Similarities and differences between younger and older disease onset patients with newly diagnosed systemic lupus erythematosus

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Abstract

Objective

Several studies show that age at onset has an impact on the clinical-serological presentation, comorbidities and disease course of patients with systemic lupus erythematosus (SLE). We evaluated whether, in patients with recent onset SLE, the age at onset correlates with clinical-serological manifestations and with comorbidities.

Methods

We analysed 171 patients with a SLE diagnosis obtained within 12 months of diagnosis enrolled in the Early Lupus project. Based on the age of onset of the first disease symptom, they were stratified into 2 groups: early onset (18–45 years) and late onset (>45 years). The analysis was replicated by stratifying patients based on age at diagnosis (fulfillment of ACR classification criteria). Each comparison was made at baseline and at 36 months of follow-up.

Results

Baseline: patients with late onset displayed comorbidities (hypertension, dyslipidaemia and osteoporosis) more frequently than early onset group. 11.4% of late onset patients had a malignancy in medical history, not recorded in the early onset cohort. The two groups differed neither in organ involvement (domain BILAG) nor in disease activity (ECLAM). Patients with early onset showed a disease with signs of higher serologic activity (higher frequency of anti-dsDNA positivity and lower mean C3 and C4 levels) and had malar rash more frequently than the late onset group (36.2% vs. 18.2%, p=0.042). Similar results were obtained by stratifying patients by age of diagnosis (18-45 years and >45 years), except for the higher frequency of discoid rash in the group with age at diagnosis >45 years (18% vs. 6.6%, p=0.045).

36 months: the 2 groups of patients independently of the stratification applied did not differ in the accumulation of damage, but showed a different pattern of 8 organ involvement. Musculoskeletal involvement was more frequent both in the late onset group (18.6% vs. 7.3%, p=0.043) and in the group with age at diagnosis >45 years (20.4% vs. 5.9%, p=0.009) compared to their counterparts, while renal involvement was more frequent in the group with age at diagnosis 18–45 years (21.4% vs. 6.1%, p=0.03).A sub analysis at 36 months on patients without hypertension and osteoporosis at enrollment showed that patients with older age at onset had a higher frequency of these comorbidities, compared to their counterparts.

Conclusion

In our cohort, younger disease SLE onset seems to correlate with a more active immunological profile, while late onset with a higher incidence of comorbidities.

Key words

systemic lupus erythematosus, comorbidities, age onset, clinical features

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease of autoimmune origin, associated to variable clinical manifestations, from skin and joint involvement to life-threatening kidney and neurological disease, and follows a relapsing and remitting course. Usually, SLE begins in women during the second to fourth decade of life, with a decline after menopause (1). An early diagnosis is very important to start a prompt treatment, whereas diagnostic delay has been associated to a worse prognosis, decrease in survival rate and worse quality of life (2-4).

Several reports have demonstrated that juvenile-onset patients may have more severe clinical and serological abnormalities than adults, while late-onset patients tend to have a less severe disease course, lower degrees of disease activity and less major organ involvement (5). This may suggest that age at onset has an impact on the clinical-serological phenotype of SLE and its comorbidity. However, previous studies on the impact of onset age on the disease course and severity of SLE showed conflicting results (6).

In order to give an answer to the question whether younger onset SLE when compared to older onset SLE patients have a different clinical and serological profile and a different disease course, we analysed the data collected in a large cohort of Italian lupus patients with recent onset disease (7-9).

Patients and methods

This is a multicentre prospective study with nine Italian centres with long-standing experience in Lupus management involved. All patients enrolled in the study aged 18 years or more, with a diagnosis of SLE according to the 1997 American College of Rheumatology (ACR) Classification Criteria (10) and a disease duration (from diagnosis until study entry) lower than 12 months. The study was approved by the Review Board of the Coordinator Centre (Comitato Etico Azienda Ospedaliero Universitaria di Cagliari prot. n° NP/2012/1312) and started on January 1st, 2012. Patient's written informed consent to participate in the study and to publish the results was obtained at the time of enrolment according to the declaration of Helsinki. All participating centres obtained local Ethics Committee approval.

In this paper we included analysis on patients enrolled until the end of June 2020 and followed regularly every six months for a 36-month period. Information on demographic characteristics, medical history, clinical symptoms, physical examinations, laboratory results, disease activity, disease damage, patient's quality of life, at the entry into the study and then every 6 months were recorded.

Global SLE disease activity was measured by the ECLAM, a validated measure of disease activity in SLE. Clinical remission was defined by ECLAM score = 0. Cumulative damage was scored according to the SLICC Damage Index, a validated measure to assess damage in SLE. Patient's quality of life was estimated by means of a Visual Analogue Scale (VAS).

Study data were collected and managed using REDCap electronic data capture tools hosted at the Italian Society for Rheumatology (11).

Autoantibody assessment

Autoantibodies were measured locally in each participating centre. The following autoantibodies (Abs) were considered in this study: ANA, anti-dsDNA, anti-SSA (Ro), anti-SSB (La), anti-Sm, anti-RNP, anticardiolipin (aCL), anti-beta2 glycoprotein I (anti-beta2GPI), Lupus Anticoagulant (LA). ANA were measured by immunofluorescence using Hep2 cells as substrate. Anti-dsDNA Abs were measured by immunofluorescence using Crithidia luciliae or Farr technique. Anti-SSA, anti-SSB, anti-Sm, anti-RNP were measured either by immunoblot technique or ELISA. Anticardiolipin antibodies and anti-beta2GPI were measured by ELISA. LA was measured by coagulometric assay. Concerning aCL and anti-beta2GPI, patients were considered to be positive when either IgG or IgM (or both) were present at medium-high titre.

Statistical analysis

For the purpose of this study, patients were stratified into two groups, ac-

Table I. Demographic characteristics of SLE patients stratified into two groups, according to age at onset (first symptom attributable to SLE) and to age at diagnosis.

	Onset				*Diagnosis*			
Baseline characteristics	Total (n=171)	18-45 (n=127)	≥45 (n=44)	*p*-value*	Total (n=171)	18-45 (n=121)	≥45 (n=50)	*p*-value*
Female, n (%)	144 (84.2%)	110 (86.6%)	34 (77.3%)	0.221	144 (84.2%)	104 (86%)	40 (80%)	0.459
Caucasian, n (%)	152 (88.9%)	112 (88.2%)	40 (90.9%)	0.887	152 (88.9%)	106 (87.6%)	46 (92%)	0.911
Smoking, n (%)	45 (66.2%)	32 (66.7%)	13 (65%)	1	45 (66.2%)	30 (66.7%)	15 (65.2%)	1
Family history of SLE, n (%)	15 (8.8%)	12 (9.5%)	3 (6.8%)	0.762	15 (8.8%)	10 (8.3%)	5 (10%)	0.769
Age				<0.001				<0.001
median (IQR)	34.8 (25.7-44.9)	29.7 (24-37.2)	54.3 (50.1-59.9)		36.4 (27.1-48)	31.3 (25.7-38.6)	55.6 (51.2-63.3)	
mean (SD)	37.2 (13.8)	30.5 (7.6)	56.6 (8.4)		38.8 (14.1)	32.1 (8.4)	57.9 (8.6)	

cording to age at onset (first symptom attributable to SLE): 1) those aged between 18 and 45 years, and 2) those aged more than 45 years.

The results of the analysis of continuous variables are indicated as mean ± standard deviation or median and interquartile range, as appropriate. Conventional chi-square and Fisher's exact test were used to analyse qualitative differences between independent samples. Student's t-test and Wilcoxon test were used to analyse mean differences. A *p*-value <0.05 was taken to indicate statistical significance. All the analyses were performed using R statistical software (The R project for statistical computing, https://www.r-project.org).

Results

At the end of June 2020, 171 patients enrolled had at least a 36-month follow-up and underwent regular follow-up visits. The cohort of these 171 patients was composed of 144 (84.2%) females, the majority (88.9%) of whom were Caucasians.

Mean and median age at diagnosis (fulfilment of ACR criteria), at disease onset (first symptom attributable to SLE), at baseline (enrolment), and disease duration (from diagnosis to enrolment) is reported in Tab I. In particular, disease duration was the same in the 2 groups.

Clinical and serological characteristics and comorbidity at study entry in patients stratified by age onset

Patients with disease onset >45 years (44 patients) had greater mean body mass index ($p<0.001$), and a greater frequency of hypertension ($p<0.001$), osteoporosis ($p=0.028$), history of cancer ($p=0.001$), familiarity for cardiovascular events ($p=0.006$), when compared to those with disease onset between 18 and 45 (127 patients).

Conversely, young disease onset patients displayed a more serologically active disease, with lower mean C3 and C4 level ($p=0.003$ and 0.013, respectively), and higher prevalence of anti-dsDNA ($p=0.037$), and more frequent disease presentation with malar rash ($p=0.042$), in comparison to patients with old disease onset. ANA were present in all patients without statistically differences among group.

No difference was found concerning history of previous infection, including tuberculosis, hepatitis B and C, human immunodeficiency virus, cytomegalovirus.

No difference was found concerning mean disease activity, quality of life, and damage between the 2 groups at study entry (Table II a-b).

Clinical and serologic characteristics and comorbidity at the 36-month follow-up in patients divided by age at onset

At the 36-months follow-up, compared to the baseline, more patients with old disease onset had developed diabetes and musculoskeletal involvement ($p=0.014$, and $p=0.043$, respectively) (Table III).

With respect to baseline, after 36 months mean disease activity decreased, from 3.2 (2.4) to 0.8 (1.1), and quality of life improved, from 53.3 (23.1) to 56.4 (28.2), with no difference between the 2 groups ($p=0.2113$ and $p=0.5925$, respectively). However, mean SLICC damage index increased, from 0.3 (0.7) to 0.6 (1.2). This increase resulted statistically significant (p-value <0.001).

We then selected, among patients with variables significantly different between the 2 study groups (younger disease onset and older disease onset) at study entry, those without those characteristics at study entry, but developed after 3 years. The analysis at 36 months showed that more patients with older disease onset developed hypertension and osteoporosis when compared to patients with younger disease onset [8 (7%) patients with younger disease onset developed hypertension *versus* 5 (21%) with older disease onset ($p=0.049$), and 1 (0.8%) with younger disease onset developed osteoporosis *versus* 3 (7.7%) with older disease onset ($p=0.047$) (Table III)].

When considering patients stratified by age at diagnosis more patients with older age at diagnosis developed diabetes and musculoskeletal involvement compared to the younger group ($p=0.025$, and $p=0.009$, respectively) at 36-months follow up. In addition, we found that patients with young age at diagnosis had more frequently renal involvement at 36-months follow-up, when comparing with patients with older age at diagnosis ($p=0.03$).

Discussion

In this study we evaluated similarities and differences between younger onset and older onset lupus patients in a cohort of recent onset SLE.

There is no agreed definition of the age cut-off for late-onset and early-onset SLE. Considering that most patients have their disease onset in the fertile period between 20 and 45 years of age, and that after 45 years women usually start to go into menopause, we defined as "young onset" those patients with disease onset between 18 and 45 years,

Table II A. Serological characteristics, clinimetry and comorbidity at study entry in patients stratified by age at onset.

	Total (n=171)	18-45 (n=127)	>45 (n=44)	*p*-value*
Comorbidity				
BMI, mean (SD)	22.8 (4)	22 (3.7)	25 (4.1)	<0.001
Diabetes, n (%)	7 (4.1%)	3 (2.4%)	4 (9.1%)	0.073
Hypertension, n (%)	28 (16.4%)	8 (6.3%)	20 (45.5%)	<0.001
Dyslipidaemia, n (%)	19 (11.2%)	11 (8.7%)	8 (18.6%)	0.093
Familial CV events, n (%)	24 (14.2%)	12 (9.5%)	12 (27.9%)	0.006
Cancer, n (%)	5 (2.9%)	0 (0%)	5 (11.4%)	0.001
Osteoporosis, n (%)	8 (4.7%)	3 (2.4%)	5 (11.4%)	0.028
Total cholesterol, mean (SD)	175.8 (45.2)	175.5 (44.4)	176.5 (48.2)	0.926
HDL, mean (SD)	52.4 (16.7)	54.3 (17.3)	47.1 (14.1)	0.135
LDL, mean (SD)	99.2 (42)	96.3 (42.5)	110.3 (41.4)	0.447
Clinimetry				
ECLAM, mean (SD)	3.2 (2.4)	3.1 (2.4)	3.2 (2.3)	0.712
QoL, mean (SD)	53.3 (23.1)	52 (24)	56.9 (20.4)	0.239
SLICC, mean (SD)	0.3 (0.7)	0.3 (0.8)	0.4 (0.7)	0.459
Serology				
C3, mean (SD)	71.7 (30.2)	68.1 (31.2)	82.3 (24.5)	0.003
C4, mean (SD)	11.8 (8.8)	10.7 (7.6)	14.9 (11.2)	0.013
anti-dsDNA, n (%)	125 (76.2%)	97 (80.8%)	28 (63.6%)	0.037
anti-Ro, n (%)	74 (46.8%)	57 (50%)	17 (38.6%)	0.269
anti-La, n (%)	31 (19.9%)	24 (21.2%)	7 (16.3%)	0.639
anti-RNP, n (%)	38 (24.7%)	27 (23.9%)	11 (26.8%)	0.871
anti-Sm, n (%)	33 (21.3%)	25 (22.1%)	8 (19%)	0.845
aCL, n (%)	36 (26.1%)	24 (23.8%)	12 (32.4%)	0.419
anti-beta2GPI, n (%)	26 (19.5%)	18 (18.2%)	8 (23.5%)	0.669
LA, n (%)	26 (19.1%)	18 (18%)	8 (22.2%)	0.76

Table II B. Clinical and serological characteristics at study entry in patients stratified by age at onset.

	Total (n=171)	18–45 (n=127)	>45 (n=44)	*p*-value*
Clinical manifestations included in the ACR classification criteria				
Malar rash, n (%)	54 (31.6%)	46 (36.2%)	8 (18.2%)	0.042
Discoid rash, n (%)	17 (9.9%)	10 (7.9%)	7 (15.9%)	0.146
Photosensitivity, n (%)	54 (31.6%)	39 (30.7%)	15 (34.1%)	0.82
Oral ulcers, n (%)	23 (13.5%)	20 (15.7%)	3 (6.8%)	0.215
Arthritis, n (%)	104 (60.8%)	78 (61.4%)	26 (59.1%)	0.926
Serositis, n (%)	46 (27.1%)	31 (24.6%)	15 (34.1%)	0.307
Renal disorder, n (%)	53 (31%)	44 (34.6%)	9 (20.5%)	0.118
Neurological, n (%)	17 (9.9%)	13 (10.2%)	4 (9.1%)	1
Haematological, n (%)	99 (57.9%)	77 (60.6%)	22 (50%)	0.292
Immunological, n (%)	161 (94.2%)	120 (94.5%)	41 (93.2%)	0.719
ANA, n (%)	171 (100%)	127 (100%)	44 (100%)	0.259
Cumulative Prednisone dose, mean (SD)				
Cum pdn dose	1671 (3079.3)	1636.9 (3009.4)	1767.7 (3304)	0.574

Frequency of comorbidity, main autoantibodies and SLE clinical manifestations in the whole sample as well as in the 2 cohorts.
BMI: body mass index; QoL: quality of life; anti-dsDNA: anti-double stranded DNA antibodies; aCL: anti-cardiolipin antibodies; anti-beta2GPI: anti-beta2 glycoprotein I antibodies; LA: lupus anticoagulant; Cum pdn dose: cumulative prednisone dosage until study entry.
Definition of clinical manifestations is according to ACR classification criteria.

and "old onset" those with disease onset after 45 years.

Our data suggest that old onset lupus patients have comorbidities such as hypertension, cancer, osteoporosis, and a higher BMI more frequently than younger onset patients. Patients with young onset, compared to the older onset group, showed a more serologically active disease (higher frequency of anti-dsDNA positivity and lower mean C3 and C4 levels), and more frequently had malar rash. Similar results were obtained by dividing patients by age at diagnosis (18–45 years and >45 years), but the frequency of discoid rash was greater in the group with old age at diagnosis compared to their counterpart.

The two groups showed no difference in disease activity, damage accrual, quality of life both at study entry and after 36 months of follow-up. Nevertheless, previous results from the Early Lupus project demonstrated that older age is independently associated with an increased risk of organ damage development (12).

However, after 36 months after onset, patients more often developed musculoskeletal involvement, diabetes, hypertension, and osteoporosis, while young onset patients more frequently developed renal disease.

Several studies showed significant differences in clinical manifestations, serological features, and severity of SLE in different age group at onset (13-16).

In particular, most data indicate that a more severe phenotype is reported in the juvenile group, as also verified in our cohort.

Literature data suggest that pulmonary involvement and serositis are more frequently observed in patients with late-onset (>50 years) SLE, whereas malar rash, photosensitivity, arthritis, and nephropathy occur less commonly in late onset SLE (17).

Boddaert *et al*., compared the patients with late-onset to those with early-onset, and described that the most frequent manifestations were arthritis, fever, and pleuritis in the late-onset group; in the early-onset group the main clinical features were malar rash and arthritis (18).

Cervera *et al*., noted pulmonary involvement in only 9% of 90 patients with late-onset SLE (>50 years) and reported a decrease in prevalence of renal involvement from 41% in early-onset to 22% in late-onset SLE patients (19).

Feng X. *et al*., reviewed the data of more than 2000 patients with SLE hospitalised from 1999 to 2009, stratified in three groups: juvenile onset (<18 years), early onset (18–45 years) and late onset (>45 years) and showed that the patients with juvenile onset (<18 years) have more mucocutaneuos but fewer musculoskeletal manifestations respect to the other groups. Major organ involvement (renal, cardiopulmonary, neuropsychiatric, gastrointesti-

Table III. Clinical and serological characteristics and comorbidity at 36-months follow-up in patients stratified by age at onset.

	Total (n=171)	18–45 (n=127)	>45 (n=44)	*p*-value*
Diabetes n (%)	7 (4.2%)	2 (1.6%)	5 (11.6%)	0.014
Dyslipidaemia, n (%)	18 (10.8%)	10 (8.1%)	8 (18.2%)	0.088
Tubercolosis, n (%)	2 (1.4%)	2 (1.9%)	0 (0%)	1
Hepatitis B, n (%)	4 (2.8%)	3 (2.8%)	1 (2.6%)	1
Hepatitis C, n (%)	0 (0%)	0 (0%)	0 (0%)	1
HIV, n (%)	1 (0.8%)	1 (1.1%)	0 (0%)	1
CMV, n (%)	3 (2.3%)	2 (2.1%)	1 (3%)	1
Total cholesterol, mean (SD)	187.1 (36.7)	183.7 (29.8)	193.9 (48.8)	0.498
HDL, mean (SD)	60.1 (16.7)	62.2 (18)	56.4 (14.4)	0.416
LDL, mean (SD)	111.4 (33.7)	107.5 (28.7)	118.7 (43.4)	0.586
ECLAM, mean (SD)	0.8 (1.1)	0.8 (1.2)	0.5 (0.7)	0.06
QoL, mean (SD)	56.4 (28.2)	54.8 (28.7)	61.6 (26.5)	0.244
SLICC, mean (SD)	0.6 (1.2)	0.5 (0.9)	0.9 (1.7)	0.091
anti-Ro, n (%)	20 (37%)	17 (39.5%)	3 (27.3%)	0.51
anti-La, n (%)	5 (9.4%)	3 (7.1%)	2 (18.2%)	0.275
anti-RNP, n (%)	15 (28.3%)	11 (26.2%)	4 (36.4%)	0.708
antiSm, n (%)	6 (11.3%)	4 (9.5%)	2 (18.2%)	0.592
anti-Cardiolipin, n (%)	6 (11.3%)	4 (9.5%)	2 (18.2%)	0.592
anti-beta2GPI, n (%)	6 (11.5%)	4 (9.8%)	2 (18.2%)	0.595
Lupus anticoagulant, n (%)	5 (10%)	4 (10%)	1 (10%)	1
Rheumatoid factor, n (%)	5 (10.4%)	3 (7.9%)	2 (20%)	0.276
Constitutional, n (%)	5 (3%)	5 (4%)	0 (0%)	0.329
Mucocutaneous, n (%)	21 (12.6%)	17 (13.7%)	4 (9.3%)	0.628
Neuropsychiatric, n (%)	2 (1.2%)	1 (0.8%)	1 (2.3%)	0.45
Musculoskeletal, n (%)	17 (10.2%)	9 (7.3%)	8 (18.6%)	0.043
Cardiorespiratory, n (%)	1 (0.6%)	0 (0%)	1 (2.3%)	0.257
Gastrointestinal, n (%)	0 (0%)	0 (0%)	0 (0%)	1
Ophtalmic, n (%)	0 (0%)	0 (0%)	0 (0%)	1
Renal, n (%)	11 (6.6%)	6 (4.8%)	5 (11.6%)	0.153
Haematological, n (%)	18 (10.8%)	15 (12.1%)	3 (7%)	0.568
Discoid rash, n (%)	16 (9.7%)	11 (9.1%)	5 (11.4%)	0.767
Photosensitivity rash, n (%)	27 (16.2%)	20 (16.3%)	7 (15.9%)	1
Oral ulcers, n (%)	14 (8.5%)	12 (10%)	2 (4.5%)	0.356
Arthritis, n (%)	53 (31.5%)	38 (30.6%)	15 (34.1%)	0.815
Serositis, n (%)	26 (15.8%)	16 (13.2%)	10 (22.7%)	0.215
Renal disorder, n (%)	28 (16.9%)	25 (20.3%)	3 (7%)	0.076
Neurological, n (%)	9 (5.4%)	7 (5.7%)	2 (4.5%)	1
Haematological, n (%)	54 (32.5%)	41 (33.6%)	13 (29.5%)	0.76
Immunological, n (%)	114 (69.1%)	87 (71.3%)	27 (62.8%)	0.397
ANA, n (%)	171 (100%)	127 (100%)	44 (100%)	1
Cum pdn dose, mean (SD)	6195.1 (5568.7)	6218.6 (5998)	6129.9 (4218.3)	0.66

Frequency of comorbidity, main autoantibodies and SLE clinical manifestations at 36 month follow-up in the whole sample as well as in the 2 cohorts. Variables significantly different at baseline were not included in the table.

BMI: body mass index; anti-dsDNA: anti-double stranded DNA antibodies; aCL: anti-cardiolipin antibodies; anti-beta2GPI: anti-beta2 glycoprotein I antibodies; LA: lupus anticoagulant; Cum pdn dose: cumulative prednisone dosage at follow-up; constitutional: constitutional symptoms; mucocutaneous: mucocutaneous symptoms; neuropsychiatric: neuropsychiatric symptoms; musculoskeletal: musculoskeletal symptoms; cardiorespiratory: cardiorespiratory symptoms; oftalmic: oftalmic symptoms; renal: renal symptoms; haematological: haematological symptoms [definition of organ/system involvement is according to the BILAG glossary (ISENBERG DA, RAHMAN A, ALLEN E *et al*. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology 2005; 44: 902-6). Bilag index was not calculated in this study].

Definition of clinical manifestations is according to ACR classification criteria.

nal, haematological and ophtalmological) was as frequent in late onset as in the other two groups. The comorbidities were much higher in the late-onset group. Regarding to serological abnormalities, anti-Sm antibodies were less frequently positive in patients with late onset disease. No differences were found in the frequency of total ANA or anti-dsDNA among these three groups of patients (20).

Some authors have suggested that neoplasia frequently occurs during SLE, but these data remain contradictory (21).

Ambrose *et al*., described the effect of age at onset of SLE on the phenotypic manifestations by assessing two large cohorts: the United Kingdom (UK) JSLE Cohort Study and the University College London Hospital (UCLH) cohort. JSLE was defined as SLE with onset before the patient's 18th birthday. Adult-onset SLE was defined as those patients 18 years or older at the time of diagnosis (from the UCLH cohort). This group was further subdivided. Adults aged 18–49 years at time of diagnosis were described as adult onset. Patients aged 50 years or older at time of SLE onset were defined as the mature-onset group. The analysis of the ACR clinical characteristics (non-renal, non-NPSLE manifestations) between cohorts showed no significant differences in percentages of patients with a lupus rash between any groups. Rashes were common both in juvenile and adult lupus. There was also no difference in prevalence of photosensitivity. Adults were significantly more likely to report arthritis and serositis. There was a non-statistically significant reduction in serositis in the older group. Mature-onset SLE patients were far less likely to have NPSLE than any other group (22).

Our cohort is composed of patients aged greater than 18 years with disease duration (from diagnosis until study entry) less than 12 months. Even if there are some differences in patients' ethnicity and disease duration, our data seem to confirm the results of similar inception cohorts reported in the literature.

Indeed, in our analysis the two groups differed neither in organ involvement (domain BILAG) nor in disease activity (ECLAM). Patients with early onset showed a disease with signs of higher serologic activity (higher frequency of anti-dsDNA positivity and lower mean C3 and C4 levels), and had malar rash more frequently than the late onset group (36.2% *vs*. 18.2%, p=0.042). We obtained comparable results by stratifying the patients by age of diagnosis (18–45 years and >45 years), with the exception of the higher frequency of discoid rash in the group with age at diagnosis >45 years (18% *vs*. 6.6%, p=0.045).

In the analysis at 36 months, patients, again stratified by age at onset and age at diagnosis, did not differ in the accumulation of damage (SLICC damage index), but showed a different organ involvement, with more frequent musculoskeletal involvement both in the late onset group (18.6% *vs*. 7.3%, p=0.043) and in the group with age at diagnosis >45 years (20.4% *vs*. 5.9%, p=0.009), while the group with age at diagnosis 18–45 years developed renal involvement more frequently (21.4% *vs*. 6.1%, p=0.03).

Our study has some limitations: first, the cut-off utilised for discriminating between younger and older onset SLE is not frequently used by other authors. We preferred to use this threshold, however reasonable, because it allowed us to have a consistent number of older onset patients, useful for maintaining the most powerful statistical tests for the comparison between the two groups. Second, the follow-up period of 36 months may be too short for a long-term consistent analysis. In addition, our cohort is mainly composed of Caucasian patients, and the results may not be applicable to different ethnicities.

In conclusion, our data show that in SLE a younger onset may be associated with a more active immunological profile, while older onset with a higher incidence of comorbidities.

References

1. DUARTE C, COUTO M, INES L, LIANG MH: Epidemiology of systemic lupus erythematosus. *In*: LAHITA RG, TSOKOS G, BUYON J, KOIKE T (Eds). Systemic lupus erythematosus. 5th ed. London: Elsevier; 2011. pp. 673-96.
2. ESDAILE JM, JOSEPH L, MACKENZIE T, KASHGARIAN M, HAYSLETT JP: The benefit of early treatment with immunosuppressive agents in lupus nephritis. *J Rheumatol* 1994; 21: 2046-51.
3. TRENTIN F, ZUCCHI D, SIGNORINI V, ELEFANTE E, BORTOLUZZI A, TANI C: One year in review 2021: systemic lupus erythematosus. *Clin Exp Rheumatol* 2021; 39: 231-41. https://doi.org/10.55563/clinexprheumatol/7gzsxp
4. FAURSCHOU M, STARKLINT H, HALBERG P, JACOBSEN S: Prognostic factors in lupus nephritis: diagnostic and therapeutic delay increases the risk of terminal renal failure. *J Rheumatol* 2006; 33: 1563-9.
5. CHOI JH, PARK DJ, KANG JH *et al*.: Comparison of clinical and serological differences among juvenile-, adult-, and late-onset systemic lupus erythematosus in Korean patients. *Lupus* 2015; 24: 1342-9. https://doi.org/10.1177/0961203315591024
6. SWAAK AJ, VAN DEN BRINK HG, SMEENK RJ *et al*.: Systemic lupus erythematosus: clinical features in patients with a disease duration of over 10 years, first evaluation. *Rheumatology* (Oxford) 1999; 38: 953-8. https://doi.org/10.1093/rheumatology/38.10.953
7. SEBASTIANI GD, PREVETE I, PIGA M *et al*.: Early Lupus Project – A multicentre Italian study on systemic lupus erythematosus of recent onset. *Lupus* 2015; 24: 1276-82. https://doi.org/10.1177/0961203315585817
8. SEBASTIANI GD, PREVETE I, IULIANO A *et al*.: Early Lupus Project: one-year follow-up of an Italian cohort of patients with systemic lupus erythematosus of recent onset. *Lupus* 2018; 27: 1479-88. https://doi.org/10.1177/0961203318777112
9. PREVETE I, ESPINOSA G, BELLISAI F *et al*.; GRUPPO DI STUDIO SIR SUL LUPUS ERITEMATOSO SISTEMICO DI RECENTE INSORGENZA-EARLY LUPUS AND REGISTRO ESPAÑOL DE PACIENTES CON LUPUS ERITEMATOSO SISTÉMICO (RELES), AUTOIMMUNE DISEASES STUDY GROUP (GEAS): Comparative study between two European inception cohorts of patients with early systemic lupus erythematosus. *Clin Exp Rheumatol* 2020; 38: 925-32.
10. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725. https://doi.org/10.1002/art.1780400928
11. HARRIS PA, TAYLOR R, THIELKE R, PAYNE J, GONZALEZ N, CONDE JG: Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377-81. https://doi.org/10.1016/j.jbi.2008.08.010
12. PIGA M, FLORIS A, SEBASTIANI GD *et al*.: Risk factors of damage in early diagnosed Systemic lupus erythematosus: results of the Italian multicentre Early Lupus Project inception cohort. *Rheumatology* (Oxford) 2020; 59: 2272-81. https://doi.org/10.1093/rheumatology/kez584
13. WARD MM, POLISSON RP: A meta-analysis of the clinical manifestations of older-onset systemic lupus erythematosus. *Arthritis Rheum* 1989; 32: 1226-32. https://doi.org/10.1002/anr.1780321007
14. WILSON HA, HAMILTON ME, SPYKER DA *et al*.: Age influences the clinical and serologic expression of systemic lupus erythematosus. *Arthritis Rheum* 1981; 24: 1230-35. https://doi.org/10.1002/art.1780241002
15. WEBB R, KELLY JA, SOMERS EC *et al*.: Early disease onset is predicted by a higher genetic risk for lupus and is associated with a more severe phenotype in lupus patients. *Ann Rheum Dis* 2011; 70: 151-6. https://doi.org/10.1136/ard.2010.141697
16. LIVINGSTON B, BONNER A, POPE J: Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: A meta-analysis. *Lupus* 2011; 20: 1345-55. https://doi.org/10.1177/0961203311416694
17. MEDLIN JL, HANSEN KE, MCCOY SS, BARTELS CM: Pulmonary manifestations in late versus early systemic lupus erythematosus: a systematic review and meta-analysis. *Semin Arthritis Rheum* 2018; 48: 198-204. https://doi.org/10.1016/j.semarthrit.2018.01.010
18. BODDAERT J, HUONG DLT, AMOURA Z, WECHSLER B, GODEAU P, AND PIETTE JC: Late-onset systemic lupus erythematosus. A personal series of 47 patients and pooled analysis of 714 cases in the literature. *Medicine* (Baltimore) 2004; 83: 348-59. https://doi.org/10.1097/01.md.0000147737.57861.7c
19. CERVERA K, KHAMASHTA MA, FONT J *et al*.; and the European Working Party on Systemic Lupus Erythematosus: Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine* (Baltimore) 1993; 72: 113-24.
20. FENG X, ZOU Y, PAN W *et al*.: Associations of clinical features and prognosis with age at disease onset in patients with systemic lupus erythematosus. *Lupus* 2014; 23: 327-34. https://doi.org/10.1177/0961203313513508
21. ABU-SHAKRA M, EHRENFELD M, SHOENFELD Y: Systemic lupus erythematosus and cancer: associated or not? *Lupus* 2002; 11: 137-44. https://doi.org/10.1191/0961203302lu182rr
22. AMBROSE N, MORGAN TA, GALLOWAY J, IONNOAU Y, BERESFORD MW, ISENBERG DA; THE UK JSLE STUDY GROUP: Differences in disease phenotype and severity in SLE across age groups. *Lupus* 2016; 25: 1542-50. https://doi.org/10.1177/0961203316644333