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Early clinical features in Systemic Lupus Erythematosus: can they be used to achieve earlier diagnosis? A risk prediction model

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Abstract

Objectives: 1) To compare the primary care consulting behaviour prior to diagnosis of people with Systemic Lupus Erythematosus (SLE) with controls, 2) to develop and validate a risk prediction model to aid earlier SLE diagnosis.

Methods: 1,739 incident SLE cases practice-matched to 6,956 controls from the UK Clinical Practice Research Datalink. Odds ratios were calculated for age, gender, consultation rates, selected presenting clinical features and previous diagnoses in the 5 years preceding diagnosis date using logistic regression. A risk prediction model was developed from pre-selected variables using backward stepwise logistic regression. Model discrimination and calibration were tested in an independent validation cohort of 1,831,747 patients.

Results: People with SLE had a significantly higher consultation rate than controls (median 9.2 vs 3.8/year) which was in part attributable to clinical features that occur in SLE. The final risk prediction model included the variables age, gender, consultation rate, arthralgia or arthritis, rash, alopecia, sicca, Raynaud's, serositis and fatigue. The model discrimination and calibration in the validation sample was good (Receiver operator characteristic curve: 0.75, 95% CI 0.73-0.78). However, absolute risk predictions for SLE were typically less than 1% due to the rare nature of SLE.

Conclusions: People with SLE consult their GP more frequently and with clinical features attributable to SLE in the five years preceding diagnosis, suggesting that there are potential opportunities to reduce diagnostic delay in primary care. A risk prediction model was developed and validated which may be used to identify people at risk of SLE in future clinical practice.

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Significance and Innovation

- People diagnosed with SLE consult their GP more than twice as frequently as controls on average in the 5 years prior to diagnosis
- People diagnosed with SLE consult their GP with clinical features attributable to SLE in the five years preceding diagnosis
- This suggests that there are potential opportunities to reduce diagnostic delay for people with SLE in primary care.
- A risk prediction model has been developed and validated which may be used to identify people at risk of SLE in future clinical practice.

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INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a multi-system autoimmune disease which can be life or organ-threatening. However, the initial symptoms can be non-specific and mimic other medical conditions, leading to diagnostic delay. A national Lupus UK survey (1) found a mean delay from first patient-reported symptom to diagnosis of 7.7 years. 50% of respondents had been given a previous diagnosis, most commonly rheumatoid arthritis (RA), but also undifferentiated connective tissue disease, renal disease and fibromyalgia. Ozbek et al.(2) reported a mean delay from first symptom to diagnosis of 21.8±30.3 months, with arthralgia being the most common presenting symptom (60%) and those with malar rash at presentation (12%) having the shortest time to diagnosis.

It is not clear where delays between symptom-onset and SLE diagnosis occur. People with symptoms may delay presenting to primary care. There may be delayed recognition of the diagnosis amongst those presenting with symptoms, leading to delayed secondary care referral. The diagnosis might be delayed in primary or secondary care due to misattribution of symptoms to an alternative disease e.g. fibromyalgia or RA. It is likely that reducing this delay will enable diagnosis and treatment at an earlier stage before severe organ involvement has occurred, thus improving outcomes and reducing healthcare costs. For example, a Danish cohort of 100 people with lupus nephritis followed for a median of 15 years found that delayed diagnosis and delayed intervention increased risk of progression to end-stage renal failure.(3) Furthermore a US health insurance database study found that diagnosis (defined as date of the first International Classification of Diseases (ICD)-9 code for SLE) delayed more than 6 months from symptom-onset (defined as the second diagnostic code for a symptom of SLE such as malar rash, photosensitivity, arthritis,

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pleurisy or an ANA test in the 12 months prior to SLE diagnosis) lead to greater flare rates, healthcare utilisation and more insurance claims (4) suggesting that earlier diagnosis may enhance patient outcomes.

We firstly aimed to examine consulting behaviour of SLE cases in primary care in the 5 years preceding diagnosis compared to controls to ascertain if consulting behaviour was a predictor for earlier diagnosis. Secondly, we developed and validated a multivariable risk prediction model to establish whether primary care consultation patterns and clinical features could be used to diagnose SLE earlier.

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METHOD

Source population

We used the Clinical Practice Research Datalink (CPRD), a longitudinal database of anonymised general practice records incepted in 1987 deemed to be representative of the UK population.(5) In January 2013 there were 660 practices contributing records for approximately 12 million people. The CPRD has been previously described and validated (6, 7), but in brief practices enter data on patient demographics, diagnoses, consultations and prescriptions using Vision Practice Management Software. Diagnoses are recorded using Read codes, a standard clinical terminology system used in general practice in the UK. Clinical information is entered contemporaneously during primary care consultations using Read codes and free text data. Only coded data were used for this study.

Participants were males and females contributing data during 1st January 1999 to 31st December 2012. They were eligible once their practice was contributing one year of data from practice registration.

Independent Scientific Advisory Committee for MHRA Database Research approval was gained for this study on 4th June 2013 (Protocol 13_092).

Study participants and study design

Cases were adult (18-100 years) incident cases of SLE identified previously.(6) In brief, participants were selected as cases if they had one of 14 Read codes for SLE or a subtype (excluding cutaneous only lupus) newly diagnosed during 1st January 1999 to 31st December 2012. Given that SLE is a rare disease we decided to include all cases with at least one code to maximise the sample size. GPs would be

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unlikely to Read code a diagnosis of SLE without confirmation from secondary care (personal communication, GD) and previous studies of other chronic autoimmune diseases have shown good accuracy in recording on the CPRD with positive predictive values >90% (8, 9). Date of first diagnosis was the index date.

Cases were randomly allocated by practice into a development (two-thirds) or validation dataset (one-third).

A case-control design was used for the development dataset as SLE is rare and this provided a straightforward approach for estimating odds ratios (OR) for clinical features in the exposure period. Four practice-matched controls per case were randomly selected from the non-SLE population. Eligible controls were aged 18-100 years and contributing at least 12 months of study time. Controls were not age or gender matched so these factors could be included in the model. After selection, controls were given an index date the same as the matched case. The study period started at the latest of registration date or 5 years prior to the index date.

A cohort design was used for model validation as this represented how the model would be used in practice and enabled direct calculation of predicted probabilities. The validation dataset included all practices containing the one-third of SLE cases plus all eligible non-SLE participants from those practices. For validation, predictor variables were assessed in the year preceding study entry and the outcome (index date) was assessed in the 1 to 5 years following study entry. Participants with less than one year of follow-up were excluded. Study entry for the validation cohort dataset was the latest of date of 18th birthday, registration date plus 1 year or 1st January 1999. For those participants with a consultation during follow-up, the first consultation date was chosen as the start date. For those participants without a

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consultation and more than 5 years of follow-up a random start date was chosen using a random number function. For those participants without a consultation and less than 5 years of follow-up study entry was the start date. Study exit was the earliest of index date (SLE diagnosis), death, transfer out of a participating practice, 31st December 2012, date of birth plus 100 years or 5 years from study entry. (Supplementary figure 1).

Predictor variables

Age (in years) and gender were chosen as important risk factors for SLE (6) and were available for every eligible participant. Consultation rate was the mean number of consultations per year (total number of consultations during the study period divided by follow-up time in years). It was hypothesised that people with SLE would consult their GP more frequently prior to diagnosis than those without SLE. Important clinical features and diagnoses that may precede a diagnosis of SLE were considered by all authors and agreement was reached by consensus. The clinical features examined were: arthralgia or arthritis, rash, alopecia, fatigue, Raynaud's phenomenon, sicca symptoms, nephrotic syndrome, serositis, general non-specific symptoms, myalgia or myositis, lymphopenia, anaemia, thrombocytopenia, miscarriage, thrombosis, fever, lymphadenopathy, abnormal weight loss, mouth ulcers, peripheral oedema, proteinuria, depression, psychosis, confusion, seizure, headache, transverse myelitis were coded as "present" or "absent". Previous differential diagnoses considered were: fibromyalgia, chronic fatigue syndrome, RA, other connective tissue disease (CTD) or Epstein-Barr virus (EBV) and a family history (FH) of autoimmune disease was also ascertained. For objective 2 fewer

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candidate predictor variables were chosen *a priori* for model development for practicality and so that a variable was less likely to be significant by chance. Age, gender, consultation rate, arthralgia or arthritis, rash, alopecia, fatigue, Raynaud's phenomenon, sicca symptoms, nephrotic syndrome, serositis and general non-specific symptoms were investigated. Consultations in the year preceding diagnosis were excluded as there was an increase in immunology blood tests and rheumatology referrals, therefore we hypothesised that GPs were considering the diagnosis of SLE and we aimed to investigate whether diagnosis could be made earlier. As the clinical feature variables were coded as either present or absent there were no missing data.

Statistical analysis

Objective 1: In the development dataset OR were calculated using logistic regression for each exposure variable. These were then adjusted for age, gender and consultation rate. Unconditional logistic regression was used as the cases and controls were only matched by practice and were felt to be a reasonable sample of people without SLE for an unmatched analysis. Using conditional logistic regression made little difference to the result. Clinical features recorded in two mutually exclusive exposure periods were explored; 0-1 years and 1-5 years preceding the index date. Differences between cases and controls in median time from clinical feature to index date were compared using the Mann-Whitney U test.

Objective 2:

Model development: Stepwise backward logistic regression used the candidate predictors to develop the prediction model. Age and gender were retained in the model as *a priori* predictors. Fractional polynomials (FP) were used to find the best

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fitting transformations for continuous variables (age and consultation rate).(10, 11) The significance of each variable and interaction between age and gender was tested using likelihood ratio (LR) tests. Variables were retained in the model if the LR test was significant ($P<0.05$). Including the FPs and interaction terms there were 16 candidate predictors and at least 10 events (cases) per candidate predictor in the development data indicating adequate sample size based on recommendations.(12)

Model validation:

To obtain the predicted risk score (risk_score) the β-coefficients for the model were applied with mean-centring in combination with a new α-coefficient. The new α-coefficient reflected the probability of SLE in the validation cohort using (13):

$$\alpha = \ln (\text{incidence}_{new}/1\text{-incidence}_{new})$$

This recalibrated the α from the developed model to the validation dataset (as the development α was biased due to it being a case-control sample).

The probability (p) of developing SLE in the validation dataset was calculated using:

$$p=\exp(\text{risk_score})/(1+\exp(\text{risk_score}))$$

The area under the receiver operating characteristic curve (ROC) tested model discrimination between those with and without the disease. Calibration was assessed with a calibration plot, graphically comparing the observed and predicted risk of SLE stratified by decile of predicted risk. Calibration-in-the-large and calibration slope statistic were calculated.(14) These should ideally be 0 and 1 respectively. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated comparing the top 5 and 10% of risk as a threshold for triggering further investigation.

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Data management and analysis was performed using StataMP4 software, version 13 (Statacorp, Texas, USA). Multiple imputation was not required as complete data were available.

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RESULTS

There were 2,635 incident cases from 571 practices; 1,739 in the development dataset (matched to 6,956 controls) and 896 (from a cohort of 2,187,974 adults) in the validation dataset. 1,831,747 of the validation participants had at least one year of follow-up from study entry of which 365 cases were diagnosed between 1 and 5 years and were therefore eligible for study inclusion. Table 1 shows the baseline demographics.

Objective 1

The OR for female gender was 5.23 (95% CI: 4.56-6.00, p<0.001). In the 5 years preceding diagnosis the median consultation rate per year was 9.2 (IQR: 5.4-14.7) for cases and 3.8 (IQR: 1.4-7.6) for controls (p<0.001). The OR was 1.098 (95% CI: 1.089-1.106, p<0.001) i.e. for every additional consultation per year the odds of having SLE increased by 9.8%. Stratifying the time before diagnosis by year there remained a significant increase in consultation rate for cases in all 5 years (Supplementary Table 1).

The OR for clinical features and diagnoses in the 5 years preceding diagnosis are in Table 2. Arthritis or arthralgia, rash, fatigue, headache and depression were the features which occurred most frequently in cases. Nephrotic syndrome, Raynaud's, thrombocytopenia, a family history of RA or a previous diagnosis of other CTD discriminated most strongly between cases and controls. Table 3 shows the comparison for 0-1 and 1-5 years preceding diagnosis.

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Table 4 summarises the median time from clinical feature to index date. Among cases only nephrotic syndrome and thrombocytopenia were recorded within a year of diagnosis on average.

Objective 2:

Model development

Table 5 gives the mutually adjusted ORs and β-coefficients for the final model. Nephrotic syndrome was excluded as there was only 1 case and no controls with this in the 1-5 years preceding diagnosis. Age and consultation rate were non-linear, therefore FP terms were used. All variables except general non-specific symptoms were significant at the 0.05 level. There was significant interaction between age and gender (p=0.0034) indicating that FP coefficients used to model the effect of age differed for men and women and therefore interaction terms were used. The ROC was 0.7850 (95% CI: 0.7733-0.7966).

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Model validation

The new α-coefficient (-8.5204) and the β-coefficients with mean-centring produced the following model:

Risk score[1]= -8.5204 + femalegenderx1.3718 + arthritisx0.6273 + rashx1.1106 + alopeciax0.6763 + raynaudx2.1359 + siccax0.4458 + fatiguex0.3451 + serositisx0.49171 + (age^2-48.9805^2) x0.0058 + [(age^2 x ln(age))-(48.9805^2 x ln(48.9815))] x-0.0004 + [(rate+1.1921e-07/ 100)$^{-0.5}$-$0.06302^{-0.5}$] x-0.0018 + [ln(rate +1.1921e-07/ 100)- ln(0.06302)]x-0.0004 + (age^2-48.9805^2) xfemalegenderx-0.0018 + [(age^2 x ln(age))-(48.9805^2 x ln(48.9815))]xfemalegenderx0.0004

Model discrimination was good (ROC 0.7538 (95% CI: 0.7295-0.7781)) (Figure 1a). The calibration plot showed good agreement between observed and predicted risks (Figure 1b). This was confirmed with the calibration-in-the-large statistic (-0.0334 (95% CI: -0.1360-0.0692)) and calibration slope (1.1495 (95% CI: 1.0331-1.2659)). The 95% CI for the calibration slope was above 1 suggesting some miscalibration; however the absolute magnitude of this was very small.

Using the top 10% as a threshold for defining high risk of SLE, the sensitivity was 33.97%, specificity 90.01%, PPV 0.07% and NPV 99.99%. Using the top 5% the sensitivity was 23.84%, specificity 95.00%, PPV 0.09% and NPV 99.98%.

[1] The best-fitting FP2 model powers for age at diagnosis were 2 and 2 i.e. age^2 and age^2 x ln(age) and for consultation rate were -0.5 and 0 i.e. $rate^{-1}$ and ln(rate). Scaling was used for consultation rate where scaled rate = unscaled rate+1.1921e-07/100 and mean-centre was 6.3021. The mean-centre for age was 48.9805.

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Used clinically, a 51 year old woman presenting to the GP three times in the past year with arthralgia, rash and Raynaud's would have a probability of developing SLE in the subsequent 1-5 years of 0.0128 (top 5%). In contrast, a 33 year old man presenting to the GP once in the past year with a rash would have a probability of developing SLE of 0.0001 in the subsequent 1-5 years (bottom 90%).

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DISCUSSION

People diagnosed with SLE consulted their GP more than twice as frequently as controls on average in the 5 years prior to diagnosis, as judged by the median consultation rate (supplementary table 1). Compared with controls people with SLE were more likely to consult with clinical features suggestive of SLE, such as arthralgia or arthritis, rash, alopecia and Raynaud's. The median time from clinical feature presentation to SLE diagnosis was greater than one year for all features except nephrotic syndrome and thrombocytopenia which are likely to prompt acute hospital admission or urgent diagnosis of SLE. This is the first study to develop a risk prediction model for SLE to identify SLE cases in the community. It had good discrimination and calibration with high specificity and NPV, but low sensitivity and PPV due to the rare nature of SLE.(6)

Previous studies of early clinical features and other rheumatological diagnoses given prior to that of SLE have largely been small single-centre analyses reliant on patient recall following diagnosis.(1, 2, 15) One US military record study(16) found in 130 people with SLE arthritis was the most frequent presenting symptom occurring a mean of 1.36 years before diagnosis. In comparison, our study was larger, from a more diverse population and included a control group. A Taiwanese insurance claims study (17) found increased use of medical care in the eight years preceding SLE diagnosis. A shorter time period was used for our study to increase the number of participants with complete data and increase the chance that clinical features were attributable to SLE. There is no primary care gate-keeper in Taiwan such as in the UK so these consultations represented self-referrals to specialists. This study considered diagnoses using ICD-9 headings such as "Disorders of the eye and adnexa" rather than presenting symptoms such as "sicca" as in our study. A UK

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paediatric study (18) found that nephritis, Black or Asian ethnicity and referral from a paediatrician to a paediatric rheumatologist were independent predictors of quicker SLE diagnosis. However, their cohort was smaller, only included children and relied on patient or parent recall of symptoms. Our early symptoms findings support the recent primary care campaign “Think LUPUS and refer” supported by Lupus UK, the Primary Care Rheumatology Society and the Royal College of General Practitioners which recommends considering a diagnosis of SLE in people with Loss of hair, Ulcers-mouth/nose, Pain – musculoskeletal, Unexplained symptoms, signs and blood test abnormalities, Sun sensitive rashes or Raynaud’s.(19)

That people ultimately diagnosed with SLE consult more frequently and with clinical features which could be attributable to SLE suggests that there are potential opportunities for earlier diagnosis of SLE in primary care. The development of a new lupus-like clinical feature should prompt the review of a previous rheumatic diagnosis. Current RA diagnostic recommendations include testing serum antinuclear antibodies (ANA) and full blood count (complete blood count).(20) A positive ANA, lymphopenia or thrombocytopenia should prompt consideration of SLE as an alternative diagnosis. Our study therefore reinforces current guidelines (25) and suggests that best practice is not always followed. To consider a multi-system disease such as SLE in a 10-minute consultation (the usual duration of a consultation in the UK) a GP needs to assimilate the current symptoms and consider the significance of previous presentations which may seem unconnected. This could contribute to diagnostic delay. The lack of rheumatology experience in GP training(21) makes educational initiatives such as the “Think LUPUS and Refer" campaign essential to increase GPs' awareness of SLE’s protean manifestations. In addition, with pressure on primary care, consultations are occurring with allied health

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professionals who may have limited training in SLE. Predictive models have gained increasing popularity in medical practice, particularly for estimating cardiovascular risk,(22, 23) osteoporosis risk(24, 25) and earlier diagnosis of malignancy.(26-28) Although there have been studies which have considered screening strategies to identify undiagnosed cases of SLE in the community (29, 30) there have been no previous risk prediction models for earlier diagnosis of SLE. The prediction model could be incorporated into primary care software so that it flags patients at risk based on symptoms entered contemporaneously and in past consultations. The model could prompt review of significant clinical features, to provide a threshold for ANA testing and if positive for onward rheumatology referral. The ROC from our prediction model compares favourably to the ROC found for the cardiovascular disease, osteoporosis and malignancy prediction models; however, comparing a threshold of people in the top 10% of risk, our sensitivity and PPV are lower than in these studies. This may be due to the rarity of SLE compared to cancer, osteoporosis and cardiovascular disease, which would result in a large number of healthy individuals being flagged as “at risk”. ANA has good sensitivity but low specificity, therefore further examining the antigenic specificities of the ANA might increase its clinical utility (31). An alternative screening test such as a more specific or inexpensive biomarker for SLE during the period of non-specific symptoms and medical visits may enhance early detection. Previous studies have suggested that if diagnosis of SLE could be made earlier patient outcomes could be improved and healthcare costs reduced(3, 4). It is hoped that tools such as this model may enable earlier diagnosis of individuals with clinical features suggestive of SLE.

The strengths of this study are the large sample size, the generalisability to the UK population, and prospective data entry which excludes recall and responder bias.

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The prediction model methodology was designed to reduce bias by the random allocation of cases by practice to development and validation datasets. FPs were used to model continuous predictors to account for non-linearity in the relationship between the predictor and risk of SLE.(10, 32) The limitations of the study are firstly we are reliant on the accuracy of data entered at the GP practice which may have been entered incorrectly or incompletely introducing misclassification bias or missing data. It may be that features such as fever and lymphadenopathy were due to infection rather than early SLE. An increase in infection rate could be due to immune system impairment preceding diagnosis which is known to occur following diagnosis(33) or could be the environmental trigger for SLE development.(34) While ethnicity is an important risk factor for SLE(6) these data are only available for a subset of individuals in the CPRD which precluded inclusion in the model. Similarly, laboratory test results were not available for a large subset and precluded inclusion of positive immunology in the model. Only clinical features in the 5 years preceding diagnosis were considered. This time was chosen to maximise participants with complete data, but may have excluded important events occurring more than 5 years preceding diagnosis. Finally, the model is not diagnostic for SLE, but provides a risk stratification which could be used to identify high risk individuals for further investigation. As SLE is a very rare disease, less than 1% will develop SLE over a period of 5 years, even among those we identify as being high risk. Before use in clinical practice the model should undergo clinical and economic evaluation.(32) The cost of ANA testing and referral of false positives needs to be balanced against the number of SLE cases that would be diagnosed earlier with the prospect of improved clinical outcomes.(35)

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In future, additional variables could be incorporated in the model such as ethnicity which may be available in future CPRD releases. Clinical features more than 5 years preceding diagnosis could be investigated, along with past exposure to infections, immunisations and presentation with further clinical features.

In conclusion, people subsequently diagnosed with SLE consult their GP more frequently and with clinical features within the SLE spectrum in the 5 years prior to diagnosis. Early clinical features may be mild and common, but presentation with two or more features should prompt clinical review and consideration of investigation such as with ANA. A risk prediction model has been developed and validated which may assist this decision-making process in future following further evaluation.

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Frances Rees had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This paper meets the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) reporting guidelines(36).

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Tables

Table 1 Dataset characteristics

	Cases	Controls	P value
Development dataset (n=8,695)			
Total number of cases	1,739	6,956	
Gender: number of females (%)	1,465 (84.2)	3,515 (50.5)	<0.001[a]
Mean age at diagnosis, years (SD)	50.5 (15.9)	48.6 (18.1)	0.0001[b]
Median time before index date, years (IQR)	6.75 (3.15-11.23)	6.76 (3.22-11.16)	0.97[c]
Validation dataset (n= 1,831,747)			
Total number of cases	365	1,831,382	
Gender: number of females (%)	312 (85.5)	937,484 (51.2)	<0.001[a]
Median age at start of follow-up, years (IQR)	43.5 (33.4-53.8)	40.1 (28.2-56.3)	0.006[c]
Median follow-up time, years (IQR)*	2.75 (1.83-3.81)	5 (3.15-5.00)	<0.001

* Follow-up was truncated at 5-years or SLE diagnosis in the validation cohort. [a]Chi-squared test, [b]Student's t-test, [c]Wilcoxon rank-sum test.

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Table 2 Odds ratios for clinical features in the 5 years prior to diagnosis

Variable	Controls (%) N=6956	Cases (%) N=1739	Univariable odds ratio (95%CI)	P value	Odds ratio adjusted for age, gender and consultation rate (95% CI)	P value
Clinical feature						
Arthritis or arthralgia	727 (10)	622 (36)	4.77 (4.21 5.40)	<0.001	3.32 (2.89 3.80)	<0.001
Rash	685 (10)	744 (43)	6.84 (6.05 7.74)	<0.001	5.60 (4.89 6.41)	<0.001
Fatigue	472 (7)	291 (17)	2.76 (2.36 3.23)	<0.001	1.64 (1.38 1.95)	<0.001
Alopecia	57 (1)	66 (4)	4.77 (3.33 6.83)	<0.001	3.31 (2.25 4.87)	<0.001
Sicca	86 (1)	102 (6)	4.97 (3.72 6.66)	<0.001	2.70 (1.93 3.78)	<0.001
Raynaud's	21 (0)	77 (4)	15.29 (9.41 24.85)	<0.001	12.28 (7.28 20.73)	<0.001
Serositis	59 (1)	72 (4)	5.05 (3.56 7.15)	<0.001	3.13 (2.12 4.64)	<0.001
Nephrotic syndrome	1 (0)	8 (0)	32.12 (4.02 257.01)	<0.001	42.00 (4.82 366.36)	<0.001
General non-	101 (1)	80 (5)	3.27 (2.43 4.41)	<0.001	1.77 (1.27 2.47)	<0.001

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specific symptoms						1				
Myalgia or myositis	0 (0)	0 (0)	-	-	-	-	-	-	-	-
Fever	62 (1)	51 (3)	3.36	(2.31	4.88)	<0.001	2.81	(1.83	4.33)	<0.001
Lymphadenopathy	74 (1)	54 (3)	2.98	(2.09	4.25)	<0.001	2.02	(1.36	2.99)	<0.001
Abnormal weight loss	26 (0)	21 (1)	3.26	(1.83	5.80)	<0.001	2.33	(1.20	4.52)	0.01
Mouth ulcers	64 (1)	58 (3)	3.71	(2.59	5.32)	<0.001	2.64	(1.76	3.96)	<0.001
Peripheral oedema	323 (5)	151 (9)	1.95	(1.60	2.39)	<0.001	1.32	(1.04	1.67)	0.02
Proteinuria	32 (0)	13 (1)	1.63	(0.85	3.11)	0.14	0.98	(0.46	2.09)	0.96
Thrombosis	50 (1)	58 (3)	4.76	(3.25	6.98)	<0.001	3.38	(2.18	5.23)	<0.001
Headache	648 (9)	296 (17)	2.00	(1.72	2.32)	<0.001	1.13	(0.96	1.33)	0.16
Depression	784 (11)	348 (20)	1.97	(1.71	2.26)	<0.001	1.07	(0.92	1.26)	0.38
Seizure	20 (0)	13 (1)	2.61	(1.30	5.26)	0.01	1.87	(0.82	4.27)	0.14
Psychosis	9 (0)	2 (0)	0.89	(0.19	4.11)	0.88	1.00	(0.17	6.00)	1.00
Confusion	27 (0)	10 (1)	1.48	(0.72	3.07)	0.29	1.07	(0.46	2.48)	0.87
Anaemia	190 (3)	151 (9)	3.38	(2.71	4.22)	<0.00	2.17	(1.70	2.77)	<0.001

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						1				
Lymphopenia	0 (0)	3 (0)	-	-	-	-	-	-	-	-
Thrombocytopenia	5 (0)	15 (1)	12.09	(4.39	33.31)	<0.001	10.54	(3.18	34.96)	<0.001
Miscarriage	58 (0)	33 (0)	2.30	(1.49	3.54)	<0.001	1.32	(0.83	2.09)	0.24
Transverse myelitis	0 (0)	0 (0)	-	-	-	-	-	-	-	-
Family history (FH)										
FH of autoimmune disease	181 (3)	61 (4)	1.36	(1.01	1.83)	0.04	0.96	(0.69	1.32)	0.80
FH of RA	1 (0)	8 (0)	32.14	(4.02	257.16)	<0.001	22.43	(2.65	189.84)	<0.001
Previous diagnoses										
Chronic fatigue syndrome	12 (0)	19 (1)	6.39	(3.10	13.19)	<0.001	2.53	(1.17	5.45)	0.02
Fibromyalgia	17 (0)	33 (2)	7.89	(4.39	14.20)	<0.001	2.56	(1.35	4.84)	<0.001
RA	31 (0)	80 (5)	10.77	(7.09	16.35)	<0.001	7.15	(4.52	11.29)	<0.001
Other CTD	22 (0)	112 (6)	21.68	(13.69	34.36)	<0.001	15.24	(9.26	25.11)	<0.001
EBV	6 (0)	2 (0)	1.33	(0.27	6.61)	0.73	1.70	(0.30	9.45)	0.55

CTD=Connective tissue disease, EBV=Epstein-Barr virus, RA=Rheumatoid arthritis

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Table 3 Odds ratios for clinical features 0-1 and 1- 5 years prior to diagnosis

Variable	Odds ratio for 0-1years N=8691 (95% CI)			P value	Odds ratio for 1-5yrs N=8291 (95% CI)			P value
Clinical feature								
Arthritis or arthralgia	8.71	(7.29	10.41)	<0.001	3.16	(2.74	3.64)	<0.001
Rash	13.75	(11.49	16.46)	<0.001	4.10	(3.56	4.72)	<0.001
Fatigue	3.52	(2.73	4.55)	<0.001	2.59	(2.16	3.10)	<0.001
Alopecia	11.60	(6.15	21.88)	<0.001	3.38	(2.15	5.31)	<0.001
Sicca	8.81	(5.10	15.22)	<0.001	3.72	(2.66	5.22)	<0.001
Raynaud's	22.01	(10.33	46.89)	<0.001	12.58	(6.55	24.19)	<0.001
Serositis	10.84	(5.57	21.09)	<0.001	3.46	(2.26	5.30)	<0.001
Nephrotic syndrome	28.09	(3.45	228.47)	<0.001	-*	-	-	
General non-specific symptoms	7.05	(4.00	12.44)	<0.001	2.64	(1.87	3.72)	<0.001
Fever	6.58	(3.52	12.29)	<0.001	2.27	(1.41	3.65)	<0.001
Lymphadenopathy	3.65	(1.96	6.80)	<0.001	2.83	(1.85	4.32)	<0.001
Abnormal weight loss	5.16	(1.92	13.88)	<0.001	2.75	(1.35	5.58)	0.01
Mouth ulcers	4.81	(2.69	8.62)	<0.001	3.23	(2.06	5.05)	<0.001
Peripheral oedema	2.58	(1.92	3.48)	<0.001	1.50	(1.17	1.91)	<0.001

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Proteinuria	1.85	(0.70	4.87)	0.21	1.33	(0.57	3.14)	0.51
Thrombosis	8.10	(4.15	15.80)	<0.001	4.18	(2.63	6.63)	<0.001
Headache	2.80	(2.23	3.53)	<0.001	1.72	(1.45	2.03)	<0.001
Depression	2.29	(1.87	2.81)	<0.001	1.84	(1.58	2.15)	<0.001
Seizure	2.67	(0.75	9.47)	0.13	2.26	(0.99	5.11)	0.05
Psychosis	1.00	(0.11	8.95)	1.00	1.00	(0.11	8.95)	1.00
Confusion	2.81	(1.07	7.38)	0.04	0.67	(0.20	2.26)	0.51
Anaemia	6.53	(4.59	9.38)	<0.001	2.39	(1.83	3.13)	<0.001
Thrombocytopenia	*-	-	-		6.01	(1.70	21.34)	0.01
Miscarriage	2.58	(1.11	5.97)	0.03	2.60	(1.60	4.22)	<0.001
Previous diagnoses								
Chronic fatigue syndrome	10.05	(3.15	32.07)	<0.001	4.91	(2.03	11.87)	<0.001
Fibromyalgia	8.06	(3.44	18.86)	<0.001	7.34	(3.51	15.36)	<0.001
RA	27.56	(12.43	61.08)	<0.001	7.41	(4.57	12.00)	<0.001
Other CTD	89.94	(28.23	286.52)	<0.001	12.19	(7.32	20.30)	<0.001
EBV	1.33	(0.14	12.82)	0.80	1.33	(0.14	12.82)	0.8

* No OR could be generated for nephrotic syndrome in the 1-5 year period or thrombocytopenia in the 0-1 year period as no controls had the clinical feature.

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Table 4 Median number of days between clinical feature onset and diagnosis

Clinical feature	Median number of days in controls (IQR)	Median number of days in cases (IQR)	P value (Mann-Whitney U test)
Fatigue	809.5 (386-1271)	729 (344-1239)	0.2907
Sicca	821 (433-1172)	687.5 (313-1250)	0.3841
Rash	858 (448-1299)	590 (173-1196)	<0.001
Arthritis or arthralgia	901 (450-1368)	574 (175-1184)	<0.001
Serositis	904 (537-1389)	513.5 (161-1193.5)	0.0031
Alopecia	750 (440-1370)	475 (143-1155)	0.0217
Raynaud's	780 (286-1094)	433 (207-1110)	0.3300
General non-specific symptoms	938 (403-1390)	509 (166-1088.5)	0.0001
Nephrotic syndrome	94 (94-94)	58.5 (42.5-98.5)	0.4386
Fever	770 (395-1322)	416 (151-797)	0.0051
Lymphadenopathy	687 (336-1128)	670.5 (337-1025)	0.9846
Abnormal weight loss	763.5 (358-915)	495 (262-837)	0.2350
Mouth ulcers	675.5 (341.5-1239)	504 (255-1036)	0.2363
Peripheral oedema	904 (393-1376)	553 (243-1237)	0.0004
Proteinuria	664.5 (244-1276.5)	552 (63-819)	0.2494
Thrombosis	835 (478-1421)	768 (272-1257)	0.4522

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Headache	916 (478-1347.5)	703.5 (308.5-1223.5)	0.0006
Depression	959 (522.5-1437.5)	954 (442.5-1419.5)	0.2592
Seizure	982.5 (647.5-1590)	836 (467-1493)	0.5072
Psychosis	490 (228-618)	882.5 (158-1607)	1.0000
Confusion	532 (237-1169)	180 (42-631)	0.1007
Anaemia	983.5 (496-1336)	503 (151-1010)	<0.001
Thrombocytopenia	729 (710-783)	338 (128-707)	0.0325
Miscarriage	1124 (445-1480)	917 (637-1499)	0.9605

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Table 5 Multivariable analysis

Variable	Multivariate mutually adjusted odds ratio (95%CI)			β-coefficient	Wald's p value
Gender	3.942	3.260	4.767	1.3718	<0.001
Age at diagnosis (FP1)[a]	1.006	1.004	1.008	0.0058	0.165
Age at diagnosis (FP2)[b]	0.999	0.998	0.999	-0.0013	0.200
Arthralgia or arthritis	1.872	1.592	2.202	0.6273	<0.001
Rash	3.036	2.598	3.549	1.1106	<0.001
Alopecia	1.967	1.193	3.241	0.6763	0.008
Raynaud's	8.465	4.106	17.452	2.1359	<0.001
Fatigue	1.412	1.156	1.725	0.3451	0.001
Serositis	1.635	1.012	2.641	0.4917	0.044
Sicca	1.562	1.050	2.324	0.4458	0.028
Consultation rate (FP1)[c]	1.000	1.000	1.000	0.0003	<0.001
Consultation rate (FP2)[d]	1.561	1.449	1.681	0.4453	<0.001
Gender*ageFP1	0.998	0.996	1.001	-0.0018	<0.001
Gender*ageFP2	1.000	1.000	1.001	0.0004	<0.001

[a]=age^2 [b]= age^2 x ln(age) [c]= $rate^{-0.5}$ [d]= ln(rate)

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Figure legends:

Figure 1:a) ROC curve and b) calibration plot in the validation dataset

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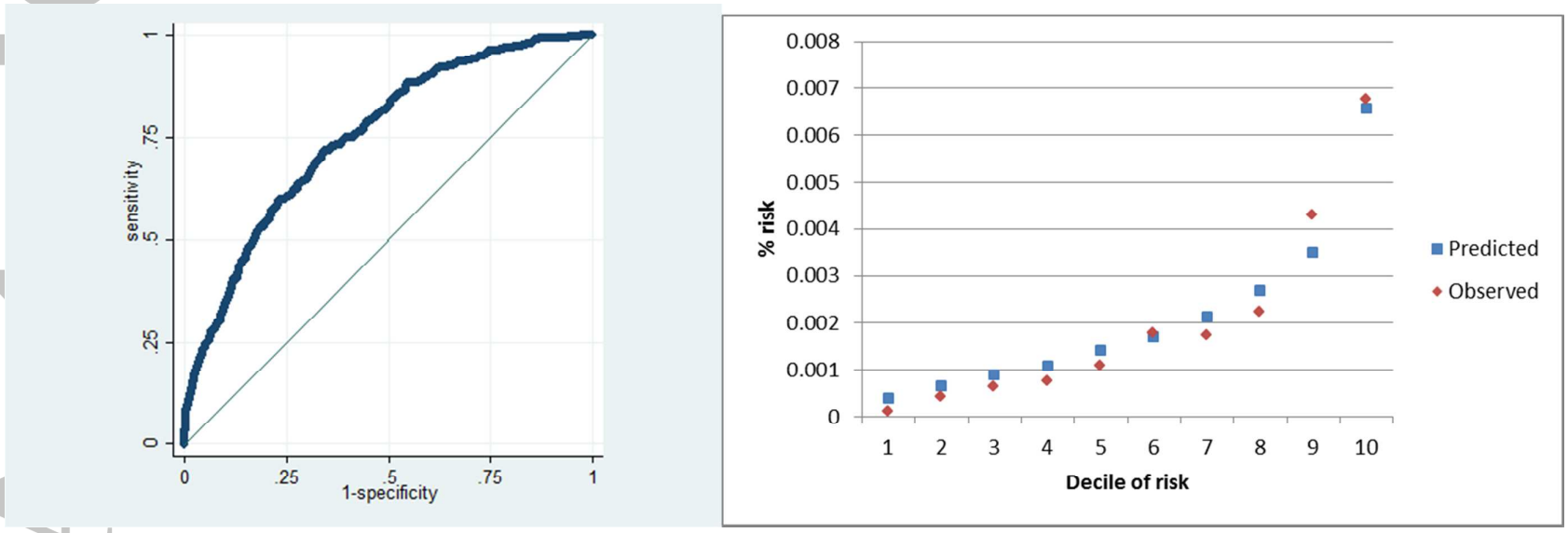

Figure 1:a) ROC curve and b) calibration plot in the validation dataset

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