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Predictors of admission to intensive care unit among systemic lupus erythematosus patients: prospective study

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Abstract

Background: Through the disease course, different prognostic factors have been addressed in patients with SLE admitted to intensive care unit. For instance, higher disease activity on admission, recent immunosuppressive therapy, infections, renal disease, and central nervous system involvement, all had negative effects on the outcome of the disease. It is still a clinical challenge for the physicians to manage this disease which has many aspects regarding its pathogenesis, clinical presentation, and its outcome remains to be explained.

The aim of our study was determining the course, outcome, and determinants of admission to intensive care unit in patients with systemic lupus erythematosus.

Results: Patients with systemic lupus erythematosus admitted to the intensive care unit in the study sample was 21.4%, and the death rate among them is 18.2%. In our study, the main causes of intensive care admission were cardiovascular causes followed by renal failure then infections. Holding the other covariates constant, a higher value of CRP, SLEDAI, and damage index value is associated with intensive care admission among lupus patients.

Conclusion: Our study showed that systemic lupus erythematosus patients with a higher value of CRP, SLEDAI, and damage index value were liable for intensive care unit admission. Good control of disease activity of SLE which in turn reduces damage of different body systems is mandatory. Periodic screening for functions of renal and cardiac systems is of great value. Proper screening and prophylaxis is recommended against variable causes of infections. Rheumatologists should be careful in controlling SLE active disease and to balance the doses of immunosuppressive especially in the presence of infection. They should focus the research on finding more accurate infection predictive index parameters to early predict the onset of infection.

Keywords: Intensive care unit, CRP, SLEDAI, CVS, Infection, Nephritis, Systemic lupus erythematosus

Background

Systemic lupus erythematosus (SLE) is a heterogeneous and complex autoimmune disease; it is associated with the production of autoantibodies and inflammatory damage of multiple organs [1]. It has a wide spectrum of clinical presentation that affects all ages and ethnicities [2]. Childbearing women most often afflicted by these diseases, but with different disease manifestations and with variable severity [3, 4].

The diagnosis of SLE is based on characteristic clinical findings of the skin, joints, kidneys, and the central nervous system, as well as on serological parameters such as antinuclear antibodies (ANA) [5].

As SLE is a heterogeneous disease, its complications may vary and the severity or intensity depends on the area affected; pulmonary hypertension, alveolar hemorrhage, thrombocytopenia, catastrophic antiphospholipid syndrome (APS), hemolytic anemia, neutropenia, blood

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cancer, and thrombotic thrombocytopenic purpura, atherosclerosis, pericardial tamponade, myocarditis, heart failure, arthritis, vasculitis, adrenal insufficiency, lupus nephritis (LN), neuropsychiatric disorders, pancreatitis, and myelitis are some of the major complications of SLE [6].

Although the survival rate of patients with SLE has improved since the 1950s due to advances in diagnosis and therapy, mortality remains high compared with the general population [7, 8]. Damage in SLE cannot be prevented completely, as SLE disease is considered an aggressive disease treated by aggressive medications [9]. Hospitalization rates and the economic burden of inpatient care are also high for SLE [10].

Approximately 50% of all critically ill SLE patients do not survive intensive care unit (ICU) admission [11]. Through the disease course, different prognostic factors have been addressed in patients with SLE admitted to ICU. For instance, higher disease activity on admission, recent immunosuppressive therapy, infections, renal disease, and CNS involvement all had negative effects on outcome [12, 13]. It is still a clinical challenge for the physicians to manage this disease which has many aspects regarding its pathogenesis, clinical presentation, and its outcomes remain to be explained [14].

From this point of view, our study aimed to determine the course, outcome, and determinants of admission in the intensive care unit (ICU) in patients with systemic lupus erythematosus (SLE) also identifying the risk factors associated with death in patients with SLE admitted to ICU.

Methods

Study design and subjects

This prospective Egyptian one center study was conducted in Rheumatology and Rehabilitation Department and the Internal Medicine Department, Zagazig University. We followed up 103 SLE patients through 1 year between January 2018 and January 2019; patients during follow-up were divided into two groups according to the admission to ICU or not. Twenty-two of our SLE patients were admitted to ICU and eighty-one were not admitted to ICU during 1 year follow-up. All patients fulfilled Systemic Lupus International Collaborating Clinics (SLICC) criteria for the classification of SLE [5]. Informed written consent was taken from all patients included in the study or their close relatives. All procedures performed in this study were following the ethical standards of the institutional and national research committee and approval number (6536). The exclusion criteria were as follows: diagnosis of SLE at or after admission to the ICU, patients with major chronic organ disease not related to SLE or terminal cancer were excluded.

Demographic and clinical data

The socio-demographic data were recorded including age, gender, smoking, disease duration, and the causes of admission to ICU of the patients of SLE who were admitted to ICU during a year of follow-up. All patients were assessed by the SLE Disease Activity Index (SLEDAI) [15] and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) [16]. Acute Physiology and Chronic Health Evaluation (APACHE) II scores were calculated [17] in the first 24 h at ICU. Patients who were admitted to ICU were followed up till the day of discharge or demise.

Laboratory and radiological investigations

Routine, specific laboratory and radiological investigations, during 1-year follow-up, were recorded and most flaring point of laboratory results during follow-up was taken including erythrocyte sedimentation rate (ESR), high sensitivity C-reactive protein (hs-CRP), liver and renal function tests, complete blood count, protein in 24-h urine, complete urine analysis, anti-nuclear antigen (ANA), anti-double-stranded DNA (anti-dsDNA) and levels of complement components C3 and C4, chest X-ray, echocardiography, chest computerized tomography, and brain magnetic resonance imaging.

Therapeutic data

We recorded the treatment used by each patient admitted to ICU or not, including corticosteroids and disease-modifying anti-rheumatic drugs (DMARDS) like azathioprine, cyclophosphamide, chloroquine, mycophenolate mofetil, and cyclosporine.

Outcome of our patients

Twenty-two of our SLE patients were admitted to ICU and eighty-one were not admitted to ICU during 1-year follow-up.

The outcome of ICU admission

Two main endpoints were documented: death in ICU or discharge from it. Each ICU admission was analyzed as a separate event with regard to clinical and laboratory predictors of the outcomes in ICU along survival time (duration between ICU admission and date of death or discharge).

Statistical analysis

All data were collected, tabulated, and statistically analyzed using SPSS 20.0 for windows (SPSS Inc., Chicago, IL, USA, 2011). Quantitative data were expressed as the mean ± SD (range), and qualitative data were expressed

as % (percentage). Percent of categorical variables were compared using the chi-square test or Fisher exact test when appropriate. All tests were two-sided. P value $\leq$ 0.05 was considered statistically significant (S), and P value > 0.05 was considered statistically insignificant (NS).

The Cox hazards model

Cox regression builds a predictive model for time-to-event data. The model produces a survival function that predicts the probability that the event of interest has occurred at a given time (t) for given values of the predictor variables. The Cox regression model extends survival analysis methods to assess the effect of several risk factors on survival time. Variable with hazard ratio > 1 is called a bad prognostic factor. A variable with a hazard ratio < 1 is called a good prognostic factor.

Proportionally, often the Cox regression model is called the proportional hazards (PH) model proportional hazard assumption by introducing an interaction of the covariate of interest with time. If T_Cov is above 0.05, then the proportional hazard assumption for Cox regression is satisfied.

Kaplan-Meier curves and log-rank tests—they describe the survival according to one factor under investigation.

The Wald chi-squared test is used to determine if explanatory variables in a model are significant.

Results

Baseline characteristics of SLE patients in the study sample are clarified in Table 1; the mean age was 29.2 years old, 88% were females and 7% were smokers. The mean disease duration was 4 years, mean SLE disease activity index 25 (range, 2-48), and SLICC damage index ranged from (0:15), APACHE II score ranged (7:39) for patients admitted to ICU.

Concerning clinical finding, 63.1% of SLE patients in the study sample had proteinuria > 0.5 g and 39.8% of them complaining hair loss; the least clinical manifestation was hemolytic anemia 17.5%, 73.8% of SLE patients in the study sample had ANA, and 71.8% of them had anti-dsDNA; least clinical manifestation was cranial nerve affection 1.9%. Concerning treatment, 78.6% of SLE patients in the study sample were treated with chloroquine, 70.9% of SLE patients in the study sample were treated with steroid only 4.9% of them were treated by cyclosporine.

In Table 2, the relations between SLE patients admitted to ICU during 1 year of follow up and their characteristics. The table indicates statistically significant relation between SLE patients admitted to ICU and leukopenia < 4000, high ESR value, abnormal CRP, high level of serum creatinine, and lupus headache ($P = 0.0001$, $p = 0.007$, p

Table 1 The demographic, clinical, and laboratory data of the study group of 103 SLE patients

Items	$N = 103$ (100%)
Demographic data	
Age mean ± SD (range, 12-45)	29.2 ± 7.4
Sex, no. (%)	
Female	91 (87.35%)
Male	12 (11.65%)
Smoking, no. (%)	
Smoker	7 (6.8%)
Non-smoker	96 (93.2)
Disease duration (years)	4-10 months
Mean ± SD	4 ± 2
Clinical features	
Malar rash, no. (%)	35 (34.0%)
Photosensitivity, no. (%)	34 (33.0%)
Oral ulcer, no. (%)	21 (20.4%)
Arthritis, no. (%)	30 (29.1%)
Pleurisy	22 (21.4%)
Pericarditis	21 (20.4%)
Proteinuria more than 0.5 g	65 (63.1%)
Vasculitis	12 (11.7%)
Fever > 38	17 (16.5%)
Seizure	11 (10.7%)
Psychosis	7 (6.8%)
Lupus headache	15 (14.6%)
CVA	13 (12.6%)
SLEDAI, mean ± SD (2-48)	18 ± 10
SLICC, mean ± SD (0-15)	5 ± 3
APACHE II score, mean ± SD (7-39)	19 ± 8
Laboratory investigations	
Hemolytic anemia	18 (17.5%)
Leukopenia less 4000	22 (21.4%)
Lymphopenia less 1500	26 (25.2%)
Thrombocytopenia	31 (30.1%)
ANA	76 (73.8%)
Anti-dsDNA	74 (71.8%)
HypoC3	37 (35.9%)
HypoC4	37 (35.9%)
Medications	
Steroid	73 (70.9%)
Azathioprine	53 (51.5%)
Cyclophosphamide	22 (21.4%)
Chloroquine	81 (78.6%)
Mycophenolate mofetil	20 (19.4%)
Cyclosporine	5 (4.9%)
Combined therapy	93 (90.2%)
Total SLE patients	**103 (100%)**
No admission to ICU	81 (78.6%)
Admitted to ICU	22 (21.4%)
Died	4 (18.2%)
Survival	18 (81.8%)

$= 0.00001$, $p = 0.017$, $p = 0.01$) respectively. Also, Table 2 indicates statistically significant relation between SLE patients admitted to ICU and Red Cell Cast, RBCs > 5/HPF urine, WBCs > 5/HPF urine, fever > 38 C, renal failure ($P = 0.001$, $P = 0.0001$, $P = 0.0001$, $P = 0.029$, $p = 0.0001$) respectively.

About their treatment, Table 2 indicates a statistically significant relation between SLE patients admitted to ICU and steroid, azathioprine, mycophenolate mofetil, cyclosporine ($P = 0.001$, $P = 0.0001$, $P = 0.023$, $P = 0.03$) respectively where a higher percentage of those who were admitted to ICU during 1 year of follow up. The mean of SLEDAI patients admitted to ICU in comparison to the mean of SLEDAI patients not admitted to ICU was statistically significant. Also, the difference between the mean of SLICC patients admitted to ICU and the mean of SLICC of the patients not admitted to ICU was statistically significant as showed in Table 2.

Table 3 shows, in total 103 SLE patients, 22 admitted to ICU after a median of 4 months (range, 1-12 month). Univariable Cox regression analysis found that leukopenia less 4000 is associated with increased risk of ICU admission, with HR (95% CI) 4.7 (2-10.8). The presence of abnormal level ESR, abnormal CRP, and high level of serum creatinine were associated with increased risk of admission to ICU HR (95% CI): 8.6 (1.2-64.3), 80 (10.7-596.6), 3 (1.1-7) respectively. SLE patients complaint of lupus headache HR (95% CI) 3.8 (1.5-9).

Also, the presence of red cell cast, RBCs > 5/HPF urine, WBCs > 5/HPF urine were associated with increased risk of admission to ICU HR (95% CI); 4 (1.6-9), 4.9 (1.95-11), 6.5 (2.7-15.8) respectively. SLE patients complaining of fever > 38 HR (95% CI), 3 (1.2-7.2). SLE patients who had renal failure HR (95% CI) of ICU admission were 5.8 (2.1-16) as shown in Table 3.

For every one-unit increase in the SLEDAI and SLICC damage index, the risk of ICU admission increases at 8.9% and 31.2% respectively. In treatment, azathioprine and chloroquine are associated with a decreased risk of admission to ICU: with HR (95% CI) 0.077 (0.018-0.33), 0.2 (0.097-0.52) but mycophenolate mofetil and cyclosporine are associated with an increased risk of admission to ICU: with HR (95% CI) 2.73 (1.14-6.5), 3.5 (1.04-12) respectively as shown in Table 3.

In Table 4, multivariable Cox regression analysis found that hazard ratio HR = 56, indicating a strong relationship between abnormal CRP value and increased risk of SLE patients ICU admission hazard ratio HR = 1.073, indicating a strong relationship between SLEDAI value and increased risk of SLE patients ICU admission hazard ratio HR = 1.15, indicating a strong relationship between SLICC damage index value and increased risk of SLE patients ICU admission. Holding the other covariates constant, a higher value of CRP, SLEDAI, and SLICC damage index value is associated with ICU admission among SLE patients (Figs. 1 and 2).

Discussion

Even though the survival rate among SLE patients has improved over the past few decades [18], there remain a host of factors that are associated with death in SLE patients, including the level of disease activity and demonstrable organ damage at presentation [19].

Exacerbations in SLE requiring ICU admission may result from acute or persistent disease activity, the side effects of treatment, or both [20].

Knowledge of the profile of patients admitted to the ICU makes management of notoriously scarce resources easier.

The immunopathology of SLE encompasses multiple innate and adaptive immunologic alterations, including hypocomplementemia, higher levels of TNF-α, IL-4, IL-6, IL-10, and type I and II interferons, with a consequent skewing toward a Th17 response, persistent B cell activation with sustained auto-antibody secretion and a deficient regulatory T cell profile [8].

Patients with SLE also have higher amounts of low-density granulocytes (LDGs), which infiltrate tissues, secrete pro-inflammatory cytokines and spontaneously produce neutrophil extracellular traps (NETs) [8]. Aside from the role of NETosis in the SLE pathogenesis, the NETs are an innate defense mechanism since they contain antimicrobial proteins including LL-37 [8].

Our data showed that age and gender have no significant difference between SLE patients admitted to ICU and other patients. On the contrary, the age at onset of SLE has also been reported as a significant predictor for survival; in three studies showed that increasing age is a risk factor for death [21–23].

CRP concentrations in patients with systemic lupus erythematosus (SLE) may contribute to defective clearance of apoptotic particles, thereby promoting the development of autoimmunity to apoptotic vesicle components. The level of CRP is rarely high in patients with SLE, even in increased disease activity levels. If a patient with SLE has increased CRP level, other causes are considered first [23].

Its intermediate outcome, in our study, by holding the other covariates constant, a higher value to predict CRP may be useful to monitor the course of the disease and of CRP value is associated with ICU admission among SLE patients, in agreement with Umare et al. [24]; hs-CRP levels among active SLE were significantly higher as compared with inactive SLE hs-CRP levels have been found elevated in SLE but its correlation with SLE disease activity was reported to be controversial [24, 25]. Lee et al.

Table 2 Comparison of clinical finding and type of treatment of SLE patients admitted to ICU and others during 1-year follow-up

Items		SLE patients admitted to ICU		SLE patients not admitted to ICU		χ^2	*P*
Age	Mean ± SD	27.95 ± 8.98		30.04 ± 6.64		$t = 1.44$	0.15
disease duration	Mean ± SD	4.96 ± 2.86		4.06 ± 1.58		MW = 1.18	0.24
		No.	%	No.	%		
Sex	Female	18	81.8	73	90.1	f	0.3
	Male	4	18.2	8	9.9		
Smoking	Yes	0	0.0	7	8.6	f	0.34
	No	22	100	74	91.4		
Oral ulcer	Yes	1	4.5	20	24.7	4.33	0.04
	No	21	95.5	61	75.3		
Seizure	Yes	2	9.1	9	11.1	0.074	0.79
	No	20	90.9	72	88.9		
Lupus headache	Yes	7	31.8	8	9.9	6.69	0.01
	No	15	68.2	73	90.1		
Fever > 38	Yes	7	31.8	10	12.3	4.76	0.029
	No	15	68.2	71	87.7		
Infections	Yes	5	22.7	1	1.2	14.6	0.0001
	No	17	77.3	80	98.8		
Hypertension	Yes	16	72.7	53	65.4	0.42	0.52
	No	6	27.3	28	34.6		
DM	Yes	1	4.5	19	23.5	3.95	0.047
	No	21	95.5	62	76.5		
CVA	Yes	0	0.0	13	16.0	4.77	0.029
	No	22	100.0	68	84.0		
Renal Failure	Yes	5	22.7	1	1.2	14.6	0.0001
	No	17	77.3	80	98.8		
Angina	Yes	0	0.0	21	25.9	7.2	0.007
	No	22	100	60	74.1		
AMI	Yes	0	0.0	13	16.0	4.04	0.044
	No	22	100	68	84.0		
CVD	Yes	0	0.0	20	24.7	6.74	0.009
	No	22	100	61	75.3		
Proteinuria more than 0.5 g	Yes	17	77.3	48	59.3		
	No	5	22.7	33	40.7	2.4	0.12
Hemolytic anemia	Yes	2	9.1	16	19.8	1.36	
	No	20	90.9	65	80.2		0.24
Leukopenia < 4000	Yes	11	50.0	11	13.6		
	No	11	50.0	70	86.4	13.66	0.0001
Thrombocytopenia	Yes	9	40.9	22	27.2		
	No	13	59.1	59	72.8	1.55	0.21
Anti-dsDNA	Yes	12	54.5	62	76.5	4.14	
	No	10	45.5	19	23.5		0.042
HypoC3	Yes	4	18.2	33	40.7	3.83	0.05
	No	18	81.8	48	59.3		
HypoC4	Yes	2	9.1	35	43.2	8.75	0.003
	No	20	90.9	46	56.8		
ESR	Abnormal	21	95.5	54	66.7	7.2	0.007
	Normal	1	4.5	27	33.3		
CRP	Abnormal	15	68.2	73	90.1	60	0.000001
	Normal	7	31.8	8	9.9		

Table 2 (continued)

Items		SLE patients admitted to ICU		SLE patients not admitted to ICU		χ^2	*P*
Serum creatinine	Abnormal	15	68.2	32	39.5	5.7	0.017
	Normal	7	31.8	49	60.5		
Red cell cast	Yes	9	40.9	8	9.9	12.09	
	No	13	59.1	73	90.1		0.001
RBCs > 5/HPF urine	Yes	9	40.9	7	8.6	19.35	0.0001
	No	13	59.1	74	91.4		
WBCs > 5/HPF urine	Yes	8	36.4	3	3.7	f	0.0001
	No	14	63.6	78	96.3		
Steroid	Yes	22	100.0	51	63.0	11.5	0.001
	No	0	0.0	30	37.0		
Azathioprine	Yes	2	9.1	51	63.0	20.1	0.0001
	No	20	90.9	30	37.0		
Cyclophosphamide	Yes	4	18.2	18	22.2	0.17	0.68
	No	18	81.8	63	77.8		
Chloroquine	Yes	11	50.0	70	86.4	13.7	0.0001
	No	11	50.0	11	13.6		
Mycophenolate mofetil	Yes	8	36.4	12	14.8	5.13	0.023
	No	14	63.6	69	85.2		
Cyclosporine	Yes	3	13.6	2	2.5	4.7	0.03
	No	19	86.4	79	97.5		
SLEDAI		25 ± 12		16 ± 8		0.002 (S)	
SLICC Damage Index		7.5 ± 4.6		3.7 ± 2		0.00004 (S)	

f Fisher exact test, χ^2 chi-square test significant for all items except SLEDAI and SLICC Mann-Whitney test, *SLE* systemic lupus erythematosus, *ICU* intensive care unit, *DM* diabetes mellitus, *CVA* cerebrovascular accident, *AMI* acute myocardial infarction, *CVD* cardiovascular disease, *C* complement, *anti-dsDNA* anti-double stranded deoxyribonucleic acid, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *RBCs* red blood cells, *WBCs* white blood cells, *SLEDAI* SLE Disease Activity Index, *SLICC* Systemic Lupus International Collaborating Clinics Damage Index

also had reported an association of hs-CRP levels with the disease activity and organ damage to the musculoskeletal system in their multiethnic cohort study including Asian SLE patients [26]. Bertoli et al. had reported that SLE patients from Hispanic, African American, and Caucasian populations show a significant association of hs-CRP levels with the disease activity [27]. It was reported that elevated hs-CRP levels are associated with multiple organ damage, including renal, cardiovascular, and musculoskeletal manifestations in SLE [28]. Also in an Egyptian study of Gheita et al., there was no difference in the level of hs-CRP according to the presence or absence of clinical manifestations. However, it was significantly higher in those with positive DNA [29].

A high level of creatinine is associated with an increased risk of admission to ICU. In agreement with studies that stated that the level of creatinine at baseline impacts the complete remission rate with immunosuppressive treatment and the prognosis of SLE is significantly affected by the serum creatinine level at baseline, and the long-term prognosis most favorable, in patients with a baseline serum creatinine level of 1.0 mg/dl [30].

In our study, SLE patients complaining of fever > 38 is associated with an increased risk of admission to ICU. Fever is a common manifestation of SLE and occurs in 36-86% of patients. In the Modified Systemic Lupus Erythematosus Disease Activity Index (M-SLEDAI), fever is taken into account as disease activity scoring. In a retrospective analysis of 160 hospitalized patients with SLE, Stahl et al. [31] identified 83 febrile episodes in 63 patients. Of these, 23% of the fevers were attributed to infections, 17% to miscellaneous causes, and 60% to lupus disease activity. Inoue et al. also reported that SLE activity was the most common cause of fever among SLE patients [32].

In our study, anti-dsDNA antibodies were present in 20 patients (27%) admitted to ICU from a total of 74 patients with positive anti-dsDNA within the sample size. Increases in circulating anti-dsDNA antibody levels often precede exacerbations of SLE, and prophylactic treatment of patients following rises in anti-dsDNA antibody levels has reduced the occurrence of subsequent disease flares [33]. Decreasing levels of C3 also correlate with increased disease activity [34, 35]. Together, these studies

Table 3 Univariate Cox regression for demographic, clinical, and laboratory characteristics and type of treatment for SLE patients admitted to ICU during 1-year follow-up

Items		SLE patients admitted to ICU	HR	95% CI	
				Lower	Upper
Age	Admitted	27.95 ± 8.98	1.03	0.86	1.36
	Not admitted	30.04 ± 6.64			
Sex	Female	18/91 (20%)	0.595	0.202	1.760
	Male	4/12 (33%)	Ref		
Smoking	Yes	0/7	0.044	0.000	48.310
	No	22/96 (23%)	Ref		
Disease duration	Admitted	4.96 ± 2.86	1.17	0.966	1.425
	Not admitted	4.06 ± 1.58			
Oral ulcer	Yes	1/21 (5%)	0.170	0.023	1.263
	No	21/82 (26%)	Ref		
Proteinuria > 0.5 g	Yes	17/65 (26%)	2.071	0.764	5.613
	No	5/38 (13%)	Ref		
Seizure	Yes	2/11 (18%)	0.816	0.191	3.493
	No	20/92 (22%)	Ref		
Lupus headache	Yes	7/15 (47%)	3.8	1.5	9
	No	15/88 (17%)	Ref		
CVA	Yes	0/13	0.039	0.000	7.545
	No	22/100 (22%)	Ref		
Fever > 38	Yes	7/17 (41%)	3	1.2	7.2
	No	15/86 (17%)	Ref		
Hypertension	Yes	16/69 (23%)	1.367	0.535	3.5
	No	6/34 (18%)	Ref		
DM	Yes	1/20 (5%)	0.177	0.024	1.32
	No	21/83 (25%)	Ref		
CVD	Yes	0/15	0.038	0.000	5.25
	No	22/88 (25%)	Ref		
Renal failure	Yes	5/6 (83%)	5.8	2.1	16
	No	17/97 (17.5%)	Ref		
Hemolytic anemia	Yes	2/18 (11%)	0.457	0.107	1.954
	No	20/85 (23.5%)	Ref		
Leuckopenia < 4000	Yes	11/22 (50%)	4.7	2	10.8
	No	11/81 (13.5%)	Ref		
Thrombocytopenia	Yes	9/31 (29%)	1.764	0.754	4.129
	No	13/72 (18%)	Ref		
Anti-dsDNA	Yes	20/74 (27%)	0.431	0.186	0.999
	No	2/29 (6.8%)	Ref		
HypoC3	Yes	4/41 (10%)	0.372	0.126	1.100
	No	18/62 (29%)	Ref		
HypoC4	Yes	2/37 (5%)	0.16	0.037	0.675
	No	20/66 (30%)	Ref		
ESR	Abnormal	21/75 (28%)	8.6	1.2	64.3
	Normal	1/38 (4%)	Ref		
CRP	Abnormal	15/23 (65%)	80	10.7	596.6
	Normal	7/80 (9%)	Ref		
Serum creatinine	Abnormal	15/47 (32%)	3	1.1	7
	Normal	7 (12.5%)			

Table 3 (continued)

Items		SLE patients admitted to ICU	HR	95% CI	
				Lower	Upper
Red cell cast	Yes	9/17 (53%)	4	1.6	9
	No	13/86 (15%)			
RBCs > 5/HPFurine	Yes	9/16 (56%)	4.9	1.95	11
	No	13/87 (15%)			
WBC > 5/HPF urine	Yes	8/11 (73%)	6.5	2.7	15.8
	No	14/92 (15%)			
SLEDAI	Admission	25 ± 12	1.089	1.046	1.135
	Non admission	16 ± 8			
SLICC Damage Index	Admission	7.5 ± 4.6	1.312	1.183	1.455
	Non admission	3.7 ± 2			
Azathioprine	Yes	2/53 (4%)	0.077	0.018	0.33
	No	20/50 (40%)	Ref		
Cyclophosphamide	Yes	4/22 (18%)	0.79	0.27	2.34
	No	18/81 (22%)	Ref		
Chloroquine	Yes	11/81 (14%)	0.2	0.097	0.52
	No	11/22 (50%)	Ref		
Mycophenolate mofetil	Yes	8/20 (40%)	2.73	1.14	6.5
	No	14/83 (17%)	Ref		
Cyclosporine	Yes	3/5 (60%)	3.5	1.04	12
	No	19/98 (19%)	Ref		

SLE systemic lupus erythematosus, *ICU* intensive care unit, *DM* diabetes mellitus, *CVA* cerebrovascular accident, *AMI* acute myocardial infarction, *CVD* cardiovascular disease, *C* complement, *anti-dsDNA* anti-double stranded deoxyribonucleic acid, *CRP* c-reactive protein, *ESR* erythrocyte sedimentation rate, *RBCs* red blood cells, *WBCs* white blood cells, *SLEDAI* SLE Disease Activity Index, *SLICC* Systemic Lupus International Collaborating Clinics Damage Index, *HR* hazard ratio

Table 4 Multivariable Cox regression models assessing factors predicting progression to ICU admission during 12-month follow-up of 103 SLE patients

	Wald	Sig.	Exp (B)	95.0% CI for exp (B)	
				Lower	Upper
CRP	15.159	0.0001	56	7	425
SLEDAI	9.927	0.002	1.073	1.027	1.12
SLICC Damage Index	5.811	0.016	1.15	1.03	1.29

The model is significant $P = 0.0001$

CRP C-reactive protein, *SLEDAI* SLE Disease Activity Index, *SLICC* Systemic Lupus International Collaborating Clinics Damage Index

demonstrate that increases in anti-dsDNA antibody levels and decreases in C3 levels represent meaningful predictors of a subsequent increase in disease activity. However, some studies have shown only a limited association between anti-dsDNA antibodies and SLE flares [36, 37].

Although the increase in anti-dsDNA antibody levels is associated with SLE exacerbations, there are limited data directly addressing the potential clinical benefit associated with reductions in anti-dsDNA antibody levels in patients with SLE.

Treatment is a pivoting factor affecting the survival of SLE. Judicious use of steroid and cytotoxic agents such as cyclophosphamide and azathioprine to achieve better control of disease activity is one of the well-recognized reasons for the improvement in survival of SLE in recent years. However, a balance between immunosuppression and disease control should be kept in mind as heavy immunosuppression with concomitant mega doses of steroids, cyclosporine, and mycophenolate mofetil were associated with an increased risk of admission to ICU.

Our result is in keeping with that from Massardo et al. [38] who also demonstrated that high dose steroids for the treatment of patients with more severe disease were associated with higher mortality in their Chilean SLE patients. Given the strong relationship between heavy immunosuppression and organ damage, efforts should assiduously be made to avoid unnecessary over immunosuppressive treatment in patients with SLE.

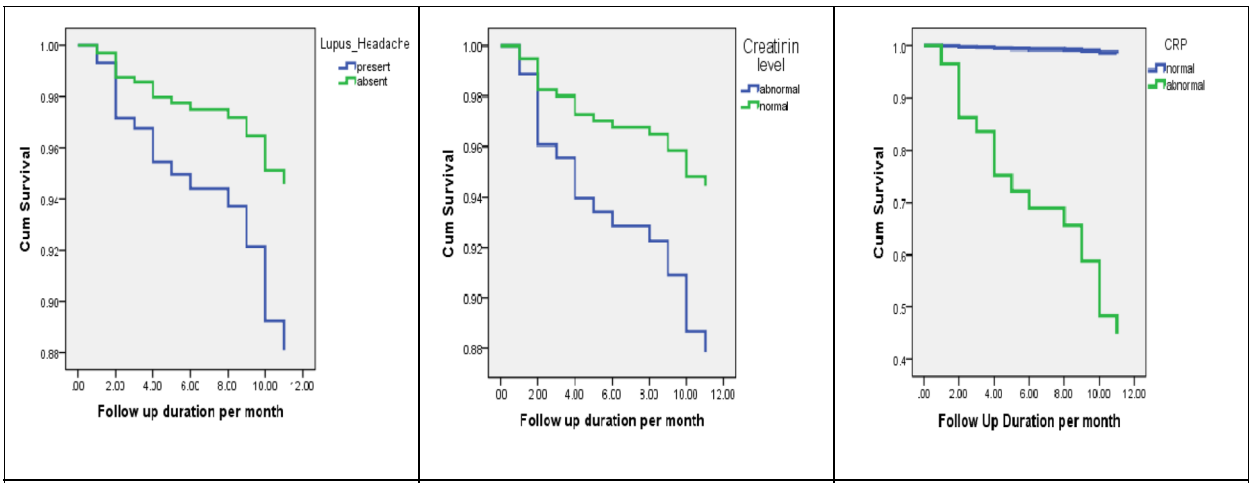

Figure (a): patients (SLE)have lupus headache lower survival curves because, they are more likely to have shorter times to admitted ICU

Figure (b): patients (SLE) have abnormal creatine lower survival curves because, they are more likely to have shorter times to admitted ICU

Figure (c): Abnormal high level CRP of SLE patients have lower survival curves because, they are more likely to have shorter times to admitted to ICU

Fig. 1 The increase of ICU admission with lupus headache (**a**), presence of abnormal creatinine (**b**), and high CRP (**c**)

The development of an infection prediction index that includes the clinical and immunological features of SLE patients is crucial to identify a group at higher risk to develop this complication. The compound measurement of B cells, Th17 cells, and TLR2 expression in monocytes is useful as an infection predictive

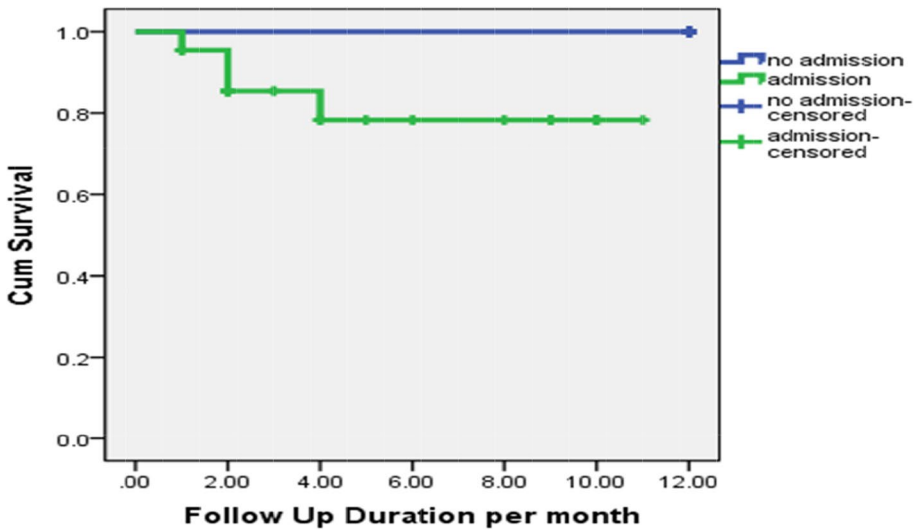

Fig. 2 Kaplan-Meier survival analysis at 12 months of follow-up for survival of 103 SLE patients stratified according to admission to ICU. Non-admitted patients have 100% of survival and admitted patients have 78.9% of survival which is statistically significant by Log-rank test $p = 0.0001$

index in SLE patients. All of the parameters included in the index are readily available using conventional flow cytometry, a technique that has demonstrated diagnostic utility as a compound measurement tool [39].

Conclusions

Our study showed that systemic lupus erythematosus patients with a higher value of CRP, SLEDAI, and damage index value were liable for intensive care unit admission. Good control of disease activity of SLE which in turn reduces damage of different body systems is mandatory. Periodic screening for functions of renal and cardiac systems is of great value. Proper screening and prophylaxis is recommended against variable causes of infections. Rheumatologists should be careful in controlling SLE active disease and to balance the doses of immunosuppressive especially in the presence of infection. They should focus the research on finding more accurate infection predictive index parameters to predict as early as possible the onset of infection.

Abbreviations

SLE: Systemic lupus erythematosus; ANA: Antinuclear antibody; APS: Antiphospholipid antibody; LN: Lupus nephritis; ICU: Intensive care unit; SLICC: Systemic lupus international Collaborating Clinics; SLEDAI: SLE Disease Activity Index; APACHE: Acute Physiology and Chronic Health Evaluation; hs-CRP: High sensitivity C-reactive protein; PH: Proportional hazards.

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Authors' contributions

SM gave the idea of the research, design of the work, and participated in writing. LI and GS contributed to writing, shared in clinical part of the research at Zagazig University Hospitals (from the Rheumatology Department, the Rheumatology Clinic and Internal Medicine Department). GD was responsible for revision the current research and also participated in writing. The authors read and approved the final manuscript.

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Availability of data and materials

The data that support the finding of this study are available at Lobna Ismaeil Kotb (the corresponding author) on reasonable request.

Declarations

Ethics approval and consent to participate

Approval of study conduction was obtained from the Research Ethical Committee at the Faculty of Medicine Zagazig University, No. 6536. All patients included in this study or their close relatives gave written informed consent to participate in this research.

Consent for publication

Non applicable

Competing interests

The authors declare that they have no competing interests.

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