ORIGINAL ARTICLE

# Association between the Duration of Steroid Therapy with Hyperglycemia in Patients with Systemic Lupus Erythematosus (SLE)

**Farahdiva Audrey Widyanrika[1], Sony Wibisono Mudjanarko[2,3*], Maftuchah Rochmanti[4], Deasy Ardiany[2,3], Putu Bagus Dharma Permana[1]**

[1]Faculty of Medicine, Universitas Airlangga Surabaya, Indonesia

[2]Department of Internal Medicine, Faculty of Medicine, Universitas Airlangga - Dr Soetomo General Academic Hospital, Surabaya, Indonesia

[3]Indonesian Association of Internal Medicine

[4]Department of Anatomy, Histology, and Pharmacology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

**ABSTRACT**

**Introduction:** Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease which primary treatment consists of steroid drugs administration. Prolonged steroid administration is often associated with an increase in blood glucose, a condition known as hyperglycemia. Hence, this study aimed to evaluate the association between the duration of steroid therapy with hyperglycemia in patients with SLE treated at a tertiary healthcare center in Surabaya, Indonesia.

**Methods:** A cross-sectional study was conducted under a purposive sampling frame from January to December of 2022 by utilizing secondary data from electronic medical health records in Dr. Soetomo General Academic Hospital, a tertiary healthcare center in Surabaya, Indonesia. The association between variables were analyzed using Fisher's exact test, chi square test, independent T-test, one-way ANOVA, Mann-Whitney, and Spearman's rank correlation.

**Results:** Out of 150 included patients, 2.67% experienced hyperglycemia following steroid therapy for SLE. There were no significant associations between clinical variables and hyperglycemia occurence in SLE patients ($p>0.05$). Patients that received higher doses of steroid did not experience any significant difference in hyperglycemia ($p=0.727$ for <6 months; $p=0.865$ for ≥6 months). Daily steroid dose was also not significantly associated with the severity of SLE manifestations based on the SLEDAI score ($p=0.081$). Overall, no significant association was identified between the duration of steroid therapy with hyperglycemia among SLE patients in the hospital ($p=0.365$).

**Conclusion:** The study found no significant correlation between clinical variables, hyperglycemia incidence, daily steroids dosage, methylprednisolone dosage, SLE severity, or steroid use duration in patients with Systemic Lupus Erythematosus.

**Keywords:** Systemic Lupus Erythematosus; steroid; hyperglycemia; autoimmune disease

**Correspondence:** Sony Wibisono Mudjanarko
E-mail: sony.wibisono@fk.unair.ac.id

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## INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a systemic autoimmune disease characterized by chronic inflammatory immune disruptions affecting various organs in the body (Andriani, 2021). Steroid therapy is one of the causes of hyperglycemia or new-onset diabetes mellitus, typically in SLE patients receiving high-dose steroid therapy. Steroids are potent immunosuppressants and anti-inflammatory agents (Aviana and Birawan, 2021). Prolonged use of steroids can lead to hyperglycemia (Hanim et al., 2018). Hyperglycemia is defined as an elevated blood glucose level leading to progressive insulin secretion decline, which can result in insulin resistance (Andriani, 2021). Population-based studies have indicated that more than 11,000 patients are at an increased risk of hyperglycemia in correlation with the daily increment in steroid dosage. The prevalence of hyperglycemia is notably high, reaching 56.8% (Sihombing and Vegas, 2016).

Risk factors for hyperglycemia can be categorized into two groups, environmental and genetic factors. Environmental factors include obesity, aging, dietary patterns, and physical activity. Women in Indonesia are a demographic at risk for hyperglycemia as they age. Basic Health Research data from 2018 indicated a prevalence of 1.78% in women and 1.21% in men, while the 2013 data showed rates of 1.7% in women and 1.4% in men. In the last five years, the prevalence of hyperglycemia in women has increased, whereas it has decreased in men (Bohari et al., 2021). The overarching objective of this study was to discern the correlation between the occurrence of hyperglycemia and the duration of steroid therapy in patients with SLE at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The research aimed to provide insights into the potential relationship between the length of steroid treatment and the prevalence of hyperglycemia among SLE patients, contributing valuable information to the understanding of healthcare outcomes in this specific context.

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## METHODS

### Study Design and Setting

This cross-sectional study was conducted from January 2022 to December 2022 in the Internal Medicine outpatient ward of Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. The statistical tests employed in this study were as follows, the association between various clinical variables and the occurrence of hyperglycemia, based on the duration of steroid treatment, was analyzed using the Chi-Square test; the association between daily steroid dosage and the incidence of hyperglycemia, considering the duration of steroid use in SLE patients, was assessed using the Mann-Whitney test; the association between daily methylprednisolone dosage and the severity of SLE was examined using the Spearman test; and the association between the occurrence of hyperglycemia and the duration of steroid use in SLE patients was investigated using the Chi-Square test.

### Study Participants

Electronic medical records documenting the demographic information, diabetic status, treatment and other related history were then retrieved from each eligible participant. The inclusion criteria for the study participants were outpatients diagnosed with SLE at the Department of Internal Medicine, Dr. Soetomo General Academic Hospital, during the period from January 2022 to December 2022; patients who are undergoing steroid therapy, including the duration of usage; and patients who have available blood glucose level data. The exclusion criteria for the study participants were patients who have experienced acute coronary syndrome and those with missing medical records data.

### Observation

Electronic medical records documenting SLE patients treated with corticosteroids ulcers were collected from the Technological, Communication, and Information Institute of Dr. Soetomo General Hospital, which were then screened based on the inclusion and exclusion criteria specified in the patient's medical records.

### Statistical Analysis

The data analysis process in this study was conducted using IBM Statistical Package for Social Sciences (SPSS) version 23 software. Statistical analysis was performed using Fisher's exact test, chi square test, independent T-test, one-way ANOVA, Mann-Whitney, and Spearman's rank correlation.

## RESULTS

Table 1 summarizes the overall clinical profile of SLE patients at Dr. Soetomo General Academic Hospital during the period from January 2022 to December 2022. In terms of gender, there were more female patients, accounting for 96.0% of the total. The median age of the patients was 37 years. The severity of SLE was categorized into five levels: none, mild, moderate, high, and very high. There were 78 patients (52.0%) with no SLE severity, 18 patients (12.0%) with mild SLE, 23 patients (15.3%) with moderate SLE, 26 patients (17.3%) with high SLE, and 5 patients (3.3%) with very high SLE severity.

Regarding steroid therapy, methylprednisolone was the most commonly used type of steroid medication, accounting for 99.3%. The most common daily dose of steroid therapy was 4

Table 1. Baseline clinical profile of the included study participants (N=30)

| Clinical Profile | n (%) |
|---|---|
| Sex | |
| Male | 6 (4.0%) |
| Female | 144 (96.0%) |
| Age, median (IQR) | 37 (17) |
| SLE Severity (SLEDAI) | |
| No SLE (0) | 78 (52.0%) |
| Mild (1-5) | 18 (12.0%) |
| Moderate (6-10) | 23 (15.3%) |
| Severe (11-19) | 26 (17.3%) |
| Very Severe (≥20) | 5 (3.3%) |
| Steroid Type | |
| Methylprednisolone | 149 (99.3%) |
| Prednisolone | 1 (0.7%) |
| Daily Steroid Dose, Mean | 4.88 |
| Methylprednisolone | |
| 2 mg | 5 (3.3%) |
| 4 mg | 123 (82.0%) |
| 8 mg | 19 (12.7%) |
| 16 mg | 1 (0.7%) |
| 48 mg | 1 (0.7%) |
| Prednisolone | |
| 15 mg | 1 (0.7%) |
| Diabetic History | |
| No History | 139 (92.7%) |
| Prediabetes | 1 (0.7%) |
| Diabetes | 10 (6.7%) |
| Diabetic Therapy | |
| None | 129 (86.0%) |
| Injection Antidiabetic | 16 (10.7%) |
| Oral antidiabetic | 5 (3.3%) |
| HDL | |
| No Data | 22 (14.7%) |
| Normal | 92 (61.3%) |
| Low | 36 (24.0%) |
| LDL | |
| No Data | 31 (20.7%) |
| Normal | 95 (63.3%) |
| High | 24 (16.0%) |
| Total Cholesterol | |
| No Data | 22 (14.7%) |
| Normal | 90 (60.0%) |
| High | 38 (25.3%) |
| Triglycerides | |
| No Data | 5 (3.3%) |
| Normal | 135 (90.0%) |
| High | 10 (6.7%) |
| Albumin | |
| No Data | 25 (16.7%) |
| Normal | 109 (72.7%) |
| High | 12 (8.0%) |
| Low | 4 (2.7%) |
| BUN | |
| No Data | 4 (2.7%) |
| Normal | 100 (66.7%) |
| High | 12 (8.0%) |
| Low | 34 (22.7%) |
| Creatinine | |
| No Data | 3 (2.0%) |
| Normal | 139 (92.7%) |
| Abnormal | 8 (5.3%) |
| SGOT | |
| No Data | 1 (0.7%) |
| Normal | 137 (91.3%) |
| Abnormal | 12 (8.0%) |
| SGPT | |
| No Data | 2 (1.3%) |
| Normal | 129 (86.0%) |
| Abnormal | 19 (12.7%) |
| Heart Rate | |
| No Data | 25 (16.7%) |
| Normal | 118 (78.7%) |
| Tachycardia | 7 (4.7%) |
| Body Mass Index | |
| No Data | 62 (41.3%) |
| Normal | 74 (49.3%) |
| Overweight | 8 (5.3%) |
| Underweight | 5 (3.3%) |
| Respiratory Rate | |
| No Data | 70 (46.7%) |
| Normal | 79 (52.7%) |
| Tachypnea | 1 (0.7%) |
| Blood Pressure | |
| No Data | 7 (4.7%) |
| Normal | 76 (50.7%) |
| Hypertension | 9 (6.0%) |
| Hypotension | 58 (38.7%) |

IQR: interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BUN: blood urea nitrogen; SGOT: serum glutamic oxaloacetic transferase; SGPT: serum glutamic pyruvic tranferase: SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

mg, with a percentage of 82.0% and a mean daily dose of 2.15. In terms of diabetes history, there were 10 patients (6.7%) with a history of diabetes, 1 patient (0.7%) with a history of prediabetes, and 139 patients (92.7%) with no available diabetes history data. Regarding diabetes therapy, 5 patients (3.3%) used oral antidiabetic medications, 16 patients (10.7%) used injectable antidiabetic medications, and 129 patients (86%) did not receive diabetes therapy.

In the lipid profile examination, which includes High-Density Lipoprotein (HDL), Low-Density Lipoprotein (LDL), total cholesterol, and triglycerides, each parameter yielded different results. For HDL, 92 patients (61.3%) had normal HDL levels, 36 patients (24%) had low HDL levels, and 22 patients (14.7%) had no available HDL data. Regarding LDL, 95 patients (63.3%) had normal LDL levels, 24 patients (16.0%) had high LDL levels, and 31 patients (20.7%) had no available LDL data. Concerning total cholesterol, 90 patients (60.0%) had normal total cholesterol levels, 38 patients (25.3%) had high total cholesterol levels, and 22 patients (14.7%) had no available total cholesterol data. For triglycerides, 135 patients (90%) had normal triglyceride levels, 10 patients (6.7%) had high triglyceride levels, and 5 patients (3.3%) had no available triglyceride data.

In the kidney function examination, consisting of Blood Urea Nitrogen (BUN) and creatinine levels, distinct results were observed. For BUN levels, 100 patients (66.7%) had normal BUN levels, 12 patients (8.0%) had high BUN levels, 34 patients (22.7%) had low BUN levels, and 4 patients (2.7%) had no available BUN data. Regarding creatinine levels, 139 patients (92.7%) had normal creatinine levels, 8 patients (5.3%) had abnormal creatinine levels, and 3 patients (2%) had no available creatinine data.

In the liver function assessment, which comprises albumin, Serum Glutamic Oxaloacetic Transaminase (SGOT), and Serum Glutamic Pyruvic Transaminase (SGPT) levels, different outcomes were observed. For albumin levels, 109 patients (72.7%) exhibited normal albumin levels, 12 patients (8.0%) had high albumin levels, 4 patients (2.7%) had low albumin levels, and 25 patients (16.7%) had no available albumin level data. Regarding SGOT levels, 137 patients (91.3%) had normal SGOT levels, 12 patients (8%) had abnormal SGOT levels, and 1 patient (0.7%) had no available SGOT data. For SGPT levels, 129 patients (86%) had normal SGPT levels, 19 patients (12.7%) had abnormal SGPT levels, and 2 patients (1.3%) had no available SGPT data.

In the variable of pulse rate, 118 patients (78.7%) exhibited a normal pulse rate, 25 patients (16.7%) lacked available data, and 7 patients (4.7%) showed signs of tachycardia. Regarding body mass index (BMI), 74 patients (49.3%) had a normal BMI, 62 patients (41.3%) lacked available data, 8 patients (5.3%) were classified as overweight, and 5 patients (3.3%) were categorized as underweight. For respiratory rate, 79 patients (52.7%) had a normal respiratory rate, 1 patient (0.7%) had tachypnea, and 70 patients (46.7%) lacked available data. In terms of blood pressure, 76 patients (50.7%) had normal blood pressure, 7 patients (4.7%) lacked available data, 9 patients (6%) had hypertension, and 58 patients (38.7%) had hypotension.

Table 2 presents the relationship between several clinical variables and the occurrence of hyperglycemia based on the consideration of the duration of steroid treatment in a bivariate analysis using the chi-square test. No significant relationship was found between clinical characteristic variables and the occurrence of hyperglycemia in SLE patients receiving steroid therapy.

Table 2. Association between Clinical Variables and Hyperglycemia

| Variable | Hyperglycemia (%) | Bivariate Analysis OR (95% CI) | p-value |
|---|---|---|---|
| Age (years), mean±SD | 38.25±12.89 | 0.879 (0.921-1.101) | 0.324 |
| HDL | | | |
| Normal | 4 (4.3%) | ref. | 0.998 |
| Low | 0 (0%) | 0 | |
| LDL | | | |
| Normal | 3 (3.2%) | ref. | 0.998 |
| High | 0 (0%) | 0 | |
| Total Cholesterols | | | |
| Normal | 4 (4.4%) | ref. | 0.998 |
| High | 0 (0%) | 0 | |
| Triglycerides | | | |
| Normal | 4 (3.0%) | ref. | 0.999 |
| High | 0 (0%) | 0 | |
| Albumin | | | |
| Normal | 4 (3.7%) | ref. | ref. |
| High | 0 (0%) | 0 | 0.999 |
| Low | 0 (0%) | 0 | 0.999 |
| BUN | | | |
| Normal | 2 (2.0%) | ref. | ref. |
| High | 0 (0%) | 0 | 0.999 |
| Low | 2 (5.9%) | 3.063 (0.414-22.63) | 0.273 |
| Creatinine | | | |
| Normal | 3 (2.2%) | ref. | ref. |
| Abnormal | 0 (0%) | 0 | 0.999 |
| SGOT | | | |
| Abnormal | 1 (8.3%) | 6.136 (0.515-73.12) | 0.151 |
| SGPT | | | |
| Normal | 2 (1.6%) | ref. | ref. |
| Abnormal | 1 (5.3%) | 3.528 (0.304-40.91) | 0.313 |
| SLEDAI, mean±SD | 5.25±4.11 | 1.018 (0.867-1.196) | 0.827 |

OR: odds ratio; CI: confidence interval; SD: Standard deviation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; BUN: blood urea nitrogen; SGOT: serum glutamic oxaloacetic transferase; SGPT: serum glutamic pyruvic tranferase: SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

Table 3 presents the relationship between daily steroid dosage and the occurrence of hyperglycemia based on the duration of steroid use in patients with SLE, utilizing the Mann-Whitney test. The analysis results revealed that there was no significant correlation between the daily steroid dosage and the severity of SLE (p=0.081).

Table 3. Association between Daily Steroid Dose with Hyperglycemia based on Duration

| Daily Steroid Dose | Hyperglycemia | | p-value |
|---|---|---|---|
| | No | Yes | |
| Duration of steroid use <6 months | | | |
| ≤4 mg | 3 (100%) | 0 (0%) | 0.727 |
| >4 mg | 73 (96.1%) | 3 (3.9%) | |
| Duration of steroid use ≥6 months | | | |
| ≤4 mg | 2 (100%) | 0 (0%) | 0.865 |
| >4 mg | 68 (98.6%) | 1 (1.4%) | |

Table 4. Association between Daily Steroid Dose with the Severity of Systemic Lupus Erythematosus (SLE)

| Daily Steroid Dose | Severity of SLE | | | | | p-value |
|---|---|---|---|---|---|---|
| | None | Mild | Moderate | Severe | Intense | |
| 2 mg | 4 (80.0%) | 0 (0%) | 0 (0%) | 1 (20%) | 0 (0%) | |
| 4 mg | 74 (60.2%) | 12 (9.8%) | 19 (15.4%) | 16 (13.0%) | 2 (1.6%) | |
| 8 mg | 9 (47.4%) | 4 (21.1%) | 3 (15.8%) | 2 (10.5%) | 1 (5.3%) | 0.081 |
| 16 mg | 0 (0%) | 0 (0%) | 0 (0%) | 1 (100%) | 0 (0%) | |
| 48 mg | 1 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | |

Table 4 presents the association between the daily dosage of methylprednisolone and the severity of SLE using the Spearman test. The analysis results indicated that there was no significant correlation between the daily steroid dosage and the severity of SLE (p=0.081).

Table 5 presents the correlation between the occurrence of hyperglycemia and the duration of steroid use in patients with SLE, utilizing the Chi-Square test. The analysis results indicated that no significant association was observed between the duration of steroid use in patients with SLE and the incidence of hyperglycemia (p=0.365).

Table 5. Association between Hyperglycemia and the Duration of Steroid Therapy

| Glucose Level | Duration of Steroid Treatment | | p-value |
|---|---|---|---|
| | <6 months | ≥6 months | |
| No Hyperglycemia | 76 (52.0%) | 70 (48.0%) | 0.365 |
| Hyperglycemia | 3 (75.0%) | 1 (25.0%) | |

## DISCUSSION

Our study found no significant association between clinical variable and hyperglycemia as there was no significant relationship between blood glucose levels and total cholesterol, HDL, LDL, and triglycerides. This is presumed to be attributed to a decline in lipoprotein lipase activity, leading to a reduction in blood lipid levels (Malau, 2014). Several factors can influence lipid metabolism, leading to varied conclusions. SLE patients with kidney disorders may exhibit elevated triglycerides and low HDL levels. Steroid therapy in SLE patients can also trigger dyslipidemia. Patients with diabetes mellitus, cardiovascular disease, liver conditions, thyroid disorders, and normal body mass index (BMI) can alter lipid profiles. Additionally, menopausal and pregnant patients may show increased total cholesterol and LDL levels (Zhou et al., 2020). In this study, the majority of patients demonstrated relatively good lipid profiles, as a significant proportion had inactive SLE, normal BMI, no history of diabetes, and normal kidney and liver function. A discovery indicates a relation between age and hyperglycemia, particularly among adults aged over 65 years. This association is linked to the aging process (Chia et al., 2018). The likely reason for the absence of hyperglycemia in the majority of patients was attributed to the median age of the subjects, which was 37 years. In kidney function, hyperglycemia is a risk factor that can lead to impaired kidney function and potentially result in kidney failure or even death (Yuliadi and Mochtar, 2014). This is due to hemodynamic changes, alterations in metabolism, and dysfunction within the kidneys (Saputra et al., 2023). The study conducted by Trilistyoati et al. in 2021 elucidates that patients with SLE exhibit elevated levels of BUN, high serum creatinine, and hipoalbuminemia in many cases. Patients with albumin levels >3.7g/dL have a more favorable prognosis (Trilistyoati et al., 2021). The likely reason for the non-significant findings in this study was speculated to be the normal kidney function observed in the majority of the patients. A considerable portion of the participants in this research did not experience hyperglycemia. In the liver function, a finding elucidates an elevation in the levels of the enzymes SGOT and SGPT in individuals with type 2 diabetes mellitus. In this study, 66.67% of the samples exhibited SGOT enzyme levels above the normal range, while 40% of the samples demonstrated SGPT enzyme levels exceeding normal values (Maulana and Kuswarini, 2022). Elevations in SGOT and SGPT can occur in patients consuming certain medications, a condition often referred to as drug-induced hepatitis. In lupus hepatitis patients, such elevations are typically minimal. Additionally, excessive oxidative stress on the liver, as seen in cases of obesity and exposure to chemicals, can contribute to increased SGOT and SGPT levels (Imran et al., 2021). The likelihood that the majority of patients in this study exhibited normal liver function was attributed to their predominantly normal BMI and the absence of a history of diabetes in the majority of cases. There was a significant association between SLE patients and the incidence of diabetes (p=0.0023). This correlation is attributed to the effects of steroid therapy, as indicated by Lin et al. (2022).

In this study, no correlation was identified between the daily steroid dosage and the severity of SLE. Steroid dosage is contingent upon the severity of the disease affecting organ systems and can vary significantly. In clinical trials, steroid dosages for induction and maintenance must be clinically limited and clearly stipulate the permissible duration of dosages. The minimal disease activity can be measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) with a score of ≤2 (European Medicines Agency, 2010). Findings reveal a significantly higher association between cumulative steroid dosage and Group I compared to Group II (p<0.01). Group I comprises SLE patients with major complications related to steroid therapy, such as bacterial pneumonia, urosepsis, myocardial infarction, ischemic stroke, hip fractures, diabetes mellitus, herpes zoster, and multiple bacterial peritonitis (Hernández, 1997). The non-significant results of this study are likely due to the relatively low cumulative dosage (4.88), with 52% of patients exhibiting minimal disease activity, and 92.7% having no history of diabetes.

In this study, no significant association was found between hyperglycemia and duration of steroid therapy. The mean daily dosage in this research was 4.88, categorized as a low dose according to the Indonesian Rheumatology Association (2019). Wardani (2023) found that several factors influenced the non-significant results, including BMI, previous history of diabetes, and cumulative dosage. Most patients in this study had a normal BMI (49.3%), the majority had no previous history of diabetes (92.7%), and the mean daily dosage was considered low. However, a previous research by Tamez-Pérez et al. (2015) suggests that prolonged steroid treatment is associated with hyperglycemia. The use of high-dose steroids can lead to hyperglycemia, with an incidence of 86% experiencing at least one episode of hyperglycemia, and the remaining 48% of the patients showing an average blood glucose level ≥ 140 mg/dL. In this study, no significant correlation was found between the daily steroid dosage and

the occurrence of hyperglycemia based on the duration of use, whether <6 months or ≥6 months. Cumulative dosage emerged as a factor that could elevate blood glucose levels. The non-significant findings are likely attributable to the predominantly low daily dosage administered to the patients, with a mean daily dosage of 4.88 (Wardani, 2023). Manson et al. (2009) study revealed that the impact of treatment duration may potentially be less influential compared to treatment dosage, thereby playing a role in treatment-related side effects. Research indicates that lower steroid dosages are equally effective as higher doses and are better tolerated. Additionally, a double-blind, randomized controlled trial involving 21 active SLE patients receiving three daily infusions of 100 or 1000 mg intravenous methylprednisolone found no difference in outcomes after three months, despite the doses falling within the high-dose steroid category. There is no definitive data supporting efficacy differences between once-daily and divided doses. However, once-daily dosing in the morning is preferable as it minimizes the likelihood of suppressing peak circadian adrenal cortisol production (Kasturi and Sammaritano, 2016). The classification of duration as <6 months and ≥6 months in this study was based on previous research guidelines by Manson et al. in 2009, covering both methylprednisolone and prednisone. In that study, both methylprednisolone and prednisone resulted in side effects such as peripheral muscle weakness, with greater muscle weakness positively correlating with the logarithm of the average daily dose (Manson et al., 2009).

In this study, it is essential to acknowledge several limitations. The incompleteness of available data in medical records introduces the possibility of variations in the measurement of SLE severity compared to the reported values. Additionally, unavailability of some variables' data raises the potential for overlooking relationships with specific confounding factors concerning the occurrence of hyperglycemia in patients with SLE who are using steroids.

## CONCLUSION

In patients with Systemic Lupus Erythematosus (SLE), we found no significant correlations between various clinical variables and the incidence of hyperglycemia; and there was no correlation between the daily dosage of steroids and the occurrence of hyperglycemia, between the daily dosage of methylprednisolone and the severity of SLE, and between the incidence of hyperglycemia and the duration of steroid use throughout the specified timeframe.

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## CONFLICT OF INTEREST

None.

## ETHICS CONSIDERATION

The research protocol has received approval and ethical clearance from the Research Ethics Committee of Dr. Soetomo General Academic Hospital with reference number 0552/KEPK/XII/2022, granted on December 27, 2022.

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## AUTHOR CONTRIBUTION

Conceptualization: FAW, SWM, MR, DA, PBD; Methodology: FAW, SWM, MR, DA, PBD; Formal analysis and investigation: FAW, SWM, MR, DA, PBD; Writing - original draft preparation: FAW, SWM, MR, DA, PBD; Writing - review and editing: FAW, SWM, MR, DA, PBD; Funding acquisition: FAW, SWM, MR, DA, PBD; Supervision: SWM, MR, DA.

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