Published in final edited form as:

Arthritis Rheumatol. 2018 November ; 70(11): 1801–1806. doi:10.1002/art.40575.

Tubulointerstitial Damage in Lupus Nephritis: A Comparison of the Factors Associated with Tubulointerstitial Inflammation and Renal Scarring

Alejandra Londoño Jimenez, MD,

Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Wenzhu B. Mowrey, PhD,

Division of Biostatistics, Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY

Chaim Putterman, MD,

Division of Rheumatology, Department of Medicine, Albert Einstein College of Medicine, Bronx, NY

Jill Buyon, MD,

Division of Rheumatology, Department of Medicine, New York University School of Medicine, New York, NY

Beatrice Goilav, MD, and

Division of Nephrology, Department of Pediatrics, Children's Hospital at Montefiore, Albert Einstein College of Medicine, Bronx, NY

Anna Broder, MD, MSc

Division of Rheumatology, Department of Medicine, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY

Abstract

Objective—To characterize and compare the factors associated with tubulointerstitial inflammation (TII) and tubulointerstitial scarring, defined as interstitial fibrosis and/or tubular atrophy (IF/TA), in patients with lupus nephritis (LN).

Methods—We identified SLE patients with a renal biopsy consistent with LN between 2005 and 2017. Clinical data was collected from the medical records. Multivariable logistic regression models were fitted to assess factors associated with TII and with IF/TA (moderate-to-severe vs. none-or-mild).

Results—Of 203 LN patients included, 41 patients (20%) had moderate-to-severe TII, 45 (22%) had moderate-to-severe IF/TA and 21 (10%) patients had both. Multivariable logistic regression models showed that moderate-to-severe TII was associated with a shorter disease duration, Black

Address correspondence and reprint requests to: Anna Broder, MD, MSc, Division of Rheumatology, Albert Einstein College of Medicine, F103N, 1300 Morris Park Ave, Bronx, NY 10461, Phone: (718) 430-8582, Fax: (718) 430-8789, abroder@montefiore.org.

Conflicts of interest: none

race, proliferative LN, and $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ at the time of biopsy. Hydroxychloroquine use was associated with significantly lower odds of moderate-to-severe TII, $\text{OR} = 0.27$, 95% CI (0.10, 0.70), $p = 0.008$. Similar to TII, factors associated with moderate-to-severe IF/TA included proliferative LN, and $\text{eGFR} < 60 \text{ mL/min/1.73m}^2$ at the time of biopsy. In addition, the presence of moderate-to-severe TII and older age were also associated with moderate-to-severe IF/TA. None of the routinely available serologic markers, including anti-dsDNA, anti-Ro/La antibodies and low complement were associated with tubulointerstitial damage (TID).

Conclusions—The use of hydroxychloroquine was strongly associated with less inflammation, while the finding of TII, proliferative LN, and low eGFR were the major determinants of the presence of tubulointerstitial scarring. Identifying modifiable factors is critical for the development of better preventive and therapeutic strategies directed towards ultimate improvement in survival in patients with lupus-related kidney disease.

The majority of studies in lupus nephritis (LN) have focused primarily on unveiling the mechanisms behind glomerular disease (1). However, glomerular-based measures of disease activity do not consistently predict adverse renal outcomes and perform poorly in identifying patients at highest risk for renal failure (2). A growing body of evidence indicates that indices of tubulointerstitial damage (TID) are better predictors of progression to renal failure than glomerular parameters (2–4). Both tubulointerstitial inflammation (TII) and tubulointerstitial scarring, namely interstitial fibrosis and tubular atrophy (IF/TA), strongly correlate with poor renal outcomes independent of the extent of glomerular damage (2, 3, 5, 6).

TII is thought to precede IF/TA but whether any differences exist in their clinical and serological profiles is unknown. Unlike glomerular disease, complement levels and elevated titers of double-stranded DNA antibodies (dsDNA) have no correlation with TID (2, 7). In Sjögren's syndrome, the presence of extraglandular manifestations, including interstitial nephritis, is associated with high titers of anti-Ro/La antibodies (8). In addition, previous studies have reported potential renoprotective effects of hydroxychloroquine (HCQ) (9, 10). However, no clinical studies to date have explored these associations specifically in TID.

Therefore, the objective of this study was to characterize and compare the factors associated with TII vs IF/TA in patients with LN. We hypothesized that TII occurs earlier in the disease course and its presence could be influenced by medication use, whereas IF/TA would largely be determined by the degree of TII, renal impairment and the presence of anti-Ro/La antibodies. Understanding the differences between TII and IF/TA is fundamental in the identification of risk factors for progression into permanent scarring and is an essential step in the development of novel preventive and targeted therapeutic strategies.

METHODS

This was a retrospective study conducted at Montefiore Medical Center (MMC). MMC is a community-based urban tertiary care center in Bronx, New York. This study was approved by the Institutional Review Board.

We identified all adult and pediatric patients who fulfilled either the American College of Rheumatology (ACR) criteria (11) or the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) criteria for SLE (12) and had a renal biopsy between January 2005 and May 2017.

Tubulointerstitial indices were defined based on the NIH activity and chronicity definitions as none-or-mild (<25%), or moderate (25–50%)-to severe (>50%) (13). The eGFR was estimated using the four-variable Modification of Diet in Renal Disease (MDRD) formula. Glomerular lesions were analyzed as proliferative (class III or class IV with or without class V) vs. class I, II or V according to the 2003 ISN/RPS classification (14)

Clinical, demographic and laboratory parameters were compared, in parallel, between patients with and without moderate-to-severe IF/TA, and patients with and without moderate-to-severe TII. Sensitivity analyses were performed in the following subgroups: patients with proliferative nephritis only, excluding patients with class I/II/V LN, patients older than 17 years of age, and patients with only mild to moderately impaired eGFR ($<30 \text{ mL/min/1.73m}^2$).

RESULTS

Study sample

A total of 236 patients who had a kidney biopsy between January 2005 and May 2017 were identified. Ten patients that had biopsy findings not consistent with LN and one patient with class I LN and lupus podocytopathy with concurrent acute tubular necrosis were excluded. In addition, 22 patients had no clinical or histological information available. Therefore, a total of 203 patients who fulfilled the ACR/SLICC SLE criteria and had complete TII and IF/TA data were included in the primary analysis.

Patient characteristics

The frequency of moderate-to-severe TII and IF/TA was 41 (20%) and 45 (22%), respectively. Moderate-to-severe IF/TA or TII were present in 65 (32%) of the 203 biopsies. Twenty-one (10%) patients had both moderate-to-severe IF/TA and moderate-to-severe TII. Twenty-four (12%) patients had moderate-to-severe IF/TA alone with no significant TII, and 20 (10%) patients had moderate-to-severe TII alone with no significant IF/TA. Twenty-one patients (47%) with moderate-to-severe IF/TA also had moderate-to-severe TII compared to only 20 patients (13%) with none-or-mild IF/TA ($p<0.01$) (Table 1).

The median, [inter-quartile range (IQR)] serum creatinine level was 0.9 (0.7, 1.4) mg/dL and the median (IQR) urine protein creatinine ratio (UPC) was 2.0 (0.96, 4.90) mg/mg.

One hundred and thirty-nine (70%) patients were receiving corticosteroids. Seventy-one patients (37%) had received immunosuppressive medications prior to biopsy. Of them, 35 (53%) received mycophenolate mofetil (MMF), while less commonly used medications included azathioprine (29%), cyclophosphamide (5%), methotrexate (5%), and others (8%), including rituximab, tacrolimus, and IVIG). Fifty-three percent of the patients were receiving HCQ at the time of biopsy.

Comparison of the factors associated with moderate-to-severe TII and moderate-to-severe IF/TA

Univariable analysis of factors associated with moderate-to-severe TII—

Patients with moderate-to-severe TII were more likely to be Black compared to patients with none-or-mild TII (68% vs 47%, $p=0.01$). Hypertension (HTN) was present in 21 (54%) and 55 (35%) of the patients, respectively, $p=0.03$. There were no differences in the frequency of diabetes or Sjögren's syndrome.

In terms of histological features, proliferative LN (class III/IV $\pm$ V) was more common in patients with moderate-to-severe TII compared to none-or-mild TII (83% and 57% respectively, $p=0.02$). Classes I/II and V were seen accompanying moderate-to-severe TII in 2 (5%) and 5 (12%) biopsies, respectively.

With regard to laboratory findings, moderate-to-severe TII was associated with a lower eGFR at the time of biopsy, $p<0.001$. The severity of TII was not associated with the degree of proteinuria, complement levels, anti-dsDNA, anti-SSA/Ro, anti-SSB/La, anti-Sm/RNP, or the presence of anti-phospholipid antibodies.

When comparing medications at the time of biopsy no differences were found with respect to angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) or immunosuppressant use between the two groups. However, patients with none-or-mild TII were more likely to be on HCQ than patients with moderate-to-severe TII (60% vs 28% respectively, $p<0.001$).

Univariable analysis of factors associated with moderate-to-severe IF/TA—

Patients with moderate-to-severe IF/TA, were significantly older at the time of their biopsy compared to patients with none-or-mild IF/TA, median (IQR) 41 (25, 53) vs 27 (19, 38) years, $p<0.001$. Black race was associated with moderate-to-severe IF/TA, similar to TII. Patients with moderate-to-severe IF/TA had a longer disease duration with a median (IQR) time from diagnosis of 54 (11, 93) months compared to 5.7 (0.7, 58) months in patients with none-or-mild IF/TA, $p<0.001$. Analogous to TII, HTN was the only comorbidity associated with IF/TA and was present in 28 (65%) of the patients with moderate-to-severe IF/TA vs 48 (31%) patients with none-or-mild IF/TA, $p<0.001$. Proliferative LN classes also predominated in the moderate-to-severe IF/TA group compared to the none-or-mild IF/TA group (84% vs 56%, $p=0.002$). Similar to TII, IF/TA was associated with a lower eGFR at the time of biopsy. In contrast to TII, IF/TA was associated with dual positivity for anti-Ro and anti-La. Co-positivity for anti-Ro and anti-La was seen in 13 (33%) of the patients with moderate-to-severe IF/TA vs 20 (14%) of patients with none-or-mild IF/TA, $p=0.008$. As in TII, there were no significant differences in complement levels, anti-dsDNA and other autoantibodies between the groups.

With regard to medications, use of immunosuppressants was more common in patients with moderate-to-severe IF/TA compared to patients with none-or-mild IF/TA (49% vs 30%, $p=0.03$). There were no differences in ACEi, ARB, NSAID or corticosteroid use between the groups but unlike TII, HCQ was not associated with milder stages of IF/TA.

Multivariable analysis of the factors associated with TII and IF/TA—In a logistic regression model comparing moderate-to-severe TII vs. none-or-mild TII (Table 2), factors associated with moderate-to-severe TII included a shorter disease duration, Black race, proliferative LN, and eGFR<60 mL/min/1.73m² at the time of biopsy. The adjusted association between history of HTN and moderate-to-severe TII was only borderline significant, odds ratio (OR) 2.68, 95% confidence interval (CI): (0.99, 7.03), $p=0.055$. HCQ use was associated with significantly lower odds of moderate-to-severe TII, OR 0.27, 95% CI (0.10, 0.70), $p=0.008$. The magnitude of the association of these variables (expressed as ORs) remained very similar in the sensitivity analyses. The association of HCQ use, eGFR and proliferative LN with lower odds of TII remained significant in all sensitivity analyses. The associations of HTN, disease duration and race with TII were not statistically significant in some of the sensitivity analyses due to loss of statistical power (data not shown).

Similar to TII, factors associated with higher odds of moderate-to-severe IF/TA in a logistic regression model included proliferative LN, and eGFR<60 mL/min/1.73m² at the time of biopsy (Table 2). In the same logistic regression model, the presence of moderate-to-severe TII and older age were also associated with moderate-to-severe IF/TA. Use of immunosuppressive medications prior to biopsy was associated with a 6-fold risk of moderate-to-severe IF/TA, suggesting the presence of more severe, refractory and/or long-standing lupus activity at the time of biopsy. Disease duration, Black race, HCQ use, and HTN were not associated with moderate-to-severe IF/TA. These findings remained unchanged in all of the sensitivity analyses (data not shown).

DISCUSSION

Multiple studies have recognized TID as a strong independent predictor of poor renal outcomes in LN (2, 3, 5, 7). However, little is known about the factors that drive its development. This hypothesis-generating study evaluates multiple clinical and serological features that are routinely available to the clinician and compares the factors associated with TII and IF/TA in patients with LN.

In the current study, both moderate-to-severe TII and IF/TA were associated with proliferative LN and eGFR, as previously described (2, 6). Black race was associated with moderate-to-severe TII. An increased frequency of TID has been previously reported in African Americans (13). Whether the poor renal outcomes in Black patients with LN are partly explained by an increased prevalence of TID deserves further study to better understand the significance of the underlying genetic and socio-demographic factors.

Moderate-to-severe IF/TA or TII were present in 32% of the biopsies. In prior studies, moderate-to-severe TID has been reported in 20–72% of the kidney biopsy specimens of patients with SLE, the large variation in its prevalence owing to differences in staining methods and definitions of significant TID (2, 3, 7). The prevalence of TID in the current study is similar to that of studies that have used routine light microscopy (3, 7). The 72% prevalence of TID reported by Hsieh *et al.* was based on CD45 staining that, although more sensitive, is not readily available in routine clinical practice.

As expected, moderate-to-severe TII was more likely to occur early in the disease course, while IF/TA were largely determined by the age, immunosuppression use (as a proxy for disease severity and/or refractory disease) and the presence of TII. The consistency of many of these findings with previous studies, supports the external validity of our results and their generalizability.

The concept of inflammation leading to fibrosis is derived from the principles of tissue repair and from previous observations that have described a close association between tubulointerstitial inflammation and scarring (2, 7). Our results are consistent with these observations and indicate that the presence of moderate-to-severe TII is independently associated with more advanced stages of IF/TA. The reversibility of TII was illustrated by Pagni *et al.* in a study that examined the evolution of tubulointerstitial changes over time (5). Consequently, there is a pressing need for early recognition of patients with TII in order to implement therapeutic strategies prior to the onset of irreversible scarring.

Several mechanisms by which glomerular disease can initiate TID have been proposed (15). However, the fact that severe TID is also seen in isolation suggests that different pathways might be implicated in its pathogenesis (3, 15). Immune complex deposition in the tubular basement membrane (TBM) and in the peritubular capillaries (PTC) is thought to arise from in-situ antibody production and binding to locally available antigens (16). This may occur early in the disease course and independently of glomerular immune complex deposition. Recent evidence suggests that the presence of TBM complexes correlates with the severity of interstitial inflammation, clinical disease activity and renal outcome (17). Unfortunately, the presence or absence of these tubular deposits was not consistently reported in the biopsies included in the current study, and therefore, we could not explore these associations.

Interestingly, HCQ was associated with a 73% decrease in the odds for moderate-to-severe TII. HCQ is known to inhibit ligation of nucleic acid with toll-like receptors (TLR) and subsequent signaling, the mechanism relating to decreased endosomal acidification and/or direct binding to nucleic acids masking their TLR-binding epitope (18). Remarkably, previous experimental studies have demonstrated the participation of renal tubular TLRs in the pathogenesis of tubulointerstitial injury being instrumental in bridging the innate and adaptive immune responses responsible for kidney damage (19). No clinical studies have evaluated the role of HCQ specifically in TII, but its association with higher rates of remission, fewer relapses and reduced renal damage has been extensively described in LN (9, 10).

In contrast to TII, we did not observe an association of HCQ with less IF/TA. Given the retrospective nature of this study, these findings may have been affected by unmeasured confounders and lack of information about the duration of treatment with HCQ and medication compliance. Since IF/TA was associated with longer SLE duration at the time of biopsy, it is possible that patients with significant IF/TA were rapid progressors and HCQ was started too late in their disease course to alter its progression. In addition, the intricate mechanisms that ultimately lead to irreversible scarring remain unknown and whether IF/TA can develop through non-inflammatory cell death is also a consideration. Rigorous

pharmacoepidemiologic studies are needed to ascertain potential benefits of HCQ in T1D. In addition, the appropriate dosing, as well as relative risks and benefits of long term HCQ use should be carefully assessed considering the concerns for ocular toxicity, especially in individuals with impaired kidney function (20). Whether longitudinally HCQ use results in less IF/TA deserves further study.

Similar to previous studies, no association was seen between complement levels, anti-dsDNA or degree of proteinuria with the severity of T1I or IF/TA (2, 7). A possible association of moderate-to-severe IF/TA with dual positivity for anti-Ro and anti-La antibodies, as shown by the results of our univariable analysis, should be investigated further.

In summary, this is the largest study to date comparing a comprehensive array of clinical and serologic factors associated with T1I and IF/TA. Our results provide compelling evidence that routinely available serological markers have no correlation with T1D and highlight the need to identify novel biomarkers and targeted therapies. The results of this study suggest that there is a window of opportunity to treat T1I before the development of fibrosis. If validated in other patient populations, these findings would strongly support the continued benefit of HCQ in lupus-related kidney disease even after initiating immunosuppressive therapy to decrease tubular inflammation. Identifying the mechanisms by which HCQ decreases tubular inflammation and exploring the effects of interstitial immune complex deposition and peritubular capillaritis on cell death may lead to the discovery of new biomarkers and development of therapies with ultimate improvement in renal survival.

Acknowledgments

Funding: NIH/NIAMS K23 AR068441 (A Broder).

References

1. Lech M, Anders HJ. The pathogenesis of lupus nephritis. *J Am Soc Nephrol.* 2013; 24:1357–1366. [PubMed: 23929771]
2. Hsieh C, et al. Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. *Arthritis care & research.* 2011; 63:865–874. [PubMed: 21309006]
3. Yu F, et al. Tubulointerstitial lesions of patients with lupus nephritis classified by the 2003 International Society of Nephrology and Renal Pathology Society system. *Kidney international.* 2010; 77:820–829. [PubMed: 20182417]
4. Yu F, Haas M, Glassock R, Zhao MH. Redefining lupus nephritis: clinical implications of pathophysiologic subtypes. *Nat Rev Nephrol.* 2017; 13:483–495. [PubMed: 28669995]
5. Pagni F, et al. Tubulointerstitial lesions in lupus nephritis: International multicentre study in a large cohort of patients with repeat biopsy. *Nephrology (Carlton).* 2016; 21:35–45.
6. Broder A, et al. Tubulointerstitial damage predicts end stage renal disease in lupus nephritis with preserved to moderately impaired renal function: A retrospective cohort study. *Seminars in arthritis and rheumatism.* 2017
7. Alsuwaida AO. Interstitial inflammation and long-term renal outcomes in lupus nephritis. *Lupus.* 2013; 22:1446–1454. [PubMed: 24097970]
8. Loch H, Pelck R, Manthorpe R. Clinical manifestations correlated to the prevalence of autoantibodies in a large (n=321) cohort of patients with primary Sjogren's syndrome: a comparison of patients initially diagnosed according to the Copenhagen classification criteria with the American-European consensus criteria. *Autoimmun Rev.* 2005; 4:276–281. [PubMed: 15990074]

9. Fessler BJ, et al. Systemic lupus erythematosus in three ethnic groups: XVI. Association of hydroxychloroquine use with reduced risk of damage accrual. *Arthritis Rheum.* 2005; 52:1473–1480. [PubMed: 15880829]
10. Kasitanon N, Fine DM, Haas M, Magder LS, Petri M. Hydroxychloroquine use predicts complete renal remission within 12 months among patients treated with mycophenolate mofetil therapy for membranous lupus nephritis. *Lupus.* 2006; 15:366–370. [PubMed: 16830883]
11. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis and rheumatism.* 1997; 40:1725.
12. Petri M, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum.* 2012; 64:2677–2686. [PubMed: 22553077]
13. Austin HA 3rd, et al. Prognostic factors in lupus nephritis. Contribution of renal histologic data. *The American journal of medicine.* 1983; 75:382–391. [PubMed: 6351607]
14. Weening JJ, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol.* 2004; 15:241–250. [PubMed: 14747370]
15. Clark MR, Trotter K, Chang A. The Pathogenesis and Therapeutic Implications of Tubulointerstitial Inflammation in Human Lupus Nephritis. *Semin Nephrol.* 2015; 35:455–464. [PubMed: 26573548]
16. Satoskar AA, et al. Discrepancies in glomerular and tubulointerstitial/vascular immune complex IgG subclasses in lupus nephritis. *Lupus.* 2011; 20:1396–1403. [PubMed: 22095887]
17. Wang H, et al. Tubular basement membrane immune complex deposition is associated with activity and progression of lupus nephritis: a large multicenter Chinese study. *Lupus.* 2018; 27:545–555. [PubMed: 28954590]
18. Kuznik A, et al. Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. *J Immunol.* 2011; 186:4794–4804. [PubMed: 21398612]
19. Benigni A, et al. Involvement of renal tubular Toll-like receptor 9 in the development of tubulointerstitial injury in systemic lupus. *Arthritis Rheum.* 2007; 56:1569–1578. [PubMed: 17469139]
20. Abdulaziz N, Shah AR, McCune WJ. Hydroxychloroquine: balancing the need to maintain therapeutic levels with ocular safety: an update. *Curr Opin Rheumatol.* 2018; 30:249–255. [PubMed: 29517495]

Table 1

Baseline demographic, clinical and LN class for the study patients in the overall sample and stratified by TII and IF/TA^a

	Total sample (n=203) ^a	Tubulointerstitial inflammation (TII)		p-value	interstitial fibrosis and/or Tubular atrophy (IF/TA)		p-value
Demographics		TII None-or-Mild (n=162)	TII Moderate-to-Severe (n=41)		IF/TA None-or-mild (n=158)	IF/TA Moderate-to-Severe (n=45)	
Age, median (IQR), years	28 (20, 42)	28 (20, 41)	33(22, 47)	0.26	27 (19, 38)	41 (25, 53)	<0.001
Female, n (%)	164 (81)	133 (82)	31(76)	0.35	129 (82)	35 (78)	0.56
Black Race, n (%)	104 (51)	76 (47)	28 (68)	0.01	76 (48)	28 (62)	0.05
Clinical characteristics							
Duration of disease, median (IQR), months	15 (1.1, 68)	17 (1.8, 70)	3.0 (0.1, 53)	0.08	5.7 (0.7, 58)	54 (11, 93)	<0.001
Comorbidities, n (%)							
Hypertension	76 (38)	55 (35)	21 (54)	0.03	48 (31)	28 (65)	<0.001
Diabetes	7 (3)	5 (3)	2 (5)	0.59	5 (3)	2 (4)	0.69
Sjögren's diagnosis, n (%)	11 (6)	10 (6)	1 (3)	0.35	9 (6)	2 (5)	0.84
Histologic characteristics							
<i>ISN/RPS^b Lupus nephritis class, n (%)</i>							
I/II	17 (8)	15 (9)	2 (5)		16 (10)	1 (2)	
III/IV	89 (44)	64 (40)	25 (61)	0.02	59 (37)	30 (67)	0.002
V	60 (30)	55 (34)	5 (12)		54 (34)	6 (13)	
Mixed III/IV + V	37 (18)	28 (17)	9 (22)		29 (18)	8 (18)	
Moderate-to-severe TII, n (%)	41 (20)	-	-	-	20 (13)	21 (47)	<0.01
Moderate-to-severe IF/TA, n (%)	45 (22)	24 (15)	21 (51)	<0.001	-	-	-
Laboratory parameters							
Serum creatinine, median (IQR), mg/dL	0.9 (0.7, 1.4)	0.8 (0.6, 1.1)	1.6 (1.0, 3.2)	<0.001	0.8 (0.6, 1.1)	1.0 (1.8, 3.1)	<0.001
eGFR ^c < 60 mL/min/1.73m ² , n(%)	58 (30)	34 (22)	24 (60)	<0.001	28 (19)	30 (70)	<0.001
Protein/Creatinine ratio (mg/mg), median (IQR)	2.0 (0.96, 4.90)	1.7 (0.9, 4.9)	2.6 (1.5, 4.9)	0.15	2.1 (0.95, 4.5)	2.0 (1.3, 5.5)	0.52
Low C3, n (%)	132 (72)	103 (71)	29 (76)	0.52	104 (72)	28 (72)	0.96
Low C4, n (%)	125 (69)	100 (70)	25 (68)	0.78	98 (69)	27 (71)	0.81

		Total sample (n=203) ^a	Tubulointerstitial inflammation (TII)		p-value	interstitial fibrosis and/or Tubular atrophy (IF/TA)		p-value
			TII None-or-Mild (n=162)	TII Moderate-to-Severe (n=41)		IF/TA None-or-mild (n=158)	IF/TA Moderate-to-Severe (n=45)	
Anti dsDNA, n (%)		115 (66)	92 (67)	23 (66)	0.92	90 (66)	25 (68)	0.87
Anti-Sm, n (%)		113 (64)	93 (65)	20 (61)	0.63	94 (67)	19 (54)	0.17
Anti-RNP, n (%)		113 (63)	91 (64)	22 (61)	0.8	94 (66)	19 (53)	0.15
Anti-Ro, n (%)		97 (51)	81 (54)	16 (40)	0.11	77 (52)	20 (49)	0.71
Anti-La, n (%)		36 (19)	27 (18)	9 (23)	0.53	22 (15)	14 (34)	0.005
Anti-Ro and anti-La, n (%)		33 (18)	24 (17)	9 (23)	0.43	20 (14)	13 (33)	0.008
ACLD IgG/IgM>40IU, n (%)		11 (6)	10 (7)	1 (3)	0.31	10 (7)	1 (2)	0.55
Lupus anticoagulant positive, n (%)		29 (17)	22 (16)	7 (19)	0.66	24 (18)	5 (14)	0.58
Anti-B2GP1 ^e >40IU, n (%)		6 (4)	4 (3)	2 (6)	0.4	5 (4)	1 (3)	0.80
Hemoglobin, mg/dl		10.6 (9.5, 11.5)	10.7 (9.7, 11.7)	10.2 (9.1, 10.8)	0.02	10.6 (9.5, 11.5)	10.3 (9.2, 11.6)	0.26
Medications								
Immunosuppression at the time of biopsy, n (%)					0.9			0.03
No		127 (66)	101 (66)	26 (67)		106 (70)	21 (51)	
Yes		66 (34)	53 (34)	13 (33)		46 (30)	20 (49)	
Ever on immunosuppression, n (%)		71 (37)	57 (37)	14 (36)	0.9	50 (33)	21 (51)	0.03
MMF ^f		35 (53)	25 (44)	10 (77)		22 (44)	13 (62)	
Hydroxychloroquine, n (%)		103 (53)	92 (60)	11 (28)	< 0.001	85 (56)	18 (44)	0.18
NSAIDS ^g , n (%)		20 (10)	18 (12)	2 (5)	0.23	18 (12)	2 (5)	0.19
Corticosteroid use, n (%)		139 (70)	113 (73)	23 (59)	0.08	104 (68)	32 (78)	0.23
Prednisone dose, median (IQR), mg		0 (10–40)	10 (0–40)	0 (0–40)	0.25	10 (0–40)	15 (0–40)	0.45
Prednisone dose, n (%)								
None		74 (38)	54 (35)	20 (51)		60 (40)	14 (34)	
10mg		31 (16)	27 (18)	4 (10)	0.29	25 (16)	6 (15)	0.88
10mg to <40mg		50 (26)	42 (27)	8 (21)		38 (25)	12 (29)	
40mg		38 (20)	31 (20)	7 (18)		29 (19)	9 (22)	
ACE ^h /inhibitors, n (%)		56 (29)	43 (28)	13 (33)	0.55	42 (27)	14 (33)	0.46

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

			Tubulointerstitial inflammation (TII)			interstitial fibrosis and/or Tubular atrophy (IF/TA)		
		Total sample (n=203) ^a	TII None-or-Mild (n=162)	TII Moderate-to-Severe (n=41)	p-value	IF/TA None-or-mild (n=158)	IF/TA Moderate-to-Severe (n=45)	p-value
ARB ⁱ , n (%)		17 (9)	12 (8)	5 (13)	0.34	12 (8)	5 (12)	0.41
ACE inhibitors or ARB, n (%)		73 (37)	55 (35)	18 (45)	0.27	54 (35)	19 (45)	0.24

^a Small variations in the percentages are due to small numbers of missing data for these variables

^b International Society of Nephrology/Renal Pathology Society

^c Estimated glomerular filtration rate

^d Anti cardiolipin

^e Anti beta-2-glycoprotein

^f Mycophenolate mofetil

^g Nonsteroidal anti-inflammatory drugs

^h Angiotensin converting enzyme inhibitors

ⁱ Aldosterone receptor blockers

Table 2

Multivariable logistic regression results

Factors associated with Tubulointerstitial Inflammation			
Variable	OR	95% CI	p value
Age at time of biopsy, per year	1.00	0.97, 1.03	0.99
Race, Black vs. other	3.22	1.27, 8.18	0.014
Duration of disease, per month	0.99	0.98, 1.00	0.024
Hypertension history	2.68	0.99, 7.03	0.055
eGFR ^a < 60 mL/min/1.73m ²	3.85	0.15, 10.0	0.005
LN ^b class (proliferative vs. other)	4.53	1.50, 13.74	0.007
Hydroxychloroquine use	0.27	0.10, 0.70	0.008
Factors associated with Interstitial Fibrosis and/or Tubular Atrophy			
Variable	OR	95% CI	p value
Age at time of biopsy, per year	1.06	1.02, 1.10	0.002
eGFR ^a < 60 mL/min/1.73m ²	4.55	1.61, 14.3	0.005
Immunosuppressive medications at biopsy	5.65	2.00, 16.3	0.001
LN ^b class, proliferative vs. other	11.32	2.68, 47.8	0.001
Positive anti-Ro and anti-La	2.45	0.79, 7.59	0.12
Tubulointerstitial inflammation	3.64	1.19, 11.1	0.02

^aEstimated glomerular filtration rate^bLupus nephritis