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Tubulointerstitial Damage Predicts End Stage Renal Disease in Lupus Nephritis with Preserved to Moderately Impaired Renal Function: a Retrospective Cohort Study

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Abstract

Objectives—The presence of tubulointerstitial damage (TID) on renal biopsy is considered to be a late sequela of lupus nephritis (LN). The objective of this study was to determine if TID predicts progression to end stage renal disease (ESRD) in LN patients without advanced kidney disease.

Methods—All SLE patients with an index biopsy consistent with LN between January 2005 and July 2015, and eGFR ≥ 30 mL/min/1.73m² were included. Moderate-to-severe TID was defined as the presence of moderate to severe tubular atrophy and/or interstitial fibrosis. Time to ESRD was defined as time from the index biopsy date to incident ESRD date; non-ESRD patients were censored at time of death or the last visit before December 2015. Time-dependent analyses were conducted to evaluate whether moderate to severe TID was predictive of ESRD progression.

Results—Of the 131 LN patients with eGFR ≥ 30 mL/min/1.73m², 17 (13%) patients progressed to ESRD. Moderate-to-severe TID was present in 13% of biopsies with eGFR ≥ 60 mL/min/1.73m² and in 33% of biopsies with eGFR between 30 and 60 mL/min/1.73m². Moderate-to-severe TID was associated with a higher risk of ESRD progression: adjusted hazard ratio (HR) = 4.1, 95% CI (1.4, 12.1), $p=0.01$ for eGFR ≥ 30 mL/min/1.73m²; HR 6.2, 95% CI (1.7, 23.2), $p=0.008$ for eGFR ≥ 60 mL/min/1.73m². There was no association between tubulointerstitial inflammation (TII) and ESRD progression.

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Conflicts of interest:

The authors declare no conflicts of interest.

Conclusions—Moderate-to-severe TID, but not TII, was a strong predictor of ESRD progression independent of eGFR or glomerular findings, therefore, providing an important window for potential early interventions.

Keywords

lupus nephritis; tubulointerstitial damage; end stage renal disease

INTRODUCTION

Lupus nephritis (LN) is one of the major manifestations of systemic lupus erythematosus (SLE). LN occurs in up to 60% of SLE, 10–30% of whom progress to end stage renal disease (ESRD) despite aggressive therapies, leading to high morbidity and mortality [1, 2]. The 2003 International Society of Nephrology and Renal Pathology (ISN/RPS) classification has been accepted as the gold standard for evaluating histology in LN and is widely used to aid in treatment decisions [3]. However, studies report conflicting data regarding prognostic value of this classification, in particular in response to therapy and progression to ESRD [4–8]. One of the main limitations of the ISN/RPS classification is that it is primarily focused on glomerular pathology, even though other renal components, such as tubules, interstitium and blood vessels may be affected in lupus nephritis [9–11].

It has been shown that tubulointerstitial damage correlated with renal function more closely than glomerular damage, and the presence of moderate to severe tubulointerstitial lesions is believed to be a “bad prognostic sign” in LN [8, 12–18]. Based on the current knowledge of LN pathophysiology, glomerular injury is considered to be the inciting event leading to proteinuria and hypoxia. Proteinuria and hypoxia trigger tubulointerstitial inflammation resulting in fibrosis and atrophy [9, 11, 19, 20]. However, it is not well understood whether TID is simply a consequence of long standing LN or occurs in parallel as an independent predictor of ESRD progression [16, 20, 21]. Some experimental evidence suggests that TID and glomerular damage may occur in parallel, and that different mechanisms may contribute to immune complex deposition in glomeruli and in tubulointerstitium [9, 11, 22].

It has not been established whether the association of TID and ESRD progression holds true in individuals with preserved to moderately impaired kidney function at the time of the renal biopsy. None of the prior studies excluded patients with advanced chronic kidney disease (CKD, eGFR < 30 mL/min/1.73m²) at the time of the index biopsy, and at least one quarter of patients in most of these studies had severe renal impairment. The objective of this study was to ascertain the prevalence of TID in clinically indicated lupus renal biopsies, and to evaluate TID as an independent predictor of ESRD in LN patients with only mild to moderate renal impairment. Understanding if TID predicts ESRD progression in this population may explain why some of these patients progress to ESRD independent of biopsy class and baseline renal function. In addition, if TID occurs independent of glomerulonephritis in early stages of LN, preventing the development of TID (in addition to treating glomerular pathology) may improve renal survival.

METHODS

To identify patients to be included in the study, we employed “Clinical Looking Glass,” a proprietary software application developed at Montefiore Medical Center (MMC), that allows clinicians and researchers to identify populations of interest from the medical center database and to gather information about laboratory data, medications, demographics, and mortality [23]. MMC is a community-based urban tertiary care center that provides primary and specialty care to over 2 million people in the Bronx, New York [24]. This project was approved by the Institutional Review Board at the Albert Einstein College of Medicine/Montefiore Medical Center.

We searched for all adult and pediatric patients who had a renal biopsy between January 2005 and July 2015 and had the words “lupus” and/or “class” anywhere in the renal pathology report. Similar to prior studies, we excluded patients with fewer than 6 glomeruli on biopsy to assure a representative biopsy sample [16, 17]. All records of patients identified by this search were subsequently reviewed by one of the two investigators (BJ or HK) and a board-certified rheumatologist (AB) to identify SLE patients who fulfilled either the American College of Rheumatology criteria [25, 26] or SLICC criteria for SLE [27]. Follow up data was collected through December 2015. To be included in the final analyses, patients had to have only mild or moderate renal impairment at the time of the index biopsy. Mild renal impairment was defined as CKD stage 1 or 2, eGFR ≥ 60 mL/min/1.73m². Moderate renal impairment was defined as CKD stage 3, eGFR ≥ 30 and <60 mL/min/1.73m² [28, 29]. GFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula [30].

Tubulointerstitial indices were defined based on the NIH activity and chronicity indices [31], similar to recent studies [15–17]. Tubular damage was defined as the presence of moderate (25–50%) to severe ($>50\%$) tubular atrophy and/or interstitial fibrosis noted on renal biopsy report. Similarly, tubulointerstitial inflammation (TII) was defined as moderate (25–50%) to severe ($>50\%$) tubular and/or interstitial inflammation.

ESRD patients were identified using the following ICD-9 codes: chronic kidney disease stage V (585.5); end stage renal disease (585.6); or admit for renal dialysis (V56.0). Subsequently, all charts were reviewed to verify patient has ESRD and exclude patients who had received hemodialysis for less than 90 days.

From the medical records of the SLE patients in our final dataset, we collected the following data: age at the time of the index biopsy, sex, race (white, black, other/multiracial), ethnicity, history of hypertension, history of diabetes, and the total number of comorbidities using the Charlson Comorbidity Index (CCI) [32]. CCI, diabetes, and hypertension history were based upon ICD-9 (International Classification of Disease) codes prior to the index biopsy. Medical charts and prescription information were reviewed to ascertain induction medications after the index biopsy. Induction therapies (in combination with corticosteroids) were recorded as follows: mycophenolate mofetil, cyclophosphamide, and “other” (rituximab, calcinurin inhibitors, methotrexate, azathioprine, and corticosteroids alone). The use of angiotensin converting enzyme inhibitors was also recorded. Mortality data in the Clinical

Looking Glass is obtained directly from hospital records and from the Social Security Administration's (SSA) Death Master File. The clinical charts were also reviewed for medication history, and laboratory data including C3, C4, dsDNA antibodies, anti-Ro antibodies, urine protein/creatinine ratio, creatinine, and eGFR at time of biopsy or within 30 days of biopsy. Glomerular lesions were analyzed as proliferative (class III or class IV with or without class V) vs. class I, II or V by the 2003 ISN/RPS classification [10].

Baseline characteristics were compared between ESRD and non-ESRD groups. Wilcoxon-Mann-Whitney tests were used to compare continuous variables, while Pearson's Chi-square tests (or Fisher's exact test when appropriate) were used to compare categorical variables. Time to ESRD onset was defined as time from the index biopsy date to incident ESRD date; non-ESRD patients were censored at time of death or the last visit.

Because the development of ESRD is a time-dependent outcome, we used survival analysis, Kaplan-Meier survival curves and Cox proportional hazards models [33], to evaluate whether TID and TII were predictive of ESRD progression. Variables were included in the multivariable Cox regression models if the p-value was ≤ 0.20 in the univariable analysis. Although age was not significantly associated with ESRD in the univariable analysis, we included it in the multivariable model because of its clinical significance. We used Cox proportional hazard models to estimate the relative likelihood of progression to ESRD at any given point in time among patients with tubulointerstitial damage compared to patients without tubulointerstitial damage. In addition, because some patients were followed for less than 12 months prior to the end of the study, and, therefore, may not have had enough time to develop ESRD, we conducted additional analyses excluding patients with less than 1 year follow-up.

Because moderate to severe TID was not seen in class I/II LN, sensitivity analyses were performed excluding 9 patients with class I/II LN. Because ESRD progression rates may be different in proliferative LN compared to other forms of LN, additional analyses were performed in a subset of patient with proliferative LN. Other analyses were limited to patients age 17 or older, and to patients with eGFR ≥ 60 mL/min/1.73m². Finally, a model with both TID and TII was created to evaluate for potential confounding.

RESULTS

Initially, 197 native kidney biopsies with ≥ 6 glomeruli were identified from the MMC EMR using CLG. Thirty-two patients had GFR < 30 mL/min/1.73m², and 5 had no laboratory data available to estimate GFR (Figure 1). Five patients were missing information on tubular atrophy or interstitial fibrosis in the biopsy reports. Ten SLE patients had biopsy findings that were not consistent with LN and included membranous glomerulonephritis (GN) without immune deposits, minimal change disease, post-infectious GN, focal segmental glomerulosclerosis, and cryoglobulinemia-related membranoproliferative GN. Fourteen patients had confirmed LN on biopsy, but no laboratory or clinical information available to document ACR or SLICC SLE criteria. These 14 patients were excluded from the main analyses, but added in the sensitivity analyses without changing the conclusions of the study

(see sensitivity analyses below). Therefore, 131 met inclusion criteria for the study and were included in the main analyses (Figure 1).

Of these 131 patients, 9 (7%) had Class I/II LN, 58 (44%) had Class III/IV, 37 (28%) had Class V, and 27 (21%) had either Class III/V or Class IV/V LN (mixed). Seventeen patients (13%) progressed to ESRD with the median (IQR) time to ESRD progression of 1.9 (1.4, 3.9) years. The baseline clinical characteristics at the time of the index biopsy for ESRD progressors and non-progressors are shown in Table 1. Eighty-eight percent of ESRD progressors had proliferative LN vs. 61% of non-ESRD, $p=0.08$. Although relatively normal in both groups, median (IQR) baseline eGFR was 65 (50, 75) mL/min/1.73m² in the ESRD group and 97 (69, 127) mL/min/1.73m² in the non-ESRD group, $p=0.001$. ESRD progressors and non-progressors had similar characteristics at baseline: there were no significant differences with respect to age, sex, race, ethnicity, comorbidity scores, induction medications, complement levels, anti-dsDNA, anti-Ro, or protein-to-creatinine ratio at index biopsy.

Moderate to severe tubular atrophy or interstitial fibrosis were present in 22 (17%) of the overall patient population: 17 had both moderate to severe tubular atrophy and interstitial fibrosis, 2 had only moderate to severe interstitial fibrosis and 3 had only moderate to severe tubular atrophy. The comparisons between patients with and without moderate to severe TID are summarized in Table 2. Moderate to severe TID and/or TII was found in 41 (31%) of patients. Six of the patients (29%) with moderate to severe TID also had moderate to severe TII, compared to only 14 (13%) of patients with none to mild TID, although the difference did not reach statistical significance, $p=0.09$. Moderate to severe TID was found in 19 (22%) of patients with proliferative LN vs. 3 (8%) of patients with class V LN, $p=0.06$. None of the patients with class I/II LN had evidence of moderate to severe TID. The severity of TID was not associated with the degree of proteinuria, complement levels, or with anti-Ro or anti-dsDNA antibody positivity. Only 2 patients in the study cohort had secondary Sjoren's syndrome, an autoimmune disease that can cause tubulointerstitial nephritis [34].

Moderate to severe TID was present in 13 (13%) of the 104 biopsies with eGFR ≥ 60 mL/min/1.73m², and in 9 (33%) of the 27 biopsies with GFR between 30 and 60 mL/min/1.73m². Seventeen patients had both moderate to severe tubular atrophy and interstitial fibrosis, and five had only tubular atrophy or interstitial fibrosis. Eight (47%) of patients who progressed to ESRD had severe TID as opposed to only 14 (12%) of patients who did not progress to ESRD, $p<0.001$. We did not find an association between ESRD and moderate to severe tubulointerstitial inflammation, 17 (16%) in non-ESRD and 3 (18%) ESRD, $p=0.74$.

Kaplan-Meier survival curves demonstrate significantly different rates to ESRD progression between moderate to severe TID compared to none or mild TID (Figure 2, log-rank p -value <0.001). In the unadjusted analyses, moderate to severe TID was associated with a 5-fold risk of ESRD progression (HR 5.2, 95% CI (2.0, 13.4), $p=0.001$) (Table 3). In the Cox proportional hazards model adjusted for age at the time of the index biopsy, LN and eGFR (as a continuous variable), moderate to severe TID was associated with a high risk of ESRD progression, HR 4.1, 95% CI (1.4, 12.1), $p=0.01$. There was no association between TII and

ESRD in unadjusted or adjusted analyses, HR (95% CI) 0.90 (0.20, 4.0), $p=0.89$ and 0.57 (0.13, 2.59), $p=0.47$, respectively. Adding TII and TID in the same model did not change the study conclusions: there was a significant association between moderate to severe TID and ESRD progression, HR 3.8, 95% CI (1.2, 11.5), $p=0.002$, but TII was not a significant predictor of ESRD, HR 0.54, 95% CI (0.15, 2.0), $p=0.35$. Adding urine protein/creatinine ratio, race, sex, history of diabetes, or hypertension into the Cox regression model one at a time did not change study conclusions. Similarly, adjusting for induction medications (mycophenolate mofetil vs. others) did not alter the association between TID and ESRD, HR 3.8, 95% CI (1.2, 11.2), $p=0.02$.

To evaluate the robustness and internal validity of our findings, we conducted several additional analyses (Table 3). TID remained an independent predictor in the following subgroups analyses: patients with $eGFR \geq 60 \text{ mL/min/1.73m}^2$, HR 6.2, 95% CI (1.7, 23.2), $p=0.008$, adjusted for age at the time of biopsy; excluding class I/II LN, HR 3.9, 95% CI (1.3, 11.7), $p=0.02$, adjusted for age, $eGFR$, LN class; patients with proliferative LN only, HR 4.6, 95% CI (1.4, 14.8), $p=0.01$, adjusted for $eGFR$ and age; limited to patients 17 and older at the time of the index biopsy, HR 3.4, 95% CI (1.1, 10.9), $p=0.04$; and excluding 11 patients with less than 1 year follow-up time, HR 4.0, 95% CI (1.3, 12.5), $p=0.02$. Adding 14 patients who had biopsies consistent with LN, but insufficient information to confirm SLE by ACR or SLICC criteria, did not change the conclusions of the study, HR 4.3, 95% CI (1.5, 12.9), $p=0.008$. Lastly, the results were similar in the subgroup of patients whose biopsy samples contained 10 or more glomeruli, HR 3.8, 95% CI (1.1, 12.7), $p=0.03$.

To evaluate external validity of our findings and to compare with the previously published data, we calculated unadjusted HRs for interstitial fibrosis and for tubular atrophy, although there was a significant overlap between these two variables. The unadjusted HR for tubular atrophy, with or without interstitial fibrosis, was 3.4, 95% CI (1.3, 9.3), $p=0.015$. The HR for interstitial fibrosis, with or without tubular atrophy, was 5.9, 95% CI (2.3, 15.3), $p<0.001$.

DISCUSSION

Numerous prior studies have shown an association between tubulointerstitial indices and renal outcomes [12–17, 35–38]. However, no prior studies focused specifically on patients with normal or only moderately impaired renal function. We have shown that moderate to severe TID is frequently seen on renal biopsies of patients without advanced CKD. Furthermore, the severity of TID in the current study was not associated with the degree of proteinuria, complement levels, or anti-dsDNA titers. Therefore, this study provides clinical evidence in support of the prior experimental findings that TID and glomerular damage may occur independently, and that different mechanisms may contribute to immune complex deposition in glomeruli and in tubulointerstitium in patients without advanced CKD [9, 11, 21].

In prior studies, both TID and TII were predictive of poor outcomes in lupus-related renal disease, while in the current study only TID, not TII, was predictive of ESRD [16, 17]. The major difference between this study and prior studies is that we included only patients with preserved renal function, while other studies included a large proportion of patients with

severe renal impairment. In our study, only 29% of patients with moderate to severe TID also had moderate to severe TII, suggesting that inflammation may occur very early in the disease course and lead to the development of fibrosis and atrophy overtime. On the other hand, our findings suggest that treating early TII may prevent the development of ESRD. If these finding are confirmed prospectively, early detection and treatment of tubulointerstitial inflammation may improve survival, independent of the glomerular disease.

The presence of TID or TII was not associated with either anti-Ro/SSA antibodies or with secondary Sjogren's syndrome. Only 2 (1.5%) of the study patients had secondary Sjogren's syndrome. This number is lower than the 6–30% prevalence of secondary Sjogren's previously reported among SLE patients [39–41]. However, the low prevalence of secondary Sjogren's in our cohort is consistent with the previous report suggesting that the prevalence of clinical renal disease is significantly lower in SLE patients with Sjogren's compared to SLE patients without Sjogren's [42]. Further studies are needed to identify factors associated with TID and TII to enable early interventions.

This study has several limitations mainly due to its retrospective design and a small number of ESRD progressors and patients with TID/TII. Complete information on disease activity and medication use was not available for all patients, and medication compliance could not be assessed, although there were no differences with respect to medications between ESRD progressors and non-progressors. The study may have been underpowered to detect important baseline differences between ESRD progressors and non-progressors, and the wide confidence intervals need to be interpreted with caution. However, this is the first study to demonstrate the impact of TID on ESRD progression in patients with normal to moderately impaired renal function where early detection and intervention may be most effective.

The current study has several important strengths. All of the biopsies included in this study were evaluated by 2 experienced renal pathologists using a standardized template to report the degree of tubulointerstitial damage for every biopsy. In contrast to most prior studies that used composite indices or immunochemical staining to define TID [14, 17, 35, 36], we used the information that is readily available to clinicians on routine renal biopsies. Only two recent studies used a similar approach to evaluate the relationship between tubulointerstitial inflammation, tubular atrophy, and interstitial fibrosis with renal function. Pagni et al. examined the evolution of tubulointerstitial changes over time in 142 White and Asian patients who underwent repeat biopsy over the course of their follow-up [15]. Yu et al. studied the association between the severity of tubulointerstitial indices and ISN/RPS classes in 313 patients from northern China [16], 25% of whom had acute renal failure at the time of their biopsy. In addition, the mean serum creatinine level in the study by Yu et al. was significantly higher, 1.3 mg/dl, compared to 0.8 mg/dl in the current study.

Additional strengths include a well characterized patient population with data on comorbidities, including hypertension and diabetes, and a relatively large number of Black and Hispanic patients with a long duration of follow-up. Although this was a single-center design, limited to the population of Bronx, New York, the unadjusted HR estimates in this study were very similar to the unadjusted HR estimates reported by Yu et al. [16], supporting

the external validity of our findings. Lastly, the study conclusions remained unchanged in several sensitivity analyses, supporting the internal validity of our findings.

Potentially, TII and early TID may be identified using previously described biomarkers, such as miRNA, vimentin, and pentraxin [21, 43–45]. Therapies directed toward treating interstitial inflammation and early fibrosis may include anti-TNF agents, as well as TWEAK (TNF-related weak inducer of apoptosis)/Fn14 inhibition, and anti-fibrotic agents [9, 11, 21, 46–48], although more evidence regarding the optimal timing and the effectiveness of these interventions is needed. Several experimental studies have suggested that mycophenolic acid, the metabolite of mycophenolate mofetil, may have anti-fibrotic effects on tubular cells that are independent of its immunomodulatory actions [11, 21, 49–51]. Further studies are needed to determine if early treatment with MMF in these patients may be beneficial to prevent TID. Novel approaches including molecular imaging, cell distance mapping, functional magnetic resonance imaging, as well as integrative biology approaches are being developed to identify early inflammatory changes, biomarkers and response to treatment in lupus nephritis [52–55].

In conclusion, TID was found in a significant number of clinically-indicated kidney biopsies in LN patients without advanced CKD. The presence of TID, but not TII, was a strong independent predictor of ESRD progression independent of eGFR or glomerular findings, therefore, providing an important window for potential early interventions. If confirmed in large prospective studies, early detection of TID may lead to the development of effective prevention strategies, and TID-directed therapeutic targets.

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Figure 1.

Inclusion/Exclusion

Abbreviations

GFR: glomerular filtration rate

TID: tubulointerstitial damage

TII: tubulointerstitial inflammation

LN: lupus nephritis

Figure 2.
Kaplan-Meier Survival Curves for ESRD Progression in Patients with eGFR > 30 mL/min/
1.73m² by the Severity of TID

Table 1

Baseline characteristics of patients with mild to moderate renal impairment at the time of the index biopsy stratified by incident ESRD Status at follow up.

	Total N=131	No incident ESRD (n=114)	Incident ESRD (n=17)	P value
Age at biopsy, median (IQR), years	26 (18, 40)	25 (17, 38)	27 (22, 41)	0.41
Pediatric patients,<17 years old, n(%)	26 (20)	23 (20)	3 (18)	0.81
Female, n (%)	108 (82)	95 (83)	13 (76)	0.49
Black race, n (%)	65 (50)	59 (52)	6 (35)	0.21
Hispanic ethnicity, n (%) (18 missing)	44 (34)	36 (37)	8 (53)	0.22
Diabetes, n (%)	7 (6)	7 (6)	1 (6)	0.98
Hypertension, n (%)	102 (78)	88 (77)	14 (82)	0.63
Carlson Comorbidity Index	3 (1, 4)	3 (1, 3)	3 (1, 4)	0.31
Low C3, n (%)	90 (69)	78 (74)	12 (80)	0.63
Low C4, n (%)	86 (66)	74 (72)	12 (80)	0.51
Elevated dsDNA, n (%)	76 (58)	67 (68)	9 (69)	0.95
Anti-Ro positive, n(%)	57 (50)	50 (53)	7 (35)	0.15
Cr (mg/dL), median (IQR)	0.8 (0.6, 1.1)	0.8 (0.6, 1.1)	1.1 (0.9, 1.7)	0.001
eGFR mL/min/1.73m ² (MDRD), median (IQR)	89 (62, 127)	97 (69, 127)	65 (50, 75)	0.001
Urine prot/creat ratio (mg/mg), median (IQR)	1.8 (0.9, 4.9)	1.8 (0.8, 4.2)	2.7 (1.5, 7.4)	0.14
LN Class, n(%)				
I, II or V	46 (35)	44 (37)	2 (12)	
III/IV with or without V	85 (65)	70 (61)	15 (88)	0.03
Induction medications				
MMF [*]	83 (63)	74 (65)	9 (53)	
Cyclophosphamide	12 (9)	8 (7)	4 (24)	0.15
ACE-I ^{**}	16 (12)	15 (13)	1 (6)	
Other	15 (11)	12 (11)	3 (18)	
Missing	5 (4)	5 (4)	0	
Follow-up time, median (IQR), years	3.6 (2.3, 5.6)	3.7 (2.6, 5.6)	1.9 (1.4, 3.9)	0.005

* MMF: mycophenolate mofetil

** ACE-I: angiotensin converting enzyme inhibitors

Table 2

Baseline characteristics of patients with mild to moderate renal impairment at the time of the index biopsy stratified by T1D and by T1D.

	T1D, none to mild N=109	T1D, moderate to severe N=22	p-value	T1D*** none to mild N=105	T1D moderate to severe N=20	p-value
Age at biopsy, median (IQR), years	24 (17, 37)	33 (22, 44)	0.10	25 (18, 40)	28 (17, 38)	0.72
Pediatric patients, <17 years old, n(%)	22 (20)	4 (18)	0.83	21 (20)	5 (25)	0.61
Female, n (%)	91 (83)	17 (77)	0.49	88 (84)	15 (75)	0.34
Black race, n (%)	53 (49)	12 (55)	0.61	48 (46)	15 (75)	0.02
Hispanic ethnicity, n (%)	38 (40)	6 (35)	0.74	47 (42)	3 (17)	0.02
Diabetes, n (%)	6 (6)	1 (5)	0.86	7 (7)	0	0.24
Hypertension, n (%)	85 (78)	17 (77)	0.94	81 (77)	16 (80)	0.78
Carlson Comorbidity Index	3 (1.3)	3 (1.4)	0.33	81 (77)	16 (80)	0.78
Low C3, n (%)	25 (25)	5 (25)	>0.99	70 (74)	14 (74)	>0.99
Low C4, n (%)	70 (71)	16 (80)	0.43	67 (72)	14 (74)	0.88
Elevated dsDNA, n (%)	61 (66)	15 (79)	0.28	61 (69)	11 (65)	0.71
Anti-Ro positive, n(%)	51 (51)	7 (35)	0.21	50 (53)	7 (35)	0.15
Cr (mg/dL), median (IQR)	0.8 (0.6, 1.1)	1.0 (0.8, 1.4)	0.01	0.8(0.6, 1.1)	0.8 (1.1, 1.3)	0.01
eGFR mL/min/1.73m ² (MDRD), median (IQR)	95 (66, 127)	68 (49, 88)	0.008	93 (64, 127)	79 (50, 100)	0.05
Urine prot/creat ratio (mg/mg), median (IQR)	1.74 (0.83, 4.86)	2.03 (1.51, 4.88)	0.62	1.58 (0.79, 4.02)	3.13 (1.88, 4.92)	0.04
LN Class, n (%)	43 (39)	3 (14)		41 (39)	4 (20)	
I/II or V	66 (61)	19 (86)	0.02	64 (61)	16 (80)	0.10
III/IV with or without V						
Induction medications						

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	TID, none to mild N=109	TID, moderate to severe N=22	p-value	TII *** none to mild N=105	TII moderate to severe N=20	p-value
MMF*	69 (63)	14 (64)		64 (61)	14 (70)	
Cyclophosphamide	9 (8)	3 (14)		11 (11)	1 (5)	
ACE-I**	14(13)	2 (9)	0.8	14 (13)	2 (10)	0.9
Other	12 (11)	3 (14)		12 (11)	2 (10)	
Missing	5 (5)	0		4 (4)	1 (5)	
Moderate to severe TII	14 (13)	6 (29)	0.09			

* MMF: mycophenolate mofetil

** ACE-I: angiotensin converting enzyme inhibitors

*** TII data unavailable for 6 patients

Table 3

Unadjusted and Adjusted Hazard Ratios for Developing ESRD in Patients with moderate to severe T1D vs. none or mild T1D.

	Unadjusted		Adjusted*	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall sample	5.2 (2.0, 13.4)	0.001	4.1 (1.4, 12.1)	0.01
In the subset of patients with GFR ≥ 60 mL/min/1.73m ²	6.4 (1.7, 23.7)	0.006	6.2 ** (1.7, 23.2)	0.008
Excluding class I/II LN	4.7 (1.8, 12.3)	0.001	3.9 (1.3, 11.7)	0.02
In the subset of patients with proliferative LN	3.6 (1.3, 10.0)	0.01	4.6 *** (1.4, 14.8)	0.01
Excluding patients younger than 17 years old	5.0 (1.8, 14.4)	0.003	3.4 (1.1, 10.9)	0.04
Excluding 11 patients with < 1 year follow-up time	3.8 (1.2, 11.6)	0.02	4.0 (1.3, 12.5)	0.02
Adding T1D into the models			3.8 (1.2, 11.5) (HR for T1D 0.54 (0.15, 2.0), p=0.35)	0.002
Including 14 patients with LN on biopsy, but insufficient information to verify ACR/SLICC criteria	5.1 (2.0, 13.3)	0.001	4.3 (1.5, 12.9)	0.008

* All models were adjusted for age, eGFR as a continuous variable, and LN class (proliferative vs. other), unless otherwise specified

** Adjusted for age only

*** Adjusted for age and eGFR as a continuous variable