Outcomes of atrial fibrillation hospitalizations in patients with systemic lupus erythematosus: a report from the national inpatient sample

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2020-001707).

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Accepted 23 December 2020

To cite: Rivera Pavon MM, Shahi A, Akuna E, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2020-001707

ABSTRACT

This study compares outcomes of patients admitted for atrial fibrillation (AF) with and without coexisting systemic lupus erythematosus (SLE). The primary outcome was inpatient mortality. Hospital length of stay (LOS), total hospital charges, odds of undergoing ablation, pharmacologic cardioversion and electrical cardioversion were secondary outcomes of interest. Data were abstracted from the National Inpatient Sample (NIS) 2016 and 2017 database. The NIS was searched for adult hospitalizations with AF as principal diagnosis with and without SLE as secondary diagnosis using International Classification of Diseases, Tenth Revision, Clinical Modification codes. Multivariate logistic and linear regression analysis was used accordingly to adjust for confounders. There were over 71 million discharges included in the combined 2016 and 2017 NIS database. 821,630 hospitalizations were for adult patients, who had a principal diagnosis of AF, out of which, 2645 (0.3%) had SLE as secondary diagnosis. Hospitalizations for AF with SLE had similar inpatient mortality (1.5% vs 0.91%, adjusted OR (AOR): 1.0, 95% CI 0.47 to 2.14, p=0.991), LOS (4.2 vs 3.4 days, p=0.525), total hospital charges ($51,351 vs $39,121, p=0.056), odds of undergoing pharmacologic cardioversion (0.38% vs 0.38%, AOR: 0.90, 95% CI 0.22 to 3.69, p=0.880) and electrical cardioversion (12.9% vs 17.5%, AOR 0.87, 95% CI 0.66 to 1.15, p=0.324) compared with those without SLE. However, SLE group had increased odds of undergoing ablation (6.8% vs 4.2%, AOR: 1.9, 95% CI 1.3 to 2.7, p<0.0001). Patients admitted for AF with SLE had similar inpatient mortality, LOS, total hospital charges, likelihood of undergoing pharmacologic and electrical cardioversion compared with those without SLE. However, SLE group had greater odds of undergoing ablation.

Significance of this study

What is already known about this subject?
- Systemic lupus erythematosus (SLE) is known to increase the risk of developing multiple adverse cardiovascular conditions.
- Atrial fibrillation (AF) is one of these cardiovascular conditions which patients with SLE are at increased risk of developing.
- It is, however, unclear if patients with SLE have worse outcomes when hospitalized for AF compared to similar AF patients without SLE.

What are the new findings?
- SLE does not increase inpatient mortality in AF hospitalizations.
- SLE does not negatively impact outcomes of hospitalizations for AF.
- Hospitalized AF patients with SLE had increased odds of receiving ablation compared with those without SLE.

How might these results change the focus of research or clinical practice?
- Further studies comparing odds of ablation in AF patients with and without coexisting SLE are needed.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease with a prevalence ranging from 0.3 to 241 per 100,000 population.[1] Cardiovascular diseases (CVD) are among the causes of premature death in patients with SLE and include coronary artery disease, valvular disease, heart failure, conduction system disturbances, and arrhythmias.[2 3] Within the tachycardias, sinus tachycardia, atrial fibrillation (AF), and atrial ectopy are among the most commonly seen.[4] AF is a common arrhythmia, and it is associated with increased morbidity and mortality.[5 6] 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.[7–9] Additionally, SLE has been identified as an independent risk factor for AF, which often develops in a younger age group compared with the general population.[10] The chronic inflammatory state, the multiple coexistent CVD comorbidities, and the known cardiotoxic effects of SLE therapeutic agents are among the multiple hypothesized mechanisms leading to cardiac involvement and atrial fibrosis that predispose to the development of AF.[11–13] A recent cohort study of US Medicaid patients reported that the incidence rate of hospitalization due to AF among patients with SLE to be approximately double than that of patients without SLE.[14] Furthermore, results associating an increased mortality in patients with SLE who develop AF have been reported.[10]

The study aims to compare outcomes of patients hospitalized for AF with and without coexisting SLE. Due to patients with SLE having multiple risk factors associated with AF, prior studies reporting a higher incidence of hospitalization rates for AF in patients with SLE, and observations of AF developing at a younger age in patients with SLE, we hypothesize that SLE might negatively impact outcomes of AF hospitalizations. We queried the latest 2 years of the National Inpatient Sample (NIS) database to answer this question.

METHODS

Data source

Hospitalizations from the NIS 2016 and 2017 with a principal diagnosis of AF with and without a secondary diagnosis of SLE were studied retrospectively. NIS is a property of the Agency for Healthcare Research and Quality. It is the largest public inpatient database in the USA.[15 16] NIS is a 20% probability sampling across different strata, designed to be representative of all acute care hospitalizations in the USA.[17] NIS maintains national representation by containing weighted discharges.[18] Each hospitalization in NIS 2016 can contain up to 30 International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) diagnosis codes and 40 for NIS 2017.[19] Diagnosis is either the principal diagnosis or secondary diagnosis.[20] A principal diagnosis is the major ICD-10 code for admission.[21] Any other diagnoses other than the principal diagnosis are secondary diagnoses.[22] This study was exempted from Institutional Review Board approval, since NIS contains depersonalized, publicly available patient data.

Inclusion criteria

We included all hospitalizations for patients≥18 years with principal diagnosis of AF with and without secondary diagnosis of SLE. We used ICD-10 codes to identify diagnoses and procedures. See online supplemental table for complete list of ICD-10 codes used.

Outcomes

The primary outcome was inpatient mortality. Hospital length of stay (LOS), total hospital charges, odds of undergoing ablation, pharmacologic cardioversion, and electrical cardioversion were secondary outcomes of interest. AF hospitalizations with ablation, pharmacologic, and electrical cardioversion were obtained using ICD procedure codes for destruction of conduction system of the heart, parenteral administration of antiarrhythmic agents, and restoration of cardiac rhythm, respectively.

Statistical analysis

Analyses were performed using STATA, V.16 (Stata, Texas, USA). A univariate logistic regression analysis using all variables and comorbidities in table 1 was used to calculate unadjusted ORs for the primary outcome. All variables with $p<0.1$ were included in a multivariate logistic regression model. $P<0.05$ were considered significant in the multivariate analysis. Literature review was used to select confounders. Charleston index was used to control for comorbidity complexity. Multivariate logistic and linear regression model with all variables and comorbidities in table 1 were used accordingly to adjust for confounders for the secondary outcomes.

RESULTS

There were over 71 million discharges included in the combined 2016 and 2017 NIS database. A total of 821,630 hospitalizations were for adult patients, who had a principal ICD-10 code for AF. A total of 2645 (0.3%) of these hospitalizations have SLE as secondary diagnosis, while 818,985 (99.7%) hospitalizations did not have SLE as secondary diagnosis. Characteristics of AF hospitalizations with and without coexisting SLE are displayed in table 1. SLE group was younger (67 vs 71 years, $p<0.0001$) and had more women (85% vs 51%, $p<0.0001$).

Around 7520 adult AF hospitalizations (0.9%) resulted in inpatient mortality. Among them, 40 (1.5%) of the deaths occurred in coexisting SLE vs 7480 (0.9%) without coexisting SLE ($p=0.1489$). Hospitalizations for AF with SLE had similar inpatient mortality (1.5% vs 0.91%, adjusted OR (AOR): 1.0, 95% CI 0.47 to 2.14, $p=0.991$), LOS (4.2 vs 3.4 days, $p=0.525$), total hospital charges ($51,351 vs $39,121, $p=0.056$), odds of undergoing pharmacologic cardioversion (0.38% vs 0.38%, AOR: 0.90, 95% CI 0.22 to 3.69, $p=0.880$) and electrical cardioversion (12.9% vs 17.5%, AOR 0.87, 95% CI 0.66 to 1.15, $p=0.324$) compared with those without SLE. Hospitalizations for AF with SLE had increased odds of undergoing ablation (6.8% vs 4.2%, AOR: 1.9, 95% CI 1.3 to 2.7, $p<0.0001$) compared with those without SLE (table 2).

DISCUSSION

In our study, AF hospitalizations with coexisting SLE accounted for only a small portion (0.3%) of total AF hospitalizations. In contrast, a large cohort study of US Medicaid patients reported the incidence rate of hospitalization for AF in patients with SLE to be approximately double than that for matched age and sex controls.[14] The increased incidence of hospitalizations was attributed to the coexistence of several other risk factors for AF in patients with SLE, including hypertension, CVD, renal disease, valvular disease, and higher Charlson comorbidity index score.[14] In the study by Lim *et al*, the incidence rates for AF were higher among the SLE group compared with the non-SLE group. This observation remained true even after multivariate adjustment for age, sex, income, and relevant comorbidities.

Table 1 Baseline characteristics of atrial fibrillation hospitalizations with and without SLE

	AF (n=821,630)		
	Without SLE (n=818,985)	With SLE (n=2645)	P value
Mean age (years)	71.0	67.0	<0.0001
Female	51.4%	85.0%	<0.0001
Race			<0.0001
White	82.3%	70.5%	
Black	7.8%	18.7%	
Hispanic	6.0%	6.6%	
Asians	1.5%	1.4%	
Native Americans	0.4%	0.2%	
Others	2.0%	2.7%	
Charlson comorbidity index			<0.0001
0	24.4%	0.0%	
1	26.3%	18.5%	
2	19.3%	21.0%	
≥3	30.4%	60.5%	
Hospital bed size			0.0127
Small	19.9%	17.9%	
Medium	30.5%	26.1%	
Large	49.6%	55.9%	
Hospital teaching status			0.0138
Nonteaching	38.0%	32.9%	
Teaching	62.0%	67.1%	
Hospital location			0.0297
Rural	11.2%	8.1%	
Urban	88.8%	91.9%	
Expected primary payer			<0.0110
Medicare	7.3%	85.3%	
Medicaid	6.2%	5.5%	
Private	21.2%	8.5%	
Self-pay	2.4%	0.6%	
Median household income (quartile)			<0.0079
First (0–25th)	70.6%	76.3%	
Second (26–50th)	6.1%	6.3%	
Third (51st–75th)	20.9%	16.4%	
Fourth (76–100th)	2.4%	0.9%	
Hospital region			<0.0017
Northeast	20.2%	19.0%	
Midwest	24.2%	18.0%	
South	40.6%	45.2%	
West	15.1%	18.0%	
Dyslipidemia	50.3%	40.6%	<0.0001
Old MI	8.3%	9.3%	0.4497
Old PCI	1.1%	0.0%	0.0198
Old CABG	7.2%	6.9%	0.8675
Old pacemaker	5.5%	5.6%	0.8244
AICD	2.9%	3.6%	0.3765
COPD	19.5%	30.1%	<0.0001
Carotid artery disease	1.3%	1.3%	0.9828
Old stroke	0.6%	0.8%	0.6751
Hypertension	48.5%	40.1%	0.0001
Peripheral vessel disease	4.2%	4.2%	0.9743
Hypothyroidism	17.3%	25.1%	<0.0001
DM type 1 and 2	28.0%	24.6%	0.0911
Obesity	19.6%	20.4%	0.6173
CHF	37.6%	43.1%	0.0099
CKD	18.1%	27.2%	<0.0001
Liver disease	2.9%	4.2%	0.1150
Electrolyte derangement	18.8%	24.2%	0.0020
Maintenance hemodialysis	2.1%	6.2%	<0.0001
O_2 dependence	3.5%	6.6%	0.0001
Smoking	27.6%	25.5%	0.2690
Anemia	15.8%	29.0%	<0.0001

AF, atrial fibrillation; CABG, coronary artery bypass graft; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; median household income, median household income for patient's zip code; MI, myocardial infarction; O_2, oxygen; PCI, percutaneous coronary intervention; SLE, systemic lupus erythematosus.

In our cohort of study population, SLE group were predominantly women, whereas the non-SLE group had near equal distribution of men and women (85% women in SLE group vs 51% in non-SLE group, p<0.0001). SLE is known to be present predominantly in women with a female to male ratio of around 9:1, especially during reproductive years.[1–3]

AF with SLE group had more chronic obstructive pulmonary disease, oxygen dependence, chronic kidney disease, maintenance hemodialysis, congestive heart failure, anemia, hypothyroidism, electrolyte derangement, and Charlson comorbidity index score of ≥3. This is similar to other studies that showed increased cardiovascular risk factors such as renal disease, and more comorbidity burden in AF with patients with SLE compared with similar patients without SLE.[14]

Our initial hypothesis that SLE might negatively impact outcomes of AF hospitalizations was based on the several studies reporting multiple mechanisms linked in the development of AF in SLE, which might make AF a more refractory disease in patients with SLE. The mechanism of AF development in SLE has not been completely elucidated. Several inflammatory processes including pericarditis and myocarditis and ischemic disease due to coronary artery disease may affect signaling pathways and lead to the development of cardiac rhythm disorders. Also, small vessel vasculitis and subsequent fibrotic changes that affect the conduction system have identified in patients with SLE.[23–25] The pathogenesis of AF includes structural remodeling due to atrial fibrosis, a process linked to inflammation, thus supporting the relationship between AF and autoimmune chronic inflammatory disorders such as SLE.[10] A possible role of anti-sjogeren's-syndrome-related antigen A autoantibodies (SSA) and anti-sjogeren's-syndrome-related antigen B autoantibodies (SSB) autoantibodies has been proposed. It has been mentioned that these autoantibodies bind to calcium channels and downregulate them, consequently causing alterations in calcium homeostasis and apoptosis of cardiomyocytes.[26] On the other hand, there have been associations between anti-Ro/SSA antibodies, with the

Table 2 Clinical outcomes of a fib hospitalizations with and without SLE

	AF with SLE (n=2645)	AF without SLE (n=818,985)	Adjusted OR (AOR)	
	% (95% CI)	% (95% CI)	(95% CI)	P value
Primary outcome				
In-hospital mortality	1.5 (0.8 to 3.0)	0.91 (0.87 to 0.96)	1.0 (0.47 to 2.14)	0.991
Secondary outcomes				
Ablation	6.8 (5.0 to 9.2)	4.2 (4.0 to 4.4)	1.9 (1.3 to 2.7)	<0.0001*
Electrical cardioversion	12.9 (10.2 to 16.0)	17.5 (17.2 to 17.9)	0.87 (0.66 to 1.15)	0.324
Pharmacologic cardioversion	0.38 (0.09 to 1.50)	0.38 (0.29 to 0.50)	0.90 (0.22 to 3.69)	0.880
			Adjusted mean difference	
LOS, mean (SE), days	4.2±0.33	3.4±0.01	0.21 (–0.44 to 0.86)	0.525
Total charge, mean, US$	51,351±3831	39,121±406	7252 (–185 to 14,689)	0.056

AF, atrial fibrillation; LOS, hospital length of stay; US$, US dollars.

development of clinical myocarditis[27] and interacting with cardiac M3 receptors causing a decrease in parasympathetic activity.[4 27] AF in SLE may also be related to therapeutic agents such as methylprednisolone and antimalarial drugs used in SLE management. A few case reports have reported possible methylprednisolone AF induction.[2] A chloroquine cumulative dose above 1207 g has been associated to structural ECG abnormalities which might lead to AF.[28]

In this nationwide 2-year retrospective study involving 821,630 adult patients hospitalized for AF, we observed there was a similar inpatient mortality in patients with SLE compared with those without SLE. These findings are in contrast with a study by Lim *et al* using the Korean Health Insurance Service National Sample Cohort database from 2008 to 2014, patients with SLE and AF had an increased risk of all-cause death compared with those with SLE without AF.[10] Difference in findings in our study could be due to better treatment modalities available to patients with SLE in the USA.

Among the two study groups, we found that patients with SLE were more likely to undergo cardiac ablation for AF when compared with those without SLE. The cardiotoxic effects of SLE therapeutic agents or atrial fibrosis in SLE might lead to recurrent or difficult to control AF resulting in increased rates of requiring invasive procedures like cardiac ablation to control AF.[11–13] There are no clear guidelines on how treatment of AF differs in patients with and without SLE. This remains a potential area of exploration and further clinical studies are required to better our knowledge on the management of AF associated with SLE.

In our study cohort, there was no statistically significant difference in rates of pharmacologic and electrical cardioversion. It is unclear if the diagnosis of SLE was considered while selecting patients for pharmacologic or electric cardioversion, and likely other factors such as associated comorbidities and prior treatment history for AF where used to make decisions concerning treatment modalities.

The large sample size which increases the study power is the major strength of our study. Our study however has some limitations. (i) NIS uses claims data based on ICD-10 codes rather than clinical data.[29] (ii) ICD-10 codes do not grade severity; therefore, we cannot discern if SLE disease severity may have had affected outcomes of AF hospitalizations. (iii) NIS database contains reports on hospitalizations, rather than individual patients.[30] (iv) Data on medication compliance are not available in NIS. (V) Choice of therapeutic intervention may be determined by indication and clinical judgment of the physician. Hence, underlying SLE may not have been considered when determine which therapeutic intervention to provide AF patients. (vi) NIS have absence of laboratory data such as inflammatory markers which may indicate underlying disease severity or activity.[31]

CONCLUSION

Although SLE increases risk of developing AF, coexisting SLE was not associated with increased inpatient mortality in AF hospitalizations in our study. SLE may be associated with increased odds of undergoing ablation in hospitalizations for AF. However, further prospective randomized studies comparing ablation in AF with and without SLE are needed.

Contributors MMRP, AS, and EA are credited with substantial contribution to the design of the work, acquisition and interpretation of the data, drafting the manuscript, revision of important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work. AT, ME, and POE are credited with substantial contribution to acquisition, analysis, and interpretation of the data, revision of critically important intellectual content, final approval of the version to be published, and agreement of accountability for all aspects of the work MU, KQ, and MWB are credited with interpretation of data, literature review, specifically for the discussion section, revision of the work for critically important intellectual content, final approval of the version published, and agreement of accountability for all aspects of the work. IRA and AWA are credited with substantial contribution to interpretation of data, literature review of all sections discussed, drafting of the manuscript, final approval of the version published, and agreement of accountability for all aspects of the work. GV, MUA, and PEO are credited with interpretation of the data, literature review of all sections, revision of important intellectual content, final approval of the version published, and agreement of accountability of all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data obtained from the National Inpatient Sample.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not

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