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Decreasing Estimated Glomerular Filtration Rate Is Associated With Increased Risk of Hospitalization After Kidney Transplantation

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Introduction: After renal transplantation, decreased renal function is associated with increased risk of cardiovascular disease, graft loss, and mortality. We investigated whether declining renal function was associated with hospitalization after transplantation.

Methods: Adult, first-time, kidney transplant recipients between 2004 and 2006 from the United Network for Organ Sharing database and hospitalizations 1 year after the 6-month posttransplant follow-up visit were examined. Generalized linear models explored the relationship between estimated glomerular filtration rate (eGFR) measured at 6 months and the number of hospitalizations in the following year.

Results: Of 15,778 kidney transplant recipients, 19.1% were admitted in the year after the 6-month follow-up visit. Among those hospitalized, the mean number of hospitalizations was 1.71, which increased with decreasing eGFR. In multivariable models, a decrease in eGFR was significantly associated with increased hospitalizations: for every 10 ml/min per 1.73 m^2 decrease in eGFR, there was an 11% increase in hospitalization rate ($P < 0.001$). Lower eGFR after the first 6 months after transplantation was associated with an increase in late hospitalizations among adult kidney transplant recipients.

Discussion: Identifying patients with declining eGFR and other risk factors may help prevent morbidity and mortality associated with hospitalization after transplantation.

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The treatment of end-stage renal disease requires renal replacement therapy in the form of dialysis or renal transplantation; transplantation is the preferred treatment, and is associated with lower mortality and improved quality of life.[1] Prior studies have shown that estimated glomerular filtration rate (eGFR) is the best predictor of long-term graft function among transplant recipients[2,3] and that declining eGFR after kidney transplantation is associated with higher health care costs;[4,5] however, the association between declining eGFR and posttransplantation hospitalization has not been examined. Hospital readmission can be used as a proxy of poor health outcomes after renal transplantation. According to an analysis of Medicare claims data from 2003 to 2004, 1 of 5 Medicare beneficiaries were rehospitalized within 30 days of discharge at a cost of $17.4 billion.[6]

Prior studies have found that 30-day readmission or "early readmission" after kidney transplantation is associated with increased morbidity, costs, and transition-of-care errors[7] in addition to increased graft loss and mortality among patients with Medicare primary insurance.[8,9] Despite a sizeable amount of research on early hospital readmission among kidney transplant recipients, to our knowledge, no study has examined eGFR as a predictor of hospital readmission beyond 6 months after transplantation. The purpose of this study was to determine whether the eGFR 6 months after renal transplantation was associated with "late" all-cause hospitalization approximately 1 year

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after the 6-month posttransplant data collection point. In addition, because prior studies of hospitalization among kidney transplant recipients have been conducted among patients receiving Medicare as primary insurance only, we sought to characterize the key risk factors for late hospital readmission among a population that is more generalizable to the entire US kidney transplant recipient population.

METHODS

Study Population and Data Sources

The United Network for Organ Sharing (UNOS) is a nonprofit organization that maintains the Organ Procurement and Transplantation Network database. Organ Procurement and Transplantation Network contains information regarding every organ donation and transplant event in the United States since 1 October 1987. For this study, we used the Standard Transplant Analysis and Research files based on Organ Procurement and Transplantation Network data for kidney, pancreas, and kidney-pancreas waiting list and transplant and/or follow-up patients between 1 October 1987 and 31 October 2011.

We restricted our analyses to data from 30 June 2004 to 1 January 2007 for adult (18 years or older), first-time, kidney-only transplant recipients where the transplant was received before 1 January 2006, based on the availability of data regarding hospitalizations during the follow-up period, which was a required field on UNOS transplant follow-up forms until 1 January 2007. Our follow-up time of 2 years after transplantation (18 months after the 6-month "baseline" for this study) was also chosen based on the availability of hospitalization data. Whereas 95% of patients had hospitalization follow-up data at 2 years after transplantation, fewer than half of participants had hospitalization data after this time point. Figure 1 shows exclusion and selection criteria. Analyses were further restricted by excluding patients with missing information on both the exposure—eGFR (n = 302)—and outcome—number of hospitalizations during the year after the 6-month post-renal-transplantation follow-up (n = 318). Next, patients who died (n = 369) or were lost to follow-up (n = 82) during the study period were similarly excluded. Unlikely, values for eGFR (>125 ml/min per 1.73 m^2) were set to missing (n = 83). The patients who were excluded for missing data on exposure or outcome were compared with those who were included in this analysis and found to be similar.

Primary Exposure

The primary exposure was eGFR collected on the UNOS transplant recipient follow-up forms at 6 months, and calculated using the 4-variable Modification of Diet in Renal Disease equation.[10] The eGFR was calculated from serum creatinine measured and reported by transplant centers to UNOS at regularly scheduled data collection time points. The 6-month posttransplant follow-up creatinine value served as the baseline time point for calculation of eGFR. Laboratory values reported between 135 and 225 days (6 months ± 45 days) after transplantation were considered to be the 6-month follow-up value. If a patient had multiple follow-up labs reported during this time period, the first value was used as the baseline.

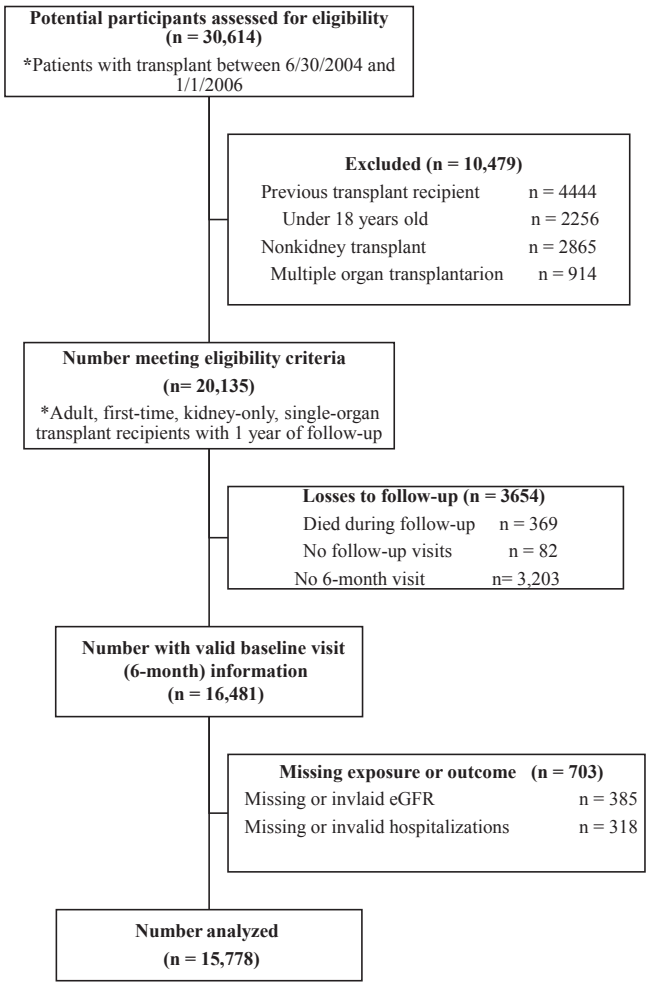

Figure 1. Flow chart of exclusion criteria for study population. eGFR, estimated glomerular filtration rate.

Primary Outcome

The primary outcome for this study was the number of hospitalizations that occurred in the year after the 6-month time point after renal transplantation, that is, hospitalizations that occurred up to 18 months after transplantation. Rehospitalization after 6 months, as opposed to 30 days, is less likely to be the result of surgical complications from the transplant procedure, as patients stabilize over time. Only hospitalizations after this baseline time point were considered for these analyses to ensure that eGFR was measured before rehospitalization.

Statistical Analyses

We performed descriptive analyses of the relationship between the 6-month eGFR and the number of late hospitalizations, controlling for several potential confounders including recipient characteristics (demographics, clinical characteristics, comorbidities), donor characteristics, transplant characteristics, and complications. Bivariate analyses by standard eGFR cut points and by the number of hospitalizations were conducted using *t*-tests to compare continuous variables and χ^2 tests for categorical variables. Covariates considered as potential confounders included *recipient characteristics*: age, race (white, black, Asian, Hispanic, other), sex, body mass index (continuous),[11] education level (high school or less, attended college, associate and/or bachelor degree, post-college graduate degree, missing), primary form of payment (private insurance, public insurance, missing), primary diagnosis (diabetes related, hypertension related, glomerular nephritis, secondary glomerular nephritis, hereditary and/or congenital disease, other), previous dialysis (yes, no), diabetes (yes, no, missing), cancer or malignancy (yes, no, missing), total serum albumin, serum creatinine; *donor characteristics:* donor age, donor height, donor type (living, deceased, deceased expanded criteria), donor diabetes (yes, no, missing), and donor hypertension (yes, no, missing); *transplant characteristics*: length of stay (at time of transplant in days), human leukocyte antigen (HLA) match level (zero to six, missing), cold ischemia time (0–10, 11–20, 21–30, >30 hours, missing), panel-reactive antibody (0, 1–20, 21–80, 80+); and *complications:* previous hospitalization (hospitalization during the first 6 months after transplantation) (yes, no) acute rejection (yes, no), delayed graft function (yes, no). "Missing" was considered as a separate response category for covariates as noted. No patients in our sample had experienced an allograft loss; therefore, loss of allograft was not included in these analyses.

The number of late hospitalizations was modeled using a zero-inflated Poisson regression (generalized linear model using SAS Proc Genmod [SAS Version 9.3, Cary, NC]). For the final multivariable model, we included variables that were significantly associated with both exposure and outcome during descriptive analyses and known potential confounders from a review of the literature.[12] The full model included the main exposure variable—eGFR—and the following variables—race, recipient age, sex, body mass index category, insurance type, education, HLA match level, cold ischemia time, length of stay (at the time of transplant), serum albumin, diabetes status, hypertension status, primary diagnosis, delayed graft function, pretransplant dialysis, before hospitalization, donor age, donor type, donor hypertension, and donor diabetes. Collinearity for this model was evaluated by assessing whether condition indices were high (>30) with variance decomposition proportions for variables excluding the intercept greater than 0.50. No variables in the full model violated these assumptions, and thus the full model included all variables stated above.

Sensitivity Analyses

We conducted several sensitivity analyses to examine the robustness of findings. First, we repeated analyses using the chronic kidney disease-Epi formula to calculate the eGFR. We also repeated analyses including patients who (i) died during the study follow-up period, (ii) had previously received a transplant, and (ii) had received a multi-organ transplant.

Statistical Significance

All tests were 2-sided, with an $\alpha = 0.05$, and analyses were conducted using SAS version 9.3 (SAS Institute, Cary, NC). The Emory Institutional Review Board approved this study.

RESULTS

A total of 15,778 adult, first-time, kidney-only transplant recipients met the inclusion criteria for this analysis. The mean age of the study population was 50 years (±13.5), 24.2% (n = 3812) were black, 60.5% were men (n = 9552), and 57.8% had public insurance (n = 9113).

Figure 2 shows the distribution of patients by eGFR category. Patients in the lowest eGFR category were more likely to be black (40.9% compared with 24.2% in the study sample as a whole), older, overweight, expanded criteria donor recipients, and publicly insured (Table 1). They were also more likely to have been readmitted to the hospital (52.7% compared with 19.1% in the study sample). On average, those with

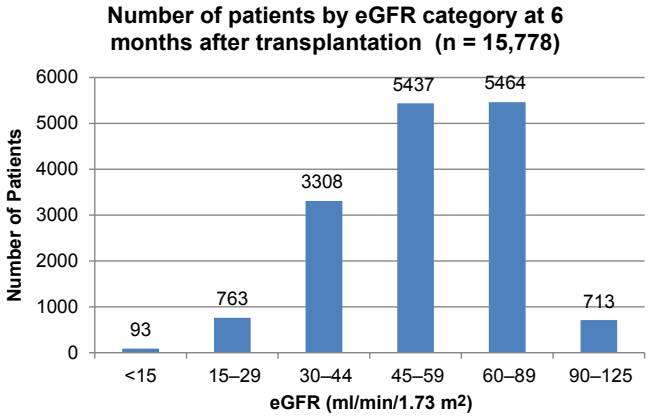

Figure 2. Distribution of study participants by estimated glomerular filtration rate (eGFR) cut point at 6 months after transplantation.

Table 1. Baseline demographic characteristics by eGFR cut points for adult, first-time, kidney-only recipients (United Network for Organ Sharing 2004–2007)

	Study population		By eGFR cut points												
			<15		15–29		30–44		45–59		60–89		90–125		
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	*P* value
	15,778		93	0.59	763	4.84	3308	20.97	5437	34.46	5464	34.63	713	4.52	
Recipient characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Age (yr)	49.6	13.5	50.0	13.5	52.9	12.8	51.9	12.8	49.9	13.2	47.7	13.8	46.6	14.3	<0.001
BMI (kg/m^2)	27.4	5.6	27.9	5.6	28.8	6.2	28.2	5.6	27.7	5.7	26.6	5.4	25.6	5.4	<0.001
Total serum albumin (g/dl)	3.9	0.6	3.9	0.5	3.9	0.6	3.9	0.6	3.9	0.6	3.9	0.6	3.9	0.7	<0.001
Serum creatinine (mg/dl)	1.5	0.7	6.3	2.4	2.8	0.7	1.9	0.3	1.4	0.2	1.1	0.2	0.8	0.1	<0.001
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Race/ethnicity															<0.001
White	8726	55.3	38	40.9	438	57.4	2042	61.7	3192	58.7	2752	50.4	264	37.0	
Black	3812	24.2	38	40.9	186	24.4	688	20.8	1189	21.9	1458	26.7	253	35.5	
Hispanic	2119	13.4	12	12.9	84	11.0	349	10.6	684	12.6	857	15.7	133	18.7	
Asian	796	5.0	3	3.2	41	5.4	157	4.8	258	4.8	285	5.2	52	7.3	
Other	325	2.1	2	2.2	14	1.8	72	2.2	114	2.1	112	2.1	11	1.5	
Sex															<0.001
Male	9552	60.5	52	55.9	403	52.8	1996	60.3	3422	62.9	3276	60.0	403	56.5	
Education[a]	2578[a]														<0.001
High school (9–12) or less	7057	53.5	42	55.3	351	55.1	1430	51.8	2361	51.9	2512	55.0	361	59.4	
Attended college/technical school	3169	24.0	19	25.0	148	23.2	650	23.5	1095	24.1	1118	24.5	139	22.9	
Associate/bachelor degree	2089	15.8	8	10.5	89	14.0	467	16.9	785	17.3	662	14.5	78	12.8	
Post-college graduate degree	885	6.7	7	9.2	49	7.7	215	7.8	307	6.8	277	6.1	30	4.9	
Insurance															<0.001
Private insurance	6,629	42.0	26	28.0	271	35.5	1446	43.7	2383	43.8	2276	41.7	227	31.8	
Public insurance	9113	57.8	67	72.0	492	64.5	1859	56.2	3045	56.0	3169	58.0	481	67.5	
Other	36	0.2	–	–	–	–	3	0.1	9	0.2	19	0.4	5	0.7	
Primary diagnosis	1719[a]														<0.001
Diabetes related	3825	24.3	23	21.5	209	26.9	683	24.5	1102	24.3	1100	23.6	168	25.8	
Hypertension related	3052	22.6	31	29.0	167	21.5	609	21.8	998	22.0	1080	23.2	167	25.6	
Glomerular nephritis	2521	18.7	15	14.0	128	16.5	509	18.2	903	19.9	855	18.4	111	17.0	
Secondary glomerular nephritis	596	4.4	2	1.9	38	4.9	106	3.8	179	4.0	234	5.0	37	5.7	
Hereditary and/or congenital diseases	1863	13.8	12	11.2	93	12.0	441	15.8	654	14.4	598	12.9	65	10.0	
Other	2202	16.3	24	22.4	141	18.2	445	15.9	701	15.5	787	16.9	104	16.0	
Previous dialysis[a]	349[a]														<0.001
Yes	12,118	79.1	92	79.3	702	85.4	2512	78.9	4025	77.1	4174	79.4	613	85.5	
Previous malignancy															0.29
Yes	562	3.8	2	2.5	32	4.8	139	4.8	206	4.4	183	3.8	24	3.8	
Diabetes[a]	303[a]														0.31
Yes	4828	31.2	25	27.5	258	34.7	1014	31.5	1644	30.8	1660	30.9	227	32.2	
Cerebrovascular disease[a]	878[a]														0.27
Yes	392	2.6	5	6.2	17	2.4	74	2.4	129	2.5	147	2.8	20	3.0	
Donor characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Donor age (yr)	39.2	14.55	43.6	15.7	48.4	14.2	45.5	14.0	40.3	13.7	34.3	13.4	29.9	12.9	0.50
Donor height (cm)	169.4	14.4	166.1	16.7	168.1	13.1	168.2	13.4	169.4	13.1	170.3	15.6	170.8	18.2	<0.001
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Donor type															<0.001
Living	6839	43.4	24	25.8	187	24.5	1348	40.8	2595	47.7	2424	44.4	261	36.6	
Deceased standard criteria	7374	46.7	46	49.5	351	46.0	1369	41.4	2354	43.3	2817	51.6	437	61.3	
Deceased expanded criteria	1565	9.9	23	24.7	225	29.5	591	17.9	488	9.0	223	4.1	15	2.1	
Donor diabetes[a]	310[a]														<0.001
Yes	452	2.88	7	5.9	64	7.6	154	4.7	125	2.3	88	1.6	14	1.9	
Donor hypertension[a]	355[a]														<0.001
Yes	2274	14.51	32	27.1	298	35.5	733	22.5	693	13.0	465	8.7	53	7.3	
Transplant characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Cold ischemic time (h)	12.9	10.76	15.5	9.0	16.8	11.0	13.8	11.3	12.2	10.5	12.3	10.6	13.2	9.9	<0.001
Length of stay at transplant (d)	7.1	11.89	10.2	9.9	9.0	7.6	7.7	18.1	6.8	7.0	6.6	8.5	7.7	24.3	<0.001

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Table 1. Baseline demographic characteristics by eGFR cut points for adult, first-time, kidney-only recipients (United Network for Organ Sharing 2004–2007) (Continued)

Transplant characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Peak PRA	8.9	22.0	15.6	29.6	10.5	24.0	9.2	22.4	7.9	20.4	9.1	22.6	10.1	23.2	<0.001
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
PRA															<0.001
0	10,712	68.36	73	61.9	538	64.1	2186	67.1	3725	69.6	3714	69.1	476	65.1	
1–20	3081	19.66	19	16.1	183	21.8	670	20.6	1048	19.6	1009	18.8	152	20.8	
21–80	1235	7.88	15	12.7	75	8.9	265	8.1	391	7.3	422	7.9	67	9.2	
80+	643	4.1	11	9.3	43	5.1	138	4.2	185	3.5	230	4.3	36	4.9	
HLA match level[a]	53[a]														<0.001
Zero	2759	17.6	21	22.8	176	23.1	589	17.9	947	17.5	906	16.7	120	16.9	
One	4267	27.1	28	30.4	233	30.5	985	29.9	1457	26.9	1368	25.1	196	27.5	
Two	2737	17.4	14	15.2	136	17.8	566	17.2	943	17.4	946	17.4	132	18.5	
Three	3211	20.4	15	16.3	117	15.3	628	19.1	1163	21.5	1153	21.2	135	19.0	
Four	1150	7.3	5	5.4	31	4.1	227	6.9	378	7.0	454	8.3	55	7.7	
Five	844	5.4	4	4.4	44	5.8	167	5.1	276	5.1	314	5.8	39	5.5	
Six	757	4.8	5	5.4	26	3.4	134	4.1	257	4.7	300	5.5	35	4.9	
Complications	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Posttransplant hospital readmissions (number)	0.3	0.9	1.2	1.7	0.7	1.3	0.4	1.0	0.3	0.8	0.3	0.7	0.3	0.8	<0.001
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	<0.001
Previous hospitalization															
Yes	3815	24.3	75	63.6	379	45.1	992	30.4	1156	21.6	1055	19.6	158	21.6	
Delayed graft function															<0.001
Yes	2534	14.3	49	32.2	314	32.0	681	18.7	750	12.6	642	10.6	98	11.3	
Acute rejection	370[a]														<0.001
Yes	816	5.3	36	28.6	160	19.2	274	8.6	204	3.9	128	2.4	14	1.9	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; PRA, panel-reactive antibody.
[a]Includes missing values.

lower eGFR also had a higher total serum albumin, cold ischemia time, serum creatinine, and length of stay at the time of transplant compared with the total study sample. The number of hospital readmissions decreased among those in higher eGFR categories.

A total of 19.1% of patients were hospitalized at least once within the year after the 6-month posttransplant follow-up visit, and 0.7% were hospitalized 5 or more times in this time period. Black race, Asian race, female sex, length of stay at the time of transplant, public insurance (vs. private insurance), standard and expanded criteria deceased donor (vs. living donors), diabetic status, and increasing donor age were associated with increased hospitalization (Table 2). Additional covariates considered are provided in Supplemental Table S1. Among those hospitalized, the mean number of hospitalizations was 1.71 (range, 0–12) and increased monotonically with decreasing eGFR. Patients who were hospitalized (n = 3009) during the year after the 6-month posttransplant follow-up had a significantly lower eGFR than those who were not hospitalized (n = 12,769) (48.79 vs. 57.45 ml/min per 1.73 m^2, respectively) (Figure 3).

In multivariable-adjusted analyses, a 10 ml/min per 1.73 m^2 eGFR was significantly associated with the total number of late hospitalizations (Rate Ratio [RR]: 0.89, 95% confidence interval [CI]: 0.89–0.89) within the year after the 6-month visit; thus, for every 10-unit increase in eGFR, there was an 11% decrease in the rate of hospitalization (Table 3). After adjusting for other covariates, transplant recipients who were diabetic, who received dialysis before transplantation, or who experienced delayed graft function were at increased risk for hospitalization compared with those who were not. Patients who had been hospitalized in the first months after transplantation were more than twice as likely to experience later hospitalization (RR: 2.33, 95% CI: 2.20–2.48), and those who were on public insurance were hospitalized 12% more than those on private insurance (RR: 1.12, 95% CI: 1.09–1.37). Those who had only attended college and/or technical school or high school or less were also at increased risk for hospitalization compared with those with a post-college degree (RR: 1.16, CI: 1.01–1.33 and RR: 1.13, CI: 0.99–1.29, respectively) (Table 3). There were no differences by donor type (living vs. deceased standard vs. deceased expanded criteria) on the number of hospitalizations.

Sensitivity Analyses

When main multivariable modeling results were repeated using the chronic kidney disease-Epi equation instead of Modification of Diet in Renal Disease, results were similar to the main effect estimates (RR: 0.9877, 95% CI: 0.9857–0.9897). Similar results were also observed when we examined the association between

Table 2. Basic demographic characteristics by the number of hospitalizations in the year after the 6-month visit for adult, first-time, kidney-only recipients (United Network for Organ Sharing 2004–2007)

			By number of hospitalizations												
	Study population (N = 15,778)		Zero (N = 12,769)		One (N = 1868)		Two (N = 623)		Three (N = 278)		Four (N = 128)		Five or more (N = 217)		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P* value
Recipient characteristics															
eGFR (ml/min per 1.73 m^2)	56.6	18.02	57.4	17.62	54.2	18.25	52.1	20.33	49.9	20.73	48.7	18.83	46.8	22.13	<0.001
Mean age (yr)	49.6	13.50	49.5	13.42	49.7	13.48	49.7	14.13	50.3	14.48	49.6	14.86	48.9	15.34	0.90
Mean BMI (kg/m^2)	27.4	5.64	27.3	5.60	27.6	5.76	27.7	5.68	27.6	6.06	27.1	5.80	27.7	5.92	0.40
Total serum albumin (g/dl)	3.9	0.60	3.9	0.59	3.9	0.66	3.8	0.59	3.8	0.52	3.9	0.52	3.9	0.50	<0.001
Serum creatinine (mg/dl)	1.5	0.65	1.5	0.57	1.6	0.70	1.7	1.08	1.8	1.20	1.8	0.80	2.0	1.25	<0.001
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Ethnicity															<0.001
White	8726	55.3	7122	55.8	1008	54.0	338	54.3	143	51.4	66	51.6	49	43.8	
Black	3812	24.2	2953	23.1	523	28.0	164	26.3	81	29.1	44	34.4	47	42.0	
Hispanic	2119	13.4	1749	13.7	227	12.2	83	13.3	35	12.6	15	11.7	10	8.9	
Asian	796	5.0	675	5.3	72	3.9	29	4.7	15	5.4	3	2.3	2	1.8	
Other	325	2.1	270	2.1	38	2.0	9	1.4	4	1.4			4	3.6	
Sex															0.04
Male	9552	60.5	7796	61.1	1103	59.1	368	59.1	158	56.8	71	55.5	56	50.0	
Education[a]	2578[a]														0.69
High school (9–12) or less	7057	53.5	5671	53.1	867	54.9	287	56.4	129	53.3	57	53.8	46	53.5	
Attended college/technical school	3169	24.0	2578	24.1	373	23.6	111	21.8	54	22.3	34	32.1	19	22.1	
Associate/bachelor degree	2089	15.8	1712	16.0	234	14.8	78	15.3	41	16.9	9	8.5	15	17.4	
Post-college graduate degree	885	6.7	717	6.7	105	6.7	33	6.5	18	7.4	6	5.7	6	7.0	
Insurance															<0.001
Private insurance	6629	42.0	5481	42.9	715	38.3	245	39.3	110	39.6	40	31.3	38	33.9	
Public insurance	9113	57.8	7256	56.8	1150	61.6	378	60.7	167	60.1	88	68.8	74	66.1	
Other	36	0.2	32	0.3	3	0.2	–	–	1	0.4	–	–	–	–	
Primary diagnosis	1719[a]														<0.001
Diabetes related	3825	24.3	2337	23.2	530	25.2	223	30.6	106	31.0	53	36.6	36	25.9	
Hypertension related	3052	22.6	2284	22.7	482	22.9	162	22.2	77	22.5	18	12.4	29	20.9	
Glomerular nephritis	2521	18.7	1952	19.4	363	17.2	107	14.7	58	17.0	21	14.5	20	14.4	
Secondary glomerular nephritis	596	4.4	442	4.4	95	4.5	30	4.1	12	3.5	6	4.1	11	7.9	
Hereditary/congenital diseases	1863	13.8	1418	14.1	288	13.7	86	11.8	42	12.3	20	13.8	9	6.5	
Other	2202	16.3	1624	16.2	348	16.5	122	16.7	47	13.7	27	18.6	34	24.5	
Diabetes[a]	303[a]														<0.0001
Yes	4828	31.2	3782	30.2	608	33.2	230	37.8	110	40.7	50	41.0	48	44.0	
Previous malignancy	1984[a]														0.02
Yes	562	3.8	465	4.2	62	3.7	26	4.7	20	8.1	8	7.1	5	5.2	
Previous dialysis[a]	349														<0.0001
Yes	12,118	79.09	8875	77.99	1951	80.89	695	83.73	319	83.73	143	87.2	135	86.54	
Cerebrovascular disease[a]	878[a]														0.15
Yes	392	2.6	301	2.5	52	3.0	24	4.2	7	2.7	5	4.2	3	2.9	
Donor characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Donor age (yr)	39.2	14.55	38.9	14.42	40.0	15.02	41.6	14.90	41.6	15.02	41.5	14.43	44.7	15.16	<0.001
Donor height (cm)	169.4	14.4	169.5	14.5	169.4	14.2	169.4	13.3	169.6	14.9	168.8	13.3	166.8	15.3	0.32
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Donor type															<0.001
Living	6839	43.4	5674	44.4	733	39.2	243	39.0	97	34.9	50	39.1	42	37.5	
Deceased standard criteria	7374	46.7	5915	46.3	924	49.5	289	46.4	142	51.1	59	46.1	45	40.2	
Deceased expanded criteria	1565	9.9	1180	9.2	211	11.3	91	14.6	39	14.0	19	14.8	25	22.3	
Donor diabetes[a]	310														<0.001
Yes	452	2.88	298	2.61	80	3.33	37	4.49	20	5.26	4	2.44	13	8.39	
Donor hypertension[a]	355														<0.001
Yes	2274	14.51	1539	13.51	407	16.94	164	19.88	82	21.75	39	23.78	43	27.56	
Transplant characteristics	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	
Cold ischemic time (h)	12.9	10.76	12.7	10.78	13.3	10.65	13.2	10.40	15.3	11.10	12.2	9.64	15.2	12.23	<0.001
Length of stay at transplant (d)	7.1	11.89	6.9	12.46	7.5	10.07	8.2	7.54	8.2	6.76	8.8	6.24	8.7	6.84	<0.001

(Continued on next page)

Table 2. Basic demographic characteristics by the number of hospitalizations in the year after the 6-month visit for adult, first-time, kidney-only recipients (United Network for Organ Sharing 2004–2007) (Continued)

Transplant characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Peak PRA	8.9	22.0	8.7	21.7	9.1	22.4	9.8	23.1	9.9	23.9	11.3	24.8	11.5	25.3	0.16
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
PRA															0.36
0	107,12	68.4	8048	68.7	1651	67.7	554	66.0	260	67.9	104	62.7	95	60.1	
1–20	3081	19.7	2268	19.4	493	20.2	169	20.1	73	19.1	36	21.7	42	26.6	
21–80	1235	7.9	907	7.8	189	7.8	76	9.1	30	7.8	19	11.5	14	8.9	
80+	643	4.1	464	4.0	105	4.3	40	4.8	20	5.2	7	4.2	7	4.4	
HLA match level[a]	53[a]														0.05
Zero	2759	17.6	2204	17.3	320	17.2	122	19.7	62	22.3	26	20.3	25	22.3	
One	4267	27.1	3409	26.8	543	29.2	171	27.5	86	30.9	30	23.4	28	25.0	
Two	2737	17.4	2200	17.3	336	18.1	110	17.7	45	16.2	27	21.1	19	17.0	
Three	3211	20.4	2620	20.6	362	19.5	134	21.6	37	13.3	31	24.2	27	24.1	
Four	1150	7.3	958	7.5	121	6.5	39	6.3	19	6.8	6	4.7	7	6.3	
Five	844	5.4	704	5.5	90	4.8	25	4.0	15	5.4	5	3.9	5	4.5	
Six	757	4.8	631	5.0	88	4.7	20	3.2	14	5.0	3	2.3	1	0.9	
Complications	N	%	N	%	N	%	N	%	N	%	N	%	N	%	
Delayed graft function															<0.001
Yes	2534	14.3	1658	12.7	460	16.5	215	21.7	106	23.5	53	25.6	42	22.2	
Acute rejection	370[a]														<0.001
Yes	816	5.3	478	4.1	167	7.0	77	9.4	40	10.3	20	11.9	34	15.7	

BMI, body mass index; eGFR, estimated glomerular filtration rate; HLA, human leukocyte antigen; PRA, panel-reactive antibody.
[a]Includes missing values.

eGFR and hospitalization in multivariable models for (i) including patients who died (RR: 0.9872, 95% CI: 0.9844–0.9900), (ii) retransplant patients (RR: 0.9865, 95% CI: 0.9839–0.9891), and (iii) multi-organ transplant recipients (RR: 0.9828, 95% CI: 0.9803–0.9854).

DISCUSSION

In this national, longitudinal study of more than 15,000 kidney transplant recipients across the United States, we found that lower eGFR was associated with a higher hospitalization rate among adult, first-time kidney-only transplant recipients, where a 10-unit decrease in the 6-month eGFR was associated with an 11% increased risk of hospitalization in the year after the 6-month transplant follow-up visit. Additional risk factors for hospital readmission included female sex, lower educational attainment, diabetes, delayed graft function, previous hospitalization, and length of stay at transplant. To our knowledge, this is the first study that identified risk factors for hospital readmission at 6 months after transplantation among a population of both publicly and privately insured kidney transplant recipients. These findings have significant implications for the identification of patients at increased risk for late hospitalization—a proxy for transplant-related poor health outcomes—such as loss of graft function and mortality. As expected, some of these risk factors, such as delayed graft function, length of stay at transplant, and previous hospitalization, may reflect complications early on that lead to later hospitalizations. Our finding that patients with fewer HLA mismatches have lower hospitalization rates may have important clinical implications; further studies are needed to determine whether policies and practices to encourage greater HLA matching may reduce health care resource utilization.

Our results are consistent with other studies that identified a series of risk factors for early hospital readmission. McAdams-Demarco *et al.*[7] found that among 32,961 Medicare primary kidney transplant

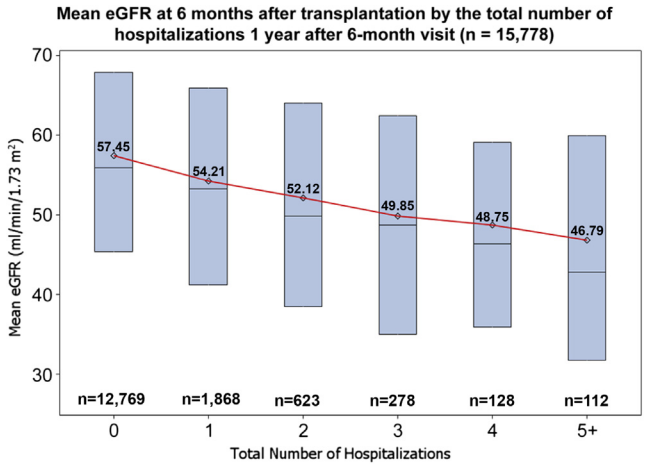

Figure 3. Mean estimated glomerular filtration rate (eGFR) at 6 months after renal transplantation by the total number of hospitalizations in 1 year after this visit among adult, first-time, kidney-only transplant recipients, United Network for Organ Sharing 2004–2006. Mean eGFR values are listed for each hospitalization number. The red line indicates the trend line for mean eGFR values from 0 to 5 or more late hospitalizations ($P < 0.0001$). The boxes represent the interquartile range of eGFR, and the horizontal line represents the median eGFR values.

Table 3. Multivariable zero-inflated Poisson modeling results for association of eGFR with number of hospitalizations among adult, first-time, kidney-only transplant recipients (United Network for Organ Sharing 2004–2007)

		95% CI		
	Adj. rate ratio	Lower	Upper	*P* value
eGFR (per 10 ml/min per 1.73 m^2)	0.89	0.89	0.89	<0.0001
Ethnicity				
White (reference)	1	–	–	–
Black	1.03	0.97	1.11	0.33
Hispanic	0.93	0.85	1.01	0.09
Asian	0.93	0.81	1.07	0.31
Time	0.94	0.76	1.15	0.53
Sex				
Male (reference)	1	–	–	–
Female	1.09	1.03	1.15	0.004
Recipient age (per 1 yr)	1.00	0.99	1.00	<0.0001
Education level				
High school or less	1.13	0.99	1.29	0.06
Attended college or technical school	1.16	1.01	1.33	0.04
Associate/bachelor degree	1.10	0.95	1.27	0.20
Post-college graduate degree (reference)	1.00	–	–	–
Education level missing	1.22	1.06	1.41	<0.001
Insurance				
Private insurance (reference)	1.00	–	–	–
Public insurance	1.12	1.05	1.19	0.004
Other	1.12	0.54	2.33	0.75
Length of stay (d)	1.00	1.00	1.01	<0.001
HLA match level				
0	1.22	1.05	1.42	0.01
1	1.08	0.93	1.25	0.31
2	1.15	0.99	1.34	0.08
3	1.18	1.01	1.37	0.03
4	1.08	0.90	1.28	0.41
5	1.04	0.86	1.25	0.67
6 (reference)	1	–	–	–
Diabetes				
No (reference)	1	–	–	–
Yes	1.18	1.25	1.11	<0.0001
Pretransplant dialysis				
Yes (reference)	1	–	–	–
No	0.87	0.80	0.94	<0.001
Missing	0.45	0.34	0.61	<0.0001
Delayed graft function				
No (reference)	1	–	–	–
Yes	1.19	1.27	1.11	<0.0001
Acute rejection episode				
No (reference)	1	–	–	–
Yes	1.09	1.19	0.99	0.07
Donor hypertension				
Yes (reference)	1	–	–	–
No	0.81	0.64	1.03	0.08
Missing	0.92	0.85	0.98	0.02
Previous hospitalizations (in first 6 mo)				
Yes (reference)	1	–	–	–
No	0.43	0.45	0.40	<0.0001

CI, confidence interval; eGFR, estimated glomerular filtration rate, HLA, human leukocyte antigen.

recipients, 31% were readmitted within 30 days of initial discharge from the transplant center. In both this study and our study, risk factors for early hospital readmission included older age, various patient comorbidities, longer length of stay, and transplant characteristics such as increased HLA mismatches. However, unlike previous studies, we did not find that donor type impacted the risk of late hospitalization. We also identified the 6-month eGFR as a novel marker for late hospitalization. Information about both early and late hospitalization may be useful in risk stratifying patients at the time of either discharge after surgery or at the 6-month posttransplant visit to monitor more closely and potentially prevent poor adverse outcomes.

This study contributes to the growing body of research investigating the association of eGFR and transplant-related health outcomes, such as allograft function[13,14] and mortality.[15–17] A meta-analysis of 105,872 participants from 14 studies found that eGFR < 60 ml/min per 1.73 m^2 is an independent predictor of all-cause mortality in the general population.[15] Furthermore, a retrospective study of 332 deceased donor kidney transplant recipients found that patients with kidneys from older donors or who experienced delayed graft function and acute rejection episodes were more likely to have deteriorating eGFR between 6 and 24 months after transplantation.[16] A similar retrospective study of 428 kidney transplant recipients with a mean follow-up of 10 years found that changes in eGFR over the first year relates to poorer long-term renal outcomes.[17]

Risk factors for decreased posttransplant renal function include increasing donor age, receipt of a deceased donor kidney, incidence of acute rejection, and delayed graft function.[18,19] As posttransplant renal function is an independent risk factor for long-term renal graft function, increased clinical scrutiny of patients with low eGFR may help reduce hospitalizations, and both decrease the incidence of poor health outcomes after transplantation and reduce cost. Closely monitoring patients with low eGFR, specifically during the first year after transplantation, may prove especially beneficial, as adverse events during that time period have been shown to predict long-term graft survival.[20] Because most transplant recipients attend a follow-up visit around 6 months posttransplant at their transplant center, identifying patients with declining eGFR at this time may allow risk stratification of patients and the potential to intervene to prevent future readmissions, graft failure, and mortality.

There were limitations to these analyses. Because hospitalization data were only collected during a limited time frame by UNOS (through 2007), we were unable to examine more recent data or hospitalizations over a longer time period. Furthermore, we could not assess early (30 days or less after surgery) versus late hospital readmissions or the length of each

hospitalization because we did not have access to hospitalization date. We also did not have admission or discharge diagnosis, and therefore cannot determine whether patients were admitted to the hospital for reasons unrelated to their kidney transplantation (e.g., elective procedures, pregnancy-related admissions, etc.). There is also the possibility that hospitalizations may be underreported to UNOS. There may be a number of potential factors that also contribute to hospitalization risk that were not captured in our multivariable analyses, such as acute rejection, immunosuppression medication, or other comorbidities that were not measured or available in the UNOS Standard Transplant Analysis and Research file data. Nevertheless, an increasing number of hospitalizations between follow-up visits may still reflect poorer health status of the patient as well as increased unplanned health costs. Exclusion of patients who died or who had incomplete follow-up may have resulted in selection bias; however, these patients had similar characteristics compared with the study sample, and sensitivity analyses including these patients showed a similar effect between eGFR and increasing hospitalization risk. Differential access to medical treatment may result in bias when hospital data are used as proxy measures[21]; however, the vast majority of transplant patients in our sample were insured. Finally, some covariates included a high number of missing values; thus, for selected covariates, we included missing values as a category.

Despite these limitations, this research had numerous strengths. The use of a nationally representative surveillance database, containing information regarding every organ donation and transplant event in the United States, resulted in a large sample size with a comprehensive set of covariates. This large sample size allowed us to detect small differences in the rate of hospitalization. In addition, risk prediction models for hospitalization status based on eGFR can be used to identify and treat patients at risk. Finally, because these data are based on a nationally representative surveillance system, they can be generalized to the US population. Other research examining hospitalization data using Medicare claims data may not be more robust; however, they are limited to a Medicare-insured population only and thus are not generalizable to the US transplant population. This is the first study that we are aware of that has examined the association between eGFR and posttransplantation hospitalization among patients with both public and private insurance, and thus results are more generalizable to all transplant recipients.

Lower eGFR measured 6 months after transplantation was significantly associated with an increase in the number of hospitalizations over time—even when adjusting for a variety of covariates—in patients who survived past 6 months. It is unclear whether there is a clinically meaningful cut point for eGFR that would help predict negative health outcomes, and whether there is an optimal time frame after transplantation to screen for changes in eGFR. As such, the findings warrant further investigation into specific cut points for eGFR that can be used as a clinical predictor of future hospitalization among kidney transplant recipients. Prediction of such preventable hospitalizations and early intervention to prevent hospitalization based on serial eGFR measurement may have significant implications in cost reduction and the prevention of morbidity and mortality associated with hospitalization after transplantation.

DISCLOSURE

All the authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Additional baseline demographic characteristics by eGFR cut points and hospitalization for adult, first-time, kidney-only recipients (United Network for Organ Sharing, 2004-2007).

Supplementary material is linked to the online version of the paper at www.kireports.org.

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