Tianjin Daxue Xuebao (Ziran Kexue yu Gongcheng Jishu Ban)/
Journal of Tianjin University Science and Technology
ISSN (Online):0493-2137
E-Publication: Online Open Access
Vol: 58 Issue: 09:2025
DOI: 10.5281/zenodo.17255173

LUPUS NEPHRITIS AND HISTOLOGY RESULTS AS PREDICTORS OF KIDNEY OUTCOMES: A SYSTEMATIC REVIEW

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Abstract

Background: In lupus nephritis (LN), glomerular class alone incompletely predicts renal outcomes. Contemporary frameworks emphasize semiquantitative activity/chronicity indices and tubulointerstitial (TI) lesions as stronger prognosticators. Objective: To synthesize original evidence on histologic predictors of kidney outcomes in LN and contextualize findings with recent guidelines and methodology updates. Methods: Following PRISMA principles, we screened the user-supplied corpus of original LN studies and performed a narrative synthesis focused on biopsy-based predictors (modified NIH activity/chronicity indices, TI inflammation/fibrosis, repeat biopsy) and clinically actionable targets (proteinuria thresholds). Results: Across cohorts, a higher modified NIH chronicity index independently predicted eGFR decline or composite renal endpoints (per-point HR =1.3). Severe TI inflammation conferred substantially higher risks of CKD/ESRD versus mild TI change, while glomerular activity alone correlated poorly with long-term failure. Repeat-biopsy cohorts showed frequent histologic non-response despite apparent clinical response, and a higher chronicity burden on follow-up biopsy tracked with worse long-term function. In membranous LN, achieving complete remission or reducing proteinuria to <1 g/g by 1 year was associated with markedly lower risk of doubling of serum creatinine. Conclusions: Histology-derived chronicity and TI metrics consistently outperform glomerular class for prognostication; structured use of repeat biopsy and proteinuria targets can refine risk and guide therapy.

Keywords: Lupus Nephritis; Renal Biopsy; Modified NIH Chronicity Index; Tubulointerstitial Inflammation; Repeat Biopsy; Proteinuria Targets.

INTRODUCTION

Renal involvement affects a large fraction of people living with systemic lupus erythematosus and remains a major driver of morbidity, CKD, and ESRD [1].

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Contemporary practice places kidney biopsy at the center of evaluation because clinical presentation often fails to mirror the underlying pathology, and treatment choices hinge on specific histologic patterns and the extent of activity and chronic damage [2,3]. The 2018 update to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification clarified lesion definitions, removed class IV sub-subclasses, and, importantly, advocated semiquantitative scoring of activity and chronicity (modified NIH indices) across classes to better capture prognostic information beyond glomerular class alone [3].

Subsequent validation work has reinforced that chronicity components, global/segmental glomerulosclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy, are closely linked to long-term renal outcome, while activity items track current inflammation and therapeutic need [4]. Clinically, LN phenotypes and outcomes have evolved over decades with earlier detection, yet the proportion progressing to ESRD remains non-trivial, underscoring the need for risk tools that reflect whole-kidney pathology, not only glomerular class [1].

Guidelines now emphasize a composite approach: biopsy-confirmed diagnosis; immunosuppression tailored to activity; and longitudinal targets including proteinuria reduction and kidney function preservation [2,11]. They also acknowledge the role of repeat biopsy in selected scenarios, refractory disease, suspected histologic discordance, or decisions about de-escalation, because clinical remission does not always equal histologic remission [7,12]. Indeed, repeat-biopsy and cohort studies show that TI inflammation and the accrual of chronic damage predict outcomes more robustly than class labels or glomerular activity scores alone [5–9,13,14].

Against this backdrop, we synthesized original studies evaluating histology-based predictors, particularly the modified NIH indices and TI lesions, and contextualized them with methodological and guideline advances to inform practical targets (proteinuria thresholds) and the potential role of repeat biopsy for risk-stratified care in LN.

METHODS

Protocol and eligibility. We prespecified inclusion of the user-supplied original LN studies that reported renal outcomes in relation to biopsy-based predictors (modified NIH activity/chronicity indices, TI inflammation/fibrosis, repeat-biopsy histology, proteinuria targets) in adult or pediatric LN [5–10,13,14]. Observational cohorts and randomized/controlled studies with extractable prognostic associations were eligible. Reviews, editorials, and guidelines were reserved for background and discussion [1–4,11,12].

Information sources and selection. All screening was performed within the provided corpus. Two stages were applied: (i) title/abstract screening for relevance to histology-outcome associations; (ii) full-text appraisal for prespecified outcomes (eGFR decline, doubling of serum creatinine, CKD/ESRD, or validated composite endpoints) and histologic exposures (modified NIH indices, TI lesions, or repeat-biopsy findings). Studies

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focused primarily on diagnostic class prediction without outcome linkage were summarized qualitatively [3,4].

Outcomes and data items. Primary outcomes were ESRD/CKD progression or validated surrogates (≥30% eGFR decline). Secondary outcomes included doubling of serum creatinine and remission status vs. long-term outcomes. Exposure variables included baseline (and when available, repeat-biopsy) activity/chronicity indices and TI inflammation/fibrosis scores. We captured adjusted effect estimates (hazard/odds ratios) when reported [5–10,13,14].

Synthesis and bias assessment. Given heterogeneity in designs, populations, histology scoring, and endpoints, we performed a narrative synthesis, highlighting adjusted associations when available and separating adult from pediatric findings where appropriate. We considered risk of bias domains relevant to prognostic cohorts (selection, measurement, confounding, missing data, and reporting). Where cohorts overlapped in theme (TI inflammation; repeat biopsy), we reported convergent findings rather than pooling [5–10,13,14].

RESULTS

Study selection and characteristics from the user-supplied original studies, we identified cohorts addressing: (i) prognostic value of tubulointerstitial inflammation (TI) and chronicity; (ii) the association of modified NIH chronicity index with renal decline; (iii) the role of repeat biopsy in revealing histologic non-response and predicting long-term outcomes; (iv) pediatric LN tubulointerstitial lesions; and (v) proteinuria targets and outcomes in membranous LN (MLN). These encompassed adult and pediatric populations with follow-up ranging from mid-term (=4–6 years) to a decade or longer, and most used multivariable models to adjust for baseline renal function and serologic activity [5–10,13,14].

Tubulointerstitial inflammation and scarring predict outcome In a University of Chicago cohort (n=68) with standardized immunohistochemical quantification of interstitial leukocytes, moderate/severe TI inflammation was common and correlated with higher serum creatinine at biopsy but not necessarily with glomerular activity scores. Crucially, TI severity, but not glomerular injury scores, identified patients at greatest risk for progression to ESRD on survival analysis [5]. When the NIH chronicity index was partitioned, only the tubulointerstitial chronicity subscore (fibrosis/tubular atrophy) predicted renal failure (HR =2.2 per unit), whereas the glomerular chronicity subscore did not add prognostic information in the same model [5].

These findings are echoed in subsequent cohorts using the modified 2018 ISN/RPS reporting framework. In a Japanese multi-year cohort re-scored with the modified NIH indices, each 1-point increase in chronicity index was independently associated with worse renal survival (HR =1.3), whereas activity indices and class subdivisions showed weaker or no independent associations after adjustment [6]. Each chronicity component,

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glomerulosclerosis, fibrous crescents, interstitial fibrosis, and tubular atrophy, retained prognostic value in alternate models [6].

A Korean cohort explicitly grading interstitial inflammation (0–3) similarly found that severe interstitial inflammation (grades 2–3) conferred a markedly higher risk of ESRD and CKD compared with mild inflammation, independent of baseline demographics and disease activity; concomitantly, higher expression of anti-apoptotic BCL-2 within intrarenal lymphocyte aggregates paralleled severe TI inflammation, suggesting a pathobiological substrate for persistence [8].

Chronicity outperforms activity for long-term prognosis Longitudinal analyses centered on modified NIH indices have consistently shown that chronicity, rather than activity, tracks with long-term kidney function loss. In a long-followed Italian cohort (n=200; median follow-up =14 years), the chronicity index and its components, but not the activity index, were significantly associated with kidney function impairment. Key predictors included baseline serum creatinine, hypertension, glomerulosclerosis, fibrous crescents, and measures of tubular atrophy/interstitial fibrosis; older age and delays from LN onset to biopsy correlated with higher baseline chronicity, reinforcing the value of timely biopsy [13]. These observations align with the Japanese study's emphasis on the modified chronicity index as a superior prognostic measure to 2003 class subdivisions or activity scoring in adjusted models [6].

Repeat biopsy reveals histologic non-response and informs outcome A prospective program incorporating repeat biopsies after induction therapy, regardless of clinical response, demonstrated frequent histologic non-response (persistent proliferative activity) even among patients labeled clinically complete or partial responders. Nearly half of apparent clinical responders still harbored active lesions on repeat biopsy, and higher chronicity at repeat biopsy associated with poorer long-term renal outcomes over =10 years, underscoring the potential added value of protocol or targeted repeat biopsy to refine risk and tailor therapy duration [7,12].

Pediatric LN: tubulointerstitial lesions matter Pediatric-onset LN carries substantial lifetime risk. In a Taiwanese pediatric cohort (n=67; mean follow-up =6.5 years), tubulointerstitial abnormalities were present in roughly one-third overall and nearly half of proliferative LN cases. Tubulointerstitial lesions in proliferative LN significantly impacted renal survival, while chronic TI changes within the chronicity index, more than the composite tubulointerstitial activity index, provided prognostic information, again emphasizing the importance of chronic scarring processes in long-term outcome [9]. Proteinuria targets and outcomes in membranous LN For MLN, a large U.S. military health system cohort of biopsy-confirmed pure MLN (n=105; mean follow-up =9 years) found that patients achieving complete remission or reducing proteinuria to <1 g/g (or <0.5 g/g) by =1 year experienced markedly lower risk of doubling of serum creatinine. Conversely, those failing to meet these early proteinuria targets were more likely to progress, transition to proliferative LN, or develop ESRD, while specific immunosuppressive regimens were not independently associated with improved outcomes after adjustment, possibly reflecting confounding by indication [10].

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Table 1: Overview of included original studies

Study	Design & n	Population	Exposure(s)	Outcome(s)	Key adjusted findings
Hsieh et al., 2011 [5]	Retrospective cohort, n=68	Adult LN	TI inflammation (IHC & light microscopy); NIH indices	ESRD	TI severity predicted ESRD; tubulointerstitial chronicity, not glomerular, drove risk
Umeda et al., 2020 [6]	Retrospective cohort, n=170	Adult LN	Modified NIH indices (2018)	≥30% eGFR decline	Chronicity index HR=1.3 per point; class/activity less predictive
Zickert et al., 2014 [7]	Prospective repeat-biopsy, n=67	Adult LN	Post-induction histology	=10-yr renal outcome	Many clinical responders had active lesions; higher repeat-biopsy chronicity predicted worse outcome
Lee et al., 2022 [8]	Retrospective cohort, n=92	Adult LN	Interstitial inflammation grade; mNIH indices	ESRD, CKD	Severe interstitial inflammation ↑ risk (Cox HRs =3–5)
Wu et al., 2020 [9]	Retrospective cohort, n=67	Pediatric LN	TI lesions; NIH & TI activity	ESRD/renal survival	TI lesions in proliferative LN worsened survival; chronic TI changes prognostic
Membranous LN cohort, 2025 [10]	Cohort, n=105	Pure MLN	Remission & 1-yr proteinuria	Doubling serum creatinine, ESRD	CR or <1 g/g by =1 yr → markedly lower risk

Table 2: Prognostic signals emphasized across cohorts

Predictor	Direction of association with adverse renal outcome
Higher modified NIH chronicity index [6,13]	Consistently ↑ risk; per-point HR =1.3
Tubulointerstitial chronicity (fibrosis/tubular atrophy) [5,6,13]	Independent predictor; outperforms glomerular chronicity
Severe interstitial inflammation [8]	Strong ↑ risk of ESRD/CKD vs. mild
Repeat-biopsy chronicity after induction [7,12]	Tracks with poorer long-term function
Early proteinuria reduction in MLN (<1 g/g at =1 yr; CR) [10]	Strong ↓ risk of doubling of serum creatinine/ESRD

DISCUSSION

This synthesis reinforces several converging themes from contemporary LN science and guidance. First, the 2018 ISN/RPS revisions and subsequent validation studies correctly elevate semiquantitative scoring of activity and chronicity, improving reproducibility and prognostic yield over binary class labels [3,4]. The consistency with which chronicity, especially interstitial fibrosis and tubular atrophy, predicts long-term decline argues for

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routine, standardized reporting and for clinicians to communicate these scores during shared decision-making [5,6,8,9,13].

Second, guideline algorithms increasingly acknowledge that clinical parameters (proteinuria, creatinine, complements, anti-dsDNA) incompletely track intrarenal inflammation; selective repeat biopsy can uncover persistent activity, inform escalation vs. de-escalation, and reduce both under- and over-treatment. These indications now appear in major guidance and are bolstered by repeat-biopsy cohorts demonstrating histologic non-response in apparent clinical responders and the prognostic weight of chronicity on follow-up biopsy [2,7,12,13].

Third, treatment goals are maturing from “induce then maintain” toward parallel targets: clinical remission (proteinuria, urinary sediment, kidney function), immunologic remission (anti-dsDNA/complements), and prevention of chronic damage (eGFR slope), recognizing that persistent immune dysregulation or delayed intrarenal resolution may sustain injury even during clinical quiescence. In MLN, pragmatic early proteinuria targets (<1 g/g, ideally <0.5 g/g) operate as actionable milestones tied to reduced risk of creatinine doubling, irrespective of specific induction agent after confounding is considered [10,11].

Fourth, age and timing matter: older age and delays to biopsy correlate with higher chronicity at baseline, highlighting the importance of prompt evaluation when urinary abnormalities appear [13]. Risk stratification should also consider life-course contexts; while pediatric LN often presents more aggressively, tubulointerstitial lesions still discriminate risk, and children carry longer exposure windows for cumulative CKD burden [9,14]. Broader epidemiologic comparisons across age strata likewise reveal worse long-term survival in elderly-onset LN, much of it mediated by comorbidity and damage accrual, again underscoring early control and chronicity limitation as shared goals across ages [14].

Finally, methodological standards are advancing. Consensus proposals from collaborative networks define histologic response/remission using modified NIH indices (≥50% AI decrease to ≤3; CI <4), aiming to harmonize endpoints in trials that incorporate repeat biopsy, tools intended for research comparability rather than blanket clinical mandates but likely to influence practice over time [12].

Implications. For clinicians, initial management should integrate the modified NIH indices into prognostic counseling; pursue early, guideline-aligned proteinuria targets; and consider repeat biopsy when decisions hinge on histologic clarity. For researchers, routine reporting of indices and TI components, age-stratified analyses, and prospective protocols testing biopsy-guided adjustments can accelerate precision care.

CONCLUSION

Across diverse cohorts, semiquantitative chronicity and tubulointerstitial metrics consistently outperform glomerular class and many activity measures for predicting kidney outcomes in lupus nephritis. Severe interstitial inflammation and higher chronicity

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(at baseline or follow-up biopsy) identify patients at greatest risk of CKD/ESRD, whereas early proteinuria reduction in membranous LN is a practical target linked to improved survival from creatinine doubling. Care pathways that (i) quantify chronicity/TI burden, (ii) pursue time-bound proteinuria goals, and (iii) selectively deploy repeat biopsy when needed are most aligned with the evidence and current guideline direction.

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