Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.59, No.1(2019). p. 1-6; doi: http://dx.doi.org/10.14238/pi59.1.2019.1-6

Original Article

Predictors of mortality in children with systemic lupus erythematosus

Fanny Listiyono, Sumadiono, Cahya Dewi Satria, Indah K. Murni

Abstract

Background Systemic lupus erythematosus (SLE) is a multisystem chronic disease with a relatively high mortality rate in children, despite improvements in prognosis and survival rate over the past decade. Studies on the predictors of mortality in children with SLE, especially in low- and middle-income countries, are limited.

Objective To determine the predictors of mortality of children with SLE.

Methods This was case-control study using data from medical records of children with SLE at Dr. Sardjito Hospital, Yogyakarta, Indonesia, between 2009 and 2017. Subjects were children aged <18 years diagnosed with SLE. Cases were those who died within one year of diagnosis; the controls were those who were discharged alive. From subjects' medical records, we collected clinical data including age, sex, date of diagnosis, nutritional status, anti-dsDNA antibody, antinuclear antibody (ANA), hypertension, disease activity based on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score, proteinuria, thrombocytopenia, mortality/survival outcome, date of death, cause of death, and clinical data including fever, seizures, antibiotic used, microbial culture outcomes, and infection-related diagnoses. We performed bivariate analysis of the association between predictor variables (SLEDAI score, proteinuria, infection, hypertension, and seizures) and mortality outcome (survival or death), followed by logistic regression analysis.

Results Eighty-four patients with SLE were included, of which 72 were female. Median age at diagnosis was 14 (range 4-18) years. Twenty-three patients (27%) died within one year after diagnosis. The most common causes of death were infection and renal failure in 8/23 and 7/23 subjects, respectively. On bivariate analysis, the variables significantly associated with mortality were hypertension (OR 3.34, 95%CI 1.22 to 9.14) and infection (OR 3.71; 95%CI 1.36 to 10.12). Seizures, proteinuria, and SLEDAI score were not found to be significantly associated with mortality. On logistic regression analysis, infection was the only significant predictor of mortality (OR 3.22; 95%CI 1.15 to 9.05).

Conclusion Among the factors studied, infection is significantly associated with mortality in children with SLE. **[Paediatr Indones. 2019;59:1-6; doi: http://dx.doi.org/10.14238/pi59.1.2019.1-6].**

Keywords: *predictor; mortality; children; systemic lupus erythematosus*

Systemic lupus erythematosus (SLE) is a chronic disease of varying degrees of severity, ranging from mild to life-threatening. Over the past few years, SLE in children has become considered a fatal disease. Some studies have reported that the prognosis of SLE in children is poorer than in adults.[1] Childhood SLE is more common in females, with a female-to-male ratio of 3:1. After puberty, this ratio increases to 9:1. The incidence of

From the Department of Child Health, Universitas Gadjah Mada Medical School/Dr. Sardjito Hospital, Yogyakarta, Central Java, Indonesia.

Corresponding author: Fanny Listiyono. Departement of Child Health, Universitas Gadjah Mada Medical School/Dr. Sardjito General Hospital, Jl. Kesehatan No.1 Sekip Utara, Yogyakarta-55284, Indonesia. Phone. +62-274-561616, +62-856-2929773, Fax. +62-274-583745. E-mail: funnemd@gmail.com.

Submitted September 28, 2018. Accepted February 5, 2019.

childhood SLE is approximately 0.3 to 0.9 per 100,000 children per year, with an average prevalence of 3.3-8.8 per 100,000 children.[2] At Dr. Sardjito Hospital, Yogyakarta, a regional referral hospital, from 2015 to April 2017 new cases accounted for 10.6% of all SLE cases.[3]

The life expectancy of SLE patients has improved in recent decades. Prior to 1955, the 5-year survival rate for SLE was less than 50%. Today, the 10-year survival rate has risen to about 90%. The increase in life expectancy is due to earlier diagnosis, more aggressive treatment with agents such as corticosteroids and cytostatics, better access to hemodialysis for patients with renal failure, and better treatment of complications such as infection, hypertension, and hyperlipidemia.[4] Race, sex, age at diagnosis, thrombocytopenia, nephritis, central nervous system involvement, and disease progression are considered to be associated with mortality in patients with SLE. In a case-control study in Mexico, the main cause of mortality was infection. Other factors associated with mortality are nephritis, therapeutic steroid index, the *SLE Disease Activity Index* (SLEDAI) score, and severe infection.[5–8]

The predictors of mortality in children with SLE has not been extensively studied in Indonesia. A study of predictors of childhood SLE mortality conducted in our hospital in 2012 found that positive anti-dsDNA antibody is a prognostic factor for mortality.[9] In the present study, we aim to provide current data on the predictors of mortality in childhood SLE patients at Dr. Sardjito Hospital.

Methods

This was a case-control study of children aged one month to 18 years diagnosed with SLE based on the 1997 American College of Rheumatology (ARC) criteria who were seen at Dr. Sardjito Hospital from January 2009 to December 2017. Cases were subjects who died within one year of diagnosis. Death was established from the medical records of subjects who died at the hospital's pediatric inpatient care unit or from reports of subjects' death from their parents. The control group consisted of subjects who were discharged from the hospital alive at least one year after diagnosis.

Data collected from the patients' medical records included age, sex, date of diagnosis, nutritional status, anti-dsDNA antibody, antinuclear antibody (ANA), and clinical variables associated with SLE at the time of diagnosis, including hypertension (systolic and/or diastolic blood pressure above the 95th percentile for sex, age, and height), disease activity, proteinuria (urinary protein $\geq$0.5 g per day or $\geq$+3 using dipstick), thrombocytopenia (platelets <100,000/mm^3), mortality outcome (survival or death), date of death, and cause of death.[10,11] We also recorded other relevant data, such as fever, seizures, antibiotic used, microbial culture outcomes, and infection-related diagnoses.

Disease activity was assessed based on *Systemic Lupus Erythematosus Disease Activity Index* (SLEDAI), a scoring system comprising 24 items. SLEDAI scores were calculated at the point of diagnosis. A score of one to ten was classified as mild-moderate disease activity, while a score of $\geq$11 was classified as severe.[12] Infection was defined as a positive microbial culture or a record of suspected new infection necessitating sampling for culture, initiation of antibiotics, or change in antibiotic regimen. Nutritional status was determined based on the *World Health Organization* (WHO) *z*-score growth charts. We used weight-for-height charts for children aged $\leq$5 years, and body mass index (BMI)-for-age charts for children aged >5 years. Subjects were classified as well-nourished if weight-for-height or BMI-for-age was >-2 standard deviations (SD) but $\leq$+2 SD, moderately malnourished if weight-for-height or BMI-for-age was <-2 SD, severely malnourished if weight-for-height or BMI-for-age was <-3 SD, overweight if weight-for-height or BMI-for-age was >+2 SD, and obese if weight-for-height or BMI-for-age was >+3 SD.

Data was entered into *Epidata software* (Epidata Association, Odense, Denmark). Statistical analysis was performed using *SPSS version 24.0* (SPSS Inc., Chicago). Univariate analysis between predictor variables and mortality outcome was done using the chi-square test. The predictor variables analyzed were disease activity using SLEDAI score, proteinuria, infection, hypertension, and seizures. The main outcome was mortality (survival or death). Variables with a P value of <0.25 were entered into a logistic regression analysis. A P value of <0.05 was considered statistically significant.

The study protocol had been approved by the Ethics Committee of the Universitas Gadjah Mada Medical School.

Results

A total of 134 children aged <18 years with SLE sought treatment at Dr. Sardjito Hospital during the study period. Eighty-four children met the inclusion criteria; 23 died and 61 survived one year after the diagnosis. Subject recruitment flow can be seen in **Figure 1**.

Out of 84 subjects included in the study, 23 died within one year after diagnosis. The cause of death was infection in 8 subjects, renal failure in 7 subjects, cardiovascular disorders in 3 subjects, neuropsychiatric SLE in 1 subject, and other cause in 2 subjects. The remaining 2 subjects died at home and in another hospital, respectively, with unknown or untraceable causes of death. Sepsis (5/8), pneumonia (2/8), and diarrhea (1/8) were the main types of infection leading to death.

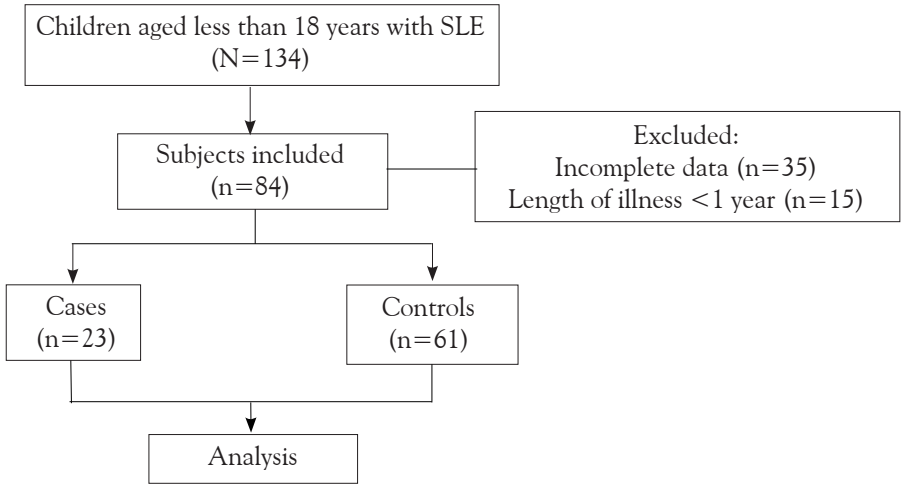

Figure 1. Subject recruitment flow

The baseline characteristics of study subjects are presented in **Table 1**. In both groups, most subjects were female. Most subjects were well-nourished; no subject was overweight or obese. Baseline characteristics appeared to be comparable between the case and control groups.

On bivariate analysis (**Table 2**), seizures (P=0.07), SLEDAI score (P=0.05), and proteinuria (P=0.09) were not significantly associated with mortality. On the other hand, hypertension (OR=3.34; 95%CI 1.22 to 9.14; P=0.02) and infection (OR 3.71; 95%CI 1.36 to 10.12; P=0.01;) significantly affected mortality. All variables studied had a P value of <0.25 and were thus included in the multivariate analysis. On logistic regression analysis, the only variable significantly associated with mortality was infection (OR 3.22; 95%CI 1.15 to 9.05; P=0.02) (**Table 2**).

Discussion

In this case-control study of factors associated with mortality in pediatric SLE, we found that hypertension and infection significantly affected of mortality. However, when all factors were considered, only infection remained as a significant associated factor. This study was done as an update to a similar study conducted at our center in 2012 by Farkhati *et al.*[9]

In the current study, we found a male-to-female ratio of 1:6. This ratio is similar to that found in Farkhati's study (1:6.9) and consistent with studies in other centers, which have reported male-to-female ratios ranging between 1:4-5 to 1:10.[6,13] The median age at diagnosis in both our case and control groups was approximately 14 (range 4 to18) years; the majority of patients in both groups were >10 years of

age (91.3% and 85.2% in the case and control groups, respectively). The median age Farkhati's study was 11.9 years.[9] A similar study in the Philippines reported a median age at diagnosis of 14 years.[14] This shows that pediatric SLE is commonly diagnosed during puberty.

Table 1. Subject characteristics

Characteristics	Died (n=23)	Survived (n=61)
Sex, n (%)		
Male	4 (17.4)	8 (13.1)
Female	19 (82.6)	53 (86.9)
Age at onset of disease, n (%)		
<10 years	2 (8.7)	9 (14.8)
≥10 years	21 (91.3)	52 (85.2)
Median age (range), years	14 (8 to 17)	14 (4 to 18)
Median time since diagnosis (range), days	62 (4-350)	1119 (365 -3772)
Median SLEDAI score (range)	19 (8-33)	13 (2-24)
Trombocytopenia		
Yes	3 (13)	13 (21.3)
No	20 (87)	48 (78.7)
ANA		
Positive	18 (78.3)	51 (83.6)
Negative	5 (21.7)	10 (16.4)
Anti ds-DNA		
Positive	17 (73.9)	47 (77)
Negative	6 (26.1)	14 (23)
Nutritional status		
Well-nourished	17 (74)	45 (74)
Moderate malnutrition	2 (9)	12 (20)
Severe malnutrition	4 (17)	4 (7)

Approximately a quarter of children with SLE died less than one year after diagnosis. The causes of death in SLE in Asia-Pacific are infections (30-80%), active SLE (19-95%), cardiovascular disorders (6-40%), and renal involvement (7-36%).[4,13,15,16] In our center, infection was the main cause of mortality in 20129 and remains the leading cause of death in the present study, accounting for 8/23 deaths, followed by renal failure (7/23) and cardiovascular disorders (3/23). The most common type of infection in this study was sepsis, which is similar to a previous report in Brazil.[6]

Although the SLEDAI score in the case group in our study was higher when compared to the control group (19 *vs.* 13), it was not significant for mortality, as well as for proteinuria. This is similar to some previous study in Malaysia.[16] Feng *et al.* in their study also reported that proteinuria and SLEDAI score were not a predictor of mortality, on the contrary it was said that seizure, as one of the manifestation of neuropsychiatry, was an independent predictor.[17] This is slightly different from our study, where the seizure are not a predictor of mortality.

Hypertension in SLE patients is associated with end-stage renal disease (ERDS) that eventually leads to death.[18,19] In the present study, hypertension was found to increase the risk of death (OR 3.34; 95%CI 1.22 to 9.14). These results are similar to those of a study in China, which reported that hypertension increased mortality risk up to threefold.[19] However, in

Table 2. Univariate and multivariate analysis of predictors and mortality among children with SLE

Parameters	Died n(%)	Survived n(%)	Bivariate analysis		Multivariate analysis	
			OR (95%CI)	P value	OR (95%CI)	P value
Hypertension						
Yes	12 (52.2)	15 (24.6)	3.34	0.02	2.83	0.05
No	11 (47.8)	46 (75.4)	(1.22 to 9.14)		(0.99 to 8.04)	
Seizures						
Yes	7 (30.4)	8 (13.1)	2.89	0.07	2.15	0.24
No	16 (69.6)	53 (86.9)	(0.91 to 9.23)		(0.59 to 7.76)	
Proteinuria						
≥+3	13 (56.5)	22 (36.1)	2.30	0.09	1.16	0.80
<+3	10 (43.5)	39 (63.9)	(0.86 to 6.17)		(0.35 to 3.92)	
SLEDAI Score						
Mild-moderate activity	22 (95.7)	45 (73.8)	7.82	0.05	5.18	0.13
Severe activity	1 (4.3)	16 (26.2)	(0.97 to 62.84)		(0.61 to 44.24)	
Infection						
Yes	14 (60.9)	18 (29.5)	3.71	0.01	3.22	0.02
No	9 (39.1)	43 (70.5)	(1.36 to 10.12)		(1.15 to 9.05)	

a previous Indonesian study, hypertension significantly increases the risk of death in lupus nephritis only when it reaches hypertensive crisis levels.[20] In our study, the association between hypertension and mortality was no longer significant upon multivariate analysis. The mechanism of hypertension in SLE is likely multifactorial and includes, among others, genetics, sex, ethnicity, the renin-angiotensin system, inflammatory cytokines, and drugs. Inflammatory cytokines play a central role in the mechanism of hypertension. Increased inflammatory cytokines will increase renal vascular resistance and reduce glomerular filtration rate (GFR). Inflammatory cytokines also mediate renal vascular changes as a result of the active renin-angiotensin system and the endothelial system, through increased oxidative stress.[21,22]

The only independent variable that remained a significant predictor of mortality after multivariate analysis was infection. Infections that occur in SLE patients may result from SLE itself or as a complication of treatment with corticosteroids and immunosuppressants. The immunocompromised condition of SLE patients brings about increased susceptibility to opportunistic infections, such as yeast infections and tuberculosis. The diagnosis of infection in SLE patients is further complicated by masking of the symptoms of infection by the clinical manifestations of SLE itself. The prevention of infection is of utmost importance for SLE patients, especially in children receiving immunosuppressant and corticosteroid treatment. Similarly, prompt and accurate diagnosis is needed, as well as adequate treatment for every SLE patient who gets an infections. Delay in the diagnosis of infections is associated with higher mortality rates in children with SLE. The most common organs affected by infection in SLE patients are the lungs, urinary tract, and joints.[6,23]

The main limitation of our study was the retrospective retrieval of information from medical records, which may lead to information bias. Since this study was based in an academic referral hospital, most cases were patients referred in poor clinical conditions. However, our results shed light on current factors affecting the mortality of children with SLE and provides data for the development of future studies on childhood SLE.

We conclude that infection is significantly associated with mortality in children with SLE. Other studied factors, including hypertension, seizures, proteinuria, and SLEDAI score are not significantly associated with mortality when all potential risk factors are taken into account.

Conflict of interest

None declared.

Funding Acknowledgment

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

References

1. Rad-Tavangar F, Ziaee V, Moradinejad M-H, Tahghighi F. Juvenile systemic lupus erythematous in Iranian children. Iran J Pediatr. 2014; 24: 365-70.
2. Weiss JE. Pediatric systemic lupus erythematosus: More than a positive antinuclear antibody. Pediatr Rev 2012; 33: 62-74.
3. Pusat Data dan Informasi Kementrian Kesehatan Republik Indonesia. Situasi Lupus di Indonesia. Jakarta: Pusdatin Kemenkes RI; 2017. [cited 2017 July 24]. Available from: www.pusdatin.kemkes.go.id.
4. Mok CC, Lee KW, Ho CT, Lau CS, Wong RW. A prospective study of survival and prognostic indicators of systemic lupus erythematosus in a southern Chinese population. Rheumatology. 2000; 39: 399-406.
5. Blancas-galicia L, Guevara-cruz M, Berrón-pérez R, Berrón-ruiz L. Survival of Mexican patients with paediatric-onset systemic lupus erythematosus and abnormal electroencephalogram. Allergol Immunopathol. 2013; 41: 108-13.
6. Faco MMM, Leone C, Campos LM, Febrônio MV, Marques HHS, Silva CA. Risk factors associated with the death of patients hospitalized for juvenile systemic lupus erythematosus. Brazilian J Med Biol Res. 2007; 40: 993-1002.
7. Hernandez-Cruz B, Tapia N, Villa-Romero AR, Reyes E, Cardiel MH. Risk factors associated with mortality in systemic lupus erythematosus. A case-control study in a tertiary care center in Mexico City. Clin Exp Rheumatol. 2001; 19: 395-401.
8. Ward MM, Pajevic S, Dreyfuss J, Malley JD. Short-term

prediction of mortality in patients with systemic lupus erythematosus: classification of outcomes using random forests. Arthritis Rheum. 2006; 55: 74-80.
9. Farkhati MY, Hapsara S, Satria CD. Antibodi Anti DS-DNA Sebagai Faktor Prognosis Mortalitas pada Lupus Eritematosus Sistemik. Sari Pediatr. 2012; 14: 2-8.
10. Sinha R, Raut S. Pediatric lupus nephritis: Management update. World J Nephrol. 2014; 3: 16.
11. Zhao H, Li S, Yang R. Thrombocytopenia in patients with systemic lupus erythematosus: significant in the clinical implication and prognosis. Platelets. 2010; 21: 380-5.
12. Iaccarino L, Larosa M, Doria A. Disease activity indices and prognosis of systemic lupus erythematosus. In: Roccatello D, Emmi L, eds. Connective tissue disease: A comprehensive guide. Cham: Springer International Publishing; 2016. p. 199-211.
13. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010; 6: 538-46.
14. Gulay CB, Dans LF. Clinical presentations and outcomes of Filipino juvenile systemic lupus erythematosus. Pediatr Rheumatol. 2011; 9: 7.
15. Jakes RW, Bae S-C, Louthrenoo W, Mok C, Navarra S V, Kwon N. Systematic review of the epidemiology of systemic lupus erythematosus in the Asia-Pacific region: prevalence, incidence, clinical features, and mortality. Arthritis Care Res. (Hoboken). 2012; 64: 159-68.
16. Teh CL, Ling GR. Causes and predictors of mortality in hospitalized lupus patient in Sarawak General Hospital, Malaysia. Lupus. 2013; 22: 106-11.
17. Feng X, Pan W, Liu L, Wu M, Ding F, Hu H, *et al.* Prognosis for hospitalized patients with systemic lupus erythematosus in China: 5-year update of the Jiangsu cohort. PLoS One. 2016; 11: 1-15.
18. Baqi N, Moazami S, Singh A, Ahmad H, Balachandra S, Tejani A. Lupus nephritis in children: a longitudinal study of prognostic factors and therapy. J Am Soc Nephrol. 1996; 7: 924-9.
19. Feng M, Lv J, Fu S, Liu B, Tang Y, Wan X, *et al*. Clinical features and mortality in Chinese with lupus nephritis and neuropsychiatric lupus: A 124-patient study. J Res Med Sci. 2014; 19: 414-9.
20. Oktadianto L, Prasetyo RV, Soemyarso NA, Noer MS. Predictors of mortality in children with nephritis lupus. Paediatr Indones. 2014; 54: 338-43.
21. Ryan MJ. The pathophysiology of hypertension in systemic lupus erythematosus. Am J Physiol Regul Integr Comp Physio. 2009; 296: R1258-67.
22. Taylor EB, Ryan MJ. Understanding mechanisms of hypertension in systemic lupus erythematosus. Ther Adv Cardiovasc. Dis. 2017; 11: 20-32.
23. Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. Curr Opin Rheumatol. 2001; 13: 345-51.