Lupus (2015) 24, 331–338
http://lup.sagepub.com

LUPUS AROUND THE WORLD

Renal outcomes among Egyptian lupus nephritis patients: a retrospective analysis of 135 cases from a single centre

GA Mahmoud, HS Zayed and SA Ghoniem
Rheumatology and Rehabilitation Department, Faculty of Medicine, Cairo University, Egypt

Objectives: The objective of this paper is to describe renal outcomes in a group of Egyptian patients with lupus nephritis and to identify variable prognostic factors. **Patients and methods:** The records of 135 patients (129 females, six males) with biopsy-proven lupus nephritis seen between 1999 and 2011 at Kasr Al-Aini Hospital, Cairo University, were reviewed and included in a retrospective analysis. Biopsies were classified according to the WHO classification. Renal outcomes were defined according to the Renal Subcommittee of Renal Insufficiency of the American College of Rheumatology. **Results:** The mean follow-up period was 55.64 ± 25.68 (range 4–156) months. Thirty-nine patients (29.9%) developed an adverse final outcome. This composite outcome, defined as persistent elevation of serum creatinine ≥ 1.2 mg/dl, chronic renal insufficiency, end-stage renal disease or death, was seen in 12 (8.9%), seven (5.2%), three (2.2%) and 17 (12.6%) patients, respectively. The overall patient survival was 93.5% and 87.5% at five and 10 years, respectively. Factors associated with an adverse outcome included male gender ($p = 0.037$), hypertension at nephritis onset ($p = 0.001$), serum creatinine ≥ 1.2 mg/dl ($p < 0.001$), urinary casts ($p = 0.006$), anticardiolipin antibodies ($p = 0.03$), class IV nephritis ($p < 0.001$), hyaline thrombosis (0.003), glomerular sclerosis ($p = 0.002$), tubular atrophy($p < 0.001$), interstitial fibrosis ($p < 0.001$) and a higher chronicity index ($p = 0.006$). Time-dependent factors associated with an adverse outcome included failure to achieve remission within the first year, uncontrolled hypertension, persistently low C3 and development of flares ($p = 0.003, < 0.001, = 0.004, = 0.003$, respectively). **Conclusion:** The association of several adverse prognostic factors with the development of poor renal outcome has been confirmed in this study. *Lupus* (2015) **24,** 331–338.

Key words: Lupus nephritis; outcome; prognostic factors; Egyptians

Introduction

Renal disease is a common and serious manifestation of systemic lupus erythematosus (SLE). The presentation may range from asymptomatic urinary abnormalities to rapidly progressive renal failure.[1] In fact, renal injury is the most important predictor of mortality in patients with SLE.[2] Demographic, social, clinical, laboratory and histopathological variables at disease presentation, therapeutic modalities as well as time-dependent factors influence disease outcome.[3] Black race,[4] male gender[5] and poor socioeconomic class,[6] hypertension, impaired renal function at the time of renal biopsy,[7,8] nephrotic-range proteinuria,[7] anemia[4,7,9] and low C3[4] have been associated with poor renal prognosis. Anti-DNA antibodies[5] and antiphospholipid nephropathy increase the risk for worse renal prognosis in lupus nephritis (LN) patients.[10] Renal histology has been the basis for classification of renal disease and is usually a guide for therapeutic decisions and prognosis.[11] Diffuse proliferative glomerulonephritis, fibrinoid necrosis, cellular crescents, interstitial fibrosis and tubular atrophy on renal biopsy are recognised as unfavourable prognostic factors,[4] as well as high activity index[4] and chronicity index.[4,12] Among the time-dependent factors, persistent hypertension,[13] a lack of achievement of complete remission and nephritic flares were associated with a poor prognosis.[9,12]

Data on the outcomes of LN in Egypt are scarce. The present study therefore aimed to describe the outcomes of biopsy-proven LN in a group of

Correspondence to: Hania Salah Zayed, 1 El-Gaber Street of Nasser El Thawra Street, Haram, Guiza, 12555 Egypt.
Emails: hania.zayed@kasralainy.edu.eg; haniasalah@yahoo.com
Received 12 July 2014; accepted 18 December 2014

10.1177/0961203314567751

Egyptian patients and to identify prognostic demographic, clinical, laboratory and histological data at presentation as well as time-dependent factors.

Patients and methods

Patients

A total of 135 patients with biopsy-confirmed LN who were followed at the Rheumatology and Rehabilitation Department of Kasr Al-Aini Hospital, Faculty of Medicine, Cairo University, between 1999 and 2011 were included in a retrospective study. All patients fulfilled at least four of the American College of Rheumatology (ACR) revised criteria for SLE.[14] The SLE disease activity index (SLEDAI) was used for assessment of disease activity. For assessment of systemic damage, the Systemic Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR DI)[15] was applied. The onset of nephritis was diagnosed at the time of appearance of significant proteinuria and/or active urinary sediment. Hypertension was defined as a persistently elevated blood pressure of $\geq 140/90$ or the use of antihypertensive drugs. Laboratory data included in the assessment of LN patients included a complete blood count, erythrocyte sedimentation rate (ESR), serum aminotransferases, serum albumin, fasting and postprandial blood sugar, serum urea and creatinine, serum albumin, complete urine analysis and 24-hour urinary proteins. Antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-DNA), anticardiolipin antibodies (aCL) and lupus anticoagulant (LA) were recorded as positive or negative. Serum complement components C3 and C4 were recorded as normal or low. The renal biopsy reports present in the patients' records were considered for analysis. The biopsies had been classified according to the World Health Organisation (WHO) classification[16] by a small team of histopathologists specialised in reporting on renal biopsies. Activity and chronicity indices were available for 80 biopsies. The demographic, clinical, laboratory and histological data obtained at the time of diagnosis of LN were recorded.

Treatment

The treatment of LN patients included two phases: induction of remission and a maintenance phase. The initial therapeutic decision was guided by the renal biopsy result and the extent of extra-renal disease. The induction phase included the use of one to three pulses of methyl prednisolone (0.5–1 g each) followed by oral prednisone in a dose of 0.5–1 mg/kg for one to two months with gradual tapering in addition to an immunosuppressive agent. Cyclophosphamide was used in patients with severe LN (III, IV or V with nephrotic-range proteinuria) or in the presence of severe extra-renal disease. It was given in six monthly intravenous (IV) pulses (0.75 g/m^2 each). Azathioprine (2–3 mg/kg) was used in classes II and V. Due to its expense, mycophenolate mofetil (MMF) was reserved for patients who failed to respond to cyclophosphamide or in whom the risk of ovarian failure was of concern. Maintenance of remission was achieved by lower doses of corticosteroids that were gradually tapered to 5–10 mg/day, cyclophosphamide quarterly pulses, azathioprine or MMF. Induction treatment was restarted in the case of flares. The medications used for induction and maintenance of remission were recorded as well as response to therapy and side effects.

Assessment of outcome of LN

The hard end point of the study was defined by death or the need for chronic dialysis. The duration of follow-up was calculated from the onset of nephritis until the endpoint was reached or the termination of the study in June, 2011. The definitions proposed by the Renal Subcommittee of Renal Insufficiency of the ACR[12] were used to describe the presentation and outcome in LN patients:

- Renal insufficiency at presentation: serum creatinine ≥ 1.2 mg/dl and creatinine clearance lower than 75 ml/minute.
- Nephrotic syndrome: proteinuria ≥ 3.5 g/24 hours with plasma albumin < 3 g/dl.
- Non-nephrotic proteinuria: proteinuria between 0.21 and 3.5 g/24 hours.
- Nephritic flare: a sudden increase in plasma creatinine of at least 30% over the last value, associated with nephritic urinary sediment and increased proteinuria.
- Proteinuric flare: an increase in proteinuria without modification of plasma creatinine. Proteinuria had to increase by at least 2 g/day if the basal proteinuria was less than 3.5 g/day, or doubled if the patient already had nephrotic proteinuria.
- Chronic renal insufficiency: doubling of plasma creatinine lasting for at least six months with a value of plasma creatinine of at least 2 mg/dl and creatinine clearance ≤ 40 ml/min without any improvement over time.
- End-stage renal disease (ESRD): renal replacement therapy by either renal transplant or dialysis lasting for at least three months

- Complete renal remission: serum creatinine $\leq$1.2 mg/dl, and 25% increase of baseline creatinine clearance if abnormal, or stable value if abnormal at baseline, proteinuria $<$ 0.2 g/24 hours, and inactive sediment defined as $\leq$ 5 white blood cells/high-power field and no cellular casts.
- Partial renal remission: serum creatinine $\leq$1.2 mg/dl, and 25% increase of baseline creatinine clearance if abnormal, or stable value if normal at baseline and proteinuria from 0.21 to 2 g/day.

According to the final outcome, patients were classified as having favourable or adverse outcome. A favourable outcome was defined as a complete or a partial remission, while an adverse outcome was defined as death, ESRD or the persistent doubling of serum creatinine.

Statistical methods

All statistical calculations were performed using the computer program SPSS (Statistical Package for the Social Science; SPSS Inc, Chicago, IL, USA) version 15 for Microsoft Windows. Data were statistically described in terms of range, mean $\pm$ standard deviation ($\pm$SD), frequencies and percentages when appropriate. Comparison of numerical variables between the study groups was performed using the Mann-Whitney *U* test for independent samples. For comparing categorical data, the Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency was less than 5. Survival analysis was conducted using Kaplan Meier statistics. A *p* value less than 0.05 was considered statistically significant.

Results

Demographic and clinical features of LN patients

This study included 135 patients with biopsy-proven lupus LN (129 females, six males). Their mean age at SLE onset and LN onset was 21.78 ± 7.97 and 24.36 ± 7.81 years, respectively. Juvenile onset of SLE was present in 26 (19.3%) cases. In 47 (34.8%) patients nephritis was part of the initial presentation of SLE while the other 88 (65.2%) patients developed nephritis after two to 204 (mean 31.06 ± 39.3) months of SLE onset. Constitutional manifestations were found in 102 (75.5%), mucocutaneous lesions in 114 (84.4%) and arthralgia/arthritis in 125 (96%) patients. Serositis was present in 74 (54.8%) patients. Neuropsychiatric manifestations were present in 40 (29.6%) patients in the form of seizures in 10, organic brain syndrome in five, psychosis in six, cerebrovascular accident in six, cranial/ peripheral neuropathy in 11 and transverse myelitis in two patients. Haematological manifestations were found in 84 (62.2%) patients in the form of haemolytic anaemia in 18, leucopenia in 65 and thrombocytopenia in 42 patients. Pulmonary involvement affecting 21 (15.6%) cases was in the form of interstitial lung disease in two, shrunken lung syndrome in one, alveolar haemorrhage in seven and pulmonary hypertension in 11 patients. Cardiac affection was found in 26 (19.3%) patients. Valvular lesions were seen in 22, myocarditis was present in two and angina pectoris in two patients. Cutaneous and retinal vasculitis were seen in 51 (37.8%) and eight (5.9%) patients, respectively.

Baseline characteristics of LN patients

At the onset of nephritis, 74 (54.8%) patients were hypertensive. The mean SLEDAI and SLICC/ACR DI scores were 30.42 ± 10.84 and 4.49 ± 9.13, respectively. The most common LN classes were Class III and IV affecting 33.3% of the patients, each. Laboratory details and WHO classification of the first renal biopsy of the studied patients are shown in Table 1.

Treatment of LN

Induction phase: 126 (93.3%) patients received methylprednisolone pulses (0.5–1 g/day for three successive days) followed by oral prednisone (0.5–1 mg/kg/day) while only nine patients were treated with oral prednisone 1–2 mg/kg/day for one to two months. For induction of remission, cyclophosphamide was used in 99 (73.3%) and azathioprine in 34 (25.2%) patients. In one patient both IV cyclophosphamide and azathioprine were used for induction of remission. In 21 patients (15.6%) MMF was used for induction of remission after failed induction by cyclophosphamide/azathioprine.

Maintenance phase: Depending on the improvement of renal and extra-renal manifestations, prednisone was gradually tapered until reaching 10 mg/day in most patients. In addition to corticosteroids, 73 patients (54.%) received cyclophosphamide pulses every two to three months for another three to six pulses followed by azathioprine later on. Forty patients were maintained on azathioprine alone and 12 patients were maintained on MMF alone.

Table 1 Laboratory data and WHO classification of renal biopsies in lupus nephritis patients

Nephrotic range proteinuria	38 (28.1)
Non-nephrotic range proteinuria	97 (71.9)
Haematuria ≥ 5 RBCs/HPF	95 (74.8)
Pyuria, ≥ 5 pus cells/HPF, infection excluded	123 (93.2)
Cellular or granular casts	90 (70.3)
Serum creatinine:	
<1.2 mg/dl	109 (80.7)
≥ 1.2 mg/dl	26 (19.3)
Haemoglobin g/dl	8.8 ± 1.98
Total leucocytic count ($\times 10^3/mm^3$)	5.56 ± 2.93
Platelet count ($\times 10^3/mm^3$)	264.91 ± 121.76
ESR (mm/1 hour)	101.85 ± 30.98
Serum albumin g/dl	2.85 ± 0.6
ANA +ve	133 (98.5)
Anti DNA +ve	97 (71.9)
aCL antibodies IgG +ve ($n=68$)	26 (38.2)
aCL antibodies IgM +ve ($n=59$)	18 (30.5)
Lupus anticoagulant +ve ($n=23$)	9 (39.1)
Low C3	118 (87.4)
Low C4	109 (80.7)
WHO class at first biopsy	
Class II	21 (15.6)
Class III	45 (33.3)
Class IV	45 (33.3)
Class V	15 (11.1)
Class III–V	5 (3.7)
Class VI	4 (2.96)

Values are expressed as mean $\pm$ SD, or no (%). WHO: World Health Organisation; RBCs: red blood cells; HPF: high-power field; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibodies; aCL: anticardiolipin antibodies; Ig: immunoglobulin; +ve: positive.

Outcome of LN patients

The follow-up period ranged from four to 156 months with a mean of 55.64 ± 25.68 months. During the study period 73 (54.1%) patients developed one or more flares. Nephritic flares occurred in 38 patients, while proteinuric flares occurred in 35 patients. Forty-eight (65.8%) patients who developed flares entered into remission with 30 and 18 patients achieving a complete or partial remission, respectively. At the end of the study, a favourable outcome, i.e. a partial or complete remission, was achieved in 96/135 (71.1%) patients, of whom 80 patients achieved a complete remission. The overall patient survival rates were 93.5% and 87.4% at five and 10 years, respectively. The cumulative renal survival, i.e. survival without dialysis, calculated from the onset of LN till ESRD, death or the last follow-up visit, was 88.9% and 87.4% at five and 10 years, respectively.

An adverse outcome (persistent elevation of serum creatinine, chronic renal insufficiency, ESRD or death) was seen in 39 (29.9%) patients. Twelve (8.9%) patients had a persistently elevated serum creatinine, seven (5.2%) had chronic renal insufficiency, and three (2.2%) patients developed ESRD, one of whom underwent renal transplantation. Seventeen (12.6%) patients had died. Ten patients died of multisystem failure associated with infection, four of renal failure, two of alveolar haemorrhage and one patient of central nervous system vasculitis.

Complications observed in the studied patients

Major infections requiring hospitalisation occurred in 42 (31.1%) and minor infections in 119 (88.1%) patients. Eight (5.9%) patients had herpes zoster infection. Ovarian failure (defined as the occurrence of menopause before 40 years) occurred in 12 (8.9%) patients, haemorrhagic cystitis in two patients, bone avascular necrosis in 17 (12.6%) patients, osteoporosis in 18 (13.3%) patients, diabetes in 12 (8.9%) patients and malignancy in one patient.

Factors associated with an adverse outcome in LN patients

Among the demographic data studied, only male gender was associated with an adverse outcome ($p=0.037$). Among the baseline clinical and laboratory data, hypertension at LN onset, a serum creatinine ≥ 1.2 mg/dl, urinary casts and aCL antibodies were associated with an adverse outcome ($p=0.001$, <0.001, 0.006 and 0.03, respectively) (Table 2). On renal biopsy, class IV nephritis was significantly associated with an adverse outcome ($p<0.001$). Individual features on renal biopsy that were associated with an adverse outcome included hyaline thrombosis, glomerular sclerosis, tubular atrophy and interstitial fibrosis ($p=0.003$, $0.002, <0.001, <0.001$, respectively). A higher chronicity index was also associated with an adverse outcome ($p=0.006$) (Table 3).

Among the time-dependent factors studied, failure to achieve remission in the first year, persistently uncontrolled hypertension and low C3 were associated with an adverse outcome ($p=0.003$, 0.001 and 0.004), respectively. The development of any flare, whether nephritic or proteinuric, was also associated with an adverse outcome ($p=0.003, <0.001, = 0.004$, respectively) (Table 4) and lower cumulative renal survival ($p=0.03$) (Figure 1).

Discussion

The overall patient survival rate in this study was 93.5% at five years and 87.5% at 10 years, which is very close to the five- and 10-year survival rates for

Table 2 Demographic, clinical and laboratory data at presentation in lupus nephritis patients with favourable or adverse outcomes

Variable	*Favourable outcome (n = 96)*	*Adverse outcome (n = 39)*	p *value*
Male gender	2 (2.1%)	4 (10.3%)	0.037
Age at SLE diagnosis	22.13 ± 8.46	20.92 ± 6.6	0.42
Juvenile-onset SLE	19 (19.8%)	7 (17.9%)	0.81
Age at onset of nephritis	24.63 ± 8.16	23.72 ± 6.96	0.73
Hypertension at LN onset	44 (45.8%)	30 (76.9%)	0.001
Haemoglobin (g/dl)	9.02 ± 2.42	8.84 ± 1.98	0.68
TLC ($\times 10^3/mm^3$)	5.56 ± 2.93	5.08 ± 2.65	0.43
PLT ($\times 10^3/mm^3$)	264.91 ± 121.76	233.77 ± 98.36	0.2
Serum albumin (g/dl)	2.85 ± 0.6	2.74 ± 0.49	0.44
Nephrotic range proteinuria	26 (27.1%)	12 (30.8%)	0.67
Serum creatinine >1.2 mg/dl	7 (7.3%)	19 (48.7%)	<0.001
Casts in urine	56 (58.3%)	34 (87.2%)	0.006
ANA+ve	95 (99%)	38 (97.4%)	0.51
Anti-DNA +ve	69 (72.6%)	28 (73.7%)	0.9
aCL	21 (21.9%)	26 (66.7%)	0.03
aCL IgG	15 (30%)	11 (61.1%)	0.06
aCL IgM	11 (25.6%)	7 (43.8%)	0.18
Lupus anticoagulant	1	5	0.32
Low C3	85 (95.5%)	33 (97.1%)	0.7
Low C4	78 (86.7%)	31 (91.2%)	0.5

Values are expresses as mean ± SD or number (%). SLE: systemic lupus erythematosus; LN: lupus nephritis; TLC: total leucocytic count; PLT: platelet count; ANA: antinuclear antibodies; Anti-DNA: anti-deoxyribonucleic acid antibodies; aCL: anticardiolipin antibodies; C3: complement component 3; +ve: positive.

Table 3 Histological features in lupus nephritis patients with favourable or adverse outcomes

Histological features	*Favourable outcome*	*Adverse outcome*	p *value*
WHO class			
II ($n = 21$)	18 (18.8%)	3 (7.7%)	<0.001
III ($n = 45$)	36 (37.5%)	9 (23.1%)	
IV ($n = 45$)	25 (26%)	20 (51.3%)	
V ($n = 15$)	14 (14.6%)	1 (2.6%)	
III–V ($n = 5$)	3 (3.1%)	2 (5.1%)	
VI ($n = 4$)	0	4(10.3%)	
Glomerular proliferation	81 (84.4)	29 (74.4)	
Fibrinoid necrosis	14 (14.6)	7 (17.9)	0.63
Cellular crescents	17 (17.7)	4 (10.3)	0.28
Hyaline thrombosis	3 (3.1)	7 (17.9)	0.003
Cellular infiltrate	73 (76)	27(69.2)	0.42
Glomerular sclerosis	27 (28.1)	22 (56.4)	0.002
Tubular atrophy	13 (13.5)	26 (66.7)	<0.001
Fibrinoid crescents	2 (2.1)	1 (2.6)	0.86
Interstitial fibrosis	9 (9.4)	24 (61.5)	<0.001
Features of APS	6 (6.3)	3 (7.7)	0.76
Activity index	8.64 ± 4.1	7 ± 4.04	0.43
Chronicity index	1.09 ± 1.22	3.25 ± 1.67	0.006

WHO: World Health Organisation; APS: antiphospholipid syndrome.

patients with LN in two large multicentre studies from Europe,[17,18] while Mok et al.[19] reported 98.4% and 94.4% survival rates in Southern Chinese patients at five and 10 years, respectively. A five-year overall survival was seen in 76% of LN patients in a study from Morocco,[20] while in South Africa, five- and 10-year survival rates were 54% and 41%, respectively.[13] In patients from Saudi Arabia, five- and 10-year survival rates were 92% and 77%, respectively.[21]

In the studied population, the cumulative renal survival, i.e. survival without dialysis, was 88.9% and 87.4% at five and 10 years, respectively. In the study by Donadio et al.,[7] survival without ESRD was 83% and 74% at five and 10 years, respectively. Cortés-Hernández et al.[22] reported a 90% renal survival at five years. Franco et al.[8] found that renal survival at five years was 95% in white patients but only 58% in black patients. In a study of Korean patients, renal survival rate at five and 10 years after LN onset was 95.9% and 91.1%, respectively.[23] A study from South Africa showed much lower renal survival rates of 48% and 21% at five and 10 years, respectively.[13] A study from Morocco reported 69.5% survival without development of ESRD at five years.[20]

This study retrospectively evaluated the prognostic role of clinical, immunological and histological characteristics in patients with LN. In agreement with other studies,[9,19,24–26] male gender was significantly associated with an adverse outcome ($p = 0.037$). While younger age at LN onset was associated with poor outcome in studies by Donadio et al.,[7] Béji et al.[27] and Cortés-Hernández et al.,[22] the age at LN onset was not associated with an adverse outcome in this study, in agreement with other authors.[9,13,25] Hypertension at the time of renal biopsy was significantly associated with an adverse renal outcome ($p < 0.001$), confirming previous reports.[7,8,13,22,26,27] An elevated baseline serum creatinine was strongly associated with an adverse outcome ($p < 0.001$), in agreement with many investigators.[7,8,12,13,27–29] Haematuria and leucocyturia at presentation indicated poor renal prognosis in one study;[30] however, in the present study only the presence of granular casts was associated with an adverse outcome ($p = 0.006$). In the present study, there was no association between thrombocytopaenia or anaemia and outcome of LN, in agreement with Ayodele et al.[13] Hypoalbuminaemia and nephrotic proteinuria were not associated with an adverse outcome in the studied patients, in agreement with some

Table 4 Time-dependent factors in lupus nephritis patients with favourable or adverse outcomes

Time-dependent factors	*Favourable outcome (n = 96)*	*Adverse outcome (n = 39)*	
Remission within one year	79 (82.3%)	16 (41%)	0.003
Flares	46 (47.9%)	27 (69.2%)	0.003
Nephritic flares	18	20	<0.001
Proteinuric flares	28	7	0.004
Persistently low C3	29 (30.2%)	22 (56.4%)	0.004
Uncontrolled hypertension	4 (4.2%)	20 (51.3%)	<0.001

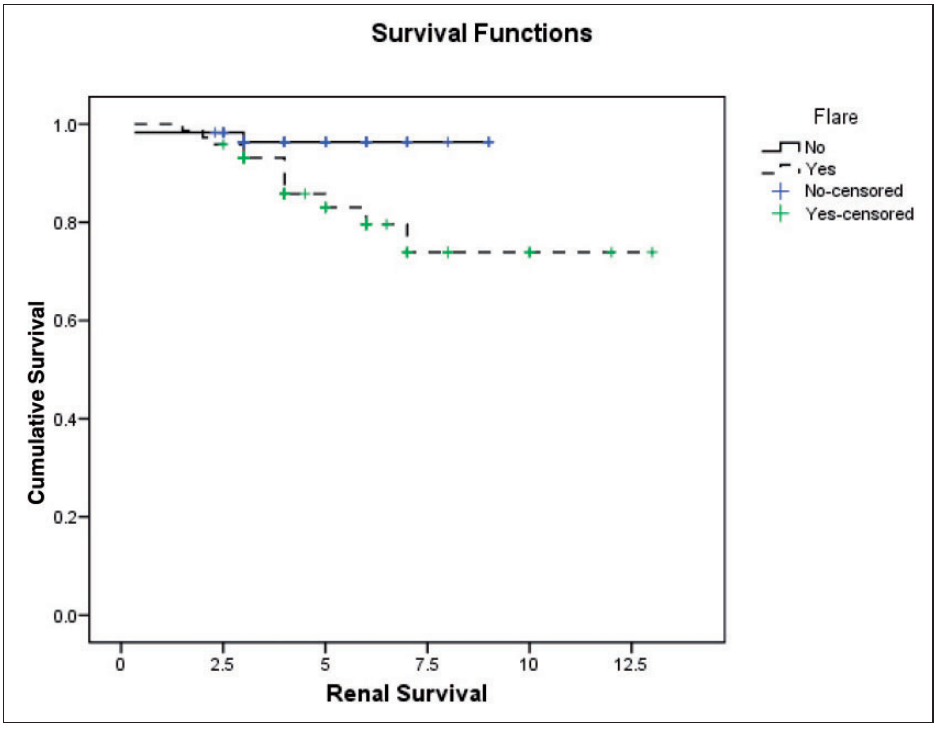

Figure 1 Survival functions.

authors.[8,13,31] No association was found in this study between hypocomplementaemia or anti-DNA positivity at the time of renal biopsy with the development of an adverse renal outcome, confirming previous reports.[8,13,31] Antiphospholipid antibodies have been associated with an increased risk of progression to renal insufficiency;[29] in the present study, aCL antibodies were associated with an adverse outcome. The presence of features related to antiphospholipid nephropathy on renal biopsy, however, was not associated with adverse outcome in this study or in other studies.[10,32] There is a well-recognised relationship between the histological features on biopsy and the clinical course of LN. The WHO classification system, the United States National Institutes of Health (NIH) histological activity and chronicity indices are well established in predicting outcomes,[11] and the WHO classification is still used in most of the pathology departments in our country. In the present study, class IV nephritis at renal biopsy was significantly associated with an adverse outcome ($p < 0.001$), in agreement with many investigators.[5,13,19] The NIH activity index focuses primarily on glomerular lesions and has been associated with poor renal prognosis in some[30] but not all studies.[12,22,31,33] In the present study, no association between the activity index and adverse renal outcome has been found. On the other hand, a higher chronicity index was found by many investigators to be predictive of progression to renal failure.[12,22,29,31,33] In this study, a higher chronicity index was significantly associated with development of an adverse outcome ($p = 0.006$). Interstitial fibrosis and tubular atrophy were significantly associated with adverse outcomes ($p = 0.002$ and <0.001, respectively), confirming previous reports.[4,31] The presence of glomerulosclerosis was also significantly associated with an adverse outcome ($p = 0.002$).

The long-term prognostic value of symptoms and signs at presentation is limited: The evolution of LN is often unpredictable, not only because of large inter-individual variation, but also because the course of the disease may be variable in the same patient.[9] Since therapy alters the natural history of the disease, it is possible that with the aggressive treatment of LN the predictive value of many disease parameters has changed;[4] the evaluation of the significance of time-dependent factors on the outcome of LN may therefore be more important. Achieving remission within the first year of the disease was associated with a favourable renal outcome ($p = 0.003$), which is in accordance with several investigators,[19,28,34,35] underscoring the importance of early detection and timely therapeutic intervention in LN before irreversible damage ensues. A persistently uncontrolled blood pressure during follow-up was associated with an adverse outcome ($p < 0.001$) in this study, in agreement with some authors.[13,22] Long-term renal outcome is strongly influenced by the occurrence of exacerbations of renal disease, especially nephritic flares, which may despite adequate therapy result in irreversible glomerular damage.[9] In this study, both nephritic and proteinuric renal flares have been found to be associated with an adverse outcome. In active lupus, C3 and C4 complement components are frequently depressed,[36] and in some groups of patients, persistently low C3 has been associated with progression of renal disease.[22,37] In the present study, persistent depression of C3 was among the time-dependent factors associated with an adverse renal outcome.

To conclude, overall five- and 10-year patient and renal survival rates are comparable to most studies. Factors related to development of an adverse outcome in this study included male gender, elevated blood pressure and serum creatinine at baseline, presence of glomerulosclerosis, tubular atrophy, interstitial fibrosis and a higher chronicity index on renal biopsy, a persistently elevated blood pressure, persistently low C3 and occurrence of renal flares during follow-up. To improve patient outcomes, strict control of blood pressure and close monitoring in order to catch and treat early and vigorously any renal flares are recommended.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1 Avihingsanon Y, Hirankarn N. Major lupus organ involvement: Severe lupus nephritis. *Lupus* 2010; 19: 1391–1398.
2 Maroz N, Segal MS. Lupus nephritis and end-stage kidney disease. *Am J Med Sci* 2013; 346: 319–323.
3 Mok CC. Prognostic factors in lupus nephritis. *Lupus* 2005; 14: 39–44.

4 Austin HA 3rd, Boumpas DT, Vaughan EM, Balow JE. Predicting renal outcomes in severe lupus nephritis: Contributions of clinical and histologic data. *Kidney Int* 1994; 45: 544–550.
5 Mok CC, Lau CS, Chan TM, Wong RW. Clinical characteristics and outcome of southern Chinese males with systemic lupus erythematosus. *Lupus* 1999; 8: 188–196.
6 Contreras G, Lenz O, Pardo V, *et al*. Outcomes in African Americans and Hispanics with lupus nephritis. *Kidney Int* 2006; 69: 1846–1851.
7 Donadio JV Jr, Hart GM, Bergstralh EJ, Holley KE. Prognostic determinants in lupus nephritis: A long-term clinicopathologic study. *Lupus* 1995; 4: 109–115.
8 Franco C, Yoo W, Franco D, Xu Z. Predictors of end stage renal disease in African Americans with lupus nephritis. *Bull NYU Hosp Jt Dis* 2010; 68: 251–256.
9 Moroni G, Quaglini S, Maccario M, Banfi G, Ponticelli C. "Nephritic flares" are predictors of bad long-term renal outcome in lupus nephritis. *Kidney Int* 1996; 50: 2047–2053.
10 Daugas E, Nochy D, Huong DL, *et al*. Antiphospholipid syndrome nephropathy in systemic lupus erythematosus. *J Am Soc Nephrol* 2002; 13: 42–52.
11 Bihl GR, Petri M, Fine DM. Kidney biopsy in lupus nephritis: Look before you leap. *Nephrol Dial Transplant* 2006; 21: 1749–1752.
12 Moroni G, Quaglini S, Gallelli B, Banfi G, Messa P, Ponticelli C. The long-term outcome of 93 patients with proliferative lupus nephritis. *Nephrol Dial Transplant* 2007; 22: 2531–2539.
13 Ayodele OE, Okpechi IG, Swanepoel CR. Predictors of poor renal outcome in patients with biopsy-proven lupus nephritis. *Nephrology (Carlton)* 2010; 15: 482–490.
14 Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
15 Gladman D, Ginzler E, Goldsmith C, *et al*. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363–369.
16 Churg J, Bernstein J, Glassock RJ. *Renal disease: Classification and atlas of glomerular disease*. Tokyo: Igaku-Shoin, 1995. pp. 151–179.
17 Cervera R, Khamashta MA, Font J, *et al*. European Working Party on Systemic Lupus Erythematosus. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: A comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore)* 2003; 82: 299–308.
18 Cervera R, Khamashta MA, Hughes GR. The Euro-lupus project: Epidemiology of systemic lupus erythematosus in Europe. *Lupus* 2009; 18: 869–874.
19 Mok CC, Lau CS, Chan TM, Wong RW. Clinical characteristics and outcome of southern Chinese males with systemic lupus erythematosus. *Lupus* 1999; 8: 188–196.
20 Haddiya I, Hamzaoui H, Tachfouti N, *et al*. Features and outcomes of lupus nephritis in Morocco: Analysis of 114 patients. *Int J Nephrol Renovasc Dis* 2013; 6: 249–258.
21 Al Durahim H, Al Ghamdi G, Al Seraya A, Alkhiari R, Al Sayyari A. Predictors of mortality and end stage renal disease in Saudi patients with lupus nephritis. *Lupus* 2011; 20: 1329–1335.
22 Cortés-Hernández J, Ordi-Ros J, Labrador M, *et al*. Predictors of poor renal outcome in patients with lupus nephritis treated with combined pulses of cyclophosphamide and methylprednisolone. *Lupus* 2003; 12: 287–296.
23 Moon SJ, Park HS, Kwok SK, Ju JH, Kim HY, Park SH. Predictors of end-stage renal disease and recurrence of lupus activity after initiation of dialysis in patients with lupus nephritis. *Clin Exp Rheumatol* 2013; 31: 31–39.
24 Resende AL, Titan SM, Barros RT, Woronik V. Worse renal outcome of lupus nephritis in male patients: A case-control study. *Lupus* 2011; 20: 561–567.
25 Hsu CY, Chiu WC, Yang TS, *et al*. Age- and gender-related long-term renal outcome in patients with lupus nephritis. *Lupus* 2011; 20: 1135–1141.
26 Schwartzman-Morris J, Putterman C. Gender differences in the pathogenesis and outcome of lupus and of lupus nephritis. *Clin Dev Immunol* 2012; 2012: 604892.
27 Béji S, Kaaroud H, Ben Moussa F, *et al*. Lupus nephritis: 211 cases [article in French]. *Rev Med Interne* 2005; 26: 8–12.
28 Korbet SM, Lewis EJ, Schwartz MM, Reichlin M, Evans J, Rohde RD. Factors predictive of outcome in severe lupus nephritis. Lupus Nephritis Collaborative Study Group. *Am J Kidney Dis* 2000; 35: 904–914.
29 Moroni G, Ventura D, Riva P, *et al*. Antiphospholipid antibodies are associated with an increased risk for chronic renal insufficiency in patients with lupus nephritis. *Am J Kidney Dis* 2004; 43: 28–36.
30 Kammoun K, Jarraya F, Bouhamed L, *et al*. Poor prognostic factors of lupus nephritis. *Saudi J Kidney Dis Transpl* 2011; 22: 727–732.
31 Hsieh C, Chang A, Brandt D, Guttikonda R, Utset TO, Clark MR. Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring. *Arthritis Care Res (Hoboken)* 2011; 63: 865–874.
32 Tektonidou MG, Sotsiou F, Nakopoulou L, Vlachoyiannopoulos PG, Moutsopoulos HM. Antiphospholipid syndrome nephropathy in patients with systemic lupus erythematosus and antiphospholipid antibodies: Prevalence, clinical associations, and long-term outcome. *Arthritis Rheum* 2004; 50: 2569–2579.
33 Hiramatsu N, Kuroiwa T, Ikeuchi H, *et al*. Revised classification of lupus nephritis is valuable in predicting renal outcome with an indication of the proportion of glomeruli affected by chronic lesions. *Rheumatology (Oxford)* 2008; 47: 702–707.
34 Houssiau FA, Vasconcelos C, D'Cruz D, *et al*. Early response to immunosuppressive therapy predicts good renal outcome in lupus nephritis: Lessons from long-term followup of patients in the Euro-Lupus Nephritis Trial. *Arthritis Rheum* 2004; 50: 3934–3940.
35 Gibson KL, Gipson DS, Massengill SA, *et al*. Predictors of relapse and end stage kidney disease in proliferative lupus nephritis: Focus on children, adolescents, and young adults. *Clin J Am Soc Nephrol* 2009; 4: 1962–1967.
36 Seshan SV, Jennette JC. Renal disease in systemic lupus erythematosus with emphasis on classification of lupus glomerulonephritis: Advances and implications. *Arch Pathol Lab Med* 2009; 133: 233–248.
37 Austin HA. Clinical evaluation and monitoring of lupus kidney disease. *Lupus* 1998; 7: 618–621.