Predictors of Infection in Children with Systemic Lupus Erythematosus: A Single Center Study in Indonesia

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Abstract
Patients with Systemic Lupus Erythematosus (SLE) are susceptible to infection due to defects in their immune system. Corticosteroids and immunosuppressant drugs used as SLE therapy also contribute to infection. This study aimed to determine predictors of infection in pediatric patients with SLE. This retrospective cohort study was conducted at Dr. Sardjito Hospital, a referral hospital in Yogyakarta, Indonesia between 2013 and 2019. Logistic regression analysis was performed to identify predictor variables for the occurrence of infection. A total of 109 SLE patients were included in this study. The incidence of infection in children with SLE was 27.5%. The most common types of infection in hospitalized SLE patients were urinary tract infections (41%), skin and soft tissue infections (20.5%), and pneumonia (20.5%). Multivariate regression analysis showed that the use of methylprednisolone pulse dose (RR 3.204; 95% CI 1.234-8.318) was a predictor of infection. Clinician should closely observe SLE patients with predictors for infection.

Keywords
infection, children, systemic lupus erythematosus, predictors

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Introduction
Systemic Lupus Erythematosus (SLE) can attack anyone, but 15% to 20% of all the SLE cases involve children and teenagers, especially girls between the ages of 12 to 16 years old.¹,² The number of SLE incidence in children is reported to be 0.3 to 0.9 per 100,000 with the prevalence of 3.3 to 24 per 100,000 children depending on the demographic area and ethnicity.² The exact number of SLE prevalence in Indonesia is still not known. Based on the registration data in the Pediatrics Allergy-Immunology Outpatient Clinic in Dr. Sardjito Hospital, the SLE prevalence in the year of 2015 was 10.6% and this number increased to 35.2% between January and September 2018.

Onset of childhood SLE occurrence showed that there is an involvement of higher major organs and a more severe disease activity, involving a worse prognosis, compared to the SLE which occurs in adult age patients, with a 5 year survival rate of 65%.³,⁴ Infection is a common cause of mortality and morbidity in SLE patients. As many as 36% of patients experience infection during the follow-up period, and it causes death in 30% within the first five years of follow-up. There are several previous studies related to factors which are associated with the occurrence of infection in SLE patients which were conducted in many other countries and the majority of those research used adult samples. The results showed that disease activity, age at onset of disease, the use of steroid, the use of cyclophosphamide, ds-DNA antibody, and the involvement of kidney, serositis, and hematologic disorders also contribute to the occurrence of the infection in SLE patients.⁵-⁸ But the majority of this research used adult samples and conducted in other countries. The results showed that disease activity was related to age at onset of disease, the

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use of steroids, the use of cyclophosphamide, ds-DNA antibody, and the involvement of the kidneys, serositis, and hematologic disorders. Meanwhile, other research conducted in 2001 using children samples concluded the opposite in which age, disease duration, disease activity, Systemic Lupus Erythematosus Disease Activity (SLEDAI) score, steroid therapy dosage at the time of infection or maximum steroid dosage, and white hematologic cell count were not correlated to the degree of infection severity.9

Currently there is very little research on the outcome of pediatric patients with SLE in Indonesia and studies that focus on infection predictor predictors in SLE child patients are still unavailable. This study aimed to identify the predictors of infection occurrence in pediatric patients with SLE so that the results can help clinicians in determining the best intervention and care for SLE child patients.

Methods

This study was an observational analytic study using a cohort retrospective design based on the 1997 American College of Rheumatology (ARC) criteria on children between the ages of 1 month old and 18 years old who have been diagnosed with SLE and who were hospitalized at Dr. Sardjito Hospital from January 1, 2013 to December 31, 2019. They should also have the follow-up of a minimum 6 months period of time since they were first diagnosed with SLE.

The data collected from the medical records of the patients include age, sex, the date of the diagnosis, SLEDAI score, nutrition status, and clinical variables which are related to SLE by the time of the diagnosis, including disease activity, disease severity, the organ involvement such as nephritis, hematologic, central nervous system, skin, joints, and serositis. The researchers also noted the types of therapy the patients received during the follow-up, including corticosteroids, cyclophosphamide, mycophenolate mofetil (MMF), cyclosporine, and chloroquine.

The events of first infection were recorded from since the SLE diagnosis was made. The infections which are referred to in this study are infections involving the organ systems, for example: respiratory tract infections, infections of the central nervous system, infections of the skin and soft tissues, infections of the musculoskeletal system, infections of the gastrointestinal system, infections of the genitourinary system, and sepsis or; infections which are caused by bacteria, viral infections of viruses, parasites, and fungi; which occurred the earliest after the SLE diagnosis was established, and caused the patient to be hospitalized, or an infection that was diagnosed during hospitalization. The diagnosis of infection was confirmed and approved by the supervisor of the immunology allergy clinic and/or supervisor of the infectious disease. The type, therapy, and outcome of all infections were recorded for each case. The following predictor variables associated with the occurrence of infection were recorded, namely, the onset of age at diagnosis, nutritional status, disease severity, disease activity, nephritis, hematological involvement, the use of MP pulse, and immunosuppressive drugs (cyclophosphamide and/or MMF).

Disease activity was assessed based on the SLEDAI score, an assessment system consisting of 24 items. Scores of 1 to 10 are classified as mild-moderate disease activity, while ≥11 are classified as severe. The disease severity of SLE is divided into mild SLE, moderate SLE, and severe SLE. SLE is mild, when it presents with skin manifestations and arthritis, and is not life-threatening. Moderate SLE is identified as SLE with mild to moderate nephritis (nephritic lupus class I and II), and thrombocytopenia (platelets 20,000-50,000/mm³). Severe SLE is identified as SLE with serosis disorders (pleuritis and pericarditis), hematologic disorders (AIHA), severe renal involvement (nephritic lupus class III and IV) and neurological disorders.10 Nutritional status was determined based on the Z score curve from the World Health Organization (WHO), using weight-for-height charts for children aged ≤5 years, and body mass index (BMI)-for-age charts for children aged >5 years. Subjects with malnutrition, stunting, obesity, and overweight belong to the malnourished category. Subjects who had received MP therapy with the dosage up to 30 mg/kg to a maximum dose of 1,000 mg/day for 1 to 3 days were grouped into MP pulse users. Subjects who had used cyclophosphamide and/or MMF were grouped into immunosuppressive users.

Data analysis was done using SPSS software version 20.0. Bivariate analysis was done to determine the relationship of each predictor variable with the infection incidence was done using the Chi-Square test or Fisher test. Predictor variables with a P-value <.25 were followed by multivariate analysis with reverse logistic regression method. The P value ≤.05 was considered statistically significant. The research protocol was approved by the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada reference number KE/FK/0224/EC/2020. The data obtained as the results of the study are confidential. The funding for the research was the responsibility of the researchers.
Results

Patients who were diagnosed with SLE during the period of January 1, 2013 until December 31, 2019 were 235 patients based on ICD code 10 M32.9 within our computer system and 109 patients met the research inclusion criteria. Among these, 30 patients experienced infection after the diagnosis of SLE was established. Figure 1 shows the subject recruitment flow.

The baseline characteristics of the study subjects are presented in Table 1. In both groups of infection and non-infection, most of the subjects were female, well-nourished, and their median age was 14 years old. At the onset of diagnosis, the majority of organ involvement in both groups were hematologic disorders (60% and 56.9%), kidney disorders (80% and 53.2%) with high disease activity. The majority of the patients in both groups received methylprednisolone (76.7% and 86.1%), cyclophosphamide (80% and 83.5%), and MMF (60% and 34.2%).

Of the 30 patients who had the occurrence of infections, the onset of infection occurred <6 months in 15 (50%) patients, and >1 year in 11 (36.7%) patients. Ten patients experienced more than 1 incidence of infection during follow-up. In addition, nine patients experienced more than one type of infection in one hospitalization period. The most common types of infection in hospitalized SLE patients were urinary tract infections (41%), skin and soft tissue infections (20.5%), and pneumonia (20.5%) (Table 2). One SLE patient died of a first-time infection which was caused by a cerebral abscess.

Microorganisms found in SLE patients who were infected were mostly bacteria and there was one case with fungal infection. There was no specimens of liquor cerebrospinal available (Table 3). Almost all (94%) cases were administered antibiotics and the most commonly used were cephalosporins (41.7%), penicillin (16.7%), and carbapenem (14.6%). The majority of patients (24 patients) used monotherapy with antibiotics, antivirals and antituberculosis regimens. Six patients used more than one type of antibiotics in 1 event of infection. During infection treatment, as many as nine patients underwent antibiotic changes adjusted to the results of microorganism specimens identified in growing cultures.

In bivariate analysis (Table 4), one significant predictor factor with $P$-value less than .05 was obtained, namely the use of MP pulse (RR 2.39; 95%CI 1.13-5.11). Predictors which had a $P$-value of <.25 were included in the multivariate analysis which consisted of disease severity, disease activity, nephritis, and MP pulse usage. In logistic regression analysis, the only variable associated significantly with infection was MP pulse usage (RR 2.39; 95%CI 1.13-5.11).

Discussion

As much as 25-50% of mortality of patients with SLE are caused by infection. In addition, in one study, 50% of

![Figure 1. Subject recruitment flow.](image-url)
the SLE patient experienced infection episodes during the history of their disease.\textsuperscript{11} From the research conducted by Listiyono et al in 2019 at Dr Sardjito Hospital, it was concluded that infection is the significant predictor of death of children with SLE.\textsuperscript{12} SLE patients are very susceptible to infection because there is a defect in their immune system, typically involving a decrease of lymphocyte T, a deficiency of complement, neutropenia, and lymphopenia. Additionally, corticosteroids and immunosuppressants which are used as SLE therapy also contribute to the occurrence of infection.\textsuperscript{12}

### Table 1. Subject Characteristics.

| Characteristics         | Infection (n = 30) | No infection (n = 79) |
|-------------------------|--------------------|----------------------|
| Sex, n (%)              |                    |                      |
| Female                  | 26 (86.7)          | 72 (91.1)            |
| Male                    | 4 (13.3)           | 7 (8.9)              |
| Median age at onset of disease (range) | 14 (4.1-17.1) | 147 (3.4-17.11) |
| Median SLEDAI score (range) | 16 (8-30)    | 14 (6-30)            |
| Nutritional Status, n (%) |                  |                      |
| Severely wasted         | 3 (10)             | 10 (12.7)            |
| Wasted                  | 3 (10)             | 9 (11.4)             |
| Normal                  | 24 (80)            | 59 (74.7)            |
| Overweight              | 0 (0)              | 1 (1.2)              |
| Disease severity, n (%) |                    |                      |
| Moderate-severe         | 27 (90)            | 58 (73.4)            |
| Mild                    | 3 (10)             | 21 (26.6)            |
| Organ involvement, n (%)|                    |                      |
| Hematology manifestation| 18 (60)            | 45 (56.9)            |
| Nephritis               | 24 (80)            | 42 (53.2)            |
| CNS Manifestation       | 6 (20)             | 16 (20.5)            |
| Serositis               | 15 (50)            | 33 (41.8)            |
| Infection at onset of disease, n (%) | | |
| Yes                     | 14 (46.7)          | 27 (34.2)            |
| No                      | 16 (53.3)          | 52 (65.8)            |
| Type of steroid, n (%)  |                    |                      |
| Prednisone              | 3 (10)             | 11 (13.9)            |
| Methylprednisolone      | 23 (76.7)          | 56 (86.1)            |
| Combination             | 4 (13.3)           | 5 (13.9)             |
| MP pulse, n (%)         |                    |                      |
| Yes                     | 23 (76.7)          | 40 (50.6)            |
| No                      | 7 (23.3)           | 39 (49.4)            |
| Median total steroid dose 1 month (mg) | 3224.92 | 2775.08 |
| Chloroquine, n (%)      |                    |                      |
| Yes                     | 18 (60)            | 45 (56.9)            |
| No                      | 5 (16.7)           | 9 (12.7)             |
| Immunosuppressive drugs, n (%) |             |                      |
| Cyclophosphamide        | 24 (80)            | 66 (83.5)            |
| Methotrexate            | 8 (26.7)           | 10 (12.7)            |
| MMF                     | 18 (60)            | 27 (34.2)            |
| Azathioprine            | 5 (16.7)           | 9 (12.7)             |
| Cyclosporine            | 4 (13.3)           | 5 (6.3)              |
| Outcome                 |                    |                      |
| Died                    | 6 (20)             | 2 (2.5)              |

### Table 2. Types of Infection.

| Types of infection       | N (%) |
|--------------------------|-------|
| Urinary tract infection  | 16 (41)|
| Soft tissue and skin infection | 8 (20.5) |
| Pneumonia                | 8 (20.5)|
| Sepsis                   | 3 (7.6)|
| Musculoskeletal infection| 1 (2.6)|
| Tuberculosis             | 1 (2.6)|
| Cerebral abscess         | 1 (2.6)|
| Dengue infection         | 1 (2.6)|
In this study, 27.5% of SLE patients had infections that required hospitalization. Previous research conducted by Al Mayouf et al in 2001 and Noel et al in 2001 showed the percentage of patients who had infections were 41% and 40%.\(^9\)\(^,\)\(^13\) The study identified 25% of the patients had an infection when diagnosed. It is associated with the presence of chemotaxis defects, functional asplenia, deficiency of complementary factors, abnormalities in the phagocytic activity of neutrophils and monocytes which then explain the high rate of infection before the use of immunosuppressive therapy.\(^7\)

The most common types of infection in this study were urinary tract infections (38%), pneumonia (19%) and skin and soft tissue infections (19%). This is in accordance with the research conducted by Khalifa et al. in 2007\(^7\) which had the same findings.\(^7\) *Escherichia coli* and *Kocuria kristinae* were the microorganisms that grew the most in urine culture in this study. In addition,

### Table 3. Microorganisms Isolated During Infection in SLE Patients.

| Specimen       | Microorganisms                                                                 |
|----------------|--------------------------------------------------------------------------------|
| Urine          | *Escherichia coli* (2), *Kocuria kristinae* (2), *Aspergillus* spp., *Enterococcus faecalis*, *Klebsiella pneumonia*, *Staphylococcus hominis*, *Staphylococcus haemolyticus*, Coagulase-negative Staphylococci |
| Pus            | *Streptococcus pyogenes*                                                       |
| Synovial fluid | *Vagococcus fluvialis*                                                         |
| Hematologic    | *Enterobacter aerogenes*, *Streptococcus epidermidis*                          |

### Table 4. Univariate and Multivariate Analyses of Predictors and Infections Among Children with SLE.

| Parameters                  | Infection n (%) | No Infection n (%) | Bivariate analysis | Multivariate analysis |
|-----------------------------|-----------------|--------------------|-------------------|-----------------------|
|                             |                 |                    | RR (95% CI)       | P value              | RR (95% CI)       | P value |
| Onset at diagnosis          |                 |                    |                   |                       |                   |         |
| Puberty                     | 26 (27.1)       | 70 (72.9)          | 0.88 (0.37-2.12)  | 0.750\(^\d\)         |
| Pre puberty                 | 4 (30.8)        | 9 (69.2)           |                   |                       |                   |         |
| Nutrition status            |                 |                    |                   |                       |                   |         |
| Malnutrition                | 6 (24)          | 19 (76)            | 0.84 (0.39-1.82)  | 0.653                 |
| Good nutrition              | 24 (28.6)       | 52 (71.4)          |                   |                       |                   |         |
| Disease severity            |                 |                    |                   |                       |                   |         |
| Moderate-severe             | 27 (31.8)       | 58 (68.2)          | 2.54 (0.84-7.66)  | 0.062\(^\d\)         |
| Mild                        | 3 (12.5)        | 21 (87.5)          |                   |                       | 1.58 (0.98-2.56)  | 0.538   |
| Disease activity            |                 |                    |                   |                       |                   |         |
| High activity               | 24 (31.6)       | 52 (68.4)          | 1.74 (0.78-3.85)  | 0.15                  |
| Mild-moderate activity      | 6 (18.2)        | 27 (81.8)          |                   |                       | 1.11 (0.96-1.26)  | 0.841   |
| Nephritis                   |                 |                    |                   |                       | 1.81 (0.98-3.35)  | 0.146   |
| Yes                         | 24 (33.3)       | 48 (66.7)          | 2.06 (0.92-4.58)  | 0.058                 |
| No                          | 6 (16.2)        | 31 (83.8)          |                   |                       | 1.81 (0.98-3.35)  | 0.146   |
| Hematology involvement      |                 |                    |                   |                       |                   |         |
| Yes                         | 19 (29.2)       | 46 (70.8)          | 1.17 (0.62-2.21)  | 0.628                 |
| No                          | 11 (25)         | 33 (75)            |                   |                       |                   |         |
| MP pulse                    |                 |                    |                   |                       |                   |         |
| Yes                         | 23 (36.5)       | 40 (63.5)          | 2.39 (1.13-5.11)  | 0.014                 |
| No                          | 7 (15.2)        | 39 (84.8)          |                   |                       | 2.39 (1.13-5.11)  | 0.017   |
| Immunosuppressive drugs     |                 |                    |                   |                       |                   |         |
| Yes                         | 28 (28)         | 72 (72)            | 1.26 (0.36-4.45)  | 1.000\(^\d\)         |
| No                          | 2 (22.2)        | 7 (77.8)           |                   |                       |                   |         |
| Chloroquine                 |                 |                    |                   |                       |                   |         |
| Yes                         | 18 (28.6)       | 45 (71.4)          | 1.09 (0.52-2.04)  | 0.774                 |
| No                          | 12 (26.1)       | 34 (73.9)          |                   |                       |                   |         |

\(^\d\) Fisher’s exact test.
there was 1 patient who was suffered from Aspergillus spp. identified in urine cultures. A similar thing was also found in the research conducted by Al-Mayouf et al. and Jung et al., which mentioned Escherichia coli as a pathogen found the most in urinary tract infections.

*Kocuria kristinae* is a gram-positive coccus bacterium that is a normal organism on the skin. Risk factors for infection by *Kocuria kristinae* are damages to the body’s defense mechanisms such as neutropenia, end-stage kidney disease, and the use of corticosteroids and immunosuppressive drugs. Herpes Zoster is the most common viral infection in SLE patients (14%-47%). In this study, 2 patients (5.1%) were reported to have Herpes Zoster. Similarly, Al-Mayouf et al. reported a 4.3% decrease in the percentage of Herpes Zoster infection in child SLE patients. Immunological studies on SLE showed abnormalities of T-cell mediated cytotoxicity and cellular immunity suppression were involved in the pathogenesis of viral reactivation in cases of Herpes Zoster.

Of the 30 patients who had the infections, 1 patient (4.2%) experienced Tuberculosis (TB) pleuritis infection based on the presence of a history of close contact with TB patients, clinical symptoms and increased ADA test result. The percentage of TB infection in SLE patients in endemic countries is approximately 5%. TB infection in SLE patients generally occurs in extrapulmonary places and may be associated with more severe pulmonary involvement. One of the immunological changes in SLE patients is damage to T cell activity (a decrease in cytotoxic T cells and suppressor T cell function), thus it can cause increased risk of infection due to intracellular pathogens such as *(Mycobacterium tuberculosis M. tuberculosis)*. Aside from that, the use of immunosuppressive drugs can reduce the number of B lymphocytes and T lymphocytes while the use of corticosteroids can inhibit the proliferation of T cells, cytotoxic T cells, and a specific immune response to antigens.

In this study, there were as many as 7.31% of extrapulmonary TB cases which were diagnosed at the same time with SLE diagnosis. This happened because *M. tuberculosis* can trigger autoimmune responses through cross-reactivity between self-antigen and the bacteria itself. The similarity between Heat Shock Protein (HSP) *M. tuberculosis* and HSP65 in humans is what triggers the autoimmune reactions in SLE patients.

The damage to various organs is described as the severity of SLE ranging from mild to severe and life-threatening. The majority of SLE patients in this study, whether infectious or non-infectious were categorized as moderate and severe SLE (90% and 73%), which corresponds to the majority of patients with kidney and hematologic disorders. In this study, the severity of SLE was not significantly related with the incidence of infection (*P* > .05). However, moderate-weight SLE patients clinically had increased risk of infection (RR > 2).

The SLE severity is associated with the severity of immune dysregulation including increased autoreactivity of T-helper cells, cytotoxic T cells, differentiation of B cells, polymorphonuclear leukocyte dysfunction, impaired production of interleukin (IL)-12 and IL-8 and deficiency of the complement system. The activity of SLE disease is a reversible clinical manifestation which is caused by the inflammatory processes underlying SLE disease. High disease activity is associated with complementary dysfunction. In this study, disease activity had no significant association with infection (*P* = .15). This finding is in line with a 2001 study in children that showed disease activity assessed with an SLEDAI score was not significantly related to the incidence of infection (*P* = .17). The opposite was found in another study which concluded that SLEDAI score > 12 when the patient was diagnosed with SLE was a risk factor for infection. This is possible due to the assessment of disease activity in this study which was only done at the beginning of diagnosis, whereas SLE patients can experience changes in disease activity into exacerbation or remission during the course of the disease.

Lupus nephritis is a manifestation of severe SLE disease that affects 35% to 60% of SLE patients. The characteristics of lupus nephritis are characterized by complex depositions of the immune system in the subendothelial and/or subepithelial glomerulus that cause extensive injury and nephron damage during the acute phase, even chronic and irreversible damage to kidney function if not adequately managed. A renal biopsy of lupus nephritis needs to be performed for classification of renal histopathological abnormalities and determine the appropriate therapy and prognosis. In this study, the basis of enforcement of the diagnosis of kidney disorders was only done clinically, due to limited resources to perform renal biopsies. This will affect the accuracy of the therapy given to the subject of this study, therefore, the therapy will be very different in different histopathological classes. Determination of lupus nephritis therapy at Dr. Sardjito Hospital is adapted to clinical and laboratory findings, such as increased hematologic pressure, creatinine levels, proteinuria, cellular cylinders, including erythrocyte cylinders, hemoglobin, granular, tubular or mixed, anti dsDNA levels and C3 C4 levels. In this study, nephritis was not statistically significantly related to the occurrence of infection (*P* = .146). This is not in line with some studies which they showed that nephritis is associated with the occurrence of infection in SLE patients. In this study’s bivariate analysis, the
results for RR > 2 even though \( P > .05 \), indicating that nephritis in SLE patients with nephritis was clinically related to the incidence of infection.

Immunosuppressive therapies including corticosteroids and cytotoxic drugs can control immunological defects and improve survival in patients with SLE, but they also increase the risk of developing serious infections.\(^9\) The results of multivariate analysis in this study showed SLE patients who received MP pulse had 2.39 times higher risk for infection than those who did not get MP pulse (\( P = .017, 95\% CI 1.19-4.82 \)). The use of very high dose steroids (100-300 mg/day) and/or MP pulse doses (300-1000 mg/day) can activate the nongenomic pathways that cause immunosuppression effects in addition to anti-inflammatory effects. MP pulse therapy is given to SLE patients with severe disease and life-threatening acute conditions such as widespread vasculitis, hemolytic anemia, lupus nephritis, and neuropsychiatric lupus.\(^10\) Based on the recommendations of the Rheumatology Society in Indonesia in 2011, MP pulse is also given to moderate-weight SLE patients. In this study, the majority of patients showed moderate-severe severity (78%) with nephritis (66%), hematologic disorders (60%) and high disease activity (69.7%) so most patients received MP pulse (58.6%).

Several studies showed the benefits of MP pulse in severe SLE patients, such as increased renal survival rate in lupus nephritis patients, improved conditions in SLE patients with central nervous system involvement, pulmonary hemorrhage, and severe thrombocytopenia.\(^20,21\) Until now MP pulse therapy has been the therapy of choice for severe and life-threatening acute conditions, although its administration increases the risk of infection in SLE patients. Accordingly, dose decision-making should take into account the level of activity of the patient’s disease at the time of initial diagnosis.

Research conducted in Singapore in 2002 concluded the use of MP pulse in lower doses, which was 500 g/day for 3 days, has a lower risk of infection but is equally effective in controlling disease activity compared to a dose of 1 g/day for 3 days (\( P < .04 \)).\(^22\) This finding can also be a consideration for administering MP pulse with lower doses to minimize the risk of infection.

In this study, the majority of SLE patients had kidney disorders (60%) and moderate-severe severity (78%), which corresponds to the use of cyclophosphamide (82.5%), as well as MMF (41.3%). In this study, the use of other immunosuppressives (cyclophosphamide and/or MMF) was not associated significantly with the incidence of infection (\( P = 1.00 \)). This may be because study subjects who had had cyclophosphamide and/or MMF therapy were included in this variable regardless of cumulative dose and length of use. Research conducted by Subedi et al. in 2015 concluded there is a significantly increased risk of bacterial infection after 47 days of MMF use. The same result was reported in relation to cyclophosphamide use, namely SLE patients who received cyclophosphamide with a cumulative dose of 9.3 g had more bacterial infections.\(^23,24\) This hydroxychloroquine can inhibit the growth of intracellular organisms by increasing the pH of the lysosome. In addition, it can inhibit 1 stage in viral replication and inhibit post-translation modification of the new proteins synthesized.\(^24\) This study, the use of hydroxychloroquine was not significantly related to the incidence of infection (\( P = .774 \)). This is thought to occur due to the protective effect of hydroxychloroquine on infections related to the short duration of use. Research conducted in Spain in 2017 concluded the use of hydroxychloroquine over 5 years increased the risk for infection.\(^8\)

In SLE, polymorphonuclear leukocyte dysfunction occurs which involves the body’s defense against infection. In SLE there is also hemolytic anemia, where the hemolysis process that occurs triggers the expression of Heme Oxigenase (HO)-1 which is used for heme solving. HO-1 will damage the oxidative neutrophil burst that plays a role in the destruction of bacteria in cells.\(^25\) In this study, hematologic disorders were not significantly associated with the occurrence of infection (\( P = .682 \)). Nutritional status correlates with the outcomes of SLE disease. Malnutrition is associated with increased susceptibility to infection, while excess nutrition is associated with an increase in pro-inflammatory cytokines that aggravates the activity level of SLE disease.\(^26,27\) In this study, malnutrition showed no significant association with the incidence of infection (\( P = .653 \)). This is likely due to the assessment of nutritional status which was performed only once at the beginning of diagnosis, whereas SLE patients can experience changes in nutritional status during the course of the disease related to side effects of immunosuppression drugs and disease comorbidities. In this study, the age at which patients were diagnosed was not found to have a meaningful relationship with the incidence of infection (\( P = .75 \)). Differences in presentation patterns during disease onset in children with SLE are influenced by genetic, immune, and hormonal factors as the parameters which cannot be controlled.

Some weaknesses of this study involve the collection of data retrospectively using data from medical records so that the accuracy of measurement data may be weak. This also includes the use of medical records which are not complete without researchers directly making confirming observations. In addition, there was an imbalance of the proportion of both groups in several
predictors, thus influencing the statistical analysis results of some predictor variables.

**Conclusion**

This study concluded that the use of MP pulse is a predictor of infection of SLE child patients. The severity of SLE and nephritis at the time of diagnosis were clinically related to the incidence of infection of the pediatric patients wia.

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**Author Contributions**

MKS: conceptualized the study, data collected, carried out the initial analyses and interpretation, drafted the initial manuscript, and revised the manuscript.

CDS and EA: conceptualized and designed the study, contributed to data analysis and interpretation, gave final approval, critically reviewed and revised the manuscript for important intellectual content.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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**References**

1. Akib A, Soepriadi M, Setiabudiawan B. Lupus Eritematosus Sistemik. In: Akib A, Munazir Z, Kurniati N, eds. Buku Ajar Allergi-Imunologi Anak. Balai Penerbit IDAI; 2010:1-152.

2. Harry O, Yasin S, Brunner H. Childhood-onset systemic lupus erythematosus: a review and update. J Pediatr. 2018;196:22-30.e2. doi:10.1016/j.jpeds.2018.01.045

3. Kamphuis S, Silverman ED. Prevalence and burden of pediatric-onset systemic lupus erythematosus. Nat Rev Rheumatol. 2010;6:538-546. doi:10.1038/nrrheum.2010.121

4. Farkhati MY, Hapsara S, Satria CD. Antibodi Anti DS-DNA Sebagai Faktor Prognosis Mortalitas pada Lupus Erimatosus Sistemik. Sari Pediatr. 2016;14:90.

5. Jeong SJ, Choi H, Lee HS, et al. Incidence and risk factors of infection in a single cohort of 110 adults with systemic lupus erythematosus. Scand J Infect Dis. 2009;41:268-274.

6. Jung J, Yoon D, Choi Y, Kim H, Suh C, Hui-yuen JS, et al. Major infections in children with systemic lupus erythematosus. Pediatr Rheumatol. 2012;10(S1):A20. doi:10.1186/1546-0096-10-S1-A20

7. Khalifa M, Kaabia N, Bahri F, Ben Jazia E, Bouajina E, Omezzine Letaief A. Infection in systemic lupus erythematosus. Med Mal Infect. 2007;37(12):792-795.

8. Rúa-Figueroa I, López-Longo J, Galindo-Izquierdo M, et al. Incidence, associated factors and clinical impact of severe infections in a large, multicentric cohort of patients with systemic lupus erythematosus. Semin Arthritis Rheum. 2017;47:38-45.

9. Al-Mayouf SM, Al-Jumaah S, Bahabri S, Al-Eid W. Infections associated with juvenile systemic lupus erythematosus. Clin Exp Rheumatol. 2001;19:748-750.

10. Kasimir Y, Handono K, Wijaya L, et al. Rekomendasi Perhimpunan Reumatologi Indonesia Untuk Diagnosis dan Pengelolaan Lupus Eritematosus Sistemik. Perhimpunan Reumatologi Indonesia; 2011.

11. Balbi GGM, MacHado-Ribeiro F, Marques CDL, Signorellia F, Levy RA. The interplay between tuberculosis and systemic lupus erythematosus. Curr Opin Rheumatol. 2018;30:395-402.

12. Listiyyono F, Sumadiono, Dewi Satria C, Murni IK. Predictors of mortality in children with systemic lupus erythematosus. Paediatr Indon. 2019;59:1-6.

13. Noël V, Lortholary O, Cassassus P, et al. Risk factors and prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Ann Rheum Dis. 2001;60:1141-1144.

14. Jung JY, Yoon D, Choi Y, Kim HA, Suh CH. Associated clinical factors for serious infections in patients with systemic lupus erythematosus. Sci Rep. 2019;9:1-8. doi:10.1038/s41598-019-46039-5

15. Chen HM, Chi H, Chiu NC, Huang FY. Kocuria kristinae: a true pathogen in pediatric patients. J Microbiol Immunol Infect. 2015;48:80-84. doi:10.1016/j.jmii.2013.07.001

16. Borba EF, Ribeiro ACM, Martin P, Costa LP, Guedes LKN, Bonfà E. Incidence, risk factors, and outcome of herpes zoster in systemic lupus erythematosus. J Clin Rheumatol. 2010;16:119-122.

17. Barber C, Gold WL, Fortin PR. Infections in the lupus patient: perspectives on prevention. Curr Opin Rheumatol. 2011;23:358-365.

18. Dahlan S. Statistik untuk kedokteran dan kesehatan. 6th ed. Epidemiologi Indonesia; 2015:40-42.

19. Parodis I, Tamirou F, Houssiau FA. Prediction of prognostic influence of infection in a single cohort of 87 adults with systemic lupus erythematosus. Arthritis Rheumatol. 2018;7:e000389.

20. Badsha H, Edwards CJ. Infections associated with juvenile systemic lupus erythematosus. Semin Arthritis Rheum. 2017;47:38-45.

21. Parker BJ, Bruce IN. High dose methylprednisolone therapy for the treatment of severe systemic lupus erythematosus. Lupus. 2009;16:387-393.

22. Badsha H, Kong KO, Lian TY, Chan SP, Edwards CJ, Chng HH. Low-dose pulse methylprednisolone for
systemic lupus erythematosus flares is efficacious and has a decreased risk of infectious complications. *Lupus.* 2002; 11:508-513.

23. Subedi A, Magder LS, Petri M. Effect of mycophenolate mofetil on the white hematologic cell count and the frequency of infection in systemic lupus erythematosus. *Rheumatol Int.* 2015;35:1687-1692.

24. Danza A, Ruiz-Irastorza G. Infection risk in systemic lupus erythematosus patients: susceptibility factors and preventive strategies. *Lupus.* 2013;22:1286-1294.

25. Stojan G, Petri M. The risk benefit ratio of glucocorticoids in SLE: have things changed over the past 40 years? *Curr Treatm Opt Rheumatol.* 2017;3:164-172.

26. Borges MC, dos Santos FMM, Telles RW, Lanna CC, Correia MI. Nutritional status and food intake in patients with systemic lupus erythematosus. *Nutrition.* 2012;28:1098-1103. doi:10.1016/j.nut.2012.01.015

27. Rytter MJH, Kolte L, Briand A, Friis H, Christensen VB. The immune system in children with malnutrition - a systematic review. *PLoS One.* 2014;9:e105017.