Paper

Kidney transplantation outcomes in lupus nephritis: A 37-year single-center experience from Latin America

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Abstract

Objective: We assessed patient and graft outcomes and prognostic factors in kidney transplantation in patients with end-stage kidney disease (ESKD) secondary to lupus nephritis (LN) undergoing kidney transplantation from August 1977 to December 2014 in a Latin American single center.

Methods: The primary endpoint was patient survival, and the secondary endpoints were death-censored graft survival for the first renal transplant and the rate of recurrent LN (RLN). Kaplan–Meier method was used for survival analysis. Factors predicting patient and death-censored graft survivals were examined by Cox proportional-hazards regression analyses.

Results: 185 patients were retrospectively evaluated. Patient survival rates were 88% at one year, 82% at three years, 78% at five years, and 67% at ten years. Death-censored graft survival for the first renal transplant was 93% at one year, 89% at three years, 87% at five years, and 80% at ten years. RLN was diagnosed in 2 patients (1.08%), but no graft was lost because of RLN. Thirty-nine (21.1%) patients died, and 65 (35.1%) patients experienced graft loss during the follow-up. By multivariable analyses, older recipient age and 1-month posttransplantation eGFR <45 ml/min/1.73m^2 were associated with lower patient survival and an increased risk of graft loss, while induction immunosuppressive therapy exerted a protective effect on patients' survival. In the subgroup of patients in whom disease activity was measured at the time of transplantation, a higher SLEDAI score was also associated with lower patient survival and an increased risk of graft loss.

Conclusion: In a mostly Mestizo population, kidney transplantation is an excellent therapeutic alternative in LN patients with ESKD. Older recipient age, an eGFR <45 ml/min/1.73m^2 at one month posttransplantation, and disease activity at the time of transplantation are predictive of a lower patient and death-censored graft survival, while induction immunosuppressive therapy has a protective effect on patient survival. RLN is rare and does not influence the risk of graft loss.

Keywords

Systemic lupus erythematosus, lupus nephritis, end-stage kidney disease, kidney transplantation, outcome, survival analyses

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Introduction

Lupus nephritis (LN) constitutes a significant cause of morbidity and mortality in systemic lupus erythematosus (SLE) patients. Up to 60% of these patients will develop LN during the first ten years of the disease, and 10 to 30% of them will progress to end-stage kidney disease (ESKD) requiring renal replacement therapy (RRT), even with aggressive treatment.[1–3] Patient survival rates with either hemodialysis or continuous ambulatory peritoneal dialysis are comparable to that of non-lupus patients with ESKD[4] and have not changed significantly over the past decades.[3]

Kidney transplantation is the best therapeutic option for ESKD, as it has been associated with a substantial improvement in survival in the all-cause ESKD population.[5] In LN-ESKD patients, kidney transplantation is associated with reduced mortality, primarily due to cardiovascular disease (CVD) and infection.[6] Furthermore, patient and graft survival rates among SLE patients are similar to those of transplant recipients with other causes of ESKD.[4,5,7–19]

The recurrence of LN (RLN) in the kidney graft remains a major concern, as it increases the risk of graft loss.[20–22] The reported rate of RLN in the graft ranges from 0 to 54%.[2,4,5,11,13,16–18,20–25] Graft loss due to RLN is uncommon with an incidence of 2 to 11% over 5 and 10 years after transplantation.[22–24,26] Risks factors for RLN in the kidney graft include African-American ethnicity, female gender, younger age, hypocomplementemia after renal transplantation, lupus anticoagulant positivity, living donors, and patients' compliance with immunosuppressive therapy.[22,23,25,27] Risk factors associated with graft failure include RLN, acute and chronic graft rejection, delayed graft function, African-American ethnicity, deceased-donor kidney graft, thrombotic events, panel-reactive antibodies $\geq$50%, and high HLA mismatch level.[7,9,22,23,28,29] Limited data are available from Latin American LN patients who underwent kidney transplantation.[11,13,16,29–32] Thus, the objective of this study was to assess patient and graft outcomes in a predominantly Mestizo Latin American population with SLE undergoing kidney transplantation in a Colombian single-center.

Materials and methods

Design and patients

This is a pragmatic retrospective cohort study of 185 LN-ESKD patients older than 14 years who underwent a kidney transplant at Hospital Universitario San Vicente Fundación (HUSVF), Medellín, Colombia, between August 1977 and December 2014.

One hundred and seventy-nine patients met the 1982 American College of Rheumatology criteria for SLE. The remaining six patients satisfied the 1971 American Rheumatism Association classification criteria for SLE and underwent kidney transplants between 1977 and 1982. Those patients who had received another organ besides the kidney were excluded. LN was diagnosed by kidney biopsy [according to the World Health Organization before 2004, or 2003 International Society of Nephrology/Renal Pathology Society classification of LN since 2004][33,34] when available, or by the presence of one or more of the following: nephrotic syndrome, proteinuria >1 g/24 h, or hematuria attributable to SLE. Patients were followed until death or until December 31, 2014, whichever came first.

Data collection

Data were obtained from archival and electronic medical records and from the database established since the beginning of the kidney transplant program at HUSVF.

The variables obtained from the database were as follows:

Recipient-related variables: age, gender, ethnicity (Mestizo, African-Latin American), comorbidities (hypertension, diabetes, CVD), time from SLE diagnosis to ESKD, time on the waiting list, pretransplant RRT, hemodialysis, time on dialysis before renal transplant, and disease activity [SLE Disease activity Index (SLEDAI)] at the time of transplantation.

Donor-related variables: age, gender, type of donor (deceased, living), serum creatinine (mg/dl).

Transplant-related variables: cold ischemia time, HLA mismatches, induction therapy [induction agents: anti-interleukin-2 (IL-2) receptor monoclonal antibodies (basiliximab, daclizumab), anti-CD52 T-cell and B-cell–depleting monoclonal antibody (alemtuzumab) or Thymoglobulin], and maintenance immunosuppressive protocols [cyclosporine A (CsA) + azathioprine (AZA) + prednisone, CsA + mycophenolate mofetil (MMF) or mycophenolic acid (MPA) + prednisone, AZA + prednisone, or tacrolimus (TAC) + MMF or MPA + prednisone).

We also collected the following outcome data: primary nonfunction, serum creatinine, and estimated glomerular filtration rate (eGFR) using the MDRD equation at discharge, at one month and one year, date of irreversible loss of transplant function (defined as the reinstitution of chronic dialysis), acute rejection episodes, delayed graft function (defined as the need for hemodialysis during the first week after transplantation), causes of death and graft failure (defined as the need to restart dialysis therapy or retransplantation), cardiovascular events, infections, malignant neoplasms,

chronic allograft nephropathy, cyclosporine toxicity, and RLN as defined by histological findings in biopsies performed based on clinical indications, and not per surveillance biopsies. The observational clinical checklist followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.

The standard immunosuppressive protocols after kidney transplantation changed throughout the retrospective study period. From 1977 to 2005, all patients received steroids plus AZA, and after 1985 CsA was added to this protocol. From 2005, AZA was changed to MMF, and induction therapy with monoclonal antibodies (basiliximab, daclizumab, or alemtuzumab) or Thymoglobulin was introduced. The HUSVF ethics committee approved this study.

Statistical analysis

The primary endpoint was patient survival. The secondary endpoints were death-censored graft survival for the first renal transplant and the rate of RLN. Patient survival was assessed from the date of transplantation until death, the end of the study period (December 2014), or the latest available follow-up. We assessed the effect of preemptive kidney transplantation on patient and graft survivals. Survival rates were generated using the Kaplan-Meier method and compared using the Mantel-Cox log-rank test. Comparison of parametric data used the Student t-test for continuous variables, Wilcoxon rank-sum tests when necessary, and Chi-squared test with Yates' correction or the Fisher exact test, whenever appropriate, for categorical variables. We performed univariable and multivariate Cox proportional hazards regression models to calculate adjusted risk estimates for patient survival and allograft censored survival. The variables included in these analyses were: recipient age, recipient sex, previous dialysis, biopsy-proven acute rejection, donor type, antibody induction therapy, 1-month post-transplantation eGFR, and SLEDAI at the time of transplantation. The univariable and multivariable analyses are reported as hazard ratios (HRs) where values ≥ 1 indicate a shorter time to the occurrence of patient death or allograft loss, while values <1 indicate a longer time; p values ≤ 0.05 were considered statistically significant. All analyses were performed using STATA Statistical Software, version 12 (College Station, TX: StataCorp LP).

Results

A total of 4,546 kidney transplants were performed between August 1977 and December 2014 at HUSVF. Among these transplants, 202 transplants were performed in 185 patients with LN-ESKD.

Patients were predominantly women (85.4%) and Mestizos (90.8%). The mean ± SD age of the recipients was 32.8 ± 10.3 years, the mean ± SD interval from SLE diagnosis to the onset of ESKD was 110.5 ± 87 months, the mean ± SD duration of dialysis before transplantation was 32.2 ± 56.4 months, and the median follow-up interval after transplantation was 10 years (IQR 5–16). Seventy-five patients (40.5%) underwent a renal biopsy before transplantation: 2 had class III LN, 6 had class III+V, 41 had class IV, 12 had class IV+V, 9 had class V, and five had class VI. In the remaining patients, the diagnosis of LN was based on clinical manifestations, laboratory findings, immunological profile, and medical records from the referring hospital. The median time on the kidney transplant waiting list was 5 months (IQR 2–12). Before renal transplantation, 60.5% of patients required RRT, and 73 (39.5%) patients underwent a preemptive transplant (patients without previous RRT). SLEDAI scores were calculated in 105 patients at the time of transplantation. Preemptively transplanted patients (n = 45) had significantly higher SLEDAI scores than non-preemptively transplanted patients (n = 60) [2 (IQR, 1–4) vs 0 (IQR 0–2), $p < 0{,}001$].

Eighty-two percent of grafts were from deceased donors. Regarding therapy, 41% of the patients received induction immunosuppressive therapy, alemtuzumab being the most commonly used (53%). Most patients (85.4%) were on triple-therapy immunosuppression [steroids, calcineurin inhibitors (CsA or TAC), and AZA or either MMF or MPA]. Steroids were continued during all follow-up examinations, and most patients continued to receive prednisone 5 mg daily. These data are summarized in Table 1.

Patient and death-censored graft survival

Thirty-nine (21.1%) patients died during follow-up, mainly due to infection (n = 18) and CVD (n = 8). There were no deaths related to allograft failure or allograft rejection (Table 1). The overall patient survival rates were 88% at one year, 82% at three years, 78% at five years, and 67% at ten years (Figure 1(a)). Patient survival rates before and after 2005, when induction therapy with monoclonal antibodies was included, were 85% and 93% at one year, 75% and 93% at three years, and 74% and 85% at five years, respectively ($p = 0.03$).

Sixty-five (35.1%) patients experienced graft loss during the follow-up. The leading cause of graft loss was chronic allograft nephropathy (n = 35), followed by the death of the patient with functioning graft

Table 1. Demographic and clinical characteristics of patients with lupus nephritis undergoing kidney transplantation between August 1977 and December 2014 at Hospital Universitario San Vicente Fundación (n = 185).*

Recipient-related variables	
Recipient age, years, mean ± SD	32.8 ± 10.3
Male sex, n (%)	27 (14.6)
Ethnic distribution, n (%)	
Mestizos	168 (90.8)
Afro-Colombians	16 (8.6)
Whites	1 (0.6)
Renal biopsy before transplantation according to WHO and/or ISN/RPS classification of lupus nephritis, n (%)	75 (40.5)
Class III	2
Class III + V	6
Class IV	41
Class IV + V	12
Class V	9
Class VI	5
Number of transplants, n (%)	202 (100)
First transplant	185 (91.6)
Second transplant	17 (8.4)
Comorbidities, n (%)	
Hypertension	146 (78.9)
Diabetes mellitus	3 (1.6)
Heart failure	2 (1.1)
The interval from SLE diagnosis to ESKD onset, months, mean ± SD	110.5 ± 87
Median of time on waiting list, months, IQR	5 (2 – 12)
Pre-transplant RRT, n (%)	112 (60.5)
Hemodialysis, n (%)	91/112 (81.3)
Peritoneal dialysis, n (%)	21/112 (18.7)
Time on dialysis before renal transplant, months, mean ± SD	32.2 ± 56.4
Pre-transplant immunosuppressive agents n (%)	
Prednisone	178 (96.2)
CyC	104 (56.2)
MMF or MPA	13 (7.0)
Rituximab	4 (2.2)
CNI (CsA or TAC)	4 (2.2)
Preemptive transplant, n (%)	73 (39.5)
Median of SLEDAI at the time of transplantation (n = 105):	1 (0–2)
Preemptive group (n = 45)	2 (1–4)
Non-preemptive group (n = 60)	0 (0–2)
Deceased patients (n = 17)	6 (4–8)
Surviving patients (n = 88)	1 (0–2)
Creatinine at one month, mg/dl, mean ± SD	1.6 ± 0.9
Creatinine at one year, mg/dl, mean ± SD	1.3 ± 0.6
BPAR, n (%)	49 (26,4%)
BPAR (BANFF category)	
Borderline	8 (9%)
IA	17 (20%)
IB	15 (18%)
IIA	6 (7%)
IIB	1 (1%)
III	2 (2%)
Other (CAN, IFTA, CNI toxicity)	35 (42%)
Recurrence of lupus nephritis, n (%)	2 (1,08%)
Death	39 (21%)

(continued)

Table 1. Continued.

Recipient-related variables	
Cause of death	
Infection	18 (46.2%)
Cardiovascular	8 (20.5%)
Others	13 (33.3%)
Death with a functioning graft	24 (61%)
Donor-related variables	
Type of donor, n (%)	
Deceased donor	152 (82.2)
Living donor	33 (17.8)
Donor age, years, mean ± SD	32.2 ± 13
Male sex, n (%)	116 (62.7)
Median of donor creatinine, mg/dl, IQR	0.91 (0.7–1.1)
Transplant-related variables	
Median of cold ischemia time, hours, IQR	20 (16–25)
HLA mismatches, mean ± SD	4.0 ± 1.1
HLA-DR mismatches, mean ± SD	1.09 ± 0.6
Induction therapy, n (%)	81 (43.8)
Induction immunosuppressive agents, n (%)	
Basiliximab/daclizumab	21 (26)
Thymoglobulin	17 (21)
Alemtuzumab	43 (53)
Maintenance therapy, n (%)	185 (100)
CsA + AZA + prednisone	74 (40)
CsA + MMF or MPA + prednisone	68 (36.8)
AZA + prednisone	19 (10.3)
TAC + MMF or MPA + prednisone	16 (8.6)
Others	8 (4.3)

WHO: World Health Organization; ISN/RPS: International Society of Nephrology/Renal Pathology Society; SD: standard deviation; IQR: interquartile range with percentile 25th and 75th; RRT: renal replacement therapy; CyC: cyclophosphamide; MMF: mycophenolate mofetil; MPA: mycophenolic acid; CNI: Calcineurin inhibitors; CsA: cyclosporine A; TAC: tacrolimus; AZA: azathioprine; BPAR: Biopsy proven acute rejection; CAN: Chronic allograft nephropathy; IFTA: Interstitial fibrosis Tubular atrophy; HLA: human leukocyte antigen.
*Data are presented as numbers and percentages, mean (standard deviation), or medium (interquartile ranges).

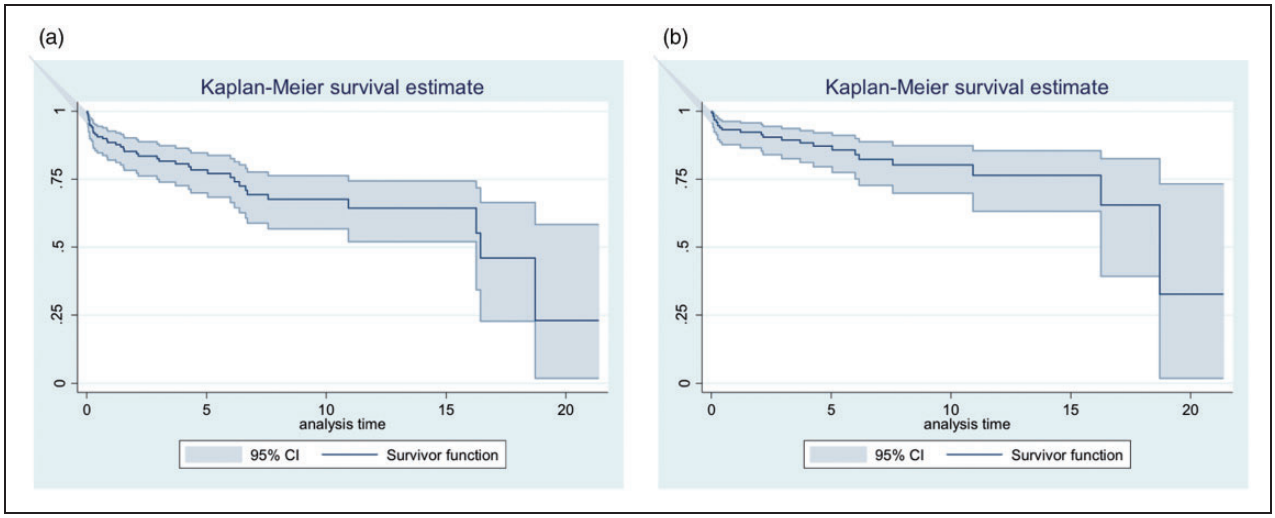

Figure 1. (a) Cumulative patient survival in years. (b) Death-censored graft survival in years.

(n = 24), acute rejection (n = 3), and others (acute humoral rejection, infection, and bleeding) (n = 3). Death-censored graft survival for the first renal transplant was 93% at one year, 89% at three years, 87% at five years, and 80% at ten years (Figure 1(b)).

Patient and death-censored graft survival rates in preemptive versus non-preemptive groups

Patient survival rates were worse in those who underwent preemptive kidney transplantation than those with non-preemptive kidney transplantation ($p = 0.015$). Patient survival rates in preemptive and non-preemptive groups were 78% and 94% at one year, 72% and 88% at three years, 66% and 85% at five years, and 56% and 73% at ten years, respectively (Table 2, Figure 2(a)).

Regarding death-censored graft survival, although there was a trend toward better graft survival rates in the non-preemptive group, there were no statistically significant differences between the groups ($p = 0.082$) (Table 3, Figure 2(b)).

Recurrence of lupus nephritis and acute renal allograft rejection

Two patients (1.08%) had a biopsy compatible with RLN during the follow-up. Both of them had histological pattern of class V LN. On the other hand, 49 (26,5%) episodes of acute rejection were demonstrated by graft biopsy, most of them mild (borderline, IA, or IB in Banff classification).[35] These data are shown in Table 1.

Table 2. Patient and graft survival rates in preemptive (without RRT) versus non-preemptive groups.

	Non-preemptive (with RRT)	Preemptive (without RRT)	*P*
Patient survival			
One year	94% (86–97)	78% (64–87)	0.015
Three years	88% (79–93)	72% (57–82)	
Five years	85% (74–91)	66% (50–78)	
Ten years	73% (57–83)	56% (39–70)	
Twenty-two years	66% (45–80)	17% (1–48)	
Death-censored graft survival			
One year	96% (89–98)	88% (75–94)	0.082
Three years	93% (84–97)	83% (68–91)	
Five years	91% (81–96)	79% (63–89)	
Ten years	84% (69–92)	72% (53–84)	
Twenty-two years	76% (51–89)	29% (1–68)	

RRT: renal replacement therapy. Values in parentheses are 95% confidence intervals. *P* values refer to those that are associated with log-rank tests comparing the survival curves.

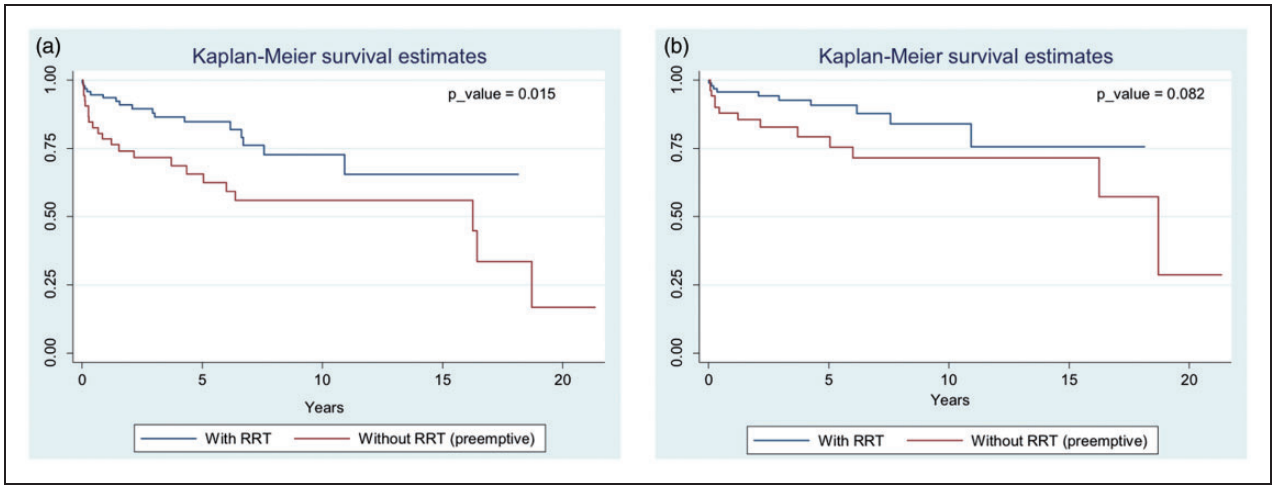

Figure 2. (a) Patient survival rates in preemptive (without RRT) versus non-preemptive groups. (b) Death-censored survival rates in preemptive (without RRT) versus non-preemptive groups. RRT: renal replacement therapy.

Table 3. Univariable and multivariable Cox analysis for overall patient survival and death-censored graft survival.

Model 1. Univariable and multivariable Cox analysis of predictors of overall patient survival in the entire population of transplant patients

	Univariable analysis			Multivariate analysis		
Variable	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
Recipient Age	1.03	1.00–1.06	0.020	1.05	1.01–1.09	0.008
Recipient sex (Male)	1.94	0.94–4.01	0.073	1.54	0.60–3.94	0.368
Afro-Colombian ethnicity	1.35	0.41–4.40	0.621	1.14	0.25–5.24	0.869
Previous Dialysis						
Yes	Reference group					
No (Preemptive)	2.18	1.14–4.16	0.018	1.65	0.74–3.67	0.220
BPAR	0.86	0.45–1.63	0.642	0.50	0.21–1.16	0.108
Donor status (Deceased donor)	1.13	0.52–2.47	0.752	1.58	0.59–4.20	0.363
Induction immunosuppressive therapy	0.55	0.25–1.18	0.124	0.35	0.13–0.94	0.038
eGFR at 1 month <45 ml/min/1.73 m^2	2.18	1.65–2.87	<0.001	2.22	1.51–3.27	<0.001

Univariate and multivariate Cox analysis of predictors of death-censored graft survival in the entire population of transplant patients

	Univariable analysis			Multivariate analysis		
Variable	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
Recipient Age	1.05	1.01–1.08	0.007	1.07	1.02–1.12	0.006
Recipient sex (Male)	1.98	0.77–5.06	0.154	1.13	0.31–4.15	0.854
Afro-Colombian ethnicity	0.74	0.10–5.51	0.768	1.01	0.12–8.33	0.992
Previous Dialysis						
Yes	Reference group					
No (Preemptive)	2.09	0.89–4.89	0.089	1.48	0.51–4.26	0.471
BPAR	0.65	0.28–1.53	0.330	0.44	0.14–1.37	0.157
Donor (Deceased Donor)	1.15	0.41–3.26	0.786	0.99	0.26–3.73	0.992
Induction immunosuppressive therapy	0.85	0.33–2.17	0.737	0.50	0.14–1.79	0.289
eGFR at 1 month <45 ml/min/1.73 m^2	2.19	1.59–3.02	<0.001	2.29	1.39–3.76	0.001

Model 2.* Univariable and multivariable Cox analysis of predictors of overall patient survival in SLE patients with SLEDAI measured at the time of transplantation

	Univariable analysis			Multivariate analysis		
Variable	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
Recipient Age	1.03	1.00–1.06	0.020	0.99	0.92–1.07	0.805
Recipient sex (Male)	1.94	0.94–4.01	0.073	1.96	0.33–11.64	0.461
Afro-Colombian ethnicity	1.35	0.41–4.40	0.621	1.00	0.12–8.13	1.000
Previous Dialysis						
Yes	Reference group					
No (Preemptive)	2.18	1.14–4.16	0.018	5.10	0.71–36.50	0.105
BPAR	0.86	0.45–1.63	0.642	0.09	0.01–0.96	0.046
Induction immunosuppressive therapy	0.55	0.25–1.18	0.124	2.58	0.27–24.83	0.413
eGFR at 1 month <45 ml/min/1.73 m^2	2.18	1.65–2.87	<0.0001	2.91	1.25–6.78	0.013
SLEDAI at the time of transplantation	1.62	1.38–1.91	<0.0001	1.71	1.27–2.31	<0.0001

Univariable and multivariable Cox analysis of predictors of death-censored graft survival in SLE patients with SLEDAI measured at the time of transplantation

	Univariable analysis			Multivariate analysis		
Variable	HR	95% CI	*P*-Value	HR	95% CI	*P*-Value
Recipient Age	1.05	1.01–1.08	0.007	1.05	0.95–1.16	0.314
Recipient sex (Male)	1.98	0.77–5.06	0.154	1.52	0.16–14.23	0.716
Afro-Colombian ethnicity	0.74	0.10–5.51	0.768	1.08	0.09–13.62	0.950

(continued)

Table 3. Continued

Previous Dialysis						
Yes	Reference group					
No (Preemptive)	2.09	0.89–4.89	0.089	5.63	0.69–45.92	0.106
BPAR	0.65	0.28–1.53	0.330	0.15	0.01–2.70	0.197
Induction immunosuppressive therapy	0.85	0.33–2.17	0.737	0.71	0.04–12.67	0.817
eGFR at 1 month <45 ml/min/1.73 m^2	2.19	1.59–3.02	<0.0001	1.91	0.78–4.66	0.157
SLEDAI at the time of transplantation	1.59	1.30–1.95	<0.0001	1.35	1.00–1.82	0.047

Model 1: the entire population of transplant patients (n = 185). Model 2: a model for patients with SLEDAI measured at the time of transplantation (n = 105).
HR: Hazard Ratio; BPAR: biopsy proven acute rejection; eGFR: estimated glomerular filtration rate; SLEDAI: SLE Disease Activity Index.
*102 patients received renal grafts from deceased donors.

Factors predicting patient and death-censored graft survival

Univariable and multivariate Cox proportional hazards regression models were performed to estimate the adjusted risk for lower patient survival and lower death-censored graft survival for the first renal transplant.

Patient survival. Univariable analyses showed that older recipient age, no previous dialysis, and 1-month eGFR <45 ml/min/1.73m^2 were associated with lower patient survival. In the multivariable analysis, older recipient age [HR 1.05 (CI 95%: 1.01–1.09, $p = 0.008$)], and 1-month eGFR <45 ml/min/1.73m^2 [HR 2.22 (CI 95%, 1.51–3.27, $p < 0.001$)] were associated with lower patient survival while induction immunosuppressive therapy exerted a protective effect on patient survival [HR 0.35 (CI 0.13–0.94, $p = 0.038$)].

Death-censored graft survival. Univariable analyses showed that older recipient age and 1-month eGFR <45 ml/min/1.73m^2 were associated with increased risk of graft loss. In the multivariable analysis, both, older recipient age [HR 1.07 (CI 95%, 1.02–1.12, $p = 0.006$)], and 1-month eGFR <45 ml/min/1.73m^2 [HR 2.29 (CI 95%, 1.39–3.76, $p = 0.001$)] remained associated with increased risk of graft loss (Table 3).

In patients with disease activity measured by the SLEDAI at the time of transplantation (n = 105), disease activity emerged as an independent predictor of lower patient survival [HR 1.71 (CI 95%, 1.27–2.31, $p < 0.0001$) and lower death-censored graft survival [HR 1.35 (CI 95%, 1.00–1.82, $p = 0.047$)] while eGFR <45 ml/min/1.73m^2 at 1 month post-transplantation remained as an independent predictor of lower patient survival [HR 2.91 (CI 95%, 1.25–6.78, $p = 0.013$)] (Table 3). SLEDAI scores at the time of transplantation were higher in deceased patients (n = 17) than in surviving patients (n = 88) [6 (IQR, 4–8) vs 1 (IQR 0-2), $p < 0.0001$] (Table 1).

We conducted a sensitivity analysis to compare patient and death-censored graft survival rates in patients with biopsy-proven LN with those with non-biopsy-proven LN. There were no statistically significant differences between the groups. Patient survival rates in biopsy-proven LN and non-biopsy-proven LN groups were 86% and 90% at one year, 84% and 82% at three years, 78% and 79% at five years, and 64% and 70% at ten years, respectively ($p = 0.377$). Death-censored graft survival rates in biopsy-proven LN and non-biopsy-proven LN groups were 91% and 94% at one year, 91% and 88% at three years, 88% and 87% at five years, and 77% and 82% at 10 years, respectively ($p = 0.598$).

Discussion

We present our single-center experience with 185 LN-ESKD patients who received a kidney transplant between 1977 and 2014. In this predominantly Mestizo cohort, we found a patient survival rate of 88% at one year, 82% at three years, 78% at five years, and 67% at ten years and a graft survival rate, censoring for patient death with a functioning graft of 93% at one year, 89% at three years, 87% at five years, and 80% at ten years.

In our population, patient survival rates were lower than those reported in other studies (Table 4).[7,9–11,15–19,22–24,27–30,32] These differences could partially be explained by different times of kidney transplant or recruitment period. In this light, the patient survival rates in our cohort at one, three, and five years after 2005 (93%, 93%, and 85%, respectively) were significantly better than those observed before 2005 (85%, 75%, 74%, respectively). We attribute this improvement in survival rates after 2005 to the use of monoclonal antibodies for induction therapy in kidney transplant recipients. Antibody induction therapy has been used in steroid-sparing protocols with optimal results in kidney transplant patients, as they reduce steroid-related comorbidities such as infection and cardiovascular events.[36,37] In fact, infection and CVD were the leading causes of mortality in our

Table 4. Summary of selected studies on kidney transplantation outcomes in recipients with end-stage kidney disease due to lupus nephritis.

Reference	Type of study, country (study dates), ethnicity (%)	KTP: number, female (%)	Age at transplant, mean ± SD years, or years (IQR)	Time since SLE diagnosis to transplantation, mean ± SD years, or years (IQR)	Dialysis as first RRT (%); time on dialysis (mean ± SD years, or years (IQR))	Deceased donor (%)	Maintenance immunosuppressive therapy (%)	Patient and graft survival	RLN (%)
Rodelo et al. (current study)	Retrospective cohort, Colombia (1977–2014), Mestizo (90.8), African ancestry (8.6), White (0.6)	185 (85.4)	32.8 ± 10.3	9.2 ± 7.2	60.5; 2.7 ± 4.7	82.2	CsA+AZA+PDN (40) CsA+MMF/MPA+PDN (36.8) AZA+PDN (10.3) TAC+MMF/MPA+PDN (8.6)	**Patient survival:** 1 year: 88.0% 5 years: 78.0% 10 years: 67.0 % **Graft survival:** 1 year: 93.0% 5 years: 87.0% 10 years: 80.0%	1.1
Albuquerque et al.[32]	Retrospective cohort, Brazil (1996–2016), Caucasians (31.6), non-Caucasians (68.4)	35 (94.7)	32.8 ± 10.9	10.3 ± 6.4	97.4; 3.9 ± 3.7	71.1	TAC (57.9), MS (52.6), EVE (15.8), SIR (2.6), MMF (10.5), CyA (5.3)	**Patient survival:** 6-months:100% 1 year: 96.9% 5 years: 92.5% **Graft survival:** 6 months: 97.1% 1 year: 84.9% 5 years: 76.3%	2.6
Ntatsaki et al.[15]	Retrospective cohort, United Kingdom (1975–2005), White (37.5), African ancestry (37.5), Asian (25)	40 (85.)	35.5 ± 11.0	NA	95; 3.6 (1.1–4.1)	55	TAC+MMF (27.5), AZA, CsA, or AZA+CsA (72.5)	**Patient survival:** 5 years: 95.0% **Graft survival:** NA	NA
Ramírez-Sandoval et al.[16]	Retrospective matched-pair cohort, Mexico (1979–2015)	74 (83.8)	31.5 ± 10.2	5 (1-9)	97.3; 2.3 (0.8–3.1)	33.8	CsA+AZA+PDN (36), AZA+PDN (4), TAC+AZA+PDN (7), TAC+MMF+PDN (52), CsA+RAP+PDN (1)	**Patient survival:** 5 years: 91.0% 10 years: 81.0% 15 years: 78.0% **Graft survival:** 5 years: 81.0% 10 years: 79.0% 15 years: 57.0%	8.1
O'Shaughnessy et al.[17]	Retrospective cohort, US Renal Data System, United States (1996–2011), White (50.8), African American (40.1), Hispanic (16.5) Asian (7.4), other (1.7), missing (3.2)	5884 (81.3)	38.3 ± 11.5	NA	89.1; 2.5 (0.9–4.7)	46.2	TAC (71.3), CsA (26.2), SIR (7.3), MMF (85.1), AZA (5.3), Steroid (95.8), missing (1.4)	**Patient survival:** 5 years: 94.5% 10 years: 89.4% 15 years: 84.1% **Graft survival:** 5 years: 81.6% 10 years: 67.8% 15 years: 57.9%	1.1

(continued)

Table 4. Continued.

Reference	Type of study, country (study dates), ethnicity (%)	KTP: number, female (%)	Age at transplant, mean ± SD years, or years (IQR)	Time since SLE diagnosis to transplantation, mean ± SD years, or years (IQR)	Dialysis as first RRT (%); time on dialysis (mean ± SD years, or years (IQR))	Deceased donor (%)	Maintenance immunosuppressive therapy (%)	Patient and graft survival	RLN (%)
Naranjo-Escobar et al.[11]	Case-control, Colombia (1996–2014), African ancestry (6.3)	65 (84.6)	34	8.7 (4–14)	94; 2.9 (1.3-5.2)	69	CsA+AZA+PDN (22) CsA+MMF/MS+PDN (45) TAC+MMF/MS+PDN (33)	**Patient survival:** 1 year: 98.0% 5 years: 98.0% 10 years: 98.0% **Graft survival:** 1 year: 92.0% 5 years: 83.0% 10 years: 79.0%	3.1
Zhang et al.[18]	Retrospective registry analysis; ANZDATA registry Australia and New Zealand; Contemporary cohort *(1998–2012)*, White (65), ATSI (4), MPI (10), Asian (17), other (4)	176 (80)	39 (31–47)	NA	87; 2.2 (1.1–4.2)	52%	NA	**Patient survival:** 1 year: 98.0% 5 years: 95.0% 10 years: 88.0% **Graft survival:** 1 year: 96.0% 5 years: 88.0% 10 years: 73.0%	2.3
Wu et al.[19]	Retrospective cohort, Taiwan (1998–2009), Chinese (100)	161 (77.6)	30.9 ± 10.7	NA	100; 4.4 ± 3.1	NA	NA	**Patient survival:** 1 year: 100.0% 5 years: 98.1% 10 years: 94.4% **Graft survival:** NA	NA
Cairoli et al.[28]	Retrospective cohort, Spain (1986–2013), Caucasians (95), Hispanic (5)	40 (80.0)	36 ± 10.4	9.8 ± 5.8	4.2 ± 4.1	58	CsA (38), TAC (54), AZA (12), MPA (76), SIR (6)	**Patient survival:** 1 year: 97.9% 5 years: 97.9% 10 years: 91.4% **Graft survival:** 1 year: 93.9% 5 years: 81.5% 10 years: 67.6%	2.5
Contreras et al.[23]	Case-control, United States (1987–2006), (UNOS database), Hispanic (16.5), White (42), Black (35.1), others (6.4)	6850 (81.8)	37 ± 11	NA	90.8; NA	61.4	CyA or TAC + AZA or MMF	**Patient survival:** NA **Graft survival:** NA	2.4

(continued)

Table 4. Continued.

Reference	Type of study, country (study dates), ethnicity (%)	KTP: number, female (%)	Age at transplant, mean ± SD years, or years (IQR)	Time since SLE diagnosis to transplantation, mean ± SD years, or years (IQR)	Dialysis as first RRT (%); time on dialysis (mean ± SD years, or years (IQR))	Deceased donor (%)	Maintenance immunosuppressive therapy (%)	Patient and graft survival	RLN (%)
Burgos et al.[22]	Retrospective cohort, United States (1977–2007), African American (65)	177 (80.0)	35.6 ± 10.0	11.2 ± 8.7	97; 3.1 ± 2.9	59	PDN (100), AZA (38), CyA (76), MMF (74), TAC (37)	**Patient survival:** 30.0% of patients died during the 30-year follow-up **Graft survival:** 39.0% of patients had graft loss during the 30-year follow-up	11.3
Signori Baracat et al.[27]	Retrospective cohort, Brazil (1984–2003)	23 (95.2)	32 ± 10.0	6 ± 3.8	100; 2.3 ± 1.5	69.5	NA	**Patient survival:** NA **Graft survival:** 1 year: 95.8% 5 years: 75.8%	13.0
Moroni et al.[9]	Case-control, Italy (1982–2004), White (100%)	33 (78.8)	34.6 ± 9.9	9.9 ± 5.5	100; 3.5 ± 3.2	78.8	CyA or TAC+ AZA or MMF +PDN (63) CyA+PDN (26) AZA+PDN (8) SIR+CyA+PDN (3)	**Patient survival:** 1 year: 100.0% 5 years: 97.0% 10 years: 97.0% 15 years: 83.0% **Graft survival:** 1 year 100.0% 5 years: 85.0% 10 years: 76.0% 15 years: 69.0%	8.6
Bunnapradist et al.[10] -deceased donors-	Retrospective registry analysis; UNOS renal registry database, United States (1996–2000), White (37.6), African American (41.0), Hispanic (14.2), other (7.2)	1170 (82.6)	<21 years (4.6%) 22–60 years (90.9%) >60 years (4.5%)	NA	NA; NA	100 (deceased) 0 (living)	MMF, CyA, or TAC	**Patient survival:** 1 year: 94.4% 3 years: 88.8% 5 years: 85.2% **Graft survival:** 1 year: 88.6% 3 years: 77.4% 5 years: 67.8%	NA
Bunnapradist et al.[10] -living donors-	Retrospective registry analysis; UNOS renal registry database, United States (1996–2000), White (50.6), African American (24.0), Hispanic (18.5), other (7.0)	789 (81.1)	<21 years (8.1%) 22–60 years (91.0%) >60 years (0.9%)	NA	NA; NA	0 (deceased) 100 (living)	MMF, CyA, or TAC	**Patient survival:** 1 year: 98.5% 3 years: 96.4% 5 years: 92.1% **Graft survival:** 1 year: 94.2% 3 years: 87.5% 5 years: 77.6%	NA

(continued)

Table 4. Continued.

Reference	Type of study, country (study dates), ethnicity (%)	KTP: number, female (%)	Age at transplant, mean ± SD years, or years (IQR)	Time since SLE diagnosis to transplantation, mean ± SD years, or years (IQR)	Dialysis as first RRT (%); time on dialysis (mean ± SD years, or years (IQR))	Deceased donor (%)	Maintenance immunosuppressive therapy (%)	Patient and graft survival	RLN (%)
Goral et al.[24]	Retrospective cohort, United States (1976–2000), African American (34), White (66)	50 (84)	33 ± 8	NA	100; 3.3 ± 3.6	54	AZA+PDN (22) CsA+AZA+PDN (48) CsA+PDN (6) CsA+MMF+PDN (18) Other (2) Data NA (4)	**Patient survival:** 1 year: 96.0% 5 years: 82.0% **Graft survival:** 1 year: 87.0% 5 years: 60.0%	30.0
Chew-Wong et al.[29]	Case-control, Mexico (1967–1997), NA	21 (90.5)	29 ± 10.0	4.2 ± 5.8	100; 1.5 ± 1.4	22	CyA+AZA+PDN (81) AZA+PDN (19)	**Patient survival:** 10 years: 81.0% **Graft survival:** 50 months: 74.0%	4.8
Ward[7] -deceased donors-	United States (1987–1994) Renal Data System, White (57.1), African American (36.1), Asian (5.7), Other (1.0)	772 (81.1)	36.1 ± 10.3	NA	NA; 1.7 years or 632.5 days (median)	100 (deceased) 0 (living)	PDN (95.1), CyA (93.3), AZA (87.6), antithymocyte globulin (23.6)	**Patient survival:** 1 year: 94.4% 3 years: 89.6% 5 years: 83.8% **Graft survival:** 1 year: 79.1 3 years: 67.0% 5 years: 58.1%	1.6
Ward[7] -living donors-	United States (1987–1994) Renal Data System, White (73.1), African American (20.8), Asian (3.6), Other (2.5)	390 (79.7)	32.6 ± 9.1	NA	NA; 0.81 years or 295.5 days (median)	0 (deceased) 100 (living)	PDN (94.2), CyA (94.5), AZA (84.6), thymoglobulin (11.9)	**Patient survival:** 1 year: 99.2% 3 years: 97.2% 5 years: 94.4% **Graft survival:** 1 year: 93.6% 3 years: 84.0% 5 years: 77.0%	0
Azevedo et al.[30]	Case-control, Brazil (1975–1994), White (91), African ancestry (4.5), Asian (4.5)	45 (78)	NA	NA	NA; NA	33	AZA+CyA+PDN	**Patient survival:** 1 year: 97.7% 5 years: 91.1% **Graft survival:** 1 year: 93.1% 5 years: 80.7%	11.1

KTP: Kidney transplant patients; RRT: renal replacement therapy; NA: data not available; CsA: cyclosporine A; AZA: azathioprine; PDN: prednisone; MMF: mycophenolate mofetil; MPA: mycophenolic acid; MS: mycophenolate sodium; TAC: tacrolimus; EVE: everolimus; SIR: sirolimus; RAP: rapamycin; ANZDATA (Australia and New Zealand Dialysis and Transplant) Registry; ATSI, Aboriginal and Torres Strait Islander; MPI, Maori and Pacific Islander; UNOS (United Network for Organ Sharing) database; RLN: recurrent lupus nephritis.

cohort, accounting for 66.7% of all deaths. Furthermore, our population was predominantly Mestizo, and to a lesser extent, of African ancestry. By and large, non-white patients have more severe forms of lupus with higher disease activity and, therefore, may be exposed to more intense immunosuppression, making them more susceptible to severe infections.[38]

In this study, death-censored graft survival rates for the first renal transplant were similar to those described by other authors (Table 4).[7,9–11,15–19,22–24,27–30,32] Studies conducted in Latin America, where SLE patients are mostly Mestizos, showed graft survival rates similar to those found in our cohort. Naranjo-Escobar et al.,[11] showed similar graft survivals in Colombian patients (92% at one year, and 83% at five years), while in a Mexican study by Ramírez-Sandoval, et al.,[16] a graft survival of 81% was found at five years and 79% at ten years. However, Moroni et al., in an Italian study, reported higher graft survival rates censored for death at one year (100%) and higher patient survival rates at one year (100%).[9] As this study included only white patients, these results may not be generalizable to other ethnic populations, particularly those of African ancestry who have a higher risk of graft failure and worse survival rates.[7,22]

In our experience, graft loss due to any cause was observed in 35% of patients after a median follow-up of 10 years, consistent with data previously reported by other authors (30–39%) in LN transplant recipients.[9,17,22] As reported in other LN studies,[9,11,18,22,28] the leading cause of graft loss was chronic allograft nephropathy (53.8%), a term that describes a progressive renal dysfunction with histological evidence of chronic interstitial fibrosis, tubular atrophy, and glomerulosclerosis.[39] Chronic graft nephropathy is the main cause of renal allograft loss in LN and non-LN transplant recipients despite the improvements in immunosuppressive therapies for renal transplantation.[9,18]

Based on the concept that lupus activity may "burn out" because of the immunosuppressive effect of pre-transplant uremia into the post-transplant period, in former times, a "waiting period" while on dialysis of at least one year before transplantation was recommended for LN-ESKD patients.[40] In this context, the effect of pre-transplant dialysis may permit lupus to become quiescent, thus reducing the risk of RLN and improving graft survival.[40] However, recent studies have shown that a longer length of dialysis is associated with worse graft outcomes among LN-ESKD patients.[20,41,42] Considering these findings, LN-ESKD patients without the clinically active disease could be transplanted without a "waiting time". Thus, preemptive kidney transplantation is preferred for those patients with LN-ESKD without active clinical disease.[2] In contrast, our results showed worse patient and graft survival rates in preemptively transplanted patients than in those previously treated with dialysis. Patient survival rates were worse in preemptive kidney transplant recipients, and preemptive kidney transplantation was associated with lower patient survival with an HR of 2.18 (95% CI 1.14–4.16, $p < 0.018$) in the univariable analysis; however, this variable was not retained in the multivariable analysis. The poorer survival among preemptive kidney transplant recipients was due to the greater number of deaths that occurred within the first year post-transplant: 11 deaths in preemptively transplanted patients versus four deaths in non-preemptively transplanted patients, serious opportunistic infections being the main cause of death in the preemptive group [cryptococcosis (n = 1), histoplasmosis (n = 1), systemic cytomegalovirus infection (n = 2), and tuberculosis (n = 3)]. This could be because some preemptive transplant recipients were still receiving immunosuppressants for the management of active LN in addition to the initial intensive immunosuppression provided by induction therapy after kidney transplantation. Our findings are consistent with data reported in the literature, which indicate that most opportunistic infections occur between 1 and 12 months after transplantation, the period of maximum immunosuppression in these patients.[43]

Although there were no significant differences in death-censored graft survival rates between preemptive and non-preemptive groups, there was a trend toward better death-censored graft survival rates in non-preemptive transplant recipients. This could be explained by the fact that of the 11 deaths in the preemptive group, five deaths were with a functioning graft; thus, these were censored.

In our cohort, two patients (1.08%) had renal biopsy-confirmed RLN during the follow-up, and both patients had histological findings consistent with membranous LN. This finding is consistent with the incidence of clinically significant RLN reported in the literature, ranging from 1.1% to 13%.[2,11,16–18,20,22,23,27–30,32] However, the incidence of RLN in our cohort could be even higher for several reasons. First, as the renal biopsies were performed for clinical indications (proteinuria, hematuria, increased serum creatinine), subclinical recurrence may have been underestimated. Second, some cases of recurrence could have been successfully treated empirically as acute rejection without a confirmatory biopsy. Finally, surveillance renal graft biopsies and routine immunofluorescence and electron microscopy studies, which could help detect subclinical cases of RLN, are not performed in our hospital. Higher recurrence rates of LN (54%) have been reported when

surveillance renal graft biopsies are performed to follow up these patients. This is partly due to the detection of subclinical disease, mainly class I or class II LN.[25] In our cohort, no patient had graft lost due to recurrence. RLN increases the risk of graft loss, but this rarely occurs, and patient and graft survival are comparable in patients with and without RLN.[2,20,22,24]

Older recipient age, and an eGFR <45 ml/min/1.73m^2 at one month post-transplantation were associated with lower patient survival and an increased risk of graft loss while induction immunosuppressive therapy had a protective effect on patient survival. Older patients have a constellation of comorbidities such as CVD, infections, malignancies, and cardiovascular risk factors which could lead to poor survival outcomes.[44] Consistent with these observations, we previously reported that the leading causes of death in kidney transplant recipients older than 60 years were CVD (38.2%), and infections (33.8%).[45] In SLE patients, life expectancy has improved over the last five decades, leading to longer disease duration and, thus, to the occurrence of different comorbidities, including CVD, malignancy, infection, and ESKD.[46] In our cohort, older age was expected to be a predictor of a poor patient and death-censored graft survival for several reasons: firstly, the absolute risk of CVD among SLE patients increases with age;[46] secondly, CVD was the second most common cause of death after infections; thirdly, 61% of the deceased recipients died with a functional graft, and 30% of these deaths were attributed to CVD; lastly, recipient age (HR, 1.7 per 10-year-increase; 95% CI, 1.09–1.25) was found to be a risk factor for 1-year graft loss after kidney transplantation in a recent meta-analysis, which is consistent with our findings.[47]

Measurement of kidney function early after transplantation is a valuable marker of graft reserve and long-term function. In a French single-center study, the 3-month eGFR <45 mL/min/1.73 m^2 was associated with lower long-term death-censored graft survival.[48] Likewise, we found that an eGFR <45 ml/min/1.73 m^2 at one month post-transplantation was a strong predictor of a lower patient and graft survival in LN patients. Our results suggest that very early risk stratification using the 1-month post-transplantation eGFR has predictive value. It may help identify patients at higher risk of graft loss and, thus, lower life expectancy and, to apply early therapeutic interventions.

We have also found that induction immunosuppressive therapy has a protective effect on patient survival but not on graft survival in kidney transplant SLE recipients. This decrease in mortality may be associated with reduced immunosuppression without increasing the risk of kidney graft loss. As stated before, monoclonal antibodies for induction therapy have a beneficial steroid-sparing effect in kidney transplant recipients as they can reduce the adverse effects of cumulative steroid dose including infections and cardiovascular events. Patients on steroid-sparing immunosuppression regimens have better control of blood pressure and serum lipids.[36,37] Induction immunosuppressive therapy may improve long-term graft survival, as it can reduce the risk of acute graft rejection.[49] However, we did not find a protective effect of this therapy on death-censored graft survival, which can be partly explained by the high number of deaths (n = 24) with a functioning graft that were censored.

The current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend that lupus activity should be clinically quiescent before transplantation.[50] Our results support this recommendation, as we have found that higher disease activity at the time of transplantation also predicted a lower patient survival and lower death-censored graft survival. In fact, we found that in patients whose SLEDAI score was calculated at the time of transplantation, those who were preemptively transplanted had significantly worse patient survival rates and higher scores than those who were non-preemptively transplanted. Furthermore, SLEDAI scores were statistically significantly higher in deceased patients than in survivors.

Our study has some limitations; as this is a retrospective single-center cohort study of a mostly Mestizo population, its findings are not generalizable to other populations. Detailed and specific SLE information was not collected uniformly for all patients, and therefore, this information could not be included in our analyses. Missing information included non-renal SLE manifestations, and autoantibodies profiles. Furthermore, the low percentage of patients (40.5%) with histological confirmation of LN in the native kidney reported in our cohort could be due to different reasons: ultrasound-guided kidney biopsy has only been widely available in our center since 1997; in patients with ESKD at SLE diagnosis, it was considered that the results of the biopsy would not change the therapeutic decision; unavailability at the referring center; and, contraindications (anticoagulation, thrombocytopenia, and uremic state). Additionally, since surveillance renal graft biopsies are not performed in our hospital, it is conceivable that the actual incidence of RLN may have been higher than the 1.08% reported in our cohort. Finally, as in any retrospective study, it was not possible to eliminate the bias corresponding to confounding or time-dependent variables that were not known at the time of transplantation and were not measured in the cohort.

Despite these limitations, the results of our study provide important information on patient and graft

outcomes in kidney transplant patients with LN-ESKD. To our knowledge, this is the largest single-center Latin American cohort of LN patients who underwent kidney transplantation with a very long follow-up (10 years). In our cohort, the patient survival rate, especially after 2005, and death-censored graft survival rate for the first renal transplant were similar to that of other cohorts. Despite the long follow-up after transplantation, the occurrence of clinically significant RLN is rare (1.08%) and does not portend a poor prognosis for graft survival. We found that, older recipient age, 1-month post-transplantation eGFR <45 ml/min/1.73m^2, and disease activity at the time of transplantation are independent predictors of lower patient and death-censored graft survival. Finally, and importantly, induction immunosuppressive therapy appears to have a protective effect on patient survival, which may be due to its steroid-sparing effect without increasing the risk of kidney graft loss in kidney transplant recipients with LN.

Declaration of conflicting interests

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