Trajectory of Damage Accrual in Systemic Lupus Erythematosus based on Ethnicity and Socioeconomic Factors

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Abstract:

Objectives: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) is associated with increased healthcare cost and mortality. We compared the trajectory of total and individual damage items of the SLICC/ACR DI in African-American vs Caucasian ethnicities in a large prospective SLE cohort. We also estimated the association between ethnicity and individual damage items after adjusting for several socioeconomic factors.

Methods: Poisson regression was used to calculate the rate of damage per year for each organ. Cox regression modeling was used to determine the association between time to the individual damage item and ethnicity.

Results: We included 2,436 patients: 43% African-American, 57% Caucasian, and 92% female. There was a linear relationship between time since diagnosis and mean SLICC/ACR DI score, with no plateau. Compared to Caucasians, African-Americans had a faster total, renal, pulmonary, and skin damage accrual rate even after adjustment for differences in socioeconomic variables.

Conclusions: The linear increase in damage in both ethnicities over time is of particular concern. African-Americans accrued more and faster damage compared to Caucasians. For a few organs, higher rates of damage in African-Americans was partially explained by socioeconomic differences, whereas for most organs, the difference persisted after adjustment for these factors.

Introduction:

In Systemic Lupus Erythematosus (SLE), a higher Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI) is associated with increased mortality (1-4), poorer health-related quality of life (5), and increased healthcare costs (6). Looking at 263 patients from the Toronto Lupus Clinic inception cohort, organ damage acquired within the first year of diagnosis increased 10-year mortality by 3-4 fold (1). In a multicenter study evaluating the economics of damage accrual in 1,687 patients who were part of the SLICC inception cohort, a SLICC/ACR DI ≥ 5 was found to accrue annual costs 12-fold higher than those with a SLICC/ACR DI of 0 (6). Mok et al. examined the effect of damage on health-related quality of life in patients with SLE (5). Compared with age- and gender- matched controls, SLE patients had lower SF-36 scores which inversely correlated with SLICC/ACR DI scores (5).

Many studies have determined ethnicity as a predictor of higher SLICC/ACR DI. In the Hopkins Lupus cohort, higher rates of damage were found in African-Americans compared to Caucasians (7). In the Carolina Lupus cohort, African-American patients were more likely than Caucasians to experience damage in almost all sub-items of the SLICC/ACR DI (8). In the LUMINA cohort, Hispanics had the highest SLICC/ACR DI scores compared to Caucasians and African-Americans (9, 10). In a retrospective analysis of medical records and SLICC/ACR DI scores of 300 patients in a multi-ethnic British cohort, African-Caribbean ethnicity was associated with increased damage (2). Different ethnicities have different damage patterns (8, 10-12). Renal and skin damage were more pronounced in African-Americans (10) and African-Canadians (8) compared to Caucasians. Mortality studies showed that mortality is higher in Black patients (13, 14). Data from the Georgia Lupus Registry suggest that Black women die earlier than their White counterparts, by an average of 13 years (14).

Only a limited number of studies have evaluated the trajectory of damage accrual in patients with SLE in different ethnicities. In a retrospective study of 300 lupus patients at the University College Hospital London, the divergence in the damage curves started early in the disease in African-Caribbean compared to Caucasian and Asian SLE patients (2). In addition, a single-center, longitudinal, inception-cohort study looking retrospectively at juvenile SLE

patients diagnosed at the pediatric lupus clinic at SickKids Hospital, Ontario, also determined African-Caribbean ethnicity as a predictor of higher initial and persistently greater damage accrual compared to Asians and Caucasians (15).

Discrepancies between different ethnicities may be due to the role of socioeconomic measures. Few studies have evaluated the effect of individual measures of socioeconomic status such as educational level and poverty on damage accrual in SLE patient (16-18). A recent study by Falasinnu et al., specifically looking at SLE related mortality in the Eight Americas, reported that race played a more important role than socioeconomic and geographical parameters (19). There was no study in the literature that looked at 3 measures of socioeconomic status simultaneously in one study population.

The aim of our study was to calculate and compare the trajectory of both total and individual organ damage accrual in the largest longitudinal prospective SLE cohort in which African-American and Caucasian ethnicities were well represented. We evaluated the role of ethnicity in damage accrual and the degree to which this was explained by socioeconomic factors.

Methods:

The Hopkins Lupus Cohort is a prospective longitudinal single-center prevalent cohort of SLE patients in Baltimore and surrounding areas. The cohort was established in 1987 and has been approved by the Johns Hopkins University School of Medicine Institutional Review Board on a yearly basis. All patients gave written informed consent to participate. This analysis was based on cohort data from its inception until January 2020.

Patients were followed up by protocol quarterly, or more often as clinically indicated. Information about SLE features since diagnosis was gathered at cohort entry by obtaining a thorough history and medical record review of the patient. This information was updated at each cohort visit. Ethnicity and the 3 socioeconomic measures were self-reported by the patient upon initial cohort entry questionnaire. Ethnicity was recorded as African-American or Caucasian. Education was reported as less than or equal to, or more than 12 years. Household income was

reported as less than $30,000, between $30,000 and $65,000 or more or equal to $65,000. Health insurance was reported as none, medical assistance, or private.

The SLICC/ACR Damage Index is a validated tool that was developed to measure damage, defined as irreversible organ dysfunction, present for 6 months or longer regardless of etiology. The index evaluates 12 organ systems (ocular, neuropsychiatric, renal, pulmonary, cardiovascular, peripheral vascular, gastrointestinal, musculoskeletal, skin, premature ovarian failure, diabetes, and malignancy), with 1–5 items per system (20, 21). The SLICC/ACR DI was calculated based on medical record review at cohort entry and updated at every cohort clinic visit. In our analysis, the SLICC/ACR DI was calculated based on organ damage that occurred after diagnosis with SLE until the last visit (20, 21). Patients whose damage occurred prior to the date of SLE diagnosis were excluded.

We plotted the mean damage score for each organ by year since SLE diagnosis stratified by ethnicity. We also plotted the percent of patients with any damage in each organ by year since SLE diagnosis and by ethnicity. To compare African-Americans to Caucasians with respect to damage rates, Poisson regression was used, allowing overdispersion for each organ system with an offset term accounting for their time followed since diagnosis. The outcome variable was the damage score of each organ system at the last available cohort visit. The associations were adjusted for sex, age, income, education, and health insurance.

We used Cox regression models approach to determine the association between time to individual damage item and ethnicity. These associations were also adjusted for sex, age, income, education, and health insurance. Associations between race and rates of damage were quantified using Rate Ratios (RR).

All analyses were performed using SAS software, version 9.4 (SAS Institute, North Carolina, United States).

Results:

A total of 2,674 patients with SLE classified according to the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria (22) or the revised American College of Rheumatology (ACR) classification criteria (23, 24), were in the cohort. Of these patients, 1,049 (39.2%) were African-American, 1,399 (52.3%) were Caucasian, and 226 (8.5%) were of other ethnicities. In this analysis, we only included African-American and Caucasian patients. We excluded 226 patients of other ethnicities and 12 patients with a missing diagnosis date.

We included 2,436 patients: 42.9% African-American, 57.1% Caucasian, and 92% female (Table 1). The mean age at SLE diagnosis was 33 years (SD=13). Forty-nine percent of these patients were classified with SLE at age younger than 30, and 33.6% were diagnosed between the age of 30 and 45 years. The cumulative classification criteria were 48% malar rash, 19% discoid rash, 52% photosensitivity, 53% oral ulcer, 72% arthritis, 49% serositis, 45% renal disorder, 12% neurological disorder, 67% hematological disorder, 79% immunological disorder and 97% ANA positivity, based on revised ACR classification criteria. Additional SLICC classification criteria included 21% direct Coombs test, 53% low C3, 47% low C4 and 16% low CH50. The mean follow-up time from diagnosis to the last clinic visit was 13.4 years (SD=9.97).

Table 1 shows a comparison of African-Americans and Caucasians with respect to demographic characteristics of the study population. They were similar in age at diagnosis, follow-up time since diagnosis and sex. African-Americans were less likely to have more than 12 years of education (59% in African-Americans vs 71% in Caucasians,) , a combined family income of $65,000 and more (22% in African-Americans vs 44% in Caucasians), and private health insurance (66% in African-Americans vs 88% in Caucasians), compared to African-Americans.

Figure 1 shows the mean total SLICC/ACR DI by time since diagnosis stratified by ethnicity. An approximately linear relationship between time since diagnosis and mean SLICC/ACR DI, with no plateau, was found. The divergence of the curve started early in the disease course.

Table 2 shows the adjusted and unadjusted associations between cumulative and individual organ system damage accrual and ethnicity. Values were adjusted for sex, age at diagnosis, years of education, health insurance, and household income. The rate of cumulative damage accrual was significantly higher in African-American compared to Caucasian patients after adjustment for socioeconomic measures (RR=1.14, 95% CI [1.03, 1.27]). Renal (RR=1.68, 95% CI [1.30, 2.16]), pulmonary (RR=1.38, 95% CI [1.09, 1.73]), and skin (RR=2.97, 95% CI [1.83, 4.85]) damage in African-American patients accumulated at a significantly higher rate compared to Caucasians after adjustments. Musculoskeletal and cardiovascular damage accumulation rate was higher in African-Americans compared to Caucasians in the univariate analysis but lost its significance after adjustment for sex, age at diagnosis, years of education, health insurance, and household income.

Table 3 examines the association between race and individual damage items in each organ system represented in the SLICC/ACR DI using a time-to-event approach. African-Americans had a higher risk of renal insufficiency, proteinuria 3.5g/24hrs, end-stage renal disease, pulmonary hypertension, pulmonary fibrosis, cardiomyopathy, pericarditis, deforming or erosive arthritis, avascular necrosis, and scarring chronic alopecia, than Caucasian patients, at any time during follow-up. On the other hand, Caucasian patients were at higher risk for osteoporosis with fracture or vertebral collapse, bowel infarction, venous thrombosis, and malignancy. African-Americans had a 40% higher risk of having renal insufficiency defined as an eGFR of < 50% (RR=1.44, 95% CI [1.16, 1.79]). In addition, African-Americans were more than twice as likely to have nephrotic proteinuria (RR=2.14, 95% CI [1.47, 3.12]) and end-stage renal disease (RR=2.09, 95% CI [1.34, 3.28]) compared to Caucasians. African-Americans had almost twice the risk of Caucasians for pulmonary hypertension (RR=1.81, 95% CI [1.30, 2.52]). The likelihood of cardiomyopathy (RR=2.52, 95% CI [1.48, 4.29]) and chronic pericarditis (RR=2.48, 95% CI [1.08, 5.71]) to develop in African-Americans was around 3 times that of Caucasians. With musculoskeletal damage, African-Americans were at double the risk of having erosive arthritis (RR=2.02, 95% CI [1.48, 2.75]) and avascular necrosis (RR=1.84, 95% CI [1.34, 2.52]), while Caucasians were at double the risk of having osteoporosis with fracture. Scarring alopecia was 6.3 times higher (RR= 6.25, 95% CI [3.16, 12.36]) in African-Americans compared to Caucasians.

Figure 2 shows the linear trends in specific organ systems. Mean pulmonary, renal, musculoskeletal, and skin damage scores were higher in African-American patients compared to Caucasian patients, at any point after SLE diagnosis. A small difference between the 2 ethnicities was also noted in cardiovascular damage. By 5 years after SLE diagnosis, 11% of African-American patient compared to 6% of Caucasian patients had renal damage. By 15 years after SLE diagnosis, 21% of African-American patients compared to 14% of Caucasians had renal damage. By 15 years after SLE diagnosis 17% of African-American patients compared to 14% of Caucasians had pulmonary damage. By 15 years after SLE diagnosis 35% of African-American patients compared to 25% of Caucasian had musculoskeletal damage. The mean musculoskeletal damage was significantly higher in African-Americans compared to Caucasians. By 15 years after SLE diagnosis, 11% of African-American patients compared to 3% of Caucasians had skin damage.

Discussion:

Our study, the largest ever done, confirmed that cumulative damage accrual is faster in African-Americans compared to Caucasians. The organ systems mostly affected by ethnicity are pulmonary, musculoskeletal, renal, and skin. The damage in these organ systems is not only more likely in African-Americans, but also occurs at a faster rate compared to Caucasians. These differences persisted after adjusting for socioeconomic factors except for musculoskeletal damage.

First, a considerable percentage of patients acquired damage by 5 years of diagnosis and continued to do so over the course of their disease. In our cohort, 40% of patients had accrued damage by 5 years with no evidence of a plateau effect. This is in agreement with other studies that showed that around 50% of SLE patients will accrue damage by 5 years of the disease regardless of the ethnicity and geographic backgrounds (10, 25). The absence of plateau effect in damage accrual in SLE patient was also demonstrated in the SLICC inception cohort (13). These findings highlight the importance of continuous follow-up and aggressive management of SLE, considering there was no flattening of the damage curve over the disease course.

Second, ethnicity was an important determinant of severity and rate of damage accrual. From the outset of the disease and thereafter throughout the course of the disease, African-

Americans accumulated more and earlier damage at a faster rate compared to Caucasians. In the Canadian juvenile SLE cohort, African-Caribbean accrued earlier and faster damage compared to Asian and White patients (15). In a large international SLE inception cohort, USA patients of African ancestry and Hispanic patients in Mexico had a higher risk of progressing from baseline damage to higher damage, while Asians had lower transition rates, compared to Caucasians in Europe or Canada (13). There are a number of possible explanations for these findings, including differences in clinical phenotype, response to therapy, comorbidities, socioeconomic factors , differences in corticosteroid use, and access to healthcare among different ethnic groups. In our study, increased rates of overall and organ-specific damage persisted after adjustment for demographics and measures of socioeconomic status. We did not adjust for corticosteroid use in comparing ethnic groups because we viewed that to be in the causal pathway from disease manifestations to damage.

Third, ethnicity plays a role in determining organ-specific damage accrual rate and pattern. Our study along with others demonstrated that renal (10, 26) and skin damage (8, 10) occurred more frequently among SLE patients of African descent compared to Asians or Caucasians. Another new finding in our study is that African-Americans accrued faster lung and musculoskeletal damage. Studies of other ethnicities also have demonstrated different patterns in organ damage. In the LUMINA multiethnic cohort, neuropsychiatric problems accounted for the greatest proportion of organ system damage in Hispanics and Caucasians (10). Hispanics were more likely than African-Americans and Caucasians to exhibit cataracts, muscle atrophy, and cognitive impairment (10). In a Chinese cohort, the main contributors to organ damage were renal insufficiency, osteonecrosis and gonadal failure (25). In a cross-sectional study from Malaysia, patients of Indian origins predominantly developed diabetes while Malays developed osteoporosis (12). The majority of patients who developed malignancy were Chinese (12).

Fourth, the difference in damage accumulation between African-Americans and Caucasians could not be explained by socioeconomic disparities. Despite contributing to organ damage in SLE (7, 8, 10, 27), socioeconomic status could not explain disparities in organ damage and mortality in SLE patients with different ethnicities in some past studies (10, 28, 29). A study conducted at the University of California, San Francisco, on 783 participants, that showed that poverty resulted in damage accumulation and that exiting poverty was associated

with lower levels of accumulated damage (17). Using the same data source, it was suggested that poverty resulted in a higher mortality in SLE by increasing organ damage (18). In 2005, Ward et al. found that among Whites, higher education was associated with lower mortality but this association was not found in Blacks (16). Our study is more in line with the Eight Americas mortality study that ethnicity plays the major role, regardless of socioeconomic status (19).

The strength of our study is that it reviewed the trajectory of damage in 2 ethnicities in a large cohort of SLE patients followed up for a mean of 13 years, taking into account the effects of socioeconomic measures. The three measures of socioeconomic status were self-reported by the patients. Socioeconomic variables were colinear and hence it was difficult to tease out any individual effect of each measure of socioeconomic status. A second, limitation is that our analysis assumes that socioeconomic status remained fixed since SLE diagnosis. While patient education is generally established after a certain age, income and health insurance could vary over time leading to some misclassifications. Determining the effect of the change in socioeconomic status on the trajectory of damage in SLE is extremely challenging and beyond the scope of this study. We did not find any study in the literature that evaluated these repercussions. Another limitation is the inability to account for potentially confounding variable, that could affect the study findings, due to their multitude. These variables include but are not limited to disease activity, corticosteroid use, medication adherence, and obesity. A final limitation is that our study was a single center predominantly consisting of African-Americans and Caucasians and cannot be generalized to other ethnicities.

Conclusion:

The linear increase in damage in both ethnicities over time is of particular concern. At any point during the disease, the SLICC/ACR DI was higher and accrued at a faster rate in African-American compared to Caucasian SLE patients. Damage in most organ systems progressed at a faster rate in African-Americans. Ethnicity, therefore, is a strong contributor to organ damage. Our study further highlights that differences between African-Americans and Caucasians in SLE organ damage are not adequately explained by disparities in socioeconomic status, similar to the Eight Americas mortality study (19).

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Table 1: Characteristics of the patients included in the study

	All (n=2436)	**African-American (n=1045)**	**Caucasian (n=1391)**
Age at SLE diagnosis (mean ±SD)	32.7±13.0	31.3±12.1	33.6±13.5
Cohort follow up time since SLE diagnosis (mean ±SD)	13.4 ± 10.0	13.6±10.2	13.3±9.8
Sex			
Female	2242 (92%)	976 (93.4%)	1266 (91.0%)
Male	194 (8%)	69 (6.6%)	125 (9.0%)
Education			
≤12 years	787 (34%)	406 (40.8%)	381 (28.7%)
>12 years	1532 (66%)	588 (59.2%)	944 (71.3%)
Family income			
<$30,000	706 (33%)	456 (49.2%)	250 (20.3%)
$30,000 - <$65,000	709 (33%)	268 (28.9%)	441 (35.8%)
≥$65,000	743 (24%)	202 (21.8%)	541 (43.9%)
Insurance			
None	57 (2%)	40 (4.0%)	17 (1.3%)
Medical assistance	451 (19%)	306 (30.2%)	145 (10.9%)
Private	1835 (78%)	667 (65.8%)	1168 (87.8%)

Table 2: Adjusted and unadjusted rates of damage accrual in total and individual organ after SLE diagnosis by ethnicity

Type of Damage	Rate of SDI per year		Rate Ratio (95% CI)	P-value	Adjusted Rate Ratio (95% CI)	p-value
	African-American	Caucasian				
Total damage	0.16	0.12	1.30 (1.18, 1.43)	**<0.0001**	1.14 (1.03, 1.27)	**0.010**
Ocular	0.015	0.015	0.99 (0.83, 1.19)	0.9474	1.06 (0.88, 1.28)	0.5483
Neuro-psychiatric	0.017	0.018	0.96 (0.78, 1.18)	0.6937	0.82 (0.65, 1.03)	0.0925
Renal	0.03	0.016	1.99 (1.58, 2.49)	**<0.0001**	1.68 (1.30, 2.16)	**<0.0001**
Pulmonary	0.016	0.011	1.47 (1.18, 1.82)	**0.0006**	1.38 (1.09, 1.73)	**0.0066**
Cardiovascular	0.012	0.009	1.32 (1.02, 1.71)	**0.0352**	1.26 (0.95, 1.68)	0.1023
Peripheral-vascular	0.0044	0.0042	1.04 (0.72, 1.52)	0.8224	0.75 (0.49, 1.16)	0.2032
Gastrointestinal	0.007	0.009	0.82 (0.59, 1.14)	0.2423	0.76 (0.52, 1.10)	0.1472
Musculoskeletal	0.03	0.02	1.31 (1.14, 1.51)	**0.0002**	1.11 (0.94, 1.30)	0.2086
Skin	0.007	0.002	4.15 (2.63, 6.55)	**<0.0001**	2.98 (1.83, 4.85)	**<0.0001**
Other	0.013	0.012	1.10 (0.90, 1.35)	0.3418	0.97 (0.79, 1.20)	0.8057

[1]adjusted for sex, age at diagnosis, years of education, insurance, and combined family income

		African-American vs. Caucasian	
SLICC/ ACR damage index items	# of events	RR[1] (95% CI)	p-value[1]
Any cataract ever	414	1.07 (0.87,1.31)	0.5123
Retinal change OR optic atrophy	101	0.91 (0.59, 1.42)	0.9512
Cognitive impairment OR major psychosis	130	0.83 (0.55, 1.23)	0.3486
Seizures requiring therapy for 6 months	57	0.58 (0.32, 1.04)	0.0678
Cerebral vascular accident ever OR resection	180	0.84 (0.60, 1.17)	0.3028
Cranial OR peripheral neuropathy	183	0.80 (0.57, 1.12)	0.1928
Transverse myelitis	15	0.79 (0.26, 2.42)	0.6816
Estimated or measured GFR < 50%	416	1.44 (1.16, 1.79)	**0.0009**
Proteinuria 3.5g/24hrs	156	2.14 (1.47, 3.12)	**<0.0001**
End-stage renal disease	112	2.09 (1.34, 3.28)	**0.0013**
Pulmonary hypertension	184	1.81 (1.30, 2.52)	**0.0005**
Pulmonary fibrosis	173	1.40 (1.00, 1.96)	**0.0521**
Shrinking lung	9	0.82 (0.18, 3.65)	0.7943
Pleural fibrosis	64	1.36 (0.78, 2.36)	0.2826
Pulmonary infarction OR resection	8	0.20 (0.02, 1.77)	0.1493
Angina OR coronary artery bypass	84	0.66 (0.39, 1.11)	0.1186
Myocardial infarction ever	97	1.03 (0.66, 1.62)	0.8943
Cardiomyopathy	79	2.52 (1.48, 4.29)	**0.0006**
Valvular disease	58	1.00 (0.56, 1.80)	0.9992
Pericarditis>6 months, OR pericardiectomy	29	2.48 (1.08, 5.71)	**0.0331**
Claudication x6 months	36	1.10 (0.51, 2.39)	0.8072
Minor tissue loss (pulp space)	14	1.73 (0.51, 5.86)	0.3765
Significant tissue loss ever	20	1.04 (0.39, 2.76)	0.9420
Venous thrombosis with swelling, ulceration, OR venous stasis	66	0.48 (0.26, 0.87)	**0.0150**
Infarction or resection of bowel	204	0.64 (0.46, 0.88)	**0.0065**
Mesenteric insufficiency	8	0.92 (0.17, 4.94)	0.9270
Chronic peritonitis	7	1.34 (0.27, 6.66)	0.7211
Stricture OR upper gastrointestinal tract surgery ever	16	2.89 (0.89, 9.35)	0.0763
Pancreatitis	9	0.23 (0.04, 1.21)	0.0818
Muscle atrophy or weakness	46	0.89 (0.46, 1.73)	0.7373
Deforming or erosive arthritis	219	2.02 (1.48, 2.75)	**<0.0001**
Osteoporosis with fracture or vertebral collapse	311	0.46 (0.35, 0.60)	**<0.0001**
Avascular necrosis	200	1.84 (1.34, 2.52)	**0.0002**
Osteomyelitis	19	0.51 (0.18, 1.44)	0.2019
Ruptured tendon	70	0.84 (0.49, 1.45)	0.5413
Scarring chronic alopecia	65	6.25 (3.16, 12.36)	**<0.0001**
Extensive scarring or panniculum other than scalp and pulp space	37	2.19 (0.99, 4.83)	0.0531
Skin ulceration (not due to thrombosis) for more than	26	0.60 (0.26, 1.42)	0.2466

Table 3: Associations between time to damage index items and ethnicity (African-American vs. Caucasian)

6 months			
Premature gonadal failure	58	0.93 (0.52, 1.65)	0.8047
Diabetes	130	1.36 (0.91, 2.03)	0.1291
Malignancy (exclude dysplasia)	248	0.74 (0.55, 0.99)	**0.0421**

[1]Adjusted for sex, age at diagnosis, years of education, income, and insurance.

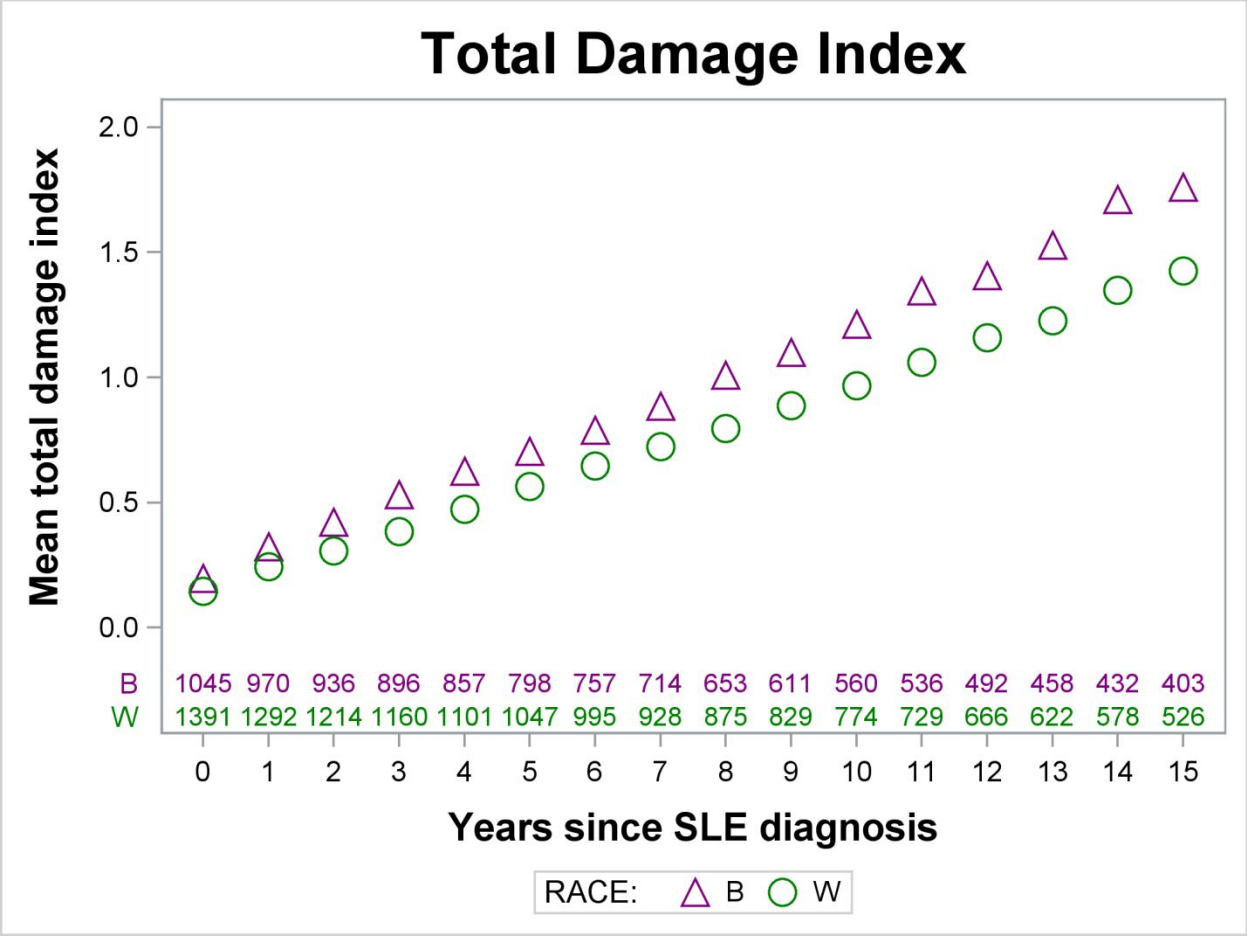

Figure 1: Mean total damage index by years since diagnosis, stratified by ethnicity

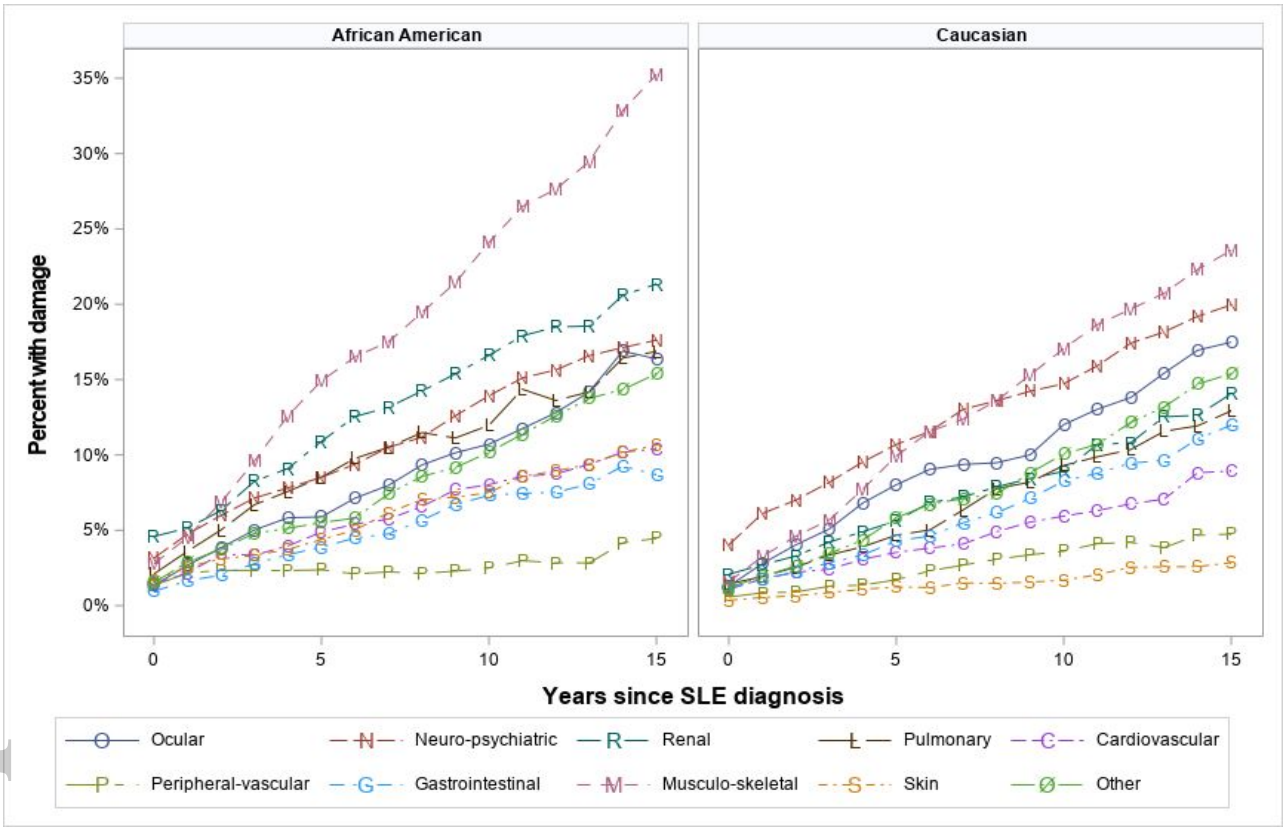

Figure 2: Damage accrual rate of each organ over time in African-American and Caucasian patients