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Kidney Transplantation and Cardiovascular Events Among Patients with End-Stage Renal Disease due to Lupus Nephritis: A Nationwide Cohort Study

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Abstract

Objective: We sought to assess the potential impact of kidney transplantation on cardiovascular (CV) events among patients with end-stage renal disease (ESRD) due to lupus nephritis (LN).

Methods: In a nationwide cohort study, we identified all patients with LN-ESRD enrolled in the United States Renal Data System who were waitlisted for a kidney transplant and enrolled in Medicare between January, 2000 and December, 2016. The primary outcome was incident CV events, including myocardial infarctions (MI) and ischemic cerebrovascular accidents (CVA). We used time-dependent Cox regression to estimate the hazard ratios (HRs) of these outcomes associated with kidney transplant as a time-varying exposure, adjusting for sex, age, race, ethnicity, geographic region, year of ESRD onset, first ESRD treatment modality (e.g., hemodialysis or peritoneal dialysis), Charlson comorbidity score, and history of prior organ transplants.

Results: Of 5,963 waitlisted patients with LN-ESRD, 3,209 (54%) had a kidney transplant during the study period. The majority were female (82%), and African Americans represented 48% of waitlisted patients and 43% of transplanted patients. Kidney transplantation was associated with a lower risk of incident CV events (adjusted HR 0.31 [95% CI 0.18–0.53]) as well as lower risks of MI and CVA (adjusted HRs 0.13 [95% CI 0.08–0.34] and 0.30 [95% CI 0.16–0.54], respectively).

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Declaration of Interest:

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Data sharing:

Data for this study are not publicly available because of a data-use agreement. For requests to access the study data, please contact the corresponding author.

Conclusion: Kidney transplantation was associated with a reduced risk of CV events, including MI and CVA, in patients with LN-ESRD. Our findings highlight the importance of identifying barriers to transplantation in this population, as improved access could reduce CV morbidity.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that disproportionately affects women and African Americans. A major complication of SLE for those with lupus nephritis (LN) is progression to end-stage renal disease (ESRD). Up to 50% of patients with lupus will develop LN, and 20% of those patients will go on to develop ESRD.[1] Both SLE and ESRD are associated with increased risks of cardiovascular (CV) events, which is a major cause of morbidity and mortality. In fact, after accounting for their younger age and predominately female sex, patients with LN-ESRD have a higher risk of CV events, including myocardial infarction (MI) and ischemic cerebrovascular accidents (CVA), than those with other causes of ESRD, with the exception of diabetes mellitus.[2]

Patients with LN-ESRD who receive a kidney transplant have a lower risk of all-cause mortality and cardiovascular-specific mortality than those who remain on the transplant waitlist.[3] However, the potential impact of kidney transplantation on the risk of atherosclerotic CV events including acute MI and ischemic stroke in patients with LN-ESRD is unknown. In this study, we sought to assess the potential impact of kidney transplantation on non-fatal and fatal CV events in a nationwide study of patients with LN-ESRD in the United States.

PATIENTS AND METHODS:

Data Source and Study Population

The primary data source was the United States Renal Data System (USRDS), a national database of nearly all patients with ESRD in the US.[4] We identified all patients with LN-ESRD who were enrolled in the USRDS from 2000–2016. The cause of ESRD is recorded by International Classification of Disease, Ninth Revision (ICD-9) codes, according to the Centers for Medicare & Medicaid Services (CMS) Medical Evidence Report form (CMS-2728). The accuracy of the LN-ESRD diagnosis (ICD-9: 710.0) in the USRDS has been previously validated, with a positive predictive value of 93%.[5] We additionally required Medicare enrollment because we assessed time-varying covariates and outcomes from linked Medicare claims. We included patients who were waitlisted for a kidney transplant, excluding those who preemptively had a transplant before receiving dialysis. We restricted our study population to those who were waitlisted to limit the potential bias of confounding by indication, since waitlisted patients are known to have fewer comorbidities and greater socioeconomic status than patients with ESRD who are not waitlisted for transplant.[3]

The data reported here have been supplied by the USRDS. The interpretation and reporting of these data are the responsibility of the authors and should not be seen as the official policy or interpretation of the U.S. government. This study was exempted from the Partners HealthCare Institutional Review Board.

Exposure

The exposure of interest was first kidney transplant. We further characterized this exposure according to donor type, including deceased-donor and living-donor kidney transplants.

Assessment of Covariates

From the USRDS, we obtained demographics, body mass index, Organ Procurement and Transplantation Network (OPTN) region, dialysis treatment modality (e.g., hemodialysis or peritoneal dialysis), comorbidities at ESRD onset, and dates of ESRD onset, waitlist entry, transplantation, and death. We additionally captured relevant time-varying comorbidities, including prior history of CVA or MI, from linked Medicare Part A and Part B claims and calculated Charlson comorbidity index (CCI) scores.

Outcomes

The outcomes of interest were non-fatal and fatal CV events, including MI and CVA. CVA included ischemic stroke and transient ischemic attack. These outcomes were captured from Medicare linked hospitalization claims, using previously validated ICD-9 codes (e.g., primary or secondary discharge diagnosis code for MI or CVA).[6,7] Fatal MI and fatal CVA were additionally captured from the USRDS when listed as the primary cause of death on the CMS ESRD Death Notification Form (CMS-2746). We additionally analyzed MI and CVA separately as secondary outcomes.

Statistical Analysis

Primary Analysis—We determined the cumulative incidence rates of CV events per 1,000 person-years and 95% confidence intervals (CI). Follow-up began at the time of waitlist entry and ended at either death, the end of the study period, the end of Medicare enrollment, or three years after the index date. We ended follow-up at three years because individuals who undergo kidney transplants will no longer automatically qualify for Medicare at three years following the transplant date. We assessed transplantation as a time-varying exposure. Thus, we allocated time on the waitlist prior to the date of receiving a kidney transplant to the not transplanted group to avoid immortal time bias, and we allocated time following the date of receiving a kidney transplant to the transplanted group. We used time-varying Cox proportional hazards models and accounted for the competing risk of death using methods described by Fine and Gray. Multivariable models adjusted for sex, age, race, ethnicity, the year of ESRD onset, first ESRD treatment modality, comorbidity score, OPTN region, and history of prior organ transplantation.

We did subgroup analyses stratified by age, sex, race, and donor type. The USRDS does not permit reporting of cells with fewer than 11 individuals to maintain privacy and confidentiality. Due to small event sizes in some subgroups and secondary outcomes, we do not report the number of events or incidence rates but only the resulting hazard ratios for these analyses.

Secondary Analysis: Sequential Cohort Matching—We additionally performed a secondary analysis using sequential stratification matching. We sequentially matched patients by age, sex, and time since initiation of dialysis on their transplant date (e.g., index

date) one-to-one with comparators who were active on the waitlist on that date. We did exact matching, using a caliper plus or minus one year for age and time since initiation of dialysis. Matched pairs with the same values of matching variables formed each stratum.[8] Follow-up began at the index date and ended at the earliest of death, end of the study period, end of Medicare enrollment, or three years following the index date. Patients in the control group were censored upon receiving a kidney transplant and would then be matched and begin follow-up time in the transplanted group. We determined CV event rates in the groups that did and did not have transplants, accounting for competing risk of death, and calculated HRs using a stratified Cox proportional hazards model. We additionally adjusted for race, ethnicity, time on the waitlist, first ESRD treatment modality, CCI score, OPTN region, and history of prior organ transplant.

We calculated E-values in a sensitivity analysis to assess the potential effect of unmeasured confounders. All p values were two-sided with a significance threshold of <0.05. Statistical analyses were performed using SAS 9.4.

RESULTS

Patient Characteristics

There were 16,807 patients with incident LN-ESRD during the study period, including 5,963 (35%) patients who were waitlisted for a kidney transplant. Of these, 3,209 (54%) received a kidney transplant (Table 1). The majority (82%) were female. The largest racial group was African Americans, representing 48% of waitlisted patients and 43% of transplanted patients. Other characteristics were similar between the waitlisted and transplanted groups, including ethnicity (23% Hispanic) and CCI (mean score 4.4). The majority of patients who had a transplant received a deceased donor transplant (62%).

Cardiovascular Events

During study follow-up, there were 119 incident CV events over 20,900 person-years. This included 19 CV events that occurred after receiving a transplant, with an incidence rate of 2.1 (95% confidence interval [CI] 1.2–3.0) per 1,000 person-years, and 100 CV events in patients who had not yet received a transplant, with an incidence rate of 8.4 (95% CI 6.8–10.1) per 1,000 person-years. The corresponding unadjusted hazard ratio (HR) was 0.31 (95% CI 0.19–0.51) (Table 2). In the fully-adjusted model, kidney transplant was associated with a 69% reduction in the risk of CV events (adjusted HR, 0.31 [95% CI 0.18–0.53]).

In subgroup analyses, we observed a similarly reduced risk of CV events associated with kidney transplant among those under age 40 years and those at least 40 years of age (adjusted HRs 0.27 [95% CI 0.13–0.56] and 0.37 [95% CI 0.17–0.78], respectively) and among patients with living donor transplants and deceased donor transplants (adjusted HRs 0.21 [95% CI 0.09–0.51] and 0.24 [95% CI 0.13–0.45], respectively) (Table 2). Kidney transplantation was associated with a reduced risk of CV events for females (adjusted HR 0.28 [95% CI 0.15–0.52]). When stratified by race, kidney transplant was associated with a lower risk of CV events among white patients (adjusted HR 0.12 [95% CI 0.04–0.32]);

a similar trend was observed among African American patients but this association was attenuated and did not achieve statistical significance (adjusted HR 0.59 [0.31–1.13]).

When the outcomes of MI and CVA were analyzed separately, there were 25 incident MIs and 129 incident CVAs (Table 3). In the fully-adjusted model, kidney transplant was associated with an 87% reduction in the risk of MI (adjusted HR, 0.13 [95% CI 0.08–0.34]) and a 70% reduction in the risk of CVA (adjusted HR 0.30 [95% CI 0.16–0.54]).

Secondary Analysis with Sequential Cohort Matching

In the secondary analysis, 1,262 patients who had a transplant were matched with 1,262 comparators. These groups were well-balanced by age, sex, and time since initiation of dialysis (Supplemental Table 1). Over an average of 2.8 years of follow up, there were 41 incident CV events. Kidney transplant was associated with an unadjusted HR of 0.28 (95% CI 0.13–0.58) and fully adjusted HR of 0.31 (95% CI 0.14–0.65) for CV events.

Sensitivity Analysis

In assessing the robustness of the association to unmeasured confounding, we determined that the observed HR of 0.31 for CV events associated with kidney transplantation in the primary analysis could be explained away by an unmeasured confounder that was associated with both the exposure (kidney transplant) and the outcome (CV events) by a HR of at least 5.91, above and beyond the measured confounders. The corresponding CI could be moved to include the null by an unmeasured confounder that was associated with both transplant and all-cause mortality by a HR of at least 3.18.

DISCUSSION

In this nationwide cohort study of patients with LN-ESRD waitlisted for a kidney transplant, we found a substantial 69% reduction in the risk of CV events associated with kidney transplantation. This benefit was seen for the risks of MI and CVA when analyzed separately and for combined CV events. Given the association of both SLE and ESRD with an independently increased risk of CV events, this is particularly relevant to the population of patients at risk for or living with LN-ESRD.

We observed similar results using two different analytic approaches, increasing the robustness of our findings. Our primary analysis using a Cox model with the time-varying exposure of first kidney transplant included all waitlisted patients with LN-ESRD and avoided immortal time bias by accounting for time spent prior to receiving a kidney transplant in the waitlisted/not transplanted arm. Our secondary analysis used sequential cohort matching to directly compare the outcomes for patients with LN-ESRD starting from the time of receiving a kidney transplant with matched patients who remained waitlisted. Patients were matched by duration of time on dialysis since this is known to be a major risk factor for CVD. This secondary analysis included a smaller sample of all waitlisted LN-ESRD since not all patients could be matched but yielded similar findings as the primary analysis.

The mechanisms of CV risk reduction with kidney transplantation among patients with LN-ESRD are likely similar as in patients with all-cause ESRD, primarily related to the prevention of accelerated progression of atherosclerosis which is known to occur with the alternative of remaining on dialysis. Longer time on dialysis has been shown to increase CV risk in patients with all-cause ESRD through mechanisms including endothelial dysfunction, dyslipidemia, uremia, and inflammation and oxidative stress.[9] Transplantation could worsen some CV risk factors through glucocorticoid use and other immunosuppressants which may worsen or lead to incident diabetes, hypertension, and hyperlipidemia.[10] However, the restoration of renal function and cessation of dialysis appear to have a net benefit of improving CV risk.

We observed lower risks of CV events in patients with LN-ESRD associated with kidney transplant regardless of living or deceased donor status and for patients older or younger than 40 years of age. Some of our subgroup analyses were limited by small sample size, which limited our ability to detect differences between the transplanted and not transplanted groups. Considerable reductions in CV risk associated with transplantation were observed in white patients. However, in the largest racial subgroup of African Americans, this effect appeared to be attenuated and did not reach significance. The cause of this potentially reduced benefit in African Americans is likely multifactorial. African Americans are known to have a higher risk of graft failure following kidney transplants, although this gap is narrowing over time.[11] In general, worse outcomes following kidney transplantation in African Americans have been attributed to a combination of biologic and socioeconomic factors including disparate access to early transplantation. Another possible factor contributing to our observations is that African Americans who are waitlisted for transplant may have lower risks of atherosclerotic events than white patients who are waitlisted, in contrast with established higher risks of CVD among African Americans with SLE, and this could reduce the potential observed benefit. Such a paradox has been previously reported in patients with all-cause ESRD.[12] Further evaluation is warranted to understand the complex interplay between race, SLE, ESRD, and CV risk.

Our findings are consistent with prior studies of kidney transplant and CV events in the general ESRD population but assess these associations in a contemporary population with LN-ESRD. In a study of US Medicare patients who were waitlisted or received a pre-emptive transplant between 1995–2002, kidney transplantation was associated with a lower risk of acute MI.[13] A study of patients with ESRD in Scotland found a lower risk of stroke associated with kidney transplant compared with hemodialysis or peritoneal dialysis.[14] Similarly, a nationwide study based in Taiwan found a lower risk of stroke in kidney transplant recipients compared with propensity score-matched patients on dialysis.[15] There may be residual confounding by indication with such comparisons, as sicker patients are less likely to be considered for transplant. However, our study strengthens this evidence for the benefit of kidney transplantation in reducing CV risk by using two approaches to minimize potential bias and adds to the literature by establishing the impact of transplantation on improving CV risk in a contemporary cohort of patients with LN-ESRD.

Our study has several strengths and limitations worth noting. The USRDS captures nearly all patients with ESRD in the United States, and over 90% are enrolled in Medicare.

Therefore, our study population is highly generalizable. We used validated definitions of LN-ESRD and CV endpoints. However, there may be misclassification as can occur with observational data. Due to a relatively small number of events, we were unable to include all potential CV risk factors as covariates but instead utilized the Charlson comorbidity index which is a composite measure of relevant comorbidities. Additionally, we lacked information on lupus treatment history prior to enrollment in the USRDS, and we lacked measures of lupus disease activity. These factors could potentially impact waitlisting for transplant and contribute to CV risk. However, our study design using two complementary analytic approaches to compare the risk of CV events associated with kidney transplant and restricting our comparator group to patients also waitlisted for kidney transplants, along with the reassuring E-value analysis, helped to minimize potential confounding and substantiate our findings.

In summary, we observed a substantial reduction in the risk of CV events associated with kidney transplantation in patients with LN-ESRD. Improved access to kidney transplants for this patient population could improve CV morbidity and mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SIGNIFICANCE and INNOVATION

- This study assesses the potential impact of kidney transplantation on non-fatal and fatal cardiovascular events in a nationwide study of patients with end-stage renal disease caused by lupus nephritis (LN-ESRD) in the United States.
- Kidney transplantation was associated with a lower risk of incident cardiovascular events including lower risks of myocardial infarction and ischemic stroke.
- Improving access to kidney transplantation for patients with LN-ESRD could significantly reduce cardiovascular morbidity in this population.

Table 1.

Baseline Characteristics of Subjects with End-Stage Renal Disease Due to Lupus Nephritis

Baseline Characteristics	LN-ESRD	All Waitlisted	Transplanted
N	16,807	5,963	3,209
Age at ESRD, n (%)			
< 30 Years	4,999 (30)	2,107 (35)	1,249 (39)
30–39 Years	3,798 (23)	1,579 (26)	826 (26)
40–49 Years	3,491 (21)	1,258 (21)	667 (21)
>50 Years	4,519 (27)	1,019 (17)	467 (15)
Female, n (%)	13,726 (82)	4,888 (82)	2,617 (82)
BMI (mean, kg/m^2)	26.8	26.3	25.8
Race, n (%)			
African American	7,853 (47)	2,938 (48)	1,395 (43)
White	6,810 (41)	2,361 (40)	1,413 (44)
Asian	1,102 (7)	416 (7)	208 (6)
Other	1,042 (6)	347 (6)	193 (6)
Hispanic, n (%)	3,194 (19)	1,344 (23)	2,473 (23)
OPTN Region, n (%)			
1 (CT, ME, MA, NH, RI, Eastern VT)	466 (3)	163 (3)	77 (2)
2 (DE, DC, MD, NJ, PA, WV, Northern VA)	1,588 (10)	589 (10)	337 (11)
3 (AL, AR, FL, GA, LA, MS)	3,402 (20)	1,44 (19)	561 (17)
4 (OK, TX)	1,744 (10)	659 (11)	367 (11)
5 (AZ, CA, NV, NM, UT)	2,662 (16)	1,029 (17)	519 (16)
6 (AK, HI, ID, MT, OR, WA)	482 (3)	151 (3)	90 (3)
7 (IL, MN, ND, SD, WI)	1,231 (7)	416 (7)	242 (8)
8 (CO, IA, KA, MO, NE, WY	705 (4)	249 (4)	170 (5)
9 (NY, Western VT)	1,191 (7)	492 (8)	263 (8)
10 (IN, MI, OH)	1,302 (8)	402 (7)	217 (7)
11 (KY, NC, SC, TN, VA)	1,993 (12)	662 (11)	362 (11)
Prior Organ Transplant, n (%)	<1	31 (<1)	<1
Prior Coronary Artery Disease or Ischemic Stroke	1315 (8)	312 (5)	149 (5)
Charlson Comorbidity Index [*], **mean (SD)**	4.2 (3.5)	4.4 (3.2)	4.4 (3.0)
Tobacco Use, n (%)	696 (4)	160 (3)	86 (3)
First Modality, n (%)			
Hemodialysis	14,266 (85)	4,990 (84)	2,665 (83)
Peritoneal Dialysis	1,935 (12)	973 (16)	544 (17)

BMI, body mass index; OPTN, organ procurement and transplant network

[*] At time of ESRD onset, waitlisting, or transplantation, respectively

Table 2.

Cardiovascular Events According to Transplant Status Among Patients with End-Stage Renal Disease Due to Lupus Nephritis

	Follow-Up (Person Years)	Events, n	Incidence Rate * (95% CI)	Unadjusted HR (95% CI)	Fully-Adjusted HR † (95% CI)
Overall	20900	119	5.7 (4.7, 6.7)		
Transplanted	9054	19	2.1 (1.2, 3.0)	0.31 (0.19, 0.51)	0.31 (0.18, 0.53)
Not Transplanted	11846	100	8.4 (6.8, 10.1)	1.0	1.0
Age at ESRD Onset					
< 40 Years	13244	60	4.5 (3.4, 5.7)		
Transplanted	-	-	1.5 (0.5, 2.5)	0.27 (0.13, 0.54)	0.27 (0.13, 0.56)
Not Transplanted	-	-	7.0 (5.1, 8.9)	1.0	1.0
≥ 40 Years	7683	59	7.7 (5.7, 9.6)		
Transplanted	-	-	3.2 (1.2, 5.1)	0.38 (0.19, 0.76)	0.37 (0.17, 0.78)
Not Transplanted	-	-	10.8 (7.8, 13.8)	1.0	1.0
Sex					
Female	17139	93	5.4 (4.3, 6.5)		
Transplanted	7400	13	1.8 (0.8, 2.7)	0.27 (0.15, 0.48)	0.28 (0.15, 0.52)
Not Transplanted	9739	80	8.2 (6.4, 10.0)	1.0	1.0
Race/Ethnicity					
African American	10255	63	6.1 (4.6, 7.7)		
Transplanted	4020	14	3.5 (1.7, 5.3)	0.57 (0.31, 1.05)	0.59 (0.31, 1.13)
Not Transplanted	6235	49	7.9 (5.7, 10.1)	1.0	1.0
White	8503	48	5.6 (4.0, 7.2)		
Transplanted	-	-	1.0 (0.0, 1.9)	0.12 (0.04, 0.33)	0.12 (0.04, 0.32)
Not Transplanted	-	-	10.0 (7.0, 12.9)	1.0	1.0
Donor Type					
Living donor	11346	100	8.8 (7.1, 10.5)		
Transplanted	-	-	2.0 (0.5, 3.5)	0.21 (0.09, 0.45)	0.21 (0.09, 0.51)
Not Transplanted	-	-	11.8 (9.4, 14.2)	1.0	1.0
Deceased Donor	16223	110	6.8 (5.5, 8.0)		
Transplanted	5597	12	2.1 (0.9, 3.4)	0.29 (0.16, 0.52)	0.24 (0.13, 0.45)
Not Transplanted	10625	98	9.2 (7.4, 11.0)	1.0	1.0

HR, hazard ratio; ESRD, end-stage renal disease

* Per 1,000 Person-years;

† Adjusted for sex, age, race, ethnicity, ESRD-onset year, first ESRD treatment modality, comorbidity score, Organ Procurement and Transplantation Network region, and history of prior organ transplant

Follow-up for the Not Transplanted group begins at the time of initial waitlisting for kidney transplantation and ends at either death, censoring at the time of kidney transplantation, three years after the index date, or the end of the study period (December 31, 2015). Follow-up for the Transplanted group begins at the time of kidney transplantation and ends at either death, three years after the index date, or the end of the study period (December 31, 2015). Person-years and event counts were suppressed to protect privacy and confidentiality and as restricted by the data use agreement for fewer than 10 events.

Table 3.

Myocardial Infarction and Ischemic Stroke According to Transplant Status Among Patients with End-Stage Renal Disease Due to Lupus Nephritis

Cardiovascular Event	Incident Rate* (95% CI)	Unadjusted HR (95% CI)	Fully-Adjusted HR† (95% CI)
Myocardial Infarction	2.1 (1.3, 2.9)		
Transplanted	1.2 (1.0, 1.6)	0.10 (0.05, 0.31)	0.13 (0.08, 0.34)
Not Transplanted	2.0 (1.2, 2.8)	1.0	1.0
Ischemic Stroke	4.2 (3.3, 5.1)		
Transplanted	1.7 (0.8, 2.6)	0.29 (0.16, 0.51)	0.30 (0.16, 0.54)
Not Transplanted	6.0 (4.6, 7.4)	1.0	1.0

HR, hazard ratio

*Per 1,000 Person-years;

†Adjusted for sex, age, race, ethnicity, ESRD-onset year, first ESRD treatment modality, comorbidity score, Organ Procurement and Transplantation Network region, and history of prior organ transplantation

Follow-up for the Not Transplanted group begins at the time of initial waitlisting for kidney transplantation and ends at either death, censoring at the time of kidney transplantation, three years after the index date, or the end of the study period (December 31, 2017). Follow-up for the Transplanted group begins at the time of kidney transplantation and ends at either death, three years after the index date, or the end of the study period.