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Systemic lupus erythematosus in Saudi Arabia: morbidity and mortality in a multiethnic population

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The objective of this study is to summarize the features of patients with Lupus erythematosus in Saudi Arabia. Racial differences of patients and predictors of mortality are assessed. Ninety-three patients treated for SLE at the University Hospital in Jeddah were reviewed. Frequencies of clinical manifestations, causes of admission and causes of death were analysed. Variables predicting mortality were assessed by logistic regression and survival probabilities were estimated by the Kaplan–Meier method. The most frequent presenting symptoms were arthritis (68%) and fever (58%). Renal involvement was seen in 61% of patients. The majority of patients (61%) showed ANA titers higher than 1:1280. C4 levels were significantly lower in patients who died during the observation period than in survivors. The overall five-year survival rate was 92%. Variables predicting early death (<2 years after diagnosis) were young age at diagnosis, male sex and skin involvement. Death after more than two years correlated with older age at diagnosis and renal involvement. Patients of African descent had higher rates of neurological involvement and renal failure. The mortality in this group was highest, though this was not statistically significant. The overall survival in our cohort compares with mortality rates reported from western countries. However, renal disease tends to be common and has a severe prognosis, and thus merits additional attention. *Lupus* (2007) **16**, 908–914.

Key words: Arab; mortality; race; SLE

Introduction

Systemic Lupus erythematosus (SLE) is an autoimmune disease with a broad spectrum of clinical manifestations. Different ethnic populations were reported to have different prevalence rates as well as different predominant symptoms.[1,2] During the last decades, prognosis has significantly improved, mostly due to early diagnosis and more appropriate immunosuppressive therapies. Studies report five-year survival rates of more than 95% in some patient cohorts,[3] whereas in other settings poor prognosis is still observed.[4]

Previous studies have indicated that mortality in SLE shows a bimodal pattern.[5] Early deaths (<2 years after diagnosis) are more often a result of active SLE or infections, whereas late deaths (>2 years) are more frequently caused by infections and diseases not directly related to SLE (e.g., atherosclerotic vascular disease). To investigate the evolution and prognosis of SLE patients in Saudi Arabia, a country with a high rate of expatriates with different ethnic background, we retrospectively analysed the presenting symptoms as well as the morbidity and mortality of SLE patients.

Patients and Methods

The study population included a random sample of 93 patients treated for SLE at the King Abdulaziz University Hospital (KAUH), during the last six years. The KAAUH is a 700-bed teaching hospital in Jeddah, Saudi Arabia. It provides free health service to the patients and is, thus, the major treating hospital for the economically weaker segments of the Saudi population as well as for expatriate workers and their families.

Files of the all patients were systematically reviewed using a standardized questionnaire. Patients were grouped according to their ethnic backgrounds as Arabs (Saudi, Yemeni, Palestinian), Africans (Eritrean, Ethiopian, Sudanese, Chadian), Southeast Asians

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(Philippines, Indonesian, Thai, Burmese) or coming from the Indian Subcontinent (India, Pakistan). The symptoms of clinical manifestation were extracted from the first visit or admission to the hospital. Whenever multiple results existed, the immunological and laboratory data of the first test were used. The hospital laboratory used commercially available routine assays for immunological and other laboratory tests. The latter file data were then assessed for the development of complications (e.g., renal failure, thrombosis, death). Diagnoses were performed on clinical grounds and verified by the appropriate techniques. When clearly documented in the records, the events were recorded. Reasons for admission were extracted both from the admission protocols and the final reports for each individual admission. They were classified as per: a) active SLE, b) infections, c) renal causes, d) vascular causes and e) other causes.

Data analysis: Statistical analysis was carried out using SPSS 10.0 for Windows. Conventional χ^2- and Fischer's exact tests were used to analyse qualitative association in exploratory univariate analysis. *P*-values <0.05 were taken to indicate statistically significant results and values <0.1 were reported as well. A logistic regression analysis was performed to assess the impact of factors in a multivariate model. For survival analysis, survival time was defined as the time interval from the date of diagnosis until death or last contact. Survival probabilities were calculated using the Kaplan–Meier lifetime analysis method. Survival probabilities in different groups were compared using a Log-rank test. To examine influence of multiple variables on survival probability a Cox proportional hazards regression model was generated. The risk ratios for multivariate models as well as their 95% confidence intervals were calculated as the exponentials of the regression coefficient of each covariate.

Results

General characteristics of the study population

The study population consisted of 84 female (90.3%) and 9 male (9.7%) patients (ratio 10:1). Fifty-six percent of the patients were Saudi nationals; 69 patients (74%) of Arabic descent, seven (8%) Africans, seven (8%) Southeast Asians and nine (10%) originated from the Indian subcontinent. Mean age at time of diagnosis was 24 ± 10 years (range 7–55 yrs); 22% of the patients were diagnosed as having SLE at an age older than 30 years. The majority of the cases (61%) were diagnosed primarily at our institution. The mean time of follow-up was 3.8 ± 0.4 years (range 0–15 yrs).

Clinical manifestations of SLE

Table 1 summarizes the patients' manifestations of SLE. Fifty nine patients (68%, CI = 58–78%) presented with arthritis affecting one or more joints, 52 (58%, CI = 47–68%) had elevated body temperature. Thirty three (37%, CI = 26–46%) presented with skin manifestations, the most frequent was 'butterfly rash', followed by phototoxicity and mucous membrane involvement. 18 patients (19%, CI = 11–28%) experienced neuropsychatic involvement of SLE. The single most frequent neurologic symptoms were seizures, seen in nine patients (10%, CI = 4–16%). Signs of nephropathy like proteinuria or urinary casts were seen in 57 patients (61%, CI = 51–72%). Nephrotic syndrome, defined as proteinuria of more than 3 g per day, was found in 19 patients (20%, CI = 12–29%). During the follow-up, 12 patients (13%, CI = 6–20%) developed renal failure, 6 patients (7%, CI = 2–12%) experienced deep vein thrombosis (with or without pulmonary embolism) and 22 patients (27%, CI = 17–37%) were found to have clinical or ultrasound findings of serositis. Hypertension, defined as multiple systolic blood pressure readings above 140 mmHg, was found in 30% of the patients (CI = 20–40%).

Treatment of SLE

The main SLE treatments during the observation period are summarized in Table 2. Oral steroids were administered to 85 patients (96%), 63 patients (78%) received doses of more than 10 mg Prednisolone/day.

Table 1 Clinical manifestations of SLE

Clinical SLE manifestation	*n*	*(%)*	*95% CI*
Any skin manifestation	33	37%	26–46%
Malar rash	33	37%	26–46%
Discoid lesions	6	7%	2–12%
Phototoxicity	19	22%	13–31%
Mucous membrane involvment	14	17%	9–25%
Arthritis	59	68%	58–78%
Nephropathy	57	61%	51–72%
Nephrotic syndrome	19	20%	12–29%
NPSLE	18	19%	11–28%
Seizures	9	10%	4–16%
Stroke	4	4%	0–9%
Movement disorders	3	3%	0–7%
Myelitis	1	1%	0–3%
Neuropathy	3	3%	0–7%
Serositis	22	27%	17–37%
Pleuritis	16	19%	10–28%
Pericarditis	11	13%	6–20%
Ascitis	7	9%	3–15%
Thrombosis	6	7%	2–12%
Fever	52	58%	47–68%

Abbreviations: 95% CI = 95% confidence interval.
NPSLE = Neuropsychiatric systemic lupus erythematosus.

Table 2 Treatment of SLE

Treatment	*n*	*(%)*	*95% CI*
Steroid	85	96%	93–100%
>10 mg/day	63	78%	70–88%
NSAID	48	63%	52–74%
Methotrexate	20	24%	15–34%
Cyclophosphamide[a]	34	40%	29–51%
Antimalarials	49	58%	47–68%
Ciclosporine	7	8%	2–14%
Azathioprine	34	40%	29–57%
Mymo	4	5%	0–9%

[a]Cyclophosphamide was given as pulse therapy only, no. of cycles 6.4 ± 3.5, range 1–15.
Abbreviations: 95% CI = 95% confidence interval.
NSAID = Non-steroidal anti-inflammatory drugs.

Antimalarial drugs were prescribed in 49 (58%), non-steroidal anti-inflammatory drugs in 48 (63%) and Azathioprine in 34 patients (40%). Cyclophosphamid was administered as i.v. pulse therapy to 34 patients. The mean number of cycles of therapy was 6.4 ± 3.5 with a range from 1 to 15 cycles.

Laboratory findings in SLE patients

The mean values of the first documented laboratory examinations of our SLE patients who either survived or died are given in Table 3. The mean Antinuclear Antibody (ANA) titer (geometric mean) was 1:948. Ninety-five percent of the patients showed initially elevated titers (>1:80) and 61% had very high titers of 1:1280 and above, ranging up to 1:5120. Anti ds-DNA antibodies were elevated in 90% of the patients.

The mean C3 and C4 levels were 0.72 ± 0.05 and 0.13 ± 0.02, respectively. The level of C3 was significantly lower in patients who died during the follow-up period than in survivors. The C4 levels were also lower in this patient group, but this difference reached borderline statistical significance, only.

Eighty-five percent of the patients had anemia with Hb levels below 12 g/dL, 33% had Hb levels below 9 g/dL. Signs of hemolytic anemia (Hb <12 g/dL and Coombs test positive) were seen in 14% of the patients. Twenty-four percent presented with leucopenia (<4000/μL), lymphopenia (lymphocytes <1500/μL) was seen in 62 % of the patients and neutropenia (neutrophiles <1500/μL) was observed in 11%. Thrombocytopenia (thrombocytes <150,000/μL) was found in 16% of the patients. The mean initial creatinine value was 94 ± 10 mmol/L. Anticardiolipin antibodies (aCL) titers were determined in 55 patients. Thirty four patients (62%) were found to be aCL-positive, while 21 (38%) were negative.

Table 3 Laboratory findings in SLE patients

	Survivor	*Death*	*P*
ANA[a]	948 ± 278	1510 ± 156	0.1
Anti dsDNA	1021 ± 113	803 ± 140	0.6
C3	0.74 ± 0.05	0.39 ± 0.13	0.054
C4	0.07 ± 0.02	0.14 ± 0.02	0.027
Hb	9.7 ± 0.9	9.8 ± 0.2	0.9
WBC	6483 ± 424	7637 ± 1111	0.4
Lymph	1320 ± 815	1633 ± 248	0.3
Neutro	4382 ± 360	6017 ± 1054	0.2
Plt	319 ± 43	255 ± 54	0.4
Crea	97 ± 11	84 ± 24	0.6

[a]Geometric mean of ANA titer.

Morbidity: Reasons for admission

During the observation period 170 admissions were recorded (Table 4). Multiple admissions for the same reason and admissions in day care wards (e.g., for cyclophosphamide infusion) were not recorded. The causes of admission were grouped as direct consequences of SLE in 33%. These included severe flares of arthritis, pneumonitis, pericarditis as well as neuropsychatric manifestations of the disease. Renal causes for admission, although consequence of SLE as well, were recorded in a separate group. The most common reasons for admission in this group were renal biopsy, nephritic syndrome, hypertensive renal disease and acute renal failure. Twenty-eight patients were admitted for infectious diseases, representing 16% of all admissions. Pulmonary infections and generalized systemic infections/sepsis represented the most frequent indication for admission in this group. Three cases of appendicitis and two cases of clinical tuberculosis were seen. Vascular causes were responsible for

Table 4 Causes for admission to hospital (total = 170 admissions)

Cause of admission	*n (%)*
I. SLE	63 (37%)
Severe arthritis (16), primary diagnosis (10), cerberitis (8), pneumonitis (5), pericarditis (6), AIHA (3), thrombocytopenia (3), facial swelling, pancytopenia, …	
II. Renal	36 (21%)
Renal biopsy (11), nephritic syndrome (10), nephritis + hypertension (4), acute renal failure (3) …	
III. Infections	28 (16%)
Pulmonary infections (8), sepsis (6), urinary tract infections (4), appendicitis (3), tuberculosis (2), abscesses (perianal, axillary) …	
IV. Vascular	10 (6%)
Thrombosis/embolism (7), myocardial infarction (2), vasculitis	
V. Others	33 (19%)
Pregnancy loss (7), delivery (4), autoimmunhepatitis (2), acute myeloic leukemia, myasthenia gravis, epilepsy, heart failure …	

10 admissions with the majority due to thrombosis/pulmonary embolism. Other reasons for admission were pregnancy loss, defined as spontaneous involuntary termination of pregnancy at any stage of gestation, as well as additional autoimmune diseases (autoimmunehepatitis, myasthenia gravis).

Patients admitted for vascular events, including thrombosis/PE, myocardial infarction and vasculitis, as described in Table 4, or for pregnancy loss had positive aCL titers more often (78%, CI = 67–89%) than patients admitted for other reasons (58%, CI = 45–71%). This difference was not statistically significant. One case of malignancy (acute myeloic leukemia) occurred during the follow-up.

Mortality and causes of death

Eight (9%, CI = 3–15%) patients died during the follow-up. Four patients died during the first two years after diagnosis, four patients died after more than two years of disease (after 3, 7, 8 and 10 years of disease). The mean age at death was 33 ± 18 years (range 14–62 yrs). In the group of the early demise, the mean age at death was 21 ± 12 years, three of the four patients were 16 years or younger at the time of death. In the group of late death the mean age was 45 ± 14 years. The deceased patients included two males (25%) and six females (75%). Five of the patients were of Arabic descent, two originated from Africa and one from Southeast Asia.

The causes of early death included pneumonitis, sepsis due to *Staphylococcus aureus*, perforated appendicitis with abdominal sepsis and one case of pulmonary embolism. The causes of late death were myocardial infarction, acute myeloic leukemia, pneumonia and sepsis of unknown origin.

Figure 1 shows the Kaplan–Meier Survival plot of the entire cohort. The overall 5-year and 10-year survival rate are 92% and 69%, respectively. The 5-year and 10-year survival rate for the Arabic patients, who represent the biggest subgroup, are 96% and 70%, respectively.

Predictive variables for mortality

In univariate analysis clinical manifestations and laboratory findings were assessed as predictive factors for early death, late death and overall death. The results of the tests are shown in Table 5. The variables with the strongest association with early death were male sex, skin involvement and age less than 16 years at diagnosis. The risk for late death was significantly higher in patients with age above 30 years at diagnosis. The relative risk for overall death was significantly higher in patients with higher age at diagnosis and in those who developed renal failure. aCL status showed no significant association with mortality.

Multiple logistic regression analysis was performed to assess predictive factors for early and late mortality. Again male sex (RR = 13.3, CI = 1.3–133, $P = 0.03$) and age at diagnosis <16 years (RR = 8.6, CI = 0.8–99, $P = 0.08$) showed correlation with early death. In contrast, age >30 years at diagnosis (RR = 13.9, CI = 1.2–160, $P = 0.03$) and renal failure (RR = 8.5, CI = 0.9–85, $P = 0.06$) were predictive variables for late death.

Analysis using Cox proportional hazards model showed that lower survival probability was associated with age >30 years at diagnosis, renal failure and skin involvement. All three variables have risk ratios significantly different from 1 (Table 6). In contrast factors predictive for early death in the univariate analysis (young age at diagnosis, male sex) were not significant predictors in this model. Figure 1(b) shows the survival curves for patients with and without renal failure.

Comparison of clinical findings in different ethnic groups

Table 7 shows the distribution of clinical symptoms and the outcome according to the ethnic group of the patients. African patients had a significantly higher incidence of neurological involvement (RR = 14, CI = 2.5–80, $P < 0.01$). In this patient group higher

Table 5 Relative risk of mortality for clinical variables in univariate analysis

Variable	*Early death*			*Late death*			*Overall death*		
	RR	*95% CI*	*P*	*RR*	*95% CI*	*P*	*RR*	*95% CI*	*P*
Age at diag. <16 yrs	8.5	0.9–85	0.06	N.A.	–	n.s.	1.6	0.35–7.2	n.s.
Age at diag. >30 yrs	1.2	0.1–12	n.s.	12.8	1.2–130	0.03	4.1	0.9–18	0.07
Male sex	11.7	1.4–95	0.04	N.A.	–	n.s.	3.5	0.6–21	n.s.
Skin involvment	N.A.	–	0.02	0.59	0.1–6	n.s.	3.4	0.8–15	n.s.
Renal failure	7.6	0.9–60	0.08	7.6	0.9–60	0.08	9.2	1.9–44	0.01

Table 6 Risk ratios for mortality using Cox proportional hazard analysis

Variable	*RR*	*95% CI*	*P*
Age at diag >30 yrs	6.2	1.2–31	0.027
Skin involvment	6.1	1.2–31	0.004
Renal failure	13.4	2.3–79	0.029

rates of serositis, nephropathy and renal failure were found: these differences were not statistically significant. These patients tended to have more multi-organ involvement and a higher risk of death than the other ethnic groups, though, this difference again did not reach statistical significance (RR = 5.1, CI = 0.8–32, $P = 0.11$).

In Southeast Asian patients as well as in patients from the Indian subcontinent milder forms of the disease were seen. Southeast Asians had significant lower rates of arthritis (RR = 6.2, CI = 1.1–34, $P = 0.03$) and both groups had lower rates of neurological and renal involvement. To compare survival probabilities of the ethnic groups, individual Kaplan–Meier lifetime analysis was performed but showed no significant differences in log-rank test. There was also no difference in the survival probability of Saudi Arabian nationals compared with expatriates.

Discussion

Our patient cohort shows demographic characteristics similar to other studies of Arabic SLE patients.[6–8] As in other reports from Lebanon and United Arabic Emirates,[9,10] the mean age of onset of the disease is lower in our patients than that found in a study of 1000 European SLE patients[3](Europe 29 years, UAE 26 years, Lebanon 25 years, our patients 24 years). The female:male ratio of 10:1 is comparable with other studies.

A relatively low rate of arthritis of 68% were observed. In European patients, 84% were reported, in Arabic patients the rate ranged from 87 to 95%.[8,9] Skin manifestations were similar in all patient populations, except for phototoxicity, which seems to be less prevalent in our patients (22%), similar to the 87 Saudi SLE patients reported by Alballa (rate 26%).[11] In the European cohort, a phototoxicity rate of 45% was found. Whether this difference is attributable to different sun exposure pattern (due to climate or to cultural dress code of women) or to racial differences remains unclear.

Like other studies from the region, we found hematological manifestations more frequently than in European patients. Signs of hemolytic anemia were seen in 14% of our patients and in other Arabic countries rates of 9–10% have been reported, whereas only 3% of European patients show this manifestation. Also, thrombopenia and leucopenia were frequently seen in our patients.

Renal involvement is frequent in Arabic patients and reported rates range around 50%. In Saudi patients, a rate of 63% has been reported[11] and we found in our patient population renal manifestation in 61%, which was significantly more common than the reported 39% in Europeans.[3] A high number of patients in our study presented with fever. In European patients, a rate of 14% has been reported, which is substantially lower than the 58% we found in our patients. The difference may be due to racial differences or to concomitant infections that are more probable in our environment.

Only limited data exist regarding the prevalence of aCL in Arab patients. In Tunisian patients, aCL were found in 66% of the patients[6] compared with a similarly high number of 62% in our patient population.

Patients admitted for vascular diseases and for pregnancy loss had an even higher rate of positive aCL titers (78%). This might be expected as these presentations form part of Hughes syndrome.

During the observation period of our study 170 admissions to the hospital were recorded. Most of the admissions were due to active SLE disease. Admissions as a consequence of renal disease were the second most common group. This reflects again the

Table 7 Clinical presentations of SLE in different racial groups

Region	*n*	*Fever*	*Cutanous involvement*	*Arthritis*	*Neurological involvement*	*Serositis*	*Nephropathy*	*Renal failure*	*Death*
African	7	57%	29%	71%	71%[a]	43%	71%	28%	28%
Arabic	69	57%	35%	72%	17%	25%	65%	14%	8%
SE Asian	7	71%	43%	29%[a]	14%	29%	43%	0%	14%
Subcontinent	9	62%	44%	63%	0%	29%	33%[b]	0%	0%
Total	92	58%	35%	68%	19%	27%	61%	13%	9%

[a]$P < 0.05$ compared with combined other subgroups
[b]$P < 0.10$ compared with combined other subgroups

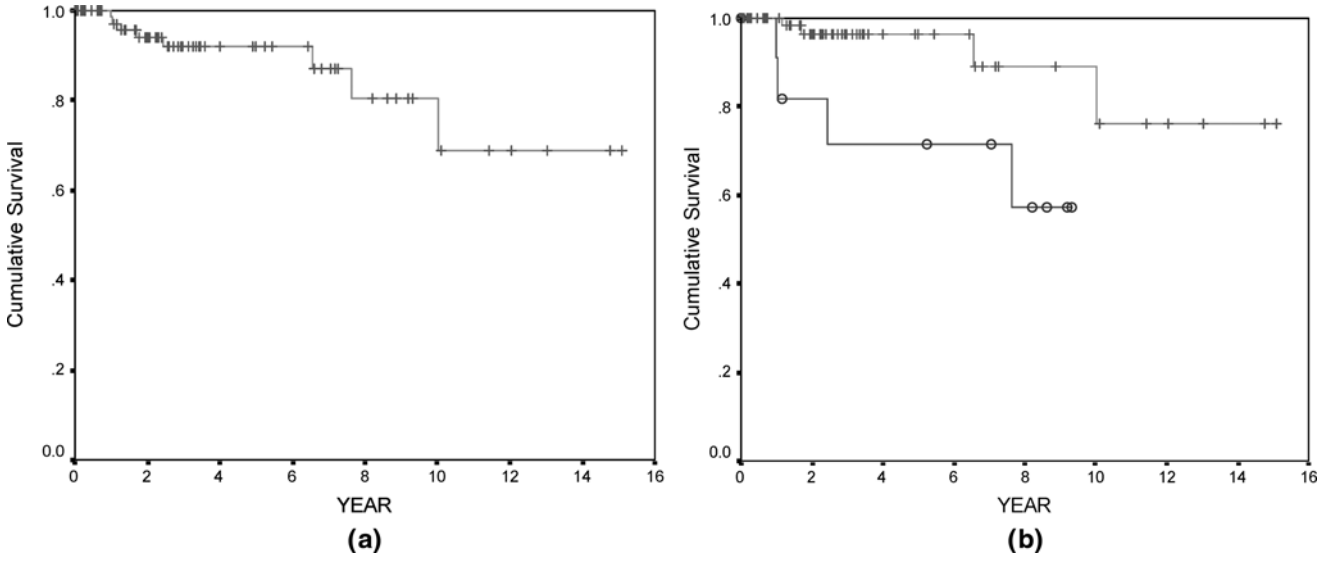

Figure 1 (a) Kaplan–Meier survival curve of all patients, (b) Kaplan–Meier survival curves of patients with (O) and without (+) development of renal failure (Log Rank test for equality of survival distributions $P = 0.0140$).

high frequency of renal involvement seen in our cohort. As in other studies, addressing associated medical problems in SLE patients[3,12] infections caused substantial morbidity in our patients.

Treatment with corticosteroid is the cornerstone for SLE treatment and it was given to 96% of our patients. It has been recommended that antimalarials should be part of the treatment regimen as well,[13,14] but only about half of our patients (58%) received this drug. Chemotherapy was given to a high number of patients–this may reflect the severity of the disease and the high proportion of renal involvement, as this was a main indication, for example, for Cyclophosphamid therapy.

We also addressed the mortality of our SLE patients. During recent decades the mortality, in general, decreased substantially in most parts of the world. Early studies showed five-year mortality rates of more than 50%,[15] but in recent investigations five-year survival rates of 90% and higher are the rule rather than the exception in western countries.[3,12] In our multiethnic population we found overall survival of 92% after five years and 69% after 10 years.

Survival rates in Arabic patients are rarely reported; to our knowledge only one study reported a five-year survival rate of 86% in 100 SLE patients, in Tunesia[6]. In our study population the 5- and 10-year survival rates in the subgroup of patients of Arabic descent were 96% and 70%, respectively.

Studies examining non-Caucasian patient populations found similar high five-year survival rates (93%) in Korean SLE patients,[16] but lower rates (82%) in Chinese, Malay and Indian patients in Malaysia, with the poorest survival rate in Indian patients.[1] In India, a study of 98 SLE patients reported a cumulative survival at five-years of 77%.[2] Black patients are known to have a poorer prognosis than Caucasians[17,18,19] – in a small study from Senegal 5 of 30 patients (17%) died even within five months after diagnosis.[4] Our African patients had a significant higher rate of neurological involvement than the other patient groups; they also had the highest rates of renal failure and death, although these differences did not reach statistical significance. As Africans in Saudi Arabia tend to be socially underprivileged, it can not be ruled out that the differences in mortality are partly due to later diagnosis and less access to health facilities.

Previous studies have shown a difference in the causes of early death (<2 years after diagnosis) and late death (>2 years after diagnosis) in SLE patients. Early death was more often caused by active disease and infection, whereas late death was caused by infection and non-SLE associated causes, like atherosclerotic disease.[5] It has further been documented that SLE patient are at higher risk for malignancy, especially for breast, lung and gynecological cancers,[20] but also for hematological diseases.[21] In our population only few deaths were observed, the most common cause was of infectious origin. The only death due to active disease (pneumonitis) occurred in the 'early death' group. In the 'late death' group, two patients died of unrelated causes, one from myocardial infarction, one from hematological malignancy. These findings are in concordance with those previously described; also the total number of events is small.

The presence of renal damage, thrombocytopenia, lung involvement, high disease activity and older age are known to be negative prognostic factors for mortality in SLE.[3,22] Also male sex has been reported to be associated with a poorer prognosis.[23] In our population, younger age at diagnosis, male and skin involvement were associated with early death. Male and young age are often associated with active disease and thus with rapid progressive courses. The skin involvement apparently represents an indicator for a more active form of multi-systemic disease. In comparison, older age at diagnosis and renal failure were associated with late death as well as with increase risk of death in the Cox hazard analysis. These two factors seem to be associated with mortality due to more chronic SLE sequelae.

In summary, our data indicate that there are racial factors influencing SLE presentation as well as the course of the disease. Patients of African descent tend to have more severe disease and more kidney disease. Renal involvement is more frequent in our setting in general and results in a poor prognosis. These patients deserve special attention.

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