

Pediatric Lupus in South Africa

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Duke Global Health Institute
in the Graduate School of Duke University

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ABSTRACT

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Abstract

Background: In North America and Europe, systemic lupus erythematosus (SLE) is more common and severe in people of African extraction than in Caucasians; however, the epidemiology of SLE in Africa is largely undetermined. Historically, the incidence of SLE in Africa was presumed to be low, but recent studies challenge this theory. In general, children present with higher disease activity, require more therapy, and accrue more organ damage than adult-onset patients. Although African children with SLE may be at high risk for poor outcomes, little research has investigated this population. We have initiated the first registry of this high risk pediatric SLE (pSLE) population in South Africa (SA). Here, we report the initial findings of the South African pSLE patients (PULSE cohort).

Methods: We conducted a cross sectional analysis (retrospective and prospective chart review) of pediatric and adult rheumatology and nephrology patients seen at two hospitals and one private center in Cape Town, South Africa from 1988-2014 meeting American College of Rheumatology criteria for pSLE. Patient age, gender, race, presenting features, clinical and serologic disease markers, and treatment were recorded for the PULSE cohort and compared to an established North American pSLE cohort. Univariable relationships between risk factors for poor outcomes (age of diagnosis,

disease duration, race/ethnicity) and severe lupus nephritis or end organ damage were assessed.

Results: Initial review of South African patients yielded 72 patients; mean age 11.5 years, 83% female. The racial distribution was 68% Coloured, 24% Black, 5% White, and 3% Asian/Indian. Most patients presented with severe lupus nephritis (LN), documented by renal biopsy performed in 58%. Of patients with LN, 88% presented with International Society of Nephrology/Renal Pathology Society (ISN/RPS) class III or higher. There were treatment differences between cohorts: patients in the South African cohort had increased use of cyclophosphamide, methotrexate, and azathioprine. The South African cohort had high disease activity at enrollment (mean Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) 20.6), compared to the North American pSLE cohort (SLEDAI 4.8). The PULSE cohort had end organ damage with 63% of the cohort having a System Lupus International Collaborating Clinic- Damage Index (SLICC-DI) score >0 (mean SLICC-DI 1.9), compared to only 23% in a previously reported US cohort of 221 pSLE patients. Within the SA cohort, 13% went on to develop ESRD, of which 9% required transplant, strikingly higher than North American peers.

Conclusions: The PULSE cohort is the largest registry of pSLE patients in Africa to date. These children present with high disease activity and progress to end organ damage at higher rates than pSLE cohorts in North America. Further research is required to

determine the burden of pSLE in South Africa, and identify risk factors for poor outcomes in this high risk population.

Dedication

This work is dedicated to the children of Africa, who continue to be my most important teachers. I dedicate this to my wonderful family for their constant support, and to my husband Andy, with enormous gratitude for his limitless encouragement and enthusiasm for this work.

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1. Introduction

SLE (systemic lupus erythematosus) is a life threatening multisystem autoimmune disease. It is the most common connective tissue disease, and currently is a chronic disease with no known cure. SLE most commonly affects females of childbearing age.¹ The burden of SLE is significant: patients with SLE have high rates of morbidity and increased risk of mortality when compared to the general population.²⁻⁴ Although death rates have improved from five year survival of 50% in the 1950s to a current rate of 88-96%, mortality is still three to five times that of the general population.⁵ SLE is a systemic disease that can affect any organ system and damage results from both inflammatory organ damage and therapy. Major morbidities include renal disease which can lead to acute or chronic renal failure, atherosclerotic disease which results in high risk for myocardial infarction and stroke, cognitive dysfunction, and osteoporosis³, but any organ system may be involved. Studies have shown that health related quality of life is poor in patients with SLE, even when compared to other subjects with chronic rheumatic diseases.⁶

In North America and Europe, SLE is more common and more severe in people of African extraction than in Caucasians.^{7,8} In a review of SLE in the United States, crude death rate was three times higher in individuals of African descent compared to whites.⁹ Despite SLE's disproportionate prevalence among individuals of African descent, only sparse published literature exists concerning the epidemiology, diagnosis and treatment

of SLE among individuals living in the African continent. In adults, there have been retrospective series of patient cases from South Africa, Nigeria, Zimbabwe and Senegal.¹⁰⁻¹³ The only pediatric SLE studies have been reported from South Africa. There are two case reports from 1981-1986 from South Africa.^{14,15} The first case report of a black child was not reported until 1991.¹⁶ This lack of data has led to perception that SLE is rare in Africa,^{17,18} although more recent studies challenge that this is likely due to under recognition, underdiagnosis, under-reporting, and access issues rather than true rarity of disease.^{19,20} A recent bibliometric review highlighted the paucity of studies published from Africa, despite the increased risk for mortality in African patients.²¹ Adult studies in South Africa show poor outcomes, with five year survival rates ranging from 69-78%, compared to rates of 88-95% in the high income countries.^{22,23} There has been one previous summary of 36 pediatric patients in South Africa, which was a retrospective review of patients who presented from 1975-2000.²⁴ The subjects in the study had high frequency of skin, musculoskeletal, and renal manifestations of disease. Disease features in the study subjects were consistent with late disease manifestations, indicating a long period of disease activity at diagnosis.

Children are at high risk for severe SLE, as they present with higher disease activity, and continue with higher activity over time than adults. Presentation in childhood occurs in 15 -20% of all SLE patients²⁵ with median age of diagnosis for pSLE patients of 12-14 years.^{26,27} Children require more therapy and accrue more damage than

adult onset SLE patients.²⁸ Children are more likely to have serious renal, neurologic, and hematologic involvement than their adult counterparts.²⁹ Mortality rates are higher in pediatric SLE patients than adults, despite having fewer comorbidities.²⁸

Lupus nephritis (LN) is renal injury that occurs as a result of inflammatory injury to the renal glomeruli.³⁰ LN is a serious complication of SLE, as it influences prognosis and life expectancy more than any other organ system involvement.^{31,32} Patients with lupus nephritis show a 15-24 year decrease in life expectancy compared to age and sex matched SLE patients without nephritis.³³ In high income countries, patients of African ancestry are two to three times more likely to develop lupus nephritis and have a more severe renal disease course than their white counterparts.³⁴ Further, African Americans SLE patients with end stage renal disease have higher mortality rates than Caucasians.³⁵ It is unclear if these differences are due to socioeconomic or biologic risk factors. Lupus nephritis is common in children: approximately 60% will have renal involvement at presentation, and 90% will develop renal disease within two years of SLE onset.³⁶ Children have higher rates of renal damage and proceed to end stage renal disease more frequently than their adult counterparts.²⁹ PSLE patients of European ancestry have decreased risk of early onset, aggressive lupus nephritis.³⁷ Lupus nephritis relapse is associated with progression to ESRD, and treatment resistance disproportionately affects African American children.³⁸ In addition, renal disease is a major cause of morbidity and mortality in SLE patients in low income nations.³⁹

Thus, pediatric SLE (pSLE) patients in Africa are potentially at high risk for poor outcomes based on race and age, yet strikingly little research has addressed this population.^{20,21,40} To date, there is only one study of pSLE in Africa and there has not been an updated report on pSLE in South Africa for the past 10 years.²⁴ If this population demonstrates expected increased disease severity, then identifying modifiable risk factors for poor outcomes could provide important information to guide monitoring and disease management in this group.

The aim of the current study is to determine if pSLE patients in the South African cohort display earlier age of onset, important differences in disease manifestations, treatment, disease activity, or disease damage compared to pSLE patients in the North American cohort. We have initiated a pSLE registry in South Africa and performed an initial cross sectional analysis at enrollment of all pediatric SLE patients who presented to care after 1988. Here, we describe this cohort and compare it to patients in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. The CARRA registry is a well-established database of pediatric patients that includes over 900 pSLE patients from 60 sites in North America.⁴¹ We attempted to control for population differences between cohorts such as age of SLE diagnosis, African ancestry, and disease duration, which could bias the results. If South African pSLE patients are at higher risk for poor outcomes than their North American comparators, identifying

modifiable risk factors could improve treatment and reduce organ damage in this population.

2. Methods

2.1 Setting

Our study was conducted in South Africa, a low to middle income, democratic nation in sub-Saharan Africa. South Africa has nine provinces and a population of 50.5 million, 23 million of whom are children.⁴² There are only 4 pediatric rheumatology providers in South Africa. Two of these are located in Cape Town (Western Cape Province), one in Johannesburg (Gauteng province), and one in Durban, (Kwa-Zulu Natal province).

We conducted our study in two medical centers that care for pSLE patients in Cape Town, South Africa: Red Cross War Memorial Children's Hospital, and Groote Schuur Hospital, and in one private practice rheumatology office in the Western Cape. Red Cross War Memorial Children's Hospital is a tertiary-care government funded teaching facility and is the only free standing children's hospital in sub-Saharan Africa. It is a 300 bed children's hospital that manages 260,000 patient visits per year.⁴³ Red Cross War Memorial Children's Hospital has provided rheumatology care and evaluation from 1980, but the rheumatology inpatient and outpatient services were established there officially in 2010. Red Cross Pediatric Rheumatology currently cares for patients from the Western Cape, Eastern Cape and Northern Cape provinces.

Groote Schuur Hospital is a government funded, tertiary-care teaching facility. It has 893 inpatient beds and an outpatient facility, both of which serve many adolescent

SLE patients. It serves the Western Cape Province of South Africa, an area with a population of approximately 6 million people.⁴² Currently, two adult rheumatologists and one pediatric rheumatologist provide inpatient and outpatient care for SLE patients at this hospital. The pediatric rheumatologist serving Groote Schuur also provides the patient care at the Red Cross War Memorial Children's Hospital. The pediatric rheumatology service provides 1000 outpatient visits per year between the two centers; there are insufficient data on the proportion of visits that are pSLE patients.

The private practice office included is staffed by two adult rheumatologists. They serve patients in the Stellenbosch region of the Western Cape, approximately 50 km outside of Cape Town, SA.

2.2 Participants

To develop the PULSE cohort, we identified patients via a search using ICD-10 codes for SLE or lupus nephritis from hospital admissions or clinic visits in the computerized databases of the two hospital centers where the study was conducted. In addition, we polled the physicians on-site to generate a list of pSLE patients. To attempt to include patients who are followed in private practice, we presented this project at one national and three local rheumatology meetings. We also sent mail-out recruitment flyers to all rheumatology offices in the Western Cape. Only one office responded with eligible participants. Inclusion criteria encompass patients age <19 years at SLE diagnosis, who met the ACR classification criteria for SLE,⁴⁴ and had received care in the

Western Cape Province, SA. The enrollment for the South African cohort was not limited by current age, but the oldest patient enrolled was 29 years of age.

The classification criteria for SLE as defined by the ACR require four of the following eleven measures to be present: malar rash, discoid rash, arthritis (present in two joints), photosensitivity (history or physician observation), oral ulcers (physician observed), serositis (history of pleuritic pain, pleural or pericardial effusion, friction rub auscultated, or EKG changes), renal disorder (3+ proteinuria or cellular casts), neurologic disorder (seizures or psychosis without other cause), hematologic disorder (leukopenia, lymphopenia, hemolytic anemia, or thrombocytopenia), positive anti-nuclear antibody test (ANA) at any point in time, and immunologic disorder (positive anti-Sm antibody, positive anti-dsDNA antibody, LE cells on smear, or false positive syphilis test, persistent for six months). We verified diagnosis of SLE via American College of Rheumatology (ACR) classification⁴⁴ through chart review.

Once identified, all living patients were approached for consent in the study by their physician or study personnel. If the patients agreed, they were consented by trained study personnel via use of approved consents prior to participation in the study. If the patients were less than 18 year old, we obtained parental consent; for patients ages 13 to 18 years, child assent was obtained. Consent was conducted in the study volunteer's language of choice (Afrikaans, isiXhosa, or English.) There were patients identified who had died prior to the initiation of the study. Deceased pSLE patient

meeting enrollment criteria were included in review, for which we obtained a waiver of consent.

For comparison, we used an existing registry: the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry. Thus, we refer to the North American cohort as the CARRA cohort. CARRA is a multicenter collaborative database which collects standardized information from 60 expert centers in North America.⁴⁵ The CARRA registry is an observational longitudinal data capture study. As of July 2012, there were over 900 children with pSLE enrolled. Patients with pSLE were eligible for inclusion if they met at least four of the eleven ACR criteria for SLE diagnosis, developed pSLE prior to age 18 years, and were less than 21 years at the time of enrollment.⁴⁶ Study information for CARRA subjects is captured via standardized data collection sheets at each study site, and entered into an online database managed at the Duke Clinical Research Institute.

2.3 Procedures

This study was conducted over 14 months (September 2013-December 2014), during which we enrolled 72 patients to the registry. We performed chart review of the entire medical record up to the most recent clinic visit. This chart review was completed either at a clinic visit or in medical record review to determine the demographic profile and current management of pSLE patients.

Data collection was performed by Dr. Lewandowski. Patients were examined by an adult or pediatric rheumatologist or nephrologist, and data from the medical record regarding features at presentation and features and treatment up to and including the date of enrollment were extracted from the chart and entered into the database. The documented physical exam and laboratory values were entered. The physical exam and serologic studies are part of standard SLE care and are not conducted for study purposes. We utilized standard CARRA study⁴¹ visit forms to collect information on patient demographics, clinical history and physical exam documented by physician, clinical variables of interest, which included SLE clinical and laboratory parameters, and current and prior medication use.

This study was approved by the Duke Medical Center Institutional Review Board and the University of Cape Town Ethics Committee.

2.4 Measures

Via chart review and data collection on review of inpatient and outpatient visits , the following clinical data were obtained utilizing standard CARRA data collection templates: presence of American College of Rheumatology (ACR) criteria for SLE diagnosis, disease manifestations at diagnosis, presence of SLE autoantibodies, renal biopsy, markers of lupus nephritis, treatment, laboratory values, disease activity as measured by SLE disease activity index (SELENA-SLEDAI) score, disease damage as measured by System Lupus International Collaborating Clinics/ACR Damage Index for

SLE (SLICC-DI) score. In addition, we documented adverse outcomes including end stage renal disease, dialysis, renal transplant, thrombosis, hemorrhage, and mortality.

2.4.1 Measure 1: Demographic Features

The following demographic features were obtained via chart review: age of disease diagnosis, gender, disease duration, and self-reported race⁴⁷. Race was reported as one of the five racial groups in employed in SA population surveys: Coloured, Black, White, Indian/Asian, and other. In South Africa, the term Coloured refers to a racially heterogeneous ethnic group who possess ancestry from Europe, Asia, Malaysia, and various Khoisan and Bantu tribes of Southern Africa. Black refers to the population with Southern African Bantu tribal ancestry. White refers to people of European descent. Indian/Asian refers to those of Indian or Asian ancestry; and other is anyone who does not identify with one of the described races.⁴⁸ As the CARRA cohort does not differentiate between Colored and Black in the racial/ethnic group of African Americans, we utilized three racial groups from SA for comparative analysis: African to describe all patients who identified themselves with African ancestry (Black and Coloured), White, and other.

2.4.2 Measure 2: Renal Histology

Lupus nephritis histology can be classified in two systems: WHO classification and ISN/RPS classification.⁴⁹ In South Africa, only ISN/RPS histologic classification is utilized. We therefore excluded CARRA patients with only WHO biopsy classification

from this comparison, as it is not possible to re-categorize these patients to an ISN/RPS group for analysis. Utilizing ISN/RPS classification, lupus nephritis classes III and IV indicate active or chronic inflammation; class IV being the more severe state. Class VI indicates prior inflammation and advanced renal scarring, as it requires >90% of glomeruli studied to be sclerosed for this classification. Class V is membranous renal disease and can be associated with heavy proteinuria, but does not always indicate inflammatory renal disease.⁵⁰ We combined all patients with active or advanced renal disease (Class III-VI) in each cohort into a new unified category for comparative analysis. We utilized this novel group to identify risk factors for high grade lupus nephritis within the South African cohort.

2.4.3 Measure 3: Antinuclear antibodies

Antinuclear antibody (ANA) testing is an assay which screens for multiple antinuclear antibodies either via immunofluorescence on Hep2 A cell lines or via ELISA. If this test is positive, specific antibodies are measured by titer.⁵¹ We captured rates of positive anti-Sm and anti-dsDNA antibodies. There are three other specific autoantibodies routinely tested in SLE patients in the CARRA cohort: Anti-Ro, anti-La, and anti-RNP antibodies. However, these have only become part of the routine assessment in the past six months in the PULSE cohort, so they were excluded from this analysis.

2.4.4 Measure 4: Treatment

Treatment was measured in the PULSE cohort via chart review. Inpatient and outpatient records were reviewed for current and prior use of therapy. All data are reported binary variables, scored as positive when the patient is receiving or had received that medication ever at time of study enrollment.

For the medications intravenous immunoglobulin (IVIg) and rituximab, the number of missing patients comprises >80% of the cohort. Patients who were taking the medication were endorsed as positive in the database, but no patients were reported as negative, yielding the large number of missing values. Therefore, those who are taking this medication are reported as positive and total numbers are presented as percentages, but P values for these medications are not reported.

2.4.5 Measure 5: Adverse Outcomes

Through chart review, we extracted data on end stage renal disease, renal disease requiring dialysis, renal disease requiring transplant, and mortality. We describe catastrophic clinical presentation in the South African patients. This is not a common definition, but a term we created to capture the extremis with which the majority of the PULSE cohort presented. This term includes stroke, seizure, blindness, pericarditis causing tamponade, or acute renal failure. There are no data available on the frequency of these drastic presentations in North American pSLE patients for comparison.

2.4.6 Measure 6: Disease activity and damage score

To measure disease activity, we employed SLE disease activity index measure (SELENA-SLEDAI),⁵² which ranges from 0-105 in scale. To measure severe and chronic disease damage, we calculated System Lupus International Collaborating Clinics/ACR Damage Index for Systemic Lupus Erythematosus (SLICC-DI) scores.⁵³ The disease manifestations must be present on two occasions six months apart to be scored in the SLICC-DI. Both measures have been validated in the pediatric population.⁵⁴

2.4.7 Measure 7 CARRA Registry Comparison

We compared this South African PULSE cohort to the CARRA cohort of patients. For patients enrolled in the CARRA registry, data captured include age, gender, ACR criteria met at diagnosis, enrollment SLE serologic and exam findings, SLEDAI scores, history of renal biopsy and grade, and treatment. SLICC-DI scores were not captured in the CARRA database; therefore comparative analysis of this measure was not performed.

The CARRAnet research group is a well-established source for data for pediatric rheumatic disease, and has published findings on pSLE and lupus nephritis in the North American population.⁴¹ We utilized raw de-identified data on 982 pSLE subjects for robust comparative analysis to determine differences between the two populations.

2.5 Analysis

We compared age of SLE diagnosis, race, presenting features, rate and class of lupus nephritis, laboratory features, SLEDAI scores, and treatment between the South African and North American patient cohorts. Characterization of the patient population was summarized using descriptive statistics with 95% confidence intervals of means and proportions for cohort comparison. We determined disease activity as measured by the SELENA-SLEDAI. We calculated percentage of each cohort with disease duration greater than or equal to two years, and age of diagnosis of SLE less than or equal to thirteen years of age. We compared ANA, anti-dsDNA, and anti-Sm antibodies amongst patients of African ancestry only between the two cohorts.

We evaluated enrollment SLEDAI scores of the PULSE cohort compared to the CARRA cohort. Where appropriate, Kruskal-Wallis, Pearson X^2 or Fisher's exact test were used to evaluate differences in both clinical and demographic features and disease scores of the two cohorts. For direct comparison of race/ethnicity between cohorts, we combined all SA patients of African ancestry into one subgroup. We also compared Coloured patients to African American and Black SA patients to African Americans independently, and found no difference in results (data not shown.)

As African ancestry, young age of onset, and long disease duration are risk factors for poor outcomes, we wanted to determine if the disproportionate number of patients in the PULSE cohort with these risk factors lent bias to our results. We

compared patients of African ancestry in the PULSE cohort to those in the CARRA cohort for all analyses. For measures of clinical features at enrollment, treatment, and outcomes, we analyzed differences between patients of young age at diagnosis and long disease duration only between cohorts. We defined young age of SLE diagnosis as age less than or equal to 13 years, and long disease duration as greater than or equal to 2 years.

As an exploratory aim, we attempted to identify risk factors for poor outcomes within the PULSE cohort. We defined poor outcomes as Class III-VI lupus nephritis, or SLICC-DI>0. We identified 5 variables of interest as possible risk factors: young age at diagnosis, African ancestry, disease duration, male gender, or positive anti-dsDNA at enrollment. We used both Fisher's exact test and generalized linear regression models to identify risk factors for poor outcomes in this population.

All calculations were performed using STATA statistical software (Stata Corp., College Station, TX).

3. Results

Enrollment characteristics are summarized in **Table 1**. Similar to the CARRA cohort, the South African PULSE cohort is largely female (83%), consistent with the known female predilection for this disease.⁵⁵ The average age of disease diagnosis of the PULSE cohort is slightly younger than the CARRA cohort (11.5 vs 12.4 years) and 75% percent of the PULSE cohort was under age 13 years at diagnosis. The racial distribution of the PULSE cohort was 68% Coloured, 26% Black, 5% White, and 3% Asian/Indian. A notable difference is that 92% of the patients in the PULSE cohort are of African descent, vs 36% of the CARRA cohort, a difference that we would expect for a group of pSLE patients from the African continent. Approximately half the South African cohort (44%) had disease duration of greater than or equal to two years at enrollment, which is significantly less than 64% of the CARRA cohort.

Table 1. Demographic Features at Enrollment

	PULSE N=72	CARRA N=982	P value (Fisher's exact)
Mean age of SLE diagnosis (mean, SD)	11.5 (3.5)	12.4 (3.2)	0.027
Average disease duration (mean, SD)	2.4 (3.2)	3.5 (3.0)	0.001
% Female (n)	82.3 (56)	82.5 (810)	0.873
% White (n)	6 (4)	45 (426)	
% African descent (n)	92 (66)	36 (339)	<0.001

% other (n)	3 (2)	20 (190)	
% age \leq 13 at diagnosis (n)	75 (53)	51 (475)	<0.001
% disease duration \geq 2 yrs (n)	44 (33)	64 (632)	0.003

SLE is an autoimmune disease characterized by the development of pathogenic autoantibodies. As seen in **Table 2**, patients in both cohorts demonstrate very high rates of positive ANA (>90%). All patients in the cohort had an ANA performed. As this is one of the ACR diagnostic criteria for SLE,⁴⁴ this result is not surprising. Nearly all the PULSE cohort (99%) and CARRA cohort (97%) had an evaluation of anti-dsDNA antibody. Anti-Sm antibody was assessed in most of the PULSE Cohort (89%) and the CARRA cohort (90%). The PULSE cohort has a higher percentage of patients with positive anti- double stranded DNA (dsDNA) antibodies, while the CARRA cohort has a larger percentage of individuals with anti-Sm antibodies.

Table 2. Antinuclear Antibody Profile at Enrollment

Antibody	PULSE N=72	CARRA N=982	P value (Fisher's exact)
% ANA positive (n)	96 (69)	91 (888)	0.065
Total N	N=72	N=982	
% Anti-dsDNA positive (n)	82 (60)	60 (576)	<0.001
Total N	N=71	N=953	
% Anti-Sm positive (n)	29 (21)	49 (482)	0.001
Total N	N=64	N=881	

We analyzed the antibody profile for patients only of African ancestry in each cohort. Again, all subjects had an ANA performed, nearly all of the PULSE (98%) and CARRA cohorts (97%) had an evaluation of anti-dsDNA antibody, and anti-Sm antibody was assessed in the vast majority of the PULSE (88%) and the CARRA cohorts (91%). We found no differences from the overall cohort assessment (**Table 3.**)

Table 3. Antinuclear Antibody Profile at Enrollment, analysis of African ancestry subjects only

Antibody	PULSE N=66	CARRA N=339	P value (Fisher's exact)
% ANA positive (n) Total N	95 (63) N=66	91 (306) N=339	0.039
% Anti-dsDNA positive (n) Total N	80 (53) N=65	61 (201) N=328	<0.001
% Anti-Sm positive (n) Total N	26 (17) N=58	65 (219) N=310	<0.001

The South African cohort had larger percentages of children enrolled with the most common pSLE disease manifestations, such as malar rash, arthritis, hematologic manifestations, and lupus nephritis (**see Table 4.**) Involvement of the renal and central nervous systems guide prognosis and therapy,^{31,56-59} and these organ manifestations show the largest difference between cohorts. In the PULSE cohort, 61% had renal involvement at enrollment, 20% more than the CARRA cohort. One in four South African pSLE patients had central nervous system involvement, much higher than the one in sixteen pSLE patients in North America. Importantly, the PULSE cohort

demonstrates high disease activity: the average SLEDAI at enrollment was 20.6, vs 4.8 in the CARRA cohort.

Table 4. Clinical Features at Enrollment

Clinical Manifestation	PULSE N=72	CARRA N=982	P value (Fisher's exact)
% Malar rash (n)	52 (38)	43 (419)	<0.001
% Renal SLE (n)	61 (44)	41 (409)	<0.001
% Central Nervous System SLE (n)	25 (17)	6 (62)	<0.001
% Arthritis (n)	63 (45)	57 (555)	<0.001
% Hematologic (n)	63 (46)	57 (563)	0.002
% Catastrophic presentation (n)	57 (40)	NR*	--
Average SLEDAI Score [range 0-105] (SD)	20.6 (9.9)	4.8 (1.9)	<0.001**

*NR indicates not reported in this cohort.

**Kruskal-Wallis

To evaluate if differences in disease presentations could be attributed to the significant difference in number of patients of African ancestry, young age at diagnosis, or long disease duration at enrollment between cohorts, we performed the same analysis, limiting to patients of African ancestry, those with age of diagnosis of SLE less than or equal to thirteen years, and those with disease duration for greater than or equal to two years. When we adjusted this analysis, there were not significant changes to the distribution of disease manifestations between cohorts for patients of African ancestry only, or patients with disease duration ≥ 2 years. (**Tables 5 and 7.**) Among the younger

patient cohort, the difference in renal disease is no longer significantly different. (Table 6.) There is no longer a difference in the rates of arthritis and hematologic manifestations in the patients who were of young age at diagnosis.

Table 5. Clinical Features at Enrollment, analysis of subjects of African ancestry only

Clinical Manifestation	PULSE N=66	CARRA N=339	P value (Fisher's exact)
% Malar rash (n)	51 (34)	34 (116)	<0.001
% Renal SLE (n)	62 (41)	42 (141)	<0.001
% Central Nervous System SLE (n)	24 (16)	7 (24)	<0.001
% Arthritis (n)	62 (41)	57 (193)	0.003
% Hematologic (n)	62 (41)	59 (200)	0.022
Average SLEDAI Score [range 0-105] (SD)	20.5 (9.3)	5.4 (6.5)	<0.001**

**Kruskal-Wallis

Table 6. Clinical Features at Enrollment, analysis of subjects age of diagnosis ≤13 years only

Clinical Manifestation	PULSE N=53	CARRA N=475	P value (Fisher's exact)
% Malar rash (n)	52 (28)	47 (222)	0.056
% Renal SLE (n)	59 (31)	43 (208)	0.058
% Central Nervous System SLE (n)	26 (14)	6 (29)	<0.001
% Arthritis (n)	60 (32)	52 (248)	0.036
% Hematologic (n)	58 (31)	58 (275)	0.124

Average SLEDAI Score [range 0-105] (SD)	20.6 (9.9)	4.8 (1.9)	<0.001**
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*Kruskal-Wallis

Table 7: Clinical Features at Enrollment, analysis of subjects with disease duration ≥ 2 yrs only

Clinical Manifestation	PULSE N=33	CARRA N=632	P value (Fisher's exact)
% Malar rash (n)	49 (16)	46 (288)	0.002
% Renal SLE (n)	63 (21)	43 (2690)	0.001
% Central Nervous System SLE (n)	36 (12)	7 (47)	<0.001
% Arthritis (n)	58 (19)	54 (339)	<0.001
% Hematologic (n)	73 (24)	56 (352)	<0.001
Average SLEDAI Score [range 0-105] (SD)	20.3 (8.7)	4.3 (5.2)	<0.001**

*Kruskal-Wallis

PULSE patients display an increased rate of severe renal disease compared to North American peers (**Table 8**). We found the rate of biopsy proven lupus nephritis to be 58% in our PULSE cohort, which is higher than the CARRA cohort (44%). In comparison with North American peers, nearly all of the biopsied patients in the PULSE cohort (88%) had ISN/RPS Class III, IV, V, or VI lupus nephritis. Seven percent of the South African cohort had Class VI LN on renal biopsy at enrollment, while none of the CARRA cohort demonstrated this class of advanced sclerosis.

Table 8. Features of Lupus Nephritis at Enrollment, ISN/RPS classification

	PULSE N=72	CARRA N=982	P value (Fisher's exact)
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% with proteinuria (n)	62 (44)	32 (242)	<0.001
% with hematuria (n)	53 (38)	15 (121)	<0.001
% with HTN (n)	40 (27)	NR*	
% who underwent biopsy (n)	58 (41)	44 (428)	0.049
% of biopsied patients with ISN classification	100 (41)	65 (280)	<0.001
% biopsied with lupus nephritis (n)	100 (41)	100 (428)	1.000
% biopsied class I (n)	0 (0)	1 (6)	0.998
% biopsied class II (n)	7 (3)	9 (39)	0.999
% biopsied class III (n)	4 (2)	22 (95)	0.020
% biopsied class IV (n)	57 (24)	26 (112)	0.001
% biopsied class V (n)	23 (9)	15 (66)	0.250
% biopsied class VI (n)	7 (3)	0	0.001

To assess whether the proclivity for more advanced nephritis was due to ancestry, young age, or disease duration, we compared the overall rates of class III-VI lupus nephritis to the rates in each sub-category (**Table 9.**) In South Africa, 53% of the cohort had high grade LN at enrollment, almost twice the rate of the North American cohort. There is no difference in distribution of higher grade LN among patients of African ancestry, young age at diagnosis, and long disease duration.

Table 9. Percentage of Cohort with Higher Grade LN (Class III-VI)

	PULSE N=72	CARRA N=982	P value (Fisher's exact)
% with Class III-VI LN, Total cohort (n)	53 (37)	22 (240)	<0.001
% of African ancestry (n)	54 (34)	20 (69)	<0.001
% of Age of diagnosis \leq 13 yrs (n)	52 (26)	24 (118)	<0.001
Disease duration \geq 2 yrs (n)	52 (16)	24 (167)	<0.001

We compared the medical management of patients in each cohort (**Table 10**). Nearly all the patients in both the PULSE (93%) and CARRA (93.5%) cohort had been treated with glucocorticoids at the time of enrollment, with no difference by location. A much larger number of patients in the CARRA cohort had been treated with an antimalarial immunosuppressive drug at the time of enrollment. Forty-two percent of the PULSE cohort had received cyclophosphamide at enrollment, compared to only 29% of the CARRA cohort. In comparison, a larger percentage of the CARRA cohort (60% vs 42%) had been treated with mycophenolate mofetil. The PULSE cohort had a higher percentage of patients using other disease modifying anti-rheumatic drugs (DMARDs), including methotrexate and azathioprine, than their North American counterparts. The percentage of patients treated with rituximab was similar between cohorts, but the PULSE cohort had a higher percentage of patients treated with IVIg.

Table 10. Treatment History at Enrollment

	PULSE N=72	CARRA N=982	P value (Fisher's exact)
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% treated with steroids (n)	93 (66)	94 (917)	0.725
% treated with antimalarial (n)	78 (54)	92 (853)	0.001
% treated with cyclophosphamide (n)	42 (30)	29 (267)	0.022
% treated with mycophenolate mofetil (n)	42 (28)	60 (556)	0.004
% treated with azathioprine (n)	61 (41)	16 (146)	0.001
% treated with methotrexate (n)	30 (19)	19 (184)	0.019
% treated with rituximab (n)	6 (4)	10 (99)	—
% treated with IVIg (n)	12 (8)	2 (17)	—

Next, we compared the medical management of patients in each cohort of African ancestry only, to determine if the large percentage of African patients in the SA cohort introduced bias to these results. (Table 11.) The percentages of subjects receiving each therapy did not vary greatly between the entire cohort and the patients of African ancestry for any therapy. In percentage of patients receiving cyclophosphamide and methotrexate therapy, the differences no longer reached statistical significance.

Table 11. Treatment History at Enrollment, analysis of subjects of African ancestry only

	PULSE N=66	CARRA N=339	P value (Fisher's exact)
% treated with steroids (n)	92 (60)	94 (320)	0.538
% treated with antimalarial (n)	77 (49)	93 (297)	<0.001

% treated with cyclophosphamide (n)	45 (29)	32 (101)	0.061
% treated with mycophenolate mofetil (n)	39 (24)	64 (205)	<0.001
% treated with azathioprine (n)	60 (37)	15 (47)	<0.001
% treated with methotrexate (n)	30 (18)	19 (59)	0.082
% treated with rituximab (n)	6 (4)	14 (49)	—
% treated with IVIg (n)	13 (8)	8 (21)	—

When we limited the analysis to subjects with young age at SLE diagnosis, we found that the percentage of patients who received cyclophosphamide in this cohort did not differ (**Table 12.**), as it did in the overall cohort analysis (**Table 10**). In patients with young age at diagnosis, we found no other differences in therapy compared to the entire cohort analysis.

Table 12. Treatment History at Enrollment, analysis of subjects age ≤ 13 years at diagnosis only

	PULSE N=53	CARRA N=475	P value (Fisher's exact)
% treated with steroids (n)	96 (51)	94 (443)	0.823
% treated with antimalarial (n)	77 (41)	91 (412)	0.007
% treated with cyclophosphamide (n)	38 (20)	35 (156)	0.652
% treated with mycophenolate mofetil (n)	44 (23)	64 (291)	0.006
% treated with azathioprine (n)	69 (36)	17 (74)	<0.001

% treated with methotrexate (n)	31 (16)	18 (78)	0.023
% treated with rituximab (n)	8 (4)	11 (52)	—
% treated with IVIg (n)	15 (8)	6 (29)	—

When assessing patients with long disease duration (**Table 13.**), we found that there was no longer a difference in the rate of antimalarial therapy between PULSE and CARRA cohorts. Again, cyclophosphamide use was higher in the PULSE cohort, but no longer a significant difference from the CARRA cohort.

Table 13. Treatment History at Enrollment, analysis of subjects with disease duration ≥ 2 yrs only

	PULSE N=33	CARRA N=632	P value (Fisher's exact)
% treated with steroids (n)	91 (29)	93 (591)	0.475
% treated with antimalarial (n)	86 (26)	92 (556)	0.304
% treated with cyclophosphamide (n)	41 (13)	33 (201)	0.444
% treated with mycophenolate mofetil (n)	40 (11)	66 (400)	0.007
% treated with azathioprine (n)	57 (16)	20 (119)	<0.001
% treated with methotrexate (n)	25 (7)	20 (119)	0.479
% treated with rituximab (n)	7 (2)	13 (81)	—
% treated with IVIg (n)	7 (2)	8 (48)	—

We identified a high rate of permanent organ damage in our cohort. SLICC-DI is a measure of irreversible organ damage in SLE patients. The South African cohort had an average SLICC-DI score of 1.9. The severe lupus nephritis demonstrated in Tables 8 and 9 in the PULSE cohort correlates with poor renal outcomes: 16% of our cohort required renal dialysis, vs 1% in the CARRA cohort (**Table 14**). South African pSLE patients with lupus nephritis also had much higher rates of renal transplant than patients in North America. In this chart review, it was clear that more than 50% of the PULSE cohort had a catastrophic clinical presentation, which we report here. This is not a common definition, but a term we created to capture the extremis with which the majority of the PULSE cohort presented. This term includes stroke, seizure, blindness, pericarditis causing tamponade, or acute renal failure. There is no data available on the frequency of these drastic presentations in North American pSLE patients for comparison. Finally, the PULSE cohort had a high mortality rate, as seven percent of this pediatric cohort was deceased prior to the time of enrollment.

As African ancestry, young age at diagnosis, and long disease duration could be associated with poor outcomes, we performed an analysis of these populations to ensure that the demographic differences in cohorts were not biasing our results. The large increase in PULSE patients requiring dialysis persisted, even among patients of African ancestry, young age, and long disease duration. For patients who required transplant,

there remained a significant difference for patients of African ancestry and young age at diagnosis, but not for patients with long disease duration.

Table 14. Disease Damage at Enrollment, analysis of subjects of African ancestry only, young age at diagnosis only, and long disease duration only.

	PULSE N=72	CARRA N=982	P value (Fisher's exact)
% requiring dialysis (n)	16 (11)	1 (11)	<0.001
African ancestry	17 (11)	1.5 (5)	<0.001
Age _≤ 13	16 (9)	0.87 (4)	<0.001
Disease duration ≥2 years	16 (5)	1.47 (9)	<0.001
% requiring transplant (n)	9 (6)	0.7 (7)	<0.001
African ancestry	9 (6)	0.3 (1)	<0.001
Age _≤ 13	11 (6)	1.3 (6)	<0.001
Disease duration ≥2 years	7 (2)	1 (7)	0.064
% ESRD (n)	13	NR*	--
Mortality % (n)	7 (5)	NR*	--
African ancestry	8 (5)	NR*	--
Age _≤ 13	4 (2)	NR*	--
Disease duration ≥2 years	0 (0)	NR*	--

*NR indicates not reported in this cohort.

As severe lupus nephritis is considered to be a predictor of poor prognosis and mortality, we evaluated risk factors for developing class III- VI lupus nephritis within the SA cohort (**Table 15**) or irreversible organ damage, defined as SLICC>0 (**Table 16**). Based on the literature, we predicted that male gender, a positive anti-dsDNA antibody, young age at diagnosis, African ancestry and long disease duration would be predictors for more severe lupus nephritis. The PULSE cohort did not have enough subjects to

provide power to predict the odds for developing more advanced lupus nephritis, or chronic severe organ disease. As these models were not powered for univariable analysis, we could not control for other variables which may act as moderators or confounders in the model.

Table 15. Odds Ratio for South African Patients Developing Class III-VI Lupus Nephritis

PULSE cohort with LN (n=42)	OR for Class III-VI LN	CI	P value
Male Gender	3.22	0.89- 11.75	0.076
dsDNA positive	2.24	0.59- 8.51	0.236
Age at diagnosis \leq 13 years	0.69	0.23- 2.07	0.517
African ancestry	1.17	0.20 -6.26	0.852
Disease duration \geq 2 yrs	1.00	0.38- 2.63	0.994

Table 16. Odds Ratio for South African Patients with Significant Organ Damage

PULSE cohort with LN (n=42)	Odds Ratio of SLICC>0	CI	P value
Male Gender	0.35	0.07-1.81	0.213
dsDNA positive	1.07	0.57- 1.99	0.837
Age at diagnosis \leq 13 years	0.94	0.28 – 3.15	0.917
African ancestry	0.39	0.04 -3.5	0.404
Disease duration \geq 2 yrs	2.61	0.80 - 8.46	0.110

4. Discussion

This study presented a cohort of 72 pSLE patients diagnosed before the age of 19 years in two medical centers and one office practice in Cape Town, South Africa. This is the largest cohort of pediatric SLE patients described in Africa to date. Although the burden of both SLE and pSLE in Africa is largely undetermined, SLE was thought to be rare in Africa. Recent studies have challenged this theory, highlighting the paucity of data and underdiagnosis.²⁰ There has only been one other study of pSLE on the African continent to date, which was a retrospective cohort of 36 patients who presented to a Johannesburg hospital between 1974-2000.²⁴ The previously reported South African cohort had a much higher proportion of white patients (42%) than the current PULSE cohort, likely reflecting shifts in recognition, diagnosis, and access to subspecialty care for Black patients.⁶⁰

The PULSE cohort is similar to the CARRA cohort in gender distribution, but differs in important measures of race, age, specific antibody profile and disease duration. Previous works suggest that earlier age of onset²⁸ and black race⁴¹ predispose to increased disease activity in pSLE patients, and may contribute to the severe disease phenotype seen in our SA cohort. Additionally, anti-dsDNA antibodies are associated with active disease and lupus nephritis, and are significantly higher in the PULSE cohort. A much larger proportion of the CARRA cohort had disease duration greater than two years at enrollment.

The PULSE cohort had higher rates of every disease manifestation studied, but the largest differences were seen in rates of renal and CNS involvement. These two organ systems have the most impact on patient health and prognosis,^{38,59,61} and therefore heavily influence treatment in pSLE.^{62,63} The PULSE cohort had high SLEDAI score at enrollment, indicating high rates of disease activity. The increased rates of all disease manifestations and the demonstration of catastrophic presentations suggest a more severe disease profile at presentation in this cohort.

It is not possible to determine if barriers to diagnosis and care influence the severity of disease profile in this cross sectional cohort study. However, there are a few features of the study setting that suggest such barriers exist. Although it has been more than twenty years since the dissolution of apartheid government, the history and politics of that era continue to have impact on access to care to date.⁶⁴ There are structural and financial barriers to persons of color and persons who live in rural areas seeking medical care in South Africa.⁶⁵⁻⁶⁷ Additionally, SLE is a chronic rheumatic disease. The health system of South Africa suffers from the burden of many diseases: HIV, other infectious diseases, and injury related disease.⁶⁸ The focus on chronic diseases has just begun. The few pediatric rheumatology providers in the country are located in urban academic centers in major cities, which could certainly limit access for patients in rural areas.

The rate of lupus nephritis in children with SLE is high, ranging from 50-67% in various cohort studies worldwide.²⁹ We found the rate of biopsy proven lupus nephritis

to be 58% in our PULSE cohort, which is higher than the CARRA cohort (44%), but consistent with previously reported pSLE data. In previously described cohorts, patients of African descent are two to three times more likely to develop lupus than white counterparts, and are more likely to have severe disease.³⁵ Previous studies in North America have indicated non-Caucasian children with lupus nephritis are more likely to progress to end stage renal disease (ESRD) than Caucasian counterparts.⁶⁹

The PULSE cohort also had higher rates of renal manifestations, hematuria, and proteinuria at enrollment. The majority of the biopsied patients in the PULSE cohort (88%) had class III-VI nephritis at enrollment, which represents more than half of the entire cohort. In contrast, 53% of biopsied North American patients had higher grade lupus nephritis, which is only 22% of the overall cohort. Also, 7% of those biopsied in the PULSE cohort had Class VI lupus nephritis, which indicates >90% sclerosis of renal glomeruli. This proclivity for advanced nephritis cannot be explained by the differences in African ancestry, young age of onset, or disease duration between cohorts.

The management of pSLE patients differs between South Africa and North America. The treatment of SLE involves glucocorticoids²⁹ and disease modifying anti-rheumatic drugs (DMARDs) to inhibit organ inflammation, prevent damage, and prevent disease flare. Both cohorts had similar rates of treatment with glucocorticoids. Antimalarial therapy has been used in SLE for decades as immunomodulation, and is now considered standard of care.⁷⁰ The choice of antimalarial drug varied by site:

hydroxychloroquine is used almost exclusively in North American, unless the patient has an allergy, while chloroquine is utilized in South Africa. Despite the low cost of chloroquine in South Africa (approximately \$1 USD per month),⁷¹ fewer patients in the PULSE cohort received antimalarial therapy. As this analysis consists of both prior and current use, discontinuation due to adverse effect does not explain the discrepancy. There are not sufficient data to determine if this difference is due to a knowledge or perception gap amongst South African providers.

More patients in the PULSE cohort received cyclophosphamide than in the CARRA cohort. Cyclophosphamide is used for induction⁶² and maintenance therapy⁷⁰ of active lupus nephritis and central nervous system SLE.⁷² Therefore the higher rates of renal and neurologic manifestations in the PULSE group may explain the increased use of this medication in South Africa. Cyclophosphamide is a potent immunosuppressant, but its use is decreasing in the management of lupus nephritis due to side effects of infertility, bone marrow suppression, and risk for infection.⁷³ The increase in mycophenolate mofetil use in the CARRA cohort could reflect this shift in prescribing practices.

A higher number of South African patients received IVIg than North American pSLE patients. This is an expensive medication,⁷⁴ and is regulated by the South African drug and therapeutics committee.⁷⁵ One explanation for the increase in the South African cohort is the high rate of hematologic manifestations in this cohort. Many of

these patients presented with hemolytic anemia or thrombocytopenia requiring transfusion and these complications are often initially managed with IVIg. This study is not powered to analyze this as a definitive cause for the differential use of this medication.

In South Africa, mycophenolate mofetil and rituximab are regulated medications that require clinical justification and motivation for use due to cost.⁷⁶ The approval process may influence the use of these medications in the PULSE cohort.

Compared with other agents used to treat SLE, methotrexate and azathioprine are inexpensive and widely available in South Africa, which may be why they are used more frequently than in North America. The odds for progression to ESRD, dialysis or transplant by treatment with either disease modifying anti-rheumatic drugs within the PULSE cohort were not statistically significant (data not shown).

We performed all of these analyses on patients of African ancestry, those with age of diagnosis less than 13 years, and those with long disease duration to see if treatment differences could be explained on differences in demographic factors between cohorts. Most of the percentages did not change dramatically, but the smaller sample sizes often did not retain statistical significance. One notable difference is the percentage of cyclophosphamide use was no longer different between cohorts in patients of young age at disease diagnosis. Infertility is a concerning adverse effect of cyclophosphamide, but the risk for infertility is greatly reduced in pre-pubertal patients. The reduction in

the risk profile could explain the more evenly distributed use between cohorts in this specific age group.

South African patients have increased rates of severe lupus nephritis and this disease severity directly translates into poor outcomes. Thirteen percent of the PULSE cohort had developed ESRD at enrollment, 16% required dialysis, and 9% required transplant. Some patients who required dialysis had acute renal failure at diagnosis, accounting for the discrepancy between those requiring dialysis and developing ESRD. The rate of renal dialysis and transplant is much higher in the South African cohort than North America, which is in keeping with the higher rates of lupus nephritis found in the PULSE cohort. However, South Africa is a resource limited setting. The use of both peritoneal and hemodialysis are tightly rationed, requiring application and approval.⁷⁷ Except for cases of acute renal failure, all patients requiring dialysis must also be suitable candidates for renal transplant. The criteria for transplantation are strict, and studies have shown that organ recipients are more likely to be white, affluent, young, and live close to a major medication center.⁷⁸ Given these factors, the increased rate in the South African cohort is surprising.

The PULSE cohort had significant non-renal permanent organ damage, as is reflected in the SLICC-DI scores. The SLICC-DI criteria require severe, permanent organ damage (such as end stage renal disease or pulmonary fibrosis) to gain positive scores. This measure is not recorded in the CARRA database, so direct comparison is not

possible. The APPLE study, which was a study of a pSLE cohort in the USA, reported only 25% of the 221 patient cohort had a SLICC score greater than 0.⁷⁹ This is vastly different from 63% of the PULSE cohort who had a SLICC score >0 at enrollment.

The mortality rate in the PULSE cohort 7%. Five year survival for pSLE patients has been reported as >95%. The reports from other lower income nations show a poorer prognosis.^{80,81} Almost all the patients (6/7) who died in the PULSE cohort had deaths related to renal disease, again reinforcing the importance of lupus nephritis management.

As lupus nephritis has such an impact on disease course and prognosis, we attempted to develop a model to identify risk factors for developing higher class renal disease. There were only 42 patients with lupus nephritis in the PULSE cohort, so the study is not powered to detect differences in risk within this cohort.

As the PULSE cohort demonstrated dramatic differences in pSLE outcomes, we also tried to develop a model for predicting organ damage in this high risk population. Again the study was not powered to detect these differences.

4.1 Implications for policy and practice

The PULSE cohort demonstrates high rates of disease activity, lupus nephritis, end stage renal disease, and organ damage compared to peers in North America. The burden of chronic rheumatic disease in South African children may be under-recognized or underdiagnosed due to the large strain that HIV, other infectious diseases, and injury

related illness place on the healthcare system. There are only four pediatric rheumatology providers to serve all of South Africa. The difference in percentage of race/ethnicity, young age at diagnosis, and disease duration does not explain the difference in disease severity between the cohorts. Improving early recognition, diagnosis, and access to treatment for pSLE patients in this setting may lead to reduction in organ damage. The South African pSLE cohort requires increased clinical monitoring, and increased vigilance for the development of lupus nephritis. In patients that develop lupus nephritis, early aggressive therapy may be indicated, as such a high percentage of the cohort goes on to develop ESRD requiring either dialysis or renal transplant. Given the limited resource of dialysis and transplant, preventing primary damage in this cohort is imperative.

4.2 Implications for further research

The PULSE cohort analysis reveals that South African pSLE patients differ from their North American peers in onset of disease, disease activity, rate and class of lupus nephritis, and progression to irreversible organ damage. These differences may be due to racial/ethnic predisposition to severe disease, barriers to health care access, or a combination of these factors.

Further prospective research in South Africa is necessary to gain better understanding of the burden of pSLE. A large, prospective study is necessary to establish the number of patients with pSLE, management, and prognosis. Such studies

will be better equipped to identify risk factors for poor outcomes. Also, qualitative research in this population could help determine the role of barriers to care, which may in part explain disease severity at onset.

We will continue to follow the PULSE cohort prospectively to help delineate the contribution of access to care, race and genetic predisposition to SLE outcomes. We will also expand the registry to other sites in South Africa to expand our understanding of the burden of pSLE in South Africa. Qualitative research is already underway to help identify barriers to care for pSLE patients.

4.3 Study strengths and limitations

This work represents the largest cohort of pSLE patients ever assembled on the continent of Africa to date. We were able to perform primary analysis of raw data comparing the African cohort to peers in North America, allowing for robust analysis. The study supports the hypothesis that patients in South Africa demonstrate earlier age of onset of disease and more severe disease, than North American comparators.

This study is limited by the number of patients enrolled in the South African cohort. Although it is the largest cohort in South Africa to date, the total number of patients is small, and does not provide power for analysis within the PULSE cohort. We performed multiple comparisons, and this may lead to an association that gains statistical significance by chance. We may need to correct for this with false discovery rates in further analysis. This study is a cross sectional analysis and therefore we are

limited by the documentation of the physician in the medical chart. It is impossible to determine if this population is representative of the country at this stage. The study is limited in geographic area to one city in South Africa. Cape Town is not representative of the entire country of South Africa, as it differs both in racial distribution and socioeconomic status. The majority of patients were recruited from two major academic medical centers. These factors may introduce bias in demographic and disease profiles.

5. Conclusion

The PULSE cohort analysis reveals that South African pSLE patients have earlier onset of disease, higher disease activity, higher rates of severe lupus nephritis, and more disease damage than their North American counterparts. The South African cohort demonstrates a striking increase in advanced lupus nephritis, poor renal outcomes, end stage renal disease, and irreversible organ damage compared to North American peers. These differences may be due to ethnic predisposition to severe disease, barriers to health care access, or a combination of these factors. Further research is warranted to investigate the burden of pSLE in South Africa, and identify risk factors for poor outcomes in this high risk pediatric population.

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