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BRIEF REPORT

Association of Lupus Nephritis With Coronary Artery Disease by ISN/RPS Classification: Results From a Large Real-world Lupus Population

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Objective. Patients with systemic lupus erythematosus (SLE) are at an increased risk for developing coronary artery disease (CAD). Several studies suggest that the presence of lupus nephritis (LN) is independently associated with CAD. The purpose of our study was to assess whether the presence of LN is independently associated with CAD in our patient population and whether this association varies by class of LN.

Methods. A retrospective cross-sectional analysis was performed using medical records of patients 18 years and older with SLE at University of North Carolina Hospitals from April 4, 2014, to December 31, 2017. Subjects were identified using *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) codes specific for SLE. LN class was defined by International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification. CAD was the outcome of interest. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs).

Results. Our sample consisted of 3732 patients with SLE, of whom 598 (16%) had LN and 537 (14%) had CAD. When adjusting for demographics and factors associated with CAD and LN, the odds of having CAD were significantly higher for patients with SLE and LN compared with patients without LN (OR 1.47; 95% CI 1.07-2.02; $P = 0.017$). Controlling for these factors, class III LN (OR 1.98; 95% CI 0.95-4.12; $P = 0.069$) and class III/V LN (OR 2.23; 95% CI 1.09-4.62; $P = 0.028$) were very strongly associated with CAD in subjects with LN compared with subjects without LN.

Conclusion. We confirm the observations of previous studies that LN is significantly associated with CAD. Our study is the first to show the association between CAD and specific classes of LN.

INTRODUCTION

Coronary artery disease (CAD) is responsible for more than 370 000 deaths in the United States annually and is the leading cause of death in patients with systemic lupus erythematosus (SLE) (1,2). Patients with SLE are at an increased risk for developing premature atherosclerosis and CAD compared with cohorts without lupus (3–5). This risk cannot be attributed to the presence of traditional cardiovascular risk factors alone among patients with lupus compared with those without the disease, suggesting that SLE is an independent risk factor for CAD (6,7).

A handful of studies have established the link between lupus nephritis (LN) and CAD. These studies have demonstrated that patients with LN have a 2.8- to 8.3-fold risk of developing CAD

compared with controls (8–10). However, literature exploring this association by specific LN class is lacking. The purpose of our study was to determine whether the presence of LN is independently associated with CAD in our cohort and whether this association varies by class of LN.

METHODS

Study subjects. A retrospective cross-sectional analysis was performed using data from the Carolina Data Warehouse for Health (CDW-H) of patients 18 years and older with SLE at University of North Carolina (UNC) hospitals from April 4, 2014, to December 31, 2017. The CDW-H is a central data repository that contains clinical, research, and administrative data sourced

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from the UNC Health Care System through Epic (electronic medical record) and is housed within the National Institutes of Health–funded North Carolina Translational and Clinical Sciences Institute at UNC.

Subjects were identified using *International Classification of Diseases, Ninth Revision* (ICD-9) and *International Classification of Diseases, 10th Revision* (ICD-10) codes for SLE. ICD-9 and ICD-10 codes, previously described in similar studies, were used to identify cases of SLE, nephritis, and CAD (myocardial infarction and unstable angina) (8–10). Patients who had at least one of the following were identified as subjects with SLE: ICD-9 code 710.0 and ICD-10 codes M32.1, M32.10-M32.19, M32.8, and M32.9.

Variables. Our main effect of interest was presence of LN (yes or no) based on ICD-9 and ICD-10 codes (ICD-9: 580.0, 580.81, 580.89, 580.9, 581.0-581.2, 581.81, 581.89, 581.9, 582.0-582.2, 582.81, 582.89, 582.9, 583.0-583.2, 583.81, 583.89, 583.9, and 580.4; ICD-10: M32.14, N00.1-N00.5, N00.7-N00.9, N01.0-N01.5, N01.7-N01.9, N03.0-N03.5, N03.7-N03.9, N05.1-N05.5, and N05.7-N05.9). LN class was defined by International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification and confirmed by a review of the renal biopsy or clinic notes (provider documentation from clinical encounters). Charts of subjects identified by our search as having LN were independently reviewed by a research staff member with formal training in lupus disease activity assessment and by EYS to ensure accuracy and true case definition.

CAD (yes or no) was the outcome of interest. CAD status was defined by presence of ICD-9 and ICD-10 diagnosis codes for CAD (ICD-9: 414.00, 414.01, 414.2-414.4, 414.8, 414.9, and V45.82; ICD-10: I25.5, I25.6, I25.82-I25.84, I25.89, and I25.9), unstable angina (ICD-9: 411.1 and 411.8; ICD-10: I20.0, I20.9, I24.0, I24.8, I24.9, I25.9, I25.10, I25.110, I25.111, I25.118, and I25.119), non-ST (ST segment elevation on EKG) segment elevation myocardial infarction, or ST segment elevation myocardial infarction (ICD-9: 410.0-410.9, 411.81, and 412; ICD-10: I21.00-I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I21.9, I22.0-I22.2, I22.8, I22.9, and I25.2).

Covariates consisted of the following: demographic factors (age [age in years at first clinical encounter during the study period], sex [male or female], and race and/or ethnicity [white, African American, Hispanic or Latino, Asian, American Indian or Pacific Islander, or other/mixed race]), CAD factors (hypertension [HTN], dyslipidemia [DLP], diabetes mellitus [DM], and smoking history), and lupus-specific factors (any steroid exposure [current or past use] and use of disease-modifying antirheumatic drugs [DMARDs]).

Smoking history (nonsmoker or current or prior smoker) was based on self-reported smoking status listed in the chart at the time of data collection. HTN was defined as an average systolic blood pressure greater than 140 mm Hg, as an average diastolic blood pressure greater than 90 mm Hg, by use of antihypertensive medication, or by the ICD-9/ICD-10 diagnostic code. Antihypertensive medications were divided into the following categories: cardioprotective (angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or beta-blockers) and noncardioprotective.

DM was defined as use of a glucose-lowering agent or by the ICD-9/ICD-10 codes. Glucose-lowering agents that were designated as cardioprotective included glucagon-like peptide-1 agonists or sodium-glucose cotransporter-2 inhibitors.

DLP was defined as an average total cholesterol level greater than 239 mg/dl, as an average low-density lipoprotein level greater than 159 mg/dl, as an average high-density lipoprotein level less than 40 mg/dl, as an average triglyceride level greater than 199 mg/dl, by use of a lipid-lowering medication, or by the ICD-9/ICD-10 codes. Lipid-lowering agents were divided into the following categories: cardioprotective (statins, PSK9 inhibitors, and ezetimibe) and others. Lipid values included fasting and nonfasting values. Medications deemed cardioprotective have been associated with reduction of cardiovascular risk. DMARDs were grouped as antimalarials (hydroxychloroquine, chloroquine, or quinacrine) or immunosuppressive agents (azathioprine, chlorambucil, cyclosporine, methotrexate, mycophenolate, cyclophosphamide, rituximab, belimumab, and tacrolimus). All covariates were categorical apart from age.

Statistical analysis. Descriptive statistics were computed using counts and percentages for categorical covariates and means and SDs for continuous variables. Multiple imputation using 10 data sets was used to address missing covariate information. Logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs), with adjustment for demographic, CAD, and lupus factors (previously defined). The odds of patients having CAD compared with controls with SLE was determined for the entire cohort with LN and was determined by individual LN class. "Class involvement" is defined as the presence of class-specific changes on the renal biopsy, whether alone or in combination with a second ISN/RPS class. Subjects with two unique ISN/RPS classes present on the renal biopsy were analyzed separately from those with only one ISN/RPS class.

To address possible effect modifiers, two-way interactions between LN and all covariates were assessed at a 0.10 level. Multiple imputation assuming missing at random was used to address missing covariate information if present in more than 5% of our sample. All statistical computations and analyses were conducted using SAS version 9.4 software (SAS Institute, Inc).

Our study was reviewed and approved by the UNC Institutional Review Board and adheres to the ethical principles of the Declaration of Helsinki. A waiver of informed consent was obtained because of the retrospective nature of our study.

RESULTS

A total of 3732 patients fit our inclusion criteria and were included in our analysis. Table 1 describes the demographic and disease characteristics of our cohort with SLE. The mean age (SD) of our population was 48 (15.2) years. Twelve percent of the sample were men, 43% were white, 38% were African American, and 6% were Hispanic or Latino. Sixteen percent had LN, and 14% had CAD. Seventy percent had HTN, 42% had DLP, 23% had DM, and 38% had a history of smoking. Sixty-eight percent took DMARDs, 65% took steroids, and 7% had end-stage renal disease (ESRD).

Of the 598 patients with SLE and LN, most had evidence of class III, class IV, or class V LN alone or in combination (class III: n = 66; class IV: n = 153; class V: n = 98; class III/V: n = 68; class IV/V: n = 53). Table 2 describes the prevalence of CAD and demographic, CAD-specific, and lupus-related factors by LN class for these patients. One hundred twenty-two of those with LN had an unknown (missing) LN class, and eight patients had evidence of class III or class IV LN on separate biopsies. These patients were not included in the class-specific analyses. The remaining subjects made up small groups belonging to other classes: class I (n = 4), class II (n = 18), class II/V (n = 3), and class VI (n = 5).

Table 3 describes our overall LN and CAD analyses. Covariates that were significantly associated with increased odds of having CAD included older age, history of smoking, HTN (ICD-9/ICD-10 codes), use of cardioprotective antihypertensives, DLP (ICD-9/ICD-10 codes), cardioprotective DLP medications, any DLP medication use, DM (ICD-9/ICD-10 codes), and noncardioprotective DM medication use. Factors strongly associated with increased odds of having CAD but that did not meet 0.05 significance, included male sex and use of noncardioprotective HTN medications. Use of antimalarials was strongly associated with decreased odds of having CAD, but this association was not significant. In our fully adjusted model, the overall odds of having CAD were significantly higher for patients with SLE and LN compared with those without LN (OR 1.47; 95% CI 1.07-2.02; P = 0.017).

Because of the low number of subjects with class I, class II, class II/V, and class VI LN, the odds of having CAD for these groups was not calculated. Of the 18 patients with class II LN,

only 3 had CAD. Two of the five patients with class VI LN had CAD. In the class-specific analyses, class III/V LN was significantly associated with CAD (OR 2.23; 95% CI 1.09-4.62; P = 0.028) compared with subjects without LN after we controlled for demographic, CAD, and LN factors (Table 4). Class III LN alone was very strongly associated with CAD (OR 1.98; 95% CI 0.95-4.12; P = 0.069). Class IV LN (OR 1.17; 95% CI 0.63-2.16; P = 0.62), class IV/V LN (OR 1.62; 95% CI 0.67-3.91; P = 0.28), and class V LN (OR 1.25; 95% CI 0.65-2.38; P = 0.50) were not associated with an increased risk of CAD in patients with LN compared with patients without LN.

DISCUSSION

The results of our large retrospective study confirm the observation that LN is independently associated with CAD after we controlled for demographics and risk factors associated with CAD and LN. We found that patients with LN were at 47% higher odds of having CAD compared with patients with SLE without LN. Our findings corroborate the observations of existing studies and further highlight the important association between LN and CAD in a real-world diverse patient population.

In our class-specific analyses, we observed that subjects with class III LN and class III/V LN have increased odds of having CAD compared with those without LN. The association between class III involvement and CAD may be explained by increased disease severity and activity in these patients compared with controls with SLE. In a study by Tang et al (11), proliferative LN was associated with higher blood pressure, increased levels of uric acid, lower complement levels, elevated double-stranded DNA levels, and significantly higher Systemic Lupus Erythematosus Disease Activity Index (SLE-DAI) scores. Nephrotic range proteinuria, a characteristic of class V LN, has been associated with premature atherosclerosis in patients with SLE, significantly higher SLEDAI scores, and increased Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index scores (12).

It is well known that progression to ESRD is associated with increased morbidity and mortality from CAD and that patients with LN are at an increased risk for developing ESRD compared with patients with SLE without LN (13). Wells and Ward (10) excluded patients with ESRD from analyses, whereas Faurschou et al (8) stratified patients by ESRD (yes or no). Although patients with ESRD experienced a significantly increased risk of ischemic heart disease (IHD)–related hospitalizations compared with those without ESRD in their study, Faurschou et al (8) found that the observed-to-expected ratio for IHD-related hospitalizations was only slightly lower for those without ESRD compared with that for the overall cohort. This led the authors to conclude that ESRD's contribution to risk of IHD-related hospitalizations was low. Hermansen et al (9) did not report whether ESRD status was considered in their analyses. We did not control for ESRD in our study because

Table 1. Demographics and CAD-specific and lupus-related factors by LN status

	Overall (N = 3732)	No LN (n = 3134)	LN (n = 598)
Demographics			
Age (range: 18-94 years), mean ± SD, y	48.0 ± 15.2	49.3 ± 15.1	40.9 ± 14.0
Male sex, n (%)	460 (12.3)	360 (11.5)	100 (16.7)
Race and/or ethnicity, n (%)			
White	1618 (43.4)	1497 (47.8)	121 (20.2)
African American	1433 (38.4)	1072 (34.2)	361 (60.4)
Hispanic or Latino	235 (6.3)	174 (5.6)	61 (10.2)
Asian	56 (1.5)	40 (1.3)	16 (2.7)
American Indian, native Hawaiian, or Pacific Islander	31 (0.8)	23 (0.7)	8 (1.3)
Other	81 (2.2)	70 (2.2)	11 (1.8)
Missing	278 (7.4)	258 (8.2)	20 (3.3)
CAD, n (%)	537 (14.4)	440 (14.0)	97 (16.2)
Myocardial infarction, n (%)[a]	220 (5.9)	185 (5.9)	35 (5.9)
HTN, n (%)	2601 (69.7)	2057 (65.6)	544 (91.0)
HTN by ICD-9/ICD-10 code, n (%)	2073 (55.5)	1626 (51.9)	447 (74.7)
Systolic blood pressure, mean ± SD, mm Hg	128.9 ± 15.3	128.5 ± 15.3	130.7 ± 15.5
Diastolic blood pressure, mean ± SD, mm Hg	74.7 ± 9.3	74.0 ± 9.0	78.2 ± 10.3
Antihypertensive medication use, n (%)	2374 (63.6)	1849 (59.0)	525 (87.8)
Cardioprotective	2008 (53.8)	1513 (48.3)	495 (82.8)
Others	1832 (49.1)	1441 (46.0)	391 (65.4)
DLP, n (%)	1574 (42.2)	1302 (41.5)	272 (45.5)
DLP by ICD-9/ICD-10 code	1044 (28.0)	855 (27.3)	189 (31.6)
Lipid-lowering medication use	1298 (34.8)	1087 (34.7)	211 (35.3)
Cardioprotective	974 (26.1)	799 (25.5)	175 (29.3)
Others	646 (17.3)	578 (18.4)	68 (11.4)
DM, n (%)	859 (23.0)	693 (22.1)	166 (27.8)
DM by ICD-9/ICD-10 code	643 (17.2)	535 (17.1)	108 (18.1)
Diabetes medication use	720 (19.3)	575 (18.3)	145 (24.2)
Cardioprotective	73 (2.0)	68 (2.2)	5 (0.8)
Others	713 (19.1)	569 (18.2)	144 (24.1)
History of smoking/tobacco use, n (%)			
Nonsmoker	2152 (57.7)	1731 (55.2)	421 (70.4)
History of or current smoking/tobacco use	1422 (38.1)	1254 (40.0)	168 (28.1)
Missing	158 (4.2)	149 (4.8)	9 (1.5)
Lupus factors, n (%)			
Steroid use	2420 (64.8)	1947 (62.1)	473 (79.1)
Disease-modifying antirheumatic drug use	2544 (68.2)	2014 (64.3)	530 (88.6)
Antimalarial	2174 (58.3)	1714 (54.7)	460 (76.9)
Immunosuppressive	1438 (38.5)	1003 (32.0)	435 (72.7)
End-stage renal disease	257 (6.9)	93 (3.0)	164 (27.4)

Abbreviation: CAD, coronary artery disease; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, 10th Revision*; LN, lupus nephritis; ST, ST segment elevation on EKG.
[a]Myocardial infarction includes non-ST elevation myocardial infarction and ST elevation myocardial infarction.

it was identified as a possible mediator in the relationship between LN and CAD. In examining the proportion of patients with ESRD by class, there was no significant difference in the proportion of patients with ESRD among those with class III LN (25.8%) or class III/V LN (22.1%) compared with subjects with other LN classes. Hence, the significant association between CAD and class III and class III/V LN cannot be explained by increased risk for ESRD in these two groups.

Table 2. Demographics and CAD-specific and lupus-related factors by ISN/RPS classification

	Class III (n = 66)	Class III/V (n = 68)	Class IV (n = 153)	Class IV/V (n = 53)	Class V (n = 101)
Demographics					
Age, mean ± SD, y	41.6 ± 14.6	40.2 ± 13.6	36.8 ± 12.5	39.1 ± 12.5	40.4 ± 14.1
Male sex, n (%)	18 (27.3)	8 (11.8)	21 (13.7)	7 (13.2)	22 (21.8)
Race and/or ethnicity, n (%)					
White	16 (24.2)	9 (13.2)	38 (24.8)	4 (7.5)	15 (14.9)
African American	39 (59.1)	45 (66.2)	75 (49.0)	38 (71.7)	64 (63.4)
Hispanic or Latino	6 (9.1)	11 (16.2)	23 (15.0)	5 (9.4)	10 (9.9)
Asian	...	1 (1.5)	7 (4.6)	1 (1.9)	3 (3.0)
American Indian, native Hawaiian, or Pacific Islander	...	...	2 (1.3)	2 (3.8)	2 (2.0)
Other	1 (1.5)	...	3 (2.0)	2 (3.8)	3 (3.0)
Missing	4 (6.1)	2 (2.9)	5 (3.3)	1 (1.9)	4 (4.0)
CAD, n (%)	13 (19.7)	15 (22.1)	16 (10.5)	7 (13.2)	16 (15.8)
Myocardial infarction[a]	5 (7.6)	4 (5.9)	5 (3.3)	2 (3.8)	7 (6.9)
HTN					
HTN by ICD-9/ICD-10 code	48 (72.7)	49 (72.1)	110 (71.9)	48 (90.6)	69 (68.3)
Antihypertensive medication use	59 (89.4)	62 (91.2)	124 (81.0)	51 (96.2)	91 (90.1)
Cardioprotective	56 (84.8)	59 (86.8)	119 (77.8)	47 (88.7)	87 (86.1)
Others	46 (69.7)	47 (69.1)	82 (53.6)	41 (77.4)	66 (65.3)
DLP					
DLP by ICD-9/ICD-10 code	20 (30.3)	27 (39.7)	38 (24.8)	15 (28.3)	36 (35.6)
Lipid-lowering medication use	20 (30.3)	25 (36.8)	45 (29.4)	19 (35.8)	41 (40.6)
Cardioprotective	14 (21.2)	23 (33.8)	37 (24.2)	12 (22.6)	35 (34.7)
Others	8 (12.1)	9 (13.2)	14 (9.2)	7 (13.2)	14 (13.9)
DM by any criteria					
DM by ICD-9/ICD-10 code	14 (21.2)	12 (17.6)	14 (9.2)	8 (15.1)	18 (17.8)
Diabetes medication use	15 (22.7)	17 (25.0)	34 (22.2)	13 (24.5)	21 (20.8)
Cardioprotective	...	...	2 (1.3)	...	2 (2.0)
Others	15 (22.7)	17 (25.0)	33 (21.6)	13 (24.5)	21 (20.8)
History of smoking/tobacco use					
Non-smoker	43 (65.2)	54 (79.4)	107 (69.9)	40 (75.5)	65 (64.4)
History of or current smoking/tobacco use	22 (33.3)	13 (19.1)	42 (27.5)	13 (24.5)	34 (33.7)
Missing	1 (1.5)	1 (1.5)	4 (2.6)	...	2 (2.0)
Lupus factors					
Steroid use	54 (81.8)	61 (89.7)	116 (75.8)	41 (77.4)	81 (80.2)
Disease-modifying antirheumatic drug use	61 (92.4)	62 (91.2)	139 (90.8)	50 (94.3)	92 (91.1)
Antimalarial	52 (78.8)	58 (85.3)	121 (79.1)	48 (90.6)	78 (77.2)
Immunosuppressive	45 (68.2)	57 (83.8)	119 (77.8)	41 (77.4)	80 (79.2)
End-stage renal disease	17 (25.8)	15 (22.1)	39 (25.5)	20 (37.7)	14 (13.9)

Abbreviation: CAD, coronary artery disease; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; ICD-9, *International Classification of Diseases, Ninth Revision*; ICD-10, *International Classification of Diseases, 10th Revision*; ISN/RPS, International Society of Nephrology/Renal Pathology Society; ST, ST segment elevation on EKG.
[a]Myocardial infarction includes non-ST elevation myocardial infarction and ST elevation myocardial infarction.

Interestingly, we did not observe any significant association between class IV or class IV/V LN and CAD in our stratified analysis. There are several factors that could have contributed to this finding. Patients may move between LN classes based on progression or remission of the disease, as seen in our own cohort. We were limited in our ability to determine the exact

Table 3. ORs and 95% CIs for association of LN with CAD

Model	OR (95% CI)[a]	P
Unadjusted	1.19 (0.93-1.51)	0.1641
Demographic model	1.96 (1.50-2.57)[b]	<0.0001
Demographic and CAD factors model	1.39 (1.02-1.89)[b]	0.0348
Demographic, CAD, and LN factors model[c]	1.47 (1.07-2.02)[b]	0.0166

Abbreviation: CAD, coronary artery disease; CI, confidence interval; DLP, dyslipidemia; DM, diabetes mellitus; HTN, hypertension; LN, lupus nephritis; OR, odds ratio.
[a]Compared with patients without LN.
[b]Age, HTN, cardioprotective HTN medications, DLP, any DLP medications, cardioprotective DLP medications, DM, any DM medications, other DM medications, and smoking history were independently significant with CAD at P = 0.05.
[c]Adjusted for age, sex, five-level race and/or ethnicity, HTN, cardioprotective HTN medications, other HTN medications, DLP, any DLP medications, cardioprotective DLP medications, other DLP medications, DM, any DM medications, cardioprotective DM medications, other DM medications, smoking history, steroid exposure, antimalarial medications, and immunosuppressive medications.

class at the time of CAD onset because of our cross-sectional study design. When comparing the prevalence of cardiovascular risk factors between subjects with class III versus class IV involvement in unadjusted analyses, subjects with class III or class III/V LN had increased odds of noncardioprotective HTN medication exposure (OR 1.53; 95% CI 0.97-2.43; P = 0.070), DLP by ICD-9/ICD-10 code (OR 1.56; 95% CI 0.97-2.50; P = 0.065), and DM by ICD-9/ICD-10 code (OR 2.01; 95% CI 1.09-3.73; P = 0.24). Although there was a difference in rates of these three factors between subjects with class III and class IV involvement, the numerical difference in percentages was small, as seen in Table 2. In addition, these factors were controlled for in our analyses, and any differences should not have affected our results. We lacked clinical data, including degree of proteinuria, serum albumin levels, estimated glomerular filtration rate (eGFR), and complement levels, that may have differed between patients with class III or III/V and class IV or IV/V LN in our cohort.

Table 4. ORs and 95% CIs for association of LN with CAD by ISN/RPS classification

LN Class Categories	OR (95% CI)[a]	P
Class III	1.98 (0.95-4.12)	0.0687
Class III/V	2.23 (1.09-4.62)	0.0276
Class IV	1.17 (0.63-2.16)	0.6223
Class IV/V	1.62 (0.67-3.91)	0.2805
Class V	1.25 (0.65-2.38)	0.5033

Abbreviation: CAD, coronary artery disease; CI, confidence interval; ISN/RPS, International Society of Nephrology/Renal Pathology Society; LN, lupus nephritis; OR, odds ratio.
[a]Compared with patients without LN after controlling for demographic, CAD, and LN factors.

Although our study did not show a significant association between class IV or class IV/V LN and CAD, the calculated ORs do show a trend that patients with class IV involvement have increased odds of having CAD. We controlled for a breadth of demographics, cardiovascular risk factors, and SLE-related factors to minimize inherent differences in our study population. It is possible that the factors that we were unable to control for (ie, medication dose and disease length) differed between patients with class III involvement and those with class IV involvement. Longitudinal studies that control for more clinical factors may be needed to detect a statistically significant association between class IV LN and CAD.

The strengths of our study include our large real-world cohort and the racial diversity of our patient population, with African American patients representing 38% of the sample. Similar studies by Hermansen et al (9) and Faurschou et al (8) that explore the association between LN and cardiovascular disease reported results from Danish cohorts and are hence limited in generalizability to more racially diverse patient populations, such as those in the United States. Another strength of our study was our ability to control for a broad range of demographic and traditional cardiovascular risk factors in our analyses. This allowed us to conclude that the observed association between LN and CAD is truly independent of traditional CAD risk factors.

Our study has several limitations that should be noted. The retrospective study design did not allow us to determine a temporal relationship between onset of LN and CAD. Therefore, we were only able to describe associations and could not assess the magnitude of risk for CAD in our cohort. In addition, we were unable to control for length of disease, cumulative medication exposure, or length of medication because of our cross-sectional study design. We were limited in clinical data regarding renal disease severity (degree of proteinuria, serum albumin levels, eGFR, and complement levels) and could not control for these factors in our study.

The results of our large observational study add to the existing literature that shows that LN is independently associated with CAD. Our study is the first to explore the association between LN and CAD by ISN/RPS classification. We have shown that there may be an association between CAD and class III LN involvement independent of demographic and other clinical characteristics. We believe that our study reveals an area of further investigation in a patient population at increased risk for CAD who may benefit from early clinical intervention. Future studies are needed to better define the relationship between LN and premature CAD by ISN/RPS classification to identify potential at-risk populations.

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AUTHOR CONTRIBUTIONS

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

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Analysis and interpretation of data. Sun, Alvarez, Sheikh.

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