



Factors Related to Infection in Systemic Lupus Erythematosus Patients Admitted to the Hospital

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ABSTRACT

Background: One of the causes of the increase in hospitalized SLE patients is infection, and it is an important factor in morbidity and mortality, so it is necessary to conduct a research to identify factors related to infection and the type of infection caused in hospitalized SLE patients. **Methods:** This study is a retrospective, categorical descriptive study utilizing medical records of SLE patients diagnosed with and treated for infection both on admission and during their stay in Hasan Sadikin General Hospital between January 2016 to June 2018. **Results:** Seventy-four patients were involved into this study. Female were 70 (94.6%), aged <40 years were 69 (93.2%) patients, and all 74 (100%) were entirely in an active disease condition with a mean Mexican systemic lupus erythematosus disease activity (MxSLEDAI) score of 9 ± 5.2 . Fifty-three (71.6%) subjects experienced major infections. Mucocutaneous and kidney were the most organs involvement found in SLE patients during infection, 63 (85.1%) and 57 (77.0%) respectively. Sixty-two (83.7%) subjects had received corticosteroids before the onset of infection, while pneumonia was the most common infection found in 33 patients (44.6%). This study also noted 12 (16.2%) patients deceased related to infection with most causes were respiratory failure (66.7%). **Conclusion:** Age less than 40-year-old, mucocutaneous and kidney involvement and previously on corticosteroids were found higher among in hospitalized SLE patients. Most experienced major infections and pneumonia is the most common type of infection.

1. Introduction

There is a tendency for an increase in the prevalence of systemic lupus erythematosus (SLE) in Asia. The prevalence of SLE in Shanghai was 70/100.000 residents, while in India, Japan, and Saudi Arabia was reported from 3.2 to 19.3/100.000 population.¹ Along with the increasing prevalence of SLE patients, there was also an increase in the number of complications and mortality in SLE patients, when compared to the general population, the mortality rate in SLE patients are 5 times higher.² Among 813 SLE patients registered in Hasan Sadikin Lupus Registry (HSLR) in 2018, there were 66 deaths

with 38% of them due to infection.³ Infections were documented around 25% - 50% as causes of mortality in SLE patients.⁶

Some SLE patients developed major infections and more than 20% had to undergo treatment.^{4,5} There have been numerous studies correlating infections and SLE, including the effects of infection as a trigger in the occurrence of SLE and conversely SLE and its medications rendering someone susceptible to infection.⁶ Various factors cause susceptibility to infection in SLE patients, including genetic factors that generate dysregulation in the immune system, an increase in disease activity, and organ

manifestations.^{7,8} Other factors include demography, age, and gender also influence the incidence of infection in SLE patients. The modality of therapy that is administered is also an affecting factor for infection in SLE patients. Corticosteroids used are significantly related to the incidence of infection.⁹ Other therapies like azathioprine may also influence the incidence of infection in SLE patients.^{9,10} However hydroxychloroquine was reported might prevent infection in SLE patients.^{7,9,11} This study aims to obtain data and discover factors related to infection in hospitalized SLE patients.

2. Methods

This is a descriptive categorical study, utilizing secondary data from medical records of SLE inpatients in Hasan Sadikin General Hospital from January 2016 to June 2018. Ages 18 and older, diagnosed with SLE based on American College of Rheumatology (ACR) 1997 or the Systemic Lupus International Collaborating Clinics (SLICC) 2012 criteria, had been admitted to hospital and diagnosed with infection whether on admission or during a hospital stay are the inclusion criteria, while SLE patients with overlap (lupus and other connective tissue diseases, like

rheumatoid arthritis or scleroderma) and inpatient subjects that are admitted only for cyclophosphamide therapy have been excluded.

Major infections are defined as those that are disseminated (septicemia), affecting deep organs, requiring hospital admission for treatment (severe soft tissue infection, disseminated herpes zoster), or causing death.⁹

The categorical variables were presented in the form of a number (n) and percentage (%), while the numerical variables were presented as mean for normally distributed data, and median for abnormally distributed data. Categorical variables were described as frequency (%) and compared using Chi-squared or Fisher exact tests, while the numerical variables were performed using t-test or Mann Whitney. Data were analyzed by SPSS software.

This study had been approved Research Ethics Committee of Hasan Sadikin Hospital (LB.02.01/X.2.2.1/781/2019). The number of SLE patients who were admitted during the study period was 243 patients. As many as 169 subjects were excluded, and 74 subjects fell under the inclusion criteria and were analyzed (Figure 1).

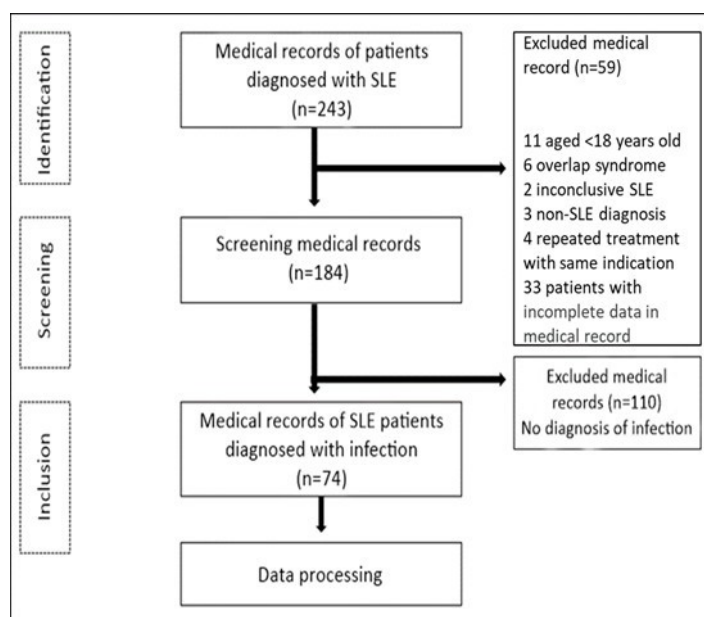


Figure 1. Study results chart

3. Results

Fifty-three (71.6%) subjects experienced major infections and 21 (28.4%) subjects had non-major infections. The age of the subjects of this study was from 18 to 57 years with a median of 25 years, 69 subjects (93.2%) were <40 years, 49 of them had

major infections. On the other hand, only 5 (6.8%) subjects were ≥ 40 years, most of them with major infections. The majority of the subjects were female 70 (94.6%) (Table 1).

Table 1. Basic characteristics of SLE hospitalized patients

Characteristics	Total n=74	Major infection n=53	Non-Major infection n=21	p
Age (years)				
Median (Min – Max)	25 (18 – 57)	24 (18-57)	25 (18-40)	0.618 ^b
< 40 years, n (%)	69 (93.2)	49 (92.5)	20 (95.2)	1.000 ^d
≥ 40 years, n (%)	5 (6.8)	4 (7.5)	1 (4.8)	
Gender, n (%)				
Male	4 (5.4)	4 (7.5)	0 (0.0)	0.572 ^d
Female	70 (94.6)	49 (92.5)	21 (100.0)	
SLE diagnosis, n (%)				
Previously known	56 (75.7)	39 (73.6)	17 (81.0)	0.505 ^c
Newly diagnosed	18 (24.3)	16 (26.4)	4 (19.0)	
Reason of admission, n (%)				
Infection	52 (70.2)	38 (71.7)	14 (66.7)	0.170 ^c
Flare	4 (5.4)	1 (1.9)	3 (14.3)	
SLE Diagnosis	7 (9.5)	6 (11.3)	1 (4.8)	
SLE Diagnosis + Infection	11 (14.9)	8 (15.1)	3 (14.3)	
Diagnosis of Infection, n (%)				
On admission	62 (83.8)	45 (84.9)	17 (81.0)	0.731 ^d
During hospital stay	12 (16.2)	8 (15.1)	4 (19.0)	
Infection day number	5 ± 3.9	5.4 ± 4.3	4 ± 1.8	
Length of stay (days)				
Median (Min-Max)	8 (2 – 45)	10 (2 – 45)	5 (3 – 20)	0.004^{b*}
Outcome. n (%)				
Discharged with improvement	59 (79.7)	39 (73.6)	20 (95.2)	0.108 ^c
Patient self-requested discharge	3 (4.1)	3 (5.7)	0 (0.0)	
Deceased	12 (16.2)	11 (20.8)	1 (4.8)	
Respiratory failure	8 (66.7)	8 (72.7)	0 (0)	
Shock	3 (25.0)	3 (7.3)	0 (0)	
Intracerebral hemorrhage	1 (8.3)	0 (0)	1 (100)	

Note: Analyzed using ^at-test, ^bMann Whitney, ^cChi Square, ^dFisher Exact

Subjects with the reason for admission due to infection were 52 (70.2%). There were 11 (14.9%) subjects admitted due to SLE diagnosis along with infection and 8 of them had major infections. The shortest length of stay was 2 days and the longest was

45 days, on a median the length of treatment was significantly longer for major infections (p 0.004). Fifty-nine (79.7%) subjects had discharged with improvement however, 12 (16.2%) subjects were decreased (Table 1).

Table 2. Types of Infection on hospital admission

Types of Infection	n = 62
Acute Bronchitis	4 (6.4)
Acute Inflammatory Diarrhea	4 (6.4)
Amoebiasis	1 (1.6)
Blepharoconjunctivitis	1 (1.6)
Cellulitis	3 (4.8)
Central line associated blood stream infection (CLABSI)	1 (1.6)
Chronic suppurated otitis media (CSOM)	1 (1.6)
Febrile Neutropenia	2 (3.2)
Herpes Zoster	1 (1.6)
Multiple Abscess	1 (1.6)
Oral candidiasis + Submandibular abscess	1 (1.6)
Otitis Externa	1 (1.6)
Pneumonia	27 (43.5)
Pulmonary abscess	1 (1.6)
Pulmonary aspergillosis + Pneumonia	1 (1.6)
Pulmonary TB	4 (6.4)
Septic Decubitus Ulcers	1 (1.6)
Septic Pneumonia	3 (4.8)
TB Meningitis + Miliary TB	1 (1.6)
Urosepsis	1 (1.6)
Urinary tract infection (UTI)	1 (1.6)
UTI + Bronchitis	1 (1.6)
Major infection	44 (71.0)
Non-major infection	18 (29.0)

Table 2 showed types of infections on admission, while table 3 showed the type of infection during hospital stay. Pneumonia was the most common type

of infection 27 (43.5%) and 6 (50%) subjects, on admission and during hospital stay, respectively.

Table 3. Types of infection during hospital stay

Types of Infection	n = 12
Acute Inflammatory Diarrhea	1 (8.3)
Catheter-associated urinary tract infection (CAUTI)	1 (8.3)
Pneumonia	6 (50.0)
Septic Pneumonia	1 (8.3)
Urosepsis	1 (8.3)
UTI	2 (16.6)
Major infection	8 (66.7)
Non-major infection	4 (33.3)

There were 70 (94.6%) subjects with anemia, with the mean hemoglobin was $6,9 \pm 2,6$ g/dl. Leukopenia was experienced by 17 (23.0%), and 22 (29.7%) had thrombocytopenia. Thirty-eight (51.4%) subjects had

neutrophil/lymphocyte count ratio (NLCR) ≥ 10 . Erythrocyte sedimentation rate (ESR) was only found in 7 (9.5%) and C Reactive Protein (CRP) in 5 (6.8%) subjects. They could not be analyzed.

Table 4. Laboratory results at the time of infection diagnosed

Lab Parameters	N=74	Major infection N=53	Non-major infection N=21	p
Hemoglobin (g/dL)				
Mean ± SD	6.9 ± 2.6	7.0 ± 3.0	7.8 ± 2.0	0.657 ^a
Hemoglobin, n (%)				
Normal	4 (5.4)	1 (1.9)	3 (14.3)	0.066 ^d
Anemia (M<14, F <12.3)	70 (94.6)	52 (98.1)	18 (85.7)	
Hematocrit (%)				
Median (Min-Max)	25 (4 – 57.4)	26 (4-50.1)	24 (17 – 57.4)	0.801 ^b
Leukocyte (/UL)				
Median (Min-Max)	9600 (400 – 34,300)	700 (400 – 34,300)	9600 (1600 – 27,900)	0.715 ^b
Leukocyte				
Leukopenia (<4500/UL)	17 (23.0)	11 (20.8)	6 (28.6)	0.770 ^c
Normal	30 (40.5)	22 (41.5)	8 (38.1)	
Leukocytosis (>11000/UL)	27 (36.5)	20 (37.7)	7 (33.3)	
Platelet (/UL)				
Mean ± SD	210,068 ± 116,545	196,038 ± 115,379	245,476 ± 114,576	0.100 ^a
Platelet				
Thrombocytopenia (<150,000/UL)	22 (29.7)	19 (35.8)	3 (14.3)	0.139 ^c
Normal	51 (68.9)	33 (62.3)	18 (85.7)	
Thrombocytosis (>450,000/UL)	1 (1.4)	1 (1.9)	0 (0)	
NLCR				
>10	38 (51.4)	28 (52.8)	10 (47.6)	0.686 ^c
<10	36 (48.6)	25 (47.2)	11 (52.4)	

Note: Analyzed using ^at-test, ^bMann Whitney, ^cChi Square, ^dFisher Exact, M male, F female

Table 5 showed that all subjects were found in active lupus condition (Mex-SLEDAI score > 2), with a mean of 9 ± 5.2. The most common organ activity was mucocutaneous 55 (74.3%), hemolysis /thrombocytopenia 44 (59.4%), kidney disorders 36 (48.6%), and neurologic disorders 17 (22.9%). The

highest involved organ was mucocutaneous 63 (85.1%), followed by kidney 57 (77.0%), hematologic 52 (70.2%), musculoskeletal 35 (47.3%), and neuropsychiatric in 20 (27.0%) subjects. There was no difference in organ manifestation in major or non-major infections.

Table 5. SLE Condition during infection

Variable	Total n=74	Major infection n=53	Non-major infection n=21	P
Lupus Activity (Mex-SLEDAI)				
Score, Mean \pm SD	9 \pm 5.2	9.7 \pm 5.1	7.3 \pm 5.3	-
Active	74 (100.0)	53 (100)	21 (100)	-
Type of Lupus Activity				
Neurologic Disorder	17 (22.9)	13 (24.5)	4 (19.0)	0.763 ^d
Kidney Disorder	36 (48.6)	29 (54.7)	7 (33.3)	0.097 ^c
Vasculitis	4 (5.4)	2 (3.8)	2 (9.5)	0.318 ^d
Hemolysis/ Thrombocytopenia	44 (59.4)	33 (62.2)	11 (52.4)	0.435 ^c
Leukopenia/Lymphopenia	14 (18.9)	9 (16.9)	5 (23.8)	0.522 ^d
Mucocutaneous	55 (74.3)	41 (77.5)	14 (66.6)	0.343 ^d
Myositis	1(1.3)	1 (1.9)	0 (0)	1.000 ^d
Arthritis	3 (4.0)	3 (5.7)	0 (0)	0.554 ^d
Serositis	14 (18.9)	12 (2.3)	2 (9.5)	0.324 ^d
Fever/Fatigue	7 (9.4)	5 (9.4)	2 (9.5)	1.000 ^d
Organ Involvement				
Neuro-Psychiatric	20 (27.0)	15 (28.3)	5 (23.8)	0.695 ^c
Hematologic	52 (70.2)	36 (67.9)	16 (76.1)	0.483 ^c
Kidneys	57 (77.0)	44 (83.0)	13 (61.9)	0.068 ^d
Mucocutaneous	63 (85.1)	46 (86.8)	17 (80.9)	0.495 ^d
Musculoskeletal	35 (47.3)	25 (47.1)	10 (47.6)	0.972 ^c
Cardio	7 (9.4)	5 (9.4)	2 (9.5)	1.000 ^d
Pulmonary	16 (21.6)	12 (22.6)	4 (19.0)	1.000 ^d

Note: Analyzed using ^at-test, ^bMann Whitney, ^cChi Square, ^dFisher Exact

Table 6. Medication received by SLE patients at the time infection occurs

Types of Therapy	N = 74	Major infection N=53	Non-major infection N=21
Corticosteroids (equivalent prednisolone) \geq 5mg/day, n (%)	62 (83.7)	44 (83.0)	18 (85.7)
Previously not administered corticosteroids	12 (16.2)	9 (16.9)	3 (14.2)
Cyclophosphamides n (%)	7 (9.4)	5 (9.4)	2 (9.5)
Median Dosage (mg) (Min - Max)	500 (500 - 1200)	500 (500 - 1200)	850 (500 - 1200)
Azathioprine n (%)	11 (14.9)	5 (9.4)	6 (28.5)
Median Dosage (mg), (Min - Max)	50 (50 - 150)	50 (50 - 150)	50 (50 - 150)
Chloroquine	3 (4.2)	1(1.9)	2 (9.5)
Median Dosage (mg), (Min - Max)	150 (150 - 250)	150 (150 - 250)	200 (150 - 250)

Sixty-two (83.7%) subjects received corticosteroid equivalent to prednisolone more than 5 mg/day. Seven (9.4%) subjects had received cyclophosphamides with a median dosage of 500 (500–1200) mg, 5 of them had major infections.

4. Discussion

This study found that the incidence of infection was more common in those aged below 40 years old and was mostly suffering from major infections. In the fourth decade of life, especially in women, there is a decrease of dehydroepiandrosterone (DHEA) and testosterone, followed with a decrease of total lymphocytes mainly B cells and CD4, decreasing immune response to infection, on the other hand, men experience this decrease in testosterone later, in the eight decades.¹² However we found most of SLE patients in younger age.

Fish et al., revealed that women carry 2 X chromosomes which express several genes involved in the body's defense mechanism, including Toll-like receptors, multiple cytokine receptors, genes involved in the activation of B cells and T cells, and transcription and translation of regulatory factors, making women more susceptible to numerous and more severe autoimmune attacks and its correlation with infection is due to excess immune response and anatomical differences with men.¹³ This study showed that the incidence of infection was more common in females, however, most of the lupus patients were female, so it is hard to conclude the infection more involved female patients.

The shortest length of stay was 2 days and the longest 45 days, with a median of 8 days. This reasonably large time span might have happened due to several factors, including the severity of infection, difficulty in diagnosis, and the severity of the involved organ manifestations. Subjects with major infections had a longer average length of stay, 10 days compared to those with non-major infections, this concurs with findings of June Lee et al.¹⁴, in their research in Canada where the average length of treatment for lupus patients with infection was 8,5 days, as did

Christine Anastasiou et al, found the mean length of treatment for SLE patients were 7,6 days.¹⁵

This study noticed 16,3% deceased cases, the most abundant cause respectively being respiratory failure. This conforms to previous studies conducted by Ruiz Irastorza et al, which stated that respiratory failure in SLE patients with pneumonia was the most common cause of death followed by septic shock.⁹

Goldblatt et al also revealed that pneumonia whether with or without sepsis is the most common cause of death in SLE patients treated with infection.⁷ Pneumonia was the most common type of infection both on admission and during hospitalization. When added, these numbers are higher than those in previous studies conducted by Ruiz Irastorza et al, 41% from 82 subjects.⁹ Another study mentioned genetics in SLE patients correlates with the incidence of pneumonia, Hispanics had a higher risk of pneumonia compared to Asians and SLE patients carrying TNF-specific genes are susceptible to pneumonia.¹⁶ Other factors causing susceptibility in SLE patients in the study were administration of corticosteroids, confirming the characteristics of subjects in this study with the majority receiving corticosteroids.

Most subjects were found with anemia at the start of their treatment with an average Hb of 6.9 ± 2.6 g/dl, whether due to inflammatory processes, hemolysis, iron deficiency, due to therapy, or hemorrhage. Giannouli et al revealed that more than 50 % of SLE patients suffered from anemia with various causes including chronic disease anemia, hemorrhage, nutrient deficiency, immune-related (hemolysis), uremia, therapy-related, and infection process.¹⁷ More than a third of the subjects had normal leukocyte levels, the rest had leukocytosis and leukopenia. Fozya Bashal, in his article, stated that leukopenia is a typical finding in SLE, with neutropenia (47%) or lymphopenia (20 – 81%), and may show disease activity, decrease in complement proteins CD55 and CD59 causing susceptibility to lysis of complements and increased production of type 1 IFN that implicates pathogenesis of neutropenia and lymphopenia in SLE

patients, other factors causing leukopenia is the use of immunosuppressants such as azathioprine and cyclophosphamide.¹⁸ Leukopenia can also happen in infection processes through a mechanism of bone marrow suppression in sepsis and is a poor prognostic factor, on the other hand, leukocytosis, mainly granulocytosis, may happen in SLE patients relating to the use of high-dose corticosteroids, flares, or left-shift infections.¹⁸ Seigel TA et al stated that 52% of 289 patients with bacteremia presented with normal leukocyte levels and 17% of them had no signs of fever,¹⁹ therefore, it can be concluded that leukocyte levels cannot definitely differentiate an infection in SLE patients, clinical evaluation and other examinations are still necessary. There were 22 (29.7%) subjects with thrombocytopenia. Thrombocytes play a role in the body's defense against infection, in some viral and bacterial infections megakaryopoiesis may be inhibited, causing thrombocytopenia.¹⁸ Thrombocytopenia also makes up 7-30% of hematologic disorder manifestations that may present in SLE patients through an increase in destruction and antibody towards thrombocytes.¹⁸

All the subjects were found in active condition based on a mean Mex-SLEDAI score of 9 + 5.2 points. These scores were recorded during the diagnosis of infection, 4 subjects were admitted with flare indications, 2 of them had an increase in the score when diagnosed with the infection. This corresponds with a study conducted by Duffy KN et al which states that infections are significantly related to disease activity on admission.²⁰ Disease activity also shows the activity of immune dysregulation, making it a risk factor for infection in SLE patients, as was stated in previous studies.^{5,7,8,20} In major infections the average Mex-SLEDAI score was 9.7 + 5.1, slightly higher compared to those in non-major infections, 7.3 + 5.3.

Kidney manifestations are proven to be related to the risk of infection.^{5,8,11} Other studies found that pulmonary involvement is the main predictor of the incidence of major infections in SLE patients.⁹ This study found that the kidney and mucocutaneous were the most involved organ in SLE patients with infection.

A study of SLE Patients in Hasan Sadikin General Hospital revealed that most organ involvements were musculoskeletally followed by mucocutaneous, hematologic, and kidneys.²¹ While in Asian SLE patients more commonly manifests in the kidneys 26-74%, skin, and musculoskeletal 45-98%, and neuropsychiatric 6-27%.²²

Most subjects 62 (83.7%) received corticosteroid therapy equivalent to prednisone >5 mg/day with a length of administration with a median of 30 (2 – 60) days before the onset of infection. Previous studies stated that the use of corticosteroids is related to gram-negative bacterial infection in the respiratory and urinary tract.²³ A retrospective study was done on 2,717 SLE patients, compared a population of corticosteroid users (n=989) and those who do not use corticosteroids (n=1728), showed that prednisone users are more susceptible to pneumonia, herpes zoster, and fungal infections.²⁴ Continuous use of corticosteroids, no matter the dosage, duration, and route of administration, still increases the risk of infection.²⁵

This study analyzed secondary data with quite a long time span of 2 years, but despite that, it still has limitations, including data of non-infection hospitalized SLE patients for comparison. Other limitations are the lack of autopsy data to define the cause of death of the subject since none of the deceased patients underwent an autopsy.

5. Conclusion

Age less than 40-year-old, mucocutaneous and kidney involvement, and previously on corticosteroids were found higher among in hospitalized SLE patients. Most experienced major infections and pneumonia is the most common type of infection.

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