

Original Article

Predictors of mortality in children with lupus nephritis

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Abstract

Background Renal involvement during the clinical course of systemic lupus erythematosus (SLE) is generally considered to be the most important factor influencing disease prognosis in terms of morbidity and mortality. Various factors have been reported to influence the prognosis of lupus nephritis (LN).

Objective To analyze clinical signs and laboratory parameters that might serve as predictors associated with mortality in pediatric LN.

Methods Retrospectively, medical records of children with LN at Soetomo Hospital from 1998 to 2011 were studied. Diagnosis of SLE was based on *Revised American Rheumatism Association* criteria, while patients with clinical manifestations of hypertension, abnormal urinalysis, and serum creatinin > 1 mg/dL were considered as lupus nephritis. Cox proportional hazard modeling was used to assess for associations of clinical signs and laboratory parameters with mortality. Kaplan-Meier survival analysis was used to assess the cumulative survival from the time of diagnosis to the outcome.

Results There were 57 children with LN of whom 43 (75%) were girls. The female-to-male ratio was 3:1. Subjects' mean age was 10.6 (SD 6.87) years. The mean time of observation was 51 (SD 74.54) months and 23 (40%) children died. Age, gender, hypertension, hematuria, proteinuria, and anemia were not significant as predictors for mortality. However, hypertensive crisis (HR=2.79; 95%CI 1.16 to 6.75; P=0.02) and initial glomerular filtration rate (GFR) of <75 mL/min/1.73m² (HR=3.01; 95%CI 1.23 to 7.34; P=0.01) were significant predictors of mortality in children with LN. The mean survival time of LN with hypertensive crisis and initial GFR <75 mL/min/1.73m² was 36.9 (SD 12.17) months.

Conclusion Hypertensive crisis and GFR <75 mL/min/1.73m² are significant predictors of mortality in children with LN. [Paediatr Indones. 2014;54:338-43].

Keywords: pediatric lupus nephritis, hypertensive crisis, low GFR, SLE

Systemic lupus erythematosus (SLE) is an autoimmune disease with various clinical manifestations. Although most common in women of childbearing age, about 10–15% of all SLE patients are diagnosed in childhood, at less than 16 years of age. Rates of organ involvement are higher in children.¹⁻³ Lupus nephritis (LN) is one of the main clinical presentations determining the course and outcome in patients with SLE. Nephritis complicates SLE in approximately 25-50% of patients and is associated with increased mortality.^{4,5} The SLE manifestation of overt nephropathy is more common in children than adults. Patients with severe histological forms of nephritis have more severe renal manifestations. Although several studies have reported on factors affecting outcomes, the results remain unclear. Possible prognostic factors are male gender, black race, onset before puberty, persistent hypertension, hypertensive crisis, impaired renal function, nephrotic syndrome, anemia, and class IV nephritis.⁶

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Several long-term studies and prognostic investigations have been performed in adult patients with SLE. However, only a few clinical studies on children with LN have been published. Those studies have been conducted to identify the predictors of children with LN, but the results are different and sometimes conflicting. Little is known about the outcomes and prognostic factors of LN in Indonesian children.⁷

The aim of this study was to analyze clinical signs and laboratory parameters in children with LN during a 14-year period and to assess for possible prognostic factors to predict patient survival.

Methods

We reviewed the medical records of all children who were initially seen by the Pediatric Nephrology Division at Dr. Soetomo Hospital, Surabaya, during a 14-year period from 1998 to 2011, and who fulfilled four or more of the *Revised American Rheumatism Association* criteria for the diagnosis of SLE (including malar rash, discoid rash, photosensitivity, oral ulcers, non-erosive arthritis, pleuritis or pericarditis, renal disorder, neurologic disorder, hematologic disorder, immunologic disorder, positive antinuclear antibody)⁸ for the diagnosis of SLE with renal manifestation. Patients with drug-induced lupus, discoid lupus, or mixed connective tissue diseases were excluded. Clinical and laboratory features with renal pathology findings [class I-VI based on the *International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification of lupus nephritis*]⁹ at the time of presentation were recorded.

Lupus nephritis was considered to be present in patients showing hypertension, abnormal urinalysis or serum creatinine >1 mg/dL. Hypertension was defined as systolic and/or diastolic blood pressure above the 95th percentile for gender, age, and height. Hypertensive crisis was defined as systolic pressure \geq 180 mmHg or diastolic pressure \geq 120 mmHg (for those > 6 year old), or blood pressure \geq 50% above the 95th percentile for gender, age, and height. Urinalysis was considered abnormal in the presence of >5 red blood cells per high power field of centrifuged specimen, urine protein >1 +, or the presence of red cell casts. Laboratory findings recorded for all patients

included white blood cell count, hemoglobin level, platelet count, albumin, complement (C3 and C4), antinuclear antibodies (ANA), anti-double stranded DNA-binding (anti-dsDNA) activity, and glomerular filtration rate (GFR) by Schwartz formula. A hemoglobin concentration of <10 g/dL, leukopenia <4000/ μ L (average from two examinations), thrombocytopenia < 100,000/ μ L, GFR <75 mL/min/1.73m², and hypoalbuminemia <2.5 g/dL were considered to be abnormal. The outcomes were classified as survived or died.

Data analyses were performed using SPSS 20.0. Cox proportional hazard modeling was used to assess for associations between clinical variables and mortality. Kaplan Meier survival analysis was used to assess for cumulative survival from the time at diagnosis to the outcome.

Results

Fifty-seven LN patients, of whom 43 (75%) were female, were included in this study. Subjects' mean age was 10.6 (SD 6.8) years. The mean time of observation was 51 (SD 7.4) months, and 23 (40%) children died. Only 2 (4%) patients had severe malnutrition (Table 1). The mean *American Rheumatism Association* (ARA) score was 5.6 (SD 1.4). Forty-two (74%) patients were under 12 years of age. Forty-four (77%) patients were referred from other hospitals.

The most common extra-renal manifestations seen in our patients were hematological abnormalities, serositis, arthritis and mucocutaneous manifestations (Table 2). Fifty-three patients (93%) had anemia, the most common clinical manifestation noted in our study. Hypoalbuminemia was observed in 33 (54%) cases. Hematuria and urinary casts were observed in 28 (49%) and 41 (71%) subjects, respectively. Complement C3 was low in 36 (63%) patients. Lupus erythematosus (LE) cells were found in 14 (25%) cases. The ANA test was positive in 33 (58%) patients and the anti-dsDNA was positive in 22 (39%) patients.

A renal biopsy was performed in 14 patients. The pathological findings included mesangial glomerulonephritis (ISN/RPS class II) in 5 patients, focal segmental proliferative glomerulonephritis (ISN/RPS class III) in 3 and diffuse proliferative glomerulonephritis (ISN/RPS class IV) in 6 patients.

The relationship between clinical and laboratory parameters to survival of LN patients is shown in **Table 3**. From all parameters analyzed by Cox models, two variables had significant correlations with the survival of LN patients, hypertensive crisis (HR=2.79; 95%CI 1.16 to 6.75; P=0.02) and GFR < 75 mL/min/1.73 m² (HR=3.01; 95%CI 1.23 to 7.34; P=0.01). Patient survival was analyzed by Kaplan-Meier survival curves (**Figures 1 and 2**).

Patients with initial GFR , 75 mL/min/1.73m² BSA had lower survival compared to those with higher GFR level (**Figure 1**), while patients with hypertensive crisis survived less then those without hypertensive crisis (**Figure 2**).

In our study, the mean time of observation was 51 (SD 7.4) months and 23 (40%) of the children

studied died. In addition, 5 (62.5%) patients with hypertensive crisis died. There were 21 (36.8%) patients with initial GFR < 75 mL/min/1.73m². The mean survival time of LN patients with hypertensive crisis and initial GFR < 75mL/min/1.73m² was 36.9 (SD 12.17) months.

Table 2. Frequency of the occurrence of extra-renal manifestations

Clinical manifestations	Number	Percentage
Mucocutaneous manifestations	37	64.4
Arthritis	22	38.6
Serositis	26	45.6
Neurological involvement	17	29.8
Hematological abnormality	54	94.7

Table 1. Demographic characteristics of subjects

Characteristics	Outcomes		All patients (n=57)
	Died (n=23)	Survived (n=34)	
Gender, n (%)			
Female	18 (78)	25 (74)	43 (75)
Male	5 (22)	9 (26)	14 (25)
Mean age (SD), years	11.3 (10)	10 (3.5)	10.6 (6.8)
Age by group, n (%)			
≤ 12 years	18 (78)	24 (71)	42 (74)
>12 years	5 (22)	10 (29)	15 (26)
Referred cases, n (%)			
No	6 (26)	7 (21)	13 (23)
Yes	17 (74)	27 (79)	44 (77)
Severe malnutrition, n (%)	0 (0)	2 (5.9)	2 (3.5)

Table 3. Clinical and laboratory parameters related to survival by Cox models

Parameters	HR	95% CI		P value
		Lower	Upper	
Hypertension	0.70	0.10	4.79	0.72
Hypertensive crisis	2.70	1.16	6.75	0.02
ANA test	0.99	0.27	3.52	0.99
Anti-dsDNA	1.59	0.04	53.28	0.79
Decreased C3 level	0.06	0.01	1.92	0.11
LE cell	1.48	0.11	19.35	0.76
Hypoalbuminemia	0.12	0.02	0.59	0.90
Decreased initial GFR	3.01	1.23	7.34	0.01
Thrombocytopenia	0.41	0.06	2.49	0.34
Leukopenia	1.05	0.30	3.67	0.93
Reticulosis	0.88	0.14	5.64	0.89
Cellular cast	0.60	0.13	2.83	0.52
Proteinuria	0.94	0.25	3.59	0.94
Hematuria	1.56	0.39	6.29	0.53
Renal biopsy	1.50	0.47	4.83	0.48

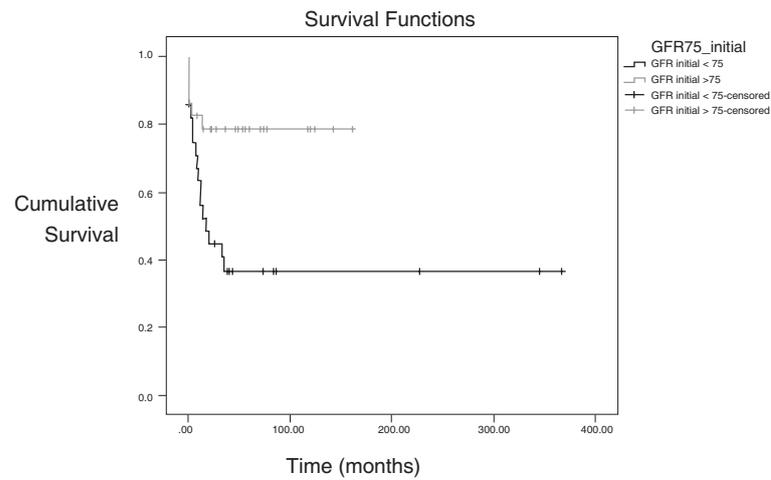


Figure 1. Survival curve of LN patients based on initial GFR

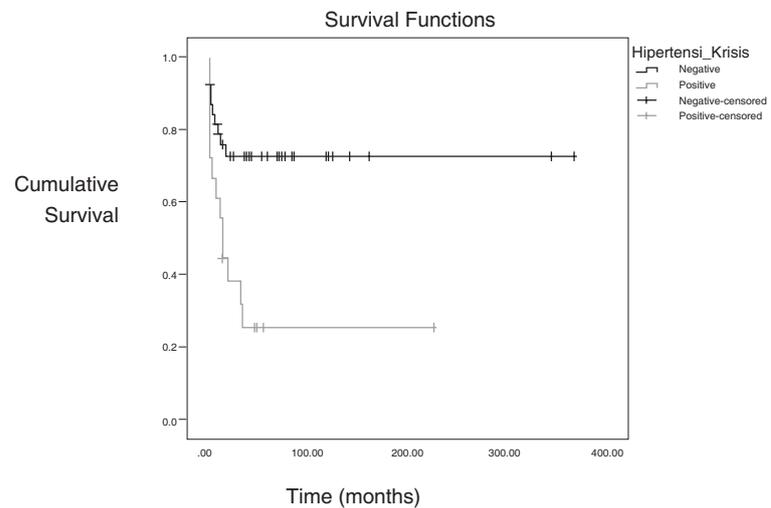


Figure 2. Survival curve of LN patients with hypertensive crisis based on occurrence of hypertensive crisis

Discussion

The clinical and laboratory parameters of 57 children with SLE were reviewed. The subjects were predominately female (75%) with female-to-male ratio of 3:1. Subjects' mean age was 10.6 (SD 6.8) years and mean time of observation was 51 (SD 7.4) months. In our study the mean age and gender distribution was similar to other studies.^{7,10-13} In contrast to previous reports, we found no statistically

significant association in male gender, or onset of disease before puberty (12 years of age) with increased risk of patient survival. This lack of association might be related to recent improvements in accessibility to health care in our patient population, differences in our referral patterns from those of other institutions, or to other as yet unrecognized factors. Whether the improved survival for younger children represents more prompt diagnosis and treatment or other factors was also unclear.¹⁴

Renal involvement is more common in children with SLE. Histological changes may precede the appearance of clinical symptoms of renal involvement, hence, early screening to improve patient management is required. Renal involvement in developed countries is seen in 30-70% of SLE patients. Proteinuria and microscopic hematuria were the most common symptoms. More than half of our children survived. Early diagnosis, better treatment protocols and aggressive management of infections all contribute to the improved outcomes in this severe disease.^{10,15,16}

Our study confirmed previous reports that elevated creatinine levels prior to the time at diagnosis increased the risk of death. The estimation of prognosis may be enhanced by considering additional features that indicate the reversibility of the renal dysfunction, including the duration of nephritis, the rate of change of serum creatinine, and the renal histology. A study reported that an elevated serum creatinine level at the time of renal biopsy was associated with an increased rate of development of renal failure and was a very strong clinical, prognostic indicator.¹⁷ Kidney biopsy evaluation offered a relatively direct appraisal of the type of disorder involved and contributed significantly to predictions of renal outcome in other studies.^{11,17,18} Unfortunately, in our study only 14 patients were performed renal biopsy, so this small number may have lead to biopsy results being deemed not significant in influencing prognosis.

In our study, hypertensive crisis and initial GFR <75 ml/min/1.73 m² were found to be associated as prognostic factors with poor survival of children with LN. Hypertensive crisis appeared to clearly define a subgroup of children at risk for progression to renal failure. In view of the importance of hypertension as an indicator of renal impairment, the blood pressure of younger children with lupus should be carefully monitored.^{19,20} In conclusion, our study confirmed that hypertensive crisis and GFR <75 mL/min/1.73 m² are the significant prognostic factors for low survival in children with LN.

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