Heterogeneity of Echocardiographic Variables in Systemic Lupus Erythematosus among Clinical Subgroups according to Non-Cardiac Involvement

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Abstract

Background − Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Cardiac involvement is important due to its impact on survival. Transthoracic echocardiography (TTE) is a sensitive technique to assess cardiac structure and function. The degree of cardiac involvement according to SLE subsets defined by non-echocardiographical manifestations remains unknown. The objective of this study was to identify differences in TTE parameters associated with different SLE clinical subgroups. **Methods and Results** − One hundred and eighty-one patients fulfilling the ACR/EULAR 2019 classification criteria for SLE and who had undergone systematic TTE at least once were included in this cross-sectional study. The earliest available TTE from the date of diagnosis was considered the baseline TTE. We defined four subsets of SLE which was based on the predominant clinical manifestations. A multivariate multinomial regression analysis was performed to determine whether TTE parameters differ between the phenotypical subsets. The first subset (n = 37) of patients showed clinical features of mixed connective tissue disease (MCTD); the second subset (n = 76) had primarily cutaneous involvement; the third subset (n = 18) exhibited serositis; the last subset (n = 50) had severe disease with significant organ involvement, including renal involvement. Forty TTE parameters were assessed in all patients. Using a multivariate multinomial regression analysis, 3 parameters differed according to groups: RV-E'(early diastolic tricuspid annular velocity, p<0.0001), RV-S' (RV-pulse DTI systolic peak wave, p = 0.0031), and RV end-diastole diameter (p = 0.0419). **Conclusion** − SLE is an heterogeneous disease. Four distinct clinical subsets based on clinical manifestations differed in terms of TTE derived parameters of right heart dysfunction and diastolic dysfunction. This SLE heterogeneity in cardiac involvement could help to tailor the follow-up required for these patients.

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Data availability statement

The data behind the conclusion of this study are available from the correspinding author upon reasonable request.

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The authors report no conflicts of interest.

Ethics approval statement

This project was approved by the local ethics committee (Approval number 21.125) and complied with the French national requirements of the "Commission Nationale Informatique et Liberté (CNIL)".

Patient consent statement

As a retrospective study, the non-opposition of patients was systematically researched.

ABSTRACT

Background –

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disease. Cardiac involvement is important due to its impact on survival. Transthoracic echocardiography (TTE) is a sensitive technique to assess cardiac structure and function. The degree of cardiac involvement according to SLE subsets defined by non-echocardiographical manifestations remains unknown. The objective of this study was to identify differences in TTE parameters associated with different SLE clinical subgroups.

Methods and Results –One hundred and eighty-one patients fulfilling the ACR/EULAR 2019 classification criteria for SLE and who had undergone systematic TTE at least once were included in this cross-sectional study. The earliest available TTE from the date of diagnosis was considered the baseline TTE. We defined four subsets of SLE which was based on the predominant clinical manifestations. A multivariate multinomial regression analysis was performed to determine whether TTE parameters differ between the phenotypical subsets.

The first subset (n = 37) of patients showed clinical features of mixed connective tissue disease (MCTD); the second subset (n = 76) had primarily cutaneous involvement; the third subset (n = 18) exhibited serositis; the last subset (n = 50) had severe disease with significant organ involvement, including renal involvement. Forty TTE parameters were assessed in all patients. Using a multivariate multinomial regression analysis, 3 parameters differed according to groups: RV-E'(early diastolic tricuspid annular velocity, $p<0.0001$), RV-S' (RV-pulse DTI systolic peak wave, $p = 0.0031$), and RV end-diastole diameter ($p = 0.0419$).

Conclusion –

SLE is an heterogeneous disease. Four distinct clinical subsets based on clinical manifestations differed in terms of TTE derived parameters of right heart dysfunction and diastolic dysfunction. This SLE heterogeneity in cardiac involvement could help to tailor the follow-up required for these patients.

KEYWORDS: Systemic lupus erythematosus – Transthoracic echocardiography – Clustering analysis – Right ventricular function – Diastolic dysfunction

INTRODUCTION

Systemic lupus erythematosus (SLE) is a heterogeneous connective tissue disease that can affect almost all organ systems. In France, the prevalence of SLE is about 50 per 100.000 individuals and women are over-represented (sex ratio 9:1).[1] SLE has varying degrees of severity depending on the involved organ systems. The diagnosis is based on clinical, biological and immunological criteria. The updated 2019 ACR/EULAR classification criteria for SLE allow an earlier diagnosis of the disease.[2] Considering the disease heterogeneity, clinical subgrouping may help to identify subsets of patients with more severe disease. To date there is no validated subgrouping of SLE that carries prognostic value, however other studies have shown certain phenotypes to be associated with more significant organ involvement. [3,4]

Cardiovascular heart disease is a leading cause of morbidity and mortality in patients with SLE. Cardiac involvement can occur in up to 50% of patients with SLE. Any part of the heart can be involved but pericardial involvement is the most common and is included among the 2019 ACR/EULAR classification criteria.[5] Other cardiac manifestations of SLE include conduction disease, valvular heart disease (Libman-Sachs endocarditis)[6]. Coronary artery disease is directly linked to chronic SLE-related inflammation and is an important prognostic factor, highlighting the need for evaluation of cardiac involvement and monitoring of cardiovascular risk factors in SLE patients in combination with optimal control of disease activity.[7,8,9]

Recent data from patients with connective tissue disease suggests that diastolic dysfunction is more frequent than in the general population and is associated with poor survival.[10] Other markers of cardiac involvement such as impairment of global longitudinal strain (GLS) or reduction of right ventricular systolic function also indicate a poorer prognosis. [11,12]

Transthoracic echocardiography (TTE) is the cornerstone for assessment of cardiac structure and function, and can detect cardiac involvement such as pericarditis, systolic and diastolic dysfunction as well as valvular lesions.

Cardiac evaluation is recommended in all SLE patients at diagnosis but the optimal follow-up strategy of cardio-vascular involvement remains to be determined.[13,14,15]

Although SLE-related cardiac involvement has been well described, there are few studies exploring to correlate TTE parameters among subgroups of SLE patients defined by non-cardiac manifestations and fulfilling the recently updated classification criteria. Defining clinical subgroups of SLE patients with specific cardiac manifestations may help identify patients who may benefit from more intensive cardiovascular follow-up and suppression of SLE activity.

The aim of this study was to identify the TTE parameters that can compare cardiac involvement among subgroups of SLE patients defined by non-cardiac manifestations in a population of patients fulfilling the updated 2019 ACR/EULAR classification criteria for SLE.

METHODS

Study population –

Patients admitted to the hospital, seen in clinics, or attending daystay at the departments of Internal Medicine and Clinical Immunology with a diagnosis of SLE were identified. Clinical data were obtained from the hospital clinical data warehouse, eHOP software, which gathers medical and paramedical files, including medical reports from Rennes University Hospital, a tertiary academic center in France.[16] From a database of 288 patients with confirmed diagnosis of systemic lupus in accordance with the ACR/EULAR 2019

criteria, 181 patients who had undergone systematic TTE at least once were included in this retrospective cross-sectional study. Patients under 18 years of age were excluded. This study was approved by the local ethics committee (Approval number 21.125) and complied with the French national requirements of the "Commission Nationale Informatique et Liberté (CNIL)".

Clinical data –

The following parameters available at the time of first TTE were recorded: clinical manifestations, autoantibodies, SLE duration, activity with the SLEDAI score, and past/current medications. Patient sociodemographic characteristics, such as age at onset and diagnosis, gender, ethnicity, along with patient history, comorbidities, body mass index (BMI), and factors leading to the diagnosis of SLE, were also documented.

Echocardiography –

The first available echocardiography (TTE) was used for the analysis. All patients underwent standard TTE using a Vivid E9 or E95 with M5Sc transducers ultrasound system (GE Healthcare, Horten, Norway). Images were digitally stored in Viewpoint and analyzed with EchoPAC (version 202, GE healthcare, Horten, Norway). Blinded interpretation of echocardiograms were analysed by a same physician (C.B.) and reviewed according to current guidelines.[17,18] Left ventricular function was assessed by ejection fraction (LVEF) using the Simpson biplane method and global longitudinal strain (GLS) using the 4-, 2- and 3-chamber views at a frame rate [?] 60frame/s. Diastolic function was evaluated following the guidelines of Nagueh et al.[18]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, the right ventricle fractional area change, systolic S' velocity of tricuspid annulus (RV-S' wave) by Doppler tissue imaging and Tricuspid annular plane systolic excursion (TAPSE) using M-mode.[19] 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 a four-level response variable.

Among available echo parameters, we selected those with less than 15% of TTE missing data. We then checked multicollinearity and excluded seven echo parameters. For the remaining 40 echo parameters, we generated five 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 generalized logits. Three logits were modeled using one level as the reference category. A multivariable model 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-square 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. A matricial table was made to explain effects of each parameters and to display the association between echocardiographic parameters and subsets.

RESULTS

Clinical Subsets defined by non-cardiac manifestations:

Twenty-five men and 156 women were included in this study. Based on the most frequently observed clinical characteristics and then the most frequently observed combinations of those characteristics, four subsets were defined. (Table 1)

The first group (A group, n=37) showed a higher prevalence of Raynaud's phenomenon and had features

corresponding to patients with mixed connective tissue disease (MCTD), less likely to have anti-DNA and anti-Sm antibodies than in other groups (p=0.06, p=0.004, respectively)

The second group (B group, n=76) had the highest proportion of patients with cutaneous involvement (100% of patients have cutaneous manifestations), including a greater prevalence of photosensitivity and malar rash. Arthralgia with or without synovitis were also more frequent. Sjogren's syndrome-related features were also overrepresented as 43% of patients of this subset had xerostomia, 35% xeropthalmia and 47% were positive for antiSSA/SSB autoantibodies. On the contrary, those patients had less frequent other organ involvement, including less frequent serositis (pericarditis or pleural effusion).

The third group (C group, n=18) was mostly defined by a high proportion of serositis (100%), including pericarditis and pleural effusions. The age at onset and at diagnosis were later in this subset and with a greater range compared to other groups (respectively 38.6 +- 19.2 and 40.9 +- 19.3 years). The proportion of Caucasian subjects is lower and there were no patients with skin involvement or malar rash in this subgroup.

The fourth group (D group, n=50) tended to have the highest prevalence of organ involvement among all the groups, notably kidney involvement, along with more frequent anti-DNA and anti-Sm autoantibodies.

TTE parameters among the 4 clinical subsets:

Forty TTE parameters were assessed in univariate analysis (Table 2A&B) in all patients from the 4 subsets described above.

There were no statistical differences between the left and right ventricle measurements, including LVEF, Left Ventricle End-Diastolic Diameter (LVEDD), and cardiac output, among the four SLE patient groups.

The LVEF was preserved (50-60% in all groups), and there were no statistical difference between the group for the right ventricle systolic function (TAPSE and RV S' wave were in normal ranges). No pulmonary hypertension was observed based on the definition using a <2.8m/s cut-off for the velocity of tricuspid regurgitation.

There was no difference between the groups of incidence of mitral or aortic regurgitation nor aortic stenosis.

Group C had the highest prevalence of clinical cardiac involvement, according with a greater prevalence of pericardial effusion (22%) and altered TTE parameters. In univariate analysis, TAPSE, Mitral lateral E'-wave, and RV-E' were lower in comparison to others subsets, measuring 20 mm, 12.44 cm/s and 10,05 cm/s, respectively.

The GLS also showed a trend of being lower in group C (-16.58%) but this did not reach statistical significance.

The multivariate multinomial regression led to three echocardiographic parameters that differed among the four subsets: Early diastolic tricuspid annular velocity (RV E', p<0.0001), RV S' wave (p = 0.0031), and RV end-diastole diameter (p = 0.0419).

A matricial table was created to explain the effects of each parameter (RVED diameter, RV S', and RV E') using pairwise comparisons across subsets. Table 3 displays the association between echocardiographic parameters and subsets.

Group C was associated with significantly lower values for these three parameters.

Figure 1 shows the main echocardiographic parameters and their mean values according to the phenogroups.

DISCUSSION

In the present study, we defined four subsets of SLE patients based on their predominant clinical manifestations. In the heterogeneous SLE population, there are various phenotypical subsets although there is no subclassification of the disease endorsed to date. Our findings demonstrate the feasibility of organizing phenotypical groups, which could provide a framework for understanding this highly diverse disease using

both clinical and biological data. Previous studies have also highlighted the distinct clinical features and outcomes associated with different phenotypical subgroups. [3,4]

When analyzing the TTE values across our groups, we observed significant differences in the values of RVS, E' and RV basal diameter between the groups, however the values of these remained within the normal range. A prospective study to assess a change over time would reveal the significance of these findings, whether these early differences predicted the development of overt cardiac dysfunction. Notably, both groups C and D had lower values for GLS suggesting LV systolic dysfunction, without significant difference between groups. Previous studies have reported a lower GLS in SLE patients versus controls with prognostic implication. [11, 20,21] Further investigation tracking the progression of these values over time would provide valuable insights.

Despite the increased risk of coronary artery disease, none of the included patients had any symptoms or signs of coronary artery disease and we did not observe silent ischaemia based on regional wall motion abnormality in TTE. Interestingly, pulmonary hypertension (PH) was observed in only six patients in our cohort, aligning with existing literature that associates PH more strongly with systemic sclerosis rather than SLE .[22]

There are limitations in our study. Firstly, the sample size of SLE patients remains limited. Secondly, while numerous parameters were analyser analysis, we applied appropriate correction methods such as backward elimination procedure and false discovery rate method to address multiple comparisons. Thirdly, due to inherent biases of a retrospective design and the risk of selection bias, our phenotypic groups need to be validated prospectively. Serial echocardiography would also reveal whether the early differences which remained within normal limits, serve as markers for progressive cardiac dysfunction. This would help answer the question of whether closer surveillance is warranted for groups C and D.

CONCLUSION

Systemic Lupus Erythematosus is a heterogeneous disease. In our study, we identified four distinct clinical subsets defined by non-echocardiographical manifestations. Although subtle differences in right heart function and diastolic function were observed, these differences remained within the normal range.

To further understand the clinical implications of these findings and their impact on patient prognosis, prospective studies are needed to validate our groupings. These studies would also help determine whether the observed differences in right heart function and diastolic function indicate a potential risk of overt cardiac dysfunction and a worse prognosis. Such insights would enable personalized follow-up strategies for patients with SLE.

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TABLE 1: Clinical characteristics across the four-level response variable

Variables	**All**	**Group A**	**Group B**	**Group C**	**Group D**	**p-value**
	N = 181	**N = 37**	**N = 76**	**N = 18**	**N = 50**	
Gender (Male)	25	21.6 (8)	6.58 (5)	16.7 (3)	18.0 (9)	0.1071
Age at onset		35.7 ± 14.6	26.8 ± 11.2	38.6 ± 19.2	30.6 ± 14.9	0.0012
Age at diagnosis		39.2 ± 15.6	28.7 ± 11.6	40.9 ± 19.3	32.3 ± 15.0	0.0004
Ethnicity Caucasian	131	75.7 (28)	75 (57)	61.1 (11)	70.0 (35)	0.0486
Black	20	16.2 (6)	6.58 (5)	5.56 (1)	16.0 (8)	
Arab	10	5.41 (2)	5.26 (4)	5.56 (1)	6.00 (3)	
Black American	7	-	3.95 (3)	22.2 (4)	-	
Asian	10	-	6.58 (5)	5.56 (1)	8.00 (4)	
SLEDAI at diagnosis		9.21 ± 6.60	11.6 ± 6.80	10.1 ± 4.05	10.3 ± 5.69	0.5092
SLEDAI-2		7.56 ± 6.30	9.52 ± 6.84	8.53 ± 4.30	9.38 ± 6.38	0.5238
Arthralgias	167	97.3 (36)	92.1 (70)	100 (18)	86.0 (43)	0.1342
Synovitis	44	27.0 (10)	19.7 (15)	38.9 (7)	24.0 (12)	0.3773
Dermatological damage	126	-	100 (76)	-	100 (50)	<.0001
Malar rash	57	-	46.0 (35)	-	44.0 (22)	<.0001
Photosensitivity	87	-	73.7 (56)	5.56 (1)	60.0 (30)	<.0001
Raynaud Disease	89	70.3 (26)	47.4 (36)	38.9 (7)	40.0 (20)	0.0284
Serositis	68	-	-	100 (18)	100 (50)	<.0001
Pleural Effusion	39	-	-	61.1 (11)	56.0 (28)	<.0001
Pericarditis	50	-	-	66.7 (12)	76.0 (38)	<.0001
Myocarditis	5	-	1.32 (1)	-	8.00 (4)	0.1218
Libman-Sacks endocarditis	1	2.70 (1)	-	-	-	0.2710
Pulmonary hypertension	6	8.11 (3)	1.32 (1)	11.1 (2)	-	0.0331
Proteinuria > 0.5 g/24h	54	13.5 (5)	22.4 (17)	50.0 (9)	46.0 (23)	0.0008
GN II	4	2.70 (1)	-	5.56 (1)	4.00 (2)	0.3296
GN III	10	2.70 (1)	3.95 (3)	5.56 (1)	10.0 (5)	0.4161

Variables	All	Group A	Group B	Group C	Group D	p-value
GN IV	7	-	3.95 (3)	5.56 (1)	6.00 (3)	0.5242
GN V	11	2.70 (1)	3.95 (3)	-	14.0 (7)	0.0459
Leukopenia	62	29.7 (11)	30.3 (23)	50.0 (9)	38.0 (19)	0.3666
Lymphopenia	53	27.0 (10)	25.0 (19)	50.0 (9)	30.0 (15)	0.2116
Thrombocytopenic Purpura	38	18.9 (7)	19.7 (15)	16.7 (3)	26.0 (13)	0.7705
Autoimmune Hemolytic Anemia	14	2.70 (1)	13.2 (10)	5.56 (1)	4.00 (2)	0.1362
MAT	7	2.70 (1)	5.26 (4)	-	4.00 (2)	0.7387
Lymphadenopathy	56	18.9 (7)	22.4 (17)	33.3 (6)	52.0 (26)	0.0017
Macrophage Activation Syndrome	8	-	1.32 (1)	-	14.0 (7)	0.0035
Central neurological disease	23	2.70 (1)	11.8 (9)	5.56 (1)	24.0 (12)	0.0215
Peripheral neuropathy	6	2.70 (1)	3.95 (3)	-	4.00 (2)	0.8426
Xerostomia	64	32.4 (12)	43.4 (33)	27.8 (5)	28.0 (14)	0.2683
Xerophthalmia	52	21.6 (8)	34.2 (26)	27.8 (5)	26.0 (13)	0.5284
Anti-ADN	138	62.2 (23)	75.0 (57)	83.3 (15)	86.0 (43)	0.0646
Anti-Sm	33	5.41 (2)	15.8 (12)	11.1 (2)	34.0 (17)	0.0047
Anti-RNP	82	48.6 (18)	42.1 (32)	50.0 (9)	46.0 (23)	0.8847
Antiphospholipides	104	43.2 (16)	57.9 (44)	66.7 (12)	64.0 (32)	0.2066
Anti - SSA/SSB	86	27.0 (10)	47.4 (36)	38.9 (7)	66.0 (33)	0.0035
Anti-Ku	8	-	5.26 (4)	11.1 (2)	4.00 (2)	0.2877
Complement CH50	75	24.3 (9)	47.4 (36)	33.3 (6)	48.0 (24)	0.0738

3 missing values for ethnicity, 1 for Raynaud GN stands for glomerulonephritis, values are percentage (frequency) or mean standard ± deviation; p-values from chi-square tests or analysis of variance

Table 2A: TTE parameters across the four-level response variable

Variable	Group A	Group B	Group C	Group D	P-value
	N = 37	**N = 76**	**N = 18**	**N = 50**	
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
RVIDd (mm)	21.15 [4.58]	20.95 [3.85]	21.08 [4.93]	20.53 [6.15]	0.9783
RV FAC (%)	29.91 [9.11]	27.98 [7.82]	26.22 [16.47]	27.03 [9.43]	0.2779
RV/LV basal ratio	0.68 [0.14]	0.64 [0.13]	0.70 [0.15]	0.63 [0.13]	0.2609
LVOT (mm)	19.80 [2.21]	19.90 [1.84]	19.97 [2.11]	19.48 [1.70]	0.8958
Valsalva (mm)	29.56 ± 3.80	29.74 ± 3.62	29.21 ± 3.25	29.52 ± 4.33	0.9574
LV EDV (BP) (mL)	80.73 ± 27.35	86.84 ± 20.96	72.56 ± 22.04	84.36 ± 22.72	0.1018
LVEF (SBP) (%)	60.00 [13.00]	56.00 [12.00]	58.00 [10.00]	56.00 [11.00]	0.2389
GLS 2D (%)	18.13 ± 3.34	18.38 ± 2.87	16.58 ± 3.49	17.45 ± 2.40	0.0716
LA Surface (cm2)	14.87 ± 4.29	15.12 ± 3.27	14.63 ± 2.99	15.19 ± 4.28	0.9391
Mitral E wave velocity (cm/s)	0.81 ± 0.20	0.85 ± 0.16	0.76 ± 0.18	0.86 ± 0.21	0.1779
EDT (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
E/A	1.30 [0.70]	1.30 [0.60]	1.10 [0.40]	1.30 [0.70]	0.1274
E/e'	6.23 [2.19]	5.97 [2.59]	7.27 [3.38]	6.19 [3.43]	0.3806
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 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

Variable	Group A	Group B	Group C	Group D	P-value
Mitral Lateral E'-wave (cm/s)	14.13 ± 5.75	15.88 ± 4.83	12.44 ± 3.68	14.51 ± 4.89	0.0394
Mitral Lateral A'-wave (cm/s)	10.60 [5.50]	9.50 [3.25]	10.50 [3.90]	9.10 [3.80]	0.2195
LVOT VTI (cm)	22.78 ± 3.94	21.45 ± 3.76	21.31 ± 4.58	21.46 ± 3.68	0.3120
Cardiac Output (mL/min)	5.26 ± 1.01	5.30 ± 1.22	5.72 ± 1.51	5.35 ± 1.43	0.6137
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 (cm2)	9.60 [2.92]	8.93 [3.73]	8.48 [3.38]	9.10 [4.31]	0.3885
RV FAC (%)	38.70 ± 13.56	43.30 ± 9.48	41.28 ± 11.55	42.40 ± 9.70	0.1919
RA indexed volume (ml/m^2)	18.00 [7.00]	18.00 [6.50]	16.00 [9.00]	19.50 [8.00]	0.4008
TAPSE	22.00 [5.00]	23.00 [4.00]	20.00 [5.00]	22.00 [5.00]	0.0222
RV-S' velocity (cm/s)	13.20 [3.60]	13.65 [2.55]	13.35 [3.60]	12.50 [2.80]	0.0709
RV-E' (cm/s)	12.79 ± 3.80	14.96 ± 3.78	10.05 ± 3.35	12.54 ± 4.19	<.0001
Isovolumic acceleration (m/s2)	0.12 ± 0.05	0.12 ± 0.04	0.11 ± 0.04	0.12 ± 0.05	0.9488
TR velocity (m/s)	2.30 [0.50]	2.20 [0.48]	2.20 [0.50]	2.24 [0.41]	0.3022
RV wall thickness (mm)	5.80 [1.62]	5.40 [1.56]	6.00 [2.20]	5.33 [1.60]	0.2123

values are mean standard ± deviation or median [interquartile range]; p-values from analysis of variance (F-test or Kruskal-Wallis test)

LVEDD: Left Ventricular end-diastolic diameter, LVESD: Left Ventricular end-systolic diameter, IVS: Interventricular septum, LVPW: Left ventricle posterior wall, RVIDd: Right ventricular internal dimension diastole, RV FAC: Right Ventricle Fractional Area Change, LVOT: Left ventricular outflow tract, LV EDV : Left Ventricle End-diastole volume, LVEF: Left Ventricle Ejection Fraction, GLS: Global Longitudinal Strain, LA: Left Atrium, EDT: E-wave deceleration time, VTI: Velocity-Time Integral, RV: Right Ventricle, RA: Right Atrium, TAPSE: Tricuspid annular plane systolic excursion, TR: Tricuspid Regurgitation

Table 2B: TTE parameters across the four-level response variable

Variable	Group A	Group B	Group C	Group D	P-value
	N = 37	**N = 76**	**N = 18**	**N = 50**	
Mitral regurgitation = 0	64.86 (24)	68.42 (52)	55.56 (10)	50.00 (25)	0.4022
Mitral regurgitation = 1	32.43 (12)	28.95 (22)	33.33 (6)	44.00 (22)	
Mitral regurgitation = 2	2.70 (1)	2.63 (2)	11.11 (2)	4.00 (2)	
Mitral regurgitation = 3	-	-	-	2.00 (1)	
Aortic regurgitation = 0	83.78 (31)	97.37 (74)	100 (18)	92.00 (46)	0.1296
Aortic regurgitation = 1	10.81 (4)	2.63 (2)	-	4.00 (2)	
Aortic regurgitation = 2	5.41 (2)	-	-	4.00 (2)	
Pericarditis	5.41 (2)	1.32 (1)	22.22 (4)	14.00 (7)	0.0060
Heart Rate (bpm)	74.8 ± 11.1	74.9 ± 11.9	79.3 ± 11.7	78.6 ± 14.4	0.2491

values are percentage (frequency) or mean standard ± deviation; p-values from chi-square tests or analysis of variance

Table 3 – Pairwise comparisons (p-value) across clinical groups adjusted for multiple comparisons

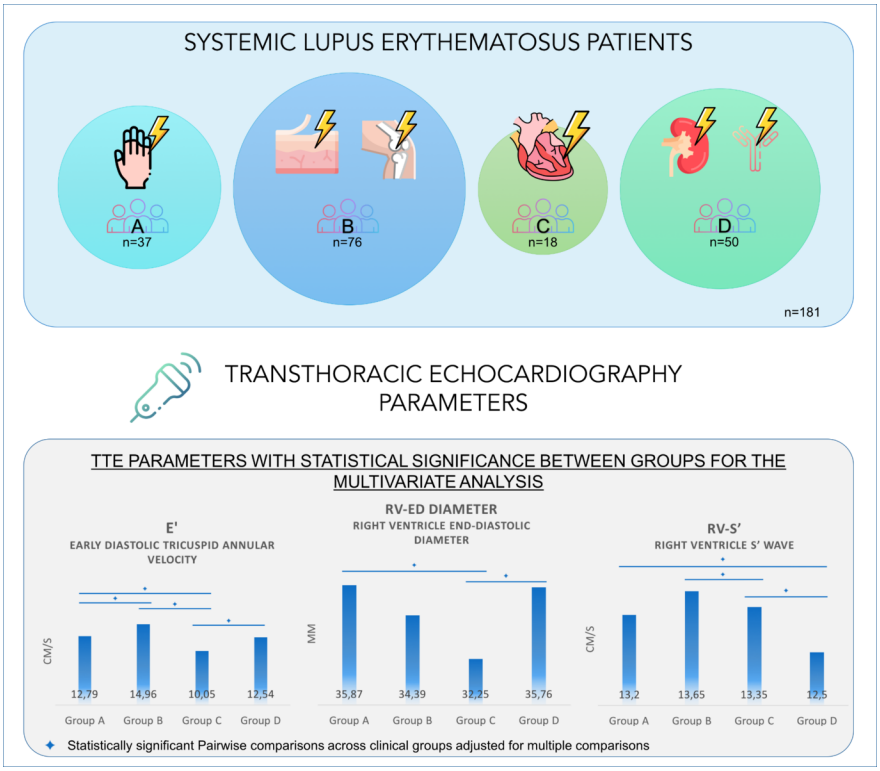
	Group B	Group C	Group D
Group A	RV E' (0.009)	RV EDd (0.035) RV E' (0.035)	RV S' wave (0.019)
Group B	-	RV S' wave (0.022) RV E' (0.002)	-
Group C	-	-	RV EDd (0.022) RV S' (0.005) RV E' (0.003)

RV E': Early diastolic tricuspid annular velocity, RV S' wave: RV-s' wave, RV EDd: RV end-diastole diameter

Central Illustration (& Figure 1) –

Upper panel: Four subsets definition according to clinical parameters in SLE patients

Lower panel: Three TTE parameters of interest in SLE patients according to subsets



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