Atrial Fibrillation/Flutter Hospitalizations among U.S. Medicaid Recipients with and without Systemic Lupus Erythematosus

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ABSTRACT

Objective

Systemic lupus erythematosus (SLE) is a multi-system chronic inflammatory autoimmune disease with high prevalence of several risk factors for atrial fibrillation/flutter (AF). However, the incidence and risk of AF in SLE have not been well quantified.

Methods

We used U.S. Medicaid Analytic eXtract from 2007-2010 to identify beneficiaries ages 18-65, with prevalent SLE, each matched by age and sex to four non-SLE general Medicaid recipients. We estimated the incidence rates (IR) per 1,000 person-years (PY) for AF hospitalizations and used multivariable Cox regression to estimate the hazard ratio (HR) for AF hospitalization.

Results

We identified 46,876 U.S. Medicaid recipients with SLE, and 187,504 age- and sex-matched non-SLE controls (93% female; mean age 41.5±12.2). Known AF risk factors such as hypertension, cardiovascular disease (CVD) and kidney disease were more prevalent in SLE patients. During a mean follow-up of 1.9±1.1 years for SLE, and 1.8±1.1 years for controls, the IR per 1,000 PY for AF was 1.4 (95% CI 1.1-1.6) among SLE patients and 0.7 (95% 0.6-0.8) among non-SLE controls. In age- and sex- matched and race-adjusted Cox models, the HR for AF was 1.79 (95%CI 1.43-2.24); after adjustment for baseline hypertension and CVD, the adjusted HR was reduced to 1.17 (95%CI 0.92-1.48).

Conclusions

SLE was associated with doubled rate of hospitalization for AF compared to age- and sex-matched general Medicaid patients. In a race-adjusted model, the risk was 80% higher. However, the AF risk factors hypertension and CVD were more prevalent among SLE patients and accounted for the excess risk.

Keywords:

Systemic lupus erythematosus

Cardiovascular disease

Atrial fibrillation

Medicaid

INTRODUCTION

Atrial fibrillation and flutter (AF), common cardiac arrhythmias, are associated with increased morbidity and mortality[1,2]. Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease characterized by autoantibody production and systemic inflammation, as well as high burden of cardiovascular disease (CVD)[3,4]. AF is also known to increase the risk of stroke[5,6], which is elevated among SLE patients[7–10]. Studies of CVD in SLE patient populations have focused mainly on the outcomes of ischemic heart disease and strokes, with little evidence regarding the risk of AF among SLE compared to the general population[11,12].

Risk factors for AF, which include hypertension, obesity, CVD, heart failure, valvular heart disease, and chronic kidney disease, are all more prevalent among patients with SLE than in the general population[13–15]. Systemic inflammation itself has been implicated in the pathogenesis of AF[16–18]. In other chronic inflammatory diseases, such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), studies have shown an increased risk of AF compared to age- and sex-matched controls, although with conflicting results after adjustment for known AF risk factors[19–22].

The objective of this study was to investigate rates, risks, and risk factors for AF among U.S. Medicaid patients with SLE and compare them to those of age- and sex-matched general Medicaid patients. As SLE patients have chronically elevated systemic inflammation, we hypothesized that the rates and risks of AF would be elevated among SLE compared to the general population related both to known AF risk factors, as well as to SLE itself.

METHODS

Data Source and Cohort Definitions

We used the Medicaid Analytic eXtract (MAX), a database that includes billing claims, demographic information and medication dispensing data for patients in Medicaid, the U.S. health insurance for low-income individuals. We identified adults aged 18-65 years residing in the 29 most populated states in the U.S., who were enrolled in Medicaid between January 1, 2007 and December 31, 2010. We did not obtain claims data for patients over age 65, as they may be dually eligible for both Medicaid and Medicare, and thus they were not included in this study.

Prevalent SLE was defined as having $\geq$ 3 International Classification of Diseases, Ninth Revision (ICD-9) codes for SLE (710.0) from hospital discharge diagnoses or physician visit claims, each $\geq$ 30 days apart, as in our prior studies[23]. A prior validation study using Canadian administrative claims showed sensitivity of 98.2% and specificity of 72.5% using $\geq$2 two SLE billing diagnoses at least 2 months apart[24]; our algorithm required at least 3 SLE billing diagnoses in an attempt to increase our specificity. We required a six-month period of continuous enrollment for collection of baseline covariable data prior to the index date, which was defined as the date that our definition of SLE was met. If the date of the third ICD-9 code for SLE occurred before the six-months of continuous enrollment criteria could be met, the next SLE-related claim allowing for a six-month baseline period thereafter was defined as the index date.

We matched each SLE patient by age at index date (within one month) and sex to four general Medicaid population patients who had ICD-9 codes for any non-SLE diagnoses from hospital discharge diagnoses or physician visit claims on the same index date as the matched SLE patient[25]. We required a six-month baseline period of continuous enrollment prior to the assigned index date, and patients with any SLE ICD-9 codes during the baseline period were excluded from the general Medicaid cohort. For both SLE and general Medicaid cohorts, the baseline period was defined as the six months before and including the index date. For both cohorts, we excluded patients with AF during the baseline period.

Baseline Covariable Assessment

Patient characteristics for all cohorts were collected during the baseline period: age, sex, self-reported race/ethnicity, U.S. region of residence, zip code-level median household income from 2010 U.S. Census data in quartiles as a proxy for socioeconomic status (SES). Using ICD-9, Diagnosis Related Group code (DRG) and/or Current Procedural Terminology (CPT) codes, we collected covariables in the baseline period, including the number of outpatient physician visits, smoking, obesity, hypertension, diabetes, hyperlipidemia, thyroid disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart failure, valvular disease, cardiac surgery, pericarditis/myocarditis using $\geq$1 ICD-9 code[1,26–30]. In the SLE cohort, lupus nephritis patients were defined as having $\geq$2 ICD-9 hospital discharge diagnoses or physician billing claims for nephritis, proteinuria, and/or renal failure, occurring $\geq$ 30 days apart, on or after the SLE criteria were met[31,32]. CVD at baseline was defined as the presence of any of the following covariables during the baseline period: acute myocardial infarction, old myocardial infarction, angina, coronary atherosclerosis, percutaneous coronary intervention, coronary artery bypass

graft, cerebrovascular accident, peripheral vascular disease, carotid artery stenosis, and heart failure[33–40].

We calculated a Charlson comorbidity index for all patients and SLE-specific risk adjustment index for SLE patients[41,42]. We identified filled prescriptions using National Drug Codes (NDC) and summed the number of unique medications filled per subject during the baseline period. We assessed baseline prescriptions filled for anticoagulants, beta-blockers, statins, and angiotensin converting enzyme inhibitor/angiotensin receptor blockers. We assessed prescriptions for glucocorticoid use (prednisone, methylprednisolone, dexamethasone, hydrocortisone, prednisolone, and cortisone defined as prednisone equivalents), hydroxychloroquine, and immunosuppressive drugs (mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab, and tacrolimus).

Outcomes

The primary outcome was incident AF hospitalization defined by ICD-9 codes 427.31 (atrial fibrillation), 427.32 (atrial flutter) for either primary or secondary hospital discharge diagnosis codes[43]. Patients were followed from index date until first AF hospitalization, death, disenrollment or end of follow-up.

Statistical Methods

We calculated unadjusted AF incidence rates (IR) per 1,000 person-years with 95% confidence intervals (CI). We used proportional hazards models accounting for competing risk of death to estimate the subdistribution hazard ratios (HR) for incident AF hospitalization in SLE,

compared to the general Medicaid cohort in sequential models, examining potential confounders of the association between SLE and AF[44]. We first ran an age- and sex-matched model adjusted for race/ethnicity in model 1. To build parsimonious models given the low number of events, we examined potential confounders individually to identify variables that changed the point estimate by ≥10%. In model 2, we additionally adjusted for the two variables that had the largest effect on the point estimate (CVD and HTN). Adjustment for other covariates that changed the point estimate by ≥10% did not further influence risk estimates. We also stratified SLE patients by baseline glucocorticoid use (yes/no) and ran our final Cox model in each group.

We performed all analyses using SAS version 9.4 using data obtained from Centers for Medicare and Medicaid Services through approved Data Use Agreements and data are presented according to Federal reporting guidelines. The Partners' Institutional Review Board approved all aspects of this study (IRB# 2013P002602).

RESULTS

The SLE cohort included 46,876 patients and the general Medicaid cohort included 187,504 patients (**Table 1**). The mean age for patients in both cohorts was 41.5 (±12.2) years and 93% were female. The mean follow-up durations were 1.9 (±1.1) years for SLE and 1.8 (±1.1) years for the general Medicaid cohorts. A higher proportion of SLE patients were African American by self-report compared to the general Medicaid population (42% compared to 22%). SLE patients had higher prevalence of baseline hypertension, hyperlipidemia, diabetes mellitus, smoking, valvular disease, CVD, thyroid disease and use of anticoagulants, beta-blockers, and

statins compared to the general Medicaid cohort. Among the SLE cohort, 41% used glucocorticoids during the baseline period compared to 6% of the general Medicaid cohort.

During the follow-up period, there were 121 AF hospitalization events in the SLE cohort (IR 1.4 per 1000 person-years [95% CI 1.1-1.6]) and 241 AF hospitalization events in the general Medicaid cohort (IR 0.7 per 1000 person-years [95% CI 0.6-0.8]) (**Table 2**). The IR of AF was higher in males and increased with age in stratified age groups for both SLE and non-SLE patients and remained higher in the SLE cohort across all age categories compared to general Medicaid. The IR of AF for both cohorts was higher among patients with hypertension, valvular disease, lupus nephritis/renal disease, and CVD.

In race/ethnicity adjusted Cox regression model, the risk of incident AF hospitalization among SLE patients was 1.79-fold higher (95% CI 1.43-2.24) than the age- and sex-matched general Medicaid population (**Figure 1**). We identified baseline CVD, hypertension, lupus nephritis/CKD, valvular disease, and Charlson comorbidity index as variables that changed the point estimate by >10% when each was separately added to the race/ethnicity adjusted model (**Supplemental Table S1**). The strongest attenuation in HR was seen when additionally adjusted for CVD, and hypertension. The risk estimate was attenuated and became non-significant in a combined model adjusting for race/ethnicity, CVD and hypertension (HR 1.17, 95% CI 0.92-1.48). No further adjustment affected risk estimates (**Supplemental Table S1**). Additionally, when we stratified SLE patients by baseline glucocorticoid use, there was no significant increased risk of AF in SLE patients with and without baseline glucocorticoid use in our adjusted models.

DISCUSSION

In this large cohort study of U.S. Medicaid patients, the IR of hospitalization for AF among SLE patients was approximately double than that of Medicaid patients matched for age and sex who did not have SLE. This increased rate of AF for patients with SLE was observed across all age groups. The relative risk of AF among SLE patients was nearly 80% higher than age-and sex-matched general Medicaid population controls when adjusted for race/ethnicity. Most of the excess risk of AF among patients with SLE was accounted for by high prevalence of hypertension and CVD, and to a lesser extent by renal disease, valvular disease, and Charlson comorbidity index. Thus, SLE is associated with increased prevalence of important risk factors for AF, including hypertension, CVD, which appear to be responsible for the increased incidence of AF hospitalizations observed.

These results have clinical and epidemiological significance for several reasons. This Medicaid cohort is the largest to assess incident AF across a broad age range of SLE patients. In a retrospective study of 235 SLE patients at a single academic center, investigators reported a prevalence of 9% for atrial fibrillation and 3% for atrial flutter[45]. A phenome-wide association study of 1,097 SLE patients demonstrated an association between SLE disease status and AF, and increased incidence of AF in male patients, a finding which was also seen in our SLE and general Medicaid patients[11]. However, the phenome-wide association study was unable to account for potential mediating factors such as hypertension and valvular heart disease.

In a recent study by Lim *et al.* using the Korean National Health Insurance Service National Sample Cohort database from 2008-2014, the IR of AF among 21,143 SLE patients was

3.69 compared to 0.94 per 1,000 person-years in age and sex-matched non-SLE controls[12]. The Korean study included both inpatient and outpatient AF, which likely explains the much higher rates of AF in both the SLE and non-SLE controls compared to our study. After multivariable adjustment, the HR for AF remained 2.84-fold higher than that of controls (95% CI 2.50-3.23) in the study by Lim *et al*. While their multivariable models adjusted for age, sex, income and many relevant comorbidities (diabetes, hypertension, dyslipidemia, COPD, end-stage renal disease, myocardial infarction, stroke and heart failure), the definition of CVD used in our multivariable adjustment included more cardiovascular variables.

Our hypothesis that the risk of hospitalizations for AF would be higher among SLE patients was based on several studies that have implicated the role of inflammation in the pathogenesis of AF. Cardiac biopsies from patients with AF have demonstrated inflammatory infiltrates on histology, and have also been observed in animal models with AF[46,47]. Key markers of inflammation, including interleukin (IL)-6, C-reactive protein, tumor necrosis factor-α, have also been found to be associated with AF[16,17,48,49], and are also known to be dysregulated in SLE[50]. Additionally, in a study of AF risk among inflammatory bowel disease patients, elevated AF risk was significantly higher during active flares and persistent activity, while there was decreased AF risk observed during periods of remission, further supporting the notion that active inflammation may be involved in the pathogenesis of AF[20].

We found that the elevated IR observed in SLE was related to the increased prevalence of hypertension, valvular disease, lupus nephritis/CKD, and CVD compared to the overall general Medicaid population. Hypertension is one of the most important risk factors for AF and adjusting for hypertension and baseline CVD accounted for a substantial portion of the elevated

risk for incident AF hospitalization. Including hypertension and CVD in the model attenuated the elevated risk for incident AF hospitalization. Our finding of attenuated risk after accounting for traditional AF risk factors do not discount the possibility that SLE-related inflammation plays an important role in increasing the risk of AF. Lupus nephritis, valvular disease, and CVD all represent states of high disease activity and inflammation in SLE and thus are likely intermediates on the pathway to higher risk of AF.

Glucocorticoids may also affect the risk of AF, but we observed no significant increase in AF risk among SLE patients in analyses stratified by glucocorticoid use during the 6-month baseline period. While it is possible that glucocorticoid dose may affect the risk of AF, glucocorticoids are frequently used in SLE management (41% of our cohort) but rarely used in non-SLE controls (6%). Thus, we did not include glucocorticoid dose in our main analysis comparing the risk of AF in SLE to non-SLE controls, as this would additionally adjust for SLE cohort status given the frequent use of glucocorticoids in SLE patients compared to the general Medicaid controls. Additionally, how the use and dose of glucocorticoids may mediate the association between SLE and AF is of interest for future studies.

Apart from inflammation, it is also possible that conditions such as valvular disease and renal disease could have led structural and metabolic mechanisms promoting higher risk of AF. Furthermore, it is unknown how the presence of antiphospholipid antibodies or the use of non-steroidal anti-inflammatory drugs which are not reliably captured in claims studies, contribute to the risk of AF.

Our study has several key strengths and some limitations. We employed ICD-9 codes to identify AF with reported sensitivity of 95%, specificity of 99%[43], and identified AF hospitalizations with primary or secondary codes without the use of outpatient claims. This likely decreased the sensitivity of capturing all incident AF, particularly as patients may present with symptoms of AF and occasionally are managed solely in the outpatient setting without requiring hospitalization. We did not include outpatient AF as algorithms for its identification have not been validated and prevalent AF diagnoses may be repeatedly observed in claims data. Thus our outcome was restricted to AF that led to hospitalization and decreased the risk of ascertainment bias as age- and sex-matched non-SLE patients may have less contact with the healthcare system, as noted by the lower frequency of outpatient visits among those without SLE in the baseline period. However, adjustment for the number of outpatient visits in our models did not significantly change our effect estimates (**Supplemental Table S1**).

Our SLE cohort was a prevalent cohort in which we excluded those with baseline AF to assess risk for incident AF. Given the short duration of follow-up and use of hospitalization codes only, these elevated IRs for AF among SLE patients are likely underestimates. We defined baseline covariates by at least one ICD-9 code, which may not accurately capture these covariates. For example, covariates without billing codes during the 6-month baseline period would not be captured while alternatively we may have captured some covariates using one ICD-9 code which may have been used for billing while ruling out a diagnosis. Due to the nature of administrative data, we were unable to assess SLE disease duration, disease activity or active inflammation. This is of importance as periods of flare activity and inflammation are likely to be involved in driving the risk of AF. We used a validated algorithm for defining lupus nephritis[32].

However, the algorithm potentially does not capture all patients with lupus nephritis due to the number of codes required to be classified. Furthermore, most Medicaid patients who develop end-stage renal disease from SLE or other causes change insurance coverage to Medicare and thus these claims could not be captured. Our study was conducted in US Medicaid recipients and we excluded patients over age 65 as we do not have claims data for patients dually eligible for both Medicaid and Medicare. While the Medicaid program represents a significant percentage of the U.S. population with a high burden of chronic diseases including SLE, this may limit the generalizability of our findings for patients with commercial insurance and those of older age.

In conclusion, we found an increased incidence of AF among SLE patients enrolled in Medicaid compared to age- and sex-matched general Medicaid population. The risk of AF for patients with SLE was double of that for patients without SLE. This risk appeared to be due to the associations between SLE and common risk factors for AF, including hypertension and CVD. Further work should target modifying the risk factors for AF identified in this study in an effort to decrease the risk of AF among patients with SLE.

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DISCLOSURES

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Figure 1. Sub-distribution hazard ratios (HRsd)* (95% CI) for incident hospitalization for atrial fibrillation/flutter among SLE compared to age- and sex-matched general Medicaid population

*HRsd: Hazard ratio for first atrial fibrillation/flutter hospitalization event, competing risk analysis taking risk of death into account
Model 1: matched on age and sex + adjusted for race/ethnicity
Model 2: Model 1 + hypertension and CVD

Table 1. Baseline* characteristics for SLE, age- and sex-matched general Medicaid cohorts, 2007-2010

	SLE	General Medicaid
Matched Cohort size (N)	**46,876**	**187,504**
Female, %	93	93
Mean age in years (age, SD)	41.5 (12.2)	41.5 (12.2)
U.S. Region of Residence, %		
West	19	27
Northeast	20	19
South	41	34
Midwest	20	20
Race/Ethnicity, %		
White	35	46
African American	42	22
Hispanic	16	25
Asian	3	3
American Indian/Alaskan Native	1	1
Lupus nephritis/Chronic kidney disease, %	19	2
Hypertension, %	37	15
Hyperlipidemia, %	12	7
Obesity, %	5	4
Smoking, %	7	4
CVD†, %	16	6
Heart failure, %	7	2
Diabetes mellitus, %	14	10
Valvular disease, %	6	1
Pericarditis/myocarditis, %	1	<1
Cardiac surgery, %	6	2
Thyroid disease, %	8	3
COPD, %	12	5
Number of outpatient visits (mean, SD)	4.7 (4.8)	1.9 (3.1)
Number of medications (mean, SD)	10.7 (10.3)	3.9 (6.0)
Anticoagulant use, %	6	<1
Beta-blocker use, %	12	5
Statin use, %	10	6
ACE inhibitor/ARB use, %	21	8
Hydroxychloroquine use, %	36	<1
Immunosuppressants‡, %	19	<1
Glucocorticoid use ≥ 10 mg/day ever, %	41	6

Charlson Comorbidity Index (mean, SD)	2.0 (1.5)	0.5 (1.3)

*Baseline is the six-month period prior to and including the index date.
†CVD: Baseline presence of any cardiovascular disease (CVD) by ICD-9 codes for acute myocardial infarction, old myocardial infarction, angina, coronary atherosclerosis, percutaneous coronary intervention, coronary artery bypass graft, cerebrovascular accident, peripheral vascular disease, carotid artery stenosis, heart failure
‡Immunosuppressant: mycophenolate mofetil, mycophenolic acid, cyclophosphamide, azathioprine, cyclosporine, methotrexate, leflunomide, rituximab and tacrolimus
SLE: systemic lupus erythematosus; CVD: cardiovascular disease; ACE inhibitor/ARB: angiotensin converting enzyme inhibitor/angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease

Table 2. Incidence rates for atrial fibrillation/flutter within the SLE and general Medicaid cohorts from 2007-2010 by baseline covariates

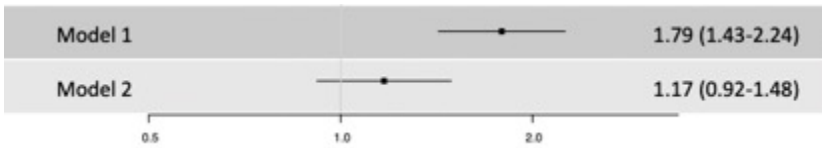
	SLE				General Medicaid			
	N	Events	Person-Years	Incidence rate (95% CI)	N	Events	Person-Years	Incidence rate (95% CI)
All patients	46,876	121	89,494	1.4 (1.1-1.6)	187,504	241	333,216	0.7 (0.6-0.8)
Age 18-39	21,139	27	39,789	0.7 (0.5-1.0)	84,461	-	-	0.1 (<0.1-0.1)
Age 40-49	12,552	29	24,153	1.2 (0.8-1.7)	50,340	42	91,389	0.5 (0.3-0.6)
Age 50-65	13,185	65	25,552	2.5 (2.0-3.2)	52,703	191	98,665	1.9 (1.7-2.2)
Sex								
Female	43,482	106	83,296	1.3 (1.1-1.5)	173,928	210	309,555	0.7 (0.6-0.8)
Male	3,394	15	6,198	2.4 (1.5-4.0)	13,576	31	23,661	1.3 (0.9-1.9)
Hypertension								
No	29,558	44	56,138	0.8 (0.6-1.1)	159,156	136	280,572	0.5 (0.4-0.6)
Yes	17,318	77	33,356	2.3 (1.9-2.9)	28,348	105	52,644	2.0 (1.6-2.4)
Valvular disease								

No	43,838	102	83,720	1.2 (1.0-1.5)	184,878	219	328,700	0.7 (0.6-0.8)
Yes	3,038	19	5,773	3.3 (2.1-5.2)	2,626	22	4,516	4.9 (3.2-7.4)
Lupus nephritis/CKD								
No	37,789	74	69,972	1.1 (0.8-1.3)	328,135	230	5,081	0.7 (0.6-0.8)
Yes	9,087	47	19,521	2.4 (1.8-3.2)	5,081	11	328,418	2.2 (1.2-3.9)
CVD†								
No	39,352	69	75,415	0.9 (0.7-1.2)	177,048	163	314,620	0.5 (0.5-0.6)
Yes	7,524	52	14,079	3.7 (2.8-4.8)	10,456	78	18,596	4.2 (3.4-5.2)
Glucocorticoid use								
No	27,664	65	51,812	1.3 (1.0-1.6)	176,722	223	315,156	0.7 (0.6-0.8)
Yes	19,212	56	37,682	1.5 (1.2-1.9)	10,782	18	18,060	1.0 (0.6-1.6)

*IR: per 1000-person years

†CVD: Baseline presence of any cardiovascular disease (CVD) by ICD-9 codes for angina, myocardial infarction, old myocardial infarction, percutaneous coronary intervention, atherosclerosis, cerebrovascular accident, coronary artery bypass graft, peripheral vascular disease, carotid stenosis, heart failure

- Cell sizes under 11 are suppressed according to Federal Reporting Requirements.



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