EARLY CARDIAC PHENOTYPING IN CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS: AN EVIDENCE-BASED MULTIMODAL DIAGNOSTIC FRAMEWORK USING MYOCARDIAL STRAIN AND CARDIAC BIOMARKERS

Oramova Sevinch
sevinchoromova57@gmail.com

Solijonova Ruxshonabonu
Ruxshonasolijonova05@gmail.com

Payziyeva Nilufar
payzievanilufar1@gmail.com
Urinov Akmal Tashkent State Medical University,
Tashkent, Republic of Uzbekistan
https://doi.org/10.5281/zenodo.22922975

Abstract

Background: Cardiovascular involvement is an important complication of childhood-onset systemic lupus erythematosus (cSLE), but clinically overt cardiac manifestations may underestimate the true extent of myocardial involvement. Conventional echocardiography may remain apparently normal despite early impairment of myocardial mechanics. This raises an important clinical question: can cardiac involvement in a child with SLE be detected before the appearance of overt cardiac symptoms?Objective: To critically evaluate the available evidence concerning subclinical cardiac involvement in cSLE and to develop an evidence-based multimodal approach integrating conventional echocardiography, myocardial strain imaging and cardiac biomarkers for earlier detection of myocardial dysfunction.Methods: A structured analytical synthesis of published clinical studies concerning cardiac involvement in cSLE was performed. Particular attention was given to paediatric studies evaluating two-dimensional and three-dimensional speckle-tracking echocardiography, global longitudinal strain (GLS), right ventricular strain, conventional echocardiographic parameters, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and cardiac troponins. Adult SLE studies were considered selectively when paediatric evidence concerning cardiac biomarkers was limited.Results: Multiple paediatric studies demonstrate that myocardial deformation may be impaired despite preserved left ventricular ejection fraction (LVEF) and absence of clinical heart failure. In a study of 50 asymptomatic children with cSLE, longitudinal and radial myocardial deformation were significantly reduced compared with healthy controls despite conventional measures being less informative. Other paediatric cohorts demonstrated reduced longitudinal strain of the left and right ventricles in clinically asymptomatic patients. More recent three-dimensional speckle-tracking studies have identified subclinical abnormalities of ventricular and atrial myocardial mechanics and suggested prognostic associations. Evidence for cardiac biomarkers is less consistent in children: NT-proBNP was not significantly different between paediatric SLE patients and controls in one prospective study, whereas adult SLE studies demonstrate abnormalities of NT-proBNP and high-sensitivity cardiac troponin even in patients without overt cardiac disease.Conclusion: The available evidence supports the concept that myocardial involvement in cSLE may precede clinically apparent cardiac disease. Conventional echocardiography and LVEF alone may therefore be insufficient for early phenotyping. Myocardial strain, particularly GLS, provides a more sensitive marker of early mechanical dysfunction, while cardiac biomarkers may provide complementary information regarding myocardial stress or injury. A multimodal strategy combining clinical risk assessment, conventional echocardiography, strain imaging and selectively interpreted cardiac biomarkers may improve recognition of early cardiac involvement. Prospective paediatric studies are required to establish age-specific reference values, diagnostic thresholds and clinically validated screening algorithms.

Keywords: childhood-onset systemic lupus erythematosus; cardiac biomarkers; echocardiography; global longitudinal strain; myocardial dysfunction

Introduction

Childhood-onset systemic lupus erythematosus is a multisystem autoimmune disease characterised by a more active disease course and a substantial risk of cumulative organ damage. Cardiovascular involvement represents an important component of this burden and may affect the pericardium, myocardium, valves, coronary circulation and pulmonary vasculature.

Population-level evidence indicates that cardiac manifestations are clinically relevant in childhood-onset SLE. In a population-based study of 297 children with incident SLE, 17.8% had at least one acute cardiac diagnosis; pericarditis or myocarditis occurred in 10.8% and valvular insufficiency in 9.1%. Nephritis was strongly associated with acute cardiac diagnoses, and childhood-onset disease was associated with a higher rate of pericarditis or myocarditis than adult-onset SLE. [1]

The clinical detection of cardiac involvement in children with SLE is challenging. Symptoms such as fatigue, reduced exercise tolerance, dyspnoea and tachycardia may be attributed to systemic inflammation, anaemia, deconditioning or active extracardiac disease. Consequently, clinically apparent cardiovascular disease may represent only a fraction of myocardial involvement.

Echocardiography is an attractive modality for paediatric assessment because it is non-invasive, widely available and does not expose the child to ionising radiation. However, conventional echocardiographic indices, particularly LVEF, may remain within the normal range despite early myocardial dysfunction.

Speckle-tracking echocardiography provides quantitative assessment of myocardial deformation. Global longitudinal strain is particularly relevant because longitudinal myocardial fibres may demonstrate functional impairment before a measurable reduction in LVEF occurs.

The central clinical question is therefore whether cardiac involvement can be identified during this subclinical stage. The objective of this analytical review was to evaluate the available evidence concerning early cardiac involvement in cSLE and to propose a multimodal diagnostic framework integrating conventional echocardiography, myocardial strain and cardiac biomarkers.

Materials and Methods

This work was designed as a structured evidence synthesis rather than an original patient-level clinical study.

Published clinical investigations evaluating cardiac involvement in childhood-onset or paediatric-onset SLE were considered, with particular emphasis on studies using echocardiography, tissue Doppler imaging, two-dimensional speckle-tracking echocardiography, three-dimensional speckle-tracking imaging and cardiac biomarkers.

Priority was given to studies involving children or adolescents with SLE without clinically overt heart failure. Adult SLE studies were used selectively to contextualise evidence concerning cardiac biomarkers when paediatric evidence was limited.

The principal outcomes considered were conventional echocardiographic measures, particularly LVEF; LV GLS and other myocardial deformation parameters; right ventricular longitudinal strain; left atrial and three-dimensional myocardial deformation; associations between myocardial strain and SLE disease activity or organ involvement; NT-proBNP and cardiac troponins; and the potential complementary value of imaging and biomarkers.

Because the included studies differed substantially in design, population, echocardiographic technology and outcome definitions, quantitative pooling of all studies was not attempted. Instead, the evidence was synthesised according to the ability of each diagnostic modality to identify abnormalities before clinically overt cardiac disease.

Results

Clinical burden of cardiac involvement

A population-based analysis of 699 youth with newly diagnosed SLE found that approximately 18% had at least one acute cardiac disease diagnosis. Echocardiography was performed in 25% during the baseline period, and regional variation in echocardiographic use was substantial. Greater

echocardiographic utilisation was associated with a higher proportion of cardiac diagnoses detected after imaging. [2]

These findings indicate that clinically recognised cardiac disease is not rare around the time of SLE diagnosis. However, administrative diagnostic codes cannot capture subtle myocardial dysfunction, and the prevalence of subclinical myocardial involvement may therefore be higher. Conventional echocardiography may underestimate early myocardial dysfunction

The principal limitation of conventional echocardiography in this setting is that global indices such as LVEF reflect relatively advanced changes in ventricular systolic function.

Leal et al. studied 50 asymptomatic patients with childhood-onset SLE and 50 healthy controls using two-dimensional speckle-tracking echocardiography. Despite normal ejection fraction, peak longitudinal systolic strain, longitudinal strain rates and radial deformation were significantly reduced in the cSLE group. Peak longitudinal systolic strain was −20.3% versus

−22.0% in controls (P<0.0001), and radial systolic strain was 33.09% versus 44.36% (P<0.0001). [3]

A separate paediatric study of 50 children with SLE and 30 healthy controls used conventional echocardiography, tissue Doppler imaging and two- and three-dimensional speckle-tracking. Several deformation parameters were significantly impaired in SLE, whereas NT-proBNP did not significantly differ between groups. [4]

These observations suggest that a normal LVEF should not be interpreted as evidence that the myocardium is unaffected.

Global longitudinal strain

GLS is one of the most consistently abnormal echocardiographic parameters in SLE.

Chang et al. evaluated 20 patients with paediatric-onset SLE and 70 healthy controls. Longitudinal strain in the apical four-chamber view was significantly reduced in pSLE compared with controls, despite many patients being in clinical remission. The authors suggested that impaired myocardial deformation may represent early myocardial damage not captured by conventional echocardiography. [5]

Leal et al. also found impaired longitudinal and radial deformation in asymptomatic children with cSLE, with peak longitudinal systolic strain negatively correlated with SLEDAI-2K (r=−0.52, P<0.0001). [3]

Adult evidence is directionally consistent. A meta-analysis of nine studies found significantly lower LV GLS in SLE patients than controls, together with abnormalities of GLS rate, circumferential strain, radial strain and right ventricular strain. [6] Adult data cannot be directly extrapolated to children, but they strengthen the biological consistency of the finding.

1. Right ventricular involvement

Early cardiac phenotyping should not be restricted to the left ventricle.

Leal et al. studied 35 children with cSLE without signs or symptoms of heart failure and 33 healthy volunteers. RV peak longitudinal systolic strain was significantly reduced in cSLE (−24.5±5.09% versus −27.62±3.02%, P=0.003). The difference persisted after excluding patients with pulmonary hypertension. [7]

This demonstrates that right ventricular myocardial dysfunction may remain clinically silent and may be missed by a left-ventricle-centred evaluation.

2. Layer-specific strain

A study of 35 drug-naive patients with new-onset SLE without cardiac symptoms and 25 healthy controls found normal LVEF and comparable conventional echocardiographic parameters, but impaired layer-specific GLS and increased peak systolic dispersion. Whole-layer GLS was −17.6±3.0% versus −19.3±2.6% (P=0.02), while endocardial GLS was

−20.0±3.2% versus −22.1±3.0% (P=0.01). [8]

More severe strain impairment was observed in patients with higher disease activity, high-risk antiphospholipid antibody profiles or renal involvement. These findings support the sensitivity of myocardial deformation imaging, although layer-specific strain is not yet sufficiently standardised for universal paediatric screening.

3. Three-dimensional speckle-tracking imaging

Three-dimensional speckle-tracking imaging may provide more comprehensive assessment of myocardial mechanics.

Feng et al. evaluated 31 children with cSLE using 3D-STI. GLS and LV twist angle were independently associated with severe disease activity. A combined 3D myocardial comprehensive index showed sensitivity of 81.4% and specificity of 94.1% for severe disease activity in that cohort. [9]

A subsequent study of 40 children with cSLE and 40 healthy controls found no significant difference in conventional echocardiographic measures, whereas lateral longitudinal strain of the LV and LA was lower in cSLE. A speckle-tracking imaging score incorporating LV mass and LV and LA strain parameters showed significant associations with clinical outcomes during six months of follow-up. [10]

These studies are relevant to early cardiac phenotyping because they show that myocardial abnormalities can be quantified even when conventional echocardiographic parameters remain apparently normal. Their small sample sizes, however, mean that the proposed indices require external validation.

Cardiac Biomarkers

NT-proBNP

NT-proBNP reflects myocardial wall stress and is widely used in the assessment of ventricular dysfunction. Its role in subclinical SLE-related myocardial involvement is less clearly established in children.

In the paediatric study described above, NT-proBNP did not differ significantly between children with SLE and healthy controls despite significant abnormalities in speckle-tracking parameters. [4] This suggests that a normal NT-proBNP concentration cannot reliably exclude early myocardial mechanical dysfunction.

Adult evidence indicates that natriuretic peptides may provide complementary information. In a study of 59 women with SLE without cardiac symptoms, BNP levels were significantly higher than in 33 healthy controls despite preserved EF in all participants. [11] Another study of 151 SLE patients without prior heart disease found elevated BNP and/or cardiac troponin I in approximately 10.6% of patients, although some abnormalities were ultimately associated with antimalarial-related cardiomyopathy. [12]

Therefore, NT-proBNP should currently be regarded as a complementary rather than standalone screening marker.

High-sensitivity cardiac troponin

Cardiac troponins are markers of myocardial injury rather than myocardial stress.

In a two-centre study of 92 asymptomatic adults with SLE, high-sensitivity troponin T was elevated compared with matched controls and was independently associated with cardiac magnetic resonance markers of myocardial inflammation. [13]

More recently, a cross-sectional study of 102 adults with SLE without known cardiac impairment found lower GLS and higher global wasted myocardial work compared with 51 controls. NT-proBNP and high-sensitivity troponin were approximately threefold and twofold higher, respectively, in SLE, although hs-troponin remained within the conventional reference range. Both biomarkers were more elevated in patients with at least moderate disease activity. [14]

These adult data support the biological plausibility of combining imaging and biomarkers, but paediatric-specific thresholds remain insufficiently established.

An Integrated Early Cardiac Phenotyping Framework

The available evidence indicates that echocardiography and cardiac biomarkers provide different types of information.

Myocardial strain primarily assesses mechanical function. NT-proBNP reflects myocardial wall stress. High-sensitivity cardiac troponin reflects myocardial injury. Conventional echocardiography evaluates structure and global ventricular performance.

A child may therefore have normal LVEF, no clinical heart failure and no major elevation of NT-proBNP while simultaneously demonstrating impaired GLS. Conversely, abnormal troponin or NT-proBNP with preserved GLS should prompt assessment for active myocardial injury, myocarditis, renal dysfunction, pulmonary hypertension or other causes of biomarker elevation. A practical four-level framework is proposed.

Level1 — Clinical risk assessment: disease duration, current activity, nephritis, antiphospholipid antibodies, hypertension, unexplained tachycardia, exercise intolerance, dyspnoea, chest discomfort and syncope or presyncope.

Level 2 — Conventional cardiac assessment: physical examination, blood pressure, ECG when indicated and transthoracic echocardiography including LVEF, ventricular dimensions, diastolic indices, valves, pericardium, RV function and pulmonary pressure estimation.

Level 3 — Myocardial deformation assessment: LV GLS should be considered the principal strain parameter, complemented where feasible by regional LV strain, RV longitudinal strain and left atrial strain.

Level 4 — Biomarker assessment: NT-proBNP and high-sensitivity cardiac troponin may be considered when clinical suspicion is increased, disease activity is high, echocardiographic findings are abnormal or other evidence suggests cardiovascular involvement.

The most informative interpretation is likely to come from the combination of biomarker trends and imaging rather than from a single isolated value.

Discussion

The principal finding of this evidence synthesis is that subclinical cardiac involvement in childhood-onset SLE can be detected using myocardial deformation imaging before conventional signs of cardiac dysfunction become apparent.

The strongest evidence concerns GLS. Multiple paediatric studies have demonstrated impaired longitudinal myocardial deformation despite preserved LVEF and absence of overt heart failure. [3–5]

The relationship between strain abnormalities and systemic disease characteristics suggests that myocardial mechanics may reflect the cumulative effects of inflammation, endothelial dysfunction, immune-mediated injury, vascular abnormalities and traditional cardiovascular risk factors.

Cardiac biomarkers should not replace echocardiographic strain. Paediatric evidence is currently insufficient to support a single biomarker as a reliable screening tool for subclinical myocardial dysfunction. The absence of a significant NT-proBNP difference in one paediatric cohort despite abnormal strain parameters illustrates this limitation. [4]

The role of biomarkers is therefore complementary. Troponin may identify myocardial injury, whereas NT-proBNP may indicate haemodynamic stress. Interpretation should account for renal function and other systemic factors.

The timing of detection is particularly relevant in childhood-onset disease because patients may experience many years of cumulative inflammatory and cardiovascular exposure. Nevertheless, prospective studies are required to determine whether identifying subclinical abnormalities and acting on them improves long-term outcomes.

Clinical Implications

The evidence does not justify interpreting every abnormal strain measurement as clinically significant cardiac disease.

Instead, the most defensible approach is longitudinal phenotyping. A child with active SLE and newly abnormal GLS could undergo confirmation of image quality and technical validity, assessment of disease activity, review of blood pressure and renal status, evaluation of cardiovascular risk factors where appropriate, consideration of NT-proBNP and high-sensitivity cardiac troponin, and repeat echocardiography when clinically indicated.

Persistent or progressive abnormalities, especially when accompanied by symptoms or biomarker abnormalities, should prompt specialist cardiovascular assessment.

This approach avoids both extremes: ignoring subtle abnormalities and overdiagnosing clinically silent myocarditis solely on the basis of an abnormal strain value.

Importantly, a reduced GLS should currently be regarded as a marker of possible subclinical myocardial involvement rather than definitive evidence of myocarditis or established heart failure.

Limitations

This evidence synthesis has several limitations. The available paediatric studies are generally small and predominantly single-centre investigations. Different echocardiographic systems and software

platforms may produce different strain measurements, limiting direct comparison between studies. Paediatric reference values for GLS and other deformation parameters vary with age, body size, sex and methodology.

Most available studies are cross-sectional or observational. Consequently, abnormal strain cannot yet be considered a validated predictor of long-term cardiovascular events in children with SLE. Evidence concerning cardiac biomarkers is substantially stronger in adults than in paediatric populations.

Finally, this work is an evidence synthesis and does not contain an independent patient cohort. Its conclusions therefore provide a clinically testable framework rather than replacing prospective validation.

Future Research

Large multicentre prospective cohorts are needed to establish age- and sex-specific reference ranges for myocardial strain in cSLE.

Longitudinal studies should determine whether abnormal GLS predicts subsequent decline in LVEF, clinical myocarditis, heart failure, persistent disease activity, cumulative organ damage or later cardiovascular events.

Future studies should evaluate whether combining GLS with NT-proBNP and high-sensitivity troponin improves diagnostic performance compared with either modality alone. Three-dimensional strain, myocardial work and left atrial strain are promising technologies but require external validation before routine paediatric implementation.

A further priority is standardisation of paediatric image acquisition and interpretation, including development of robust and, where possible, vendor-independent thresholds.

Conclusion

Childhood-onset systemic lupus erythematosus may involve the cardiovascular system before overt cardiac symptoms or conventional echocardiographic abnormalities become evident.

The most consistent evidence concerns myocardial deformation imaging. Reduced LV GLS, impaired RV strain and abnormalities detected by advanced three-dimensional speckle-tracking techniques have been demonstrated in paediatric patients who may remain clinically asymptomatic and retain preserved conventional systolic function.

Cardiac biomarkers provide complementary information but currently lack sufficient paediatric evidence to serve as standalone screening tests.

The available evidence therefore supports a multimodal concept of early cardiac phenotyping in cSLE: clinical risk assessment should be complemented by conventional echocardiography and, where feasible, myocardial strain assessment, with cardiac biomarkers used selectively to evaluate myocardial stress or injury.

The central clinical implication is that a normal LVEF should not be considered sufficient evidence that the myocardium is unaffected in a child with SLE.

Prospective multicentre paediatric studies are required to determine whether early detection of these abnormalities translates into improved long-term cardiovascular outcomes.

Declarations

Ethics approval: Not applicable. This manuscript is an evidence synthesis based exclusively on previously published studies and does not involve direct research on human participants.

Consent for participation: Not applicable.

Funding: No external funding was received for this work.

Conflict of interest: The author declares no conflicts of interest related to this manuscript. Data availability: No original patient-level dataset was generated or analysed in this study.

Author contributions: The author conceived the manuscript, performed the literature synthesis, interpreted the evidence and prepared the manuscript.

References

1. Chang JC, Xiao R, Mercer-Rosa L, Knight AM, Weiss PF. Child-onset systemic lupus erythematosus is associated with a higher incidence of myopericardial manifestations compared to adult-onset disease. Lupus. 2018;27(13):2146-2154. doi:10.1177/0961203318804889.
2. Chang JC, Knight AM, Xiao R, Mercer-Rosa LM, Weiss PF. Use of echocardiography at diagnosis and detection of acute cardiac disease in youth with systemic lupus erythematosus. Lupus. 2018;27(8):1348-1357. doi:10.1177/0961203318772022.
3. Leal GN, Silva KF, Lianza ACL, Giacomin MF, Andrade JL, Kozu K, Bonfá E, Silva CA. Subclinical left ventricular dysfunction in childhood-onset systemic lupus erythematosus: a two-dimensional speckle-tracking echocardiographic study. Scand J Rheumatol. 2016;45(3):202-209. doi:10.3109/03009742.2015.1063686.
4. Emara M, Hafez MA, El-Bendary A, El Razaky O. Speckle tracking echocardiography for the evaluation of left ventricular function in children with systemic lupus erythematosus. Lupus. 2020;29(11):1449-1455. doi:10.1177/0961203320942296.
5. Chang JC, Wang Y, Xiao R, Fedec A, Meyers KE, Tinker C, Natarajan SS, Knight AM, Weiss PF, Mercer-Rosa L. Echocardiographic strain analysis reflects impaired ventricular function in youth with pediatric-onset systemic lupus erythematosus. Echocardiography. 2020;37(12):2082-2090. doi:10.1111/echo.14872.
6. Di Minno MND, Forte F, Tufano A, Buonauro A, Rossi FW, De Paulis A, Galderisi M. Speckle tracking echocardiography in patients with systemic lupus erythematosus: a meta-analysis. Eur J Intern Med. 2020;73:16-22. doi:10.1016/j.ejim.2019.12.033.
7. Leal GN, Silva KF, França CMP, Lianza AC, Andrade JL, Campos LMA, Bonfá E, Silva CA. Subclinical right ventricle systolic dysfunction in childhood-onset systemic lupus erythematosus: insights from two-dimensional speckle-tracking echocardiography. Lupus. 2015;24(6):613-620. doi:10.1177/0961203314563135.
8. Luo T, Wang Z, Chen Z, Yu E, Fang C. Layer-specific strain and dyssynchrony index
9. alteration in new-onset systemic lupus erythematosus patients without cardiac symptoms. Quant Imaging Med Surg. 2021;11(4):1271-1283. doi:10.21037/qims-20-859.
10. Feng X, Zhou P, Ding Y, Peng J, Wang T. Three-dimensional speckle-tracking imaging for the
11. prognosis of childhood-onset systemic lupus erythematosus: a pilot study. Front Pediatr. 2025;13:1510852. doi:10.3389/fped.2025.1510852.
12. Feng X, Zhou L, Zhou P, Xiong Y, Wang S, Wu Y, Peng J. Prognostic value of speckle-
13. tracking imaging score for patients with childhood-onset systemic lupus erythematosus. Int J Cardiol. 2026;444:133978. doi:10.1016/j.ijcard.2025.133978.
14. Karadag O, Calguneri M, Yavuz B, Atalar E, Akdogan A, Kalyoncu U, Kiraz S, Aksoyek S,
15. Ozmen F, Ertenli AI. B-type natriuretic peptide (BNP) levels in female systemic lupus erythematosus patients: what is the clinical significance? Clin Rheumatol. 2007;26(10):1701-1704. doi:10.1007/s10067-007-0575-4.
16. Tselios K, Gladman DD, Harvey P, Akhtari S, Su J, Urowitz MB. Abnormal cardiac biomarkers in patients with systemic lupus erythematosus and no prior heart disease: a consequence of antimalarials? J Rheumatol. 2019;46(1):64-69. doi:10.3899/jrheum.171436.
17. Winau L, Hinojar Baydes R, Braner A, Drott U, Burkhardt H, Sangle S, D'Cruz DP, Carr-White G, Marber M, Schnoes K, Arendt C, Klingel K, Vogl TJ, Zeiher AM, Nagel E, Puntmann VO. High-sensitive troponin is associated with subclinical imaging biosignature of inflammatory cardiovascular involvement in systemic lupus erythematosus. Ann Rheum Dis. 2018;77(11):1590-1598. doi:10.1136/annrheumdis-2018-213661.
18. Kadoglou NPE, Dimopoulou A, Korakianitis I, Parperis K. Advanced parameters of myocardial strain and cardiac biomarkers indicate subclinical systolic myocardial dysfunction in patients with systemic lupus erythematosus. Biomedicines. 2024;12(11):2638. doi:10.3390/biomedicines12112638.