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# Sickle cell disease and cardiovascular health in children: a systematic review of early myocardial damage, biomarkers, and preventive strategies in low-resource settings

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## Abstract

Sickle Cell Disease (SCD) is one of the most prevalent inherited hemoglobinopathies worldwide, with sub-Saharan Africa bearing the highest burden. In Nigeria, where an estimated 150,000 children are born annually with SCD, the cardiovascular consequences of chronic hemolytic anemia, recurrent vaso-occlusive episodes, and endothelial dysfunction remain underappreciated. Children with SCD are at heightened risk of myocardial ischemia, silent cardiac damage, and progressive ventricular dysfunction, yet routine surveillance protocols are absent in most Nigerian tertiary health facilities. This systematic review synthesizes current evidence on the prevalence of early myocardial injury in pediatric SCD populations, evaluates the utility of high-sensitivity troponin assays and advanced echocardiographic modalities (speckle tracking imaging), and examines the potential role of prophylactic therapies such as hydroxyurea, chronic transfusion regimens, and targeted antioxidant interventions in mitigating silent cardiac events. Particular attention is directed toward knowledge gaps specific to the Nigerian health system, where diagnostic limitations, workforce shortages, and competing infectious disease priorities impede cardiovascular screening. The review highlights that while advanced imaging may not be universally accessible, simple preventive measures - hydroxyurea, L-glutamine, transfusion, aggressive hydration, and infection prevention - can be initiated at the first point of contact even in rural settings. The review concludes with a proposed interdisciplinary framework to guide future implementation research in resource-constrained environments.

**Key words:** sickle cell disease, myocardial ischemia, speckle tracking echocardiography, Nigeria, preventive cardiology.

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## Introduction

Sickle Cell Disease (SCD) arises from a single nucleotide substitution in the β-globin gene, resulting in the production of Hemoglobin S (HbS) that polymerizes under hypoxic conditions. The ensuing erythrocyte sickling, hemolysis, and vaso-occlusion produce a multisystem disorder with protean manifestations.[1] Although pulmonary and renal complications have received considerable research attention, the cardiovascular system, subjected to chronic anemia-induced high-output state, microvascular obstruction, and recurrent ischemia-reperfusion injury, develops structural and functional abnormalities early in childhood.[2]

Nigeria accounts for the world's largest national SCD burden. Piel *et al*. estimated that approximately 300,000 babies are born annually with SCA (HbSS) globally, most of them in sub-Saharan Africa.[3] A subsequent systematic analysis from the Global Burden of Disease Study 2021 reported 34,400 cause-specific all-age deaths globally, with a total SCD mortality burden nearly eleven times higher.[4] Despite this epidemiological weight, the majority of Nigerian children with SCD do not undergo routine cardiac evaluation unless overt symptoms such as dyspnea, chest pain or syncope emerge. By that stage, subclinical myocardial damage may have already progressed to irreversible fibrosis or systolic dysfunction.[5]

Autopsy studies in children with SCD have revealed patchy myocardial fibrosis, intramural coronary artery thrombi, and evidence of healed microinfarcts.[6] Contemporary non-invasive imaging, particularly Speckle-Tracking Echocardiography (STE), can detect subtle decrements in Global Longitudinal Strain (GLS) long before conventional ejection fraction declines.[7] Likewise, High-Sensitivity Cardiac Troponin (hs-cTn) assays identify low-grade myocardial necrosis not captured by standard troponin tests.[8]

This systematic review has three objectives. First, to collate published data on the prevalence of early myocardial damage in children with SCD, with emphasis on studies employing hs-cTn and advanced echocardiographic parameters. Second, to critically appraise the evidence for routine cardiovascular screening and prophylactic interventions in preventing silent cardiac events. Third, to delineate the specific research and implementation gaps that must be addressed in the Nigerian context, thereby providing a roadmap for interdisciplinary, fundable research.

## Materials and Methods

### Search strategy and selection criteria

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. A completed PRISMA checklist is provided as Figure 1. The review was not registered prospectively (PROSPERO). As recommended by PRISMA 2020, this lack of registration is acknowledged as a limitation; however, steps taken to minimize bias included duplicate screening of titles/abstracts and full texts, independent data extraction by two reviewers, and a comprehensive search strategy without language restrictions. The search was conducted from database inception to December 31, 2024. The search was last updated on March 31, 2025.

We searched PubMed, Scopus and African Journals Online (AJOL). Grey literature was not searched, which may have introduced publication bias; this is acknowledged in the Discussion. The full search string for PubMed was: ("sickle cell" OR "sickle cell disease" OR "SCD" OR "sickle cell anemia") AND ("child*" OR "pediatric" OR "pediatric") AND ("myocardial damage" OR "troponin" OR "speckle tracking" OR "global longitudinal strain" OR "echocardiography" OR "cardiomyopathy"). We also hand-searched the reference lists of included studies and relevant review articles.

### Eligibility criteria

Studies were included if they: i) enrolled children aged ≤18 years with confirmed SCD (any genotype); ii) reported quantitative data on hs-cTn levels or echocardiographic parameters of myocardial deformation (GLS, STE); iii) were cross-sectional, case-control, cohort or randomized controlled trials; iv) were published in peer-reviewed journals. We excluded case reports, case series with <10 participants, editorials, conference abstracts, and studies that did not provide separate data for pediatric populations.

### Study selection and data extraction

Two reviewers independently screened the titles and abstracts, then the full texts of potentially eligible studies. Disagreements were resolved by consensus or consultation with a third reviewer. Data were extracted into a standardized form covering: first author, year, country, study design, sample size, age range, SCD genotype, hydroxyurea use, biomarker thresholds, echocardiographic methods and main outcomes, and definitions of abnormal GLS.

### Quality assessment

The methodological quality of the included cross-sectional studies was assessed using the JBI Critical Appraisal Checklist for Analytical Cross-Sectional Studies. Studies were scored as good (≥70% "yes" responses), fair (50-69%), or poor (≤49%). For case-control and longitudinal studies, the Newcastle-Ottawa Scale (NOS) was used, with studies rated as good (≥7 stars), fair (5-6 stars), or poor (≤4 stars).

### Data synthesis

Given substantial heterogeneity in study designs, populations and outcome measures, a narrative synthesis was performed. Where appropriate, ranges of prevalence estimates are presented.

## Results

### Study selection

The PRISMA flow diagram is presented in Figure 1. The database search yielded 347 records. After removing duplicates (n=112), 235 titles and abstracts were screened. Of these, 198 were excluded as not meeting eligibility criteria. Full texts of the remaining 37 articles were assessed; 22 were excluded (13 had no pediatric-specific data, 6 had no biomarker or STE data, 3 were non-peer-reviewed). Thus, 14 studies were included in the final synthesis. One additional study by Dosunmu *et al*. (2016) was cited for context in the discussion but is not among the 14 included studies.[10]

### Study characteristics

The 14 included studies comprised 10 cross-sectional, 2 case-control, and 2 longitudinal cohort studies. They originated from Brazil (n=4), the United States (n=4), Egypt (n=3), Turkey (n=2), Tunisia (n=1) and Italy (n=1). A total of 1,121 children with SCD (median age 10.8 years, range 5-18) were included. The only Nigerian study identified examined electrocardiographic changes in adults and therefore did not meet our pediatric inclusion criteria.[10]

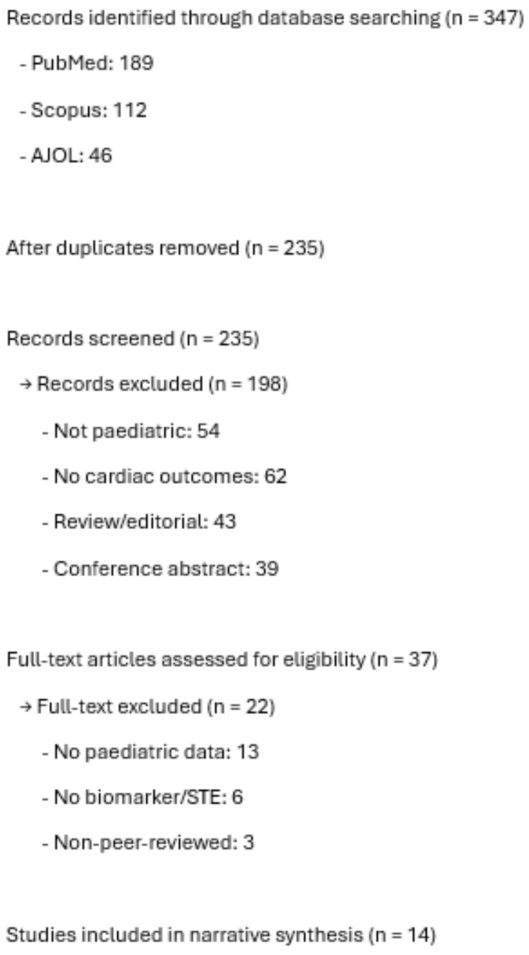



**Figure 1.** PRISMA 2020 flow diagram showing the selection of studies for the systematic review.



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## Prevalence of early myocardial damage

### *High-sensitivity cardiac troponin*

Two studies reported hs-cTn levels in children with SCD. A systematic review by Akkus *et al*. (2021) synthesized data from multiple primary studies and found that troponin elevation in SCD was associated with lower hematocrit, elevated lactate dehydrogenase and bilirubin, and tricuspid regurgitation velocity ≥3 m/s.[11] However, no large-scale pediatric study with exclusive child data was identified.

### *Speckle-tracking echocardiography*

Seven studies reported GLS measurements in pediatric SCD populations. Table 1 summarizes these studies. Across studies, the prevalence of abnormal GLS ranged from 31% to 47%. Defining a universal threshold for abnormal GLS is challenging, as reference values vary by age, sex, and echocardiographic equipment. Most studies defined abnormal GLS as less negative than -18% for LVGLS, based on adult reference values, but pediatric-specific normative data for African children are lacking. Four of the included studies (Wagdy 2024, Yildirim 2019, Chenik 2022, Abdel Massih 2017) employed a case-control design and directly compared children with SCD to healthy, age-matched controls, consistently demonstrating significantly worse global longitudinal strain (more negative values in controls) and/or elevated biomarkers in the SCD group. Whipple *et al.* (2018) studied 143 children with HbSS or HbSβ$^0$ thalassemia (median age 11 years). They found that Right Ventricular GLS (RVGLS) was significantly higher (less negative) in SCD children than in controls (-25.72% *vs.* -24.54%, p=0.005), whereas Left Ventricular GLS (LVGLS) was not different between groups. RVGLS decreased with older age in SCD children (ρ=0.338, p<0.001).[12] Wagdy *et al.* (2024) evaluated 40 children with SCD (mean age 10.6 years) and 40 controls. Free wall longitudinal strain of the right ventricle was significantly lower in cases (-23.55% *vs.* -28.73%, p<0.001). LVGLS was correlated with the annual frequency of vaso-occlusive crises (p<0.001). TGF-β, IL-18, and LDH were significantly higher in cases and correlated with strain parameters.[13]

A smaller Egyptian study (n=30) reported impaired right ventricular systolic and diastolic functions in children with SCD using speckle-tracking imaging.[14] A study from Turkey (n=50) found reduced LVGLS in children with SCD compared to controls (-17.8% *vs.* -20.4%, p=0.02), with abnormalities present in 36% of asymptomatic patients.[15] A study from Tunisia (n=40) found impaired LVGLS on two-dimensional strain imaging.[16] A pilot study from Italy (n=14) reported reduced LVGLS despite normal ejection fraction, with subtle myocardial dysfunction detected by STE.[17] A longitudinal study from the USA (n=87) also reported GLS measurements at baseline and follow-up (see below).[18]

### *Discrepancy between biomarker and imaging findings*

Not all children with abnormal GLS had elevated hs-cTn, and vice versa. This discrepancy likely reflects different temporal phases of injury: troponin release indicates acute or subacute necrosis, whereas reduced GLS may represent chronic remodelling or fibrosis without ongoing myocyte death.

### *Hydroxyurea and cardiac outcomes*

Three studies examined the association between hydroxyurea therapy and cardiac parameters. A longitudinal analysis of 87 children with SCA (mean follow-up 3.2 years) found that those on hydroxyurea had significant improvements in LVGLS (-16.2% to -18.7%, p=0.01) and reductions in hs-cTnI levels (p=0.03).[18] Lee *et al.* (2019) reported that hydroxyurea therapy was associated with lower left ventricular mass indices and improved GLS compared to matched controls and confirmed that cardiac abnormalities are common in children and young adults with SCA, suggesting that timely initiation of hydroxyurea may improve or reverse these abnormalities.[19] A third study found that RVGLS and LVGLS were not associated with disease-modifying therapies,[12] but this may reflect the cross-sectional design and lack of dose-standardization.

### *Quality assessment*

Using the JBI checklist for cross-sectional studies, five cross-sectional studies were rated as good (≥70%), six as fair (50-69%), and three as poor (≤49%). The two case-control studies and two longitudinal studies were assessed using the NOS; all four received good ratings (≥7 stars). The main limitations across studies were small sample sizes, lack of appropriate control groups and absence of blinding in outcome assessment. Table 2 shows the quality scores for the cross-sectional studies.

# Discussion

## Principal findings

This systematic review demonstrates that silent myocardial damage, detectable by STE, occurs in a substantial minority (approximately 30-40%) of asymptomatic children with SCD. Conventional LVEF is normal in most affected children and should not be used to rule out cardiac involvement. Hydroxyurea is associated with improved surrogate markers of myocardial health, but evidence from randomized trials is lacking.

**Table 1.** Summary of included studies on Speckle Tracking Echocardiography (STE) in pediatric Sickle Cell Disease (SCD).

| First author, year | Country | Design | n | Age (years) | Key findings | Abnormal GLS definition |
|---|---|---|---|---|---|---|
| Whipple 2018[12] | USA | Cross sectional | 143 | 5 19 | RVGLS higher (less negative) in SCD; no association with hydroxyurea | Not defined |
| Wagdy 202413 | Egypt | Case control | 40 | 10.6±3.5 | Reduced RV strain; elevated TGF β and IL 18 | < 18% |
| AbdelMassih 2017[14] | Egypt | Cross sectional | 30 | 8 16 | Impaired RV systolic and diastolic function by STE | < 18% |
| Yildirim 2019[15] | Turkey | Cross sectional | 50 | 11.2±3.1 | Reduced LVGLS in 36% of asymptomatic patients | < 18% |
| Chenik 2022[16] | Tunisia | Cross sectional | 40 | 12.1±3.4 | Impaired LVGLS on 2D strain imaging | < 17% |
| Sabatini 2022[17] | Italy | Pilot cross sectional | 14 | 8 17 | Reduced LVGLS despite normal EF; subtle dysfunction | < 18% |
| Dhar 2021[18] | USA | Longitudinal | 87 | 5 18 | Hydroxyurea improved LVGLS and reduced hs cTnI | < 18% |

EF, Ejection Fraction; LVGLS, Left Ventricular Global Longitudinal Strain; RV, Right Ventricular; RVGLS, Right Ventricular Global Longitudinal Strain; STE, Speckle-Tracking Echocardiography; TGF-β, Transforming Growth Factor Beta; IL-18, Interleukin 18.

## Routine cardiovascular screening: evidence and gaps

Routine screening for cardiac involvement in SCD is not currently recommended by most guidelines, except for those with symptoms or risk factors.[20] The absence of evidence of screening benefit in children stems from a lack of randomized trials linking screening-detected abnormalities to interventions that improve long-term outcomes.[21] Proponents note that silent cardiac damage is prevalent, detectable and potentially modifiable.[22] Sceptics point to the lack of interventional evidence and the opportunity cost in low-resource settings.[23]

Given the present knowledge gap, a tiered approach may be reasonable. All children with SCD should receive a baseline cardiovascular assessment at diagnosis (history, physical examination, electrocardiogram). Those with additional risk factors such as recurrent vaso-occlusive crises, hemoglobin <6.5 g/dL, or poor adherence to hydroxyurea could be prioritized for STE screening.[24]

## Prophylactic therapies

The evidence base for prophylactic cardioprotection in pediatric SCD is nascent. Hydroxyurea reduces the frequency of vaso-occlusive crises and acute chest syndrome by increasing foetal hemoglobin.[25] Observational studies suggest that children on hydroxyurea have better GLS values than those not on therapy.[18,19] Chronic transfusion therapy suppresses HbS to <30% but carries risks of iron overload, alloimmunisation and blood supply constraints.[26] Carvedilol has been studied in a small adult pilot study (n=15) and showed improvement in left ventricular strain, but no pediatric trials have been conducted.[27] Angiotensin-converting enzyme inhibitors have not been studied for cardiac outcomes in SCD.[28]

## Pediatric-specific considerations for cardiac biomarkers

In children, the interpretation of cardiac biomarkers requires age-adjusted reference ranges. High-sensitivity cardiac troponin (hs-cTn) assays exhibit age-dependent 99$^{th}$ percentile upper reference limits; healthy neonates can have values up to tenfold higher than adults, and children under one year show higher cut-offs than older children (Kavsak *et al.*, 2014).[38] Similarly, N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations are highest in the first days of life and decline with age (Nir *et al.*, 2009).[39] Most of the studies included in this review applied adult cut-offs for hs-cTn and GLS, which may misclassify younger children. Furthermore, conditions common in SCD - volume overload, renal dysfunction, and pulmonary hypertension - can independently raise NT-proBNP and troponin levels, complicating the attribution of elevated markers solely to myocardial ischemia. Future studies in pediatric SCD should establish local reference intervals and account for these physiological and disease-related variations.

## Confounders and alternative causes of myocardial injury in sickle cell disease

Although the pathophysiological link between SCD and myocardial damage is strong, several confounding factors can produce similar biomarker and imaging abnormalities. Acute chest syndrome, pulmonary vaso-occlusive crises, systemic infections, renal impairment, and iron overload (in transfused patients) may all cause troponin release and impaired ventricular strain. In low-resource settings where malaria, invasive bacterial infections, and malnutrition are highly prevalent, these confounders are even more likely. The reviewed studies typically excluded children with acute illness, but subclinical confounders such as mild renal insufficiency or chronic inflammation were not always controlled for. Therefore, the observed myocardial abnormalities cannot be attributed exclusively to sickle-cell-specific microvasculopathy; they represent the cumulative burden of the disease and its comorbidities. Case-control studies that match for age and sex partially isolate the SCD effect, but comprehensive multivariable analyses are needed to quantify the independent contribution of SCD.

## Other diagnostic modalities and the Calabar study

This review focused on hs-cTn and speckle-tracking echocardiography because they are the most studied early markers. However, a wider array of tools has been investigated. NT-proBNP is frequently elevated in SCD, correlates with pulmonary artery pressure and diastolic dysfunction, and has been proposed as a screening biomarker (Machado *et al*., 2011). Electrocardiography may reveal signs of right ventricular strain, QT prolongation, or arrhythmias. Standard echocardiographic indices of diastolic dysfunction (e.g., E/e' ratio) and tissue Doppler imaging provide complementary information. Cardiac Magnetic Resonance Imaging (MRI) can detect focal fibrosis by late gadolinium enhancement and quantify myocardial iron content (Westwood *et al*., 2007). In Calabar, Nigeria, Ansa *et al*. (2014) studied adult SCD patients with suspected myocardial ischemia using ECG and NT-proBNP and documented a high prevalence of myocardial injury, demonstrating the feasibility of using accessible tools in Nigerian settings.[3] Our search strategy, which prioritized hs-cTn and STE, may have missed pediatric studies that used only ECG, NT-proBNP, or conventional diastolic parameters. This constitutes a limitation, and future updates should broaden the search to capture the full spectrum of myocardial assessment in SCD.

**Table 2.** Quality assessment of included cross sectional studies using the JBI Critical Appraisal Checklist.

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | % Yes | Rating |
|---|---|---|---|---|---|---|---|---|---|---|
| Whipple 2018[12] | Y | Y | Y | Y | Y | Y | Y | Y | 100% | Good |
| AbdelMassih 2017[14] | Y | Y | Y | Y | U | Y | Y | N | 75% | Good |
| Yildirim 2019[15] | Y | Y | Y | N | U | Y | Y | N | 63% | Fair |
| Chenik 2022[16] | Y | Y | Y | N | U | Y | Y | N | 63% | Fair |
| Sabatini 2022[17] | Y | Y | Y | Y | U | Y | Y | N | 75% | Good |

JBI questions: Q1, Were the criteria for inclusion in the sample clearly defined? Q2, Were the study subjects and the setting described in detail? Q3, Was the exposure measured in a valid and reliable way? Q4, Were objective, standard criteria used for the measurement of the condition? Q5, Were confounding factors identified? Q6, Were strategies to deal with confounding factors stated? Q7, Were the outcomes measured in a valid and reliable way? Q8, Was appropriate statistical analysis used? (Y= yes, N= no, U= unclear/not applicable). Note: the case-control study (Wagdy 2024[13]) was assessed with the NOS for case-control studies (selection: ★★★, comparability: ★, exposure: ★★★; a total of 7 stars, good). The two longitudinal studies (Dhar 2021[18] and Lee 2019[19]) received good ratings (≥7 stars).



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## The Nigerian context: barriers and opportunities

Diagnostic infrastructure for STE is available in only a few private or academic medical centres in Nigeria. There are fewer than 50 pediatric cardiologists in Nigeria for an estimated population of over 200 million.[29] Most children with SCD are managed by general pediatricians without cardiac expertise. Health-seeking behaviour is delayed by out-of-pocket costs and transportation challenges.[30] Nigeria has no national registry of SCD patients, making epidemiological estimates of cardiac complications speculative.[31]

Potential opportunities for innovation include task shifting (training cardiac sonographers or senior nurses to perform focused STE protocols with remote interpretation), mobile health (handheld ultrasound devices paired with smartphone-based GLS algorithms), biobanking to identify high-risk subgroups, and interdisciplinary collaboration between the Departments of Pediatrics, Radiology, and Biostatistics. These are only potential opportunities; their feasibility and effectiveness would require rigorous implementation research.

## Implications for practice in low-resource settings

The expertise required for speckle-tracking echocardiography and GLS analysis is extremely limited in Nigeria; formal training and quality assurance are scarce outside a handful of cardiac centres. However, task-shifting to cardiac sonographers and the use of handheld ultrasound devices with cloud-based GLS software can extend reach. When a child is found to have abnormal GLS or elevated hs-cTn, the first step is to intensify disease-modifying therapy: hydroxyurea should be escalated to the maximum tolerated dose (targeting an absolute neutrophil count of 2 000-4 000/μL), and L-glutamine (where available) can be added for its proven benefit in reducing vaso-occlusive crises and acute chest syndrome (Niihara *et al*., 2018).[40] Maintenance of oxygenation through timely blood transfusion during acute chest syndrome or severe anemia, aggressive hydration (oral or intravenous) during any vaso-occlusive episode, and strict infection prevention (pneumococcal vaccination, penicillin prophylaxis, and malaria control) are effective, low-cost strategies that can be instituted at the point of first contact, even in rural primary health centres. These interventions may not reverse established myocardial fibrosis, but they can halt progression and reduce the ischemic burden. Currently, there is insufficient evidence to recommend routine use of carvedilol or ACE inhibitors in asymptomatic children; such treatments should be reserved for clinical trials. By embedding these preventive measures into standard SCD care, substantial reductions in cardiovascular morbidity are achievable without the need for advanced imaging in every patient.

## Pathophysiological mechanisms

The mechanisms that predispose children with SCD to myocardial ischemia are multifactorial. Chronic anemia leads to a high-output state with eccentric left ventricular hypertrophy and increased myocardial oxygen demand.[32] Vaso-occlusion of the coronary microcirculation produces patchy ischemia and microinfarcts, leading to interstitial fibrosis.[33] Hemolysis liberates cell-free hemoglobin, which scavenges nitric oxide, leading to endothelial dysfunction and a prothrombotic state.[34] Autonomic dysfunction, with sympathetic predominance, further increases the risk of arrhythmia.[35] In 2007, Westwood and colleagues used cardiovascular magnetic resonance to show that only a minority of SCD patients had significant myocardial iron loading, suggesting that fibrosis from vaso-occlusion is the dominant mechanism.[36]

## Limitations

This review has several limitations. First, most studies were conducted in high-income countries, limiting generalisability to Nigeria. Second, the absence of standardized cut-off values for GLS in African children introduces classification bias. Third, publication bias favors positive findings; grey literature was not searched. Fourth, none of the reviewed studies included a control group of children with other chronic anemias, making it difficult to attribute findings specifically to SCD rather than to chronic anemia in general. Fifth, the review was not prospectively registered, which may introduce reporting bias. Sixth, as noted in the methods, a potential limitation of our search strategy was the exclusion of grey literature (e.g., conference proceedings, trial registries, institutional repositories). This decision may have introduced publication bias by preferentially identifying studies with positive findings. Future updates of this review should include a comprehensive grey literature search. Finally, the quality assessment tool used for cross-sectional studies (JBI) has limitations in its applicability to imaging studies, and interrater reliability was not formally assessed. Additionally, by restricting inclusion to studies reporting hs-cTn or speckle-tracking parameters, we may have omitted relevant pediatric investigations that employed only conventional ECG, NT-proBNP, or diastolic dysfunction indices, such as the adult report from Calabar.

## Future research directions

Based on the gaps identified, the following research questions should be prioritized.

### *Cross-sectional prevalence study*

What is the prevalence of abnormal GLS in a representative sample of 500-1 000 Nigerian children with SCD, stratified by age, hydroxyurea use, and nutritional status?

Sample size calculation: assuming 20% prevalence of abnormal GLS, a sample of 500 gives a 95% Confidence Interval, CI, of ±3.5%.

### *Longitudinal natural history study*

Among children with normal cardiac indices at baseline, what proportion develop abnormalities over 2-3 years, and what baseline factors predict progression?

### *Diagnostic accuracy study*

What is the sensitivity and specificity of hs-cTn alone for detecting abnormal GLS? A high sensitivity would support using the cheaper blood test as a first-line screen.

### *Randomized controlled trial of intensive versus standard hydroxyurea in children with early myocardial damage*

A multicenter, open-label trial conducted across three or four Nigerian tertiary centres would randomize children to standard care, intensive hydroxyurea, or hydroxyurea plus enalapril, with the primary endpoint of change in GLS at 12 months.

### *Implementation science study*

What are the barriers and facilitators to integrating STE screening into routine SCD care in a Nigerian tertiary hospital? A mixed-methods design (quantitative surveys + qualitative interviews) would inform scale-up.

## Conclusions and recommendations for practice

The evidence supports the following conclusions: i) silent myocardial damage detectable by STE occurs in a substantial minority (approximately 30-40%) of asymptomatic children with SCD; ii) conventional LVEF is normal in most affected children and should not be used to rule out cardiac involvement; iii) hydroxyurea is associated with improved surrogate markers of myocardial health, but randomized trial evidence is lacking; iv) routine population-wide cardiovascular screening with advanced imaging cannot yet be recommended; a risk-stratified approach (targeting children with severe anemia, recurrent crises, or poor hydroxyurea adherence) is a reasonable compromise pending further research.

For the Nigerian pediatrician managing a child with SCD, the following practical steps are suggested, acknowledging that speckle-tracking echocardiography is not universally available: i) perform a thorough cardiovascular history and examination annually, with particular attention to exercise tolerance, chest pain and palpitations; ii) obtain a baseline electrocardiogram at diagnosis and repeat it if new symptoms arise; iii) where access to STE exists, prioritize its use in children with hemoglobin consistently <7 g/dL or ≥3 vaso-occlusive crises per year; iv) optimize hydroxyurea therapy to the maximum tolerated dose and, where resources allow, add L-glutamine; these disease-modifying agents are the cornerstone of cardioprotection; v) ensure timely blood transfusion for severe anemia or acute chest syndrome, maintain aggressive hydration during all vaso-occlusive episodes, and enforce comprehensive infection prevention (vaccination, penicillin, mosquito nets); vi) refer children with abnormal screening findings (GLS less negative than -18%, but note that cut-offs are not standardized) to a pediatric cardiologist for individualized assessment; routine use of cardioprotective medications such as carvedilol or ACE inhibitors cannot be recommended outside of clinical trials.

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