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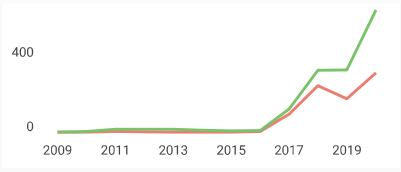

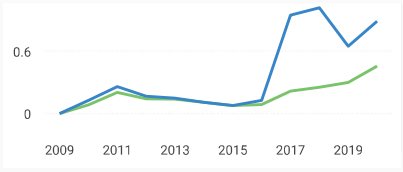

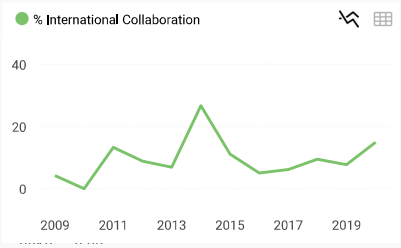

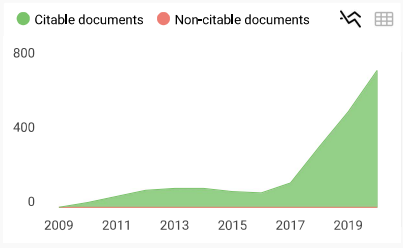

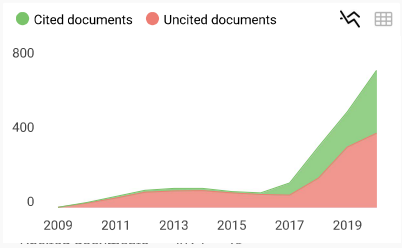

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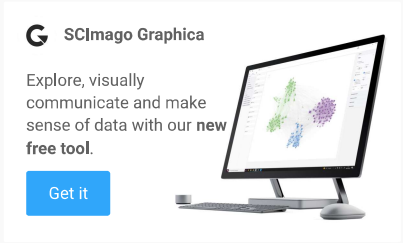

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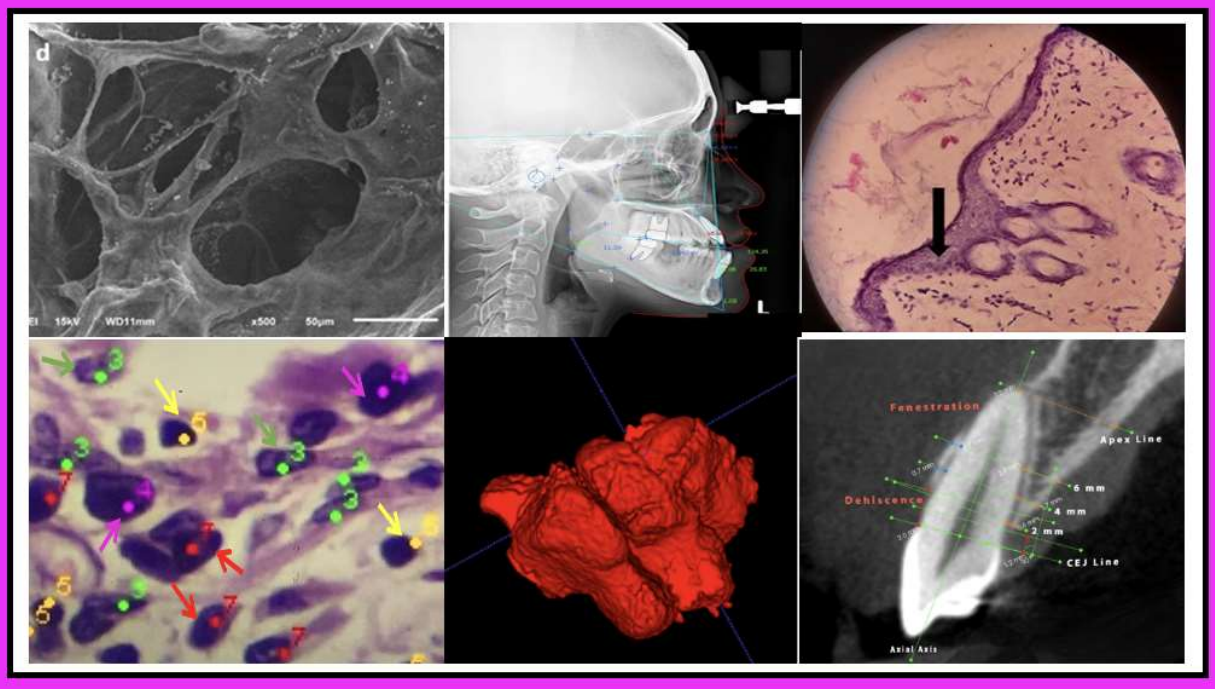

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Natural Killer Cell in Mild and Severe Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by acute relapses that affect numerous organ systems. The purpose of this study was to compare the number of natural killer (NK) cells and the proportion of activated NK cells in patients with mild and severe SLE based on CD69 expression.

The design of this study was cross-sectional. Patients with SLE in this study were patients who met four criteria out of 11 criteria for the 1997 ACR. Patients were examined for the number of NK cells, the percentage of activated NK cells, and SLE disease activity assessed by the Score Systemic Lupus Activity Measure (SLAM) index. All patients were female, 17 patients in the mild SLE group (47.2%) and 19 patients in the severe SLE group (52.8%). The mean age of the SLE group was 30.76 ± 10.146 years, and the severe SLE group included 27.89 ± 7.527 years. In this study, the mean body mass index (BMI) in the mild SLE group was 20.859 ± 2.3203 kg/m^2, while BMI in the severe SLE group was 21.900 ± 3.1213 kg/m^2. The mean number of NK cells in the mild SLE group (161.94 ± 113.004 cells/μL) was higher than the severe SLE group (63.16 ± 54.851 cell /μL) (p = 0.006). The mean percentage of activated NK cells in the severe SLE group (4.00 ± 3.45cells/μL) was higher than the mild SLE group (1.90 ± 0.94cells/μL) (p = 0.141).

There was a significant difference in the number and percentage of activated NK cells between the mild SLE group and the severe SLE group.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with acute periodic recurrences affecting multiple organ systems, characterized by loss of tolerance to nucleic acids, and has a wide variety of clinical manifestations, leading to potentially life-threatening complications.[1–3] SLE is well known as a disease characterized by the formation of autoantibodies. Subsequent studies have shown that SLE also can affect the innate and adaptive immune system. The latest study on pathogenesis of SLE have shown a formation of Neutrophil Extracellular Trap (NET), Interferon (IFN) signatures, changes in Dendritic Cell (DC), changes in T cells, and changes in Natural Killer (NK) cells.[4,5] NK cells are lymphocytes in innate immune system that has a contribution to autoimmune diseases.[6] Currently, there have been several studies studying the effect of SLE disease activity on NK cell counts and NK cell cytotoxic activity,[7–9] but the results are still controversial.

Recent studies on the pathogenesis of SLE have reported the presence of an IFN signature and also NET. The presence of NET will cause more antigen presentation so that excessive autoantibodies are formed, and immune complexes are deposited in various body tissues, which causes disease activity to worsen. This is due to the reduced role of NK cells as immunoregulators due to the influence of IFN. SLE patients show differences in clinical

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manifestations or disease activity due to the molecular signature that causes the IFN signature.[10–13] This interferon signature and NET causes inflammation in various organs due to immune complex activation because the presence of NET will form many autoantigens.[5,14–16]

NET causes the number and function of NK cells to decrease, which causes impaired immune system regulation related to disease activity.[6–9,15,17] Previous studies reported that a decrease in the number of NK cells was not associated with SLE disease activity. The different results of this study were due to differences in the activity parameters and the number of NK cells used.[18–20]

The problems in SLE patients cannot be underestimated. Until now, the mortality rate for SLE is still relatively high. The incidence of SLE worldwide ranges from 0.3–23.7 per 100,000 people per year, while the prevalence of SLE ranges from 6.5–178 per 100,000 population. Data on SLE sufferers in Indonesia have not been collected integratively. However, based on the Data and Information Center of the Ministry of Health of the Republic of Indonesia in 2017, it is estimated that the prevalence of SLE in Indonesia is 0.5% of the total population or around 1,250,000 patients.[21,22]

The role of NK cells in the pathogenesis of SLE is widely studied nowadays since it is believed that variations in NK cell deficiency are related to SLE. This study is intended to compare the number and percentage of activated NK cells in mild and severe SLE.

Materials and methods

This is analytic observational study with a cross-sectional research design. The study location is in the Inpatient and Outpatient Installation of Dr. Soetomo Hospital, Surabaya, Indonesia, from October 2019 to January 2020. The population of this study was all patients diagnosed with SLE based on the criteria of the 1997 American College Rheumatology (ACR) in the Inpatient and Outpatient Installation of Dr. Soetomo Hospital, Surabaya, Indonesia.

Sample

The sample in this study was part of all SLE patients in the Inpatient and Outpatient Installation of Dr. Soetomo Hospital, Surabaya, who met the inclusion criteria, and no exclusion criteria were found. The inclusion criteria of this study were 16-50 years old, new SLE patients (who had not received therapy) who met the 1997 criteria clinically, laboratories and radiologists in inpatients, and SLE patients with a minimum length of calm for one year in an outpatient installation. In comparison, the exclusion criteria were SLE patients who overlapped with other connective tissue diseases (scleroderma, rheumatoid arthritis, dermatomyositis), people with diabetes mellitus, and who had a history of or were suffering a malignancy. The minimum total sample size in this study is calculated based on the following formula:

$$N = \frac{2 \times \sigma^2 \times (Z\alpha + Z\beta)^2}{(\mu 1 - \mu 2)^2}$$

The sample size required for each group based on the above calculation is 9.6, rounded off to 10 people. Thus, the minimum sample size is 20 people. Sampling was done by consecutive sampling from SLE patients to obtain a predetermined large number of samples.

Patients with SLE in this study were patients who met four criteria out of 11 criteria for the 1997 ACR. Samples were obtained from inpatient and outpatient installations. The immunological tests measured in this study were ANA and anti-double-stranded deoxy nucleic acid (anti-dsDNA). This was classified into 3 levels, namely negative (<20 units/ml), moderate positive (20-60 units/ml), strong positive (>60 units/ml), measured by the ANA hybrid method. Anti ds-DNA was classified into 4 levels, namely negative (<92.6 WHO units/ml), borderline (92.6–138.9 WHO units/ml), moderate positive (139.9-370 WHO units/ml), strong positive (>370.4 WHO unit/ml), measured by the Enzyme Immuno Assay (EIA) titer method. The examination of the number of NK cells was also carried out at the Clinical Pathology Laboratory, Dr. Soetomo Hospital, Surabaya, Indonesia, expressed in units of cells/μL, while the percentage of NK cells to the number of lymphocytes is displayed in a ratio scale.

In this study, the percentage of activated NK cell is measured based on CD69 expression. The examination was carried out in the calibrated laboratory of Clinical Pathology at Dr. Soetomo Hospital, Surabaya. The variable percentage of

activated NK cells will appear as a ratio scale. While SLE disease activity was assessed using the Score Systemic Lupus Activity Measure (SLAM) index. This scoring system assigns a score of 0–3 for each parameter. The total score value ranges from 0 to 86. The meaning of this score is that if the score is higher, the degree of disease will be more active or severe.[23] This variable is a nominal scale with mild and severe categories. SLE was classified into mild SLE (SLAM Score 0-19) and severe SLE (SLAM Score >20).

Data analysis

Data processing was performed using the IBM® SPSS® version 25 programme. Data were analyzed using descriptive statistics and presented in the form of a frequency distribution table. Statistical analysis of the difference in the number of NK cells and the percentage counting of activated NK cells between the two subject groups were carried out. Test data distribution was done using Shapiro Wilk, where if p >0.05 indicates normal data distribution. A comparative test for 2 sample groups was also conducted, namely two independent samples of the non-parametric test.

Results

General Characteristics of Research Subjects

This study took a sample of 36 patients in outpatient and inpatient units at the Department of Internal Medicine, Dr. Soetomo Hospital, Surabaya. The study subjects were divided into two groups: the mild SLE group (low SLAM) and the severe SLE group (high SLAM). All subjects of this study were female. The age group for mild SLE included a mean age of 30.76 ± 10.15 years, with the youngest age being 17 years and the oldest being 47 years. For the severe SLE group, the mean age was 27.89 ± 7.52 years, with the youngest age being 19 years and the oldest being 47 years old. The mean Body Mass Index (BMI) in the mild SLE group was 20.86 ± 2.32 kg/m^2, with the lowest BMI was 17.5 kg/m^2 and the highest BMI was 22.5 kg/m^2. Meanwhile, BMI in the severe SLE group had a mean value of 21.90 ± 3.12 kg/m^2 with the lowest value of 16.8 kg/m^2 and the highest value of 27 kg/m^2.

Table 1 displays the laboratories parameter of subjects. The mean random blood glucose (RBG) was 89.71 ± 22.66 mg/dL for the mild SLE group and 115.95 ± 30.74 mg/dL for the severe SLE group. Sequentially from mild SLE to severe SLE, the mean erythrocyte sedimentation rate (ESR) included 35.47 ± 19.88 and 35.74 ± 24.24. The mean CRP levels were 0.32 ± 0.28 for the mild SLE group and 3.98 ± 4.33 for the severe SLE group. The complement test showed that the mean level of C3 for the mild SLE group was 73.54 ± 28.29, and the severe SLE group was 44.28 ± 34.79. Meanwhile, the mean C4 level for the mild SLE group was 25.61 ± 12.08, and the severe SLE group was 20.66 ± 21.39.

Characteristics	Mild SLE (n=17)	Severe SLE (n=19)
Hemoglobin (g/dL)		
Mean ± SD	11.80 ± 1.72	8.11 ± 3.14
Median (range)	12.10 (8.8-14.1)	8.70 (2.3-14.8)
Leukosit (cell/µL)		
Mean ± SD	6814.71 ± 2145.49	8190.00 ± 5029.40
Median (range)	7210.00 (3390-11290)	7930.00 (2420-21990)
Limfosit (cell/µL)		
Mean ± SD	1631.18 ± 847.14	1053.16 ± 538.68
Median (range)	1800.00 (240-3300)	1200.00 (270-1960)
Trombosit (cell/µL)		
Mean ± SD	306000.00 ± 75790.83	167368.42 ± 116779.09
Median (range)	285000 (188000-486000)	139000 (6000-458000)
Random Blood Glucose (mg/dL)		
Mean ± SD	89.71 ± 22.66	115.95 ± 30.74
Median (range)	91.00 (21-136)	113.00 (77-196)
LED		
Mean ± SD	35.47 ± 19.88	35.74 ± 24.24
Median (range)	34.00 (5-72)	33.00 (2-84)
CRP		
Mean ± SD	0.32 ± 0.28	3.98 ± 4.33
Median (range)	0.20 (0.1-0.9)	2.00 (0.0-14.0)
C3		
Mean ± SD	73.54 ± 28.29	44.28 ± 34.79
Median (range)	82.00 (19.0-120.0)	33.80 (16.4-144.0)
C4		
Mean ± SD	25.61 ± 12.08	20.66 ± 21.39
Median (range)	27.20 (6.0-47.5)	15.70 (3.0-90.6)
SLAM Score		
Mean	4.24 ± 4.87	26.26 ± 4.82
Median (range)	2.00 (1-19)	24.00 (20-36)

Table 1. Laboratories Parameter of Subjects.
SLE: Systemic lupus erythematosus; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SLAM: Systemic Lupus Activity Measure.

The examination of the number of NK cells in each group of mild and severe SLE is shown in Table 2. The average number of NK cells in the mild SLE group was higher than the average number of NK cells in the severe SLE group. The lowest number of NK cells in the mild

SLE group was 7, while the highest was 388. The lowest number of NK cells in the severe SLE group was 10, while the highest was 222. The range of minimum and maximum values in both groups was also quite large, as indicated by the standard values. The very high deviation was 113.00 in patients with mild SLE scores and 54.85 in patients with severe SLE.

Group	N	□□□□□□□□□ (cells/µL)	□□□□□□□(cells/µL)
Mild SLE	17	161.94 ± 113.00	140.00
Severe SLE	19	63.16 ± 54.85	54.851

Table 2. Number of NK Cells in mild and severe SLE. SLE: Systemic lupus erythematosus.

Percentage of activated NK cells in mild and severe SLE

The examination of the percentage of activated NK cells in each group of mild and severe SLE is shown in Table 3. The average percentage of activated NK cells in the severe SLE group was higher than that of activated NK cells in the mild SLE group. The lowest percentage of activated NK cells was 0.55 in the mild SLE group, and the highest percentage of NK cells was in the severe SLE group at 13.25. The range of minimum and maximum values in both groups was also quite large, indicated by a very high standard deviation value, namely 0.94 in patients with mild SLE scores and 3.45 in patients with severe SLE scores.

Group	N	Mean ± SD (cells/µL)	Median (cells/µL)
Mild SLE	17	1.90 ± 0.94	1.90
Severe SLE	19	4.00 ± 3.45	2.21

Table 3. Percentage of activated NK cells on mild and severe SLE.
SLE: Systemic lupus erythematosus.

Research Data Normality Test

Examination of the distribution of NK cells and the percentage of activated NK cells in SLE patients was carried out using the Shapiro Wilk method. Based on the Shapiro Wilk test results for the variable number of NK cells and the percentage of activated NK cells in each sample group, the resulting p-value is 0.46; 0.01; 0.09; 0.00; which means normally distributed.

Comparative test comparison of the number of NK cells for each SLE group

The results of the comparative test for the mean number of NK cells in patients with mild SLE (161.94 ± 113.00 cells/µL) and severe SLE (63.16 ± 54.85 cells/µL) obtained a p-value of 0.006. It can be concluded that there is a significant difference in the number of NK cells in the mild and severe SLE groups. The mean value of the number of NK cells was higher in the mild SLE group than in the severe SLE group, which indicated a negative relationship between the SLAM score of SLE and the number of NK cells, as illustrated in the scatter diagram in Figure 1.

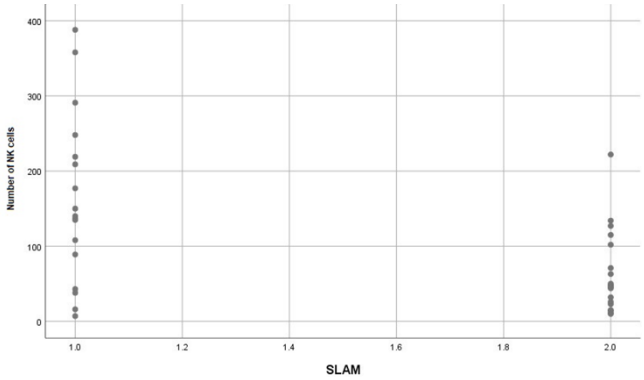

Figure 1. Scatter diagram comparing the number of NK cells with the SLAM score.
Note: 1.0 = mild SLE, 2.0 = severe SLE.

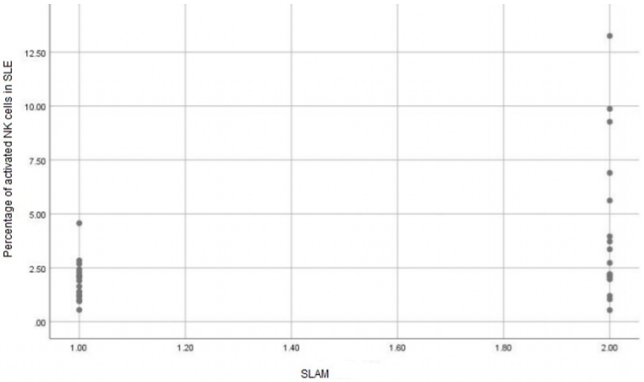

Figure 2. Scatter diagram comparing the percentage of activated NK cells in SLE.
Note: 1.0 = mild SLE, 2.0 = severe SLE.

Comparative test of the percentage of activated NK cells in each group

The results of the comparison test of the percentage of NK cells in patients with mild SLE (1.90 ± 0.94 cells/µL) and severe SLE (4.00 ± 3.45 cells/µL) obtained a p-value of 0.032. Consequently, it can be concluded that there was significant difference in the percentage of activated NK cells in SLE patients in the mild and severe SLAM groups. The mean value of the percentage of activated NK cells was greater in the severe SLE group than the mild SLE group, indicating a positive relationship between the

SLAM score of SLE and the percentage of NK cells, as illustrated in the scatter diagram in Figure 2.

Discussion

The results of this study suggested that the number of NK cells in the mild and severe SLE groups was significantly different. This study also tested the correlation between mild SLE scores and severe SLE scores with the number of NK cells using a scatter diagram showing the direction of linear and negative correlation. This means that the lower the SLAM score, the higher the number of NK cells. According to the comparison analysis, both groups had a significant decrease in NK cells. This is consistent with the theory that the more active SLE disease, the more NK cells undergo apoptosis. This causes autoantigens' availability that triggers more intense inflammation, which is reflected in the activity of SLE disease. Additionally, IFN-a released by plasmacytoid (p) DC causes cell death in individuals with active SLE as a result of circulating NK cell activation, ultimately contributing to the loss of circulating NK cells. A recent study suggested that $CD56^{bright}$ NK cells might contribute to the pathogenesis of SLE. Serum IL-15 levels are elevated in SLE patients, especially those with active SLE.[24,25] Meanwhile, in SLE patients, an increase in peripheral blood Ki67 + $CD56^{bright}$ NK cells was significantly associated with an increase in serum IL-15 clinical severity and active nephritis.[26]

This study discovered that severe SLE patients had a higher percentage of activated NK cells than those with mild SLE based on CD69 expression. In addition, the scatter diagram shows that the higher the SLAM score, the higher the percentage of activated NK cells. The percentage of activated NK cells in the peripheral circulation is not same in the target tissue of the inflamed organ. Many NK cells in the periphery go to the tissue by releasing cytokines and chemokines that aim to control inflammation, but in tissues that have experienced inflammation due to the presence of NK cells, it turns out that the tissue will experience more intense inflammation so that the tissue cells will be more numerous which is damaged and causes spreading epitope, which explains the worsening of organ function disorders or the emergence of inflammation in other organs.[27,28]

Due to the interactions between chemokines and their receptors, NK cells are rapidly attracted from the peripheral circulation to the wounded tissue during pathological situations, such as inflammation.[29,30] After reaching at the site of inflammation, NK cells are activated to carry out their functional functions. Activation of NK cells can occur in response to a variety of different cues. These include signals transmitted by multiple NK cell activating receptors in response to the recognition of specific ligands expressed on tumor cells, or signals generated in response to stimulation via toll-like receptors (TLRs) that are constitutively expressed on NK cells and enable them to react to pathogen-derived products.[31,32] Additionally, NK cells can be activated via cytokines released by other cell types. Indeed, while NK cells can recognize altered cells directly, recent research has showed that the microenvironment and interactions with other immune cells, particularly DCs, can play a significant role in ensuring proper NK cell priming. For instance, the synthesis of cytokines (such as IL-12) by activated DCs augments NK cell proliferation, IFN production, and antitumor cytotoxicity.[33]

The majority of research on the role of NK cells in SLE has been conducted on peripheral blood, but little is known about NK cell function in the target tissue. Recent studies using the mouse SLE model have shown that NK cells infiltrate the kidney in an active disease state, which in this case, due to the influence of the microenvironment, the NK cells in the tissue will be activated and cause inflammation in lupus nephritis.[6]

Several further investigations have established that NK cells have a role in the pathogenesis of SLE. Experiments in rats have shown that NK cell deficiency triggers the autoimmune disease.[34] Subsequent studies observed the cytotoxic activity and cytokine profile of NK cells in the pathogenesis of SLE. Increased cytotoxicity and pro-inflammatory phenotype of NK cells are correlated with changes in cytotoxic activity in NK cells, including downregulation of CD3x expression in SLE patients accompanied by increased caspase-3 activity compared to healthy controls, resulting in downregulation of CD3x expression in cells which are pro-inflammatory phenotypes.[35] Other studies have also shown changes in the phenotype, distribution, and function of NK cells

in SLE. The proportion of NK cells, namely CD56^{dim} NK cells, was lower, but CD56^{bright} NK cells were higher in the peripheral blood of SLE patients when compared to healthy controls.[6,15] As is well known, NK-dimmed CD56 NK cells in active SLE patients exhibit increased IFN-g production and exhibit an active phenotype in the presence of increased activating receptors (e.g., NKp44, NKp46, and CD69) and decreased CD158a/h/g expression.[36] A decrease in the number of circulating CD56^{dim} NK cells in SLE patients can be related to the rapid migration of CD56^{dim} NK cells from peripheral circulation to target organs, such as the kidneys, resulting in local tissue damage. Numerous factors contribute to CD56^{dim} NK cell migration, including increased expression of NKG2D ligands, such as ribonucleic acid export (RAE)-1 and UL16 binding in mouse transcript-like protein (MULT)-1, CD226 ligands (e.g., CD112 and CD115), proinflammatory cytokines (e.g., TNF-a), and chemoattractant chemokines, for example, the C-X3-Cligan-patterned chemokine (CX3CL) in kidney tissue that contributes to CD56^{dim} NK cell migration. Migratory NK cells have also been observed in animal models of SLE, in which circulating DX5 + NK cells (mostly CD226 +) infiltrate rat kidneys and are responsible for the kidney injury observed in SLE.[37,38]

Increased IL-15 levels in SLE are associated with increased type I IFN production, which activates DCs; moreover, IL-15 promotes Ki67 expression on NK cells, stimulating NK cell proliferation and contributing to the pathogenesis of SLE. The precise mechanisms by which CD56^{bright} NK cells induce SLE or cause tissue harm, however, remain unknown. The inflamed tissue is expected to recruit NK cells and alter their effector function by transforming the phenotypic of CD56^{bright} NK cells, which should have low cytotoxicity, to CD56^{bright} cytotoxicity via an unknown mechanism.[31]

This research has several limitations. First, this study used a cross-sectional design to measure the number of NK cells, and the percentage of activated NK cells was only done once. Second, the exclusion criteria in this study were only based on anamnesis, physical examination, and simple laboratory results. Third, the difficulty in controlling the confounding variables of the study, including the drugs used and the duration of suffering from SLE. Fourth, NK cell measurements were not differentiated in a subset of CD56^{dim} NK cells and CD56^{bright} NK cells. Fifth, the measurement of the percentage of activated NK cells based on CD69^{+} expression was only carried out at baseline without any in vitro stimulation.

Conclusions

There was a substantial difference in the number of NK cells and the percentage of activated NK cells between mild SLE group and severe SLE group based on CD69 expression.

Declaration of Interest

The authors declare no conflict of interest.

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KOMITE ETIK PENELITIAN KESEHATAN
RSUD Dr. SOETOMO SURABAYA

KETERANGAN KELAIKAN ETIK
(" ETHICAL CLEARANCE ")

1500/KEPK/Ix/2019

KOMITE ETIK RSUD Dr. SOETOMO SURABAYA TELAH MEMPELAJARI SECARA SEKSAMA RANCANGAN PENELITIAN YANG DIUSULKAN, MAKA DENGAN INI MENYATAKAN BAHWA PENELITIAN DENGAN JUDUL :

" Perbandingan Jumlah dan Persentase Sel NK Teraktivasi dengan Aktivitas Systemic Lupus Erythematosus "

PENELITI UTAMA : Wita Kartika Nurani, dr., Sp.PD

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DINYATAKAN LAIK ETIK

Berlaku dari : 10/09/2019 s.d 10/09/2020
Surabaya, 10 September 2019
KETUA

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) Sertifikat ini dinyatakan sah apabila telah mendapatkan stempel asli dari Komite Etik