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5 Year Survival of Systemic Lupus Erythematosus (SLE) Patients at RSCM and Predispose Factors: A Retrospective Cohort Study

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A B S T R A C T

Background: Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease characterized by widespread inflammation involving almost all organ systems. This disease attacks young women with a peak incidence aged 15-40 years. The clinical manifestations of SLE vary depending on the organs involved. The risk of death in SLE patients increases if it is not diagnosed and treated appropriately.

Methods: This study is a retrospective cohort study using medical record data from patients diagnosed with SLE for the first time in 2014-2019 at RSCM. Survival analysis was carried out on age, gender, hemolytic anemia, thrombocytopenia, NPSLE, high anti ds-DNA, low C3 and C4, high dose glucocorticoids, lymphopenia, positive Anti Cardiolipin Antibody (ACA), cardiovascular disease, and lupus nephritis. Multivariate analysis with cox regression was carried out.

Results: There were 448 subjects studied. The five-year survival of SLE patients at RSCM is 88%. Mean survival 56 months (95% CI : 55-57). In the multivariate analysis, it was found that NPSLE [p=0,000 ; HR 3,595 (95%CI 1,932-6,688)], low C3 and C4 [p=0,004 ; HR 2,501 (95%CI 1,330-4,701)], cardiovascular disease [p=0,018 ; HR 2,851 (95%CI 1,198-6,787)], and hemolytic anemia [p=0,023 ; HR 2,106 (95%CI 1,008-4,404)] had a significant effect on patient survival.

Conclusion: The 5-year survival of SLE patients was 88% with neuropsychiatric lupus (NPSLE), low C3 dan C4, cardiovascular disease, dan hemolytic anemia have a significant effect on the SLE survival patients at RSCM.

1. Introduction

Systemic Lupus Erythematosus (SLE) is an autoimmune rheumatic disease characterized by widespread inflammation involving almost all organ

systems.¹ This disease attacks young women with a peak incidence aged 15-40 years during the reproductive period with a female to male ratio of 5:1. The prevalence of SLE in various countries ranges between 2.9/100,000 - 400/100,000.² SLE found in certain races such as Negroes,

Chinese and Filipinos.² SLE often found in urban areas than rural areas. The prevalence of SLE in Indonesia is known. Based on recapitulation data on rheumatology clinic in several hospitals in Indonesia, there has been an increase of SLE patient number, 17,2-27,2% of the total number of patients (2015), 18,7-31,5% of the total number of patients (2016), and 30,3-58% of the total number of patients (2017).^{3,4} The clinical manifestations of SLE depend on the organs involved. The risk of death in SLE patients increases if it is not diagnosed and treated appropriately.⁴ The 5-year and 10-year survival rates of SLE patients have increased in the last 5 decades, from 74,8% and 63,3% to 94,8% and 91,4%. In Asia, the 5-year survival rate of SLE patients has reached 87,9%.⁵ A study conducted by Mok CC, et al. and Wang Z, et al. showed that there was an increased in SLE survival in the last 10 years and 20 years.^{6,7} Research in Indonesia that conducted by Juariah N, Kasjmir Y, and Sukmana N at RSCM in 2008 showed that the survival rate of SLE patients in the last 5 years was 88%.⁸ Various studies have been conducted to determine the predictor factors that influence the survival of SLE patients such as age, gender, hemolytic anemia, thrombocytopenia, NPSLE, high anti ds-DNA, low C3 and C4, high dose glucocorticoids, lymphopenia, positive Anti Cardiolipin Antibody (ACA), cardiovascular disease, and lupus nephritis.^{11,12,17-19} Over the past 15 years, there have been changes in SLE management recommendations including therapeutic strategies with glucocorticoids that are immediately tapered down to minimize long term side effects and more diverse immunosuppressive therapeutic strategies such as wider use of mycophenolate and calcineurin inhibitor drug groups.^{1,2} The JKN service affects the ease of access to examination, treatment, and SLE patients referral.^{3,4} Both of them encourage researchers to conduct SLE survival research and hoped that it can be compared with survival 15 years ago.⁸

2. Methods

This retrospective cohort study was performed at the Department of Internal Medicine, Dr. Cipto Mangunkusumo National Hospital, Jakarta, Indonesia, from January to July 2024. The participants were patients diagnosed with SLE for the first time in 2014-2019 at RSCM using medical record.

The minimum sample size required was 200, with a power of 95% confidence level. The inclusion criteria were all SLE patient with a disease onset of > 18 years that fulfilled ACR criteria 1997 or SLICC 2012. The exclusion criteria were incomplete patients data in medical record and patients with *overlap syndromes*. The sample was taken by consecutive sampling method.

We collect medical record data of patients diagnosed with Systemic Lupus Erythematosus who meet the inclusion criteria, screening for completeness of subject monitoring in 2014-2019, if the data is complete, the subject is included in the study. Data collection was carried out such as age, gender, hemolytic anemia, thrombocytopenia, NPSLE, high anti dsDNA, low C3 and C4, high dose glucocorticoids, lymphopenia, positive Anti Cardiolipin Antibody (ACA), cardiovascular disease, lupus nephritis, and type and number of immunosuppressants used in the first 1 year of treatment. If the subject last outcome status is unknown, the subject is confirmed by telephone. The subject family/subject was given informed consent first. Then, we asked about the subject current condition. If the subject/family is not connected by telephone, the researcher will enter the data as *loss to follow up*. Recapitulation and data processing to obtain survival data and find contributing factors. Finally, we conduct sensitivity analysis to determine whether loss to follow up affects the research results. The collected data is kept confidential.

Statistical analysis was conducted using SPSS v.25. The characteristics of participants were presented as percentages for categorical data and mean (standard deviation) or median (min-max) for continuous data. Survival analysis was carried out on age, gender, hemolytic anemia, thrombocytopenia, NPSLE, high anti ds-DNA, low C3 and C4, high dose glucocorticoids, lymphopenia, positive *Anti Cardiolipin Antibody* (ACA), cardiovascular disease, and lupus nephritis. Variables that were significant in the bivariate analysis included in the multivariate analysis with *cox regression*. The protocol of this study was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Indonesia (KET-220/UN2.F1/ETIK/ PPM.00.02/2024).

3. Results

A total of 674 subjects were collected in the study based on ICD 10 diagnosis. A total of 192 subjects were included in the exclusion criteria because the final diagnosis was not

Systemic Lupus Erythematosus and 34 subjects were included in the exclusion criteria because the final diagnosis was *overlap syndrome*. A total of 448 subjects were obtained who met the inclusion and exclusion criteria and could be included in this study (Figure 1) with the following details: 45 subjects died, 336 subjects were alive, and 67 subjects were lost to follow up because the subject's number was not active when contacted.

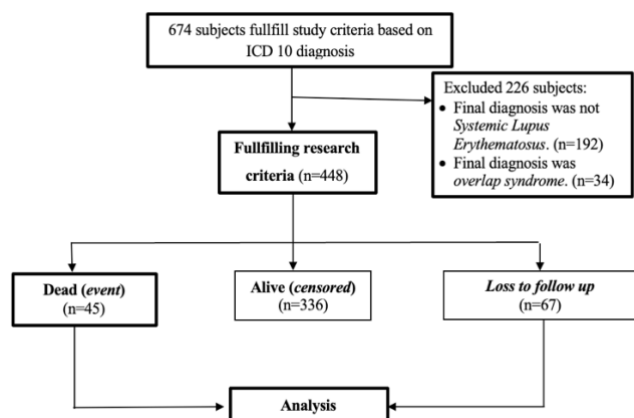


Figure 1. Flow chart of patient recruitment

In this study, the majority of 448 patients were 18-50 years (97,3%) with median age was 29 years (19-63 years). Most subjects were female (97,3%) and the most frequent comorbid was hypertension (25,7%). The most frequent drugs that consumed by SLE patients beside corticosteroids are hydroxychloroquine (67,4%), mycophenolate mofetil (44,2%), and azathioprine (14,7%). Sociodemographic characteristics are presented in Table 1.

Table 1. Sociodemographic characteristics of participants (n = 448)

Sociodemographic Characteristics	Total (n = 448 (%))
Age (years)**	29 (19-63)
18-50 years	436 (97.3)
> 50 years	12 (2.7)
Gender, n (%)	
Male	12 (2.7)
Female	436 (97.3)
Comorbid	
Hypertension	115 (25.7)
Type 2 Diabetes	13 (2.9)
Asthma	4 (0.9)
Cardiovascular disease	23 (5.1)

Chronic Kidney Disease stage 5 on Hemodialysis	4 (0.9)
Dislipidemia	41 (9.2)
Thalassemia	3 (0.7)
Liver disease	8 (1.7)
Hepatitis B	3 (0.6)
Hepatitis C	4 (0.9)
Liver Cirrhosis	1 (0.2)
Thyroid disease	5 (1.1)
Malignancy	7 (1.6)
Cystic Ovarian Neoplasm	3 (0.7)
Uterine Myoma	2 (0.5)
Lung Adenocarcinoma	1 (0.2)
Leiomyosarcoma	1 (0.2)
No Comorbidities	271 (60.5)
Drugs	
Hydroxychloroquine	302 (67.4)
Corticosteroids	448 (100)
Mycophenolat Mofetil	198 (44.2)
Azathioprine	66 (14.7)
Metotrexate	25 (5.6)
Cyclosporine	27 (6.0)
Tacrolimus	1 (0.2)
Cyclophosphamide	2 (0.4)
Rituximab	1 (0.2)

Data are presented in percentage for categorical variables (%), *Data are presented in mean (standard deviation), **Data are presented in median (min-max)

The most frequent clinical manifestations were mucocutan (92,2%) and musculoskeletal (96,9%). Then, the most frequent laboratory manifestations were positive ANA (100%), high anti ds-DNA (69,4%), and hemolytic anemia (18,3%). (**Table 2**).

Table 2. Clinical and laboratory manifestation of participants (n = 448)

Clinical dan Laboratory Manifestations	Total (n = 448 (%))
Constitutional	111 (24,8)
Fever	73 (16.3)
Weight loss	8 (1.8)
Fatigue	30 (6.7)
Mucocutan	413 (92.2)
Malar rash	365 (81.5)
Discoïd rash	58 (12.9)
Photosensitivity	105 (23.4)
Alopecia	326 (72.8)
Paniculitis lupus	1 (0.2)
Oral ulcer	53 (11.8)
Musculoskeletal	434 (96.9)
Serositis	30 (6.7)
Pleural Effusion	25 (5.6)
Pericard Effusion	5 (1.2)

Pulmonology	1 (0.2)
Interstitial Fibrosis	1 (0.2)
Hematology	289 (64.5)
Hemolytic anemia	82 (18.3)
Leucopenia	72 (16.1)
Lymphopenia	63 (14.1)
Trombocytopenia	72 (16.1)
Neuropsychiatric	57 (12.7)
Gastrointestinal	2 (0.4)
Lupus Nephritis	125 (27.9)
Lupus nephritis class I	-
Lupus nephritis class II	30 (6.7)
Lupus nephritis class III	45 (10.0)
Lupus nephritis class IV	40 (8.9)
Lupus nephritis class V	10 (2.3)
Immunology	448 (100)
Positive ANA	448 (100)
High anti ds-DNA	311 (69.4)
Low Complement	272 (60.7)
Low C3	268 (59.8)
Low C4	173 (38.6)
Low C3 dan C4	163 (36.4)
Antiphospholipid Antibody	125 (27.9)
Positive lupus anticoagulant	122 (27.2)
High or medium anticardiolipin (IgA, IgM, atau IgG)	59 (13.2)
Positive <i>Anti beta 2-glycoprotein I</i> (IgA, IgG or IgM)	53 (11.8)

Most SLE patients received combination of 2 drugs (51,6%). The most frequent combination of 2 drugs used was corticosteroids + hydroxychloroquine (24,6%). The most frequent combination of 3 drugs used was hydroxychloroquine + corticosteroids + mycophenolate mofetil (27,0%). In this study, the most frequent causes of SLE patients being treated were high SLE disease activity (flare) (34,2%), infection (6,7%), and obstetric gynecologic abnormalities (6,5%). (Table 3).

Table 3. Cause of SLE patients treated at RSCM (n = 448)

Cause	Total (n = 448 (%))
High SLE disease activity (Flare)	153 (34.2)
Obstetry-Gynecology	29 (6.5)
Intra Uterine Fetal Death (IUFD)	3 (0.7)
Pregnancy	21 (4.7)
Premature rupture of membranes	1 (0.2)
Oligohydramnion	3 (0.7)
Abortus	1 (0.2)
Surgery	11 (2.3)

Osteoarthritis	2 (0.4)
Avascular Necrosis	5 (1.1)
Cholelithiasis	1 (0.2)
Osteomyelitis	2 (0.4)
Anal Fistel	1 (0.2)
Deep Vein Thrombosis (DVT)	2 (0.4)
Anaemia	1 (0.2)
Severe Trombocytopenia	5 (1.1)
Infection	31 (6.7)
Septic Arthritis	1 (0.2)
Miliary / Lung TB	6 (1.3)
Septic/Septic Shock	6 (1.3)
Pneumonia	10 (2.2)
Abscess	2 (0.4)
Dengue Hemorrhagic Fever	1 (0.2)
Urinary Tract Infection	1 (0.2)
COVID-19	4 (0.9)
Cardiovascular	7 (1.4)
Acute heart failure	2 (0.4)
Acute coronary syndrome	2 (0.4)
Pulmonary hypertension	1 (0.2)
Syncope	1 (0.2)
Emergency hypertension	1 (0.2)

The most frequent causes of death in this study were infection (51,1%) and neuropsychiatric lupus (33,3%). Other causes is shown in table 4.

Table 4. Cause of death SLE patients at RSCM (n = 448)

Cause of Death	Total (n = 45 (%))
Lupus related	17 (37.8)
Neuropsychiatric lupus	15 (33.4)
Lupus nephritis	2 (4.4)
Infection	23 (51.1)
Severe Community Pneumonia	10 (22.8)
Hospital Associated Pneumonia	8 (17.7)
COVID-19	2 (4.2)
Miliary TB	1 (2.2)
Septic Shock e.c Complicated Intra Abdomen Infection	2 (4.2)
Another cause	5 (11.1)
Pulmonary Embolism	3 (6.7)
Cardiovascular disease	1 (2,2)
Severe metabolic acidosis e.c linezolid induced	1 (2,2)

In this study, the results of the sensitivity analysis showed that there was a significant difference in the cyclosporine variable so that loss to follow up could affect the research results if lost to follow up included in survival analysis. (Supplementary table). The 5-year survival of SLE

patients was 88%. (Figure 2). Mean survival 56 (55-57) months.

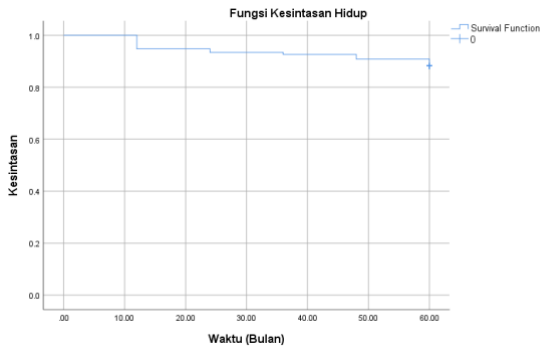


Figure 2. 5 year survival of SLE patients at RSCM

Log rank analysis in this study found that NPSLE ($p=0,000$), low C3, C4 levels ($p=0,000$), cardiovascular disease ($p=0,027$), hemolytic anemia ($p=0,006$), thrombocytopenia ($p=0,013$), and high anti ds-DNA ($p=0,000$) had a statistically significant difference in 5-year survival of SLE patients at RSCM. (Figure 3).

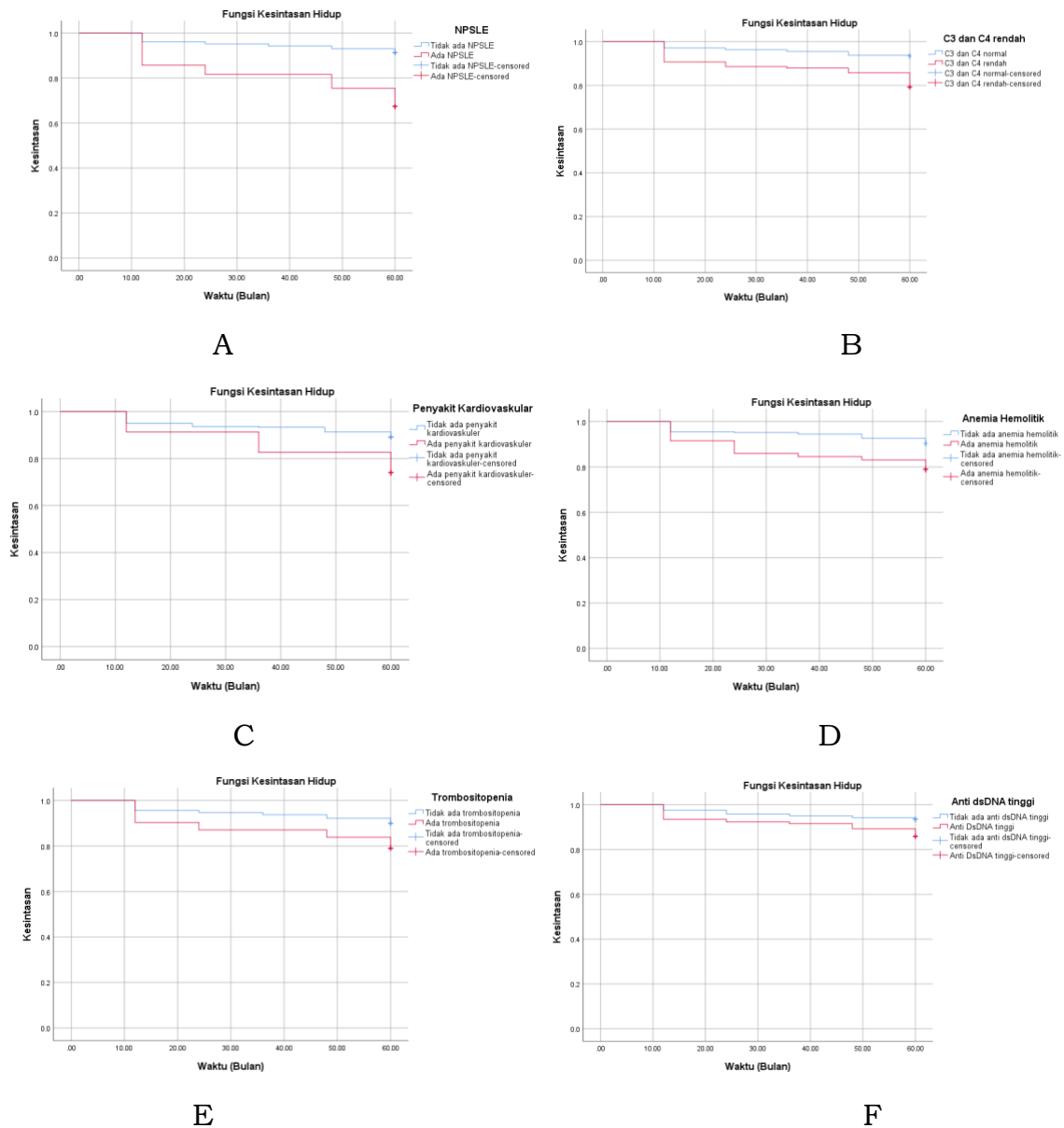


Figure 3. Variable that impact in 5 year survival of SLE patients at RSCM. A. The impact of NPSLE in 5 year survival of SLE patients at RSCM; B. The impact of low C3 and C4 in 5 year survival of SLE patients at RSCM; C. The impact of cardiovascular disease in 5 year survival of SLE patients at RSCM; D. The impact of hemolytic anemia in 5 year survival of SLE patients at RSCM; E. The impact of

In the bivariate analysis, the significant value were found in hemolytic anemia [p= 0,037 ; HR 2,026 (95% CI 1,042-3,941)], thrombocytopenia [p= 0,018 ; HR 2,184 (95%CI 1,146-4,162)], and NPSLE [p= 0,000 ; HR 3,615 (95%CI 1,934-6,757)]. Other significant results were found in low C3 and C4 levels [p= 0,018 ; HR 2,266 (95%CI 1,152-4,461)], high anti ds-DNA [p= 0,042 ; HR 2,208 (95%CI 1,028-4,741)], and cardiovascular disease [p= 0,020 ; HR 3,393 (95%CI 1,191-7,520)]. (Supplementary table).

Variables that had $p < 0.25$ in the bivariate analysis were continued to the initial multivariate cox regression model, the highest p was removed one by one until $P < 0.05$ was obtained in the final multivariate model. In the final multivariate model, significant values were found in NPSLE [p= 0,000 ; HR 3,595 (95%CI 1,932-6,688)], low C3 and C4 levels [p= 0,004 ; HR 2,501 (95% CI 1,331-4,701)], cardiovascular disease [p= 0,018 ; HR 2,851 (95% CI 1,198-6,787)], and hemolytic anemia [p= 0,023 ; HR 2,106 (95%CI 1,008-4,404)]. (Supplementary table).

4. Discussion

In this study, most subjects were 18-50 years (97,3%) with median age was 29 years (19-63 years) which was productive age. In addition, SLE is a disease that often attacks women (97,3%) with female: male ratio of 36:1. This result are similar to the study conducted by Juariah, et al. at RSCM, Laniyati, et al. at Hasan Sadikin General Hospital, and Yuliasih, et al. at Soetomo Hospital.^{9,10} Other countries with similar results are China, South Korea, Turkey, Hong Kong, and Libya.^{6,7,9-12} Then, the most frequent comorbid was hypertension (25,7%). The results of this study are similar from the study conducted by Zaid FE in Libya (51,6%) and Pamuk ON in Turkey (21,5%).^{10,11}

The most frequent clinical manifestations were mucocutaneous (92,2%) and musculoskeletal (96,9%). The results of this study are similar to the study conducted by Juariah N, et al. at RSCM, Laniyati, et al. at Hasan Sadikin General Hospital and other countries such as China, South Korea, Turkey, Hong Kong, and Libya.⁶⁻¹³ In this study, most patients

received hydroxychloroquine (67,4%), mycophenolate mofetil (44,2%), and azathioprine (14,7%) beside corticosteroids. Most of them received combination of 2 drugs (51,6%) where the most frequently used was corticosteroids + hydroxychloroquine (24,6%). The other received combination of 3 drugs where the most frequently used was hydroxychloroquine + corticosteroids + mycophenolate mofetil (27,0%). The results of this study are similar to the study conducted by Juariah N, et al. at RSCM, Laniyati, et al. at Hasan Sadikin General Hospital but different from the study conducted by Yuliasih et al. at Soetomo Hospital.⁸⁻¹⁰

In this study, the most frequent cause of SLE patients being treated were high SLE disease activity (flare) (34,2%) and infection (6,7%). The results of this study are similar from the study conducted by Alhassan N, et al. in Saudi Arabia (68,4% flare and 20% infection) and Aldarmakki R, et al. in United Arab Emirates.^{14,15} However, a study conducted by Lee J, et al. in Canada showed that the number of SLE patients being treated due to high SLE disease activity (flare) (17,5%) and infection (10%) was lower compared to this study, Alhassan N, et al. in Saudi Arabia, and Aldarmakki R, et al. in United Arab Emirates.¹⁶

The most frequent cause of death in this study were infection (51,1%) and neuropsychiatric lupus (33,3%). The results of this study are similar to study conducted by Juariah N, et al. at RSCM, Laniyati, et al. at Hasan Sadikin Hospital and other countries such as China, South Korea, Turkey, Hong Kong, United States of America, Italy, Libya, and others.^{5-13,17-22} However, study in Sweden for 20 years showed that the most frequently cause of death SLE patients was cardiovascular disease (51,7%).²³ This can be explained by the bimodal pattern of death in SLE patients where infection and high SLE disease activity (flare) are considered the main causes of death in developing countries where socioeconomic status is lower and limited diagnostic tools availability in SLE diagnosis while cardiovascular disease and malignancy are considered the main causes of death in most developed countries.²³

Based on observations of SLE patients first diagnosed from 2014-2019, 45 subjects were died, 67 were lost to follow up, and 336 subjects were alive. The results of this study are better than study conducted by Juariah N, et al.⁸

The 5-year cumulative survival of SLE patients was 88% with mean survival 56 (55-57) months. The results of this study are similar to the study conducted by Juariah N, et al. in 2008 (88%) but higher than Libya and lower than Italy, United States, China, Sweden, and South Korea.^{6-8,12,17-22} The current survival at RSCM is better than Libya because the study in Libya was conducted in the rheumatology clinic with sample size was 79 samples.¹² Other countries such as Italy, United States of America, China, Sweden, and South Korea have better survival than Indonesia and Libya because use of glucocorticoids wisely, earlier use of steroid sparing agents such as cyclophosphamide which is more frequently used, and strict routine treatment supervision.¹⁷⁻²²

In this study, SLE patients with hemolytic anemia had significant results with HR 2,106 (95%CI 1,008-4,404) and p value = 0,023. The results of this study are similar to the study conducted by Pamuk ON, et al. and Artım-Esen B, Cene E, Sahinkaya Y, Erdugan M, et al. that hemolytic anemia is one of the predictive factors of SLE survival within 1 year of observation from from the initial diagnosis of SLE.^{11,24} A similar study was conducted by Jin Z, et al. in China showed that anemia caused by chronic disease, kidney involvement, drugs, and infections was related to disease activity that contributed greatly to SLE patients mortality with different disease activities.²⁵ SLE patients with NPSLE had significant results with HR 3,595 (95%CI 1,932-6,688) and p value = 0,000. The results of this study consistent with study conducted by Zhang S, Li M, Zhang L, Wang Z, et al and Juan Z, Jiahao Q, Liyuan L, Xiaoqing C, et al. which SLE patients with NPSLE had a lower survival rate than SLE patients without NPSLE.^{26,27} Neuropsychiatric SLE is one of the most severe clinical manifestations of SLE and is associated with a poor prognosis.²⁶

In this study, SLE patients with cardiovascular disease had significant results with HR 2,851 (95%CI 1,198-6,787) and p value= 0,018. The results of this study are similar to the study conducted by Yafasova, et al. which SLE patients with cardiovascular disease have a higher mortality rate compared to SLE patients without cardiovascular disease.²⁸ This study is also

supported by Li D, Yoshida K, Feldman CH, Speyer C, et al. which SLE patients with cardiovascular disease have increased risk of death significantly with HR 3,1 (95%CI 2,49-3,89).³⁸ This is caused by the inflammatory process in the pathogenesis of SLE having a major role in the occurrence of rapid atherosclerosis with the result in SLE patients are 2-7 times developing cardiovascular disease and increases the risk of death.^{11,29} SLE patients with low C3 and C4 had significant results with HR 2,501 (95%CI 1,330-4,701) and p value = 0,004. The results of this study are similar to the study conducted by Kasitanon N, Magder LS, Petri M which low C3 and C4 are predictive factors for survival of SLE patients based on 1 year observation starting from the initial diagnosis of SLE.²⁶ As we know, the complement system plays an important role in the pathogenesis of SLE through 2 mechanisms.^{30,31} One of them is complement deficiency related to disease activity and clinical manifestations that appear in SLE.^{26,31}

The advantage of this study is first study at RSCM to assess the factors that influence the survival of SLE patients and cumulative survival of SLE patients in JKN era with retrospective cohort method. This study also uses comprehensive statistics such as bivariate and multivariate analysis so that it can determine the factors that influence the 5-year survival of SLE patients at RSCM. This study also has several limitations, first, loss to follow up was 15%. Loss to follow up occurs because the subject phone number was not active when contacted to confirm whether the subject is alive or dead. Second, this study was only conducted in one hospital in Indonesia (single center).

5. Conclusion

The 5 year survival cumulative of SLE patients at RSCM is 88% with neuropsychiatric lupus (NPSLE), low C3 and C4, cardiovascular disease, and hemolytic anemia have a significant effect on the survival of SLE patients at RSCM.

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