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Original Article

Factors associated with pericardial effusion in pediatric systemic lupus erythematosus

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Abstract

Background Cardiovascular involvement in systemic lupus erythematosus (SLE) has been reported to range from 4-78%. Complications can affect all structures of the heart, including the endocardium, myocardium, pericardium, and valves. Pericarditis is the most common manifestation, with an incidence of 11-54% in SLE patients. Pericardial effusion is often observed in patients with pericarditis, and can be confirmed by echocardiography.

Objective To determine factors associated with pericardial effusion in children with SLE.

Methods We conducted a restrospective cross-sectional study by reviewing medical records of children with SLE aged less than 18 years who underwent echocardiography at the Dr. Sardjito Hospital. Yogyakarta, from January 2011 to March 2018. Patients with congenital heart disease or incomplete medical records were excluded. A multivariate logistic regression analysis was done to determine factors that independetly associated with pericardial effusion.

Results Among 165 children with SLE, 73 fulfilled the inclusion criteria. The prevalence of pericardial effusion was 54.8%. Median age was 13 (range 5-17) years and the female-to-male ratio was 8:1. Hemolytic anemia (OR=4.135; 95%CI 1.039 to 16.453; P=0.044) was significantly associated with pericardial effusion.

Conclusion Hemolytic anemia is significantly associated with pericardial effusion in children with SLE. **[Paediatr Indones. 2018;58:227-32; doi: http://dx.doi.org/10.14238/pi58.5.2018.227-32]**.

Keywords: *lupus; children; pericardial effusion; pericarditis*

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disorder in which 20% of patients are diagnosed in childhood. Childhood-onset SLE is associated with higher morbidity and mortality than adult-onset SLE. The number of SLE patients in the Department of Pediatrics, Dr Sardjito Hospital, Yogyakarta has increased at an average of 5-6 patients per year, with 65% survival by the fifth year.[1]

Cardiovascular manifestations of SLE cause high morbidity and mortality.[2] The incidence of pericarditis and pericardial effusion documented by echocardiographic examination varied from 11% to 54%. A much higher incidence of pericardial involvement in SLE was reported in autopsy studies in which histological examination was performed.[3] Nowadays, cardiac manifestations are often mild and asymptomatic. However, they can be frequently recognized by echocardiography and other noninvasive tests. Echocardiography is a sensitive and specific technique in detecting cardiac abnormalities, particularly mild pericarditis, valvular lesions, and myocardial dysfunction.[4]

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In high-income countries, echocardiography is routinely performed for early detection of cardiovascular disorders in SLE, as pericarditis is often asymptomatic.[5] However, in low- and middle income countries including our center, echocardiography has not been a routine examination. In previous studies, the factors associated with pericarditis in SLE were hemolytic anemia, proteinuria, lymphadenopathy, anti-Smith antibodies, Raynaud's syndrome, pleuritis, positive anti-double stranded-deoxyribonucleate (anti-ds-DNA), and low levels of complement-3 (C3). We aimed to determine possible factors associated with pericardial effusion in children with SLE.

Methods

This retrospective study was conducted in the Department of Pediatrics, Dr Sardjito Hospital, Yogyakarta. Data were obtained from patients' medical records. We included children with SLE, based on *American College of Rheumatology* (ACR) 1997 and Systemic Lupus International Collaborating Clinics (SLICC) criteria,[6,7] aged ≤18 years, from January 2011 to March 2018 who underwent echocardiography at the initial diagnosis. In our hospital, we performed echocardiography if there was abnormality that suspected cardiac involvement, it was not a routine procedure. We excluded children with congenital heart disease or incomplete medical records. Among eligible subjects for inclusion, we devided into pericardial effusion and no pericardial effusion group. The minimum required number of subjects was calculated with 0.95 confidence level and 80% power. The study subjects were recruited consecutively.

The subjects' basic characteristics were age at diagnosis, sex, parental education, parental socio-economic, nutritional status, and SLE protocol. The outcomes were classified pericardial effusion and no pericardial effusion based on echocardiography. The independent variables were age at diagnosis, gender, nutritional status, parental education level, parental socio-economic status, and clinical manifestations including proteinuria, hemolytic anemia, and immunological parameters [positive anti-ds-DNA, antinuclear antibodies (ANA) test, and low C3], while the independent variables were the status of pericardial effusion. Pericardial effusion was diagnosed by echocardiography, which was defined as abnormal fluid accumulation in the pericardial space.[3,4,8]

Nutritional status based on WHO 2006 criteria which was defined as abnormal nutritional status, consisted of severe malnutrition (WHZ or BMI for age Z<-3SD), mild to moderate malnutrition (WHZ or BMI for age -3SD<Z<-2SD), overweight/obesity (WHZ or BMI for age Z>+2SD) and normal nutritional status if there was good nutritional status (WHZ or BMI for age -2SD<Z<+2SD). Proteinuria and hemolytic anemia were defined by the ACR 1997 criteria.[7,9-11] Proteinuria was defined as excess protein in the urine, protein excretion higher than 0.5 grams/day or >+3 by dipstick procedure.[9,11] Hemolytic anemia was defined as abnormalities of hemoglobine level based on age and followed by positive Coomb's test.[9-11]

We use some protocols for SLE treatment, consisting of lupus nephritis, severe SLE, and standard SLE protocol. Lupus nephritis protocol was defined as clinical and laboratory manifestations that met ACR criteria consisted of persistent proteinuria >0.5 gram per day or greater than +3 by dipstick, and/or cellular casts including red blood cells (RBCs), hemoglobin, granular, tubular, or mixed.[12] Severe SLE protocol was defined as organ involvement may lead to irreversible damage in the affected organ. For example, gastrointestinal involvement (pancreatitis, vasculitis), lung involvement causing shortness of breath (pulmonary hypertension, pulmonary hemorrhagic), cardiac involvement may develop heart failure (valvular insufficiency, pericardial tamponade), lupus nephritis may develop rapidly progressive renal failure (nephrotic syndrome, kidney failure), CNS disease (psychosis, confusion, disorientation, paresthesias, seizure, cognitive dysfunction, severe unremitting headache, cerebrovascular accident, transient ischemic attack, retinal vasculitis), severe skin involvement (scarring, alopecia, ulcers) and hematology involvement (severe anemia or thrombocytopenia may be life threatening).[13.,14] And standard SLE protocol for patients with SLE who have mild and stable disease (those without major organ involvement and/or comorbidity).[13,14]

Baseline data and outcomes were described using mean, median, or proportion, as appropriate. Chi-square test was used to analyze categorical variables.

Fisher's exact test was used when >20% of the cells in the 2×2 contingency table had a frequency <5. The significance level (α) was 0.05 for two-tailed tests. Multivariate analysis was done by logistic regression test. The ORs and 95%CIs were computed to compare the strength of the association. Statistical analyses were performed with *SPSS software version 20* . This study was approved by the Ethics Committee for Medical Research, Universitas Gadjah Mada Medical School.

Results

Eighty-seven children with SLE underwent echocardiography but 14 had incomplete medical record data (5 without C3 level, 1 without ds-DNA level, 4 without ds-DNA and C3 level, and 4 without ds- DNA/ANA/C3 level). Hence, 73 patients were included in the study, of whom 40 (54.8%) had pericardial effusion (**Figure 1**). The characteristics of subjects are shown in **Table 1**.

Bivariate analysis showed that proteinuria (OR 3.913; 95%CI 1.097 to 13.693; P=0.036) and hemolytic anemia (OR 4.815; 95%CI 1.237 to 18.737; P=0.022) were significantly associated with pericardial effusion. However this study showed that age at diagnosis (pubertal status), sex, anti-ds-DNA,

Table 1. Characteristics of children with SLE

Characteristics	N=73
Median age at diagnosis (range), years	13 (5.0-17.0)
Sex, n(%)	
Male	8 (11)
Female	65 (89)
Nutritional status, n (%)	
Severe malnutrition	7 (9.6)
Mild to moderate malnutrition	12 (16.4)
Good nutritional	51 (69.9)
Overweight	3 (4.1)
SLE protocol, n (%)	
Standard SLE	18 (24.7)
Severe SLE	35 (47.9)
Lupus nephritis	20 (27.4)

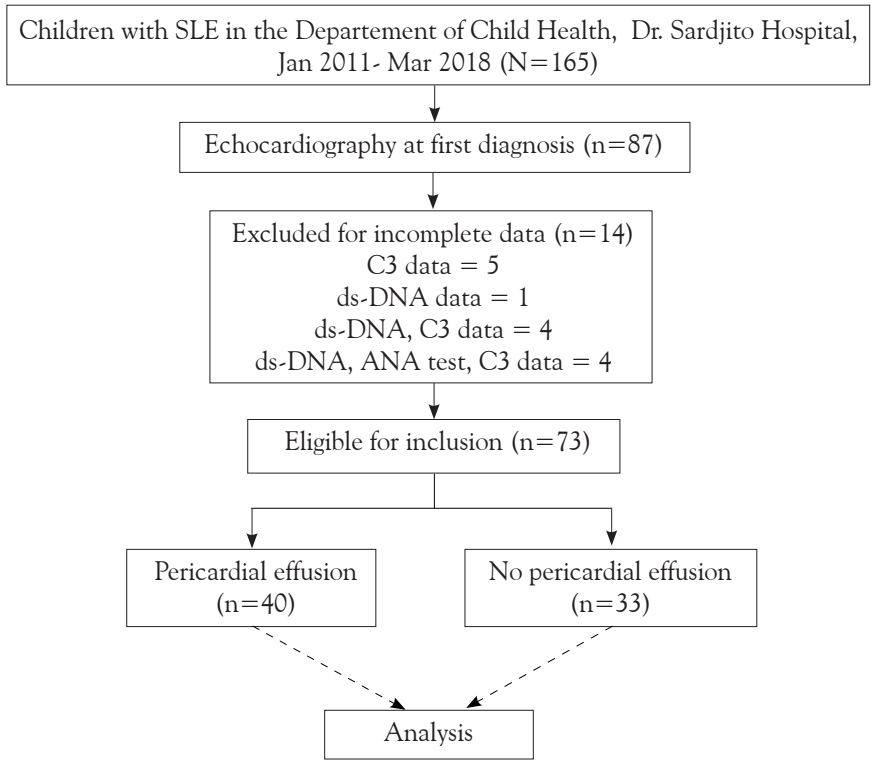

Figure 1. Study flow diagram

ANA test, and C3 at diagnosis were not significantly associated with pericardial effusion (**Table 2**). Multivariate logistic regression analysis showed that hemolytic anemia was an independent factor associated with pericardial effusion (OR 4.135; 95%CI 1.039 to 16.453; P=0.044), but proteinuria was not (OR 3.258; 95%CI 0.885 to 11.998; P=0.076) (**Table 2**).

Discussion

Cardiovascular involvement was prevalent in children with SLE, as about half of our subjects had pericardial effusion. This finding was consistent with previous studies with pericarditis prevalences of around 8-53%.[15-18] Also, characteristics and immunological profiles are similar among children with SLE.[18]

We found that age and biological sex were not associated with pericardial effusion, similar to a previous study in which age and sex were not significantly associated with serositis.[3] Another study noted that pericarditis was not associated with sex, but associated with age at diagnosis.[15] SLE is prevalent during puberty due to the influence of estrogen and androgen hormone inactivity.[1] These hormones affect the pituitary to activate the immune system and cytokine production.[17]

Nutritional status was not associated with pericardial effusion. In contrast, a study conducted in United Kingdom (UK) found that the amount of organ damage was closely related to age at diagnosis, as well as nutritional status.[19] Another study conducted in Brazil, showed that there was relationship between nutritional status and immunity. Malnutrition and obesity can both lead to immunosuppression, which may affect the degree of inflammation already present in SLE.[19,20]

A previous published study in China found no significant differences in laboratory parameters, including proteinuria, in adult-onset SLE patients in terms of pericarditis.[21] We also found that proteinuria was not associated with pericardial effusion

Table 2. Bivariate analysis of possible variables associated with pericardial effusion

Variables	Pericardial effusion (n=40)	No pericardial effusion (n=33)	Bivariate analysis			Multivariate analysis		
			OR	95%CI	P value	OR	95%CI	P value
Pubertal status, n(%)			0.907	0.306 to 2.694	0.861			
Prepubertal	9 (22.5)	8 (24.2)						
Pubertal	31 (77.5)	25 (75.8)						
Sex, n(%)			3.735	0.514 to 14.569	0.280#			
Male	6 (15)	2 (6.1)						
Female	34 (85)	31 (93.9)						
Nutritional status, n(%			0.583	0.213 to 1.598	0.292			
Abnormal	10 (25)	12 (36.4)						
Normal	30 (75)	21 (63.6)						
Clinical manifestation								
Proteinuria, n(%)			3.913	1.097 to 13.963	0.036#	3.258	0.885 to 11.998	0.076
Positive	36 (90)	23 (69.7)						
Negative	4 (10)	10 (30.3)						
Hemolytic anemia, n(%)			4.815	1.237 to 18.737	0.022#	4.135	1.039 to 16.453	0.044
Positive	13 (32.5)	3 (9.1)						
Negative	27 (67.5)	30 (90.9)						
Immunological profile								
Anti-ds-DNA, n(%)			1.280	0.412 to 3.887	0.663			
Positive	32 (80)	25 (75.8)						
Negative	8 (20)	8 (24.2)						
ANA test, n(%)			2.202	0.485 to 10.002	0.306			
Positive	37 (92.5)	28 (84.8)						
Negative	3 (7.5)	5 (15.2)						
C3, n(%)			1.526	0.458 to 5.086	0.492			
Positive	34 (85)	26 (78.8)						
Negative	6 (15)	7 (21.2)						

#Fisher's exact test

on multivariate analysis. However, a study in China found that positive anti-ds-DNA was associated with renal involvement and pericarditis.[22] In addition, another study in South Korea found that proteinuria was associated with pericarditis.[15]

In our study, hemolytic anemia was the only variable significantly associated with pericardial effusion on multivariate analysis, consistent with several previous studies. Another study conducted in United States (US) noted that having hemolytic anemia increased the risk of pericarditis.[10] Moreover, another study in South Korea found that patients with hemolytic anemia had twice the risk of pericarditis.[15] Another study conducted in US observed a strong relationship between hemolytic anemia with IgM or IgG anti-phospholipid (aPL) antibodies. Another study conducted in Italy about heart involvement in SLE, explained that several autoantibodies, such as aPL antibodies, anti- SSA/Ro antibodies, and anti-endothelial cells antibodies, can mediate heart damage.[23] These autoantibodies can directly affect the heart tissue or trigger a mechanism that can cause heart involvement.[15,23,24]

We found that immunological status with regards to anti-ds-DNA, ANA test, and C3 were not associated with pericardial effusion. Consistent with a previous study, positive anti-ds-DNA was not associated with pericarditis.[22] Likewise, another study found no significant differences in laboratory parameters (ANA test, anti-ds-DNA, C3) in patients <15 years of age with regards to pericarditis.[21] In contrast, a previous study noted a significant association between anti-ds-DNA and pericardial effusion by multivariate analysis.[15] A Kuwaiti study in children with SLE found that serologic profiles with positive ANA test, positive anti-ds-DNA, and positive C3 were associated with heart damage.[17] Also, a study conducted in China showed significant associations between positive anti-ds-DNA and C3 with serositis.[25]

This study had several limitations. We used a retrospective design, therefore, risk factors and outcomes were taken from one point of time, and depended on the completeness of medical record data. Also, the small sample size limited the strength of the study. Furthermore, we did not use Kappa test to assess the agreement among examiners who performed echocardiography. However, this study provides preliminary data that may be useful to determine cardiovascular status of SLE patients at the time diagnosis.

In conclusion, pericardial effusion is associated with hemolytic anemia in children with SLE. We suggest performing echocardiography in SLE patients with hemolytic anemia.

Conflict of Interest

None declared.

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