Sex Differences in Disease Severity Among Patients With Systemic Lupus Erythematosus

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ABSTRACT

Background: Systemic lupus erythematosus (SLE), a prototypical autoimmune disease, often results in comorbidities from exposure to medications as well as from chronic inflammation. Identification of gender-based differences in comorbidities and disease severity may assist health practitioners in providing optimum care for those living with SLE.

Objective: The purpose of this study, which utilized hospital discharge data collected during a 7-year period to garner a large SLE patient sample, was to determine the effect of gender on SLE comorbidities and disease severity.

Methods: Patients were hospitalized in the Dallas-Fort Worth metropolitan statistical area between 1999 and 2005 and had a diagnosis of SLE. The sample consisted of 14,829 patients with SLE, 10% of which were male. ANOVAs were conducted to test for differences between males and females for disease severity, age, length of stay in the hospital, total hospital charges, and number of autoimmune diseases. Disease severity was measured with the SLE comorbidity index, which weights 14 conditions in SLE. We identified the top 30 comorbidities as well as the odds of experiencing the secondary illnesses by gender.

Results: Male patients had significantly greater disease severity compared with female patients. Additionally, female patients had more autoimmune diagnoses compared with male patients. Male patients were more likely to have cardiovascular and renal comorbidities compared with female patients. Female patients had significantly greater odds of diagnoses of urinary tract infection, hypothyroidism, depression, esophageal reflux, asthma, and fibromyalgia.

Conclusions: Although the prevalence of SLE among males is rare, male patients have the potential for greater disease severity and are more likely to suffer from cardiovascular and renal disease. Gender differences in disease severity should be further evaluated, but with the added recommendation to develop an index with conditions more indicative of active SLE. (*Gend Med.* 2011;8:365–371)

Key words: comorbidities, disease severity, gender, lupus, SLE.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is the prototypical autoimmune disease, with prevalence in the United States ranging from 1 to 2 million.[1,2] This chronic disease can affect any organ system of the body, but initial manifestation is often vague symptomatology (eg, fatigue, low grade fever, joint pain) that may delay accurate diagnosis. However, treatment and detection of SLE have improved significantly over the last several decades, thus improving the lifespan of patients.[3] As a consequence of improved treatment, a greater number of comorbidities has been identified as a result of exposure to medications, as well as chronic inflammation attributed to SLE itself. For instance, non-Hodgkin lymphoma is the most common cancer observed among patients with SLE, and more aggressive subtypes occur in patients with SLE owing to the use of immunosuppressive medications.[4]

High disease severity, measured by the extent and number of comorbidities, is predictive of poorer prognosis and early mortality.[5] Identification of gender-based differences in comorbidities and disease severity may assist health practitioners in providing optimum care for those living with SLE. Historically, the ratio of female to male patients with SLE has been 9:1; as such, it is difficult to obtain data on male patients to achieve adequate statistical power for comparison. Consequently, conflicting results have been presented regarding gender differences among SLE patients.

According to studies conducted by several researchers,[6–10] no difference in organ involvement has been reported between female and male patients with SLE. However, Pande et al[11] have reported less severe disease among male patients with SLE, whereas others have suggested poorer prognosis for male patients.[12–15] Given the equivocal findings for gender-based differences on disease severity, the present study used hospital discharge data collected during a 7-year period to garner a large SLE patient sample. The purpose of this study was to determine the effect of gender on SLE comorbidities and disease severity.

METHODS

Hospital discharge data were obtained from the Dallas-Fort Worth Hospital Council. Patients for this study were hospitalized in the Dallas-Fort Worth metropolitan statistical area between 1999 and 2005 and had a diagnosis of SLE (*International Classification of Diseases, Ninth Revision, Clinical Modification* 710.0). Deterministic linkage was used to certify each case as unique, yielding a sample of 14,829 patients with SLE.

Descriptive analyses were performed to determine mean age, total charges, length of stay, and the number of autoimmune diseases (of the 21 most prevalent). Separate 1-way ANOVAs were conducted to test for differences between males and females for disease severity, age, length of stay in the hospital, total hospital charges, and number of autoimmune diseases. Disease severity was measured with the SLE comorbidity index (SLE-CI), which weights 14 conditions adapted from the Charlson comorbidity index.[16] The comorbidities (weighted score) are as follows: 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 (2), peripheral vascular disease (6), pleuritis (2), severe liver disease (8), and thrombocytopenia (4). The SLE-CI is scored from 0 to 36, though it is impossible for a patient to have a score of 1. According to the researcher who developed the SLE-CI,[16] scores >10 are uncommon and generally predict in-hospital mortality.

Analyses were performed to identify the top 30 comorbidities observed among female and male patients with SLE. Furthermore, a series of multiple logistic regression analyses were performed to identify the odds of experiencing the top 30 comorbidities by gender. Because only 10% of the sample was male, all males (n = 1412) were included and a random selection of female patients (n = 2824) was selected for comparison. In the analyses, males were coded to 1 and females were coded to 0 (reference). Additionally, gender frequencies were noted for the 14 comorbidities on the SLE-CI and multiple logistic regressions were performed to determine the effect of gender on the SLE-CI. All regression results by gender were adjusted for the effect of age, race, and

Table I. ANOVA of gender on age at discharge, cost of hospitalization (US$ 1999–2005), length of hospitalization, systemic lupus erythematosus (SLE) comorbidity index, and number of autoimmune diseases

Parameter	n	Mean	SD	*F*	*P*
Age, y				10.35	0.001
Female	13,417	47.17	16.23		
Male	1412	48.64	16.55		
Total charge				3.90	0.048
Female	13,417	$27,198	$49,040		
Male	1412	$29,889	$45,226		
Length of stay, d				.61	0.435
Female	13,417	6.54	8.45		
Male	1412	6.72	7.33		
SLE comorbidity index		165.76	.000		
Female	13,417	1.64	2.13		
Male	1412	2.42	2.57		
No. of autoimmune diseases				24.23	0.000
Female	13,417	1.17	0.43		
Male	1412	1.12	0.33		

ethnicity on the presence of comorbidities. Level of significance was set at $P < 0.01$; the level of significance for the logistic regression results is assumed as $P < 0.0001$ unless otherwise noted.

RESULTS

The majority of patients with SLE were female (90.5%), which supports previous findings in the literature. As shown in **Table I**, the average age for SLE patients was 47 (16.26) years, and ages ranged from 18 to 96 years. The average length of stay was 6.56 (8.35) days, and length of stay ranged from 1 to 190 days. From 1999 to 2005, total hospitalization costs averaged $27,454 ($48,694), with a minimum recorded charge of $0 and a maximum charge of $1,253,662. Patients had an average of 1.17 (0.42) autoimmune diseases with a maximum of 4 autoimmune disease diagnoses. The average disease severity score as measured by the SLE-CI was 1.71 (2.19), and scores ranged from 0 to 18.

Separate 1-way ANOVAs (F-tests) were conducted to identify differences between males and females on age at time of discharge, total charge of hospitalization, length of stay, disease severity (SLE-CI), and the number of autoimmune diagnoses. Mean and SD values are presented in **Table I**. The results revealed significant gender differences by age (F [1, 14,827, the degrees of freedom for the ANOVA statistical test] = 10.35; $P < 0.001$), as male patients with SLE were significantly older (48.64 [16.55] years) than female patients with SLE (47.17 [16.23] years).

The results indicated a significant gender difference in disease severity (SLE-CI) (F [1, 14,827] = 165.76; $P < 0.001$). Male patients had significantly greater disease severity (2.42 [2.57]) compared with female patients (1.64 [2.13]). The results also revealed significant gender differences in the number of autoimmune diagnoses, (F [1, 14,827] = 24.23; $P < 0.001$), with female patients having more autoimmune diagnoses (1.17 [0.43]) compared with male patients (1.12 [0.33]). The results failed to reveal significant gender effects on length of stay (F [1, 14,827] = 0.02; $P = 0.435$).

The most common diagnoses for female and male patients with SLE are provided in **Table II**. Being male increased the odds for 12 of the top comorbidities and was a protective factor for 6 comorbidities. In general, male patients with SLE were more likely to have cardiovascular and renal comorbidities compared with female patients with SLE. When adjusted for age, race, and ethnicity,

Table II. Frequency and adjusted odds ratios (OR) (95% CI) for comorbidities among male (M) and female (F) patients with systemic lupus erythematosus

		Males n = 1412	Females n = 13,417	Adjusted OR/95% CI (M = 1412, F = 2824)			
Rank M/F	Diagnosis	No. (%)	No. (%)	OR (M = 1, F = 0)	Lower	Upper	*P*
1/1	Essential hypertension	480 (34.0)	4357 (32.5)	1.02	0.89	1.17	0.765
2/2	Anemia	324 (22.9)	3489 (26.0)	0.84	0.72	0.98	0.026
3/5	Congestive heart failure	271 (19.2)	1602 (11.9)	**1.67**	1.40	2.00	0.0001
4/9	Coronary atherosclerosis	205 (14.5)	1154 (8.6)	**1.69**	1.37	2.07	0.0001
5/4	Hypertensive kidney disease	197 (14.0)	1621 (12.1)	1.19	0.98	1.45	0.075
6/12	Nephritis/nephropathy (acute/chronic not specified)	176 (12.5)	1079 (8.0)	**1.60**	1.29	1.98	0.0001
7/17	Cardiac arrhythmias	169 (12.0)	925 (6.9)	**1.84**	1.47	2.31	0.0001
8/14	COPD	160 (11.3)	1018 (7.6)	**1.60**	1.28	2.01	0.0001
9/3	Diabetes	155 (11.0)	1743 (13.0)	0.79	0.64	0.96	0.021
10/10	Pneumonia	136 (9.6)	1143 (8.5)	1.00	0.80	1.24	0.979
11/21	Acute renal failure	110 (7.8)	658 (4.9)	**1.72**	1.32	2.24	0.0001
12/13	Volume depletion	100 (7.1)	1065 (7.9)	0.79	0.62	1.01	0.059
13/25	Chronic nephritis	90 (6.4)	587 (4.4)	**1.52**	1.14	2.02	0.004
13/NR	Cardiomyopathy	90 (6.4)	408 (3.0)	**2.38**	1.74	3.24	0.0001
14/29	Chronic renal failure	88 (6.2)	527 (3.9)	**1.59**	1.19	2.12	0.002
15/28	Thrombocytopenia (secondary/unspecified)	84 (5.9)	540 (4.0)	**1.65**	1.23	2.22	0.001
16/NR	Venous embolism and thrombosis	79 (5.6)	388 (2.9)	**2.20**	1.59	3.05	0.0001
17/27	Cellulitis and abscess	78 (5.5)	561 (4.2)	1.42	1.05	1.91	0.022
18/16	Seizures	77 (5.5)	951 (7.1)	0.79	0.60	1.04	0.088
19/8	Depression	76 (5.4)	1218 (9.1)	**0.52**	0.40	0.68	0.0001
20/23	Septicemia	74 (5.2)	618 (4.6)	1.22	0.91	1.64	0.187
21/26	Hyperlipidemia (unspecified)	72 (5.1)	570 (4.2)	0.98	0.73	1.31	0.889
22/6	UTI (site not specified)	70 (5.0)	1393 (10.4)	**0.45**	0.34	0.59	0.0001
23/20	Obesity	69 (4.9)	682 (5.1)	0.96	0.72	1.29	0.794
24/15	Asthma	68 (4.8)	990 (7.4)	**0.60**	0.45	0.80	0.0001
24/11	Esophageal reflux	68 (4.8)	1129 (8.4)	**0.57**	0.43	0.75	0.0001
25/NR	Stroke	67 (4.7)	485 (3.6)	1.31	0.96	1.81	0.093
25/NR	Disorders of kidney and ureter (unspecified)	67 (4.7)	387 (2.9)	**1.75**	1.25	2.45	0.001
26/30	Sodium deficiency	65 (4.6)	518 (3.9)	1.25	0.91	1.72	0.172
27/24	Osteoarthrosis	63 (4.5)	605 (4.5)	1.04	0.76	1.43	0.802
27/18	Chest pain	63 (4.5)	724 (5.4)	0.72	0.53	0.97	0.028
27/NR	Pleuritis	63 (4.5)	470 (3.5)	1.11	0.81	1.52	0.512
NR/7	Hypothyroidism (unspecified)	42 (3.0)	1266 (9.4)	**0.25**	0.18	0.35	0.0001
NR/19	Hypopotassemia	49 (3.5)	693 (5.2)	0.66	0.48	0.92	0.015
NR/22	Fibromyalgia	19 (1.3)	636 (4.7)	**0.29**	0.18	0.47	0.0001
NR/30	Osteoporosis	33 (2.3)	518 (3.9)	0.65	0.43	0.97	0.035

COPD = chronic obstructive pulmonary disease; NR = not ranked; UTI = urinary tract infection. Significant findings are highlighted in bold font.

the male patients had 2.4 and 2.2 times the odds of having cardiomyopathy (odds ratio [OR] = 2.38; confidence interval [CI], 1.74–3.24) and venous embolism and thrombosis (OR = 2.2; CI, 1.59–3.05), respectively. Male patients also had greater odds of cardiac arrhythmias (OR = 1.84; CI, 1.47–2.31), acute renal failure (OR = 1.72; CI, 1.32–2.24), coronary atherosclerosis (OR = 1.69; CI, 1.37–2.07), congestive heart failure (OR = 1.67; CI, 1.4–2.0), thrombocytopenia (secondary/unspecified) (OR = 1.65; CI, 1.23–2.22; $P < 0.001$), nephritis (acute/chronic not specified) (OR = 1.6; CI, 1.29–1.98), and chronic obstructive cardiopulmonary disease (OR = 1.6; CI, 1.28–2.01). The female

Table III. Frequency and adjusted odds ratios (OR) (95% confidence interval [CI]) for systemic lupus erythematosus comorbidity index (SLE-CI) diagnoses

	Males N = 1412	Females N = 13,417	Adjusted OR/95% CI (M = 1412, F = 2824)			
SLE-CI Category	No. (%)	No. (%)	OR (M = 1, F = 0)	Lower	Upper	*P*
Nephritis	337 (23.9)	2128 (15.9)	**1.77**	1.50	2.10	0.0001
Diabetes	155 (11.0)	1743 (13.0)	0.79	0.64	0.96	0.021
Congestive heart failure	271 (19.2)	1602 (11.9)	**1.67**	1.40	2.00	0.0001
Thrombocytopenia	108 (7.6)	717 (5.3)	**1.61**	1.24	2.08	0.0001
Chronic renal failure	88 (6.2)	527 (3.9)	**1.59**	1.19	2.12	0.002
Stroke	67 (4.7)	485 (3.6)	1.31	0.96	1.81	0.093
Pleuritis	63 (4.5)	470 (3.5)	1.11	0.81	1.52	0.512
Malignancy	98 (6.9)	441 (3.3)	**2.36**	1.75	3.19	0.0001
Pericarditis	34 (2.4)	268 (2.0)	1.33	0.86	2.07	0.197
Peripheral vascular disease	43 (3.0)	216 (1.6)	**2.23**	1.43	3.47	0.0001
Acute myocardial infarction	56 (4.0)	201 (1.5)	**2.73**	1.81	4.13	0.0001
Metastatic cancer	16 (1.1)	121 (0.9)	1.07	0.58	1.98	0.830
Severe liver disease	5 (0.4)	37 (0.3)	0.87	0.30	2.52	0.798
HIV/AIDS	7 (0.5)	30 (0.2)	4.06	1.18	13.96	0.026

Significant findings are highlighted in bold font.

patients had significantly greater odds of diagnoses for urinary tract infection (OR = 0.45; CI, 0.34–0.59), hypothyroidism (OR = 0.25; CI, 0.18–0.35), depression (OR = 0.52; CI, 0.40–0.68), esophageal reflux (OR = 0.57; CI, 0.43–0.75), asthma (OR = 0.60; CI, 0.45–0.80), and fibromyalgia (OR = 0.29; CI, 0.18–0.47).

Frequencies and adjusted ORs for the SLE-CI are provided in **Table III**. The frequencies of nephritis and thrombocytopenia are higher for the SLE-CI due to the combination of diagnoses for the index. Male patients with SLE had increased odds for 7 of the comorbidities on the SLE-CI. When adjusted for age, race, and ethnicity, the most significant effects by gender (male) were found for acute myocardial infarction (OR = 2.73; CI, 1.81–4.13), malignancy (OR = 2.36; CI, 1.75–3.19), peripheral vascular disease (OR = 2.23; CI, 1.43–3.47), and nephritis (OR = 1.77; CI, 1.50–2.10). Specific to the malignancy category of the SLE-CI, non-Hodgkin lymphoma was the most frequent cancer diagnosis among patients in this study. Adjusted for age, race, and ethnicity, male patients with SLE were >4 times more likely to have a diagnosis of non-Hodgkin lymphoma (OR = 4.27; CI, 2.55–7.15; $P < 0.0001$).

DISCUSSION

Gender Effect on Individual Comorbidities

Overall, male patients with SLE were more likely to have cardiovascular and renal comorbidities. Although cardiomyopathy (13th) and venous embolism and thrombosis (16th) were among the most common comorbidities for male patients (**Table II**), these diagnoses were not among the most common diagnoses for female patients with SLE. Furthermore, the male patients were 84% more likely to have a diagnosis of cardiac arrhythmia, 69% more likely to have a diagnosis of coronary atherosclerosis, and 67% more likely to have a diagnosis of congestive heart failure. These findings are consistent with results from another study,[17] which indicated that male patients with SLE were 82% more likely to have cardiovascular complications compared with female patients.

In the present study, the male patients had 72% greater odds of acute renal failure and 59% greater odds of chronic renal failure (**Table II**). Nephritis (acute/chronic not specified), chronic nephritis, and disorders of the kidney and ureter (unspecified) were also more common among male patients. Overall, these findings are supported by prior studies, indicating that male patients with SLE are at greater risk of renal dis-

ease.[14,17–19] Life-threatening infections can occur in renal patients,[20] and these patients should be closely monitored. Of the most common diagnoses, urinary tract infection, hypothyroidism (unspecified), depression, esophageal reflux, asthma, and fibromyalgia were the most common among female patients with SLE.

Gender Effect on SLE-CI

SLE disease severity was measured with the SLE-CI, which consists of 14 weighted comorbidities. Male patients were more likely to have greater disease severity scores and had greater odds of 7 of the 14 diagnoses on the SLE-CI. The greatest gender effect occurred for acute myocardial infarction, peripheral vascular disease, nephritis, and malignancy (**Table III**). Non-Hodgkin lymphoma was the most frequent cancer diagnosis among the patients in this study, and male patients were >4 times more likely than female patients to have this diagnosis.

The comparison of our results to other studies is problematic because different instruments/methodologies were used to measure disease severity. Additionally, these studies had small samples of males in comparison to females, making it difficult to detect statistically significant differences between genders. Molina et al[14] defined disease severity as the number of patients with renal disease, cardiovascular disease, and neurologic involvement (N = 1209; males = 107). According to the researchers, males experienced more renal disease and vascular thrombosis compared with females. These findings are supported by results from the present study. In contrast, Voulgari et al[19] employed the European Consensus Lupus Activity Measurement and damage index and reported no difference in damage index scores between genders. Importantly, the number of males included in the study was quite small (n = 68) and thus lacked the statistical power to reveal a gender effect. In another study, researchers measured disease severity using the SLE Disease Activity Index and found no difference in severity between genders (N = 1214; males = 123). However, male patients generally had worse health outcomes and were significantly more likely to have renal and cardiovascular complications.[17]

Limitations

Although this study had the largest sample of male patients with SLE to date and suggests that male patients are more likely to have serious comorbidities, there were some limitations. The data set was very large and some minimal differences revealed statistical significance. To account for this, a random sample of female patients with SLE was selected for comparisons with the male SLE patient population. Patient histories, medications, and long-term data were not available in the secondary database, limiting any conclusions to be drawn about disease severity over time. Although this information was not available, we assumed that high disease severity would be related to the diagnoses provided in the hospital data. Future studies could involve the review of principal and secondary diagnoses to provide a more thorough evaluation of acute disease activity.

CONCLUSIONS

In the population studied, this study indicated a significant effect by gender on SLE disease severity and individual comorbidities indicative of a more serious prognosis. The study used a larger sample of male patients (n = 1412) compared with other SLE gender studies and yielded some interesting findings. Some of the comorbidities on the SLE-CI are not considered to be associated with SLE (eg, severe liver disease, AIDS), whereas other commonly associated conditions of SLE severity (eg, sepsis, systemic inflammatory response syndrome, seizures) are not included on the index. Thus, disease severity specific to patients with SLE may be underestimated in this study. Although the prevalence of SLE among males is rare, males have the potential for greater disease severity and are more likely to suffer from cardiovascular and renal disease. Gender differences in disease severity should be further evaluated, but with the added recommendation to develop an index more in line with conditions indicative of active SLE.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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Drs. Crosslin and Wiginton designed and monitored the study. Dr. Wiginton performed the statistical analyses. Dr. Crosslin authored the Introduction, Methods, and Discussion sections; Dr. Wiginton authored the Results section.

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