

# Systemic Lupus Erythematosus Is Associated With a High Risk of Venous Thromboembolism in Hospitalized Patients Leading to Poor Outcomes and a Higher Cost: Results From Nationwide Inpatient Sample Database 2003-2011

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**Objective.** Venous thromboembolism (VTE) is a major cause of mortality and morbidity in hospitalized patients, particularly those with autoimmune disorders. The Nationwide Inpatient Sample (NIS) database was analyzed to determine trends in the rate of hospitalization, mortality from VTE, epidemiology, and outcomes in hospitalized patients with systemic lupus erythematosus (SLE) to assess its impact.

**Methods.** The 2003-2011 NIS database of the Healthcare Cost and Utilization Project was queried to identify all adults (age 18 years and older) hospitalized with SLE and VTE. Demographic characteristics and in-hospital outcomes of this population were compared with those of patients with SLE without a VTE diagnosis. A multivariate logistic regression analysis was used to obtain the adjusted odds ratio (OR).

**Results.** The total number of hospitalized patients with SLE was 299595, of whom 9175 (3.06%) had VTE. After adjusting for potential confounders, compared with those without VTE, patients with SLE and VTE had significantly higher inpatient mortality (5% vs. 2.0%; OR 2.35 [95% confidence interval (CI) 2.10-2.62];  $P < 0.001$ ), greater disability at discharge (34% vs. 26%; OR 1.53 [95% CI 1.46-1.62];  $P < 0.001$ ), a longer length of stay (LOS) by 3.57 days, and higher cost of hospitalization by \$25400. In this database, patients with SLE and VTE were younger and of male sex. Also, African American race and a higher number of comorbidities were associated with an increased risk of VTE in patients with SLE.

**Conclusion.** VTE in hospitalized patients with SLE is associated with significantly higher inpatient mortality, greater disability at discharge, an increased LOS, and higher cost of hospitalization. This cross-sectional study helps with quantifying the risk of VTE in hospitalized patients with SLE and provides information on the immense human and material cost this complication leads to. These data can be very useful in the development and implementation of appropriate prophylactic strategies in the high-risk population with SLE.

## INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE) are manifestations of potentially lethal venous thromboembolism (VTE). Among hospitalized patients, VTE is a major cause of mortality and morbidity and remains one of the major reasons for poor outcomes and increased cost in these patients. The risk of VTE is increased further in these patients by comorbid conditions, such as diabetes, cerebrovascular accident, malignancy, heart failure, and, in particular, autoimmune disorders. Among the autoimmune disorders, it is well proven that there is a high risk of VTE with systemic lupus erythematosus (SLE), especially when associated

with antiphospholipid antibodies (APLAs). Yet this increased risk and in-hospital outcomes have not been well characterized in hospitalized patients with SLE.

VTE is caused by one of three factors according to the Virchow triad: stasis, vessel wall abnormalities, including endothelial dysfunction, and/or a prothrombotic/altered coagulation state (1,2). There are a number of inherited and acquired causes of altered coagulation states and endothelial dysfunction that include age, APLA syndrome, Factor V deficiency, trauma, surgery, malignancy, heart failure, and systemic inflammatory disorders, such as SLE (1,2). Among acquired risk factors, advancing age, prolonged immobilization, heart failure, lower-extremity fracture or surgery,

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No potential conflicts of interest relevant to this article were reported.

There was no financial support/funding for this project/manuscript.

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and cancer have most frequently been associated with VTE (3–6). Among the systemic inflammatory diseases, SLE, inflammatory bowel disease, rheumatoid arthritis, and vasculitides, especially granulomatosis with polyangiitis, are associated with an increased risk of VTE (7–9).

Furthermore, it is also felt that VTE is a major cause of mortality and morbidity in hospitalized patients with these disorders. Multiple cohort studies in patients with SLE have shown that they are at a higher risk of VTE, especially when associated with APLAs. Notably, Mok et al (10) found a 11.9-fold higher risk of VTE in patients with SLE than in the general population, and this association has been replicated in other studies (10–14). Patients with SLE have a higher risk for VTE in the first year after diagnosis (15). Risk factors for arterial thromboembolism and VTE in patients with SLE have also been well defined (16). However, there is paucity of data on the in-hospital outcomes of these patients. In this study, the Nationwide Inpatient Sample (NIS) database was analyzed to determine trends in the rate of hospitalization and in mortality from VTE in hospitalized patients SLE and to assess its impact on length and cost of hospitalization.

## METHODS

**Data source.** We used the NIS database for years 2003–2011. The NIS contains data on inpatient hospitalization stay from states participating in the Healthcare Cost and Utilization Project (N = 46 in 2011). The NIS is the largest publicly available database in the United States and is designed to approximate a 20% stratified sample of discharges from US community hospitals, defined as “all non-federal, short-term, general, and other specialty hospitals excluding rehabilitation and long-term acute care hospitals.” Discharge weights provided by the NIS allow extrapolation to calculate expected national hospitalization rates. Criteria used for stratified sampling of hospitals include ownership, bed size, teaching status, urban or rural location, and US region. All discharges from sampled hospitals are included in the NIS database. The NIS is an all-payer database that covers all patients, including those covered by Medicare, Medicaid, and private insurance and those who are uninsured. Inpatient stay records in the NIS include one primary and up to 24 secondary discharge diagnoses together with demographic and patient disposition. An overview of the NIS database is available online (Healthcare Cost and Utilization Project; online at <http://www.hcup-us.ahrq.gov/nisoverview.jsp>). In accordance with institutional policy, this study used publicly available data and was exempted from institutional review board approval.

**Study population.** Our study included all patients 18 years of age and older with a diagnosis of SLE who were identified from the NIS database between 2003 and 2011 using the Clinical Classification Software (CCS) codes. The CCS is a categorization scheme that groups the *International Classification of*

*Diseases, Ninth Revision* (ICD-9) codes into mutually exclusive categories. CCS code 710.0 represents all diagnoses of SLE. From this cohort, we identified patients with a diagnosis of VTE using ICD-9 codes for DVT (453.2, 453.3, 453.40, 453.41, 453.42, 453.82–453.89, 453.9, 453.0, 325, and 452), PE (415.11, 415.12, 415.13, and 415.19), and phlebitis and thrombophlebitis (451.11, 451.19, 451.2, 451.83, 451.81, 451.84, and 451.89). Patients with superficial upper- and lower-extremity VTE were excluded. Only patients with VTE as one of the top three discharge diagnoses were included in the cohort. The comparison group included hospitalized patients with SLE who did not have a diagnosis of VTE.

**Patient and hospital characteristics.** NIS-defined patient demographic and clinical characteristics used for our study included age, race, sex, insurance type, comorbidities (diabetes, hypertension, chronic heart failure, chronic renal disease, chronic liver disease, connective tissue disease, chronic lung disease, and valvular heart disease), length of stay (LOS), inpatient mortality, discharge status, and total charges. We also used NIS-defined hospital characteristics, such as location (rural vs. urban) and teaching status (teaching vs. nonteaching). Discharge status is reported in the NIS database as routine home discharge, home health care, short-term hospital or other hospital facility (including intermediate care and skilled nursing home), or death. We classified routine discharge as none to minimal disability, and we classified all other discharges as moderate to severe disability, which has previously been described (17–19).

**Outcomes.** The primary outcomes of this study were inpatient mortality, trends of hospitalization, and the inpatient mortality rate over the study period (2003–2011). Secondary outcomes were LOS, cost of hospitalization, and disability at discharge.

**Statistical analysis.** A bivariate comparison between patients with SLE with and without VTE was done using Mann-Whitney *U* tests with a 2-tailed hypothesis for continuous variables and Pearson's  $\chi^2$  test for categorical variables to detect any significant univariate associations. Binary outcomes (in-patient mortality and disability at discharge) were modeled using binomial families with logit links, with results being reported as probabilities and odds ratios (ORs). Likewise, LOS and total charges were modeled with gamma family and identity links, with results being reported on the natural scale. Trend plots were constructed using fully adjusted models that showed the marginal outcomes, and the trend analysis was conducted using year as a continuous variable and interacting with VTE, when appropriate. All models were adjusted for age, sex, race, teaching status of the hospital, hospital location, and presence of comorbid conditions. Adjustments were made (because of NIS sample schemes) using NIS guidelines. Namely, all results were probability weighted and stratified on established NIS weighting and stratification variables. All analyses were performed with Stata version 15.1 (StataCorp LLC).

**Table 1.** Weighted descriptive characteristics of patients older than 18 years with systemic lupus erythematosus, NIS (January 2003 through December 2011)

Variable	All Patients	VTE	No VTE	P
	N = 299 595	n = 9175	n = 290 420	
Age, mean (SD), y	50.00 (25.00)	48.00 (25.00)	51.00 (25.00)	<0.001
Sex, n (%)				
Female	266 969 (89)	7769 (85)	259 200 (89)	...
Male	32 626 (11)	1406 (15)	31 220 (11)	...
Race, n (%)				<0.001
White	132 649 (54)	3670 (48)	128 979 (54)	...
African American	71 151 (29)	2706 (35)	68 445 (29)	...
Hispanic	29 582 (12)	948 (12)	28 634 (12)	...
Asian	5258 (2)	127 (2)	5131 (2)	...
Native American	1498 (1)	46 (1)	1452 (1)	...
Other	5699 (2)	187 (2)	5512 (2)	...
No. of comorbidities, mean (SD)	3.00 (2.00)	4.00 (3.00)	3.00 (2.00)	<0.001
Hospital location, n (%)				<.001
Urban	269 880 (91)	8436 (92)	261 444 (91)	...
Rural	29 715 (9)	739 (8)	28 976 (9)	...
Teaching status, n (%)				<.001
Nonteaching	149 853 (50)	4225 (46)	145 628 (50)	...
Teaching	149 742 (50)	4950 (54)	144 792 (50)	...

Abbreviation: NIS, Nationwide Inpatient Sample; VTE, venous thromboembolism.

## RESULTS

Between 2003 and 2011, 299595 patients with SLE were hospitalized, of whom 9175 (3.06%) had an accompanying diagnosis of VTE, as defined previously, and were included in the analysis. There were 290420 patients with SLE without a diagnosis of VTE who served as comparators in the control cohort. Of the study population, 89% were women. The mean age of the study population was 50 years. The mean age was slightly lower in patients who had VTE (48 vs. 51 years;  $P < 0.001$ ). Overall, a higher proportion of patients were white (54%); however, the VTE rate was higher in African American patients compared with white patients (3.8% vs. 2.7%;  $P < 0.001$ ). Similarly, the VTE rate was higher in men compared with women (4.3% vs. 2.9%;  $P < 0.001$ ). The total number of comorbid conditions was higher in patients with VTE (4 vs. 3;  $P < 0.001$ ). Other baseline characteristics of the patients and hospital characteristics are listed in Table 1.

Patients with VTE had worse outcomes in terms of inpatient mortality, LOS, total charges, and disability at discharge compared with patients without VTE, as shown in Table 2. After adjusting for age, primary payer, weekend versus weekday admission, comorbidities, and other potential confounders, compared with patients with SLE without VTE, those with VTE had significantly higher rates of inpatient mortality (5% vs. 2%; adjusted OR 2.35; 95% confidence interval [CI] 2.10-2.62;  $P < 0.001$ ), longer expected LOS (9 vs. 6 days; adjusted  $\beta$  3.57; 95% CI 3.32-3.83;  $P < 0.001$ ), higher total expected charges (\$67 000 vs. \$41 600; adjusted  $\beta$  \$25 400; 95% CI \$23 000-\$27 900;  $P < 0.001$ ), and moderate to severe disability at discharge (34% vs. 26%; adjusted OR 1.53; 95% CI 1.46-1.62;  $P < 0.001$ ). Table 3 shows the multivariate regression analysis of the study outcomes.

A sudden spike in VTE rates was observed from 2004 to 2005 (OR 1.64;  $P < 0.001$ ) (Figure 1); however, trends both before and after this period were stable (OR 0.98 [ $P = 0.812$ ] and OR

**Table 2.** Outcomes of VTE in hospitalized patients with systemic lupus erythematosus

Variable	All Patients	VTE	No VTE	P
Inpatient mortality, n (%)	6132 (2)	429 (5)	5703 (2)	<0.001
LOS, median (IQR), d	4.00 (5.00)	6.00 (7.00)	4.00 (4.00)	<0.001
Total charges, median (IQR), US \$10 000	2.31 (3.19)	3.61 (5.81)	2.28 (3.13)	<0.001
Moderate to severe disability at discharge, n (%)	77 904 (26)	3117 (34)	74 787 (26)	<0.001

Abbreviation: IQR, interquartile range; LOS, length of stay; VTE, venous thromboembolism.

**Table 3.** Multivariate analysis predicting individual outcomes and adjusting for other variables<sup>a</sup>

Variable	Adjusted Estimate (95% CI)	P
Inpatient mortality for VTE vs. no VTE	OR = 2.35 (2.10-2.62)	<0.001
Expected additional LOS for VTE vs. no VTE, d	3.57 (3.32-3.83)	<0.001
Expected additional charges for VTE vs. no VTE, \$	25 400 (23 000-27 900)	<0.001
Moderate to severe disability at discharge for VTE vs. no VTE	OR = 1.53 (1.46-1.62)	<0.001

Abbreviation: CI, confidence interval; LOS, length of stay; OR, odds ratio; VTE, venous thromboembolism.

<sup>a</sup>Adjustment was made for age, sex, primary expected payer, teaching status of the hospital, hospital location, and presence of comorbid conditions.

0.99 [ $P = 0.401$ ], respectively) (Figure 1). A trending decrease in year mortality rates was observed for patients both with and without VTE was also observed (OR 0.90 per year;  $P < 0.001$ ) (Figure 2). There was no difference in yearly mortality trends between patients with and without VTE ( $P = 0.348$ ).

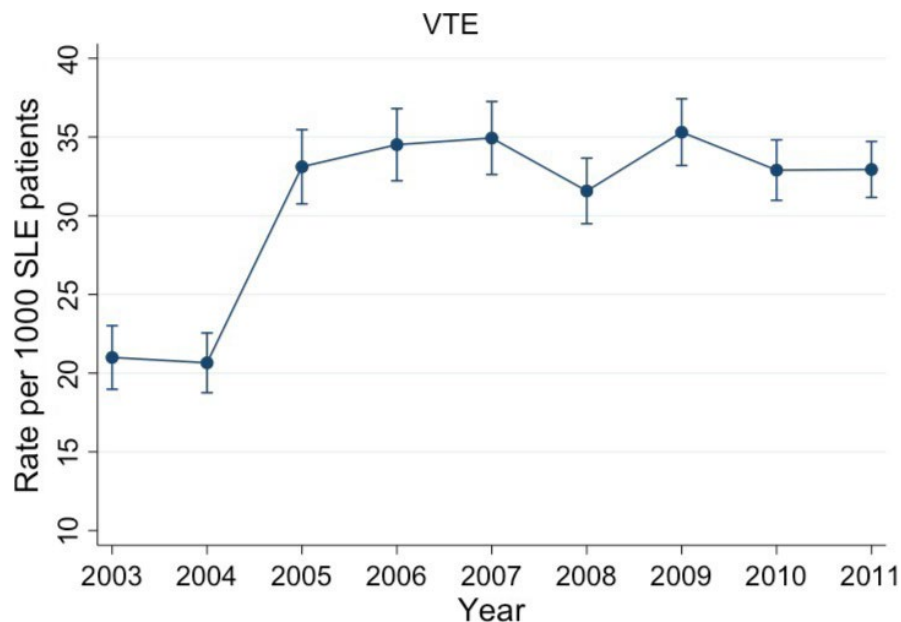
These results highlight that the risk of VTE is significantly increased in hospitalized patients with SLE. Furthermore, VTE in hospitalized patients with SLE is associated with adverse outcomes and leads to a higher morbidity and mortality as well as a prolonged LOS and higher cost of admission.

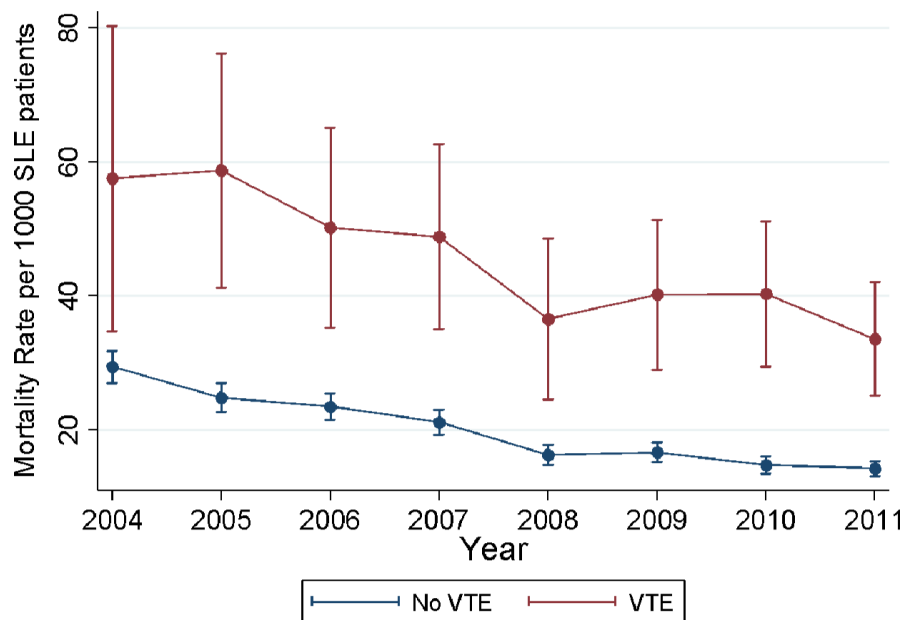
## DISCUSSION

VTE is a major health care burden in the US population, with an annual incidence of one to two cases per 1000 people and increasing prevalence (20). Studies have shown an increased risk of thromboembolism in patients with SLE as well as an increased mortality associated with VTE in these patients (21,22). Risk of PE during the first year after admission for SLE in a Swedish registry was significantly high (21). Similar results were reported in a Chinese and a Canadian cohort with SLE, with an increased risk of developing DVT or a PE in the patient group with SLE (23,24). In a 10-year prospective cohort study of patients, thrombosis was one of the leading causes (26.5%) of deaths, with thrombosis dominating the second 5-year period of follow-up (22).

However, there continues to remain an understanding gap between well-defined overall association of VTE in the general population with SLE and information on the hospitalized patients with SLE. This analysis focuses on the hospitalized patients with SLE and provides significant insight into this association for these patients. Results from our study showed a significantly high risk of mortality in patients admitted with VTE in SLE (OR 2.35), thereby corroborating the association between the two disease processes. We also found that in this subset of hospitalized patients with SLE, prevalence of VTE is increased over the period of follow-up, almost doubling from 2003-2004 to the period thereafter and then remaining stable from 2005 to 2011. This finding is similar to results of previous studies in the general population (20).

There are a number of possible explanations for this association of a higher prevalence of VTE in hospitalized patients with SLE. The biggest contributing factor is likely the presence of APLAs (8–10,16). However, there are other factors, such as

**Figure 1.** Annual rate of venous thromboembolism (VTE) in hospitalized patients with systemic lupus erythematosus (SLE).



**Figure 2.** Mortality rate of hospitalized patients with systemic lupus erythematosus (SLE) with and without venous thromboembolism (VTE).

endothelial dysfunction from inflammatory processes in SLE that causes microvascular thrombosis and alteration in cytokines that promotes procoagulant activity, downregulation of anticoagulants, and suppression of fibrinolysis (10). There is a high prevalence of corticosteroid use in these patients, which increases the risk of hemostasis and could contribute to risk of VTE in SLE (25). There is also increased prevalence of hypertension, diabetes mellitus, and dyslipidemia patients with SLE, and all of these factors have been associated with thrombosis (26).

Another highlight of the analysis was the decrease in mortality of hospitalized patients with SLE both with and without VTE, giving a reassuring insight into the advances in the care of these patients. The results also show that increased risk is significantly affected by both age and race. The patients with VTE and SLE were younger than the ones who did not develop VTE. This may reflect the severity of disease in these patients. Also, the percentage of VTE in hospitalized patients with SLE was higher for African American patients, and white patients had a lower likelihood of developing VTE (35% vs. 29% for African American patients and 48% vs. 54% for white patients). In addition, the VTE rate was significantly higher in men compared with women (4.3% vs. 2.9%) possibly because of more severe disease. The presence of comorbid conditions significantly raised the risk of VTE in these patients. Those with VTE had a higher number of comorbidities than those without VTE (4 vs. 3). There also were minor differences in the risk based on hospital setting (rural vs. urban and teaching vs. nonteaching hospital). As mentioned previously, this analysis provides major insight into the epidemiology of VTE in hospitalized patients with SLE.

Furthermore, the analysis quantifies and sheds light on the huge morbidity and mortality as well as cost to the health system

that occurrence of VTE in these patients leads to. The patients with VTE were 2.5 times more likely to die and had a significant increase in moderate to severe disability at discharge (34% vs. 26%). Development of VTE led to three additional days of hospital stay and increased cost by about \$25400.00 in this analysis.

The strength of this study is a large sample of patients over a span of 9 years. This is one of the largest retrospective analysis of VTE hospitalizations for patients with SLE and provides huge confidence that the results likely reflect a true prevalence. The NIS also collects data from a number of centers across the geographic United States, and hence the analysis is likely to be free of geographic bias and is applicable to the US population with SLE.

Despite a large number of patients available in the NIS database, which gives the analysis a high power, there are significant limitations to our study secondary to the database being based on administrative coding. Accuracy of certain variables may be influenced by hospital coding practices. The NIS is a discharge-level database; hence, it was impossible to distinguish whether VTE was the primary reason for admission or a hospital-acquired complication during the patient's stay. We limited our selection of the cohort with VTE to patients with VTE as a top three discharge diagnosis to avoid potential bias. This is a well-accepted methodology to minimize coding bias. A number less than three is likely to miss a significant number of cases, and a higher number is likely to add miscoded cases, thereby inflating numbers. However, there is no definite way to ensure that the sample is completely accurate. This is a descriptive cross-sectional study across each hospitalization, and thus we were unable to draw any causal inference.

Because the NIS does not collect medication data, our study was not able to ascertain whether this large number of at-risk

patients did indeed receive VTE treatment or prophylaxis, thus limiting insight or inference on inpatient practice in this population. Despite clear practice guidelines, many eligible patients either receive no or suboptimal prophylaxis (27,28). In addition, there is no information on the severity of SLE, major organ involvement (especially lupus nephritis and APLA serology), all known risk factors for VTE as well as prognosis of patients with SLE, which are potential confounders. To overcome this limitation, the multivariate analysis included adjustments for coagulopathies and chronic kidney disease. VTE events were not further adjudicated in this analysis because of the potential of introducing coding errors in the analysis and the potential of decreasing the power of the analysis to obtain relevant results. By repeating this analysis using *International Classification of Diseases, 10th Revision (ICD-10)* data, the study may be able to overcome this limitation.

These results, however, call for increased awareness about the prevalence of VTE in SLE. Further longitudinal studies that evaluate the role of known risk factors, such as APLAs and their routine evaluation in hospitalized patients with SLE, will be very useful. Increased vigilance to detect VTE and risk factors for VTE in SLE and implementation of preventive intervention in such patients can limit mortality associated with VTE. Despite these limitations, our findings are very likely reflective of true trends and outcomes of VTE in hospitalized patients with SLE.

In conclusion, this analysis suggests that the risk of VTE is significantly increased in hospitalized patients with SLE. Furthermore, VTE in hospitalized patients with SLE is associated with adverse outcomes and leads to a higher morbidity and mortality as well as prolonged LOS and higher cost of admission. Based on these results, we recommend that hospitalized patients with SLE be considered for VTE treatment with prophylaxis as appropriate and be monitored for development of this serious complication. We also recommend additional analytic studies in other databases to confirm these findings, to further quantify the risks, and to also develop an appropriate monitoring and prophylactic strategy in the hospitalized population with SLE.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published.

**Study conception and design.** Kishore, Mittal, Majithia.

**Acquisition of data.** Kishore, Lirette, Mittal, Majithia.

**Analysis and interpretation of data.** Kishore, Jatwani, Malhotra, Lirette, Majithia.

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