was 4 (2, 34) days. Six hundred and sixty-eight subjects were male (62.8%), and 193 were African American (AA; 18.1%). Patients who required hospital readmissions were more likely to be AA ($p < 0.01$), to have longer pre-transplant dialysis time ($p < 0.01$), less likely to have pre-emptive ($p = 0.03$) and/or living donor kidney transplantation ($p < 0.01$). Furthermore, these patients had higher prevalence of coexisting psychiatric diagnosis ($p < 0.01$), higher prevalence for smoking history ($p = 0.01$), and were less likely to have private health insurance ($p = 0.01$). At the time of transplantation, they received more often kidneys from expanded criteria donors (ECD; $p < 0.01$) and donors after cardiac death (DCD; $p < 0.01$), had more HLA mismatches ($p < 0.01$), experienced more delayed graft function (DGF; $p < 0.01$), and required longer initial inpatient stay ($p < 0.01$).

Causes and predictors of hospital readmissions

The most common diagnosis justifying early readmissions was surgical complications accounting for 32.4% of all readmissions, followed by infection (20.1%), acute kidney injuries/acute rejection (13.0%), CVE (11.0%), fluid and electrolyte issues (11.5%), gastrointestinal complaints (5.7%), deep vein thrombosis (1.3%), and others (5.0%). Although there were more readmissions related to

Table 1. Demographic and baseline characteristics of study population

	Hospital readmissions			
	None, n = 778	Once, n = 204	Twice or more, n = 82	p
Recipient characteristics				
Age, yr (SD)	49.2 (13.1)	46.7 (14.0)	49.8 (12.3)	0.88
Gender, male (%)	489 (62.9)	125 (62.7)	54 (65.9)	0.77
Race, African American (%)	126 (16.2)	51 (25.0)	22 (26.8)	<0.01
BMI, kg/m^2 (SD)	28.4 (5.6)	28.5 (5.6)	29.0 (6.9)	0.67
Dialysis duration, yr (SD)	2.2 (2.6)	3.0 (3.0)	3.3 (3.2)	<0.01
Diabetes mellitus, yes (%)	259 (33.3)	82 (42.2)	27 (32.9)	0.17
Smoking history, yes (%)	367 (47.2)	117 (57.4)	49 (59.8)	0.01
Alcohol abuse history, yes (%)	79 (10.2)	23 (11.3)	13 (15.9)	0.28
Drug abuse history, yes (%)	91 (11.7)	25 (12.3)	12 (14.6)	0.73
Chronic opioid use history, yes (%)	71 (9.1)	26 (12.8)	11 (13.4)	0.19
Psychiatric history, yes (%)	216 (27.8)	67 (32.8)	40 (48.8)	<0.01
College education, yes (%)	389 (50.0)	90 (44.1)	31 (37.8)	0.05
Private insurance, yes (%)	352 (45.2)	76 (37.3)	24 (29.3)	0.01
Employed, yes (%)	332 (42.7)	79 (38.7)	31 (37.8)	0.46
First transplant, yes (%)	671 (86.3)	176 (86.3)	71 (86.6)	0.99
Pre-emptive transplant, yes (%)	211 (27.1)	43 (21.1)	13 (15.9)	0.03
Positive HCV serology, yes (%)	29 (3.7)	12 (5.9)	7 (8.5)	0.08
PRA, >20% (%)	169 (21.7)	51 (25.0)	15 (18.3)	0.42
Donor characteristics				
Age, yr (SD)	39.5 (13.4)	39.8 (12.7)	39.6 (15.6)	0.96
Gender, male (%)	408 (52.4)	99 (48.5)	51 (62.2)	0.11
Living donor, yes (%)	413 (53.1)	84 (41.2)	34 (41.5)	<0.01
Expanded criteria donors, yes (%)	83 (10.7)	44 (21.6)	13 (15.9)	<0.01
Donors after cardiac death, yes (%)	42 (5.4)	27 (13.2)	8 (9.8)	<0.01
Transplant characteristics				
HLA mismatches, n (SD)	3.1 (1.9)	3.6 (1.8)	3.5 (1.9)	<0.01
Cold ischemia time, hours (SD)	7.7 (6.9)	8.7 (6.7)	8.6 (7.0)	0.14
Delayed graft function, yes (%)	92 (11.8)	45 (22.1)	18 (22.0)	<0.01
	160 (20.6)	34 (16.7)	22 (26.8)	0.15
CMV D+/R−, yes (%)				
Calcineurin inhibitors, CsA (%)	718 (92.3)	182 (89.2)	77 (93.3)	0.28
rATG induction, yes (%)	184 (23.7)	46 (22.6)	24 (29.3)	0.47
Initial hospital stay, days (SD)	5.1 (3.3)	6.7 (5.7)	6.5 (4.2)	<0.01

surgical and infectious complications among patients with frequent early readmissions, the overall pattern was similar between patients with isolated and frequent readmissions (Fig. 1). Longer initial inpatient stay (days), a positive self-reported psychiatric history, being an AA patient, receiving an ECD kidney transplant, having higher HLA mismatches and having a positive smoking history were variably associated with high likelihood of readmissions (once and/or twice or more) within the initial 30 d (Table 2).

Baseline renal function and episodes of acute rejection during the two time periods

Patients who required early readmissions achieved significantly lower baseline transplant renal function (eGFR: 61.6 ± 16.1, 57.4 ± 17.1 and 59.1 + 18.4 mL/min, ANOVA, $p < 0.01$). Similarly, patients with early readmissions also had more frequent episodes of biopsy-documented acute rejection (3.0%, 15.7%, and 13.4%, χ^2, $p < 0.01$).

Long-term clinical outcomes

There were four cases of death and/or kidney failure within 30 d. They were excluded from subsequent survival analyses. During follow-up, 147 patients died and 80 kidney grafts were lost (death censored). The most common causes of death were CVE (37.4%), infections (27.9%), and malignancies (10.2%). However, a large fraction of death had unknown or otherwise non-specified causes (25.4%). The predominant causes of graft loss were acute and/or chronic rejection (75.0%) followed by infectious (7.5%) and other/or non-specified causes (17.5%). Patients who had early readmissions displayed inferior clinical outcomes,

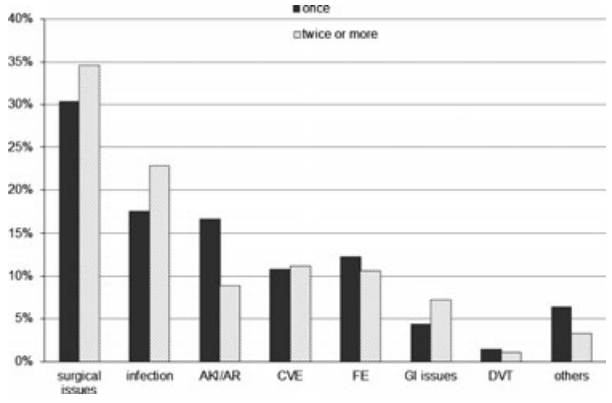

Fig. 1. Causes of early readmission among patients with isolated or frequent readmissions during the first 30 d.

defined as patient (Fig. 2A, log-rank, $p < 0.001$) and death-censored kidney survival (Fig. 2B, log-rank, $p < 0.001$). Cox proportional regression analyses, either univariate or multivariate models adjusting for various demographic characteristics, as well as baseline renal function achieved and occurrence of biopsy-documented early acute rejection, confirmed the statistically significant association between frequent hospital readmissions (twice or more) and increased risk of death and death-censored kidney failure: a 75% increase in the risk of death (AHR 1.75, 95% CI 1.19, 2.59, $p = 0.01$ for frequent readmissions) and more than 100% increase in the risk of death-censored kidney failure (AHR 2.20, 95% CI 1.33, 3.64, $p < 0.01$ for frequent readmissions; Table 3), respectively. Numerically, more patients from zero readmission group than from isolated and frequent readmission groups died of CVE (42.0% vs. 33.3% and 23.5%, respectively), and more patients from readmission groups (isolated and frequent) than from zero readmission group died of infectious causes (33.3% and 35.3%, respectively, vs. 23.9%). However, these differences were not statistically significant ($p = 0.47$). Similarly, no significant difference was found in the causes of kidney graft loss among the groups although more patients from frequent readmission group lost kidney due to infection (21.4% vs. 12.5% and 2.0% among patients with isolated and zero readmission, respectively, $p = 0.09$).

Additional variables associated with an increased risk of death included old patient age, longer dialysis vintage, presence of diabetes mellitus as comorbidity, a history of alcohol abuse and chronic opioid usage prior to transplantation, and longer initial hospital stay at transplantation. Having a higher baseline renal function, on the other hand, was associated with lower risk of death. Finally, an increased risk for death-censored kidney failure was observed for AA patients, patients with a positive smoking history, and patients who had DGF, whereas old patient age, receiving first transplant, having higher baseline renal function and private health insurance were associated with a reduced risk for death-censored kidney failure (Table 3).

Discussion

The present study shows that unplanned hospital readmissions following index kidney transplantation are very common early post-transplantation and negatively associated with both short- and long-term post-transplant clinical outcomes. In particular, frequent hospital readmissions, twice or more, during the initial 30 d were associated with

Table 2. Predictors of early hospital readmissions[a]

	Once			Twice or more		
Variables	AOR	95% CI	p	AOR	95% CI	p
Initial hospital stay, d	1.08	1.04, 1.12	<0.01	1.07	1.02, 1.12	0.01
Psychiatric history, yes	1.24	0.88, 1.74	0.22	2.45	1.53, 3.92	<0.01
African American, yes	1.65	1.13, 2.42	0.01	1.98	1.15, 3.39	0.01
ECD, yes	1.94	1.27, 2.96	<0.01	1.21	0.63, 2.36	0.57
Smoking history, yes	1.48	1.07, 2.03	0.02	1.52	0.95, 2.44	0.08

AOR, adjusted odds ratios; ECD, expanded criteria donors.
[a]Patients with no readmission as reference group.

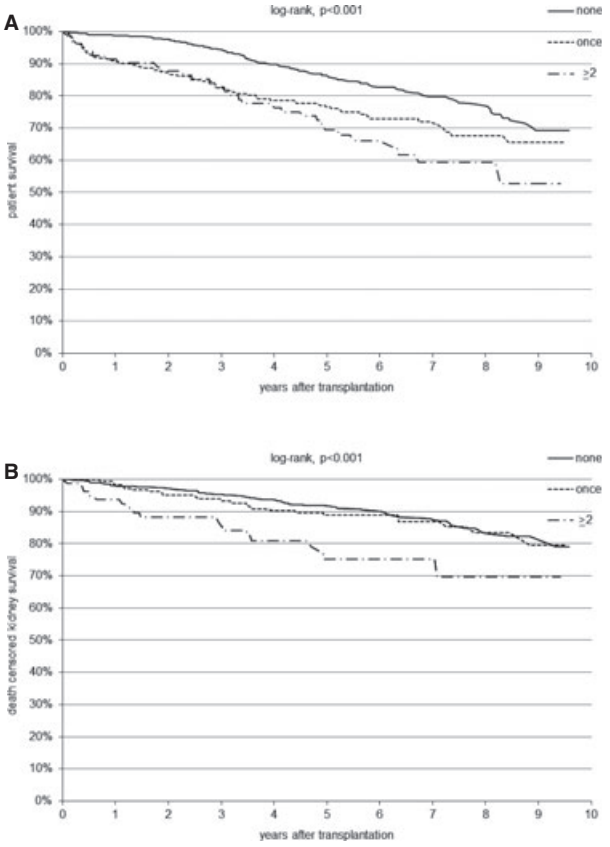

Fig. 2. Kaplan–Meier conditional survival analysis: (A) patient survival and (B) death-censored kidney survival.

75% higher risk of death and more than 100% higher risk of death-censored kidney failure.

Kidney transplantation is considered an elective surgical procedure given the availability of dialysis for patients with end-stage renal disease. Nevertheless, this elective surgical procedure faces unique challenges as the patient population served by kidney transplantation often carries significant burden of medical and/or surgical comorbidities including diabetes mellitus, hypertension, coronary artery disease, and peripheral vascular occlusive disease. These patients also require long-term use of immunosuppressive medications post-transplantation, which in turn can lead to various adverse effects ranging from infections to metabolic de-arrangements and malignancy (17–19). Our observed readmission rate of 36% during the initial 30 d is close to the 31% overall early hospital readmission rate reported recently by McAdams-DeMarco et al. using national data (6). Similarly, the reasons for readmissions, observed in our study that included surgical complications, infection, acute kidney injuries/acute rejection, and CVE, are also in line with their findings as well as other previous reports and consistent with the nature of the index hospitalization, the overall state of immunosuppression, and the increased cardiovascular burden of kidney transplant patients (5–7, 12, 14). The presence and severity of these comorbidities likely affect the risk for readmissions, as evidenced by studies involving both general and kidney transplant patient population, although the practice patterns of individual hospitals (a center effect) could influence the readmission rates as well (1, 6, 20, 21). There was no significant difference in the pattern for the reasons of readmission between patients with isolated and frequent early readmission, although numerically, surgical complication and infection contributed more to the frequent readmission early after transplantation. Furthermore, we observed positive association between various demographic and baseline characteristics and the readmissions. Some of them were similar to those reported by the previous studies such as length of initial hospital stay, AA race, and receiving an ECD kidney, whereas others were not, like a pre-transplant history of reported psychiatric conditions and smoking habit. It remains unclear why patients with a positive psychiatric history were more likely to have frequent readmissions. After a detailed review, only five readmissions among four patients were related psychological diagnosis as the primary reason. During subsequent follow-up, a positive history of psychiatric illness was not associated with increased risk of death or kidney graft loss (data not shown).

Table 3. Association between early readmissions, various baseline characteristics, and risk of death and death-censored kidney graft failure

	Death			Graft failure		
Variables	HR	95% CI	p	HR	95% CI	p
Early readmission [a,b]						
Once	1.56	1.16, 2.10	0.01			ns
Twice or more	2.21	1.49, 3.26	0.01	2.49	1.50, 4.14	0.01
Early readmission [a,c]						
Once			ns			ns
Twice or more	1.75	1.19, 2.59	0.01	2.20	1.33, 3.64	<0.01
eGFR, mL/min	0.99	0.98, 1.00	0.01	0.97	0.96, 0.98	<0.01
Recipient age, yr	1.05	1.04, 1.07	<0.01	0.98	0.96, 0.99	<0.01
Dialysis duration, yr	1.07	1.02, 1.13	0.01			ns
African American, yes			ns	1.89	1.27, 2.80	<0.01
Diabetes mellitus, yes	2.35	1.81, 3.05	<0.01			ns
History of alcohol abuse, yes	1.72	1.23, 2.41	<0.01			ns
History of opioid usage, yes	1.57	1.09, 2.27	0.02			ns
Initial hospital stay, d	1.04	1.01, 1.06	<0.01			ns
First transplant, yes			ns	0.42	0.28, 0.63	<0.01
Private health insurance, yes			ns	0.59	0.41, 0.87	0.01
Delayed graft function, yes			ns	1.57	1.02, 2.42	0.04
Positive smoking history, yes			ns	1.72	1.20, 2.46	<0.01

ns, not significant.
[a]Patients with no readmission as reference group.
[b]Univariate analysis.
[c]Multivariate analysis including only baseline characteristic with $p \leq 0.10$ in univariate analysis.

We observed lower achieved baseline renal function and higher incidence of acute rejection during the early periods among patients who required hospital readmissions. It is possible that conditions leading to hospital readmissions could be either related to poorer renal function/acute rejection or contribute to poorer renal function. An interesting and potentially useful observation derived from our study, however, is the independent negative association of frequent rather than isolated early readmissions post-transplantation with future clinical outcomes. There could be at least two possible explanations for this finding. First, the conditions that led to frequent early readmissions were directly responsible for subsequent occurrence of clinical events. The finding of higher numbers of death and kidney graft loss as a result of infection among patients with isolated and/or frequent early readmissions would support such speculation although relatively lower numbers of events (death and/or graft loss) likely prevented a statistically meaningful comparison. Alternatively, patients who required frequent early hospital readmissions had underlying medical, surgical, and social conditions that increased the risk for future clinical events. Our findings would suggest that frequent hospital readmissions early after transplantation can be a marker of increased risk for inferior long-term transplant outcomes and that infection, as a cause for readmission, likely played a major detrimental role. More studies are needed to confirm our observations and to investigate the utility of interventions such as dedicate and individualized predischarge planning, post-discharge telephone call, timely follow-up appointment in the outpatient clinic, and prompt referral to specialist clinics such as infectious disease and cardiology clinics, etc. for patients who required frequent early readmissions as means to improve long-term outcomes (4).

Among other baseline variables, we found unique negative association between a positive history of alcohol abuse and chronic opioid usage prior to transplantation and risk of death, as we reported previously (22). On the other hand, we did not find any negative impact of early acute rejection on the long-term clinical outcomes, either in univariate or multivariate analyses, with and/or without early hospital readmissions in the model. We speculate that early episodes of acute rejection were more likely diagnosed promptly, treated accordingly and effectively.

Our study has several limitations. First, it is a retrospective observational study, and thus, a causal relationship between various variables examined in the study and the frequency of hospital readmissions and undesirable clinical outcomes cannot be ascertained by the study design. Second, although a specific diagnosis was identified for each readmission, such diagnoses may not be the

primary or only reason for readmission as individual physicians may use different readmission criteria and possess different thresholds for hospital admission for patients with a similar diagnosis. Third, as both patient and center effects play an important role in determining early hospital readmission rate (6), the generalizability of a single-center experience such as ours remains uncertain. Fourth, many of the pre-transplant baseline information were self-reported by patients during the transplant evaluation process, such as habit of illicit drug and/or chronic opioid use, psychiatric conditions, etc.; thus, caution should be taken at interpreting any positive association with outcomes observed in our study. Finally, while all patients received their transplant surgery in our hospital, our measurement of readmission may not represent the readmission rate for each patient as some patients may have been admitted to community hospitals for kidney-related or no medical problems that were not captured in our dataset. This study will require replication, possibly using larger regional or national data adjusting for the center effects (such as transplant volume, geographic location, etc.), if we are to determine clinical interventions that address the population of kidney transplant patients who experience frequent early readmissions for transplant-related surgical and/or medical complications to promote more positive long-term clinical outcomes.

In summary, frequent hospital readmissions within 30 d post-kidney transplantation identify kidney transplant patients at risk for future negative clinical outcomes. More studies are needed to confirm our observation and to understand the underlying mechanisms of this negative association.

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