ORIGINAL ARTICLE

Burden of comorbidities in South Africans with systemic lupus erythematosus

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Abstract

Introduction To investigate the prevalence and spectrum of comorbidities in South Africans with systemic lupus erythematosus (SLE).

Patients and methods A nested case-control study of a known alive group (AG) and deceased group (DG) of 200 and 40 patients, respectively, matched for age and sex, attending a tertiary Lupus Clinic. Comorbidities that were documented included, but not restricted to, those listed in the Charlson comorbidity index (CCI). Lupus disease severity was assessed using the lupus severity index (LSI).

Results Patients were mainly black female (94%), and the median age (IQR) and median disease duration (IQR) were 33 (25–42) and 6 (3–11) years, respectively. Overall, 191 (79.5%) patients experienced ≥ 1 comorbidities. The median (IQR) LSI and CCI scores were significantly higher in the DG than the AG (8.5 (6.7–9.1) vs 6.3 (5.2–8.3), $p < 0.001$ and 1 (1–3) vs 0 (0–2), $p = 0.002$, respectively). The commonest comorbidities were hypertension (42%), serious infections (36.6%) and tuberculosis (TB) (18.8%), the latter two being significantly more common in the DG (OR = 7.34, $p < 0.0001$ and OR = 3.40, $p = 0.001$, respectively). Of the CCI comorbidities, congestive cardiac failure (OR = 10.39, $p = 0.0003$), cerebrovascular disease (OR = 7.29, $p = 0.01$) and chronic kidney disease (OR = 3.08, $p = 0.02$) were more common in the DG. Both serious infections and TB were independent predictors of death.

Conclusion In this study of predominantly black South African SLE patients, comorbidities were common, with serious infections and TB amongst the commonest comorbidities. Unlike in industrialised Caucasian populations, cardiovascular comorbidities were rare in spite of a high prevalence of HPT.

Keywords Africa · Comorbidities · Infections · SLE · Tuberculosis

Introduction

Systemic lupus erythematosus (SLE) is a rare multisystem autoimmune disease which is most common and aggressive in young females of African descent [1]. The worldwide incidence and prevalence of SLE has been increasing with time and is highest in people of black ethnicity and lowest in people of white ethnicity [2].

In industrialised countries, there appears to be a bimodal pattern of mortality, with early deaths attributed mainly to infections and disease activity and late deaths, beyond 5 years, mainly attributable to malignancies and cardiovascular disease (CVD) [3]. This pattern is less apparent in developing countries including South Africa where most deaths are due to infections, renal disease and overall disease activity, regardless of disease duration [4, 5].

The use of potent drugs including corticosteroids (CS) and immunosuppressive agents has been associated with an increased risk of comorbidities in SLE [6]. Comorbidities impact not only on health-related quality of life (HRQOL), but also contribute to reduced life expectancy in SLE [7]. The commonest chronic comorbidities observed in industrialised countries are CVD, type 2 diabetes (T2DM) and cancer [8, 9].

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Infections are a common acute comorbidity, and in one European study, the incidence of serious infections was 29.2 infections/1000 person years [10]. There are also ethnic differences in the spectrum of comorbidities [11], and in the USA, African-Americans with SLE have a higher risk of stroke compared to Caucasians [12].

In the absence of any published studies on comorbidities in SLE in sub-Saharan Africa, we investigated the prevalence and spectrum of comorbidities in patients with SLE attending a tertiary Lupus Clinic in South Africa. The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M1409790).

Patients and methods

A retrospective nested case-control study of 200 randomly selected known alive patients (alive group, AG), and 40 deceased patients (deceased group, DG), matched for age and sex, with SLE, attending the Chris Hani Baragwanath Hospital Connective Tissue Diseases Clinic between 30 June 1990 and 31 May 2015. Inclusion criteria were age ≥ 16 years at diagnosis, fulfilling the 1997 American College Rheumatology (ACR) classification criteria for SLE [13] and a follow-up period of ≥ 6 months.

Data abstracted from the case records included demographics, disease duration (defined as the period from diagnosis of SLE by an internist or rheumatologist to last visit or death), clinical and serological features of SLE, drug therapy and comorbidities. Clinical features of SLE were defined according to the ACR classification criteria. The Charlson comorbidity index (CCI), a validated weighted cumulative comorbidity score used to predict mortality [14], was used to score the cumulative burden of comorbidity. The scoring for connective tissue diseases in the CCI was modified for the study to include connective tissue diseases (CTD) other than SLE, principally anti-phospholipid syndrome and Sjogrens syndrome. Other comorbidities not listed in the CCI that were documented included hypertension (HPT), tuberculosis (TB), serious infections (defined as acute infections that necessitated hospitalisation and/or parenteral antibiotic therapy), avascular necrosis (AVN) and osteoporosis (OP). The lupus severity index (LSI) was used to assess overall disease severity. This instrument is derived from a weighted scoring of the 1997 ACR SLE classification criteria [15]. Pulse intravenous methylprednisone therapy (IVCS) was administered in doses varying between 250 and 1000 mg daily for 3 days.

Statistical methods

Data was captured on an Excel spreadsheet and statistical analysis was done using Medcalc (version 17.9.7). The Mann-Whitney test was used to compare continuous variables between groups and the chi-square test and, where indicated, the two-tailed Fisher's exact test were applied to compare categorical variables. Multivariate stepwise logistic regression was used to determine independent predictors of comorbidities and death. Only variables that achieved a $p < 0.15$ in the univariate analysis were included in the multivariate analysis. A p value < 0.05 was deemed to be significant.

Results

The demographic and clinical characteristics of the patients are shown in Table 1. Overall, most patients were black female (94%) with a median (IQR) age at diagnosis and disease duration of 33 (25–42) and 6 (3–11) years, respectively. The commonest clinical features of SLE were arthritis, haematological disorder and renal disorder reported as 70.8%, 65.8% and 47.5%, respectively. Of those with nephritis who had renal biopsies, histology showed class III/V in 33% and class V disease in 46.5% [16], respectively. Compared to the AG, the DG had more severe disease as evidenced by a significantly shorter disease duration, higher LSI scores and higher cumulative frequencies of nephritis and anti-dsDNA antibodies. Most patients had been treated with chloroquine (94.2%) and corticosteroids (88.8%), of whom 40% had received IVCS. Immunosuppressive agents included methotrexate (32.5%), azathioprine (35.4%), mycophenolate mofetil (25.4%) and cyclophosphamide (22.5%).

The spectrum of comorbidities is shown in Table 2. The median (IQR) CCI in the DG of 1 (0, 2) was significantly higher than in the AG of 0 (0, 1). Whilst the frequency of ≥ 1 comorbidities at presentation was similar between the groups (9 (36%) vs 55 (27.5%) in the DG and AG, respectively), the cumulative frequency was significantly higher in the DG (40 (100%) vs 112 (56%), respectively, $p < 0.001$).

Hypertension was the commonest comorbidity overall. Of the comorbidities included in the CCI, peptic ulcer disease, diabetes, chronic kidney disease (CKD), CTD and HIV were the most common (Table 2). A significantly higher proportion of patients in the DG suffered from congestive cardiac failure (CCF), cerebrovascular disease and CKD. Of note, there were no cases of lymphoma or other haematological malignancies, and in spite the high prevalence of HPT, myocardial infarction was distinctly rare.

Acute and chronic infections were amongst the most common comorbidities overall. Of the 88 patients who had serious infections, one third had multiple episodes during the course of their disease, with a mean of two episodes/patient. A third of the 45 TB cases had extra-pulmonary disease. Moreover, 75% of the DG had serious infections and were also more likely to have TB than the AG (Table 2). Serious infections were also the commonest cause of death, either as the sole

Table 1 Demographic and clinical features of 200 alive and 40 deceased South African SLE patients

Variable	Cumulative frequency - overall n (%)	Cumulative frequency - alive group n (%)	Cumulative frequency - deceased group n (%)	p value
Age of onset in years, median (IQR)	33 (25–42)	33 (26–42)	34.5 (23–43.3)	0.78
Duration of disease in years, median (IQR)	6 (3–11)	7 (3.25–12)	3 (1–7)	0.0001
Female gender	226 (94)	188 (94)	38 (95)	1.0
Black ethnicity	228 (95)	188 (94)	40 (100)	0.47
LSI score, median (IQR)	6.9 (5.2–8.3)	6.3 (5–8.2)	8.5 (6.7–9.1)	< 0.001
Malar rash	104 (43)	90 (45)	14 (35)	0.25
Discoid rash	106 (44)	91 (45.5)	15 (37.5)	0.35
Oral ulcers	75 (31.3)	64 (32)	11 (27.7)	0.57
Photosensitivity	95 (39.5)	82 (41)	13 (32.5)	0.32
Arthritis	170 (70.8)	148 (74)	22 (55)	0.02
				OR = 0.43 (0.21–0.86)
Serositis	55 (22.9)	41 (20.5)	14 (35)	0.05
				OR = 2.09 (1.00–4.35)
Renal disorder	114 (47.5)	86 (43)	28 (70)	0.003
				OR = 3.10 (1.49–6.43)
Neurologic disorder	40 (16.7)	32 (16)	8 (20)	0.54
Haematological disorder	158 (65.8)	136 (68)	22 (55)	0.14
Antinuclear antibody	239 (99.5)	199 (99.5)	40 (100)	1.0
Anti-dsDNA antibody	100 (41.7)	76 (38)	24 (60)	0.01
				OR = 2.45 (1.22–4.90)
Anti-Sm antibody	139 (57.9)	115 (57.5)	24 (60)	0.86
Anti-Ro antibody	123 (51.3)	105 (52.5)	18 (45)	0.39
Anti-La antibody	64 (26.7)	53 (26.5)	11 (27.5)	1.0
Anti-cardiolipin IgG antibody	60 (25)	50 (25)	10 (25)	1.0
Anti-cardiolipin IgM antibody	47 (19.6)	42 (21)	5 (12.5)	0.22
Lupus anticoagulant	11 (4.6)	10 (5)	1 (2.5)	0.49
C3/C4 hypocomplementaemia	128 (53.3)	108 (54)	20 (50)	0.64

CCI Charlson comorbidity index; *LSI* lupus severity index

cause in 17 (42.5%) or in combination with chronic renal failure (CRF) in 6 (15%) cases.

Less than half of the deaths were solely due to non-infectious causes—these included CRF in 4 (10%), CVD in 3 (7.5%), CCF in 1 (2.5%) and oesophageal cancer in 1 (2.5%) patients. No death was attributed to coronary artery disease.

Table 3 lists the independent predictors of death and the most frequent comorbidities of HPT, serious infections and TB. Nephritis was associated with an increased risk of HPT and serious infections. There was a notable strong interaction between the risk for serious infections and TB and both were independent predictors of death. Disease severity as measured by the LSI was also an independent predictor of death. Of the therapeutic interventions, IVCS use was associated with an increased risk of both serious infections and death.

Conversely, the use of chloroquine was associated with reduced risk of death.

Discussion

Like in other populations, we found comorbidities to be common in this cohort of predominantly black South African females with SLE. Just over a third of patients had ≥1 comorbidities at diagnosis, and this figure rose to almost 80% after an average follow-up period of 6 years. However, in contrast to studies in Caucasians in industrialised countries, where CVD and malignancies are common comorbidities, the commonest comorbidities were HPT, serious infections and TB.

The comorbidities observed in the present study largely mirror the causes of death previously reported in mortality

Table 2 Spectrum of comorbidities in 200 alive and 40 deceased South African SLE patients

Variable	Cumulative frequency - overall	Cumulative frequency - alive group	Cumulative frequency - deceased group	p value
	n (%)	n (%)	n (%)	
Comorbidities in the Charlson comorbidity index (CCI)				
Myocardial infarction	3 (1.3)	3 (1.5)	0 (0)	0.81
Congestive cardiac failure	11 (4.6)	4 (2)	7 (17.5)	0.0003
				OR = 10.39 (2.88–37.28)
Peripheral vascular disease	2 (0.8)	1(0.5)	1 (2.5)	0.31
Cerebrovascular disease	7 (2.9)	3 (1.5)	4 (10)	0.01
				OR = 7.29 (1.57–33.99)
Dementia	0 (0)	0 (0)	0 (0)	1.0
Chronic obstructive pulmonary disease	5 (2.1)	5 (2.5)	1 (2.5)	1.0
Peptic ulcer disease	21 (8.8)	17 (8.5)	4 (10)	0.76
Connective tissue disease	37 (15.4)	31 (15.5)	6 (15)	0.41
Diabetes mellitus uncomplicated	10 (4.2)	9 (4.5)	1 (2.5)	1.0
Diabetes mellitus complicated	2 (0.8)	2 (1.0)	0 (0)	1.0
Chronic kidney disease	23 (9.6)	15 (7.5)	8 (20)	0.02
				OR = 3.08 (1.21–7.87)
Hemiplegia	2 (0.8)	2 (1.0)	0 (0)	0.42
Solid tumour localised	7 (2.9)	5 (2.5)	2 (5)	0.33
Mild liver disease	12 (5.0)	12 (6)	0 (0)	0.25
Moderate/severe liver disease	2 (0.8)	1 (0.5).0	1 (2.5)	0.31
HIV infection	21 (8.6)	19 (9.5)	2 (5)	0.54
CCI - median (IQR)	0 (0–2)	1 (1–3)	0 (0–2)	0.002
Comorbidities not included in the CCI				
Hypertension	101 (42)	87 (43.5)	14 (35)	0.32
Serious infections	88 (36.7)	58 (29)	30 (75)	< 0.0001
				OR = 7.34 (3.37–15.99)
Tuberculosis	45 (18.8)	30 (15)	15 (37.5)	0.001
				OR = 3.40 (1.61–7.19)
Osteoporosis	9/54 (16.7)	6/14 (42.8)	3/40 (0.8)	0.15
Avascular necrosis	5 (2.1)	5 (2.5)	0 (0)	0.58

studies of South African patients with SLE [4, 5]. In the present study and previous studies in South Africa, the majority of deaths have been found to be due to infections and CRF (16.4%), and only the minority being caused by CV events.

The burden of serious infections and TB is evident in our study. Serious infections occurred in over a third of patients, many of whom had multiple admissions, and accounted for two-thirds of deaths. Moreover, there was a strong interaction between TB and serious infections with patients with serious infection having an almost threefold risk of developing TB. These findings are similar to those observed in a Durban study, where 35.2% and 17.7% of admissions were attributed to infections and a combination of infection and active disease and in whom 14.4% died from serious infections [5]. As regards TB, our findings are comparable with the Durban study in which 12% of hospital admissions in SLE patients

were TB-related [5]. In a previous study from our centre that focussed specifically on TB in SLE patients, we found that one in six patients contracted TB [17]. These findings are not surprising, given that South Africa has one of the highest incidence rates of TB in the world [18]. Whilst isoniazid preventative therapy (IPT) is recommended by the WHO for the prevention of TB in patients with HIV infection [19], the role of IPT in SLE in TB endemic areas is less clear [20]. A study by Gaitonde et al. in India showed that IPT reduced the risk of TB from 11 to 2%, while Mok et al. were unable to show any benefit of IPT in a Hong Kong study [21, 22].

The risk of serious infections was independently associated with nephritis and the use of IVCS, the latter are commonly used to treat acute severe lupus flares. Both these factors and TB were independent predictors of death. Several studies in recent years have shown that CS, and in particular high dose

Table 3 Independent predictors of the common frequent comorbidities and death in South African SLE patients

Outcome	Variable	Multivariate analysis		
		OR	95%CI	p value
Hypertension	Age of onset	1.07	1.04–1.10	< 0.0001
	Duration of disease	1.08	1.03–1.13	0.0006
	Renal disorder	3.07	1.65–5.70	0.0004
Serious infection	Pulse IV steroids	2.48	1.41–4.35	0.002
	Renal disorder	2.00	1.14–3.5	0.02
Tuberculosis	Serious infection	2.90	1.42–5.92	0.004
	Hypertension	0.34	0.17–0.80	0.01
	Disease duration	1.05	1.00–1.10	0.03
	Arthritis	0.48	0.23–0.98	0.04
Death	Severe infection	5.11	2.12–12.30	0.0003
	Tuberculosis	4.11	1.64–10.33	0.003
	Pulse IV steroids	3.03	1.24–7.43	0.02
	Lupus severity index	1.41	1.06–1.88	0.02
	Chloroquine use	0.07	0.02–0.30	0.0003

CS, are associated with organ damage and future mortality [23]. Although almost 10% of patients in the present study were known to have HIV infection, this was not associated with an increased risk of TB, serious infections or death.

The prevalence of HPT was much higher than reported in European studies [6], in part a reflection of the larger public health challenge of HPT in South Africa [24], but also related to the high frequency of lupus nephritis. Despite HPT being common, CVD and in particular myocardial infarction, was rare, unlike the experience in industrialised countries [25]. There were also no cases of lymphoma, a relatively common comorbidity in Caucasians [26]. The commonest malignancy in the present study was cervical cancer, which has been recognised in SLE and thought to be related to immune dysregulation from the disease and use of immunosuppressive agents like cyclophosphamide [27].

The CCI, which has been extensively validated in many chronic diseases to predict mortality, was significantly higher in the DG than the AG. In a Swedish study, the CCI score was an independent risk factor for mortality and demonstrated a direct relationship between comorbidities and mortality in SLE [14]. However, in our setting, the CCI appears to be less useful. It did not perform well as an independent predictor of death, mainly because the CCI does not include comorbidities like HPT, TB and serious infections and that there was a low prevalence of CVD and malignancies. By contrast, the LSI, which has been shown to predict early mortality in an American cohort, performed better [15]. The LSI scores were significantly higher in the DG and was the only independent disease-related predictor of death.

Limitations of the study include a relatively small sample size and the retrospective nature of the study where missing data is often a shortcoming. In particular, we had incomplete anthropometric data like heights and weights, thus not allowing us to calculate body mass index in the majority of cases. Obesity is an important morbidity, which not only impairs functional capacity, but also increases inflammation [28]. We were unable to calculate the cumulative dose of CS, which is known to increase the risk of certain comorbidities such OP and CVD. DEXA scans were often not available and CD4 counts were not recorded in the files.

Notwithstanding the aforementioned limitations, our findings provide further evidence that infections, both acute infections and TB, and nephritis, pose a major challenge in the management of SLE patients in developing countries like South Africa. Greater access to and availability of acute high care facilities and timeous renal dialysis therapy are likely to improve HRQOL and reduce mortality. Large prospective studies are needed to better elucidate the role of IPT in reducing the burden of TB in endemic areas.

Compliance with ethical standards

Ethical standards The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (clearance certificate number M1409790), and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Disclosure None.

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