Nephritis and the risk of acute myocardial infarction in patients with systemic lupus erythematosus

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Abstract

Background

Patients with systemic lupus erythematosus (SLE) have an increased risk of acute myocardial infarction (AMI). We examined if nephritis or other clinical manifestations of SLE identified patients at increased risk.

Methods

In this population-based case-control study, we identified patients with SLE hospitalized with an AMI in California in 1996-2000. We compared the frequency of six manifestations of SLE (nephritis, pleuritis, hemolytic anemia, thrombocytopenia, psychosis/major depression, seizures) and of venous thrombosis/pulmonary embolism, in this group (n=535) to the frequency of these manifestations in two control groups: patients with SLE hospitalised for pulmonary disease (n=529), and patients with SLE hospitalised for gastrointestinal bleeding (n=349).

Results

Nephritis was present in 23.7% of patients with AMI, 11.0% of patients with pulmonary disease and 25.2% of patients with gastrointestinal bleeding. In adjusted analyses, nephritis was more common in the AMI group (odds ratio (OR) 2.85, 95% confidence interval (CI) 1.97–4.14; p<.0001) than in the pulmonary disease control group. Among women, nephritis was more common in the AMI group (OR 2.83; 95% CI 1.33–6.01; p=0.007) than in the gastrointestinal bleeding control group. Psychosis/major depression was less common among patients with AMI.

Conclusions

Among patients with SLE, nephritis was associated with 2.8-fold increased risk of AMI.

Key words

Systemic lupus erythematosus, myocardial infarction, cardiovascular disease, lupus nephritis

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Introduction

Patients with systemic lupus erythematosus (SLE) have an increased risk of cardiovascular disease. In epidemiological studies, the risk of acute myocardial infarction (AMI) was 2.67 to 10 times higher among patients with SLE than the general population (1-7). These risk estimates represent the average risk among all patients, but the risk may be concentrated in some subsets of patients. Several studies have sought to identify risk factors for cardiovascular disease in patients with SLE. These studies were limited in having few patients with events, including from 4 to 35 patients with AMI (3, 8-16). Some studies combined AMI with other vascular diseases such as stroke or peripheral arterial disease (11-16). While these diseases share many risk factors, the relative importance of hypertension, smoking, diabetes mellitus, and hyperlipidemia differ among different types of vascular disease (17-19). These studies also focused on traditional cardiovascular risk factors and medications, and less often on the clinical manifestations of SLE. We considered that the risk of AMI may differ among patients with different clinical manifestations of SLE, and hypothesised that the risk of AMI may differ between patients with lupus nephritis and those without nephritis. We examined these associations in a large population-based case-control study.

Methods

Data source

Data used in this study were obtained from the California Office of Statewide Health Planning and Development. All acute-care, non-federal hospitals in California are mandated to provide this agency with discharge abstracts on each hospitalisation. The discharge abstracts are prepared from medical and billing records, and include information on demographic characteristics, the principal diagnosis (defined as the condition chiefly responsible for the hospitalisation, by International Classification of Diseases, 9th Revision-Clinical Modification (ICD-9-CM) codes), up to 24 additional diagnoses, and disposition. Information on laboratory tests and medications are not included. Patients were anonymous, although a unique patient identifier was included to allow identification of repeat hospitalisations of the same patient. The average number of hospitalisations was 3.6 million annually.

Before being released, data are subjected to extensive reliability and consistency checks, and data fields with error rates > 0.1% are returned for correction (20). Reabstraction studies that compared these discharge abstracts with original medical records found specificities for diagnoses, including AMI, of 0.98 to 1.00, and sensitivities of 0.88 to 1.00, although non-acute conditions such as hypertension are often not listed (21-24).

The study protocol was exempted from human subjects review by the National Institutes of Health Office of Human Subjects Research.

Patients

We used data from 1996 to 2000, the most recent year in which the unique patient identifier was included. This identifier was required to construct the hospitalisation history of each patient, which provided information on the exposures in this study. We identified all hospitalisations of patients age ≥18 who had SLE (ICD-9-CM 710.0) as any of their discharge diagnoses. We limited the study to patients who had a diagnosis of SLE recorded on at least two hospitalisations, to further ensure the accuracy of the diagnosis. We excluded hospitalisations for which the patient identifier was missing, patients with only one hospitalisation, and hospitalisations that resulted from inter-hospital transfers (to avoid double-counting). We also excluded patients with end-stage renal disease (ICD-9-CM codes 585, 586) because the known increased risk of cardiovascular disease in these patients may be due to renal failure rather than SLE (25, 26). The resulting dataset included 54,876 hospitalisations among 9094 patients.

Among these patients, we identified as cases those who had an unscheduled hospitalisation with a principal diagnosis of AMI (ICD-9-CM code 410) at an acute-care hospital. If a patient had

more than one eligible hospitalisation, we used the first hospitalisation. We used two control groups: patients without AMI during 1996–2000 who had an unscheduled acute-care hospitalisation for asthma or chronic obstructive pulmonary disease (ICD-9-CM codes 491, 492, 493, 496; hereafter pulmonary disease), and patients without AMI during 1996–2000 who had an unscheduled acute-care hospitalisation for gastrointestinal (GI) bleeding (ICD-9-CM codes 531, 532, 533, 534, 535, 578). We chose these diagnoses because they were common reasons for hospitalisation, would likely be treated by internists or family practitioners (and therefore, in contrast to surgical conditions or trauma, likely have the exposures recorded with a similar sensitivity as patients hospitalised with AMI), and were similar to AMI in not being direct complications of immunosuppressive treatment. Using conditions that could be complications of immunosuppression (*e.g.* pneumonia) to define control groups could have led to an overrepresentation among controls of the clinical indication for which the immunosuppressive was given.

We abstracted information on age, type of medical insurance, gender, race (white, black, other) and Hispanic ethnicity.

Exposure variables. We searched the discharge diagnoses of all hospitalisations prior to and including the index hospitalisation for the following manifestations of SLE, by ICD-9-CM code: nephritis (580–584, 403.91), pleuritis (511, 786.52), hemolytic anemia (283.9), thrombocytopenia (284.8, 284.9, 287.3, 287.4, 287.5), seizures (345, 780.3), and psychosis/major depression (293, 294.9, 296, 297, 298, 323.8, 323.9; transient organic psychotic conditions, organic brain syndrome, affective psychosis, paranoid states, other non-organic psychosis, and other encephalitis, respectively). Because thrombophilia may be a risk factor for cardiovascular events and may occur in patients with antiphospholipid syndrome, we also included deep venous thrombosis and/or pulmonary embolism (451.1, 451.2, 453.8, 453.9, 415.1) (27-31). There is no unique ICD-9-CM code for antiphospholipid syndrome, so this diagnosis could not be tested as a risk factor specifically. We categorised each exposure variable as present or absent, depending on whether it was listed at least once as a discharge diagnosis.

Table I. Characteristics of cases hospitalized with acute myocardial infarction and of controls hospitalized with either pulmonary disease or gastrointestinal bleeding.

	Acute Myocardial Infarction (n=535)	Pulmonary Disease (n=529)	Gastrointestinal Bleeding (n=349)
Age, years*	62.9 ± 14.5	56.9 ± 15.8	55.7± 18.1
Women, %	71.6	89.6	76.8
White, %	75.0	77.3	67.3
Black, %	13.1	14.0	16.9
Other race, %	11.9	8.7	15.8
Hispanic ethnicity, %	12.9	15.9	17.8
Type of health insurance			
Medicare, %	53.6	49.0	44.4
Other public, %	15.5	21.7	20.3
Private, %	28.2	27.0	31.0
No insurance, %	2.7	2.3	4.3

*Mean ± standard deviation.

Statistical analysis

We examined if any of the seven clinical manifestations were over- or underrepresented among AMI cases compared to controls using logistic regression analysis. Separate comparisons were done using each control group to test the consistency of associations. We adjusted for differences between groups in age, gender, race, and Hispanic ethnicity. We first tested the association of each exposure separately, and then tested models that included all exposures. The goodness of fit of each model was satisfactory, as indicated by the results of the Hosmer-Lemeshow test. SAS programs (SAS Institute, Cary, NC) were used for analysis. All hypothesis testing was two-tailed, and p-values ≤ 0.05 were considered statistically significant.

We used classification trees as a second method to identify exposures associated with AMI. A classification tree is a hierarchical procedure that uses recursive partitioning to subset patients into groups (32). The procedure iteratively tests each exposure for the one that best separates cases from controls, and repeats this process for each subgroup until all patients are classified or subgroups of sufficient homogeneity are found. The procedure is nonparametric, not model-based, and can be useful for identifying combinations of exposures associated with case or control status. We used demographic characteristics and the 7 clinical manifestations as candidate independent variables in the classification tree, with 10-fold cross-validation. This analysis was done using R programs (version 2.2.0, The R Foundation for Statistical Computing).

Results

We identified 535 patients with SLE hospitalized with AMI as our cases, 529 patients with SLE hospitalised with pulmonary disease as one control group, and 349 patients with SLE hospitalised with GI bleeding as the second control group. Patients were predominantly middle-aged women, although the AMI patients were older and included a higher proportion of men than the control groups (Table I). Data on clinical manifestations of SLE were obtained from a median of 3 hospitalisations per patient in each group. Nephritis was more common among cases with AMI than among controls with pulmonary disease (23.7% versus 11.0%) (Table II). Adjusting for differences in demographic characteristics and other SLE manifestations between groups, cases with AMI were 2.85 times more likely than the pulmonary controls to have had nephritis. In contrast, a history of psychosis/major

Table II. Associations of clinical manifestations with cases of acute myocardial infarction, compared to controls with pulmonary disease. Odds ratios (OR) greater than 1.0 indicate the manifestation was more common among cases than controls.

	Proportion among cases with AMI	Proportion among controls	Unadjusted OR (95% CI)	OR adjusted for demographic characteristics (95% CI)	OR adjusted for demographic characteristics and other clinical manifestations (95% CI)
Nephritis	23.7	11.0	2.53 (1.80 – 3.55)	2.79 (1.94 – 4.00)	2.85 (1.97 – 4.14) (p<.0001)
Pleuritis	9.2	8.3	1.11 (0.72 – 1.71)	1.02 (0.65 – 1.61)	0.91 (0.57 – 1.46) (p=.71)
Haemolytic anemia	1.1	1.0	1.19 (0.36 – 3.92)	0.99 (0.27 – 3.57)	1.10 (0.29 – 4.19) (p=.89)
Thrombocytopenia	11.4	7.2	1.66 (1.09 – 2.55)	1.58 (1.01 – 2.47)	1.41 (0.89 – 2.25) (p=15)
Venous thrombosis/pulmonary embolism	4.9	4.5	1.08 (0.60 – 1.90)	1.09 (0.59 – 1.98)	1.14 (0.61 – 2.13) (p=.68)
Psychosis/Major depression	7.1	15.1	0.43 (0.28 – 0.65)	0.43 (0.27 – 0.67)	0.39 (0.24 – 0.61) (p<.0001)
Seizures	9.2	10.0	0.91 (0.60 – 1.37)	1.00 (0.64 – 1.56)	1.04 (0.65 – 1.68) (p=.86)

Table III. Associations of clinical manifestations with cases of acute myocardial infarction, compared to controls with gastrointestinal bleeding. Odds ratios (OR) greater than 1.0 indicate the manifestation was more common among cases than controls.

	Proportion among cases with AMI	Proportion among controls	Unadjusted OR (95% CI)	OR adjusted for demographic characteristics (95% CI)	OR adjusted for demographic characteristics and other clinical manifestations (95% CI)
Nephritis	23.7	25.2	–	–	–
Men without nephritis				1.00 (reference)	1.00 (reference)
Men with nephritis				0.58 (0.30 – 1.09)	0.55 (0.28 – 1.04) (p=.07)
Women without nephritis				0.62 (0.42 – 0.91)	0.61 (0.41 – 0.91) (p=.02)
Women with nephritis				2.41 (1.15 – 5.05)	2.83 (1.33 – 6.01) (p=.007)
Pleuritis	9.2	10.9	0.83 (0.52 – 1.29)	0.77 (0.47 – 1.22)	0.77 (0.47 – 1.26) (p=.30)
Haemolytic anemia	1.1	2.3	0.48 (0.16 – 1.41)	0.44 (0.14 – 1.34)	0.42 (0.13 – 1.29) (p=.13)
Thrombocytopenia	11.4	17.5	0.61 (0.41 – 0.90)	0.64 (0.42 – 0.96)	0.67 (0.44 – 1.01) (p=.06)
Venous thrombosis/pulmonary embolism	4.9	7.4	0.63 (0.36 – 1.12)	0.64 (0.35 – 1.15)	0.70 (0.38 – 1.27) (p=.24)
Psychosis/Major depression	7.1	12.9	0.52 (0.32 – 0.82)	0.56 (0.34 – 0.90)	0.56 (0.34 – 0.92) (p=0.03)
Seizures	9.2	11.8	0.76 (0.48 – 1.18)	0.84 (0.52 – 1.33)	0.91 (0.56 – 1.47) (p=.71)

depression was less common among cases with AMI than pulmonary controls (adjusted odds ratio (OR)=0.39). Cases with AMI were more likely than controls to have a history of thrombocytopenia in the unadjusted analysis, but this association was not significant in the adjusted analysis. Cases and controls did not differ in other clinical manifestations of SLE or venous thrombosis/pulmonary embolism. Older age, male gender, and having Medicare (versus private insurance) were also significantly associated with risk of being in the AMI group.

Comparing cases with AMI to controls with GI bleeding, we found a significant interaction between nephritis and gender (Table III). Among men, cases with AMI were somewhat less likely than controls to have had nephritis, but among women, cases with AMI were substantially more likely to have had nephritis (adjusted OR=2.83). Cases with AMI were again less likely than controls to have a history of psychosis/major depression, and somewhat less likely to have thrombocytopenia. Other clinical manifestations did not differ between cases and controls.

The classification tree analysis supported the results of the logistic regression models. Comparing cases with AMI and controls with pulmonary disease, the initial classifier was gender, with men over-represented in the AMI group (Fig. 1). Among women, AMI was more common among older patients, but both younger and older women were more likely to be AMI cases if they had had nephritis. Among older women without nephritis, AMI cases were more likely among those without a history of psychosis/major depression. Age, psychosis, and thrombocytopenia were the main classifiers in a classification tree comparing cases with AMI to controls with GI bleeding (data not shown).

Discussion

Case-control studies provide an efficient design for identifying risk factors for uncommon conditions. We used a statewide hospitalisation database to assemble a large number of cases of AMI among patients with SLE, and examined risks for AMI associated with different clinical manifestations of SLE. A history of nephritis was associated with 2.8-fold increased risk of AMI compared to each of two control groups (among all patients compared to pulmonary controls, and among women compared to GI bleeding controls). Previous studies have not demonstrated consistent or strong associations between nephritis and risk of AMI in patients with SLE, possibly due to their sample size or use of a combined vascular disease outcome. In a previous cohort study, nephritis was associated with a 50% increase in risk of coronary events (AMI or new-onset angina) (3).

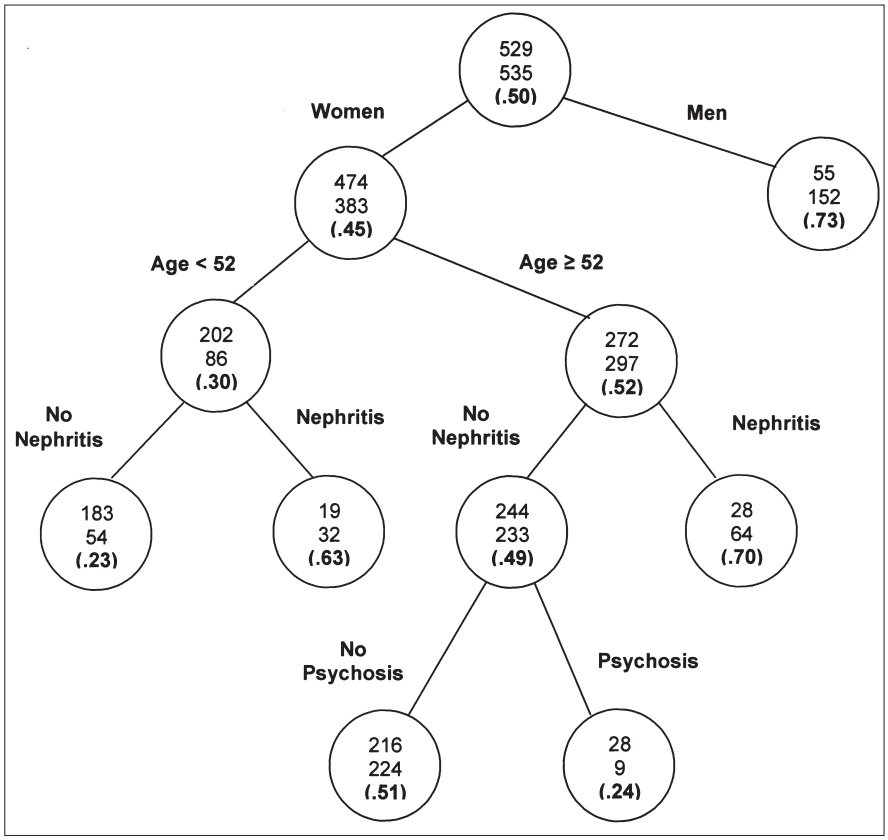

Fig. 1. Classification tree separating cases with acute myocardial infarction from controls with pulmonary disease. Demographic and clinical variables that split the group of 535 cases and 529 controls into subgroups enriched in either cases or controls are noted for each branch. Within each node are the number of controls (top number) and cases (bottom number) in the subgroup, along with the percentage of cases in the subgroup (in bold).

This increase, and the association in the only other cohort study that specifically examined coronary events, was not statistically significant, perhaps due to limited power (8). In three of six other studies, nephritis or renal insufficiency was associated with an increased risk of vascular disease (AMI, angina, cerebrovascular accident, or peripheral arterial disease), with odds ratios that ranged from 1.4 to 2.0 (11-16). Because many patients in these studies had events other than AMI, we cannot be sure that nephritis was associated with the risk of AMI, or that the specific risk for AMI was not higher. Renal insufficiency has been associated with more severe subclinical atherosclerosis or aortic stiffness in some, but not all, studies, while other markers of renal involvement, such as proteinuria, have generally not been associated with subclinical atherosclerosis in the setting of SLE (33-38). Differences among these studies may be due in part to different definitions of renal disease and to consideration only of patients' current, rather than past, renal involvement.

Nephritis was associated with the risk of AMI in both men and women when using the pulmonary disease control group, but nephritis was associated with AMI only among women when using the GI bleeding control group. The difference between the two analyses indicates that the nature of the control group was an important factor, and suggests that the risk of hospitalisation for GI bleeding in the setting of nephritis differs between men and women in a way that is not present for hospitalisation for chronic pulmonary disease. The association between nephritis and AMI was consistent for women using either control group.

Nephritis may increase the risk of AMI through several possible mechanisms. Nephritis often causes hypertension, a well-established risk factor for AMI. Nephritis also represents one of the major sources of inflammation in SLE, and persistent systemic inflammation is a risk factor for vascular events (44, 45). Hypercoagulability associated with nephrotic syndrome may result in AMI (46). Metabolic changes associated with renal insufficiency also contribute to AMI risk (47). However, nephritis may only be a marker of the true risk factor, which could include other closely associated conditions, or medications used to treat nephritis. Systemic corticosteroids are the most commonly used treatment, and the duration or cumulative dose of corticosteroid therapy has been associated with risk of vascular events in some studies (2, 3, 8, 9, 12-15). Distinguishing whether nephritis or corticosteroid treatment is the predominant risk factor may be difficult, and both factors may be important. We did not have information on these factors to be able to examine this question. Nephritis may also be treated with immunosuppressants such as azathioprine and cyclophosphamide. These medications, which have not otherwise been implicated in promoting atherosclerosis, were reported in previous studies to have been used more often by patients with vascular events, suggesting that the indication for treatment (*e.g.* nephritis) was an important risk factor (12, 14).

We also found that patients with a history of psychosis/major depression were less likely to be in the AMI group than patients without this history. These conditions, or factors associated with them such as particular treatments, may be protective, although the mechanisms are unclear. In contrast, seizures were not associated with risk of AMI, indicating that all neuropsychiatric manifestations of SLE do not carry the same risk. In two previous studies of this association, neuropsychiatric manifestations of SLE were found to be more frequent among patients with vascular events, although both the exposure (all neuropsychiatric diagnoses) and the disease (vascular events including stroke and transient ischemic attacks) were different from those in our study (14, 16). Subclinical atherosclerosis has also been reported to be more common among patients

with SLE treated with antidepressants, although again differences in both the exposure and the disease make it difficult to compare these results with our study (34). Thrombocytopenia was less common among patients with AMI than those with GI bleeding, likely reflecting an increased risk of bleeding associated with thrombocytopenia than a protective association for AMI. We did not find associations with other clinical manifestations, including a history of venous thrombosis or pulmonary embolism, which might have included many patients with antiphospholipid syndrome.

The strengths of this study include the large population-based sample, rigorous criteria to identify patients with SLE and suitable controls, consistency of results across two control groups, and support of the results of the logistic regression analysis by classification trees. We also examined AMI events using a database in which the accuracy of diagnosis had previously been validated (21-24). We did not combine AMI with other vascular events, because etiologic exposures may be very specific (48, 49). However, our study is limited in the depth of clinical information available about the exposures. For example, we do not know how the manifestations of nephritis might have varied among patients, or whether the duration or severity of nephritis was associated with risk of AMI. We did not have information about current or past treatments, some of which might have contributed to the risk attributed to nephritis. We also did not have information on traditional cardiac risk factors, but apart from the association of hypertension with nephritis, these are not known to be associated with the SLE manifestations we examined. Additionally, although the controls did not have an AMI during the five years we examined, we do not know if they had had an AMI before the study period. However, any misclassification of disease status would tend to reduce the strength of association with exposures. Lastly, we examined only hospitalised patients, and the results may not apply to patients who are not hospitalised or who die before reaching the hospital.

Our findings indicate that patients with nephritis appear to have particularly increased risk of AMI. Studies should examine if the risk of AMI in patients with SLE, relative to patients without SLE, is concentrated in patients with nephritis, or if patients without a history of nephritis or psychosis/major depression also have an increased risk. The identification of subgroups of patients with different levels of risk helps clinically to aid prognosis, and provides insights into the pathogenic processes that may be most important. Future studies to refine the risk factors for AMI in patients with SLE should include a focus on nephritis and its treatments. Given that coronary artery disease takes years to develop, it will be key to examine information on the duration of exposures.

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