ORIGINAL ARTICLE

Causes and predictors of mortality in biopsy-proven lupus nephritis: the Sarawak experience

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Abstract

Background: Lupus nephritis (LN) is a serious manifestation of systemic lupus erythematosus that can be fatal if left untreated. The causes and prognostic predictors of mortality in LN have been well studied in developed countries but evidence is lacking for developing countries. The objective of this study was to investigate the causes and predictors of mortality in a cohort of Malaysian patients with biopsy-proven LN.

Methods: We retrospectively studied all patients with biopsy-proven LN treated in Sarawak General Hospital during the period of 2000–15. Demographic data, clinical features and outcomes were collected. Cox regression analysis was carried out to determine the independent predictors of mortality.

Results: There was a total of 250 patients with 259 renal biopsies available for our analysis. Our patients were of multi-ethnic origins with a female predominance (90%). Their mean ± standard deviation age was 37.7 ± 12.8 years. The patients had a mean disease duration of 135.6 ± 81.9 months. Nephrotic syndrome was the most common presentation (29.6%) and acute renal failure was evident at initial presentation in 16% of patients. Class IV LN was the predominant biopsy class within the cohort (66.8%). The majority of patients achieved remission (81.2%) and had normal renal function (83.9%) at the last follow-up. The 5-, 10-, 15- and 20-year survival rates for our cohort were 93%, 88%, 82% and 77%, respectively. There were 37 deaths (14.8%), of which the main causes were: infection and flare (52.7%), infection alone (25.0%) and other causes (22.3%). Independent predictors of mortality in our cohort of LN patients were: the presence of acute kidney injury at presentation [hazard ratio (HR) 3.41; confidence interval (CI) 1.50–7.76], failure to achieve remission at 1-year post-induction therapy (HR 2.99; CI 1.35–6.65) and non-compliance with treatment (HR 1.89; CI 1.22–2.96). Age, ethnicity, class of LN and type of immunosuppressant used were not predictive of mortality.

Conclusions: Survival and renal outcomes in our LN cohort were comparable to most LN studies reported worldwide. Both flare and infection remained the main causes of death. The presence of acute renal failure at presentation, failure to achieve remission at 1 year post-treatment and non-compliance with treatment were independent prognostic predictors of mortality in LN.

Key words: dialysis, lupus nephritis, mortality, outcome, systemic lupus erythematosus

Introduction

Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) with significant morbidity and mortality. LN is reported to affect approximately 60% of SLE patients, with 10% progressing to end-stage renal disease (ESRD) [1, 2]. Asians have been reported as having a higher incidence of LN [3].

Survival in LN has shown marked improvement over the past 50 years. With the advent of advanced therapies, the 5-year survival rate of LN patients has shown continuous improvement from 44% in 1953–69, 82% in 1990–95, to nearly 96% today [4–6]. Prognosis of LN has improved over the past few decades in industrialized countries but the outlook for developing countries is less optimistic. The causes and prognostic predictors of mortality in LN have been well studied in developed countries but evidence is lacking in developing countries.

This study aimed to evaluate the causes of mortality in LN patients and to investigate the predictors of mortality within a cohort of Malaysian patients with biopsy-proven LN.

Materials and methods

This study was a retrospective review of all biopsy-proven LN patients treated at the Sarawak General Hospital Department of Medicine over a 15-year period (1 January 2000 to 31 December 2015). Sarawak General Hospital is a tertiary public hospital providing nephrology and rheumatology services in Sarawak.

All biopsy-proven LN cases were identified using outpatient records located at the nephrology and rheumatology clinics. The diagnosis of SLE was made according to the American College of Rheumatology (ACR) classification [7]. LN was classified according to the nomenclature of the International Society of Nephrology and Renal Pathology [8]. Demographics of patients, date of SLE diagnosis, number of ACR criteria present and comorbidities including hypertension, diabetes mellitus and dyslipidaemia were collected. Clinical presentation of LN, laboratory investigations and renal biopsy results were also collected.

Patients were divided according to the clinical presentation of LN: nephrotic syndrome, nephritic syndrome, mixed nephrotic and nephritic syndrome, proteinuria, and mixed proteinuria and haematuria. Renal function was measured using serum creatinine, which was ascertained from the patient records. Patients were divided into groups based upon the presence or absence of acute kidney injury (AKI) at presentation [9]. Urinary protein creatinine ratio (uPCR) was used to assess the level of proteinuria and haematuria was assessed using urinalysis.

IV methyprednisolone pulses (0.5–1 g/day for 3 successive days) followed by high-dose oral prednisolone of 0.5–1 mg/kg/day was the standard induction therapy for severe LN cases in this centre. In addition to corticosteroids, patients with Class III or Class IV LN were given induction immunosuppressive treatment that comprised of either cyclophosphamide [National Institutes of Health (NIH) regime or Euro-Lupus regime] or mycophenolate mofetil, followed by maintenance immunosuppression using low-dose prednisolone and either azathioprine or mycophenolate mofetil. Patients with mixed Class III + Class V received treatment for Class III and Class IV + Class V LN were treated as Class IV. Azathioprine (2–3 mg/kg) was used in Classes II and V. Class V LN with severe proteinuria was treated with mycophenolate mofetil, cyclosporine A or both. All patients received hydroxychloroquine at a dose of 200–400 mg/day unless contraindicated. Antihypertensive agents, diuretics and angiotensin-converting enzyme inhibitors were given as and when needed. Non-compliance was defined by documentation within the medical records of any non-adherence to medical therapy during the study period.

Response to therapy was assessed at 1-year post-induction therapy and again at the final follow-up. Partial remission was defined as a stabilization (±25%) or improvement of serum creatinine plus a ≥ 50% decrease in uPCR, proteinuria <3 g/day and a change from active to inactive urinary sediment. Complete remission was defined as return of serum creatinine to previous baseline, plus a decline in the uPCR to <500 mg/g (<50 mg/mmol) [10]. Remission status (complete or partial remission) was assessed based on serum creatinine level at 1-year post-induction therapy.

The primary outcome was mortality due to any cause. The secondary outcome was ESRD, defined as dialysis dependence for >3 months. Data were collected until either the patients' final follow-up or until 31 December 2015, whichever occurred later. Risk factors for poor outcome (mortality or ESRD) were determined and hazard ratios (HR) were calculated.

Analysis was performed using SPSS version 10.0, (SPSS, Chicago, IL, USA). Results have been presented as frequencies and percentages for categorical variables and as means and standard deviations for continuous variables. Patient and renal survival patterns of the study population were analysed and survival curves were constructed using the Kaplan–Meier method. The risk factors associated with mortality and ESRF were assessed using multivariate Cox regression analysis adjusted for sex and age at diagnosis. A two-tailed P < 0.05 was used as the threshold for significance.

Results

Patient characteristics

A total of 250 patients with 259 renal biopsies were available for analysis. Nine patients had repeat renal biopsies during the study period. The earliest recorded renal biopsy was done in 1982 and the last in 2014. The majority of patients (92.4%) fulfilled the ACR criteria for SLE. Our patients were of multi-ethnic origins with a female predominance (225 females versus 25 males). The patients had a mean age of 37.7 ± 12.8 years. The mean age at SLE diagnosis was 26.9 ± 11.5 years (range 3–64.5 years) and the mean disease duration was 135.6 ± 81.9 months as illustrated in Table 1. In all, 42 patients were diagnosed as having SLE before the age of 17 years whilst 11 patients had elderly onset SLE (defined as onset after age 50). Only nine patients had antiphospholipid syndrome.

The time interval between the diagnosis of SLE and LN was 19.0 ± 37.4 months (range 0–216 months). However, LN was evident at the time of SLE diagnosis in 139 patients (56.3%). The extrarenal manifestations in our patients were: mucocutaneous lesions in 151 (60.6%), haematological in 136 (54.4%) and arthritis in 91 (36.4%) patients. Serositis was present in 39 (15.6%) patients and neurological manifestations were present in 35 (14.0%) patients. Anti-nuclear antibody was positive in 232 (92.8%) patients and anti-dsDNA was positive in 169 (67.6%) patients. Low complement levels were found in 32% of patients.

Clinical presentation

Nephrotic syndrome was the most frequent clinical presentation [74 (29.6%)] of LN in our patients followed by mixed nephrotic/nephritic syndrome [64 (25.6%)] and proteinuria

Table 1. Demographic characteristics of patients (N = 250)

Age (years)	37.7 ± 12.8
Sex (male/female), *n* (%)	25/225 (10/90.0)
Ethnicity, *n* (%)	
Chinese	108 (43.2)
Malay	70 (28.0)
Iban	43 (17.2)
Bidayuh	20 (8.0)
Others	9 (3.6)
Years between SLE and LN diagnosis (months)	19.0 ± 37.4
Duration of follow-up (months)	135.6 ± 81.9
Lupus nephritis class, *n* (%)	
I	1 (0.4)
II	28 (11.2)
III	17 (6.8)
IV	167 (66.8)
V	35 (14.0)
VI	2 (0.8)
Hypertension, *n* (%)	136 (54.4)
Antiphospholipid syndrome, *n* (%)	9 (3.6)

Values are represented as mean ± standard deviation, unless otherwise mentioned.

Table 2. Induction therapy for LN according to LN class

LN class	Induction						Aza + CSA		
	NIH	Euro-Lupus	MMF	Aza	CSA	Oralcyclo		Pred	Total
1	0	0	0	0	1	0	0	0	1
2	0	0	0	20	1	0	0	7	28
3	13	1	3	0	0	0	0	0	17
4	127	22	17	0	0	1	0	0	167
5	0	0	9	14	4	0	1	7	35
6	0	0	0	0	0	0	0	2	2
Total	140	23	29	34	6	1	1	16	250

Euro-Lupus, Euro-Lupus regime; MMF, mycophenolate mofetil; Aza, azathioprine; CSA, cyclosporine A; Oralcyclo, oral cyclophosphamide; Aza + CSA, azathioprine plus cyclosporine A; Pred, prednisolone alone.

[46 (18.4%)]. The remaining patients presented with nephritic syndrome [43 (17.2%)] and mixed proteinuria and haematuria [23 (9.2%)].

A total of 142 patients had normal renal function at initial presentation. In all, 40 (16.0%) had AKI Stages 2 and 3 at presentation while 68 had AKI Stage 1. Hypertension was present in 136 (54.4%) LN patients during their initial presentation.

Class IV [167 (66.8%)] was the most common LN class identified in this cohort followed by Class V [35 (14.0%)] and Class II [28 (11.2%)]. Of the nine patients who underwent repeated renal biopsies, four patients showed transformation to Class IV LN.

Treatment

Induction and maintenance therapies for the patients are illustrated by Tables 2 and 3. In all, 114 patients (45.8%) received IV methyprednisolone pulses followed by oral prednisolone of 0.5–1 mg/kg/day. The remaining 136 (54.2%) patients were treated with oral prednisolone 1–2 mg/kg/day alone for 1–2 months during the induction period. The majority of patients with LN Class IV (89.2%) and LN Class III (82.4%) received cyclophosphamide as induction therapy. Most of these patients received cyclophosphamide as per the NIH regime (76.0% of Class IV and 76.2% of

Table 3. Maintainance therapy for LN according to LN class

LN class	Maintainance						
	MMF	Aza	CSA	**MMF + CSA**	Pred	**Aza + CSA**	Total
1	0	0	1	0	0	0	1
2	0	20	1	0	5	1	27
3	5	8	0	0	4	0	17
4	59	67	2	4	18	0	150
5	3	15	4	5	5	1	33
6	0	0	0	0	2	0	2
Total	67	110	8	9	34	2	230

MMF, mycophenolate mofetil; Aza, azathioprine; CSA, cyclosporine A; MMF + CSA, mycophenolate mofetil plus cyclosporine A; Pred, prednisolone alone; AZA + CSA, azathioprine plus cyclosporine A.

Class III). The NIH regime consisted of induction therapy using monthly cyclophosphamide infusion at 0.75–1 g/m^2 for 6 months. The mean total dose of cyclophosphamide received by patients on the NIH regime was 4.46 g. Only 22 patients with Class IV and 1 patient with Class III received cyclophosphamide per Euro-Lupus regime, with a standard dose of 500 mg every 2 weeks for 3 months. A total of 17 Class IV patients and 3 Class III patients received mycophenolate mofetil with a mean daily dose of 1.8 g. The mean duration of induction therapy in this patient cohort was 5.35 months.

During the last follow-up, the majority of our patients were on hydroxychloroquine [238 (95.6%)]. The immunosuppressants used were: azathioprine [92 (36.9%)], mycophenolate mofetil [75 (30.0%)], cyclosporine A [38 (15.3%)] and cyclophosphamide [11 (4.4%)]. A total of 169 (67.9%) patients were still on prednisolone. Non-compliance with treatment was documented for 33 patients (13.2%).

Outcome

The 5-, 10-, 15- and 20-year survival rates of our cohort were 93%, 88%, 82% and 77%, respectively. There were a total of 37 deaths (14.8%) with the main causes being infection and flare [20 (54.0%)] and infection alone [10 (27.0%)]. Seven (19.0%) patients died from other causes, of which three died from stroke, one died of lung cancer, one due to a motor vehicle accident, one from burns and one due to pulmonary hypertension. Five of these seven patients had a disease duration in excess of 5 years.

In all, 16 patients (43.2%) died within the first 5 years of disease onset due to both flare of LN and infection. All of the patients had septicaemic shock for which they received broad-spectrum antibiotics and treatment in intensive care. The organisms isolated from patients with sepsis included *Streptococcus pyogenes* (two patients), *Streptococcus pneumonia* (one patient), *Staphylococcus aureus* (one patient), *Escherichia coli* (one patient), *Salmonella typhi* (one patient) and *Pseudomonas aeroginosa* (one patient).

Age, gender, ethnicity, disease duration, class of LN, treatment given, presence of hypertension and complement levels were not predictive of mortality for this cohort. The independent predictors of mortality identified for this cohort of LN patients were: the presence of AKI at presentation [HR 3.41; confidence interval (CI) 1.50–7.76], failure to achieve either complete or partial remission at 1-year post-induction therapy (HR 2.99; CI 1.35–6.65) and non-compliance with treatment (HR 1.89; CI 1.22–2.96) as illustrated by Table 4. Figure 1 shows the survival patterns according to the presence or absence of AKI at presentation.

Table 4. Multivariate analysis of the risk factors for mortality in patients with lupus nephritis

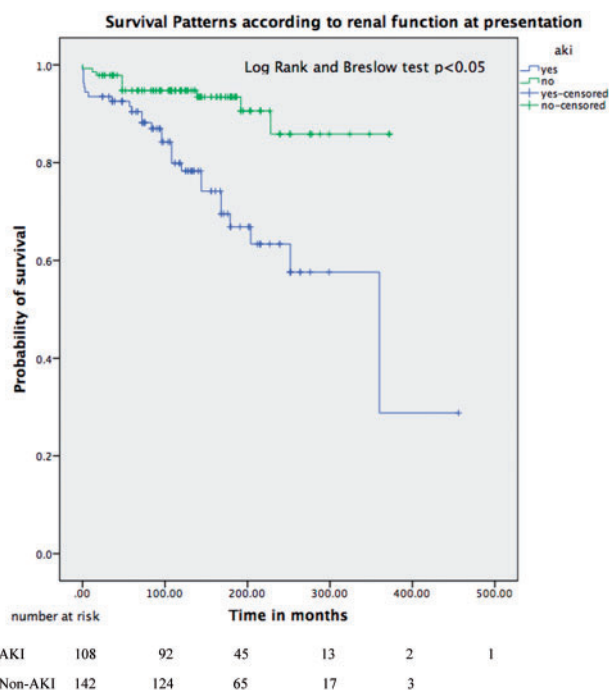| Risk factors	HR	95% CI		P-value
		Lower	Upper	
Age	0.997	0.962	1.034	0.886
Gender	1.630	0.494	5.371	0.422
Ethnic group	1.308	0.996	1.716	0.053
AKI	3.414	1.502	7.757	0.003
Hypertension	0.816	0.354	2.265	0.816
LN class	1.210	0.659	2.221	0.539
Induction therapy	0.866	0.669	1.120	0.272
Failure to achieve remission at 1 year	2.994	1.348	6.647	0.007
Non-compliance	1.898	1.216	2.964	0.005

Fig. 1. Survival patterns according to the status of renal function at presentation.

Subgroup analysis of the 37 deaths showed that different treatment modalities were not predictive of death due to infection. Neither usage of methylprednisolone nor different immunosuppressants were predictive of death due to infection.

A total of 173 (81.2%) patients were in complete remission during their last follow-up. At the end of study period, 16 patients showed progression of LN, while 12 had relapsed LN. Partial remission had occurred in 12 patients.

The renal survival rates at 5-, 10-, 15- and 20 years were 97%, 93%, 88% and 86%, respectively. In all, 201 patients (94.4%) remained dialysis-free while 12 patients were in ESRD. Seven patients were on haemodialysis, four were on peritoneal dialysis and only one patient received renal transplant. Table 5 shows the independent predictors of ESRD in this cohort of LN patients were: failure to achieve remission 1 year post-induction therapy (HR 10.59; CI 2.64–42.56), the presence of AKI at presentation (HR 6.35; CI 1.64–24.55) and non-compliance with treatment (HR 2.64; CI 1.36–5.13). Figure 2 shows the renal survival patterns according to remission status at 1-year post-induction therapy.

Discussion

This study found that the majority of LN patients in our centre were young females with Class IV LN. LN was prevalent at the time of SLE diagnosis in more than half of the cases, a figure much higher than others previously reported in the literature [1–3, 11]. Ethnic differences in disease expression have most likely contributed to the increased incidence of LN. Clinicians need to be vigilant in monitoring the renal function and urinalysis in every SLE patient so as to diagnose LN earlier on.

The 5-, 10-, 15- and 20-year survival rates of 93%, 88%, 82% and 77%, respectively, for these patients were comparable to survival rates previously reported in the literature [6, 12, 13]. Improved socio-economic conditions, earlier diagnosis, modern immunosuppressive therapies and better supportive care have increased the survival rates in LN patients, irrespective of diagnosis and class.

In contrast to other studies from well-developed countries [5, 6, 11–14], the main causes of death among these patients were flare of LN and concomitant infection. Both of these causes contributed to >50% of deaths. Infection alone contributed to another 25% deaths for this cohort. The majority of deaths during the first 5 years of disease were from flare of LN and infections. Our findings corroborate studies from other developing countries [15–18] showing that infection remains the main cause of death in patients with severe active LN. Control of active LN, prevention and treatment of infection remain the main therapeutic challenges in LN patients within developing countries.

Cardiovascular complications and malignancy have been reported as emerging causes of mortality in LN [5, 11]. However, we only found three deaths due to stroke and one death due to lung cancer in our centre. Early mortality due to active LN complicated by infection remained the primary cause of deaths in this cohort.

Multiple demographic, clinical and laboratory variables have been associated with poor outcome in LN. Age, gender, ethnicity, disease duration, uncontrolled hypertension, anaemia, elevated serum creatinine, high rate of decline in glomerular filtration rate and chronic renal scarring have all been associated with poor outcome in LN [12–14].

Attainment of a response or remission in proteinuria is the ultimate aim of treatment in LN. Failure to achieve remission at 1-year post-induction therapy has been found to be the strongest negative prognostic factor amongst our LN patients. This is in keeping with previous studies showing that patients who fail to achieve remission have poorer outcomes. Long-term follow-up of patients in the Euro-Lupus Nephritis Trial showed that early response to therapy at 6 months (defined as a decrease in serum creatinine level and proteinuria <1 g/24 h) was the best predictor of good long-term renal outcome [19]. Proteinuric remission is an independent predictive prognostic marker of good renal survival and mortality, regardless of the interval from biopsy to remission, recurrence of proteinuria after remission, renal function status at remission or haematuria remission [20, 21].

The presence of AKI at presentation is also a poor prognostic factor in our patients. Previous studies have shown that poor renal function at presentation is associated with poor outcomes [12, 22–24]. This is not surprising as renal damage has been consistently found to be independent predictor of mortality in SLE. Faurschou et al. have reported that serum creatinine >140 μmol/L increased the risk for ESRD by 3.5 times [24].

Table 5. Multivariate analysis of the risk factors for ESRF in patients with lupus nephritis

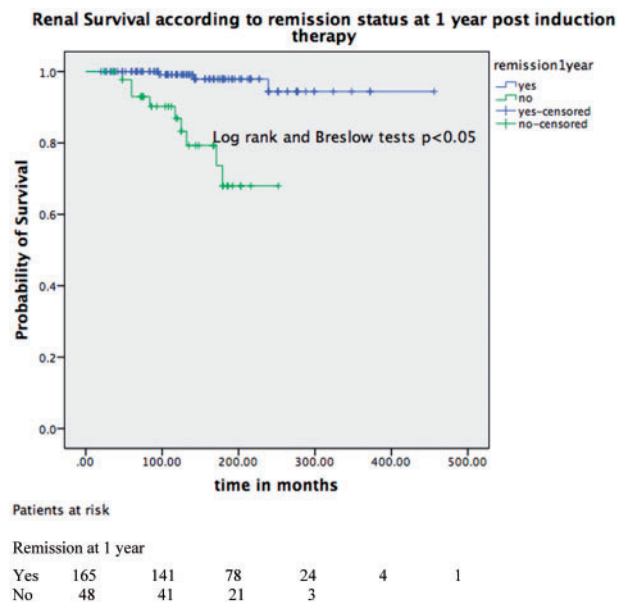| Risk factors	HR	95% CI Lower	Upper	P-value
AKI	6.350	1.643	24.550	0.007
Failure to achieve remission at 1 year	10.591	2.636	42.561	0.001
Non-compliance	2.636	1.355	5.130	0.004

Fig. 2. Renal survival patterns according to remission status at 1 year post-induction therapy.

Non-compliance with treatment has been identified as an independent predictor for mortality and ESRD in this cohort. This finding highlights the need to educate our patients about their disease and the importance of compliance with treatment and follow-up. This needs to be reinforced consistently to ensure compliance in order to prevent poor outcomes.

Hydroxychloroquine improved the complete renal remission rate in conjunction with mycophenolate mofetil therapy for membranous LN [25] and reduced LN flare incidence by 74% in another study [26]. In this study, >90% of patients received hydroxychloroquine as part of their treatment regimes. This most probably contributed to the improved survival as hydroxychloroquine has been found to be beneficial in LN. Hydroxychloroquine, therefore, may protect against the onset of LN, relapses of LN and ESRD [27, 28].

Age, gender, ethnicity, disease duration, class of LN, treatment given, presence of hypertension, antiphospholipid syndrome, anaemia and complements levels were not predictive of mortality for this cohort. As this study was retrospective, there was some inevitable inherent bias. We were unable to correlate the histopathological activity and chronicity indexes of renal biopsies with outcomes in our patients due to inadequate data. This study did not assess the socio-economic status or education levels of our patients, which may have affected the outcomes.

In summary, we have found that active LN and concomitant infection contributing to early mortality remain the main therapeutic challenge in a multi-ethnic Asian population with LN.

Independent predictors of mortality in our cohort of LN patients were the presence of AKI at presentation, failure to achieve remission at 1-year post-induction therapy and non-compliance with treatment.

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Authors' contributions

All authors were involved in conception, design, analysis and interpretation of data. C.L.T. and C.H.-H.T. were involved in drafting the article, revising it and providing intellectual content of critical importance to the work described. All authors approved the final version of the manuscript.

Conflict of interest statement

None declared.

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