CAUSES AND OUTCOMES OF PATIENTS ADMITTED TO THE INTENSIVE CARE UNIT WITH SYSTEMIC LUPUS ERYTHEMATOSUS

Naveed Haroon Rashid, Maria Ali Khan, Salman Bin Mahmood, Muhammad Aziz, Safia Awan, Ali Bin Sarwar Zubairi

Aga Khan University Hospital Karachi Pakistan

ABSTRACT

Objective: To identify the causes and outcome of patients admitted with systemic lupus erythmatosus (SLE) requiring intensive care unit care in a tertiary care hospital.
Study Design: Retrospective record review study.
Place of Duration of Study: Aga Khan University Hospital, 15 years from Jan 2001 to Dec 2015.
Material and Methods: Medical record of past fifteen years (from 2001 till December 2015) was reviewed for all adult patients (age ≥16) admitted to intensive care unit with SLE. At the time of ICU admission patients were evaluated for demographics characteristics, clinical and laboratory parameters, length of ICU stay, Acute Physiology and Chronic Health Evaluation II (APACHE II) score and mortality.
Results: During the study period, 58 patients were admitted to ICU; 47 (81%) were females and 11 (19%) were males. Out of them 42 (72%) patients died, predominantly with septic shock. The mean age was 36.1 ± 13.3 years. The main reason for ICU admission was respiratory (74%), neurological (50%), renal (18.9%), and cardiogenic (15.5%). Patients who had septic shock and multiorgan dysfunction syndrome had a higher mortality.
Conclusion: Patients with higher APACHE II score, septic shock and multiorgan dysfunction syndrome at the time of admission in ICU had a higher mortality.

Keywords: ICU, Lupus, Mortality.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder of unknown etiology that provokes inflammation in various organs of the body. This is due to the production of antibodies forming immune complexes and complement activation that attack host organs including the skin, muscles, joints, blood, kidneys and brain[1]. The disease mostly affects young females resulting in significant morbidity and mortality[2], mainly secondary to causes like renal failure, circulatory system diseases, pneumonia, and septicemia[3]. Patients can experience frequent episodes of exacerbation which requires treatment with corticosteroids and other immunosuppressive medications[4].

Patients with SLE are at an increased risk of infection secondary to the disease process itself and the use of immunosuppressants. These infections have been attributed to different abnormalities in immunological mechanisms including defects in phagocytosis, chemo-taxis and deficiency in complement[5]. Infection is one of the most common causes of admission to the intensive care unit (ICU) and mortality among patients with SLE[6]. One study has identified inadequate treatment of nosocomial infections as an independent risk factor for mortality[7].

Patients also require ICU admission secondary to severe illnesses such as thrombo-embolic disorder and flare-up of disease that can involve cardiopulmonary, central nervous system or renal function. A bimodal distribution of mortality in SLE has been reported, with the first peak within the first year after diagnosis, mostly attributable to active disease and infections, and a second peak occurring later and mainly due to cardiovascular events[8] where high levels of cystatin C and low estimated glomerular filtration rate (e-GFR) based on cystatin C emerged as strong predictors for all

Correspondence: Dr Naveed Haroon Rashid, Department of Medicine Aga Khan University Hospital, Karachi Pakistan
Email: naveed.rashid@aku.edu
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outcomes[9]. A retrospective analysis performed on patients with SLE admitted to ICU in Spain from 1999-2007 showed that long term survival was negatively affected with age >45 years, presence of any chronic disease, higher APACHE II score (>18) and higher doses of corticosteroids during hospitilization[10].

Despite the serious nature of this disease, there is a dearth of studies on SLE patients admitted to the ICU, especially from the developing world and our study is the first in Pakistan to evaluate ICU admissions in SLE. The main objective of our study was to determine the causes and outcome of patients diagnosed with SLE, who were admitted to the ICU in a largest tertiary care private hospital in Pakistan.

MATERIAL AND METHODS

Total 58 participants were included in this retrospective record review study. Medical record of past fifteen years (from 2001 till December 2015) was reviewed. All the cases coded as 710.0 according to ICD-9 codes (International Classification of Diseases, 9th revision) system and for whom there were sufficient retrievable demographic and laboratory data at the time of admission to the hospital and to the intensive care unit were reviewed. All adult patients; aged ≥16 admitted to intensive care unit (ICU) at the Aga Khan University Hospital with a diagnosis of SLE (n=58) were included. There were no repeat admissions and no patients were missed during the study period. Patients aged less than 16 were excluded.

Table-I: Baseline characteristics of the patients admitted to the intensive care unit with systemic lupus erythematosus (n=58).

Characteristics	Number of cases (%)
Gender	
Male	11 (19.0)
Female	47 (81.0)
Age (years)	
Mean ± SD	36.1 ± 13.3
disease duration (years)**	
Median (Range)	1 (0-20)
Active organ involvements prior to admission*	
Kidney	22 (37.9)
Hematologic	8 (13.8)
Muco-cutaneous	13 (22.4)
Pulmonary	6 (10.3)
Musculoskeletal	6 (10.3)
Neuropsychiatric	12 (20.7)
Cardiovascular	5 (8.6)
Gastrointestinal	3 (5.2)
Patients on steroids before admission	40 (69)
Dose equivalent to prednisolone (mg)	
Median (range)	15 (0-80)
APACHE II score	
Mean ± SD	20.1 ± 7.9
Duration of ICU stay(days)	
Median (Range)	4 (1-30)

*Total number of patients with organ involvement does not add up to 58 because many patients had more than one organ involvement, **The duration is mentioned in years and patients diagnosed on current admission may result in negative values

Ethical approval from the Hospital Ethical Research Committee was taken before the commencement of this study.

The recorded data included demographics (table-I) age, gender, disease duration before admission, known organ involvement prior to admission and APACHE II score within first 24 hours of admission in MICU. The initial laboratory data included complete blood picture, urinalysis, biochemistry, arterial bllod gases and radiological investigations including chest Xray and MRI brain.

Variables recorded during ICU admission were duration of ICU stay, treatment administered, complications and survival. Patients were categorized as survivors if they were discharged and as non-survivors if they expired during their hospital stay.

Definitions of indications for ICU admission employed at our institution are classified as follows: (a) Septic shock is defined as sepsis-induced hypotension persisting despite adequate fluid resuscitation, after the administration of 30 mL/kg crystalloid or 4mmol/L of lactated ringer's[11]; (b) Respiratory failure is defined as arterial oxygen tension/inspired fractional oxygen (PaO2/FiO2) ratio <300 or requiring a ventilator[11]; (c) Acute kidney injury is defined as an abrupt (within 48 hours) absolute increase in the serum creatinine concentration of ≥0.3 mg/dL from baseline; a percentage increase in the serum creatinine concentration of ≥50 percent; or oliguria of <0.5 mL/kg per hour for more than six hours[12]; (d) Altered mental status including seizures, paralysis, encephalopathy (defined as glasgow coma scale score <8, or alterations in

Table-II: Causes of the patients admitted to the intensive care unit with systemic lupus erythematosus (n=58).

Cause of Admission	Number of cases (%)
Cardiogenic	9 (15.5)
Arrhythmia	4 (6.9)
Cardiogenic shock	4 (6.9)
Infective endocarditis	1 (1.7)
Pulmonary	43 (74.1)
Pneumonia	5 (8.6)
Respiratory Failure	36 (62.1)
Alveolar Hemorrhage	2 (3.4)
Neurologic	29 (50.0)
Seizures	4 (6.9)
Encephalopathy	25 (43.1)
Renal	11 (18.9)
Acute Kidney Injury	9 (15.5)
Acute on Chronic Renal Failure	1 (1.7)
Lupus Nephritis	1 (1.7)
Infection	8 (14)
Sepsis	6 (10.3)
Pulmonary Tuberculosis	1 (1.7)
Others	6 (10.3)
Serositis	3 (5.2)
DVT	1 (1.7)
Pancreatitis	1 (1.7)
Autoimmune Hemolytic Anemia	1 (1.7)

mental status)[13]; (e) and need for hemodynamic monitoring not fulfilling the above criteria.

SPSS version 19 was used to enter and analyze data. Patient demographics (table-I) were expressed as frequency and percentages or mean and standard deviation. The Fischer exact test was used to compare categorical data, and Mann Whitney U test (non parametric test) was used for continuous variables. Risk factors associated with non-survival were analyzed. A *p*-value of <0.05 was taken to be statistically significant.

RESULTS

Fifty-eight patients diagnosed with SLE were admitted in medical ICU from January 2001 to December 2015, out of which 81% were female. The mean age (SD) of the patients was 36.1 ± 13.3 years. The median duration of SLE disease before admission to ICU was 1 year (range 0-20 year). SLE was first diagnosed in 18 patients during their stay in the ICU. In this group, the mean duration of ICU stay was 7 days and the survival rate was 16.6% (n=3).

Table-III: Comparison of factors (categorical variables) associated with survival and non-survival patients with SLE admitted to ICU (n=58).

Characteristics	Survivor n=16	Non-Survivor n=42	*p*-value
Gender Male Female	 4 (36.4) 12 (25.5)	 7(63.6) 35 (74.5)	0.353
Previous medications			
Steroid	12 (30.0)	28 (70.0)	0.391
Azathioprine	2 (18.2)	9 (81.8)	0.357
Cyclophosphamide	0 (0.0)	1 (100.0)	0.724
Mycophenolate mofetil	0 (0.0)	4 (100.0)	0.264
Known organ involvement			
Renal	7 (31.8)	15 (68.2)	0.393
Muco-cutaneous	0 (0.0)	13 (100.0)	0.008
Musculoskeletal	0 (0.0)	6 (100.0)	0.130
Neuropsychiatric	3 (25.0)	9 (75.0)	0.567
Cardiovascular	2 (40.0)	3 (60.0)	0.424
Gastrointestinal	0 (0.0)	3 (100.0)	0.372
Hematologic	1 (12.5)	7 (87.5)	0.287
Pulmonary	1 (16.7)	5 (83.3)	0.466
Intervention			
Need for Vasopressors	8 (17.8)	37 (82.2)	0.004
Ventilator	16 (27.6)	42 (72.4)	*p*-value not computed
Dialysis	4 (22.2)	14 (77.8)	0.391
Need for steroids	16 (27.6)	42 (72.4)	*p*-value not computed
Immunosuppressant	5 (100.0)	0 (0.0)	0.001
Surgical intervention	1 (16.7)	5 (83.3)	0.466
Causes of ICU admission			
Neurologic	5 (17.2)	24 (82.8)	0.070
Infection	0 (0.0)	7 (100.0)	0.090
Renal	2 (18.2)	9 (81.8)	0.357
Pulmonary	12 (27.9)	31 (72.1)	0.605
Cardiogenic	1 (10.0)	9 (90.0)	0.165

Out of 58, most patients had renal involvement (n=22), followed by muco-cutaneous (n=13) and neuropsychiatric (n=12) on ICU admission. The mean APACHE II score was 20.1 on presentation to ICU.

Forty patients (69%) were on corticosteroids before admission with a median dose equivalent to 15 mg/day of prednisolone (table-I). Eighteen (31%) received immunosuppressive therapy other than steroids out of which 11 (61%) were on azathioprine, 4 (22%) on mycophenolate mofetil, 4 (22%) on methotrexate and 1 (5.5%) on cyclophosphamide. Moreover, 2 (11.1%) patients received hydroxychloroquine. All immunosuppressants other than steroids were stopped on ICU admission.

The major indications for ICU admission were respiratory failure on presentation in 36 (62%) patients, encephalopathy in 25 (43%) patients and acute kidney injury (AKI) in 9 (15.5%) patients. Other indications for admission to ICU are listed in table-II.

Infection was found in forty eight (83%) of our patients. UTI was the major nosocomial infection in 26 patients (54%) followed by pneumonia in 25 patients (52%), bacteremia (positive blood cultures) in 15 (31.25%) and CNS infection in 4 (8.3%). The focus of infection could not be identified in 2 patients. Microbial agents were identified in 32 (66.6%) patients out of which the commonest one was Acinetobacter baumannii 7 (21.8%) followed by Escherichia coli 6 (18.7%) and Pseudomonas aeruginosa 4 (12.5%). Fungus was isolated in 24 (50%) patient admitted with SLE out of which 17 (70.83%) were Candida albicans followed by Aspergillus flavus 3 (12.5%).

All 58 patients needed mechanical ventilator support mainly due to respiratory failure, encephalopathy and acute kidney injury AKI. In addition, 78% required vasopressor therapy and 31% required dialysis. All patients were treated with systemic corticosteroids while 5 patients were managed with additional immunosuppressant therapy. Twenty six patients (45%) received pulse steroid therapy with a median dose of 3000mg during admission in ICU.

The most common complication encountered during ICU stay in our patients was pulmonary (40%), acute worsening of chronic kidney disease (AKI on CKD) (26%) and encephalopathy (24%). Other complications included cardiopulmonary

Table-IV: Comparison of factors (continuous variables) associated with survival and non-survival patients with SLE admitted to ICU.

Characteristics	Survivor (n=16) Mean Rank	Non-Survivor (n=42) Mean Rank	*p*-value	Mean Differences
Age	23.06	31.95	0.073	-1.793
ICU stay (days)	28.19	30.00	0.713	-0.367
Floor stay	41.06	25.10	0.001	-3.248
APACHE II	16.06	34.62	0.000	-3.747
Disease duration (years)	29.72	29.42	0.948	-0.065
Hospital stay in days	36.72	26.75	0.044	-2.013

Non parametric -Mann-Whitney Test applied.

Table-V: Comparison of factors (continuous variables) associated with survival and non-survival patients with SLE admitted to ICU with crude OR.

Characteristic	Survivor n=16	Non-Survivor n=42	Crude OR	(95% CI)	*p*-value
Need for vasopressors					
No	8 (61.5)	5 (38.5)	1*	1	
Yes	8 (17.8)	37 (82.2)	7.40	1.911, 28.651	0.004

*Reference category.

arrest (14%), gastrointestinal bleeding (9%), disseminated intravascular coagulation (DIC) (10%) and AKI (12%).

Table-III shows comparison between survivors and non-survivors. A total of 16 patients (28%) survived. The major causes of mortality were septic shock (n=30), respiratory failure (n=6). Intracerebral bleed (n=4) and cardiogenic shock (n=2). There was a significant difference in need of vasopressors in the non-survivor group as compared to survivor (82.2% vs 17.8%) with a *p*-value of 0.004.

As shown in table-IV, ward stay, hospital stay and APACHE II score were significantly associated with survival of patients. The mean APACHE II score was 16.06 in survivors and 34.62 in non survivors (*p*-value <0.001).

As shown in table-V, mortality of patient was significantly associated with need for Vasopressors. Out of 58 patients of SLE, 37 (82.2%) patients were in need for vasopressors in the non-survivor group. Need for Vasopressors was seven times higher as compare to those with survivors [Crude Odd Ratio (COR) 7.4; 95% CI: 1.911, 28.651; *p*-value: 0.004].

DISCUSSION

We found a high mortality rate in our SLE patients (72%) who were admitted to the medical ICU. This was reportedly higher than other studies found in literature where the mortality ranged from approximately 30-60%[14-17]. Differences in incidence, prevalence and mortality from SLE between and within ethnic groups have been reported by several authors, suggesting that these disparities are due to genetic or environmental effectors[18] including population parameters, APACHE II scores in the first 24 hours of ICU admission and reasons for admission to ICU.

A number of factors may have contributed to the higher mortality rate in our study. Eighteen (31%) patients were newly diagnosed with SLE during ICU admission in comparison to 9 (14.8%) by Siripaitoon et al[17]. These patients presented with flare-up of the disease. In those who were on maintenance therapy, this might have contributed to immunosuppression leading to development of infectious complications as evident in 48 of our patients. Majority of the patients also had known organ involvement prior to admission. Hence, both disease and treatment related factors may have contributed to the risk of acquiring a critical illness.

Septic shock was the most common cause of death, responsible for mortality in 52% of patients, with pneumonia as the most frequent source of infection. This is in comparison to a studies done in North India[19] and Malaysia[20] in which active SLE and/or infection caused most patient deaths. A greater proportion of non-survivors developed infection during ICU stay and this finding is consistent with results reported previously as demonstrated by a 40% mortality rate of SLE patients with infection versus 11% in SLE patient without infection as reported by Han et al[6].

We found a non-significant association between higher APACHE II scores and mortality (22.6 ± 6.7 vs 13.5 ± 7.1, *p*=0.649). This association has been evaluated previously in literature with inconsistent results. Some studies have found a significant association[7,14,16] while others demonstrated little or no evidence in this regard[16,21].

Another independent risk factor associated with mortality was the need for vasopressor therapy (OR=7.40, 95% CI= 1.911-28.651, *p*=0.004). Both of these findings are consistent with those reported by Namendys-Silva et al[15] from Mexico. Other reported factors associated with mortality are lupus nephritis[21], GI bleed, intracranial bleed and septic shock[16]. However, our study found no association between these factors and the risk of mortality.

The survivors exhibited a higher rate of receiving immunosuppressant in addition to steroids (100% vs 0%, *p*=0.001), although the small number (n=5) is not enough to comment on this finding.

A study done by Kang et al. analyzed the mean cumulative prednisolone dose and the mean prednisolone dose during 1 month before death in SLE patients with early and late deaths. There was no significant difference in the mean dose during 1 month before death, while the cumulative dose was significantly higher in patients with early death than in those with late deaths[22]. In our study, the association between use of steroids and survival rates was nonsignificant. Interestingly, our results demonstrated significant muco-cutaneous involvement in non-survivor patients prior to ICU admission (p=0.008).

The major strength of our study was that APACHE II scores were calculated for every patient upon admission to ICU within 24 hours. Also, this is the first study of its kind from this region of the world.

A major limitation of this study was its retrospective design due to which we were not able to calculate the modified SLEDAI-2K scores to correlate disease activity with prognosis[23]. We were also not able to test the hypothesis for some parameters. For example, even though the overall effect on survival of immunosuppressant was significant, we could not test the effect of individual agents separately due to the limited number of subjects. Siripaitoon et al. demonstrated a survival benefit of patients taking azathioprine 3 months prior to admission (OR=0.10, 95% CI= 0.02–0.49, p=0.001)[17].

CONCLUSION

Patients with higher APACHE II score, septic shock and multiorgan dysfunction syndrome at the time of admission in ICU had a higher mortality.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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