Categorization of Patients With Systemic Lupus Erythematosus Using Disease Activity, Patient-Reported Outcomes and Transcriptomic Signatures

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Abstract

Objective

Patients with systemic lupus erythematosus (SLE) display symptoms that are not always related to disease activity and may distort clinical trial results. Recently, a clinical categorization based on the presence of type 1 (inflammatory manifestations) and/or type 2 (widespread pain, fatigue, depression) symptoms has been proposed in SLE. Our aim was to develop a type 2 score derived from the Short-Form health survey (SF-36) to categorize SLE patients and to compare immunological and transcriptomic profiles between groups.

Methods

Seventeen items from the SF-36 were selected to build a type 2 score for 50 SLE patients (100 visits; LUPUCE cohort) and the SLEDAI was used to define type 1 symptoms. Patients were categorized in four groups: minimal (no symptoms), type 1, type 2 and mixed (both type 1 and type 2 symptoms). Clinical, immunological and transcriptomic profiles were compared between the groups.

Results

Type 2 scores ranged from 0 to 31, with a cut-off value of 14 (75th percentile). The sample categorization was: minimal in 39%, type 1 in 37%, type 2 in 9% and mixed in 15%. Type 2 patients were older than minimal patients and had a longer disease duration than type 1 and mixed patients. Immunological data and modular interferon signatures did not differ between the groups.

Conclusion

Patients with SLE can be categorized into four clinical groups using the SLEDAI score and our SF-36-derived type 2 score. This categorization is non-redundant with immunological or transcriptomic profiles and could prove useful to stratify patients in clinical trials.

Significance And Innovations

- A score derived from selected items of the SF-36 can be used to identify SLE patients with type 2 symptoms according to the Duke University categorization.
- Using the SLEDAI and this type 2 score, SLE patients can be categorized in four clinical groups.
- This categorization is not related to immunological activity or blood transcriptome profiles (and not to the interferon signature in particular).

- This categorization could be useful in the daily care of patients as well as in clinical trials, for upstream patient stratification or for the interpretation of results.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease, characterized by a wide range of symptoms. Some SLE symptoms are related to systemic and local inflammation resulting from disease activity, while others can affect quiescent patients. Although survival has been improved dramatically with medications (1), patients with SLE suffer from a persistently altered health-related quality of life (HRQoL) (2, 3), mainly influenced by fatigue, reported by 67–90% of patients (4–7), chronic pain and depression (8). These symptoms correlate poorly with disease activity (7), do not respond to conventional immunosuppression, and are often difficult to manage. In addition, they can lead to the failure of therapeutic candidates to improve HRQoL in clinical trials (9). Recently, categorization of SLE symptoms between two non-exclusive types was proposed by Duke University (10) and tested in a cohort of 212 patients (11). Type 1 symptoms include inflammatory manifestations related to disease activity, such as nephritis, arthritis, rash, serositis and cytopenia; type 2 symptoms include widespread pain, fatigue, sleep disturbance, cognitive dysfunction and depression. This allowed the categorization of patients at the time of clinical assessment into four distinct groups (11): (i) “type 1”: patients displaying only type 1 symptoms; (ii) “type 2”: patients displaying only type 2 symptoms; (iii) “mixed”: patients displaying both type 1 and type 2 symptoms; (iv) “minimal”: patients with no symptoms. This classification was built upon the SLEDAI score (type 1 symptoms), which is widely available in SLE studies, and on American College of Rheumatology (ACR) fibromyalgia criteria (12) (type 2 symptoms) (11), which are less commonly used in SLE and are rarely available retrospectively.

Our aim was to determine whether selected items from the SF-36 questionnaire could allow the identification of type 2 symptoms and the retrospective categorization of patients from different SLE cohorts. We then aimed to evaluate whether these categories were associated with distinct immunological and transcriptomic profiles. In particular, we compared the interferon (IFN) modular scores of samples from these four groups through a modular framework of analysis described previously (13).

Patients And Methods

Patients and Ethics

This study involved data from patients included in the LUPUCE study (NCT00920114) and the PSY-LUP study (NCT03913754). All patients gave their written informed consent before any study-related procedure. The study was conducted according to the Declaration of Helsinki.

LUPUCE was a transcriptomic study (13–15) comprising 62 consecutive SLE patients, of whom 50 had completed the self-administered SF-36 questionnaire on at least at one visit and were included in the present study. Clinical, biological and transcriptomic data were recorded at each visit. The study was

approved in France by the Comité de Protection des Personnes Sud Méditerranée 1 (IDRCB 2009-A00257-50) and in the USA by the Institutional Review Boards (IRBs) of the Baylor Institute of Immunology Research (IRB 011–173) and the Benaroya Research Institute (IRB 12085).

PSY-LUP (NCT03913754) is a study evaluating the psycho-social consequences of SLE. One-hundred SLE patients responded to several quality of life (QoL) questionnaires including the SF-36. The study was approved by the Comité de Protection des Personnes Ile de France I (IDRCB A02747-48).

Assessment of type 1 and type 2 symptoms

Patients were considered to have type 1 symptoms if they had a SLEDAI ≥ 6 , a clinical SLEDAI ≥ 4 , or active lupus nephritis documented by kidney biopsy (11).

The presence of type 2 symptoms was defined using a score built from the responses to specific items of the SF-36 questionnaire (16) (detailed in Table 1). Three physicians experienced in SLE (RA, LC and NJC) manually selected 17 items/questions they considered the most relevant to express widespread pain, fatigue and depression. Responses to these items were weighted and the global type 2 score ranged from 0 to 42. The 75th percentile of this score in the LUPUCE cohort was chosen as the threshold to consider that a patient displayed significant type 2 symptoms.

Table 1
Detailed type 2 score, built from the responses to 17 items of the SF-36.

Questions	0	1	2	3	Points
In general, would you say your health is:	Excellent, very good or good	Fair	Poor		/2
How TRUE or FALSE is each of the following statements for you?	True, or don't know	Mostly false	Definitely false		/2
- <i>I am as healthy as anybody I know</i>	True, or don't know	Mostly false	Definitely false		/2
- <i>My health is excellent</i>					
The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	No, not limited at all	Yes, limited a little	Yes, limited a lot		/2
- <i>Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports</i>	No, not limited at all	Yes, limited a little	Yes, limited a lot		/2
- <i>Climbing several flights of stairs</i>	No, not limited at all	Yes, limited a little	Yes, limited a lot		/2
- <i>Walking more than a mile</i>					
During the past 4 weeks, to what extent have your physical health or emotional problems interfered with your normal activities with family, friends, neighbours, or groups?	Not at all or slightly	Moderately	Severe	Very severe	/3
During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)	A little bit or none of the time	Some of the time	Most of the time	All of the time	/3
How much bodily pain have you had during the past 4 weeks?	None, very mild or mild	Moderate	Severe	Very severe	/3
During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all or a little bit	Moderately	Quite a bit	Extremely	/3
These questions are about how you feel and how things have been with you during the last 4 weeks. For each question, please give the answer that comes closest to the way you have been feeling.					

Questions	0	1	2	3	Points
How much of the time during the past 4 weeks:	All, most, a good bit or some of the time	A little bit of the time	None of the time	All of the time	/2
- Did you feel full of pep?		A good bit of the time	Most of the time	All of the time	/3
- Have you felt so down in the dumps that nothing could cheer you up?	Some, a little bit or none of the time	A little bit of the time	None of the time	All of the time	/2
- Did you have a lot of energy?		A good bit of the time	Most of the time	All of the time	/3
- Have you felt downhearted and blue?	All, most, a good bit or some of the time	A good bit of the time	Most of the time		/2
- Did you feel worn out?		A good bit of the time	Most of the time		/3
- Have you been a happy person?	Some, a little bit or none of the time	A little bit of the time	None of the time		
- Did you feel tired?		A good bit of the time	Most of the time		
	Some, a little bit or none of the time				
	All, most, a good bit or some of the time				
	Some, a little bit or none of the time				
Total Score					/42

Immunological activity

Immunological activity was evaluated by the levels of the complement fractions C3 and/or C4 and of anti-dsDNA antibodies.

Blood modular transcriptional repertoire analyses

Whole-blood transcriptomic data collected in the LUPUCE study were investigated (13). RNA was processed as described elsewhere using Illumina beadchips (13). Data are deposited in the NCBI Gene Expression Omnibus (GEO, <http://www.ncbi.nlm.nih.gov/geo>, GEO Series accession number GSE49454). Analyses were performed using the second generation of a modular framework as described previously (13, 17). The level of regulation of each module was calculated as the percentage difference: % upregulated probes – % downregulated probes. A module was considered activated (up-regulated) or inhibited (down-regulated) if its value was, respectively, $\geq 20\%$ or $\leq -20\%$. A modular IFN score was

calculated depending on the activation of three IFN modules (M1.2, M3.4 and M5.12). The IFN signature was absent, mild, moderate or strong if 0, 1, 2 or 3 IFN modules were active ($\geq 20\%$) respectively (13).

Statistical analysis

Quantitative variables are described as median and interquartile range (IQR), or mean $\pm$ standard deviation (SD); categorical variables are described as numbers and percentages.

The four clinical groups were compared for patient characteristics, immunological activity and level of regulation of IFN modules (modules M1.2, M3.4 and M5.12) using the Kruskal Wallis test and Tukey's test for pairwise comparisons. Categorical patient characteristics, frequency of IFN signature and active modules were compared between the four clinical groups using the Chi² test or Fisher's exact test. Exploratory analysis compared levels of regulation of all modules between the four clinical groups using the Kruskal-Wallis test with false discovery rate (FDR) correction for multiplicity. Similarly, the presence of modules was compared using Fisher's exact test with FDR correction. Statistical tests were two-tailed and significance was set at $p < 0.05$. All statistical analyses were conducted using IBM SPSS Statistics 20.

Results

Type 2 score and patient distribution between clinical groups

All visits ($n = 100$) at which patients from the LUPUCE cohort answered a SF-36 questionnaire were considered to calculate the type 2 score (Table 1). The type 2 score ranged from 0 to 31, with a median of 6 and interquartile range [IQR] of 3–14. The threshold to define type 2 symptoms was > 14 . Median SLEDAI was 4 [IQR: 0–22] and patients exhibited type 1 symptoms at 52 visits. Patients from the LUPUCE cohort were categorized into four clinical groups: minimal in 39%, type 1 in 37%, type 2 in 9% and mixed in 15% (Table 2).

Table 2
Distribution (%) of SLE patients from different cohorts in the four clinical groups.

Clinical groups	LUPUCE cohort (N = 100)	Duke University cohort (N = 212)	PSY-LUP cohort (N = 100)
Minimal	39	49	ND
Type 1	37	30	ND
Type 2	9	8	23
Mixed	15	13	
ND: not determined (the SLEDAI was not recorded in the PSY-LUP cohort)			

The type 2 score was calculated in an independent cohort of 100 SLE patients (PSY-LUP cohort). This showed a similar pattern of values to the LUPUCE cohort (Fig. 1): the score ranged from 0 to 33, with a median of 8.3, and 23% of patients were above the threshold of 14. The distribution of patients from the LUPUCE cohort was compared with that from Duke University (11), in which type 2 symptoms were defined by ACR fibromyalgia criteria. A similar distribution was found in the two cohorts (Table 2).

The characteristics of patients from the LUPUCE cohort at their first visit (n = 50 unique patients) and the characteristics of patient-by-visit by clinical groups are summarized in Table 3. The median time between each visit was 124 days [IQR: 20–130]. Patients in the “type 2” group were older (52 vs. 31 years, $p = 0.016$) and more often menopausal (66.7% vs. 17.9%, $p = 0.031$) than patients in the “minimal” group, and they had a longer disease duration than patients in the “type 1” and “mixed” groups (10 vs. 5 years and 10 vs. 2 years, $p = 0.011$, respectively).

Table 3

Characteristics of patients at their first visit (unique patient, N = 50) and of patient-by-visit (N = 100 visits) in the four clinical groups.

	Total patients <i>n</i> = 50	Minimal <i>n</i> = 39	Type-1 <i>n</i> = 37	Type-2 <i>n</i> = 9	Mixed <i>n</i> = 15	Total visits <i>n</i> = 100	p value
Number of visits	2 [1–5]	2 [1–4]	2 [1–4]	1 [1–3]	1 [1–3]	1.5 [1–5]	
Sex, female	43 (86)	31 (79.5)	33 (89.2)	9 (100)	10 (66.7)	83 (83)	0.119
Age (years)	38 [18–70]	31 [18–54]	36 [20–67]	52 [39–70]	44 [25–56]	37 [18–70]	0.016 ^a
Ethnicity	44	35	30	9	15	89	0.636
Caucasian	(88)	(89.7)	(81.1)	(100)	(100)	(89)	
Black	3 (6)	2 (5.1)	2 (5.4)	0 (0)	0 (0)	4 (4)	
Asian	3 (6)	2 (5.1)	5 (13.5)	0 (0)	0 (0)	7 (7)	
Hypertension	21 (42)	17 (43.6)	17 (45.9)	5 (55.6)	9 (60)	48 (48)	0.723
Smoking	16 (32)	11 (28.2)	17 (45.9)	1 (11.1)	7 (46.7)	36 (36)	0.126
Menopause	16 (32)	7 (17.9)	13 (35.1)	6 (66.7)	4 (26.7)	30 (30)	0.031 ^a
Antiphospholipid Sd	5 (10)	7 (17.9)	5 (13.5)	0 (0)	2 (13.3)	14 (14)	0.670
Disease duration (years)	7 [0–40]	7 [1–24]	5 [0–30]	10 [3–40]	2 [0–22]	7 [0–40]	0.011 ^{b,c}

Values shown are median [IQR], or n (%).

SLE: systemic lupus erythematosus; Hb: haemoglobin.

p value: comparison between SLE subtypes (Kruskal Wallis test), significant pairwise comparisons (Tukey test): ^a: Minimal < Type 2; ^b: Type 1 < Type 2; ^c: Mixed < Type 2; ^d: Minimal < Type 1; ^e: Minimal < Mixed; ^f: Type 2 < Type 1; ^g: Type 2 < Mixed; ^h: Type 1 < Mixed; ⁱ: Type 1 < Minimal; ^j: Mixed < Minimal; ^k: Mixed < Type 1; ^l: Type 2 < Minimal

	Total patients <i>n</i> = 50	Minimal <i>n</i> = 39	Type-1 <i>n</i> = 37	Type-2 <i>n</i> = 9	Mixed <i>n</i> = 15	Total visits <i>n</i> = 100	p value
SLEDAI	4 [0–22]	2 [0–4]	10 [4–22]	2 [0–4]	14 [4–22]	4 [0–22]	< 0.001 ^{d,e,f,g,h}
Flaring SLE	27 (54)	5 (12.8)	32 (86.5)	1 (11.1)	15 (100)	55 (55)	< 0.001 ^{b,c,i,j}
Cutaneous flare	13 (26)	2 (5.1)	14 (37.8)	1 (11.1)	6 (40)	23 (23)	0.001 ^{d,e}
Articular flare	10 (20)	0 (0)	11 (29.7)	0 (0)	5 (33.3)	16 (16)	0.001 ^{d,e}
Haematological flare	4 (8)	1 (2.6)	5 (13.5)	0 (0)	2 (13.3)	8 (8)	0.190
Renal flare	17 (34)	0 (0)	19 (51.4)	0 (0)	12 (80)	31 (31)	< 0.001 ^{d,e,f,g}
Serum creatinine (μmol/l)	70 [42–514]	71 [42–150]	61 [48–100]	73 [58–122]	102 [51–514]	70 [42–514]	0.087
CKD	10 (20)	6 (15.4)	6 (16.2)	3 (33.3)	3 (20)	18 (18)	0.596
AKI	5 (10)	0 (0)	1 (2.7)	0 (0)	5 (33.3)	6 (6)	< 0.001 ^{e,h}
Nephrotic Sd	10 (20)	0 (0)	7 (18.9)	0 (0)	6 (40)	13 (13)	< 0.001 ^{d,e}
Anti-dsDNA +	34 (68)	23 (60.5)	22 (59.5)	8 (88.9)	10 (71.4)	63 (64.3)	0.377
Anti-dsDNA level	43 [0–578]	24 [0–465]	34 [1–578]	60 [2–110]	47 [1–400]	39 [0–578]	0.446

Values shown are median [IQR], or n (%).

SLE: systemic lupus erythematosus; Hb: haemoglobin.

p value: comparison between SLE subtypes (Kruskal Wallis test), significant pairwise comparisons (Tukey test): ^a: Minimal < Type 2; ^b: Type 1 < Type 2; ^c: Mixed < Type 2; ^d: Minimal < Type 1; ^e: Minimal < Mixed; ^f: Type 2 < Type 1; ^g: Type 2 < Mixed; ^h: Type 1 < Mixed; ⁱ: Type 1 < Minimal; ^j: Mixed < Minimal; ^k: Mixed < Type 1; ^l: Type 2 < Minimal

	Total patients <i>n</i> = 50	Minimal <i>n</i> = 39	Type-1 <i>n</i> = 37	Type-2 <i>n</i> = 9	Mixed <i>n</i> = 15	Total visits <i>n</i> = 100	p value
Anti-RNP +	12 (24)	5 (12.8)	6 (16.2)	2 (22.2)	4 (26.7)	17 (17)	0.568
Anti-Sm +	7 (14)	5 (12.8)	2 (5.4)	2 (22.2)	3 (20)	12 (12)	0.233
Anti-SSA +	18 (36)	13 (33.3)	18 (48.6)	2 (22.2)	7 (46.7)	40 (40)	0.368
Anti-SSB +	4 (8)	1 (2.6)	4 (10.8)	0 (0)	1 (6.7)	6 (6)	0.405
Low C3	21 (42)	15 (38.5)	21 (56.8)	3 (33.3)	4 (26.7)	43 (43)	0.171
Low C4	14 (28)	12 (30.8)	14 (37.8)	3 (33.3)	5 (33.3)	34 (34)	0.954
Low C3 or C4	23 (46)	15 (38.5)	23 (62.2)	3 (33.3)	6 (40)	47 (47)	0.148
Hb < 12 g/dL	18 (36)	9 (23.7)	8 (21.6)	3 (33.3)	9 (60)	29 (29.3)	0.042 ^{b,e,h}
Hydroxychloroquine	28 (56)	21 (53.8)	24 (64.9)	6 (66.7)	6 (40)	57 (57)	0.357
Corticosteroids	43 (86)	34 (87.2)	32 (86.5)	9 (100)	14 (93.3)	89 (89)	0.835
Corticosteroids (mg/day)	8 [0–90]	5 [0– 20]	15 [0– 60]	8 [5– 8]	20 [0– 90]	8 [0– 90]	0.003 ^{e,g}

Values shown are median [IQR], or n (%).

SLE: systemic lupus erythematosus; Hb: haemoglobin.

p value: comparison between SLE subtypes (Kruskal Wallis test), significant pairwise comparisons (Tukey test): ^a: Minimal < Type 2; ^b: Type 1 < Type 2; ^c: Mixed < Type 2; ^d: Minimal < Type 1; ^e: Minimal < Mixed; ^f: Type 2 < Type 1; ^g: Type 2 < Mixed; ^h: Type 1 < Mixed; ⁱ: Type 1 < Minimal; ^j: Mixed < Minimal; ^k: Mixed < Type 1; ^l: Type 2 < Minimal

	Total patients <i>n</i> = 50	Minimal <i>n</i> = 39	Type-1 <i>n</i> = 37	Type-2 <i>n</i> = 9	Mixed <i>n</i> = 15	Total visits <i>n</i> = 100	p value
Cyclophosphamide	4 (8)	0 (0)	4 (10.8)	0 (0)	1 (6.7)	5 (5)	0.171
Azathioprine	14 (28)	14 (35.9)	11 (29.7)	5 (55.6)	6 (40)	36 (36)	0.526
Mycophenolate Mofetil	7 (14)	7 (17.9)	4 (10.8)	0 (0)	3 (20)	14 (14)	0.515
Physical functioning	80 [5-100]	95 [60-100]	90 [28-100]	60 [10-90]	45 [5-85]	85 [5-100]	< 0.001 ^{f,j,k,l}
Social functioning	63 [0-100]	75 [50-100]	63 [25-100]	38 [0-75]	50 [13-88]	63 [0-100]	< 0.001 ^{f,j,k,l}
Role physical	75 [0-100]	100 [0-100]	100 [0-100]	25 [0-100]	0 [0-100]	100 [0-100]	< 0.001 ^{f,j,k,l}
Role emotional	100 [0-100]	100 [0-100]	100 [0-100]	0 [0-100]	33 [0-100]	100 [0-100]	0.003 ^{f,j,l}
Mental health	60 [24-96]	64 [28-92]	64 [28-88]	40 [28-80]	44 [24-96]	60 [24-96]	0.014 ^l
Vitality	45 [0-90]	55 [15-100]	50 [30-100]	30 [10-45]	25 [0-55]	48 [0-100]	< 0.001 ^{f,j,k,l}

Values shown are median [IQR], or *n* (%).

SLE: systemic lupus erythematosus; Hb: haemoglobin.

p value: comparison between SLE subtypes (Kruskal Wallis test), significant pairwise comparisons (Tukey test): ^a: Minimal < Type 2; ^b: Type 1 < Type 2; ^c: Mixed < Type 2; ^d: Minimal < Type 1; ^e: Minimal < Mixed; ^f: Type 2 < Type 1; ^g: Type 2 < Mixed; ^h: Type 1 < Mixed; ⁱ: Type 1 < Minimal; ^j: Mixed < Minimal; ^k: Mixed < Type 1; ^l: Type 2 < Minimal

	Total patients <i>n</i> = 50	Minimal <i>n</i> = 39	Type-1 <i>n</i> = 37	Type-2 <i>n</i> = 9	Mixed <i>n</i> = 15	Total visits <i>n</i> = 100	p value
Bodily pain	61 [0–100]	84 [22–100]	62 [22–100]	32 [0–74]	41 [0–52]	62 [0–100]	< 0.001 ^{f,j,k,l}
General health	54 [10–100]	57 [32–100]	57 [25–82]	25 [15–55]	25 [10–77]	54 [10–100]	< 0.001 ^{f,j,k,l}
Physical component summary	47 [16–65]	52 [42–65]	50 [30–62]	36 [23–43]	30 [16–40]	48 [16–65]	< 0.001 ^{f,j,k,l}
Mental component summary	43 [19–60]	46 [25–59]	45 [19–59]	36 [20–43]	40 [22–60]	43 [19–60]	0.008 ^{f,j,k,l}
Type 2 score	6 [0–31]	4 [0–13]	4 [0–14]	18 [15–31]	20 [15–31]	6 [0–31]	< 0.001 ^{a,b,e,h}
Values shown are median [IQR], or <i>n</i> (%).							
SLE: systemic lupus erythematosus; Hb: haemoglobin.							
p value: comparison between SLE subtypes (Kruskal Wallis test), significant pairwise comparisons (Tukey test): ^a : Minimal < Type 2; ^b : Type 1 < Type 2; ^c : Mixed < Type 2; ^d : Minimal < Type 1; ^e : Minimal < Mixed; ^f : Type 2 < Type 1; ^g : Type 2 < Mixed; ^h : Type 1 < Mixed; ⁱ : Type 1 < Minimal; ^j : Mixed < Minimal; ^k : Mixed < Type 1; ^l : Type 2 < Minimal							

Clinical groups and immunological activity

Immunological activity (elevated anti-dsDNA antibodies, anti-dsDNA level, low C3 and/or C4) did not differ between the four clinical groups (Table 3).

Clinical groups and transcriptomic signatures

Modular IFN score, number of activated IFN modules and level of regulation of each IFN module did not differ between the four clinical groups (Table 4). In the analyses of all modules, the values of two modules (M3.3, cell cycle signature, and M4.14, monocyte signature) were slightly higher in patients in the “mixed” group compared to other groups, but these modules were not significantly activated (Supplementary Tables S1 and S2).

Table 4
Blood modular IFN signature and SLE clinical groups.

	Minimal <i>(n = 39)</i>	Type 1 <i>(n = 37)</i>	Type 2 <i>(n = 9)</i>	Mixed <i>(n = 15)</i>	Total <i>(n = 100)</i>	p value
IFN signature						0.747
Absent	6 (15.4)	6 (16.2)	1 (11.1)	1 (6.7)	14 (14)	
Mild	3 (7.7)	7 (18.9)	1 (11.1)	2 (13.3)	13 (13)	
Moderate	22 (56.4)	14 (37.8)	6 (66.7)	6 (40.0)	48 (48)	
Strong	8 (20.5)	10 (27.0)	1 (11.1)	6 (40.0)	25 (25)	
IFN modules						
M1.2	33 (84.6)	31 (83.8)	8 (88.9)	14 (93.3)	86 (86)	0.918
M3.4	30 (76.9)	24 (64.9)	7 (77.8)	12 (80.0)	73 (73)	0.611
M5.12	8 (20.5)	10 (27.0)	1 (11.1)	6 (40.0)	25 (25)	0.396
IFN modules						
M1.2	69.4 [-22.2-92]	69 [-11.1-88.9]	69.4 [-8.3-91.7]	77.8 [0-88.9]	69.4 [-22.2-92]	0.337
M3.4	38.7 [-6.5-79]	31 [-1.6-75.8]	37.1 [-4.8-71]	50 [0-69.4]	38.7 [-6.5-79]	0.255
M5.12	6 [-2-65]	8 [-2-76]	5 [0-62]	19 [0-62]	6 [-2-65]	0.175
Values shown are median [IQR], or n (%)						
p value: comparison between SLE subtypes using Kruskal-Wallis test and Fisher's exact test.						

Discussion

This is the first study using items from the SF-36 to assess the ability of a type 2 score to categorize SLE patients according to the presence of symptoms of fatigue, widespread pain and depression. Using the SLEDAI score to define type 1 symptoms, SLE patients from the LUPUCE cohort were categorized into the four groups defined by Duke University, with a similar patient distribution. The differences between these groups were then explored and apart from clinical differences, no significant immunological or transcriptomic profiles associated with the categories were found.

The initial definition of type 2 symptoms relied on the ACR fibromyalgia criteria (12). Although these criteria are likely to reflect type 2 symptoms accurately, they are rarely available in clinical trials and in historical SLE cohorts. In contrast, SF-36 is widely used to assess HRQoL in SLE (3), as in many chronic diseases (18), and an item-level analysis has been shown to be useful to interpret HRQoL variations in SLE patients (17). We chose to select the most relevant items from the SF-36 questionnaire to define type 2 symptoms and build a score that was easy to use in other cohorts. The values of the type 2 score observed in the LUPUCE cohort were very similar to those from an independent cohort of SLE patients, the PSY-LUP cohort. In addition, the proportions of patients categorized into each of the four clinical groups using the SLEDAI and the type 2 score were almost the same in the LUPUCE cohort and in the cohort described by Duke University. This constitutes an external validation of the SF-36-derived type 2 score and could allow standardization of the clinical categorization of SLE patients into different cohorts. Until now, the clinical segregation of SLE patients was heterogeneous between different studies. Before the first description of type 1/type 2 symptoms by Duke University (10), some studies described SLE patients with active/inactive disease and high/low fatigue (7) and found quite similar proportions as with the type 1/type 2 categorization (19).

Interestingly, as in the cohort from Duke University, no significant difference was observed between the immunological profiles of the four clinical groups. This highlights the fact that categorization into these four clinical groups, instead of providing redundant information, is a complimentary tool for the care of SLE patients and for patient stratification in clinical trials. Patients with type 2 symptoms, regardless of clinical activity, are likely to report higher activity levels than that evaluated by physicians, which can result in discordant measures (10) challenging the interpretation of clinical trial results.

This is the first study to investigate the association between transcriptional signatures, particularly IFN signature, and clinical type 1/type 2 SLE categorization. We could have expected a higher IFN signature in patients with active SLE (type 1 and mixed groups). However, there was no significant difference in IFN signatures between patients with active SLE and patients with inactive SLE. Alternatively, we could also have expected higher IFN signatures in patients reporting fatigue (type 2 group). Indeed, IFN signature was elevated in patients with fibromyalgia (20, 21), and therapeutic IFN is associated with neuropsychiatric side-effects such as fatigue and depression (22). In contrast, we have previously shown a paradoxical association between HRQoL and IFN signatures, patients with higher IFN scores displaying better HRQoL in some SF-36 domains (mental health and vitality) (14). However here, although a majority of patients from the type 2 group had a moderate IFN score, no significant difference was observed with the other groups. This is consistent with the report of an absence of correlation between pro-inflammatory cytokines (including IFN) and HRQoL in SLE patients (23). The same has been observed in patients with primary Sjögren syndrome in whom there was no correlation between IFN signature and HRQoL/fatigue (24). Thus, the IFN signature, as an immunological marker, is not relevant to discriminate type 1 from type 2 profiles.

Our study has some limitations. First, we used items from the SF-36 questionnaire to assess fatigue and depression, and not more specific questionnaires dedicated to SLE patients (such as SLEQOL, LIT, L-QOL,

LupusQOL, LupusPRO) (25). However, the SF-36 has been used for a long time and more widely than specific scales and it is well validated in SLE (26) and widely available, even retrospectively, in SLE cohorts. Second, the limited number of patients could lead to a loss of power after the division of the cohort into the four clinical groups. New studies with larger populations are therefore needed to confirm our results. Cohorts such as the LUPUCE cohort, providing well-characterized clinical, immunological, transcriptomic and HRQoL data, are very much needed.

Conclusion

A score derived from the SF-36 can be used to identify SLE patients with type 2 symptoms, and, with the use of the SLEDAI, to categorize patients into four clinical groups. This categorization, which is not related to immunological activity or blood transcriptomic profiles, could be useful in the daily care of patients, as well as in clinical trials, for the upstream stratification of patients and for the interpretation of results.

List Of Abbreviations

ACR: American College of Rheumatology

HRQoL: health-related quality of life

IFN: interferon

SF-36: 36-item short form survey

SLE: systemic lupus erythematosus

SLEDAI: SLE disease activity index

Declarations

Ethics approval and consent to participate

This study involved data from patients included in the LUPUCE study (NCT00920114) and the PSY-LUP study (NCT03913754). All patients gave their written informed consent before any study-related procedure. The study was conducted according to the Declaration of Helsinki. The LUPUCE study was approved in France by the Comité de Protection des Personnes Sud Méditerranée 1 (IDRCB 2009-A00257-50) and in the USA by the Institutional Review Boards (IRBs) of the Baylor Institute of Immunology Research (IRB 011–173) and the Benaroya Research Institute (IRB 12085). The PSY-LUP study was approved by the Comité de Protection des Personnes Ile de France I (IDRCB A02747-48).

Availability of data and materials

Transcriptomic data from the LUPUCE study are deposited in the NCBI Gene Expression Omnibus (GEO, <http://www.ncbi.nlm.nih.gov/geo>, GEO Series accession number GSE49454). The analyses performed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

R.A., L.C. and N.J.-C. elaborated the type 2 score. E.J. performed the analyses and made the tables and figure. All authors discussed and interpreted the results. R.A. wrote the first draft of the manuscript. L.C. and N.J.-C. corrected the manuscript. All authors approved the final version of the manuscript and agreed to its publication.

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Figures

Figure 1

Distribution of type 2 scores in the LUPUCE and PSY-LUP cohorts.

Supplementary Files

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- [LUPUCEType1Type2modulesSupplementaryTables.docx](#)