The Impact of Race and Ethnicity on Disease Severity in Systemic Lupus Erythematosus

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Objectives: Systemic lupus erythematosus (SLE) can result in comorbidities and high disease severity. The aim of this study was to evaluate the effects of age, sex, race, ethnicity, cost of hospitalization, length of stay, and payor source on SLE disease severity scores.

Design: Epidemiological study.

Setting: Hospital discharge data were obtained from the DFW Hospital Council (DFWHC), for 65,535 patients hospitalized in the North Texas Dallas-Fort Worth (DFW) Metropolitan Statistical Area (MSA) from 1999–2005 with at least one autoimmune disease.

Patients: Of the 65,535 autoimmune patients, 14,829 patients had SLE as a diagnosis. The sample was assessed for disease severity according to the SLE comorbidity Index.

Main outcome: Disease severity, SLE comorbidities.

Results: SLE patients were younger and more than five times more likely to have multiple autoimmune diseases. More than one third of Hispanic patients were on Medicaid or self-pay and more likely to have higher disease severity. Race (Caucasian), sex (female), and payor source (PPO/POS) predicted lower disease severity scores. SLE was predictive of eight of the fourteen SLE-CI diseases, with greatest effects observed for nephritis (OR=3.30, $P<.0001$), chronic renal failure (OR=3.36, $P<.0001$), pericarditis (OR=3.2, $P<.0001$), and pleuritis ($OR=2.06$, $P<.0001$). Non-Caucasian patients were more likely to have chronic renal failure, nephritis, congestive heart failure, pericarditis and pleuritis.

Conclusions: The comorbidities that exist in SLE vary according to ethnicity. It is paramount for physicians to be cognizant of these disparities and make appropriate referrals. (*Ethn Dis*. 2009;19:301–307)

Key Words: Lupus, Disease Severity, Autoimmune Disease, Chronic, Comorbidities, Autoimmunity, Epidemiology

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Introduction

Systemic lupus erythematosus (SLE) is a non-organ specific disease that strikes women nine times more often than men.[1] The exact prevalence of SLE is unknown, though estimates range from one to two million cases in the United States.[2,3] Of the current cases, more than 100,000 SLE patients are hospitalized every year.[4] Although SLE has the potential to target any system, the most commonly affected are the cardiovascular, respiratory, musculoskeletal, renal, and central and peripheral nervous systems. SLE may initially present in flares of vague symptomology, including fatigue, anemia, skin rash, muscle aches, sensitivity to cold, weight loss, fever, and diarrhea. Comorbidities of SLE include congestive heart failure, nephritis and renal failure, osteoporosis, seizures, non-Hodgkin's lymphoma, diabetes, infections, and myocardial infarction.[5–8] Improvements in organ specific treatments have allowed more patients to survive the acute phases of SLE, but vascular problems such as coronary artery disease may develop from chronic inflammation.[9] Now recognized as a major complication of SLE, premature accelerated atherosclerosis increases the risk for angina, myocardial infarction, peripheral vascular disease, and cerebrovascular disease.[10] Long-term management of the disease also carries substantial social and financial implications, such as poor quality of life, increased healthcare costs, and loss of productivity.[4]

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High disease severity, as measured by the extent and number of comorbidities, indicates an ongoing inflammatory response that could predict early mortality.[11] As documented in the literature, Hispanic and African American patients with SLE experience greater disease severity when compared with Caucasian patients.[11,12] Additional studies have reported on the disproportionate SLE mortality rates when compared by ethnicity, as well as certain social determinants like income and access to care.[13–17] The purpose of this study was to utilize a large database of autoimmune patients to evaluate the effect of payor source, race, ethnicity, age, sex, number of autoimmune diagnoses, cost of hospitalization, and length of hospital stay on disease severity among SLE patients.

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Methods

Study Population and Design

The data include 65,535 patients hospitalized in the North Texas Dallas-Fort Worth (DFW) Metropolitan Sta-

tistical Area (MSA) from 1999–2005 with at least one of the following 21 autoimmune diseases listed as a diagnosis: SLE, discoid lupus erythematosus (DLE), rheumatoid arthritis (RA), juvenile RA, Graves' disease, Hashimoto's thyroiditis, autoimmune hepatitis, primary thrombocytopenia (ITP), multiple sclerosis (MS), myasthenia gravis, Raynaud's syndrome, systemic sclerosis, Sjögren's disease, Crohn's disease, ulcerative colitis, primary biliary cirrhosis, celiac disease, IgA nephropathy, dermatomyositis, polymyositis, and autoimmune disease (not otherwise specified). Hospital discharge data were obtained from the DFW Hospital Council (DFWHC), which is a consortium of hospitals in the 12-county DFW MSA that share data to improve quality and clinical outcomes. Utilizing deterministic linkage, patient records were matched and each case was certified as unique. This dataset was chosen for its large sample size, as well as for the multiple ethnicities represented in the DFW area. Variables included in analyses were: ICD-9-CM diagnostic codes (1–9), race, ethnicity, sex, age, length of hospitalization, payor source, cost of hospitalization, and number of autoimmune diseases from the list of 21 diseases. Only patients who were 18 years of age or older were included in the study, and patients with missing data were excluded from analyses. Of the larger sample, 14,829 patients were hospitalized with SLE as a diagnosis (ICD-9-CM 710.0), making it the second most common autoimmune diagnosis from the 21 diseases.

Instrumentation and Analyses

The sample was assessed for disease severity as measured by the SLE Comorbidity Index (SLE CI), which is a total score for the following 14 weighted health conditions: HIV/AIDS (3), any malignancy (4), cerebrovascular accident (2), chronic renal failure (2), congestive heart failure (2), diabetes mellitus (2), nephritis (2), metastatic disease (3), myocardial infarction (3), pericarditis (3), peripheral vascular disease (6), pleuritis (2), severe liver disease (8), and thrombocytopenia (4). Scores on the SLE CI are a weighted sum, ranging from 0 to 46, though it is not possible to have a score of one and scores over 10 are considered to be uncommon. The risk for in-hospital mortality increases as the score on the SLE CI increases. Stepwise linear regressions were utilized to determine if race, ethnicity, age, sex, payor type, number of autoimmune diagnoses, cost of hospitalization, and length of hospitalization are predictive of disease severity in patients with SLE. Additionally, a series of multiple logistic regressions were conducted to examine predictors of individual comorbidities from the SLE Comorbidity Index.

Table 1. Descriptive characteristics of SLE subsample (*N*=14,829)

	Frequency	Percentage
Sex		
Female	13417	90.5
Male	1412	9.5
Race		
African American	5271	35.6
Caucasian	7933	53.5
American Indian/Eskimo/Aleut	19	0.1
Asian or Pacific Islander	197	1.3
Other	1405	9.5
Ethnicity		
Hispanic origin	1788	12.1
Not of Hispanic origin	13037	87.9
Payor Source		
Self pay	1293	8.8
PPO/POS	4341	29.5
HMO	1976	13.5
Medicare	5379	36.6
Medicaid	1459	9.9
Worker's compensation	36	0.2
Unknown	207	1.4

RESULTS

Demographics

As shown in Table 1, the ratio of female to male patients with SLE was 9:1, over half of SLE patients were Caucasian (53.5%), over one third were African American (35.6%), and approximately 12% were Hispanic. The average age for SLE patients was 47 years (SD=16.26) and ranged from 18 to 96 years. The average length of stay was 6.56 days (SD=8.35) and ranged from 1 to 190 days. Total hospitalization charges averaged $27,454 (SD=$48,694), with a minimum recorded charge of $0 and a maximum charge of $1,253,662. SLE patients had an average of 1.17 autoimmune diseases (SD=0.42) with a minimum of one and a maximum of four.

Payor source or method of payment was delineated into the following seven groups: 1) Medicare part A and B (36.6%); 2) PPO/Point of service (POS; 29.5%), 3) HMO (13.5%); 4) Medicaid (9.9%); 5) self-pay (8.8%); 6) unknown (1.4%); and 7) worker's compensation and other federal programs (0.2%). While the most common payor source for all races was Medicare, Caucasian SLE patients had the highest percentage of PPO/POS (33.7%) and the percentage of African American patients on Medicaid was more than two times that of Caucasians (13.7% vs 6.5%). The percentage of Hispanic SLE

Table 2. Multiple regression analyses predicting SLE Comorbidity Index Scores (*N*=14,829)

	b	SE	Beta	*t*	*p*
Caucasian	−0.368	0.04	−0.084	−9.50	.000
Hispanic	0.190	0.06	0.028	3.43	.001
Female	−0.744	0.06	−0.099	−12.30	.000
Age	0.013	0.00	0.094	10.04	.000
Total charge	0.000	0.00	0.126	10.06	.000
Autoimmune diagnoses	−0.015	0.04	−0.003	−0.35	.725
Length of stay	0.010	0.00	0.036	2.89	.004
Self pay	−0.052	0.13	−0.007	−0.42	.676
PPO/POS	−0.286	0.12	−0.059	−2.48	.013
HMO	−0.229	0.12	−0.036	−1.90	.058
Medicare	0.122	0.11	0.027	1.06	.287
Medicaid	−0.119	0.12	−0.016	−0.96	.338

patients on self-pay (18.9% vs 7.4%) and Medicaid (17.6% vs 8.9%) was disproportionate to that of non-Hispanics.

Predictive Factors of SLE

A multiple logistic regression analysis was conducted to examine predictors of SLE. The model used the entire SLE sample and a random sample of 14,829 patients without SLE for the control group. The predictors included: race (Caucasian vs non-Caucasian); ethnicity (Hispanic vs non-Hispanic); sex (female vs male); age at discharge; total hospital charges; number of autoimmune diagnoses; length of stay; disease severity (as measured by the SLE Comorbidity Index); self-pay; PPO/POS; HMO; Medicare; and Medicaid.

The results indicated that Caucasian patients were 47% less likely to have SLE (adjusted OR=0.53, $P<.001$). The odds of having SLE decreased 3.7% per yearly increase in age (OR=0.963, $P<.001$). In addition, having PPO/POS (OR=0.79, $P<.05$), HMO (OR=0.70, $P<.01$), or Medicaid (*OR*=0.78, $P<.05$) predicted lower odds of having SLE. Female patients were nearly three times more likely to have SLE (OR=2.92, $P<.001$) and those with multiple autoimmune diseases were over five times more likely to have SLE (OR=5.34, $P<.001$). This is significant given the fact that all patients in the control group also had at least one autoimmune disease. Additionally, greater total charges and greater disease severity predicted a diagnosis of SLE.

Predictive Factors of Disease Severity

A multiple regression analysis was conducted to examine predictors of disease severity among patients with SLE as measured by SLE Comorbidity Index scores. The predictors included: race (Caucasian vs non-Caucasian); ethnicity (Hispanic vs non-Hispanic); sex; age at discharge; total hospital charges; number of autoimmune diagnoses; length of stay; self-pay; PPO/POS; HMO; Medicare; and Medicaid (Table 2). Results indicated that being Caucasian ($P<.001$), being female ($P<.001$), and having PPO/POS ($P<.05$) predicted lower disease severity scores. Greater disease severity was predicted by being Hispanic ($P<.01$), being older ($P<.001$), having greater total charges ($P<.001$), and having a longer length of hospitalization ($P<.01$).

Predictive Factors of Individual Comorbidities

Using the entire autoimmune patient population ($N=65,535$), a series of multiple logistic regression analyses were conducted to determine the effect of SLE on individual comorbidities from the SLE CI, when adjusted for other covariates (Table 3). For the regressions, age was entered as a continuous covariate and the following were dummy coded to 1 for 'yes' and 0 for 'no': SLE diagnosis, sex (female), race (non-Caucasian), ethnicity (Hispanic). Results indicated that SLE was predictive of eight of the comorbidities and protective of four. SLE had no effect on diabetes or malignancy. SLE patients were over three times more likely to have nephritis (OR=3.30, $P<.0001$), chronic renal failure (OR=3.36, $P<.0001$), and pericarditis (OR=3.2, $P<.0001$), and were over two times more likely to have pleuritis (OR=2.06, $P<.0001$). Additionally, when adjusted for other covariates, SLE patients were 84% more likely to have congestive heart failure, 59% more likely to have had a stroke, 36% more likely to have a diagnosis for acute MI, and 27% more likely to have peripheral vascular disease (PVD). SLE was a protective factor for metastatic disease, thrombocytopenia, severe liver disease, and AIDS.

Another series of logistic regressions were conducted with the SLE patient cohort ($N=14,829$) to evaluate the effect of the following covariates on the individual comorbidities: age, sex (female), race (non-Caucasian), ethnicity (Hispanic). Non-Caucasian SLE patients were more than two times more likely to have chronic renal failure (OR=2.26, $P<.0001$) and nearly two times more likely to have nephritis (OR=1.96, $P<.0001$) and congestive heart failure (*OR*=1.93, $P<.0001$). Additionally, being non-Caucasian predicted increased odds of pericarditis (OR=1.64, $P<.0001$), diabetes (OR=1.41, $P<.0001$), and pleuritis (OR=1.34, $P<.01$). Adjusted for other covariates, Hispanic SLE patients were 62% more likely to have chronic renal failure (OR=1.62, $P<.0001$), 61% more likely to have nephritis (OR=1.61, $P<.0001$), and 55% more likely to have diabetes (OR=1.55,

Table 3. Adjusted odds ratios (OR) and 95% confidence intervals (CI) for individual comorbidities based on SLE (*N*=65,535) and other covariates (*N*=14,829)

Covariates	Malignancy	Metastatic Cancer	Severe Liver Disease	AIDS	Stroke	Pleuritis	Acute MI
SLE							
OR	0.95	0.63†	0.36†	0.16†	1.59†	2.06†	1.36†
CI	0.86–1.05	0.52–0.76	0.26–0.50	0.11–0.22	1.45–1.75	1.83–2.32	1.18–1.58
Age							
OR	1.030†	1.030†	1.028*	0.958*	1.028†	0.989†	1.044†
CI	1.024–1.035	1.020–1.041	1.008–1.047	0.934–0.983	1.023–1.033	0.983–0.995	1.036–1.052
Female							
OR	0.47†	0.83	0.82	0.41	0.90	0.77	0.39**
CI	0.37–0.59	0.49–1.40	0.32–2.08	0.18–0.93	0.70–1.16	0.58–1.00	0.29–0.52
Non-Caucasian							
OR	1.00	1.10	0.93	1.94	1.21	1.34*	1.12
CI	0.83–1.21	0.76–1.58	0.48–1.80	0.94–4.02	1.03–1.43	1.12–1.60	0.85–1.47
Hispanic							
OR	0.55*	0.90	1.27	0.21	0.91	1.13	1.27
CI	0.38–0.80	0.49–1.64	0.49–3.28	0.14–1.53	0.69–1.19	0.88–1.45	0.85–1.90

Covariates	Thrombo-cytopenia	Pericarditis	PVD	Diabetes	Congestive Heart Failure	Nephritis	Chronic Renal Failure
SLE							
OR	0.57†	3.20†	1.27*	1.01	1.84†	3.30†	3.36†
CI	0.53–0.62	2.67–3.85	1.10–1.46	0.96–1.07	1.73–1.96	3.09–3.53	2.95–3.82
Age							
OR	0.989†	0.970†	1.040†	1.037†	1.041†	0.968†	0.984†
CI	0.984–0.993	0.961–0.978	1.032–1.048	1.034–1.040	1.037–1.044	0.965–0.971	0.979–0.990
Female							
OR	0.67†	0.80	0.55**	1.29*	0.58†	0.56†	0.60†
CI	0.55–0.83	0.55–1.15	0.39–0.76	1.08–1.54	0.50–0.67	0.49–0.64	0.48–0.76
Non-Caucasian							
OR	1.00	1.64†	1.10	1.41†	1.93†	1.96†	2.26†
CI	0.86–1.15	1.28–2.09	0.84–1.44	1.27–1.57	1.73–2.15	1.78–2.15	1.89–2.70
Hispanic							
OR	1.12	1.22	1.03	1.55†	0.68†	1.61†	1.62†
CI	0.92–1.38	0.90–1.66	0.67–1.58	1.34–1.80	0.57–0.82	1.43–1.82	1.31–1.99

* $P < .01$
† $P < .0001$

$P<.0001$). Hispanic SLE patients were less likely to have a malignancy and congestive heart failure.

When adjusted for other covariates, being female was a protective factor for malignancy, acute MI, thrombocytopenia, PVD, congestive heart failure, chronic renal failure, and nephritis. Diabetes was the only comorbidity among SLE patients for which sex (female) was predictive. Older age predicted malignancy, metastatic cancer, stroke, acute MI, PVD, diabetes, congestive heart failure, and severe liver disease. Adjusted for other covariates, younger SLE patients were more likely to have pleuritis, thrombocytopenia, pericarditis, nephritis, chronic renal failure, and AIDS.

DISCUSSION

Autoimmune diseases (ADs) disproportionately affect females,[18] and the results of this study support the female-to-male ratio of 9:1 among SLE patients. When adjusted for other covariates, female patients were three times more likely to have SLE. Additionally, younger patients were more likely to be hospitalized with SLE as a diagnosis. Although all patients in the study had at least one autoimmune disease, patients with SLE were more than five times more likely to have multiple ADs. Several research studies have indicated hormones may play a significant role in the greater distribution of SLE among females, along with a common genetic model that may explain the unique etiology of multiple ADs.[18,19] For

When adjusted for other covariates, female patients were three times more likely to have SLE.

example, researchers reported that one particular gene controlled the expression of four individual ADs, such as rheumatoid arthritis, SLE, type 1 diabetes, and Hashimoto's thyroiditis.[20]

The co-existence of additional ADs in SLE may increase the risk for high disease severity and complicate the treatment plan. According to Chambers and colleagues, disease accrual and organ damage was greater in SLE patients with additional ADs when compared to patients with only SLE.[21] Because SLE is non-organ specific, it should be noted that initial flares may result in a diagnosis of an organ specific autoimmune disease. In this study, it is unknown whether SLE was the primary diagnosis which then predisposed patients to secondary ADs, if ADs occurred simultaneously with the SLE diagnosis, or if the SLE diagnosis occurred after another autoimmune diagnosis. However, recognition of the potential for multiple AD diagnoses among SLE patients is important for optimum treatment.

Hispanic, African American, and Asian individuals are two to three times more likely to develop SLE when compared with Caucasians.[22] Consistent with findings from other studies of ethnicity, being Caucasian was a protective factor for SLE in this study. Although genetic predisposition is a factor in the etiology of SLE,[23,24] certain environmental exposures may contribute to the development of SLE. For example, results from studies of identical twins indicate the sibling of an SLE patient has a 24%–69% chance of developing SLE.[24]

Ethnicity also increases the odds of comorbidities indicative of heightened disease severity. Results from this study revealed Hispanic patients with SLE were more likely to have greater disease severity. Though there are many possibilities for this occurrence, Hispanics are three times more likely to be uninsured than other ethnic groups[25] and, in this study, nearly one in five Hispanic SLE patients had self-pay as their payor source. In the U.S., Hispanics are the fast growing ethnic group,[26] as well as the lowest paid minority group.[27] In North Texas, persons of Hispanic origin comprised more than 20% of the total population and more than 40% of uninsured individuals.[28] The lack of economic resources may result in fewer physician visits, lack of access to a rheumatologist and, ultimately, inadequate self-management of the disease. Clearly, social factors such as unemployment, income, and access to health insurance influence the etiology and prognosis of SLE.

The social determinants that factor into disease severity for Hispanic SLE patients are more pronounced when compared to a population with fewer barriers to health care. For example, Puerto Rican SLE patients do not experience as severe a disease state when compared with Hispanics from Texas, despite the genetic predisposition from African American and Native American admixtures and exposure to the sun. Puerto Rican SLE patients have greater access to affordable health care, more formal education, and a better overall SES than Hispanic SLE patients in Texas.[29]

Older age and longer length of hospitalization also predicted greater disease severity. Longer hospital stays were observed in patients with Medicaid when compared to patients with other payor types. Patients with Medicare and self-pay also had longer lengths of stay, while patients with PPO/POS or HMO insurance had the shortest hospital stays. This may suggest that patients with PPO/POS or HMO insurance received ongoing medical care to better manage their disease, thus reducing the potential for active disease states.

In this study, SLE was a significant predictor of eight of the fourteen SLE CI diseases, with the greatest effects for nephritis, chronic renal failure, pericarditis, pleuritis, and congestive heart failure. Except for chronic renal failure, all were among the top 25 principal discharge diagnoses from national SLE inpatient data.[30] The consequences of unmanaged comorbidities may result in hospitalization and increased morbidity or mortality. In this study, congestive heart failure was fourth and coronary atherosclerosis was seventh among all diagnoses for SLE patients. Although not included on the SLE CI, the odds of coronary atherosclerosis were 46% more likely among SLE patients when compared with other autoimmune disease patients. The findings for congestive heart failure and coronary atherosclerosis support prior results indicating increased risk for heart disease in SLE patients when compared with controls.[31,32] Vascular inflammation may result in the progression of SLE, while other factors (e.g., side effects from medications) may also play a role in the advancement of heart disease among SLE patients. Ultimately, SLE patients should receive prompt diagnostics for cardiovascular, pulmonary, and renal complications when symptoms present.

SLE was protective of certain diseases, including AIDS, metastatic cancer, and severe liver disease. Because the SLE CI is a weighted instrument, disease severity specific to SLE may be misrepresented by a score that includes diagnoses for AIDS, metastatic disease, and severe liver disease. Although not represented on the SLE CI, complications resulting from infection are leading causes of hospitalization, multisystem organ failure, and mortality among SLE patients.[10,30] Results from this study revealed that septicemia, bacteremia, and SIRS/sepsis were ranked

22nd, 78th, and 99th among diagnoses of SLE patients, respectively. SLE patients were 74% more likely to have septicemia, 89% more likely to have bacteremia, and over two times more likely to have SIRS/sepsis when compared with other autoimmune disease patients.

The results from the series of SLE patient regressions on individual comorbidities by race indicated non-Caucasian patients were more likely to have chronic renal failure, nephritis, congestive heart failure, pericarditis, diabetes, and pleuritis. Adjusted for other covariates, Hispanic SLE patients were more likely to have chronic renal failure, nephritis, and diabetes, and less likely to have a malignancy and congestive heart failure. For those conditions where SLE was a predictive factor, younger SLE patients were more likely to have nephritis, pericarditis, chronic renal failure, and pleuritis. Because certain groups may be more susceptible to renal and cardiopulmonary complications, it is paramount for physicians to be cognizant of these disparities and make appropriate referrals.

Future research should continue to explore the factors associated with high disease severity in SLE. While the SLE CI is a validated instrument used to predict in-hospital mortality, some illnesses (ie, AIDS) are not common comorbidities in SLE and may underestimate disease severity scores. Researchers should attempt to refine this instrument to better predict disease severity in SLE patients.

Patient histories, medications, and other ambulatory care data were not available in the secondary database, limiting the conclusions related to disease severity prior to hospitalization. However, it is assumed that high disease severity would be related to the diagnoses provided in the hospital data. Considering all patients in the comparison group had at least one autoimmune disease, the effect of SLE on individual comorbidities needs to be evaluated in that context. Using a comparison group more representative of the general population may yield even greater effects for SLE on certain diseases.

In conclusion, improved treatment has lengthened the lifespan of patients with SLE, while also increasing the possibility of additional comorbidities. SLE predicted several comorbidities, such as nephritis, chronic renal failure, pericarditis, congestive heart failure, and pleuritis. Although certain factors had significant effects on SLE disease severity scores, future evaluation of disease severity measures for SLE should include infection related complications.

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AUTHOR CONTRIBUTIONS

Design concept of study: Crosslin, Wiginton
Acquisition of data: Crosslin, Wiginton
Data analysis and interpretation: Crosslin, Wiginton
Manuscript draft: Crosslin, Wiginton
Statistical expertise: Crosslin, Wiginton
Acquisition of funding: Crosslin, Wiginton
Administrative, technical, or material assistance: Crosslin, Wiginton
Supervision: Crosslin, Wiginton