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REVIEW

Left ventricular systolic function assessed by standard and advanced echocardiographic techniques in patients with systemic lupus erythematosus: A systemic review and meta-analysis

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ABSTRACT

Objectives: Aim of the study was to perform a systemic review and meta-analysis of the current case-control studies based on the assessment of the left ventricular (LV) systolic function with standard and advanced echocardiographic methods.

Materials and methods: Objectives of the study, methods of statisticalanalysis, literature search strategy, inclusion andexclusion criteria, and outcome measurementswere defined according to Cochrane Collaborationsteps, 13 including recommendations for metaanalysisof observational studies in epidemiology (MOOSE).

Results: A total of 850 papers were collected. Of those, eight papers (10 groups) including 174,442 SLE patients and 45,608,723 controls with heart failure (HF), 20 papers including 1,121 SLE patients and 1,010 controls with an evaluated LV ejection fraction (LVEF), and eight studies (nine groups) including 462 SLE patients and 356 controls with a measured LV global longitudinal strain (LVGLS) met the predefined inclusion criteria. HF rate in SLE patients was 2.39% (4,176 of 174,442 patients with HF), and SLE patients showed a 3.4 times higher risk for HF compared to controls. SLE patients had a lower LVEF compared to controls. LVGLS was more impaired in SLE patients compared to controls, irrespective of two-dimensional or three-dimensional speckle tracking echocardiography.

Conclusion: Heart failure rate in SLE patients is high, and SLE patients showed a 3.4 times higher risk in patients with SLE compared to controls. LV systolic function, as measured by LVEF and LVGLS, is significantly affected in SLE patients, and LVGLS potentially represents a new tool for the early assessment of LV function.

Keywords: Heart failure, left ventricular global longitudinal strain, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease associated with high cardiovascular morbidity and mortality. Changes in cardiac structure and function have been shown to predict the clinical outcomes in cardiovascular diseases. Both traditional and disease-related factors contribute to the development of cardiovascular disease in SLE patients.[1-3] Long-term inflammatory burden and the immune system abnormalities can result in several forms of cardiovascular involvement, including valvular heart disease, myocarditis, myocardial fibrosis, pericarditis, inflammatory, atherosclerotic, and thromboembolic changes in the vascular system, leading to early coronary artery disease (CAD), congestive heart failure (HF), electrical disturbances, arrhythmias, conduction abnormalities, pulmonary embolism, and cerebrovascular accidents.[4,5]

Patients with SLE undergo extensive left ventricular (LV) remodeling, which can lead to dysfunction of the left ventricle. Therefore, to evaluate and predict cardiac function in SLE patients is of great clinical significance. Changes in cardiac function is reflection of manifestation of changes in cardiac anatomy, electrocardiography,

myocardial contractility as well as the complex blood flow state and hemodynamic changes within the heart cavity.[6]

Left ventricular ejection fraction (LVEF) is the most commonly used index for estimating cardiac function. However, cardiac involvement, particularly at an early stage of the disease, is largely underdiagnosed due to the nonspecific nature of the symptoms and low sensitivity of current diagnostic tools, such as two-dimensional (2D) conventional echocardiography derived LVEF. Studies based on autopsy have shown myocardial involvement in 40 to 50% of SLE patients,[7,8] while only 7 to 10% of SLE patients are clinically diagnosed with myocardial injury.[9] Subclinical HF is common in SLE and is seen in up to 61% of SLE patients based on cardiac magnetic resonance imaging.[10] On the other hand, speckle tracking echocardiography (STE) derived LV global longitudinal strain (LVGLS) using 2D or three-dimensional (3D) techniques has shown to be a reliable and sensitive tool for the diagnosis of subtle myocardial changes in various entities (Figure 1).[11,12]

MATERIALS AND METHODS

Based on the fact that it is a review and meta-analysis of already published data, informed consent was not required, institutional review board's approval was not necessary, and new patients were not recruited for the analysis. Objectives of the study, methods of statistical analysis, literature search strategy, inclusion and exclusion criteria, and outcome measurements were defined according to Cochrane Collaboration steps,[13] including recommendations for meta-analysis of observational studies in epidemiology (MOOSE).[14] PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis) flow diagram was used to depicts the flow of information through the different phases of a systematic review.

Literature search criteria

Electronic databases of PubMed MEDLINE, Cochrane Library, and MD Consult were used to obtain sources of published data. A literature search was performed in July 2022, including articles from all regions in the English language.

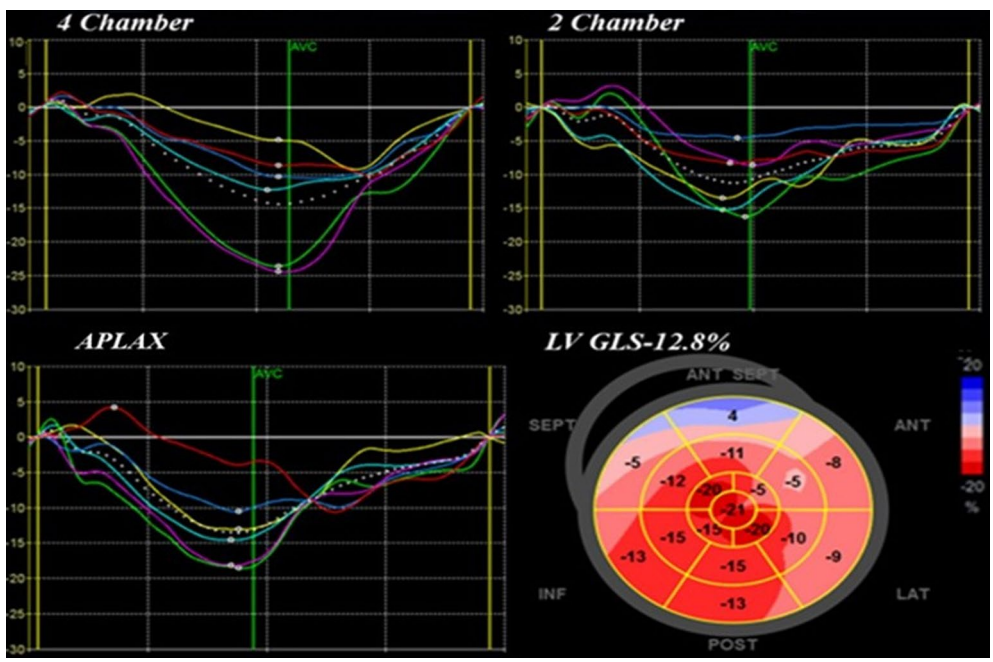

Figure 1. An example of the assessment of LVGLS by STE in SLE patients displayed with color-coded Bull's eye plots for longitudinal strain (LVGLS= –12.8%). Curves of longitudinal strain per segment and averaged among the segments (dotted line for the three-, four-, and two-chamber apical views) are also displayed in the figure.

APLAX: Apical long-axis; LVGLS: Left ventricular global longitudinal strain; STE: Speckle tracking echocardiography; SLE: Systemic lupus erythematosus.

The search criteria included the following search terms in all possible combinations from January 1, 1999, to March 25, 2022: "heart failure in SLE" OR "LV systolic function in patients with SLE" OR "LVGLS in SLE" OR "LVEF in SLE."

Inclusion and exclusion criteria

Inclusion criteria for the studies were defined as follows: *(i)* original studies with a case-control (not case matched) design that compared SLE patients with healthy controls; *(ii)* no history of previous cardiac diseases, such as congenital heart disease, rheumatic heart disease, and CAD; *(iii)* detailed mean and standard deviation of LVEF or LVGLS, as well as the incidence of HF.

The exclusion criteria for the meta-analysis included *(i)* studies with incomplete general information, such as sex, age, and history of cardiac disease; *(ii)* studies without original data of transthoracic echocardiographic parameters; *(iii)* studies that are published in non-English journals.

In addition, the reference lists of all retrieved articles were manually reviewed. Retrieved citations were screened independently by two authors using the title and keywords of the articles, followed by a full-text review for the final inclusion.

Data extraction and outcomes of interest

Data included in this study were extracted and summarized by two independent authors. Studies were carefully analyzed for clinical parameters including prevalence of HF and echocardiographic measures of LV systolic function: LVGLS and LVEF in SLE patients and controls. In each study, data regarding sample size, major clinical and demographic variables, and values of LVEF and STE-derived LVGLS were extracted for cases and controls.

As the primary analysis, we evaluated the incidence of HF in SLE patients in reported studies; additionally, we evaluated mean values of LVGLS and LVEF in SLE patients and in controls without SLE.

Quality assessment

Analysis was done according to an established protocol of the Cochrane collaboration steps and MOOSE recommendations. The methodological quality of case-control studies was independently assessed by two reviewers using the modified Newcastle-Ottawa scale.[14-16] A score ranging from 0 to 9 was calculated for each study. Studies achieving 6 or above were considered to be of high quality.

Statistical analysis

All analyses were performed using the Review Manager 5.0 (Cochrane Collaboration, Oxford, UK) and IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA). The standardized mean difference (SMD) and odds ratio (OR) were used to compare continuous and dichotomous variables, respectively. All results were reported with 95% confidence intervals (CIs). Statistical heterogeneity between studies was formally assessed using the chi-square test with significance set at $p<0.10$, and heterogeneity was quantified using the inconsistency index *(I^2)* statistic. Heterogeneity (a lack of homogeneity) was considered to be significant with an I^2 ≥50%. The random-effect model was used if there was heterogeneity between studies; otherwise, the fixed-effects model was adopted.[17,18] Sensitivity analysis was performed using both models. Publication bias was performed by Egger's test, and the significance was considered if a p-value <0.05 was achieved.

RESULTS

A total of 850 papers were collected according to our searching criteria. Of those, 811 publications were unrelated and therefore excluded from the study. The flow diagram of the selection process is shown in Figure 2. Finally, from the selected 39 studies, eight papers including 174,442 SLE patients and 45,608,723 controls with HF, 20 papers including 1,121 SLE patients and 1,010 controls with measured LVEF, and eight papers including 462 SLE patients and 356 controls with measured LVGLS met the predefined inclusion criteria and were used for this systemic review. All studies in our meta-analysis were case-control (not case matched) studies (evidence level 3b) with a high quality (quality score above 6).

We performed meta-analysis for each of the following abnormalities: HF incidence and LVEF and LVGLS in SLE patients. Meta-analysis for HF,

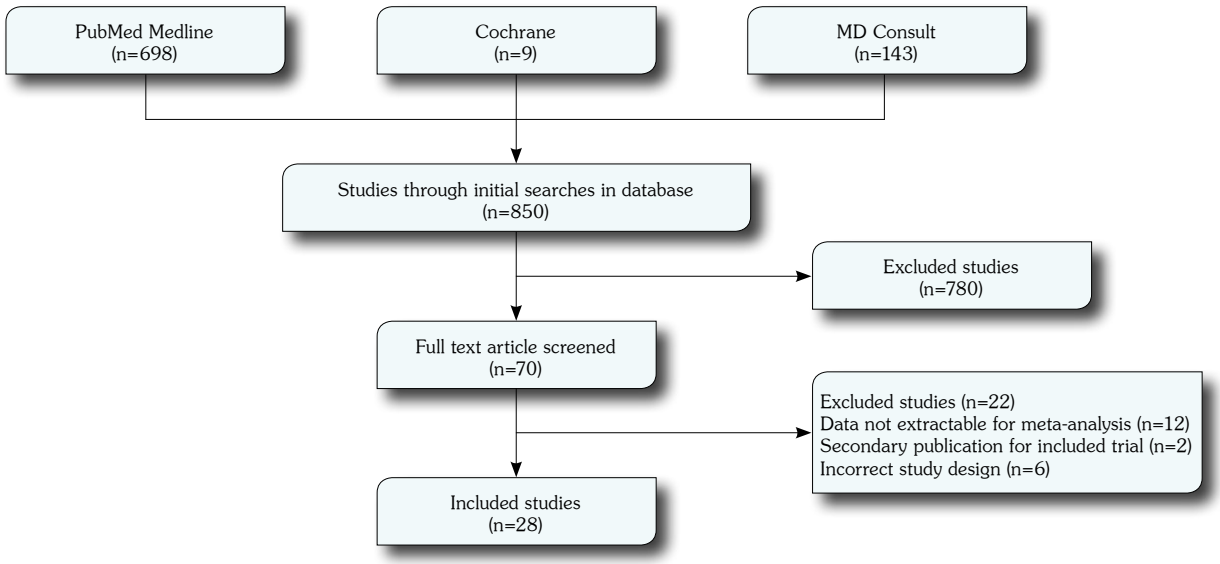

Figure 2. Flow diagram of studies identified, included, and excluded.

LVEF, and LVGLS were heterogeneous (I^2 >50%). Thus, a random model was used for the analysis of these three parameters.

Heart failure and alterations in left ventricular systolic function

Prevalence of HF was reported in eight papers, including 174,442 SLE patients and 45,608,723 controls. The mean age of the participants was 47.9±7.1 years, and 16,888 of the participants were male, whereas 157,554 were female. HF rate in SLE patients was 2.39% (n=4,176) and showed 3.4 times higher risk in patients with SLE compared to controls (OR=3.41, 95% CI: 2.51-4.65, p<0.00001, Figure 3). Prevalence of HF in controls was 0.19% (n=86,214).

Left ventricular ejection fraction was evaluated in 1,121 SLE patients and in 1,010 controls from the selected 20 studies. The mean age of the participants was 36.7±10.7

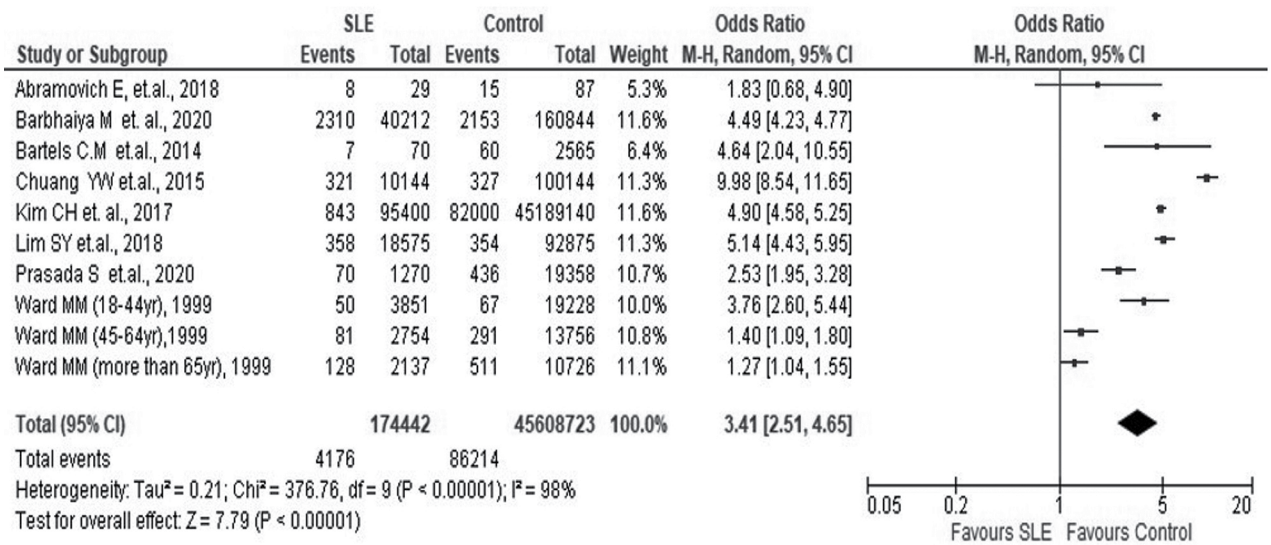

Figure 3. Forest plot and meta-analysis of HF prevalence in patients with SLE.
SLE: Systemic lupus erythematosus; M-H: Mantel-Haenszel method; CI: Confidence interval; HF: Heart failure.

years, and 135 of the participants were male, whereas 986 were female. We found that patients with SLE overall had a lower value of LVEF compared to controls (SMD=-0.41, 95% CI: −0.60 to −0.23, p<0.0001, Figure 4). Subgroup analysis showed that LVEF

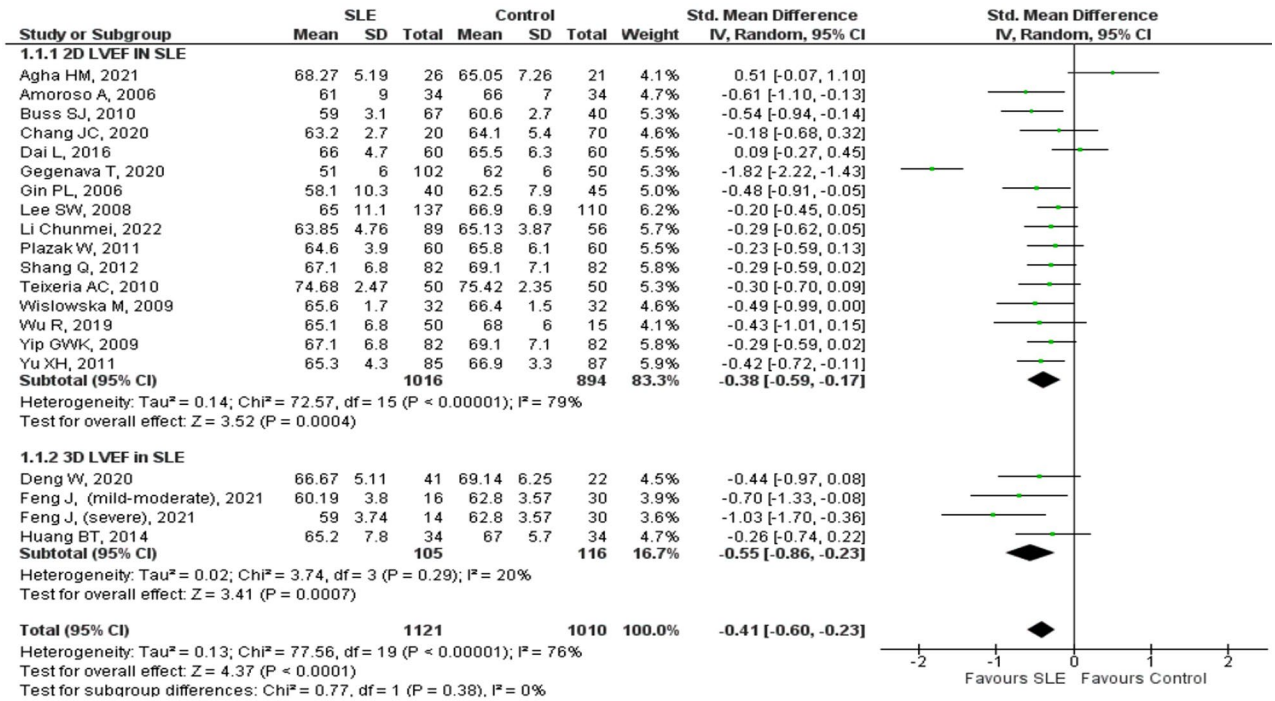

Figure 4. Forest plot and meta-analysis of LVEF in patients with SLE.

SLE: Systemic lupus erythematosus; SD: Standard deviation; LVEF: Left ventricular ejection fraction; IV: Inverse variance method; CI: Confidence interval.

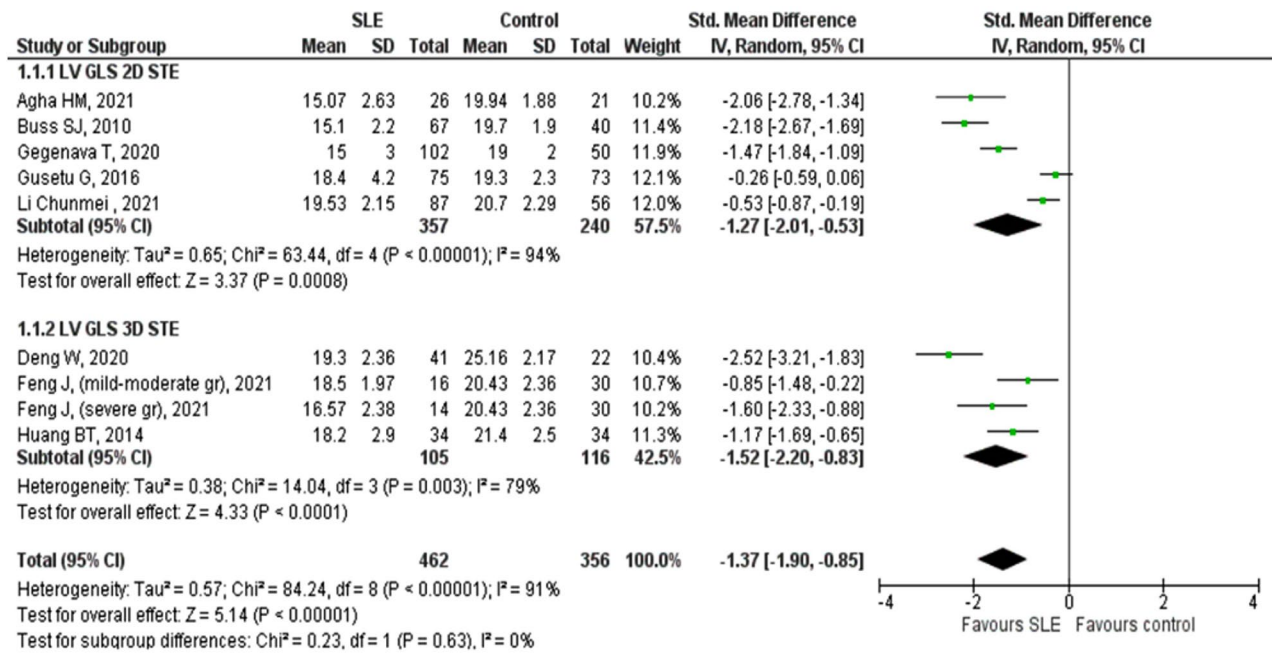

Figure 5. Forest plot and meta-analysis of LV GLS in patients with SLE

SLE: Systemic lupus erythematosus; SD: Standard deviation; IV: Inverse variance method; CI: Confidence interval; LV GLS: Left ventricular global longitudinal strain; STE: Speckle tracking echocardiography.

was lower in the study group independently of 2D (SMD= −0.38, 95% CI: −0.59 to −0.17, p<0.0004) or 3D (SMD= −0.55, 95% CI: −0.86 to −0.23, p<0.0007) echocardiographic technique (Figure 4).

Eight selected studies measured the LVGLS of 462 SLE patients and 356 controls. The mean age of the participants was 36.7±10.9 years, and 50 of the participants were male, whereas 412 were female. LVGLS was more deteriorated in SLE patients compared to controls (SMD= −1.37, 95% CI: −1.90 to −0.85, p<0.00001, Figure 5). Three studies (four groups) from selected publications had performed a 3D STE-derived LVGLS assessment.[19-21] Subgroup analysis showed that 2D (SMD=−1.27, 95% CI: −2.01 to −0.53, p<0.0008) and 3D (SMD=−1.52, 95% CI: −2.20 to −0.83, p<0.0001) STE-derived LVGLS was significantly lower in SLE patients compared to healthy controls (Figure 5).

Sensitivity analysis and publication bias

In sensitivity analysis, the findings were similar regardless of the models used, fixed or random effect. Egger's test was performed for the evaluation of publication bias, and a significant difference (p<0.05) was not detected in any case, HF, LVEF, or LVGLS.

DISCUSSION

In the present meta-analysis, we investigated 176,025 SLE patients from 31 studies for the presence of HF and LV systolic function assessment with the help of standard (LVEF) and advanced echocardiographic (LVGLS) methods. To the best of our knowledge, this is the first paper providing complex assessment of LV systolic function using different echocardiographic modalities and assessing prevalence of the HF in these patients. Based on the meta-analysis, our study showed that patients with SLE have a higher risk of HF compared to controls. LVEF and LVGLS (irrespective of 2D or 3D STE mode) are significantly more affected in SLE patients as compared to controls too.

Heart failure in patients with SLE

Cardiovascular involvement and cardiovascular complications are highly prevalent in SLE patients.[3] Long-term inflammatory burden and the immune-system abnormalities can result in several forms of cardiovascular involvement, including congestive HF.[7,22-30] Potential effects of autoimmunity on cardiovascular health are likely to be much broader than originally thought, probably due to effects on connective tissue and small vessels, cardiomyocytes, and some of the treatments commonly used to treat autoimmunity.

Data about the prevalence of HF in SLE patients are controversial and often underestimated owing to the nonspecific nature of the symptoms. According to our meta-analysis based on the published literature, patients with SLE overall have 3.41 times higher prevalence of HF compared to controls (OR varies from 1.27 to 9.98). Microvascular inflammation, endothelial activation, reduction in nitric oxide, adenosine triphosphate, and cyclic guanosine monophosphate all together lead to microvascular ischemia, LV remodeling, and fibrosis.[31,32] Medications (e.g., chloroquine and hydroxychloroquine) used for long term in patients with SLE causes deficiency in lysosomal cells that lead to intracellular accumulation of glycogen and membrane phospholipids, inducing cardiac structural and functional abnormalities and possibly leading to HF.[33] Moreover, thrombotic microvasculopathy, attributed to antiphospholipid antibodies, is responsible for myocardial ischemia, even in the absence of obstructive CAD.[34,35]

Speckle tracking echocardiography

Two-dimensional echocardiography may be limited by its low sensitivity to detect subtle myocardial dysfunction, leading to underestimation of cardiac involvement in SLE patients. The use of advanced echocardiographic techniques, particularly speckle tracking imaging, is currently proposed as a more sensitive and reproducible approach to detect subtle myocardial systolic dysfunction as compared to conventional echocardiographic measure such as LVEF.[36,37] STE is a valuable technique that allows the evaluation of ventricular and atrial myocardial deformation by dimensionless parameters without the need of any geometrical assumption. Therefore, it is considered a promising tool for the assessment of regional

and global atrial and ventricular systolic and diastolic functions. Using this imaging technique, LVGLS can be measured, and this parameter showed to be clinically useful for the early detection of myocardial dysfunction and risk stratification in several cardiovascular diseases, including cardiac involvement in autoimmune disorders.[11] Moreover, some studies showed significant association between deteriorated LVGLS and cardiovascular events.[12] According to current recommendations based on the recent meta-analysis that included 24 studies with 2,597 healthy subjects, normal values for GLS ranged from 15.9 to 22.1% (mean: 19.7; 95% CI: 20.4-18.9%). Values are somewhat vendor dependent, but a GLS <16% represents reduction in LV systolic function and a GLS between 16% and 18% represents borderline values.[38,39]

In the present study, changes in echocardiographic parameters, including decreased systolic function of the left ventricle, were important features in SLE patients. LVEF was significantly lower in almost every reported study in our meta-analysis, with very few exceptions.[20,21,40-52]

Left ventricular systolic function assessment with STE derived LVGLS showed consistently lower levels in every reported study without exceptions.[40,41,53,54] Interestingly, these findings are confirmed and extended by the subgroup analyses, showing similar results both in studies using 2D STE and in those using 3D STE modalities.[19,20]

The precise mechanism of decreased LV systolic function remains unclear. It may relate to myocarditis or CAD, which may be activated due to traditional and disease-related factors. STE-derived LVGLS assessment outlines the presence of subclinical changes in the myocardium even before the HF symptoms manifest.

Some limitations of this meta-analysis must be acknowledged. All studies included were case-control studies, although most of them were of high quality. Studies showed a heterogeneity >50%, significant heterogeneity between selected studies can be explained by differences observed in age, sexes, races, disease courses, and disease activities in included studies. Adopting the random effects model may reduce the effect of heterogeneity, but it does not avoid it. Furthermore, only one study with 3D STE echocardiography measurements was included. Echocardiography and STE have their limitations; however, both are inexpensive, reproducible, noninvasive, and nonradioactive techniques, and it has been proved that these are reliable methods and they may remain practical tools for the diagnosis of cardiac involvement in patients with SLE.

In conclusion, the rate of HF in SLE patients is high, and SLE patients showed a 3.4 times higher risk for HF compared to controls. LV systolic function as measured by LVEF and LVGLS is significantly affected in SLE patients. Data from this meta-analysis suggest that STE-derived LVGLS potentially represents a new tool to improve the early evaluation of LV function and may improve risk stratification in patients with SLE.

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