Lupus nephritis outcomes when kidney biopsy is not feasible: findings from a tertiary centre inception cohort

F. Kharouf[1,2], P. Mehta[1], Q. Li[1], D.D. Gladman[1], Z. Touma[1], L.P. Whittall Garcia[1]

[1]University of Toronto Lupus Clinic, Division of Rheumatology, Schroeder Arthritis Institute, Krembil Research Institute, University Health Network, Toronto, ON, Canada;
[2]Rheumatology Unit, Department of Medicine, Hadassah Medical Center and Faculty of Medicine, Hebrew University of Jerusalem, Israel.

Abstract

Objective

Baseline kidney biopsy is the gold standard for diagnosing lupus nephritis (LN). However, in certain cases, biopsy may not be feasible due to medical, technical, or patient-related factors, leading to a clinical diagnosis of LN. This study compares outcomes between biopsy-confirmed and clinically diagnosed LN to inform clinical decision-making in scenarios where a kidney biopsy is not feasible.

Methods

This retrospective study included patients with SLE enrolled between 2000 and 2024 who developed incident LN in an inception cohort at a tertiary centre. Inclusion began in 2000 to reflect treatment changes following the introduction of mycophenolate mofetil. Outcomes included: (1) complete proteinuria recovery (CPR) at 6 months and one year, and (2) a sustained ≥30% eGFR decline, end-stage kidney disease (ESKD), or death (composite outcome). Time-to-event outcomes were assessed using Kaplan-Meier curves and Cox proportional hazards regression.

Results

Among 127 patients with incident LN, 84 (66.1%) had biopsy-confirmed and 43 (33.9%) clinically diagnosed LN. Clinically diagnosed patients were younger, with lower baseline proteinuria and disease activity. CPR at 6 months and one year, as well as the composite outcome, did not differ significantly between groups. Individual events, including ≥30% eGFR decline, ESKD, and death, were also not statistically different.

Conclusion

Renal outcomes were not statistically different between biopsy-confirmed and clinically diagnosed LN when managed with standard treatment in a tertiary care setting. These findings offer reassurance in cases where biopsy is not feasible; however, biopsy remains the diagnostic gold standard and should be pursued whenever possible.

Key words
systemic lupus erythematosus, lupus nephritis, kidney biopsy

Fadi Kharouf, MD
Pankti Mehta, MD
Qixuan Li, MSc
Dafna D. Gladman, MD
Zahi Touma, MD, PhD
Laura P. Whittall Garcia, MD, MSc

Please address correspondence to:
Laura P. Whittall Garcia
Toronto Western Hospital Lupus Clinic,
Division of Rheumatology,
University Health Network, EW, 1-412,
399 Bathurst Street,
Toronto (ON) M5T 2S8, Canada.
ORCID iD: 0000-0002-5762-4469
E-mail: laura.whittallgarcia2@uhn.ca

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease marked by multisystem involvement, with a wide range of clinical features (1, 2). Lupus nephritis (LN), one of the most serious visceral manifestations of SLE, affects about 50% of patients and carries significant prognostic implications (3-6). The clinical spectrum of LN is highly variable, ranging from mild proteinuria to end-stage kidney disease (ESKD) (3, 6-8). Although laboratory findings, such as changes in serum creatinine, albumin, complement levels, anti-dsDNA antibodies, and urinary abnormalities including proteinuria and active urine sediment (*e.g.* casts, haematuria, pyuria), can support the diagnosis, kidney biopsy remains the gold standard for definitive diagnosis and classification (3, 6, 9, 10). When performed by skilled clinicians in specialised centres, percutaneous ultrasound-guided renal biopsy is considered safe, with a low incidence of adverse events (11, 12). The most significant complication is bleeding, particularly in patients with thrombocytopenia or impaired renal function (11, 13). Importantly, nephropathologic assessment provides detailed information on disease activity and chronicity and allows identification of alternative or coexisting non-immune complex-mediated nephropathies (9, 14). However, once LN is confirmed, it is important to note that the treatment of most cases, particularly proliferative (Classes III, IV), membranous (Class V), and mixed forms, shares many similarities, especially with the widespread use of mycophenolate mofetil (MMF) (6, 15-17). Although the diagnostic value of kidney biopsy – including repeat biopsies – in LN is well established (18, 19), real-world clinical practice often presents challenges that may preclude biopsy. These barriers may include medical contraindications, technical limitations, patient preferences, or resource constraints. In such situations, especially at specialised centres, close coordination between rheumatologists and nephrologists is essential to guide diagnosis and management. Given the limited data on outcomes in patients with newly diagnosed LN who do not undergo kidney biopsy, we conducted this study to compare the clinical characteristics and outcomes of patients with biopsy-confirmed LN to those with clinically diagnosed LN in whom biopsy was not feasible.

Patients and methods

Study design

We conducted a retrospective analysis of prospectively collected data from an inception cohort of SLE patients, enrolled within one year of diagnosis, who developed incident LN at or after clinic entry.

Setting

Since 1970, patients have been enrolled in the Toronto Lupus Cohort if they meet established classification criteria for SLE, including the revised 1997 American College of Rheumatology (ACR) criteria and, more recently, the 2019 European Alliance of Associations for Rheumatology (EULAR)/ACR SLE classification criteria (20, 21). Following enrollment, patients are longitudinally followed at the Toronto Lupus Clinic, with scheduled visits every 2 to 6 months for ongoing clinical monitoring and data acquisition. At each visit, a detailed clinical history and physical examination are conducted, alongside standardised assessments of disease activity and organ damage. The SLE Disease Activity Index-2000 (SLEDAI-2K) is completed at every visit (22), while the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SDI) is assessed annually (23).

Blood tests and untimed urine samples are routinely collected, with laboratory results generally available within 24 hours. If results reveal a spot urine protein-to-creatinine ratio (UPCR) ≥0.5 g/g, abnormal urine sediment, or an unexplained decrease in estimated glomerular filtration rate (eGFR), patients are advised to complete a 24-hour urine collection for accurate protein quantification.

In the SLEDAI-2K, the three renal descriptors – proteinuria, pyuria, and red blood cell or heme-granular casts – are recorded only when they are attributed to SLE disease activity, based on the clinical judgment of the treating team. All clinical and laboratory data are securely stored in an electronic database.

Kidney biopsy

At our centre, decisions regarding kidney biopsy are made through a shared decision-making process involving the patient, rheumatologist, and nephrologist. In accordance with accepted clinical recommendations (10), a kidney biopsy is pursued in any patient with suspected inflammatory renal involvement to ensure accurate diagnosis and classification, assess glomerular, tubulointerstitial, and vascular compartments, quantify activity and chronicity indices, and rule out non-inflammatory aetiologies. However, certain scenarios can make kidney biopsy acquisition challenging. These include medical contraindications such as severe thrombocytopenia or bleeding diathesis; technical limitations like extreme obesity; patient preference to avoid an invasive procedure; or situations in which the rheumatology and nephrology teams elect to proceed without pursuing a kidney biopsy. The latter is particularly common when the clinical presentation, supported by extra-renal manifestations and serologic findings, is strongly suggestive of LN or when proteinuria is mild. In such cases, the diagnosis is made clinically based on the presence of proteinuria associated with disease activity, often accompanied by abnormal urinary sediment and/or a decline in renal function. The majority of biopsies are performed at the clinic's affiliated centre by nephrologists or interventional radiologists using percutaneous ultrasound-guided techniques and are interpreted by experienced renal pathologists. Some biopsies are performed at external centres across Ontario. All pathology reports follow the revised International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification criteria (24), and the Lupus Clinic team ensures consistent validation and recording of histological data.

Patient selection

We identified patients from the University of Toronto Lupus Cohort (2000–2024) who developed LN at or following their initial clinic visit. Patient inclusion began in 2000 to reflect treatment changes associated with the introduction of MMF. For each patient, the baseline (LN onset) visit was defined as the earliest date when abnormal renal parameters were recognised and treatment for active LN was initiated by the managing team. All participants provided informed consent for the collection and use of clinical and laboratory data. This study was approved by the University Health Network Research Ethics Board in Toronto, Ontario, Canada, and conducted in accordance with the Declaration of Helsinki.

Outcomes

The following outcomes were used:

1. complete proteinuria recovery (CPR) at 6 months and one year, defined as proteinuria <0.5 g/day (24-hour collection) or UPCR <0.5 g/g;
2. adverse composite outcome: a sustained (observed over at least two consecutive visits) ≥30% decline in eGFR, ESKD (eGFR <15mL/min/1.73m^2, dialysis, or kidney transplant), or death.

These outcomes (and time to outcomes) were evaluated and compared between the two study groups.

Statistical analysis

Descriptive statistics were used to summarise baseline cohort characteristics. Categorical variables were reported as frequencies and percentages, with group comparisons conducted using the Chi-squared test. Continuous variables were summarised as medians with interquartile ranges (IQR), and comparisons between groups were performed using the Mann-Whitney U-test.

Time-to-event outcomes were analysed using Kaplan-Meier (KM) curves and log-rank tests. Patients were censored at the time of the event or at a maximum follow-up of 5 years. To account for differences in follow-up duration between groups, all analyses were restricted to the first 5 years after LN onset. Associations between biopsy-confirmed and clinically diagnosed LN and clinical outcomes were evaluated using Cox proportional hazards models, adjusted for baseline proteinuria and other imbalanced variables, including age, SLEDAI-2K, and SDI, based on their relevance to the outcome. A sensitivity analysis was subsequently performed, restricting the cohort to patients with baseline proteinuria ≥1.5 g/day to filter out milder cases, given baseline differences in proteinuria between groups. All statistical tests were two-sided, with a significance threshold of $p<0.05$. Missing data were minimal (<5% across all model variables); therefore, a complete-case analysis was performed, as this degree of missingness was unlikely to materially affect the results.

Analyses were performed using R software, v. 4.2.2.

Results

Patient characteristics

This inception cohort included 127 patients with incident LN, of whom 84 (66.1%) had biopsy-confirmed LN, and 43 (33.9%) were clinically diagnosed in the absence of a kidney biopsy (Table I). The overall median age was 34.5 years, and 11.8% were male. The cohort was racially diverse, with the largest proportions identifying as White (39.2%) or Black (28.0%). Median duration of SLE at LN onset was short (0.4 years), consistent with the inception design.

Compared to those with biopsy-confirmed LN, clinically diagnosed LN patients were numerically younger (median 28.4 *vs*. 36.4 years, $p=0.09$). They also had significantly shorter total follow-up (median 5.4 *vs*. 9.4 years, $p<0.01$), higher serum albumin levels (36.0 *vs*. 33.0 g/L, $p=0.01$), lower disease activity at onset (median SLEDAI-2K 12.0 *vs*. 16.0, $p<0.01$), and greater baseline damage (SDI, $p=0.01$) (Table I). To further characterise baseline damage, we added a breakdown of SDI items at baseline as Supplementary Table S1. The most frequent SDI items were musculoskeletal and neurologic.

While proteinuria levels were lower in clinically diagnosed LN patients (median 1.4 [IQR: 1.0–3.5] *vs*. 2.0 [1.1–4.0] g/day; $p=0.13$; mean 2.2±1.7 *vs*. 2.9±2.3 g/day; $p=0.12$), the differences were not statistically significant. Rates of haematuria, baseline renal function (creatinine and eGFR), complement levels, and anti-dsDNA positivity were comparable between groups (Table I).

Among patients who underwent biopsy, class IV LN (including IV+V) was

Table I. Baseline characteristics at LN onset in patients with clinically diagnosed and biopsy-confirmed LN.

Variable	Overall (n=127)	Clinically diagnosed (n=43)	Biopsy-confirmed (n=84)	*p*-value
Age in years, median [IQR]	34.5 [25.6, 43.8]	28.4 [21.5, 41.6]	36.4 [27.2, 44.7]	0.09
Sex, male, n (%)	15 (11.8)	6 (14.0)	9 (10.7)	0.81
Race				
Black, n (%)	35 (28.0)	12 (28.6)	23 (27.7)	
White, n (%)	49 (39.2)	17 (40.5)	32 (38.6)	0.81
Chinese, n (%)	17 (13.6)	4 (9.5)	13 (15.7)	
Other, n (%)	24 (19.2)	9 (21.4)	15 (18.1)	
SLE duration in years, median [IQR]	0.4 [0.2, 1.0]	0.4 [0.2, 4.4]	0.4 [0.1, 0.9]	0.20
Hypertension, n (%)	86 (67.7)	29 (67.4)	57 (67.9)	1.00
Hyperlipidaemia, n (%)	102 (80.3)	37 (86.0)	65 (77.4)	0.35
Diabetes mellitus, n (%)	8 (6.3)	2 (4.7)	6 (7.1)	0.87
Haematuria, n (%)	74 (58.3)	21 (48.8)	53 (63.1)	0.18
Creatinine, µmol/L, median [IQR]	69.0 [56.5, 90.5]	67.0 [57.5, 88.5]	69.5 [56.8, 92.0]	0.58
eGFR, mL/min/1.73 m², median [IQR]	96.5 [74.4, 121.7]	99.0 [80.0, 121.8]	95.5 [69.5, 119.7]	0.38
Serum albumin, g/L, median [IQR]	33.0 [29.0, 37.0]	36.0 [31.0, 39.0]	33.0 [27.0, 36.0]	**0.01**
Low complement, n (%)	84 (67.2)	30 (73.2)	54 (64.3)	0.43
C3, g/L, median [IQR]	0.75 [0.55, 1.02]	0.73 [0.59, 0.96]	0.77 [0.52, 1.03]	0.67
C4, g/L, median [IQR]	0.13 [0.08, 0.22]	0.13 [0.08, 0.22]	0.12 [0.08, 0.21]	0.71
Positive anti-dsDNA, n (%)	91 (71.7)	33 (76.7)	58 (69.0)	0.48
Positive APLA, n (%)	15 (11.8)	8 (18.6)	7 (8.3)	0.16
Proteinuria, g/day, median [IQR]	1.9 [1.0, 3.6]	1.4 [1.0, 3.5]	2.0 [1.1, 4.0]	0.13
Proteinuria, g/day, mean (SD)	2.6 (2.2)	2.2 (1.7)	2.9 (2.3)	0.12
SLEDAI-2K, median [IQR]	14.0 [10.0, 18.0]	12.0 [8.0, 16.0]	16.0 [12.0, 20.0]	**<0.01**
SDI, median [IQR]	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 0.0]	**0.01**
Biopsy class (n=84) † §				
I or II, n (%)	2 (2.4)	—	2 (2.4)	
III, n (%)	14 (16.7)	—	14 (16.7)	
III+V, n (%)	7 (8.3)	—	7 (8.3)	NA
IV, n (%)	25 (29.8)	—	25 (29.8)	
IV+V, n (%)	15 (17.9)	—	15 (17.9)	
V, n (%)	21 (25.0)	—	21 (25.0)	
NIH Activity index, median [IQR]	5.0 [0.0, 8.0]	—	5.00 [0.0, 8.0]	NA
NIH Chronicity index, median [IQR]	3.0 [1.0, 3.0]	—	3.0 [1.0, 3.0]	NA
Glucocorticoid use, n (%)	127 (100.0)	43 (100.0)	84 (100.0)	1.00
Glucocorticoid dose during first year, median [IQR] *	19.2 [14.4, 26.7]	19.2 [15.5, 25.0]	19.3 [14.0, 27.9]	0.73
Use of immunosuppressives during first year, n (%)	123 (96.9)	43 (100.0)	80 (95.2)	0.36
Mycophenolate mofetil, n (%)	97 (76.4)	37 (86.0)	60 (71.4)	0.11
Cyclophosphamide, n (%)	17 (13.4)	4 (9.3)	13 (15.5)	0.49
Azathioprine, n (%)	36 (28.3)	8 (18.6)	28 (33.3)	0.13
Other (Cyclosporine, Tacrolimus, Rituximab, Belimumab), n (%)	17 (13.4)	7 (16.3)	10 (11.9)	0.68
Antimalarial use, n (%)	97 (76.4)	36 (83.7)	61 (72.6)	0.24
ACEi or ARB use during first year, n (%)	86 (67.7)	28 (65.1)	58 (69.0)	0.80

LN: lupus nephritis; SLE: systemic lupus erythematosus; IQR: interquartile range; eGFR: estimated glomerular filtration rate; dsDNA: double-stranded DNA; APLA: antiphospholipid antibody; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SDI: SLICC/ACR Damage Index; NA: not applicable; NIH: National Institutes of Health; ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.
Statistically significant *p*-values are in bold ($p<0.05$). Biopsy class and NIH indices only available for patients who underwent kidney biopsy.
Hypertension is defined as high blood pressure (systolic >130 mmHg or diastolic >80 mmHg) on two consecutive visits or taking anti-hypertensive drugs
Hyperlipidaemia is defined as high cholesterol or receiving Lipid lowering treatment
The median duration of follow-up was 7.3 years (IQR 4.7–12.0) overall, 5.4 years (IQR 2.4–7.6) in the clinically diagnosed group (n=43), and 9.4 years (IQR 5.8–12.5) in the biopsy-confirmed group (n=84) ($p<0.01$).
† Mixed classes (III+V and IV+V) are reported separately in the table but are included within classes III and IV, respectively, when summarised in the text.
§ Five patients had overlapping Sjögren's syndrome (all in the biopsy-confirmed group). All had proliferative LN on kidney biopsy, and four also had tubulointerstitial lesions.
* The 5-year cumulative glucocorticoid dose was not significantly different between patients who underwent a kidney biopsy (median 125.1 mg [IQR: 75.8, 212.5]) and those who did not (median 111.0 mg [IQR: 73.0, 148.8]; $p=0.07$).

the most common histologic subtype (47.6%), followed by class III LN (including III+V) (25.0%) and pure class V (25.0%) (Table I). All patients received glucocorticoids, and MMF was the most commonly used immunosuppressive in both groups.

Outcomes

- CPR

At 6 months, CPR was achieved in 30.4% overall, including 34.9% of clinically diagnosed LN patients and 28.0% of biopsy-confirmed LN patients ($p=0.56$) (Table II). The proportion of patients achieving CPR at one year was 58.4% overall, with 65.1% in the clinically diagnosed LN group and 54.9% in the biopsy-confirmed group ($p=0.36$) (Table II).

The overall median time to CPR was 0.8 years [IQR 0.3–2.2], with no sig-

Table II. Outcomes of patients with clinically diagnosed and biopsy-confirmed lupus nephritis, restricted to 5 years.

Outcomes	Overall (n=127)	Clinically diagnosed (n=43)	Biopsy-confirmed (n=84)	*p*-value
CPR at 6 months, n (%) [§]	38 (30.4)	15 (34.9)	23 (28.0)	0.56
CPR at 1 year, n (%) [§]	73 (58.4)	28 (65.1)	45 (54.9)	0.36
Time to CPR, years, median [IQR]	0.8 [0.3, 2.2]	0.9 [0.3, 1.7]	0.8 [0.5, 2.3]	0.81
Sustained ≥30% decline in eGFR, ESKD, or death [†] (composite outcome), n (%)	24 (19.2)	7 (16.7)	17 (20.5)	0.79
Time to composite outcome, years, median [IQR]	5.0 [2.2, 5.0] [*]	3.4 [1.4, 5.0]	5.0 [3.9, 5.0]	0.93

CPR: complete proteinuria recovery; ESKD: end-stage kidney disease; eGFR: estimated glomerular filtration rate; IQR: interquartile range.
[§] Two patients had missing proteinuria outcome data at 6 months and 1 year; percentages were calculated using available data.
[†] Observed over at least two consecutive visits.
[*] Median time to composite outcome not reached due to low event rates; 5.0 years represents censoring at end of follow-up.

nificant difference between groups (p=0.81). KM survival analysis demonstrated no significant difference in time to CPR between the two groups (p=0.81) (Fig. 1A).

In the multivariable Cox proportional hazards model, adjusted for baseline age, proteinuria, and SDI, biopsy-confirmed LN was not significantly associated with CPR (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.76–1.84, p=0.45) (Table III).

- Adverse composite outcome (a sustained ≥30% eGFR decline, ESKD, or death)

Over a 5-year follow-up period, 19.2% (n=24) of patients developed the composite outcome, which included sustained ≥30% eGFR reduction, ESKD, or death (Table II; see also Supplementary Table S2 for breakdown). The event occurred in 16.7% (n=7) of clinically diagnosed LN patients and 20.5% (n=17) of biopsy-confirmed LN patients (p=0.79). The overall median time to the composite outcome was not reached (censored at 5 years), with the upper quartile extending to the end of follow-up (Table II). KM survival analysis revealed no significant difference in time to the composite outcome between groups (p=0.93) (Fig. 1B).

In multivariable Cox proportional hazard models, adjusted for baseline age, proteinuria, and SDI, biopsy-confirmed LN was not significantly associated with the composite outcome (HR 0.91, 95% CI 0.38–2.19, p=0.83) (Table II).

Sensitivity analysis

To address baseline differences in proteinuria, a sensitivity analysis was per-

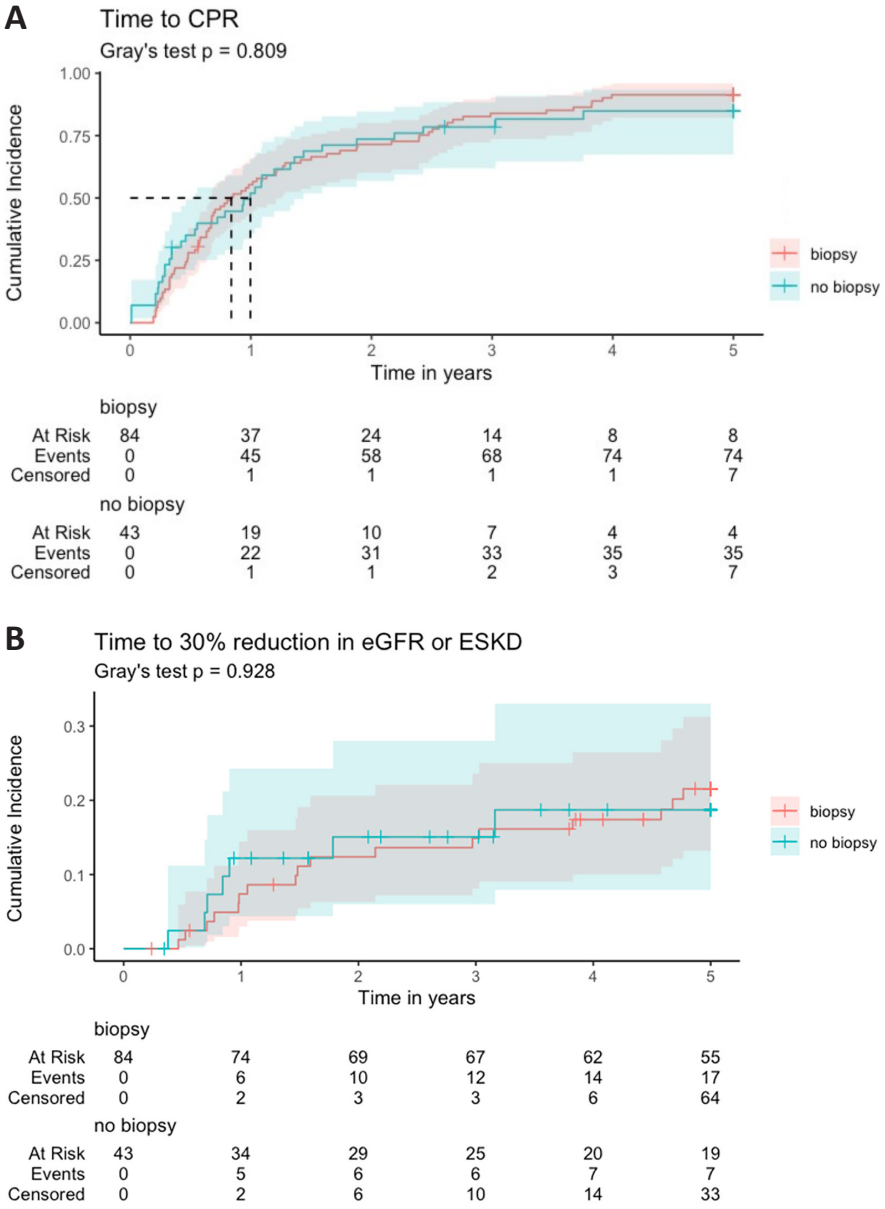

Fig. Kaplan-Meier curves showing the differences between the biopsy and no biopsy groups in:
A: Time to CPR
B: Time to a sustained ≥30% decline in eGFR, ESKD, or death
CPR: complete proteinuria recovery; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease

Table III. Univariable and multivariable Cox proportional hazard models comparing biopsy-confirmed *vs*. clinically diagnosed lupus nephritis.

Outcome	Model	Exposure: biopsy-confirmed *vs*. clinically diagnosed LN	*p*-value
CPR	Univariable	HR 1.05 (95% CI: 0.69–1.60)	0.80
	Multivariable*	HR 1.19 (95% CI: 0.76–1.84)	0.45
Sustained ≥30% decline in eGFR,	Univariable	HR 1.05 (95% CI: 0.44–2.52)	0.91
ESKD, or death (composite outcome)	Multivariable*	HR 0.91 (95% CI: 0.38–2.19)	0.83

CPR, complete proteinuria recovery; ESKD, end-stage kidney disease; eGFR, estimated glomerular filtration rate; HR, hazard ratio.
*Adjusted for baseline age, proteinuria, and SDI.

formed among patients with baseline proteinuria ≥1.5 g/day (n=77, 60.6%), including 20 (46.5%) clinically diagnosed and 57 (67.9%) biopsy-confirmed LN patients (p=0.033). In multivariable Cox models, biopsy-confirmed LN was not significantly associated with CPR (HR 0.90, 95% CI 0.50–1.64, p=0.73) or with the composite outcome (HR 0.88, 95% CI 0.25–3.11, p=0.84) (Suppl. Table S3).

Discussion

In this inception cohort-based observational study, approximately one third of patients with incident LN were diagnosed based on clinical judgment because kidney biopsy could not be performed due to medical, technical, or patient-related factors. Patients who were clinically diagnosed tended to present with lower baseline proteinuria, higher serum albumin, and lower disease activity, suggesting a generally milder phenotype. Importantly, when managed according to established treatment protocols within a specialised lupus clinic at a tertiary care centre, these patients experienced outcomes not statistically different from those with biopsy-confirmed LN. Furthermore, a sensitivity analysis restricted to patients with baseline proteinuria ≥1.5 g/day yielded consistent results, reinforcing the robustness of our findings.

Kidney biopsy remains the gold standard for diagnosing LN, as it provides essential information for confirming the diagnosis, classifying LN, assessing disease activity and chronicity, identifying compartmental involvement, directing therapy, and even informing prognosis (3, 6, 9, 10, 14, 25). In addition, biopsy may reveal alternative or coexisting renal pathologies – such as thrombotic microangiopathy or lupus podocytopathy – that require different therapeutic approaches (26-29). Furthermore, renal impairment in SLE may be multifactorial (*e.g.* diabetic or hypertensive nephropathy, renovascular disease, or drug-induced injury) (26), and biopsy may help distinguish these causes from inflammatory LN, thereby guiding appropriate treatment.

The most recent treatment guidelines and recommendations for SLE, including those provided by the EULAR, ACR, Kidney Disease: Improving Global Outcomes (KDIGO), and EULAR/European Renal Association – European Dialysis and Transplant Association (ERA-EDTA), provide valuable direction for managing LN, with particular emphasis on proliferative, membranous, and mixed forms of LN (10, 15, 18, 30-33). In these cases, MMF plays a central role in both induction and maintenance therapy and has become a mainstay of treatment in both real-world practice and randomised clinical trials, either as a standalone immunosuppressive agent or as part of a multitarget regimen (32-36). The widespread use of MMF across LN classes has raised the question of whether treatment may sometimes be initiated without histologic confirmation (16, 37). While the consensus is clearly in favour of biopsy whenever feasible (10, 16, 31), it is plausible that increased availability and perceived reliability of MMF might have influenced clinical decisions in certain contexts, particularly when technical, logistical, or resource constraints limit biopsy accessibility. In such scenarios, as seen in our cohort, applying standard LN treatment protocols may lead to outcomes that are not substantially different from those observed in biopsy-confirmed LN. However, it is important to emphasise that this strategy carries important trade-offs, including the risk of unnecessary immunosuppression with its associated toxicities and the potential for misdiagnosis or oversight of non-inflammatory causes of renal dysfunction (16).

While this study focused on incident LN events and baseline biopsies, it is important to acknowledge another evolving aspect of LN management: the role of repeat kidney biopsies, including those performed per protocol (38-40). This approach addresses the known discordance between clinical and histopathologic findings and may guide treatment decisions, particularly during response assessment or therapy tapering (9, 19, 40, 41). Importantly, the absence of a baseline biopsy should not preclude biopsy later in the disease course, particularly during disease flares, when histologic evaluation can help distinguish active inflammation from chronic damage and guide therapy (19, 40).

Our study has several strengths, including its multiracial representation and the structured and well-documented nature of the data. A key advantage is the use of an inception cohort, which allowed us to focus specifically on incident LN events and corresponding baseline biopsies, rather than disease flares. We also limited the observation period to the era beginning in 2000 to reflect the adoption of contemporary treatment protocols, particularly the availability and widespread use of MMF.

Nonetheless, several limitations should be acknowledged. These include the relatively small sample size and its single-centre retrospective design. The proportion of patients without biopsy is also relatively high; however, this reflects the inclusion of an inception subgroup dating back to 2000. In more recent years, kidney biopsy has been consistently pursued whenever feasible in our centre. Furthermore, the study results are applicable to a specialised tertiary care setting, where advanced care delivery and follow-up are typically well coordinated. Notably, some pa-

tients in the clinically diagnosed group may not have had true LN but rather alternative causes of renal impairment, potentially associated with different prognoses. It is also possible that milder, non-proliferative cases were more likely to be managed without biopsy, supported by the low frequency of Class I–II LN in our cohort. Although baseline proteinuria was adjusted for as a key confounder, other unobserved variables may have influenced the relationship between biopsy status and outcomes, such as sociodemographic factors. Despite these limitations, the descriptive findings appear to provide useful insights into real-world treatment patterns and outcomes.

In conclusion, kidney biopsy remains the gold standard for diagnosing LN, as endorsed by current guidelines and expert consensus (16, 18, 30, 31, 37). However, if biopsy is not feasible, clinically diagnosed LN cases managed in specialised tertiary care settings may achieve outcomes that are not statistically different from those with biopsy-confirmed disease when treated according to standard protocols. While these findings provide reassurance, they are limited to situations where biopsy is contraindicated or unavailable and should never replace the recommendation to perform biopsies.

Take-home messages

- Kidney biopsy is the gold standard for diagnosing LN.
- In cases where a kidney biopsy is not feasible, initiating standard treatment protocols may still optimise clinical outcomes

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