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CAUSES AND PREDICTORS OF DEATH IN SOUTH AFRICANS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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A research report submitted to the Faculty of Health Sciences, University of the Wiwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch of Internal Medicine

Johannesburg, 2005

Declaration

I, Shoyab Wadee declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

……

…….day of …….., 2005

Dedication

For My Family
Nazreen
Muhammed
Fatima Zahra
2005

Presentations arising from this study

1. Wadee S; Tikly M. Deaths in lupus patients at the Chris Hani Baragwanath Hospital, Soweto. Oral paper presentation. Annual congress of South African Rheumatology and Arthritis Association.2003 May; Gauteng
2. Wadee S, Tikly M. Contribution of nephritis to lupus mortality in an indigent black population. Poster presentation. 3rd World Congress of Nephrology. 2005 June 26-30. Singapore.

Abstract

Little is known about the epidemiological and mortality patterns of systemic lupus erythematosus (SLE) in Africa. Aims of this study- to determine the demographics, clinical features and causes and predictors death in patients attending the Lupus clinic at the Chris Hani Baragwanath hospital in Soweto. Methods- the records of 226 patients who fulfilled American College of Rheumatism criteria for the diagnosis of SLE were reviewed. The mean (± SD) age at presentation was 34 (± 12.5) years. The female to male ratio was 18:1. The commonest clinical feature found was arthritis in 70.4% of patients. Nephritis was present in 43.8% and CNS lupus in 15.9% of patients. 55 patients in this group had died and 64 were lost to follow up. The 5-year survival was 57% uncensored and 72% if censored for loss to follow up. Infection (32.7%) was the commonest cause of death followed by renal failure (16.4%). Nephritis, CNS lupus and hypocomplementaemia were associated with mortality on univariate analysis. Lupus nephritis was the only independant predictor of mortality on multivariate analysis. Conclusion- this study confirms the poor outcome of SLE in the developing world and demonstrates that renal disease is a factor commonly implicated in mortality. The 5-year survival and pattern of mortality is similar to that reported elsewhere in the developing world.

Acknowledgements

Professor Mohammed Tikly for his close support and supervision

Dr. Mark Hopley and Dr Beverly Traub for their support and especially to Mark for his assistance with the statistical analysis.

Professor Saraladevi Naicker for her patience and support.

The past and present staff from the Lupus clinic at the Chris Hani Baragwanath hospital, as well as the administration of the hospital for allowing me to examine the records.

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Abbreviations

ACR	American College of Rheumatology
ANF	Antinuclear factor antibodies
ANOVA	Analysis of variance
anti –RNP	Anti ribonuclear protein antibodies
anti-dsDNA	anti-double stranded DNA antibodies
anti-Sm	Anti -Smith antigen antibodies
APL	Antiphospholipid
BILAG	British Isles lupus assessment group
C1q	Complement factor 1q
C2	Complement factor 2
C4	Complement factor 4
CHBH	Chris Hani Baragwanath Hospital
DNA	Deoxyribonucleic acid
HIV	Human Immunodeficiency Virus
HLA	Human Leucocyte Antigen
ICU	Intensive Care Unit
LE	Lupus erythematosus
LN	Lupus nephritis
MHC	Major histocompatibility complex
mts	Months
No.	Number
NS	Not Significant
S Africa	South Africa
SD	Standard Deviation
SLAM	Systemic lupus activity measure
SLE	Systemic lupus erythematosus
SLEDAI	Systemic lupus erythematosus disease activity index
SLICC	Systemic Lupus International Co-operative Clinics
TB	Tuberculosis
TNF	Tumour Necrosis Factor
UK	United Kingdom
USA	United States of America
UV	Ultra violet
WHO	World Health Organization
WR	Wasserman reaction
yrs	Years

1.Introduction

1.1 Background and history

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disorder caused by tissue damage resulting from antibody and complement-fixing immune complex deposition (Wallace and Hahn, 2002). The disease is the result of a complex interplay between genetic factors, hormones, autoantibodies and environmental factors (Isenberg, 1997). It is characterized by immunologically mediated, clinical and serological phenomena. It may resemble any of a variety of infectious, inflammatory, nutritional, malignant and metabolic disorders.

'Lupus' which means wolf in Latin was probably first used by Hebernus of Tours in the tenth century to describe a skin lesion (Smith and Cyr, 1988). Because of the preponderance of cutaneous manifestations and the high prevalence of tuberculosis (TB) at the time, some of the earlier descriptions of the disease were attributed to cutaneous TB (Wallace and Hahn, 2002). Biett and Cazenave coined the term 'lupus erythemateaux' (Holubar and Fatovic-Ferencic, 2001, Smith and Cyr, 1988) and Wilson later noted that the non-ulcerating skin lesion called 'lupus' was commoner in women. Kaposi called for a clear segregation between 'lupus vulgaris' and 'lupus

erythematosus' (LE). He described the former as an ulcerating lesion that was a manifestation of TB and the latter as a separate condition. After the discovery of the tubercle bacillus and the failure to isolate the organism from LE lesions, the association with TB waned (Wallace and Hahn, 2002).

In 1895, Osler described a group of patients some of whom had LE and visceral disease and had a relapsing and remitting pattern. He called this condition 'erythema exudativum multiforme'(Wallace and Hahn, 2002). In 1902, Sequira and Balean published a series of patients with discoid and systemic LE (Smith and Cyr, 1988).This period, during which the systemic nature of the condition was being described, is known as the 'neoclassical' period of the history of SLE (Hochberg, 1991).

By the fifth decade of the twentieth century several immunological phenomena were described. The value of these tests lay in their ability to assist in making the diagnosis of SLE when the classic skin lesions were absent (Wallace and Hahn, 2002). This heralded the onset of the 'modern' period in the history of the disease (Hochberg, 1991). These features included the discovery of the false positive WR, by Reinhart in 1909, the LE cell phenomenon, by Hargraves in 1948, the lupus anticoagulant by Conley

and Hartman,in 1952, and antinuclear antibodies (ANA) by Miescher and Fauconnet in 1954 (Wallace and Hahn, 2002).

1.2 Classification criteria

1.2.1 Development of classification criteria

As researchers probed this disease it was recognized that other conditions have overlapping clinical features. Criteria to help classify the disease were needed especially to facilitate research. Early criteria were described by Siegel and Lee in an attempt to standardize diagnosis (Siegel *et al*., 1962). By 1971 the American College of Rheumatology (ACR) considered 74 criteria as potentially useful. 14 were selected as diagnostic criteria (Cohen and Canoso, 1972). One of the aims of these criteria was to differentiate the disease from rheumatoid arthritis. Four criteria were needed to confirm the diagnosis. In 1982 a positive ANA test was added to the, then revised, ACR criteria, and the total number of criteria was reduced to 11 (Tan *et al*., 1982). Further adjustments were proposed by Hochberg to include antiphospholipid antibodies (Hochberg, 1997). The 1997 revised criteria are shown in Appendix 1.

1.2.2 Use and limitations of ACR classification criteria

Levin *et al* have pointed out some limitations of these criteria if used as a diagnostic tool. Only 50% of their patients fulfilled the 1982 criteria at the onset of the disease (Levin *et al.*, 1984). However after 5 and 7 years respectively this increased to 78.5% and 83%. All of their patients eventually fulfilled the criteria, requiring up to 20 years in some instances. Alarcon *et al* report that the mean time to accrual of four criteria was 29.4(±52) months from first presentation in their cohort (Alarcon *et al.*, 2004). Davis and Stein applied criteria to 18 Zimbabwean SLE patients, for which they found the sensitivities to be 83% and 94% for the 1971 and 1982 criteria, respectively (Davis and Stein, 1989). Patients with SLE, especially with milder disease and at initial presentation may be undiagnosed if the 'diagnostic' criteria are used to define diagnoses, but may contribute to the burden of the disease and may need similar therapy (Levin *et al.*, 1984).

In addition to the ACR classification criteria, numerous instruments have been developed to measure disease activity, including the SLE disease activity index (SLEDAI), systemic lupus activity measure (SLAM) and British Isles lupus assessment group (BILAG) scores. These instruments are important from therapeutic and prognostic perspectives. The ACR Systemic Lupus International Co-operative Clinics damage (SLICC) score is used to

measure irreversible damage that results from both disease activity and drug toxicity (Wallace and Hahn, 2002).

1.3 Epidemiology of disease and clinical features

1.3.1 Disease incidence and prevalence

Systemic lupus erythematosus occurs in all populations, with the highest prevalence described in African -American women. As with type I diabetes, the prevalence varies along what is termed a tropical gradient, with the highest figures in temperate regions and lowest in the tropics (Bae *et al*., 1998). The annual incidence of the disease varies between 3.3 and 8.7/100000 people. (Table 1)

Table 1 – Incidence of SLE in selected countries

Study	Country	Year	No	Incidence *
Gudmundsson (Gudmundsson and Steinsson, 1990)	Iceland	1990	76	3.3
Nossent (Nossent, 1992)	Curacao	1992	94	4.6
Hopkinson (Hopkinson *et al*., 1993)	United Kingdom	1993	23	3.7
Uramoto (Uramoto *et al*., 1999)	USA	1992	48	5.56
Vilar (Vilar and Sato, 2002)	Brazil	2002	43	8.7

* per 100 000 people per year

Several groups have documented an increase in the incidence of the disease over the latter part of the twentieth century (Uramoto *et al*., 1999, Gudmundsson and Steinsson, 1990). Similarly the prevalence of the disease in different parts of the world varies widely from 12 to 254 per 100 000. The differences in prevalence may relate to differences in the study populations relating to age, sex, ethnicity and environment or differences in the methodology of the studies and the criteria used for diagnosis (Wallace and Hahn, 2002).

1.3.2 Incidence of the disease in Africans

There are no published studies on the rates of occurrence of SLE in Africa, although several centres have reported their experience with SLE. The disease is thought to be less common in tropical Africa because of the high prevalence of tropical infectious diseases, particularly malaria. This phenomenon may be mediated by the presence of immunosuppressive mediators like tumour necrosis factor alpha and nitric oxide in patients with chronic infection (Adebajo, 1997, Greenwood, 1968). It is also likely that poor access to health services contributes to under diagnosis in Africa. Nevertheless, population surveys together with increasing reporting suggest that the disease may not be as uncommon in sub-Saharan Africa as once believed (Seedat *et al*., 1994, Ka *et al*., 1998b, Houman *et al*., 2004, Adebajo and Davis, 1994). Certainly, patients of ethnic African descent living in Western countries appear to be quite commonly afflicted with this condition (Bae *et al*., 1998, Molokhia *et al*., 2003). Systemic lupus erythematosus has been reported to be commoner in Southern Africa than in central and West-Africa (McGill and Oyoo, 2002, Symmons, 1995). There is also some suggestion that Asian populations are more prone to the disease than whites (Samanta *et al*., 1992). Table 2 shows some of the reports from Southern Africa.

Table 2. Selected studies from Southern Africa reporting SLE

Study	Year	Place	Period	No. of patients	Comment	Ref
Dessein	1988	Pretoria	12 yrs	30	20 of the cases in 2 years; all black	(Dessein *et al.*, 1988)
Ansell	1996	Johannesburg	10.5 yrs	30	Critical care requiring	(Ansell *et al.*, 1996)
Sutej	1989	Johannesburg	Cross sectional	92	Prospective study examining photosensitivity	(Sutej *et al.*, 1989)
Jessop	1973	Cape Town	11yrs	130	Only 60% fit 1971 criteria;mostly white and coloured	(Jessop and Meyers, 1973)
Seedat	1977	Durban	6 yrs	30	17 Indian, 13 black	(Seedat and Pudifin, 1977)
Stein	1990	Harare	6 mts	18	Prevalent patients seen at clinic	(Stein and Davis, 1990)
Tikly	1996	Soweto	Cross sectional	111	Survey of autoantibodies	(Tikly *et al.*, 1996)
Mody	1994	Durban	6 yrs	85	Hospitalised	(Mody *et al.*, 1994)

1.3.3 The role of gender and age

Female sex has consistently been associated with the disease, with a female predominance approaching 90% (Wallace and Hahn, 2002). Outside the childbearing years the incidence of SLE in males approaches the rate in females although it remains higher in females. These differences are thought to relate to hormonal influences (Mayor and Vila, 2003). The median age of disease onset is between 37 and 50 years in white women (Wallace and Hahn, 2002). Several comparative studies have, however, shown that the peak age of onset is lower in black women (Hochberg, 1985, Hopkinson *et al*., 1994). The disease has been reported to occur later in affected males (Pistiner *et al*., 1991, Wallace and Hahn, 2002).

1.3.4 Genetic factors related to disease.

Familial clustering of patients with SLE has been noted. Hochberg in a case control analysis reported that 10% of patients with SLE have at least one first degree relative with the disease compared to 1% of age, gender and race matched controls (Hochberg, 1987a). A concordance rate between monozygotic twins that is about ten times the concordance rate between dizygotic twins or non-twin siblings is evident (Bengtsson *et al*., 2002, Cooper *et al*., 2002a). Both major histocompatibility complex (MHC) and

non-MHC related genes have been linked to SLE susceptibility (Wallace and Hahn, 2002). An extensive review of the genes associated with SLE is beyond the scope of this report but some of the most consistent are listed below.

- HLA DR2 in Caucasians, Asians and Africans (Wallace and Hahn, 2002, Rudwaleit *et al.*, 1995). HLA DR3 in many Caucasian populations and in some studies in Africans (Reveille *et al.*, 1998, Wallace and Hahn, 2002).
- HLA DR2 and DR3 have been associated with the presence of Anti-Ro (SSA) and Anti-La (SSB) antibodies (Arnett *et al.*, 1989).
- Antiphospholipid antibodies were associated with HLA DR7, DR4 and DRw53 (Wallace and Hahn, 2002).
- Deficiencies in complement components 2 (C2) and 4 (C4) have both been associated with SLE in different populations (Arnett *et al.*, 1990, Ayed *et al.*, 2004).
- Tumour Necrosis Factor (TNF) gene polymorphisms have been associated with SLE but may be due to gene linkage (Bettinotti *et al.*, 1993, Rudwaleit *et al.*, 1996).
- Several non-MHC encoded loci have been associated with SLE. They have in common the fact that they involve genes coding for

participants in the immune system and include C1q genes, T-cell receptor genes, Fc receptor genes, cytokine genes and TNF receptor genes (Wallace and Hahn, 2002).

- Researchers from Africa have demonstrated several genes associated with SLE. Kachru *et al* in 1984 described associations with HLA DR2 and DR3 in African patients (Kachru *et al*., 1984). Klemp *et al* demonstrated that HLA DR2 was associated with a higher risk of SLE in Cape Coloured patients (Klemp *et al*., 1988). Rudwaleit *et al* in a group of 49 patients from our clinic also demonstrated the association with DR2 in black patients (Rudwaleit *et al*., 1995). Davies *et al* showed an association between SLE and mannose-binding protein gene polymorphisms in patients from South Africa (Davies *et al*., 1998).

1.3.5.Environmental aspects implicated in disease causation

Despite the above strong evidence for genetic factors that predispose to SLE, there exists also strong evidence that environmental factors are partly responsible for the development of the disease. An example of environmental influence is the observation that in Africa (especially West Africa) the disease is uncommon while in people of African extraction living

in the developed world the incidence is very high (Molokhia *et al.*, 2001). Several environmental factors have been commonly linked with autoimmune disease. These include:

- Chemical factors including aromatic amines and hydrazines- these are metabolized by acetylation and 'slow acetylators' are at particular risk. Exposure to heavy metals including gold and mercury are also implicated(Cooper et al., 2004a, Cooper et al., 2004b)
- Exposure to sunlight especially the UV fraction.(Nived et al., 1993)
- Infectious agents including Herpes group viruses, and bacterial elements have been indirectly linked to autoimmune disease. (Wallace and Hahn, 2002, Cooper et al., 2002a).

1.3.6 Differences in clinical features and clinicoserologic correlations

The manifestations of SLE differ significantly among individuals. Several epidemiological studies have been performed to look at clinical features and their distribution in different populations around the world. The following are a few examples. Various studies have revealed a clustering of clinical and serological features in particular populations.

- Naiker *et al* have demonstrated a prevalence of 45% for anticardiolipin antibodies in a population of South African

patients with lupus nephritis (Naiker *et al*., 2000). This association has also been described by others along with associations of Lupus nephritis with anti-dsDNA antibodies and anti-Sm antibodies (Alba *et al*., 2003).

- Comparison of patients with and without renal involvement in a study from Tunisia showed that lupus nephritis was significantly associated with pericarditis, hypertension, cryoglobulinemia and antiphospholipid syndrome (Houman *et al*., 2004).
- Ribosomal–P autoantibodies have been associated with neurological lupus but this has not been a consistent finding (Arnett et al., 1996, Gerli et al., 2002).
- Font *et al*, in their group of 600 Spanish patients with SLE, described numerous correlations including associations between renal disease, haemolytic anaemia and anti-dsDNA antibodies (Font *et al*., 2004).
- Tikly *et al* also found positive clinicoserological associations which included the combination of anti-dsDNA antibodies and low complement factor 4 (C4) levels with renal disease; anti-dsDNA antibodies with cutaneous vasculitis; anti-Sm antibodies with psychosis; anti-RNP antibodies with Raynaud's phenomenon

and anti-Ro antibodies with renal disease, psychosis and malar rash (Tikly *et al.*, 1996).

Furthermore racial and ethnic groups may differ in the pattern of manifestations associated with SLE. Cooper *et al* analyzed racial differences in the Southeastern USA and found more discoid lupus, more nephritis and a higher prevalence of anti-Sm and anti-RNP antibodies in black patients as well as less photosensitivity or mucosal ulcers in black patients (Cooper *et al.*, 2002b). A similar finding as regards photosensitivity was reported in South African Blacks by Jacyk *et al* (Jacyk and Steenkamp, 1996). Several other investigators have noted the increased incidence of renal disease in black patients (Bastian *et al.*, 2002, Hochberg *et al.*, 1985).Gender differences have also been described. These include an older age of onset in males as well as a greater tendency to renal failure and a higher prevalence of serositis. (Mayor and Vila, 2003).

The commonest clinical manifestations reported are articular and cutaneous disease. Haematological and renal involvements are also common. The table below summarizes the prevalence of these manifestations in studies from the

developing world (Dessein *et al*., 1988, Jessop and Meyers, 1973, Seedat and Pudifin, 1977, Houman *et al*., 2004, Vila *et al*., 1999).

Table 3: Clinical manifestations in selected studies

Study	**Jessop (Cape Town)**	**Dessein (Pretoria)**	**Seedat (Durban)**	**Houman (Tunisia)**	**Vila (Peurto Rico)**
Year	**1973**	**1988**	**1976**	**2004**	**1999**
Number	130	30	30	100	134
Articular	74%	90%	97%	78%	67.5%
Skin	78%	60%	73%	>63%	76.9%
Renal	58.5%	60%	87%	43%	16.2%
Haematological					
1.Haemolytic anaemia	14.5%				12.7%
2.Leukopaenia	22.3%	63%	12%		41.8%
3.Thrombocytopaenia	17.7%	10%	3%		
ANA (or positive LE)*	90.8%*		100%*	100%	93.3%

1.3.7 Incidence of lupus nephritis (LN) and different classes of LN

The frequency of renal involvement varies in different populations studied with both ethnic and geographic variation reported. In a recent study done in Tunisia, 43% of patients were diagnosed with lupus nephritis (LN) (Houman *et al*., 2004), while LN was found to be uncommon in an ethnically similar Arab population in Israel (Habib and Saliba, 2002). Various studies have demonstrated a higher incidence of LN in black patients (Bastian *et al*., 2002, Alba *et al*., 2003). In a study done at Queens medical center in Nottingham (UK) by Hopkinson and colleagues only 22% of patients had LN (Hopkinson *et al*., 1993).The histological patterns of lupus nephritis as defined by the WHO are shown as appendix 2 in simplified form. The table below demonstrates the prevalence of the different subtypes in several studies (Seedat *et al*., 1994, Mok *et al*., 1999, Bates *et al*., 1991, Bastian *et al*., 2002, Neumann *et al*., 1995).

Table 4: WHO subtype in selected studies

WHO subtype		N	I	II	III	IV	V	VI
Bates *et al*(1991)	S Africa	55	-	11%	24%	58%	7%	-
Seedat *et al*(1994)[$]	S Africa	43	5%	35%	7%	40%	9%	-
Neumann *et al*(1995)[#]	USA	150	0.6%	7%	13%	46%	11%	5%
Mok *et al*(1999)	S China	183	1%	5%	25%	55%	14%	-
Bastian *et al*(2002)[*]	USA	43	-	21%	33%	35%	41%	-

$ 1 biopsy showed interstitial nephritis; # 10% classification not determinable; * In this study where two classes of LN were reported both were counted.

1.4 Mortality data

1.4.1. Trends in Mortality

In the preceding five decades significant advances have been made in the management of SLE. Initial strides in improving diagnosis, especially with serology, allowed appropriate treatment. The prognosis of SLE has improved with the widespread use of corticosteroids. The advent of other immune suppressants in the last few decades has conversely allowed us to diminish the overall exposure to steroids while maintaining efficacy of immunosuppression to further improve outcomes. Better supportive care in the form of ICU services, dialysis, transplantation and antibiotics have contributed to improving survival (Wallace and Hahn, 2002).

An observational study done in 1956 by Dubois' group, which included patients from the pre-steroid era, demonstrated a five year survival of only 40%, a study by Ginzler *et al* showed a 77% 5 year survival in 1982 while more recent studies have demonstrated 5 year survival figures exceeding 90% in developed countries (Dubois, 1956, Ginzler *et al*., 1982, Cervera *et*

al., 1999). Studies in the developing world, from India, Curacao, Tunisia and Thailand have shown that survival has not been as good in these countries (Malaviya *et al*., 1997, Nossent, 1993b, Kasitanon *et al*., 2002). In South Africa Jessop *et al* described a 5 year survival rate of 65.5% in 130 patients in Cape Town in 1973 (Jessop and Meyers, 1973). Dessein *et al*, in 30 patients from Pretoria, reported their five year mortality as 78% (Dessein *et al*., 1988). A study from Durban also revealed a high mortality rate in hospitalized patients with SLE (Mody *et al*., 1994). Similarly Ansell *et al* showed a high mortality in a group of critically ill patients with SLE in Johannesburg (Ansell *et al*., 1996) as did Whitelaw in Cape Town (Whitelaw *et al*., 2005). Even in more developed nations however, patients with SLE are still more likely to die than those without the disease (Urowitz *et al*., 1997).

1.4.2 Causes of death

Before the advent of corticosteroids and immunosuppressants, disease activity was the commonest cause of death with most deaths occurring soon after diagnosis (Wallace *et al*., 1982, Dubois *et al*., 1978). More recently, mortality in the developed world seems to follow an established, disease duration related pattern. Early deaths (within 5 years) are more often due to

disease activity or infections. Deaths after this are more likely to be due to malignancy or vascular disease (Cervera *et al*., 2003, Moss *et al*., 2002). The increased incidence of cardiovascular disease is not fully explained by traditional risk factors alone (Gorman and Isenberg, 2004).

Several studies from the developing world, although mostly consisting of small numbers of patients, have demonstrated that infection and active disease, particularly with renal involvement or renal failure, are the major causes of death and that the early mortality (within five years) is higher than that in the developed world (Kasitanon *et al*., 2002, Houman *et al*., 2004, Seedat *et al*., 1994). Table 5 demonstrates the causes of death as reported in various selected studies from around the world (Moss *et al*., 2002, Seedat and Pudifin, 1977, Abu-Shakra *et al*., 1995a, Jacobsen *et al*., 1998, Ka *et al*., 1998a, Cervera *et al*., 2003)

Table 5: Causes of death in SLE –selected studies											
Study	Country	Year	Number	Deaths	Infections	Renal	Cardiovascular	Malignancy	Activity	unknown	Other
Seedat	S.Africa	1977	30	6	-	33%	15%	-	-	33%	-
Abu Shakra	Canada	1995	665	124	40%	4.8%	15.4%	6.5%	16%	10.5%	14.6%
Jacobsen	Denmark	1998	513	122	20.4%		26.2%	7.3%	28.6%		17.2%
Ka	Senegal	1998	30	8	25%	37.5%	-	-	-	-	37.5%
Moss	UK	2002	300	41	17%	15%	17%	20%	-	10%	22%
Cervera	Spain	2003	1000	68	25%				26.5%		26.5%

1.4.3. Predictors of mortality

Several investigators have attempted to define features that predict a poor outcome. Conflicting data regarding the effect of age at diagnosis have been reported. Kaslow commented on the effects of increasing age on mortality (Kaslow and Masi, 1978). More recently Abu Shakra also reported that increasing age was independently associated with mortality (Abu-Shakra *et al*., 1995b). However older age has not been consistently found to be a predictor of mortality in all studies. Gender differences in mortality are also inconsistent but some studies have noted a poorer prognosis in males (Molina *et al*., 1996, Mayor and Vila, 2003). Others have found no effect on mortality of male sex (Hochberg, 1987b). Black race has been shown to be associated with poorer outcome as has non-white race in other series (Walsh *et al*., 1996, Ward *et al*., 1995). This is confounded by the finding that lower socioeconomic status has also been associated with poorer outcome in some of these studies.(Alarcon et al., 2001, Lotstein et al., 1998)

Several studies have demonstrated renal disease to be a poor prognostic feature (Abu-Shakra *et al*., 1995b, Bellomio *et al*., 2000).In addition patients with more advanced renal disease as evidenced by more severe

hypertension, higher degrees of proteinuria, proliferative disease or fibrosis on biopsy and renal dysfunction have the worst prognosis (Donadio *et al*., 1995, Mok *et al*., 1999). Black patients may also have a poorer outcome of nephritis (Dooley *et al*., 1997, Nossent, 1993a). Thrombocytopenia, lung involvement, neurological involvement, cardiac disease, antiphospholipid antibodies, SLE disease activity index (SLEDAI) score and high damage scores are other factors which have been reported to be predictors of poor outcome in several studies (Wallace and Hahn, 2002).

1.5 Aims and Objectives

In view of paucity of data on causes and predictors of death in Africans, we undertook a retrospective study of Black South African patients attending the Lupus clinic at Chris Hani Baragwanath Hospital (CHBH), the major tertiary referral facility that serves the people of Soweto and surrounding areas of southern Gauteng.

2. Patients and Methods

2.1 Description of study and inclusion criteria

A retrospective review of available clinical records of patients fulfilling the 1997 ACR criteria for SLE or features of SLE-like disease (3 criteria) and attending the Lupus clinic at CHBH was performed. Only records of patients who were admitted or who were seen on more than one occasion were included in the analysis.

2.2 Clinical and laboratory data abstraction

Demographic, clinical and serological data was abstracted from the clinic records. The clinical and laboratory features present, which corresponded to the ACR classification criteria for SLE, were recorded if clearly noted in the records. Clinical features were further stratified according to whether they were present at diagnosis (or within one month of presentation) or whether they developed subsequently. Laboratory features were however only recorded as being present or absent at any time.

Serological tests that were documented included the anti-nuclear antibody (ANA) test, antibodies to the extractable nuclear antigens RNP, SM, Ro and La, anti double stranded-DNA antibodies and anti-phospholipid antibodies

(either a positive IgG or IgM anticardiolipin antibody test or a positive test for lupus anticoagulant). The presence of hypocomplementaemia (low C3 or C4) was also recorded. Appendix 3 is an example of the form used to record data.

2.3 Recording outcomes

Outcomes were recorded as known or unknown. Known outcomes were further stratified as known alive or known dead. Causes of death were determined from the available records in patients known to have died. The causes were classified as follows:

- Infections (sepsis) – where the cause of death was found to be definitively caused by an infective aetiology or by a syndrome characteristic of infection (e.g. pneumonia with raised white cells and C-reactive protein).
- Renal failure -where patients had markedly deranged creatinine and were thought to have died as a result of renal metabolic complications.
- Active disease - where death occurred directly as a result of a serious manifestation of SLE but not renal failure.
- Other - where death was not directly attributable to SLE but was caused by any other condition (e.g. cardiovascular disease).

The causes of deaths were assigned into one of the above categories by careful review of the records by Dr S Wadee and Professor M Tikly. Where no cause of death was recorded in the file this was classified as unknown. Indirect contributors to mortality were assessed based on a subjective assessment of the records at the time of death.

2.4 Statistical Methods

The Chi-square test and Student's t- test or ANOVA analysis were applied to compare nominal and continuous variables, respectively, between patient subgroups. Kaplan-Meier survival curves were constructed to assess the overall survival figures and for subgroups of patients. A multivariate logistic regression analysis of the variables that were associated with mortality was performed using the Cox proportional hazard model. Statistical analyses were performed using Statistica v6 (Statistica.com). A p value < 0.05 was defined as being statistically significant.

3.0 Results

3.1 Overview of files reviewed

Of 280 patients reviewed, 10 were excluded either because records were inadequate (3), the diagnosis was not SLE (2) or records were not traceable at the time of the analysis (5). Of the remaining 270 patients, 226 patients fulfilled at least 4 ACR classification criteria for a diagnosis of SLE while 44 patients met 3 criteria and were defined as 'SLE like'. The records dated from January 1986 to July 2003. Figure 1 below shows the breakdown of the records reviewed. The demographic description of the population studied is summarized in table 6 below

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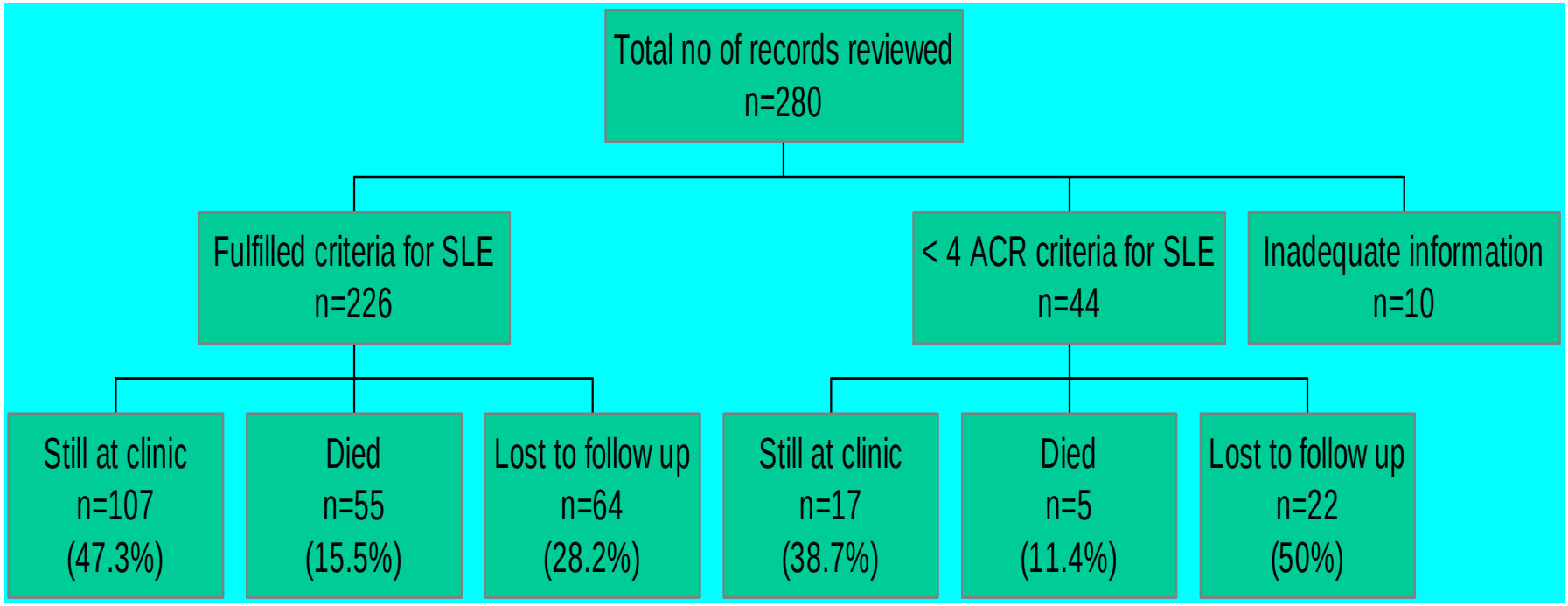


Figure 1 –Overview of records reviewed

3.2 Demographic analysis

The demographic and outcome data are summarized in table 6. The mean age at presentation was 34 years. The mean age at presentation in males with SLE (38.9yrs) was not significantly different from that in females (33.7 yrs). Differences between the SLE group and SLE like group are also shown. The mean follow up was significantly shorter ($p<0.0001$) in the SLE-like group. Half of the SLE-like patients were lost to follow up. A significantly higher proportion of the patients classified as SLE-like were lost to follow up (Chi Squared -$p<0.01$).

TABLE 6: Demographic data			
	SLE (no=226)	SLE-like (no=44)	Overall (n=270)
Male: Female	1:18	1:15	1:16
Mean(±SD) age (years)	34(±12.5)	35.9(±13.4)	34.3(±12.7)
Mean(±SD) follow up(months)	59.4(±49)*	27.3(±31.3)	54.2(±48)
Known deaths	55(24.3%)	5(11.4%)	60(22.2%)
Lost to follow up	64(28.3%)$	22(50%)	86(31.9%)

*p<0.0001 versus SLE like group; $p<0.01 versus SLE like group

3.3 Prevalence of clinical features and differences between groups based on outcome.

The clinical features found at presentation are displayed in table 7 and the cumulative incidences of various ACR clinical and serological criteria are shown in Table 8 below. The demographic and clinical features of the subgroups of known alive, known dead and patients lost to follow up at the time of analysis, are summarized in table 8.

TABLE 7 - Frequencies of clinical features found at initial presentation in 226 patients with SLE	
Clinical Feature	**Frequency**
Malar rash	105 (46.5%)
Discoid rash	79 (35%)
Photosensitivity	80 (35.4%)
Oral ulcers	50 (22.1%)
Arthritis	115 (50.9%)
Nephritis	77 (34.1%)
Neurological disease	20 (8.8%)
Serositis	38 (16.8%)

Table 8 Cumulative frequency of clinical and laboratory findings in 226 patients fulfilling ACR criteria for SLE

ACR criteria/feature	Total (226)	Dead (55)	Known alive (107)	Lost to follow up (64)	p-value[1]
Mean age ±SD (yrs)	33.9 ±12.5	34 ±14.3	33.7 ±11.1	34.4 ±13.3	NS
Mean follow up ±SD (mts)	59.4 ±49	46.7 ±43.3	82.2 ±46.3	32.3 ±39.5	0.0001[2]
Malar rash	132 (58.4%)	34 (61.8%)	60 (56.1%)	38 (59.3%)	NS
Discoid lupus	94 (41.5%)	19 (34.5%)	47 (43.9%)	28 (43.8%)	NS
Oral ulcers	87 (38.5%)	28 (50.9%)	39 (36.4%)	20 (31.3%)	NS[3]
Photosensitivity	88 (38.9%)	20 (36.3%)	37 (34.6%)	31 (48.4%)	NS
Serositis	41 (18.1%)	12 (21.8%)	16 (14.9%)	13 (20.3%)	NS
Arthritis	159 (70.4%)	35 (63.6%)	83 (77.5%)	41 (64.1%)	NS
Neurological disease	36 (15.9%)	14 (25.4%)	12 (11.2%)	10 (15.6%)	NS[4]
Nephritis	99 (43.8%)	35 (63.6%)	39 (36.4%)	25 (39.1%)	0.01
Haematological disease *Thrombocytopaenia*	118 (52.2%) *29(12.8%)*	21 (38.2%) *6(10.9%)*	65 (60.7%) *12(11.2%)*	32 (50%) *11(17.2%)*	0.025 *NS*
ANA positive	224 (99.1%)	55 (100%)	105 (98.1%)	64 (100%)	NS
Any other immunological criteria(dsDNA,Sm orAPL)	179 (79.2%)	45 (81.8%)	83 (77.5%)	51 (79.6%)	NS
Anti-dsDNA antibodies	125 (55.3%)	33 (60%)	61 (57%)	31 (48.4%)	NS
Anti-Sm antibodies	92 (40.7%)	23 (41.8%)	41 (38.3%)	28 (43.8%)	NS
Antiphospholipid antibodies	61 (27%)	16 (29.1%)	32 (29.9%)	13 (20.3%)	NS
Hypocomplementaemia	147 (65%)	44 (80%)	67 (62.6%)	36 (56.3%)	0.025

1.All p values above reflect results when analysis includes all 3 groups.

2. Known alive vs Lost to follow up and Known alive Vs Known Dead. (1-way ANOVA)

3. Not significant overall but $p< 0.05$ if dead compared to (known + unknown) together (Chi-squared)

4. Not significant overall but $p< 0.05$ if dead compared to (known + unknown) together (Chi-squared)

Arthritis was the commonest presenting clinical feature. Cutaneous manifestations of SLE were also common presenting clinical features. While 78% of patients with nephritis had it at presentation only 56% of patients with CNS lupus presented with it. As shown in table 8 nephritis, neurological disease and hypocomplementaemia were significantly more common in patients who were known to have died compared to the known alive and lost to follow up group. Mean follow up was significantly longer in the known alive group (1-way ANOVA $p<0.0001$). On multivariate analysis using the Cox proportional hazard regression model for all the factors in table 8 only nephritis was independently associated with death. The relative risk of death in patients with renal disease was 2.07 (95% confidence interval = 1.11-3.84) $p<0.0007$.

Table 9 below shows the cumulative clinical and serological features in the SLE-like group. The difference in follow up of the patients known to be alive was statistically significantly longer than that for the other groups ($p<0.004$). None of the other differences between the three subgroups in the table were statistically significant.

Table 9 Cumulative frequency of clinical and laboratory findings in 44 patients not fulfilling ACR criteria for SLE (SLE-Like)					
ACR criteria/feature	**Total (44)**	**Dead (5)**	**Known alive (17)**	**Lost to follow up (22)**	**p- value**
Mean Age ± SD years	35.9±13.4	32.2±8.7	36.8± 10.7	36±16.2	NS
Mean Follow up ±SD mts	27.3±31.3	11.4±9.9	46.9±35.4	15.8±22.8	<0.004
Malar rash	3 (6.8%)	0	0	3 (13.6%)	NS
Discoid lupus	7 (15.9%)	2 (40%)	1 (5.9%)	4 (18.2%)	NS
Oral ulcers	2 (4.5%)	0	1 (5.9%)	1 (4.5%)	NS
Photosensitivity	4 (9%)	0	1 (5.9%)	3 (13.6%)	NS
Serositis	2 (4.5%)	0	1 (5.9%)	1 (4.5%)	NS
Arthritis	26 (59.1%)	3 (60%)	13 (76.5%)	10 (45.4%)	NS
Neurological	1 (2.3%)	1 (20%)	0	0	NS
Renal	9 (20.5%)	1 (20%)	2 (11.8%)	6 (27.2%)	NS
Haematological	7 (15.9%)	1 (20%)	4 (23.5%)	2 (9.1%)	NS
ANA positive	41 (93.2%)	5 (100%)	15 (88.2%)	21 (95.5%)	NS
Immunological criteria(dsDNA,Sm,APL)	18 (41%)	1 (20%)	7 (41.2%)	10 (45.4%)	NS
Hypocomplementaemia	16 (36.3%)	2 (40%)	9 (52.9%)	5 (22.7%)	NS

3.4 Causes of death

A total of 55 patients (24.3%) with SLE were known to have died. The mean (±SD) age at the time of death was 37.8 (±13.9) years. Table 10 below demonstrates the causes of death as classified. The cause of death was known in 40 patients. The largest proportion of patients (32.7%) died as a result of infections. Infections ranged from Tuberculosis and pneumonia to staphylococcal septicaemia. The details of the causes of infective deaths are shown in Table 11. There were no known viral causes of infective deaths however two patients who succumbed to sepsis also had associated HIV infection. Renal failure in 16.4% of patients was the second commonest known cause of death. Of seven deaths in the 'other' group only one was from a presumed atherosclerotic cause - a myocardial infarct, three were from cardiomyopathies, two were from pulmonary vascular diseases and one was pregnancy related. The relative causes of death within 5 years of presentation and thereafter are also shown in Table 10. No death due to malignancy was recorded. Active lupus and renal disease were the main indirect contributors to death where they were not themselves the cause of death. In the group of lupus-like patients 5 deaths occurred. Three were due to infection, one due to renal failure and in one the cause was unknown.

Table 10 - Causes of death in patients with SLE			
Causes of death	<5years	>5 Years	Total
Infection	13	5	18 (32.7%)
Renal	6	3	9 (16.4%)
Active disease	4	2	6 (10.9%)
Other	5	2	7 (12.7%)
Acute cardiovascular[1]	1	0	
Pulmonary circulatory[2]	1	1	
Pregnancy related[3]	1	0	
Cardiomyopathies	2	1	
Unknown	12	3	15 (27.3%)
Total	40 (72.7%)	15 (27.3%)	55

Notes-table 10.

1. Myocardial infarct at 43 years of age after 53 months of follow up in patient with positive anti-phospholipid antibodies and previous stroke.
2. One pulmonary embolus after 3 months of follow up and one patient with chronic progressive pulmonary hypertension
3. Complications resulting from foetal loss in a patient with recurrent foetal losses

Table 11- Details of infective causes of death			
Type of infection	**<5 years**	**>5years**	**Total**
Sepsis/Septicaemia unspecified	4	2	6
Pneumonia unspecified	4	1	5
Tuberculosis[1]	1	2	3
PCP pneumonia	1		1
Meningitis	1		1
Post surgical sepsis	1		1
Pyomyositis	1		1
Total[2]	13	5	18

Notes –Table 11

1. Two of the three patients had drug resistant TB. TB also contributed to death in one other patient whose primary cause of death was due to a cardiomyopathy.
2. HIV infection was a possible co-factor in two infective deaths, one with TB and one with Pneumonia.

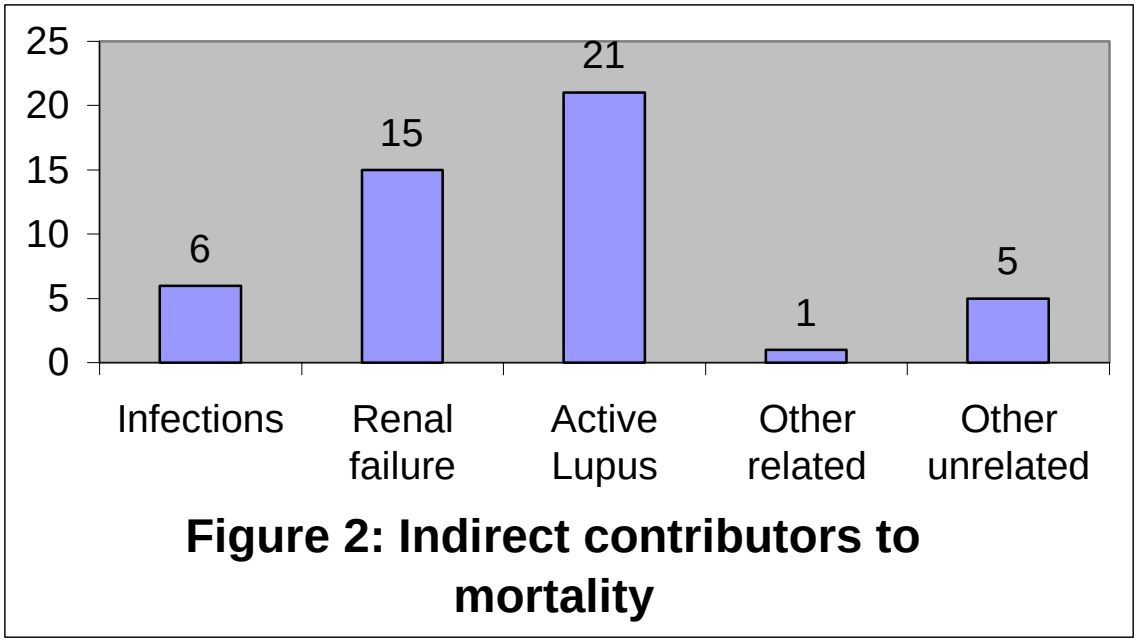


Figure 2: Indirect contributors to mortality

Figure 2 above shows the indirect contributors to mortality in the opinion of the reviewers. These were factors which were present in patients who died in addition to the assigned cause of death.

3.5 Survival curves

The Kaplan Meier survival curves for patients with SLE demonstrate an overall 5-year survival rate of 57% (figure 3). Five-year survival if censored for those lost to follow up is 72% (figure 4). Figure 5 indicates the magnitude of the survival difference between those with or without renal disease censored for patients lost to follow up. It is stratified as to whether disease was present at initial presentation, developed during follow up, or was never noted. It can be seen that the survival is worst for those that develop the disease early but that renal disease at any time is a poor prognostic indicator. These differences were statistically significant ($p=0.002$). CNS disease and hypocomplementaemia were also associated with poorer survival. ($p=0.007$ and $p=0.031$ respectively).

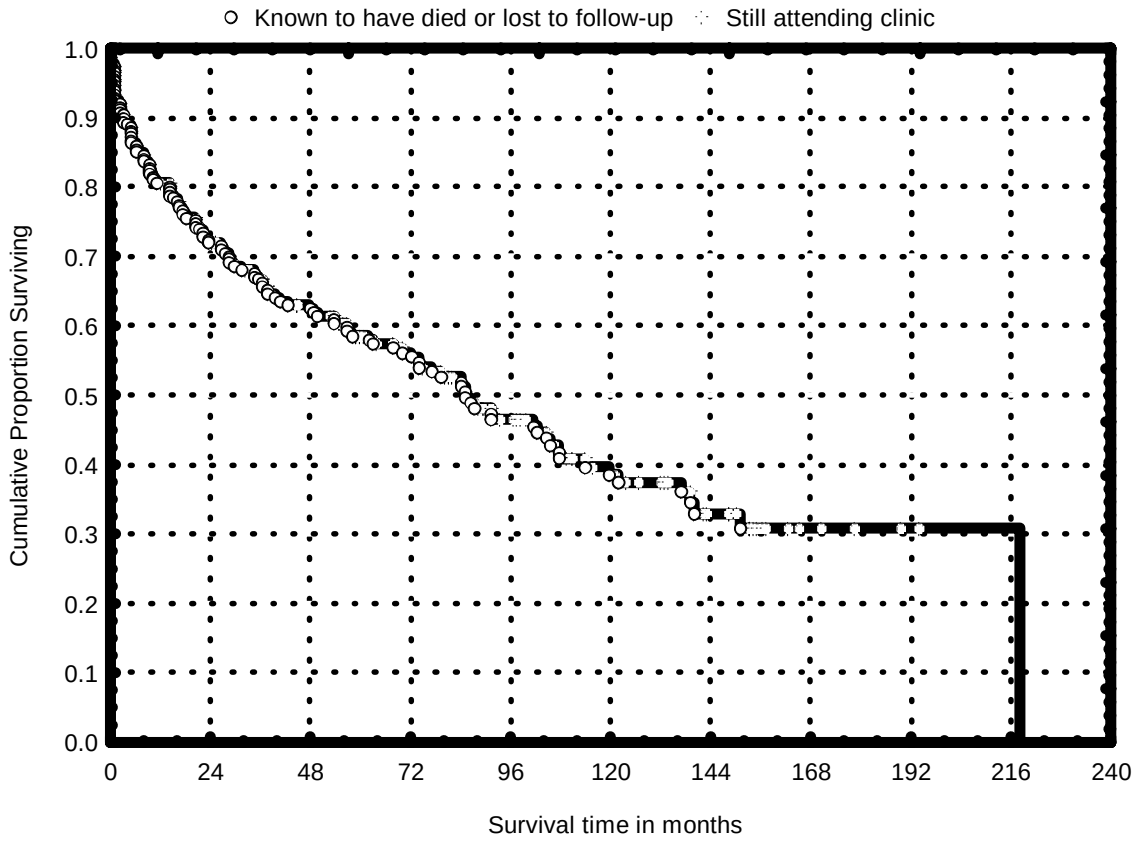


Figure 3- Survival of patients at clinic

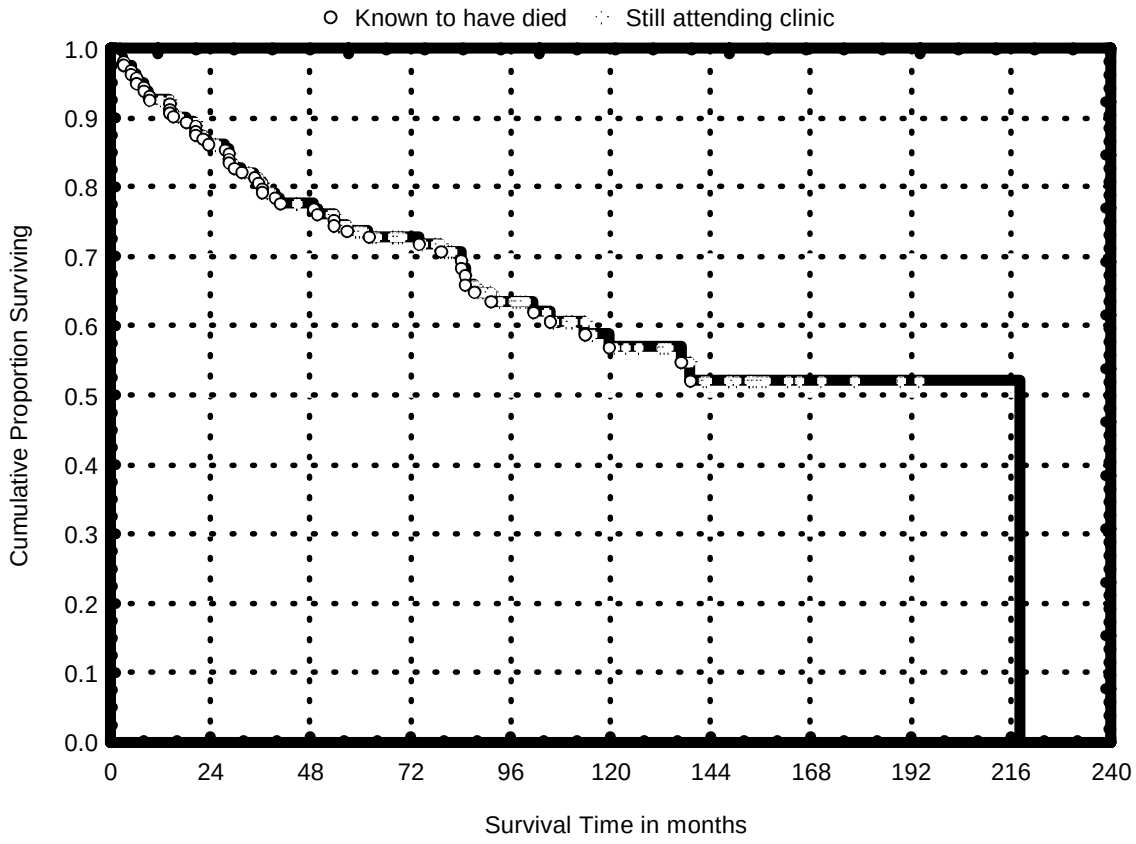


Figure 4- Patient survival excluding lost to follow up group

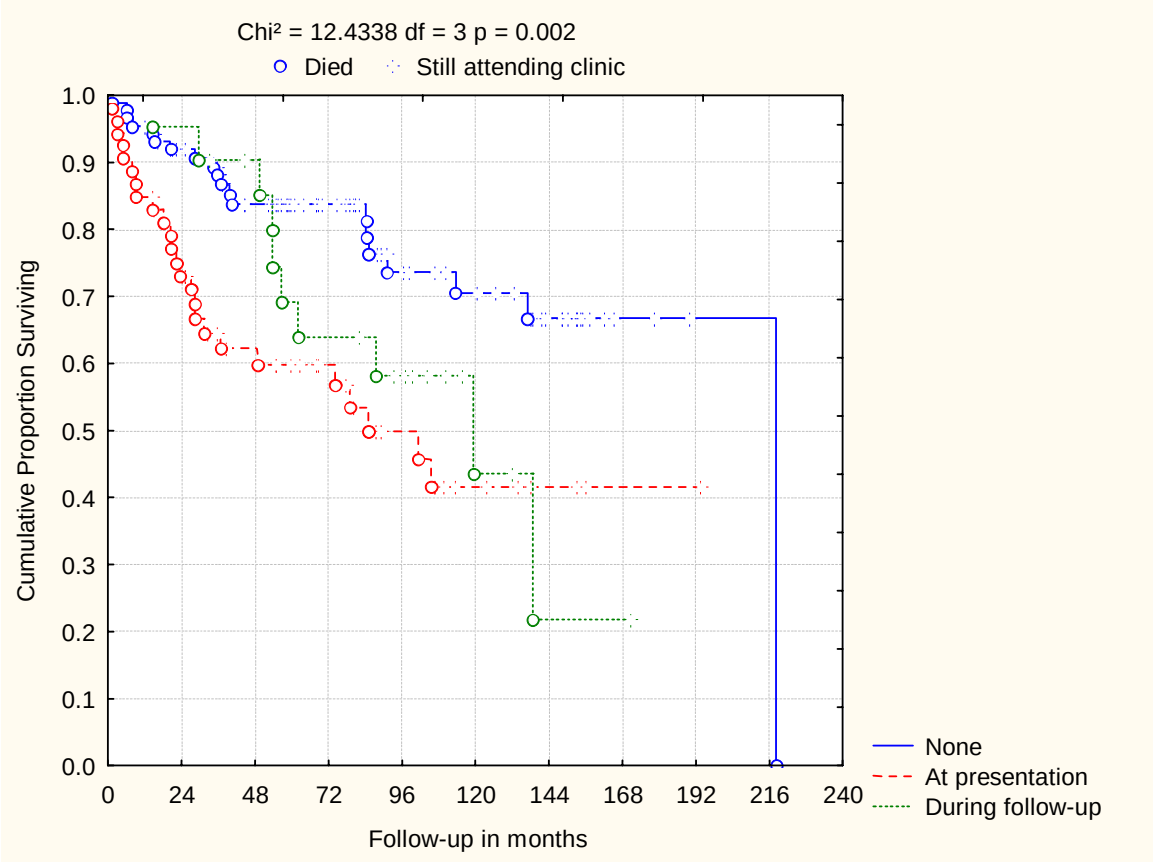


Figure 5- Survival with and without nephritis (lost to follow up group excluded)

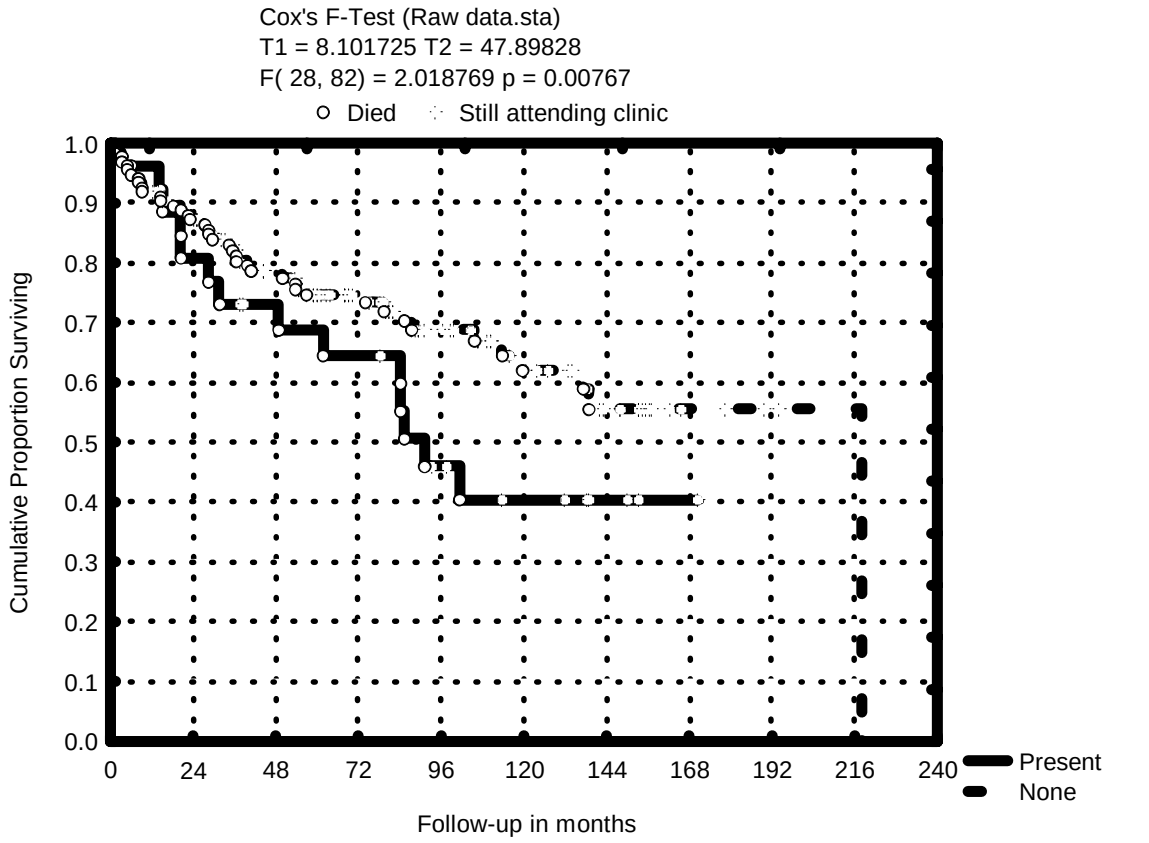


Figure 6- Survival with and without CNS disease (lost to follow up group excluded)

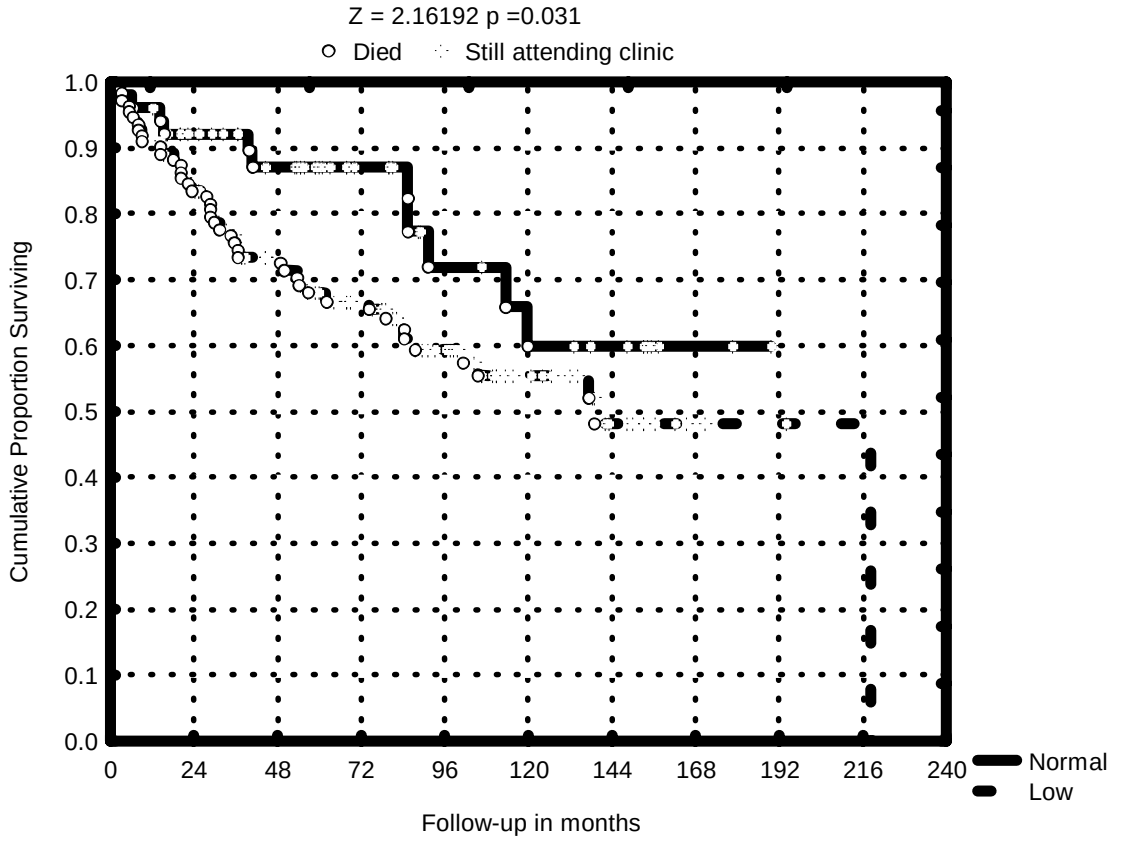


Figure 7- Survival with and without hypocomplementaemia disease (lost to follow up group excluded)

4.Discussion

This review of patients from Soweto in Gauteng Province, South Africa consists of an analysis of 270 patients for whom records were available. The analysis spans a period of more than sixteen years. This analysis constitutes the largest single group of patients reported in South Africa. Two hundred and twenty six of these patients fulfilled the ACR criteria for SLE out of the 270 files examined.

4.1 Demographic features and classification by outcome.

The age at presentation of the patients diagnosed with SLE is well within the range reported elsewhere. The disease overwhelmingly is one affecting young females, usually in their thirties. Only 12 of 226 patients were male (5.3%). This exceeds the degree of female predominance in most reports (Wallace and Hahn, 2002). The reason for this is not clear but may reflect variation in the female predominance in our population. It is possible that the well-known female preponderance in this condition leads to missed diagnosis in some males with the disease. The mean age of presentation was similar in males and females. On closer analysis however it can be noted that the ages of presentation in the males were skewed towards the very young and the old. Only 3 of the 12 males presented between the ages of 20-40

years compared to the almost 60% of females who presented in this age group. This would be partly in keeping with other studies that have demonstrated an older age of onset for males. The average follow up at just over five years reflects the fact that this is an established clinic with the longest follow up of a patient being for a period of over 16 years. This review is unable to provide any estimate of the true prevalence or incidence of the disease in our population. This is due to several reasons. The population in Soweto has been in major flux over the past few decades and has been further impacted on by the arrival in South Africa of several immigrant groups from neighboring countries. It is also likely that several patients with SLE from Soweto presented to and received treatment at other hospitals in the public or private sectors. Further, estimates of occurrence of the disease are complicated by the fact that many of our patients are known to be from other areas within the broader referral base of the Chris Hani Baragwanath hospital.

4.2 Clinical features

The most prevalent clinical feature in this group is arthritis. This finding does not conflict with findings from elsewhere in South African populations

(Dessein *et al*., 1988, Seedat and Pudifin, 1977). Skin manifestations were also common. Photosensitivity was previously reported to be less common in black patients and was reported in 38.9% of patients. This is however higher than the prevalence of 13% reported by Dessein *et al* in his cohort of 30 black patients (Dessein *et al*., 1988). The presence of this feature is often subjectively assessed based on the experience of the patient. Oral ulcers were also reported in <40% of patients. It is possible that this clinical feature may be missed as these are usually painless ulcers and may not be reported by the patient.

Neurological disease is the least common clinical feature found in this group (15.9%). This however represents only new onset seizures or psychosis. It is likely that the total burden of neurological disease is higher if commoner lesions like neuropathies are included. Renal disease occurred commonly but was not as common as that (>60%) reported by Seedat *et al*, Dessein *et al* or Jessop and Meyers from previous South African series (Jessop and Meyers, 1973, Dessein *et al*., 1988, Seedat *et al*., 1994). The prevalence of renal and neurological disease is also less than that reported by Mody in a hospitalized group of patients. This likely indicates that those requiring hospitalization were more likely to have major organ involvement.(Mody *et al*., 1994)

Renal disease, neurological disease and hypocomplementaemia were associated with mortality. Renal, and neurological diseases are areas in which disease may directly lead to death via major dysfunction of these organs. It is likely that hypocomplementaemia represents a surrogate for disease activity. Haematological disease, which in various previous reviews has been associated with mortality, was in fact statistically significantly commoner in patients known to be still alive. Thrombocytopaenia specifically, which has particularly been a poor prognostic factor in some studies was also less common in patients who died.

4.3 Causes of Death

Infection was the commonest cause of death. Contrary to findings in industrialized nations this remained so even for deaths after 5 years (late deaths). This is similar to the findings elsewhere in the developing world (Kumar *et al.*, 1992, Malaviya *et al.*, 1997, Kasitanon *et al.*, 2002). The predisposition to infection is a well documented feature of SLE (Gladman *et al.*, 2002). This may be attributed to both disease and treatment related features. In the developed world early deaths are also mostly due to infection and reflect the active nature of the disease early on and the high exposures to

immunosuppressant medication. The patients in these populations who survive beyond 5 years have been selected out and have a separate set of morbidities to deal with. They are more likely to have accrued a cumulative amount of damage from SLE as well as from exposure to immunosuppression, which may manifest (at least in the industrialized world) as malignancy and cardiovascular disease (Moss *et al*., 2002, Abu-Shakra *et al*., 1995a).

In our setting the high background prevalence of tuberculosis and HIV disease make these constant threats. Only two of the deaths had co-existent HIV at the time of death. However HIV disease increases the incidence of TB, respiratory illnesses, gastroenteritis and other communicable diseases.

Renal disease was also a common cause of mortality and reflects the somewhat limited availability of dialysis. This is similar to the findings from elsewhere in Africa (Ka *et al*., 1998a). One of the problems is that the co-morbidities in these patients may make dialysis difficult. Another problem in our setting contributing to increased mortality from infection as well as from renal disease is the somewhat limited availability of appropriate intensive care facilities. Even if patients are admitted to an ICU Ansell *et al* and

recently Whitelaw *et al* have demonstrated a high mortality in these patients in South African settings(Ansell *et al.*, 1996, Whitelaw *et al.*, 2005). The Chris Hani Baragwanath hospital was until the end of the apartheid dispensation deliberately under-resourced and this is likely a further factor contributing to the finding of a poor outcome in these patients.

The background prevalence of ischaemic heart disease is thought to be lower in South African black patients. However the rising prevalence of diabetes mellitus, smoking and obesity means that this is changing. As disease patterns in our population change and if deaths from other causes can be prevented more effectively this may be a future challenge for our population (Seedat, 1996, Bradshaw *et al.*, 2002, Walker *et al.*, 2004).

Active disease as a direct cause of death was recorded in 5 patients. However active disease contributed to death in many more patients essentially by predisposing to infection or major organ failure.

4.4 Survival curves

The five-year survival at the clinic is poor and is similar to that in other developing nations. It is possible that this is an underestimate of patients truly surviving. This is because of the relatively large group of patients lost to follow up. 28.3% of our patients were lost to follow up. These patients may possibly have moved to another centre, gone to the private sector or died. An intriguing possibility is that many of these patients may have had mild disease and may be being followed up at local general practitioners or clinics. Interestingly the mean follow up of these lost to follow up patients was only just over half that of the group that are known to be alive (this difference was statistically significant -$p<0.0001$)). However it was not quite statistically different from those who died, although it was shorter. Given these observations it is difficult to comment on whether these patients are still alive and if they died, when they died. It is notable however that in terms of clinical features this group did not have any statistically significant differences when compared to the known alive group. It could however be argued that given more time (i.e longer follow up) some of these patients may have accrued major organ involvement.

For similar reasons the five-year survival if the lost to follow up group are excluded is likely to be an overestimate. Bearing these points in mind then,

we can only confidently say that the true five-year survival (both in the clinic and/or the community) lies between these two figures. This would still mean that at least a quarter of our patients die within five years. This somber detail means that the outcome of SLE in our population is as bad as in other areas in the developing world (Malaviya *et al*., 1997).

By ten years the survival at the clinic is less than 40%. In the sense of survival from this disease we are still lagging behind the developed world. I believe that this reflects partly the overall health of our systems of patient care. There is however also the indication from studies worldwide that the outcome of the disease is poorer in people of African origin and with poor socioeconomic circumstances. The disease may occur earlier, be more active and have a higher incidence of major organ (particularly renal involvement) (Alarcon *et al*., 2001, Kaslow and Masi, 1978, Mody *et al*., 1994).

As indicated in figure 5, survival in patients with renal disease was significantly worse than those without renal disease. If this graph is not censored for those lost to follow up however, this difference is not significant. This is because most of the patients lost to follow up did not have renal disease yet they did not ‘survive’ at the clinic. Further it can be

seen that death occurred as a consequence of the nephritis. In the patients who only got nephritis later in their disease the initial survival curve matches that of those without renal disease. Later however it 'catches up with the poorer curve of those who had renal disease at initial presentation.

4.5 The SLE-like group

As discussed earlier the classification criteria are not necessarily for diagnostic use and several of the patients who are 'SLE-like' may be indistinguishable in their clinical course from those defined as SLE (Alarcon *et al*., 2004). The suggestion that these are patients who are evolving into definitive SLE may have merit. The mean follow up of these patients was only 27.3 months, less than half the follow up of the 'SLE' group of 60.4 months. Only 5 of 44 of these patients had been followed up for more than five years. Of all the records reviewed only these 5 of 102 patients (4,9%) who were followed up for more than 5 years in our clinic did not fulfill 4 ACR criteria. In the earlier mentioned work by Levin *et al* and Alarcon *et al*, some patients (though a very small fraction) required more than 20 years to achieve a 'diagnosis' of SLE (Levin et al., 1984, Alarcon et al., 2004). Furthermore half of our 'SLE-like' patients were lost to follow up. Another factor influencing their diagnostic status is the quality of record keeping and

reporting of features by clinicians in the files of these patients. It certainly is possible that clinical features were overlooked or inadequately recorded which would have conferred a 'diagnosis' of SLE on these patients (for better or worse). Even though they did not fulfill clinical criteria for SLE, 5 of these patients died. The causes of death were also related to infection and kidney disease. The prevalence of neurological, renal or haematologic features were all lower than in the SLE group. This suggests that these patients may have had milder disease overall, at least during the period they were followed up. Before they were lost to follow up almost 40% of these patients however, had nephritis. It is possible that some of these patients may have reached end stage renal failure and may be on renal replacement therapy. Some studies have shown that renal failure may attenuate SLE disease activity and these patients may therefore have stopped coming to lupus clinic (Coplon *et al.*, 1983).

The intention of this review however, was to assess clinical and outcome measures in patients with 'diagnosed' SLE. This allows us to compare this population's features with that of other populations. While the limited results

of the lupus-like group allow us to make the point of their contribution to the burden of the disease they do not form a major focus of this paper.

4.6 Limitations

Any retrospective review is prone to certain types of error. The most obvious is that there is likely to be problems with the data recorded. Missing information, inconsistencies in data recording in the records by different clinicians and problems with interpretation of data recorded may occur. This may particularly affect the descriptive aspects of this study. While this may occur in a random fashion certain aspects of the analysis may be disproportionately affected. An example is the possibility that certain clinical features (like oral ulcers), which may cause less discomfort may be under recorded.

This review may also be prone to various types of statistical error. Because recorded variables may have a small effect and sample size is not set beforehand, Type 2 errors cannot be excluded (i.e. the tests may be under-powered).

Another limitation of this particular review is the fact that treatments were not recorded on the database and the impact of the different therapies on survival, clinical features and morbidity is not reported. This was done because of the difficulty recording the actual therapy that patients received, especially as in-patients. The standards of care in terms of the therapy available also changed over this period. The difficulty of this task however may be overcome and it is possible that with a more intensive search through other hospital records future comments could be made on the impact of therapy in this group. Patient data recording organ damage and SLEDAI scores were also not done routinely and the impact of these factors on mortality could not be assessed.

The large number of patients lost to follow up also interferes with our ability to interpret the data correctly. The nature of these patients is unclear and their actual outcomes unknown.

4.7 Conclusions

Some important conclusions can be drawn from this study despite the above limitations.

1. The demographic distribution of patients with SLE in this study resembles that from other areas in the world although with a stronger female predominance, especially in the childbearing period. Males may have an older age of onset but the numbers were too small to draw firm conclusions.
2. Joint and skin involvement are the commonest manifestations of the disease.
3. Renal involvement is independently associated with poor outcome on this analysis.
4. Infection is the commonest cause of death both in the initial period as well as later in the disease course. Renal failure is also a common cause of death.
5. Survival is poor in our patients over this period and is in keeping with data from elsewhere in the developing world. Loss to follow up is a further serious problem that we face.

Systemic lupus erythematosus is certainly not a rare disease in South Africa. From the above study it can clearly be appreciated that the disease contributes significantly to the poor survival of people who have it.

Further research in this area that is needed includes:

1. Population-based studies to adequately assess the incidence of this disease and the amount of a burden it places on our society.
2. Prospective studies to assess the influence of various features on outcome as well as the impacts of therapy on the disease.
3. Basic science investigations to answer the questions of how to identify patients at risk for this condition using genetic and other markers.

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APPENDICES

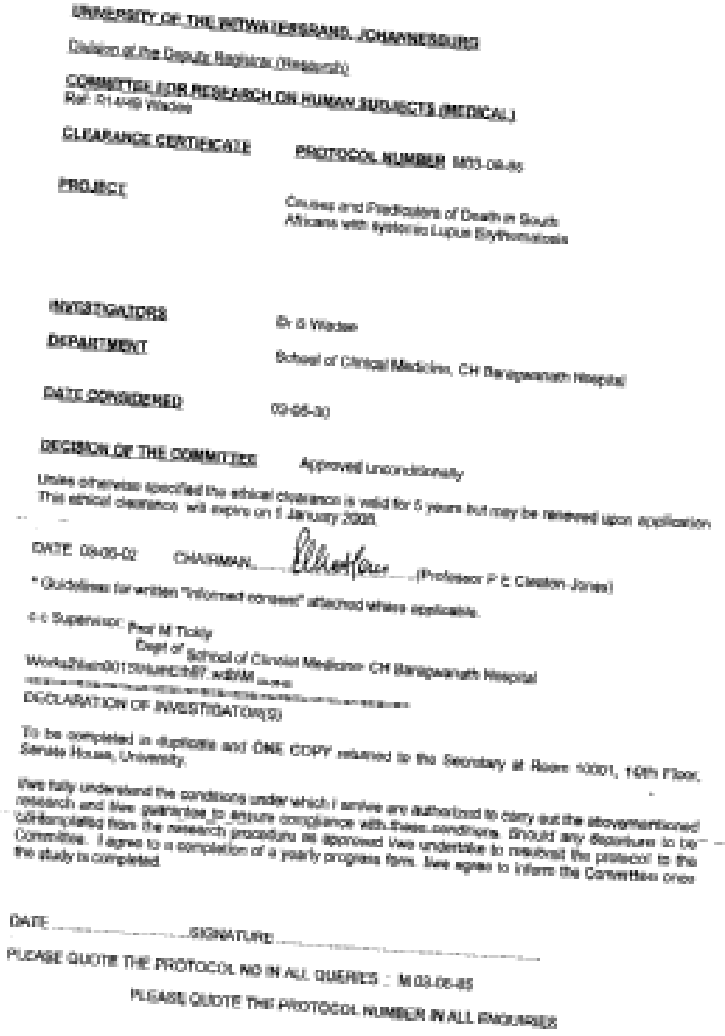
Appendix 1 **The 1997 revised ACR criteria for the diagnosis of SLE**	
Criterion	**Description**
1.Malar rash	Fixed malar erythema, flat or raised
2.Discoid rash	Erythematous-raised patches with keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions
3.Photosensitivity	Skin rash as an unusual reaction to sunlight, by patient history or physician observation
4.Oral ulcers	Oral or nasopharyngeal ulcers, usually painless, observed by physician
5.Arthritis	Non erosive arthritis involving two or more peripheral joints, characterized by tenderness swelling or effusion
6.Serositis	a. Pleuritis (convincing history of pleuritic pain or rub heard by physician or evidence of pleural effusion) or b. Pericarditis (documented by ECG , rub, or evidence of pericardial effusion)
7.Renal disorder	a. Persistent proteinuria (>0,5g/d or 3+) b. Cellular casts of any type
8.Neurologic disorder	a. Seizures (in the absence of other causes) or b. Psychosis (in the absence of other causes)
9.Haematologic	a. Haemolytic anaemia or

disorder	b. Leukopaenia (<4000/mm^3 on two or more occasions) or c. Lymphopaenia (<1500/mm^3 on two or more occasions or d. Thrombocytopaenia (<100 000/mm^3 in the absence of offending drugs)
10.Immunologic disorder	a. Anti double stranded DNA or b. Anti –Sm or c. Positive finding of antiphospholipid antibodies based on (1) abnormal serum level of IgG or IgM anticardiolipin antibodies, (2) a positive test for lupus anticoagulant ,or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test
11.Antinuclear antibody (ANA)	Abnormal titre of ANA by immunofluorescence or equivalent assay at any time and in the absence of drugs known to be associated

Appendix 2 WHO classification of Lupus nephritis	
WHO Lupus Class	Description
I	Normal
II	A: Mesangial deposits B: Mesangial hypercellularity
III	Focal segmenal GN(<50%)
IV	Diffuse GN(>50%)
V	Membranous GN
VI	Advanced sclerosis

APPENDIX 3 -Copy of Ethics approval

PROTOCOL NUMBER M03-08-85



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Wilkins

CLEARANCE CERTIFICATE PROTOCOL NUMBER M03-08-85

PROJECT Causes and Predictors of Death in South Africans with systemic Lupus Erythematosus

INVESTIGATORS Dr G Wilkin

DEPARTMENT School of Clinical Medicine, CH Baragwanath Hospital

DATE CONSIDERED 03-05-30

DECISION OF THE COMMITTEE Approved unconditionally

Unless otherwise specified the ethical clearance is valid for 5 years but may be renewed upon application
This ethical clearance will expire on 1 January 2009

DATE 03-05-02 CHAIRMAN (Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c.c Supervisor Prof M Tickly
Dept of School of Clinical Medicine CH Baragwanath Hospital

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we undertake to ensure compliance with these conditions. Should any departure to be considered from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. I agree to a completion of a yearly progress form. I/we agree to inform the Committee once the study is completed.

DATE SIGNATURE

PLEASE QUOTE THE PROTOCOL NO IN ALL QUERIES : M 03-08-85

PLEASE QUOTE THIS PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 4 -SAMPLE OF DATA RECORDING SHEET

Num	Age at presentation	Sex	Date of Presentation	last seen	Months FU	Status	Malar rash	discoid lupus	photosensi	oral ulcers	serositis	arthritis	renal	haem	CNS	ANF	comp	dsDNA	Sm	Apl
1	12	f	11/1/95	1/1/97	15	d	1	1	1	0	0	0	1	1	0	640	1	10	1	0
2	14	f	2/1/00	3/1/00	3	d	1	0	0	0	0	0	1	0	0	1280	2	0	1	
3	15	f	7/1/94	1/1/02	91	u	0	0	0	1	1	0	1	1	0	640	1	640	0	0
4	15	f	7/1/89	7/1/03	169	k	2	0	0	2	0	0	2	1	1	1280	1	640	1	1
5	15	f	2/1/87	3/1/92	62	d	1	0	0	1	0	2	2	0	2	640	1	160	0	0
6	16	f	3/1/02	7/1/03	17	k	1	1	0	1	0	1	0	0	0	640	0	0	1	0
7	16	f	2/1/94	1/1/00	72	u	1	0	1	1	0	1	1	0	0	640	2	640	1	0
8	16	f	5/1/02	7/1/03	15	k	1	0	1	0	0	2	1	0	0	1280	1	10	1	0
9	16	f	5/1/98	9/1/00	28	d	0	0	0	0	0	0	1	1	0	640	2	80	0	1
10	16	f	4/1/96	6/1/03	87	d	1	0	0	2	0	0	2	1	0	640	1	0	1	0
11	16	f	8/1/95	10/1/00	63	u	1	1	1	0	0	2	1	0	2	640	2	640	0	1
12	16	f	6/1/00	7/1/03	38	k	1	0	0	0	0	1	0	1	2	1280	1	640	1	0
13	17	f	5/1/92	1/1/01	104	d	1	0	0	1	0	0	1	1	0	640	1	640	0	0
14	17	f	5/1/95	7/1/03	99	k	1	2	1	1	0	1	2	1	0	160	2	160	0	1
15	17	f	6/1/94	7/1/03	110	k	0	0	0	0	0	2	2	1	0	640	1	0	1	0
16	17	f	8/1/00	6/1/01	11	u	1	0	0	1	0	0	0	1	1	640	2	640	0	0
17	17	f	5/1/95	11/1/95	7	d	1	1	0	1	0	0	0	1	1	40	0	0	0	1
18	18	f	11/1/93	4/1/98	54	d	1	1	1	2	0	0	2	0	0	640	1	160	1	1
19	19	f	10/1/00	11/1/00	3	u	1	0	0	0	0	0	0	1	0	640	0	0	1	0