EXTENDED REPORT

# Changing patterns in clinical–histological presentation and renal outcome over the last five decades in a cohort of 499 patients with lupus nephritis

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## ABSTRACT

**Objectives** To evaluate changes in demographic, clinical and histological presentation, and prognosis of lupus nephritis (LN) over time.

**Patients and methods** We studied a multicentre cohort of 499 patients diagnosed with LN from 1970 to 2016. The 46-year follow-up was subdivided into three periods (P): P1 1970–1985, P2 1986–2001 and P3 2002–2016, and patients accordingly grouped based on the year of LN diagnosis. Predictors of patient and renal survival were investigated by univariate and multivariate proportional hazards Cox regression analyses. Survival curves were compared using the log-rank test.

**Results** A progressive increase in patient age at the time of LN diagnosis ($p<0.0001$) and a longer time between systemic lupus erythematosus onset and LN occurrence ($p<0.0001$) was observed from 1970 to 2016. During the same period, the frequency of renal insufficiency at the time of LN presentation progressively decreased ($p<0.0001$) and that of isolated urinary abnormalities increased ($p<0.0001$). No changes in histological class and activity index were observed, while chronicity index significantly decreased from 1970 to 2016 ($p=0.023$). Survival without end-stage renal disease (ESRD) was 87% in P1, 94% in P2% and 99% in P3 at 10 years, 80% in P1 and 90% in P2 at 20 years ($p=0.0019$). At multivariate analysis, male gender, arterial hypertension, absence of maintenance immunosuppressive therapy, increased serum creatinine, and high activity and chronicity index were independent predictors of ESRD.

**Conclusions** Clinical presentation of LN has become less severe in the last years, leading to a better long-term renal survival.

## INTRODUCTION

Lupus nephritis (LN) is a frequent and severe manifestation of systemic lupus erythematosus (SLE) and is characterised by a relapsing and remitting clinical course.[1–4] Renal involvement occurs at the time of SLE diagnosis or during the course of the disease in up to two-thirds of patients.[5 6] Clinical presentation varies from asymptomatic urinary abnormalities to chronic irreversible renal insufficiency.[7] Although renal involvement is still considered a strong predictor of death and end-stage renal disease (ESRD),[8 9] both patient and renal survival have significantly improved in the last few decades[10–13] and the rate of renal flares has considerably decreased over time as well.[3] The improvement in LN prognosis has been attributed to many factors including the better understanding of SLE pathogenesis, new treatment options and strategies, and improved management of hypertension, infections and other comorbidities.[14]

To the best of our knowledge, no studies have evaluated whether changes in demographic, clinical and histological features at the time of LN presentation have occurred over the last decades and whether these changes have had an influence on the disease management and outcome.

The objective of our study was to examine the changes in demographic, clinical and histological features at the time of LN onset in a large cohort of patients during a 46-year follow-up. We looked at changes in LN prognosis during the course of the follow-up and searched for the prognostic factors associated with patient and renal outcomes.

## PATIENTS AND METHODS

Four hundred and ninety-nine patients were included in this retrospective study of prospectively collected data. Inclusion criteria were American College of Rheumatology criteria-based diagnosis of SLE[15] and biopsy-proven LN performed between January 1970 and December 2016. Patients were followed in four Italian referral centres: Renal Divisions of Ospedale Maggiore Milano, San Carlo Hospital Milano and University of Parma, and Rheumatology Unit of Padova University. Since the 1980s, according to the good clinical practice, patients undergoing renal biopsy in Italy signed informed consent that includes the consent for using clinical data for scientific purposes, while in previous years no consent was required for this type of studies. The study was approved by the local ethics committees. The 46-year follow-up was subdivided into three periods (P), 15 years each: P1 from January 1970 to December 1985, P2 from January 1986 to December 2001 and P3 from January 2002 to December 2016, and patients



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accordingly grouped based on the year of LN diagnosis. Detailed data on the source population and study design are reported in table 1 and online supplementary text S1. Notably, 70.3% of the overall source population had biochemical and/or urinary abnormalities of lupus nephritis. The high proportion of patients with LN is due to the fact that three of the four centres participating in this study were Nephrology Units.

All patients received a renal biopsy that was classified according to the International Society of Nephrology/Renal Pathology Society (IRS/RPS) classification criteria.[16] Since 2003, all renal biopsies performed before 2002 were reclassified according to the same IRS/RPS classification criteria by the clinicians and pathologists based on written reports of light microscopy and immunofluorescence or the re-evaluation of slides, where necessary. Activity and chronicity indices were calculated according to the score proposed by Austin *et al*.[17] Estimated glomerular filtration rate (eGFR) was calculated according to the Cockcroft and Gault formula based on gender, serum creatinine, age and body weight of the patients. Normal renal function was defined as serum creatinine ≤1 mg/dL and eGFR >60 mL/min that correspond to the definition of CKD 1 and 2. Proteinuria was measured by benzethonium chloride on the urine collected over 24 hours expressed as grams per 24 hours. Arterial hypertension was defined as the mean of three consecutive measurements

**Table 1** Description of source population and features of patients included in the study

| | Overall | P1 | P2 | P3 | P values |
|---|---|---|---|---|---|
| (A) Source population | | | | | |
| All patients with SLE, N | 793 | 162 | 249 | 382 | – |
| Patients with LN, N (%) | 557 (70.2) | 124 (76.5) | 174 (69.8) | 259 (67.8) | ns |
| Patients with renal biopsy, N (%)* | 499 (89.6) | 106 (85.5) | 158 (90.8) | 235 (90.7) | ns |
| Patients without renal biopsy, N (%)* | 58 (6.1) | 18 (14.5) | 16 (9.2) | 24 (9.3) | ns |
| Lost to follow-up, N (%) | 21 (3.7) | 2 (1.2) | 6 (2.4) | 13 (3.4) | ns |
| (B) Clinical features of patients with renal biopsy | | | | | |
| | Overall 499 patients | P1 106 patients | P2 158 patients | P3 235 patients | |
| Gender, female, N (%) | 427 (85.6) | 99 (93.4) | 139 (88) | 189 (80.4) | 0.004 |
| Age at SLE diagnosis, years | 28.11±12.0 | 27±10.3 | 26.3±11.2 | 29.8±13 | 0.01 |
| Age at LN diagnosis, years | 31.4±12.5 | 28.4±10.4 | 29±11.5 | 34.4±13.3 | 0.001 |
| Disease duration before LN diagnosis, years | 3.3±5.3 | 1.3±1.3 | 2.6±4.5 | 4.6±6.3 | <0.0001 |
| Follow-up duration, years | 12.7±9.8 | 20.5±13 | 15.8±7.8 | 6.8±4.3 | |
| Weight, kg | 61.7±12.2 | 57.4±10.4 | 62±11.2 | 63.3±13.1 | ns |
| Hypertension, N (%) | 240 (48.2%) | 56 (52.8%) | 77 (48.7%) | 107 (45.9%) | ns |
| Serum creatinine, mg/dL | 1.2±1.1 | 1.8±1.8 | 1.2±0.8 | 1.0±0.7 | <0.0001 |
| Creatinine clearance, mL/min | 86.3±41 | 72.2±45.1 | 83.7±36.6 | 94.1±40.2 | 0.0001 |
| Proteinuria, g/24 hours | 4.1±3.7 | 3.6±2.7 | 4.5±4.0 | 4.1±3.9 | ns |
| Urinary erythrocytes/HPF | 27.7±45.7 | 18.6±18.6 | 24.2±24.3 | 34.1±61.9 | 0.01 |
| Serum albumin, g/dL | 3.0±0.7 | 2.7±0.7 | 3.0±0.7 | 3±0.7 | 0.005 |
| Haematocrit, % | 33.5±6.2 | 33.3±7.3 | 33.8±5.5 | 33.4±6 | ns |
| White blood cells/$10^3$/mL | 6252±3223 | 6258±2842 | 6180±2888 | 6299±3603 | ns |
| Platelets/109/L | 240 302±96 198 | 230 422±103 282 | 252 193±97 365 | 236 641±91 640 | ns |
| C3, mg/dL | 62.1±25.4 | 65.1±22.6 | 58.7±25.4 | 63.1±26.3 | ns |
| C4, mg/dL | 13.7±14.3 | 20.7±20.2 | 14.7±15.8 | 10.2±8 | 0.001 |
| Anti-dsDNA, positive N (%) (NA 25) | 414 (87.3) | 82 (93.6) | 128 (85.3) | 204 (90.3) | ns |
| Urinary abnormalities | 203 (40.7) | 28 (26.4) | 60 (38) | 115 (48.9) | <0.0001 |
| Nephrotic syndrome | 174 (34.9) | 32 (30.2) | 59 (37.3) | 83 (35.4) | ns |
| Nephritic syndrome | 92 (18.4) | 31 (29.2) | 32 (20.3) | 29 (12.4) | 0.0001 |
| Rapidly progressive renal insufficiency | 30 (9.0) | 15 (14.2) | 7 (3.9) | 8 (3.4) | <0.0001 |
| Histological classes, N (%) | | | | | |
| II | 22 (4.4) | 5 (4.8) | 4 (2.5) | 13 (5.5) | ns |
| III† | 115 (23.1) | 23 (21.9) | 28 (17.8) | 64 (27.2) | ns |
| IV† | 267 (53.7) | 56 (53.3) | 91 (58) | 120 (51.1) | ns |
| V | 93 (18.7) | 21 (20) | 34 (21.7) | 38 (16.2) | ns |
| VI | 2 (0.4) | 1 (0.9) | 1 (0.6) | 0 (0) | ns |
| Activity index | 6.4±4.9 | 6.2±4.9 | 6.6±4.9 | 5.9±4.5 | ns |
| Chronicity index | 2.0±2.2 | 2.6±2.5 | 2.0±2.2 | 1.6±2 | 0.0023 |

(A) Number of patients with SLE followed in the four centres (three Nephrology Units and one Rheumatology Unit) and number of patients with clinical diagnosis of lupus nephritis who underwent or did not undergo renal biopsy, overall and subdivided according to the different periods. (B) Clinical features at the time of lupus nephritis diagnosis in patients who underwent renal biopsy, overall and according to the three different periods. P values refer to t-test, Kruskal-Wallis test or $\chi^2$ test (with 2 df), according to the type and distribution of variables.
*Percentages refer to the number of patients who received renal biopsy (n=557).
†Class III+V: overall, four patients; P1, three patients; P2, one patient, P3, no cases. Class IV+V: overall, 31 patients; P1, 2 patients, P2, 8 patients; P3, 21 patients.
P, period; P1: 1970–1985; P2: 1986–2001; P3: 2002–2016.
C3/C4, complement components; HPF, high-power field; LN, lupus nephritis; NA, not available; N, number; ns, not significant; SLE, systemic lupus erythematosus.



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of systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg in sitting position. Data on death were obtained from hospital charts for patients who died in hospital and through information obtained from relatives for other patients.

### Definitions

Clinical syndromes at presentation were defined as follows:

- Isolated urinary abnormalities: normal renal function, proteinuria <3.5 g/24 hours and >0.5 g/24 hours, and/or microscopic haematuria (urinary red blood cells >5/high-power field (HPF)) after having excluded non-renal causes;
- Nephrotic syndrome: normal renal function, proteinuria >3.5 g/24 hours and serum albumin <3.5 g/dL;
- Acute nephritic syndrome: acute renal dysfunction (serum creatinine >1 mg/dL and eGFR <60 mL/min), macroscopic or severe microscopic haematuria (urinary red blood cells >20/HPF) and/or erythrocyte casts, arterial hypertension and variables degrees of proteinuria;
- Rapidly progressive renal insufficiency: rapid deterioration of renal function leading to CKD stage 3 to 5 within a few weeks, with oliguria, arterial hypertension and severe haematuria.
- Renal states at last observation were defined as follows: complete renal remission, serum creatinine <1 mg/dL with eGFR >60 mL/min, proteinuria <0.5 g/day and inactive urinary sediment; partial renal remission, serum creatinine <1 mg/dL with eGFR >60 mL/min and proteinuria <3.5 g/day and ≥0.5 g/day; CKD, serum creatinine >1.0 mg/dL with eGFR <60 mL/min and inactive urinary sediment, confirmed by at least three determinations; ESRD, the need of renal replacement therapy; Poor renal outcome, CKD or ESRD.

### Statistical analysis

Mean±SD or median and IQR were used for descriptive statistics, according to variable distribution. Temporal trends of clinical parameters were tested through Pearson or Spearman correlation analysis, according to parametric or non-parametric variable distribution. Survival curves were drawn using the Kaplan-Meier estimate and compared using the log-rank test. Univariate and multivariate proportional hazards Cox regression analyses were used to investigate the prognostic value of continuous and binary (dichotomised) variables. Patients lost to follow-up were 2/106 (1.9%) in P1, 6/158 (3.8%) in P2 and 13/235 (5.5%) in P3. These low numbers of patients and the lack of a significant clinical deterioration at their last available follow-up suggest that censoring due to loss to follow-up was likely to be minimal and non-informative. The statistical package S-Plus was used to analyse sample data.[18]

## RESULTS

### Demographic characteristics

Four hundred and ninety-nine patients (427 women, 85.6%) were included in the study; they were followed for a median period of 10.6 years (IQR 4–18). All but 51 (10.2%) patients were Caucasian. Demographic, clinical and histological features of the cohort at the time of LN diagnosis are reported in table 1. The cohort was subdivided into three groups according to the year of LN diagnosis: group 1 included 106 patients (21%) diagnosed with LN in P1; group 2 encompassed 158 patients (32%) diagnosed with LN in P2; group 3 comprised 235 patients (47%) diagnosed with LN in P3.

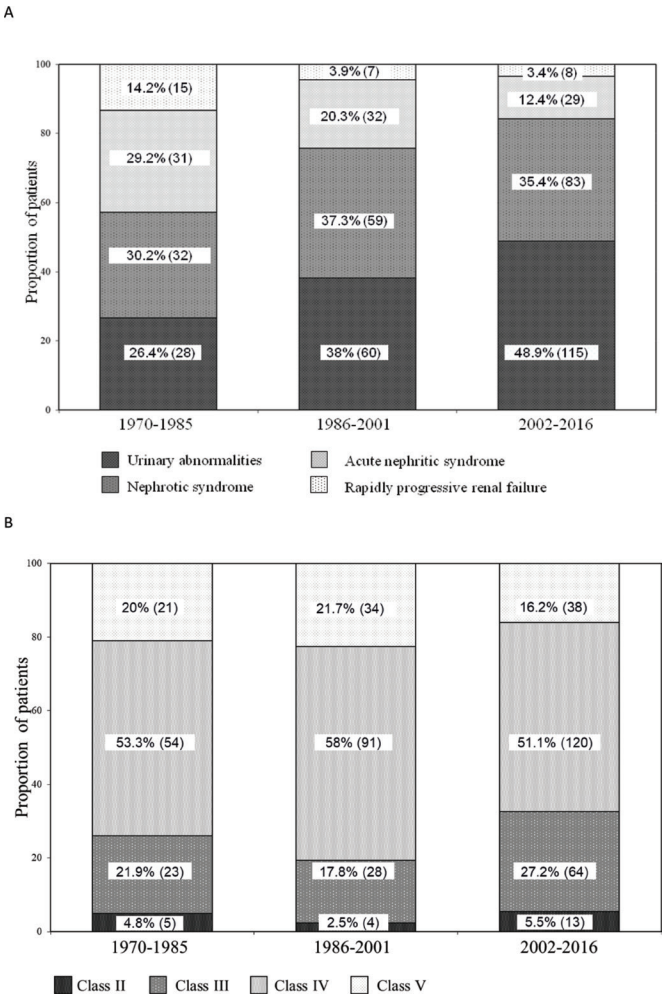


**Figure 1** (A) Clinical syndrome at presentation of lupus nephritis in three different periods. (B) Histological classes at renal biopsy in three different periods.

The number of male patients progressively increased over the three periods: 6.6% in P1, 12% in P2 and 19.6% in P3 (p=0.004). The lag time between SLE and LN diagnosis (p<0.0001) progressively increased from 1970 to 2016. The mean age at the time of LN occurrence increased from 28.4±10.4 in P1 to 29±11.5 in P2, and to 34.4±13.3 in P3 (p<0.001).

### Clinical and histological presentation

The mean values of serum creatinine progressively decreased overtime: 1.8±1.8 mg/dL in P1, 1.2±0.8 mg/dL in P2 and 1.0±0.7 mg/dL in P3 (p<0.0001). Consistently, a significant decrease in the frequency of acute nephritic syndrome (p=0.0001) and rapidly progressive renal insufficiency (p=0.0001) was observed, together with a significant increase in the prevalence of isolated urinary abnormalities from the first to the third period (p<0.001) (figure 1A). The rate of nephrotic syndrome presentation was similar in the three periods. Creatinine serum levels, eGFR, proteinuria and urinary red blood cells in patients with the different clinical syndromes at the time of LN diagnosis by the three periods are reported in online supplementary table S1.

No differences in the percentage of histological classes in the three periods were observed (table 1 and figure 1B). Interestingly, an increase in mixed forms (class III+IV and IV+V) from P1 (4.7% of cases) to P2 (12.6%) and P3 (17.4%) (p=0.006) was



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**Table 2** Induction and maintenance therapy, and outcomes in all patients and according to the three different periods

| | Overall 499 patients | P1 106 patients | P2 158 patients | P3 235 patients | P values |
|---|---|---|---|---|---|
| Methylprednisolone pulses, N (%) | 351 (70.3) | 63 (67.7) | 120 (83.9) | 168 (73.7) | 0.01 |
| Immunosuppressive drugs, induction | | | | | |
| None, N (%) | 66 (13.2) | 28 (29) | 26 (17.9) | 12 (5.4) | <0.0001 |
| Cyclophosphamide, N (%) | 258 (51.7) | 49 (51) | 95 (65.5) | 114 (51.3) | 0.016 |
| Azathioprine, N (%) | 42 (8.4) | 15 (15.6) | 18 (12.4) | 9 (4.0) | <0.0001 |
| Mycophenolate, N (%) | 79 (15.8) | 0 | 4 (2.7) | 75 (33.8) | <0.0001 |
| Others*, N (%) | 17 (3.4) | 3 (3.1) | 2 (1.4) | 12 (5.4) | ns |
| Immunosuppressive drugs, maintenance | | | | | |
| None, N (%) | 140 (28) | 66 (68.7) | 50 (34) | 24 (10.9) | <0.0001 |
| Cyclophosphamide, N (%) | 7 (1.4) | 1 (1) | 5 (3.4) | 1 (0.45) | ns |
| Azathioprine, N (%) | 152 (30.4) | 27 (28) | 58 (39) | 67 (30.6) | ns |
| Mycophenolate, N (%) | 143 (28.6) | 1 (1) | 22 (15.1) | 120 (54.8) | <0.0001 |
| Others*, N (%) | 18 (3.6) | 0 | 11 (7.5) | 7 (3.2) | ns |
| Outcomes† | | | | | |
| Partial renal remission, N (%) | 122 (25.5) | 7 (6.9) | 43 (28.1) | 72 (32.1) | <0.0001 |
| Complete renal remission, N (%) | 246 (51.4) | 41 (49.6) | 74 (48.4) | 131 (58.5) | 0.01 |
| CKD, N (%) | 31 (6.4) | 8 (7.9) | 13 (8.5) | 10 (4.5) | <0.0001 |
| ESRD, N (%) | 42 (8.8) | 25 (24.8) | 14 (9.1) | 3 (1.3) | <0.0001 |
| Death, N (%) | 37 (7.7) | 20 (19.8) | 9 (5.9) | 8 (3.6) | <0.0001 |

P, period; P1: 1970–1985; P2:1986–2001; P3: 2002–2016. P values refer to $\chi^2$ test with 2 df.
*'Others' includes ciclosporin A, methotrexate, rituximab.
†Outcome was available in 478 patients (P1, 101 patients; P2, 153 patients; P3, 224 patients).
CKD, chronic kidney disease; ESRD, end-stage renal disease.

noted. Activity index did not significantly change over the three periods either when all the classes were considered (table 1) or when patients with class III (4.95±2.9 in P1, 5.6±3.1 in P2 and 5.9±4.5 in P3, p=ns) and class IV (9.4±4.9 in P1, 9.4±3.7 in P2 and 9.4±3.8 in P3, p=ns) were separately analysed. Conversely, chronicity index significantly decreased (p=0.0023) from P1 to P3 (table 1).

### Treatment

More than two-thirds of patients in each period were treated with methylprednisolone pulses as induction therapy. In P1, 29% of patients received corticosteroids alone for induction therapy in comparison with 17.9% in P2% and 5.4% in P3 (p<0.0001). Immunosuppressive drugs were added to corticosteroids for maintenance therapy in 30.5% of patients in P1, 65.5% in P2% and 89.1% in P3 (p<0.0001). The immunosuppressive drugs used in induction and maintenance therapy during the three periods are reported in table 2. More than 50% of patients in each period received cyclophosphamide as induction therapy (online supplementary table S2). A decrease in the use of azathioprine as induction therapy from P1 to P3 was counterbalanced by an increase in the use of mycophenolate mofetil (MMF). As far as maintenance therapy is concerned, the proportion of patients receiving azathioprine remained stable in the first two periods and decreased in the third period (p<0.0001), while MMF use significantly increased in the last period compared with the previous ones (p<0.0001). Notably, the proportion of patients who were not treated with induction therapies progressively decreased over time (p<0.0001).

### Renal outcome and predictors of renal survival

Outcome was available in 478 patients (95.8%) (table 2). At last observation, complete renal remission was observed in 49.6% of patients in P1, 48.4% in P2% and 58.5% in P3 (p=0.01) (table 2). CKD and ESRD occurred in 7.9% and 24.8% of patients in P1, in 8.5% and 9.1% in P2 and in 4.5% and in 1.3% in P3, respectively (p<0.0001 for all comparisons). Twenty patients in P1 died (19.8%), in comparison with 9 (5.9%) in P2 and 8 (3.6%) in P3 (p<0.0001). The CKD-free survival at 10 and at 20 years was 75% and 66% in P1, 85.5% and 80.2% in P2%, and 91.5% in P3, respectively (p=0.0069) (figure 2A). The ESRD-free survival at 10 and at 20 years were respectively 87% and 80% in P1, 94% and 90% in P2%, and 99% in P3, respectively (p=0.0019) (figure 2B). Predictors of CKD and ESRD at univariate analyses are reported in table 3.

At multivariate analysis, carried out in the entire cohort, several factors at the time of the diagnosis of LN were independently associated with poor renal outcomes (CKD or ESRD) including baseline serum creatinine, high activity and chronicity index, arterial hypertension and the absence of maintenance immunosuppressive therapy (table 4). In addition, male gender, older age and high serum creatinine were predictors of death (table 4).

## DISCUSSION

Our study outlines the most significant changes observed during the last five decades in demographic, clinical and histological features of LN at presentation. These results were drawn from a large multicentric cohort of patients followed in four Italian referral centres from 1970 to 2016. In order to identify changes in LN presentation, the whole observational time was subdivided into three periods, 15 years each.

Historically, from 1970 to 1985 (P1) corticosteroid monotherapy was progressively replaced by combination treatment of corticosteroids with either azathioprine or cyclophosphamide probably due to the results of a pooled analysis that showed the superiority of combined immunosuppressive regimens over corticosteroids alone.[19] Intravenous methylprednisolone pulses were also largely used in this period.[20 21] From 1986 to 2001 (P2), high-dose intravenous cyclophosphamide was commonly used as



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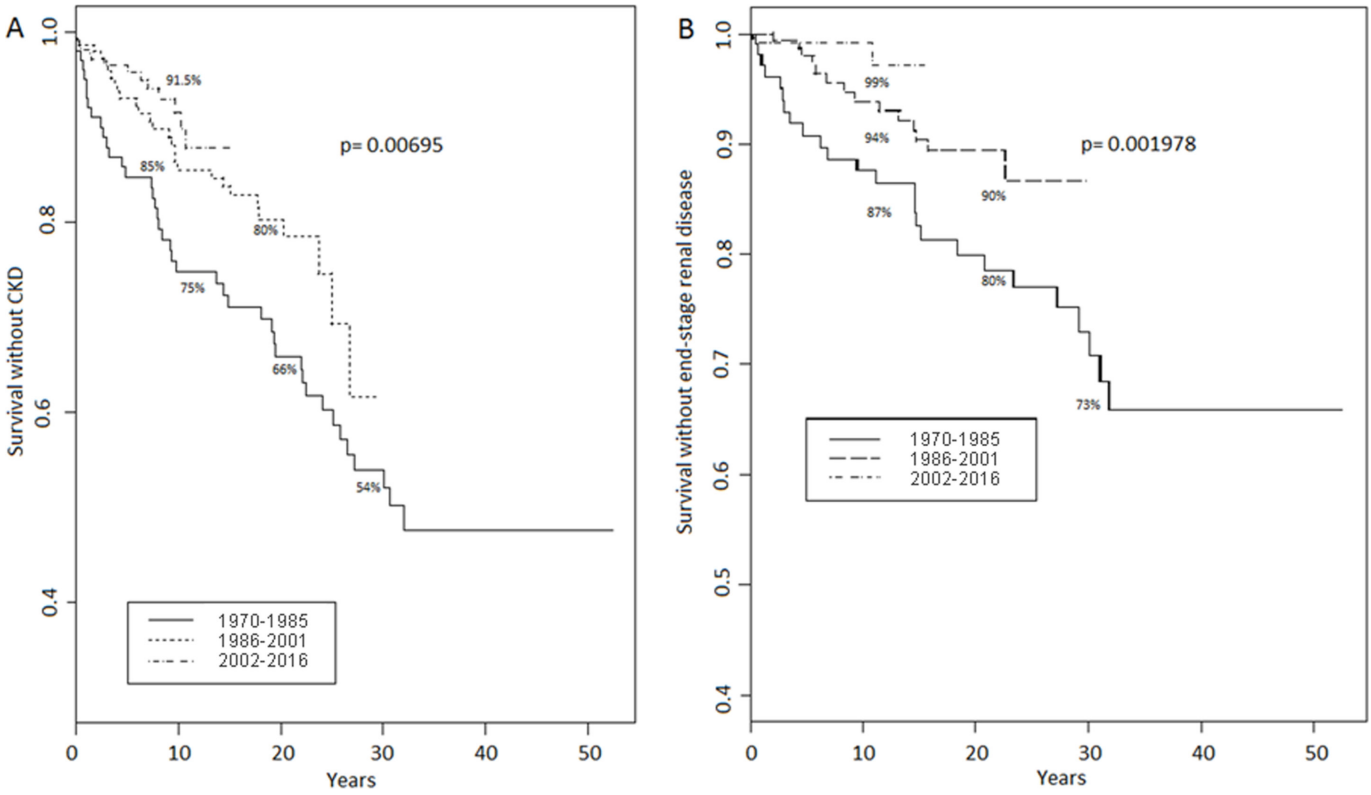


**Figure 2** (A) Survival without chronic kidney disease (CKD) in three different periods. (B) Survival without end-stage renal disease in three different periods.

induction and maintenance therapy following the positive results of long-term controlled trials carried out at the National Institutes of Health.[22] In the same period, the use of a combined oral immunosuppressive regimen as maintenance therapy became progressively more popular.[23] Interestingly, the proportion of our patients who received steroids alone as induction therapy decreased from 29% in P1% to 18% in P2 and further declined to 5% in P3. Finally, from 2002 to 2016 (P3), the evidence that MMF has a similar efficacy compared with cyclophosphamide in the induction phase and is more effective than azathioprine in the maintenance phase led to an increase in the use of MMF for induction as well as for maintenance therapy.[24–26]

The age of our patients at LN diagnosis progressively increased from 1970 to 2016 and LN developed progressively later after the onset of SLE. These changes may result from an earlier diagnosis of SLE, which leads to a closer surveillance of LN over time and, in turn, allows the identification of mild disease phenotypes, as well as from the earlier and more appropriate therapeutic intervention that includes the extensive use of antimalarial drugs,[27 28] MMF[29 30] and biological drugs[31 32] capable of hindering the development of LN.

The most interesting and innovative observation of our study is the progressively milder clinical presentation of LN from P1 to P3. Presentation with isolated urinary abnormalities significantly increased from 25% in P1 to about 50% in P3. This finding was accompanied by the progressive decrease in the frequency of renal insufficiency at presentation, while the percentage of nephrotic syndrome did not significantly change over time. The decreased severity in clinical presentation from 1970 to 2016 is in keeping with the progressive decline in serum creatinine at the time of LN diagnosis, which is one of the most important predictors of renal adverse outcome in short-term and long-term follow-up.[17 33 34]

Nevertheless, the distribution of the renal histological classes was similar in the three periods regardless of clinical presentation. Class IV accounted for more than 50% of cases in all periods, followed by class III in 25%, class V in around 20% and class II in a minority of patients. There was a significant increase from P1 to P3 in mixed classes (class III+Vand class IV+IV) that are considered to be associated with the worst prognosis in some [35 36] but not all studies.[37 38] Activity index remained unchanged from P1 to P3 either when we considered all histological classes or class III and IV separately. These data are consistent with the discrepancy between clinical and histological severity of LN at presentation reported in previous studies.[7] Proliferative forms of LN were observed even in the absence of urinary abnormalities,[39 40] suggesting that a certain amount of time is required for histological lesions to give rise to clinical manifestations. On the other hand, the early diagnosis of renal involvement in recent years can account for the lower severity of clinical presentation, which is in accordance with the significant progressive decrease in the chronicity index from P1 to P3. Moreover, in the last decades, the indication to renal biopsy has become wider due to the decrease in post-biopsy complications, which has led to perform renal biopsy in a number of patients with less severe urinary abnormalities. The increasing number of class III and class IV LN diagnosed with isolated urinary abnormalities, yet with high activity index (unchanged over the three periods), has important implications in clinical practice. Indeed, this result emphasises once again the importance of renal biopsy in defining the prognosis and tailoring therapeutic approaches to LN. Notably, high activity and chronicity indexes were independent predictors of ESRD and CKD at multivariate analysis. Due to the decreasing trend of LN presentation with severe renal dysfunction, these histopathological variables remain a valuable tool aiding the physician in defining prognosis and taking treatment decisions in all patients.[41]



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**Table 3** Univariate Cox proportional hazard regression analysis among the clinical characteristics at presentation of lupus nephritis for end-stage renal disease and chronic kidney disease

| | Univariate analysis ESRD | | | Univariate analysis CKD | | |
|---|---|---|---|---|---|---|
| | RR | 95% CI | P values | RR | 95% CI | P values |
| Year of LN diagnosis | 0.941 | 0.914 to 0.967 | **<0.0001** | 0.964 | 0.945 to 1.058 | **0.00017** |
| Male gender | 1.84 | 0.810 to 4.188 | 0.14 | 1.53 | 0.824 to 2.836 | 0.18 |
| Age at diagnosis of LN | 0.998 | 0.969 to 1.027 | 0.9 | 1.01 | 0.987 to 1.026 | 0.5 |
| Duration of SLE before diagnosis of LN | 0.925 | 0.835 to 1.024 | 0.13 | 0.961 | 0.906 to 1.019 | 0.19 |
| Histological classes: II+V vs III+IV | 3.01 | 1.067 to 8.456 | **0.037** | 1.79 | 0.987 to 3.251 | 0.055 |
| Activity index* | 1.15 | 1.085 to 1.26 | **<0.0001** | 1.11 | 1.065 to 1.167 | **<0.0001** |
| Chronicity index* | 1.39 | 0.935 to 1.531 | **<0.0001** | 1.3 | 1.197 to 1.414 | **<0.0001** |
| Urinary abnormalities+nephrotic syndrome vs nephritic syndrome+rapidly progressive renal insufficiency | 3.19 | 2.202 to 4.620 | **<0.0001** | 2.35 | 1.88 to 2.943 | **<0.0001** |
| Log serum creatinine† | 5.03 | 3.52 to 7.26 | **<0.0001** | 3.72 | 2.838 to 4.838 | **<0.0001** |
| Creatinine clearance | 0.967 | 0.864 to 1.082 | **<0.0001** | 0.974 | 0.967 to 0.981 | **<0.0001** |
| Proteinuria g/24 hours | 1.04 | 0.969 to 1.110 | 0.28 | 1.03 | 0.979 to 1.083 | 0.24 |
| Urinary erythrocytes | 0.996 | 0.984 to 1.008 | 0.56 | 1.002 | 0.997 to 1.006 | 0.46 |
| Serum albumin | 0.551 | 0.36 to 0.84 | 0.0058 | 0.716 | 0.53 to 0.96 | 0.026 |
| Arterial hypertension | 8.35 | 3.277 to 21.177 | **<0.0001** | 4.15 | 2.480 to 6.900 | **<0.0001** |
| Haematocrit | 0.91 | 0.875 to 0.946 | **<0.0001** | 0.926 | 0.899 to 0.953 | **<0.0001** |
| White blood cell count | 1 | 1.000 to 1.000 | **<0.0001** | 1 | 1.000 to 1.000 | **0.008** |
| Platelet count | 1 | 1.000 to 1.000 | 0.33 | 1 | 1.000 to 1.000 | 0.07 |
| C3 | 0.993 | 0.979 to 1.005 | 0.26 | 0.997 | 0.988 to 1.005 | 0.5 |
| C4 | 0.998 | 0.977 to 0.995 | 0.8 | 0.997 | 0.982 to 1.011 | 0.68 |
| Methyprednisolone pulses/oral prednisolone | 1.01 | 0.45 to 2.26 | 0.97 | 0.913 | 0.530 to 1.571 | 0.74 |
| Immunosuppressive induction therapy | 2.23 | 1.079 to 4.623 | **0.03** | 0.724 | 0.420 to 1.244 | 0.24 |
| Immunosuppressive maintenance therapy | 0.693 | 0.34 to 1.41 | 0.31 | 0.857 | 0.53 | 1.38 |

*For any unit increase in activity or in chronicity index.
†For any unit increase in log serum creatinine.
Significant P values are given in bold.
C3/C4, complement components; CKD, chronic kidney disease; ESRD, end-stage renal disease; LN, lupus nephritis; SLE, systemic lupus erythematosus.

Arterial hypertension was another important predictor of both ESRD and CKD.[34 42–44] Thus, the effective control of blood pressure is of paramount importance in the management of LN. In keeping with previous reports,[45–48] male gender was associated with worse renal outcome in our cohort; however, according to a recent critical review of the literature, there is limited evidence supporting the worse prognosis in male than in female patients.[49]

**Table 4** Predictors of chronic kidney disease, end-stage renal disease and death at multivariate Cox proportional hazards regression analysis

| | Coefficient | RR | 95% CI | P value |
|---|---|---|---|---|
| Dependent variable: chronic kidney disease | | | | |
| Logarithm of serum creatinine | 0.8708 | 2.39* | 1.57 to 3.65 | <0.0001 |
| Activity index | 0.0611 | 1.06† | 1 to 1.13 | 0.038 |
| Chronicity index | 0.1188 | 1.13† | 1.01 to 1.26 | 0.034 |
| Hypertension | 1.4243 | 4.16 | 2.15 to 8.03 | <0.0001 |
| No immunosuppressive drugs for maintenance | 0.7341 | 2.08 | 1.14 to 3.82 | 0.018 |
| Dependent variable: end-stage renal disease | | | | |
| Logarithm of serum creatinine | 1.0001 | 2.72* | 1.5 to 4.92 | 0.00095 |
| Male gender | 1.2057 | 3.34 | 1.25 to 8.93 | 0.016 |
| Activity index | 0.0936 | 1.1† | 1.02 to 1.19 | 0.02 |
| Chronicity index | 0.2545 | 1.29† | 1.11 to 1.49 | 0.00069 |
| Hypertension | 1.7835 | 5.95 | 1.99 to 17.75 | 0.0014 |
| No immunosuppressive drugs for maintenance | 1.1106 | 3.04 | 1.37 to 6.74 | 0.0063 |
| Dependent variable: death | | | | |
| Logarithm of serum creatinine | 0.6355 | 1.8* | 1.1 to 3.25 | <0.0001 |
| Male gender | 1.0584 | 2.88 | 1.17 to 7.1 | <0.0001 |
| Older age | 0.0711 | 1.07‡ | 1.04 to 1.11 | <0.0001 |

Clinical characteristics at presentation of lupus nephritis were analysed as independent variables.
*For any unit increase in log serum creatinine.
†For any unit increase in activity or in chronicity index.
‡For any increase in 1 year of age.
RR, relative risk.



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We observed that the proportion of male patients progressively increased over time, but we have no explanation for the increase in number of men diagnosed in the last decades and we think that this preliminary result needs to be confirmed in large multicentre studies. Another interesting result of our study is the significant and progressive improvement of renal survival from P1 to P3, which confirms previous data[10–13] and is probably the result of a wider indication to renal biopsy and improved treatment of LN over the last decades.[48]

We are aware of a number of limitations of this study. It is a retrospective study of prospectively collected data and no information is provided on the number of patients who achieved remission after induction therapy, the duration of remission, the number of flares and the need of repeated renal biopsy. The majority of our patients were Caucasian; hence, the results may not be applied to other ethnic groups.

In conclusion, the clinical presentation at the time of kidney biopsy for suspected LN has apparently become less severe in the last years and is now characterised by an increase in isolated urinary abnormalities and a decrease in renal insufficiency. However, a concomitant decrease in histological active lesions was not observed. This emphasises once again the importance of performing renal biopsy in the management of LN. The progressive improvement in renal survival in our cohort is the result of a comprehensive approach, which includes a prompt diagnosis of renal involvement, a wider indication to renal biopsy, treatment based on renal biopsy and increased clinical experience in the management of LN.

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