Risk factors of progression from discoid lupus to severe systemic lupus erythematosus: a registry-based cohort study of 164 patients.

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Background: No study has assessed the risk factors of progression from discoid lupus erythematosus (DLE) to severe systemic lupus erythematosus (sSLE) (defined as requiring hospitalization and specific treatment).

Objective: To identify the risks factors of and generate a predicting score for progression to sSLE among patients with isolated DLE or associated with systemic lupus erythematosus with mild biological abnormalities.

Methods: In this registry-based cohort study, multivariable analysis was performed using risk factors identified from literature and pruned by backward selection to identify relevant variables. The number of points was weighted proportionally to the odds ratio (OR).

Results: We included 30 patients with DLE who developed sSLE and 134 patients who did not. In multivariable analysis, among 12 selected variables, an age of <25 years at the time of DLE diagnosis (OR, 2.8; 95% CI, 1.1-7.0; 1 point), phototype V to VI (OR, 2.7; 95% CI, 1.1-7.0; 1 point), and antinuclear antibody titers of ≥1:320 (OR, 15; 95% CI, 3.3-67.3; 5 points) were selected to generate the score. Among the 54 patients with a score of 0 at baseline, none progressed to sSLE, whereas a score of ≥6 was associated with a risk of approximately 40%.

Limitations: Retrospective design.

Conclusion: In our cohort, an age of <25 years at the time of DLE diagnosis, phototype V to VI, and antinuclear antibody titers of ≥1:320 were risk factors for developing sSLE. (J Am Acad Dermatol 2023;88:551-9.)

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CAPSULE SUMMARY

- Our study aimed to assess the risk factors of developing severe systemic lupus erythematosus among patients with discoid lupus erythematosus.
- In this cohort of 164 patients with DLE, we developed a 3-item score, including an age at DLE diagnosis of <25 years, phototype V-VI, and ANA titer of ≥1:320 at baseline, which may predict progression to sSLE.

INTRODUCTION

Lupus erythematosus (LE) is an autoimmune disease that may present as a limited skin disease, such as cutaneous lupus erythematosus (CLE),[1] or a systemic disease with manifestions ranging from biological abnormalities or mild symptoms to a potentially life-threatening disease with multiorgan involvement, as in systemic lupus erythematosus (SLE). Among CLE cases, discoid lupus erythematosus (DLE) is the most common subtype and accounts for approximately 80% of cases.[2,3]

At the time of diagnosis, a majority of patients with DLE do not have associated SLE; however, some of them will secondarily develop SLE during the follow-up period.[2-5]

In a systematic literature review, the risk of progression from DLE to SLE ranged from 6% to 21%.[5] Widespread DLE lesions, arthralgia, nail changes, anemia, leucopenia, high erythrocyte sedimentation rates, and high titers of antinuclear antibodies (ANA) were identified as potential risk factors for progression from DLE to SLE.[5] However, no statistical analyses were performed.

Moreover, previous studies were based on the previous American College of Rheumatology (ACR) 1982 or 1997 SLE classification criteria,[3,4,6] however, a new set of classification criteria that is more sensitive for the diagnosis of SLE has been published in 2019.[7]

Because these former criteria included several cutaneous items, patients with DLE who developed SLE frequently have mild disease limited to the skin or mild biological abnormalities, such as leucopenia.[8]

More recently, in 2 studies including 93 and 107 patients with CLE, using respectively the Systemic Lupus International Collaborating Centers 2012 and the ACR/European Alliance of Associations for Rheumatology (EULAR) 2019 criteria, respectively, between 3% and 11% of the patients developed SLE after a median follow-up of 3.5 years.[9,10] In these studies, patients with CLE frequently developed the following during their clinical course: leucopenia, thrombocytopenia, and ANA items; however, none of them developed severe systemic lupus erythematosus (sSLE).

The challenge for dermatologists is specifically to identify patients with DLE who have high risk of developing sSLE features requiring hospitalization and/or a specific treatment. Indeed, patients with DLE associated with "mild SLE" based on biological abnormalities (leucopenia, low C3 or C4, positive anti-dsDNA or anti-Sm antibodies) will not require any specific treatment for these abnormalities.

To our knowledge, only 1 study has assessed the risk of progression from CLE to sSLE.[4] In this study, only 5 (7%) of 74 patients with CLE developed moderate or sSLE[4] after a mean follow-up of 2.81 years. However, this study included different CLE subtypes and did not investigate the risk factors for progression to sSLE.

The aims of this study were, first, to identify risks factors for progression from DLE (isolated DLE or DLE with mild biological SLE) to sSLE using the ACR/EULAR 2019 SLE classification criteria and, second, to develop a score that may help to predict this progression to sSLE.

MATERIALS AND METHODS

Study design and setting

This registry-based cohort included patients with DLE identified in 3 dermatology departments and 2 internal medicine departments of French university hospitals between January 1997 and April 2021.

Definitions

DLE with mild biological SLE was defined by the presence of ≥10 points using the ACR/EULAR 2019 SLE classification, with DLE as the only clinical feature associated with the presence of biological abnormalities, including leucopenia, decreased C3 and/or C4 levels, and presence of specific autoantibodies, with no specific treatments regarding these abnormalities.

Severe SLE was defined as follows: (1) by the occurrence of at least 1 of the following features: SLE fever, serositis (pericarditis or pleural effusion), lupus nephritis, neuropsychiatric manifestation,

Abbreviations used:

ACR:	American College of Rheumatology
ANA:	antinuclear antibody
CI:	confidence interval
CLE:	cutaneous lupus erythematosus
DLE:	discoid lupus erythematosus
EULAR:	European Alliance of Associations for Rheumatology
LE:	lupus erythematosus
NPV:	negative predictive value
OR:	odds ratio
PPV:	positive predictive value
SLE:	systemic lupus erythematosus
sSLE:	severe systemic lupus erythematosus

autoimmune hemolysis, or autoimmune thrombocytopenia and (2) the need for a specific treatment with systemic corticosteroids (>0.5 mg/kg), immunosuppressant drug, and/or hospitalization related to SLE, defining a severe flare.[11]

Participants and eligibility criteria

Patients were included if they had DLE with pathologic confirmation,[12,13] with isolated DLE or mild biological SLE at the time of diagnosis using the ACR/EULAR 2019 SLE classification criteria.[7] Patients with DLE and associated sSLE features at the time of diagnosis or those developing SLE features <2 months after the DLE diagnosis were excluded. The starting point for measuring the duration of progression to sSLE was the date of DLE diagnosis.

Patients who developed sSLE features at least 2 months after the diagnosis of DLE (see definition section) were referred as patients with DLE-sSLE. Patients with DLE-sSLE were compared with those with DLE with or without mild biological SLE identified in the same cohort who did not develop sSLE features after at least 4 years of follow-up.

Data collection

Data collection was performed retrospectively from January 2020 to April 2021. Demographic data recorded included sex and age at the time of the diagnosis of DLE, body mass index, smoking status (active, past, or nonsmokers), Fitzpatrick phototype (from extremely fair, type I, to very dark, type VI) and familial lupus history. All patients with phototypes V to VI were of Sub-Saharan African descent from Africa or West Indies. Data recorded from physical examination included localized DLE (restricted to head and neck region) versus generalized DLE (that occurs both above and below the neck). Similar to previous studies,[6,14] arthralgia without arthritis was not considered as a symptom of SLE. Baseline biologic and immunological data, including ANA levels, anti−SS-A, anti−SS-B, anti-dsDNA, anti-Sm, anti-U1RNP, antiphospholipid autoantibodies, leucopenia, and decreased C3 and C4 fraction levels, were collected. Treatment history and treatments received at the time of progression from DLE to sSLE were recorded and categorized as antimalarials, systemic corticosteroids, and immunosuppressant drugs.

The ACR 2019 SLE classification criteria score was calculated for all patients with a cut-off of ≥10 points for SLE diagnosis.[7]

Outcomes

The main outcome at the end of the follow-up period was LE status for patients with DLE-sSLE versus those without DLE-sSLE.

Using variables identified via a literature review in PubMed (MEDLINE) using keywords discoid lupus, systemic lupus, progression, and development (Supplementary Table I, available via Mendeley at https://data.mendeley.com/datasets/fjdxk3cjps/3), we aimed to identify the risk factors of progression to DLE-sSLE and obtain a score associated with the risk of progression. We selected a priori age at DLE diagnosis,[15] sex, phototypes V or VI,[16] generalized DLE lesions,[4,6,14,16,17] presence of arthralgia,[6,14] a baseline ANA titer of ≥1:320,[18] presence of anti-dsDNA, anti-SSA, and anti-Sm antibodies,[9,16] presence of anemia[6,19,20] or lymphopenia,[6,19] and being classified as "mild" SLE at baseline[4,16] as potential risk factors for progression to sSLE. Age was dichotomized as ≤25 years or >25 years on the basis of the mean age at the time of DLE diagnosis in different SLE cohorts in the literature.[21]

Because the presence of mild biological SLE at baseline may be a severe confounder associated with the risk of progression toward sSLE, sensitivity analyses were performed among patients with isolated DLE and those with mild biological SLE.

Statistical analysis

Continuous variables were reported as medians with ranges and compared using Student *t* tests or Mann-Whitney tests, as appropriate. Categorical variables were reported as numbers with percentages and compared using the Fisher exact or χ^2tests. Odds ratio (OR) and 95% confidence intervals (CIs) were estimated to examine the association between risk factors and LE status.

The multivariable model was pruned by backward selection model using the Bayesan information criteria to simplify it with minimal loss of accuracy. The results of this data-driven approach were evaluated by a clinician (FC) for clinical relevance. Parameters from the literature associated with an

Table I. Clinical and biological parameters of patients with discoid lupus erythematosus at baseline

Features	Overall population (n = 164)
Sociodemographic data, *n* (%)	
Female sex	133 (81)
Age at DLE diagnosis, median (range), years	33 (9-79)
BMI. median (range, years)	23.1 (15.4-53.3)
Active smoking at diagnosis of DLE	74 (45)
Ethnicity, phototype and familial history, *n* (%)	
Caucasian	91 (55)
Sub-Saharan Africa or West Indies	44 (27)
Asia	14 (8)
Other	15 (10)
Phototype I-IV/ V-VI	120 (73)/ 44 (27)
Familial lupus	21 (13)
Clinical characteristics of DLE patients, *n* (%)	
Localized/ Generalized DLE	93 (57)/ 71 (43)
Scarring alopecia	108 (66)
Hand and foot lesions	38 (23)
Associated other CLE subtypes[†]	47 (29)
Raynaud's phenomenon	27 (16)
Arthralgias	62 (38)
Biological features at baseline, *n* (%)	
ANA ≥1/80	111 (68)
High ANA titers ≥1/320	87 (53)
Anti-dsDNA abs	51 (31)
Anti-SSA abs	52 (33)
Anti-SSB abs	7 (4)
Anti-U1 RNP abs	32 (20)
Anti-Sm abs	24 (15)
Low C3	22 (14)
Low C4	34 (22)
Lymphopenia	40 (26)
Treatments taken between DLE diagnosis and DLE-sSLE or last visit, *n* (%)	
Hydroxychloroquine ever	160 (98)
Systemic glucocorticoids ever	63 (38)
Immunosuppressive agents* ever	21 (13)
Treatment at time of DLE-sSLE or last visit	
Hydroxychloroquine	159 (97)
Systemic corticosteroids	51 (31)
Thalidomide	39 (24)
Lenalidomide	14 (9)
Immunosuppressive agents[‡]	21 (13)
DLE/SLE ACR/EULAR 2019 classification	
SLE at baseline according to ACR 2019	78 (48)
Number of baseline ACR 2019 criteria, median (range)	7 (0-23)
Number of final ACR 2019 criteria, median (range)	10 (0-31)
Follow-up data, *n* (%)	
Follow-up duration, median (range), y	12.1 (2.6-48.6)
DLE ± mild SLE who did not develop severe SLE	134 (81.7)
DLE who develop severe SLE	30 (18.3)

ACR, American College of Rheumatology; *ANA*, antinuclear antibody; *BMI*, body mass index; CLE, cutaneous lupus erythematosus; *DLE*, discoid lupus erythematosus; *EULAR*, European Alliance of Associations for Rheumatology; *SLE*, systemic lupus erythematosus; *sSLE*, severe systemic lupus erythematosus.

*DLE-sSLE: isolated DLE or DLE with mild SLE who develop severe SLE;

[†]including associated subacute CLE *n* = 14 (9%), lupus tumidus *n* = 14 (9%), chilblain lupus *n* = 14 (9%), lupus panniculitis *n* = 8 (55) and acute CLE n = 3 (2%).

[‡]methotrexate, mycophenolate mofetil, salazopyrine, azathioprine.

increased risk of sSLE progression with minimum Bayesan information criteria in the first model (model 1) were selected for creating the predictive score (model 2). The number of points assigned to each score variable was weighted proportionally to its OR by approximating the decimal points to the nearest unit.[22]

Statistical analyses were performed using JMP 15 (SAS Institute Inc).

RESULTS

Patients' characteristics

We included 30 patients with DLE-sSLE and 134 patients with DLE who did not develop sSLE features. Patients' characteristics are described in Table I. Most patients were women (81%), and the median age at the time of DLE diagnosis was 33 years (range, 9-79 years). The median follow-up duration was 12.14 years (range, 2.64-48.56 years).

All but 4 patients (98%) had received antimalarials during their DLE history; 63 (38%) patients had received systemic glucocorticoids, and 21 (13%) patients had received immunosuppressive agents.

At baseline, 86 (52%) patients were classified as having DLE only and 78 (48%) patients were classified as having DLE associated with mild biological SLE.

Table II. Severe SLE manifestations and treatments at time of discoid lupus erythematosus—severe systemic lupus erythematosus

Features	DLE-sSLE (*n* = 30)
Severe systemic manifestations, *n* (%)	
Renal manifestations	14 (47)
Proteinuria > 0.5 g/24 h*	3 (10)
Renal biopsy class II lupus nephritis	2 (7)
Renal biopsy Class V lupus nephritis	6 (20)
Renal biopsy Class III or IV lupus nephritis	3 (10)
SLE Fever	11 (37)
Acute pericarditis	8 (27)
Pleural effusion	3 (10)
Neurologic manifestations	3 (10)
Delirium	2 (7)
Fahr syndrome	1 (3)
Autoimmune haemolysis	2 (7)
Kikuchi syndrome	2 (7)
Autoimmune thrombocytopenia	1 (3)
Macrophage activation syndrome	1 (3)
Other systemic manifestations	
Interstitial pneumonia	1 (3)
Autoimmune erythroblastopenia	2 (7)
Lupus enteritis	1 (3)
Systemic manifestations requiring hospitalization	30 (100)
Severe flare according to SELENA-SLEDAI Flare Index (SFI)†	30 (100)
Follow-up data, *n* (%)	
Follow-up duration, median (range), y	13.98 (2.64-26.55)
Time to develop SLE, median (range), y	5.7 (0.33-20.4)
Treatment at time of DLE-sSLE	
Hydroxychloroquine	27 (90)
Systemic glucocorticoids	16 (53)
Thalidomide	4 (13)
Lenalidomide	3 (10)
Immunosuppressive agents‡	5 (17)

ANA, Antinuclear antibody; *BMI*, body mass index; CLE, cutaneous lupus erythematosus; *DLE*, discoid lupus erythematosus; *sSLE*, severe systemic lupus erythematosus.
*No renal biopsy was performed
†SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment—Systemic Lupus erythematosus disease activity index
‡Methotrexate, azathioprine, salazopyrine, immunoglobulin therapy, dapsone.

Description of CLE-sSLE features

Patients' characteristics are described in Table II. Among the 30 patients who developed sSLE manifestations, 27 (90%) were women, with a median age of 23.5 (range, 10-72 years) at the time of DLE diagnosis and a median age of 33.8 years (range, 16.3—73.9 years) at the time of sSLE diagnosis. The median duration to develop sSLE was 5.7 years (range, 0.33-20.4 years). At baseline, 6 (20%) patients were classified as having isolated DLE and 24 (80%) patients were classified as having mild SLE. Conversely, 54 of 78 (69%) patients with DLE who were classified as having mild SLE at baseline never developed sSLE features during the follow-up period.

The most common SLE features that developed in patients with DLE were renal involvement (47%), serositis (37%), and SLE fever (37%). Neurologic manifestations were observed in 3 (10%) patients. All patients required hospitalization upon presenting severe symptoms and fulfilled the severe flare definition according to the SELENA-SLEDAI Flare Index.[11]

Development of the predictive score for progression to sSLE

Univariable analyses of the association between all recorded variables and the progression from DLE toward sSLE are presented in Table III. The median follow-up duration was 13.98 years (range, 2.64-26.54 years) in the DLE-sSLE group and 11.60 years (range, 4.12-48.56 years) in the non—DLE-sSLE group (P = .80). The results of these univariable analyses were consistent with the choice of the selected variables based on literature review. Neither the presence of associated CLE subtypes nor any CLE subtypes assessed individually were statistically associated with progression to DLE-sSLE. Of note, 2 of 3 (66%) patients with acute CLE (P = .08) and none with tumidus lupus (P = .07) developed sSLE.

We created the first model (model 1) considering all selected variables based on literature review (Table IV). In this model, the following variables were selected using backward elimination to generate the score: an age of ≤25 years at the time of DLE diagnosis (OR, 4.4; 95% CI, 1.5-13.4; P = .006), phototype V or VI (OR, 4.0; 95% CI, 1.2-13.4; P = .02), and an ANA titer of ≥1:320 (OR, 7.4; 95% CI, 1.2-46.3; P = .02). In the second model (model 2), which included only these 3 variables, we found an OR of 2.8 (95% CI, 1.1-7.0) for an age of ≤25 years at the time of DLE diagnosis, an OR of 2.7 (95% CI, 1.1-7.0)

Table III. Clinical and biological parameters at baseline associated with the progression from discoid lupus erythematosus with or without mild systemic lupus erythematosus to severe systemic lupus erythematosus

Features	DLE ± mild SLE who did not develop sSLE (*n* = 134)	DLE-sSLE† (*n* = 30)	Univariable	
			OR (95% CI)	*P* value
Sociodemographic features				
Female	106 (79%)	27 (90%)	2.38 (0.67-8.33)	.21
Age at diagnosis of DLE <25 years old	**31 (23%)**	**16 (53%)**	**3.80 (1.67-8.64)**	**.001**
Body mass index, median (range)*	23.2 (15.4-53.3)	22.3 (16.2-41.1)	0.96 (0.88-1.05)	.28
Active smoking at diagnosis of DLE	63 (47%)	11 (37%)	0.65 (0.29-1.48)	.30
Phototype V-VI	**31 (23%)**	**13 (43%)**	**2.54 (1.11-5.8)**	**.03**
Familial lupus history	15 (11%)	6 (20%)	1.98 (0.7-5.6)	.21
Clinical features				
Generalized DLE	**51 (38%)**	**20 (67%)**	**3.23 (1.41-8.33)**	**.0043**
Scarring alopecia	84 (63%)	24 (80%)	2.38 (0.91-6.22)	.06
Hand and foot lesions	**25 (19%)**	**13 (43%)**	**3.33 (1.44-7.74)**	**.006**
Other subtypes of DLE	40 (30%)	7 (23%)	0.72 (0.28-1.8)	.47
Raynaud phenomenon	**17 (13%)**	**10 (33%)**	**3.44 (1.38-8.58)**	**.01**
Arthralgias	**43 (32%)**	**19 (63%)**	**3.62 (1.58-8.26)**	**.018**
Biological features at baseline (presence)				
ANA titers ≥ 1:320	**59 (44%)**	**28 (93%)**	**17.80 (4.07-77.75)**	**<.001**
Anti-dsDNA	**35 (26%)**	**16 (57%)**	**3.77 (1.63-8.75)**	**.0019**
Anti-SSA	**38 (29%)**	**14 (50%)**	**2.44 (1.07-5.62)**	**.036**
Anti-SSB	5 (4%)	2 (7%)	1.94 (0.36-10.54)	.61
Anti-U1RNP	**20 (15%)**	**12 (43%)**	**4.16 (1.7-10.1)**	**.0021**
Anti-Sm	**13 (10%)**	**11 (39%)**	**5.92 (2.29-15.32)**	**.0003**
Low C3	15 (11%)	7 (26%)	2.70 (0.98-7.46)	.0651
Low C4	25 (19%)	9 (33%)	2.12 (0.85-5.27)	.12
Lymphopenia	**28 (22%)**	**12 (43%)**	**2.65 (1.12-6.25)**	**.0287**
Anemia	9 (7)	4 (13)	2.14 (0.61-7.47)	.25
DLE/SLE ACR/EULAR 2019 classification				
SLE according ACR 2019 at baseline	**54 (40%)**	**24 (80%)**	**5.93 (2.27-15.46)**	**<.0001**
ACR 2019 total baseline median (extreme)*	**4 (0-23)**	**16 (4-22)**	**1.19 (1.11-1.28)**	**<.0001**
Follow-up data				
Follow-up duration, median (range), years	11.60 (4.12-48.56)	13.98 (2.64-26.54)	-	.80

Statistically significant variables have been highlighted in bold.

ACR, American College of Rheumatology; *ANA*, antinuclear antibody; *DLE*, discoid lupus erythematosus; *EULAR*, European Alliance of Associations for Rheumatology; *OR*, odds ratio; *SLE*, systemic lupus erythematosus; *sSLE*, severe systemic lupus erythematosus.

*OR are expressed in per unit change in regressor.

†DLE-sSLE: progression from DLE to severe SLE.

for phototypes V or VI, and an OR of 15 (95% CI, 3.3-67.3) for ANA titers of ≥1:320. We proportionally weighted each variable according to its OR by rounding the decimal points to the nearest unit and, therefore, assigned 1 point for the variables age of ≤25 years at the time of DLE diagnosis and phototypes V or VI each and 5 points for ANA titers of ≥1:320.

The performances of the score are summarized in Fig 1. Among the 54 patients with a score of 0, none developed DLE-sSLE. Conversely, 1 (6%) of 17 patients with a score of 1, 1 (17%) of 6 patients with a score of 2, 6 (18%) of 33 patients with a score of 5, 18 (39%) of 46 patients with a score of 6, and 4 (50%) of 8 patients with a score of 7 developed DLE-sSLE. Using a receiver operating characteristic curve,

Table IV. Generation of a **s**core associated with progression from discoid lupus erythematosus to severe systemic lupus erythematosus

	Model 1*		Model 2†		
Features	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**	**Points**
Sociodemographic features					
Age at diagnosis of DLE < 25 y	4.4 (1.5-13.4)	.0061	2.8 (1.1-7.0)	.0243	1
Female sex	4.1 (0.4-42.2)	.1822			
Phototype V-VI	4.0 (1.2-13.4)	.0189	2.7 (1.1-7.0)	.0364	1
Clinical features					
Generalized DLE	1.3 (0.4-4.2)	.6492	-	-	
Arthralgias	1.5 (0.4-5.1)	.5183	-	-	
Biological features at baseline (presence)			-	-	
ANA titers ≥ 1:320	7.4 (1.2-46.3)	.0188	15 (3.3-67.3)	<.0001	5
Anti-dsDNA	2.5 (0.6-10.4)	.1987	-	-	
Anti-SSA	2.0 (0.7-6.1)	.1999	-	-	
Anti-Sm	3.0 (0.8-11.0)	.0990	-	-	
Anemia	1.9 (1.2-22.4)	.6027	-	-	
Lymphopenia	1.2 (0.4-3.6)	.7596	-	-	
DLE/SLE ACR/EULAR classification					
SLE according ACR 2019 at baseline	2.3 (0.3-16.1)	.3837	-	-	

ACR, American College of Rheumatology; *ANA*, antinuclear antibody; *DLE*, discoid lupus erythematosus; *EULAR*, European Alliance of Associations for Rheumatology; *OR*, odds ratio; *SLE*, systemic lupus erythematosus.
*Model 1 includes all variables selected from the literature review (see Supplementary Table I).
†Model 2 includes variables selected by backward elimination.

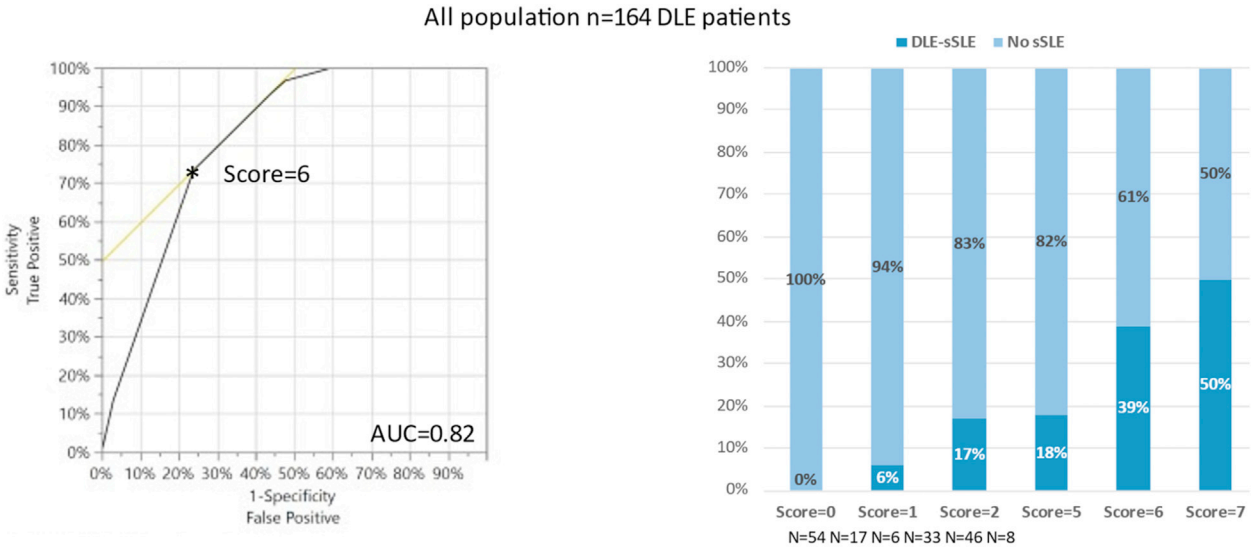
a score of 6 had the best cut-off with a sensitivity of 73% and a specificity of 76% (Youden's index: sensitivity − [1 − specificity] = 0.49) for predicting progression to DLE-sSLE (Fig 1) with a positive predictive value (PPV) of 41% and a negative predictive value (NPV) of 93%. Moreover, a score ≤1 was associated with a NPV of 100%. Subgroup analyses including only patients with isolated DLE or with DLE associated with "mild" SLE are presented in Supplementary Figs 1 and 2 (available via Mendeley at https://data.mendeley.com/datasets/fjdxk3cjps/3), respectively. Among patients with isolated DLE, a score of ≤2 was associated with a NPV of 100% but with a low PPV of 22%. Similarly, among patients with DLE associated with "mild" SLE, a score of ≤1 was associated with a NPV of 100% and a PPV of 31%, whereas a score of 6 was associated with a NPV of 89% and a PPV of 47%.

DISCUSSION

In this cohort study including 164 patients with DLE, using potential risk factors identified via a literature review (Supplementary Table I), we developed a simple score using the following 3 items: an age of ≤25 years at the time of DLE diagnosis, ANA titers of ≥1:320, and phototype V or VI—which may be useful to predict a risk of progression to sSLE (DLE-sSLE). This score has a high NPV, and a score of 0 was associated with no risk of developing sSLE. Conversely, a score of ≥6 was associated with a much-increased risk but with a low PPV of 41%. Of importance, the performance of this score was similar among patients with isolated DLE and those with DLE with "mild" SLE.

To our knowledge, no study has aimed to assess the risk factors of developing sSLE features. Previous studies have found generalized DLE, arthralgia, titers positive for ANA or high titers of ANA, and a greater number of ACR/Systemic Lupus International Collaborating Centers criteria as risk factors of progression from DLE to SLE.[4,6,14,17,19,20] However, developing SLE is not necessarily associated with the need of increasing treatment and, therefore, may not be clinically meaningful. Indeed, for example, in our study, among the 78 patients with DLE fulfilling the ACR 2019 classification criteria for SLE, more than two-third never developed sSLE features, with a median follow-up duration of 14 years.

Regarding the risk factors of progression that we identified, a previous study in pediatric lupus found that the risk of progression to SLE was 29%,[15] which is higher than that in the adult population.[8] Moreover, among patients with SLE, a younger age at the time of DLE diagnosis was found to be a risk factor for developing lupus nephritis and, therefore, sSLE.[23] Regarding the black phototype, it has already been shown to be a risk factor for sSLE features[24] and for progression to lupus nephritis.[25] Finally, considering ANA titers, a recent study found that a titer of ≥1:320 had a PPV of 84.0% for the diagnosis of



Score Values	Number of patients/Number of DLE -sSLE (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
0	54/0 (0%)	100	0	18	NA
1	17/1 (6%)	100	40	27	100
2	6/1 (17%)	97	52	31	99
5	33/6 (18%)	93	56	32	97
6	46/18 (39%)	73	76	41	93
7	8/4 (50%)	13	97	13	97

Fig 1. ROC curve and performances of the score among overall population. *PPV*, Positive predictive value; *NPV*, negative predictive value; *AUC*, area under the curve.

systemic autoimmune rheumatic diseases, including SLE, in accordance with our results.[26]

The limitations of the study include its retrospective design and the limited number of included patients. In particular, baseline DLE activity using the Cutaneous LE Disease Area and Severity Index was not available in most cases. Moreover, our study design did not allow assessment of the prevalence of patients with DLE who developed sSLE features. Of importance, there is no validated definition of sSLE, and we have used in part the SELENA-SLEDAI Flare Index,[11] which defined sSLE flare, which is different from sSLE. However, our aim was to use a pragmatic definition associated with the development of extracutaneous SLE features requiring a specific treatment. Finally, it will be necessary to assess the performance of our score in a prospective validation cohort to confirm its potential use in a real-life setting.

Overall, in our cohort of 164 patients with DLE with or without associated mild SLE, an age <25 years at the time of DLE diagnosis (OR, 2.8; 95% CI, 1.1-7.0), phototypes V to VI (OR, 2.7; 95% CI, 1.1-7.0), and ANA titers of ≥1:320 (OR, 15; 95% CI, 3.3-67.3) were identified as risk factors for developing sSLE. Using these 3 criteria, we developed a score with a high NPV, which may allow clinicians to reassure patients with DLE with a score of ≤1, even among those who fulfilled the ACR/EULAR 2019 criteria for SLE. Moreover, patients with DLE with a score of ≥6 may require closer monitoring in particular urinalysis. This score should be validated in an external prospective cohort to confirm these preliminary data.

Conflict of interest

None disclosed.

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