Lupus (2010) 19, 1573–1578
http://lup.sagepub.com

LUPUS AROUND THE WORLD

Early renal damage assessed by the SLICC/ACR damage index is predictor of severe outcome in lupus patients in Pakistan

MA Rabbani[1], HB Habib[2], M Islam[2], B Ahmad[2], SMA Shah[2], S Tahir[3], D Merchant[1] and A Ahmad[1]
[1]Department of Nephrology, the Kidney Center, Post Graduate Training Institute, Karachi, Pakistan; [2]Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan; and [3]Sind Medical College, Karachi, Pakistan

We investigated patients with systemic lupus erythematosus with the objective of assessing whether early damage accrued in systemic lupus erythematosus as measured by the SLICC/ACR Damage Index predicts mortality in lupus patients that have been followed prospectively in a single center. Patients with systemic lupus erythematosus from Aga Khan University hospital presenting between 1992 and 2007 were included. This enabled all patients to be potentially followed for at least 10 years. Yearly SLICC/ACR Damage Index scores were determined for each patient. Early damage was defined as a score ≥ 1, and no damage as a score of 0 at the initial assessment. Kaplan–Meier and Log rank tests were used to compare the survival experience between those with and without damage, with all patients being assessed at 10 years. In this inception cohort 198 patients were identified and were followed for 10 years. Of these, 47 (23.7%) patients had a SLICC/ACR Damage Index score of 0 (no damage) while 151 patients (76.3%) had at least one SLICC/ACR Damage Index item scored (early damage). Mean renal damage score at 1, 5 and 10 years was 0.16, 0.34 and 0.67, respectively. Of lupus patients who exhibited renal damage at their first SLICC/ACR Damage Index assessment, 31% died within 10 years of their illness as compared with only 13% who had no early renal damage ($p < 0.003$). Mean renal damage score at 1 year after diagnosis was a significant predictor of death within 10 years of diagnosis ($p < 0.002$). *Lupus* (2010) **19,** 1573–1578.

Key words: SLE; organ damage; mortality

Introduction

Systemic lupus erythematosus (SLE) is still a significant cause of morbidity and increased mortality.[1] However, relevant changes in the spectrum of lupus complications, both in quantitative and qualitative terms, have occurred in the past decades. Review of recent literature suggests remarkable improvement in prognosis of patients with SLE in the western world over 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, despite the overall improvement in survival, the incidence of SLE has nearly tripled and 10–25% of patients still succumb within 10 years of disease onset.[5] Severe organ involvement related to SLE itself and infections remain common causes of mortality.[6] Poor survival of SLE is still reported in certain ethnic groups such as Asians,[6,7] Black Caribbeans[8] and Hispanics.[9]

The SLICC/ACR Damage Index was developed in 1992.[10] It was created to assess an ongoing reflection of disease activity in patients with SLE and hence to measure irreversible damage resulting from SLE disease activity and its treatment. Since 1992, a number of investigators have used the Damage Index in their clinical studies. The new concept of irreversible organ damage in SLE has been defined as irreversible changes in organ or systems accrued during the course of lupus, although not necessarily caused by SLE (i.e. could be the result of treatment or concurrent conditions), and persisting for at least 6 months.[11]

Organ damage occurs in 50% of patients within 5 years of diagnosis of SLE,[12,13] and is associated

Correspondence to: Malik Anas Rabbani, Associate Professor and Consultant Nephrologist, Program Director, Post Graduate Training in Renal Medicine, The Kidney Center, Post Graduate Training Institute, Karachi-75530, Pakistan.
Email: anasrabbani@yahoo.com
Received 21 April 2010; accepted 20 May 2010

10.1177/0961203310375704

with increased mortality.[14] Risk factors for damage include older age at diagnosis,[12–14] longer duration of SLE,[12] African-Caribbean or Asian ethnicity,[14] high disease activity at diagnosis,[12,13] and greater overall activity during the disease course.[15,16] Although SLE is not an uncommon disease in South Asia, no data exist about organ damage and its impact on patient survival in Pakistan. This study was therefore conducted to assess organ damage accrued in SLE, as assessed by the SLICC/ACR Damage Index, and its impact on the survival of these patients.

Methods

Patients

An inception cohort of all of our patients with SLE in whom the diagnosis was established at least 10 years prior to November 2007, and who had subsequently attended a specialist clinic, was studied. At each outpatient consultation, detailed clinical and serological information was recorded. Case note documentation, assessment of disease activity, generation of damage scores and definition of disease flares were standardized, and patients were seen by the same group of nephrologists and rheumatologists throughout. Patients were followed-up prospectively 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 (DS) in each system and mortality data were recorded during the disease course of our patients. Disease activity was measured by the SLEDAI.[17] SLEDAI scores were obtained at the time of first presentation and subsequent visits. Assessment of organ damage was made using the SLICC/ACR index.[10] Damage was defined as irreversible impairment that was present after the diagnosis of SLE and persistent for more than 6 months, irrespective of whether it was related to disease activity or treatment. For patients whose SLE was diagnosed before 1998, DS were obtained retrospectively. After 1998, the Damage Index was scored yearly. The total cumulative DS were summated for each patient at the end of the study. In case of a lethal outcome, the last DS was determined 6 months before death. The weighted total DS was calculated by multiplying the neuropsychiatric, renal and cardiovascular DS by four, the ocular, pulmonary, peripheral vascular and malignancy DS by three, and the gastrointestinal and musculoskeletal DS by two, resulting in a potential maximum of 133 points.[11] Every patient was carefully reviewed for evidence of having had a severe outcome within 10 years after diagnosis, defined as either death or end-stage renal failure (ESRF) necessitating dialysis. If a patient had moved and had not been attending our outpatient clinic, attempts were made to contact her/him and their physicians to obtain the necessary data.

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 of the variables selected for the building of the multivariate model have biologically important *p*-values of less than 0.25 in univariate analysis. A *p*-value less than 0.05 (two sided) was considered as statistically significant.

Results

The group studied comprised 198 patients, 174 females and 24 males. A total of 147 patients fulfilled the ARA criteria[18] for diagnosis of SLE (4/11 criteria). The remaining 49 patients fulfilled three of the 11 ARA criteria, and were diagnosed on the basis of a high clinical suspicion of the disease, renal or skin biopsy suggestive of SLE, positive anti-dsDNA antibodies and clinical response to treatment. Mean age at presentation was 31 years (range 14–76 years). Mean duration of follow-up was 34 months (range 4–179 months). Mean SLEDAI score at disease presentation was 11.7 ± 0.40 (range 4–33).

Cutaneous manifestations of SLE (46%) were relatively less common in our sample. Malar rash was present in 56 patients (29%), discoid lupus in 27 (14%), photosensitivity in 12 patients (6%) and alopecia in 44 patients (22%). A total of 105 patients (53%) were febrile at the time of presentation. There were variable occurrences of renal,

central nervous system (CNS), serosal, hematological and articular involvement. Of the patients, 33% ($n = 65$) had renal involvement at presentation. Of these 65 patients, 50% had raised serum creatinine at the time of presentation (normal 0.8–1.3 mg/dl), 74% had proteinuria detectable on urine dipstick, and 55% had nephritic-range proteinuria at presentation. Renal biopsy findings revealed that 64% of the patients had WHO class 4, 17% had class 5, 14% had class 3, and 5% had class 2 histological findings. Serosal involvement was noted in 44 (22%) patients. Pleural effusion was seen in 33 patients (17%) and pericardial effusion in 18 patients (9%). Articular involvement was noted in 76 patients (38%). Regarding hematological parameters, 26% of patients had thrombocytopenia, 22% had leucopenia and 54% had significant lymphopenia. Some 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. We found that 86% of the patients were ANA positive ($n = 168$). Anti-dsDNA test results were positive in 74% of patients ($n = 146$).

Regarding immunosuppressive treatment, 178 (90%) were treated with oral corticosteroids, and 39 (20%) received intravenous pulse methylprednisolone therapy. An initial high-dose regimen (oral prednisone $\geq$1 mg/kg/day or intravenous pulse methylprednisolone therapy), mainly indicated for renal, CNS and hematological disease, was received by 52% of patients. The cumulative numbers and percentages of patients who received azathioprine and cyclophosphamide were 81 (41%) and 27 (14%), respectively. Two patients received chlorambucil. Cyclosporin was used in only seven patients.

Of our patients, 76% had organ damage at the time of data analysis; 30% had a SLICC score of 1, 32% of patients had a SLICC score of 2, and 14.5% had SLICC score of 3 or more. The kidneys were the commonest organ being damaged (37.5%), followed by the CNS (28%), skin (28.5%) and musculoskeletal systems (25.5%). Median SLICC score of the whole cohort was 1 (range 0–5) and for those who had damage, median SLICC score was 2 (range 1–5). No significant difference in DS could be demonstrated between female and male patients ($p < 0.84$). Age at disease onset and disease duration did not correlate with SLICC scores ($p < 0.42$ and $p < 0.02$, respectively).

Univariate and multivariate analysis were performed to study the predictive factors for damage. Alopecia ($p < 0.000$), discoid lesions ($p < 0.01$), seizures ($p < 0.048$), renal disease ($p < 0.000$), and musculoskeletal system ($p < 0.014$) involvement were univariately associated with damage. Logistic regression (multivariate analysis) with outcome being damage, and the prevalence of other clinical features, auto-antibodies, demographic data (e.g. age and sex) and drug treatment being predictor variables, showed that only alopecia ($p < 0.009$) and renal disease ($p < 0.002$) were independent predictors for damage (Table 1).

As renal damage was the most commonly seen organ damage in our patients a separate logistic regression analysis was performed, with outcome being renal damage and other clinical variables as described above being predictors. It was found that anemia at onset ($p = 0.018$) and malar rash ($p = 0.031$) were independent risk factors for renal damage.

Twenty-seven patients died within 1 year; however, damage could be scored at 1 year after diagnosis in all 198 patients. At 5 years a further 15 patients had died. At 10 years four more patients had died, and the DS could be determined in only 142 patients. Thus, by the end of the study, l0 years after establishing the diagnosis of SLE, 46 patients had died while 12 patients had developed ESRF.

Mean renal DS at 1 year was 0.16 (15%), and it progressively increased to 0.34 (29%) and 0.67 (37%) at 5 and 10 year time intervals, respectively. Table 2 shows that although mean DS in neuropsychiatry was significant at 1 year and it did show rise in cumulative DS at 5 and 10 years, it did not however predict mortality ($p = 0.067$). The mean renal DS at 1 year in surviving patients was significantly lower compared with those who had died ($p < 0.002$). Survival at 10 years in patients with early renal involvement was less than 60% compared with 85% in those with normal renal function (Figure 1). Similarly, the mean renal DS at

Table 1 Multivariate analysis of predictors for damage in our cohort of patients

		95% confidence interval (CI)	
Variables	*Significance* (p-*value*)	*Lower CI*	*Upper CI*
Serum Creatinine	0.002	2.258	44.158
Seizures	0.067	0.902	19.535
Alopecia	0.009	1.950	115.317
Pleuritis	0.083	0.836	18.203

Table 2 Progression of damage scores (DS) and cumulative prevalence of damage over time

	DS (mean) Cumulative prevalence of damage at		
	1 year	*5 years*	*10 years*
Total DS (unweighted)	0.57	1.13	1.83
Weighted DS (Total)	1.47	3.10	5.51
Renal DS	0.16; 15%	0.34; 29%	0.67; 37%
Neuropsychiatry DS	0.04; 7.5%	0.12; 13.2%	0.27; 28%
Pulmonary DS	0.02; 2.5%	0.02; 3.9%	0.05; 4%
GI DS	0.02; 2%	0.02; 2%	0.02; 2%
Cardiovascular DS	0.01; 2.5%	0.03; 3.7%	0.04; 4.5%
Musculoskeletal DS	0.15; 14%	0.2; 20%	0.26; 25%
Skin DS	0.14; 13%	0.28; 23%	0.34; 28%
Gonadal DS	0.00; 0%	0.00; 0%	0.00; 0%
Ocular DS	0.00; 0%	0.02; 2.4%	0.02; 2.4%
Peripheral	0.03	0.08	0.12
Endocrine/Malignancy DS	0.00; 0%	0.02; 2.4%	0.04; 4%

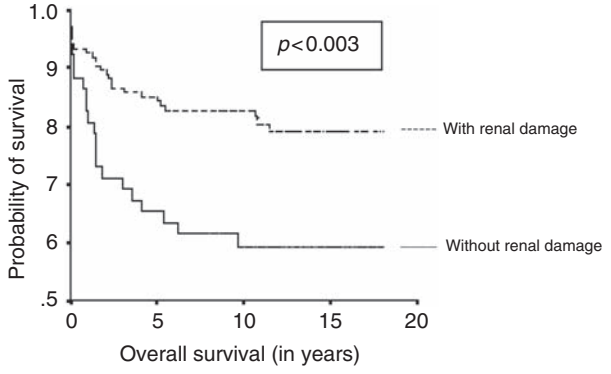

Figure 1 Probability of survival in patients with and without renal damage.

1 year of those patients developing ESRF was significantly higher than the corresponding mean in patients with no ESRF up to 10 years after diagnosis ($p = 0.008$). Table 2 outlines the significant differences in renal, neuropsychiatry, pulmonary, total and weighted DS at 1, 5 and l0 years.

Discussion

During the last decade, the emergence of better techniques for diagnosis, the availability of novel and more refined immunosuppressive agents and hence better disease management have significantly improved the survival of patients with SLE. However, research has shown that majority of patients with SLE sustain permanent damage in one or more organs because of the disease itself, its treatment, or co-morbid processes.[13,14,19] Moreover, by definition, the SLICC/ACR Damage Index scores cumulative damage since the onset of SLE and are therefore likely to increase with disease progression. In this study the mean renal DS 1 year after diagnosis significantly predicted death. The relevant item in those who died was elevated serum creatinine. The mean renal DS at 1 year also significantly correlated with the development of ESRF. These findings correspond with the fact that reduced glomerular filtration rate or proteinuria is a predictor for poor renal outcome.[20,21] Moreover, a significantly higher renal DS after 5 and 10 years in patients with ESRF appears to corroborate these findings. These findings, in accordance with the literature,[20–22] demonstrate the prognostic validity of the renal item of the SLICC/ACR Damage Index. Despite the fact that interstitial lung disease[22] and pulmonary hypertension in SLE[23] are known to increase mortality, mean pulmonary DS at 1, 5 and 10 years after diagnosis did not prove statistically significant to predict death. Other organ DS, for example in the neuropsychiatric or the cardiovascular systems, and the total DS did not show prognostic value in the present study.

Our report is the first in our region to describe the prognostic validity of the SLICC/ACR Damage Index in a Pakistani population. Moreover, compared with Caucasians and Afro-Caribbeans,[24–26] significantly higher mean renal DS at 5 and 10 years were found in our population. We also found significantly lower occurrence of ESRF in our population, compared with other ethnic groups.[27] Moreover, compared to Caucasian and Afro-Caribbean patients, a lower mean neuropsychiatric DS 5 years after diagnosis was found. We noted a rather low prevalence of different organ involvement, e.g. 13.2% neuropsychiatric disease at 5 years and 28% at 10 years after diagnosis compared with figures of CNS involvement of 12–59% reported by other groups.[28] However, it is worth mentioning that SLICC/ACR Damage Index scores only those items likely to be relevant to outcome. Neurological problems such as migraine, a frequent neuropsychiatric finding in patients with SLE, will not score as damage. In addition, a symptom/finding has to be present continuously for at least 6 months to score. Subtle changes such as cognitive impairment will only be scored when they are clinically overt, and hence impairment demonstrable with detailed neuropsychiatric testing or magnetic resonance imaging will

not be counted as damage in a patient who seems clinically unaffected. This is probably because assessment by the SLICC/ACR Damage Index is designed to be feasible for all physicians to complete, being based on clinical examination and simple investigations (urinalysis, creatinine, X-ray of the chest).

The percentage of early organ damage and the mortality rate during the initial phase of disease is much higher in our cohort as compared with that of other recently reported major cohorts.[14] However, direct comparison of the survival rates and organ DS 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 patterns may also influence the survival rates. However, we believe that delayed referrals to tertiary care hospitals, non-availability of immunosuppressive agents in the past, poor socioeconomic status and non-compliance are some of the possible factors responsible for high organ damage and mortality rate seen during the initial phase of the disease in our cohort.

We also believe that our population has an elevated risk of progression similar to African-American and Hispanic patient, and given the results of multivariate analyses, much of the poorer prognosis of our patients may be due to socioeconomic rather than biological or genetic factors. Indeed, the relative importance of genetic factors may be amplified by environmental factors that are associated with poverty. It has been postulated that differences in severity of SLE may be related to different genotypes.[29] As many genes have been identified, it may well be that lupus in Pakistan has a different genetic etiology, responsible for varying disease susceptibility and expression. Furthermore, Pakistan has a very high rate of consanguineous marriages. In Pakistan, over 60% of marriages are between first and second cousins,[30,31] which will lead to a conservation of certain genotypes causing the disease, and impede their transmission to other races. Further studies will be required to explain the contributing role of environmental and genetic factors in order to explain ethnic difference in lupus susceptibility and its expression in our local population.

In conclusion, in this study, renal DS at 1, 5 and 10 years after diagnosis were significantly higher than other organ DS in our patient population. Severe outcome in terms of ESRF and mortality in patients with SLE correlates significantly with a higher mean renal DS at 1 year.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors have no conflicts of interest to declare.

References

1 Ippolito A, Petri M. An update on mortality in SLE. *Clin Exp Rheumatol* 2008; 26: 72–79.
2 Merrell M, Shulman LE. Determination of prognosis in chronic disease, illustrated by systemic lupus erythematosus. *J Chronic Dis* 1955; 1: 12–32.
3 Gripenberg M, Helve T. Outcome of systemic lupus erythematosus: a study of 66 patients over 7 years with special reference to the predictive value of anti-dsDNA antibody determination. *Scand J Rheumatol* 1991; 20: 104–109.
4 Pistiner M, Wallace DJ, Nessim S, Metzger Al, Klineberg JR. Lupus erythematosus in the 1980's: a survey of 570 patients. *Semin Arthritis Rheum* 1991; 21: 55–64.
5 Ward MM, Pyun E, Studenski S. Mortality risks associated with specific clinical manifestations of systemic lupus erythematosus. *Arch Intern Med* 1996; 156: 1337–1344.
6 Rabbani MA, Habib HB, Islam M, *et al*. Survival analysis and prognostic indicators of systemic lupus erythematosus in Pakistani patients. *Lupus* 2009; 18: 848–855.
7 Rabbani MA, Tahir MH, Siddiqui BK, Ahmad B, Shamim A, Shah SM, Ahmad A. Lupus in Pakistan. *Lupus* 2005; 13: 820–825.
8 Nossent JC. Course and prognosis of systemic lupus erythematosus disease activity in Black Caribbean patients. *Semin Arthritis Rheum* 1993; 23: 16–21.
9 Lopez-Acuna D, Hochberg M, Gittelsohn A. Do persons of Spanish heritage have an increased mortality from systemic lupus erythematosus compared to other Caucasians? *Arthritis Rheum* 1982; 25: S67.
10 Gladman D, Ginzlcr E, Goldsmith C, *et al*. Systemic lupus international collaborative clinics: development of a damage index in systemic lupus erythematosus. *J Rheumatol* 1992; 19: 1820–1821.
11 Gladman D, Goldsmith C, Urowitz M, *et al*. Derivation of a weighting scale for the SL1CC/ACR damage index – preliminary results. *Arthritis Rheum* 1994; 37(Suppl 9): S326.
12 Karlson EW, Daltroy LH, Lew RA, *et al*. The relationship of socioeconomic status, race, and modifiable risk factors to outcomes in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 47–56.
13 Zonana-Nacach A, Camargo-Coronel A, Yáñez P, *et al*. Measurement of damage in 210 Mexican patients with systemic lupus erythematosus: relationship with disease duration. *Lupus* 1998; 7: 119–123.
14 Stoll T, Seifert B, Isenberg DA. SLICC/ACR damage index is valid, and renal and pulmonary organ scores are predictors of severe outcome in patients with systemic lupus erythematosus. *Br J Rheumatol* 1996; 35: 248–254.
15 Becker-Merok A, Nossent HC. Damage accumulation in systemic lupus erythematosus and its relation to disease activity and mortality. *J Rheumatol* 2006; 33: 1570–1577.

16 Andrade RM, Alarcón GS, Fernández M, *et al*. Accelerated damage accrual among men with systemic lupus erythematosus: XLIV. Results from a multiethnic US cohort. *Arthritis Rheum* 2007; 56: 622–630.
17 Gladman DD, Goldsmith CH, Urowitz MB, *et al*. Sensitivity to change of 3 systemic lupus erythematosus disease activity indices: international validation. *J Rheumatol* 1994; 21: 1468–1471.
18 Tan EM, Cohen AS, Fries JF, *et al*. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; 25: 1271–1277.
19 Petri M, Barr SG, Zonana-Nacach A, Magder L. Measures of disease activity, damage, and health status: the Hopkins Lupus Cohort experience. *J Rheumatol* 1999; 26: 502–503.
20 Levey AS, Lan SP, Corwin HL, *et al*. Progression and remission of renal disease in the lupus nephritis collaborative study. *Ann Intern Med* 1992; 11: 114–123.
21 Esdaile JM, Abrahamowicz M, MacKenzie T, Hayslett JP, Kashgarian M. The time-dependence of long-term prediction in lupus nephritis. *Arthritis Rheum* 1994; 37: 359–368.
22 Weinrib L, Sharma OP, Quismorio Jr FP. A long-term study of interstitial lung disease in systemic lupus erythematosus. *Semin Arthritis Rheum* 1990; 20: 48–56.
23 Guillevin L. Vasculopathy and pulmonary arterial hypertension. *Rheumatology (Oxford)* 2009; 48(Suppl 3): iii54–57.
24 Reveille JD, Bartolucci A, Alarcon GS. Prognosis in SLE. Negative impact of increasing age at onset, black race and thrombocytopenia, as well as causes of death. *Arthritis Rheum* 1990; 33: 37–48.
25 Ward MM, Studenski S. Clinical manifestations of systemic lupus erythematosus. Identification of racial and socioeconomic influences. *Arch Intern Med* 1990; 150: 849–853.
26 Hochberg MC, Boyd RE, Ahearn JM, *et al*. Systemic lupus erythematosus: a review of clinico-laboratory features and immunogenetic markers in 150 patients with emphasis on demographic subsets. *Medicine* 1985; 64: 285–295.
27 Alarcon GS, McGwin Jr G, Petri M, *et al*. Time to renal disease and end-stage renal disease in PROFILE: a multiethnic lupus cohort. *PLoS Med* 2006; 3: e396.
28 Wallace DJ. The clinical presentation of SLE. In: Wallace DJ, Hahn BH (eds), *Dubois' lupus erythematosus*, 4th edn. Philadelphia and London: Lea and Febiger; 1993. p. 317–321.
29 Arnett FC. Genetic studies of human lupus in families. *Int Rev Immunol* 2000; 194: 297–317.
30 Hakim A. Comments on 'consanguineous marriages in Pakistan'. *Pak Dev Rev* 1994; 33: 675–676.
31 Afzal M, Ali SM, Siyal HB. Consanguineous marriages in Pakistan. *Pak Dev Rev* 1994; 33: 663–674.