Evaluation of left ventricular systolic function in children with sickle cell anemia: contribution of 2D strain

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Abstract

Background: Children with sickle cell anemia (SCA) are at an increased risk of cardiovascular complications. The aim of this study was to assess the role of speckle tracking echocardiography in detecting subclinical myocardial damage in children with SCA.

Methods: A cross-sectional case–control study was conducted at the echocardiography laboratory of the military hospital of Tunis between July and December 2018. Thirty patients with SCA were included. A control (C) group including 30 normally developing children was selected and matched to the SCA group by sex and age. We compared between the two groups: conventional echocardiographic parameters including cardiac output, left ventricular ejection fraction (LVEF), thickness and the global longitudinal strain (GLS). The echocardiographic measurements were indexed according to body surface area. The left ventricular (LV) GLS association with clinical characteristics and echocardiographic parameters were also evaluated.

Results: Patients and controls were matched for age and sex: the mean age was (11± 2years) in SCA group versus (12± 1 years) in C group with a sex ratio of (1.31 versus 1.27, respectively). Body surface area was comparable. LV hypertrophy and dilation were revealed in the SCA group, whereas measurements were normal in the C group. No significant differences were observed for cardiac output (p=0.4). LVEF were preserved in both groups. However, two-dimensional (2D) LVGLS
was impaired in 46% of SCA group (n=14) with mean value of (-21%±3.07 vs -25%±2.98; p<0.01). In SCA group, impaired LVGLS was significantly associated with LV mass (r = - 0.399, p<0.01), LV tele diastolic diameter (r = -0.419, p<0.01) and left atrial volume (r = - 0.399, p< 0.04). In multivariate analysis, LV mass was the only independent factor.

Conclusions:
In the present study, LVGLS measurement revealed subclinical LV systolic impairment in patients with SCA. Therefore, 2D strain could be beneficial to detect the natural history of LV dysfunction in SCA.

Keywords
sickle cell anemia; heart disease; echocardiography; Speckle tracking echocardiography. Global longitudinal strain; Left ventricular systolic function; child.
List of abbreviations
2D: Two-dimensional
C: Control
DTI: Pulsed Doppler tissue
GLS: Global longitudinal strain
IVST: Interventricular septal wall thickness
LV: Left ventricular
LVEDD: Left ventricular end-diastolic diameter
LVEF: Left ventricular ejection fraction
LVESD: Left ventricular end-systolic diameter
LVGLS: Left ventricular global longitudinal strain
LVM: Left ventricular mass
MAPSE: Mitral annular plane systolic excursion
PWT: Posterior wall thickness
S': Systolic mitral annulus velocity
SCA: Sickle cell anemia
TM: Time Movement (TM)
TTE: Transthoracic echocardiography

Introduction
Sickle cell disease or sickle cell anemia (SCA) is an autosomal recessive genetic disease linked to a hemoglobin abnormality leading to the deformation of red blood cells. The disease affects more than 50 million people worldwide, particularly in sub-Saharan Africa and the Mediterranean region. Globally, hemoglobin disorders are responsible for about 3.4% of death among children under 5 years old. The prognosis of this serious chronic disease depends on the occurrence of complications, particularly cardiovascular diseases. However, these complications usually occurred in adulthood, largely due to a lack of regular cardiological follow-up during childhood. The development of cardiac complications in SCA are multifactorial including anemia related chronic volumetric overload, endothelial dysfunction, altered microcirculation, and myocardial iron overload. All these mechanisms contribute to severe clinical manifestations, ranging from pulmonary arterial hypertension to left ventricular diastolic dysfunction and dilated or hypertrophic cardiomyopathy. Nowadays, with the advent of new echocardiographic techniques such as two-dimensional (2D) strain, it is possible to detect systolic and diastolic dysfunction earlier than with conventional echocardiography.

The advent of 2D strain has provided early detection of cardiac damage in many chronic diseases and has increasingly become essential to stratify prognosis. In fact, it is a new technique that studies myocardial motion by tracking speckles, which are acoustic markers of the myocardium. Local tissue motion is represented by the geometric displacement of each speckle. Several software packages have been developed to allow temporal and spatial processing of the image obtained by the 2D strain.

The aim of the present study was to assess the contribution of 2D strain to the detection of subclinical left ventricular (LV) myocardial damage in children with SCA.
Methods

Study design

A cross-sectional case-control study was conducted in the cardiology department at the Military Hospital of Tunis between July and December 2018.

Study population

- **Sample size calculation:**

Knowing that 2.4% of patients followed up on at the pediatric department were referred for pediatric cardiology consultation during the study period, it was deemed that a sample size of 35 patients, calculated using a predictive formula, would be required to achieve statistical significance (power: 0.8; alpha: 0.05).7

- **SCA group:**

Inclusion and non-inclusion criteria: The SCA group included children (2-18 years) followed up at the pediatric department of the military hospital of Tunis for homozygous SCA during the study period. Patients with a history of heart disease or those who had undergone cardiac surgery were not included.

Exclusion criteria: The patients with poor echogenicity on transthoracic echocardiography (TTE) and those who were lost to follow-up during the study period were excluded.

- **Control group:**

For the control (C) group, we selected 30 children with no history of cardiovascular or respiratory pathology or presenting anemia at the time of the study. Those children were hospitalized in the pediatric department and referred to a pediatric cardiologist for assessment of a heart murmur or for exploration of atypical chest pain. All the control patients had normal echocardiography. Then, the control group was matched with the SCA group based on age and gender.

Data collection

Data were collected by a single physician (? For example SC or AN ...) using the patient information sheet. Parents accepted to participate in the study and informed consents were given. They also accepted that their children underwent an echocardiographic examination since it is noninvasive.

- **Clinical and anthropometric data**

Data collected were age, sex, medical history, age of onset of disease, hemoglobin level, rate of transfusion, complications, and current treatment. The height was measured with a standing stadiometer (Seca 217), barefoot or in socks, in a standing position, heels joined, well balanced, and back straight. Weight (±1 kg) was measured with a digital scale (Tanita TBF-300 body composition analyzer), and then body surface area (m²) was calculated.8

- **Echocardiography**

TTE was performed in all patients by a single experienced pediatric cardiologist (same who ? initials) using a vivid E7 ultrasound system (GE Healthcare, Horten, Norway) with a S5-1 probe according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.9

All echocardiographic examinations were analyzed by the same cardiologist who was not aware about the collected clinical data (blind analysis). Measurements were performed in the parasternal long axis, parasternal short axis, and apical views (two, three, and four chamber views). An electrocardiogram with a velocity scale between 12 and 20 cm/sec was performed to avoid aliasing.

Each incidence was performed so that the angle between the examined myocardial wall and the ultrasound beam did not exceed 30 degrees. All echocardiographic data were stored on a central memory unit, allowing post processing and adjustment of measurements, including pulsed Doppler tissue imaging (DTI), measured, and averaged over 3 to 5 continuous cardiac cycles.
Left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal wall thickness, and posterior wall thickness (PWT) were measured with 2D targeted M-mode tracing. The left ventricular mass (LVM) was estimated using the Devereux formula.\textsuperscript{10}

Left ventricular ejection fraction (LVEF) was calculated using Simpson’s biplane method of discs, and systolic mitral annulus velocity (S’) was assessed using DTI in 2D mode of the mitral annulus in the four-chamber view.\textsuperscript{10}

**Figure 1.** Analysis of longitudinal deformations of the apical incidence of 4 cavities in a healthy population.

**Figure 2.** Segmental and global left ventricular longitudinal strain in a healthy population.
• **Strain analysis by speckle-tracking echocardiography:** myocardial deformation assessment

Speckle tracking analysis was performed offline on views of the four apical chambers, the apical long axis, and the apical two chambers that were previously stored in Digital Imaging and Communications in Medicine format. Analysis of echocardiographic images was performed offline using Echo PAC (GE Medical Systems, Norway). Three cardiac cycles were recorded in cine loop format at a frame rate between 50 and 80 frames per second as 2D grayscale views.

One end systolic frame is selected by the operator to perform the manual tracing of the endocardial border of the LV. This tracing is then used by the software to create a region of interest. The myocardium is automatically divided into segments according to the standard 16-segment model of the LV. The quality of myocardial tracking was visually checked in real time and then manually corrected to ensure optimal tracking. The software then tracks the deformation of the myocardium during the cardiac cycle to calculate peak systolic segmental strain. The global longitudinal strain (GLS) is determined as the average of the segmental strains (Figures 1, 2). The mean LVGLS estimated in healthy children at -20.2% (95% CI: -19.5%, -20.8%) was used as the cutoff level.

**Statistical analysis**

All statistical analyses were conducted using SPSS 25.0 software (IBM SPSS Inc., Chicago, Illinois, USA). Quantitative variables were tested for normal distribution using the Shapiro-Wilk tests and then expressed as medians and interquartile. Qualitative variables were expressed as numbers and percentages. For the case-control study, the Mann-Whitney test was used to compare categorical data. The optimal cutoff value of GLS in the SCA group was determined based on receiver-operator characteristics (ROC) curve analysis.

A linear regression model was used to evaluate the relationship between impaired LVGLS and clinical and echocardiographic measurements. Pearson correlation analysis and Spearman rank correlation analysis were performed to assess dependence.

The multivariate linear regression for assessing independent correlations in the impaired GLS was performed by including significant variables from the univariate model. A p<0.05 indicated statistical significance.

**Literature review**

For bibliographic research, we used PubMed through MESH research based on the following keywords: Sickle cell anemia, heart disease, echocardiography, speckle tracking echocardiography, global longitudinal strain, left ventricular systolic function, and child. We included publications in French and English between 1970 and 2020.

**Ethics and consent**

The study was approved by the ethics committee of the military hospital in Tunis. Written informed consent was collected from the parents. Anonymity was respected during data treatment.

**Results**

• **Baseline characteristics of the two groups**

Patients and controls were matched for age and sex (Table 1). The mean age of children with SCA was 12±4 years including 13 girls (43%) and 17 boys (57%). The mean age of the control group was 11±3 years.

| Variable          | SCA group | C group | p-value |
|-------------------|-----------|---------|---------|
| Age (years)       | 12±4      | 11±3    | 0.23    |
| Sex ratio         | 0.76      | 0.67    | 0.15    |
| Mean weight (kg)  | 35±14.7   | 31.2±12.3 | 0.43    |
| Mean height (cm)  | 131±31.8  | 138.5±24.6 | 0.521   |
| Mean body surface area (m²) | 1.16±0.31 | 1.11±0.28 | 0.528   |
| Hemoglobin (g/dl) | 8.5±0.5   | 12.8    | 0.001*  |

SCA: Sickle cell anemia group, C group: Control group.
*p<0.05.
(18 boys and 12 girls). In terms of body surface area, there was no statistically significant difference between the two groups.

The average hemoglobin level in the SCA group was 8.6±0.5 g/dl. The mean serum ferritin value was 824±32 μg/l. The treatment received by SCA children included intravenous penicillin in 43% (n=13), Hydroxycarbamide in 46% (n=14), Deferoxamine in 16% (n=5) and vitamin E in 96% (n=29) of the patients. All patients received folic acid.

The symptoms of the SCA group and reported complications are summarized in Table 2.

- **Echocardiographic measurements**

Morphological characteristics and LV systolic function are summarized in Table 3. LV dimensions and mass were significantly greater in the SCA group than in the C group. However, the LVEF measured by the Teicholtz method, was preserved in both groups. A significant difference in the mean LVEF value was noted: 58±12% for the SCA group versus 63±5% for the C group.

No significant differences were revealed between the 2 groups for mitral annular plane systolic excursion (MAPSE) and LV systolic mitral annulus velocity (S') wave measurements. The calculation of the indexed cardiac output was comparable in both groups.

### Table 2. Clinical findings and complications in the SCA group (N=30).

|                          | Number of patients (n) | Frequency (%) |
|--------------------------|------------------------|---------------|
| Dyspnea on exertion      | 14                     | 47%           |
| Chest pain               | 9                      | 30%           |
| Lipothymia               | 3                      | 10%           |
| Complications:           |                        |               |
| Splenomegaly             | 12                     | 40%           |
| Vaso-occlusive crisis    | 28                     | 93%           |
| Osteonecrosis            | 3                      | 10%           |
| Splenic sequestration    | 10                     | 33%           |
| Stroke                   | 5                      | 16%           |
| Splenectomy              | 12                     | 40%           |
| Acute thoracic syndrome  | 21                     | 70%           |

SCA: Sickle cell anemia.

### Table 3. Comparison of LV morphological parameters and LV systolic function in the two groups.

|                              | SCA group (N=30) | C group (N=30) | P     |
|------------------------------|------------------|----------------|-------|
| LVtdD indexed (mm/m²)        | 39.3±14.6        | 28.9±5.03      | 0.001*|
| ISW (mm)                     | 7.09±1.7         | 6.2±1.2        | 0.037*|
| LVM ind (g/m²)               | 98.7±34.2        | 62±16.5        | <0.0001*|
| RWT                          | 0.29±0.03        | 0.39±0.05      | 0.035*|
| LVEF (%)                     | 58±5.6           | 63.2±4.9       | <0.01 |
| S’LV (cm/s)                  | 9±2.6            | 8.7±1.7        | 0.685 |
| MAPSE (mm)                   | 14.6±3           | 13±3.3         | 0.429 |
| Cardiac output (l/min/m²)    | 3.93±2.1         | 4.08±3         | 0.464 |

SCA: Sickle cell anemia group, C group: Control group, LVtdD: Telediastolic diameter of the left ventricle, ISW: Interseptal wall, LVMind: Indexed left ventricular mass, RWT: Wall Relative Thickness, LVEF: Left ventricular ejection fraction, S’: Systolic mitral annulus velocity in DTI, MAPSE: Mitral annular plane systolic excursion.

*p<0.05.
Study of longitudinal myocardial deformation using the speckle tracking technique

According to this study, the optimal cutoff value of GLS was -21.3% (AUC 0.79, 95% CI [0.68–0.90], p<0.001).

The sensitivity, specificity, positive predictive value, and negative predictive value were 48%, 82%, 96%, and 65%, respectively, for predicting altered LV contractile function (Figure 3).

In the SCA group, LVGLS was estimated at -21.2±3%. It was significantly reduced (-20%) in 46% of the children (n=14), whereas it was significantly higher (-25.03±2.9%) in the C group with no decreased value (Figure 4).

Univariate and multivariate analyses of factors associated with abnormal LVGLS

In the SCA group, impaired LVGLS was significantly associated with left ventricular mass (LVM), LV tele diastolic diameter, and left atrial volume (Table 4).

Figure 3. Curve receiver operating characteristic (ROC) of left ventricular strain.

Figure 4. Comparison of the left ventricular global longitudinal strain in the two groups.
No significant correlations were noted between the altered LVGLS, clinical symptoms, complications, and hemoglobin level. The multivariate analysis found a correlation between LVM and impaired GLS ($b=-0.082$, $p<0.001$).

**Discussion**

The main finding of the present study was that performing 2D speckle echocardiography in SCA patients may allow early detection of subclinical left ventricular morphological modifications such as hypertrophy and dilation. Even though both groups had preserved LVEF, the systolic function as measured by 2D speckle tracking imaging was impaired in 46% of the SCA group.

In fact, the greater dilation of the LV in the SCA group could be explained by several mechanisms. First, the chronic anemia due to hemolysis leads to an increase in cardiac output, systolic ejection volume, and baseline heart rate. All these contribute to a significant dilation of the LV. In addition, the chronic intravascular hemolysis is commonly associated with vaso-occlusive event that also results in hypoxia and further increase in cardiac output. In some studies, the degree of LV dilation has been described as proportional to the degree of anemia. However, increased cardiac output in non-sickle cell anemia usually occurs when the hemoglobin level is less than or equal to 7 g/100 ml. A few studies have been performed using hemodynamic measurements of cardiac output in homozygous SCA and have confirmed the existence of a significant increase in resting cardiac output in most patients, even for hemoglobin levels of 9 to 10 g/100 ml. Thus, for the same hemoglobin level, resting cardiac output was higher in sickle cell patients than that of persons with chronic anemia from other etiologies. This is most likely due to hypoxemia caused by hemoglobin S’s decreased affinity for oxygen and intrapulmonary shunts caused by vaso-occlusive crisis. Therefore, this increase in cardiac output has long been implicated in the prime cause of cardiac damage in sickle cell patients. It has been also associated with morbidity and mortality in these patients.

This study has also revealed features of left ventricular eccentric hypertrophy in SCA patients. The LVM may expand in the setting of SCA to accommodate the increase in tele diastolic diameter of LV. In addition, iron overload may develop during transfusions and boost myocardial development.

In this study, LV systolic function was preserved in all patients with a decreased mean value of LVEF in the SCA group. No significant differences were found for the rest of parameters, including cardiac output value. This result was in line with several studies and meta-analyses. For example, no significant difference in LVEF was also observed in a meta-analysis involving 841 patients with SCA and 554 controls. Otherwise, Lamers et al. have reported a decreased in fractional shortening in SCA children while studying myocardial contractility. Several studies that have assessed left ventricular systolic function in sickle cell patients have concluded that myocardial contractility was impaired independently of left ventricular preload and after load. The load-dependent parameters would be compensated at early stage and would progressively deteriorate with age. Chronic left ventricular volume overload and repeated ischemic events represent the main mechanisms of cardiomyopathy in SCA patients. It leads to myocardial dilation and remodeling that progressively impair left ventricular systolic function overtime.

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**Table 4. Echocardiographic parameters according to impaired LVGLS in sickle cell anemia patients.**

| Echocardiographic parameters | Impaired GLS | R  | P      |
|-----------------------------|--------------|----|--------|
| LVtdD                       | -0.419       | 0.001*|
| LVM                         | -0.414       | 0.001*|
| Left atrial volume          | -0.399       | 0.004*|
| LVEF                        | 0.226        | 0.089 |
| PAPS                        | -0.389       | 0.003*|
| Em                          | 0.156        | 0.427 |
| Am                          | 0.575        | 0.000*|
| E/Am                        | 0.060        | 0.768 |

GLS: Global longitudinal strain, LVM: Left ventricular mass, LVtdD: Telediastolic diameter of the left ventricle, LVEF: Left ventricular ejection fraction, PAPS: Systolic pulmonary artery pressure, Am: Mitral A wave, Em: Mitral E wave.

*p<0.05.
The present study revealed that the LVGLS was significantly impaired in sickle cell patients compared to controls. Indeed, LVGLS is a more specific predictor of myocardial remodeling than LVEF. It is extremely sensitive in detecting early systolic function impairment despite a preserved LVEF. In fact, altered strain in sickle cell patients could be the result of myocardial ischemia, fibrosis, myocardial iron deposition, and ventricular hypertrophy which could be associated with a preserved LVEF during the early stage of the disease. Therefore, LVGLS could indicate the progression to cardiac disorders and myocardial damage at a subclinical stage.

In line with this study result, Sachdev et al. described a correlation between impaired LVGLS and LV dilation and hypertrophy. Thus, the GLS seems to be a useful tool for the follow-up of sickle cell patients. Recent genetic studies in SCA have identified certain genotypes associated with cardiovascular disease. Therefore, it is maybe important to couple echocardiography with genetic analyses in order improve the follow-up and long-term prognosis of SCA patients.

Conclusion
This study primarily supports the use of 2D strain in the assessment of LV function in SCA. However, the interpretation of these results was limited by the absence of recognized standard norms of strain in the pediatric population and by the complexity of using Z-score reference values in the morphological analysis of the LV. Larger scale studies are therefore required to improve the role of LV strain for early evaluation of myocardial damage in children with SCA and to predict the risk of progression to heart failure in these patients.

Consent
Written informed consent was obtained from the parents.

Author contributions
Each author has contributed to this work as follows:

Sarra Chenik: Conceptualization, Data Curation, Methodology, Resources, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Aymen Noamen: Data Curation, Methodology, Resources, Validation, Writing – Original Draft Preparation

Abyr Bouslimi: Data Curation, Methodology, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Houaida Mahfoudhi: Supervision, Validation, Visualization, Writing – Review & Editing

Sadok Hannachi: Conceptualization, Data Curation, Methodology, Resources, Supervision, Validation, Writing – Original Draft Preparation, Writing – Review & Editing

Hager Barakizou: Resources, Validation, Visualization

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Tasnim Znegui: Visualization, Writing – Review & Editing

Wafa Fehri: Supervision, Validation, Visualization, Writing – Review & Editing

Data availability
Underlying data
Figshare: ECHOCARDIOGRAPHIC EVALUATION IN CHILDREN WITH SICKLE CELL ANEMIA: CONTRIBUTION OF 2D STRAIN.xlsx. https://doi.org/10.6084/m9.figshare.20949031.v1.

Data are available under the terms of the Creative Commons Attribution 4.0 International license (CC-BY 4.0).
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The authors have addressed the raised points in an appropriate way. The manuscript is well improved. Then, the current version of paper is suitable for indexing.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiovascular disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

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I have reviewed the submitted paper entitled “Evaluation of left ventricular systolic function in
children with sickle cell anemia: contribution of 2D strain”. The authors showed that left ventricular global longitudinal strain is significantly altered in the SCD-group. They also suggested that treatment with hydroxycarbamide is a predictive factor.

This paper is not well written and not suitable for indexing in the current form. Major revision is required before being considered for further evaluation. Herein, I addressed the main points:

1. English editing is needed through all the manuscript.

2. The authors must define each abbreviation before its first use in the text (C means control in the abstract section).

3. Conclusion in abstract section is out of nowhere.

4. In the introduction section, the authors should cite the potential cardiac complications of sickle cell disease and explain in detail the two-dimensional strain technique.

5. Methods section. It is completely unclear how the authors have performed this study. First, it is a case control study. Inclusion and exclusion criteria are not well defined. They mentioned among inclusion criteria: “having SCA and a performed TTE”, then they mentioned in the text that they performed TTE for all patients. So why do they fix the performance of TTE during follow-up as an inclusion criterion? When have they performed TTE? Did they compare the performed TTE to the previous ones?

6. What was the indication for TTE in SCA or controls group? What was the indication for hospital admission in controls group?

7. A comparative table with 4 columns should be added in the result section (Variable, SCA-group, C-group, p-value). This table should figure baseline characteristics (age, sex, BMI, laboratory values (Hb), treatment, dose, mean of LVGLS, LVEF, etc.).

8. How much was the proportion of patients with impaired LVGLS? Also, a clear definition of impaired LVGLS is lacking.

9. Multivariable logistic regression investigating the association between impaired LVGLS and other parameters (Hydroxycarbamide dose, osteonecrosis, splenomegaly) was not performed. Then, a conclusion only based on bivariate analysis is extremely weak.

10. I suggest putting 3 main tables in the results section: Table 1 (point 6), Table 2 (Impaired LVGLS vs normal LVGLS), Table 3 (multivariable logistic regression).

11. Was a single TTE performed to each study participant? Or were repeated TTE performed?

12. Clear definitions of left ventricular dilation and hypertrophy were missed. All these terms must be defined in the method section including for threshold of normal LVGLS.

13. The authors should mention in the result section that LVGLS was normal in all study participants in C-group.
14. It is true that there was a significant difference in echocardiographic parameters between study groups, but the represented values are within range of normal in both groups. They were not suitable for neither hypertrophic nor dilated cardiomyopathy diagnosis.

15. The authors should represent their results in the first paragraph of the discussion section. Then, they must focus on discussing their findings based on literature data.

16. They claim that hydroxycarbamide treatment is the predictor of LVGLS impairment, but in fact, the hydroxycarbamide dosage differs significantly between study groups. In the concerned table, the authors differ hydroxycarbamide treatment from hydroxycarbamide dose.

17. The authors should explain what this study adds to what is already known in the field. Previous studies investigate the role of LVGLS to predict cardiac outcomes in SCD patients.

18. Re-write the conclusion (rephrase the first sentence which must highlight your take-home message).

19. It is unclear if a LVGLS below -20% is a predictor for cardiac disease in the future. It could be an incidental finding without clinical relevance. Usually, A GLS higher than 18% is considered normal.

Is the work clearly and accurately presented and does it cite the current literature?  
No

Is the study design appropriate and is the work technically sound?  
Partly

Are sufficient details of methods and analysis provided to allow replication by others?  
Partly

If applicable, is the statistical analysis and its interpretation appropriate?  
Yes

Are all the source data underlying the results available to ensure full reproducibility?  
Partly

Are the conclusions drawn adequately supported by the results?  
Partly

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Cardiovascular disease

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.
Author Response 22 Nov 2022

Tasnim Znegui, Military Hospital of Tunis, Tunis, Tunisia

1. English editing is needed through all the manuscript.
   We revised the manuscript.

2. The authors must define each abbreviation before its first use in the text (C means control in the abstract section).
   We rectified all abbreviations in the text.

3. Conclusion in abstract section is out of nowhere.
   We corrected the conclusion in the abstract section.

4. In the introduction section, the authors should cite the potential cardiac complications of sickle cell disease and explain in detail the two-dimensional strain technique.
   We added a paragraph to explain this.

5. Methods section. It is completely unclear how the authors have performed this study. First, it is a case control study. Inclusion and exclusion criteria are not well defined. They mentioned among inclusion criteria: “having SCA and a performed TTE”, then they mentioned in the text that they performed TTE for all patients. So why do they fix the performance of TTE during follow-up as an inclusion criterion? When have they performed TTE? Did they compare the performed TTE to the previous ones?
   It's a cross sectional case-control study
   The (SCA) group included children followed up at the pediatric department of the Tunis military hospital for sickle cell disease during the study period. We did not include patients with SCA with history of heart diseases, or those who had undergone cardiac surgery.
   The control (C) group selected 30 children with no history of cardiovascular or respiratory pathology and not presenting anemia at the time of the study. Then, C group was matched to the SCA group by age, sex and body mass index.

6. What was the indication for TTE in SCA or controls group? What was the indication for hospital admission in controls group?
   These children had been hospitalized in the pediatric department and referred to a pediatric cardiology consultation for assessment of a heart murmur or for exploration of atypical chest pain, and who had a normal echocardiography.

7. A comparative table with 4 columns should be added in the result section (Variable, SCA-group, C-group, p-value). This table should figure baseline characteristics (age, sex, BMI, laboratory values (Hb), treatment, dose, mean of LVGLS, LVEF, etc.).
   We added a table untitled ‘Comparison of baseline characteristics of the two groups’.

8. How much was the proportion of patients with impaired LVGLS? Also, a clear definition of impaired LVGLS is lacking.
   In SCA group, LVGLS was estimated at -21.2±3%. It was significantly decreased (< -20%) in 46% of children (n=14) referring to ‘Reference Ranges of Left Ventricular Strain Measures by
Two-Dimensional Speckle-Tracking Echocardiography in Children A Systematic Review and Meta-Analysis. J Am Soc Echocardiogr. 2016 Mar;29(3):209-225.e6. Epub 2015 Dec 30.

9. Multivariable logistic regression investigating the association between impaired LVGLS and other parameters (Hydroxycarbamide dose, osteonecrosis, splenomegaly) was not performed. Then, a conclusion only based on bivariate analysis is extremely weak. In multivariate analysis we found a correlation between LVM and impaired GLS (b = -0.082, p<0.001)

10. I suggest putting 3 main tables in the results section: Table 1 (point 6), Table 2 (Impaired LVGLS vs normal LVGLS), Table 3 (multivariable logistic regression). We have organized the results section.

11. was a single TTE performed to each study participant? Or were repeated TTE performed? A single TTE was performed to each study participant.

12. Clear definitions of left ventricular dilation and hypertrophy were missed. All these terms must be defined in the method section including for threshold of normal LVGLS. We revised the methodology.

13. The authors should mention in the result section that LVGLS was normal in all study participants in C-group. We mentioned this result.

14. It is true that there was a significant difference in echocardiographic parameters between study groups, but the represented values are within range of normal in both groups. They were not suitable for neither hypertrophic nor dilated cardiomyopathy diagnosis. We added a Table to compare the LV morphological parameters and LV systolic function in the two groups.

15. the authors should represent their results in the first paragraph of the discussion section. Then, they must focus on discussing their findings based on literature data. We corrected the first paragraph of the discussion section.

16. they claim that hydroxycarbamide treatment is the predictor of LVGLS impairment, but in fact, the hydroxycarbamide dosage differs significantly between study groups. In the concerned table, the authors differ hydroxycarbamide treatment from hydroxycarbamide dose. We corrected the correlation between treatment and LVGLS impairment.

17. the authors should explain what this study adds to what is already known in the field. Previous studies investigate the role of LVGLS to predict cardiac outcomes in SCD patients.
The aim of this study was to assess the contribution of 2D strain to the detection of subclinical LV myocardial damage in children with SCA and to reveal associated factors with abnormal LVGLS.

18. Re-write the conclusion (rephrase the first sentence which must highlight your take-home message).
We have corrected the conclusion.

**Competing Interests:** No competing interests were disclosed.

Author Response 23 Nov 2022

Tasnim Znegui, Military Hospital of Tunis, Tunis, Tunisia

We are grateful to the reviewers for their insightful comments.

**Competing Interests:** No competing interests were disclosed.

Reviewer Report 31 October 2022

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**Hassen Ibn Hadj Amor**

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Sickle cell disease is endemic in north Africa. It used to be a life-threatening disease with reduced life expectancy which improved in the recent years due to healthier lifestyles, medical monitoring, and new therapies. Nevertheless, we attest to an increase of chronic multi-systemic complications in addition to acute complications, mainly cardiovascular ones. The authors highlighted in this paper the importance of early detection of myocardial damage using echocardiographic techniques such as two-dimensional (2D) strain during childhood. It is a patient control study with a predictive factor analysis for alteration of the global longitudinal strain of the left ventricle. Generally, the manuscript is well written and the topic is quite interesting for the reader. The paper seems suitable for indexing in its actual version.

**Is the work clearly and accurately presented and does it cite the current literature?**
Yes

**Is the study design appropriate and is the work technically sound?**
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: cardiology, echocardiography

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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