Age at Onset and Its Association With Damage Accrual in Systemic Lupus Erythematosus (SLE): Insights From 5 Registries in the Lupus Federated Data Network (LupusNet)

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Key Takeaways

- **SLE diagnosis before and after 50 years of age was associated with distinct clinical and damage profiles**
  - **Patients with SLE diagnosed at ≥50 years of age were less likely to have severe disease activity but more likely to have damage present at baseline and follow-up**
- **Among patients with no damage at registration, new damage accrual was associated with greater severity of disease activity in patients diagnosed at <50 years of age but not in patients diagnosed at ≥50 years of age**
  - **The rate of new damage accrual did not differ by age in patients without damage at baseline**
- **Age at SLE diagnosis was associated with certain types of damage**
  - **Features such as osteoporosis, cataracts, myocardial infarction, and diabetes were overrepresented in patients diagnosed at ≥50 years of age**
- **The differences observed in damage accrual patterns may reflect a difference in age-related risks**
- **These findings underscore the need for age-specific management strategies to prevent damage accrual in SLE**

Background

- Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is associated with a significant disease burden and increased risk for mortality[1–3]
- Age of SLE onset is associated with differences in disease severity, organ manifestations, and mortality[4,5]
- Late-onset SLE, diagnosed at ≥50 years of age, typically presents as a milder disease (ie, lower disease activity scores), with fewer renal and neurological manifestations and more musculoskeletal and serosal involvement[4]; however, it is also associated with greater damage accrual and lower survival rates[5]

Objective

To describe organ damage in patients with late-onset SLE versus patients with earlier-onset SLE and to analyse patterns and determinants of organ damage accrual using data from the Lupus Federated Data Network (LupusNet)

Methods

Data Source

- LupusNet is the largest existing federated SLE data network, with data from 5 large, longitudinal observational registries across North America, Latin America, Europe, and Asia Pacific mapped in LupusNet: The National Data Bank for Rheumatic Diseases (FORWARD), Grupo Latino Americano De Estudio del Lupus (GLADEL 2.0) and Rheumatology Department of the Hospital Guillermo Almenara Irigoyen (Almenara), Lupus Register of the Spanish Society of Rheumatology (RELESSER), and Asia Pacific Lupus Collaboration (APLC), respectively[6]
  - Registries included both incident and prevalent patients
  - Registry datasets were harmonised using the Observational Medical Outcomes Partnership Common Data Model v5.4, a standard representation of healthcare experiences and common vocabularies for coding clinical concepts, which enables consistent analyses across data sources and improves the characterisation of clinical presentation and global SLE outcomes

Study Assessments

- Baseline characteristics were collected at registration (ie, a 30-day window before and after enrolment into the registry)
- Disease activity was collected at registration and subsequent follow-up visits using the following:
  - Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K): Almenara, APLC, GLADEL 2.0, and RELESSER
  - Systemic Lupus Activity Questionnaire (SLAQ): FORWARD
- Accumulated organ damage was measured at registration and subsequent follow-up visits using the following:
  - Systemic Lupus International Collaborating Clinics Damage Index (SDI): Almenara, APLC, GLADEL 2.0, and RELESSER
  - Brief Index of Lupus Damage (BILD): FORWARD

Data Analyses

- Patients were grouped by age at SLE diagnosis (diagnosis at ≥50 or <50 years of age)
- Patients were classified by their highest SLEDAI-2K scores between baseline and Year 3 (mild: ≤4; moderate: >4 to <10; severe: ≥10) and by SLAQ severity categories (mild: <4; moderate: ≥4 to <7; severe: ≥7)
- The proportion of patients with damage (SDI score >0) in each group was calculated at baseline (registry entrance date) and Year 3, and new onset damage from baseline to Year 3 (SDI score change from 0 to >0) was assessed
- Unadjusted relative risk (RR) of damage was estimated to evaluate the association of onset age and severity of disease activity with damage

Results

Patient characteristics: onset age at registration, disease duration

- A total of 4122 patients in LupusNet with necessary follow-up data were included in the analysis (n=3734 from Almenara, APLC, GLADEL 2.0, and RELESSER; n=388 from FORWARD)
- Most patients (89% [3668/4122]) were diagnosed at <50 years of age
  - Patients diagnosed at ≥50 years of age entered registries at a mean age of 64.0 years, whereas those diagnosed at <50 years of age entered at a mean age of 40.6 years
  - Mean time from diagnosis to registration was shorter for those diagnosed at ≥50 years of age (7.2 years) versus those diagnosed at <50 years of age (11.6 years)

Association of age at diagnosis and disease duration with severity of disease activity through 3 years of follow-up

- Patients diagnosed at ≥50 years of age were less likely to have severe disease activity (SLEDAI-2K score ≥10 or SLAQ score ≥7) between registration and Year 3 of follow-up (16% [74/454]) versus those diagnosed at <50 years of age (28% [1020/3668]; **Table 1**)
  - In both groups, individuals with more severe SLEDAI-2K (but not SLAQ) activity were younger at the time of registration (**Figure 1**)
- More severe SLEDAI-2K (but not SLAQ) activity was linked to shorter disease duration prior to registration, regardless of age at diagnosis (**Figure 2**)

Table 1: Disease activity severity by age group

	Individuals with SLEDAI-2K activity		Individuals with SLAQ activity		Combined	
Severity, n (%)	≥50 years of age (n=388)	<50 years of age (n=3346)	≥50 years of age (n=66)	<50 years of age (n=322)	≥50 years of age (n=454)	<50 years of age (n=3668)
Mild	216 (56)	1450 (43)	38 (58)	155 (48)	254 (56)	1605 (44)
Moderate	113 (29)	955 (29)	13 (20)	88 (27)	126 (28)	1043 (28)
Severe	59 (15)	941 (28)	15 (23)	79 (25)	74 (16)	1020 (28)

Mild: SLEDAI-2K score ≤4 or SLAQ score <4; moderate: SLEDAI-2K score >4 to <10 or SLAQ score ≥4 to <7; severe: SLEDAI-2K score ≥10 or SLAQ score ≥7.
***SLAQ**=Systemic Lupus Activity Questionnaire, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.*

Figure 1: Mean age at registration by age at diagnosis and (A) maximum SLEDAI-2K score or (B) maximum SLAQ score over follow-up

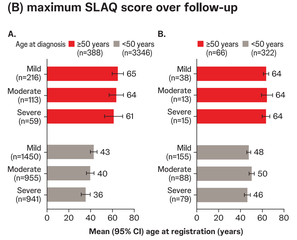
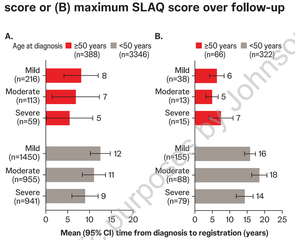


Figure 2: Mean time from diagnosis to registration by age at diagnosis and (A) maximum SLEDAI-2K score or (B) maximum SLAQ score over follow-up

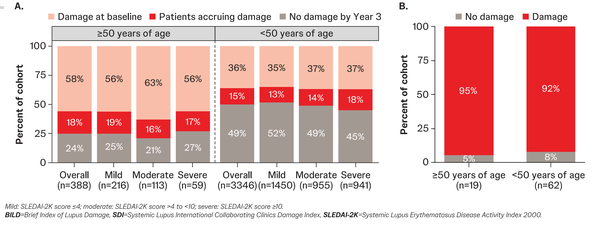


Mild: SLEDAI-2K score ≤4 or SLAQ score <4; moderate: SLEDAI-2K score >4 to <10 or SLAQ score ≥4 to <7; severe: SLEDAI-2K score ≥10 or SLAQ score ≥7.
***CI**=confidence interval, **SLAQ**=Systemic Lupus Activity Questionnaire, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.*

Association of age at diagnosis and severity of disease activity with damage accrual through 3 years of follow-up

- Patients diagnosed at ≥50 years of age were more likely to have any SDI damage (score >0) at registration (58% [226/388]) versus those diagnosed at <50 years of age (36% [1215/3346]; **Figure 3A**)
  - By Year 3 of follow-up, patients diagnosed at ≥50 years of age were more likely to have SDI damage than those diagnosed at <50 years of age (76% [295/388] vs 51% [1703/3346], respectively; unadjusted relative risk [RR]: 1.49; 95% confidence interval [CI]: 1.39–1.60)
  - However, patients diagnosed at ≥50 years of age without damage at registration were not significantly more likely to newly accrue damage (score increase from 0 to >0) from baseline to Year 3 compared with those diagnosed at <50 years of age (18% [69/388] vs 15% [488/3346], respectively; unadjusted RR: 1.22; 95% CI: 0.97–1.53)
- The proportion of patients diagnosed at ≥50 and <50 years of age with BILD damage (score >0) in the FORWARD registry at Year 3 was 95% and 92%, respectively (**Figure 3B**)

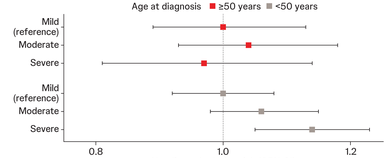
Figure 3: Percent of patients who accrued (A) SDI damage from baseline to Year 3 by age at diagnosis and maximum SLEDAI-2K score over follow-up and (B) BILD damage at Year 3 by age at diagnosis



Mild: SLEDAI-2K score ≤4; moderate: SLEDAI-2K score >4 to <10; severe: SLEDAI-2K score ≥10.
***BILD**=Brief Index of Lupus Damage, **SDI**=Systemic Lupus International Collaborating Clinics Damage Index, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.*

- Among patients diagnosed at <50 years of age, those with severe SLEDAI-2K activity were more likely to have damage present at Year 3 compared with those with mild activity (unadjusted RR: 1.14; 95% CI: 1.05–1.23; **Figure 4**)
  - Among patients diagnosed at ≥50 years of age, SLEDAI-2K severity did not have a significant correlation with the presence of damage at Year 3 (unadjusted RR for severe activity versus mild: 0.97; 95% CI: 0.81–1.14)

Figure 4: Unadjusted RR of SDI damage at Year 3 of follow-up by age at diagnosis and maximum SLEDAI-2K score over follow-up

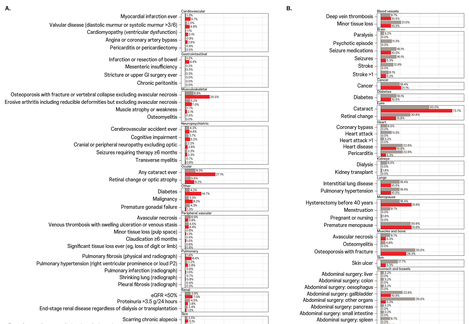


Mild: SLEDAI-2K score ≤4; moderate: SLEDAI-2K score >4 to <10; severe: SLEDAI-2K score ≥10.
***CI**=confidence interval, **RR**=relative risk, **SDI**=Systemic Lupus International Collaborating Clinics Damage Index, **SLEDAI-2K**=Systemic Lupus Erythematosus Disease Activity Index 2000.*

Association of age at diagnosis and types of organ damage at Year 3

- SDI damage types varied by age at diagnosis (**Figure 5A**)
  - Osteoporosis (27% in patients diagnosed at ≥50 years of age vs 9% in those diagnosed at <50 years of age; unadjusted RR: 3.2; 95% CI: 2.7–3.8) and cataracts (25% vs 9%, respectively; unadjusted RR: 3.1; 95% CI: 2.7–3.6) were more frequent in patients diagnosed at ≥50 years of age and were the most common types of organ damage in both groups
  - Other damage types, including myocardial infarction, valvular disease, cardiomyopathy, angina, bowel infarction, mesenteric insufficiency, cognitive impairment, retinal change/optic atrophy, diabetes, malignancy, claudication ≥6 months, and pulmonary fibrosis, were also more prevalent in patients diagnosed at ≥50 years of age
  - In contrast, premature gonadal failure, avascular necrosis, and severe proteinuria were more common in patients diagnosed at <50 years of age

Figure 5: Prevalence of (A) SDI damage and (B) BILD damage at Year 3 by age at diagnosis



- Among BILD damage types, cataracts and hysterectomy before 40 years of age occurred more frequently in patients diagnosed at ≥50 years of age, whereas other damage types were evident more frequently in those diagnosed at <50 years of age (**Figure 5B**)

***BILD**=Brief Index of Lupus Damage, **eGFR**=estimated glomerular filtration rate, **GI**=gastrointestinal, **P2**=pulmonic valve closure sound, **SDI**=Systemic Lupus International Collaborating Clinics Damage Index.*

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