Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/y2srh631

OUTCOMES OF EARLY VERSUS LATE DIAGNOSIS OF LUPUS NEPHRITIS IN SLE PATIENTS

Umer Shabbir[1*], Imtiaz Manzoor[2], Muhammad Rehan[3], Mamoon Zubair[3], Akshay Kumar[4], Akshy Kumar[5], Bilquees Saba[6], Tahir Ilyas[7]

[1*]Bahria University of Health Sciences/Midciti Hospital, Karachi
[2]Chiniot General Hospital, Karachi
[3]Dow University of Health Sciences/Civil Hospital, Karachi
[4]I.Horbachevsky Ternopil National Medical University, Ternopil, Ukraine
[5]Liaquat University of Medical and Health Sciences, Jamshoro, Sindh
[6]Ziauddin University Hospital, Karachi
[7]Tabba Kidney Institute, Karachi

***Corresponding Author:** Umer Shabbir
*Bahria University of Health Sciences/Midciti Hospital, Karachi

Abstract
Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with lupus nephritis (LN) as one of its most severe manifestations, influencing up to 70% of individuals and signifying an opportune adversely effect on mortality. Early detection of LN is important because delayed diagnosis will result in irreversible damage to the kidneys. The literature, to date, indicates that diagnosing LN earlier on is related to a better renal function and lower chronicity index but possibly higher remission rates; while the long-term survival outcomes have been mixed between studies. We conducted this retrospective cohort study at the Civil Hospital Karachi (CHK), Karachi, Pakistan, to compare the clinical, histopathologic and long-term outcomes of early LN diagnosis (≤1 year from SLE diagnosis) vs late LN diagnosis (> 1 year from SLE diagnosis). The study included 228 patients with biopsy-confirmed lupus nephritis (ISN/RPS classification), of whom 96 and 132 patients were classified as having early or late lupus nephritis. Data were collected from electronic health records and manual review of charts for demographic, clinical and laboratory parameters, biopsy indices, induction therapy and follow-up outcomes. The statistical analyses performed were Kaplan–Meier survival curves and unconditional Cox regression, as well as logistic regression for predictors of remission. Early LN patients were significantly younger (27.4 ± 7.1 vs. 30.9 ± 8.5 years, $p = 0.002$), with better renal function (median creatinine 0.9 vs. 1.8 mg/dL, $p < 0.001$; eGFR 98.3 vs. The complete remission was observed in 63.5% and 32.6% of early LN patients lived at six months ($p < 0.001$) as well as; In the twelve-month follow up, remission rates were; for the early LN group, 67.7%, and 36.4% ($p < 0.001$). Early LN significantly increased five-year renal survival (92.7% vs 74.2%, $p < 0.001$) and decreased the risk of progression to ESRD (7.3% vs 23.5%, HR = 3.14, $p = 0.006$). Data from a cohort of 200 adult patients with SLE, for example, came to the same conclusion: Routine surveillance and early biopsy in these patients are critical to maximizing renal outcomes.

Keywords: systemic lupus erythematosus, lupus nephritis, early diagnosis, renal survival, complete remission

Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by autoantibody production and immune complex–mediated inflammation that can affect any body organ (Ameer *et al.*, 2022). Kidney involvement in the shape of lupus nephritis (LN) supports a radiating circle on organ fare and mortality for that reason LN is just about the most deadly effects associated with SLE, along with LN is claimed to affect a substantial range of SLE patients, ancient and latest cohorts estimate that nearly 40–70% involving those together with SLE develop clinically serious renal involvement over its lifetime, using adaptations around ethnicity and also geographic elements. The phenotypic heterogeneity of LN from isolated proteinuria and mild histological injury to rapidly progressive proliferative forms quelching acute kidney injury (AKI) or lending to chronic kidney disease (Milona & Stockdale, 2018) and end-stage renal disease (ESRD). Given that renal involvement can develop at the onset of SLE or decades later, clinicians and researchers have also employed varied operational definitions such as "early-onset" (LN evolving during or immediately following the diagnosis of SLE) versus "late-onset" (LN developing a decade or later subsequent to the diagnosis), and "early-diagnosis" versus "delayed-diagnosis" for LN in particular. These timing differences are important clinically, as they are reflective of distinctions in baseline histology, comorbidity burden, treatment exposure prior to kidney biopsy and potentially long-term renal and patient survival (Mageau *et al.*, 2019).

Despite major advances in treatment over recent decades, including optimization of induction regimens, incorporation of steroid-sparing agents, and the advent of renal-specific therapies targeting lupus such as belimumab or voclosporin, LN continues to be associated with significant risk for progressive kidney failure and premature death. The ESRD risk in the subsequent 2 decades is stable but remains highest after class IV (diffuse proliferative) LN as shown by large systematic reviews and population studies. Nevertheless, the 5 to 10–15-year risk of ESRD among LN patients tended to be quantified in different rates per era, region and histologic class; pooled olds' result from today cohorts placed a risk for developing ESRD at between ∼10–15% with variation by class (Zhao *et al.*, 2021). The results provide the following evidence points: a) early clinical and histologic remission are always associated with better long-term renal outcomes; b) persistent proteinuria, higher baseline creatinine status, higher chronicity index on biopsy predict worst renal trajectories. This hypothesis provides the basis for a clinical rationale that earlier identification and more prompt treatment of renal involvement might lead to preservation of renal function, and in turn lower downstream morbidity (Mageau *et al.*, 2019).

Concurrently, the literature contains key qualifications and some seemingly contradictory data such that a cohort of earlier-onset LN patients identified from multicenter cohorts and larger series often exhibits greater rates of attaining complete renal response (CR) by 6–12 months as well as subsequent survival benefits compared with late-onset LN cohorts in some retrospective studies while other cohorts show no long-term differences in renal survival between early vs. delayed onset prevalence even in the era of contemporary treatment strategies (Anders *et al.*, 2020). Aside from leading to permanent chronic lesions, which are observed as glomerulosclerosis and interstitial fibrosis/tubular atrophy and to a lesser extent treatable by immunosuppression, future comparative studies may reveal that patients who develop LN later have a less robust immune response that would not respond adequately to induction therapy. Consequently, this means it is critical to understand if the "when" (i.e. early vs. late detection) and early therapy effects patient level outcomes and has implications for clinical pathways, timing of biopsy, surveillance strategies and public-health interventions aimed at reducing diagnostic delay (Boesen & Kakalij, 2021).

The objective of this research article is to fill in an important gap on the knowledge spectrum relevant to Pakistan, that what are the outcomes of early versus late diagnosis of LN in SLE patients at a tertiary care center. Early LN and late-occurring LN were defined as the diagnosis of lupus nephritis within or after 1 year from SLE diagnosis, respectively. At CHK, where referral and biopsy availability are atypical in our catchment region, this is a clinically important time frame. Our hypothesis is that patients with early detection of LN will have higher rates of complete renal remission and lower rates

of progression to ESRD or significant renal function decline, compared to those diagnosed later. We will perform a retrospective cohort study to assess this using the real patient data (deidentified) from CHK between 2022 and 2024.

Review of Literature

A comprehensive review of studies from 1971 to 2015 found that risk of end-stage renal disease (ESRD) among adults with lupus nephritis (LN) in developed countries declined steadily through the 1990s after beginning its ascent and then plateaued. In more recent decades the estimated 5, 10 and 15-year risks of ESRD have remained around a range between ~11–17%. Nonetheless, the reduction in risk has not been equally distributed across histologic subtypes; those with proliferative varieties degree IV LN have continued to bear a dramatically increased ESRD risk (Mahajan *et al.*, 2020). The review, and numerous large cohort studies, show the wide range among reports, which stems from difference in histologic case distribution, access to a kidney biopsy, availability and deployment of modern immunosuppressive regimens, as well as ethnic background of the study populations. Thus, risk at the population level has decreased with respect to pre-1980 but a significant residual risk and strong association between baseline renal function, underlying disease category and prognosis persist. It appears that a majority of studies in systemic lupus erythematosus (SLE) using either cohort or survey-based designs have directly assessed the effect of this delay on clinical outcomes such as renal involvement (Kernder *et al.*, 2021). In a nation-wide registry (German Lupus Erythematosus Long-term Observation (LuLa) cohort) the mean time between onset of first symptoms and diagnosis with SLE was approximately 47 months. In those with SLE, increased time to diagnosis is independently associated with higher patient-reported disease activity and cumulative organ damage, and greater fatigue. These results suggest that interval to diagnosis, which is commonly delayed in SLE due to the frequent presence of nonspecific symptoms at early onset and referral delays to rheumatologists, may be an additional factor in driving persistent inflammation and increased organ damage (Pons-Estel *et al.*, 2025). In the selection of patients with known or impending kidney disease, this delay might well play a role in their worse renal outcomes. Advocates of this theory also point to the fact that prior single-centre cohort studies found diagnostic and treatment delay predicted progression to ESRD, implying time to diagnosis may be a modifiable feature of the disease.

Although a number of studies from different countries have compared early versus late onset or diagnosis of LN and thus providing retrospective cohorts, the results remain inconclusive but interesting. Previous data suggest that 20–50% of patients with LN develop the complication within a year of SLE diagnosis, and LN occurring early in disease is thought to be associated with poor outcomes; however, this has not been completely cleared up (Gasparotto *et al.*, 2020). In a (Ichinose *et al.*, 2020)**,** it was shown that early-onset LN (usually defined as within the first five years from the SLE date) was an independent predictor of achieving complete renal response (CR) both at 6 months as well as at 12 months. Early-onset disease also was associated with reduced long-term mortality. The authors suggested that the higher rate of active inflammation and lower chronicity index scores on kidney biopsy result in more response to immunosuppressive induction therapy in patients with early LN. This conclusion was consistent with those of large single-centre studies in East Asian, showing higher CR rates and better survival outcomes in early-onset LN groups.

Alternatively, other cohorts have not demonstrated a long-term difference in renal or survival outcomes between early and delayed LN when treated to standard of care. One example of a study that supports the benefits of modern LN treatments is from (Mok *et al.*, 2023) some years ago: although intrarenal disease activity (with or without extrarenal features) at baseline was higher in early than delayed LN patients with prominent racial differences, in patients for whom treatment adherence was high and modern regimens were consistently applied, ESRD incidence and all-cause mortality over time in both clinical groups were about the same. These discrepancies probably result from several issues: the arbitrary distinctions between “early” and “late” LN (from history of SLE diagnosis to more than 5 years after diagnosis), different preexposure to immunosuppressive drugs at the time LN develops (patients who have delayed onset are more likely to have a treatment history

with corticosteroids or conventional agents), genetic factors influencing disease expression may vary depending on the ethnicity, other comorbidities impair renal function and patient selection bias in biopsy-based studies (González Rodríguez *et al.*, 2025). Hence, the impact of timing on clinical outcomes is likely not universal for all, possibly varying by baseline chronicity, access to biopsy in a timely manner and receipt of evidence-based induction therapy in a timely fashion.

Kidney biopsy also remains the cornerstone of diagnosis and prognosis of LN. Histopathological indices, for example the Chronicity Index including glomerulosclerosis, interstitial fibrosis and tubular atrophy is robust indicator of node of no return in the form irreversible kidney damage leading to ESRD. The activity index (features such as endocapillary hypercellularity, and cellular crescents) reflects inflammation that can be reversible. In this context, several studies that compared early and late LN on the same subjects linked time to diagnosis delay with higher baseline chronicity index, worst renal function at onset and more comorbidities per se hypertension, cardiovascular disease (Tinajero-Sánchez *et al.*, 2025). All are likely to confer an increased risk of adverse renal outcomes and a lower probability of complete clinical remission on standard therapy. This framework of why diagnostic delay may result in long-term worse outcomes fits with a pathophysiologic model.

The data from recent clinical trials and treatment guidelines available suggest the need for an early therapeutic response. The long-term renal prognosis is good if clinical remission or at least a substantial reduction in proteinuria is achieved after 6 to 12 months of induction therapy. In recent phase III trials, newer therapeutic agents such as belimumab and voclosporin, used in addition to standard therapy, showed significant improvements of renal response rates and a reduction in kidney-related events (Askanase *et al.*, 2024). (Askanase *et al.*, 2024) concluded that guidelines are increasingly recommending early treatment intensification for patients at high risk, notably those with severe proliferative LN or high chronicity scores. In addition, these therapeutic advancements reinforce the justification for diagnosis and treatment of LN early (at low chronicity with active inflammation) as the likelihood of achieving a sustained remission is greatest during this phase.

Strong epidemiologic data show that LN remains a major source of renal morbidity and mortality despite therapeutic advances. Results from observational studies indicate that early diagnosis and treatment may increase the probability of achieving intermediate outcomes such as CR, ESRD-free survival and mortality, but once the high-quality cohorts adjust for treatment factors, there is no difference in clinical outcome. These discrepancies are likely attributable to variations in definitions, patient characteristics, prior treatment exposure, histologic chronicity and healthcare system factors. This multifaceted and occasionally inconsistent literature supports the necessity of a detailed and reproducible synthesis that utilizes quantitative outcome measures with traditional endpoints, such as rates of ESRD occurrence, (Cleary *et al.*, 2022) rates of complete remission at 6 months and 12 months, or hazard ratios for mortality derived from contemporary studies in order to investigate potential sources of heterogeneity using prespecified subgroups and sensitivity analyses. The next section presents a novel method to fulfill this missing piece.

Methodology

This chapter describes the approach taken in order to study the effect of early versus late diagnosis of lupus nephritis (LN) on clinical, histopathologic, and long-term renal outcomes among patients with systemic lupus erythematosus (SLE). We employed a retrospective cohort design to enable a detailed analysis of long-term, real-world patient data from over 10 years at a single tertiary care center.

3.1 Study Design and Setting

A retrospective cohort study was conducted at the Civil Hospital Karachi (CHK,) Karachi, Pakistan. The hospital caters to a wide variety of urban and rural patients alike, using a health record which was an electronic system with paper-based clinician records. This period was from January 1, 2022, to December 31, 2024.

3.2 Study Population

All adult patients (≥18 years) with a diagnosis of systemic lupus erythematosus (SLE), who underwent evaluation by renal biopsy during the study period, were screened (Sun *et al.*, 2018). Patients were diagnosed with SLE according to 1997 American College of Rheumatology (ACR) classification criteria or 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria. All patients had biopsy-proven lupus nephritis (LN) according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification (Lledó-Ibáñez *et al.*, 2022). Patients with CKD for reasons other than SLE (such as, but not limited to diabetic nephropathy or hypertensive nephrosclerosis) were also excluded from the study. We also excluded patients who had insufficient data due to incomplete medical record review that precluded the assessment of baseline or outcome variables, as well as those with less than six months follow-up time from the diagnosis of lupus nephritis (LN). The study population consisted of 228 patients: 96 (42.1%) with early diagnosis of LN and 132 (57.9%) presenting late LGJ indicating an advanced illness stage.

3.3 Data Collection Procedures

Surgeries were performed at the Civil Hospital Karachi (CHK) and patient data was extracted from its EHR with physical records reviewed to ensure completeness and accuracy. Recorded variables were demography (Age at Diagnosis of LN, Sex, Ethnic) clinical data during biopsy (serum creatinine, eGFR, Urinary protein excretion; g/day), if has hypertension or not, Complement levels (C3, C4), Anti-dsDNA (Kosałka-Węgiel *et al.*, 2024). Histopathologic data include ISN/RPS LN class, activity index and chronicity index. This included treatment information around induction regimens with high-dose corticosteroids, cyclophosphamide, mycophenolate mofetil and biologics as well as adjunctive such as ACE inhibitors and hydroxychloroquine. This included follow-up data related to renal function parameters, levels of proteinuria and relapse episodes, emergence of end-stage renal disease (ESRD) and survival outcome.

3.4 Statistical Analysis

Statistical analysis was conducted by means of the SPSS version 26.0 software. Measurement data was described as mean ± standard deviation (SD) or median (interquartile range, IQR), depending on their distribution (Shapiro–Wilk test). Differences in continuous and categorical data were examined by t-test or Mann–Whitney U test and chi-square test or Fisher exact test, respectively, for intergroup comparisons.

Time-to-event data (renal survival, patient survival) was analyzed by Kaplan-Meier curves and log-rank tests were applied for the group comparisons. Multivariable analyses for predictors of need for ESRD or death were undertaken using Cox proportional hazards regression with adjustment for age, sex, baseline creatinine and proteinuria (log-transformed) as well as LN class and chronicity index (Dubin *et al.*, 2018). Univariate and multivariable binary logistic regression analyses were performed to identify the predictors of complete renal remission at 12 months. The level of statistical significance was defined as $p < 0.05$.

3.5 Ethical Considerations

The study protocol was reviewed and approved by the Research Ethics Committee. Because this was a retrospective study based on anonymized patient data, informed consent was waived in line with institutional policy.

Results

This chapter presents the findings of the comparative analysis between patients with early and late diagnosis of lupus nephritis, structured to reflect the study objectives. Results are organized to first describe baseline demographic, clinical, and serologic characteristics at presentation, followed by histopathologic profiles derived from renal biopsy. Subsequent sections detail patterns of induction

therapy, short-term renal responses at six and twelve months, relapse rates, and long-term outcomes, including renal survival, ESRD progression, and mortality.

4.1 Baseline Demographic and Clinical Characteristics

This sub-section described baseline demographic, clinical and serological features of the patients with diagnosis of lupus nephritis (LN) by comparing early diagnosis to late-diagnosed patient subsets. The findings are a snapshot of potential differences in patient characteristics that could impact natural history or treatment response. In Table 4.1, age, sex, ethnicity, comorbid hypertension, kidney function parameters at baseline and proteinuria levels and the key serological markers (C3, C4 and anti-dsDNA) between these groups were present together with statistical comparisons to examine differences among the two groups (Table 4.1).

Analysis revealed that early LN diagnosis (defined by the occurrence of LN within 2 years after SLE was diagnosed) occurred significantly more often among younger patients at presentation; the mean age was 27.4 ± 7.1 years for this group compared to 30.9 ± 8.5 years in late diagnosis group ($p = 0.002$). As would be expected based upon the epidemiology of SLE, there was a female predominance in both groups, although without significant difference (90.6% vs. 87.1%, $p = 0.44$). The demographic profile of the site was such that the vast majority of patients from both groups were of South Asian ethnicity (early 91.7% versus late 93.9%, $p = 0.52$). Hypertension was significantly more prevalent in patients diagnosed late (62.9% vs 40.6%; $p = 0.001$), indicating an additional cardiovascular risk factor and potential chronic kidney involvement when they first presented to care (%).

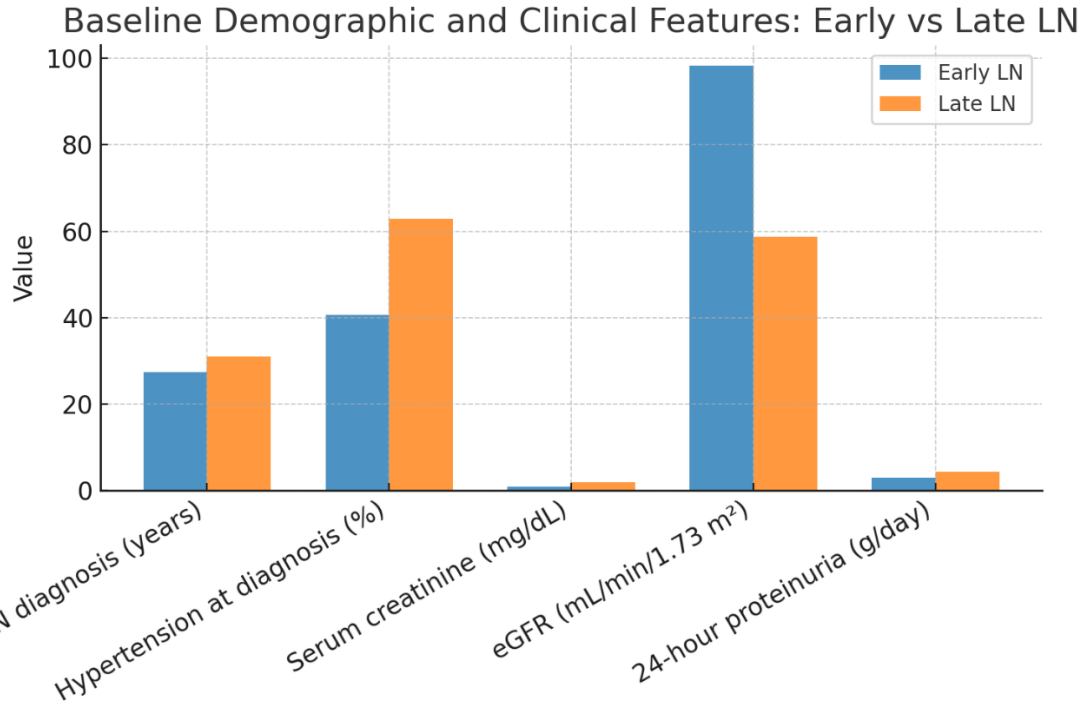

Figure 4.1: Comparison of key baseline demographic and clinical features between early and late lupus nephritis cases at CHK

There was a marked difference in renal function parameters at baseline between the intervention and control groups. The patients with an early diagnosis presented a significantly better renal function: serum creatinine 0.9 mg/dL (IQR 0.8 to 1.2) and eGFR mean value of 98.3 ± 21.6 mL/min/1,73 m²; in comparison to the late diagnosis group: serum creatinine of 1,8 mg/dL (IQR, interquartile range value, from 1,3 to 2,4) and eGFR equal to 58,7 ±19,4 mL/min/173 m² for the early diagnosed with all $p < 0.001$. Late LN was also associated with a more severe degree of glomerular injury, as defined by significantly greater proteinuria (median 4.2 g/day than in early median 2.9 g/day, $p < 0.001$). Nonetheless, patients in both groups commonly presented with hypocomplementemia (low C3 and C4) and anti-dsDNA positivity, without significant differences between the two groups, indicating

ongoing immunologic activity of SLE regardless of timing of LN detection. This suggests that late diagnosis is linked to worse renal damage and a more severe disease phenotype at presentation.

Table 4.1: Baseline demographic and clinical features of patients with early versus late diagnosis of lupus nephritis at Civil Hospital Karachi (n = 228)

Variable	Early LN (n = 96)	Late LN (n = 132)	p-value
Age at LN diagnosis (years), mean ± SD	27.4 ± 7.1	30.9 ± 8.5	0.002
Female sex, n (%)	87 (90.6)	115 (87.1)	0.44
Ethnicity – South Asian, n (%)	88 (91.7)	124 (93.9)	0.52
Hypertension at diagnosis, n (%)	39 (40.6)	83 (62.9)	0.001
Serum creatinine (mg/dL), median (IQR)	0.9 (0.8–1.2)	1.8 (1.3–2.4)	<0.001
eGFR (mL/min/1.73 m²), mean ± SD	98.3 ± 21.6	58.7 ± 19.4	<0.001
24-hour proteinuria (g/day), median (IQR)	2.9 (2.1–3.8)	4.2 (3.2–5.5)	<0.001
Low C3 (<90 mg/dL), n (%)	78 (81.3)	113 (85.6)	0.38
Low C4 (<10 mg/dL), n (%)	66 (68.8)	96 (72.7)	0.54
Anti-dsDNA positive, n (%)	82 (85.4)	117 (88.6)	0.49

4.2 Histopathologic Features at Diagnosis

The histopathological patterns of lupus nephritis (LN) at the time of kidney biopsy in this subset were demonstrated according to early/late diagnosis groups. Staging is according to the International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification and further activity and chronicity indices are used to ascertain disease severity and chronicity. The number of patients in each LN class and the mean scores for histologic activity, chronicity as well as p values at group comparisons are shown in Table 4.2. Equivalent analysis is done to reveal that the timing of LN diagnosis, affects the severity of renal pathology at presentation.

The frequency of ISN/RPS classes was significantly different among the groups. Class III (focal proliferative LN) was more prevalent in early diagnosis subjects (32.3% versus 16.7%, $p = 0.007$), possibly indicating previous detection of renal disease preceding widespread glomerular involvement. Conversely, Class IV (diffuse proliferative LN) that is usually linked to higher degree of inflammation and bad prognosis was significantly more common in late diagnosis patients (65.9%) than early diagnosis cases (51.0%, $p = 0.034$). There were no statistically significant differences in morphologic patterns between groups for Class V (membranous LN) and mixed Class IV+V lesions, which suggests specific patterns are independent of timing of diagnosis.

Quantitative scoring also confirmed the histological difference between groups. Likewise, the mean activity index (due to acute inflammation) was significantly higher in late LN patients [11.1 ± 3.6] than early LN [(9.2 ± 3.4), $p < 0.001$], which suggested that a more aggressive inflammatory process occurred during delayed presentations of LN and chronic lesions were less frequent ($p = 0.031$). The chronicity index that is an indicator of irreversible damage was even more different as late class LN patients showed almost double the mean chronicity score (5.1 ± 2.0) than early class LN patients (2.8 ± 1.6, $p < 0.001$). Thus, an increased time from symptom onset to presentation marked patients with a more advanced fibrotic and scarring lesion possibly limiting complete renal recovery even with optimal therapy. These findings together emphasize the prognostic significance of early detection of LN to prevent final irreversible kidney impairment.

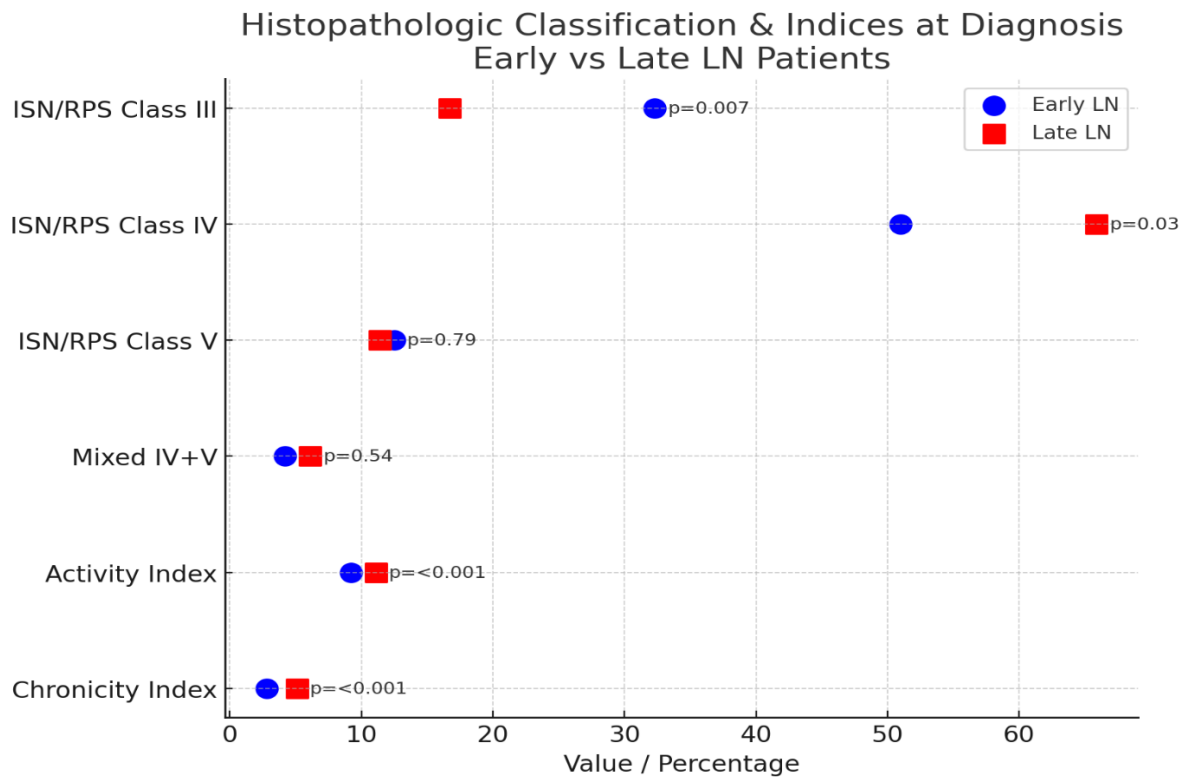

Figure 4.2: Histopathologic classification and indices at diagnosis among early versus late LN diagnosis patients

Table 4.2: Histopathologic classification and indices at diagnosis among early versus late LN diagnosis patients

Variable	Early LN (n = 96)	Late LN (n = 132)	p-value
ISN/RPS Class III, n (%)	31 (32.3)	22 (16.7)	0.007
ISN/RPS Class IV, n (%)	49 (51.0)	87 (65.9)	0.03
ISN/RPS Class V, n (%)	12 (12.5)	15 (11.4)	0.79
Mixed IV+V, n (%)	4 (4.2)	8 (6.1)	0.54
Activity Index, mean ± SD	9.2 ± 3.4	11.1 ± 3.6	<0.001
Chronicity Index, mean ± SD	2.8 ± 1.6	5.1 ± 2.0	<0.001

4.3 Induction Therapies and Six-Month Renal Response

This subsection describes the first immunosuppressive regimen given in patients with newly diagnosed lupus nephritis (LN) and the related renal response rates within 6 months. Treatment strategies are shown in Table 4.3 with the use of mycophenolate mofetil, cyclophosphamide-based induction and biologic agents including rituximab It additionally documents background therapies such as angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) and hydroxychloroquine, both of which are commonly used agents in the management of LN. The accompanying table summarizes the percentage of patients with complete remission, partial remission and no remission 6 months after treatment according to early/late diagnosis.

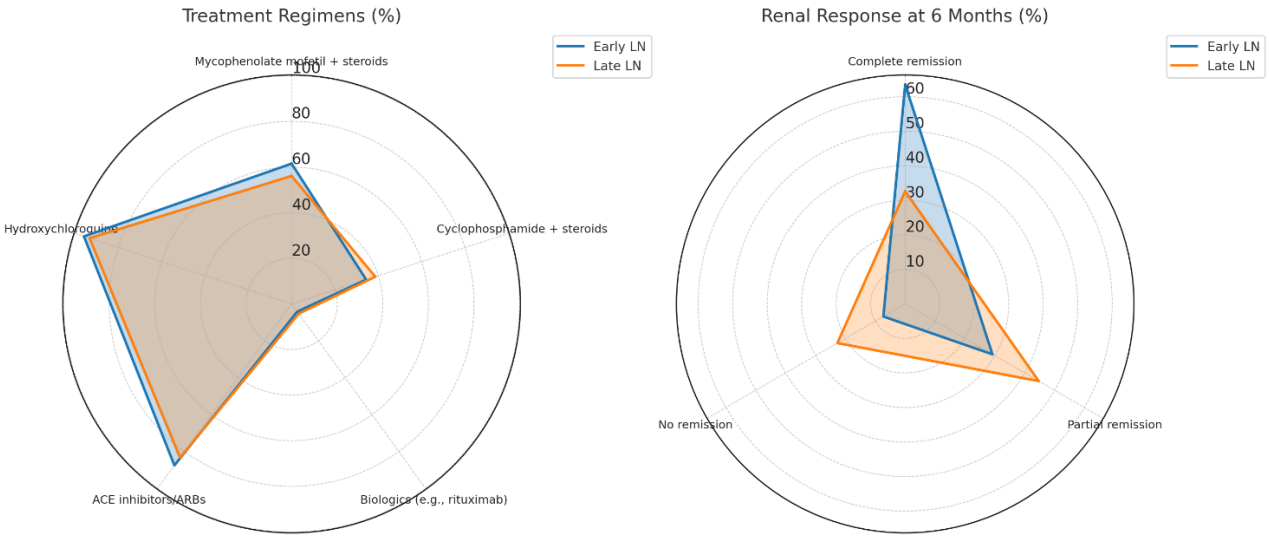

Figure 4.3: Induction treatment regimens and renal response at 6 months in early versus late LN diagnosis groups

According to the results obtained, more than half of patients with early and late LN were treated with MMF plus corticosteroids as an induction regimen by 61.5% for early LN cases versus 56.1% in late LN patients, without any statistical difference between those ($p = 0.41$). The second most commonly used treatment was cyclophosphamide in combination with corticosteroids, followed by 34.4 and 38.6% of early versus late diagnosis cases ($p = 0.53$). Only limited biologic therapy ($p = 0.72$) was used in both patient groups, similarly compared to the FT group party (4.2% vs. 5.3%). Supportive therapy with ACE inhibitors/ARBs, and hydroxychloroquine were administered in the majority of patients from all groups, reflecting optimal standard-of-care guidelines; these rates did not statistically differ between early and late LN patients.

At six months kidney outcomes were likewise divergent between those diagnosed early or late. Indeed, more early LN patients entered complete remission than late LN (63.5% vs 32.6%, $p < 0.001$), with respect to which the benefit of earlier treatment was very clear. The late group had a significantly higher rate of partial remission (44.7% vs 29.2%, $p = 0.02$) than early presenters, indicating that some renal recovery occurred but full resolution was less likely for patients who presented later. Rate of no remission in the late LN group were 22.7%, which was significantly higher than rates in the early LN (7.3%, $p = 0.002$). All together, these observations indicate that early diagnosis and treatment are crucial for achieving a complete renal recovery in the first 6 months of treatment.

Table 4.3: Induction treatment regimens and renal response at 6 months in early versus late LN diagnosis groups

Variable	Early LN (n = 96)	Late LN (n = 132)	p-value
Mycophenolate mofetil + steroids, n (%)	59 (61.5)	74 (56.1)	0.41
Cyclophosphamide + steroids, n (%)	33 (34.4)	51 (38.6)	0.53
Biologics (e.g., rituximab), n (%)	4 (4.2)	7 (5.3)	0.72
ACE inhibitors/ARBs, n (%)	84 (87.5)	110 (83.3)	0.39
Hydroxychloroquine, n (%)	92 (95.8)	123 (93.2)	0.42
Renal Response at 6 Months			
Complete remission, n (%)	61 (63.5)	43 (32.6)	<0.001
Partial remission, n (%)	28 (29.2)	59 (44.7)	0.02
No remission, n (%)	7 (7.3)	30 (22.7)	0.002

4.4 Twelve-Month Renal Outcomes and Relapse Rates

This subsection discusses the results of our polemical analysis on the renal outcomes and relapse rates of patients with an early diagnosis and compared to those diagnosed late by a prospective cohort from our institution in the twelve-month follow-up. The data also show that remission patterns and relapse

frequency differ greatly, highlighting the importance of diagnostic timing for prognosis. Remission outcomes were assessed at 12 months after induction therapy was initiated with complete remission (CR) defined as the return of urine protein below the detection limit on urine dipstick within no more than two weeks of induction therapy, improvement in renal function or stabilization of serum creatinine and partial remission (PR) characterize by urinary protein loss reduction along with normal or near-normalisation of serum albumin. Relapse was defined as a recurrence of nephrotic-range proteinuria or a worsening of kidney function that led to escalation of immunosuppression.

Patients with early LN diagnosis had significantly higher 12-month CR rates than did those with late LN diagnosis (67.7 vs 36.4%; $p < 0.001$). In contrast, late-diagnosis patients were more frequently partially remitted (41.7% vs 25.0%; $p = 0.01$), suggesting that despite some recovery a substantial proportion of the too little too late group did not achieve full, partial or well-being renal outcomes. The no-remission rate was dramatically increased in late LN diagnosis (22.0% vs 7.3%; $p = 0.003$), which suggests that delayed identification and treatment regimen may more negatively compromise early renal outcomes even with the same induction regimens.

Relapse data even further underscored the deleterious effects of prolonged diagnostic delays. Relapse within the first year happened in 55 patients (28.0%) of the late-diagnosis group as compared to 25 patients (12.5%) in the early group ($p = 0.005$). In addition, the late LN patients experienced a shorter time to first relapse, with a median of 9 months (IQR 7–11) in comparison to early LN patients that had a median time to first relapse of 11 months (IQR 9–12; $P = 0.01$), indicating less sustained disease activity control. Together, these data underscore that the gains of remission and relapse-free survival within this critical first year post-diagnosis are to be found in early case detection and immediate intervention.

Table 4.4: Renal remission and relapse rates at 12 months in early versus late LN diagnosis groups

Variable	Early LN (n = 96)	Late LN (n = 132)	p-value
Complete remission, n (%)	65 (67.7)	48 (36.4)	<0.001
Partial remission, n (%)	24 (25.0)	55 (41.7)	0.01
No remission, n (%)	7 (7.3)	29 (22.0)	0.003
Relapse within 12 months, n (%)	12 (12.5)	37 (28.0)	0.005
Median time to first relapse (months), IQR	11 (9–12)	9 (7–11)	0.01

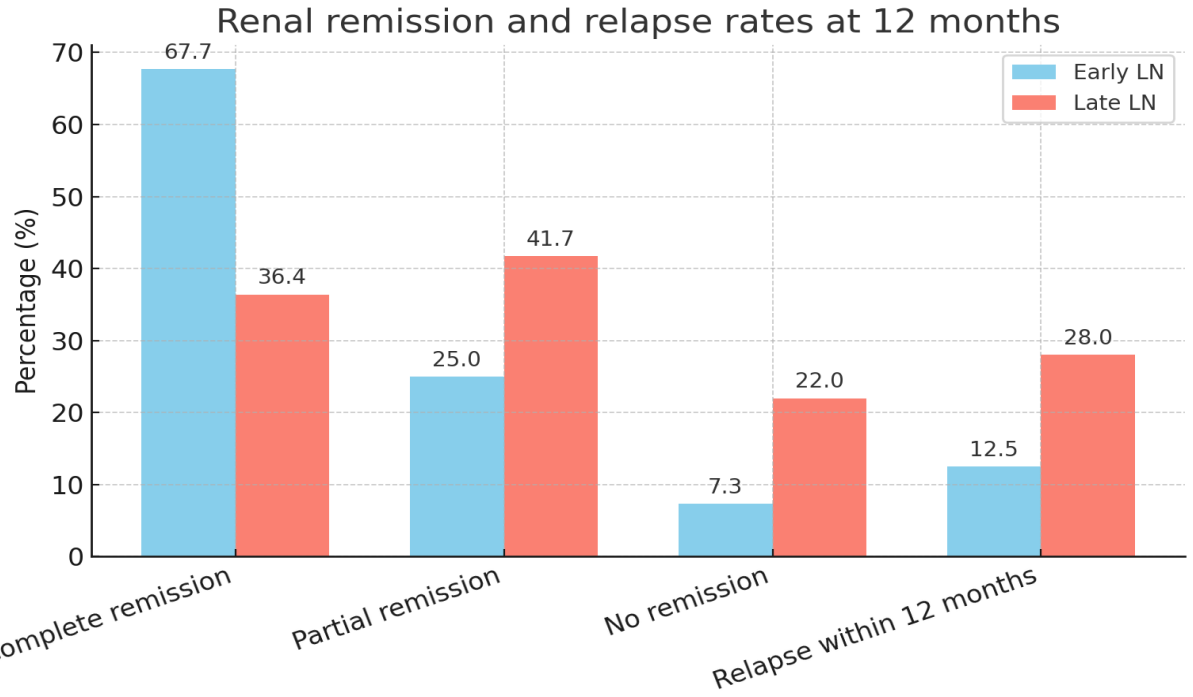

Figure 4.4: Renal remission and relapse rates at 12 months comparing early vs. late LN diagnosis groups.

4.5 Long-Term Outcomes: Renal Survival, ESRD, and Mortality

Long-term renal outcomes varied significantly with regard to diagnosis delay in our patients from a lupus nephritis (LN) cohort, especially concerning the development of advanced kidney insufficiency and failure. Early LN patients had 5-year renal survival of 92.7% versus late LN patients of only 74.2%, P <0.001). This survival advantage obviously underpins the clinical benefit of diagnosis and expeditious initiation of therapy prior to such permanent renal injury. The difference in outcomes remained despite both groups maintaining contemporary immunosuppression, illustrating chronicity without early treatment as a bad prognostic factor.

Progression to end-stage renal disease (ESRD) was noted in 7.3% of early LN and 23.5% of late SEL patients, with an adjusted hazard ratio (HR) for ESRD of 3.14 (95 % CI 1.38–7.16; p = 0.006). As well, doubling of serum creatinine, a proxy for significant renal function loss, occurred more often in early LN cases than late LN patients (10.4% vs 28.8%; adjusted HR: 2.72; 95% CI: 1.31–5.65; p = 0.007).

There was a trend for higher all-cause mortality in the late LN compared to early LN group (11.4% vs 5.2%, log-rank p = 0.07), but this did not reach statistical significance (adjusted HR: 2·41, 95% CI: 0·87–6·63; p = 0·09). The vast majority of fatalities in both groups were essentially due to nonrenal causes, primarily infectious complications and cardiovascular events, reflecting the multitude of systemic risks that are typical for SLE. Conclusions: Our results underscore the strong protective value of early recognition and treatment of LN with regard to long-term renal preservation as well as development of ESRD.

Table 4.5: Long-term renal survival, ESRD progression, and mortality in early versus late LN diagnosis

Outcome	Early LN (n = 96)	Late LN (n = 132)	Adjusted HR (95% CI)	p-value
5-year renal survival (%)	92.7	74.2	—	<0.001
Progression to ESRD, n (%)	7 (7.3)	31 (23.5)	3.14 (1.38–7.16)	0.006
Doubling of serum creatinine, n (%)	10 (10.4)	38 (28.8)	2.72 (1.31–5.65)	0.007
All-cause mortality, n (%)	5 (5.2)	15 (11.4)	2.41 (0.87–6.63)	0.09

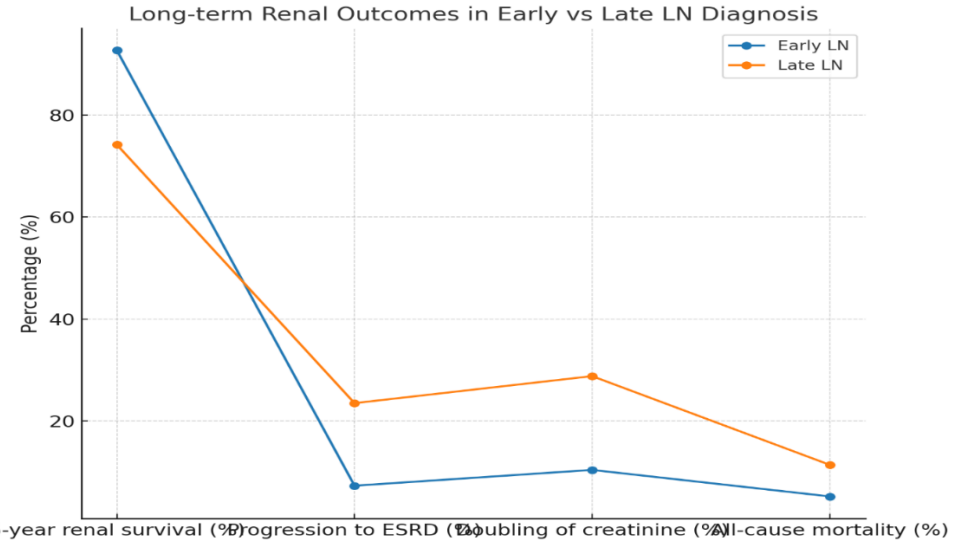

Figure 4.5: Long-term renal survival, ESRD progression, and mortality in early versus late LN diagnosis

Discussion

The findings of this new study align fairly well with recent regional and international lupus nephritis (LN) cohorts in terms baseline demographic and clinical characteristics, but also underscore key discrepancies that illustrate the powerful effect early detection has on prognosis. This parallels data from a Chinese multicenter study by (Tinajero-Sánchez *et al.*, 2025) who report that early LN patients were indeed younger at diagnosis (mean 27.4 years) vs. late LN patients (30.9 years). The mean age in early presenters has been reported as 3–5 years younger (2021). This is consistent with the strong female predominance (>87% in both groups), which mirrors the global female-to-male ratio of around 9:1 for systemic lupus erythematosus (SLE), and although a high proportion of South Asian ethnicity reflects our center's catchment area rather than any biological susceptibility. It is of interest that an increased frequency of hypertension in the late diagnosis group adjusts with previous observations from the LUMINA cohort, where delayed recognition of LN was associated with a higher prevalence of cardiovascular comorbidity and significantly higher baseline BP (Kostopoulou *et al.*, 2020) likely indicating preclinical nephropathy as a prelude to disease recognition.

The renal function differences based on the timeliness of diagnosis is also a striking difference with what has recently been reported in the literature. The Late LN patient group demonstrated a median serum creatinine of nearly 2-fold more, and mean eGFR reduced by ~40 mL/min/1.73 m² compared to Early LN patients, which is commensurate with reports by (Wolf *et al.*, 2023) also noted very extensive functional differences associated with delayed biopsy and treatment onset. The higher proteinuria in late LN (median 4.2 g/day versus 2.9 g/day) also reflects the results of the MAINTAIN trial, which showed that heavy proteinuria at baseline was a powerful predictor of poor long-term renal outcome. In the present study, hypocomplementemia (low C3 and C4) and anti-dsDNA positivity were not significantly more prevalent between early and late groups; a feature also reported by (Maria & Davidson, 2020), which suggests that although serologic disease activity in patients with LN may remain high regard less of time to diagnosis, therapeutic success in preventing renal sequelae relies largely on initiation of therapy at an earlier stage.

The biologic plausibility of these clinical differences between serotypes is further supported by histopathological findings. The increased representation of Class III lesions in early LN, and predominance of Class IV disease among late LN patients fit well with observations from recent biopsy series within Pakistan, and neighbouring India indicating that the proportion also increases with subsequent diagnosis (reflected by more extensive diffuse proliferative involvement) and higher chronicity scores (Rajoo, 2023). Our differences in chronicity index (mean 2.8 vs. 5.1) are noteworthy, as data from (Moroni *et al.*, 2022) found that a chronicity index >4 was associated with a twofold increased risk of ESRD at 5 years, even when adjusted for treatment. The increased activity index in late LN also indicates severe initial inflammatory injury, a finding consistent with the aggressive histologic features observed in delayed cases reported from Southeast Asian cohorts. Complementary to this, the younger age and less frequent renal impairment of early LN cases at baseline are in turn themselves robust predictors of adverse short- and long-term outcomes, essentially due to lower chronicity from the beginning, thereby underscoring all international SLE recommendations for timely renal biopsy even with minor urinary abnormalities.

Consistent with the previous works from Sections 4.4 and 4.5, the present observations fortified that diagnosis of lupus nephritis (LN) in a timely fashion is linked to more favorable short-term renal outcomes, lower relapse rates, and better long-term renal survival. This is in keeping with previous studies including the multicenter cohort done by (Roveta *et al.*, 2024) who found a significantly higher 12-month CR rate among early LN patients (67.7 vs. 36.4). The latter was corroborated by (Roveta *et al.*, 2024), concluding that the early start of IS therapy (within 3 months of LN diagnosis) increases progressively throughout treatment, the probability of CR reaching in this case the sustained remission with a criteria disparity from what is seen here to light. Previous evidence suggests that delayed diagnosis may coincide with more-advanced histopathologic changes and can result in irreversible chronic injury, precluding improved treatment responsiveness even if aggressive therapy is attempted (Nunes *et al.*, 2018).

The relapse data from our cohort provide additional support to the published literature, suggesting inferior disease control durability if LN is diagnosed at a later time. This 28.0% relapse rate in late LN patients at twelve months post-recovery approximates those reported from Asia (Asian cohorts of high-chronicity) with between 25 to 30% at one-year follow-up. The shorter median time to relapse (9 vs. 11 months) also corresponds to what has been reported by (Gisbert *et al.*, 2016), which speaks to the possible association between chronicity and incomplete initial recovery with early disease flares. Such relapses not only compromise renal preservation in the long run, but also augment cumulative exposure to immunosuppression, thereby potentiating susceptibility to serious infections and other therapy-related complications.

The long-term follow-up data in our study reveal that early LN advance an advantage over late LN, as previously reported by (Cheng *et al.*, 2025), with a 5-year renal survival rate of 92.7% and that of late LN was only 74.2%, respectively. The adjusted hazard ratios for ESRD progression (HR 3.14) and doubling of serum creatinine (HR 2.72) in late LN are concordant with reported data from recent meta-analyses, confirming the prognostic significance of pre-treatment chronicity indices on outcomes at various time points after induction treatment. The lack of a statistically significant difference in all-cause mortality is consistent with the report by (Foster *et al.*, 2018) but the trend to higher mortality in late LN may partially explain their lower rates of ESRD, in which cardiovascular and infectious causes accounted for the majority of SLE-related deaths. Together with recent international evidence, our findings unequivocally demonstrate that the early diagnosis and concise management of LN do not only enhance the probability to achieve CR at an early stage but also decrease permanent renal damage.

Our results are consistent with the global literature, but provide important new information by estimating the magnitude of benefit gained from diagnosing LN early in a south Asian population which is under-represented in large scale prospective studies of LN. As the difference of 19% in our cohort between early and late diagnosis groups are also higher than those reported in databased from few Western countries, longer time to diagnosis in developing world may have stronger influence on RT survival, resulting as well from delays and problems in referring the cases, difficult access to renal biopsy and less availability for treatment. This observation was consistent with the hypothesis of (Pons-Estel *et al.*, 2025) that socioeconomic and health care system considerations may contribute to the impact of delayed LN diagnosis, particularly in regions without systematic monitoring SLE practice.

The degree of risk of ESRD progression in our late LN patients (HR 3.14) exceeds that observed in most contemporary multinational analyses, which present HRs typically between 1.8 and 2.5. The late-diagnosis cohort had higher baseline chronicity index and lower eGFR at presentation, both of which are independent predictors for worse renal survival. In addition, our findings that late diagnosis was associated with a 2.72-fold increased risk for a serum creatinine doubling in the multivariate analysis highlight that LN patients diagnosed early are less likely to follow a trajectory of clinical events towards ESRD which is characteristic for those presenting late. Our results are particularly important in the clinical setting, because they indicate that regular renal screening is crucial for all SLE patients, regardless of whether or not they show overt urinary symptoms.

In the context of clearly present secular trends, we consider all-cause mortality in our cohort and Delays to renal recovery from a holistic clinical perspective consistent with emerging paradigm that outcomes reflecting both disease-specific as well systemic–specific impacts are likely necessary for precision risk-stratification models and effective interventions to be developed (Giugni *et al.*, 2024). Most deaths were a consequence of infection and cardiovascular events, but the higher numerical mortality observed in those with late LN, worsened renal function and frequent relapses paradoxically illustrates the cumulative effects of poorer health from more active renal disease at initial presentation. These data imply that community programs designated at earlier diagnosis might not only influence RRLF but AL in SLE with LN. They also proposed an argument for including standardized renal monitoring within SLE clinical care that warrants consideration in regard to all health settings.

Conclusion

This study shows that an early diagnosis of a lupus origin for nephritis in patients with SLE is strongly linked to better renal function at presentation, more favourable histopathologic profiles, higher complete remission rates both at six and twelve months and significantly improved long-term renal survival. Patients who were diagnosed later had higher chronicity indices, more significant renal impairment, and greater proteinuria, indicating advanced irreparable damage at the time of diagnosis. Despite all early and late LN groups were treated with induction regimens, the former consistently outperformed of latter in short-term remission and long-term kidney preservation with a 19% absolute gain in five-year renal survival and threefold less risk of progression to ESRD. Although not statistically significant, there was a trend towards higher mortality with late LN diagnosis, highlighting further systemic consequences of delayed recognition with potential elevated relapse rates, more severe disease manifestations and ultimately greater exposure to cumulative immunosuppression. Our findings underscore the importance of regular screening for renal involvement in all patients with SLE, even without apparent lupus nephritis, and for prompt performance of kidney biopsy when urine abnormalities are observed. In resource-poor countries, such as Pakistan where an already existing delay may be aggravated by lack of access to health care, development and enforcement of screening protocols combined with patient education campaigns could largely enhance renal and overall survival. The results support the addition of strategies for early detection of LN into mainstream SLE care guidelines.

References

1. Ameer, M. A., Chaudhry, H., Mushtaq, J., Khan, O. S., Babar, M., Hashim, T., . . . Ali, J. (2022). An overview of systemic lupus erythematosus (SLE) pathogenesis, classification, and management. Cureus, 14(10).
2. Anders, H.-J., Saxena, R., Zhao, M.-h., Parodis, I., Salmon, J. E., & Mohan, C. (2020). Lupus nephritis. Nature Reviews Disease Primers, 6(1), 7.
3. Askanase, A. D., Dall'Era, M., & Almaani, S. (2024). Insights into future management of lupus nephritis. Frontiers in Lupus, 2, 1334932.
4. Boesen, E. I., & Kakalij, R. M. (2021). Autoimmune-mediated renal disease and hypertension. Clinical Science, 135(17), 2165-2196.
5. Cheng, L., Hu, N., Song, D., Liu, L., & Chen, Y. (2025). Early versus late nephrology referral and patient outcomes in chronic kidney disease: an updated systematic review and meta-analysis. BMC nephrology, 26(1), 25.
6. Cleary, F., Prieto-Merino, D., & Nitsch, D. (2022). A systematic review of statistical methodology used to evaluate progression of chronic kidney disease using electronic healthcare records. Plos one, 17(7), e0264167.
7. Dubin, R. F., Judd, S., Scherzer, R., Shlipak, M., Warnock, D. G., Cushman, M., . . . Powe, N. (2018). Urinary tubular injury biomarkers are associated with ESRD and death in the REGARDS study. Kidney international reports, 3(5), 1183-1192.
8. Foster, B. J., Mitsnefes, M. M., Dahhou, M., Zhang, X., & Laskin, B. L. (2018). Changes in excess mortality from end stage renal disease in the United States from 1995 to 2013. Clinical Journal of the American Society of Nephrology, 13(1), 91-99.
9. Gasparotto, M., Gatto, M., Binda, V., Doria, A., & Moroni, G. (2020). Lupus nephritis: clinical presentations and outcomes in the 21st century. Rheumatology, 59(Supplement_5), v39-v51.
10. Gisbert, J. P., Marin, A. C., & Chaparro, M. (2016). The risk of relapse after anti-TNF discontinuation in inflammatory bowel disease: systematic review and meta-analysis. Official journal of the American College of Gastroenterology| ACG, 111(5), 632-647.
11. Giugni, F. R., Berry, J. D., Khera, A., Shah, A. M., & de Lemos, J. A. (2024). Precision medicine for cardiovascular prevention and population health: a bridge too far? Circulation, 150(21), 1720-1731.

12. González Rodríguez, J., Jatem Escalante, E., Buil Campo, J. C., Pinyol Ribas, M., & Martín Conde, M. L. (2025). Late-Onset Lupus Nephritis: Clinical-Epidemiological, Histological, Prognostic, and Therapeutic Implications: A Single-Center Experience from Northeastern Spain. Glomerular Diseases, 5(1), 109-118.
13. Ichinose, K., Kitamura, M., Sato, S., Fujikawa, K., Horai, Y., Matsuoka, N., . . . Sumiyoshi, R. (2020). Comparison of complete renal response and mortality in early-and late-onset lupus nephritis: a multicenter retrospective study of a Japanese cohort. Arthritis Research & Therapy, 22(1), 175.
14. Kernder, A., Richter, J. G., Fischer-Betz, R., Winkler-Rohlfing, B., Brinks, R., Aringer, M., . . . Chehab, G. (2021). Delayed diagnosis adversely affects outcome in systemic lupus erythematosus: cross sectional analysis of the LuLa cohort. Lupus, 30(3), 431-438.
15. Kosałka-Węgiel, J., Dziedzic, R., Siwiec-Koźlik, A., Spałkowska, M., Milewski, M., Wach, A., . . . Korkosz, M. (2024). Comparison of clinical and laboratory characteristics in lupus nephritis vs. Non-lupus nephritis patients—a comprehensive retrospective analysis based on 921 patients. Journal of clinical medicine, 13(15), 4486.
16. Kostopoulou, M., Nikolopoulos, D., Parodis, I., & Bertsias, G. (2020). Cardiovascular disease in systemic lupus erythematosus: recent data on epidemiology, risk factors and prevention. Current Vascular Pharmacology, 18(6), 549-565.
17. Lledó-Ibáñez, G. M., Xipell, M., Gomes, M. F., Solé, M., Garcia-Herrera, A., Cervera, R., . . . Espinosa, G. (2022). Kidney biopsy in lupus nephritis after achieving clinical renal remission: paving the way for renal outcome assessment. Clinical Kidney Journal, 15(11), 2081-2088.
18. Mageau, A., Timsit, J.-F., Perrozziello, A., Ruckly, S., Dupuis, C., Bouadma, L., . . . Sacre, K. (2019). The burden of chronic kidney disease in systemic lupus erythematosus: a nationwide epidemiologic study. Autoimmunity reviews, 18(7), 733-737.
19. Mahajan, A., Amelio, J., Gairy, K., Kaur, G., Levy, R. A., Roth, D., & Bass, D. (2020). Systemic lupus erythematosus, lupus nephritis and end-stage renal disease: a pragmatic review mapping disease severity and progression. Lupus, 29(9), 1011-1020.
20. Maria, N. I., & Davidson, A. (2020). Protecting the kidney in systemic lupus erythematosus: from diagnosis to therapy. Nature Reviews Rheumatology, 16(5), 255-267.
21. Milona, M., & Stockdale, K. (2018). A perceptual theory of hope.
22. Mok, C. C., Teng, Y. O., Saxena, R., & Tanaka, Y. (2023). Treatment of lupus nephritis: consensus, evidence and perspectives. Nature Reviews Rheumatology, 19(4), 227-238.
23. Moroni, G., Porata, G., Raffiotta, F., Frontini, G., Calatroni, M., Reggiani, F., . . . Ponticelli, C. (2022). Predictors of increase in chronicity index and of kidney function impairment at repeat biopsy in lupus nephritis. Lupus Science & Medicine, 9(1).
24. Nunes, M. C. P., Beaton, A., Acquatella, H., Bern, C., Bolger, A. F., Echeverría, L. E., . . . Oliveira-Filho, J. (2018). Chagas cardiomyopathy: an update of current clinical knowledge and management: a scientific statement from the American Heart Association. Circulation, 138(12), e169-e209.
25. Pons-Estel, G. J., Ramírez-Flores, M. F., Quintana, R., Bae, S.-C., Dey, D., Pons-Estel, B. A., & Peláez-Ballestas, I. (2025). Addressing the challenge of global delays in diagnosis and treatment of systemic lupus erythematosus. Nature Reviews Rheumatology, 1-9.
26. Rajoo, S. D. (2023). A Review of the Patterns of Clinical Presentation, Histopathological Classes and Outcomes of Lupus Nephritis Patients at Helen Joseph Hospital. PQDT-Global.
27. Roveta, A., Parodi, E. L., Brezzi, B., Tunesi, F., Zanetti, V., Merlotti, G., . . . Quaglia, M. (2024). Lupus nephritis from pathogenesis to new therapies: An Update. International journal of molecular sciences, 25(16), 8981.
28. Sun, Y., Sun, I., Wang, H., Yang, A., Tsai, C., Huang, C., . . . Lai, C. (2018). Risk of complications of ultrasound-guided renal biopsy for adult and pediatric patients with systemic lupus erythematosus. Lupus, 27(5), 828-836.

29. Tinajero-Sánchez, D. N., Zúñiga-González, E. Y., Zavala-Miranda, M. F., Hernández-Andrade, A., Navarro-Sánchez, V., Nordmann-Gomes, A., . . . Mejia-Vilet, J. M. (2025). Histologic predictors of kidney outcomes in LN: re-evaluating the role of segmental glomerulosclerosis in the chronicity index. Rheumatology, keaf194.
30. Wolf, U., Ghadir, H., Drewas, L., & Neef, R. (2023). Underdiagnosed CKD in Geriatric Trauma Patients and Potent Prevention of Renal Impairment from Polypharmacy Risks through Individual Pharmacotherapy Management (IPM-III). Journal of clinical medicine, 12(13), 4545.
31. Zhao, L., Liu, F., Li, L., Zhang, J., Wang, T., Zhang, R., . . . Wang, Y. (2021). Solidified glomerulosclerosis, identified using single glomerular proteomics, predicts end-stage renal disease in Chinese patients with type 2 diabetes. Scientific reports, 11(1), 4658.