

Poor Outcomes After Acute Myocardial Infarction in Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* Systemic lupus erythematosus (SLE) is associated with higher risk for acute myocardial infarction (MI); but the post-infarction outcomes among these patients are unknown. Our objective was to compare post-acute MI outcomes in patients with SLE to those with diabetes mellitus (DM) and those with neither condition.

Methods. We analyzed the risk for prolonged hospitalization and in-hospital mortality following acute MI in the 1993–2002 US Nationwide Inpatient Sample. We used logistic regression to calculate odds ratios (OR) for prolonged hospitalization and Cox proportional hazards regression to calculate hazard ratios (HR) for in-hospital mortality with and without adjustments for age, sex, race/ethnicity, socioeconomic status, and presence of congestive heart failure.

Results. For the SLE (n = 2192), DM (n = 236,016), SLE/DM (n = 474), and control (n = 667,956) groups, the in-hospital mortality rates were 8.3%, 6.2%, 5.7%, and 4.7%, respectively. In multivariable regression models, all 3 disease groups had higher adverse outcome risk compared to control. The OR for prolonged hospitalization was higher for those with SLE (OR 1.48, 95% CI 1.32–1.79) compared to those with DM (OR 1.30, 95% CI 1.28–1.32). A similar pattern was observed for hazard ratios for in-hospital mortality as well (SLE, HR 1.65, 95% CI 1.33–2.04; DM, HR 1.11, 95% CI 1.07–1.14).

Conclusion. SLE, like DM, increases risk of poor outcomes after acute MI. These patients need to be triaged appropriately for aggressive care. (First Release Jan 15 2009; J Rheumatol 2009; 36:570–5; doi:10.3899/jrheum.080373)

Key Indexing Terms:

SYSTEMIC LUPUS ERYTHEMATOSUS
ACUTE MYOCARDIAL INFARCTION

DIABETES MELLITUS
LENGTH OF HOSPITAL STAY MORTALITY

In recent years, the short-term mortality rate has improved substantially in patients with systemic lupus erythematosus (SLE)¹. Yet morbidity and mortality from early-onset coronary artery disease remain problems in these patients. Although investigators have found that the association between coronary artery disease, atherogenesis, and SLE is independent of traditional cardiovascular risk factors^{2–10}, little is known about the risk for adverse outcomes after the incidence of acute myocardial infarction (MI) among people with SLE. To our knowledge, only one study has explored the risk of post-acute MI mortality in patients with SLE. That study, published in 2004, used the discharge database of California hospitals and examined the post-acute MI outcomes in 519 patients with SLE⁹. It did not find a statistically significant difference between the in-hospital mortality risk of patients with SLE and that of patients without

SLE⁹. That study did not address post-acute MI morbidity or compare outcomes of patients with SLE to those with other diseases.

Some investigators have used diabetes mellitus (DM) as an analogy for explaining atherogenesis in chronic inflammatory autoimmune diseases such as rheumatoid arthritis (RA)¹¹. This is based on the premise that persistent inflammatory insult due to RA, like persistent hyperglycemia in DM, leads to atherosclerosis and subsequent acute MI^{10,12–14}. While this analogy is appealing, it raises another question — is SLE, like DM, associated with excess post-acute MI morbidity and mortality, and if so, is the quantum of adverse events comparable to that associated with DM^{15,16}? Our study was designed to estimate and compare the risk of post-acute MI morbidity and mortality outcomes in patients with SLE, patients with DM, patients with both SLE and DM, and patients with neither disease (controls). Because SLE is a rare disease and because acute MI and subsequent death are even rarer events, we chose to use a large, population-representative hospitalization dataset from the Nationwide Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project for our investigation.

MATERIALS AND METHODS

Data source. The NIS is the largest all-payer inpatient care database that is

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publicly available in the United States. The database contains demographic and clinical data one would typically find in a hospital discharge summary from 12–15 million hospital discharges from nonfederal short-stay US hospitals that are part of the American Hospital Association. The NIS data are structured as annual national cross-sectional data and, due to privacy concerns, information that can be used for tracking an individual from one hospitalization to the next is not available. The hospitals participating in this study are chosen using a multistage sampling strategy. This involved stratifying hospitalizations by state and ZIP code (60 strata) and then randomly choosing a 20% systematic random sample of hospitals within the state-ZIP code stratum. The sample was so designed that 2 hospitals were chosen from each stratum. We used the data from the years 1993–2002. This de-identified data set has been made publicly available (<http://www.hcup-us.ahrq.gov/nisoverview.jsp>). Detailed information on the statistical design of the NIS and the magnitude of sampling errors associated with the estimates has been published¹⁷.

Case selection and data collection. The NIS database provides information on demographic data, the principal diagnosis and up to 14 secondary diagnoses, the principal hospital procedure and up to 14 secondary procedures, and admission and discharge status. Codes for diagnoses and procedures are based on the International Classification of Diseases–Clinical Modification (ICD-9-CM)¹⁸.

We looked at all 15 possible discharge codes for each hospital discharge and classified hospitalizations into 4 mutually exclusive groups — SLE, DM, SLE and DM, and neither SLE nor DM (controls). SLE hospitalizations were those having an ICD-9-CM code¹⁹ of 710.0. Patients with DM were those having an ICD-9-CM code of 250.XX. Patients with both SLE and DM were those having both codes. Patients without SLE or DM (controls) were those having neither code. Presence of the ICD-9-CM codes 410.XX and 480.XX was used to identify hospitalizations of individuals where acute MI and congestive heart failure (CHF), respectively, were recorded.

For each patient, we had 2 dichotomous outcomes of interest (prolonged hospitalization and in-hospital mortality) and sociodemographic data, including age, sex, race/ethnicity, and residential ZIP code. We subsequently categorized race/ethnicity as White, Black, Hispanic, or other/unknown. We determined the median household income for individuals residing in a patient's ZIP code and used that information as a proxy for the patient's socioeconomic status as 3 strata: < \$25,000, \$25–\$35,000, and > \$35,000. The ZIP code is a well validated socioeconomic variable in mortality studies in the US²⁰.

Statistical analyses. For all statistical analyses, we used Stata version 8 (Stata Corp., College Station, TX, USA). To assess differences in proportions and means across different groups, we used Pearson's chi-square test and analysis of variance (ANOVA). All continuous variables were used as such in our analyses unless specified otherwise.

Primary analyses. We first identified hospitalizations for adults (age 18 to 70 yrs) with acute MI as those discharge records where acute MI was listed as one of the first 3 diagnoses. We then excluded hospitalizations that were related to maternity. A hospital length of stay (LOS) of 6 days coincided with 75th percentile of the distribution of LOS and so was designated as the cutoff value for the definition of "prolonged hospitalization." To determine the risk of prolonged hospitalization, we used logistic regression analyses with and without adjustments for the effects of age, sex, race/ethnicity, socioeconomic status, and the presence of CHF. To evaluate in-hospital survival data, we used Cox proportional hazards regression models with and without adjustments for the above covariates²¹. In these survival models, the observation time started on the day of hospitalization and ended at the time of death. The observations that did not end in deaths were censored at the last day of the hospitalization. Cox models were also used to perform trend tests to determine if the mortality risk changed over the time period of this study. These models were fitted separately for the 4 study categories; calendar year was used as continuous variable, age and sex alone were adjusted.

Sensitivity analyses. The primary analyses were based on a set of premises and case definitions, the validity of which were tested in a set of secondary sensitivity analyses. The first premise was that of the definition of acute MI hospitalizations. Use of the ICD-9-CM code for acute MI anywhere in the 15 diagnostic code fields would have yielded very high sensitivity but would have resulted in very poor specificity, especially since a history of acute MI would be counted as an incident acute MI. On the other hand, restricting the case definition to the principal diagnosis would have increased the specificity but at the cost of excluding several acute MI hospitalizations that presented as pulmonary edema, shock, etc. We therefore chose to use the first 3 diagnostic positions for defining acute MI. However, we performed secondary analyses including only those hospitalizations where acute MI was the principal diagnosis. Lastly, given the short followup period in our study, we reran the analyses using logistic regression models.

Effect modification. A review of the literature suggested that the outcomes after acute MI may vary with diabetes and CHF^{15,16}. We wished to explore such an effect for SLE and CHF and DM and CHF in our dataset. Therefore we performed 2-way interaction analyses (SLE–CHF; DM–CHF) to explore and adjust for any differential role for CHF in the setting of SLE, diabetes, and both.

RESULTS

Study population. During the study period (1993–2002), 906,638 patients were admitted to the hospital with acute MI listed as one of the first 3 diagnoses. Of these patients, 667,956 had neither SLE nor DM (control group), 2192 had SLE without DM (SLE group), 236,016 had DM without SLE (DM group), and 474 had both SLE and DM (SLE/DM group). Analyses of sociodemographic characteristics (Table 1) indicated that patients with SLE were younger and more likely to be female than patients in the other groups.

Race, disease category, and mortality. Analyses of mortality rates indicated that the study population had an overall in-hospital mortality rate of 5.1%. Mortality rates were the highest among those with SLE regardless of race and sex (Table 2). There was a trend toward lower mortality rate for those with both SLE and diabetes, but the numbers of subjects (n = 474) and events (n = 27) were too few to have a robust estimate of rate difference. The overall mortality rate was highest in the SLE group and DM group (8.3% and 6.2%, respectively), compared with the control group (4.7%).

In bivariate Cox regressions where death was the dependent variable and race (White/Black) the independent variable, being Black conferred a hazard ratio of 1.45 (95% CI 1.39–1.52) among the control group, 1.13 (95% CI 1.07–1.20) among the diabetes group, 1.31 (95% CI 0.88–1.98) among the SLE group, and 1.1 (95% CI 0.41–2.9) among the SLE and diabetes group. On sex-specific analyses among those with SLE, being Black increased mortality risk among men (hazard ratio 3.0, 95% CI 1.2–7.9), but not among women (hazard ratio 1.08, 95% CI 0.70–1.69). This was in contrast to the control group, where both Black men and women were at higher risk of death compared to Whites (OR 1.4 and 1.3, respectively; p < 0.001). Diabetics, on the other hand, had a mortality risk

Table 1. Sociodemographic characteristics of patients hospitalized for acute myocardial infarction.

Characteristic	Control, n = 667,956	SLE Group, n = 2192	DM Group, n = 236,016	SLE/DM Group, n = 474	p
Age in yrs, mean (\pm SD)	56.7 (9.5)	52.7 (10.8)	59.1 (8.4)	56.3 (9.2)	< 0.001
Female, %	27	78	39	83	< 0.001
Race/ethnicity, %					
White	69	59	62	54	< 0.001
Black	7	16	10	20	< 0.001
Hispanic	4	4	7	10	< 0.001
Other/unknown	20	20	21	16	< 0.001
Median income category, %					
< \$25,000	69	77	74	78	< 0.001
\$25,000–\$35,000	16	13	15	13	< 0.001
> \$35,000	14	10	11	9	< 0.001

DM: diabetes mellitus; SD: standard deviation; SLE: systemic lupus erythematosus.

Table 2. In-hospital mortality rates of patients hospitalized for acute myocardial infarction. Data are percentage (no.).

	Control	DM	SLE	SLE and DM
Men				
Black	5.6 (25,298)	6.0 (11,020)	15.2 (46)	0.0* (13)
Hispanic	4.2 (19,046)	5.8 (9,398)	5.6 (18)	0.0* (6)
White	4.0 (313,434)	5.5 (85,474)	5.6 (286)	2.0 (49)
Women				
Black	8.2 (14,573)	8.1 (12,072)	10.2 (284)	7.8 (77)
Hispanic	7.7 (5,889)	7.6 (6,196)	11.6 (69)	5.1 (39)
White	6.2 (110,818)	7.6 (50,828)	9.4 (942)	7.1 (197)

* Too few events to calculate. DM: diabetes mellitus; SLE: systemic lupus erythematosus.

profile similar to the SLE group, with a statistically significant odds ratio for men (OR 1.1, 95% CI 1.0–1.9) but not for women (OR 1.07, 95% CI 0.99–1.15). Hispanic race did not emerge as a statistically significant correlate of mortality in any of these analyses. Additional analyses adjusting for age did not significantly change the results.

CHF and mortality. Overall, CHF was present in 19% of all hospitalizations for acute MI. The prevalence was striking among diabetics (31%) and those with diabetes and SLE (34%). The prevalence among the SLE group was 20% and among the control group 15%. Overall, the mortality rate among those with CHF was 11%, while the corresponding rate for those without CHF was 4% ($p < 0.001$). The mortality rate for those with and without CHF within the SLE group was 17.9% and 5.8%, respectively ($p < 0.001$). A similar pattern of excess mortality rate associated with CHF was observed in all the other 3 patient groups.

In separate bivariate analyses, CHF was a statistically significant predictor of mortality among the control group (HR 3.7, 95% CI 3.6–3.8), diabetics (HR 2.27, 95% CI 2.20–2.35), and the SLE group (HR 3.5, 95% CI 2.6–4.8). There was no racial difference in the prevalence of CHF in the SLE group (Whites 21%, Blacks 22%) and diabetic group (Whites 32%, Blacks 34%), while the prevalence of

CHF was higher among Blacks in the control group, 20% compared to 15% among Whites.

Length of hospitalization. Analyses of LOS (Figure 1) indicated that patients in the SLE groups had an overall mean LOS greater than that of the control group, regardless of race and sex ($p < 0.001$). The overall mean LOS was 5.6 days (SD 7.25). Of all the hospitalizations studied, 34% met our criteria for prolonged hospitalization (≥ 6 days).

Multivariable analyses for adverse hospital outcomes. Analyses of the risks of poor outcomes are shown in Table 3. Compared with the control group, the SLE group and the diabetic group were more likely to have prolonged hospitalization, as indicated in both the unadjusted logistic regression model and the logistic regression model adjusted for age, sex, race/ethnicity, socioeconomic status, and CHF. Addition of an interaction term for CHF and the disease group did not change the results. Patients in the SLE group were also more likely to die in hospital, as indicated in both the unadjusted and the adjusted Cox models. Compared with the control group, the diabetic group was more likely to have a prolonged hospitalization. However, the diabetes and SLE group did not have excess mortality compared with the control group, likely due to the small sample size ($n = 474$). The confidence intervals of the risk estimates for the dia-

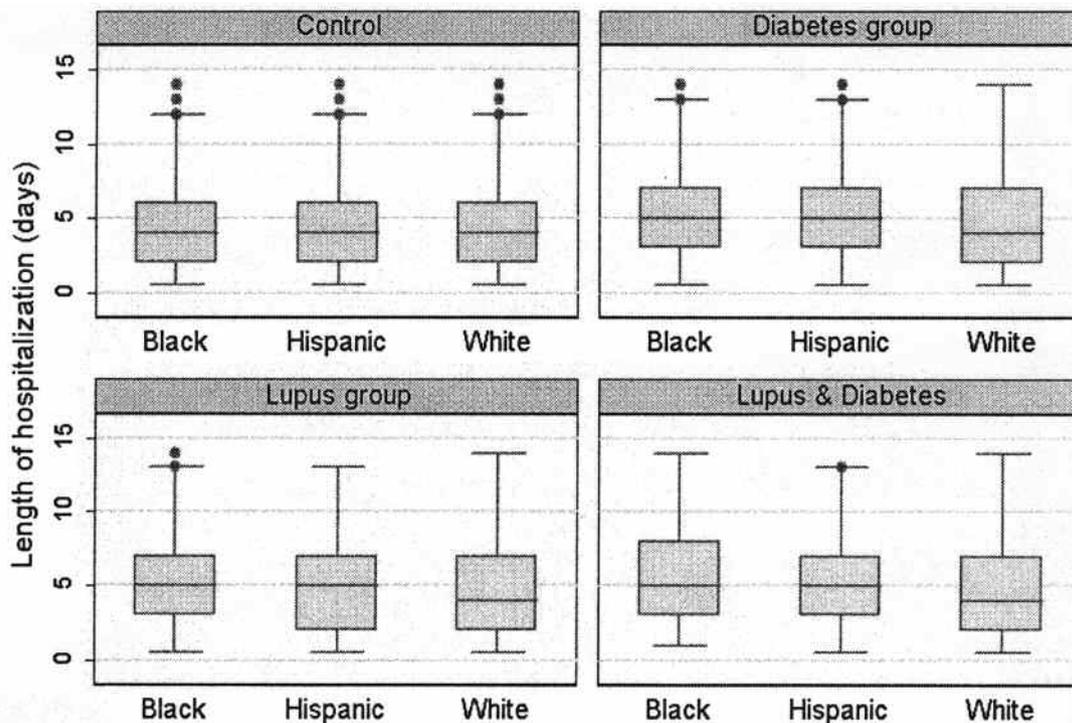


Figure 1. Distribution of length of hospitalizations of the 4 study groups. Horizontal line in the box shows the median value; lower and upper edges of the box indicate 25th and 75th quartiles. Upper and lower whiskers denote the largest and smallest non-outlier observation value.

Table 3. Risks of poor outcomes in patients hospitalized for acute myocardial infarction. The control group was the group of comparison (n = 667,956).

	Control, n = 667,956	DM Group, n = 236,016	SLE Group, n = 2192	DM and SLE Group, n = 474
Prolonged hospitalization, odds ratio (95% CI)				
Unadjusted	1.00	1.46 (1.45–1.47)	1.41 (1.29–1.53)	1.56 (1.30–1.87)
Adjusted for age, sex, race/ ethnicity, income, and CHF	1.00	1.17 (1.16–1.19)	1.46 (1.31–1.61)	1.32 (1.07–1.63)
In-hospital mortality, hazard ratio (95% CI)				
Unadjusted	1.00	1.16 (1.14–1.18)	1.54 (1.34–1.79)	0.91 (0.62–1.32)
Adjusted for age, sex, race/ ethnicity, income, and CHF	1.00	1.00 (0.97–1.02)	1.68 (1.43–2.04)	0.75 (0.50–1.12)

CHF: congestive heart failure; DM: diabetes mellitus; SLE: systemic lupus erythematosus.

betes and SLE group did not overlap, indicating that the magnitude of excess risk for SLE was significantly greater than that for diabetes.

Time trends in mortality. Age-sex adjusted trend analyses using Cox models showed an increasing trend in in-hospital mortality among the control group during the study period ($p < 0.001$). Among the diabetic group the mortality risk declined annually ($p < 0.001$). Such changes were not observed among the SLE group ($p = 0.197$) or the SLE and diabetes group ($p = 0.469$).

Sensitivity analyses. In order to test the effect of coding issues on determining the cause of hospitalization, we performed multivariable analyses with adjustment for inter-

action with CHF, as above, on the subset of individuals where acute MI was the primary (first) diagnosis in the hospitalization records. There were 773,431 such hospitalizations. The odds ratios of prolonged hospitalization for the diabetics was 1.28 (95% CI 1.26–1.30), that for SLE group was 1.44 (95% CI 1.27–1.68), and for those who had both, 1.35 (95% CI 1.02–1.81). In Cox regression models, diabetics had a hazard ratio of 1.12 (95% CI 1.08–1.6) and the SLE group had a hazard ratio of 1.61 (95% CI 1.24–2.09). The confidence intervals overlapped, suggesting no statistical differences in hazard ratios. The group with both SLE and DM had a statistically insignificant hazard ratio, 0.94 (95% CI 0.45–1.98). Our other observations regarding the

racial patterns remained robust. Reanalyses of data using logistic regressions instead of Cox regressions did not change the results.

DISCUSSION

Diabetes is well known to be a major risk factor for adverse outcomes after acute MI^{22,23}. In our study the magnitude of risk for SLE was slightly higher than that for diabetes, an observation that has not been reported before. This means that a person with SLE presenting to the emergency room with an acute MI must be considered as a high-risk MI and triaged accordingly. Our results differ from those of an earlier study that compared post-acute MI outcomes in patients with and without SLE⁹. That study examined patients who were hospitalized with acute MI in California during the period 1996–2000, and found no difference in the risks of prolonged hospitalization and in-hospital mortality of patients with SLE and patients without SLE⁹. However, that study was smaller than ours (519 vs 2192 patients with SLE, respectively).

What could be the pathophysiological explanations for our observations? Patients with SLE are known to have a substantially increased risk for atherosclerosis that cannot be fully explained by traditional risk factors². Current explanations for the pathogenesis of atherosclerosis and coronary heart disease in patients with SLE include chronic inflammation^{13,24}, corticosteroid therapy^{25,26}, antiphospholipid antibodies^{27,28}, immune complexes^{29,30}, coronary aneurysms³¹, vasculitis^{4,32}, and endothelial dysfunction^{33,34}. Whether these factors associated with incidence of premature atherosclerosis lead to increased thrombogenesis, increased infarct size, and consequently increased case fatality is unknown. An important piece of data on the symptom onset-to-emergency room time is not available in our dataset; it may well be that MI is unrecognized among patients with lupus. Given the structure of our data source, analyses of potential pathophysiological pathways could not be performed.

The inflammatory process has been shown to be a strong risk factor for cardiovascular events in SLE, a disease characterized by chronic inflammation³⁵. The net effect of treatments for SLE on risk of coronary artery disease is not well studied. Corticosteroids have antiinflammatory properties that help reduce disease activity in SLE, but can themselves increase atherogenesis¹². On the other hand, used as treatment for acute MI, corticosteroids have not been known to increase the risk for adverse cardiovascular outcomes³⁶. Hydroxychloroquine, a medication very commonly used for SLE, is associated with improved lipid profile and better glycemic control, at times to the extent of countering the effects of corticosteroids^{37–39}. The effect of other medications such as mycophenolate mofetil and azathioprine on the atherosclerotic and thrombotic risk is unclear.

Blacks are well known to be at higher risk for SLE and

for coronary artery disease. We found that Blacks with SLE had higher mortality than Whites and other groups. Within the SLE group, however, the mortality risk disparity was present among men but not among women. The reasons for this could be the gender difference in the effect of ethnicity on the risk of incidence of SLE. Alternatively, Black men might have greater prevalence of adverse prognostic factors such as smoking, hyperlipidemia, etc., a hypothesis that needs to be addressed in future studies.

The strength of our analysis is that it is based on data from the NIS, a large, nationwide population-based survey in which rigorous sampling techniques reduced the likelihood of sampling bias. By its design, this data source does not provide detailed clinical information on disease severity. These variables are important for determining why post-MI outcomes are poor among patients with SLE; the objective of our study was to determine whether such differences exist, and if so, their absolute and relative magnitude. One limitation of our study is that the NIS does not include all types of data that would be helpful in controlling for other factors that contribute to poor outcomes in patients hospitalized for acute MI. Another is that we could not confirm the diagnosis of SLE recorded in the discharge abstracts. However, studies of the NIS found good overall reliability of the diagnostic information in the database^{40,41}. It is possible that the database misses those individuals with inactive or relatively mild SLE. These people are at risk for acute MI nevertheless. The effect of such a bias would be to exaggerate the post-MI risk estimation. On the other hand, subjects may be misclassified as having SLE when they did not. This potential bias will work in the opposite direction. Another source of bias was the heterogeneity of control groups. Ideally this group should be free of all diseases except MI; but many in the control group had other risk factors/conditions such as insulin resistance. On the other hand patients with SLE are often taking glucocorticoids; we did not have detailed data on these. However, the excess post-MI risk attributed to SLE in this study may be an underestimate.

The prevalence of poor post-acute MI outcomes is higher among patients with SLE than in those with diabetes. Because atherosclerotic risk factor recognition and management are currently inadequate in patients with SLE⁴², we join our colleagues in calling for more aggressive efforts at early detection and management of atherosclerosis in these patients⁴³.

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