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Systemic Lupus Erythematosus Features in Rheumatoid Arthritis and Their Impact on Overall Mortality

Murat Icen, MD¹, Paulo J. Nicola, MD², Hilal Maradit-Kremers, MD, MSc¹, Cynthia S. Crowson, MS³, Terry M. Therneau, PhD³, Eric L. Matteson, MD, MPH⁴, and Sherine E. Gabriel, MD, MSc^{1,4}

¹ Division of Epidemiology, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

² Instituto de Medicina Preventiva², Faculdade de Medicina de Lisboa, Lisbon, Portugal

³ Division of Biostatistics, Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota

⁴ Division of Rheumatology, Department of Medicine, Mayo Clinic, Rochester, Minnesota

Abstract

OBJECTIVE—Systemic lupus erythematosus (SLE) features are commonly observed in patients with rheumatoid arthritis (RA). However, their frequency and clinical significance are uncertain. We examined the frequency of SLE features in RA and their impact on overall mortality.

METHODS—We assembled a population-based incidence cohort of subjects aged ≥ 18 years first diagnosed with RA (1987 American College of Rheumatology [ACR] criteria) between 1955–95. Information regarding disease characteristics, therapy, comorbidities and SLE features (1982 ACR criteria) were collected from the complete inpatient and outpatient medical records. Cox regression models were used to estimate the mortality risk associated with lupus features.

RESULTS—The study population comprised 603 incident RA subjects (mean age 58 years, 73% female) with a mean follow-up time of 15 years. By 25 years after RA incidence, ≥ 4 SLE features were observed in 15.5% of the RA subjects. After adjustment for age and sex, occurrence of ≥ 4 SLE features was associated with increased overall mortality (hazard ratio [HR] 5.54, 95% confidence interval [CI] 3.59–8.53). With further adjustment for RA characteristics, therapy and comorbidities, the association weakened but remained statistically significant (HR: 2.56, 95% CI 1.60–4.08). After adjustment for age, sex, RA characteristics, therapy and comorbidities, thrombocytopenia (2.0, 95% CI: 1.2, 3.1) and proteinuria (1.8, 95% CI: 1.3, 2.6) were significantly associated with mortality.

CONCLUSION—SLE features were common in RA, given sufficient observation time. Subjects with RA who developed ≥ 4 SLE features had an increased risk of death. Proteinuria and thrombocytopenia were individually associated with an increased mortality risk.

Keywords

Rheumatoid arthritis; systemic lupus erythematosus; mortality

All correspondence and requests for reprints should be sent to the Corresponding Author: Sherine E. Gabriel, MD, MSc, Professor of Medicine and Epidemiology, Chair, Department of Health Sciences Research, Mayo Foundation, 200 First St. SW, Rochester, MN 55905, (507) 284-1696, (507) 284-1516 fax, gabriel.sherine@mayo.edu.

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INTRODUCTION

Clinicians have long recognized that systemic lupus erythematosus (SLE) features occur sporadically in patients with rheumatoid arthritis (RA). It has been debated whether this reflects the presence of a single disease with features of both, or the occurrence of two distinct diseases in an individual subject(1–7). Recent genetic studies have identified various loci associated with increased risks for both RA and SLE(8–11), along with candidate genes associated with predisposition to autoimmune diseases in general(12,13), supporting the hypothesis of ‘shared autoimmunity’. These findings suggest a common genetic susceptibility underlying the clustering of systemic and organ specific autoimmune disorders among members of the same family or sometimes in the same person (14). Therefore we postulated that RA patients who develop SLE features over the course of their disease represent a high risk subset with a worse long term prognosis. To date, most studies of SLE features in RA patients are cross-sectional and provide little information as to the occurrence of these features and their impact over the entire life span(3,15,16).

The purpose of this study is to examine the frequency of SLE features in an incidence cohort of subjects with RA and their impact on overall mortality.

PATIENTS AND METHODS

We studied a previously described(17) inception cohort of 603 Rochester, MN residents $\geq$ 18 years of age, who fulfilled the 1987 American College of Rheumatology (ACR) criteria for RA(18) between 1/1/1955 and 1/1/1995. The entire inpatient and outpatient medical records of study subjects from all health care providers in Olmsted County were reviewed using the medical records-linkage system of the Rochester Epidemiology Project(19).

Data collection was performed longitudinally starting at 18 years of age (or date of migration into Rochester, MN) and continuing until death, migration from Olmsted County, or date of abstraction (conducted between 2001–2003). Medical records were reviewed for RA disease characteristics, RA therapy, comorbidities and SLE disease features, as described below.

Data regarding RA characteristics included rheumatoid factor (RF) seropositivity, radiographic erosions and/or destructive changes of the joints, as well as evidence for any of the following: rheumatoid vasculitis, rheumatoid nodules, Felty’s Syndrome, rheumatoid myocarditis, rheumatoid lung disease, Sjögren’s Syndrome and other RA complications. Data was also collected regarding use of disease modifying antirheumatic drugs (DMARDs), biologic therapies and corticosteroids for RA. Start and stop dates for all therapies were collected.

Comorbidities were ascertained using Charlson comorbidity classification(20) and included cardiovascular disease, chronic pulmonary disease, peptic ulcer disease, all grades and complications of diabetes mellitus, cancer, cancer chemotherapy, renal disease, liver disease and dementia.

We also reviewed the medical records for the presence and the dates of all the first occurrences of clinical and laboratory features of SLE as defined in the 1982 ACR criteria for SLE classification(21), with the exception of urinary cell casts, as it was not feasible to reliably abstract the cellular composition of the casts from the urinalysis reports. SLE features included malar rash, discoid rash, photosensitivity, oral or nasopharyngeal ulcers, pleuritis (defined by a history of pleuritic pain or rub heard by a physician or evidence of pleural effusion) or pericarditis (defined by ECG or rub, or evidence of pericardial effusion), neurologic disorders (seizure or psychosis as recorded by physician, in the absence of

offending drugs or known metabolic derangements), renal disorders (proteinuria, defined as urine protein level > 500mg/24h or > 3+ on a dipstick), hematological disorders (hemolytic anemia defined as documented physician diagnosis of hemolytic anemia, with the presence of elevated reticulocytes; leucopenia defined as white blood cell counts <4000/ml on two or more occasions; lymphopenia defined as lymphocyte counts <1500/ml on two or more occasions, thrombocytopenia defined as platelet counts <100,000/mm in the absence of offending drug), antinuclear antibodies (depending on the laboratory, reported as positive either at a titer of 1:40 or 1:80) and immunologic disorders (anti-dsDNA antibody, anti-Sm antibody, false positive syphilis serology and LE cells).

Various methods were used over the years for testing for autoantibodies. Antinuclear antibodies were detected by indirect immunofluorescence on mouse liver substrates since 1965, and on human epithelial (HEp2) cell lines since mid 1980s, and more recently by enzyme immunoassay methods. Anti-dsDNA was detected by immunoprecipitation of radiolabeled DNA since 1975, by enzyme immunoassays on microtiter plates starting in early 1980s and later by commercial ELISA kits. Anti-Sm antibodies were detected by immunoprecipitation on agar gel since 1975 and with commercial ELISA kits since early 1990s. LE cell detection was performed after 1955. As most of these laboratory tests required assays not available during the entire study period, subjects were only considered "at risk" for laboratory criteria during those time periods when the tests for these criteria were clinically available. In each case, we recorded whether the laboratory tests had been performed, as well as the result. Percentages of subjects who developed immunological features were calculated in two ways: by considering only subjects in whom the laboratory tests were performed and by considering all subjects under observation, irrespective of whether testing was performed.

Statistical methods

Descriptive statistics including percentages, means and standard deviations were used to summarize the data. Kaplan-Meier methods were used to compute the cumulative incidence of SLE features, including SLE features present at or before RA incidence date (baseline), as well as those that developed during follow-up. Cox models were used to examine the risk of mortality associated with SLE features. These models used an age time-scale and were stratified by sex. Dichotomous time-dependent covariates were used to model the SLE features, RA disease characteristics, therapy exposures and comorbidities, which developed during follow-up. The potential adjustment variables for each group of adjusters (RA disease characteristics, RA therapy and comorbidities) were examined univariately to determine their association with mortality risk. Then a subset of significant adjusters was selected from each group using backward selection removing any variables with p-values >0.10. These subsets of variables were then used as adjusters in the models reported in Tables 2 and 3. For laboratory SLE features, subjects who never received the test were excluded from these analyses. Describing mortality following SLE features which develop throughout follow-up is complex. We used landmark analyses to obtain the results displayed in Figure 2. In these analyses, RA patients were categorized by the number of SLE features they have developed at the start of the curves (in this case, at 1, 2, 5 or 10 years after RA incidence) and survival of these groups was then estimated and compared using Kaplan-Meier methods.

RESULTS

The study population comprised 603 (mean age 58.0±15.2 years, 73.1% women) incident RA subjects diagnosed between 1955 and 1995 and followed up for a mean duration of 15.0 years (total 9066 person-years). Table 1 shows occurrence of SLE characteristics at baseline and during the follow up period in the cohort. The most common clinical SLE feature

observed in the RA cohort was pleuritis/pericarditis (6.5%) and the most common laboratory features were lymphopenia (79.8%) and antinuclear antibodies (47.1% of all tested subjects and 32.3% of all subjects observed after the test was available). Of the 481 RA subjects who developed lymphopenia, 38 had Sjogren's syndrome and 55 had keratoconjunctivitis sicca only. Of the 189 RA subjects with ANA positivity, 22 had Sjogren's syndrome and 26 had keratoconjunctivitis sicca only. A total of 266 subjects (44.1%) had at least 1 SLE feature (in addition to arthritis) and 2 (0.3%) subjects had physician diagnosis of SLE at RA incidence.

Figure 1 shows the cumulative incidence of 2, 3, 4, and 5 SLE features involving different organ systems as defined in the 1982 ACR criteria in the RA cohort after RA incidence. The percentage of RA subjects estimated to have developed a second SLE feature (in addition to arthritis) was 87.8% at 20 years and 89.5% at 25 years. Over 25 years of follow up, an estimated 54.5% of the RA subjects developed 3 SLE features, 15.5% developed 4 features and 5.0% developed 5 SLE features. During this period, only 9 (1.5%) subjects had a physician diagnosis of SLE, of whom 2 had a physician diagnosis of SLE at RA incidence date (baseline). We also examined whether subjects with RA diagnosed in recent years were more or less likely to develop SLE features than those diagnosed in earlier years. Although the development of SLE clinical features did not change over time ($p=0.62$), overall SLE features, including laboratory features, were more likely to be detected in RA subjects diagnosed in later years than in earlier years. In age and sex-adjusted models, RA subjects first diagnosed after 1975 were 58% more likely (Hazard ratio [HR]: 1.58, 95% confidence interval [CI]: 1.33, 1.89) to develop 2 and 79% more likely to develop 3 (HR: 1.79, 95% CI 1.39, 2.30) SLE features, suggesting that increased availability of laboratory testing over time may have resulted in a higher likelihood of detection of SLE features in RA subjects. However, RA subjects diagnosed after 1975 were not significantly more likely to develop 4 (HR: 1.07, 95%CI 0.65, 1.77) or 5 SLE features (HR: 0.73, 95%CI 0.28, 1.87).

We then examined the mortality risk according to the number of SLE features. The association with the number of SLE features and mortality was examined using Cox proportional hazards models, adjusting for age, sex, RA therapy, RA characteristics and comorbidities (Table 2). The age and sex adjusted HR for mortality in subjects with 2–3 and 4 or more SLE features compared to those having only arthritis were 1.85 (95% CI: 1.37, 2.49), and 5.54 (95% CI: 3.59, 8.53), respectively. A statistically significant increase in mortality risk persisted after further adjustment for use of RA therapy in subjects with 2–3 SLE features (HR 1.67, 95%CI: 1.23, 2.26) and 4 or more SLE features (HR 4.74, 95%CI: 3.04, 7.39). Occurrence of 2–3 features was no longer associated with mortality after further adjustment for RA disease characteristics (HR 1.29, 95%CI: 0.94, 1.78). However, occurrence of 4 or more SLE features remained significantly associated with a 2.56 (95% CI: 1.60, 4.08) fold higher risk of mortality, even after further adjustment for comorbidities. Figure 2 illustrates the mortality risk of subjects who had 2, 3 or ≥ 4 SLE features at 1, 2, 5 and 10 years after RA incidence. At each time point (landmark), increasing number of SLE features were associated with higher mortality risks.

We then examined the mortality risk associated with individual SLE features. Table 3 shows the mortality risk associated with individual SLE features, after adjustment for age, sex (column 1), RA therapy (column 2), RA characteristics (column 3) and comorbidities (column 4). All SLE features except for photosensitivity and false positive syphilis serology were individually associated with mortality, after adjusting for age and sex. Features most strongly associated with mortality in age and sex adjusted analyses were neurologic disorders (HR 5.9, 95% CI: 3.1, 11.5), hemolytic anemia (4.1, 95% CI: 1.8, 9.3), lymphopenia (2.8, 95% CI: 2.1, 3.7), oral/nasopharyngeal ulcers (2.9, 95% CI: 1.4, 6.2), and thrombocytopenia (2.3, 95% CI: 1.5, 3.5). The significant associations between individual SLE features and mortality were sustained following further adjustment for RA therapy and

characteristics, except for malar/discoid rash, oral/nasopharyngeal ulcers and leucopenia. After further adjustment for comorbidities, proteinuria (1.8, 95% CI: 1.3, 2.6) and thrombocytopenia (2.0, 95% CI: 1.2, 3.1) remained as statistically significant predictors of mortality.

DISCUSSION

This study provides a comprehensive description of the incidence of SLE features over a follow up period exceeding 40 years in a population-based inception cohort of RA subjects. We extend the findings of previous cross-sectional studies by describing the overlap between RA and SLE features and, for the first time, report the potential impact of SLE features on mortality in RA. Our findings demonstrate that SLE features are common in the lifetime course of RA and are significantly associated with an increased mortality risk, even after adjusting for well-described RA-specific predictors of mortality. Indeed, for some SLE features (e.g., neurological features, hemolytic anemia), the risk may be as high as six fold. These findings emphasize the overlap between RA and SLE and provide further evidence for a common autoimmunity background in these diseases.

There are at least four possible explanations for the high incidence of individual SLE features in subjects with RA. First, SLE features may simply be coincidental occurrences in RA subjects. After RA incidence and throughout the course of the disease, individual SLE features occurred sporadically and the number rose continuously over time. More than three quarters of the subjects in the RA cohort experienced at least one SLE feature (besides arthritis) and 15% experienced 4 SLE features by 25 years after RA diagnosis. Theoretically, 15% of RA subjects who experienced four or more SLE features fulfilled criteria for SLE, as the 1982 SLE criteria clearly states that “a person shall be said to have systemic lupus erythematosus if any 4 or more of the 11 criteria are present, serially or simultaneously, during any interval of observation(21).” Yet, the number of subjects in our cohort who received a physician’s diagnosis of SLE was only 9 (1.5%), indicating a large difference between the number of subjects fulfilling the criteria and those having a clinical diagnosis. The dispersed occurrences of these features over a long period may prevent easy recognition of these symptoms as a constellation. Even if they were recognized, the physician may be reluctant to consider an additional diagnosis in an established RA subject and interpret the symptoms as extraarticular manifestations. Another explanation for the large discrepancy between the number of subjects fulfilling the criteria and receiving clinical diagnosis may be the arbitrary and nonspecific nature of classification criteria, which were developed in cross-sectional analysis of subjects with established disease. This study highlights the limitations of the classification criteria when assessing symptoms collected over a long time frame, considering the dynamic nature of the autoimmune disorders. Although only 9 subjects in the RA cohort received a physician’s diagnosis of SLE, this rate was considerably more than what would be expected based on the incidence of SLE(22) alone. The incidence of SLE in this community has been reported to be 5.56 per 100,000; thus ≤ 1 new case would have been expected in this RA cohort if members of the cohort were at the same risk of SLE as the general population. A similar observation was also reported by Cohen et al. in their case series where the 11 subjects having the diagnosis of both RA and SLE comprised 3.6% of the SLE cohort whereas the predicted prevalence of RA in this SLE cohort was 1% or less(6). Therefore, it is unlikely that these are coincidental occurrences.

Second, it is possible that SLE features represent extra-articular manifestations of RA or, they are associated with DMARD, glucocorticoid or NSAID therapy, and thus, should not be interpreted as features of SLE. Proteinuria may be the result of drug induced nephropathy and thrombocytopenia may be due to drug induced immune reactions. Although leucopenia and lymphopenia were associated with seropositivity and exposure to DMARD (all $p \leq 0.01$),

we observed quite substantial numbers of leucopenia and lymphopenia cases occurring among seronegative RA patients or patients who were never exposed to DMARDs or glucocorticoids. Therefore, although therapy might have contributed to the occurrence of some SLE features, it does not appear to account for all features.

A third possible explanation is that these subjects represent a particular subset of SLE or RA subjects, or even a distinct clinical entity, such as 'rheupus syndrome' (2). It is long recognized that features of RA and SLE may coexist in individual patients, reflecting either the presence of a single disease with features of both, or the occurrence of two distinct diseases in an individual patient (1–4,6,7). It remains controversial as to whether rheupus is a true overlap between SLE and RA (16,23), a variant of either condition (e.g., lupus arthropathy) (3,4,7,15,23) or corresponds to a clinically and immunologically distinctive entity (3,24). In our study, although the number of patients who fulfilled the diagnostic criteria for SLE were much higher, RA subjects who had a physician's diagnosis of SLE comprised only a small proportion of the cohort (1.5%). It is quite likely that physicians are reluctant to consider the diagnosis of SLE as a second disease in patients with established RA, and rather view the disease features of SLE in these patients as part of the disease spectrum of RA (e.g., extra-articular manifestations) or therapy. Furthermore, the long time interval between the occurrence of individual SLE features makes physician recognition of SLE in the clinical setting difficult.

Finally, the presence of SLE features in RA subjects may support the hypothesis of "shared autoimmunity", i.e. that RA is not a specific, independent disease construct, but rather part of a broad clinical spectrum of autoimmune disease (12). Shared autoimmunity is defined as occurrence of various forms of autoimmune disorders in several members of the same family, coincidence of autoimmune rheumatic and non-rheumatic diseases in the relatives of patients, presence of autoantibodies in the healthy relatives of subjects and the occurrence of more than one autoimmune disorder in the same subject (25). For instance, family members of patients with SLE are as likely to develop RA as family members of patients with RA (26). Both RA and SLE patients frequently have other autoimmune diseases. Indeed, in a recent study 33% of the subjects in a retrospective SLE cohort have at least one other autoimmune disorder (3.49% of the cohort have RA) (27). Sjögren's syndrome is reported to occur in 11% to 31% of RA patients (28). In our cohort, 58 subjects had Sjögren's syndrome, with a cumulative incidence of 11.4% over 30 years (29). Several studies have reported that positive rheumatoid factor and anti-citrullinated peptide antibodies are found commonly in patients with SLE (30).

Genetic studies also support the concept of shared autoimmunity. The genetic risk in RA is associated with the shared epitope HLA-DRB1 on 6p21.3 especially in populations of European ancestry. In addition to the shared epitope, Anaya et al (31) demonstrated that gene variants TAP2*0201 (RA and SLE) and TNF-308A (RA, SLE and Sjögren's syndrome) on the same chromosomal region increased the susceptibility risk for multiple autoimmune disorders. A genome wide scan of multiplex RA families found that the risk of RA was significantly associated with genes implicated in other autoimmune disorders including D1S235 (SLE), D4S1647, D5S1462, D16S516 (inflammatory bowel disease), D12S1052 (multiple sclerosis) and D16S516 (ankylosing spondylitis) (32). Various other candidate genes have also been proposed as the underlying predisposing factor for the development of multiple autoimmune disorders. Among these genes, PDCD1 (8), PTPN22 (11), FCRL3 (10) and STAT4 (9) have been associated with both RA and SLE. Our clinical findings are clearly supported by these genetic studies and provide further evidence for the shared autoimmunity hypothesis.

These four possibilities can only be disentangled with a deeper understanding of the common and distinctive pathologies in these autoimmune diseases, and with prospective studies designed specifically to examine these hypotheses. Our study, taking advantage of the extended time span, where not all DMARD therapies were available, provides some indication that RA-related therapy and/or RA severity may not completely explain the occurrence of SLE features found in subjects with RA. Altogether, our observations do not support the possibility that the co-existence of RA and SLE may simply be the coincidental occurrence of two independent diseases, or even a rare phenomenon.

In this study, we also examined the association of SLE features with overall mortality in RA subjects. Our findings underscore the significance of SLE features as predictors of mortality in RA. Indeed, previous mortality studies in SLE populations have identified neurologic involvement, thrombocytopenia, hemolytic anemia and renal involvement among the strong risk factors for mortality(33–36). Some of the laboratory features we investigated are rather nonspecific findings. Proteinuria is a predictor of cardiovascular disease and mortality in the general population(37), similar to our findings in RA subjects. Proteinuria may be functional (due to fever, strenuous exercise, exposure to cold and pregnancy), or it may develop related to various disease processes including urinary tract infections, hypertension, congestive heart failure, diabetes mellitus, plasma cell dyscrasias and SLE(38). In subjects with RA, amyloidosis, NSAID or DMARD related nephropathy and mesangial glomerulonephritis resulting from immune complex deposition are other potential causes of proteinuria(39–41). In our RA cohort, there were 7 subjects who had renal disease at baseline and 49 additional subjects who developed renal disease during the course of RA. Even though our definition of proteinuria is consistent with the 1982 ACR criteria for SLE diagnosis, information on the potential causes of proteinuria or renal biopsy results are not available. Our findings also indicate that thrombocytopenia is another nonspecific feature associated with mortality. Thrombocytopenia is not a common feature of RA but it generally develops as a result of drug induced immune reaction. Similarly, we did not collect information about the possible immune reactions underlying thrombocytopenia in this cohort. Although proteinuria and thrombocytopenia are relatively nonspecific features, they may still be useful in identifying RA subjects with a higher risk of mortality.

Our study has several potential limitations that should be considered. First, this is a retrospective study and only SLE features that came to medical attention and were recorded in the medical records were ascertained. We were unable to consistently ascertain urinary cellular casts, which is an important feature of renal disorders in SLE and we did not collect information on antiphospholipid antibodies which are included in 1997 revised criteria(42). Furthermore, subjects who had a single negative laboratory test result may not have been retested to determine if they later had a positive test. These limitations may contribute to underestimation of the true number of SLE features in RA subjects. Second, this is a historical study and the RA population was ascertained between 1955 and 1995 with a follow-up until 2001–2003. Although the long follow-up period allows comprehensive description of SLE features over time, these findings may not reflect the clinical characteristics of the contemporary RA patients. Third, we assumed that SLE features, once present, would identify that subject as ‘exposed’ from that point forward, in agreement with the methodology for how SLE classification criteria were defined. However, as some of these manifestations may be transient and and/or modifiable by therapy (e.g., serositis), we may have over estimated the true number of SLE features in RA subjects that are present at a particular time point. On the other hand, laboratory abnormalities such as leucopenia or lymphopenia may have been exacerbated by therapy in some RA subjects. Assays for anti-dsDNA and anti-Sm antibodies are more robust features of SLE. However, they were not available throughout the study period and methods to detect these antibodies changed over time. Although the use of these assays increased over time, data on these variables was

available in only a small subset of the RA cohort and therefore, provided limited power to examine their role on mortality. Finally, the predominance of Caucasians in the Olmsted County population may limit the generalizability of our findings to more ethnically diverse RA populations.

Our results have important implications for future research. Longitudinal studies with long follow up are necessary to understand the overlap between autoimmune diseases. This overlap and the transient aspect of especially laboratory features should be taken into account in the future development of classification criteria for autoimmune diseases, in particular for RA and SLE. Longitudinal studies can provide a more robust and clinically meaningful approach than cross-sectional studies and can capture the dynamic nature of these two diseases. Finally, subjects who develop several features of apparently different autoimmune diseases such as RA, SLE and Sjögren's syndrome may provide a better understanding of the underlying susceptibility for autoimmunity.

Our observations may also have implications for clinical practice. Physicians should remain alert to manifestations of autoimmunity, and overlapping disease features, even well after the diagnosis of RA is established. Physicians should take into account the entire spectrum of RA disease manifestations as well as overlapping SLE features when considering therapeutic strategies, recognizing that the therapeutic approach may change as autoimmune manifestations evolve over time. Most importantly, SLE features may help to identify RA subjects at a higher mortality risk.

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Figure 1.
Cumulative incidence of developing 2, 3, 4 and 5 or more SLE features over the course of RA
Arthritis is considered as one feature and assumed present in all RA subjects.

Figure 2. Mortality risk associated with 2, 3 or ≥ 4 systemic lupus erythematosus features at 1 (Fig 2a), 2 (Fig 2b), 5 (Fig 2c) and 10 (Fig 2d) years after RA incidence.

Table 1

Occurrence of SLE Features at Baseline and over Follow Up (9066 person-years) in 603 RA subjects

	Baseline (RA incidence date)	Ever
	N(%)	N(%)
SLE clinical features		
Malar or Discoid rash	4 (0.7%)	8 (1.3%)
Photosensitivity	5 (0.8%)	10 (1.7%)
Oral/nasopharyngeal ulcers	1 (0.2%)	10 (1.7%)
Pleuritis/Pericarditis	15 (2.5%)	39 (6.5%)
Neurological disorder (seizure, psychosis)	4 (0.7%)	11 (1.8%)
Total number of patients	28 (4.6%)	69 (11.4%)
SLE laboratory features		
Renal disorder (proteinuria)	11 (1.8%)	72 (11.9%)
Hematological disorder	198 (32.8%)	488 (80.9%)
Hemolytic anemia	2 (0.3%)	8 (1.3%)
Leucopenia	29 (4.8%)	119 (19.7%)
Lymphopenia	189 (31.3%)	481 (79.8%)
Thrombocytopenia	6 (1.0%)	35 (5.8%)
Antinuclear antibodies *	79 (22.1%/17.4%)	189 (47.1%/32.3%)
Immunologic disorder *	32 (6.0%/5.5%)	54 (10.1%/9.0%)
Anti-dsDNA antibody *	5 (5.9%/1.6%)	12 (10.5%/2.3%)
Anti-Sm antibody *	1 (3.1%/0.3%)	2 (4.6%/0.4%)
False positive syphilis serology *	10 (2.1%/1.7%)	10 (2.1%/1.7%)
LE cells *	16 (5.2%/2.6%)	35 (11.4%/5.8%)
RA subjects with at least 1 SLE criteria in addition to arthritis	266 (44.1%)	
MD diagnosis of SLE	2 (0.3%)	9 (1.5%)

* These laboratory tests were not available over the entire span of the study (antinuclear antibodies available after 1965; anti-dsDNA and anti-Sm after 1975; LE cell detection after 1955). First value in the paranthesis for these features shows the percentage of positive results among those subjects tested. The second value is the percentage of positive results among all subjects observed after the test became available, assuming untested subjects as negative.

RA= rheumatoid arthritis; SLE=systemic lupus erythematosus

Table 2

Association between the number of systemic lupus erythematosus (SLE) features and the risk of mortality in the rheumatoid arthritis (RA) cohort

No. of SLE features	Hazard Ratio (HR [95%CI]) adjusted for			
	Age and sex	Age, sex and RA therapy	Age, sex, RA therapy & RA characteristics	Age, sex, RA therapy, RA characteristics and comorbidities
1 (arthritis)	1	1	1	1
2–3	1.85 (1.37, 2.49)	1.67 (1.23, 2.26)	1.29 (0.94, 1.78)	1.13 (0.82, 1.57)
4	5.54 (3.59, 8.53)	4.74 (3.04, 7.39)	3.29 (2.08, 5.21)	2.56 (1.60, 4.08)

Table 3

Association between the individual SLE features and the risk of mortality in the rheumatoid arthritis (RA) cohort

Hazard Ratio for mortality (HR [95%CI]) adjusted for				
	Age & sex	Age, sex & RA therapy	Age, sex, RA therapy & RA characteristics	Age, sex, RA therapy, RA characteristics & comorbidities
Malar/discoid rash	2.2 (1.0, 4.9)	2.5 (1.1, 5.6)	0.8 (0.3, 2.0)	0.8 (0.3, 2.1)
Photosensitivity	1.1 (0.4, 2.6)	1.2 (0.5, 2.8)	1.0 (0.4, 2.6)	0.6 (0.2, 1.5)
Oral/nasopharyngeal ulcers	2.9 (1.4, 6.2)	2.3 (1.1, 5.0)	1.5 (0.7, 3.5)	1.1 (0.5, 2.4)
Pleuritis/pericarditis	1.9 (1.3, 2.8)	1.9 (1.3, 2.8)	1.9 (1.3, 2.9)	1.3 (0.9, 2.1)
Neurologic disorders	5.9 (3.1, 11.5)	6.4 (3.3, 12.4)	4.7 (2.2, 10.1)	2.1 (0.9, 4.9)
Proteinuria	2.1 (1.5, 2.8)	2.0 (1.5, 2.7)	1.8 (1.3, 2.5)	1.8 (1.3, 2.6)
Hemolytic anemia	4.1 (1.8, 9.3)	4.6 (2.0, 10.7)	4.0 (1.6, 9.9)	1.4 (0.5, 3.6)
Leucopenia	1.3 (1.0, 1.7)	1.2 (1.0, 1.6)	0.9 (0.7, 1.3)	0.6 (0.5, 0.9)
Lymphopenia	2.8 (2.1, 3.7)	2.6 (1.9, 3.5)	1.8 (1.3, 2.5)	1.4 (1.0, 1.9)
Thrombocytopenia	2.3 (1.5, 3.5)	2.1 (1.4, 3.1)	2.4 (1.5, 3.8)	2.0 (1.2, 3.1)
Antinuclear Antibody	1.8 (1.4, 2.3)	1.6 (1.3, 2.1)	1.4 (1.1, 1.8)	1.3 (1.0, 1.7)
False (+) Syphilis serology	1.7 (0.9, 3.3)	1.6 (0.9, 3.1)	1.6 (0.8, 3.1)	1.0 (0.5, 1.9)
Lupus erythematosus cells	2.2 (1.5, 3.3)	2.3 (1.5, 3.3)	1.7 (1.2, 2.6)	1.6 (1.0, 2.4)