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Systemic lupus erythematosus and the risk of perioperative major adverse cardiovascular events

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Abstract

Background—Systemic lupus erythematosus (SLE) is a significant risk factor for cardiovascular disease. The relationship between SLE and perioperative cardiovascular risks following non-cardiac surgery is uncertain.

Objectives—We investigated associations between a diagnosis of SLE and outcomes following major non-cardiac surgery in a large national database from the United States.

Patients/Methods—Patients age ≥ 18 years requiring major non-cardiac surgery were identified from Healthcare Cost and Utilization Project's National Inpatient Sample data from 2004 to 2014. Systemic lupus erythematosus (SLE) and perioperative major adverse cardiovascular events (MACE; myocardial infarction, ischemic stroke or death) were defined by ICD-9 diagnosis codes. Perioperative MACE events were reported for SLE patients stratified by age and sex.

Results—From 2004 to 2014, a total of 17,853,194 hospitalizations for major non-cardiac surgery met study inclusion criteria. SLE was identified in 70,578 (0.4%) hospitalizations. Overall, the frequency of perioperative MACE was higher in patients with versus without SLE (2.4% vs. 2.0%, $p < 0.001$; adjusted OR [aOR] 1.25; 95% CI 1.18–1.31). Perioperative MACE associated

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This is an analysis of previously collected, publicly available, de-identified administrative data. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required. This article does not contain any studies with animals performed by any of the authors.

with SLE was largely driven by increased death (aOR 1.58 95% CI 1.40 – 1.77) and myocardial infarction (aOR 1.32; 95% CI 1.05 – 1.66) in younger patients with SLE. The increased risk of perioperative MACE associated with SLE in younger patients was attenuated with increasing age.

Conclusions—A diagnosis of SLE is associated with increased risk of perioperative MACE, particularly among younger patients. Efforts to improve the perioperative management and outcomes of patients with SLE are needed.

Keywords

Cardiovascular; Lupus; Perioperative Period; Surgery; Systemic lupus erythematosus; Thrombosis

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease that affects approximately 20 to 150 per 100,000 adults in the United States (US), with a higher prevalence in women and non-white populations.[1–3] SLE is associated with significant morbidity and mortality, driven by infectious, renal, and cardiovascular complications. Although the pathogenesis remains incompletely understood, systemic cardiovascular effects of SLE appear to be mediated by chronic inflammation, increased platelet activity, a hypercoagulable state, and vascular dysfunction.[4, 5]

Nearly 300 million non-cardiac surgeries are performed annually in the US. While perioperative cardiovascular events are on the decline, 3% of patients 45 years of age hospitalized for surgery still develop MI, stroke, or death in the perioperative period.[6] However, data in surgical patients with SLE are limited and thus it remains unknown whether declining trends are also applicable to this population. Two prior studies noted that SLE was associated with an increased risk of adverse perioperative outcomes.[7, 8] However, data were from surgeries performed in Taiwan or in the United States nearly two decades ago, cohorts of SLE patients undergoing surgery were relatively small, analyses excluded men, and did not investigate outcomes by age. Accordingly, this study was initiated to investigate the relationship between a diagnosis of SLE and adverse cardiovascular outcomes following major non-cardiac surgery in a large contemporary nationwide database from the United States.

Methods

Patients age 18 years requiring major non-cardiac surgery were identified from Healthcare Cost and Utilization Project's National Inpatient Sample data from 2004 to 2014, using previously described methodology.[6] Systemic lupus erythematosus was identified using *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis code 710.0. As described previously, perioperative major adverse cardiovascular events (MACE) were defined by death and ICD-9 diagnosis codes for acute myocardial infarction and ischemic stroke (Table 2 footnote). Multivariable logistic regression models were generated to estimate odds of perioperative events, adjusted for patient demographics, cardiovascular risk factors, and surgery type. Statistical analyses were performed using SPSS 20 (IBM SPSS Statistics, Armonk, NY). P-values < 0.05 were considered to be statistically significant.

Results

From 2004 to 2014, a total of 17,853,194 hospitalizations for major non-cardiac surgery met study inclusion criteria and SLE was identified in 70,578 (0.40%). Patients with a diagnosis of SLE were younger, more likely to be female (90.3% vs. 64.7%, $p<0.001$), black (20.1% vs. 9.6%, $p<0.001$), more frequently had hypertension, end-stage renal disease, heart failure, and were less likely to have diabetes and hyperlipidemia than patients without SLE (Table 1). Patients with SLE were more likely to undergo vascular or orthopedic surgery, and were less likely to undergo surgery during an elective hospitalization than patients without SLE. Overall, patients with SLE had a higher frequency of perioperative MACE in comparison to patients without SLE (2.4% vs. 2.0%, $p<0.001$) (Table 2). After multivariable adjustment, SLE remained associated with perioperative MACE overall (adjusted OR [aOR] 1.25; 95% CI 1.18–1.31) and in both women (aOR 1.29; 95% CI 1.22–2.37) and men (aOR 1.17; 95% CI 1.03–1.33). The frequency of MACE by age and sex is shown in Figure 1. Observed increases in perioperative MACE associated with SLE were largely driven by increased risk of death (aOR 1.58 95% CI 1.40 – 1.77) and myocardial infarction (aOR 1.32; 95% CI 1.05 – 1.66) in patients with SLE age <50 years. The increased risk of perioperative MACE, death, and MI associated with SLE was attenuated in older patients (Table 2). No differences in perioperative acute ischemic stroke were identified in patients with and without SLE.

Discussion

In this analysis of patients undergoing non-cardiac surgery, men and women with SLE had higher risks of perioperative MACE and in-hospital mortality than those without SLE, with the greatest increases in risk observed in the youngest patients. The vast majority of SLE patients undergoing non-cardiac surgery were women, and in the subgroup of women age 18–49, MACE was approximately 5-fold higher in patients with SLE in unadjusted analyses, with a 27% increase in risk of MACE associated with SLE after adjusting for clinical covariates. There was a higher frequency of MI among the younger patients age 18–49 (of both sexes) in the analysis, although confidence intervals of adjusted odds ratios for MI were wide in subgroups stratified by sex. The increased risk of perioperative MI and MACE associated with SLE observed in younger patients was attenuated in the older subgroup. This may be attributed to the competing risks of age-related cardiovascular disease in older cohorts, or a survival bias of SLE patients with less severe disease. SLE was not associated with a signal for increased perioperative stroke in this analysis, a surprising finding in light of the increased risk of arterial thrombosis in patients with SLE.[9]

There are several notable limitations of this study. Analyses were based on administrative coding data, which is subject to reporting bias and coding errors. It is unknown whether patients met either the American College of Rheumatology or SLE international cooperating clinics (SLICC) classifications.[10, 11] Medical therapy, including immunosuppressive and antithrombotic regimens, were not available from this dataset, nor were levels of anti-phospholipid antibodies. Similarly, data on perioperative antiplatelet, anticoagulant, and statin use were not available. Causes of death could not be determined and may have been related to infectious complications. Finally, the sequence of cardiovascular complications following non-cardiac surgery cannot be firmly established from ICD-9 coding.

In conclusion, a diagnosis of SLE was associated with increased incidence of perioperative MACE and in-hospital mortality, particularly among younger women hospitalized for non-cardiac surgery. Mechanisms of death among SLE patients undergoing non-cardiac surgery are uncertain. Patients with SLE may require careful consideration during pre-operative cardiovascular risk assessment, and antithrombotic and lipid lowering therapies indicated for atherosclerotic cardiovascular disease may be beneficial. Trials of medical therapy to improve the perioperative outcomes of young patients with SLE require further study.

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References

1. Lawrence RC, Helmick CG, Arnett FC, Deyo RA, Felson DT, Giannini EH, Heyse SP, Hirsch R, Hochberg MC, Hunder GG, Liang MH, Pillemer SR, Steen VD, Wolfe F. Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis and rheumatism*. 1998; 41:778–99. 10.1002/1529-0131(199805)41:5<778::AID-ART4>3.0.CO;2-V. [PubMed: 9588729]
2. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis and rheumatism*. 2007; 56:2092–4. DOI: 10.1002/art.22641 [PubMed: 17530651]
3. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Seminars in arthritis and rheumatism*. 2010; 39:257–68. DOI: 10.1016/j.semarthrit.2008.10.007 [PubMed: 19136143]
4. Nhek S, Clancy R, Lee KA, Allen NM, Barrett TJ, Marcantoni E, Nwaukoni J, Rasmussen S, Rubin M, Newman JD, Buyon JP, Berger JS. Activated Platelets Induce Endothelial Cell Activation via an Interleukin-1beta Pathway in Systemic Lupus Erythematosus. *Arteriosclerosis, thrombosis, and vascular biology*. 2017; 37:707–16. DOI: 10.1161/ATVBAHA.116.308126
5. Rahman A, Isenberg DA. Systemic lupus erythematosus. *N Engl J Med*. 2008; 358:929–39. DOI: 10.1056/NEJMra071297 [PubMed: 18305268]
6. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative Major Adverse Cardiovascular and Cerebrovascular Events Associated With Noncardiac Surgery. *JAMA Cardiol*. 2017; 2:181–7. DOI: 10.1001/jamacardio.2016.4792 [PubMed: 28030663]
7. Yazdanyar A, Wasko MC, Scalzi LV, Kraemer KL, Ward MM. Short-term perioperative all-cause mortality and cardiovascular events in women with systemic lupus erythematosus. *Arthritis care & research*. 2013; 65:986–91. DOI: 10.1002/acr.21915 [PubMed: 23213026]
8. Lin JA, Liao CC, Lee YJ, Wu CH, Huang WQ, Chen TL. Adverse outcomes after major surgery in patients with systemic lupus erythematosus: a nationwide population-based study. *Annals of the rheumatic diseases*. 2014; 73:1646–51. DOI: 10.1136/annrheumdis-2012-202758 [PubMed: 23740232]
9. Glueck HI, Kant KS, Weiss MA, Pollak VE, Miller MA, Coots M. Thrombosis in systemic lupus erythematosus. Relation to the presence of circulating anticoagulants. *Arch Intern Med*. 1985; 145:1389–95. [PubMed: 3927865]
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis and rheumatism*. 1982; 25:1271–7. [PubMed: 7138600]
11. Petri M, Orbai AM, Alarcon GS, Gordon C, Merrill JT, Fortin PR, Bruce IN, Isenberg D, Wallace DJ, Nived O, Sturfelt G, Ramsey-Goldman R, Bae SC, Hanly JG, Sanchez-Guerrero J, Clarke A,

Aranow C, Manzi S, Urowitz M, Gladman D, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis and rheumatism*. 2012; 64:2677–86. DOI: 10.1002/art.34473 [PubMed: 22553077]

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Figure 1.
Frequency of perioperative major adverse cardiovascular events in patients undergoing major non-cardiac surgery among women (1A) and men (1B).

Table 1

Baseline characteristics of patients with and without a diagnosis of Systemic Lupus Erythematosus undergoing non-cardiac surgery in the United States.

	Diagnosis of Systemic lupus erythematosus		P Value
	Present (n=70,578)	Absent (n=17,782,616)	
Age	52.1 ± 15.8	53.7 ± 19.6	<0.001
Female Sex	63724 (90.3%)	11475349 (64.7%)	<0.001
Race/Ethnicity			<0.001
White NH	37298 (52.8%)	10550320 (59.3%)	
Black NH	14208 (20.1%)	1705118 (9.6%)	
Hispanic	6048 (8.6%)	1647672 (9.3%)	
Other	3142 (4.5%)	888463 (5%)	
Unknown	9882 (14%)	2991043 (16.8%)	
Hypertension	37604 (53.3%)	7264726 (40.9%)	<0.001
Hyperlipidemia	11872 (16.8%)	3525380 (19.8%)	<0.001
Diabetes	11066 (15.7%)	2966240 (16.7%)	<0.001
End-Stage Renal Disease	6661 (9.4%)	324883 (1.8%)	<0.001
Coronary Artery Disease	8295 (11.8%)	2080422 (11.7%)	0.66
Heart Failure	4783 (6.8%)	782566 (4.4%)	<0.001
Peripheral Artery Disease	3471 (4.9%)	835493 (4.7%)	0.01
Prior DVT or PE	4602 (6.5%)	337978 (1.9%)	<0.001
Elective Surgery	38341 (54.5%)	10167006 (57.4%)	<0.001
Surgery Type			<0.001
General	14183 (20.1%)	3534864 (19.9%)	
Endocrine	821 (1.2%)	181364 (1%)	
ENT	531 (0.8%)	164972 (0.9%)	
Genitourinary	2797 (4%)	1041279 (5.9%)	
Gynecologic	4761 (6.7%)	1317021 (7.4%)	
Skin/Burn	3481 (4.9%)	657098 (3.7%)	
Neurosurgery	2995 (4.2%)	875635 (4.9%)	
Obstetric	4610 (6.5%)	2931194 (16.5%)	
Orthopedic	25225 (35.7%)	5421326 (30.5%)	
Thoracic	1437 (2%)	297678 (1.7%)	
Transplant	1362 (1.9%)	48375 (0.3%)	
Vascular	8375 (11.9%)	1311810 (7.4%)	

Table 2

Perioperative outcomes with and without a diagnosis of Systemic Lupus Erythematosus.

Age Group	All Patients			Men			Women		
	SLE	without SLE	aOR (95% CI) ^{a,b}	SLE	without SLE	aOR (95% CI) ^a	SLE	without SLE	aOR (95% CI) ^a
MACE ^c									
Age < 50	1.6%	0.5%	1.35 (1.22 – 1.48)	2.9%	1.2%	1.26 (0.98 – 1.61)	1.5%	0.3%	1.27 (1.14 – 1.41)
Age 50	3.0%	3.1%	0.90 (0.85 – 0.96)	4.2%	3.6%	0.93 (0.79 – 1.08)	2.8%	2.8%	0.9 (0.84 – 0.96)
Total [†]	2.4%	2.0%	1.25 (1.18 – 1.31)	3.7%	2.9%	1.17 (1.03 – 1.33) [‡]	2.2%	1.5%	1.29 (1.22 – 1.37)
Death									
Age < 50	1.0%	0.3%	1.58 (1.40 – 1.77)	1.9%	0.8%	1.37 (1.01 – 1.84)	1.0%	0.2%	1.50 (1.32 – 1.71)
Age 50	1.9%	1.8%	1.00 (0.93 – 1.08)	2.6%	2.0%	1.00 (0.82 – 1.21)	1.8%	1.5%	1.01 (0.93 – 1.09)
Total [†]	1.5%	1.2%	1.43 (1.34 – 1.52)	2.3%	1.7%	1.28 (1.08 – 1.50) [‡]	1.4%	0.8%	1.51 (1.41 – 1.62)
Myocardial Infarction ^d									
Age < 50	0.3%	0.1%	1.32 (1.05 – 1.66)	0.7%	0.2%	1.56 (0.95 – 2.53)	0.2%	0.03%	1.20 (0.92 – 1.56)
Age 50	0.8%	0.9%	0.79 (0.71 – 0.89)	1.2%	1.1%	0.86 (0.65 – 1.13)	0.7%	0.8%	0.78 (0.69 – 0.89)
Total [†]	0.6%	0.6%	1.09 (0.99 – 1.21)	1.0%	0.8%	1.16 (0.91 – 1.48)	0.5%	0.4%	1.10 (0.99 – 1.23)
Ischemic Stroke ^e									
Age < 50	0.4%	0.1%	0.96 (0.80 – 1.16)	0.6%	0.3%	1.07 (0.65 – 1.77)	0.4%	0.1%	0.90 (0.74 – 1.11)
Age 50	0.7%	0.7%	0.85 (0.75 – 0.96)	0.9%	0.8%	0.94 (0.68 – 1.28)	0.6%	0.6%	0.83 (0.73 – 0.95)
Total [†]	0.5%	0.5%	1.02 (0.92 – 1.13)	0.8%	0.7%	1.05 (0.81 – 1.38)	0.5%	0.4%	1.01 (0.90 – 1.13)

^a Adjusted for race, tobacco use, obesity, hypertension, hyperlipidemia, diabetes mellitus, end-stage renal disease, coronary artery disease, prior revascularization (PCI or CABG), peripheral artery disease, valvular heart disease, heart failure, pulmonary disease, drug abuse, alcohol abuse, malignancy, anemia, elective/urgent surgery, surgery type and year of hospitalization.

^b Additionally adjusted for sex

[†] Additionally adjusted for age

^c Composite of death, myocardial infarction, and ischemic stroke

^d Defined by ICD9 diagnosis codes 410.x1

^e Defined by ICD9 diagnosis codes 33.x1, 434.x1, 436, and 437.1