

# Association of Lupus Nephritis Histopathologic Classification With Venous Thromboembolism—Modification by Age at Biopsy



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**Introduction:** Lupus nephritis (LN) is an independent risk factor for venous thromboembolism (VTE). The risk of VTE has not been analyzed by International Society of Nephrology/Renal Pathology Society or World Health Organization LN class. Study goals were to measure VTE incidence in an LN patient cohort, to evaluate associations between VTE and LN class, and to investigate factors modifying associations between VTE and LN class.

**Methods:** A retrospective analysis was performed using Glomerular Disease Collaborative Network data. Image-confirmed VTE was compared between patients with any LN class V lesion and patients with only LN class III or IV. Logistic regression was used to calculate odds ratios and 95% confidence intervals. Effect modification was assessed between main effect and covariates.

**Results:** Our cohort consisted of 534 LN patients, 310 (58%) with class III/IV and 224 (42%) with class V with or without class III/IV, including 106 with class V alone. The VTE incidence was 62 of 534 (11.6%). The odds of VTE were not significantly different between patients with class III/IV and class V in adjusted analyses (odds ratio [OR] = 0.82, 95% confidence interval [CI] = 0.45–1.48). An age interaction was observed ( $P = 0.009$ ), with increased odds of VTE with class III/IV diagnosed at a younger age (2.75, 0.90–8.41 estimated at age 16 years) and decreased odds with class III/IV diagnosed at an older age (0.23, 0.07–0.72 estimated at age 46 years), compared to class V.

**Conclusions:** The VTE incidence was similar among patients with LN classes III/IV and V, suggesting that VTE risk is not limited to class V–related nephrotic syndrome and that age may modulate LN class-specific VTE risk.

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KEYWORDS: lupus; lupus nephritis; renal biopsy; systemic lupus erythematosus; venous thromboembolism

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Patients with systemic lupus erythematosus (SLE), like those with other autoimmune diseases, are at increased risk for venous thromboembolism (VTE) due to hypercoagulability and inflammation, which are

general features of these disease states.<sup>1</sup> Compared to the general population, patients with SLE have a 3.14- to 3.55-fold risk of developing VTE, based on several cohort studies using large population-based databases.<sup>1,2</sup> Furthermore, in a 10-year prospective cohort study of patients with SLE, venous and arterial thrombotic events accounted for 26.5% of deaths.<sup>3</sup>

Additional factors that increase the risk for VTE in SLE patients include antiphospholipid antibodies and glucocorticoids, which are commonly used to treat various manifestations of SLE.<sup>4</sup> Notably,

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hydroxychloroquine, which is also commonly used in the management of SLE, has antithrombotic effects.<sup>5</sup>

Lupus nephritis (LN) has been identified as an independent risk factor for VTE among patients with SLE, based on multivariable analyses in several studies.<sup>6,7</sup> However, studies to date have focused primarily on the association of nephrotic syndrome with thrombosis.<sup>8,9</sup> Furthermore, literature exploring the association of LN with VTE risk by specific LN class is lacking. Sun *et al.* recently demonstrated that the association of LN with another SLE-related outcome, namely, coronary artery disease, varies by specific class of LN.<sup>10</sup> Determining whether a class-specific effect exists for LN and VTE risk could help risk-stratify the need for VTE prophylaxis, anticoagulation duration, and diagnostic testing among patients with SLE.

To our knowledge, the risk of VTE has not been analyzed by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN or World Health Organization (WHO) classification system.<sup>11</sup> The goals of this study were as follows: (i) to measure the incidence of VTE in our cohort of patients with LN (class, III, IV, and/or V); (ii) evaluate the association between VTE and LN class, specifically among patients with or without LN class V; and (iii) investigate factors that modify the association between VTE and LN class. The specific focus on the rates of VTE in patients who had evidence of LN class V relative to other LN classes is based on its association with nephrotic syndrome (a known risk factor for VTE), whereas LN classes III/IV are more strongly associated with nephritic syndrome.<sup>9,12–14</sup>

## MATERIALS AND METHODS

### Study Population

A retrospective analysis was performed using data from patients in the Glomerular Disease Collaborative Network (GDCN). The GDCN is a longitudinal, glomerular disease patient registry and biobank repository that has been ongoing for more than 35 years. Patients are primarily identified by renal biopsy diagnosis in the University of North Carolina Nephropathology Division. The GDCN includes patients followed at University of North Carolina hospitals as well as from private practice nephrologists throughout the southeastern United States. Patients referred to any GDCN physician who meet the biopsy requirements are also invited to participate in the cohort even if their biopsy specimen was not evaluated at the University of North Carolina (<10% of the cohort).

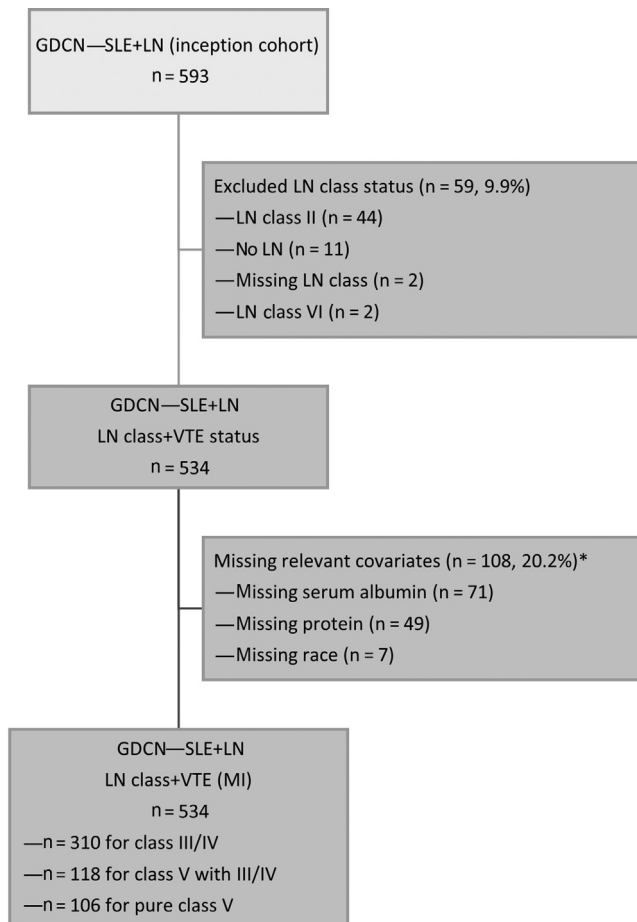
The GDCN inception cohort of patients with SLE and LN, with initial renal biopsy between 1977 and 2016, was used for this study. Our analyses included patients

who had a biopsy diagnosis of lupus nephritis class III, class IV, or class V (with or without additional evidence of class III or IV), as defined by either ISN/RPS or WHO criteria. Biopsy diagnosis was taken from the final reported pathology diagnosis rather than from a retrospective re-evaluation, so that the study would rely on real-world pathology diagnoses. The majority of available biopsy samples (88%) had both immunofluorescence (IF) and electron microscopy (EM) for evaluation. Patients excluded from the study were those with no LN, or with LN class not specified because of insufficient data, and those with LN class II or class VI (because of the low prevalence).

The outcome of interest was image-confirmed VTE, inclusive of deep vein thrombosis (DVT), pulmonary embolism (PE), and superficial VTE (including fistula or graft thromboses). Imaging was done at the discretion of the treating clinician when there was a clinical concern for VTE, and not as part of a regular screening protocol. The VTE could have occurred before or after the date of the initial renal biopsy. The primary objectives were to evaluate the association between VTE and LN class, specifically among patients with LN class V as compared to other LN classes without concomitant class V, and to investigate factors that modify the association between VTE and LN class. The 2 comparison groups were as follows: (i) patients with LN class V with or without class III/IV; and (ii) patients with only LN class III or only LN class IV (no class V). More than half of the patients with a class V lesion also had concomitant proliferative lesions (118 of 224, 52.7%), so they were included in the class V comparison group for the primary analysis. Subsequent sensitivity analyses evaluated a pure Class V group. Covariates of interest included age at biopsy, sex, race (White, African American, Hispanic or Latino, or other), hormonal contraception use, serum albumin, proteinuria, and use of hydroxychloroquine.

### Statistical Analyses

Descriptive statistics were calculated using counts and percentages for categorical covariates and means and standard deviations (SDs) for continuous variables. Multiple imputation was used to address missing covariate information with missing values assumed to be missing at random. Imputed values accounted for no more than 15% missing individually, with an overall missing of 20%. Multiple imputation of 25 datasets was used during model analysis. Logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (95% CI), adjusted for continuous age, sex, race, hormonal contraception use, serum albumin, proteinuria, and use of hydroxychloroquine. Effect modification was assessed by backward elimination and



**Figure 1.** Description of study cohort. GDCN, Glomerular Disease Collaborative Network; LN, lupus nephritis; SLE, systemic lupus erythematosus; VTE, venous thromboembolism.

testing of all 2-way interactions between the main effect and other covariates and considered statistically significant if  $P$  was  $<0.05$ .

In a sensitivity analysis, the comparison groups were redefined as follows: (i) patients with LN class V alone; (ii) patients with LN class V with class III/IV; and (iii) patients with only LN class III/IV (no class V).

Subsequent sensitivity analyses consisted of models with a more conservative VTE outcome and other covariates to consider the impact of missing data as follows: (i) VTE definition including only DVT or PE as the outcome modeled; (ii) inclusion of antiphospholipid antibody positivity (lupus anticoagulant, anticardiolipin antibodies, and/or anti- $\beta_2$ -glycoprotein-1 antibodies) as an additional covariate that was not included in the main analysis because of high level of missing data (39%); and (iii) inclusion of thrombotic microangiopathy (TMA) as an additional covariate of interest.

This study was approved by the UNC Institutional Review Board (UNC IRB 18-3339) and adhered to the ethical principles of the Declaration of Helsinki. A

waiver of informed consent was issued by the UNC Institutional Review Board.

## RESULTS

The cohort included 593 patients (Figure 1). A total of 59 patients were excluded because they had LN class II ( $n = 44$ ), LN class VI ( $n = 2$ ), no LN ( $n = 11$ ), or LN class information was missing ( $n = 2$ ). The remaining 534 patients comprised the cohort included in this study: 103 (19.3%) with LN class III, 207 (38.8%) with LN class IV, 106 (19.9%) with LN class V, and 118 (22.1%) with LN class V with class III/IV. A total of 108 patients (20.2%) had missing data, including 71 missing serum albumin values, 49 missing urine protein values, and race information missing for 7 patients. Table 1 describes the demographic and other relevant baseline characteristics of the study population by LN class. The mean  $\pm$  SD age of the study population at biopsy was  $31.2 \pm 15.1$  years (range, 6–79 years) and tended to be somewhat older among the group comprising LN class V patients, with or without class III/IV patients ( $34.3 \pm 14.5$  years,) compared with the group comprising only LN class III/IV (no class V) patients ( $28.9 \pm 15.2$  years). In all, 25% of the study population were men, 58% were African American, 28% were White, and 8% were Hispanic or Latino. The total number of image confirmed VTEs was 62 (including superficial VTEs [ $n = 4$  plus 1 co-occurring with DVT] and fistula or graft thromboses [ $n = 3$  plus 2 co-occurring with DVT]). The number of DVTs or PEs was 55 (10.3% of the study cohort; DVT  $n = 33$  plus 2 co-occurring with fistula or graft thrombosis and 1 co-occurring with superficial VTE; PE  $n = 9$ ; co-occurring DVT and PE:  $n = 10$ ). The majority (65%; 40 of 62) of the VTEs occurred after the initial renal biopsy, but 35% (22 of 62) occurred before the date of the initial biopsy. Most (85%; 51 of 60) of the VTEs occurred after the SLE diagnosis, but 15% (9/60) occurred before the date of the SLE diagnosis.

In unadjusted analyses based on total number of VTEs, the odds of having a VTE were not significantly different for patients with only LN class III/IV (no class V) compared to those with LN class V with or without class III/IV (OR = 0.74; 95% CI = 0.44–1.27). When adjusted for covariates, the odds of having a VTE remained similar between patients with LN class III/IV and patients with LN class V with or without class III/IV (OR = 0.82, 95% CI = 0.45–1.48).

Assessment for effect modification of LN class on VTE by covariates indicated an effect modification by age at biopsy at an  $\alpha$  level of 0.05 (Figure 2). This analysis demonstrated increased odds of VTE with LN class III/IV diagnosed at a younger age (among patients

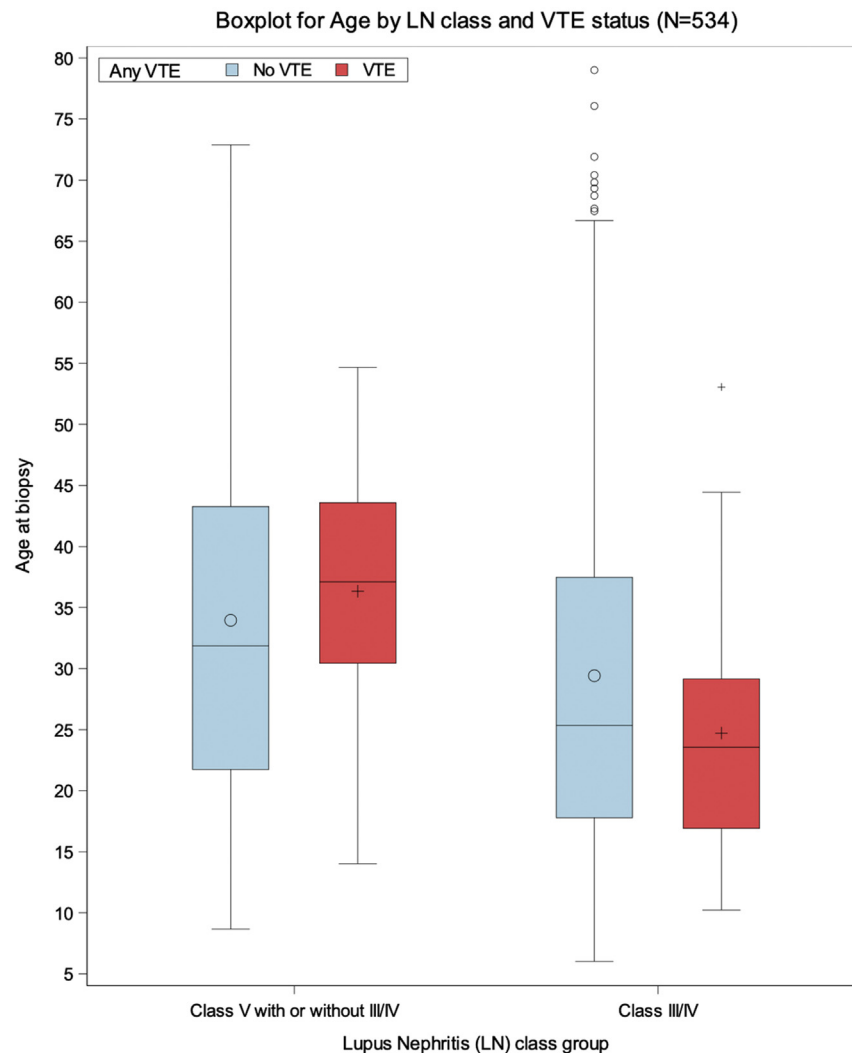
**Table 1.** GDCN lupus nephritis cohort descriptive statistics

Characteristic	Lupus nephritis class group							
	Overall (n = 534)		Class III or IV (n = 310)		Class V with III/IV (n = 118)		Class V (n = 106)	
Age at biopsy (yr), mean ± SD	31.2 ± 15.1		28.9 ± 15.2		32.9 ± 13.9		35.8 ± 15.0	
	N	%	n	%	n	%	n	%
Male sex	132	24.7	82	26.5	22	18.6	28	26.4
Hormonal contraceptive use	94	17.6	54	17.4	23	19.5	17	16.0
Hydroxychloroquine use	334	62.5	178	57.4	81	68.6	75	70.8
African American	307	57.5	157	50.6	72	61.0	78	73.6
White	147	27.5	102	32.9	25	21.2	20	18.9
Hispanic or Latino	43	8.1	26	8.4	14	11.9	3	2.8
Other	30	5.6	21	6.8	4	3.4	5	4.7
Serum albumin <2.5 g/dl	173	32.4	91	29.4	47	39.8	35	33.0
Serum albumin (g/dl), mean ± SD	2.73 ± 0.76		2.77 ± 0.73		2.58 ± 0.74		2.75 ± 0.89	
Protein (mg/24 hr), median (IQR)	3000 (1300–5756)		2400 (1000–4867)		4099 (2132–6860)		3900 (1816–6300)	
Total number of VTE events <sup>a</sup>	62	11.6	32	10.3	16	13.6	14	13.2
VTE events (DVT or PE only) <sup>b</sup>	55	10.3	29	9.4	12	10.2	14	13.2
TMA at time of first biopsy	10	1.9	6	1.9	4	3.4	0	0

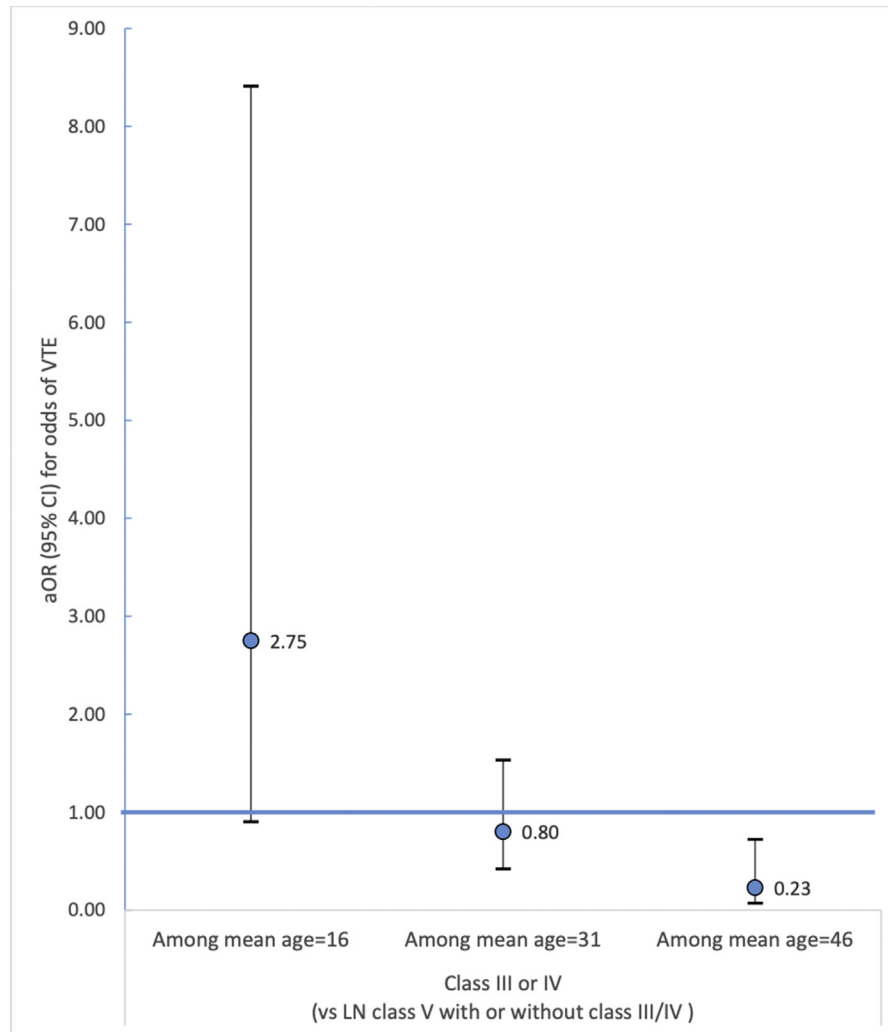
DVT, deep vein thrombosis; GDCN, Glomerular Disease Collaborative Network; IQR, interquartile range; TMA, thrombotic microangiopathy; VTE, venous thromboembolism.

<sup>a</sup>Image-confirmed; includes superficial VTEs (n = 4 plus 1 co-occurring with DVT) and fistula or graft thromboses (n = 3 plus 2 co-occurring with DVT)

<sup>b</sup>DVT: n = 33 plus 2 co-occurring with fistula or graft thrombosis and 1 co-occurring with superficial VTE; PE: n = 9; co-occurring DVT and PE: n = 10



**Figure 2.** Age distribution by lupus nephritis (LN) class and venous thromboembolism (VTE) status (N = 534).



**Figure 3.** Venous thromboembolism (VTE) odds ratio by lupus nephritis (LN) class and age at biopsy.

with mean age of 16 years at biopsy (OR = 2.75, 95% CI = 0.90–8.41 versus LN class V with or without class III/IV) and decreased odds of VTE with LN class III/IV diagnosed at an older age (among patients with mean age of 46 years at biopsy: OR = 0.23, 95% CI = 0.07–0.72 vs. LN class V with or without class III/IV) (Figure 3). There were no overall sex differences in odds of VTE and no effect modification of such by age.

These findings remained robust in sensitivity analyses described in Table 2. In the sensitivity analysis, results remained consistent even when compared to LN class V only instead of LN class V with or without class III/IV. Odds of VTE remained higher for LN class III/IV among younger patients and lower for LN class III/IV among older patients when compared to patients with LN class V only. With the VTE definition limited to only DVT and PE or including antiphospholipid antibody positivity or TMA separately, results were similar, demonstrating increased odds of VTE in patients with LN class III/IV diagnosed at a younger age (mean age of 16 years at biopsy) and decreased odds of

VTE in patients with LN class III/IV diagnosed at an older age (mean age of 46 years at biopsy), compared with LN class V with or without class III/IV.

Not all participants in our analysis had available activity and chronicity indices (294 and 295 participants, respectively, or only 55%). Among these participants with non-missing indices, the median activity index was 8 (interquartile range [IQR] = 5–11) and the chronicity index was 2 (IQR = 1–4). No evidence of association was found between activity index and odds of VTE (unadjusted OR = 1.02, 95% CI = 0.92–1.12) for a 1-unit increase in activity index). Some evidence of association, albeit not statistically significant at 0.05, was found between chronicity index and odds of VTE (unadjusted OR = 1.23, 95% CI = 0.98–1.56, for a 1-unit increase in chronicity index). Of 522 participants (98%) with this information available, the median creatinine at the time of first kidney biopsy was 1.00 (IQR = 0.76–1.80) mg/dl.

The time interval between diagnosis of SLE and diagnostic biopsy for LN was available for 509 of 534

**Table 2.** Adjusted aORs and 95% CIs for association of LN class III/IV versus LN class V with or without class III/IV with VTE<sup>a</sup>

Model	Estimated at age at biopsy		
	Age 16 yr (−1 SD)	Age 31 yr (mean)	Age 46 yr (+1 SD)
	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Main model <sup>b</sup>	2.75 (0.90–8.41)	0.80 (0.42–1.53)	<b>0.23 (0.07–0.72)</b>
LN class sensitivity analysis			
M1: 3-level LN group definition			
LN class III/IV (vs. LN class V)	4.21 (0.78–22.7)	1.04 (0.42–2.54)	<b>0.25 (0.07–0.89)</b>
LN class V with III/IV (vs. LN class V)	1.93 (0.28–13.1)	1.59 (0.60–4.25)	1.31 (0.36–4.77)
Subsequent sensitivity analyses			
M2: VTE defined as DVT or PE only <sup>c</sup>	<b>5.53 (1.49–20.5)</b>	1.11 (0.54–2.26)	<b>0.22 (0.07–0.72)</b>
M3: including APLab covariate <sup>d</sup>	2.90 (0.93–9.01)	0.79 (0.41–1.52)	<b>0.22 (0.07–0.68)</b>
M4: including TMA covariate <sup>e</sup>	3.05 (0.97–9.59)	0.79 (0.41–1.53)	<b>0.21 (0.06–0.66)</b>

aOR, adjusted odds ratio; APLab, antiphospholipid antibodies; CI = confidence interval; DVT, deep vein thrombosis; LN, lupus nephritis; PE, pulmonary embolism; TMA, thrombotic microangiopathy; VTE, venous thromboembolism.

Bolded values indicate a 95% CI where the null effect of odds ratio = 1 is not included, at a 0.05  $\alpha$ -level of significance.

<sup>a</sup>Odds shown are for class III/IV versus class V/V combinations, with the exception of M1

<sup>b</sup>Model is stratified by of birth decade and biopsy decade and includes 25 imputed datasets, n = 534 (adjusted for age at biopsy, sex, 4-level race/ethnicity, hormonal contraceptive use, hydroxychloroquine use, proteinuria, and serum albumin).

<sup>c</sup>VTE outcomes were reduced from 62 to 55.

<sup>d</sup>Fifty imputed datasets were used to account for missingness of APLab.

<sup>e</sup>TMA is significantly associated with VTE.

participants, or 95% of the cohort. Among these 509 participants, the median time between SLE diagnosis and diagnostic biopsy was 64 (IQR = 1–991) days. [Supplementary Table S1](#) outlines the frequency and percentage of immunosuppressive and immunomodulatory medication and anticoagulant use in patients who developed VTE. Of these, the most common medications were prednisone (81%), Plaquenil (71%), cyclophosphamide IV (66%), and mycophenolate mofetil (65%). The indication for immunosuppressive therapy (i.e., renal vs. extrarenal) was not able to be extracted from the data set. From the data we have available (also shown in [Supplementary Table S1](#)), only 2 individuals were on aspirin at the time of the event, and 1 patient was on rivaroxaban, and no other patients were on prophylactic anticoagulation at the time of the event. However because of the limitations of the dataset and concern for potential missing data, we cannot conclusively comment on status of prophylactic anticoagulation at the time of VTE event for the entire cohort.

## DISCUSSION

In this study, VTE occurred in approximately 10% of patients. This is similar to an incidence of 8.4% reported among another large (n = 1930) multiethnic cohort of patients with SLE (31% of whom had LN).<sup>6</sup> In our study, the risk of VTE was similar among patients with LN class III or class IV compared with LN class V, even when adjusting for covariates. Our findings were consistent even when we excluded patients with “mixed” lesions and compared patients with class III/IV to those with only class V. These results suggest that the observed association between LN and VTE in this

and other studies is not limited to class V–associated nephrotic syndrome.

A small number of other studies have examined the association of LN with VTE risk, but ours is the first, to our knowledge, to analyze that association by LN class. For example, in a large, multi-ethnic cohort of patients with SLE (n = 1930), a history of nephritis was identified as a risk factor for thrombosis, but neither frequency nor risk by specific LN class was analyzed.<sup>6</sup> Among a smaller cohort of German patients of White ethnicity with SLE, nephritis (defined by ACR criteria, with only a subgroup having renal biopsy samples) was determined to be a risk factor for thromboembolic events; but, again, no analysis by LN class was provided (relative risk [RR] = 1.4, 95% CI = 1.0–2.0).<sup>6,7</sup> Both of these studies included arterial (e.g., stroke, myocardial infarction) and venous (e.g., DVT, PE) thromboembolic events, unlike our study, which analyzed only VTEs. In 2 other small studies in SLE patients with antiphospholipid antibodies, there were higher incidences of thrombotic events among patients with LN than in those without, but distribution of incidences by LN class was not indicated in either study.<sup>15,16</sup> The distribution of thrombotic events across LN classes has been reported in a smaller retrospective study of 200 patients with SLE and LN, of whom only 147 were diagnosed by biopsy, and 53 by presence of proteinuria and/or alterations in urinary sediment.<sup>11</sup> However, no statistical analysis was provided regarding the potential association of LN class with VTE risk in that study.

An interesting finding from our study was the effect LN class on VTE frequency by age at biopsy—specifically, increased odds of VTE with class III/IV diagnosed at a younger age, and decreased odds of VTE

with class III/IV diagnosed at an older age. These estimates remained robust in sensitivity analyses. Although the clinical significance, if any, of this finding is unknown at this time, it is interesting to speculate regarding possible mechanisms. The heavy proteinuria and low serum albumin associated with nephrotic syndrome are predictive of VTE risk in LN.<sup>9</sup> The effect of LN on VTE risk may be mediated by different mechanisms in class III/IV than in class V—perhaps related to the inflammatory nature of overall SLE disease in individuals with class III/IV rather than to the renal lesion itself that plays a role in VTE risk among class V nephrotic syndrome patients. Alternatively, perhaps younger patients with class III/IV have a heightened VTE risk related to the likely longer duration of disease and exposure to immunosuppression, increased rate of infection and hospitalization, and more advanced progression toward end-stage kidney disease.

Our cohort was somewhat unbalanced in terms of age distribution among LN classes, with more older patients with LN class V with or without class III/IV and more younger patients with LN class III/IV alone. The literature is lacking regarding age distribution among various LN classes. One small retrospective study of 173 hospitalized patients with LN in China reported very similar mean ages among patients with class II ( $27.49 \pm 13.26$ ), class III and IV ( $26.38 \pm 13.65$ ), and class V ( $28.27 \pm 13.83$ ) LN.<sup>17</sup>

Study limitations include the retrospective study design, inability to control for disease duration or severity, cumulative medication exposure, or length of treatment, and the inability to evaluate class change over time, or to adjust for aspirin use. Anti-phospholipid antibody data availability was also limited (39% missing data), which is an important consideration in the evaluation of thromboembolic disease. Other variables for which we could not adjust and that could potentially have an impact on VTE risk differences (or lack thereof) between LN classes include medication differences between classes (e.g., use of immunosuppression) and possible management differences for those with class V. For example, given the broadly accepted VTE risk with nephrotic syndrome, those patients may undergo a higher rate of screening or imaging for thrombosis and/or more frequently receive antiplatelet therapy or other VTE prophylaxis. In this study, however, VTEs were assessed by clinically determined studies and not as part of a regular screening protocol, introducing the possibility of underdiagnosing asymptomatic patients with VTE. Finally, as noted above, the use of a combined category of LN class (class V with or without class III/IV) may have affected our findings. However, we would expect

this classification scheme to bias our results toward minimizing any observed differences. In our sensitivity analyses, we excluded patients with combined lesions and noted consistent relationships between age, LN class and VTE.

Strengths of our study include a relatively large real-world cohort, a racially diverse patient population, biopsy data for all individuals, and an outcome of interest based on verified clinical events (VTE) in a real-world setting.

The results of our observational study add to the limited existing literature demonstrating that LN is an independent risk factor for VTE. Our study is the first to analyze the association between LN and VTE risk by class, and our results suggest that the increased VTE risk in LN is not limited to LN class V. The age-specific analysis demonstrating increased odds of VTE with class III/IV LN diagnosed at a younger age and decreased odds of VTE with class III/IV LN diagnosed at an older age may suggest the presence of an age-sensitive modulation of LN class-specific VTE risk.

Future studies are needed to better define the relationship between LN and VTE risk to identify potential at-risk populations. Future research should also examine the relationship between age at biopsy and LN class-specific rate of VTE, to determine whether the effect modification of age is present in other large LN cohorts.

## DISCLOSURE

SZS has served as a consultant on an Advisory Board for GlaxoSmithKline and has received a research grant from Pfizer. VKD has received consultant fees from Bayer, Novartis, and Retrophin and honoraria from UpToDate. All the other authors declare no competing interests.

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## AUTHOR CONTRIBUTIONS

The following authors contributed to study conception, design, supervision, data collection, statistical analysis, interpretation, writing and revision of manuscript: IC, VKD, KLG, CA, CJP, LNB, AL, SLH, SZS. JCJ and RJF contributed to revision of the manuscript. All authors revised the manuscript and approved the final report.

## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Table S1.** Frequency and percentage of medication use in patients who developed VTE

**STROBE Statement**

## REFERENCES

1. Aviña-Zubieta JA, Vostretsova K, De Vera MA, et al. The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus: a general population-based study. *Semin Arthritis Rheum.* 2015;45:195–201.
2. Jorge A, Lu L, Choi H. The risk of pulmonary embolism and deep venous thrombosis in systemic lupus erythematosus in the united kingdom: a population-based study. *Ann Rheum Dis.* 2016;75(Suppl 2):550–551.
3. Cervera R, Khamashta MA, Font J, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. *Medicine (Baltimore).* 2003;82:299–308.
4. Al-Homood IA. Thrombosis in systemic lupus erythematosus: a review article. *ISRN Rheumatol.* 2012;2012:428269.
5. Belizna C. Hydroxychloroquine as an anti-thrombotic in anti-phospholipid syndrome. *Autoimmunity Rev.* 2015;14:358–362.
6. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. *Ann Rheum Dis.* 2009;68:238–241.
7. Manger K, Manger B, Repp R, et al. Definition of risk factors for death, end stage renal disease, and thromboembolic events in a monocentric cohort of 338 patients with systemic lupus erythematosus. *Ann Rheum Dis.* 2002;61:1065–1070.
8. Hinojosa-Azaola A, Romero-Diaz J, Vargas-Ruiz AG, et al. Venous and arterial thrombotic events in systemic lupus erythematosus. *J Rheumatol.* 2016;43:576–586.
9. Mahmoodi BK, ten Kate MK, Waanders F, et al. High absolute risks and predictors of venous and arterial thromboembolic events in patients with nephrotic syndrome: results from a large retrospective cohort study. *Circulation.* 2008;117:224–230.
10. Sun EY, Alvarez C, Sheikh SZ. Association of lupus nephritis with coronary artery disease by ISN/RPS classification: results from a large real-world lupus population. *ACR Open Rheumatol.* 2019;1:244–250.
11. Zaldivar-Alcantara H, Herrera-Jimenez LE, Dehesa-Lopez E, et al. Risk factors for the development of thrombotic complication in patients with lupus erythematosus and lupus nephropathic. *Rev Invest Clin.* 2013;65:199–208.
12. Almaani S, Meara A, Rovin BH. Update on lupus nephritis. *Clin J Am Soc Nephrol.* 2017;12:825–835.
13. Gomez Mendez LM, Cascino MD, Katsumoto TR, et al. Outcome of participants with nephrotic syndrome in combined clinical trials of lupus nephritis. *Lupus Sci Med.* 2019;6, e000308.
14. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. *Kidney Int.* 1985;28:429–439.
15. Domingues V, Nwaukoni J, Buyon JP, et al. History of lupus nephritis is an independent risk factor for thrombosis in systemic lupus erythematosus patients with antiphospholipid antibodies [abstract]. *Arthritis Rheumatol.* 2016;68(suppl 10). Available at: <https://acrabstracts.org/abstract/history-of-lupus-nephritis-is-an-independent-risk-factor-for-thrombosis-in-systemic-lupus-erythematosus-patients-with-antiphospholipid-antibodies/>. Accessed January 7, 2020.
16. Choojitarom K, Verasertniyom O, Totemchokchayakarn K, et al. Lupus nephritis and Raynaud's phenomenon are significant risk factors for vascular thrombosis in SLE patients with positive antiphospholipid antibodies. *Clin Rheumatol.* 2008;27:345–351.
17. Tang Y, Zhang W, Zhu M, et al. Lupus nephritis pathology prediction with clinical indices. *Sci Rep.* 2018;8:10231.