From first symptoms to diagnosis of systemic lupus erythematosus: mapping the journey of patients in an observational study

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Abstract

Objective

Although increased awareness for systemic lupus erythematosus (SLE) has reduced diagnostic delay, the average time from symptom onset to diagnosis is still long, potentially resulting in adverse outcomes. We mapped the journey of lupus patients from onset of symptoms to disease diagnosis.

Methods

We carried out an observational study of 275 SLE patients with disease duration <6 years. Data were collected from patient charts, interviews and in-person clinical visits. Total delay was divided in i) time from symptom onset to first physician visit, ii) time from first visit to assessment by rheumatologist, and iii) time from initial rheumatologist assessment to final diagnosis. Early diagnosis was defined as diagnosis within 6 months from symptom onset.

Results

Most common initial symptoms were arthritis/arthralgia (74.5%) and rashes (61.8%). Median (IQR) total delay between symptom onset and SLE diagnosis was 24 (54) months. An "early" diagnosis was achieved only in 28.4% of patients, while 55.6% were diagnosed after 12 months, with patients consulting an average of 3 different physicians before reaching diagnosis. Oral ulcers (OR 3.55; 95% CI 1.45–8.70) and malar rash (OR 1.99; 95% CI 1.00–3.94) as initial symptoms, and first medical assessment by orthopaedic (OR 5.18; 95% CI 1.47–18.20) were independently associated with a delayed diagnosis. The latter was also associated with increased SDI at the time of diagnosis (OR 2.42; 95% CI 1.03–5.69), attributed mainly to neuropsychiatric and thrombotic events.

Conclusion

Diagnosis of SLE is delayed by more than 6 months in three quarters of patients and is associated with more damage accrual.

Key words

systemic lupus erythematosus, delay, diagnosis, Attikon cohort, onset

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a broad spectrum of clinical manifestations (1, 2). Its onset is often insidious, with clinically evident disease developing over years (3-7). At early stages, many patients present with only a few features that can resemble other autoimmune, infectious or haematological diseases. Constitutional, cutaneous, musculoskeletal and haematological features are common initial manifestations (7-14). Also, clinical presentation may differ according to age at onset (15-17) and sex (18-20). This paucity of specific manifestations, insidious onset and wide range of potential organ involvement often lead patients to a variety of specialists, who may focus on different aspects of the disease (3, 4). Accordingly, evaluation of patients with early signs of lupus by non-specialists may lead to diagnostic delays.

Although the time between onset of symptoms and SLE diagnosis has decreased from approximately 50 months before 1980 to approximately 24 months thereafter, the time lag is still long (21, 22). This diagnostic delay may lead to delayed treatment initiation, which may in turn increase the likelihood of organ damage and affect short- and long-term outcomes (23-28). Accordingly, early diagnosis of SLE can be beneficial, by allowing early intervention and a better prognosis (2, 21-28). Unlike rheumatoid arthritis, in SLE a universally accepted definition of early diagnosis is lacking, and a "window of opportunity" has not been clearly defined. Nevertheless, several studies suggest that patients diagnosed within 6 months from symptom onset experience lower rates of flares, hospitalisations, healthcare utilisation costs and disease-related damage (21-28).

In the present study, we sought to explore the initial symptoms of the disease and map the journey of patients from first symptoms to final diagnosis. To this end, we calculated distinct components of diagnostic delay between symptom onset and definitive SLE diagnosis. We also sought to identify factors associated with a delayed diagnosis (defined as diagnosis >6 months after first symptoms) and, further, to assess whether this delay is associated with more damage accrual at the time of disease diagnosis.

Materials and methods

Study design, patients and data collection

We screened 441 patients from the 'Attikon' lupus cohort (29), which as of June 2021 includes 869 SLE patients (all Caucasian). In our cohort, SLE diagnosis is established clinically, combined with fulfilment of at least one of the three existing classification criteria (ACR-1997, SLICC-2012, EULAR/ACR-2019) (30-32). For the purpose of the present study, patients with a diagnosis prior to 2015 were excluded to minimise recall bias, as were those with inadequate data or lost-to-follow up. A total of 275 consecutive SLE patients were finally included in the study and enrolment was completed in June 2021. The study was approved by the local Ethics Committee.

All data were collected using a combination of medical chart review and structured interview during patient visits. Patients were asked for the presenting symptoms and signs which ultimately led to diagnosis of SLE. To this end, standardised forms were used, which included classification criteria (30-32) and additional non-criteria features (3) translated in lay language; patients were also offered the option to recall symptoms not captured in the structured forms. A physician (NK) then linked the patient-reported symptoms with disease features, based on clinical judgment and data from the patient's file, and these features were documented in chronological order. For each symptom, the duration between its first appearance and the timepoint of definite SLE diagnosis was calculated. To increase reliability of the data, symptoms/signs with >10 years duration prior to diagnosis were included only if accompanied by a physician note from the time of symptom appearance.

Definitions used and journey of patients from symptom to diagnosis

Onset of symptoms was defined as the timepoint of first appearance of any symptom/sign attributed to SLE. Time

of SLE diagnosis was defined as the time of first documentation of a diagnosis of SLE. Since the 'Attikon' cohort was established in 2015, same year with the starting date of the present study, the majority of patients were diagnosed in our centre. A few patients were referred to our centre from other physicians shortly after being diagnosed or with a clinical suspicion, and diagnosis was confirmed at our site.

Using questionnaire-based forms completed by a physician (NK) with the patient present, we recorded for each patient the interval time between (a) symptom onset to first physician visit (T1), (b) first physician visit to first assessment by rheumatologist (T2), and (c) first rheumatologist assessment to definite SLE diagnosis (T3). The respective lag times in the patient journey to diagnosis were calculated for each patient. Additional questions included the specialty of the first physician, as well as the number of physicians the patient visited until reaching the diagnosis of SLE. Patients were also asked for possible alternative diagnosis(-es) they were initially given.

The total time between onset of symptoms and diagnosis of SLE was used to divide the study population in "early diagnosis" (*i.e.* diagnosis within 6 months from symptom onset) and "delayed diagnosis" (*i.e.* >6 months from symptom onset). This cut-off was chosen based on available data mainly from administrative database analyses, which suggest that patients diagnosed within 6 months from symptom onset have improved prognosis, with lower rates of flares and hospitalisations (21-28). The Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI) was used to document irreversible damage being present already at the time of diagnosis (33).

Statistical analysis

Descriptive statistics were obtained using standard statistical methods, with means (SD) or median (IQR) used for continuous variables normally and non-normally distributed, respectively. Frequencies and proportions were reported for categorical data. Chi-square or Fisher's exact test were used to compare categorical variables; one-way analysis of variance (Kruskal-Wallis non-parametric test), followed by *post-hoc* pairwise comparisons, was used to compare continuous variables between three age groups. Kaplan-Meier curves were constructed to evaluate the time from symptom onset to diagnosis and log rank test was implemented to compare groups based on age at diagnosis or other parameters. Finally, logistic regression models were used to identify factors that were independently associated with a delayed diagnosis >6 months. All variables with a *p*-value <0.100 in univariable analyses qualified for further analysis in age- and sex-adjusted multivariable models. *p*-values, odds ratios (ORs) and their 95% confidence intervals (95% CI) were computed. A stepwise backward selection was performed to eliminate non-significant factors. For all comparisons, a *p*-value of <0.05 was considered statistically significant. All analyses were performed using SPSS v. 24.0.

Table I. Initial symptoms attributed to SLE prior to definitive diagnosis (n=275).

Symptoms	Present as first symptom n (%)	Present prior to diagnosis* n (%)	Mean time† (±SD)	Median time‡ (IQR)
Arthralgias/arthritis§	141 (51.3)	205 (74.5)	58.6 (82)	24 (65)
Photosensitive rash§	103 (37.5)	151 (54.9)	68.4 (96)	26 (60)
Malar rash§	73 (26.5)	104 (37.8)	75.6 (100.4)	36 (96)
Discoid rash§	3 (0.1)	6 (2.2)	29.2 (25.3)	27 (44)
Subacute rash§	7 (2.5)	15 (5.6)	55.4 (66.8)	24 (91)
Other rash¥	15 (5.4)	41 (14.9)	131.2 (333.8)	36 (72)
Ulcers§	50 (18.2)	71 (25.8)	76.8 (97.4)	36 (108)
Alopecia§	72 (26.2)	112 (40.8)	53.7 (81.6)	24 (48)
Unexplained fever**	25 (9)	60 (21.8)	42.5 (83.8)	12 (32.5)
Haematological abnormalities§	31 (11.2)	84 (30.5)	43.9 (71)	9 (60)
Fatigue¥	81 (29.4)	131 (47.6)	43.7 (62.6)	14 (41)
Weight loss/anorexia¥	0 (0)	7 (2.5)	38 (64.9)	8 (46)
Urine abnormalities§	2 (0.7)	17 (6.2)	51.5 (117.2)	3 (23.5)
Pleurisy/pericarditis§	10 (3.6)	32 (11.6)	13.8 (19.3)	5 (23)
Sicca¥	12 (4.4)	21 (7.6)	52 (59.5)	24 (36)
Neuropsychiatric††	6 (2.2)	15 (5.5)	44.5 (74.3)	11 (58)
Raynaud's phenomenon¥	37 (13.4)	85 (30.9)	75.2 (118)	24 (60)

*In any chronologically order among initial symptoms reported in the time from symptom onset to diagnosis; †the mean time (months) from symptom onset to diagnosis; ‡the median time (months) from symptom onset to diagnosis; § according to SLICC-2012 classification criteria for Systemic Lupus Erythematosus (31); ¥ defined as in J.P. Maddison *et al*. (3); **according to EULAR/ACR-2019 classification criteria for Systemic Lupus Erythematosus (32); †† according to ACR-1997 classification criteria for systemic lupus erythematosus (30).

Results

Demographics and clinical features of patients at diagnosis

The mean (SD) age of the 275 patients (85.8% females) at SLE diagnosis was 45.6 (15.3) years. Conversely, mean (SD) age at onset of symptoms was 41.0 (16.3) years. Nineteen (6.9%) patients were diagnosed with childhood-onset (defined as ≤17 years of age) SLE and 79 patients (28.7%) with late-onset (defined as ≥50 years of age) SLE. Clinical manifestations and immunological profile at diagnosis are summarised in Supplementary Table S1.

Initial symptoms reported by patients

The most frequent initial symptoms reported by patients prior to SLE diagnosis are summarised in Table I. Most common were arthritis/arthralgia (74.5%), followed by skin rashes (61.8% cumulatively; photosensitive rash 54.9%; malar rash 37.8%) and hair loss (40.8%). Fatigue and Raynaud's phenomenon -not present in any set of classification criteria- were particularly prevalent, reported by 47.6% and 30.9% of patients, respectively. Notably, one fifth (21.8%) of patients presented with unexplained fever. Supplementary Figure S1 and Supplementary Table S2 shows the prevalence of initial symptoms according to age group at onset and sex. Compared to late-onset patients, those with childhood-onset SLE presented more commonly with unexplained fever ($p<0.01$),

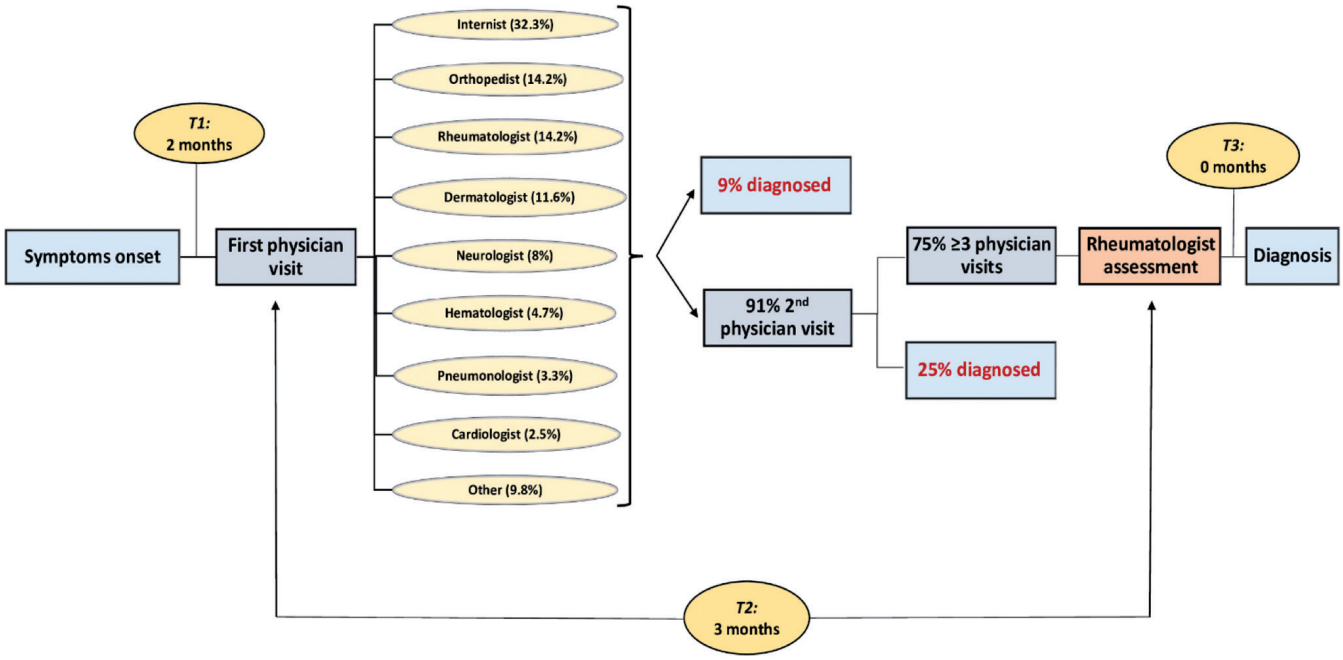

Fig. 1. The journey of patients from first symptoms to SLE diagnosis. Overall, the median (IQR) interval from symptom onset to SLE diagnosis was 24 (57) months, while the time between symptom onset and first physician visit (T1) was 2 (11.5) months. Internists were the most common first consultants (32.3%). The median (IQR) interval between the first physician visit and first assessment by a rheumatologist (T2) was 3 (12) months, while the median (IQR) time from rheumatologist assessment to definite diagnosis (T3) was 0 (3) months. SLE patients consulted an average of 3 different physicians before the definite diagnosis, which in 97.4% was established by rheumatologists.

malar rash ($p<0.01$), ulcers ($p<0.01$) and fatigue ($p<0.01$). Females tended to present more often with arthralgias ($p<0.01$), alopecia ($p<0.01$), ulcers ($p<0.05$) and fatigue ($p<0.01$), while males reported more frequently serositis as presenting manifestation ($p<0.05$).

Patient journey from onset of symptoms to diagnosis

Overall, the median (IQR) interval from symptom onset to SLE diagnosis was 24 (54) months. Median (IQR) lag time between symptom onset and first physician visit (T1) was 2 (11.5) months, with internists being the most common first physicians (32.3%) followed by orthopedics (14.2%) and rheumatologists (14.2%). The median (IQR) T2 interval (*i.e.* first physician visit to first rheumatologist evaluation) was 3 (12) months, while median (IQR) T3 lag (rheumatologist assessment to definite SLE diagnosis) was 0 (3) months. The longer median overall interval compared to the sum of individual medians (T1 + T2 + T3) is explained by the skewed distribution of values for all intervals (Suppl. Fig. S2).

To assess the association of particular initial symptoms/signs with time to diagnosis, we calculated mean times from symptom to diagnosis for the most common symptoms reported by patients as appearing first (Suppl. Fig. S3A). Because 25.1% and 38.2% of patients presented with 2 and ≥3 concomitant symptoms, Supplementary Figure S3B shows the mean time to diagnosis for patients manifesting 1, 2, or ≥3 concomitant symptoms prior to diagnosis. Of note, presence of >1 symptom was not associated with an earlier diagnosis. On average, SLE patients consulted 3 different physicians before reaching diagnosis; in the majority (97.4%), diagnosis was established by rheumatologists. Approximately half patients (n=135, 49%) reported they had initially received an alternative diagnosis, most commonly infectious disease (n=25, 18.5%) and rheumatoid or non-specific arthritis (n=23, 17%). Thirty-eight patients (13.8%) received more than one alternative diagnoses. The patient journey from symptom onset to diagnosis is illustrated in Figure 1.

Delay in diagnosis

An early diagnosis was established in 28.4% of patients, while more than half patients (55.6%) reached diagnosis >12 months from symptom onset (Fig. 2A). Time to diagnosis increased in parallel to the total number of physicians seen until final diagnosis, from median (IQR) 12 (34) months in patients consulting 1 physician to 60 (156) months in patients consulting >5 physicians (Fig. 2B). When patients were divided in 3 groups according to age at diagnosis (≤30, 31–49 and ≥50 years), we found significant differences in total delay from symptom onset to diagnosis between groups ($p<0.05$), with a greater delay recorded in older patients compared to patients aged ≤30 years at diagnosis (Fig. 2C). We found no statistically significant difference in lag time per sex and per presenting symptom (data not shown).

Factors associated with delay in SLE diagnosis

To identify possible factors contributing to a delayed diagnosis, we performed univariable and multivariable analyses (Table II). Importantly, none of the most common initial clinical features was associated with a reduced likelihood for delayed diagnosis. In contrast, ulcers (OR 3.55; 95% CI 1.45–8.70) and malar rash (OR 1.99; 95% CI 1.00–3.94) as initial symp-

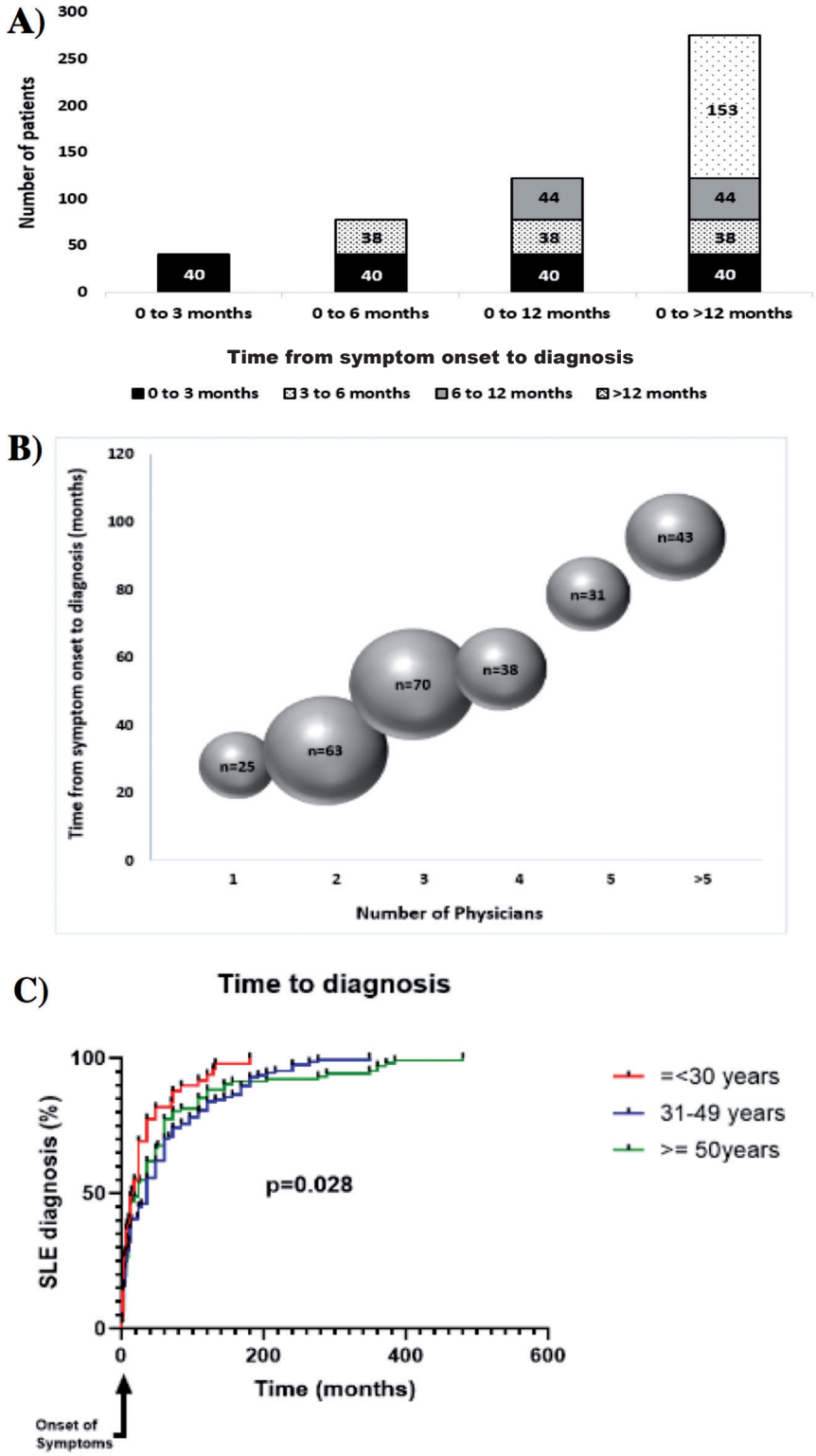

Fig. 2. A: Distribution of SLE subjects according to time from symptom onset until diagnosis (n=275). First bar: within 3 (0 to 3) months; second bar: within 6 (0 to 6) months; third bar: within 12 (0 to12) months; fourth bar: more than 12 (0 to >12) months from symptom onset. More than half of the patients (55.6%) were diagnosed after 12 months from disease onset, while only 28.4% were diagnosed within 6 months of symptom presentation (early diagnosis).
B: Mean interval (months) from symptom onset to definite SLE diagnosis per number of physicians consulted before the final diagnosis (n=275). Time (mean ±SD) to diagnosis increased in parallel to the number of physicians seen before the final diagnosis, from 28 ±38.4 months (median 12, IQR 34) in patients consulting one physician to 95.5 ±103.8 (median 60, IQR 156) in patients consulting >5 physicians.
C: Kaplan-Meier curve for time interval between symptom onset and SLE diagnosis according to age at diagnosis. Log-rank (Mantel-Cox) test was used to compare three groups of patients: i) ≤30 years of age at diagnosis (red), ii) 31-49 years (blue), iii) ≥50 years (green); p=0.028. Median (IQR) total delay was 18 (44) months for subjects aged ≤30 years at diagnosis, 36 (78) months for those between 30–50 years, and 24 (53) months for patients diagnosed after 50 years of age (Kruskal-Wallis test: p<0.001).

toms were found to be independently associated with a delayed diagnosis in multivariable analyses. Low complement levels were associated with an almost 50% increased likelihood for early diagnosis (OR 0.54), though only in univariable analysis. Finally, regarding the specialty of first physician visit, initial evaluation from an orthopaedic was independently associated with a delayed diagnosis (OR 5.18; 95% CI 1.47–18.20).

Outcomes

At the time of diagnosis, 1 of 6 patients (16.4%) had irreversible organ damage (*i.e.* SDI ≥1), mostly attributed to neuropsychiatric manifestations and thrombotic events. When we divided the study population in early *versus* late diagnosis, 9% and 19.3% of patients with early and delayed diagnosis, respectively, had disease-related damage at the time of diagnosis. Univari-

Table II. Factors associated with delay in SLE diagnosis > 6 months.

	Univariable		Multivariable	
Variable	*OR*	*95% CI*	*OR*	*95% CI*
Female sex	1.71	0.85–3.48	1.06	0.48–2.34
Age at diagnosis	1.01	0.99–1.03	**1.03**	**1.01–1.05**
Education ≤12 years	1.16	0.64–2.08		
Initial features				
Arthralgias*	**2.25**	**1.27–4.00**		
Malar rash*	**3.13**	**1.69–5.80**	**1.99**	**1.00–3.94**
Photosensitive rash*	1.42	0.83–2.40		
Ulcers*	**4.88**	**2.12–11.21**	**3.55**	**1.45–8.70**
Alopecia*	**2.54**	**1.42–4.54**		
Fatigue†	**1.96**	**1.14–3.36**		
Raynaud's†	**2.31**	**1.23–4.36**		
Sicca†	2.51	0.72–8.78		
Serology				
Presence of ANA§	0.82	0.37–1.83		
Low complement§	**0.54**	**0.31–0.94**		
Initial physician				
Internist	0.63	0.37–1.09		
Orthopaedic	**5.59**	**1.67–18.73**	**5.18**	**1.47–18.20**
Neurologist	0.50	0.20–1.23		
Cardiologist	0.29	0.06–1.30		

*According to SLICC-2012 classification criteria for Systemic Lupus Erythematosus (31); † defined as in J.P. Maddison *et al*. (3); § according to EULAR/ACR-2019 classification criteria for Systemic Lupus Erythematosus (32); ANA: antinuclear antibodies.

able regression analysis showed that a delay >6 months in diagnosis was associated with an OR 2.42 (95% CI 1.03–5.69) for an SDI >0 at diagnosis.

Discussion

Although increased physician awareness for SLE has reduced diagnostic delay, still the average time from symptom onset to diagnosis is approximately 2 years. At the same time, prompt recognition of the disease is essential for early initiation of treatment, aiming to improve short- and long-term outcomes. In this study, we explored initial symptoms, evaluated diagnostic delays, and defined associated factors, in a well-established cohort of Caucasian lupus patients.

In accordance with previous published studies (5-14), arthritis/arthralgia was the most frequent manifestation at onset, followed by cutaneous rashes and fatigue. Notably, fever was recorded as a chief complaint in approximately one fifth of our study population, underlying the value of this feature towards early diagnosis. Concerning childhood-onset SLE, initial disease phenotype in our experience was not as severe as indicated in previous studies, which suggest increased incidence of severe organ involvement as presenting manifestation, nephritis being more prominent (15-17, 34, 35). Consistent with earlier reports (18-20, 34, 35), male patients had a lower prevalence of musculoskeletal symptoms and reported more frequently serositis at disease onset, compared to females.

The median lag time between onset of symptoms and diagnosis of SLE was 2 years in our cohort, corroborating data from previous studies (8-14, 21, 22). Our data indicate increased diagnostic delay in patients ≥50 years, compared to patients aged below 30 at diagnosis. This is in accordance with earlier reports (13-17, 36-38) suggesting that patients with late-onset lupus have a longer time from symptom onset to diagnosis (up to 50 months) in comparison with younger patients, possibly due to the lower diagnostic suspicion of SLE, as well as a more insidious presentation with less specific symptoms and low incidence of severe disease manifestations.

There was a slight variation in the respective lag times during the journey of patients towards diagnosis. Delay in diagnosis was driven mainly by the time lag between first physician visit and assessment by rheumatologist, although this was sooner compared with published studies (12-14, 23, 28), possibly reflecting ethnic and socioeconomic characteristics and differences in healthcare systems. Importantly, Greece does not have a well-structured primary care network and examination by a general practitioner is not mandatory prior to specialist examination. Accordingly, rheumatologist examinations represent either referrals by other specialists, or often self-referrals. Our patients consulted an average of 3 different physicians, with internists being the most common first specialists encountered. Owing to the multisystem nature of the disease, with an often consecutive rather than simultaneous involvement of different organ systems (2-5), patients may first present to a variety of specialists, each focusing on a different disease aspect. Indeed, increased healthcare utilisation has been reported in previous studies, indicating a median of 10 consultations of 3 different physicians before definite diagnosis, and an increase in physician visits during the period close to diagnosis (12-14, 23, 28). One could speculate that training campaigns in primary care to increase awareness in early manifestations such as arthritis, could possibly optimise prompt referral to rheumatologists and further contribute to earlier diagnosis.

Of note, most of our study population were diagnosed with significant delay (>6 months from symptom onset), with more than half patients receiving a diagnosis more than 12 months after symptom onset. "Late-diagnosed" patients were more likely to be initially evaluated by orthopedics and presented with non-specific features, such as mucosal ulcers, but also malar rash. This observation highlights the fact that lupus typically starts with non-specific symptoms, shared by many diseases. Further, even signs that are considered more typical for the disease, like the malar rash, in clinical practice are rarely "typical" in appearance (*i.e*. "textbook" malar rash). In our experience, non-rheumatologists often fail to recognise subtle evidence for lupus such

as faint or transient malar rashes, mild arthritis, asymptomatic mucosal ulcers, or to elicit a history of SLE-related features (*e.g.* photosensitivity, Raynaud's phenomenon) that are not present at the time of evaluation. Recognising that certain manifestations may be attributable to underlying SLE, careful history taking for lupus features in the past, together with detailed clinical examination, are of great importance for a timely referral to a rheumatologist. Importantly, delay in diagnosis >6 months from symptom onset was associated with significant increase in disease-related damage, enhancing the current urge to diagnose SLE earlier.

Our study is limited by its retrospective data extraction in a significant proportion of the study population. Nevertheless, the 'Attikon' cohort is a well-established and comprehensive registry for lupus patients, in which data collection derives from detailed structured forms and medical records, thus reducing possible data completeness bias. By default, data referring to initial symptoms were patient-reported; thus, there remains some uncertainty whether the initial symptoms reported by patients were indeed attributable to later diagnosed SLE. To minimise this risk, we excluded patients with a diagnosis before 2015, performed personal interviews and asked patients for detailed physician notes prior to diagnosis. We acknowledge that accurate recall of the timing of symptoms depends on several parameters, thus the possibility of recall and outcome bias cannot be excluded. Nevertheless, our distribution of symptoms was consistent with results from similar studies (8-14, 23, 28). Also, the relatively high number of ANA-negative patients at first presentation (13%) may be explained by the fact that ANA titers tend to fluctuate over time, and a proportion of patients may be negative at baseline, depending also in the assay used (39). Over the course of follow-up (median follow-up until last visit was 3 years), five more patients became ANA-positive, reaching overall ANA positivity of approximately 90% in this cohort. In the established 'Attikon' cohort, cumulative ANA positivity is ~ 96–97% (29).

Conclusions

Our data suggest that arthritis and cutaneous features were the most frequent initial SLE-related manifestations, while age at onset and sex impact on disease presentation. In our cohort, a median diagnostic delay of 2 years was recorded, with the half of patients being diagnosed after 12 months. A diagnosis more than 6 months from symptom onset was associated with more damage already present at diagnosis, underlying the need for earlier SLE diagnosis and treatment initiation.

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