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# Survival analysis and prognostic indicators of systemic lupus erythematosus in Pakistani patients

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To aim of this study is to analyse the survival rate and prognostic indicators of systemic lupus erythematosus (SLE) in Pakistani population. A total of 198 patients with SLE diagnosed between 1992 and 2005 were reviewed retrospectively. Clinical features at presentation, subsequent evolving features, autoantibody profile, damage scores and mortality data were obtained. Prognostic factors for survival were studied by statistical analysis. Of 198 SLE patients studied, 174 were women and 24 were men. The women to men ratio was 7.2:1. Mean age at presentation was 31 years (range 14–76). Mean duration of symptoms before diagnosis was 2.8 years. Mean duration of follow-up was 34.21 months (±33.69). Mean disease duration was 15.6 years. At diagnosis, arthritis, malar rash, oral ulcers and alopecia were the commonest features. During the follow-up, the prevalence of nephritis, arthritis, neurological and hematological disease increased significantly. About 76% ($n$ = 151) of the patients had organ damage at the time of data analysis, and renal disease was the commonest cause. Univariate analysis revealed that renal disease ($P$ = 0.000), seizures ($P$ = 0.048), pleural involvement ($P$ = 0.019), alopecia ($P$ = 0.000) and discoid lesions ($P$ = 0.005) were predictors for damage. Multivariate model, however, revealed that only renal disease was independent risk factor for damage ($P$ = 0.002). During the study period, 47 patients (24%) died (five due to disease-related complications and rest as a result of infections). The 3-, 5-, 10-, 15- and 20-year survival rates of our cohort were 99, 80, 77, 75 and 75%, respectively. Cox regression analysis revealed that renal involvement ($P$ = 0.002) and infections ($P$ = 0.004) were independent risk factors for mortality. The survival of our Pakistani SLE patients was significantly lower compared to that of the Caucasian series reported in last decade. Nephritis not only contributes to organ damage but also acts a major determinant for survival. Infection remains the commonest cause of death. Renal involvement and infections are independent risk factors for mortality. Judicious use of immunosuppressive agents is necessary to improve the short-term survival of lupus patients. *Lupus* (2009) **18,** 848–855.

**Key words:** lupus; prognosis; prognostic indicators; survival

## Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that predominantly affects women of childbearing age. It is also a major cause of mortality and morbidity in young population.[1] The prognosis of SLE in the Western world has improved remarkably in the past few decades, from a 5-year survival rate of only 50% in the 1950s[2] to a 10-year survival rate of nearly 90% in the last decade.[3,4] However, poor survival of SLE is still reported in certain ethnic groups such as Indians,[5] Black Caribbeans[6] and Hispanics.[6]

In the last three decades, we have seen an important increase in the survival of SLE patients, especially in those patients with renal involvement. Management with immunosuppressive drugs, such as intravenous cyclophosphamide or azathioprine has changed the prognosis in these patients. These results demonstrate that our patients with SLE increased their life expectancy but are now faced with new types of morbidity because of the sequelae related to the disease itself.[7]

The improvement of SLE survival can be attributed to a number of factors such as the early diagnosis of renal disease, better serological monitoring, more judicious use of corticosteroids and cytotoxic agents,

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availability and advancement of renal replacement therapies, and better management of associated complications like infection, hyperlipidemia and hypertension.

Despite the overall improvement in the survival of patients with SLE, 10–25% of patients still succumb within 10 years of disease onset.[8] Severe organ involvement related to SLE itself[4,9] and infection[10] remain the main causes of early mortality. It has been reported that Asian SLE patients living in the United States and UK have more serious organ manifestations and higher mortality.[11] Whether this is also related to the poorer socio-economic status of the Asian-Americans remains to be confirmed. Although there have been few studies on survival patterns in Indian and Thai patients with SLE,[12,13] data on survival patterns of SLE is scarce in other Southeast Asian countries including Pakistan in international literature. In a study from India, the cumulative percentage survival at 1, 5 and 10 years was found to be 89, 77 and 60%, respectively.[13] The Markov chain predicted a life expectancy of 13.9 years. Central nervous system (CNS) and renal involvement were poor prognostic factors. Proteinuria (>0.5 g/day) caused a 50% reduction in life expectancy but increased disease activity at onset did not predispose to a poor outcome.[13]

In the current study, we, retrospectively, followed a cohort of SLE patients; however, as the study was conducted retrospectively, selection bias and incompleteness of records were inevitable.

## Patients and methods

The Aga khan University Hospital is a tertiary care referral center. Case note documentation, assessment of disease activity, generation of damage scores and definition of disease flares are standardized and patients are seen by the same group of nephrologists and rheumatologists throughout.

Between January 1992 and March 2005, 198 patients were admitted with diagnoses of SLE. While 50% of patients were admitted through emergency department, approximately 45% were admitted through out-patient consultant clinics and a small percentage (5%) of patients was reffered by different primary and secondary care units. Majority of patients fulfilled at least four of the revised American College of Rheumatology (ACR) criteria for the classification of SLE.[14] The following informations were obtained from all patients at presentation: age, sex, clinical presentation and organ involvement, disease activity scores and autoantibody profile. Patients were followed up at regular intervals of 6–8 weeks. More frequent follow-up was arranged for patients who had severe organ involvement, who had just had a disease flare or who were receiving intensive immunosuppression. Damage scores in each system and mortality data were recorded during the disease course of our patients. Disease activity was measured by the SLE disease activity index (SLEDAI).[15] SLEDAI scores were obtained at the time of first presentation and at subsequent visits. Assessment of organ damage was made using the Systemic Lupus International Collaborating Clinics/ACR (SLICC/ACR) index.[16] Damage was defined as irreversible impairment that was present after the diagnosis of SLE and persisted for more than 6 months irrespective of whether it was related to disease activity or treatment. For patients whose SLE was diagnosed before 1998, damage scores were obtained retrospectively. After 1998, the damage index was scored yearly. The total cumulative damage scores were summated for each patient at the end of the study.

A total of 42 patients, in this cohort of 198 patients with SLE, were considered lost-to-follow-up. Postal and residential addresses of these patients were obtained from medical record files and were contacted and encouraged to return to out-patient clinics for an evaluation or to answer a questionnaire by telephone. For patients who died during the follow-up period, the cumulative damage scores just before their death were taken for analysis.

### *Laboratory evaluation*

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence. Anti-dsDNA was assayed using a standard radio-immunoassay procedure (normal value 0.0–6.0 IU/ml). Anti-extractable nuclear antigen (ENA) antibodies (Ro, La, nRNP and Sm) were studied by standard enzyme-linked immunosorbent assay (ELISA-Euro). Serum C3 was measured by nephelometry (normal range 0.88–2.07 g/l). Lupus anticoagulant was screened by mixing studies and dilute Russell viper venom test. Anticardiolipin antibodies (IgG and IgM) were assayed using a standard ELISA kit (Eliza EURO). A positive test was defined as a value of >10 IU/ml on at least two occasions more than 3 months apart. ANA and anti-ENA were obtained at the time of diagnosis of SLE and were not routinely repeated. Anti-dsDNA and serum C3 levels were assayed at the time of initial visit and during period of suspected disease-flare up. Anticardiolipin antibodies (IgG, IgM) and lupus anticoagulant were tested for most patients during the course of the disease, especially during periods of disease activity.

*Statistical analysis*

Statistical package for social science (SPSS) version 13.0 was used for data analysis. Results are presented as mean ± standard deviation for quantitative variables and number (percentages) for qualitative variables. Univariate analysis was performed by using independent sample *t*-test to compare the means and differences in proportion were assessed by using Pearson Chi-Square test. Logistic regression analysis was used to identify the independent risk factors for damages. The probability curves of survival were calculated according to the Kaplan–Meier method and compared by the log rank test. Multivariate analysis was performed by using Cox proportional hazard model, to identify the independent risk factor for poor survival. All the variables with biologically important *P*-value of <0.25 in univariate analysis were selected for the multivariate model building. A *P*-value of <0.05 (two sided) was considered as statistically significant.

## Results

Between 1992 and 2005, at the Aga Khan University Hospital, 198 in-patients had SLE listed as a discharge diagnosis. Of these patients, 174 were women and 24 were men. Of all, 149 patients met the ACR criteria (4 of the 11 criteria) for the diagnosis of SLE. The remaining 49 patients fulfilled 3 out of 11 ARA criteria and were diagnosed on basis of high index of suspicion for the disease, renal or skin biopsies suggestive of SLE, positive anti-dsDNA antibody titers and response to therapy. The mean age at presentation was 31 years with a range of 14–76 years. Mean duration of follow-up was 34 months (±33.69). Mean SLEDAI score at disease presentation was 11.7 ± 0.40 (range 4–33).

Cutaneous manifestations of SLE were relatively less common in our sample. Malar rash was present in 60 patients (30%), discoid lupus in 30 (15%), photosensitivity in 12 patients (6%) and alopecia in 44 patients (22%). About 53% ($n = 105$) were febrile at the time of presentation.

There were variable occurrences of renal, CNS, serosal, hematological and articular involvement. Approximately 45% of the patients ($n = 89$) had renal involvement at presentation. Of these 89 patients, 50% of patients had raised serum Cr. At the time of presentation (normal 0.8–1.1 mg/dl), 67% patients had microscopic hematuria, 87% had active urinary casts, 74% had proteinuria detectable on urine dipstick, whereas 55% had nephrotic-range proteinuria at presentation. Renal biopsy findings revealed that 64% of the cases had WHO class IV, 17% had WHO class V, 14% had WHO class III and 5% had class II histology. Serosal involvement was noted in 44 patients (22%). Pleural effusion was seen in 33 patients (17%) and pericardial effusion in 18 patients (9%). Arthritis was present in 76 patients (38%). Symptomatic arthralgias were noted at some stage in almost all patients. Regarding hematological parameters, 28% of patients had thrombocytopenia, 22% had leukopenia and 54% had significant lymphopenia. About 5% of the patients presented with pancytopenia ($n = 9$). CNS involvement was noted in 26% of patients ($n = 52$). Of these 52 patients, 15% presented with frank psychosis and 14% had seizures at some stage during the course of illness. About 84% of the patients were ANA-positive ($n = 168$), anti-dsDNA test results were positive in 74% of patients ($n = 146$) and anti-Sm was positive in 50% of patients. No other antibodies, such as rheumatoid factor (RF), anti nuclear cytoplasic antibody (ANCA) or antiphospholipid antibodies, were found in clinically significant titers.

The overall mortality was 24% ($n = 47$). There was no significant gender difference in the prevalence of major organ manifestations.

About 76% of our patients had organ damage at the time of data analysis. While 30% of patients had a SLICC score of one, 32% had a SLICC score of two and 38% had SLICC score of 3 or more. Table 1 shows the number of patients with damage in various systems. The kidneys were the commonest organ being damaged, followed by the CNS, skin and musculoskeletal systems. The median SLICC score of the whole cohort was 1 (range 0–5) and for those who had damage, the median SLICC score was 2 (range 1–5).

Regarding immunosuppressive treatment for our cohort of patients, 178 (90%) were treated with oral corticosteroids, 39 (20%) received intravenous pulse methylprednisolone therapy. Around 52% of patients initially received a high-dose regimen

**Table 1** Proportion of patients with damage in various systems in our SLE cohort ($n = 198$)

| *Target organ* | *Number of patients (%)* |
|---|---|
| Renal | 75 (37.5) |
| Neuropsychiatric | 56 (28) |
| Gonadal | 0 (0) |
| Skin | 57 (28.5) |
| Musculoskeletal | 51 (25.5) |
| Cardiovascular | 9 (4.5) |
| Peripheral vascular | 4 (2) |
| Pulmonary | 0 (0) |
| Ocular | 2 (1) |
| Endocrine | 8 (4) |
| Gastroenterological | 2 (1) |
| Malignancy | 0 (0) |

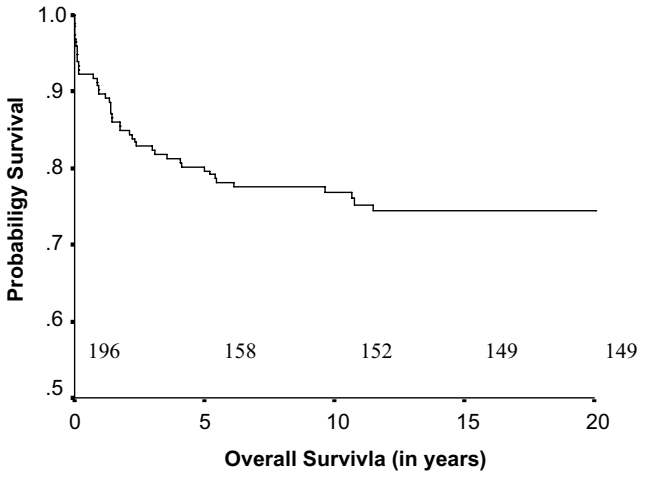


**Figure 1** Cumulative probability of survival in our cohort of SLE patients ($n = 198$).

(oral prednisone ≥1 mg/kg/day or intravenous pulse methylprednisolone therapy), which was mainly indicated for renal, CNS and hematological disease. The cumulative percentages of patients who received azathioprine and cyclophosphamide were 81 (41%) and 27 (14%), respectively.

Twelve patients developed end-stage renal failure and were dialyzed and two patients received kidney transplant. All of these dialyzed patients survived. Figure 1 shows the survival analysis of our cohort of patients. The 3-, 5- and 10-, 15- and 20-year survival rates were 99, 80, 77, and 75 and 75%, respectively.

During follow-up, 47 (24%) of our patients died, 7 due to disease-related complications (pulmonary hemorrhage, cerebrovascular accident, acute myocardial infarction secondary to embolic occlusion of left anterior descending coronary artery, ischemic enteritis leading to bowel perforation, lupus cerebritis) and the rest as a result of infections (nocardial and tuberculosis meningitis in four, disseminated cytomegalovirus infection in one, disseminated tuberculosis in one, bronchopneumonia in 6, neutropenic fibril illness in 7 and septicemia with and without disseminated intravascular coagulation in the remaining 21 patients).

Risk factors for survival were studied by both univariate (Kaplan–Meier method and compared by the log rank test) and multivariate analysis (Cox proportional hazard model), using the prevalence of various clinical features, demographic data such as age and sex, autoantibodies and presence of damage as predictor variables. In univariate model, infections ($P = 0.008$), renal disease ($P = 0.010$) and thrombocytopenia ($P = 0.037$) were associated with poor prognosis (Table 2); however, in multivariate model only renal involvement ($P = 0.002$) was found to be an independent risk factor predicting mortality

**Table 2** Independent risk factors for mortality (univariate model)

| | *Dead (%)* | *Alive (%)* | P *value* | *OR (95% CI)* |
|---|---|---|---|---|
| Infections | 21.4 | 78.6 | 0.008 | 0.27 (0.1–0.74) |
| None | 7.0 | 93 | | |
| Renal involvement | 23.5 | 76.5 | 0.010 | 2.75 (1.24–6.07) |
| None | 10 | 90 | | |
| Raised creatinine | 35 | 65 | 0.000 | 4.7 (2.1–10.5) |
| Normal creatinine | 10 | 90 | | |
| Seizures | 28.6 | 71.4 | 0.05 | 2.43 (0.96–6.14) |
| None | 14.1 | 85.9 | | |
| Thrombocytopenia | 28 | 72 | 0.037 | 2.4 (1.03–5.8) |
| Normal platelets | 14 | 86 | | |
| Alopecia | 25 | 75 | 0.07 | 2.11 (0.93–4.8) |
| None | 13.6 | 86.4 | | |

(Table 3). Figure 2A–D shows the survival curves of our patients. Impaired renal function and presence of organ damage were associated with poor survival.

## Discussion

This was a retrospective study of the survival and prognostic indicators of SLE in a Pakistani population. In the autoantibody profile, percentage of ANA in most studies[15,17,18] approached hundred but we only found 86% of our patients to be ANA positive. Use of different laboratory technique and dilution method in 1990s and different substrate which might have been antigenically inadequate is possible reason for low ANA positivity in this study. Besides, in some patients, immunosuppression was initiated before ANA testing which might have influenced ANA results. There was no difference in the prevalence of other antibodies like dsDNA as compared to Chinese,[19] Caucasians,[20] Blacks,[16,21,22] Hispanics[23] and Indians.[24] Compared to Caucasians, our patients had a higher prevalence of anticardiolipin antibodies.[19] However, this may not be reliable as only 14% of our patients underwent anticardiolipin antibody screening.

The overall 5-year survival rate of our SLE patients was 80%. The survival of our SLE cohort is less as compared to that of the recently reported Caucasian and Asian series.[3,4,24] SLE mortality tends to vary among different geographical areas and ethnic

**Table 3** Independent risk factors for mortality (multivariate model)

| | | | *95.0% CI for OR* | |
|---|---|---|---|---|
| | P-*value* | *Adjusted Odds Ratio* | *Lower* | *Upper* |
| CR ≥ 1.4 | 0.002 | 3.2 | 1.5 | 6.8 |

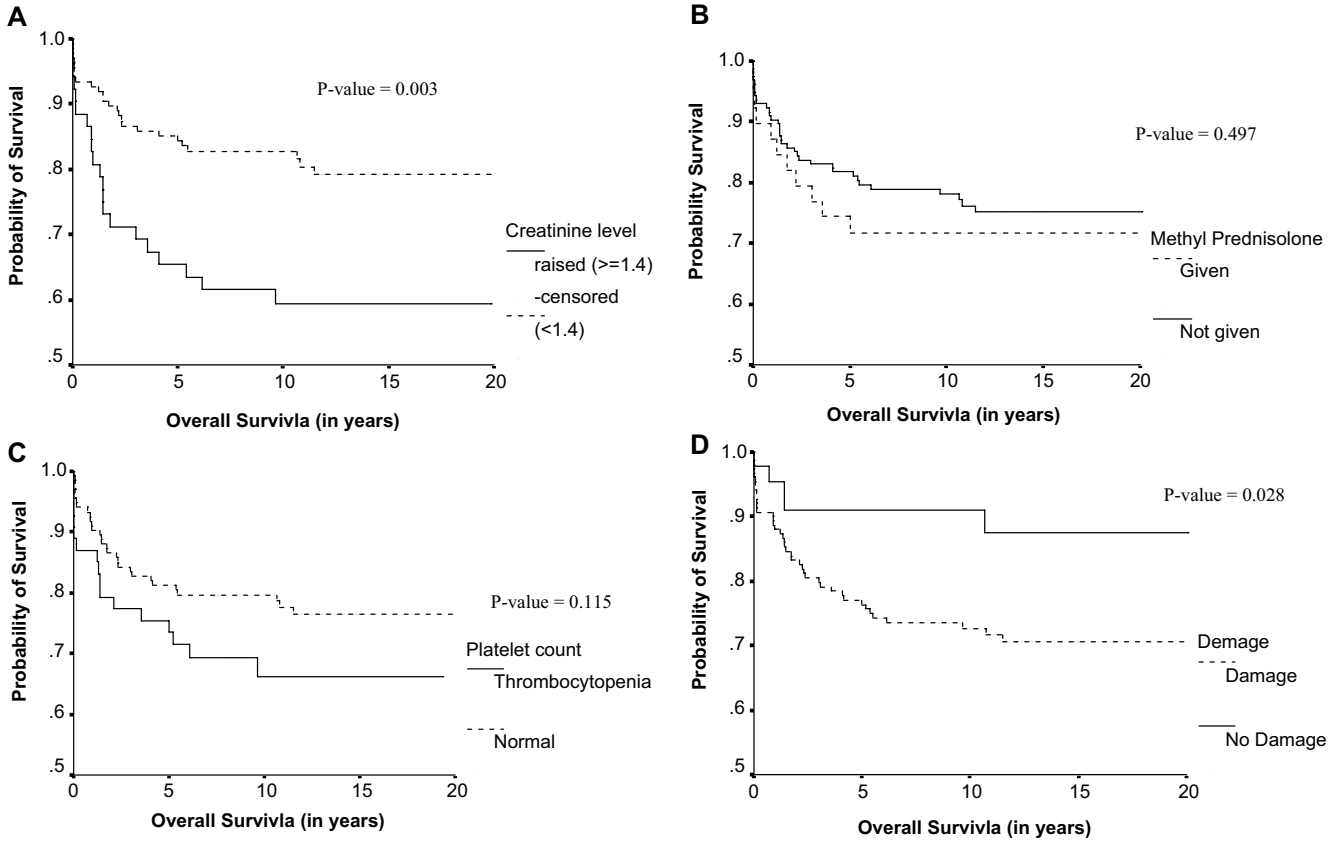


**Figure 2** (A) Probability of survival in SLE patients with and without renal disease. (B) Probability of survival in SLE patients who were and were not initially treated with high-dose corticosteroid. (C) Probability of survival in SLE patients with and without thrombocytopenia. (D) Probability of survival in SLE patients with and without damage.

groups. Direct comparison of the survival rates among different studies is not easy because of the discrepancies in patient selection and treatment protocols. Most published survival studies of SLE have been retrospective, and selection bias and incompleteness of medical records are major flaws. Moreover, the proportion of patients with severe organ manifestations included in different series as a result of referral pattern may also influence the survival rates. Prospective studies are, therefore, necessary. However, as with many other diseases, socioeconomic status (SES) is an important risk factor for progression of lupus, independent of race/ethnicity.[25,26] We believe that our population has an elevated risk of progression similar to African-Americans and Hispanics and given the results of multivariate analyses, much of the poorer prognosis of our patients may be due to socio-economic rather than biological or genetic factors. Indeed, the relative importance of genetic factors may be amplified by environmental factors that are associated with poverty. We believe that social and economic causes of inequity across income and race/ethnicity should be aggressively investigated and studies that aim to find putative major genes or haplotypes to explain race/ethnic disparities should consider SES. Patients with SLE have an approximately fivefold increased risk of mortality compared with the general population.[27] Many studies have described the causes of death of SLE patients.[28,29] Death occurs both early and late in the course of disease and follows a bimodal pattern.[29] Early mortality of SLE is often due to complications related to the active SLE process itself and infection, while vascular events and end organ failure unrelated to active SLE contribute to late mortality.[4] The main causes of death in our patient cohort were infection and active SLE with severe organ involvement, which are consistent with those reported in other series.

A number of lupus- and non–lupus related factors have been described in association with the prognosis of SLE.[21] Major organ manifestations, particularly CNS and renal diseases, have long been identified as markers of poor prognosis.[30] Patients who die of active SLE are more likely to have CNS disease.[29]

Organic brain syndrome was reported to be a poor prognostic indicator for survival in an early study by Esters and Christian.[30] Moreover, seizure was found to be associated with a poorer overall survival of SLE in a study by Ward, *et al.*[8] Lupus nephritis, especially diffuse proliferative glomerulonephritis, carries a poor prognosis in most studies.[8,18,31–33] Elevated serum creatinine, reduced creatinine clearance and progressive WHO class of lupus nephritis were associated with decreased survival. Our data demonstrated CNS (seizures) and renal disease to be significant predictors for survival in our cohort. All our six patients who developed end-stage renal failure survived on dialysis, indicating availability of improved renal replacement therapies. Hematological manifestations, in particular thrombocytopenia, have also been cited as adverse factor for poor outcome in SLE.[18,33] However, we could not find any relationship between low platelet count and outcome (Figure 2C). Apart from two patients, one died of pulmonary hemorrhage, which was thought to be caused by fulminant vasculitis, and another one who died of massive gastrointestinal (GI) bleed, no other patient suffered from significant morbidity and mortality secondary to bleeding complications. WHO class IV was associated with poor prognosis, which in turn was the main indication for heavy immunosuppressive therapy at the time of diagnosis of SLE.

Treatment is a pivoting factor affecting survival of SLE patients. Judicious use of steroid and cytotoxic agents such as cyclophosphamide and azathioprine to achieve a better control of disease activity is one of the well-recognized reasons for the improvement in survival of SLE patients in recent years. However, heavy immunosuppression, such as mega doses of steroid, may adversely affect short-term survival of SLE because of the risk of infection. Although in the current study, we have shown that initial treatment with high-dose oral prednisone or intravenous methylprednisolone bolus is not a significant risk factor for damage and mortality in both the univariate and multivariate models (Figure 2B), high-dose steroid treatment is, however, associated with a number of side-effects such as susceptibility to opportunistic infection, avascular bone necrosis, cataract, glaucoma, secondary diabetes, osteoporosis and its complications, which contributed significantly to morbidity in our cohort. Our result is in keeping with that from Massado, *et al.*[33] who also demonstrated that over immunosuppression for the treatment of patients with more severe disease was associated with higher mortality in their Chilean SLE patients. Given the strong relationship between heavy immunosuppression and bone marrow suppression and serious opportunistic infections leading to high mortality rates, efforts should assiduously be made to avoid unnecessary over-immunosuppressive treatment in patients with SLE.

Race appears to play a role in disease prognosis in SLE, although it is difficult to separate the effect of race from socio-economic status. Non-White populations residing in Hawaii, which were exclusively Asians, were found to have more serious SLE and mortality than Whites.[34] This may possibly be related to the lower socio-economic condition of the Asian-Americans. Black patients, when compared with Whites, also have more severe organ manifestations and poorer survival.[1,35] However, a multicenter study of a large cohort of SLE patients demonstrated that apparent racial differences in survival could be accounted for by differences in medical insurance status between Blacks and Whites.[32] Moreover, Ward, *et al.*[36] also showed that socio-economic status, instead of race, is a strong indicator for survival.

The age at onset of SLE has also been reported as a significant predictor for survival, although currently available data are conflicting. In the multicenter study by Ginzler, *et al.*[32] better 1- and 5-year survival rates were demonstrated in older SLE patients. Moreover, pediatric-onset SLE patients have been associated with a worse prognosis.[37] However, a study comparing the outcome of adult- and childhood-onset SLE patients did not reveal any difference in the 5-year survival rates.[38] On the contrary, two recent studies showed that increasing age is a risk factor for death.[18,36] This is in contradiction to the common observation that late-onset SLE often runs a more benign disease course.[39] The effect of gender on SLE survival is also controversial. Male SLE patients were reported to have more severe renal disease and reduced survival[40] when compared with their female counterparts. However, other studies failed to show a gender difference in damage and mortality rates of SLE.[18,41,42] We were unable to demonstrate a contribution of either age at onset or sex to survival in our patients ($P = 0.2126$). No gender differences in major organ manifestations, damage scores ($P = 0.84$) and survival rates ($P = 0.2126$) could be demonstrated.

There is still little information in the literature regarding the relationship between damage and survival in SLE patients. In a retrospective study by Stoll, *et al.*[43] that involved an inception cohort of 80 SLE patients, it was reported that the mean renal and pulmonary scores at 1 year after the diagnosis of SLE predicted for renal failure and mortality, respectively, within 10 years. Because of the problem of obtaining reliable damage scores retrospectively for some of our patients at 1 year post-diagnosis of SLE and the small

number of patients who developed renal failure ($n = 10$) within a relatively short period of follow-up, statistical analysis of our data regarding damage scores at 1 year and subsequent outcome was not feasible. However, we were able to demonstrate that the cumulative SLICC score was a predictor for survival in both the univariate and multivariate models (Figure 2D).

Renal damage was the commonest form of organ damage in our cohort. Renal disease was not only a predictor for damage but was also an independent risk factor for survival ($P = 0.002$). Of the 89 (45%) patients with renal disease in our cohort, 75 (84%) had renal damage. This suggests that most patients with nephritis did not respond well to treatment, and it is, therefore, because of this poor therapeutic response that renal disease was shown to be a strong predictor for renal damage in logistic regression analysis ($P = 0.002$).

In summary, this is the first study of the survival of Pakistani SLE patients ever reported in the English literature. The long-term survival of our patients is comparable to that of the Caucasian series in the 1990s.[44] Renal disease not only contributes to organ damage but is also a strong determinant for survival. Infection remains the main cause of death in this cohort ($P = 0.004$). Seizures, alopecia and thrombocytopenia are independent risk factors for mortality in the univariate model. Although, lupus survival has significantly improved in the recent decade, further improvement should be pursued. Judicious use of corticosteroids and cytotoxic agents to prevent over-immunosuppression, particularly in patients with serious disease manifestations, is essential. Continuous follow-up of our cohort of SLE patients is necessary to accrue data on long-term survival of the disease.

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