International Journal of Rheumatic Diseases

WILEY

International Journal of Rheumatic Diseases

ORIGINAL ARTICLE OPEN ACCESS

Coexisting Tubulointerstitial Inflammation and Damage Is a Risk Factor for Chronic Kidney Disease in Patients With Lupus Nephritis

Hyemin Jeong[1] | Sung-Eun Choi[1] | Ji-Hyoun Kang[1] | Ji Shin Lee[2] | Yoo-Duk Choi[2] | Dong-Jin Park[1] | Shin-Seok Lee[1]

[1]Division of Rheumatology, Department of Internal Medicine, Chonnam National University Medical School and Hospital, Gwangju, Republic of Korea | [2]Department of Pathology, Chonnam National University Medical School & Hospital, Gwangju, Republic of Korea

Correspondence: Dong-Jin Park (dongjin02@hanmail.net) | Shin-Seok Lee (shinseok@chonnam.ac.kr)

Received: 14 August 2024 | **Revised:** 4 November 2024 | **Accepted:** 25 November 2024

Funding: This study was supported by a grant (BCRI19034) from the Biomedical Research Institute of Chonnam National University Hospital.

Keywords: chronic kidney disease | lupus nephritis | outcome | tubulointerstitial nephritis

ABSTRACT

Objective: This study aims to determine whether the concurrent presence of tubulointerstitial inflammation (TII) and tubulointerstitial damage (TID) predicts the progression of chronic kidney disease (CKD) in patients with lupus nephritis (LN).

Methods: Data from 175 LN patients, collected at the time of renal biopsy, were analyzed. Patients were stratified into two groups based on the presence or absence of coexisting TII/TID. Uni- and multivariable Cox proportional hazard regression models were utilized to identify independent risk factors for CKD in LN patients.

Results: Of 175 patients, 110 (62.9%) exhibited coexisting TII/TID, whereas 65 (37.1%) did not. Patients with coexisting TII/TID tended to be older and presented with higher levels of ESR and 24-h proteinuria, as well as lower levels of eGFR and hemoglobin compared to those without coexisting TII/TID. Over a mean follow-up period of 89.9 months, CKD and end-stage renal disease occurred more frequently in patients with coexisting TII/TID. Notably, the presence of coexisting TII/TID was associated with a higher risk of CKD progression, with adjusted hazard ratios of 2.667 (95% CI: 1.333, 5.335, $p = 0.006$) for all LN patients, 3.265 (95% CI: 1.451, 7.345, $p = 0.004$) for those with class III, IV, and V LN, and 3.045 (95% CI: 1.289, 7.195, $p = 0.011$) for those with class III, IV, V LN, and eGFR $\geq 30\,mL/min/1.73\,m^2$.

Conclusions: LN patients with coexisting TII/TID are at a heightened risk of kidney function deterioration at LN onset and subsequent development of CKD over the long term.

1 | Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting multiple organs, including the joints, skin, cardiovascular system, kidneys, gastrointestinal tract, lungs, nervous system, hematologic system, and eyes. Renal involvement, occurring in up to 50% of SLE patients, is a significant manifestation of the disease [1]. Approximately 20%–40% of lupus nephritis (LN) patients develop chronic kidney disease (CKD), with 10%–20% progressing to end-stage renal disease (ESRD) [2]. CKD resulting from LN significantly increases morbidity and mortality in SLE patients, serving as a risk factor for cardiovascular diseases such as myocardial infarction, congestive heart failure, and stroke, further contributing to mortality [3].

Recognizing poor prognostic factors of LN is crucial for clinicians to initiate intensive immunosuppressive therapies when necessary. Factors such as race, pathology, proteinuria, mean

Hyemin Jeong and Sung-Eun Choi contributed equally to this study.

arterial pressure, and baseline serum creatinine are well-established prognostic indicators [4, 5]. Histopathological findings from kidney biopsies, especially those categorized by the 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification and assessed using activity and chronicity indexes, aid in predicting renal outcomes [6]. However, current classification systems primarily focus on glomerular lesions, potentially overlooking important tubulointerstitial changes.

Recent studies suggest that tubulointerstitial lesions may provide valuable prognostic insights into long-term renal outcomes in LN patients. Tubulointerstitial inflammation (TII) has emerged as a significant risk factor for the development of renal failure [7, 8], whereas moderate-to-severe tubulointerstitial damage (TID), but not TII, has been specifically linked to the progression to ESRD [9]. However, in other studies, neither TII nor TID alone was statistically associated with the development of CKD in patients with LN [10, 11]. These conflicting findings regarding the association between tubulointerstitial lesions and long-term LN outcomes may arise from the separate analysis of TII and TID, despite their frequent coexistence.

Considerable evidence indicates that TII may lead to chronic damage and subsequent CKD development, with TID and declining kidney function exacerbating inflammatory processes. This interaction creates a feedback loop of kidney injury and functional loss [12]. To address discrepancies in previous studies and explore the combined prognostic value of TII/TID, we aimed to investigate whether coexisting tubulointerstitial lesions predict CKD progression in LN patients.

2 | Methods

2.1 | Population and Study Design

We assessed 202 patients with available clinical data at the time of renal biopsy from the KORean lupus NETwork (KORNET) registry. KORNET is a nationwide, multi-institutional, hospital-based registry used to evaluate the clinical characteristics of SLE and the outcomes of Korean patients. Study enrollment was restricted to patients with LN who visited Chonnam National University Hospital within 6 months of diagnosis, because of data availability regarding long-term outcomes. All patients met the 1997 revised criteria for the classification of SLE [13]. Inclusion criteria required a minimum 1-year follow-up period, while patients were excluded if biopsy specimens were inadequate or biopsy findings were inconsistent with LN. Patients with uncertain medical records or follow-up periods of less than 12 months were also excluded. Ultimately, 175 patients were enrolled in this study (Figure 1). All patients were followed up at 1- to 3-month intervals, from the time of renal biopsy until at least 1 year later, via the KORNET database. We divided the enrolled patients into two groups: those with coexisting TII/TID and those without, and compared demographic, clinical, histological, and laboratory findings, as well as long-term prognosis. The development of the electronic case report form and data management for this study were conducted using the internet-based Clinical Research and Trial management system (iCReaT; http://icreat.nih.go.kr). This system is established by the Centers for Disease Control and Prevention, Ministry of Health and Welfare, Republic of Korea (iCReaT Study No. C140018). The Institutional Review Board of Chonnam National University Hospital approved this study (CNUN-2014-239), and informed consent was obtained from all participants before registry enrollment.

2.2 | Patient Data Collection

Baseline characteristics were examined at the time of renal biopsy, encompassing demographic data such as age at LN onset, gender, duration of SLE at LN onset, education level, smoking history, and the presence of hypertension and diabetes mellitus. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg on two or more occasions, and/or self-reported use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level ≥ 126 mg/dL or the use of insulin or hypoglycemic agents. The SLE Disease Activity Index (SLEDAI)-2000 was also calculated at the time of biopsy [14].

Laboratory data obtained included white blood cell count, lymphocyte count, hemoglobin level, platelet level, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum albumin level, serum creatinine level, urinalysis results, and urinary protein excretion (g/day) at the time of renal biopsy. The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) study equation: eGFR (mL/min/1.73 m^2) = 186 × (S_{Cr} [mg/dL])$^{-1154}$ × (age)$^{-0.203}$ × (0.742 if female). Serological markers, including anti-nuclear antibody, complement (C3, C4), and various autoantibodies (Smith, ribonucleoprotein, Ro/SS-A, La/

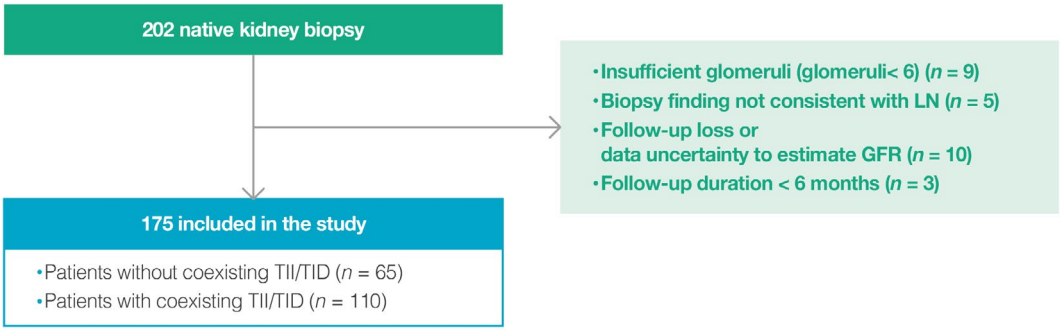

FIGURE 1 | Flow diagram for enrolled patients.

SS-B, nucleosome, histone, and ribosomal-P), were assessed by enzyme-linked immunosorbent assays (ELISA) using a commercial kit (Alegria; ORGENTEC Diagnostika, Mainz, Germany). Anti-dsDNA antibody was determined by radioimmunoassay using a commercial kit from Trinity Biotech PLC (Wicklow, Ireland). The presence of antiphospholipid antibody (aPL), including lupus anticoagulant (LAC), anti-cardiolipin (aCL), and anti-beta2-glycoprotein I (β_2GPI), was also determined. LAC was measured using the modified Russell's viper venom time test, with confirmation by mixing studies. IgG/M aCL and IgG/M anti-β_2GPI antibodies were analyzed by ELISA (Alegria; ORGENTEC Diagnostika, Mainz, Germany), and positivity was determined if the titer was medium to high. Patients were considered aPL-positive if they tested positive for at least one of these autoantibodies.

To gather pathological data, biopsy specimens were independently reclassified by two renal pathologists according to the ISN/RPS classification, regardless of any previous World Health Organization (WHO) or ISN/RPS classification [15]. Both renal pathologists were blinded to the patients' previous renal biopsy findings and clinical conditions. Mixed-type cases according to the ISN/RPS classification were assigned to a predominant class based on agreement between the two pathologists: III + V cases were assigned to type III, and IV + V cases were assigned to type IV. Tubulointerstitial indices were defined according to the NIH scoring system for activity and chronicity indices [16]. TII was defined as the presence of > 25% tubular and/or interstitial inflammation. Similarly, TID was defined as the presence of > 25% tubular atrophy and/or interstitial fibrosis noted on the renal biopsy report. In this study, patients with coexisting TII/TID refer specifically to those with both TII and TID.

2.3 | Treatments and Patient Outcome

Treatment was determined at the discretion of the attending rheumatologist and typically involved glucocorticoids combined with either high-dose intravenous cyclophosphamide (CYC; 500–1000 mg/m^2 body surface area monthly, for 6 cycles) or glucocorticoids with an oral immunosuppressant such as mycophenolate mofetil (MMF; up to 3 g/day), azathioprine (AZA), cyclosporine (CsA), or tacrolimus (TAC), followed by quarterly intravenous CYC or oral immunosuppressant. Glucocorticoids were administered at a dose of 30–60 mg prednisolone per day, with or without intravenous methylprednisolone pulse therapy (500–1000 mg/day for 3 days). Patients with LN types I and II received low-to-moderate doses of prednisone (0.5 mg/kg/day), alone or combined with oral immunosuppressants if renal response was inadequate. For induction therapy in patients with types III/IV ± V or type V LN, high-dose intravenous CYC or MMF was the preferred treatment. However, in cases where MMF and CYC were unavailable, patients were treated with AZA or CsA. Typically, induction treatment lasted for approximately 6 months, based on the clinical judgment of the treating rheumatologist.

Treatment responses after 12 months were assessed using the ACR 2006 clinical trial criteria [17]. A complete renal response (CR) was defined as an eGFR > 90 mL/min/1.73 m^2, a urine protein-to-creatinine ratio < 0.2, and inactive urinary sediment. A partial response (PR) was characterized by a stable eGFR, urinary protein-to-creatinine ratio ranging from 0.2 to 2.0, and absence of urinary sediment. No response (NR) indicated failure to meet remission criteria. Renal relapse was defined as > 25% decline in eGFR, ≥ 50% increase in proteinuria, or appearance of urinary sediment in patients previously achieving CR or PR. CKD was defined as eGFR < 60 mL/min/1.73 m^2 for ≥ 3 months. ESRD or renal failure was identified as either GFR < 15 mL/min/1.73 m^2 (typically accompanied by uremic symptoms) or the need for kidney replacement therapy such as dialysis or transplantation [18]. Additionally, besides renal response, occurrences of death from any cause were recorded during follow-up.

We also examined past and current medications utilized in induction and maintenance therapies, including hydroxychloroquine (HCQ), CYC, MMF, and other immunosuppressive agents. Additionally, the use of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARB) to mitigate proteinuria was reviewed. In Korea, belimumab has been covered by insurance since February 2021, anifrolumab is not currently planned for launch in Korea, and rituximab lacks an indication for lupus nephritis and is therefore used off-label. As a result, data on these therapies were not included in our analysis. Additionally, to maintain consistency in treatment regimens, we excluded patients participating in clinical trials involving these biologics.

2.4 | Statistical Analysis

We conducted statistical analysis using SPSS software version 20 (SPSS Inc., Chicago, IL, USA). Patients were categorized into two groups at the time of renal biopsy: those with and without coexisting TII/TID. Results are presented as means ± standard deviation for continuous variables and as percentages for categorical variables. Continuous variables were compared using Student's *t*-test, while categorical variables were compared using the Chi-squared test. Multivariable logistic regression analysis was performed to assess the association between coexisting TII/TID and clinical variables. Additionally, multivariable Cox proportional hazards regression analysis was conducted to identify predictors for developing CKD in patients with coexisting TII/TID. Variables with a significance level of $p < 0.05$ in Student's t-test or Chi-square test, based on a comparison between LN patients with and without CKD progression (see Table S1), were included in the multivariable analysis. The difference in the development of CKD over time between patients with coexisting TII/TID and those without TII/TID was examined using the log-rank test. Statistical significance was defined as *p*-values < 0.05.

3 | Results

3.1 | Baseline Characteristics

The baseline characteristics of the two groups at the time of renal biopsy are presented in Table 1. The cohort had a mean age of 33.5 ± 14.7 years, with 153 (87.4%) patients being

TABLE 1 | Baseline characteristics and laboratory findings of LN patients stratified by their TII/TID status at the time of renal biopsy.

	All patients ($N=175$)	Patients with coexisting TII/TID ($N=110$)	Patients without coexisting TII/TID ($N=65$)	p
Age at onset of LN, years	33.5 ± 14.7	35.9 ± 14.2	29.4 ± 13.4	0.003
Women (%)	153 (87.4)	96 (87.3)	57 (87.7)	0.936
SLE disease duration at onset of LN, months	32.4 ± 53.3	34.0 ± 57.8	29.8 ± 44.9	0.611
Education, years	12.5 ± 3.73	12.2 ± 4.10	13.1 ± 2.99	0.118
Current smoking (%)	9 (6.1)	7 (6.4)	2 (3.1)	0.283
Hypertension at onset of LN (%)	58 (33.1)	41 (37.3)	17 (26.2)	0.131
Diabetes mellitus at onset of LN (%)	8 (4.6)	6 (5.5)	2 (3.1)	0.374
SLEDAI-2000	13.1 ± 5.75	13.1 ± 5.56	13.2 ± 6.10	0.933
Laboratory findings				
White blood cells, /mm^3	5995.4 ± 3507.3	6205.4 ± 3468.9	5640.0 ± 3569.9	0.304
Lymphocytes, /mm^3	1069.5 ± 650.0	1219.1 ± 674.8	1085.7 ± 601.5	0.190
Hemoglobin, g/dL	10.4 ± 1.92	10.1 ± 1.90	10.9 ± 1.87	0.008
Platelet, $\times 10^3/\mu L$	202.2 ± 105.1	208.4 ± 109.7	191.9 ± 96.9	0.319
ESR, mm/h	45.5 ± 35.7	49.0 ± 39.7	38.1 ± 26.0	0.018
CRP, mg/dL	0.72 ± 1.10	0.75 ± 1.05	0.67 ± 1.19	0.643
Serum creatinine, mg/mL	0.96 ± 0.66	1.09 ± 0.78	0.72 ± 0.29	< 0.001
eGFR (MDRD), mL/min/1.72 m^2	95.7 ± 45.8	81.9 ± 38.9	118.9 ± 47.4	< 0.001
eGFR (MDRD) < 60 mL/min/1.72 m^2 (%)	34 (19.4)	30 (27.3)	4 (6.2)	< 0.001
Proteinuria, g/24 h	3.37 ± 3.11	3.79 ± 3.50	2.65 ± 2.17	0.009
Active urine sediment (%)	113 (64.6)	71 (64.5)	42 (64.6)	0.993
Complement levels, mg/dL				
C3	52.3 ± 27.7	54.7 ± 28.7	48.2 ± 25.4	0.127
C4	10.6 ± 10.7	10.9 ± 8.45	10.1 ± 13.8	0.635
Autoantibodies				
Anti-nuclear (%)	169 (96.6)	105 (95.5)	64 (98.5)	0.291
Anti-dsDNA, IU/mL	580.7 ± 1281.7	548.7 ± 1385.6	672.4 ± 1110.4	0.518

(Continues)

TABLE 1 | (Continued)

	All patients ($N=175$)	Patients with coexisting TII/TID ($N=110$)	Patients without coexisting TII/TID ($N=65$)	p
Anti-Sm (%)	66 (37.7)	35 (31.8)	31 (47.7)	0.036
Anti-RNP (%)	76/174 (43.7)	49/109 (45.0)	27/65 (41.5)	0.660
Anti-Ro/SS-A (%)	113 (64.3)	66 (60.0)	47 (72.3)	0.100
Anti-La/SS-B (%)	48 (27.4)	30 (27.3)	18 (27.7)	0.952
Anti-nucleosome (%)	124 /167 (74.3)	75/103 (72.8)	49/64 (76.6)	0.590
Anti-ribosomal-P (%)	58/167 (34.7)	29/104 (27.9)	29/63 (46.0)	0.017
Anti-Histone (%)	81/161 (50.3)	49/100 (49.0)	32/61 (52.5)	0.670
Anti-phospholipid (%)	54/162 (33.3)	37/100 (37.0)	17/62 (27.4)	0.209

Notes: Unless otherwise indicated, data are shown as mean ± standard deviation.
Abbreviations: CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; LN, lupus nephritis; MDRD, modification of diet in renal disease; SLEDAI, systemic lupus erythematosus disease activity index; TII, tubulointerstitial inflammation; TID, tubulointerstitial damage.

women. The mean duration of SLE at the onset of LN was 32.4 ± 53.3 months. Among the 175 patients identified in this study, 110 (62.9%) had LN with coexisting TII/TID, while 65 (37.1%) did not. Patients with coexisting TII/TID were older than those without ($p=0.003$). However, other characteristics such as disease duration, percentage of women, education status, proportion of current smoking, hypertension, diabetes mellitus, and disease activity measured by SLEDAI-2000 at the onset of LN did not show statistically significant differences between the groups (all $p>0.05$). In terms of laboratory findings, patients with coexisting TII/TID had lower hemoglobin levels than those without (10.1 ± 1.90 vs. 10.9 ± 1.87, $p=0.008$), higher ESR levels (49.0 ± 39.7 vs. 38.1 ± 26.0, $p=0.018$), higher 24-h proteinuria (3.79 ± 3.50 vs. 2.65 ± 2.17, $p=0.009$), and a higher proportion of eGFR (MDRD) < 60 mL/min/1.72m^2 (27.3% vs. 6.2%, $p<0.001$) compared to those without coexisting TII/TID. When comparing baseline autoimmune markers between the groups, patients with coexisting TII/TID had lower frequencies of anti-Sm (31.8% vs. 47.7%, $p=0.036$) and ribosomal-P antibodies (27.9% vs. 46.0%, $p=0.017$).

3.2 | Renal Pathologic Findings

Table 2 shows the renal pathologic features, encompassing the ISN/RPS classification and NIH activity/chronicity index. A significant difference was observed in the distribution of ISN/RPS classification between the two groups ($p=0.033$). Patients with coexisting TII/TID exhibited a higher prevalence of proliferative type LN compared to those without (77.3% vs. 63.1%, $p=0.043$). Moreover, the proportion of chronicity scores > 4 was greater among patients with coexisting TII/TID than those without (19.1% vs. 0%, $p<0.001$). The presence of interstitial inflammation (100% vs. 49.2%, $p<0.001$), tubular atrophy (85.5% vs. 10.8%, $p<0.001$), and interstitial fibrosis (93.6% vs. 10.8%, $p<0.001$) was significantly more frequent in patients with coexisting TII/TID compared to those without.

3.3 | Treatments for LN and Renal Outcome

Table 3 illustrates the current and previous treatments for LN and the renal outcomes. MMF was the most commonly prescribed immunosuppressive agent in both groups (43.6% in patients with coexisting TII/TID and 35.4% in those without). However, there was no significant difference in the immunosuppressive agents used for induction therapy between the two groups ($p=0.064$). Furthermore, at the time of LN diagnosis, 87 patients were taking HCQ and 32 patients were taking immunosuppressives, but these medications were not associated with the presence of coexisting TII/TID (both $p>0.05$). Additionally, the use of ACEi or ARB for the treatment of LN did not differ significantly between the two groups ($p>0.05$). During a mean follow-up of 89.9 months, the incidence of CKD (45.5% vs. 18.5%, $p<0.001$) and ESRD (14.5% vs. 3.1%, $p=0.012$) was more prevalent in patients with coexisting TII/TID compared to those without. However, the proportions of CR at 1 year after LN diagnosis, relapse during follow-up, and death due to any cause during follow-up did not differ significantly between the two groups (all $p>0.05$).

TABLE 2 | Comparison of renal pathologic findings of LN patients stratified by their TII/TID status.

	All patients ($N=175$)	Patients with coexisting TII/TID ($N=110$)	Patients without coexisting TII/TID ($N=65$)	p
ISN/RPS classification (%)				0.033
I	13 (7.4)	8 (7.3)	5 (2.9)	
II	17 (9.7)	10 (9.1)	7 (10.8)	
III	45 (25.7)	26 (23.6)	20 (30.8)	
IV	80 (45.7)	59 (53.6)	21 (32.7)	
V	19 (10.9)	7 (6.4)	12 (18.5)	
Proliferate type	126 (72.0)	85 (77.3)	41 (63.1)	0.043
Mix type	26 (14.9)	16 (14.5)	10 (15.4)	0.880
NIH activity/chronicity index (%)				
Activity score (>12)	73 (41.7)	51 (46.4)	22 (33.8)	0.105
Chronicity score (>4)	21 (12.0)	121 (19.1)	0 (0.0)	<0.001
Tubulointerstitial lesions				
Interstitial inflammation	142 (81.1)	110 (100)	32 (49.2)	<0.001
Tubular atrophy	101 (57.7)	94 (85.5)	7 (10.8)	<0.001
Interstitial fibrosis	110 (62.9)	103 (93.6)	7 (10.8)	<0.001

Abbreviations: ISN/RPS, International Society of Pathology/Renal Pathology Society; LN, lupus nephritis; NIH, National Institutes of Health; TID, tubulointerstitial damage; TII, tubulointerstitial inflammation.

3.4 | Predictors of Coexisting TII/TID in Patients With LN

Table 4 presents the results of multivariable logistic regression analysis conducted to identify predictors of coexisting TII/TID in patients with LN. This analysis employed a stepwise inclusion methodology utilizing variables such as age, gender, disease duration, and those significant at $p<0.05$ in univariable analysis (hemoglobin, ESR, eGFR $<60\,mL/min/1.73\,m^2$, urinary protein excretion g/24 h, anti-Sm antibody, anti-ribosomal P antibody, and proliferative type LN). Among these variables, age at LN onset (odds ratio [OR] = 1.035, 95% confidence interval [CI]: 1.007–1.064; $p=0.015$), ESR (OR = 1.016, 95% CI [1.004–1.028]; $p=0.011$), eGFR $<60\,mL/min/1.73\,m^2$ (OR = 3.851, 95% CI [1.191–12.453]; $p=0.024$), proliferative type LN (OR = 2.837, 95% CI [1.271–6.335]; $p=0.049$), and anti-ribosomal P antibody (OR = 0.448, 95% CI [0.217–0.925]; $p=0.030$) were found to be significantly associated with the presence of coexisting TII/TID in patients with LN.

3.5 | Predictors of Developing CKD in Patients With LN

Table 5 presents the results of multivariable Cox-proportional regression analysis aimed at identifying hazard ratios (HR) for developing CKD in patients with LN. In the unadjusted analysis, patients with coexisting TII/TID exhibited a substantially higher risk of CKD progression (HR 3.590, 95% CI [1.853–6.955], $p<0.001$). Furthermore, in the Cox proportional hazards model adjusted for age, gender, and disease duration at the time of renal biopsy, patients with coexisting TII/TID demonstrated an elevated risk of developing CKD (HR 2.706, 95% CI [1.384–5.290], $p=0.004$). In the multivariable Cox-proportional regression analysis, conducted using a stepwise inclusion methodology with age, gender, disease duration, and variables significant at $p<0.05$ in univariable analysis (including education, diabetes mellitus, hypertension, eGFR $<60\,mL/min/1.73\,m^2$, anti-phospholipid antibody, anti-ribosomal P antibody, chronicity >4, LN flare), the coexisting TII/TID group exhibited a higher risk of CKD progression (HR 2.667, 95% CI [1.333–5.335], $p=0.006$). To validate the robustness of our findings, additional analyses were conducted. Even after excluding patients with class I/II LN from the cohort, the coexisting TII/TID group remained at a higher risk of developing CKD (HR 3.265, 95% CI [1.451–7.345], $p=0.004$). Moreover, excluding patients with both class I/II LN and eGFR $<30\,mL/min/1.73\,m^2$, the risk of progression to CKD remained significant (HR 3.045, 95% CI [1.289–7.195], $p=0.011$). Finally, Kaplan–Meier survival curves indicate a significantly elevated incidence of CKD in LN patients with coexisting TII/TID compared to those without (Figure 2, Log-rank $p<0.001$).

4 | Discussion

In this study, LN patients with concurrent TII/TID exhibited reduced renal function at the time of kidney biopsy and were at an elevated risk of developing CKD during long-term follow-up. Importantly, even after excluding patients with class I/II LN and an eGFR $<30\,mL/min/1.73\,m^2$ from the cohort, the presence of coexisting TII/TID remained a significant predictor of CKD development. These findings underscore the crucial role of coexisting TII/TID in renal biopsies for predicting renal outcomes.

TABLE 3 | Comparison of treatments and outcomes of LN patients stratified by their TII/TID status.

	All patients ($N=175$)	Patients with coexisting TII/TID ($N=110$)	Patients without coexisting TII/TID ($N=65$)	p
Treatment (%)[a]				
Induction therapy				0.064
CYC	62 (35.4)	42 (38.2)	20 (30.8)	
MMF	71 (40.6)	48 (43.6)	23 (35.4)	
Others	42 (24.0)	20 (18.2)	22 (33.8)	
HCQ at LN diagnosis	87 (49.7)	51 (46.4)	36 (55.4)	0.249
Immunosuppressants[b]	32 (18.4)	22 (20.0)	10 (15.4)	0.445
ACEi or ARB	126 (72.0)	82 (74.5)	44 (67.7)	0.329
Outcomes (%)				
CR at 1 year	101 (57.7)	66 (60.0)	35 (53.8)	0.426
Relapse	71 (40.6)	43 (39.1)	28 (43.1)	0.604
CKD	62 (35.4)	50 (45.5)	12 (18.5)	<0.001
ESRD	18 (10.3)	16 (14.5)	2 (3.1)	0.012
Death due to any cause	5 (2.9)	5 (4.5)	0 (0.0)	0.095

Abbreviations: ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; CR, complete remission; CYC, cyclophosphamide; ESRD, end-stage renal disease; HCQ, hydroxychloroquine; LN, lupus nephritis; MMF, mycophenolate mofetil; TII, tubulointerstitial inflammation; TID, tubulointerstitial damage.
[a]When a specific medication has been used in the preceding 6 months, it is defined as having been used.
[b]Immunosuppressants used at the time of renal biopsy, not as a part of induction therapy.

TABLE 4 | Multivariable logistic regression analyses to identify predictors of coexisting TII/TID in LN patients.

	Multivariable analysis	
Variables	**OR (95% CI)**	p
Age at LN onset	1.035 (1.007–1.064)	0.015
ESR	1.016 (1.004–1.028)	0.011
eGFR $<60\,mL/min/1.73\,m^2$	3.851 (1.191–12.453)	0.024
Proliferative type LN (Class III or IV)	2.837 (1.271–6.335)	0.049
Anti-ribosomal P antibody	0.448 (0.217–0.925)	0.030

Abbreviations: ESR, erythrocyte sedimentation rate; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; OR, odds ratio; TID, tubulointerstitial damage; TII, tubulointerstitial inflammation.

While current LN classification systems prioritize glomerular lesions, such as inflammation and scarring, studies indicate that these glomerular measures often fail to accurately predict the subsequent clinical course of LN [11, 19]. Instead, emerging evidence suggests that tubulointerstitial lesions are more closely correlated with diminished renal function and the risk of CKD in LN patients. Park et al. demonstrated that the severity of TII serves as a prognostic indicator for the progressive deterioration of renal function [20]. Similarly, Hill et al. identified TII as one of the critical histologic factors associated with renal outcomes [21], and in another study, they established that the tubulointerstitial activity index was predictive of kidney function decline in LN patients [22]. Furthermore, Esdaile et al. emphasized that tubulointerstitial disease serves as a significant prognostic marker for progression to renal failure [23], while Kwon et al. underscored the importance of TID as a predictive factor for renal prognosis in LN patients [24]. However, conflicting findings exist in the literature, as demonstrated by O'Dell et al., who found that the presence of tubulointerstitial activity or interstitial sclerosis did not provide additional predictive value beyond clinical data or glomerular biopsy results [25]. Similarly, in cohort studies, both TII and TID were not statistically associated with the development of CKD in LN patients [10, 11]. Additionally, a retrospective study showed that none of the individual tubulointerstitial factors reached statistical significance in predicting ESRD in pediatric LN patients [26]. Notably, a recent study identified the extent of TII as an independent predictor of renal survival, whereas TID did not exhibit predictive value [27]. In

current studies exploring the prognostic roles of TII and TID in LN patients, these two factors have typically been analyzed separately, potentially contributing to inconsistencies in the results obtained. Tubulointerstitial injury initiates as an inflammatory process that, if unchecked, can progress to irreversible tubulointerstitial fibrosis and atrophy. Therefore, both TII and TID should be comprehensively considered to assess their association with renal outcomes. From this perspective, our study is significant as it examines the renal outcomes of patients with coexisting TII/TID.

TABLE 5 | Multivariable Cox-proportional regression analysis to identify hazard ratios for developing CKD in LN patients with coexisting TII/TID.

	Multivariable analysis	
Variables	**HR (95% CI)**	***p***
Unadjusted	3.590 (1.853–6.955)	< 0.001
Age, gender, disease duration adjusted	2.706 (1.384–5.290)	0.004
Full adjustment[a]	2.667 (1.333–5.335)	0.006
Full adjustment excluding class I/II LN	3.265 (1.451–7.345)	0.004
Full adjustment excluding class I/II LN and eGFR < 30 mL/min/1.73 m^2	3.045 (1.289–7.195)	0.011

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; LN, lupus nephritis; TII, tubulointerstitial inflammation; TID, tubulointerstitial damage; HR, hazard ratio.
[a]Adjustments was made for age, gender, disease duration, and variables significant at $p < 0.05$ in univariable analysis (including education, diabetes mellitus, hypertension, eGFR < 60 mL/min/1.73 m^2, anti-phospholipid antibody, anti-ribosomal P antibody, chronicity > 4, LN flare).

In the present study, even after excluding LN patients with decreased kidney function at the time of diagnosis, the presence of TII/TID remained a significant predictor of developing CKD. As mentioned earlier, tubulointerstitial injury leads to the accumulation of inflammatory cells in the interstitium, exacerbating hypoxia and causing further renal damage [12, 28]. Additionally, tubular damage reduces functional nephrons, exposing the remaining nephrons to increased metabolic demand and making them more susceptible to disease. Tubular atrophy also contributes to a reduction in GFR and worsens glomerulosclerosis. Consequently, these events create a cycle of injury, cellular activation, and misguided repair, ultimately driving progression to CKD [12, 28]. Therefore, the link between coexisting TII/TID and CKD progression in LN may stem from this feed-forward loop of kidney injury and gradual loss of kidney function. Given its significance in early identification of individuals at risk of renal dysfunction, including CKD or ESRD, histologic classification considering tubulointerstitial lesions holds promise for predicting renal outcomes in LN.

In our study, we observed that LN patients with coexisting TII/TID were more likely to exhibit severe renal disease activity and a higher proportion of proliferative type LN compared to those without such coexisting lesions. Specifically, in our analysis, elevated ESR, eGFR < 60 mL/min/1.73 m^2, proliferative type LN, and higher levels of 24-h proteinuria were associated with the presence of coexisting TII/TID. This finding aligns with a prior study indicating that LN patients with coexisting tubulointerstitial lesions tended to have a higher prevalence of proliferative type LN compared to those without tubulointerstitial lesions. O'Dell et al. noted an intimate correlation between TII and diffuse proliferative glomerulonephritis, accompanied by elevated serum creatinine levels at the time of renal biopsy and an increased prevalence of proteinuria both at the initial biopsy and during follow-up [25]. Similarly, ter Borg et al. suggested that severe tubular dysfunction frequently manifests in active proliferative LN [29].

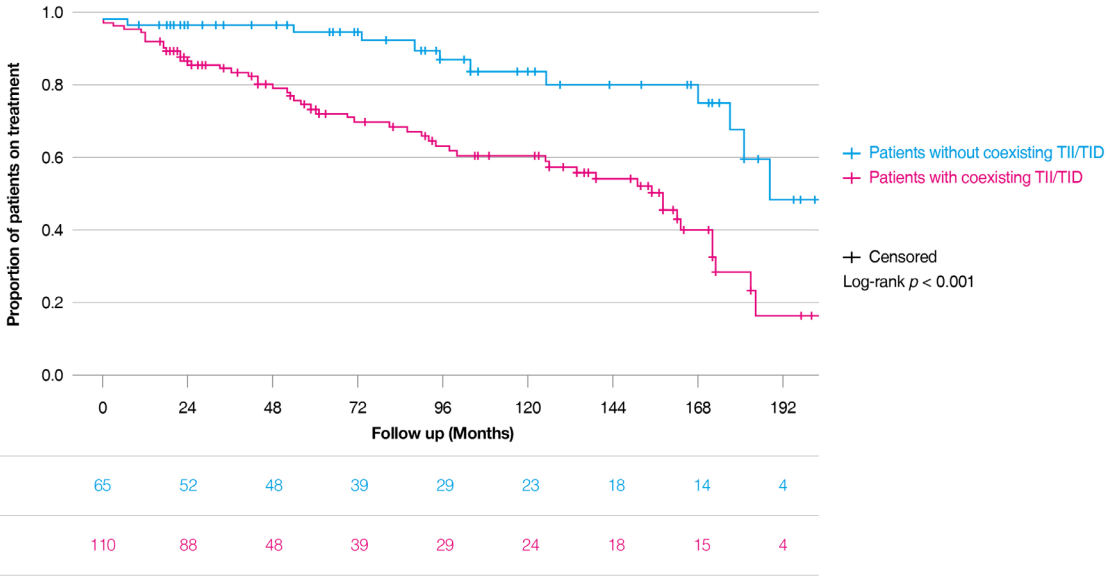

FIGURE 2 | Kaplan–Meier survival curve was used to assess the disparity in chronic kidney disease development between LN patients with coexisting TII/TID and those without. LN, lupus nephritis; TII, tubulointerstitial inflammation; TID, tubulointerstitial damage.

Our study has several limitations. First, because of its conduct within routine clinical practice, the treatment of LN could not be standardized. Second, as we included only patients with a minimum follow-up period of 1-year, non-responders to immunosuppressive drugs were disproportionately excluded compared to responders. Third, patients in the coexisting TII/TID group exhibited lower eGFR at baseline compared to those without TII/TID, potentially influencing disparate renal outcomes, although adjustments were made. Fourth, we were unable to analyze data from the perspective of follow-up renal biopsies. Given the potential reversibility of chronicity, a prospective study incorporating follow-up renal biopsies could offer more accurate insights into predicting renal response to immunosuppressive treatments in LN patients. Fifth, because of the sample size, we could not fully evaluate the clinical impact of TII/TID extent on renal outcomes in LN. While not shown in a table, we conducted a subgroup analysis categorizing patients into three groups: those with TII/TID $\geq 50\%$, those with TII/TID $\geq 25\%$ but TII $< 50\%$ or TID $< 50\%$, and those without coexisting TII/TID. This analysis suggested a higher HR in the TII/TID $\geq 50\%$ group compared to the TII/TID $\geq 25\%$, but TII $< 50\%$ or TID $< 50\%$ group, though the difference was not statistically significant. This limitation, likely due to the small sample size ($n = 5$) in the TII/TID $\geq 50\%$ group, highlights the need for larger studies to validate our findings and understand the impact of higher TII/TID levels on renal outcomes. Sixth, although not shown in a table, we found that TII alone was not a significant risk factor for CKD progression, whereas TID alone (with mild or no TII) was associated with increased CKD risk. While the difference in HR between TID alone and coexisting TII/TID was modest, the slightly higher HR with coexisting TII/TID suggests potential added prognostic value of having both present. It is also notable that TID was prevalent among most patients in our cohort, aligning with findings from studies such as Feng Yu et al. [30] The high prevalence of TID may limit its role as a differentiator. Our study therefore focused on assessing whether coexisting TII and TID offered additional prognostic insights beyond TID alone. The frequent presence of TID may partly result from delayed LN diagnosis, leading to more advanced tubulointerstitial damage at biopsy and complicating the assessment of TID's independent prognostic significance. Finally, our study was conducted within a single, homogeneous population, necessitating further investigation in heterogeneous populations to validate our findings.

5 | Conclusion

In conclusion, our study results suggest that LN patients with coexisting TII/TID face an elevated risk of CKD progression. Hence, recognizing poor prognostic biopsy results and implementing intensive treatment strategies for these patients is crucial.

Author Contributions

Guarantor: Shin-Seok Lee. Conceptualization: Hyemin Jeong, Dong-Jin Park, Shin-Seok Lee. Methodology: Ji Shin Lee, Yoo-Duk Choi. Formal analysis: Hyemin Jeong, Sung-Eun Choi, Ji-Hyoun Kang, Ji Shin Lee, Yoo-Duk Choi, Dong-Jin Park, Shin-Seok Lee. Investigation: Hyemin Jeong, Sung-Eun Choi, Ji-Hyoun Kang, Ji Shin Lee, Yoo-Duk Choi, Dong-Jin Park, Shin-Seok Lee. Writing – original draft: Hyemin Jeong. Writing – review and editing: Dong-Jin Park, Shin-Seok Lee. Project administration: Hyemin Jeong, Dong-Jin Park, Shin-Seok Lee. Funding acquisition: Dong-Jin Park, Shin-Seok Lee. All authors have read and agreed to the published version of the manuscript.

Acknowledgments

We thank the patients and their families for their participation.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data presented in this study are available from the corresponding author upon reasonable request.

References

1. C. C. Mok, D. Y. Yap, S. V. Navarra, et al., "Overview of Lupus Nephritis Management Guidelines and Perspective From Asia," *International Journal of Rheumatic Diseases* 16, no. 6 (2013): 625–636.

2. M. G. Tektonidou, A. Dasgupta, and M. M. Ward, "Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971–2015: A Systematic Review and Bayesian Meta-Analysis," *Arthritis & Rhematology* 68, no. 6 (2016): 1432–1441.

3. M. L. Hermansen, J. Lindhardsen, C. Torp-Pedersen, M. Faurschou, and S. Jacobsen, "The Risk of Cardiovascular Morbidity and Cardiovascular Mortality in Systemic Lupus Erythematosus and Lupus Nephritis: A Danish Nationwide Population-Based Cohort Study," *Rheumatology (Oxford, England)* 56, no. 5 (2017): 709–715.

4. O. E. Ayodele, I. G. Okpechi, and C. R. Swanepoel, "Predictors of Poor Renal Outcome in Patients With Biopsy-Proven Lupus Nephritis," *Nephrology (Carlton, Vic.)* 15, no. 4 (2010): 482–490.

5. G. Contreras, V. Pardo, C. Cely, et al., "Factors Associated With Poor Outcomes in Patients With Lupus Nephritis," *Lupus* 14, no. 11 (2005): 890–895.

6. K. E. Sada and H. Makino, "Usefulness of ISN/RPS Classification of Lupus Nephritis," *Journal of Korean Medical Science* 24, no. Suppl (2009): S7–S10.

7. A. O. Alsuwaida, "Interstitial Inflammation and Long-Term Renal Outcomes in Lupus Nephritis," *Lupus* 22, no. 14 (2013): 1446–1454.

8. C. Hsieh, A. Chang, D. Brandt, R. Guttikonda, T. O. Utset, and M. R. Clark, "Predicting Outcomes of Lupus Nephritis With Tubulointerstitial Inflammation and Scarring," *Arthritis Care & Research (Hoboken)* 63, no. 6 (2011): 865–874.

9. A. Broder, W. B. Mowrey, H. N. Khan, 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* 47, no. 4 (2018): 545–551.

10. S. J. Moon, S. K. Kwok, J. H. Ju, et al., "Predictors of Chronic Kidney Disease in Korean Patients With Lupus Nephritis," *Journal of Rheumatology* 38, no. 12 (2011): 2588–2597.

11. D. J. Park, J. H. Kang, J. W. Lee, et al., "Risk Factors to Predict the Development of Chronic Kidney Disease in Patients With Lupus Nephritis," *Lupus* 26, no. 11 (2017): 1139–1148.

12. M. R. Clark, K. Trotter, and A. Chang, "The Pathogenesis and Therapeutic Implications of Tubulointerstitial Inflammation in Human Lupus Nephritis," *Seminars in Nephrology* 35, no. 5 (2015): 455–464.

13. M. C. Hochberg, "Updating the American College of Rheumatology Revised Criteria for the Classification of Systemic Lupus Erythematosus," *Arthritis and Rheumatism* 40, no. 9 (1997): 1725.

14. D. D. Gladman, D. Ibanez, and M. B. Urowitz, "Systemic Lupus Erythematosus Disease Activity Index 2000," *Journal of Rheumatology* 29, no. 2 (2002): 288–291.

15. J. J. Weening, V. D. D'Agati, M. M. Schwartz, et al., "The Classification of Glomerulonephritis in Systemic Lupus Erythematosus Revisited," *Kidney International* 65, no. 2 (2004): 521–530.

16. H. A. Austin, 3rd, L. R. Muenz, K. M. Joyce, et al., "Prognostic Factors in Lupus Nephritis. Contribution of Renal Histologic Data," *American Journal of Medicine* 75, no. 3 (1983): 382–391.

17. Renal Disease Subcommittee of the American College of Rheumatology Ad Hoc Committee on Systemic Lupus Erythematosus Response C, "The American College of Rheumatology Response Criteria for Proliferative and Membranous Renal Disease in Systemic Lupus Erythematosus Clinical Trials," *Arthritis and Rheumatism* 54, no. 2 (2006): 421–432.

18. A. S. Levey, J. Coresh, E. Balk, et al., "National Kidney Foundation Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification," *Annals of Internal Medicine* 139, no. 2 (2003): 137–147.

19. O. C. Kwon, Y. Park, J. S. Lee, et al., "Non-albumin Proteinuria as a Parameter of Tubulointerstitial Inflammation in Lupus Nephritis," *Clinical Rheumatology* 38, no. 1 (2019): 235–241.

20. M. H. Park, V. D'Agati, G. B. Appel, and C. L. Pirani, "Tubulointerstitial Disease in Lupus Nephritis: Relationship to Immune Deposits, Interstitial Inflammation, Glomerular Changes, Renal Function, and Prognosis," *Nephron* 44, no. 4 (1986): 309–319.

21. G. S. Hill, M. Delahousse, D. Nochy, et al., "A New Morphologic Index for the Evaluation of Renal Biopsies in Lupus Nephritis," *Kidney International* 58, no. 3 (2000): 1160–1173.

22. G. S. Hill, M. Delahousse, D. Nochy, et al., "Predictive Power of the Second Renal Biopsy in Lupus Nephritis: Significance of Macrophages," *Kidney International* 59, no. 1 (2001): 304–316.

23. J. M. Esdaile, C. Levinton, W. Federgreen, J. P. Hayslett, and M. Kashgarian, "The Clinical and Renal Biopsy Predictors of Long-Term Outcome in Lupus Nephritis: A Study of 87 Patients and Review of the Literature," *Quarterly Journal of Medicine* 72, no. 269 (1989): 779–833.

24. O. C. Kwon, Y. M. Cho, J. S. Oh, et al., "Factors Associated With Aggravation of Tubulointerstitial Damage on Repeated Biopsies in Lupus Nephritis Patients With Treatment Failure," *Clinical and Experimental Rheumatology* 38, no. 2 (2020): 239–244.

25. J. R. O'Dell, R. C. Hays, S. J. Guggenheim, and J. C. Steigerwald, "Tubulointerstitial Renal Disease in Systemic Lupus Erythematosus," *Archives of Internal Medicine* 145, no. 11 (1985): 1996–1999.

26. C. Y. Wu, H. P. Chien, H. Y. Yang, et al., "Role of Tubulointerstitial Lesions in Predicting Renal Outcome Among Pediatric Onset Lupus Nephritis - A Retrospective Cohort Study," *Journal of Microbiology, Immunology, and Infection* 53, no. 1 (2020): 33–41.

27. M. F. Gomes, C. Mardones, M. Xipell, et al., "The Extent of Tubulointerstitial Inflammation Is an Independent Predictor of Renal Survival in Lupus Nephritis," *Journal of Nephrology* 34, no. 6 (2021): 1897–1905.

28. K. S. Hodgkins and H. W. Schnaper, "Tubulointerstitial Injury and the Progression of Chronic Kidney Disease," *Pediatric Nephrology* 27, no. 6 (2012): 901–909.

29. E. J. ter Borg, P. E. de Jong, S. S. Meijer, and C. G. Kallenberg, "Tubular Dysfunction in Proliferative Lupus Nephritis," *American Journal of Nephrology* 11, no. 1 (1991): 16–22.

30. F. Yu, L. H. Wu, Y. Tan, et al., "Tubulointerstitial Lesions of Patients With Lupus Nephritis Classified by the 2003 International Society of Nephrology and Renal Pathology Society System," *Kidney International* 77, no. 9 (2010): 820–829.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.