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# openheart Heterogeneity of right ventricular echocardiographic parameters in systemic lupus erythematosus among four clinical subgroups, as stratified by clinical organ involvement in observational cohort

Corentin Bourg <sup>1,2</sup>, Erwan Le Tallec,<sup>3</sup> Elizabeth Curtis,<sup>1</sup> Charlotte Lee,<sup>4</sup> Guillaume Bouzille,<sup>2</sup> Emmanuel Oger,<sup>5</sup> Alain Lescort,<sup>3,6</sup> Erwan Donal <sup>1,2</sup>

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For numbered affiliations see end of article.

**Correspondence to**  
Dr Erwan Donal; erwan.donal@chu-rennes.fr

## ABSTRACT

**Background** Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Cardiac involvement in SLE is rare but plays an important prognostic role. The degree of cardiac involvement according to SLE subsets defined by non-cardiac manifestations is unknown. The objective of this study was to identify differences in transthoracic echocardiography (TTE) parameters associated with different SLE subgroups.

**Methods** One hundred eighty-one patients who fulfilled the 2019 American College of Rheumatology/EULAR classification criteria for SLE and underwent baseline TTE were included in this cross-sectional study. We defined four subsets of SLE based on the predominant clinical manifestations. A multivariate multinomial regression analysis was performed to determine whether TTE parameters differed between groups.

**Results** Four clinical subsets were defined according to non-cardiac clinical manifestations: group A (n=37 patients) showed features of mixed connective tissue disease, group B (n=76 patients) had primarily cutaneous involvement, group C (n=18) exhibited prominent serositis and group D (n=50) had severe, multi-organ involvement, including notable renal disease. Forty TTE parameters were assessed between groups. Per multivariate multinomial regression analysis, there were statistically significant differences in early diastolic tricuspid annular velocity (RV-Ea,  $p<0.0001$ ), RV S' wave ( $p=0.0031$ ) and RV end-diastolic diameter ( $p=0.0419$ ) between the groups. Group B (primarily cutaneous involvement) had the lowest degree of RV dysfunction.

**Conclusion** When defining clinical phenotypes of SLE based on organ involvement, we found four distinct subgroups which showed notable differences in RV function on TTE. Risk-stratifying patients by clinical phenotype could help better tailor cardiac follow-up in this population.

## INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous connective tissue disease

### WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Systemic lupus erythematosus is a heterogeneous connective tissue disease.
- ⇒ Cardiac involvement plays a role in patient prognostication.

### WHAT THIS STUDY ADDS

- ⇒ Four subsets of patients were defined based on clinical manifestations.
- ⇒ Transthoracic echocardiography parameters were compared among these different subsets.
- ⇒ Subtle differences in right heart function and diastolic function were identified.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ Patients with visceral organ involvement should have closer cardiology follow-up.
- ⇒ Right heart morphology and function should be of interest in this disease.

which can involve almost all organ systems. Although dermatological, haematological, renal, musculoskeletal and nervous manifestations of SLE are most common, cardiovascular disease is an underappreciated manifestation of the disease. In France, the prevalence of SLE is 50 per 100 000, and females are predominately affected (9:1 female-to-male ratio).<sup>1</sup> Currently, the diagnosis of SLE is based on clinical, biological and immunological criteria per 2019 American College of Rheumatology (ACR)/EULAR guidelines.<sup>2</sup> However, given the clinical heterogeneity of SLE, additional subgrouping may help identify subsets of patients who are more likely to develop cardiac involvement. Although there is currently no validated subgrouping

of SLE, recent studies have shown that certain phenotypes may be associated with more significant organ involvement.<sup>3 4</sup>

Stratifying risk categories holds important prognostic significance, as cardiovascular disease is the leading cause of morbidity and mortality in patients with SLE. Cardiac involvement occurs in up to 50% of patients and most commonly involves the pericardium.<sup>5</sup> However, SLE can affect nearly every part of the heart, and less common manifestations include conduction system disease, valvular heart disease (Libman-Sacks endocarditis), coronary artery disease and myocardial dysfunction.<sup>6</sup> When present, coronary artery disease is directly linked to chronic SLE-related inflammation and impacts prognosis, highlighting the need for cardiac surveillance and risk factor modification, even in patients with optimal control of SLE activity.<sup>7-9</sup> In addition, recent data from patients with connective tissue disease suggest that diastolic dysfunction is more frequent than in the general population and is associated with poor survival.<sup>10</sup> Other markers of cardiac involvement, such as reductions in global longitudinal strain (GLS) or right ventricular systolic function, may also indicate a poorer prognosis.<sup>11 12</sup>

Given these potential implications, cardiac evaluation via transthoracic echocardiography (TTE) is typically performed at the time of SLE diagnosis and allows for thorough assessment of cardiac structure, systolic and diastolic function, pericardial involvement and valvular lesions. However, beyond baseline TTE, the management and surveillance of SLE-related cardiovascular disease remains to be determined.<sup>13-15</sup>

Moreover, there exist very few studies correlating the SLE subgroups (as defined by non-cardiac parameters) with TTE parameters. Elucidating the SLE subgroups more likely to suffer from specific cardiac manifestations may help target patients for more intensive disease control and cardiovascular follow-up. Therefore, the aim of this study was to identify the TTE parameters that can compare cardiac involvement among subgroups of patients with SLE defined by clinical manifestations in a population of patients fulfilling the updated 2019 ACR/EULAR classification criteria for SLE.

## METHODS

### Study population

We retrospectively studied 181 patients carrying a diagnosis of SLE who were either seen in clinic or admitted to medicine services at Rennes University Hospital between 2006 and 2020. We used the hospital's electronic medical record and data warehouse software (eHOP)<sup>16</sup> to identify 288 patients with a confirmed diagnosis of SLE per ACR/EULAR 2019 criteria. Among the 288 patients, we excluded patients who were under 18 years of age, as well as those without TTE, giving a final sample size of 181 patients.

### Clinical data

Among the 181 patients, we recorded the following parameters at the time of the first TTE: SLE clinical manifestations, SLE autoantibodies, SLE duration, SLE Disease Activity Index score and current or past disease-modifying medications. Demographic information including age, comorbidities, body mass index and factors leading to SLE diagnosis were also recorded.

### Echocardiography

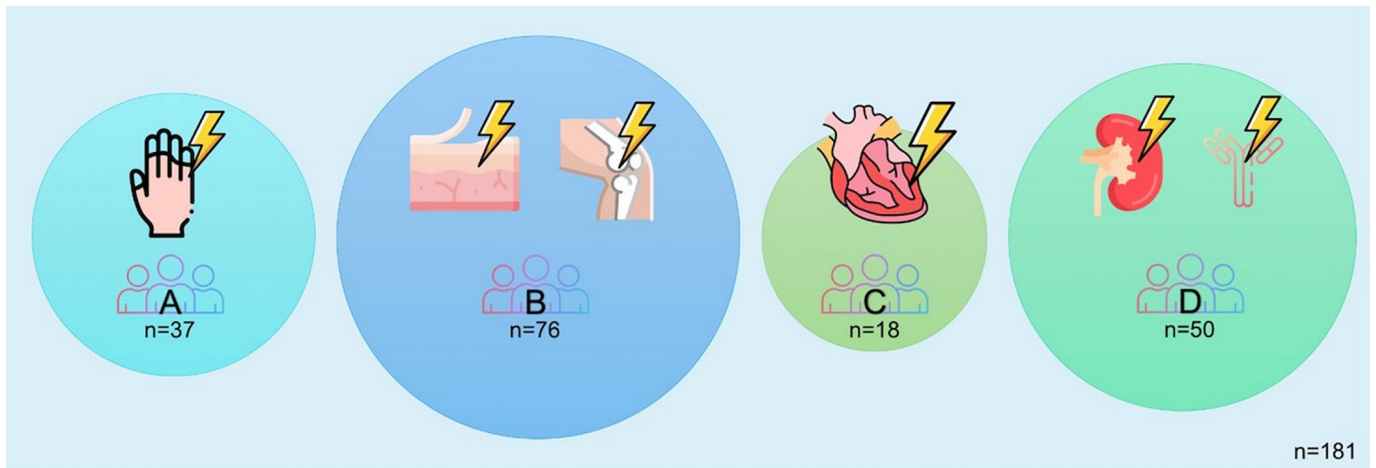
For the purposes of analysis, we reviewed the first available TTE on file for each patient. All TTEs were performed using a Vivid E9 or E95 ultrasound system with M5Sc transducers (GE Healthcare, Horten, Norway). Images were digitally stored in ViewPoint and analysed with EchoPAC v202 (GE Healthcare). A single, blinded physician (CB) was responsible for reviewing all TTE according to current guidelines.<sup>17 18</sup>

Left ventricular (LV) systolic function was assessed by biplane ejection fraction (LVEF) and by GLS based on four-chamber, two-chamber and three-chamber views at a frame rate  $\geq 60$  frames per second. LV diastolic function was evaluated using mitral E wave, A wave, e' septal and lateral velocities according to current guidelines.<sup>18</sup> Left and right atrial volumes were measured using the disk-method and indexed to surface body area. Right heart evaluation was performed on dedicated views to obtain end-diastolic basal and mid-diameters of the right ventricle (RV), the RV fractional area change (FAC), systolic S' velocity of tricuspid annulus (tricuspid S' wave) by Doppler tissue imaging and tricuspid annular plane systolic excursion (TAPSE) using M-mode. Peak systolic velocity of tricuspid regurgitation was measured by continuous-wave Doppler. Mitral and aortic regurgitation were characterised as no regurgitation (0), mild (1), moderate (2), severe (3). Aortic stenosis was described using peak velocity, mean pressure gradient and aortic valve area. Pericardial effusion was reported as present or absent.

### Statistical analysis

Based on the most frequently observed clinical characteristics and then the most frequently observed combinations of those characteristics, we defined four clinical SLE subgroups by the logistic procedure (SAS System). Patients were grouped by clinical symptoms rather than by autoantibodies given that the presence of autoantibodies does not always correspond with disease pleiotropy. Within these four clinically defined subgroups, patients with  $>15\%$  of TTE missing data were excluded. We then checked multicollinearity and excluded seven echo parameters. For the remaining 40 echo parameters, we generated 5 datasets with imputed missing values (Monte-Carlo Markov Chain).

Considering that levels of the response variable had no essential ordering, we performed a logistic regression on the generalised logits. Three logits were modelled using one level as the reference category. A multivariable model



**Figure 1** Graphical description of the four clinical subgroups of systemic lupus erythematosus established and analysed in the present study.

was fitted with all echo parameters associated with the response variable in univariate analysis at a 0.20 significance threshold. A backward elimination procedure retained only parameters with a Wald  $\chi^2$  test  $<0.05$ . For clarity purpose, we provided adjusted least-square means for those selected parameters. For pairwise comparisons across the four-level response variable, we used the false discovery rate method to adjust for multiple comparisons.

## RESULTS

### Clinical subsets defined by non-cardiac manifestations

Among the 181 patients included in this study, there were 25 (13.8%) men and 156 (86.2%) women. Analysis of the most frequently observed clinical findings and the most frequently observed combinations of these findings resulted in the creation of four key groups: those with predominance of Raynaud's phenomenon (group A), those with predominant cutaneous manifestations and arthralgias (group B), those with predominant pericarditis (group C) and those with predominant lupus nephritis and autoantibodies (group D) (figure 1, table 1).

Patients in group A (n=37) had the highest rate of Raynaud's phenomenon (n=26 patients, 70.3%) relative to the other groups (between 38.9% and 47.4%) prevalence. These patients also had more features corresponding with mixed connective tissue disease, such as arthralgias (36 patients, 97.3%) and anti-RNP antibodies (18 patients, 48.6%). Compared with other groups, they were less likely to have anti-DNA and anti-Smith antibodies (p=0.06 and p=0.004, respectively) (table 1).

Patients in group B (n=76) had high rates of cutaneous involvement (n=76, patients, 100%), including a greater prevalence of photosensitivity (n=56, 73.7%) and malar rash (n=35, 46.0%). Arthralgia with or without synovitis was also more frequent (n=70, 92.1%). Additionally, there were high rates of Sjögren syndrome-related features in this group (43% patients had xerostomia, 35% had xerophthalmia and 47% were positive for anti-SSA/SSB

autoantibodies). On the contrary, patients in group B had less frequent involvement of other organs, including less frequent serositis (pericarditis or pleural effusion) (table 1).

Patients in group C (n=18) were mostly defined by high rates of serositis (n=18, 100%), including pericarditis (n=12, 66.7%) and pleural effusions (n=11, 61.1%) (table 1).

Patients in group D (n=50) had the highest rates of multi-organ involvement, including the highest rates of cutaneous involvement (n=50, 100.0%), pericarditis (n=38, 76.0%), lymphadenopathy (n=26, 52.0%), thrombotic thrombocytopenic purpura (n=13, 26.0%), central nervous system involvement (n=12, 24.0%) and myocarditis (n=4, 8.0%). Additionally, they also had the second highest rate of proteinuria (n=23, 46.5%). Regarding antibodies, patients in group D had the highest percentage of anti-DNA (n=43, 86.0%), anti-Smith (n=17, 24.0%) and anti-SSA/SSB (n=33, 66.0%) antibodies (table 1).

### TTE parameters among groups A, B, C and D

Among the 40 TTE parameters assessed, there were no statistically significant differences in the vast majority of LV and RV structural and functional indices. Notably, there were no differences in LV end-diastolic diameter, LV end-diastolic volume, LVEF, LV GLS or cardiac output (p>0.05 each). Additionally, mean LVEF was preserved (>55%) in all four groups. Regarding right heart indices, there were no significant differences in RV basal and mid-cavitary diameters, RV FAC or tricuspid S' (p>0.05 each, table 2). Although TAPSE differs significantly between the groups (p=0.022), the differences in TAPSE were clinically insignificant (median TAPSE values all >20 mm) (table 2).

Regarding valves, there were no significant differences in the rates of tricuspid regurgitation, mitral regurgitation or aortic regurgitation or stenosis (p>0.05 each). Additionally, when defining pulmonary hypertension based on a tricuspid regurgitation maximum velocity

**Table 1** Demographic, clinical and laboratory characteristics across the four clinical subgroups of SLE

Variable	Group A (Raynaud-predominant) (n=37)	Group B (skin/arthritis-predominant) (n=76)	Group C (serositis-predominant) (n=18)	Group D (multi-organ-predominant) (n=50)	P value*
Male sex	8 (21.6%)	5 (6.6%)	3 (16.7%)	9 (18.0%)	0.1071
Age at symptom onset (years)	35.7±14.6	26.8±11.2	38.6±19.2	30.6±14.9	<b>0.0012</b>
Age at SLE diagnosis (years)	39.2±15.6	28.7±11.6	40.9±19.3	32.3±15.0	<b>0.0004</b>
Ethnicity†					
Caucasian	28 (75.7%)	57 (75.0%)	11 (61.1%)	35 (70.0%)	<b>0.0486</b>
Black	6 (16.2%)	5 (6.6%)	1 (5.6%)	8 (16.0%)	
Arab	2 (5.4%)	4 (5.3%)	1 (5.6%)	3 (6.0%)	
African-American	0 (0%)	3 (3.9%)	4 (22.2%)	0 (0%)	
Asian	0 (0%)	5 (6.6%)	1 (5.6%)	4 (8.0%)	
SLEDAI at SLE diagnosis	9.2±6.6	11.6±6.8	10.1±4.1	10.3±5.7	0.5092
SLEDAI-2	7.6±6.3	9.5±6.8	8.5±4.3	9.4±6.4	0.5238
Arthritis	36 (97.3%)	70 (92.1%)	18 (100.0%)	43 (86.0%)	0.1342
Synovitis	10 (27.0%)	15 (19.7%)	7 (38.9%)	12 (24.0%)	0.3773
Cutaneous manifestations	0 (0%)	100 (76)	0 (0%)	50 (100.0%)	<b>&lt;0.0001</b>
Malar rash	0 (0%)	35 (46.0%)	0 (0%)	22 (44.0%)	<b>&lt;0.0001</b>
Photosensitivity	0 (0%)	56 (73.7%)	1 (5.6%)	30 (60.0%)	<b>&lt;0.0001</b>
Raynaud's phenomenon‡	26 (70.3%)	36 (47.4%)	7 (38.9%)	20 (40.0%)	<b>0.0284</b>
Serositis	0 (0%)	0 (0%)	18 (100.0%)	50 (100.0%)	<b>&lt;0.0001</b>
Pleural effusion	0 (0%)	0 (0%)	11 (61.1%)	28 (56.0%)	<b>&lt;0.0001</b>
Pericarditis	0 (0%)	0 (0%)	12 (66.7%)	38 (76.0%)	<b>&lt;0.0001</b>
Myocarditis	0 (0%)	1 (1.3%)	0 (0%)	4 (8.0%)	0.1218
Libman-Sacks endocarditis	1 (2.7%)	0 (0%)	0 (0%)	0 (0%)	0.2710
Pulmonary hypertension	3 (8.1%)	1 (1.3%)	2 (11.1%)	0 (0%)	0.0331
Renal involvement					
Proteinuria (>0.5g/24 hours)	5 (13.5%)	17 (22.4%)	9 (50.0%)	23 (46.0%)	<b>0.0008</b>
GN II	1 (2.7%)	0 (0%)	1 (5.6%)	2 (4.0%)	0.3296
GN III	1 (2.7%)	3 (3.9%)	1 (5.6%)	5 (10.0%)	0.4161
GN IV	0 (0%)	3 (3.9%)	1 (5.6%)	3 (6.0%)	0.5242
GN V	1 (2.7%)	3 (3.9%)	0 (0%)	7 (14.0%)	<b>0.0459</b>
Haematological manifestations					

Continued

Table 1 Continued

Variable	Group A (Raynaud-predominant) (n=37)	Group B (skin/arthralgia-predominant) (n=76)	Group C (serositis-predominant) (n=18)	Group D (multi-organ-predominant) (n=50)	P value*
Leukopenia	11 (29.7%)	23 (30.3%)	9 (50.0%)	19 (38.0%)	0.3666
Lymphopenia	10 (27.0%)	19 (25.0%)	9 (50.0%)	15 (30.0%)	0.2116
Thrombocytopenic purpura	7 (18.9%)	15 (19.7%)	3 (16.7%)	13 (26.0%)	0.7705
Autoimmune haemolytic anaemia	1 (2.7%)	10 (13.2%)	1 (5.6%)	2 (4.0%)	0.1362
Thrombotic microangiopathy	1 (2.7%)	4 (5.3%)	0 (0%)	2 (4.0%)	0.7387
Lymphadenopathy	7 (18.9%)	17 (22.4%)	6 (33.3%)	26 (52.0%)	<b>0.0017</b>
Macrophage activation syndrome	0 (0%)	1 (1.3%)	0 (0%)	7 (14.0%)	<b>0.0035</b>
Central neurological disease	1 (2.7%)	9 (11.8%)	1 (5.6%)	12 (24.0%)	<b>0.0215</b>
Peripheral neuropathy	1 (2.7%)	3 (3.9%)	0 (0%)	2 (4.0%)	0.8426
Xerostomia	12 (32.4%)	33 (43.4%)	5 (27.8%)	14 (28.0%)	0.2683
Xerophthalmia	8 (21.6%)	26 (34.2%)	5 (27.8%)	13 (26.0%)	0.5284
Antibodies					
Anti-dsDNA	23 (62.2%)	57 (75.0%)	15 (83.3%)	43 (86.0%)	0.0646
Anti-Smith	2 (5.4%)	12 (15.8%)	2 (11.1%)	17 (34.0%)	<b>0.0047</b>
Anti-RNP	18 (48.6%)	32 (42.1%)	9 (50.0%)	23 (46.0%)	0.8847
Antiphospholipid antibodies	16 (43.2%)	44 (57.9%)	12 (66.7%)	32 (64.0%)	0.2066
Anti-SSA/SSB	10 (27.0%)	36 (47.4%)	7 (38.9%)	33 (66.0%)	<b>0.0035</b>
Anti-Ku	0 (0%)	4 (5.3%)	2 (11.1%)	2 (4.0%)	0.2877
Low CH50	9 (24.3%)	36 (47.4%)	6 (33.3%)	24 (48.0%)	0.0738

Bold values denote significant difference.  
 \*P values derived from  $\chi^2$  tests or analyses of variance.  
 †Three missing values for ethnicity.  
 ‡One missing value for Raynaud's phenomenon.  
 dsDNA, double-stranded DNA; GN, glomerulonephritis; RNP, ribonucleoprotein; SLE, systemic lupus erythematosus; SLEDAI, SLE Disease Activity Index.

**Table 2** Baseline echocardiography parameters across the four clinical subgroups of SLE

Parameter	Group A (Raynaud-predominant) (n=37)	Group B (skin/arthritis-predominant) (n=76)	Group C (serositis-predominant) (n=18)	Group D (multi-organ-predominant) (n=50)	P value*
Heart rate (bpm)	74.8±11.1	74.9±11.9	79.3±11.7	78.6±14.4	0.2491
LA and LV geometry					
LA surface (cm <sup>2</sup> )	14.87±4.29	15.12±3.27	14.63±2.99	15.19±4.28	0.9391
LVEDD (mm)	44.93±5.41	45.82±4.47	45.26±8.78	44.82±4.48	0.7191
LVESD (mm)	30.72 (5.74)	32.03 (6.84)	30.83 (9.07)	31.40 (7.15)	0.3159
IVS (mm)	8.79±2.17	8.62±1.53	8.76±1.60	9.03±2.06	0.6765
LVPW (mm)	8.61±1.52	7.85±1.62	7.95±1.85	8.21±1.47	0.1101
LVOT (mm)	19.80 (2.21)	19.90 (1.84)	19.97 (2.11)	19.48 (1.70)	0.8958
Sinus of Valsalva (mm)	29.56±3.80	29.74±3.62	29.21±3.25	29.52±4.33	0.9574
RA and RV geometry					
RA indexed volume (mL/m <sup>2</sup> )	18.00 (7.00)	18.00 (6.50)	16.00 (9.00)	19.50 (8.00)	0.4008
RVIDD (mm)	21.15 (4.58)	20.95 (3.85)	21.08 (4.93)	20.53 (6.15)	0.9783
RV basal diameter (A4C) (mm)	35.87±6.10	34.39±4.80	32.25±4.05	35.76±5.90	0.0578
RV mid-cavity diameter (A4C) (mm)	30.56±5.86	29.32±5.08	28.11±3.50	29.61±5.55	0.4153
RV longitudinal dimension (A4C) (mm)	69.97 (15.69)	71.84 (10.92)	69.03 (6.02)	74.35 (9.05)	0.1782
RV end-systolic area (cm <sup>2</sup> )	9.60 (2.92)	8.93 (3.73)	8.48 (3.38)	9.10 (4.31)	0.3885
RV/LV basal ratio	0.68 (0.14)	0.64 (0.13)	0.70 (0.15)	0.63 (0.13)	0.2609
RV wall thickness (mm)	5.80 (1.62)	5.40 (1.56)	6.00 (2.20)	5.33 (1.60)	0.2123
LV systolic function					
LV EDV (biplane) (mL)	80.73±27.35	86.84±20.96	72.56±22.04	84.36±22.72	0.1018
LVEF (biplane) (%)	60.00 (13.00)	56.00 (12.00)	58.00 (10.00)	56.00 (11.00)	0.2389
2D LV GLS (%)	18.13±3.34	18.38±2.87	16.58±3.49	17.45±2.40	0.0716
LVOT VTI (cm)	22.78±3.94	21.45±3.76	21.31±4.58	21.46±3.68	0.3120
Cardiac output (L/min)	5.26±1.01	5.30±1.22	5.72±1.51	5.35±1.43	0.6137
LV diastolic function					
Mitral E-wave velocity (cm/s)	0.81±0.20	0.85±0.16	0.76±0.18	0.86±0.21	0.1779
Mitral E-wave deceleration time (ms)	180.0 (57.00)	177.5 (58.00)	155.5 (87.00)	175.0 (50.00)	0.4299
Mitral A-wave velocity (cm/s)	0.70 (0.20)	0.60 (0.22)	0.70 (0.10)	0.60 (0.30)	0.4601
Mitral E/A ratio	1.30 (0.70)	1.30 (0.60)	1.10 (0.40)	1.30 (0.70)	0.1274
Mitral average E/e'	6.23 (2.19)	5.97 (2.59)	7.27 (3.38)	6.19 (3.43)	0.3806

Continued

Table 2 Continued

Parameter	Group A (Raynaud-predominant) (n=37)	Group B (skin/arthralgia-predominant) (n=76)	Group C (serositis-predominant) (n=18)	Group D (multi-organ-predominant) (n=50)	P value*
Mitral septal S wave (cm/s)	8.20 (2.40)	8.60 (1.70)	8.30 (2.40)	8.05 (2.32)	0.7398
Mitral septal E' wave (cm/s)	10.82±4.21	11.52±3.12	8.95±2.49	11.30±4.18	0.0562
Mitral septal A' wave (cm/s)	10.00 (3.70)	9.59 (3.00)	10.58 (3.80)	9.40 (3.10)	0.0865
Mitral lateral S wave (cm/s)	9.20±2.36	9.42±2.30	9.14±2.32	9.20±2.36	0.9300
Mitral lateral E' wave (cm/s)	14.13±5.75	15.88±4.83	12.44±3.68	14.51±4.89	<b>0.0394</b>
Mitral lateral A' wave (cm/s)	10.60 (5.50)	9.50 (3.25)	10.50 (3.90)	9.10 (3.80)	0.2195
E' lateral/E' septal ratio	1.34±0.40	1.37±0.35	1.40±0.44	1.31±0.26	0.7340
RV systolic function					
RV FAC (%)	38.70±13.56	43.30±9.48	41.28±11.55	42.40±9.70	0.1919
TAPSE	22.00 (5.00)	23.00 (4.00)	20.00 (5.00)	22.00 (5.00)	<b>0.0222</b>
RV S' velocity (cm/s)	13.20 (3.60)	13.65 (2.55)	13.35 (3.60)	12.50 (2.80)	0.0709
RV diastolic function					
RV-Ea (cm/s)	12.79±3.80	14.96±3.78	10.05±3.35	12.54±4.19	<0.0001
Valvular function					
TR velocity (m/s)	2.30 (0.50)	2.20 (0.48)	2.20 (0.50)	2.24 (0.41)	0.3022
MR grade					
None (0)	64.86 (24)	68.42 (52)	55.56 (10)	50.00 (25)	0.4022
Mild (1)	32.43 (12)	28.95 (22)	33.33 (6)	44.00 (22)	
Moderate (2)	2.70 (1)	2.63 (2)	11.11 (2)	4.00 (2)	
Severe (3)	–	–	–	2.00 (1)	
AR grade					
None (0)	83.78 (31)	97.37 (74)	100 (18)	92.00 (46)	0.1296
Mild (1)	10.81 (4)	2.63 (2)	–	4.00 (2)	
Moderate (2)	5.41 (2)	–	–	4.00 (2)	
Pericarditis	5.41 (2)	1.32 (1)	22.22 (4)	14.00 (7)	<b>0.0060</b>

P values are mean±SD or median (IQR); p values from analysis of variance (F-test or Kruskal-Wallis test). EDT, E-wave deceleration time; LV EDV, left ventricle end-diastole volume; RV FAC, right ventricle fractional area change; GLS, global longitudinal strain; IVS, interventricular septum; LA, left atrium; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricle ejection fraction; LVESD, left ventricular end-systolic diameter; LVOT, left ventricular outflow tract; LVPW, left ventricle posterior wall; RA, right atrium; RV, right ventricle; RVIDd, right ventricular internal dimension diastole; SLE, systemic lupus erythematosus; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VTI, velocity-time integral.



**Table 3** Pairwise comparisons across four clinical subgroups of SLE, adjusted for multiple comparisons, with significant values highlighted in yellow

	Group B	Group C	Group D
Group A	RV-Ea (p=0.009) RVEDD (NS) RV S' wave (NS)	RV-Ea (p=0.035) RVEDD (p=0.035) RV S' wave (NS)	RV-Ea (NS) RVEDD (NS) RV S' wave (p=0.019)
Group B	RV-Ea (NS) RVEDD (NS) RV S' wave (NS)	RV-Ea (p=0.002) RVEDD (NS) RV S' wave (p=0.022)	RV-Ea (NS) RVEDD (NS) RV S' wave (NS)
Group C	RV-Ea (NS) RVEDD (NS) RV S' wave (NS)	RV-Ea (NS) RVEDD (NS) RV S' wave (NS)	RV-Ea (p=0.003) RVEDD (p=0.022) RV S' wave (p=0.005)

NS, not significant; RV, right ventricle; RV-Ea, early diastolic tricuspid annular velocity; RVEDD, RV end-diastolic diameter; SLE, systemic lupus erythematosus.

>2.8 m/s, there was no pulmonary hypertension across the four groups.

Overall, group C (serositis-predominant group) had the highest prevalence of cardiac involvement, as defined by a greater prevalence of pericardial effusion (n=4, 22.2%) and altered TTE parameters. When compared with other groups, median TAPSE, mean mitral lateral E' wave and mean RV-Ea were lower in group C (20 mm, 12.44 cm/s and 10.05 cm/s, respectively) (p<0.05 each). Mean 2D GLS was also lower in group C (-16.58±3.49%), however, this did not reach statistical significance (p=0.072, table 2).

Multivariate, multinomial regression revealed three echocardiographic parameters which differed among the four groups: early diastolic tricuspid annular velocity (RV-Ea, p<0.0001), RV S' wave (p=0.0031) and RV end-diastolic diameter (RVEDD) (p=0.0419). Table 3 is created to demonstrate pairwise comparisons among the above parameters (RV-Ea, RVEDD and RV S' wave) across the three groups. Notably, group C exhibited the

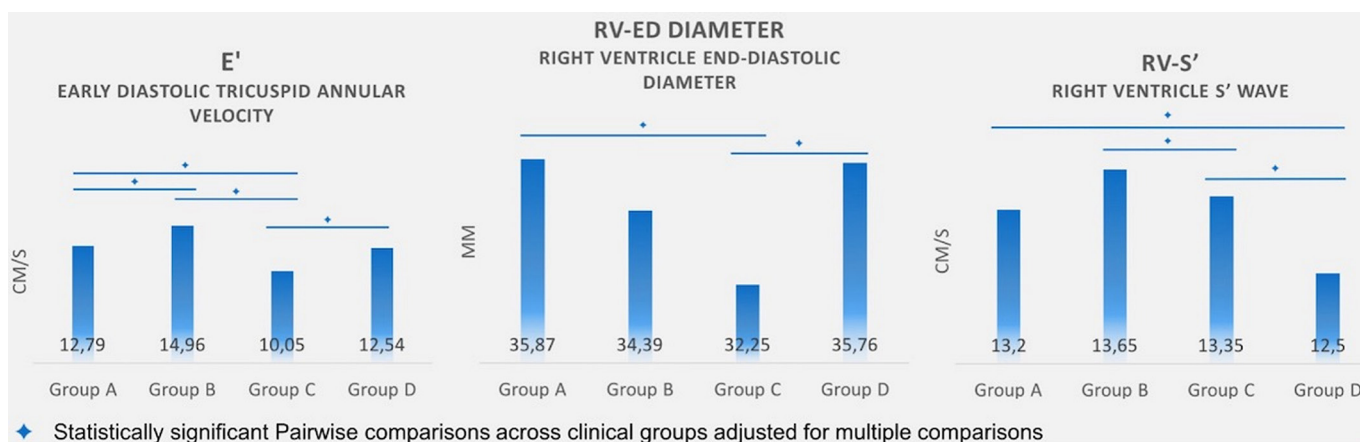
lowest values for each of the three variables (p<0.05 each, table 3, figure 2).

## DISCUSSION

SLE is a heterogenous autoimmune disease affecting multiple organ systems, including the cardiovascular system. Although to date, there is no validated subclassification of the disease based on clinical phenotypes, we demonstrated that our study population (n=181 patients) could successfully be divided into four clinical cohorts. In statistical analysis, group A was characterised by prominent Raynaud's phenomenon, group B was characterised by cutaneous and musculoskeletal involvement, group C was characterised by prominent serositis and group D was characterised by prominent multi-organ involvement (notably renal disease and high rates of corresponding antidouble-stranded DNA antibodies). In multivariate analysis, we subsequently found that group C (serositis group) was statistically more likely to develop cardiac involvement.

These results are of utmost importance, as there is currently no literature to suggest which patients with SLE are most likely to develop cardiac manifestations. Nonetheless, pericardial involvement is a highly prevalent disease manifestation, described in up to 50% of autopsy series and up to 25% of clinical series.<sup>5</sup> In our cohort of n=181 patients with SLE, the rate of pericardial involvement was 27%, which is consistent with this literature.

Moreover, as demonstrated by Sade and Akdogan and Mavrogeni *et al*, the evidence regarding the intensity of cardiac screening and surveillance in patients with SLE is not well defined.<sup>19,20</sup> It is well known that chronic inflammation, antiphospholipid antibodies, immune complex deposition, vasculitis, microvascular dysfunction and renal dysfunction all contribute to myocardial damage in SLE. These features may in turn provoke irreversible heart failure, ventricular arrhythmias and sudden cardiac death. Despite being subclinical most of the time, the development and progression of cardiac involvement is variable and unpredictable. We purport that dividing



**Figure 2** Transthoracic echocardiography (TTE) parameters demonstrating statistically significant differences among the four clinical subgroups of systemic lupus erythematosus.

patients into clinical subgroups may help combat this unpredictability, as groups C (serositis group) and D (multi-organ involvement group) had higher rates of pericardial effusion and altered TTE parameters.

More specifically, while not reaching the cutoffs for 'abnormal', we showed that group C had lower parameters for several indices of right heart systolic function (TAPSE) and diastolic function (RV-Ea and RVEDD) when compared with other groups. Interestingly, group C also had smaller RV basal and mid-cavitary diameters ( $32.35 \pm 4.05$  and  $28.11 \pm 3.50$  mm, respectively). While not pathological, and all groups remained within the normal range, it is unclear what this signifies. Regarding other RV systolic functional indices, group D had the lowest mean RV S', which could indicate early RV systolic dysfunction. Among left heart functional indices, group C had the lowest and group D had the second lowest mean GLS ( $16.58 \pm 3.49\%$  and  $-17.45 \pm 2.40\%$ ,  $p=0.07$ ). With a larger number of patients, it is likely this result would become statistically significant and would become of clinical interest, as GLS can be used to detect subclinical LV dysfunction. Moreover, these results corroborate prior studies demonstrating lower GLS in patients with SLE.<sup>11 21</sup>

Just as a decrease in GLS may be a marker of interest in this population, a lower GLS may be explained by pericardial damage resulting in impaired diastolic filling and compliance. This is observed with a statistically significant alteration in mitral lateral E' wave compared with the other groups. Mitral septal E' wave also showed a tendency to decrease compared with the other groups, but this was not statistically significant. Also, the ratio between these two parameters (E' lateral/E' septal) was slightly higher in group C, which may reflect lower compliance and therefore predominant pericardial damage in explaining the resulting dysfunction.

Taken together, these results suggest that patients with serositis-predominant SLE and/or diffuse SLE (with renal features) may have lower baseline functional indices, increasing their risk for future cardiac involvement. While recent studies<sup>3 4</sup> have demonstrated that patient outcomes depend on the clinical subgroup of SLE, this is the first study to approximate cardiac risk by correlating SLE subgroups with baseline TTE. Our findings that patients with the clinical phenotypes above (groups C and D) have lower baseline RV function and lower LV GLS are of key importance to cardiology and rheumatology communities. Clinicians who identify patients with these phenotypes can more appropriately recommend repeat cardiology follow-up (eg, serial TTE) and intensive SLE-specific therapy. Rather than suggesting cardiology follow-up in all patients, tailoring the degree of follow-up based on SLE phenotype would allow for better utilisation of time and resources.

To our knowledge, this is the first study to assess 40+ TTE parameters in SLE, which allowed us to determine the most relevant TTE parameters for the disease. Our findings suggest systolic RV function and diastolic RV

and LV function may be of unique importance. Although prior literature has demonstrated LV impairment in SLE, there are no studies which characterise RV function in patients with the disease.<sup>5 11 12</sup> Thorough analysis of the RV is a key message of our work, and this is physiologically justified by the prevalence of lung involvement of SLE, which impacts of RV afterload. Borlaug *et al*<sup>22</sup> have also demonstrated the importance of pulmonary pressures in patients with HFpEF.

There are several key limitations in our study. First, the sample size of our cohort was relatively small ( $n=181$  patients), and this was a single-centre analysis. However, our database was very complete with clinical, laboratory and imaging results, which led to accurate characterisation of our patients into clinical subsets. Second, we performed our cardiac evaluations using only TTE, and as such, we did not identify coronary artery disease despite the fact it occurs with higher frequency in patients with active SLE. Importantly, none of the patients in our cohort had signs or symptoms of coronary artery disease, and we did not observe silent ischaemia based on regional wall motion abnormalities on TTE.

Third, we retrospectively analysed SLE subgroups and TTE parameters in our patients. The four phenotypic groups that we purport must be validated, preferably in multicentric cohorts. Additionally, the correlation of SLE subgroups and TTE parameters with clinical outcomes must be validated in a prospective format. This would require long-term follow-up to assess which patient cohorts develop the highest rates of heart failure.

## CONCLUSION

Although SLE is a heterogenous disease with 'clustered' organ involvement, there are currently no validated schema to clinically subclassify patients with SLE. Based on non-cardiac manifestations, we defined four distinct SLE phenotypes and demonstrated differences in right heart function and diastolic function among each. In future guidelines, risk-stratifying patients with SLE based on clinical phenotype may help tailor the degree of recommended cardiology follow-up. Further studies are needed to describe the prognostic value of early TTE changes as they relate to the development of heart failure and patient survival.

### Author affiliations

<sup>1</sup>Department of Cardiology, CHU Rennes, Rennes, France

<sup>2</sup>Laboratoire du traitement du signal et de l'image LTSI, INSERM UMR 1099, Rennes, France

<sup>3</sup>Department of Internal Medicine and Clinical Immunology, University of Rennes 1, Rennes, France

<sup>4</sup>University of Pennsylvania, Philadelphia, Pennsylvania, USA

<sup>5</sup>EA Reperes, CHU Rennes, Rennes, France

<sup>6</sup>Irset (Institut de Recherche en Santé Environnement et Travail)—UMR\_S 1085, Rennes, France

X Charlotte Lee @kcharlottelee and Erwan Donal @DonalErwan

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#### ORCID iDs

Corentin Bourg <http://orcid.org/0000-0001-7074-4839>

Erwan Donal <http://orcid.org/0000-0003-2677-3389>

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