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Echocardiography Myocardial Work and Cardiac Biomarkers Indicate Subclinical Systolic Myocardial Dysfunction in Patients with Systematic Lupus Erythematous

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Abstract: Background: Systemic lupus erythematosus (SLE) is characterized by inflammation and cardiovascular complications. Our study aimed to investigate subclinical and early indicators of systolic myocardial dysfunction in SLE patients using advanced echocardiographic methods and biomarkers. **Methods:** In this cross-sectional study, we enrolled 102 SLE patients without known cardiac impairment and 51 healthy controls. Demographics, disease characteristics, laboratory results, disease activity (SLEDAI) and organ damage (SDI) indices were recorded. Left ventricular global longitudinal strain (GLS) and myocardial work indices were assessed by utilizing speckle tracking echocardiography. In addition, high sensitivity C-reactive protein (hsCRP), high sensitivity troponin (hsTn) and N-terminal-pro B-type natriuretic peptide (NT-proBNP) levels were measured in blood samples. **Results:** In comparison to controls, SLE patients had significantly higher GLS (-19.94±2.71%vs-21.15±1.55%, p<0.001) and global wasted work (GWW) (94±71mmHg%vs71±49 mmHg%, p=0.025). Notably, NT-proBNP and hsTn were threefold and twofold higher in SLE group compared to control group, respectively (p<0.001). Within SLE cohort, patients with at least moderate disease activity (SLEDAI≥4) both biomarkers were significantly elevated than those with low disease activity (SLEDAI<4). **Conclusion:** Advanced echocardiographic parameters combined with specific biomarkers have a promising role in detecting systolic dysfunction at an early phase in SLE patients, potentially enabling timely interventions to mitigate cardiovascular risk.

Keywords: systematic lupus erythematous; echocardiography; myocardial work; speckle tracking echocardiography; high sensitivity troponin; natriuretic peptide

1. Introduction

Systemic lupus erythematosus is a prototypic autoimmune disease characterized by systemic inflammation and dysfunction of various organs, including the cardiovascular system [1]. Cardiac manifestations are commonly observed in SLE patients and can involve any part of heart including the myocardium, valves, conduction system, pericardium and coronary arteries [2]. Myocardial disease can be present in 8-14% SLE patients, and the nonspecific nature of associated signs and symptoms often confused with SLE clinical manifestations may lead to underdiagnosis of myocardial dysfunction, heightening the risk of morbidity and mortality [3]. Heart failure (HF) is a common complication in SLE patients negatively impacting their prognosis [4]. While HF with reduced ejection fraction (HFrEF) occurs less frequently, the prevalence of subclinical left ventricular (LV) systolic dysfunction or HF with preserved ejection fraction (HFpEF) is speculated to be higher in the SLE population. The connection between SLE and HF is primarily attributed to immume-mediated mechanisms, and the presence of traditional cardiovascular risk factor, such as hypertension and hyperlipidemia [5].

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The introduction of speckle tracking echocardiography (STE) has conferred a great advantage in the early detection of subtle reduction in LV systolic function [6,7]. It has been demonstrated that the impairment of LV deformation becomes detectable before the development of an overt systolic dysfunction, especially among patients with auto-immune diseases [8]. To date, a limited number of studies has investigated the presence of subtle systolic dysfunction in SLE patients utilizing STE [9], [10]. The latter studies implicate the early development of myocardial dysfunction before becoming apparent clinically or with the classical echocardiographic indices, like LV ejection fraction (LVEF), in comparison to healthy controls.

The main disadvantage of GLS calculation is its dependence on blood pressure measurement. A novel advancement in STE is its ability to calculate myocardial work (MW), proposed as an early marker of cardiac damage, independent of blood pressure level. MW is an evolving echocardiographic tool linked with the pathophysiology of myocardial function, but more studies are required to clarify its clinical impact, its advantages over STE and set its limitations [11]. A recently published study has demonstrated MW as a more sensitive tool for detecting subclinical LV systolic dysfunction in SLE population [12].

Cardiac biomarkers such as natriuretic peptides and troponin have long been used as considerable tools for diagnostic and prognostic purposes among patients with suspected or established HF, respectively [13]. Limited studies have documented elevated blood concentrations of both those biomarkers in SLE patients [14]. Therefore, a diagnostic strategy that integrates STE, MW assessment, and cardiac biomarkers could enhance early detection of subclinical systolic myocardial dysfunction in SLE patients. This integrated strategy would enable clinicians to initiate treatment earlier, potentially leading to better patients' outcome.

This study examined the hypothesis that SLE negatively impacts LV myocardial systolic function at a subclinical level in SLE patients without overt cardiovascular disease (CVD). It aimed to: (1) evaluate LV myocardial systolic function using STE, MW and cardiac biomarkers (natriuretic peptides and troponin), (2) explore the relationships of the latter parameters between them, with disease activity, organ damage indices and other clinical parameters in order to subclinical LV myocardial systolic dysfunction.

2. Materials and Methods

Participants

We recruited 102 adult patients diagnosed with SLE from 2 centers over the period from September 2022 to October 2023. SLE diagnosis was based on the SLICC 2012 classification criteria [15]. The history of any SLE-related complication was retrieved from the medical records. Among exclusion criteria were: concurrent cardiovascular diseases such as coronary artery disease (CAD), heart failure with reduced ejection fraction (HFrEF), peripheral artery disease, or other cardiomyopathies and patients with concomitant significant kidney or liver impairment, chronic diseases associated with poor prognosis (e.g. cancer) or recent infection, surgery or trauma which might have increased the inflammatory burden. Additionally, patients with echocardiographic images of poor quality, which could question the interpretation of echocardiography analysis, were not included in the final enrolment.

Furthermore, 51 sex- and age-matched healthy individuals without any chronic disease were recruited as controls. The study adhered to the ethical guidelines of the Declaration of Helsinki. The study obtained approval from the national bioethical committee (EEBK/EP/2019/03). Before entering the study, all participants provided a signed complete informed consent.

Study Design

We conducted an observational, cross-sectional study. We obtained a complete medical history, including demographic data, disease duration, organ involvement, current or previous treatments, and disease activity and damage indices. The disease activity was analyzed by Safety of Estrogens in Lupus Erythematosus National Assessment–SLEDAI instrument score (SELENA-SLEDAI) and

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organ damage by the SLICC/ACR Damage Index (SDI) [16], [17]. In the context of medical history, we recorded medications and cardiovascular risk factors, including active smoking, hypertension, diabetes mellitus (DM), dyslipidemia and family history of premature CAD. We also measured body weight and blood pressure and we calculated the body mass index (BMI).

Further, all eligible participants underwent echocardiography conducted by an experienced echocardiographer, and image analysis for speckle tracking and MW was performed. Subsequently, blood samples were collected for the measurement of high sensitivity C-reactive protein (hsCRP), high-sensitive cardiac troponin I (hs-cTnI) and N-terminal-pro B-type natriuretic peptide (NT-proBNP). The echocardiographic and laboratory methods are described in the following sections.

Global Longitudinal Stain (GLS) and Myocardial Work (MW)

We examined the LV myocardial deformation by calculating the LV global longitudinal stain (GLS) formula using the following steps: During breath-holding, we recorded 2 consecutive cardiac cycles of the 4-chamber, 2-chamber and 3-chamber apical views. The frame rate frequency was above 60 frames/s. Longitudinal strain was measured from 3 apical views, with each wall subsequently divided into 3 segments (basal, mid and apical), resulting in a total of 17 segmental strain curves. This analysis was performed using the EchoPAC Version 203 software package (GE Vingmed Ultrasound, Norway). GLS was calculated as the average value of the three apical strain peak values. Two experienced cardiologists made the calculations, blinded to patients' medical history. The intra and inter-observer reliability of strain analysis by our group has been previously reported and found to be very low (<2.5%) [18].

Blood pressure was considered equivalent to LV pressure. To build up a global LV pressure-strain loop adjusted on valvular timing events, the vendor-specific software integrated a global LV strain curve with a non-invasively predicted LV pressure curve. The MW was quantified by computing the region myocardial shortening rate and multiplied by LV pressure during the LV isovolumic contraction and ejection period. The regional constructive work (CW) generated during segmental shortening, while the regional segmental elongation comprised the regional wasted work (WW). We also calculated: 1) global work index (GWI, mmHg%): total MW within the area enclosed in the LV pressure-strain loop (from mitral valve closure through to mitral valve opening). 2) global constructive work (GCW, mmHg%): total MW of 17 segments generated during myocardial shortening in systole and lengthening in isovolumic relaxation. 3) global wasting work (GWW, mmHg%): total MW of 17 segments generated during myocardial lengthening in systole and shortening in isovolumic relaxation. 4) global wasting efficiency (GWE, %): The ratio of GCW/(GCW + GWW) [19], [20].

Blood Assays

Blood samples were promptly collected after overnight fasting and subjected to centrifugation, after which the resulting serum was stored in a deep freezer at -80°C. The measurements of serum hsCRP, hs-cTnI and NT-proBNP and were conducted using the Alinity analyzer from Abbott Diagnostics (Abbott Park, Illinois, USA). This process involved a two-step immunoassay conducted in human serum, utilizing chemiluminescent microparticle immunoassay (CMIA) technology.

According to the manufacturer's specifications, the precision of the hs-cTnI and NT-proBNP assay at low concentrations is adequate, enabling the assessment of various thresholds with a coefficient of variation (CV) of 3.2% in our laboratory.

Statistical Analysis

Before conducting the analysis, the normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± SD, and group comparisons were carried out using Student's t-test. Categorical variables were expressed as numbers or frequencies (%) and were compared using the Chi-square test. The assessment of SLE activity involved stratification into 2 categories: at least moderate activity (defined as SELENA-SLEDAI≥ 4)

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or low disease activity (defined as SELENA-SLEDAI < 4). Based on SDI we divided patients into subgroups with organ damage (SDI≥ 1) or not (SDI<1).

To investigate the relationship of parameters of LV systolic function (GLS, MW indices) and biomarkers (hs-cTnI and NT-proBNP) with clinical parameters and SLE activity, univariate analysis was performed using Pearson correlation. Subsequently, for multivariate regression analysis was conducted. The data analysis was carried out using SPSS version 25, with statistical significance set at a p-value of ≤ 0.05.

3. Results

A total of 126 patients with SLE were selected for the study. Following a comprehensive clinical and echocardiographic assessment, 102 consecutive patients diagnosed with SLE (with a mean age of 51, of whom 90% were women) were considered eligible for participation in this study. A significant proportion of SLE patients were on prednisolone (41.5%) and hydroxychlorokine (82%). Based on medical records 24.5% among SLE patients reported nephritis and/or 13.7% pericarditis in the past. None of the SLE patients had a history of cardiovascular disease (e.g. myocardial infarction, myocarditis), significant kidney impairment or acute pericarditis. Almost 25% of SLE patients were on medications for hypertension and a similar percentage had hyperlipidemia (Table 1).

Table 1. Comparison between patients with SLE and healthy controls.

	SLE patients (N=102)	Healthy controls (N=51)	P-value
Age (years)	51±15	50±7	0.352
Males/females (n)	10 / 92	6/45	0.720
Hypertension (n)	25 (25.5%)	0	-
Dyslipidemia (n)	25 (25.5%)	0	-
Diabetes (n)	3 (2.9%)	0	-
Nephritis (n)	25 (25.5%)	0	-
Pericarditis (n)	14 (13.7%)	0	-
Duration SLE (years)	13±8	-	-
SLEDAI ≥ 4 (n)	39 (38.2%)	-	-
SDI ≥ 1 (n)	19 (18.6%)	-	-
SBP (mmHg)	135±17	131±13	0.189
DBP (mmHg)	81±13	82±8	0.833
HR (bpm)	73±11	72±9	0.703
Echocardiography			
LVEF (%)	65±7	66±7	0.205
E/A ratio	1.22±0.53	1.19±0.29	0.753
E/E' ratio	7.37±5.32	6.11±1.56	0.134
TAPSE (cm)	2.2±0.3	2.5±0.4	<0.001
RVS' (m/s)	0.77±2.48	0.14±0.02	0.133
TRVmax (m/s)	2.17±0.41	2.71±2.88	0.159
LAVI (ml/m²)	33.1±17.3	34.4±13.5	0.669
GLS (%)	-19.84±2.51	-21.35±1.25	<0.001
GWI (mmHg%)	2072±421	2080±346	0.899
GWW (mmHg%)	94±71	71±49	0.025

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GCW (mmHg%)	2401±475	2397±365	0.960
GWE ratio (%)	95.64±2.73	96.33±2.26	0.143
Biomarkers			
Troponin (pg/mL)	3.33±2.10	1.56±1.02	<0.001
NT-proBNP (pg/ml)	163.71±86.82	58.55±23.87	<0.001

Abbreviations: DBP, Diastolic blood pressure; E/A ratio, E transmitral flow velocity / A transmitral flow velocity; E/E', E transmitral flow velocity / E' tissue; GLS, Global longitudinal strain; GCW, Global constructive work; GWE, Global work efficiency; GWI, Global work index; GWW, Global wasted work; HR, Heart rate; LAVI, Left atrial volume index; LVEF, Left ventricular ejection fraction; n, Number; b NT-proBNP, N-terminal pro–B-type natriuretic peptide; RVS', Right ventricular systolic excursion velocity by tissue Doppler; SBP, Systolic blood pressure; SDI, SLICC/ACR Damage Index; SLE, Systematic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TAPSE, Tricuspid annular plane systolic excursion; TRVmax, Maximal tricuspid regurgitation velocity.

Additionally, a control group consisting of 51 individuals (mean age: 50 years, 88% women) was included in the study. Those healthy control participants did not have any chronic illnesses and were not on any chronic medication regimens. The comparative evaluation of those groups showed no significant differences between them concerning gender distribution, vital signs, and BMI. Regarding the assessment of SLE activity, all relevant parameters were evaluated. Using the Systemic Lupus Erythematosu s Disease Activity Index (SELENA-SLEDAI), 39 patients were identified as having high disease activity (SELENA-SLEDAI ≥ 4), and when employing the SDI, 19 patients were categorized as having organ damage (SDI ≥ 1).

Echocardiographic Findings and Cardiac Biomarkers

Most of the classical echocardiographic indices did not significantly differ between groups, as shown in Table 1. However, a small proportion of SLE patients (4%) exhibited diastolic dysfunction (defined as E/A < 0.8, E/E' > 8, and left atrium dilatation), and 4% had left ventricular hypertrophy (LVH). Surprisingly, SLE patients had lower levels of tricuspid annular plane systolic excursion (TAPSE), but its levels remained within normal range compared to controls ($p < 0.001$).

Concerning the novel echocardiographic markers, SLE patients exhibited higher values of GLS ($p < 0.001$) and GWW ($p = 0.025$) compared to controls. No significant differences were observed in the rest of MW parameters.

hs-cTnI concentrations were twofold higher in SLE patients compared to controls, while NT-proBNP concentrations were almost threefold higher in the SLE group compared to the control group ($p<0.001$). Within the SLE group, patients with previous nephritis and/or pericarditis tended to have higher hs-cTnI levels (3.53pg/ml vs. 2.78pg/ml, $p = 0.126$) and NT-proBNP levels (170 ± 100 pg/ml vs. 148 ± 100 pg/ml, $p = 0.293$) than complication-free counterparts, but those differences did not reach statistical significance.

Comparison based on Disease Activity or Organ Damage

The SLE group was further subdivided into subgroups of patients with at least moderate disease activity and low disease activity using the cutoff values SELENA-SLEDAI ≥ 4, and into patients with damage and no damage using the cutoff value SDI ≥ 1. When applying the cutoff value (SELENA-SLEDAI ≥ 4), we observed non-significant differences in LVEF and novel echocardiographic findings between subgroups, apart from GCW, which was reduced in the subgroup with higher disease activity. Furthermore, patients with at least moderate disease activity had significantly higher troponin and NT-proBNP levels. Non-significant differences were observed in the rest of parameters between subgroups. All clinical, echocardiographic, and biochemical characteristics of both groups are depicted in Table 2.

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Table 2. Comparison within SLE group of patients with moderate and high disease activity vs low disease activity.

	Subgroup A (SLEDAI <4) N=63	Subgroup B (SLEDAI ≥4) N=39	P- value
Age (years)	51±17	51±12	0.827
Duration (years)	16±14	13±11	0.439
Hypertension (n)	13 (20.6%)	12 (30.4%)	0.091
Dyslipidemia (n)	14 (22.2%)	11 (28.2%)	0.287
Diabetes (n)	2	1	-
Nephritis (n)	14 (22.2%)	11 (28.2%)	0.287
Pericarditis (n)	7 (11.1%)	7 (17.9%)	0.074
BMI (Kg/m²)	24.97±4.52	25.96±4.68	0.191
SBP (mmHg)	135±14	137±16	0.212
DBP (mmHg)	81±12	82±14	0.959
LVEF (%)	66±6	65±6	0.743
GLS (%)	-20.11±2.99	-19.52±2.30	0.327
GWI (mmHg%)	2065±453	2086±365	0.806
GWW (mmHg%)	93±69	95±45	0.858
GCW (mmHg%)	2489±398	2231±356	0.049
GWE ratio (%)	96.30±4.35	95.91±2.19	0.503
Troponin (pg/mL)	2.89±1.50	4.01±2.76	0.008
BNP (pg/ml)	122.2±70.4	200.3±112.6	<0.001

Abbreviations: BNP, Brain natriuretic peptide; BMI, Body-mass index; DBP, Diastolic blood pressure; GLS, Global longitudinal strain; GCW, Global constructive work; GWE, Global work efficiency; GWI, Global work index; GWW, Global wasted work; LVEF, Left ventricular ejection fraction; n, Number; SBP, Systolic blood pressure; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

The subdivision of SLE cohort based on SDI levels did not reveal significant differences between subgroups, perhaps to the unequivocal distribution of participants (data not shown).

Correlations

In univariate analysis of cardiac biomarkers, we observed notable correlations. Hs-cTnI displayed significant associations with several key variables, including the SELENA-SLEDAI, SDI, GLS, and NT-proBNP. Similarly, NT-proBNP exhibited considerable correlations with SLEDAI, SDI, GLS, Left Atrial Volume Index (LAVI), and troponin. Variables with significant univariate associations with either hs-cTnI or NT-proBNP entered the multivariate regression analysis. SLEDAI, GLS and NT-proBNP remained independent predictors of hs-cTnI as the dependent variable (R^2=0.242, p<0.001). In parallel, SELENA-SLEDAI, GLS and troponin independently predicted NT-proBNP levels among SLE patients (R^2=0.371, p<0.001). The results are presented in Table 3a,b.

Table 3. (**a**) Associations between troponin (dependent variable) and other variables in SLE patients. (**b**) Associations between NT-proBNP and other variables in SLE patients.

Characteristics	Univariate analysis		Multivariate analysis	
	β (SE)	p	β (SE)	P
NT-proBNP	0.511 (0.232)	0.002	0.237 (0.095)	0.029

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SELENA-SLEDAI	0.312 (0.121)	<0.001	0.210 (0.068)	0.012
GLS	-0.488 (0.113)	<0.001	-0.322 (0.096)	0.004
SDI	0.110 (0.109)	0.041		
Characteristics	**Univariate analysis**		**Multivariate analysis**	
	β (SE)	**p**	**β (SE)**	**P**
Troponin	0.589 (0.110)	0.002	0.348 (0.062)	0.002
SELENA-SLEDAI	0.282 (0.101)	0.002	0.164 (0.056)	0.031
GLS	-0.432 (0.174)	<0.001	-0.266 (0.091)	0.007
SDI	0.252 (0.156)	0.035		
Nephritis	0.259 (0.179)	0.037		

Abbreviations: GLS, Global longitudinal strain; NT-proBNP, N-terminal pro–B-type natriuretic peptide; SDI, SLICC/ACR Damage Index; SLEDAI, Systematic Lupus Erythematosus Disease Activity Index. GLS, Global longitudinal strain; LAVI, Left Atrial Volume Index; SDI, SLICC/ACR Damage Index; SLEDAI, Systematic Lupus Erythematosus Disease Activity Index.

We also examined the relationships of disease activity (expressed by SELENA-SLEDAI) and organ damage (expressed by SDI) with the rest of variables. It is noteworthy that, despite an initial univariate correlation between SELENA-SLEDAI and GCW, this association did not persist when subjected to the multiple linear regression analysis.

4. Discussion

In the present study, the comparative evaluation of SLE patients without CVD versus healthy controls revealed impaired GLS and GWW of myocardial work in SLE patients, indicating subtle cardiac dysfunction in this patient group. Elevated circulating levels of hs-cTnI and NT-proBNP were detected in SLE patients, even in the absence of overt CVD, underscoring the potential cardiac involvement in SLE. Furthermore, both cardiac biomarkers, hs-cTnI and NT-proBNP, demonstrated independent associations with GLS in SLE patients. In the subgroup of SLE patients with at least moderate disease activity (SELENA-SLEDAI ≥ 4), we observed a reduction in GCW and significantly higher hs-cTnI and NT-proBNP levels compared to the low disease activity counterparts.

One of the major complications of SLE associated with a poor prognosis is the cardiac systolic dysfunction [9]. That is primarily associated with the duration and the severity of the disease [21]. There are two main underlying causes related to systolic dysfunction. Firstly, the reasons of premature CAD include precipitated atherosclerosis, thrombosis, endothelial damage, inflammation, renal impairment, hypertension, dyslipidaemia, and corticosteroid administration. A second cause is myocarditis, induced by inflammatory insult such as immune-mediated mechanisms. Previous studies have reported a very low incidence of HFrEF among SLE patients [22], while diastolic dysfunction may be more common [23]. In our study, a very small number of SLE patients exhibited significant diastolic dysfunction. It is worth noting that the sensitivity of classical echocardiographic parameters in detecting minor systolic dysfunction is very low, especially in the early stages of CAD or in patients with minimal myocarditis spread in limited area. Regarding the impact of SLE on myocardial function, there is a growing body of evidence indicating that subclinical LV dysfunction among SLE patients is common finding [12,13]. This dysfunction is typically identified through GLS measurements despite preserved LVEF [24,25]. In line with a recent meta-analysis of 9 studies [26], we confirmed lower GLS values in SLE patients compared to age- and sex-matched healthy controls. Notably, our SLE cohort had low cardiovascular risk profile, with no previous atherothrombotic CVD or myocarditis recorded. Moreover, a small proportion of patients had nephritis or pericarditis in the

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past without any remaining disorders. What adds significant value to our results is the detection of reduced GLS in otherwise cardiac uncomplicated patients. This finding indicates the early involvement of SLE in myocardial dysfunction, which may alter the management of those patients. Lower strain values indicate subclinical impairment of the myocardium and have been linked to a higher incidence of cardiovascular adverse events, as observed in both HFpEF [27] and SLE populations [28]. However, the link between STE and clinical end-points in SLE cohort needs further investigation.

The dependence of GLS on afterload can affect its accuracy in assessing LV systolic function. However, the calculation of stain-pressure loop using the recently proposed MW indices may overcome this disadvantage of GLS. Extensive research has shed light on the clinical applicability of MW across a wide spectrum of cardiomyopathies [29,30]. In a previous study on SLE patients conducted by He W et al., GWW and GWE appeared with abnormal values, along with an independent association of GWE with SLE activity measured by SLEDAI-2K index [12]. To our knowledge, this is the second study reporting higher GWW in SLE patients than controls. The markedly elevated GWW in SLE may represent a compensatory mechanism to maintain LV systolic function in the face of increased afterload. This increase in GWW points towards the presence of systolic dysfunction at an early stage. While approximately one-fifth of our SLE patients had hypertension, in the vast majority of them blood pressure was well-controlled and only 4% presented with LV hypertrophy. Consequently, we did not anticipate a substantial impact of hypertension without LVH on the MW indices.

We further examined whether disease activity may drive the considerable difference in GLS and GWW within SLE group. We realized that the difference was not attributed to the current disease activity. In this context, we failed to demonstrate an independent relationship of SELENA-SLEDAI with GLS or any MW index in multiple regression analysis, in contrast to previous results from He et al [12]. Within the SLE group, patients with more active disease had lower GCW, while the rest of classical and novel echocardiographic indices were not affected by the level of disease activity. Regarding the limitations in GCW calculation, our results do not provide robust evidence about the interplay between disease activity and myocardial strain. In contrast, previous authors reported a linear relationship of myocardial strain impairment with disease activity [31], [32]. Plausible explanations for this inconsistency derive from the inherent limitations of SELENA-SLEDAI score to quantify disease activity. Compared to previous studies, our cohort was at low cardiovascular risk since none had known CVD or significant chronic kidney dysfunction, a small percentage of patients had prior nephritis / pericarditis, and our patients had smaller duration of SLE. In addition to this, there was a lower average degree of disease activity, which was predominantly moderate, since only 3% appeared with high disease activity (SELENA-SLEDAI≥10). We believe that a longer follow-up and the recruitment of patients with cardiovascular complications and more severe disease activity could clarify whether the inflammatory burden (disease activity) could directly affect myocardial function even at a subclinical level. Finally, the index of organ damage, the SDI, did not differentiate the echocardiographic findings at all.

In comparison with previous studies [33], one could argue that our SLE patients did not exhibited systolic dysfunction due to the preserved LVEF and the slight reduction in GLS levels, which remained within normal range (<-18%) [29]. This raises the question about the clinical significance of the differences in myocardial strain between SLE and healthy control groups. To limit the potential random effects of participants selection, we simultaneously examined the circulating levels of biomarkers of myocardial injury (hs-cTnI) and myocardial overload (NT-proBNP). To the best of our knowledge, this is the third study examining the concentrations of troponin in SLE patients. In a smaller study of 63 SLE patients with low CV risk profile like ours, high hs-troponin levels were associated with the presence of carotid atherosclerotic lesions [34]. In another study, Sabio JM et al (2023) demonstrated higher arterial stiffness in SLE patients with detectable values of hs-troponin compared to controls [35]. Notably, both studies used the dichotomous values of detectable and non-detectable hs-troponin levels for analysis. In our study, we analysed hs-cTnI as continuous variable, thereby increasing its sensitivity. Although the observed values of hs-cTnI in our study

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remained within the normal range, they were two times higher than those in the control group indicating myocardial involvement.

Recently, natriuretic peptides have emerged as biomarkers of cardiac disorders in SLE patients [36]. From a clinical perspective, BNP elevation has traditionally been interpreted as a result of SLE-induced cardiac complications, such as pulmonary hypertension or heart failure with HFrEF [37]. In the context of the low CV risk profile of our SLE cohort, the observed remarkable elevation in NT-proBNP is of paramount importance, since it is by far the most sensitive biomarker of increased intra-cardiac pressure and overt cardiac dysfunction [38]. Even after excluding patients with prior lupus nephritis, a considerable difference in NT-proBNP levels remained between SLE patients and healthy controls. Like hs-cTnI, NT-proBNP is a well-established independent predictor of future CV events [39]. Therefore, utilizing a combination of these biomarkers in routine clinical assessments has the potential to better evaluate cardiovascular risk in SLE patients, even in the early stages of their disease.

Both hs-cTnI and NT-proBNP levels were influenced by disease activity, aligning with prior studies reporting higher levels of those biomarkers in patients with autoimmune diseases without cardiac symptoms [40,41]. Although hs-cTnI provides significantly higher sensitivity, it comes at the cost of decreased specificity. The upper reference limits (URLs) can introduce variability in studies investigating myocardial injury, rather than ischemia [42]. After excluding confounding comorbidities, measurements of hs-cTnI below the 99th-percentile may still maintain their diagnostic [43] and prognostic value [44]. After the exclusion of acute or subacute myocarditis or pericarditis, we found that the increased levels of hs-cTnI and NT-proBNP in our SLE patients were linked to GLS and disease activity. This suggests that cardiac biomarkers can help to detect and quantify ongoing myocardial injury and subtle cardiac dysfunction in SLE patients due to disease activity. Determining specific cutoff values for these biomarkers will assist to detect SLE-related cardiac effects, but large prospective trials are unambiguously required.

There are some limitations in the present study. Firstly, the small sample size and the cross-sectional design may introduce some bias into our results. We anticipate that future prospective studies will confirm the prognostic value of our findings. Secondly, we did not have access to a more sensitive imaging modality, like cardiac magnetic resonance (CMR), which could provide more detailed assessment of the myocardial texture and function. If CMR was available to all participants, we could detect objectively cases of past myocarditis. Furthermore, the present study was a two-centre study, and larger studies are needed to provide insights into the clinical implementation of our findings.

5. Conclusions

In conclusion, our study revealed that SLE patients without known CVD had subtle systolic impairment compared to healthy controls, even though the classical echocardiographic parameters of systolic and diastolic function did not differ from those in healthy controls. One of the most striking findings of our study was the remarkable elevation of circulating levels of both hs-cTnI and NT-proBNP, which remained unaffected by co-morbidities and age, and paralleled higher GLS and GWW levels in SLE patients. Notably, those biomarkers were independently associated with disease activity, implicating that they could serve as valuable indicators of myocardial insult in case of moderately or highly active disease. Future studies will investigate the prognostic implications of our findings and the potential integration into the management of SLE patients.

Author Contributions: NPEK: Conceptualization, Methodology, Validation, Writing—Review & Editing, Supervision; AD: Formal Analysis, Investigation, Data Curation, Original Draft Preparation; IK: Investigation, Resources, Data Curation, Original Draft Preparation; KP: Methodology, Writing—Review & Editing, Supervision. All authors have read and agreed to the published version of the manuscript.

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