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Risk Factors of Worsening of Systemic Lupus Erythematosus in Patients at Two Tertiary Hospitals in Jakarta

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Abstract

Systemic Lupus Erythematosus (SLE) is a prototypical multiorgan autoimmune disease with a fluctuating and chronic disease course. As an emerging disease in this century, SLE will burden stakeholders and the country. This study was conducted to determine the prognostic factors for SLE worsening, especially in ambulatory patients. This ambispective study used logistic regression to view the risk factors for worsening SLE in patients. Anemia, age, body mass index, education level, employment status, marital status, hydroxychloroquine, and immunosuppressants were the independent variables in this study. This study concludes that anemia is statistically significant and, therefore, a risk factor for worsening SLE in patients (RR = 5.31; p-value<0.005), while age, body mass index, education level, employment status, marital status, hydroxychloroquine, and immunosuppressants are not statistically significant.

Keywords: anemia, risk factor for flare, systemic lupus erythematosus

Introduction

Systemic Lupus Erythematosus (SLE) is a chronic, systemic, and debilitating multiorgan autoimmune disease. Five million people have lupus worldwide.[1] The history of lupus begins with Hippocrates describing ulcers (suspected to be lupus) as herpes esthiomenos in 200 BC.[2] The SLE can attack various organs: the skin, with manifestations of malar rash; the kidneys (nephritis); blood, with manifestations of autoimmune hemolytic anemia or thrombocytopenia; the musculoskeletal system (arthritis); and the central nervous system (myelitis, psychosis).[2] Currently, no drug has been found to cure SLE. Management of this disease aims to keep it under control or in remission, although there has been no clear definition of remission in SLE. Women of reproductive age suffer from SLE more than men.[3]

In SLE, many autoantibodies are produced by B lymphocytes, and the diagnosis of SLE is usually based on their presence. Some autoantibodies seem to attack specific organs. As a protein produced by the body (but which attacks the body itself), the antibodies lose the ability to recognize themselves (self-recognized) and combine with blood complement to form immune complexes that deposit in tissues and trigger inflammation. This is what underlies the concept of autoimmunity.[4]

Experts have developed many instruments to assess lupus disease activity globally. Some instruments, like the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG), include questions about the conditions of the organs affected by lupus, which are given the appropriate score (weighted).[5] End organ damage or organ damage in lupus occurs due to continuous attacks by autoantibodies. This commonly happens in uncontrolled SLE or flares. The damage may occur in various systems, such as neuropsychiatry, renal, or hematology. Besides the disease activity, organ damage can be due to lupus therapy, such as glucocorticoids, which trigger osteoporosis, or hydroxychloroquine, which leads to retinal disorders.[6]

Corticosteroids have become the main choice for treating lupus in the last 60 years. Pulse steroid doses adopted by internists for kidney transplant patients have become the standard therapy for lupus patients experiencing a flare. While, oral administration is still favorable, but the side effects of steroids remain a problem for SLE patients. Other medicines taken to treat lupus are immunosuppressants, such as azathioprine, cyclosporine, and antimalarial hydroxychloroquine. They have been taken for a long time for the SLE treatment.[7]

Based on the 2013 Indonesian Ministry of Health

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reports, there is no prevalence of SLE in the Indonesian people.[8] Crude prevalence was around 4.3 to 45.3 per 100,000 people.[9] Mok, *et al.*, reported that Asian SLE has different variations of Fcγ receptors from Caucasian SLE, which causes Asian SLE patients to have higher organ damage scores than Caucasian patients.[10] It is related to IgG and lupus nephritis; while, renal outcomes and levels of immunosuppressant usage among Asians are the same as among African people. It means that they also experience worse conditions than Caucasians. Besides, socioeconomic factors, including access to health facilities, education, cultural factors, and beliefs, also affect the overall outcomes of SLE patients in Asia.[11] A previous study stated that conditions including cytopenia or major organ involvement, such as nephritis, trigger flares in lupus.[12]

Crampton proposed a pathophysiological model of SLE (Figure 1).[13] It was a presentation of an unknown antigen to MHC class II that would cause the priming of CD4 cells, leading to class switching and maturation of B cells in the germinal center. They were autoreactive, becoming plasma cells that produced soluble IgG isotype autoantibodies. The autoantibodies would bind to autoantigens and become immune complexes or bind to complement and Fcγ receptors on other cell types. This supports inflammation and tissue damage by recruiting inflammatory cells to the tissue. Cells that undergo apoptosis will be taken by macrophage cells and be a new autoantigen that continues to lymphocyte priming and auto activity. Also, TLR activation by environmental influences like a viral infection or cell damage by ultraviolet (UV) light contributes to the above process through the secretion of IFN-1 and other cytokines that trigger the autoreactivity of lymphocytes and network damage.[13]

Human leukocyte antigens, or HLA-DR (D-antigen related), is a group of genes on chromosome 6 that produce proteins on the cell surface called major histocompatibility complex class II (MHC class II).[13] They are originally associated with organ transplantation. A study in Saudi Arabia found that the HLA-A*29 gene was related to SLE (OR = 2.07; 95% CI = 1.03–7.08), HLA-DRB1*15 haplotype (OR = 2.01; 95% CI = 1.20–3.68, P = 0.008), and HLA-DQB1*06 (OR = 1.67; 95% CI = 1.19–3.36, P = 0.0032). HLA-DRB1*16 is negatively associated with SLE disease (OR = 0.18; 95% CI = 0.02–1.3, P = 0.055).[14] While, a study in Malaysia found that HLA-DR2, DQB1*0501, and DQB1*0601 had a significant relationship with SLE (pcorr=0.03, rr = 3.83; pcorr = 0.0036 rr = 4.56; pcorr = 0.0048, rr = 6).[15]

This study aimed to look for risk factors for the worsening of SLE in patients undergoing outpatient care. The risk factors were based on the patients' ages, education levels, employment status, hemoglobin levels, and

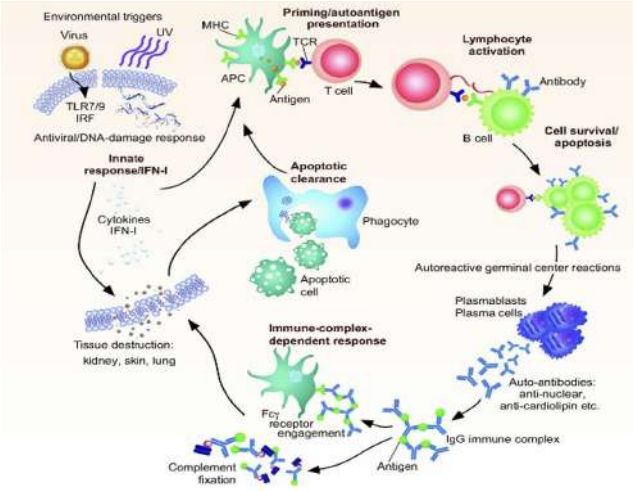

Figure 1. Disease Model and Mechanism[13]

administration of hydroxychloroquine and immunosuppressants. Due to the absence of genetic data on SLE patients in Indonesia, the genotyping analysis will be carried out on the subpopulation of study subjects as a form of descriptive data.

Method

The participants were 82 patients with SLE followed in an ambispective cohort study. A total of 22 subjects followed in a prospective cohort study, and 60 followed in a retrospective cohort study. The inclusion criteria were SLE patients diagnosed with the American College of Rheumatology 1997 criteria. While, the criteria for worsening was an increase in the SLEDAI, with a score of three or higher with a minimum of three months between the first and second measurements. The examined variables were anemia—defined as hemoglobin level <10 g/dL)—education level, hydroxychloroquine, immunosuppressants, and employment status. The bivariate and multivariate methods aimed to check the significance of the relationship between the variables. The genotyping examination used the DNA typing PCR-based labeled sequence-specific oligonucleotide (SSO) that can read up to two digits.

Results

All of 82 participants were female (100%). Their average age was 33.3, with a maximum age of 55, and the youngest was 19. As many as 62 subjects (75.61%) were under 40, and 20 (24.39%) were over 40. Most respondents attended high school (47.56%), did not work formally (80.49%), and were married (60.98%). As many as 28.05% had a body mass index (BMI) of

≥25 (abnormal). Most respondents were not anemic (84.15%), and 64.63% received treatment with hydroxychloroquine. While, 68.29% received treatment with immunosuppressants, and 14.63% experienced an increase in the SLEDAI by three points.

Patients with SLE aged <40 years had a 1.61 times higher risk of worsening than those aged ≥40. Patients with SLE who work were at a 1.55 times higher risk, and patients without higher education were at a 1.48 times higher risk of worsening. While, based on the results of this study, being single/a widower/a widow was a protective factor against worsening, with an RR of 0.59 compared to married patients, and abnormal BMI (BMI≥25) was also a protective factor against worsening of SLE disease activity, with RR 0.24; however, all the variables above were statistically insignificant, with p-value>0.05.

Another factor, anemia, was a risk factor for worsening in SLE patients with RR 5.31. However, in treating patients with the medicine, patients not given hydroxychloroquine had 1.31 times the flares/worsening, but immunosuppressants were protective factors against disease worsening, with RR 0.43. Statistically, the results of this bivariate analysis were only significantly related to the anemia variable, with a p-value of 0.003.

In contrast, other variables, such as age, education level, employment status, marital status, BMI, hydroxychloroquine, and immunosuppressants, produced p-values of >0.05, which were not statistically significant statistics. In this study, the predictor factor for worsening SLE activity in patients was statistically significant anemia. Patients who were anemic (indicated by Hb <10) had a higher risk of worsening the SLEDAI score (95% CI = 0.02–0.29).

Table 1. Respondents' Characteristic (N = 82)

Variable	Category	N	%
Age	≥40 years	20	24.39
	<40 years	62	75.61
Education	Elementary school	3	3.66
	Junior high school	6	7.32
	Senior high school	39	47.56
	Higher education	34	41.46
Employment status	Unemployed	66	80.49
	Employed	16	19.51
Marital status	Married	50	60.98
	Single/Widow/Widower	28	34.15
	Missing (no data)	4	4.88
BMI	BMI ≥25	55	67.07
	BMI >25	23	28.05
	Missing (no data)	4	4.88
Anemia	Not Anemia (Hb ≥10)	69	84.15
	Anemia (Hb <10)	13	15.85
Medication	Without Hydroxychloroquine	29	35.37
	With Hydroxychloroquine	53	64.63
	Without Immunosuppressant	26	31.71
	With Immunosuppressant	56	68.29
Genotype HLA (N = 19)	DRB1*12 DRB1*12	3	15.79
	DRB1*15 DRB1*15	6	31.58
	DRB1*12 DRB1*14	2	10.53
	DRB1*12 DRB1*15	2	10.53
	DRB1*7 DRB1*16	1	5.26
	DRB1*8 DRB1*15	1	5.26
	DRB1*7 DRB1*15	1	5.26
	DRB1*7 DRB1*12	1	5.26
	DRB1*14 DRB1*15	1	5.26
	DRB1*8 DRB1*12	1	5.26

Notes: Hb = Hemoglobin, BMI = Body Mass Index, HLA DR = Human Leucocyte Antigen

Table 2. Incidence of Worsening/Flare (N = 82)

Variable	Category	N	%
Worsening (Flare)	Not Flare	70	85.37
	Flare	12	14.63

Discussion

All respondents in this study were women. A previous study stated that women with lupus have a higher frequency than men (9:1 ratio).[16] This is generally associated with differences in hormones and chromosomes; however, no studies can explain this with certainty. The average age of the respondents was 33.3. Although SLE can affect women in all age groups, a cross-sectional study in Germany showed an increased incidence of SLE in women in the 20–25 age group, with a rate of 3.6 per 100,000 persons per year (95% CI = 2.9–4.3).[17] However, there is a second peak of incidence at menopause (95% CI = 1.5–3.8).[18]

The most vulnerable age group for SLE was 20–39 years for women.[19] The age demographic in this study is not very different from the previous study. However, a study in Hong Kong stated that Asian SLE patients have a higher possibility of experiencing renal complications than Caucasians.[10] Asian lupus patients tend to have higher organ damage scores due to late diagnosis. It is also necessary to think about the availability of access to health facilities.[10]

It is estimated that 20–25% of lupus patients will experience flares in the first 1–2 years, and 40–60% will experience them after 5–10 years.[20] While, a study in Italy reported an incidence of flares in SLE patients who were followed for the first year (5– 7%).[21] The incidence of flares (worsening) in this study was 14%, which is rather high compared to the incidence of flares in the Italian population. A previous study reported that in the Caucasian population, education level also affects the mortality of SLE patients.[11] Caucasian lupus patients with high educational levels have lower mortality rates, but this phenomenon is not found in other ethnic groups (African-American and Asia-Pacific Islander).[11]

Table 3. Correlation between Worsening of Lupus (Flare) with Age, Education Level, Employment Status, Marital Status, Body Mass Index, Anemia, Hydroxychloroquine, and Immunosuppressants Status (N = 82)

Variable	Category	Flare				RR	95% CI	p-value
		Yes		No				
		N	%	N	%			
Age	<40 years	10	16.13	52	83.87	1.61	0.39–6.75	0.721
	≥40 years*	2	10	18	90			
Education	Lower education	7	14.58	41	85.42	0.99	0.71–6.01	0.237
	Higher education*	5	14.71	29	85.29			
Employment	Employed	4	25	12	75	2.06	0.34–2.86	1.000
	Unemployed*	8	12.12	58	87.88			
Marital status	Single/Widow/Widower	3	10.71	25	89.29	0.67	0.19–2.32	0.737
	Married*	8	16	42	84			
BMI	BMI >25	1	4.35	22	95.65	0.24	0.03–1.76	0.160
	BMI ≤25*	10	18.18	45	81.82			
Anemia	Anemia (Hb<10)	6	46.15	7	53.85	5.31	2.02–13.92	0.003*)
	Not anemia (Hb≥10)*	6	8.70	63	91.30			
Medication	Without HCQ	5	17.24	24	82.76	1.31	0.46–3.75	0.746
	With HCQ*	7	13.21	46	86.79			
	Without Immunosuppressants	2	7.69	24	92.31	0.43	0.10–1.83	0.322
	With Immunosuppressants*	10	17.86	46	82.14			

Notes: RR = Relative Risk, CI = Confidence Interval, HCQ = Hydroxychloroquine, Hb = Hemoglobin, BMI = Body Mass Index, *Reference, *) Significant (p-value<0.05)

Table 4. Multivariate Analysis for Predictor Factors for Worsening Systemic Lupus Erythematosus Patients

Variable	RR Adjusted	95% CI	SE	p-value
Anemia	5.3	2.02–13.91	0.701	0.00

Notes: RR = Relative Risk, CI = Confidence Interval, SE = Standard Error

Table 5. Mean Size of The Erythrocyte Index in 15 Subjects with Anemia

	MCV (fl)	MCH (pg)	MCHC (g/dL)
Mean	69.4	26.3	32.4

Notes: MCV = Mean Corpuscular Volume, MCH = Mean Corpuscular Hemoglobin, MCHC = Mean Corpuscular Hemoglobin Concentration

In this study, the variable that affected the worsening condition of the SLEDAI score (flare) was anemia, defined as Hb<10 g/dl. Voulgarelis stated that anemia of chronic disease, autoimmune anemia, and iron deficiency anemia are often found in SLE patients.[22] Iron deficiency anemia is associated with SLE disease activity.[22] In contrast, anemia of chronic disease tends to be stable with no remission, regardless of other components of disease activity.[22] While, autoimmune anemia is due to a severe decrease in hemoglobin levels.[22] Inflammatory cytokines, such as tumor necrosis factor α, interferon β, and interleukin 1, seem to influence anemia, especially anemia of chronic disease, by inhibiting the proliferation of erythroblast progenitors, altering iron metabolism, and suppressing erythropoietin production. Immunohistochemical studies in lupus nephritis patients also found CD4 lymphocytes and macrophages infiltration in the kidney's interstitial areas, suppressing renal erythropoietin production.[22]

From Table 5, the result of the calculation of the average MCV in 15 subjects is 79.2 fl. Djulbegovic stated that an MCV value of lower than 100 has a high specific value for iron deficiency anemia (although a definite diagnosis requires bone marrow examination).[23] The iron deficiency anemia in the subjects seems to be related to Voulgarelis' statement that iron deficiency anemia is affected by disease activity. In contrast, anemia of chronic disease is more stable during observation.[22] However, differentiating iron deficiency anemia from anemia of chronic disease is not easy. The mechanism of why cytopenia (anemia in this study) causes a flare in lupus patients may have many different pathways. Considering pro-inflammatory cytokines may cause anemia, it could be hypothesized that anemia is only the surrogate factor for predicting flare in lupus patients.

The Indonesian Ministry of Health reports show that anemia prevalence in women aged ≥15 years is 22.7%.[24] Assuming that this population is at risk of becoming afflicted with SLE in the future, it is expected that the burden of treatment could rise. In this study, two other variables (being employed or working and younger age) also posed a higher risk for lupus worsening (flare). Although not statistically significant, this could be explained by the theory that UV B induced apoptosis of keratinocytes in the skin; autoantibodies in lupus patients

may recognize autoantigens from this apoptotic cell, which then induced inflammation in the respondents who were working (with more sun exposure than the nonworking subjects); and subjects of a younger age had relatively more active estrogen (estrogen is known to modulate immune system function) compared to older respondents, which in turn caused a higher chance of flares.[20,21]

In this study, genotyping was done on 19 subjects, with the examination target of the HLA DR gene. The highest frequency of the HLA gene was class 2, HLA DRB1*15 DRB1*15, with a frequency of 18.75%. While, Niu, *et al.*, stated that the HLA DR-3 gene is related to SLE.[25] A study in Malaysia used the PCR method and found HLA DR2 and DQB 1 to be associated with lupus.[15] With the high variation of HLA genes in lupus, it should be considered that the HLA genes have high polymorphism. Therefore, the immune system can recognize different kinds of peptides. Later, the immune system can recognize various strange peptides, which will be presented to T lymphocytes.[26] The HLA gene DRB1*15 is commonly associated with multiple sclerosis, an autoimmune disease that primarily attacks the nervous system, especially the myelin membranes, and which is characterized by fatigue, pain, balance disorders, and paralysis.[27]

The time for the second SLEDAI examination for prospective and retrospective cohorts in this study was set independently. Looking for the risk factors for flares in SLE patients is recommended so that future studies follow the subjects in a prospective cohort starting from a low SLEDAI score or remission until they have an increased SLEDAI score (flare). This step must be ethically reviewed. It is also necessary to consider the quantity factor of the frequency of repetition of the scoring tool or instrument to monitor disease activity. In this study, the SLEDAI tool and complement levels were only repeated twice. Also, there was a high risk of bias because it was an ambispective cohort carried out in two hospitals.

Conclusion

The risk factor for worsening (flare) of systemic lupus erythematosus was anemia, defined as a hemoglobin level of less than 10 g/dL, with RR = 5.31, p-value = 0.03, 95% CI = 2.02–13.92. While, age, body mass index, education level, employment status, marital status, hydroxychloroquine, and immunosuppressants are not statistically significant risk factors for worsening (flare) of systemic lupus erythematosus.

Abbreviations

SLE: Systemic Lupus Erythematosus; SLEDAI: Systemic Lupus Disease Activity Index; BMI: Body Mass Index; MCV: Mean Corpuscular Volume.

Ethics Approval and Consent to Participate

This study was carried out after ethical approval was obtained from the Ethics Committee of the Faculty of Public Health, Universitas Indonesia, No. 814/UN2.F10/PPM.00.02/2018.

Competing Interest

The authors declare that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

All datasets generated and analyzed are available in the article.

Authors' Contribution

GA, RD, MKS, and S contributed to the conception and design, acquisition analysis and interpretation of data, and drafting and revising of the manuscript.

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