Mortality and Cardiovascular Burden of Systemic Lupus Erythematosus in a US Population-based Cohort

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ABSTRACT. ***Objective.*** To examine the mortality and cardiovascular disease (CVD) burden among a population-based cohort of patients with systemic lupus erythematosus (SLE) with previously described late mean onset and low rates of organ-threatening disease.

Methods. This retrospective population-based cohort study investigated incident cases of SLE diagnosed from 1991–2008 and followed through March 2009 to examine rates of death and CVD events: myocardial infarction, stroke, or congestive heart failure hospitalization. Cases were identified using the 1997 update of the 1982 American College of Rheumatology SLE criteria. Searches included electronic records, chart audits, and state death matches, with physician review. Age-matched and sex-matched population comparisons facilitated relative event rate calculations.

Results. Seventy incident SLE cases had late mean onset (52 years), with an incidence of 5 cases per 100,000/year. Matched comparisons showed similar baseline rates of hypertension, hyperlipidemia, and diabetes. However, patients with SLE experienced more CVD in the 2 years preceding SLE diagnosis (OR 3.8, 95% CI 1.8, 8.0). The estimated 10-year mortality rates were 26% for SLE subjects versus 19% for comparisons, hazard ratio (HR) 2.1, $p < 0.01$. Adjusted for prior CVD, SLE cases still demonstrated increased hazards of mortality (HR 1.9, $p = 0.01$) and CVD event or death (HR 1.8, $p = 0.01$).

Conclusion. This incident SLE cohort demonstrated nearly doubled mortality and CVD event hazards compared to age-matched and sex-matched comparisons, even after accounting for higher CVD events in the 2 years preceding SLE diagnosis. This raises research questions regarding delayed SLE diagnosis versus accelerated CVD prior to SLE, particularly in older-onset SLE. (First Release Feb 15 2014; J Rheumatol 2014;41:680–7; doi:10.3899/jrheum.130874)

Key Indexing Terms:
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While early survival among patients with systemic lupus erythematosus (SLE) has improved, epidemiological studies still show an increased mortality rate and cardiovascular disease (CVD) events[1,2,3,4,5]. Reports regarding longterm outcomes of SLE frequently stem from patients of urban clinical referral centers[1,2,3], and many argue that these reports do not reflect SLE as it is commonly encountered elsewhere[6,7], including older adults in whom mortality and CVD event excesses are less clear. Few studies have examined survival in US population-based SLE inception cohorts[8,9], with the most recent concluding followup in 1997. To our knowledge, no prior studies have systematically examined the CVD burden among a US population-based cohort of patients with SLE.

Using the 1997 update of the 1982 American College of Rheumatology (ACR) SLE classification criteria[10], we assembled a population-based cohort of patients with SLE newly diagnosed between January 1, 1991, and December 31, 2008. Specifically, we combined a previously identified incident SLE cohort diagnosed from 1991 to 2001[11] with new incident cases observed in the same population through 2008. Our objective was to examine the mortality burden and rates of CV events within this population-based cohort

of patients with SLE, which had demonstrated later onset and milder SLE disease than many other SLE cohorts[9].

MATERIALS AND METHODS

Population sample. This retrospective cohort study investigated all incident cases of SLE diagnosed from 1991 to 2008 in a geographically defined population to examine rates of death and fatal and nonfatal CVD events including myocardial infarction (MI), stroke, and hospitalization for congestive heart failure (CHF). The SLE study cohort was established within the Marshfield Epidemiologic Study Area (MESA), a defined region of 24 postal codes within the service area of a single healthcare system in north-central Wisconsin, USA. The MESA resource was established in 1991 to facilitate population-based epidemiologic and clinical research. Nearly all MESA residents receive healthcare from Marshfield Clinic, its 42 regional centers, and affiliated hospitals. Patient information dating back to 1991 or earlier is archived in electronic medical records, and detailed administrative files include cohort enrollment, healthcare encounters, and links to state death files. Validation efforts indicated the recording of > 90% of healthcare encounters and 99% of deaths among the residents of central MESA[11]. The 2000 US Census data indicated that roughly 97% of the 77,280 residents of this area were white non-Hispanic. The study area population is remarkably stable geographically, with < 5% annual out-migration of the original cohort. The Marshfield Clinic Institutional Review Board approved our study.

SLE and comparison cohort definitions and exclusions. A prior study in this population described 44 incident SLE cases diagnosed between 1991 and 2001, from among 239 potential cases reviewed[11]. In our new study, inpatient and outpatient encounters were again searched for International Classification of Diseases, 9th ed (ICD-9) SLE diagnosis codes (710.0). In total, 128 individuals with at least 1 SLE ICD-9 code were reviewed, including 28 who had insufficient criteria for definite SLE in the 2001 review but had subsequent SLE-coded encounters, plus 100 new potential cases from 2002 to 2008. Chart reviews were completed by trained medical record abstractors with adjudication by study physicians, including 2 board-certified rheumatologists. "Definite lupus" was defined by the 1997 update of the 1982 ACR revised SLE classification criteria[10]. Antinuclear antibody (ANA) was considered positive at ≥ 1:80. Nonspecific urinary casts were omitted to improve specificity. Rash or mucosal symptoms and arthritis required documented physician verification by history or examination. Possible antiphospholipid antibody syndrome status was assessed by the presence of antiphospholipid laboratory abnormalities and thrombosis history confirmed by study physician review of clinical clotting event descriptions[12]. Questions were resolved by physician reviewer consensus.

To be considered incident cases, subjects with definite SLE were required to have resided in the MESA region at the time of their earliest diagnosis of SLE. The diagnosis "baseline" date was interpreted as the first date the patient met at least 4 ACR diagnostic criteria as per physician encounter notes. Cases with prior SLE diagnosis while residing outside this geographic region, miscoded diagnoses, or incomplete documentation were excluded. Discoid SLE in isolation or drug-induced SLE cases, defined by either formal diagnosis or documented use of culprit medications, were excluded.

The comparison group was defined to include all age-matched (same birth month/year) and sex-matched MESA cohort members with health encounters on the date of the matched SLE case's diagnosis date (n = 2565). The baseline date for comparisons was defined as the date of corresponding SLE case diagnosis. Individual comparisons were linked with a single SLE case in a weighted fashion to account for variable numbers of matched comparisons (n = 3–65) for each SLE case. SLE cases and comparisons were evaluated to confirm MESA residence and assess other comorbid diagnoses 24 months preceding baseline date to verify the robustness of the population-based cohort and to facilitate baseline CVD risk and comorbidity assessment.

Data sources. Data sources included clinical and administrative electronic records, matches to clinic and state death files, and SLE patient paper and electronic chart audits by trained abstractors using a pretested tool with study physician adjudication. A 20% random sample of cases underwent reabstraction including chart review by a second abstractor to assure quality. Electronic clinical data warehouse files were reviewed to ascertain encounter diagnosis codes and laboratory data. Administrative data files were searched to verify residency information, and death dates were verified between state vital statistics records and local mortality files.

Variables and outcomes. Baseline CVD risk characteristics were ascertained by electronic search for both cases and comparisons. Two or more ICD-9 coded encounters in 24 months indicated presence of diabetes, hypertension (HTN), or hyperlipidemia respectively[13,14]. Administrative search strategies developed by the Center for Medicare Services for the Chronic Condition Data Warehouse were used to evaluate the presence or absence of ischemic heart disease, acute myocardial infarction (AMI), stroke, or heart failure in the 2 years prior to SLE diagnosis or index comparison date[15]. Prior "nonfatal CVD" was defined as at least 1 hospitalization code for AMI, stroke, CHF, or ischemic heart disease with or without revascularization, or 2 or more outpatient codes within 24 months prior to baseline date. The same criteria were applied to screen "new" CVD events when searching from baseline diagnosis date through the earliest censoring date of date of death, migration, or the end of the followup period (March 21, 2009). New CV events and deaths in SLE cases were then confirmed based on queries of electronic medical record data, medical chart review, and state vital statistics data, with MD verification. New MI events in SLE cases were confirmed using the American Heart Association universal definition including presence of (1) positive troponin or creatine kinase, muscle and brain subunits plus chest pain, acute Q-waves or ST elevation, or imaging wall motion abnormalities; (2) angioplasty or bypass; (3) postmortem confirmation of myocardial injury; or (4) sudden death in the presence of chest pain[16]. New heart failure and stroke events in SLE cases were reviewed using Framingham Study CHF criteria and registry definitions of stroke including new focal or global neurologic impairment confirmed with imaging, or death with only a vascular cause[17,18]. Chart audits by 2 MD investigators using these standard clinical/registry criteria confirmed 90% of CVD events that occurred in subjects with SLE during the observed period, validating the automated algorithm that had been applied to compare CVD events between SLE cases and comparisons. Smoking status (current, former, or never) was ascertained by manual review for the SLE cases.

Statistical analysis. Population-based SLE incidence density was calculated as number of new diagnoses per total person-time observed. Baseline demographics and CV risk factors were summarized for cases and comparisons using descriptive statistics. For comparisons, "weighted" statistics were calculated, corresponding to a hypothetical population of matched comparisons having the same age and sex distribution as the case population. Baseline CV risk factors adjusted for age and sex were compared using stratified OR and Cochran-Mantel-Haenszel p-values.

All-cause mortality and a composite endpoint of death or CVD event were examined by means of weighted Kaplan-Meier (K-M) estimates. The weighted estimates may be considered the estimated cumulative incidence of CVD events for a hypothetical population drawn from the comparison group but having the same age and sex distribution as the case population. Event rates were compared using HR from a stratified Cox proportional hazards model and stratified log-rank p-values. Individuals were censored at the earliest of the date they left regional membership, died, or data cutoff on March 21, 2009. In a posthoc analysis, the analysis was repeated with comparisons matched to cases on baseline prior CVD status, in addition to age and sex. K-M curves for SLE cases and weighted comparisons with and without prior CVD were presented with HR to compare CVD risk in 2 groups after accounting for age, sex, and baseline status of prior CVD.

RESULTS

Patient characteristics. From 1991 to 2008, there were a

total of 70 incident SLE cases with a mean onset age of 52 years and females outnumbering males 4:1 (Table 1). Population-based SLE incidence was 5.03 cases per 100,000 persons per year. The SLE cases had mean followup of 7.7 years for a total of 540 SLE patient-years observed. Similar to earlier published results[11], SLE disease was mild, including only 2 cases (3%) of central nervous system (CNS) disease and 23% with renal disease (Figure 1). Most were ANA-positive (99%), and hematologic abnormalities (80%) and arthritis (61%) were among the most common disease manifestations. Additionally, 75% had received hydroxychloroquine (HCQ) and 25% received steroid-sparing disease-modifying drugs beyond HCQ. Another 73% had received steroids and at least 56% had ever received steroids in excess of 10 mg daily for more than 2 months. Antiphospholipid syndrome was found in 20%, and 38% of these patients with SLE had received 2 or more months of anticoagulation therapy for various reasons.

Most traditional CVD risk factors at baseline were similar between SLE cases and comparisons, including rates of diagnosed HTN, hyperlipidemia, and diabetes (Table 1). However, patients with SLE were more likely than comparisons to have received CVD diagnosis codes in the 2 years prior to their SLE diagnosis (OR 3.8, 95% CI 1.8, 8.0). Significant excesses were seen in prevalent ischemic heart disease, heart failure hospitalizations, and stroke, which carried the highest estimated OR (5.1, 95% CI 1.4, 19) for greater baseline prevalence in patients with SLE compared to age-matched and sex-matched comparisons.

New CVD events and deaths. From 1991 to March 2009, in the SLE cohort, there were 17 subjects who experienced 23 nonfatal CVD events, and 19 deaths were observed among the 70 patients with SLE during 540 patient-years of followup. Compared to age-matched and sex-matched comparisons observed over 21,181 person-years, subjects with SLE had about twice the hazards of all-cause mortality and of composite death and new CVD events, with HR 2.09, p = 0.002 and HR 1.83, p = 0.006, respectively (Figure 2). Estimated mortality rates for the SLE cohort at 5, 10, and 15 years after diagnosis were 13%, 26%, and 41%, versus 10%, 19%, and 27% for matched comparisons (data not shown). The estimated rate for the composite endpoint of death or CVD event at 10 years after diagnosis was 33% for the SLE cohort compared to 26% for matched comparisons. Leading causes of death in SLE subjects included 32% (n = 6) cardiovascular, 16% (n = 3) renal failure, 16% (n = 3) infection, and 11% (n = 2) malignancy, with remaining deaths attributed to gastrointestinal bleeding (n = 1), respiratory failure/interstitial lung disease (n = 1), hepatic failure (n = 1), and 11% (n = 2) recorded "failure to thrive" without a further death etiology documented in these 2 cases. The most common nonfatal CVD events in SLE cases were CHF hospitalizations (n = 11), followed by stroke (n = 7), and nonfatal MI (n = 4).

Posthoc, the survival and composite death or CVD event analyses were repeated with stratification by baseline CVD status. K-M estimates were computed for subjects with SLE and comparisons with and without baseline CVD (Figure 3) to estimate the additional hazard observed in the SLE cohort not accounted for by age, sex, and baseline CVD status. As shown in Figure 3, similar to Figure 2, all-cause mortality was highest in SLE cases with prior CVD (dashed black line), which exceeded comparisons with prior CVD (dashed grey line), and also higher in SLE cases without prior CVD

Table 1. Baseline descriptives SLE cases and comparisons.

Characteristics	SLE, n = 70	Comparisons, n = 2565	Weighted Controls	OR (95% CI)
Onset age, yrs, mean (SD)	51.6 (21.2)	45.3 (19.2)	51.6 (21.0)	Matched
Age categories, yrs (%)				
18–25	8 (11)			Matched
25– < 35	12 (17)			Matched
35– < 50	15 (21)			Matched
50– < 65	15 (21)			Matched
65+	20 (29)			Matched
Female, n (%)	57 (81)	2144 (84)	81%	Matched
Hypertension, n (%)	17 (24)	354 (14)	19%	1.5 (0.8,2.8)
Hyperlipidemia, n (%)	9 (13)	369 (14)	18%	0.6 (0.3,1.3)
Diabetes, n (%)	5 (7)	136 (5)	7%	1.0 (0.4,2.6)
Prior CVD, n (%)	16 (23)	166 (7)	10%	3.7 (1.8,7.9)*
Acute MI	2 (3)	16 (0.6)	1%	2.8 (0.6,12)
Ischemia	11 (16)	127 (5)	8%	2.8 (1.3,6.1)*
CHF	7 (10)	60 (2)	4%	2.9 (1.2,7)*
Prior stroke	3 (4)	17 (0.7)	1%	5.1 (1.4,19)*
Mean followup, yrs	7.7	8.3	8.1	

* p < 0.05. SLE: systemic lupus erythematosus; CVD: cardiovascular disease; MI: myocardial infarction; CHF: congestive heart failure.

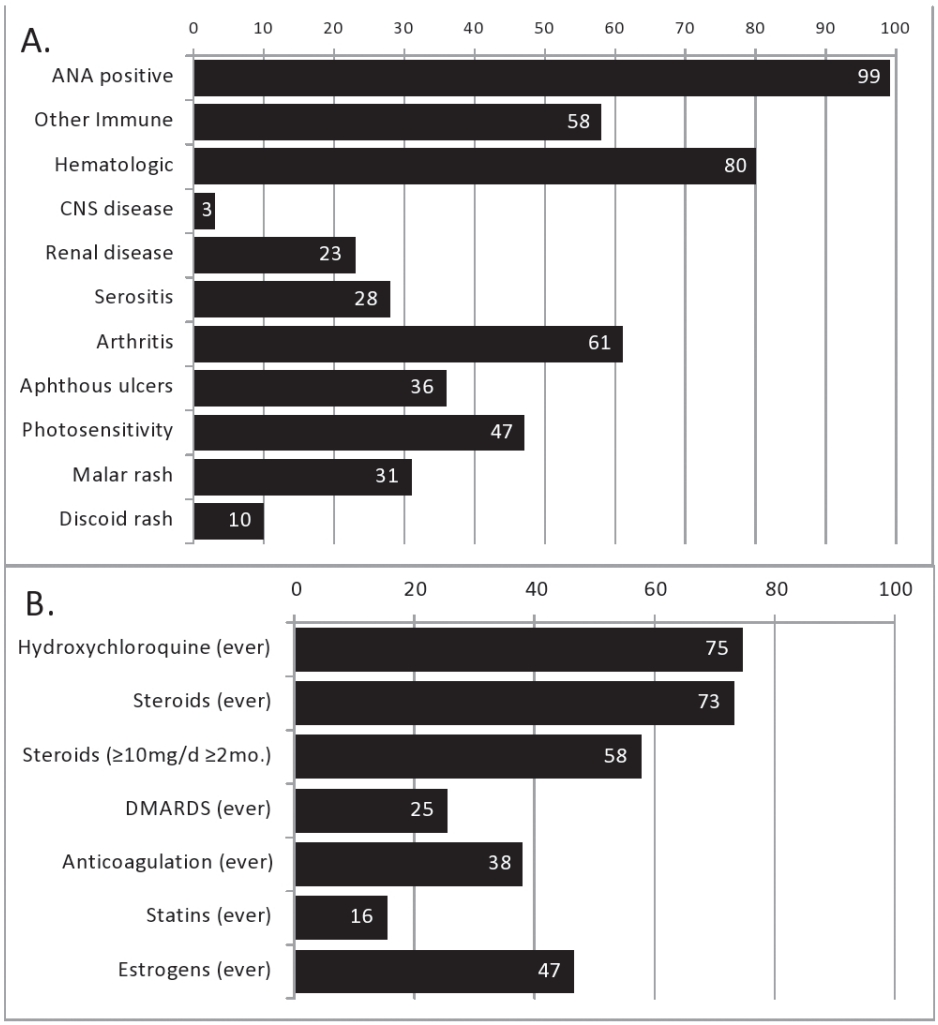

Figure 1. Clinical systemic lupus erythematosus (SLE) features at baseline (A) and medication exposure history (B). Values reflect percentage of SLE patients (n = 70) with each feature. ANA: antinuclear antibody; CNS: central nervous system; DMARD: disease-modifying antirheumatic drugs.

(solid black) than in comparisons without prior CVD (solid grey). The HR for SLE cases compared to population comparisons, after matching by age, sex, and baseline CVD status, were 1.91, p = 0.01 for mortality and HR 1.76, p = 0.01 for the composite of death or new CVD event, similar to the unstratified analysis that yielded HR of 2.09 and 1.83, respectively. Although sample size was limited to n = 13 men with SLE, interaction of SLE and sex was not detected, and mortality HR were not significantly different from women.

Lastly, SLE cases were also assessed for tobacco use and lipid testing as additional CVD risk factors. In the patients with SLE, at the time of diagnosis, 16.2% were current smokers, 36.8% were past smokers, and 47.1% indicated they had never smoked. There were no deaths among current smokers, and there was no indication of increased risk of mortality or death/CVD composite among current or past smokers compared to SLE cases who had never smoked (p = 1.0). Lipid tests were ever performed in only 66% of patients with SLE over a mean observation time of > 7 years. Overall 84% of SLE men and only 61% of women were ever tested. Gaps in hyperlipidemia diagnosis and statin treatment (< 20%) were also observed, suggesting suboptimal control of traditional CV risk particularly in women with SLE, although this was not compared to population comparison subjects.

DISCUSSION

Among 70 incident SLE cases with a mean age of 52 years at diagnosis, SLE cases experienced increased mortality and CVD event rates. Cases had about twice the hazard of death or CVD events compared to age-matched and sex-matched comparisons. Although baseline rates for other traditional CV risk factors were similar between cases and comparisons, SLE cases had nearly 4 times the odds of baseline CVD 2 years prior to SLE diagnosis. Even after accounting

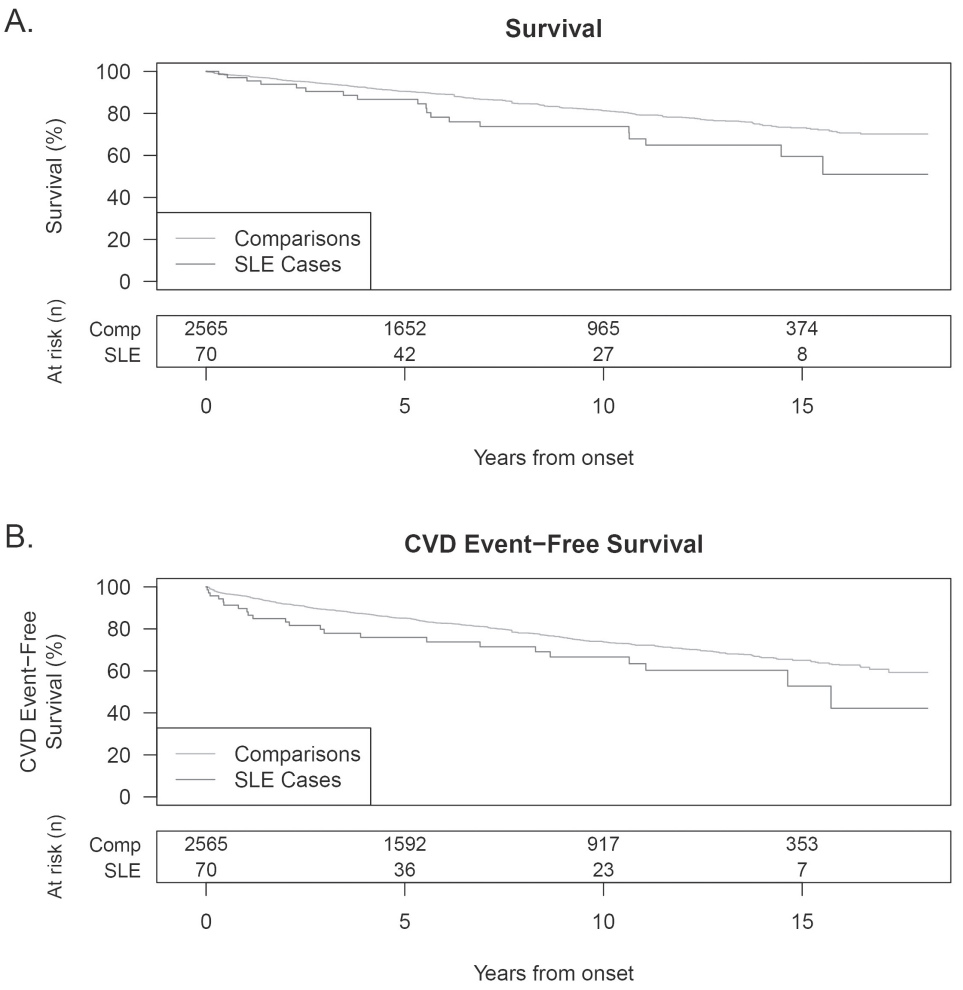

Figure 2. Kaplan-Meier estimates for systemic lupus erythematosus (SLE) cases and their age-matched and sex-matched comparisons for (A) all-cause mortality and (B) the composite of death or cardiovascular disease (CVD) event. Subjects with SLE had 2-fold increased hazards for each endpoint (A and B).

for prior CVD status, in addition to matching age and sex, we observed HR of SLE cases versus comparisons that remained significantly elevated. This shows that the differences in observed rates of mortality and new CVD events in patients with SLE are not fully accounted for by differences in prior CVD, although that observation also deserves more study.

Our findings fit with published literature including a summary by Lim, *et al* describing reported US population-based SLE incidence rates ranging from 3.4 to 7.6 per 100,000[19]. One US population-based study from the Mayo Rochester Epidemiology Project defined an SLE incidence cohort similar to ours including a mean age of 49 years, and incidence estimates of 3.1–5.6/100,000 in another predominantly white Midwestern cohort[9]. They too noted increased mortality; however, that study concluded followup in 1997 and did not specifically measure CVD events[9].

Reports on late-onset SLE, defined as onset after age 50, also support our findings by describing lower female to male ratios of 3–4:1, white race predilection, more arthritis, less renal disease, and high mortality[5,20,21]. In our incident SLE cohort, 50% of new cases were > 50 years old at first SLE diagnosis and 61% had arthritis; renal and CNS disease were rare. Accordingly, use of medications beyond HCQ or steroids was infrequent, yet SLE was associated with increased mortality and CVD event hazards. Our 10-year SLE survival rate of 74% was nearly identical to a recent late-onset SLE cohort from Spain[5], although most SLE studies with younger mean age cite > 90% 10-year survival[3], likely reflecting age-related hazards rather than disease severity. While our cohort size did not allow multivariate modeling, patients more often received steroids than other immunosuppression, and a recent Hopkins Lupus Cohort correlated steroid use to SLE CVD events more strongly than SLE activity[22]. Likewise, surveillance studies regarding atherosclerosis progression in SLE have reported that risk factors such as age, HTN, and steroid exposure may interact to compound risk[23,24].

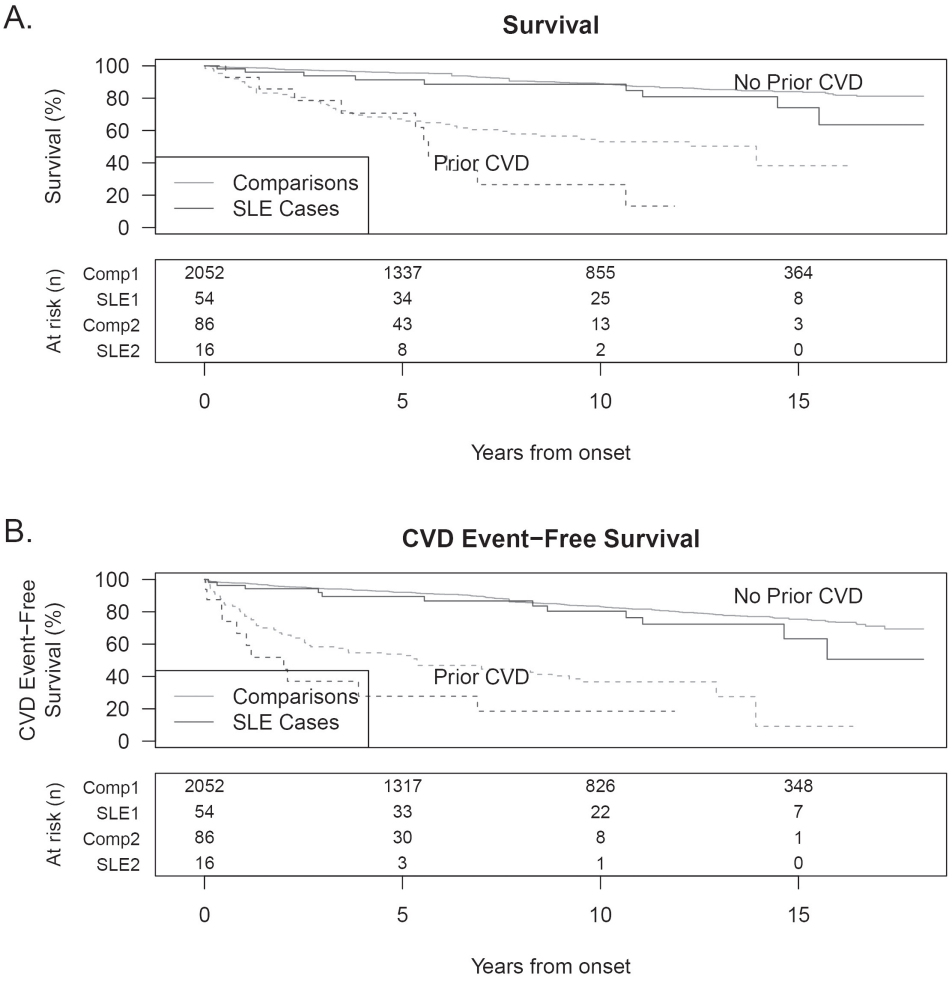

Figure 3. Kaplan-Meier estimates for systemic lupus erythematosus (SLE) cases and their age-matched and sex-matched comparisons for (A) all-cause mortality and (B) the composite of death or cardiovascular disease (CVD) event endpoints stratified by baseline CVD status. Increased hazard ratios of SLE for event risk remained even after stratifying for baseline CVD status.

CVD remains a major cause of excess SLE deaths[2,25,26]. A frequently cited study demonstrated that women with SLE between 35 and 44 years of age had a hazard for cardiac events that was elevated 50-fold compared to age-matched peers[27]. However, prior studies have drawn disparate conclusions regarding relationships between age at onset, sex, and SLE mortality[2,3,4], driving our interest in examining the CVD burden and mortality among this older, more sex-balanced cohort. Moreover, SLE patients with baseline CVD have often been excluded from studies examining the link between SLE and CVD[27]. To our knowledge, no prior studies have systematically recorded CVD diagnosis and events preceding SLE diagnosis.

In light of higher observed CVD event rates in the 2 years preceding SLE diagnosis, we must also consider possible explanations such as rapid atherosclerotic acceleration upon, or even prior to, disease onset in subclinical disease states, or perhaps delayed SLE diagnoses. Rural patients often have fewer healthcare encounters[28]. Moreover, with older onset and male sex, an SLE diagnosis may be considered less frequently[29]. Conversely, early accelerated CVD may be an inherent feature of this predominantly older SLE cohort.

As with any study, some limitations are inherent in this analysis, and findings such as increased CVD events prior to SLE diagnosis should be reexamined in larger SLE populations beyond our well-described population-based cohort. We may have missed patients with SLE who did not receive care or whose encounters used alternate ICD-9 codes including unspecified connective tissue disease or misclassified/attributed disease to drug-induced SLE. Next, although ascertainment of CVD risk factors and events used established algorithms, determination of CVD risk factors and outcomes may have been incomplete. Manual audits for the > 21,000 comparison patient-years were not feasible, but could have offered improved CVD event ascertainment

beyond the validated CVD event ICD/procedure code algorithms used to compare SLE cases and comparison subjects. Moreover, the 2 SLE cases with reported "failure to thrive" as a source of out-of-hospital death, and perhaps also in some comparison cases, may have been misclassified as noncardiac. As cardiac risks, we did not systematically examine obesity, activity levels, and comparison smoking rates. However, smoking rates in SLE subjects did not differ significantly from regional smoking rates[30]. Sensitivity analysis showed that all SLE cases with current tobacco use were alive at last observation, with no evidence of increased risk of mortality or CV events in smokers. This finding suggests that smoking cannot explain observed differences. Also, although subjects were censored at the date they were known to have left the regional MESA population, CVD events may have been missed owing to subject migration or acute management outside the region. Lastly, the region is 97% non-Hispanic white race, and our cases had a mean age of onset of 51 years; care should be taken in applying the conclusions to other SLE patient populations. Important strengths of our approach include systematic ascertainment of nearly all SLE cases in a geographically defined population and strong clinical data systems to record residence, medical encounters, CV events, and mortality.

Overall, our study offers an updated look at survival among a US population-based SLE inception cohort, and serves as a comparison to many tertiary clinical cohort survival reports. It offers a novel examination of CVD diagnoses and event codes preceding SLE diagnosis and suggests new hypotheses regarding the timing of SLE diagnoses and atherosclerosis.

We observed increased mortality and CVD events despite mild, late-onset SLE disease. This SLE effect was independent of observing higher prior CVD at baseline, supporting the need for further CVD prevention efforts in patients with SLE. Higher rates of CVD events in the 2 years preceding SLE diagnosis in patients with SLE versus comparisons draw attention to questions of delayed SLE diagnosis versus early rapidly accelerated CVD in this predominantly older SLE cohort, and future work should explore these possibilities.

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