Ratio of Mitral Peak Velocity of Early Filling to Early Diastolic Mitral Annular Velocity is More Sensitive than the Ratio of Mitral Peak Velocity of Early Filling to Mitral Peak Velocity of Late Filling in Detection of Left Ventricular Diastolic Dysfunction in Systemic Lupus Erythematous

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Abstract

Background: SLE linked to cardiovascular issues, including myocarditis, valve diseases, and conduction abnormalities. E/A ratio for LV diastolic function assessment has limitations. E/E' ratio offers promise as an alternative, less affected by preload changes. Conventional echocardiography's role in evaluating diastolic function and related factors unclear.

Objectives: A study compared the sensitivity of two ratios to detect LV diastolic dysfunction in patients with SLE: E/A ratio and E/ É ratio.

Patients and Methods: Transthoracic echocardiography was conducted on a group of 100 patients with systemic lupus erythematosus (SLE) who did not have heart failure or angina symptoms. The results were then compared to a control group of 40 individuals who were matched in terms of age and sex. Myocardial tissue peak velocities at the lateral and septal angles of the mitral annulus were measured using conventional 2D echocardiography and pulsed wave (PW) tissue Doppler echocardiography.

Results: In SLE cases, Mitral E velocity didn't significantly differ from controls, while A velocity showed a notable increase. E/A ratio remained similar between cases and controls, although cases exhibited a higher frequency of E/A ratio <1. Septal E velocity didn't show a significant difference, but the septal E/E ratio was higher in cases, particularly with more ratios >8 and>15. Lateral E velocity and E/E ratio didn't significantly differ between the two groups, yet cases displayed a higher frequency of ratios >8.

Conclusions: The E/E' ratio is more responsive than the E/A ratio in identifying left ventricular diastolic dysfunction in individuals with systemic lupus erythematosus (SLE).

Keywords: Systemic lupus erythematosus; Tissue Doppler imaging; Left ventricle; Diastolic dysfunction.

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Introduction

SLE is a complicated autoimmune illness that mostly affects young women and is distinguished by its unpredictable course **(Han et al., 2023).** Despite advances in SLE management, cardiovascular disease (CVD) remains a major issue, affecting up to 50% of patients. Patients with SLE have a much higher chance of experiencing severe cardiovascular problems, including myocardial infarction, stroke, and heart failure. This risk is up to nine times greater than that of the general population.. This has prompted an investigation into the SLE-specific variables that contribute to this phenomenon **(Luo et al., 2020).**

Traditional methods for assessing LV diastolic function have intrinsic limitations, pushing researchers to look for other indications. When compared to the standard E/A ratio, the E/E' ratio appears as a more sensitive approach for diagnosing LV diastolic dysfunction in SLE patients **(Gegenava et al., 2020; Li et al., 2023).**

The E/A ratio's drawbacks include its vulnerability to higher LV filling pressures, which results in E velocity and E/A ratios above 0.8. The existence of mitral regurgitation (MR) increases confounding factors, underlining the need for a more trustworthy indication of LV diastolic dysfunction, especially in the setting of SLE **(Li et al., 2023).**

Assessing LV diastolic function using the E/A ratio faces several challenges that limit its sensitivity. Firstly, the E/A ratio depends on heart rate and can be influenced by conduction abnormalities. Secondly, when LV filling pressure rises, the E velocity also increases, leading to an E/A ratio greater than 1. Additionally, changes in mitral inflow patterns, especially in the presence of MR, can result in a misinterpretation of a restrictive mitral filling pattern. These factors collectively diminish the reliability of the E/A ratio as a sensitive indicator of LV diastolic function **(Chan et al., 2023; Obokata et al., 2020).**

Cardiovascular complications are prevalent in SLE patients, with conditions such as pericarditis, myocarditis, valve diseases, and conduction system problems being common outcomes **(Alghareeb et al., 2022).** Lupus myocarditis adversely affects the conducting system and overall heart function. Furthermore, adults with SLE may experience various conduction abnormalities, including tachyarrhythmia, bradyarrhythmia, AV nodal blocks, and QT prolongation **(Du Toit et al., 2023; Ward et al., 2022).**

Interestingly, in studies comparing SLE individuals to control groups, the traditional E/A ratio did not exhibit significant differences, suggesting that it may lack the necessary sensitivity to detect early diastolic dysfunction in SLE patients. The E/ É ratio, However, shows potential as an alternative to the E/A ratio, with less vulnerability to preload fluctuations and other affecting variables **(Liang et al., 2020; Mitter et al., 2017**). This shows that it has the potential to be a more accurate predictor of LV filling pressure, It serves as a valuable technique for identifying diastolic dysfunction in individuals with SLE. Thus, in the setting of SLE, the E/E' ratio may provide a better diagnostic strategy for detecting LV diastolic dysfunction **(Pazoki et al., 2022).**

The research sought to evaluate and compare the sensitivity of two diagnostic indices, namely the E/A ratio

and the E/ É ratio, in detecting left ventricular diastolic dysfunction.

Patients and Methods

Study Population

This comparative study included 100 patients (94 females, 6 males) who were diagnosed with SLE and had preserved LV systolic function (EF% > 50%) and 40 individuals, matched for age and sex (38 females, 2 males), who haven't any disease except for controlled hypertension and did not have any autoimmune conditions, were chosen as the control group. The study was conducted at the Outpatient Clinic of the Internal Medicine Department, Faculty of Medicine, South Valley University Hospitals. The patients were evaluated using pulsed wave tissue Doppler from February 2022 to September 2023. All participants satisfied the 2012 criteria set by the SLICC (Petri et al., 2012). The duration of the illness was determined as the period from the diagnosis of SLE to the execution of echocardiography.

The research received approval from the ethics committee at South Valley University (SVU /MED/MED018/1/22/2/345)

- **Patient agreement: -** All participants in the study were provided with comprehensive information on the purpose and specifics of the research, and signed agreement was acquired from everyone.

Inclusion criteria: Participants had to meet two criteria: they had to be at least 18 years old and have a confirmed diagnosis of SLE. In addition, they required a regional wall motion index of 1, which indicates a healthy left ventricular function, combined with normal end-diastolic and end-systolic dimensions.

Exclusion criteria: Individuals under 18, those with drug-induced lupus, discoid lupus without systemic manifestations, comorbidities, concurrent malignancies, pregnancy, significant valvular heart diseases, or LV systolic dysfunction (EF% < 50%). Patients with COPD or non-compliance were also ineligible.

All patients were subjected to the following

I. History and Clinical Examination:

1. Comprehensive medical history assessment, including age, gender, tobacco and alcohol use, presence of other concurrent disorders such high blood pressure, diabetes mellitus, stroke, medication usage, cardiac history, peripheral artery disease, and family medical history.
2. Comprehensive Clinical Examination: evaluating the overall state of the patient, as well as measuring vital indicators such as pulse, blood pressure, respiration rate, and temperature. An examination was conducted on the abdomen, chest, and heart, with particular attention given to identifying signs of cardiac illness. Hypertension was characterized by a blood pressure that is equal to or above 140/90 mmHg. **(Whelton et al., 2018).**
3. Anthropometric measures were conducted to determine the height and weight of the individuals. The Body Mass Index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters.

II. Laboratory Investigations:

Blood samples were collected for a range of tests, including complete blood counts (hemoglobin concentration, RBCs, WBCs, and platelet count), fasting blood glucose, postprandial 2-

hour oral glucose tolerance test, HbA1c, renal function tests (serum creatinine and urea), and albumin to creatine ratio (ACR) calculated from urine samples. Immunological markers (ANA, anti-dsDNA, Coomb's test), C3, C4, and ESR were recorded. Hematologic manifestations such as hemolytic anemia, leucopenia, thrombocytopenia, and lymphopenia were also documented**.**

III. Medications

The medications given to individuals with SLE were those prescribed for a minimum duration of half a year (6 months) before the echocardiography procedure. High-dose glucocorticoid therapy was defined as a dosage over 10 mg per day, whereas low-dose glucocorticoid treatment was described as a dosage below 10 mg per day.

IV. Twelve-lead electrocardiogram (ECG):

The FUKUDA device will record a standard 12-lead ECG with a paper speed of 25 mm/s and a gain of 10 mm/mV.

V. Echocardiography:

The echocardiographic pictures were acquired using a GE Vivid S5 ultrasound machine equipped with a 3.5-MHz transducer. Both patients and controls had comprehensive cardiac examinations, including conventional 2D echocardiography using established techniques such as PW Doppler, color flow Doppler, and M-mode echocardiography. Additionally, PW TDI was performed according to a standardized research protocol. Echocardiographic measures were conducted with the patient lying on their left side, as advised by the American Society of Echocardiography. All measurements were made by a same investigator using the same machine.

1-Conventional echocardiography

2D pictures were used to get precise measurements of the dimensions of the LA, the diameters of the LV, and the thicknesses of the LV walls at the level of the mitral valve tips. The measurements were made in a way that ensured their alignment with the ventricle's longitudinal axis. The LV LVEF was evaluated by 2D echocardiography employing M-mode.

The Apical Doppler method was used to capture the blood flow entering the mitral valve, specifically at the locations where the mitral leaflets meet. A total of five to 10 cardiac cycles were observed. The measured parameters of the mitral inflow velocities consisted of the peak velocity of the E and A diastolic filling. The E/A ratio was computed. The tricuspid regurgitant velocity was used to compute an approximation of the pulmonary artery systolic pressure **(Yock and Popp, 1984).**

2-Tissue Doppler Parameters

We used a GE Vivid S5 ultrasound apparatus equipped with a 2.5-MHz PW tissue Doppler transducer to evaluate all aspects. Doppler recordings were obtained from standard apical views using the highest possible frame rate while the person was in a lateral position. The filter setting was decreased, and the Nyquist limit was adjusted to 15–20 cm/s. Gain reduction decreased the level of background noise and enhanced the clarity of the tissue signal. The scanning velocity ranged from 50 to 100 millimeters per second, while the Doppler velocity spanned from negative 30 to positive 30 centimeters per second. Echocardiographic Doppler parameters were estimated by averaging the results from three to five cycles. The velocities of peak longitudinal systolic

(S'), early diastolic (E'), and late diastolic (A) were measured in centimeters per second (cm/s). For these measurements, a sample volume of 2-5 mm was positioned at the two mitral annular regions, which divide the left ventricle into septal and lateral segments. This was done using the apical four-chamber view.

TDI also gathered average E/E' disparities (early diastolic trans-mitral flow velocity to tissue velocity).

Statistical analysis

The data underwent processing and analysis using SPSS version 24, developed by SPSS Inc. in Chicago, IL, USA. Mean and standard deviation were shown for continuous variables. The categorical variables were represented using frequency and percentage. A nonparametric independent t-test was used to compare continuous variables between SLE patients and controls. The chi-square test was used to assess the frequencies of sex, hypertension, and cardiac performance in patients with systemic lupus erythematosus (SLE) and the control group. The Mann-Whitney U test was used to evaluate cardiac functions, namely the E/A and E/E' ratios, between SLE patients and controls. The analysis was corrected for pre-echocardiography medications. The odds ratio was computed using binary logistic regression. A p-value less than 0.05 indicates statistical significance in the statistical analysis.

Results

Patients' and controls characteristics

There were no disparities in age or gender distribution between the patients and controls. However, there was a notable discrepancy in BMI between the two groups. Specifically, patients with SLE had a significantly lower BMI compared to the control group (P =0.0049). A significantly higher number of SLE patients had been diagnosed with hypertension (27% vs 17.5%) (P =0.0002) and had been prescribed anti-hypertensive medication. Hypertension was effectively controlled on treatment and maintained within the normal range in both patients and controls, (**Table.1**).

Table 1. Demographic characteristics of patients with SLE and controls

Variables	Cases (N = 100)	Controls (N = 40)	P. Value
Age (Years)[a]	27.93 ± 6.25	29.3 ± 6.31	0.2446
SEX			
Female	94 (94%)	38 (95%)	0.8179
Male	6 (6%)	2 (5%)	
BMI (Kg/m^2) [a]	21.73 ± 1.39	22.48 ± 1.43	0.0049*
HTN	27 (27%)	7 (17.5%)	0.0002*
Blood pressure (mmHg)			
SBP[a]	115.75 ± 11.92	114.75 ± 8.91	0.6325
DBP[a]	71.28 ± 8.07	70.13 ± 7.3	0.4421

[a]Values are expressed as mean ± standard deviation, unless otherwise indicated.

Clinical presentation and laboratory findings in SLE patients

The duration of SLE ranged from 9 months to 6 years with a mean of 3.45 ± 2.55. The most frequent clinical presentation of SLE was arthritis (59%), and other common clinical presentations included malar rash (57%), oral ulcers (55%), and serositis (53%). Additionally, a significant percentage of patients

exhibited clinical manifestations such as autoimmune hemolytic anemia (AIHA) (32%), thrombocytopenia (26%), and leukopenia (17%). Alopecia was observed in 48% of patients, while vasculitis was less common (7%). Laboratory findings showed that 92% of patients had a positive ANA, 89% had a positive anti-ds DNA, 46% had consumed C3, and 38% had consumed C4, **(Table.2**)

Table 2. Duration of disease, Clinical presentation and laboratory data in patients with SLE

Variables	Cases (N = 100)
Duration of disease (Years)[a]	3.45 ± 2.55
Clinical manifestations	
AIHA	32 (32%)
Thrombocytopenia	26 (26%)
Leukopenia	17 (17%)
malar rash	57 (57%)
Photosensitivity	31 (31%)
Oral ulcers	55 (55%)
Arthritis	59 (59%)
Serositis	53 (53%)
Proteinuria	42 (42%)
Hematuria	20 (20%)
Alopecia	48 (48%)
Vasculitis	7 (7%)
Lab Data	
ANA Positive	92 (92%)
Anti -ds DNA Positive	89 (89%)
Consumed C3	46 (46%)
Consumed C4	38 (38%)

[a]Values are expressed as mean ± standard deviation, unless otherwise indicated.

Medications that SLE patients have received

As shown in (**Table.3**), 52% of patients administered high-dose glucocorticoid treatment, while 48% of them administered a low-dose glucocorticoid treatment. 46% of patients received ACEI or ARB for treatment of hypertension and proteinuria of lupus nephritis. Azathioprine was prescribed to 57% of patients, and hydroxychloroquine was used by a majority at 65%. Mycophenolate mofetil was taken by 42% of patients, and cyclosporin was used by 5% of patients. Notably, only one patient (1%) received cyclophosphamide, while only a small percentage received aspirin (3%) or anticoagulants (2%).

Table 3. Medications that SLE patients have received.

Medications	Cases (N = 100)
Steroid use	
Low dose steroid	48 (48%)
High dose steroid	52 (52%)
ACEIs or ARBs	46 (46%)
Aspirin	3 (3%)
Anticoagulant	2 (2%)
Azathioprine	57 (57%)
Cyclophosphamide	1 (1%)
Hydroxy chloroquine	65 (65%)
Mycophenolate mofetil	42 (42%)
Cyclosporin	5 (5%)

Echocardiographic data between SLE patients and controls

(**Table. 4A)** displays the echocardiography measurements for both groups. **2D and M-mode echocardiography** revealed that patients diagnosed with SLE display a significant higher left ventricular septal end-systolic and posterior end-diastolic wall thickness when compared to the control group. However, there were no significant changes observed between the two groups in metrics such as LA diameter or LVEF.

Conventional Doppler echocardiography showed tricuspid regurgitating velocity was significant higher in SLE patients compared with controls ($P < 0.05$).

Data of **tissue doppler imaging** showed that SLE On Mitral E vel. m/sec was significantly no differance in cases compared to controls (0.75 ± 0.14cm/sec vs. 0.74 ± 0.09 cm/sec, p = 0.4858). A vel. m/secalso showed a significant increase in cases (0.59 ± 0.13 cm/sec) compared to controls (0.56 ± 0.07 cm/sec, p = 0.079). E/A ratio in cases (1.31 ± 0.35) compared to controls (1.33 ± 0.18, p = 0.7258). Frequency of E/A ratio < 1 (%) in cases (13 (13%)) and in control (2 (5%)) . In terms of Septal E` velocity, cases hadn't a significantly different value (10.63 ± 2.76 cm/sec) compared to controls (11.38 ± 1.79 cm/sec, p = 0.1144), The septal E/ E` ratio was significantly higher in cases (7.43 ± 2.7) compared to controls (6.55 ± 0.73, p = 0.0443*), with a higher frequency of ratios >8 (32% vs. 5%, p = 0.0008*) and >15 (3% vs. 0%, p = 0.5576). lateral E`velocity did not show a significant difference between cases (10.95 ± 2.6 cm/sec) and controls (11.22 ± 1.63 cm/sec, p = 0.5402). The lateral E/ E` ratio did not show a significant difference (7.51 ± 2.62 in cases vs. 6.63 ± 0.76 in controls, p = 0.1739), but the frequency of ratios >8 (30% vs. 5%, p = 0.0015*) was significantly higher in cases. Septal E/ E`ratio was significantly higher in cases, with a higher frequency of ratios >8 and >15. Lateral E/ E`ratio did not significantly differ, but the frequency of ratios >8 was higher in cases.

As shown in (**Table, 4B**), **Two-dimensional and color doppler echocardiography**, showed that the majority of SLE patients had no amount of pericardial effusion enough to cause hemodynamic changes (47%), with and

mild PE (53%). When it comes to valvular lesions, a significant percentage of cases had no mitral regurgitation (MR) (55%) and had no aortic regurgitation (AR) (81%) or tricuspid regurgitation (TR) (42%). mild MR (41%), mild AR (18%) and mild TR (52%) , with moderate MR (4%), moderate AR (1%) and moderate TR(6%). There were no cases with severe valvular lesions in any cardiac valve.

Table .4A. Echocardiographic data between patients with SLE and controls

Parameters	Cases (N = 100)	Controls (N = 40)	P. Value
Two-dimensional and M-mode echocardiography			
LA diameter mm	32.26 ± 3.53	31.6 ± 3.99	0.3373
LVEDD mm	44.59 ± 9.1	46.93 ± 3.38	0.1169
LVESD mm	29.5 ± 5.19	31.15 ± 2.01	0.0534
Septal End -Systolic Thickness mm	11.99 ± 1.2	11.8 ± 0.85	0.0039*
Septal End -Diastolic Thickness mm	8.33 ± 1	8.05 ± 0.85	0.1196
PW End -Systolic Thickness mm	10.36 ± 1.31	10.78 ± 0.92	0.0703
PW End -Diastolic Thickness mm	8.79 ± 1.39	8.28 ± 0.75	0.0282*
LVEF %	65.89 ± 6.2	66.53 ± 4.32	0.5548
Conventional Doppler echocardiography			
On Mitral E vel. m/sec	0.75 ± 0.14	0.74 ± 0.09	0.4858
A vel. m/sec	0.59 ± 0.13	0.56 ± 0.07	0.079
E/A ratio	1.31 ± 0.35	1.33 ± 0.18	0.7258
Frequency of E/A ratio < 1 (%)	13 (13%)	2 (5%)	0.1198
On Tricuspid TR vel. m/sec	2.53 ± 0.38	2.17 ± 0.3	0.0364*
PASP (RV pressure) mm Hg	26.62 ± 6.86	28.86 ± 5.98	0.072
Tissue Doppler Imaging			
Septal S` vel. cm/sec	9.25 ± 1.4	9.78 ± 0.92	0.0491*
Lateral S` vel. cm/sec	9.41 ± 1.3	9.53 ± 0.78	0.0001*
Septal E` vel. cm/sec	10.63 ± 2.76	11.38 ± 1.79	0.1144
Lateral E` vel. cm/sec	10.95 ± 2.6	11.22 ± 1.63	0.5402
Septal A` vel. cm/sec	9.1 ± 2.43	8.08 ± 1	0.0109*
Lateral A` vel. cm/sec	8.87 ± 2.67	7.95 ± 0.99	0.0364*
Septal E/E` Ratio	7.43 ± 2.7	6.55 ± 0.73	0.0443*
Frequency of Septal E/E` Ratio >8	32 (32%)	2 (5%)	0.0008*
Frequency of Septal E/E` Ratio >15	3 (3%)	0 (0%)	0.5576
Lateral E/E` Ratio	7.51 ± 2.62	6.63 ± 0.76	0.1739
Frequency of Lateral E/E` Ratio > 8	30 (30%)	2 (5%)	0.0015*
Frequency of Lateral E/E` Ratio > 15	1 (1%)	0 (0%)	0.99

[a]Values are expressed as mean ± standard deviation, unless otherwise indicated.
P-Value less than 0.05 was considered significant and less than 0.01 was considered highly significant.

Table (4B). Echocardiographic data among patients with SLE

Two-dimensional and color doppler echocardiography	Cases (N = 100)
PE	
No	**47 (47%)**
Mild	**53 (53%)**
MR	
No	**55 (55%)**
Mild	**41 (41%)**
Moderate	**4 (4%)**
AR	
No	**81 (81%)**
Mild	**18 (18%)**
Moderate	**1 (1%)**
TR	
No	**42 (42%)**
Mild	**52 (52%)**
Moderate	**6 (6%)**

Comparison of SLE patients` characteristics and cardiac functions between patients receiving and not receiving ACEIs or ARBs

The patients with SLE were categorized into two groups based on whether they were taking ACEIs or ARBs (receiving group) or not (non-receiving group), (**Table.5).** No significant disparities were seen in terms of age, sex distribution, illness duration, BMI, or steroid usage between the two groups. 58.7% of patients who were prescribed ACEIs, or ARBs had hypertension. While SLE patients who were not prescribed ACEIs, or ARBs did not have hypertension.

Patients who were administered ACEIs or ARBs had a significant higher LVEF (69.63 ± 5.58) compared to those who did not receive ACEIs or ARBs, whose LVEF was (62.7 ± 4.78) ($P < 0.01$). Nevertheless, there were no notable disparities in the E/A ratio (1.28 ± 0.33 vs 1.34 ± 0.38) or in the E/E` ratio of the septal or lateral regions (7.77 ± 2.75 vs 7.13 ± 2.65, 7.48 ± 2.97 vs 6.89 ± 1.82, respectively) between the two groups.

Table 5. Comparison of cardiac functions between patients with SLE receiving and not receiving ACEI or ARB

Variables	On ACEIs or ARBs (N = 46)	Not on ACEIs nor ARBs (N = 54)	P. Value
Patients` Characteristics			
AGE (Years) [a]	29.15 ± 6.36	26.89 ± 6.02	0.0708
SEX			
Female	41 (89.13%)	53 (98.15%)	0.5843
Male	5 (10.87%)	1 (1.85%)	
BMI (Kg/m^2) [a]	21.7 ± 1.42	21.75 ± 1.38	0.8468

HTN	27 (58.7%)	0 (0%)	
Blood pressure (mmHg)			
SBP	121.41 ± 13.02	110.93 ± 8.36	<0.0001*
DBP	73.91 ± 8.43	68.94 ± 7.02	0.002*
Duration of disease (Years)[a]	3.86 ± 2.71	3.1 ± 2.38	0.1344
Steroid Use			
Low dose steroid	24 (52.17%)	24 (44.44%)	0.441
High dose steroid	23 (50%)	30 (55.56%)	0.579
Cardiac Functions[a]			
LVEF %	69.63 ± 5.58	62.7 ± 4.78	<0.0001*
E/A Ratio	1.28 ± 0.33	1.34 ± 0.38	0.4118
Frequency of E/A Ratio < 1 (%)	6 (13.04%)	7 (12.96%)	0.7321
Septal E/E` Ratio	7.77 ± 2.75	7.13 ± 2.65	0.2387
Frequency of Septal E/E` Ratio >8	16 (34.78%)	16 (29.63%)	0.582
Frequency of Septal E/E` Ratio >15	1 (2.17%)	2 (3.7%)	0.655
Lateral E/E` Ratio	7.48 ± 2.97	6.89 ± 1.82	0.2252
Frequency of Lateral E/E` Ratio > 8	12 (26.09%)	18 (33.33%)	0.4306
Frequency of Lateral E/E` Ratio > 15	1 (2.17%)	0 (0%)	0.46

[a]Values are expressed as mean ± standard deviation, unless otherwise indicated.

Case presentation

Case (1):

Interpretation (Fig.1)

-Systolic myocardial velocity (S`) at the lateral & septal mitral annulus is a measure of longitudinal LV systolic function and is correlated with measurements of LV ejection fraction. Septal & Lateral S` are within normal ranges & correlated with LV EF=68% as above.

-The E/A ratio is ≥ 2 but the septal E`/A` ratio is < 1 indicating a pattern of pseudo-normalization suggestive of moderate to severe LV diastolic dysfunction with decreased relaxation & compliance. LV DD is confirmed by E/E` ratio ≥ 15 that indicating elevated LV end-diastolic filling pressure & IVRT (between 60-100 ms).

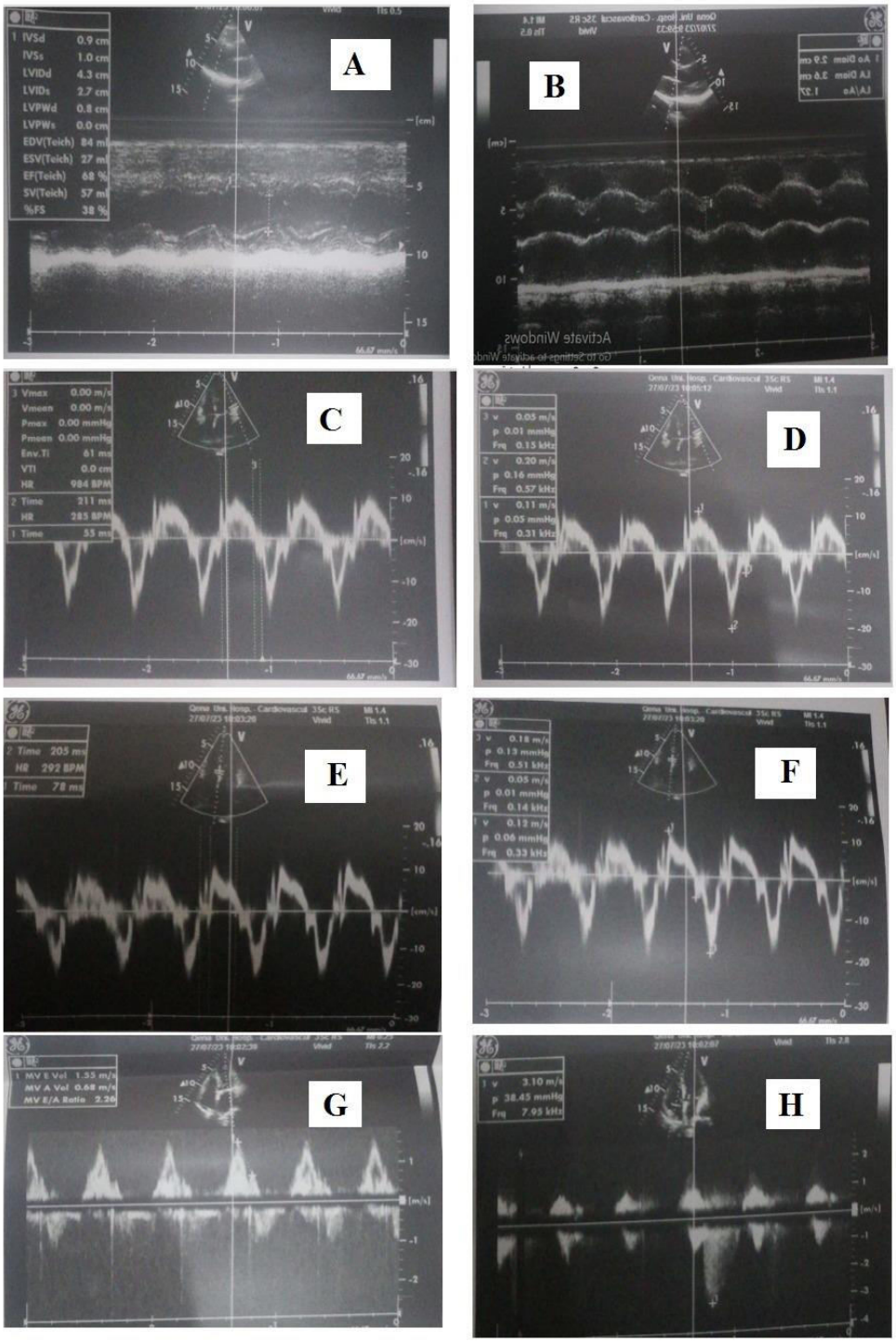

Fig.1. TDI Dimensions: A: By M-Mode, Normal LV dimensions & systolic function**.B: By M-Mode,** Normal LA & Aortic Root dimensions. **C: By TDI Lateral aspect** show IVRT =55ms, ET= 211ms, IVCT= 61ms **D: By TDI Lateral aspect** show S`=0.11m/s, E`=0.20m/s, A`=0.05m/s**. E: By TDI Septal aspect** show IVRT =78ms, ET= 205ms, IVCT= --ms**. F: By TDI Septal aspect** show S`=0.12m/s, E`=0.05m/s, A`=0.18m/s**. G: By Pulsed doppler,** MV E vel.=1.55m/s, MV E/A ratio ≥ 2**. H: By Cont. doppler,** TR jet vel.=3.10m/s, TR jet pressure=38 mmHg, PASP=48 mmHg

Case (2)

Interpretation (Fig.2)

-Systolic myocardial velocity (S`) at the lateral & septal mitral annulus is a measure
of longitudinal LV systolic function and is correlated with measurements of LV ejection fraction. Septal & Lateral S` are within normal ranges & correlated with LV EF=65% as above.

-The E/A ratio is ≥ 2 that indicating presence of restrictive pattern of LV diastolic dysfunction but the septal E` velocity cm/s ≥ 10, E`/A` ratio is >1, E/E` ratio is ≤ 8, IVRT (between 50-100 ms) indicating normal LV diastolic function with normal relaxation & compliance & normal LV end-diastolic filling pressure.

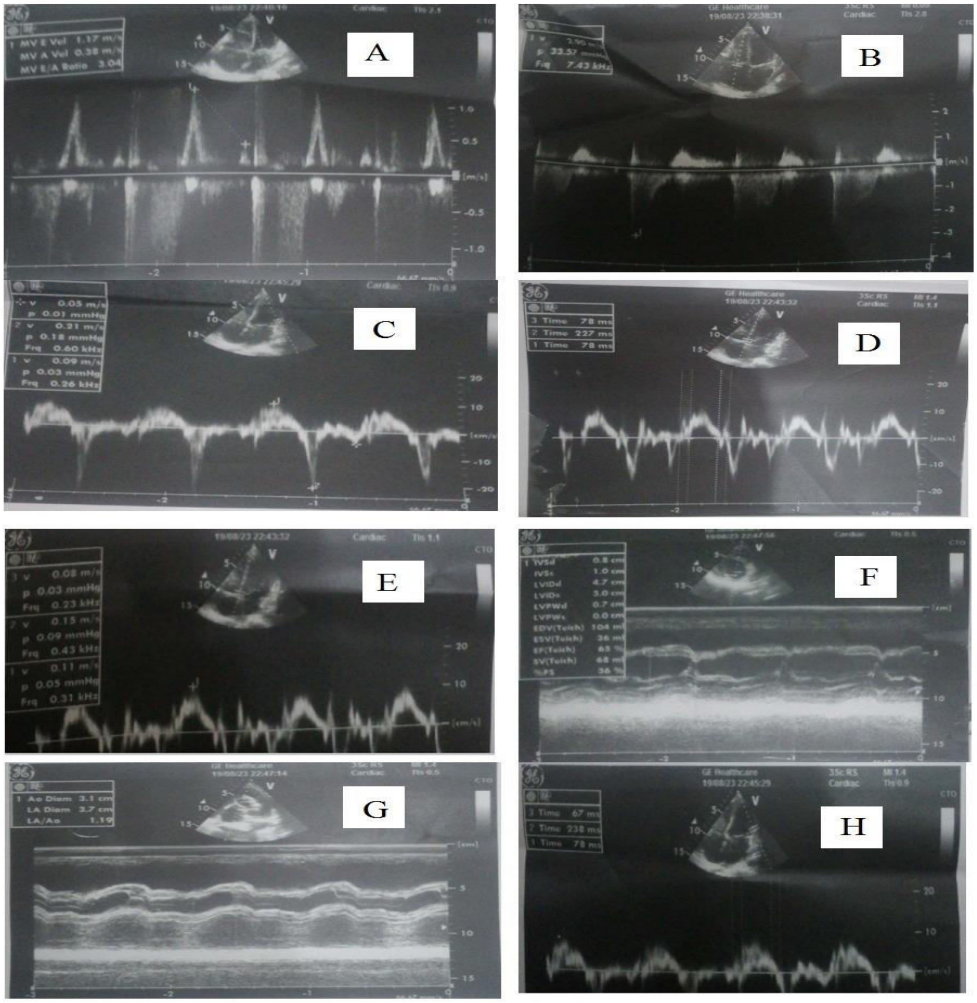

Fig.2. TDI Dimensions: A: By Pulsed doppler, MV E vel.=1.17m/s, MV E/A ratio ≥ 2**. B: By Cont. doppler,** TR jet vel.=2.9m/s, TR jet pressure=33 mmHg, PASP=43 mmHg**. C: By TDI Lateral aspect** show S`=0.09m/s, E`=0.21m/s, A`=0.05m/s**. D: By TDI Septal aspect** show IVRT =78ms, ET= 227ms, IVCT= 78ms.**. E: By TDI Septal aspect** show S`=0.11m/s, E`=0.15m/s, A`=0.08m/s**. F: By M-Mode,** Normal LV dimensions & systolic function**.. G: By M-Mode,** Normal LA & Aortic Root dimensions. **H: By TDI Lateral aspect** show IVRT =78ms, ET= 238ms, IVCT= 67ms

Discussion

This comparative study was conducted at the Internal Medicine Department of Qena University Hospitals, Qena, Egypt. The research cohort consisted of 140 participants, 100 of whom were diagnosed with SLE and 40 were control.

We found that SLE patients displayed a significantly lower BMI (mean of 21.73 ± 1.39 kg/m^2) compared to the control group (mean of 22.48 ± 1.43 kg/m^2), that is matched with previous studies, which demonstrated increased fat metabolism and reduced BMI is prevalent in SLE patients **(Kipen et al., 1999; Kipen et al., 1998).** Additionally, the prevalence of hypertension was notably higher among SLE patients, compared to the control group, indicating the relevance of this condition in SLE (27% vs 17.5%, P < 0.01).

The over representation of female SLE patients in our study is a consistent epidemiological finding **(Zhang, 2020).**

Also, the higher prevalence of hypertension in SLE patients can be explained by various disease-related factors. Lupus nephritis can lead to hypertension due to impaired regulation of blood pressure and sodium balance. Additionally, the chronic inflammation characteristic of SLE can cause endothelial dysfunction and arterial stiffness, both of which are risk factors for hypertension. Some medications used to manage SLE, particularly corticosteroids, may also contribute to hypertension as a side effect. Furthermore, SLE is marked by autoimmunity, where the immune system mistakenly targets healthy tissues, including blood vessels. This autoimmune response can lead to vascular damage and increased blood pressure **(Lu et al., 2021; Munguia-Realpozo et al., 2019).**

In terms of On Mitral E velocity, cases hadn't a significantly different value (0.75 ± 0.14cm/sec) compared to controls (0.74 ± 0.09 cm/sec, p = 0.4858), while A vel. m/secvelocity also showed a no significant increase in cases (0.59 ± 0.13cm/sec) compared to controls (0.56 ± 0.07cm/sec, p = 0.079). Frequency of E/A ratio < 1 (13 %) vs. (5%). Septal E` velocity, although not statistically significant, exhibited a decreasing trend in cases (10.63 ± 2.76 cm/sec) compared to controls (11.38 ± 1.79 cm/sec, p = 0.1144). Similarly, lateral E` velocity did not show a significant difference between cases (10.95 ± 2.6 cm/sec) and controls (11.22 ± 1.63 cm/sec, p = 0.5402). The septal E/ E` ratio was significantly higher in cases (7.43 ± 2.7) compared to controls (6.55 ± 0.73, p = 0.0443*), with a higher frequency of ratios >8 (32% vs. 5%, p = 0.0008*) and >15 (3% vs. 0%, p = 0.5576). The lateral E/ E` ratio did not show a significant difference (7.51 ± 2.62 in cases vs. 6.63 ± 0.76 in controls, p = 0.1739), but the frequency of ratios >8 (30% vs. 5%, p = 0.0015*) was significantly higher in cases. Septal E/ E`ratio was significantly higher in cases, with a higher frequency of ratios >8 and >15. Lateral E/ E`ratio did not significantly differ, but the frequency of ratios >8 was higher in cases.

Our results were coordinated with the study conducted by **(Ciurzyński et al., 2021)** in 2021 which included 66 patients with SLE of which 57 (86.37%) were female, with a wide age range from 20 to 75 years, were evaluated alongside 27 age-matched healthy subjects. They observed that the E/A ratio exhibited little fluctuation

between patients with SLE and healthy persons, suggesting a significant similarity in the velocities of early to late diastolic filling. However, the group of patients with SLE had a statistically significant higher E/E' ratio, which is an indicator of diastolic dysfunction, in comparison to the control group. This finding underscores the presence of impaired diastolic function in persons with SLE, as seen by the significance of the E/E' ratio in identifying this impairment.

Also, we were in line with **(Myhr et al., 2022)** study in 2022, which spanned a five-year pursuit period and conjoined 108 SLE patients, predominantly females (90%) with a mean age of 46 ± 13 years and a median disease duration of 14 years (range 7–21), several significant findings emerged. The presence of left atrial calcification (LAC) was shown to be linked to indicators of diastolic function and the gradual enlargement of the LV over a period of 5 years. Therefore, LAC may serve as an indicator of cardiac impairment in people with SLE. The E/E` ratio emerged as a key focal point. Although other diastolic measurements showed improvement throughout the follow-up period, such as a drop in the E/A ratio (from 1.4 ± 0.5 to 1.3 ± 0.5, p = 0.002), the E/E` ratio was particularly important in evaluating diastolic function. Specifically, the levels were much higher in patients with SLE in comparison to the control group (7.5 (4–22) vs. 6.8 (1.6–9.4), p = 0.018). Furthermore, the E/E` ratio served as a robust predictor of impaired diastolic function, as seen by its correlation with reduced E/A ratio and increased left ventricular atrial volume index at the beginning of the study. This study highlights the importance of using the E/E` ratio to assess diastolic function in SLE patients over a long period of observation. It offers crucial insights into how the illness affects the cardiovascular system.

(Gegenava et al., 2020) showed that, the all 102 examined SLE patients had positive antinuclear antibodies (ANA), demonstrating their universal presence in this SLE cohort. Additionally, 58% of the patients tested positive for anti-double-stranded DNA (DS DNA) antibodies, and 14% showed positivity for anti-Smith antibodies. In their investigation, patients with SLE exhibited a significant impairment in LV systolic function, as measured by LV GLS, which was found to be closely linked to subsequent cardiovascular events. In comparison to control subjects, those with SLE displayed compromised LV systolic function, both in terms of LV ejection fraction (51 ± 6% vs. 62 ± 6%, P < .001) and LV GLS (−15 ± 3% vs. −19 ± 2%, P < .001). Over a median follow-up period of 2 years (interquartile range, 1–6 years), 38 patients (37%) experienced cardiovascular events, which indicated a significant occurrence of LV diastolic dysfunction in individuals diagnosed with SLE. The E/E' ratio has been shown to be more sensitive in detecting left ventricular diastolic dysfunction than the E/A ratio in patients with SLE. A retrospective analysis was conducted on a cohort of 137 patients diagnosed with SLE, which was then compared to a control group of 110 individuals of the same age and sex. The LV ejection percentages and mean E/A ratio did not vary between the two groups. Nevertheless, the average E/E' ratio of the patients was greater than that of the controls (10.4 +/- 4.0 vs 7.7 +/- 2.1, P < 0.01). Patients with SLE who were

treated with ACEIs or ARBs had notably greater left ventricular ejection fractions and lower E/E' ratios compared to those who did not receive this treatment ($P < 0.05$).

While, **(Gin et al., 2006)** employed TDI to assess cardiac function in SLE patients and identified a discernible trend towards LV dysfunction within this group. Although not reaching statistical significance, the SLE cohort exhibited lower LV ejection fraction and peak systolic TDI of the mitral annulus.

(Elnady et al., 2016) study indicates that individuals with SLE exhibit subclinical dysfunction in both the left and right ventricles. The findings emphasize the importance of regular follow-up and early screening for SLE patients. Specifically, the study highlights lower E and A values in right ventricular diastolic function, particularly in the medial annulus of the tricuspid valve.

Also, **(Leone et al., 2020)** research brings to light the existence of early-stage diastolic dysfunction in individuals with severe SLE, which may remain clinically silent. Their findings suggest that despite the absence of overt clinical symptoms, patients with severe SLE may already be experiencing subtle impairments in diastolic function.

The E/E' ratio is a crucial echocardiographic parameter that evaluates diastolic dysfunction. In a healthy cardiac state, the E/E' ratio remains within a certain physiologic range. However, when diastolic dysfunction occurs the E/E' ratio may deviate from this norm **(Chan et al., 2023; Dal Canto et al., 2022).**

The increased E/E' ratio found in several SLE patients in our research indicates compromised LV relaxation during diastole. Nevertheless, the conventional E/A ratio did not exhibit any notable disparities between the two groups. This indicates that the E/A ratio, which is often used to evaluate diastolic function, may not possess the necessary sensitivity to identify early diastolic impairment in persons with SLE.

On the other hand, the E/E' ratio may be a very sensitive and accurate indicator for assessing left ventricular diastolic dysfunction. Changes in preload have an impact on the E/A ratio, whereas the E/E' ratio stays unaltered. Furthermore, the velocity of the E' stays diminished regardless of changes in the patterns of mitral input. Despite the influence of other variables like elevated left atrial pressure or mitral valve incompetence, the E' velocity in tissue Doppler imaging (TDI) stays reduced when LV filling pressure rises. As a result, the E/E' ratio rises, serving as a definitive sign of LV diastolic dysfunction. These findings indicate that the E/E' ratio might serve as a more dependable measure of LV filling pressure **(Ommen et al., 2000; Sohn et al., 1997).**

In our study, Hydroxychloroquine was the most frequently prescribed drug, used by 65% of patients. Azathioprine was prescribed to 57% of patients, and 52% received high-dose glucocorticoid treatment, while 48% received low-dose glucocorticoids. A smaller proportion of patients received other medications such as mycophenolate mofetil (42%) and cyclosporine (5%), while only 1% received cyclophosphamide.

Hydroxychloroquine, an antimalarial drug with immunomodulatory properties, effectively reduces inflammation, alleviates symptoms, prevents flares, and safeguards against organ damage in autoimmune diseases like SLE **(Schrezenmeier et al., 2020).** Azathioprine also serves as a vital

immunosuppressant in SLE treatment. It suppresses the overactive immune response, controlling inflammation. Azathioprine is especially valuable when hydroxychloroquine alone is insufficient or to reduce reliance on glucocorticoids, thus helping manage the disease and protect against organ damage **(McKeon et al., 2020).**

In 2021, the study conducted by (**Loureiro et al., 2021**) aimed to analyze LV diastolic dysfunction in adolescents with juvenile SLE, it is evident that hydroxychloroquine was extensively employed in the treatment of juvenile SLE. Among the 49 adolescents with juvenile SLE included in the study, an overwhelming majority, with only 4.08% as an exception, used hydroxychloroquine throughout the study period.

Our results were consistent with **(Elgohari, 2022)** case-control study which involved 100 participants divided into two groups: 50 non-SLE individuals in the Control group and an SLE group. The study found significant differences in global longitudinal strain (GLS) and the E/E` ratio between the Control and SLE groups ($p<0.05$), suggesting the potential use of these parameters in identifying cardiac function variations in SLE. Additionally, a significant difference in GLS was noted concerning the duration of SLE ($p<0.05$), indicating the evolving cardiac impact of SLE over time. However, significantly no differences were observed in ejection fraction (EF) or the E/A ratio between the Control and SLE groups, suggesting their limited sensitivity in detecting cardiac issues in SLE.

(Pazoki et al., 2022) did a research with the objective of detecting subclinical left ventricular diastolic impairment in individuals with SLE during the first phase of the disease. The findings indicated that there was no notable disparity in LVEF, as assessed using conventional echocardiography, between the patients with SLE and the group of individuals without any health issues. However, they observed significant differences in E velocity, A velocity, and the E/E` ratio, all of which were higher in people with SLE. These findings highlight the importance of employing more precise criteria, such as the E/E` ratio, to detect mild cardiac dysfunction in patients with SLE, even when conventional measurements like LVEF may not show significant variations.

Similarly, **(Farah et al., 2020)** study on asymptomatic SLE patients. These asymptomatic SLE patients exhibited lower E, A, and E/A ratio values compared to the control group, signifying potential early diastolic dysfunction. Moreover, significant alterations in E/A and E/E` ratios suggested impaired diastolic function even in the absence of symptoms.

In our investigation, we conducted a subgroup analysis to examine SLE patients who were administered either ACEIs or ARBs, contrasting them with those who did not receive prescriptions for these medications. The comparison revealed that individuals utilizing ACEIs, or ARBs exhibited elevated levels of SBP and DBP in comparison to those who were not utilizing these pharmaceuticals. Additionally, their LVEF demonstrated a substantial increase (69.63 ± 5.58 vs. 62.7 ± 4.78, $P < 0.01$).

The significantly higher LVEF in the group on ACEIs or ARBs may be attributed to the beneficial effects of these medications on the heart. ACEIs and ARBs can help improve cardiac

function and prevent adverse remodeling of the heart, which is often seen in conditions like SLE. As a result, the higher LVEF indicates better pumping ability of the heart, potentially reducing the risk of heart failure and related complications in SLE patients **(Khurana and Goswami 2022; Lo and Tsai 2022).**

Conclusion

Our research has demonstrated that the E/E' ratio, which measures the ratio of the velocity of early filling of E to the early diastolic velocity of the mitral annulus (E'), is a more sensitive indicator for detecting left ventricular diastolic dysfunction in patients with SLE compared to the conventional E/A ratio, which is based on the ratio of E to the velocity of late filling of the mitral valve (A). This finding highlights the importance of including E/E' ratio assessment into the diagnostic criteria for evaluating cardiac involvement in systemic lupus erythematosus (SLE), as it provides increased sensitivity in detecting early diastolic problems. Adopting this strategy has the potential to result in prompt therapies that attempt to reduce cardiovascular problems in patients with SLE.

Study limitations

There are certain constraints that must be taken into account in our investigation. Initially, the number of SLE patients and controls included in the study was rather limited, potentially restricting the applicability of our results to a larger population. Furthermore, our research used a cross-sectional design, which hindered our ability to establish causal correlations between variables. Longitudinal investigations would provide a more thorough comprehension of the cardiac alterations in SLE over a period of time. Furthermore, the evaluation of diastolic function using echocardiography was based only on one method. Incorporating additional imaging modalities, such as cardiac magnetic resonance imaging, might have enhanced the validity of our results. Finally, although we saw notable disparities in cardiac parameters, more research is necessary to explore the clinical ramifications and prognostic significance of these results. This will help inform clinical decision-making and improve patient care.

Recommendations

- We recommend incorporating the E/E' ratio as a sensitive indicator for the early detection of left ventricular diastolic dysfunction. By including this parameter, clinicians can identify cardiac involvement at an earlier stage, allowing for timely interventions to mitigate cardiovascular complications in SLE patients.
- It's recommended that SLE patients undergo regular cardiac screening, which should include echocardiography with a specific focus on assessing diastolic function using the E/E' ratio. Routine monitoring is essential to detect and manage cardiac abnormalities promptly, which can lead to improved patient outcomes and a reduced risk of adverse cardiovascular events.
- It's recommended that future research efforts include longitudinal studies with larger cohorts of SLE patients. These studies can provide a more in-depth understanding of the progression of cardiac abnormalities over time and help elucidate the natural history of cardiac involvement in SLE.

Long-term data can guide clinical decision-making and improve patient care.

- We recommend exploring the utility of multimodal imaging approaches in diagnosing and monitoring cardiac involvement in SLE. Combining echocardiography with other imaging techniques, such as cardiac magnetic resonance imaging, may offer a more comprehensive assessment of cardiac function. Investigating the synergies between these modalities can enhance the accuracy of cardiac evaluations.
- It's recommended that further research investigates the clinical implications and prognostic value of the observed cardiac changes in SLE patients. Understanding how these findings correlate with patient outcomes will provide valuable insights for tailoring treatment strategies and optimizing the overall care of individuals with SLE-related cardiac involvement.

Abbreviations:

A	Mitral peak velocity of late filling
2D	Two-Dimensional
ACEIs	Angiotensin-Converting Enzyme Inhibitors
ACR	Albumin To Creatine Ratio
AIHA	Autoimmune Hemolytic Anemia
ANA	Antinuclear Antibody
Anti-dsDNA	Anti-Double-Stranded DNA Antibody
AR	Aortic Regurgitation
ARBs	Angiotensin II Receptor Blockers
ARBs	Angiotensin Receptor Blockers
BMI	The Body Mass Index
C3	Complement Component 3
C4	Complement Component 4
COPD	Chronic Obstructive Pulmonary Disease
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
DBP	Diastolic Blood Pressure
E'	Early diastolic mitral annular velocity
E	Mitral peak velocity of early filling
ECG	Electrocardiogram
EF	Ejection Fraction
ESR	Erythrocyte Sedimentation Rate
GLS	Global Longitudinal Strain
HTN	Hypertension
LA	Left Atrium
LAC	Lupus anticoagulant
LV	Left Ventricular
LVEDD	Left Ventricular End-Diastolic Dimension
LVEF	Left Ventricular Ejection Fraction
LVESD	Left Ventricular End-Systolic Dimension
LVIDd	Left Ventricular Internal Diameter In Diastole
LVIDs	Left Ventricular Internal Diameter In Systole
MHz	Megahertz
MR	Mitral Regurgitation
NS	Not Significant
RBCs	Red Blood Cells
SBP	Systolic Blood Pressure
SLE	Systemic Lupus Erythematosus
SLICC	Systemic Lupus International Collaborating Clinics
SPSS	Statistical Package For The Social Sciences
TDI	Tissue Doppler Imaging
The E/È ratio	The Ratio Of Early (E) To Late Diastolic Filling

	Velocities
TR	Tricuspid Regurgitation
WBCs	White Blood Cells

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