Published in final edited form as:

Ann Intern Med. 2019 February 19; 170(4): 240–247. doi:10.7326/M18-1570.

Renal Transplantation and Survival Among Patients With Lupus Nephritis:

A Cohort Study

April Jorge, MD*, Na Lu, MPH

Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch 165, Boston, MA 02114.

Zachary S. Wallace, MD, MSc*, Yuqing Zhang, DSc, Hyon K. Choi, MD, DrPH

Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, 100 Cambridge Street, Suite 1600, Boston, MA 02114.

Abstract

Background: Patients with end-stage renal disease (ESRD) due to lupus nephritis (LN) have high rates of premature death.

Objective: To assess the potential effect on survival of renal transplant among patients with ESRD due to LN (LN-ESRD) in the United States.

Design: Nationwide cohort study.

Setting: United States Renal Data System, the national database of nearly all patients with ESRD.

Participants: Patients with incident LN-ESRD who were waitlisted for a renal transplant.

Measurements: First renal transplant was analyzed as a time-varying exposure. The primary outcomes were all-cause and cause-specific mortality. Time-dependent Cox regression analysis was used to estimate the hazard ratio (HR) of these outcomes associated with renal transplant in

Corresponding Author: April Jorge, MD, Instructor in Medicine, Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Bulfinch 165, Boston, MA 02114, AMJorge@mgh.harvard.edu.

Author Contributions: Conception and design: A. Jorge, Z.S. Wallace, N. Lu, Y. Zhang, H.K. Choi.

Analysis and interpretation of the data: A. Jorge, Z.S. Wallace, N. Lu, Y. Zhang, H.K. Choi.

Drafting of the article: A. Jorge, Z.S. Wallace, N. Lu, H.K. Choi. Critical revision of the article for important intellectual content: A. Jorge, Z.S. Wallace, N. Lu, Y. Zhang, H.K. Choi.

Final approval of the article: A. Jorge, Z.S. Wallace, N. Lu, Y. Zhang, H.K. Choi.

Statistical expertise: Z.S. Wallace, N. Lu, Y. Zhang, H.K. Choi. Obtaining of funding: Z.S. Wallace.

Administrative, technical, or logistic support: A. Jorge, Z.S. Wallace, N. Lu, H.K. Choi.

Collection and assembly of data: Z.S. Wallace, H.K. Choi.

*Drs. Jorge and Wallace contributed equally to this work.

Disclosures: Dr. Jorge reports grants from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH during the conduct of the study. Dr. Wallace reports personal fees from Teva Pharmaceuticals and Gilead Sciences outside the submitted work. Authors not named here have disclosed no conflicts of interest. Disclosures can also be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M18-1570.

Reproducible Research Statement: Study protocol and statistical code: Available from Dr. Jorge (e-mail, AMJorge@mgh.harvard.edu). Data set: Availability is subject to approval by the USRDS. Interested readers may contact USRDS@usrhs.org to place a data request.

Current author addresses and author contributions are available at Annals.org.

the primary analysis. Sequential cohort matching was used in a secondary analysis limited to patients with Medicare, which allowed assessment of time-varying covariates.

Results: During the study period, 9659 patients with LN-ESRD were waitlisted for a renal transplant, of whom 5738 (59%) had a transplant. Most were female (82%) and nonwhite (60%). Transplant was associated with reduced all-cause mortality (adjusted HR, 0.30 [95% CI, 0.27 to 0.33]) among waitlisted patients. Adjusted HRs for cause-specific mortality were 0.26 (CI, 0.23 to 0.30) for cardiovascular disease, 0.30 (CI, 0.19 to 0.48) for coronary heart disease, 0.41 (CI, 0.32 to 0.52) for infection, and 0.41 (CI, 0.31 to 0.53) for sepsis.

Limitation: Unmeasured factors may contribute to the observed associations; however, the E-value analysis suggested robustness of the results.

Conclusion: Renal transplant was associated with a survival benefit, primarily due to reduced deaths from cardiovascular disease and infection. The findings highlight the benefit of timely referral for transplant to improve outcomes in this population.

Primary Funding Source: National Institutes of Health.

Lupus nephritis (LN) affects 30% to 50% of all patients with systemic lupus erythematosus (SLE) and leads to end-stage renal disease (ESRD) in up to 20% of affected patients (1–4). Those with ESRD due to LN (LNEsRD) have a substantially higher risk for premature death than other patients with SLE—up to 26 times higher in 1 study (5)—and double the risk for hospital mortality compared with patients with all-cause ESRD (6). African Americans with LN-ESRD have further increased mortality rates versus white, Asian, and Hispanic patients (7).

Renal transplantation has been associated with improved survival in the all-cause ESRD population (8, 9). However, patients with LN-ESRD may have a heightened risk for certain posttransplant complications (10, 11), including infections partly attributed to extensive pretransplant immunosuppression, graft thrombosis related to antiphospholipid antibody syndrome, and recurrent LN affecting the allograft (12). Furthermore, although small-scale studies have reported improved survival for patients who have a transplant compared with those who continue to receive dialysis (13, 14), these studies were confounded by indication, because healthier patients had a transplant. As such, the potential survival benefit associated with renal transplant remains unclear among patients with LN-ESRD.

To address this issue, we examined the association between renal transplant and risk for all-cause and cause-specific mortality among patients with LN-ESRD in a national registry.

METHODS

Data Source and Study Sample

Our source population was the United States Renal Data System (USRDS), the national database of nearly all U.S. patients with ESRD. We identified all patients with incident LN-ESRD (International Classification of Diseases, Ninth Revision, code 710.0) enrolled between 1 January 1995 and 31 December 2014. Patients with LN-ESRD were identified by the Centers for Medicare & Medicaid Services (CMS) Medical Evidence Report

(CMS-2728). Attending nephrologists are required by law to submit this form (including the cause of ESRD according to International Classification of Diseases, Ninth Revision, codes) within 45 days of a patient starting a new ESRD treatment. The accuracy of the LN-ESRD diagnosis in this database has been previously validated, with a positive predictive value of 93% (15). This study was exempted from review by the Partners HealthCare Institutional Review Board.

Our primary study sample comprised all patients with LN-ESRD who were waitlisted for a renal transplant between 1 January 1995 and 31 December 2015 ($n = 9890$). We excluded those who preemptively had a transplant before receiving hemodialysis or peritoneal dialysis ($n = 214$) or who had missing covariates ($n = 17$); this left 9659 patients in our primary sample. We restricted the sample to those waitlisted for a transplant to remove confounding by contraindication, because they are generally younger and have fewer comorbid conditions and greater socioeconomic status than those not waitlisted for a transplant (8).

Our secondary study sample was the Medicare-enrolled subset of the primary sample, because assessment of time-varying comorbid conditions was possible in this population. This analysis included 2963 patients who had a transplant and 2963 comparators sequentially matched by age, sex, and duration of dialysis in the USRDS database (Appendix Figure, available at [Annals.org](https://www.annals.org)).

Exposure

The exposure of interest was first renal transplant. We also determined donor status (that is, living vs. deceased).

Covariates

We obtained relevant variables from the USRDS, including demographics, race (white, African American, Asian, or other), ethnicity (Hispanic or non-Hispanic), body mass index, lifestyle factors (such as tobacco use), Organ Procurement and Transplantation Network geographic region (16), relevant comorbid conditions at the time of ESRD onset, first ESRD treatment method (hemodialysis, peritoneal dialysis, or renal transplant), history of a nonrenal organ transplant, and date of entry onto the waitlist. Relevant comorbid conditions, such as diabetes mellitus, were used to calculate a weighted comorbidity score developed specifically for patients with ESRD (17). In our secondary matched cohort analysis, we also obtained time-varying comorbid conditions from linked Medicare claims data to comprise the same comorbidity score at the time of transplant or matching (17).

Outcomes

Our primary outcome was all-cause mortality, documented by mandatory completion of the CMS ESRD Death Notification form (CMS-2746). Our secondary outcome was the primary cause of death (cardiovascular disease [CVD], including coronary heart disease and stroke; infection, including pneumonia and sepsis; cancer; or another cause), also documented on CMS-2746.

Statistical Analysis

Primary Analysis—We determined mortality rates per 1000 person-years. Follow-up began at the initial date of entry onto the waitlist and ended at death or the end of the study period, 31 December 2015. We assessed transplantation as a time-dependent exposure, allocating time spent before a renal transplant to the group that did not have transplants and time spent after to the group that did (8). This time-dependent approach avoids immortal time bias (18). Cumulative incidence rates were calculated to compare overall and cause-specific mortality, and the competing risk for death was accounted for using the methods described by Fine and Gray (19, 20). We calculated mortality hazard ratios (HRs) using time-dependent Cox proportional hazards modeling while adjusting for relevant covariates at the time of enrollment in the USRDS (that is, ESRD onset). After confirming the proportional hazards assumption, we proceeded with the final Cox model. We also did subgroup analyses stratified by age, sex, race/ethnicity, year of ESRD onset (between 1995 and 2004 or between 2005 and 2014), and Medicare enrollment status.

Secondary Analysis With Sequential Cohort Matching for Time-Varying Variables—To incorporate time-varying variables, such as duration of dialysis and current comorbid conditions, we did a secondary analysis with sequential stratification matching (21) limited to the waitlisted patients who were enrolled in Medicare. On the basis of age, sex, and time since initiation of dialysis, we sequentially matched patients on their transplant date (index date) one-to-one with comparators who remained active on the waitlist on that date. We did exact matching, using a caliper of age ± 1 year and time since initiation of dialysis ± 1 year. Follow-up began at the date of transplant or matching and ended at the time of death, end of the study period, or transplant (control group only, at which point a participant would be matched and begin follow-up time in the transplant group). We determined mortality rates in the groups that did and did not have transplants and calculated HRs using a stratified Cox proportional hazards model, adjusting for time-varying comorbid conditions and the variables used in the primary analysis. Pairs with the same values of matching variables formed each stratum (22). In this analysis, we also examined the effect of renal transplant donor status (living vs. deceased) on all-cause mortality for participants who had versus did not have a transplant.

We calculated E-values in a sensitivity analysis to assess the potential effect of unmeasured confounders (23). All *P* values were 2-sided, with a significance threshold of 0.05. Statistical analyses were done using SAS, version 9.4 (SAS Institute).

Role of the Funding Source

The National Institutes of Health had no role in the design or conduct of the study or the reporting of results. 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.

RESULTS

Patient Characteristics

The sample comprised 20 974 patients who had incident LN-ESRD between 1995 and 2014. Of these, 9659 (46%) were waitlisted for a renal transplant and 5738 (59%) had a transplant during follow-up (Table 1). Waitlisted patients were younger at the time of ESRD onset and had a lower mean comorbidity score. The average age at entry onto the waitlist was 38 years, and the average age at transplant was 39 years. Most waitlisted patients were female (82%), 48% were African American, and 21% were Hispanic. Hypertension was the most common comorbid condition, affecting 79% of waitlisted patients. Deceased-donor transplants were done in 3720 participants (65%) and living-donor transplants in 2015 (35%) (donor status was unknown in 3 participants).

All-Cause Mortality of LN-ESRD

During follow-up, 973 patients who had a transplant and 1697 who did not died, resulting in mortality rates of 22.5 (95% CI, 21.2 to 24.0) per 1000 person-years and 56.3 (CI, 53.7 to 59.1) per 1000 person-years, respectively (HR, 0.29 [CI, 0.26 to 0.32]) (Table 2). After adjustment for covariates, renal transplant was associated with a 70% reduction in risk for death (adjusted HR, 0.30 [CI, 0.27 to 0.33]) (Table 2).

The lower risk for all-cause mortality associated with renal transplant was similar across African Americans, Asians, Hispanics, and whites (Table 2). Our results also persisted across other characteristics, including age at ESRD onset, sex, year of ESRD onset, and Medicare enrollment status (Table 2).

Cause-Specific Mortality of LN-ESRD

When competing risks were accounted for, renal transplant was associated with a 74% lower risk for CVD death (adjusted HR, 0.26 [CI, 0.23 to 0.30]) (Table 3). Patients who had a transplant had a 70% lower risk for death due to coronary heart disease and a 61% lower risk for death due to stroke (adjusted HRs, 0.30 [CI, 0.19 to 0.48] and 0.39 [CI, 0.24 to 0.61], respectively) (Table 3). In a subgroup analysis including only African American patients with LN-ESRD, the adjusted HR for death due to CVD associated with renal transplant was 0.40 (CI, 0.32 to 0.49).

The risk for death due to infection was also lower among patients who had a transplant than among those who remained waitlisted (adjusted HR, 0.41 [CI, 0.32 to 0.52]). This included a 59% lower risk for death due to sepsis (adjusted HR, 0.41 [CI, 0.31 to 0.53]). We found no statistically significant association between renal transplant and risk for death due to cancer.

Secondary Analysis With Sequential Cohort Matching for Time-Varying Variables

In our secondary analysis using sequential stratification matching, we included 2963 patients who had a transplant and 2963 matched comparators. These groups were well-balanced by age, sex, time since initiation of dialysis, and time since entry onto the waitlist (Appendix Table 1, available at [Annals.org](https://annals.org)). During follow-up, 470 patients who had a transplant and 608 who did not died, resulting in mortality rates of 21.1 per 1000 person-years and 77.1 per

1000 person-years, respectively (HR, 0.24 [CI, 0.21 to 0.28]) (Appendix Table 2, available at [Annals.org](https://annals.org)). After adjustment for covariates, the HR was 0.26 (CI, 0.22 to 0.30). The adjusted mortality HRs were 0.32 (CI, 0.29 to 0.36) for deceased-donor transplants and 0.24 (CI, 0.21 to 0.27) for living-donor transplants.

Finally, in a sensitivity analysis assessing the robustness of the association to unmeasured confounding, we determined that the observed HR of 0.30 for all-cause mortality associated with renal transplant could be explained away by an unmeasured confounder that was associated with both the exposure (renal transplant) and the outcome (all-cause mortality) by an HR of at least 6.1, above and beyond the measured confounders, but not by weaker confounding. 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 an HR of at least 5.5 (23).

DISCUSSION

In this large population study of nearly all U.S. patients with LN-ESRD waitlisted for a renal transplant in a recent 2-decade period, we found a substantial improvement in survival associated with renal transplant. The survival benefit persisted in key subgroups, including African Americans, Hispanics, and Asians, as well as in both sexes, in all age groups, and throughout the study period. For cause-specific deaths, renal transplant was associated with a 74% lower risk for CVD death among all waitlisted patients with LN-ESRD; the risk reduction among African Americans was 60%. The protective association was similarly substantial for deaths due to infection, particularly sepsis.

Renal transplant has been found to be associated with a survival benefit of 47% to 80% in the all-cause ESRD population in the United States and other countries (8, 9, 24). However, concerns have arisen about potentially worse outcomes after renal transplant among patients with LN-ESRD, relating to certain SLE features and associated treatments (10, 11, 25–27). For example, some studies (although not all [28–30]) have suggested higher rates of allograft failure among patients with LN-ESRD than among those with other causes of ESRD (10, 11, 25, 27). Patients with LN-ESRD may have higher risk for infection due to the intensive immunosuppression used to treat LN and other disease manifestations (31). Associated antiphospholipid antibody syndrome is also a concern among patients with LN-ESRD because it may increase risk for graft thrombosis (12). Furthermore, recurrent LN in the allograft is a risk, although it rarely leads to graft loss (28). These unique concerns have limited the extrapolation of renal transplant outcomes from other groups of patients with ESRD to those with LN-ESRD. To that end, our study provides evidence for a substantial survival benefit of renal transplant among patients with LN-ESRD.

We could not identify a similarly large study of patients with LN-ESRD who were eligible to have a kidney transplant. Although several studies with small sample sizes (patients with LN-ESRD who had a transplant: $n = 40$ [32], $n = 65$ [14], and $n = 17$ [13]) also suggested the potential benefits of renal transplant in this population, their comparison groups were treated with long-term peritoneal dialysis or hemodialysis regardless of eligibility for a transplant. As such, these studies have been highly vulnerable to confounding by

contraindication because sicker patients tend to continue long-term dialysis without moving to a transplant waitlist (8). This was evident in our patients with LN-ESRD: Those waitlisted for a transplant tended to be younger and have fewer comorbid conditions than those not waitlisted (Table 1). By restricting our study population in this way, we were able to minimize this important confounding issue.

Renal transplant was associated with substantially lower risks for cardiovascular death and death due to infection among patients with LN-ESRD, which largely explains the all-cause mortality benefit. Many previous studies have found an increased risk for CVD among patients with LN-ESRD, including both myocardial infarction and stroke (33, 34). Underlying SLE disease activity, treatment of SLE with corticosteroids, and hemodialysis have all been believed to contribute to this risk (35, 36). Similarly, LN and ESRD are associated with higher risk for serious infections, including sepsis and pneumonia (37, 38). Our findings suggest that timely referral for transplant in this population may alleviate both CVD mortality and infection-related mortality. Our study period was a time of substantial treatment advances, especially for patients having an organ transplant, which may have contributed to the substantial survival benefit (39).

We found that African American, Asian, Hispanic, and white patients had similar mortality benefits associated with renal transplant. African American patients have previously been shown to have higher risks for death and cardiovascular events than white, Asian, and Hispanic patients with LN-ESRD (7). Although we also show higher overall crude mortality rates among African Americans, our study is the first to our knowledge to identify the same relative improvement with renal transplant among this group. Asian and Hispanic patients have been previously shown to have lower absolute risks for death and cardiovascular events than white patients with LN-ESRD (7), as we also found here.

Our study has several strengths and limitations. The USRDS is a generalizable nationwide database that captures nearly all U.S. patients with ESRD. As mentioned, the classification of LN-ESRD has been previously validated with a high level of accuracy (15). In addition to restricting our analysis to waitlisted patients to minimize confounding by contraindication, we treated renal transplant as a time-varying exposure to avoid immortal time bias. Whereas our primary sample of all eligible patients with ESRD was adjusted for variables only at the time of ESRD onset, our secondary analysis limited to Medicare patients was matched on the basis of duration of dialysis and additionally adjusted for time-varying comorbid conditions, resulting in a similar level of survival benefit. Finally, the E-value sensitivity analysis for the potential effect of unmeasured confounders also supported the robustness of our findings. We adjusted for important factors, including known geographic variability in renal transplantation by Organ Procurement and Transplantation Network region (39, 40). However, the USRDS does not capture measures of SLE disease activity, which could have affected waitlisting practices. Whether the same benefits would be seen if consideration of renal transplant had been expanded to all patients with LN-ESRD remains unclear, because our findings are directly generalizable to waitlisted patients. Nevertheless, a considerable proportion of waitlisted patients died before having a renal transplant, suggesting the need for improved access to renal transplantation for patients with LN-ESRD.

In summary, this nationwide cohort study of patients with LN-ESRD found that renal transplant is associated with a considerable survival benefit, largely due to a reduction in deaths caused by CVD and infection. Therefore, timely consideration of renal transplant should be a part of routine care for patients with LN-ESRD, and improved access to renal transplantation for this population may considerably improve outcomes.

From Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts (A.J., Z.S.W., N.L., Y.Z., H.K.C.).

Acknowledgment:

The authors thank Dr. Eliot Heher of the Massachusetts General Hospital Transplant Center for his contributions to overall study design.

Financial Support: Dr. Jorge is supported in part by the Ruth L. Kirschstein Institutional National Research Service Award (T32-AR-007258). Dr. Wallace receives funding from the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (NIH) (K23AR073334), the Rheumatology Research Foundation (Scientist Development Award), the Executive Committee on Research at Massachusetts General Hospital (Fund for Medical Discovery), and the NIH Loan Repayment Program. Dr. Zhang and Dr. Choi are supported in part by the NIH (P60-AR-047785).

Appendix

Appendix Figure.

Creation of the study cohort for primary and secondary study samples.

Appendix Table 1.

Characteristics of Participants Who Had a Transplant and Matched Comparators With LN-ESRD

Patient Characteristic	Participants Who Had a Transplant (n = 2963)	Matched Comparators (n = 2963)	Standardized Difference [*]
Mean age at transplant or matching, y	38	38	0.00
Female, %	88	88	0.00
Mean BMI, kg/m ²	26	26	0.10
Race/ethnicity, %	—	—	0.08
White	44	35	—
African American	45	54	—
Asian	6	5	—
Other	5	6	—
Hispanic, %	21	21	0.01
Organ Procurement and Transplantation Network region, %	—	—	0.02
1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, eastern Vermont)	3	3	—
2 (Delaware; Washington, DC; Maryland; New Jersey; Pennsylvania; West Virginia; northern Virginia)	12	11	—
3 (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi)	17	18	—
4 (Oklahoma, Texas)	11	10	—
5 (Arizona, California, Nevada, New Mexico, Utah)	15	18	—
6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington)	4	2	—
7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin)	8	7	—
8 (Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming)	5	4	—
9 (New York, western Vermont)	7	9	—
10 (Indiana, Michigan, Ohio)	7	8	—
11 (Kentucky, North Carolina, South Carolina, Tennessee, Virginia)	11	10	—
Comorbidity score [†]	7.0	7.3	0.07
First treatment method, %	—	—	0.04
Hemodialysis	82	84	—
Peritoneal dialysis	18	16	—
Prior organ transplant, %	<1	<1	0.03
Mean time receiving dialysis (SD), y	3.4 (2.0)	3.4 (2.5)	0.02
Mean time on waitlist (SD), y	2.3 (2.0)	2.1 (1.9)	0.12

BMI = body mass index; LN-ESRD = lupus nephritis due to end-stage renal disease.

^{*} Estimated using the approach of Austin (41).

[†] At time of transplant or matching.

Appendix Table 2.

All-Cause Mortality According to Transplant Status Among Matched Patients With LN-ESRD

Status	Total Follow-up, person-years [*]	Deaths, <i>n</i>	Mortality Rate (95% CI) [†]	Unadjusted HR (95% CI)	Adjusted HR (95% CI) [‡]
Had transplant	22 331	470	21.1 (19.2–23.0)	0.24 (0.21–0.28)	0.26 (0.22–0.30)
Did not have transplant	7889	608	77.1 (71.1–83.4)	1.0	1.0

ESRD = end-stage renal disease; HR = hazard ratio; LN-ESRD = ESRD due to lupus nephritis.

^{*} Follow-up for the group that had transplants begins at the time of renal transplant (index date) and ends at either death or the end of the study period (31 December 2015). Follow-up for the group that did not have transplants begins at the date of matching with a participant who had a transplant (index date, which occurs while waitlisted for renal transplant) and ends at death, censoring at the time of renal transplant, or the end of the study period (31 December 2015).

[†] Matched by age, sex, and time receiving dialysis.

[‡] Additionally adjusted for race/ethnicity, year of ESRD onset, first ESRD treatment method, comorbidity score, Organ Procurement and Transplantation Network region, and history of organ transplant.

References

1. Sabucedo AJ, Contreras G. ESKD, transplantation, and dialysis in lupus nephritis. *Semin Nephrol* 2015;35:500–8. doi:10.1016/j.semnephrol.2015.08.011 [PubMed: 26573552]
2. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol* 2017;12:825–35. doi:10.2215/CJN.05780616 [PubMed: 27821390]
3. Alarcón GS, McGwin G Jr, Bastian HM, Roseman J, Lisse J, Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups. VII [correction of VIII]. Predictors of early mortality in the LUMINA cohort. LUMINA Study Group. *Arthritis Rheum* 2001;45:191–202. [PubMed: 11324784]
4. Hanly JG, O’Keeffe AG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, et al. The frequency and outcome of lupus nephritis: results from an international inception cohort study. *Rheumatology (Oxford)* 2016;55:252–62. doi:10.1093/rheumatology/kev311 [PubMed: 26342222]
5. Yap DY, Tang CS, Ma MK, Lam MF, Chan TM. Survival analysis and causes of mortality in patients with lupus nephritis. *Nephrol Dial Transplant* 2012;27:3248–54. doi:10.1093/ndt/gfs073 [PubMed: 22523116]
6. Sule S, Fivush B, Neu A, Furth S. Increased hospitalizations and death in patients with ESRD secondary to lupus. *Lupus* 2012;21: 1208–13. doi:10.1177/0961203312451506 [PubMed: 22736748]
7. Gómez-Puerta JA, Feldman CH, Alarcón GS, Guan H, Winkelmayer WC, Costenbader KH. Racial and ethnic differences in mortality and cardiovascular events among patients with end-stage renal disease due to lupus nephritis. *Arthritis Care Res (Hoboken)* 2015; 67:1453–62. doi:10.1002/acr.22562 [PubMed: 25624071]
8. Wolfe RA, Ashby VB, Milford EL, Ojo AO, Ettenger RE, Agodoa LY, et al. Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant. *N Engl J Med* 1999;341:1725–30. [PubMed: 10580071]
9. Oniscu GC, Brown H, Forsythe JL. Impact of cadaveric renal transplantation on survival in patients listed for transplantation. *J Am Soc Nephrol* 2005;16:1859–65. [PubMed: 15857921]
10. Stone JH, Amend WJ, Criswell LA. Outcome of renal transplantation in systemic lupus erythematosus. *Semin Arthritis Rheum* 1997; 27:17–26. [PubMed: 9287386]
11. Stone JH, Amend WJ, Criswell LA. Outcome of renal transplantation in ninety-seven cyclosporine-era patients with systemic lupus erythematosus and matched controls. *Arthritis Rheum* 1998;41: 1438–45. [PubMed: 9704643]

12. Golebiewska J, Debska-Slizien A, Bullo-Piontecka B, Rutkowski B. Outcomes in renal transplant recipients with lupus nephritis—a single-center experience and review of the literature. *Transplant Proc* 2016;48:1489–93. doi:10.1016/j.transproceed.2016.02.061 [PubMed: 27496433]
13. Kang SH, Chung BH, Choi SR, Lee JY, Park HS, Sun IO, et al. Comparison of clinical outcomes by different renal replacement therapy in patients with end-stage renal disease secondary to lupus nephritis. *Korean J Intern Med* 2011;26:60–7. doi:10.3904/kjim.2011.26.1.60 [PubMed: 21437164]
14. Naranjo-Escobar J, Manzi E, Posada JG, Mesa L, Echeverri GJ, Duran C, et al. Kidney transplantation for end-stage renal disease in lupus nephritis, a very safe procedure: a single Latin American transplant center experience. *Lupus* 2017;26:1157–65. doi:10.1177/0961203317696591 [PubMed: 28420067]
15. Broder A, Mowrey WB, Izmirly P, Costenbader KH. Validation of systemic lupus erythematosus diagnosis as the primary cause of renal failure in the US renal data system. *Arthritis Care Res (Hoboken)* 2017;69:599–604. doi:10.1002/acr.22972 [PubMed: 27390299]
16. Organ Procurement and Transplantation Network. Regions Accessed at <https://optn.transplant.hrsa.gov/members/regions> on 3 8 2018.
17. Liu J, Huang Z, Gilbertson DT, Foley RN, Collins AJ. An improved comorbidity index for outcome analyses among dialysis patients. *Kidney Int* 2010;77:141–51. doi:10.1038/ki.2009.413 [PubMed: 19907414]
18. Lévesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ* 2010;340:b5087. doi:10.1136/bmj.b5087 [PubMed: 20228141]
19. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;94:496–509.
20. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016; 133:601–9. doi:10.1161/CIRCULATIONAHA.115.017719 [PubMed: 26858290]
21. Schaubel DE, Wolfe RA, Port FK. A sequential stratification method for estimating the effect of a time-dependent experimental treatment in observational studies. *Biometrics* 2006;62:910–7. [PubMed: 16984335]
22. Greenland S Applications of stratified analysis methods. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology* 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:283–302.
23. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;167:268–274. doi:10.7326/M16-2607 [PubMed: 28693043]
24. Kaballo MA, Canney M, O’Kelly P, Williams Y, O’Seaghdha CM, Conlon PJ. A comparative analysis of survival of patients on dialysis and after kidney transplantation. *Clin Kidney J* 2018;11:389–93. doi:10.1093/ckj/sfx117 [PubMed: 29942504]
25. O’Shaughnessy MM, Liu S, Montez-Rath ME, Lenihan CR, Lafayette RA, Winkelmayer WC. Kidney transplantation outcomes across GN subtypes in the United States. *J Am Soc Nephrol* 2017;28:632–44. doi:10.1681/ASN.2016020126 [PubMed: 27432742]
26. Chelamcharla M, Javaid B, Baird BC, Goldfarb-Rumyantsev AS. The outcome of renal transplantation among systemic lupus erythematosus patients. *Nephrol Dial Transplant* 2007;22:3623–30. [PubMed: 17640941]
27. Clark WF, Jevnikar AM. Renal transplantation for end-stage renal disease caused by systemic lupus erythematosus nephritis. *Semin Nephrol* 1999;19:77–85. [PubMed: 9952283]
28. Horta-Baas G, Camargo-Coronel A, Miranda-Hernández DG, González-Parra LG, Romero-Figueroa MDS, Pérez-Cristóbal M. Renal transplantation in systemic lupus erythematosus: comparison of graft survival with other causes of end-stage renal disease. *Reumatol Clin* 2017. doi:10.1016/j.reuma.2017.07.006
29. Nieto-Ríos JF, Serna-Higuaita LM, Builes-Rodríguez SA, Restrepo-Correa RC, Aristizabal-Alzate A, Ocampo-Kohn C, et al. Clinical outcomes of kidney transplants on patients with end-stage renal disease secondary to lupus nephritis, polycystic kidney disease and diabetic nephropathy. *Colomb Med (Cali)* 2016;47:51–8. [PubMed: 27226665]

30. Ward MM. Outcomes of renal transplantation among patients with end-stage renal disease caused by lupus nephritis. *Kidney Int* 2000;57:2136–43. [PubMed: 10792635]
31. Ponticelli C, Moroni G. Renal transplantation in lupus nephritis. *Lupus* 2005;14:95–8. [PubMed: 15732296]
32. Cairoli E, Sanchez-Marcos C, Espinosa G, Glucksmann C, Ercilla G, Oppenheimer F, et al. Renal transplantation in systemic lupus erythematosus: outcome and prognostic factors in 50 cases from a single centre. *Biomed Res Int* 2014;2014:746192. doi:10.1155/2014/746192 [PubMed: 25013800]
33. Sinicato NA, da Silva Cardoso PA, Appenzeller S. Risk factors in cardiovascular disease in systemic lupus erythematosus. *Curr Cardiol Rev* 2013;9:15–9. [PubMed: 23463953]
34. Gustafsson JT, Herlitz Lindberg M, Gunnarsson I, Pettersson S, Elvin K, Öhrvik J, et al. Excess atherosclerosis in systemic lupus erythematosus,—a matter of renal involvement: case control study of 281 SLE patients and 281 individually matched population controls. *PLoSOne* 2017;12:e0174572. doi:10.1371/journal.pone.0174572
35. Lewandowski LB, Kaplan MJ. Update on cardiovascular disease in lupus. *Curr Opin Rheumatol* 2016;28:468–76. doi:10.1097/BOR.0000000000000307 [PubMed: 27227346]
36. Cucchiari D, Graziani G, Ponticelli C. The dialysis scenario in patients with systemic lupus erythematosus. *Nephrol Dial Transplant* 2014;29:1507–13. doi:10.1093/ndt/gft420 [PubMed: 25053848]
37. Feldman CH, Hiraki LT, Winkelmayr WC, Marty FM, Franklin JM, Kim SC, et al. Serious infections among adult Medicaid beneficiaries with systemic lupus erythematosus and lupus nephritis. *Arthritis Rheumatol* 2015;67:1577–85. doi:10.1002/art.39070 [PubMed: 25772621]
38. Dalrymple LS, Go AS. Epidemiology of acute infections among patients with chronic kidney disease. *Clin J Am Soc Nephrol* 2008; 3:1487–93. doi:10.2215/CJN.01290308 [PubMed: 18650409]
39. United States Renal Data System. 2018 USRDS annual data report: epidemiology of kidney disease in the United States Bethesda: National Institutes of Health and National Institute of Diabetes and Digestive and Kidney Diseases; 2018 Accessed at www.usrds.org/2018/view/Default.aspx on 5 December 2018.
40. Saunders MR, Lee H, Alexander GC, Tak HJ, Thistlethwaite JR Jr, Ross LF. Racial disparities in reaching the renal transplant waitlist: is geography as important as race? *Clin Transplant* 2015;29:531–8. doi:10.1111/ctr.12547 [PubMed: 25818547]
41. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–107. doi:10.1002/sim.3697 [PubMed: 19757444]

Table 1.

Baseline Characteristics of Participants With LN-ESRD

Baseline Characteristic	LN-ESRD (n = 20 974)	All Waitlisted (n = 9659)	Had Transplant (n = 5738)
Age at ESRD onset, %			
<30 y	30	35	38
30–39 y	23	28	28
40–49 y	21	22	21
>50 y	26	15	13
Female, %	82	82	82
Mean BMI, kg/m ²	26.2	26.0	25.6
Race/ethnicity, %			
White	42	40	44
African American	48	48	44
Asian	4	6	6
Other	6	6	6
Hispanic, %	18	21	22
Organ Procurement and Transplantation Network region, %			
1 (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, eastern Vermont)	3	3	3
2 (Delaware; Washington, DC; Maryland; New Jersey; Pennsylvania; West Virginia; northern Virginia)	10	11	11
3 (Alabama, Arkansas, Florida, Georgia, Louisiana, Mississippi)	20	18	16
4 (Oklahoma, Texas)	10	10	10
5 (Arizona, California, Nevada, New Mexico, Utah)	16	18	17
6 (Alaska, Hawaii, Idaho, Montana, Oregon, Washington)	3	3	3
7 (Illinois, Minnesota, North Dakota, South Dakota, Wisconsin)	7	7	8
8 (Colorado, Iowa, Kansas, Missouri, Nebraska, Wyoming)	4	4	5
9 (New York, western Vermont)	7	8	8
10 (Indiana, Michigan, Ohio)	8	8	8
11 (Kentucky, North Carolina, South Carolina, Tennessee, Virginia)	12	10	10
Prior organ transplant, %	<1	<1	<1
Comorbid conditions, % [*]			
Diabetes	7	5	4

Baseline Characteristic	LN-ESRD (n = 20 974)	All Waitlisted (n = 9659)	Had Transplant (n = 5738)
Hypertension	79	79	77
CAD	6	3	3
CHF	18	10	8
CVA	5	3	3
Tobacco use	4	2	2
Cancer	2	1	1
Comorbidity score *	0.9	0.6	0.5
First treatment method, %			
Hemodialysis	85	83	82
Peritoneal dialysis	12	17	18
Enrolled in Medicare, %	75	77	80

BMI = body mass index; CAD = coronary artery disease; CHF = congestive heart failure; CVA = cerebrovascular accident; ESRD = end-stage renal disease; LN-ESRD = ESRD due to lupus nephritis.

* Based on the Centers for Medicare & Medicaid Services medical evidence form.

Table 2.

All-Cause Mortality According to Transplant Status Among Patients With LN-ESRD

Status	Total Follow-up, <i>person-years</i>	Deaths, <i>n</i>	Mortality Rate (95% CI)*	Unadjusted HR (95% CI)	HR Adjusted for Age, Sex, and Year of ESRD Onset (95% CI)	Fully Adjusted HR (95% CI)†
Overall	73 349	2670	36.4 (35.1–37.8)	–	–	–
Had transplant	43 207	973	22.5 (21.2–24.0)	0.29 (0.26–0.32)	0.28 (0.26–0.31)	0.30 (0.27–0.33)
Did not have transplant	30 139	1697	56.3 (53.7–59.1)	1.0	1.0	1.0
Age at ESRD onset						
<30 y	26 547	739	27.8 (25.9–29.9)	–	–	–
Had transplant	16 436	288	17.5 (15.6–19.7)	0.29 (0.24–0.34)	0.27 (0.23–0.32)	0.30 (0.25–0.36)
Did not have transplant	10 111	451	44.6 (40.7–48.9)	1.0	1.0	1.0
30–39 y	21 571	684	31.7 (29.4–34.2)	–	–	–
Had transplant	12 625	250	19.8 (17.5–22.4)	0.30 (0.25–0.36)	0.29 (0.24–0.34)	0.32 (0.27–0.39)
Did not have transplant	8946	434	48.5 (44.2–53.3)	1.0	1.0	1.0
40–49 y	16 134	662	41.0 (38.0–44.3)	–	–	–
Had transplant	9465	249	26.3 (23.2–29.8)	0.28 (0.24–0.34)	0.27 (0.22–0.32)	0.27 (0.23–0.33)
Did not have transplant	6669	413	61.9 (56.2–68.2)	1.0	1.0	1.0
50 y	9128	585	64.1 (59.1–69.5)	–	–	–
Had transplant	4711	186	39.5 (34.2–45.6)	0.30 (0.24–0.37)	0.28 (0.22–0.34)	0.27 (0.22–0.33)
Did not have transplant	4417	399	90.3 (81.9–99.7)	1.0	1.0	1.0
Sex						
Male	12 996	494	38.0 (34.8–41.5)	–	–	–
Had transplant	8145	193	23.7 (20.6–27.3)	0.25 (0.20–0.31)	0.24 (0.19–0.30)	0.24 (0.19–0.30)
Did not have transplant	4851	301	62.0 (55.4–69.5)	1.0	1.0	1.0
Female	60 384	2176	36.0 (34.6–37.6)	–	–	–
Had transplant	35 091	780	22.2 (20.7–23.8)	0.30 (0.27–0.33)	0.29 (0.26–0.32)	0.31 (0.28–0.35)
Did not have transplant	25 293	1396	55.2 (52.4–58.2)	1.0	1.0	1.0
Race/ethnicity						
White	30 529	999	32.7 (30.8–34.8)	–	–	–
Had transplant	19 786	438	22.1 (20.2–24.3)	0.30 (0.26–0.35)	0.29 (0.25–0.33)	0.29 (0.25–0.34)
Did not have transplant	10 743	561	52.2 (48.1–56.7)	1.0	1.0	1.0

Status	Total Follow-up, person-years	Deaths, <i>n</i>	Mortality Rate (95% CI) [*]	Unadjusted HR (95% CI)	HR Adjusted for Age, Sex, and Year of ESRD Onset (95% CI)	Fully Adjusted HR (95% CI) [†]
African American	33 483	1416	42.3 (40.1–44.6)	–	–	–
Had transplant	17 688	446	25.2 (23.0–27.7)	0.29 (0.26–0.33)	0.29 (0.25–0.33)	0.30 (0.27–0.35)
Did not have transplant	15 795	970	61.4 (57.7–65.4)	1.0	1.0	1.0
Asian	4219	100	23.7 (19.3–28.8)	–	–	–
Had transplant	2359	30	12.7 (8.6–18.2)	0.29 (0.17–0.47)	0.29 (0.18–0.49)	0.35 (0.21–0.58)
Did not have transplant	1860	70	37.6 (29.8–47.6)	1.0	1.0	1.0
Hispanic	15 709	412	26.2 (23.8–28.9)	–	–	–
Had transplant	9112	143	15.7 (13.3–18.5)	0.26 (0.20–0.32)	0.25 (0.20–0.31)	0.28 (0.22–0.35)
Did not have transplant	6597	269	40.8 (36.2–46.0)	1.0	1.0	1.0
Non-Hispanic	57 517	2238	38.9 (37.3–40.6)	–	–	–
Had transplant	34 028	824	24.2 (22.6–25.9)	0.29 (0.27–0.33)	0.29 (0.26–0.32)	0.30 (0.27–0.34)
Did not have transplant	23 489	1414	60.2 (57.1–63.4)	1.0	1.0	1.0
Calendar year of ESRD onset						
1995–2004	49 582	1995	40.2 (38.5–42.0)	–	–	–
Had transplant	33 250	843	25.4 (23.7–27.1)	0.29 (0.26–0.32)	0.29 (0.26–0.32)	0.30 (0.27–0.34)
Did not have transplant	16 332	1152	70.5 (66.5–74.7)	1.0	1.0	1.0
2005–2014	23 978	675	28.2 (26.1–30.4)	–	–	–
Had transplant	9986	130	13.0 (11.0–15.5)	0.25 (0.20–0.30)	0.25 (0.20–0.30)	0.28 (0.22–0.34)
Did not have transplant	13 812	545	39.5 (36.3–42.9)	1.0	1.0	1.0
Medicare enrollment status						
Enrolled	57 863	2148	–	–	–	–
Had transplant	34 325	790	23.0 (21.4–24.7)	0.28 (0.25–0.31)	0.27 (0.24–0.30)	0.29 (0.26–0.33)
Did not have transplant	23 538	1358	57.7 (54.7–60.9)	1.0	1.0	1.0
Not enrolled	15 517	522	–	–	–	–
Had transplant	8911	183	20.5 (17.7–23.7)	0.34 (0.27–0.42)	0.33 (0.27–0.41)	0.34 (0.27–0.42)
Did not have transplant	6605	339	51.3 (46.0–57.1)	1.0	1.0	1.0

ESRD = end-stage renal disease; HR = hazard ratio; LN-ESRD = ESRD due to lupus nephritis.

^{*} Per 1000 person-years.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Adjusted for sex, age, race/ethnicity, year of ESRD onset, first ESRD treatment method, comorbidity score, Organ Procurement and Transplantation Network region, and history of organ transplantation. Follow-up for participants who did not have a transplant begins at entry onto the waitlist for renal transplant and ends at death, censoring at the time of renal transplant, or the end of the study period (31 December 2015). Follow-up for participants who had a transplant begins at the time of renal transplant and ends at either death or the end of the study period (31 December 2015).

Table 3.
Cause-Specific Mortality According to Transplant Status Among Patients With LN-ESRD

Status	Deaths, <i>n</i>	Unadjusted HR (95% CI)	HR Adjusted for Age, Sex, and Year of ESRD Onset (95% CI)	Fully Adjusted HR (95% CI)*
CVD overall				
Had transplant	273	0.33 (0.28–0.38)	0.31 (0.26–0.36)	0.26 (0.23–0.30)
Did not have transplant	675	1.0	1.0	1.0
Coronary heart disease				
Had transplant	28	0.32 (0.21–0.49)	0.30 (0.20–0.46)	0.30 (0.19–0.48)
Did not have transplant	77	1.0	1.0	1.0
Stroke				
Had transplant	27	0.42 (0.27–0.65)	0.39 (0.25–0.61)	0.39 (0.24–0.61)
Did not have transplant	72	1.0	1.0	1.0
Infection overall				
Had transplant	124	0.40 (0.32–0.65)	0.39 (0.25–0.61)	0.41 (0.32–0.52)
Did not have transplant	277	1.0	1.0	1.0
Sepsis				
Had transplant	94	0.40 (0.31–0.52)	0.38 (0.29–0.50)	0.41 (0.31–0.53)
Did not have transplant	221	1.0	1.0	1.0
Pneumonia				
Had transplant	17	0.54 (0.28–1.04)	0.60 (0.31–1.17)	0.62 (0.32–1.20)
Did not have transplant	26	1.0	1.0	1.0
Cancer				
Had transplant	42	0.86 (0.57–1.29)	0.94 (0.63–1.42)	0.96 (0.63–1.45)
Did not have transplant	40	1.0	1.0	1.0

CVD = cardiovascular disease; ESRD = end-stage renal disease; HR = hazard ratio; LN-ESRD = ESRD due to lupus nephritis.

* Adjusted for sex, age, race/ethnicity, year of ESRD onset, first ESRD treatment method, comorbidity score, Organ Procurement and Transplantation Network region, and history of organ transplant.