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LUPUS AROUND THE WORLD

Predictors and outcome of systemic lupus erythematosus (SLE) admission rates in a large teaching hospital in sub-Saharan Africa

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Although it was previously believed that systemic lupus erythematosus was uncommon among Africans, it has become increasingly apparent that the incidence is higher, and socioeconomic challenges such as physician shortages, poor medical facility access, and poor health literacy may worsen prognosis. This retrospective study examines characteristics and outcomes of hospitalized systemic lupus erythematosus patients over a two-year period and serves as a baseline for comparison for future studies to examine the outcomes with the provision of more dedicated care. There were 51 patient admissions over a two-year period, with a mean duration from start of illness to admission of approximately two years. Duration of admission ranged from one to 140 days with a mean period of 26.12 days (SD ± 26.6). There were 22 deaths (43.1% of admissions), which were mainly due to infections and renal complications. Factors associated with risk of death in regression analysis were: infections, fever, disease flare, musculoskeletal involvement, amenorrhea, depression, a clinical finding of hepatomegaly, and chest infection. Understanding the effect and outcome of systemic lupus erythematosus across different countries can elucidate the role of genetic, environmental, and other causative factors in the progression of the disease. *Lupus* (2018) **27,** 336–342.

Key words: Systemic lupus erythematosus; infections; hospitalization; mortality; Africa

Introduction

Systemic lupus erythematosus (SLE) is a multisystem connective tissue disorder characterized by the presence in the blood of antibodies directed against components of cell nuclei driven by a defective clearance of antigens through apoptosis.[1,2] The exact cause is unknown; however, it is believed to be an interaction between genetic and environmental factors.[3–6]

The prevalence of SLE varies worldwide with substantial age and racial disparities.[7–10]

Until recently, SLE was thought to be rare in sub-Saharan Africa.[11] However, recent evidence suggests that people of African descent develop the condition and at an earlier age. In addition, people of African descent in general have more than twice the incidence rate as compared to Caucasians.[12] Comparatively, people of African descent have an increased burden of renal disease and are more likely to progress to end stage renal disease (ESRD).[13]

Owing to the relative lack of awareness among the general public and health professionals, SLE cases in Africa are usually diagnosed late, resulting in poor outcomes.[14–16]

The mortality rate associated with SLE is substantial, although recent reports have shown significant improvement due to better treatment and supportive management over the past decade.[17]

SLE patients have one of the highest hospital admission and readmission rates compared to those with other chronic illnesses, as well as higher in-hospital mortality and opportunistic infections.[18–20]

Other factors that may influence frequent admissions and outcome include non-adherence to

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treatments, presence of active lupus nephritis, and multisystem disease.[21]

Environmental, socioeconomic/demographic, psychosocial, genetic, and clinical factors obviously play an important role in SLE outcomes worldwide. These disparities in disease expression are due to the interaction between genetic and non-genetic (environmental, socioeconomic-demographic, cultural, and behavioral) factors, as has been shown in the LUMINA (Lupus in Minorities: Nature vs nurture) cohort.[22]

Other challenges in caring for SLE patients in sub-Saharan Africa include poor diagnostic and hospital facilities, lack of experience by physicians in the management of SLE, the use of substandard drugs and antibiotics and lack of proper treatment for the underlying immune condition, and inadequate hospital support such as intensive care units (ICUs).[23]

The present study examined the demographic characteristics of critically ill SLE patients who were admitted to a teaching hospital in Ghana to determine the clinical presentation, examination, and laboratory findings and describe the final diagnosis confirmed on admission and clinical outcome of management.

The present retrospective study examined outcomes of SLE before the establishment of a rheumatology unit and a trained rheumatologist, as a baseline for comparison for future studies to look at the outcomes with the provision of more dedicated care.

Defining the burden of SLE across different countries can elucidate the role of genetic, environmental, and other causative factors in the progress of the disease, and help define possible clinical, therapeutic, and societal concerns across different areas of the world.

Method

A retrospective study with prospective follow up of hospitalizations between 2007 and 2009 at the Korle bu Teaching Hospital was conducted of patients with SLE meeting the revised American College of Rheumatology (ACR) criteria.[24] Data were collected on patients admitted during the two-year period to describe the characteristics, outcome, the incidence and risk factors for hospitalization in SLE in sub-Saharan Africa. Data were obtained from the hospital folders and those on admission and were followed up until discharge or death, if that was the final outcome on the ward. The following patient information was recorded: age, sex, time course of SLE, lupus organ involvement profile, number of admissions per patient, reasons for hospital admissions, and the outcome, including the length of hospital stay, readmission or death, medical records, and discharge reports for each patient. Ethical approval was not required at the time for this sort of chart review or consent from patients. SPSS capturing data used for analysis are available for review.

Analysis of results. The analyses were conducted in three stages using SPSS 20. First, frequencies, means, standard deviations, and percentages were conducted on the sociodemographic characteristics of the patients (Table 1). Second, descriptive analyses of the various prospective predictors were carried out (see Tables 2 through 5). Finally, multiple logistic regression analyses for dichotomous outcome were performed to determine which risk factors predict death and disability. As several risk factors were investigated, the analyses employed a

Table 1 Age and sex characteristics of SLE patients admitted on the medical ward of the Korle bu Teaching Hospital

Age group (years)	*Gender*		*Total*
	Male n *(%)*	*Female* n *(%)*	
10–19	1 (16.7)	5 (11.1)	6 (11.8)
20–29	1 (16.7)	22 (48.9)	23 (45.1)
30–39	1 (16.7)	9 (20.0)	10 (19.6)
40–49	2 (33.3)	6 (13.33)	8 (15.7)
50–59	1 (16.7)	2 (4.4)	3 (5.9)
60–69	0 (0.0)	1 (2.2)	1 (2.0)
Total	6 (100)	45 (100)	51 (100)

SLE: Systemic lupus erythematosus.

Table 2 Systems involved at presentation by SLE patients admitted to the Korle bu Teaching Hospital

	Yes Frequency (n = *51*)	*No Frequency* (n = *51*)	*Yes (%)*
	Complaints and system involved		
General flare	44	7	86.3
Cardiovascular system	26	25	51.0
Nervous system	21	30	41.2
Musculoskeletal system	32	19	62.7
Mucocutaneous	35	16	68.6
Gastrointestinal system	11	40	21.6
Respiratory system	17	34	33.3
Genito-urinary system	23	28	45.1
Infections	29	22	56.9

SLE: Systemic lupus erythematosus.

Table 3 Medical history of SLE patients admitted to the Korle bu Teaching Hospital

	Yes Frequency (n = *51*)	*No Frequency* (n = *51*)	*Percentage Yes (%)*
Morning stiffness	2	49	3.9
Nodules	0	50	0.0
Skin rash	39	9	76.5
Thrombosis	1	47	2.0
Raynaud's phenomenon	5	43	9.8
Ulcers	3	40	5.9
Fatigue	38	9	74.5
Fever	35	13	68.6
Depression/anxiety	24	24	47.1
Seizures	11	37	21.6
Significant infection	21	27	41.2
Disability (writing, dressing)	29	19	56.9
Amenorrhea	29	13	56.9
Contraceptive use	6	41	11.8
Acute flares	31	20	60.8
Environment precipitant	4	47	7.8
Food precipitant	1	50	2.0
Medication precipitant	1	50	2.0
Other	4	47	7.8
No known precipitant	41	10	80.4
Family history of SLE	3	48	5.9
Smoking	0	51	0.0
Alcohol use:			
No	41		80.4
Yes, but not significant	6		11.8
Significant use (14–21 units/week)	3		5.9

SLE: Systemic lupus erythematosus.

Table 4 Clinical and laboratory findings in SLE patients admitted to the Korle bu Teaching Hospital

	Yes Frequency (n = *51*)	*No Frequency* (n = *51*)	*Percentage Yes (%)*
Clinical features			
Pallor	46	4	90.2
Rash	35	15	68.6
Chest consolidation	15	34	29.4
Chest infections	23	26	45.1
Splenomegaly	5	44	9.8
Hepatomegaly	12	37	23.5
Paraparesis or plegia	12	37	23.5
Myopathy	8	40	15.7
Meningism	4	45	7.8
Ascites	14	35	27.5
Serositis	12	37	23.5
Fibrosis	4	45	7.8
Endocarditis	1	48	2.0
Pericarditis/pleural effusion	4	45	7.8
Hypotension	1	48	2.0
Heart failure	17	32	33.3
Hypertension	10	39	19.6
Large joints	1	50	2.0
Generalized	29	22	56.9
PIP Joint involved	18	33	35.3
DIP joint involved	1	50	2.0
Laboratory features			
ANA	41	10	80.4
dsDNA	27	24	53.0
ENA	6	45	11.8
Low hemoglobin	41	10	80.4
Low WBC	4	46	8.7
High WBC	14	37	30.4
Low platelets	13	28	25.5
High urea	25	26	49.0
High creatinine	24	27	47.1
High ESR	21	30	41.2
Low total protein	10	41	19.6
Low albumin	29	22	56.9
Drugs used			
Prednisolone	45	6	88.2
Antibiotics	39	12	76.5
Immunosuppressive drugs	18	33	35.3
Ace inhibitors	26	21	51.0
Diuretics	27	20	53.0
Proton pump inhibitors	40	7	78.4
Calcium supplements	9	38	17.6
Anticoagulation	16	35	31.4
Hematinics	20	27	42.6

PIP: proximal interphalangeal joints; DIP: distal interphalangeal joints; WBC: white blood cells; ANA: antinuclear antibodies;dsDNA: double stranded deoxyribonucleic acid; ENA: extractable nuclear antigen; ESR: erythrocyte sedimentation rate; SLE: systemic lupus erythematosus.

bootstrapping procedure; specifically, a backward elimination to yield a parsimonious model. The odds ratios of each of the risk factors on death and disability are presented in Table 6.

Results

Socio-demographic characteristics of the respondents

Fifty-one patients (51) were involved in the present study, of which 45 (86.5%) were females.

Females constituted most of the patients, 86.5% ($n = 45$). Overall, the female to male ratio was 7.5 : 1.

The mean age of the males was 36.5 (SD ± 13.9) years and females 30.4 (SD ± 11.4) years, and among all patients, 31.1 (SD ± 11.7) years with a range of 14 to 68 years. The majority of them, 56.9% ($n = 29$), were single, with 36.5% of them never having been married. The rest of them were separated.

The majority of the patients, 28.8% ($n = 15$), were students. Approximately 38% (20) of the patients had professions, mainly in the sales, trading, and services sector. A total of 7.7% ($n = 4$) of the patients were unemployed and 23.1% ($n = 12$) of the patients had attained at least basic education.

About 23.1% ($n = 12$) of the patients had attained at least basic education, and 67.3% were

Table 5 Final diagnosis and clinical outcome among critically ill suspected SLE patients admitted to the Korle bu Teaching Hospital

	Patient's sex		
Characteristic	*Male (%)*	*Female (%)*	*Total no (%)*
Diagnosis			
SLE	5 (83.3)	38 (84.4)	43 (84.3)
MCTDx	1 (16.7)	7(15.6)	8 (15.7)
Total	6 (100.0)	45 (100.0)	51 (100.0)
Outcome			
Died	0 (0.0)	22 (48.8)	22 (43.1)
Alive	5 (83.3)	23 (51.2)	28 (54.2)
Disabled	1 (16.7)	0 (0.0)	1 (2.1)
Total	6 (100.0)	45 (100.0)	51 (100.0)

MCTDx: mixed connective tissue disease; SLE: systemic lupus erythematosus.

Table 6 Multiple logistic analysis of predictors (risk factors) for death and disability

Risk factor	*Odds ratio*	*95% (CI)*	p
Musculoskeletal	1.30	(1.00–.86)	0.35
PIP pain	1.64	(1.01–2.18)	0.03
Fever	1.60	(0.00–0.84)	0.02
Cardiovascular	8.77	(0.94–81.49)	0.06
Fatigue	38.39	(0.80–1838.82)	0.66
Depression	70.98	(11.75–85.80)	0.01
Parity	491.12	(132.63–895.14)	0.07
Amenorrhea	9.69	(2.86–27.95)	0.02
Pallor	1.02	(.01–.79)	0.86
Consolidation	1.04	(.12–1.29)	0.71
Chest infection	95.84	(2.44–98.61)	0.00
Hepatomegaly	49.70	(2.35–101.37)	0.01
Nervous system defect	8.95	(.95–84.31)	0.06
Paresis/plegia	11.03	(1.40–86.66)	0.72
Calcium	1.05	(.00–1.22)	0.66
Hematinics	71.65	(1.88–172.37)	0.02

CI: confidence interval; PIP: proximal interphalangeal joint.

educated. The majority did not drink alcohol, 82% ($n=41$).

The socio-demographic characteristics are reported in Table 1.

The cause of admission, as stated in admission diagnosis, was clinical flare of SLE in 86.3% and infection in 56.9% (some had multiple diagnoses). Duration, in weeks, from the start of symptoms to their diagnosis of SLE ranged from four to 572 weeks, with a mean of 100.6 (SD $\pm$ 125.9) weeks.

Duration of admission ranged from one to 140 days with a mean of 26.12 (SD $\pm$ 26.6). There were 22 deaths (43.8% of admissions). The deaths were mainly due to infection and renal complications.

Flares were reported in 61.7% ($n=31$); however, 78.7% did not know the cause of their flare. A total of 60.4% ($n=29$) reported that they were depressed.

The majority of the patients (95.7%; $n=45$) were treated with some form of steroid whilst 81.2% ($n=39$) received antibiotics during their stay and 32% ($n=16$) were anticoagulated. Low hemoglobin (<9 g/dl) was common: 89.1% ($n=41$).

Using multiple logistic regression analyses, chest infections ($p=0.00$); fever ($p=0.03$); disease flare—usually manifesting with musculoskeletal involvement, usually PIP joint involvement ($p=0.03$); amenorrhea ($p=0.03$); and self-reported depression ($p=0.01$); a clinical finding of hepatomegaly ($p=0.01$); and chest infection ($p=0.00$) were associated with risk of death.

Discussion

We report on 51 SLE patients seen over a two-year period, focusing on only those who were critically ill and required admission. Compared to earlier figures in Ghana, the prevalence of SLE increased from an estimated 2.4/1000 previously reported to a prevalence of 5.28/1000.[14]

Systemic lupus erythematosus (SLE) is said to be rare in people of African ancestry.[25] To our knowledge, there are no records of SLE before the 1960s that document the incidence in sub-Saharan Africa, and it had been reported to be rare in West Africa.[26] In contrast, SLE is reported to be high in Afro-Caribbean populations and West Africans who have relocated to Western countries such as the United Kingdom (UK) and the United States of America (USA).[27]

Most reports show increasing numbers over time.[28,29] In the 1980s, Kanyerezi et al. reported on 21 patients with SLE in 11 years at the Mulago Hospital, Uganda, and 31 cases over a six-year period in Zimbabwe.[30]

In Ghana, the largest numbers were recorded by Affram and Neequaye in 1991, describing 11 cases of SLE and other rheumatic disorders admitted over a six-year period in Ghana.[31] Adelowo and Oguntona also described 66 cases of SLE in 2009 in Nigeria over a period of time.[15]

Recent reports from South Africa show even larger numbers.[32,33] These reported studies suggest an increasing prevalence with time and the accounts of a high prevalence of SLE in recent migrants from West Africa to the West suggest that the disease might not be rare in West Africa.[34] Other factors

that might account for the higher numbers may be improved diagnosis due to increased awareness in primary care, improved access to health care, better access to diagnostics, and some improvement in the numbers of specialist physicians.

The most common causes for admission in our study were a flare, in 86.3%, and infections, in 56.9%, with overlap. The most common systems associated with a flare were the musculoskeletal (62.7%), mucocutaneous (68.6%), cardiovascular (51.0%), and renal (45.1%).

In the Hopkins Lupus Cohort, activity of SLE accounted for 35% of admissions and infections were responsible for 14% of admissions.[35] Infections play a major role in morbidity and mortality in SLE; they are common in hospitalized SLE patients and related to overall disease activity.[20,36] Infections are a major predictor of death (OR 7.3, $p < 0.01$) and young patients with coexistent infections are most likely to die from the disease.[37] Our patient population was young, with mean age of 31.1 (SD $\pm$ 11.7) years and a range between 14 and 68 years.

Studies show most SLE initial hospitalization usually occurs 0–3 years after diagnosis and it is basically due to lupus flare without visceral involvement. Later admissions are usually due to infections. Hence, patients with very active disease at the initial stage should be monitored closely.[38] Most of our patients had a disease duration from four to 572 weeks with a mean of 100.6 (SD 125.9); a mean of about two years from diagnosis and 61.7% reported previous flares suggesting active disease.

Duration of admission ranged from one to 140 days with a mean of 26.12 (SD 26.6). This is higher than most studies worldwide have reported.[37–39] This may be due to the inadequate health care services and lack of ICU services or the more complicated visceral organ involvement at the time of admission and high infection rate requiring a protracted hospital stay.[14]

Renal involvement was common among our admitted patients and accounted for the second most common cause of death. The African American race has been associated with ESRD in SLE[40] and, coupled with poor health systems, might account for the very high mortality rate.

Ethnic differences occur in SLE in terms of disease expression and outcome. Environmental, socioeconomic/demographic, psychosocial, genetic, and clinical factors play an important role as contributing factors in the ethnic differences observed. Measures aimed at eliminating these disparities are needed through research to clarify the source of these disparities and how changes can be made to reduce those that are modifiable, such as reducing the impact of poverty and poor access to treatment.[41]

Erythrocyte sedimentation rate, Complement C3 and C4, and anti-dsDNA (double stranded deoxyribonucleic acid) can be used in the evaluation and management of patients with SLE.[42] Most of our patients were not able to have their serological tests due to cost constraints and an absence of diagnostic laboratories specialized in carrying out such tests at the time of data collection. Of the total number of patients, ANA (antinuclear antibodies) were positive in 91.1% and dsDNA was positive in 35.7% (19.2% did not do the test).

Prednisolone and other forms of steroids were used in 95.7% of patients and antibiotics in 81.3%, suggesting more patients were treated for infections than alluded to in their admission diagnosis. Only 38.3% were on additional immunosuppressive drugs and it was not clear if this was due to intercurrent illness, that is infections, or unavailability of the drugs due to cost constraints as well as substandard drugs in sub-Saharan Africa.

There were 22 deaths (43.1% of admissions), a very large proportion even compared to other studies from Africa.[16] Most deaths were due to renal and infectious complications. Factors that were associated with the risk of death from multiple logistic regression analyses include factors associated with systemic infections, namely fever, a clinical finding of hepatomegaly (which may be a manifestation of systemic infection or cardiovascular compromise), and chest infection. Disease flare manifested typically with musculoskeletal involvement (frequently PIP joint involvement), amenorrhea (which is known to be common with severe disease),[43] and self-reported depression.

These data were collected when there was no fully trained rheumatologist in Ghana. Hospitalization at a hospital experienced in the treatment of SLE patients, compared to hospitalization at a less experienced hospital, is associated with decreased in-hospital mortality in all groups of patients with SLE, and this was not linked to the general quality of medical care.[44] This could have influenced the high mortality observed in our patients.

Hospital mortality in hospitals that treat larger numbers of SLE patients is lower than the expected number of deaths among such patients. Some studies also report that physicians' experience in treating SLE is more crucial in determining in-hospital mortality than a hospital's annual SLE caseload.[44] Rheumatology as a subspecialty has only been

active in Ghana over the past six years, with only two specialists currently serving the whole country. These data may have an impact on the development of policies aimed at eliminating health disparities in the management of these conditions and argue for the training of more personnel.

Conclusion

Infections cause death and should be one of the priorities of treatment when SLE patients are hospitalized. Patients with active disease at diagnosis should be monitored closely as they are more likely to be admitted. There is a high proportion of lupus nephritis among patients in Ghana, and follow up studies should be conducted to determine factors that may help improve outcome in patients and determine possible reasons for the apparent increasing prevalence of SLE in sub-Saharan Africa. Further, ways need to be found to reduce the high mortality in hospitalized patients. We hope to replicate this study in the future to determine if the presence of a dedicated team of trained rheumatologists would improve patient outcome.

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