



## Risk Factors for Skin Infection in Patients with Systemic Lupus Erythematosus (SLE)

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### Abstract

**Background:** Systemic lupus erythematosus (SLE) is an autoimmune chronic disease that sometimes leads to serious life-threatening condition. The occurrence of SLE was about 5 million worldwide by 2022. The overall frequency of SLE across Asian countries ranged from 0.9 to 3.1 per 100,000. Infection is one of the grave condition in SLE patients. This study intended to evaluate risk factors for skin infections in patients with systematic lupus erythematosus. **Material & Methods:** This observational prospective study was carried out in the Department of Rheumatology, BSMMU, Dhaka, Bangladesh from November 2014 to April 2016. A total of 131 patients with systematic lupus erythematosus were enrolled in this study as study subjects following the inclusive criteria. Data were collected using the predesigned semi-structured questionnaire. Proper written consent was taken from all the participants, before recruiting. Completed data forms were reviewed, edited, and processed for computer data entry. The data analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 25.0. Univariate and multivariate analyses were performed to identify the predictive of infection in patients with systemic lupus erythematosus (SLE) where  $P < 0.05$  was considered as the level of significance with 95% CI. **Results:** Among the total study population ( $N=131$ ), skin infections were found in 27% of cases ( $n=35$ ) whereas 73% of cases were non-infected ( $n=96$ ). In the infected group, the mean age of the respondents was  $28.2 \pm 8.7$  years. Taeniasis was the most common skin infection (15, 42.9%), and herpes infection was found in 12 patients (34.3%). Higher SELENA SLEDAI scores were more frequent in skin infected group than that in the non-infected group. Skin infections were significantly higher among the participants who used I.V. cyclophosphamide. In skin infected group, immunosuppressive drugs were used significantly in higher frequency (94.3% versus 24.0%) than in the non-infected group. In the multivariate analysis, higher disease activity (SELENA-SLEDAI score  $>3$ , ( $P=0.049$ )) ( $OR=21.44$ ), higher daily doses of prednisolone intake ( $>10\text{mg/day}$ ,  $P=0.046$ ) ( $OR=16.69$ ), low serum C3/C4 ( $P=0.004$ ) ( $OR=147.82$ ) and use of any immunosuppressive drugs either in



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present or previously (P value= 0.042) (OR=22.58) were found as significant risk factors. **Conclusion:** In this study, taeniasis and herpes infections were found as the most common skin infections among patients with systemic lupus erythematosus (SLE). Higher disease activity, a higher dose of prednisolone, use of any immunosuppressive therapy either present or past and low complement level were the risk factors for skin infections.

**Keywords:-** SLE, Diagnosis, Drugs, Skin Infection.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that leads to a life-threatening condition.<sup>[1]</sup> The scientific inception of SLE arises from the interaction between genetic predisposition and immunological, environmental and hormonal influences with a strong preference for women of reproductive age.<sup>[2]</sup> SLE is a heterogeneous disease, commonly affecting young women.<sup>[3]</sup> Sex distribution before the puberty and late in life do not show this marked female preponderance.<sup>[4]</sup> SLE is an autoimmune disease that affects nearly every organ and can be treated with immunomodulation and immunosuppression. SLE patients have an inherently dysfunctional immune system which is exacerbated by disease activity and leaves them susceptible to infections.<sup>[5]</sup> Treatment with immunosuppression raises susceptibility to infection, while hydroxychloroquine use decreases this risk. Infectious diseases are the prime reason behind hospitalization and death.<sup>[6]</sup> Infections which are associated with distinct risk factors included the lupus activity state, the use of immunosuppressive agents, abnormal white blood cells ( $<4 \times 10^9/L$  or  $>10 \times 10^9/L$ ), and low levels of the complete immune system.<sup>[7]</sup> Infection is one of the causes of morbidity and mortality in SLE patients

which are the cause of death in up to 25% of cases. Their high prevalence, mortality and morbidity have been attributed to the use of immunosuppressive agents and the action of the autoimmune disease itself.<sup>[8]</sup> Some other factors such as neutropenia are associated with infectious complications.<sup>[9]</sup> The association between persistently low CD4+ lymphocytes, cryptococcosis, & aspergillosis etc are termed as infection threats.<sup>[10]</sup> Prophylactic treatment with trimethoprim or sulfamethoxazole has been suggested for patients with lymphopenia to avoid infections.<sup>[11]</sup> Respiratory tract infections are the most common infections and bacteraemia is the major cause of mortality some pathogenic bacteria are usually intricate infections, followed by fungi and viruses.<sup>[12]</sup> In a Spanish study, skin and mucous membrane infection was the most frequent (16%) infection among the SLE patient.<sup>[13]</sup> Skin infection was the second most common infection (23%) following urinary tract infection of outpatients with systemic lupus erythematosus in a Mexican study.<sup>[14]</sup> In clinical practice, it is frequently problematic to identify whether SLE patients are with infections or without. The study intended to evaluate risk factors for skin infections in patients with systematic lupus erythematosus.



## Objectives

### General objective

To determine the risk factors for infections in patients with systematic lupus erythematosus infections.

### Specific objective

- To identify the frequency of skin infections in SLE patients
- To identify the risk factors for skin infections in SLE patients.

## MATERIAL AND METHODS

This was an observational prospective study which was carried out in the Department of Rheumatology, BSMMU, Dhaka, Bangladesh from November 2014 to April 2016. A total of 131 patients with systematic lupus erythematosus were enrolled in this study as study subjects following the inclusive criteria. Data were collected using the predesigned semi-structured questionnaire. Proper written consent was taken from all the participants before recruiting. A nonprobability consecutive sampling technique was followed. Ethical clearance was taken from the mentioned institution. The study coordinators performed random checks to verify data collection processes. Completed data forms were reviewed, edited, and processed for computer data entry. Frequencies, percentages and cross-tabulations were used for descriptive analysis. The data analysis was performed using univariate, multivariate and Fisher's exact t test by Statistical Package for the Social Sciences (SPSS) Version 25.0. The significance level of  $<0.05$  was considered for all tests. The inclusion and exclusion criteria were as follows:

## Inclusion Criteria

- Diagnosed SLE patient on the basis of ACR criteria
- Willing to be a participant in the study

## Exclusion Criteria

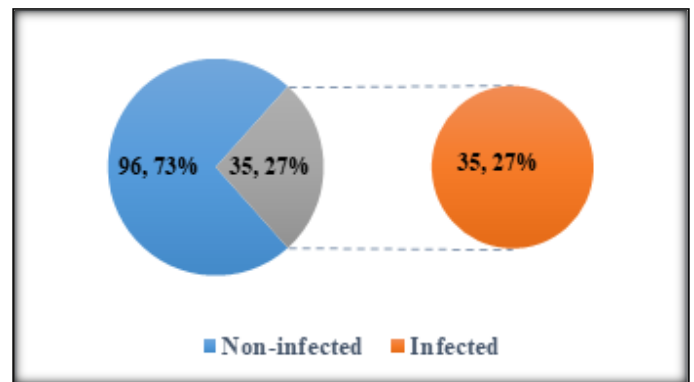
- SLE with other connective tissue diseases, e.g. systemic sclerosis, dermatomyositis/polymyositis, rheumatoid arthritis, etc.
- The patients who were unable to give their complete history regarding the onset and course of the disease.
- The patients who were mentally unstable and who have lost their medical documents.

## RESULTS

Among the study population (N=131), skin infections were found among 27% of cases (n=35) whereas 73% of cases were non-infected (n=96). In the infected group mean age of the respondents was  $28.2 \pm 8.7$  years. Of thirty-five infected patients, all were female (35,100.0%). Twenty-nine (29) infected respondents (82.9%) were married and 70 non-infected respondents were housewives (72.9%). Around three-fifths of the infected patients (21, 60.0%) were from the urban areas and there were no significant differences between the infected and non-infected groups ( $p > 0.05$ ) [Table 1]. Taeniasis was the most common skin infection (15, 42.9%), and herpes infection was found in 12 patients (34.3%) [Table 2]. Higher SELENA SLEDAI scores were more frequent in skin infected group than in the non-infected group. There were no significant differences in WBC counts in between skin-infected and non-infected groups but there were significant

differences in ESR, CRP, anti-dsDNA and low complement level [Table 3]. Renal disease activities were more frequent in the infected group than that in the non-infected group (62.9% versus 9.4%) and extra-renal disease activities were also more frequent (45.7% versus 8.3%) in the infected group than that of the non-infected group [Table 4]. There were significant differences in the daily dosage of prednisolone (>10 mg/day) used by both the infected groups (74.29%) and non-infected group (7.29%) and higher mean cumulative dosage of prednisolone (3148.11 ± 2349.98 and 1390.06 ± 2341 mg) were taken by the skin infected group than that of the non-infected group respectively [Table 5]. Skin infections were significantly higher among the participants who used I.V cyclophosphamide, AZA but no differences were found in the infected or non-infected group who used MMF and MTX. Skin infected group significantly used immunosuppressive drugs (94.3% versus 24.0%) than that of the non-

infected group at present [Table 6]. In the multivariate analysis, higher disease activity (SELENA-SLEDAI score >3, P=0.049), higher daily doses of prednisolone intake (>10mg/day, P=0.046), low complements level (P=0.004) and use of anyone immune-suppressive drugs either in present or previously (P value= 0.042) were found as significant risk factors [Table 7].



**Figure 1:** Frequency of infection among total participants (N=131)

**Table 1:** Socio-demographic findings between infected & non-infected patient group (N=131).

Characteristics	Categories	Infected	Non-infected	p-value
		(n=35)	(n=96)	
Age (year)**	Mean ± SD	28.2±8.7	29.0±8.6	0.619***
	Median, Range	27,18-50	28,18-50	
Sex	Male	0	5 (5.2)	0.324***
	Female	35(100)	91(94.8)	
Marital status	Married	29(82.9)	74(77.1)	0.316***
	Unmarried	3(8.6)	18(18.8)	
	Others	3(8.5)	4(4.2)	
Occupation	Housewife	31(88.6)	70(72.9)	0.310***
	Student	4(11.4)	13(13.5)	
	Others##	0	13(13.5)	
Religion	Islam	35(100)	90(93.8)	0.504***
	Others	0	6 (6.2)	
Educational status	Up to Primary	20(57.1)	37(38.5)	0.391*
	Secondary	8(22.8)	26(27.1)	
	More than secondary	7(20)	33(34.4)	





Residence	Urban	21(60)	60(62.5)	0.890***
	Semi-urban	2(5.7)	4(4.2)	
	Rural	12(34.2)	32(33.3)	

**Table 2:** Distribution of the study population based on type of infection (n=35).

Skin infections		(n, %)
Taeniasis	Onychomycosis	5,14.3%
	Tinea versicolor	5,14.3%
	Tinea pedis	4,11.4%
	Tinea corporis	1,2.9%
Total		15,42.9%
Herpes	Herpes zoster	7,20.0%
	Herpes labialis	4,11.4%
	Genital herpes	1,2.9%
Total		12,34.3%
Others	Paronychia	7,20.0%
	Scabies	6,17.1%
	Multiple-skin abscess	3,8.6%
Total		16,45.7%

**Table 3:** Clinical and laboratory findings between infected & non-infected groups (N=131).

Characteristics	Category	Infected	Non-infected	p-value	
		(n=35)	(n=96)		
		(n, %)	(n, %)		
SELENA SLEDAI score	SLE DAI score <3	2(5.7)	79(82.3)	0.000*	
	SLE DAI score >3	33(94.3)	17(17.7)		
WBC Count	<4000/cmm	1(2.9)	1(1.0)	0.320*	
	4000-11000/cmm	30(85.7)	89(92.7)		
	>11000/cmm	4(11.4)	6(6.3)		
ESR	Raised	9(25.7)	68(70.8)	0.000**	
	Normal	26(74.3)	28(29.2)		
CRP	Normal	12(34.3)	31(32.3)	0.013*	
	Raised	10(28.6)	5(5.2)		
Anti dsDNA	Positive	30(85.7)	44(45.8)	0.000*	
	Negative	4(11.4)	44(45.8)		
Serum C3/C4	Normal	9(25.7)	79(82.3)	0.000**	
	Reduced	25(71.4)	9(9.4)		
SELENA SLEDAI score	SLE DAI score <3	2(5.7)	79(82.3)	0.000*	
	SLE DAI score >3	33(94.3)	17(17.7)		
WBC Count	<4000/cmm	1(2.9)	1(1.0)	0.320*	
	4000-11000/cmm	30(85.7)	89(92.7)		



	>11000/cmm	4(11.4)	6(6.3)	
ESR	Raised	9(25.7)	68(70.8)	0.000**
	Normal	26(74.3)	28(29.2)	
CRP	Normal	12(34.3)	31(32.3)	0.013*
	Raised	10(28.6)	5(5.2)	
Anti dsDNA	Positive	30(85.7)	44(45.8)	0.000*
	Negative	4(11.4)	44(45.8)	
Serum C3/C4	Normal	9(25.7)	79(82.3)	0.000**
	Reduced	25(71.4)	9(9.4)	

\*Fisher's exact test, \*\*X<sup>2</sup> test

**Table 4:** Renal activity distribution between infected & non-infected groups (N=131)

Renal disease activity	Infected	Non-Infected	p value
	n=35	n=96	
	(%)	(%)	
Present	22(62.9)	9(9.4)	0
Absent	13(37.1)	87(90.6)	
Extra renal disease activity			
Present	16 (45.7)	8(8.3)	0
Absent	19(54.3)	88(91.7)	

\*Univariate analysis, # renal disease activity defined as proteinuria (0.5 gm/day) and/or haematuria/pyuria with or without cast excluding infection and other causes.

**Table 5:** Doses of prednisolone distribution between infected & non-infected groups (N=131)

Doses	Category	Infected	Non-Infected	p-value
		n=35	n=96	
		(%)	(%)	
Dose of prednisolone	>10 mg/day	26 (74.3)	7 (7.3)	0
	<10 mg/day	7 (20)	67 (69.8)	
Cumulative dose intake	Mean ±SD	3148.11±2349.98	1390.06±2341	0.000*
	Range	(0-9325)	(0-9581)	

\*Univariate analysis, SD standard deviation

**Table 6:** Distribution of immunosuppressive drug uses between infected & non-infected group (N=131)

Immunosuppressive drugs		Infected	Non-infected	p-value
		n=35	n=96	
Drugs	Dose	n (%)	n (%)	
Usage of immunosuppressive drugs				
At least one drug	Yes	33 (94.3)	23 (24.0)	0

	Not taken	2 (5.7)	73 (76.0)	
<b>Immunosuppressive drugs used</b>				
Cyclophosphamide	500 mg/m <sup>2</sup> /BSA	2(5.7)	0 (0.0)	0
	501-700 mg/m <sup>2</sup> /BSA	2(5.7)	1(1.0)	
	701-1000 mg/m <sup>2</sup> /BSA	16(45.7)	3(3.1)	
AZA	1 mg/kg/day	5(14.3)	5 (3.82)	0.003
	1.1-2 mg/kg/day	8(22.6)	6 (4.5)	
MMF	0.5-1 g/day	1(2.9)	2(2.0)	0.423
	1.1-1.5 g/day	1 (2.9)	3(3.1)	
	1.6-2 g/day	1 (2.9)	0	
MTX	10-15 mg/week	0	1(1.0)	0.548

\*Univariate analysis, \*\* Percentage values are in parenthesis# use of any immunosuppressive drugs at present at past.

**Table 7:** Distribution of the study population based on risk factors (N=131)

Variables	Regression Co-efficient (B)	OR	95% CI	p- value
Disease activity (SELENA-SLEDAI score $\geq$ 3)	3.066	21.447	1.01-451.88	0.049
Anti dsDNA positivity	0.879	2.409	0.17-32.54	0.508
Low serum C3/C4	4.996	147.828	4.93-4425.8	0.004
Dose prednisolone (>10mg/day)	2.815	16.694	1.05-265.15	0.046
Cumulative doses of prednisolone	0	1	1.00-1.001	0.789
Any immunosuppressive drug use	3.117	22.58	1.12-452.39	0.042

\*Multivariate analyses

## DISCUSSION

Skin infection can be caused by a wide range of germs and symptoms can differ from mild to severe. These can include bacterial, fungal, and/or parasitic infections. Mild infections may be treatable with over-the-counter medications and home remedies whereas other infections may require medical attention. In this current analysis, skin infections were found in 27% of SLE patients which was similar to another meta-analysis (26.0%).<sup>[15]</sup> but was a little higher than that of the findings (16%) of another study.<sup>[16]</sup> In this present study, Taeniasis was the most frequent finding (42.8%) in SLE patients whereas another meta-analysis suggested that,

tinea capitis is the most common dermatophyte.<sup>[17]</sup> In this study, other tinea infections were tinea versicolor, tinea pedis, and tinea corporis. Though to date, no tinea versicolor reported in SLE patients, 14.3% tinea versicolor was found in this series. Bangladesh is a hot and humid country as well as SLE somehow is an immunocompromised state may be the cause of the development of tinea versicolor, this prevalence is also high (12.81%) in the general population.<sup>[18]</sup> Though to date, no published report on tinea pedis in SLE yet it was found in 11.4% of this study. Most of the participants of this study were female housewives who use excessive water in household work. Humidity and temperature

are also well-known factors affecting fungal penetration through the skin.<sup>[19]</sup> In this series, tinea corporis was found in 2.9% of SLE patients. Other two similar studies,<sup>[20,21]</sup> found 7% and 2.5% tinea corporis respectively in their settings. A related analysis described that, while tinea corporis occurred universally, it is most frequently found in tropical regions.<sup>[22]</sup> The lifetime threat of acquiring tinea corporis is approximately 10-20%. Tinea corporis occurred most usually in post-pubertal children and young adults.<sup>[23,24]</sup> In this present series, herpes infection was found in 12 patients (34.3%). Another similar study found that the prevalence of herpes was 30.5% and the incidence was 14.3 cases per 1000 person-years.<sup>[25]</sup> Another meta-analysis depicted that, patients with SLE were at greater risk of severe herpes infection.<sup>[26]</sup> A study carried out in Bangladesh found 2.5% of genital herpes in their study which was consistent with our findings.<sup>[27]</sup> In this series, paronychia was found in 20% of cases. This finding was higher than that of the finding (10%) of a study conducted in Pakistan and the finding (2.5%) of another study conducted in Bangladesh.<sup>[20,27]</sup> Skin abscess was found in 8.6% of patients in this series. A related article found 5% of cellulitis and abscesses which was comparable with our findings.<sup>[20]</sup> In this current content, scabies was found in 17.1% (out of six patients three had a family history of scabies) of SLE patients. A contradictory finding suggested that 92.7% of Pakistani SLE patients had scabies.<sup>[28]</sup> In this current analysis, there were significant differences in ESR, CRP, anti-dsDNA, and low complement levels. Higher SELENA SLEDAI scores were more frequent in skin infected group than in the non-infected group in this current content. Another article published that;

anti-ds-DNA was positive in 78.3% of patients. SLEDAI score was  $\geq 6$  in 87% of patients. Elevated ESR, Anti-dsDNA, and low complement levels were significantly positively correlated with infection.<sup>[29]</sup> Several factors may increase the risk of infections in SLE patients. Higher disease activity, both renal and extra-renal disease activity, a higher dose of prednisolone ( $>10$  mg kg/day), usage of any immunosuppressive therapy either present or past, and low serum complement level was identified as the risk factors for skin infections in this series in multivariate analysis. On the other hand, another related article found a significant association with the presence of disease activity, SLEDAI score, renal activity, prednisolone dose, and IV cyclophosphamide in univariate analysis but in multivariate analysis, only SLEDAI score ( $>4$ ) was associated with skin infection.<sup>[30]</sup> Another article found that daily oral doses of over 7.5 mg of prednisolone were independent risk factors for severe herpes infection.<sup>[26]</sup> SLE may be triggered by colds and other infections, fatigue, stress, smoking, chemicals, and certain drugs. Some research suggests an association between Epstein-Barr virus (EBV), the cause of mononucleosis, and increased risk for SLE.<sup>[31]</sup>

## CONCLUSIONS

SLE is an autoimmune disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage to affected organs. It can affect joints, skin, brain, lungs, kidneys and blood vessels. In this finding, Taeniasis and herpes infection was the most common skin infection. A higher frequency of herpes zoster may be for the lack of vaccination facilities in Bangladesh. Higher disease activity, a higher dose of prednisolone,



use of any immunosuppressive therapy either present or past and low complement levels were found as the risk factors for skin infections.

### Recommendations

We would like to recommend the judicious use of steroids and other immune suppressants along with the management of other risk factors

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