

# Recurrence of Lupus Nephritis after Kidney Transplantation

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## ABSTRACT

The frequency and outcome of recurrent lupus nephritis (RLN) among recipients of a kidney allograft vary among single-center reports. From the United Network for Organ Sharing files, we estimated the period prevalence and predictors of RLN in recipients who received a transplant between 1987 and 2006 and assessed the effects of RLN on allograft failure and recipients' survival. Among 6850 recipients of a kidney allograft with systemic lupus erythematosus, 167 recipients had RLN, 1770 experienced rejection, and 4913 control subjects did not experience rejection. The period prevalence of RLN was 2.44%. Non-Hispanic black race, female gender, and age <33 years each independently increased the odds of RLN. Graft failure occurred in 156 (93%) of those with RLN, 1517 (86%) of those with rejection, and 923 (19%) of control subjects without rejection. Although recipients with RLN had a fourfold greater risk for graft failure compared with control subjects without rejection, only 7% of graft failure episodes were attributable to RLN compared and 43% to rejection. During follow-up, 867 (13%) recipients died: 27 (16%) in the RLN group, 313 (18%) in the rejection group, and 527 (11%) in the control group. In summary, severe RLN is uncommon in recipients of a kidney allograft, but black recipients, female recipient, and younger recipients are at increased risk. Although RLN significantly increases the risk for graft failure, it contributes far less than rejection to its overall incidence; therefore, these findings should not keep patients with lupus from seeking a kidney transplant.

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The frequency and clinical impact of recurrent lupus nephritis (RLN) in the kidney allograft of recipients with systemic lupus erythematosus (SLE) varies considerably in both prospective and retrospective studies.<sup>1–25</sup> In 1996, Mojciak and Klippel<sup>26</sup> pooled data from a total of 366 allografts transplanted in 338 recipients. In that review, histologic RLN was present in 3.8% of the grafts. Contrasting, in the studies by Goral *et al.*<sup>27</sup> and Nyberg *et al.*,<sup>10</sup> RLN was reported in a much higher proportion: 30 and 44% of recipients, respectively.

The clinical consequences of RLN on patient and allograft survival have ranged from no effect to a significant increase in the risk for graft loss and patient mortality.<sup>24,27–31</sup> In this case-control study, we estimated the period prevalence of RLN in kidney

transplant recipients who had ESRD secondary to lupus nephritis and received a transplant between October 1987 and October 2006. We assessed the

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effects of RLN on graft failure and recipient survival and the risk factors leading to the development of RLN.

## RESULTS

The study included 6850 recipients with SLE. Recipients were predominantly young women (81.8%) at a mean age of 37 years. They received a higher percentage of kidney allografts from deceased (61.4%) compared with living (38.6%) donors. Overall, 167 (2.44%) recipients developed RLN: 82 (3.19%) of 2563 before January 1996 and 85 (1.98%) of 4287 after December 1995 ( $P = 0.0016$ ). Rejection also occurred in 83 (50%) of 167 of the patients with RLN. A total of 1770 (25.84%) recipients developed rejection without evidence of RLN. In the remaining group (others group) of 4913 recipients, the transplant centers did not ascertain recurrence or rejection events during the study period. When comparing the group of recipients who had RLN (including the ones with RLN and rejection) with those in the rejection and others groups, RLN recipients were younger and more commonly were female, and black non-Hispanic and needed dialysis before transplantation compared with the others group. Recipients in the RLN group commonly received a deceased-donor kidney allograft with high levels of HLA-A locus and HLA-B locus mismatch, had a high frequency of zero-haplotype match with their living donors, and had high frequency of increased panel-reactive antibodies (PRA; Table 1). By multivariate logistic regression analysis, only black non-Hispanic race (odds ratio [OR] 1.88; 95% confidence interval [CI] 1.37 to 2.57), female gender (OR 1.70; 95% CI 1.05 to 2.76), and age <33 years (OR 1.69; 95% CI 1.23 to 2.31) were independently associated with the development of RLN (Table 2). By univariate logistic regression analysis, use of biological agents for induction compared with other agents (OR 0.92; 95% CI 0.63 to 1.36) as well as the use of cyclosporine compared with tacrolimus (OR 1.11; 95% CI 0.74 to 1.67) and azathioprine compared with mycophenolate (OR 1.38; 95% CI 0.90 to 2.11) for maintenance did not affect significantly the odds for RLN. Recipients' median time to development of RLN was 1561 days (range 1 to 5594 days) after transplantation (Figure 1).

During follow-up, 156 (93.4%) recipients in the RLN group and 1517 (85.7%) recipients from the rejection group lost their allografts. In addition, 923 (19.1%) recipients in the others group also lost their kidney allografts. By survival analyses, recipients' allograft survival was significantly lower in the RLN, rejection, and RLN with rejection groups compared with the others group (RLN *versus* others,  $P < 0.000001$ ; rejection *versus* others,  $P < 0.000001$ ; RLN with rejection *versus* others,  $P < 0.000001$ ; Figure 2). Recipients in the RLN and RLN with rejection groups had a similarly poor allograft survival; therefore, recipients with RLN alone and RLN with rejection together were included in one single group in the proportional hazard regression models. By proportional hazard regression analyses, RLN (hazard ratio [HR] 4.09; 95% CI 3.41 to 4.92 *versus* others group), rejection (HR 3.97; 95% CI 3.63 to 4.34 *versus* others group), delayed graft function (DGF; HR 1.72;

95% CI 1.55 to 1.90), black non-Hispanic race (OR 1.38; 95% CI 1.13 to 1.69 *versus* others recipients), deceased-donor kidney allograft (HR 1.16; 95% CI 1.05 to 1.28 *versus* living-donor kidney allograft), PRA  $\geq 50\%$  (HR 1.13; 95% CI 1.00 to 1.27 *versus* PRA <50%), and HLA mismatch level (HR 1.05; 95% CI 1.02 to 1.07 per level) were independently associated with increased risk for allograft failure (Table 3). The estimated attributable risks (ARs) for allograft failure of rejection, black non-Hispanic race, DGF, deceased-donor kidney allograft, RLN, and PRA  $\geq 50\%$  were 43, 12, 10, 9, 7, and 1%, respectively (Table 3). During the 19 years of follow-up, 867 of 6850 recipients died: 27 in the RLN group, 313 in the rejection group, and 527 in the control group. By survival analysis, overall recipient survival was significantly lower only in the rejection group compared with the others group ( $P = 0.0001$ ; Figure 3). Although recipients' cumulative survival was lower in the RLN group, particularly in the RLN with rejection group compared with the others group, differences were not statistically significant by survival analysis ( $P > 0.05$ ).

## DISCUSSION

The results of this study indicate that RLN is uncommon. Although RLN is associated with a high relative risk (RR) for kidney allograft failure, its overall AR for allograft loss is small. RLN is not associated with reduced recipient survival. The data suggest that race/ethnicity, gender, and age of recipients are independent factors associated with RLN.

In this study, 2.44% of recipients with SLE developed RLN after transplantation. The previously reported incidence of RLN after transplantation has ranged from 0 to 44%.<sup>3–12,26,27</sup> This wide range is probably due in part to the differences among centers in the use of complete examination of biopsies in recipients with SLE, the performance of serial biopsies, the period of observation, the population characteristics, and the immunosuppressive regimen used. Particularly, the use of light microscopy alone in the examination of biopsy specimens would likely yield a low rate of RLN diagnosis. Transplant kidney biopsy specimens from patients with a history of ESRD as a result of SLE must additionally be evaluated by both immunofluorescence and electron microscopy. The diagnosis of RLN ideally should be based on the complete examination of the biopsy using the World Health Organization (WHO) or the International Society of Nephrology/Renal Pathology Society histologic classifications,<sup>32,33</sup> including a positive immunofluorescence microscopy or the presence of electron-dense deposits in the electron microscopic examination. Goral *et al.*<sup>27</sup> reported RLN in 30% of recipients using a complete histologic examination of biopsies. Nyberg *et al.*<sup>10</sup> reported RLN in 44% of recipients who underwent serial biopsies that were read using the WHO classification including electron-dense deposits by electronic microscopy. In our study, we were unable to confirm the histologic diagnosis of RLN because the United Network for Organ Sharing (UNOS) method of collecting data

**Table 1.** Baseline characteristics of kidney allograft recipients with SLE according development of recurrence, rejection, or neither of those events

Characteristic	All Recipients (n = 6850; 100%)	Others Group (n = 4913; 71.72%)	Rejection Group (n = 1770; 25.84%)	Recurrence Group (n = 167; 2.44%)	P
Age (years; mean ± SD)	37 ± 11	38 ± 12 <sup>a</sup>	34 ± 11	33 ± 11	<0.00001
Female gender (n [%])	5605 (81.8)	4010 (81.6)	1447 (81.8)	148 (88.6)	0.069460
Race/ethnicity (n [%])					<0.00001
white non-Hispanic	2878 (42.0)	2109 (42.9)	713 (40.3)	56 (33.5)	
black non-Hispanic	2406 (35.1)	1581 (32.2)	744 (42.0)	81 (48.5)	
Hispanic	1132 (16.5)	879 (17.9)	232 (13.1)	21 (12.6)	
Rest	434 (6.4)	344 (7.0)	81 (4.6)	9 (5.4)	
Pretransplantation dialysis status (n [%]) <sup>b</sup>					<0.00001
yes	6069 (90.8)	4267 (88.6)	1646 (96.5)	156 (93.4)	
no	541 (8.1)	479 (10.0)	53 (3.1)	9 (5.4)	
unknown	75 (1.1)	66 (1.4)	7 (0.4)	2 (1.2)	
recipients treated for hypertension (n [%]) <sup>c</sup>	3302 (73.3)	2735 (73.6)	494 (72.2)	73 (70.9)	0.520156
Donor type (n [%])					<0.00001
deceased	4205 (61.4)	2839 (57.8)	1265 (71.5)	101 (60.5)	
living	2645 (38.6)	2074 (42.2)	505 (28.5)	66 (39.5)	
Deceased-donor transplant HLA-A locus mismatch level (n [%]) <sup>d</sup>					0.00018
2	1747 (41.6)	1201 (42.3)	495 (39.2)	51 (50.5)	
1	1618 (38.5)	1036 (36.5)	547 (43.3)	35 (34.7)	
0	834 (19.9)	599 (21.1)	220 (17.4)	15 (14.9)	
Deceased-donor transplant HLA-B locus mismatch level (n [%]) <sup>d</sup>					0.02018
2	1895 (45.1)	1280 (45.1)	571 (45.3)	44 (43.6)	
1	1498 (35.7)	976 (34.4)	483 (38.3)	39 (38.6)	
0	806 (19.2)	581 (20.5)	207 (16.4)	18 (17.8)	
Deceased-donor transplant HLA-DR locus mismatch level (n [%]) <sup>e</sup>					0.028968
2	1102 (26.6)	750 (26.7)	330 (27.0)	22 (22.2)	
1	1851 (44.8)	1223 (43.5)	583 (47.7)	45 (45.5)	
0	1183 (28.6)	841 (29.9)	310 (25.3)	32 (32.3)	
Deceased-donor transplant HLA mismatch level (n [%]) <sup>f</sup>					<0.00001
6	397 (9.6)	288 (10.2)	100 (8.2)	9 (9.1)	
5	907 (21.9)	621 (22.1)	262 (21.4)	24 (24.2)	
4	1018 (24.6)	689 (24.5)	306 (25.0)	23 (23.2)	
3	776 (18.8)	482 (17.1)	275 (22.5)	19 (19.2)	
2	402 (9.7)	254 (9.0)	138 (11.3)	10 (10.1)	
1	159 (3.8)	96 (3.4)	58 (4.7)	5 (5.1)	
0	475 (11.5)	383 (13.6)	83 (6.8)	9 (9.1)	
Living-donor transplant haplotype match level (n [%]) <sup>g</sup>					0.000127
2.0	413 (17.6)	348 (19.0)	58 (12.8)	7 (11.9)	
1.5	71 (3.0)	61 (3.3)	9 (2.0)	1 (1.7)	
1.0	1251 (53.3)	931 (50.8)	288 (63.6)	32 (54.2)	
0.5	92 (3.9)	81 (4.4)	8 (1.8)	3 (5.1)	
0.0	519 (22.1)	413 (22.5)	90 (19.9)	16 (27.1)	
Blood ABO type (n [%]) <sup>h</sup>					0.274332
identical	6082 (88.8)	4341 (88.4)	1588 (89.8)	153 (91.6)	
compatible	716 (10.5)	533 (10.9)	171 (9.7)	12 (7.2)	
incompatible	49 (0.7)	37 (0.8)	10 (0.6)	2 (1.2)	

Table 1. Continued

Characteristic	All Recipients (n = 6850; 100%)	Others Group (n = 4913; 71.72%)	Rejection Group (n = 1770; 25.84%)	Recurrence Group (n = 167; 2.44%)	P
Most recent PRA (%; mean $\pm$ SD) <sup>i</sup>	14 $\pm$ 26	12 $\pm$ 25 <sup>a</sup>	17 $\pm$ 29	16 $\pm$ 29	<0.00001
Previous pregnancies (mean [range]) <sup>j</sup>	1 (0 to 6)	1 (0 to 6)	1 (0 to 6)	1 (0 to 6)	0.60485
DGF (n [%])	1045 (15.3)	606 (12.3)	424 (23.9)	15 (8.9)	<0.00001
Follow-up time (years; mean $\pm$ SD)	4.95 $\pm$ 3.94	4.56 $\pm$ 3.87 <sup>a</sup>	5.89 $\pm$ 3.96	6.34 $\pm$ 3.69	<0.00001

<sup>a</sup>P < 0.05, others group versus rejection or recurrence groups adjusted for multiple comparisons.

<sup>b</sup>A total of 165 missing values.

<sup>c</sup>A total of 2626 missing values.

<sup>d</sup>A total of six missing values.

<sup>e</sup>A total of 69 missing values.

<sup>f</sup>A total of 71 missing values.

<sup>g</sup>A total of three missing values.

<sup>h</sup>A total of 258 missing values.

<sup>i</sup>A total of 1258 missing values.

<sup>j</sup>A total of 1948 missing values.

Table 2. Factors associated with increased risk for recurrence of lupus nephritis in the allografts

Factor	OR	95% CI
Black non-Hispanic race/ethnicity	1.88	1.37 to 2.57
Female gender	1.70	1.05 to 2.76
Age <33 years	1.69	1.23 to 2.31

Logistic model adjusted for type of transplant (deceased versus living donor), preemptive transplantation, and rejection.

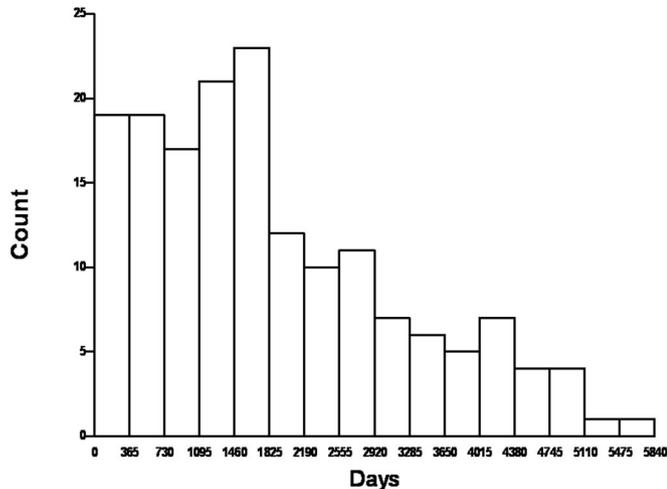


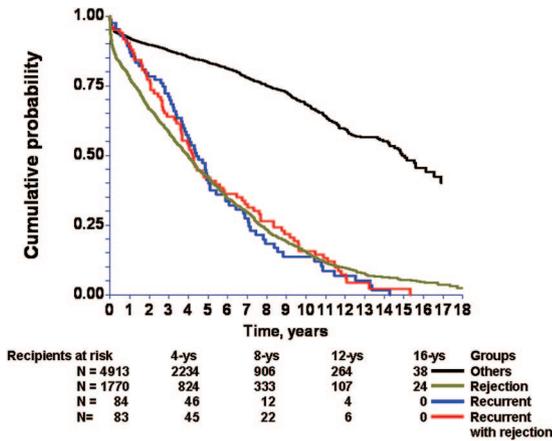
Figure 1. Recurrent lupus nephritis can occur as early as the first week to as late as 16 years after transplantation, with most events occurring during the first 10 years of receiving a kidney allograft. The y axis represents the count of recipients with recurrence of lupus nephritis.

does not require that the transplant centers enter whether a confirmatory biopsy is done or includes a field to report the histologic class of lupus nephritis. In our study, the period of observation seems to matter in determining the incidence of RLN. Comparing recipients who received the kidney allograft before January 1996 with those received a transplant thereaf-

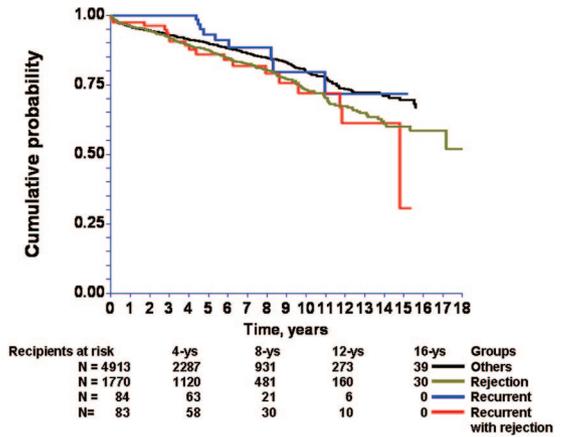
ter, the development of RLN was more frequent in the first period (3.19%) compared with the second period (1.98%), which marked the introduction of mycophenolate use as immunosuppressive agent. Consistent with that finding, maintenance azathioprine compared with mycophenolate was associated with a higher risk for RLN with an OR of 1.38; however, that association was NS as a result of a relatively wide 95% CI (0.90 to 2.11), which included 1.

Factors associated with RLN may be identified before transplantation. Black non-Hispanic and female recipients had 1.88- and 1.70-fold increased odds for the development of RLN. Also, recipients who were younger than 33 years had 1.69-fold increased odds for development of RLN. In agreement with the study by Burgos *et al.*,<sup>24</sup> black non-Hispanic race was the strongest predictor of the development of RLN. Onset of SLE at a younger age in a black woman usually predicts a more aggressive form of this disease that can be prone to recurrence<sup>34,35</sup> at anytime after transplantation. Other potential risk factors for the development of RLN, such as need for dialysis before transplantation, deceased-donor kidney allograft, occurrence of rejection, lack of induction with biological agents, and type of maintenance immunosuppressive agent, seemed less important in the analyses.

In this study, recipients with RLN had a significantly higher RR for allograft failure compared with control subjects. This finding agrees with Burgos *et al.*<sup>24</sup> and our own center's experience but contrasts with Goral *et al.*,<sup>27</sup> who reported that allograft failure as a consequence of RLN was rare. In the study by Goral *et al.*, 53% of the recipients with RLN had WHO class II lesions. By contrast, in our own center's review of biopsies from recipients with RLN, only 17% of the recipients had WHO class II, whereas most of the recipients had aggressive histologic forms of lupus nephritis with 58% demonstrating WHO class IV and 25% demonstrating WHO class V. This contrasting effect of RLN on the risk for graft loss is probably due in part to the differences among centers in their population risk relationship with



**Figure 2.** Long-term kidney allograft survival is lower in the recurrent lupus nephritis, rejection, and recurrent lupus nephritis with rejection groups compared to the others group. Overall  $P < 0.000001$ ;  $P < 0.000001$  for the others group versus the recurrent disease group;  $P < 0.000001$  for the others group versus the rejection group;  $P < 0.000001$  for the others group versus the recurrence with the rejection group.



**Figure 3.** Long-term survival of recipients is lower in the rejection group compared to the others group. Overall  $P = 0.0006$ ;  $P = 0.0001$  for the others group versus the rejection group;  $P = 0.08$  for the others group versus the recurrence with rejection group;  $P = 0.38$  for the others group versus the recurrent disease group;  $P = 0.11$  for the recurrent disease group versus the rejection group;  $P = 0.15$  for the recurrent disease alone group versus the recurrence with rejection group;  $P = 0.69$  for the rejection group versus the recurrence with rejection group.

**Table 3.** RR for allograft failure associated with recurrence of lupus nephritis, rejection, and other important factors

Variable	Unadjusted (RR [95% CI])	Model 1 Adjusted (RR [95% CI])	Model 2 Adjusted (RR [95% CI])	AR
Recurrence versus others group	2.30 (1.96 to 2.71)	4.26 (3.59 to 5.05)	4.09 (3.41 to 4.92)	7
Rejection versus others group	3.96 (3.67 to 4.29)	4.35 (4.00 to 4.72)	3.97 (3.63 to 4.34)	43
Black non-Hispanic versus rest		1.46 (1.20 to 1.76)	1.38 (1.13 to 1.69)	12
DGF versus none			1.72 (1.55 to 1.90)	10
Deceased- versus living-donor kidney allograft			1.16 (1.05 to 1.28)	9
PRA $\geq 50$ versus $< 50\%$			1.13 (1.00 to 1.27)	1
HLA mismatch level, per level			1.05 (1.02 to 1.07)	–

Proportional hazard models: Model 1 adjusted for age, gender, race/ethnicity, and rejection. Model 2 adjusted for all variables in model 1 as well as for DGF (the need for dialysis within the first week of transplantation), donor type (deceased versus living), the most recent PRA before transplantation, HLA match level, and preemptive transplantation. Estimates of potential risk factors were not included when probability values were  $> 0.05$  in the models.

allograft failure and the type of histologic form of lupus nephritis recurring in the allograft.

In this study, there was no difference in kidney allograft survival between the RLN and rejection groups. Also, the risk relationship between RLN and allograft failure was as strong as the one between rejection and allograft failure, with RR values in general above 2 in the unadjusted and adjusted analyses; however, rejection compared with RLN was a much more frequent event. The prevalence of rejection was 25.84%, 10 times higher than the 2.44% prevalence of RLN; therefore, 43% of the total allograft failure could be attributed to rejection compared with only 7% from RLN. Overall in this study, rejection was the most important event determining allograft failure, a finding that is in agreement with other studies.<sup>30,36</sup> Other independent risk factors associated with allograft failure, such as black non-Hispanic race/ethnicity, deceased-donor kidney allograft, PRA  $\geq 50\%$  and high HLA mismatch level were moderately strong, with RR  $< 2$ .

Patients who have SLE and undergo kidney transplantation

have similar survival compared with recipients without SLE<sup>28,29</sup>; however, the development of rejection can reduce recipient survival.<sup>30</sup> In this study, the recipients in the RLN group had a lower survival rate compared with the others group; however, recipient survival was not significantly different between those two groups. During the 19 years of follow-up, only 27 recipients with RLN died in the studied population of 6850 recipients. Even though RLN can lead to allograft failure, the availability of dialysis support or another kidney transplant can reduce the risk relationship between RLN and recipient mortality.

Our study has several limitations worth mentioning. First, we cannot completely attribute RLN as the sole cause of allograft failure in the RLN group because in 50% of those recipients, rejection was also ascertained during follow-up; however, the group with RLN alone had similarly poor allograft survival compared with the groups with rejection alone and rejection with RLN together. Second, the use of complete and serial kidney biopsies in the ascertainment of the type of RLN is not

required in the UNOS program; therefore, the prevalence of RLN may be underestimated in this study. It very likely, however, that the UNOS Standard Transplant Analysis and Research (STAR) files capture mostly severe forms of RLN. Third, the study design is retrospective; therefore, our findings may not be adequate to establish cause–effect associations between the risk factors and outcomes. Fourth, associations between immunosuppressive drugs and RLN are limited because of missing data. Of the total of 6850 recipients, only 4134 had data specifying the type of immunosuppressive agent in the UNOS files. In addition, associations between the immunosuppressive drugs and RLN can be confounded by the lack of adherence data. In the UNOS database, the immunosuppressive drugs data also reflected the use of particular drug combinations over time throughout many centers in the relatively uncontrolled setting of clinical practice as opposed to a clinical trial conducted in a carefully predefined population. Fifth, we were not able to assess the risk relationship among autoantibody titers, complement component levels, and extrarenal disease SLE activity level with the development of RLN because of lack of that information in the UNOS database.

Individuals who have a history of SLE and receive a kidney transplant rarely develop severe RLN. Although the RR for RLN for kidney allograft failure is strong, its overall AR for allograft loss is small and these findings should not keep patients with SLE from seeking a kidney transplant if they need one. RLN is much less important than rejection in reducing the long-term function of renal allografts. RLN more commonly develops in young black non-Hispanic female recipients of a kidney allograft. RLN can occur as early as the first week to as late as 16 years after transplantation, with most events occurring during the first 10 years of receiving a kidney allograft. RLN should be considered in the differential diagnosis of particularly high-risk transplant recipients who have SLE with allograft dysfunction and whose transplant biopsies require a complete evaluation by light, immunofluorescence, and electron microscopy.

## CONCISE METHODS

### Patients

The study population consisted of patients who had ESRD secondary to lupus nephritis, received a kidney transplant between October 1987 and October 2006, and had complete records in the UNOS STAR files. For the purpose of this study, the first and second kidney allografts were used as the index transplant in 6442 and 408 recipients, respectively, whose records were complete for analyses. For most recipients, RLN occurred in the first kidney allograft, except in nine recipients, in whom RLN occurred in the second allograft.

### Data Collection

UNOS maintains the STAR database, which includes baseline information such as recipient age, gender, race/ethnicity, history of the need for dialysis before transplantation, history of preoperative hypertension, history of pregnancies, date of transplantation, type of

transplant (living- or deceased-donor kidney), ABO compatibility with the donor, PRA, the MHC for the HLA loci mismatch level with the donor, and haplotype match level with the living-related donor. Data regarding postoperative DGF (the need for dialysis within the first week of transplantation), recurrent disease, episodes of rejection, and date of allograft failure (return to dialysis or need for another transplant) as well as patient death were extracted from the same STAR files.

## Definitions

### Cases

Each transplant center reported recipients who had SLE with RLN to the UNOS database system; no biopsy or clinical data were required to categorize the recurrence. Subjects with rejection were recipients who had SLE and were categorized with rejection by their transplant center. The definition of rejection includes hyperacute, acute, and chronic rejection on the basis of histologic classifications used by the individual centers. Recipients who had SLE without recurrence or rejection were included in the “others” control group.

### Outcomes

Allograft failure as defined as the return to dialysis or the need for another kidney transplant was the primary outcome in this study. Recipient survival was the secondary outcome.

Biological agents for induction immunosuppression included polyclonal antibodies and mAbs anti-CD3, anti-CD20, and anti-IL-2. Mycophenolate formulations for maintenance included mycophenolate mofetil and mycophenolate sodium.

## Statistical Analysis

Initially, the prevalence of RLN was estimated during the period between 1987 and 2006. Baseline characteristics were summarized as frequencies and proportions for categorical variables and as means  $\pm$  SD for continuous variables. The baseline characteristics at the time of the transplantation were compared among recipients with RLN or rejection and those without RLN or rejection (others group). Comparisons of categorical variables among groups were performed using  $\chi^2$  tests. Comparisons of continuous variables among groups were performed using ANOVA and for pair groups using the *t* test or the Aspin-Welch test as appropriate. Factors associated with the development of RLN were assessed by univariate and multivariate logistic regression models and data are presented as ORs with 95% CIs. Associations between the type of induction or maintenance immunosuppressive agents and RLN were also assessed by logistic regression models. We limited the extracted data of immunosuppressive agents only to the file containing the transplant hospitalization data to ensure that the type of immunosuppressive agent used preceded the development of RLN. Subsequently, survival statistics were used to estimate the effects of RLN on the primary and secondary outcomes. The allograft survival was censored when recipients were lost to follow-up or died. Recipient survival was censored when recipients were lost to follow-up. The cumulative survival curves were derived by the Kaplan-Meier method, and the differences among survival curves were compared by the log-rank test. Two multivariate proportional hazard regression models were constructed to assess the independent

influences of RLN on the risk for allograft failure. Model 1 adjusted for rejection, age, gender, and race/ethnicity. Model 2 adjusted for all variables in model 1 as well as for DGF (need for dialysis within the first week of transplantation), type of transplant allograft (deceased versus living), most recent PRA before transplantation, HLA mismatch level, and preemptive transplantation. Risk factors included in the models were selected *a priori* because of their potential prognostic value in determining allograft survival.<sup>37,38</sup> Models data are presented as RRs with 95% CIs. Finally, we estimated the AR of each dichotomized risk factor associated with allograft failure using the prevalence (P) of the risk factor and the adjusted RR of model 2. We used the following formula to estimate the AR:  $AR = P*(RR - 1)/1 + P*(RR - 1)$ . All statistical analyses, except for the AR, were conducted using the NCSS 2000 software package, and statistical significance was considered at  $P < 0.05$ .

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## DISCLOSURES

None.

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