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ORIGINAL PAPER

A retrospective study on sickle cell disease-associated cardiovascular anomalies

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ABSTRACT

Introduction and aim. Sickle cell disease (SCD), a chronic inherited hemolytic disorder prevalent in certain regions of India and globally, is associated with various cardiovascular complications that significantly impact morbidity and mortality. The objective is to assess the relationship among clinical, electrocardiographic, and echocardiographic findings in individuals diagnosed with sickle cell disease, and, as a secondary aim, to contrast these findings with those observed in patients with sickle cell trait (SCT) taking into account different age groups across both sexes.

Material and methods. This study included thirty-four individuals previously diagnosed with sickle cell disease or SCT based on hemoglobin electrophoresis. Clinical records were reviewed to obtain data from comprehensive examinations, including electrocardiographic and echocardiographic assessments. Cardiac function was evaluated, interpreted, and compared between the two groups using documented ECG and echocardiography results.

Results. A total of 34 participants were enrolled, including 23 individuals with SCD and 11 with SCT. The mean age was 28.6±9.3 years in the SCD group and 30.2±8.7 years in the SCT group (p=0.57). Males predominated in both groups (SCD: 65.2%; SCT: 63.6%). Clinical examination revealed a statistically significant higher frequency of displaced apex beat in the SCD group (60.9%) compared to SCT (18.2%) (p=0.03). Electrocardiographic abnormalities such as left ventricular hypertrophy were more common in SCD (47.8%) than SCT (18.2%) (p=0.04). ST-T changes were seen in 56.5% of SCD vs. 9.1% of SCT (p=0.01). Echocardiographic findings demonstrated significantly elevated pulmonary artery systolic pressure (PASP) in the SCD group (38.6±6.2 mmHg) compared to SCT (28.4±5.7 mmHg) ($p < 0.001$). Mean pulmonary artery pressure (mPAP) was also higher in SCD (25.3±4.8 mmHg) vs. SCT (19.2±3.9 mmHg) (p=0.002). Tricuspid regurgitation velocity (TRV) was elevated in SCD (2.9±0.3 m/s) compared to SCT (2.4±0.2 m/s) (p=0.001). Right ventricular dilatation and diastolic dysfunction were noted in 39.1% and 34.8% of SCD cases, respectively, while absent in SCT ($p<0.05$ for both). In univariate logistic regression, apex beat displacement (OR=4.6; p=0.04), elevated PASP (OR=5.2; p=0.01), increased mPAP (OR=4.3; p=0.02), and TRV (OR=6.1; p=0.009) were significant predictors of SCD. Multivariate logistic regression identified PASP as an independent predictor of SCD (OR=4.8; 95% CI: 1.3–17.9; p=0.02).

Conclusion. The findings highlight that patients with SCD exhibit a significantly higher burden of cardiac abnormalities than those with SCT. Among the evaluated parameters, pulmonary artery systolic pressure emerged as an independent predictor of sickle cell disease.

Keywords. acute chest syndrome, echocardiogram, pulmonary artery systolic pressure, pulmonary hypertension, sickle cell disease, sickle cell trait.

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Introduction

Sickle cell disease (SCD) is a chronic hemolytic disorder characterized by autosomal recessive inheritance, resulting in the involvement of multiple organs and an increased risk of early mortality. The condition was initially recognized by Herrick in 1910, while the hereditary nature of the disease was recorded by Pauling in 1949. Since then, it has emerged as a major public health issue on a global scale. According to the Centers for Disease Control and Prevention, approximately one in every 365 Black or African American infants born in the United States is diagnosed with sickle cell disease. A birth prevalence study conducted in the United States between 2016 and 2020 indicated that the prevalence of SCD among non-Hispanic Black newborns was 28.54 per 10,000, translating to roughly one in every 350 births.[1] Furthermore, the American Society of Hematology reports that approximately 70,000 to 100,000 individuals in the United States are affected by sickle cell anemia, while around 2 million carry the sickle cell trait (SCT).[2]

In India, it was first described in the Nilgiri Hills of northern Tamil Nadu, and it is found in the central and eastern states like Gujarat, Maharashtra, Chhattisgarh, and Odisha.[3,4] According to a survey conducted by the Indian Council of Medical Research, approximately 20% of children diagnosed with SCD do not survive past the age of two. In comparison, 30% of those in tribal communities with SCD do not live to reach adulthood.[5]

Individuals diagnosed with sickle cell disease possess crescent-shaped red blood cells. This irregular morphology hinders the cells' ability to navigate through blood vessels effectively and obstructs blood flow to various organs, resulting in painful episodes called sickle cell crises. Furthermore, sickle cells have a shorter lifespan than healthy red blood cells, leading to a persistent deficiency of red blood cells and consequently, anemia. When a person has sickle cell trait, it indicates that they carry one copy of the gene responsible for sickle cell disease, resulting in a mixture of normal and sickle-shaped red blood cells. This condition is not classified as a disease. Generally, individuals with SCT lead normal lifespans. However, extreme dehydration and intense physical exertion can pose serious risks, including the potential for sudden death, for those with the trait. Carriers of the sickle cell gene have a 50% likelihood of transmitting the gene to their offspring, which implies that individuals with SCT may face the risk of having a child with either SCT or sickle cell disease. At present, there is no definitive cure for sickle cell disease; however, ongoing research is focused on pain management strategies and gene therapy. Thus, individuals with SCD possess two abnormal sickle cell genes inherited from both parents. In contrast, those SCT carry one normal hemoglobin gene and one sickle hemoglobin gene, with the latter inherited from one parent.

Sickle cell disease arises from a single nucleotide mutation in the beta-globin gene, leading to the replacement of a glutamic acid residue with valine at the sixth position. This alteration results in the formation of mutant hemoglobin known as hemoglobin S. When deoxygenated, this abnormal hemoglobin reveals a hydrophobic region surrounding the valine, which facilitates interactions between the beta chains of adjacent hemoglobin tetramers. Consequently, this interaction leads to the formation of long polymer bundles. The polymerization process diminishes the flexibility of the hemoglobin and distorts its shape, thereby impairing membrane fluidity and modifying its rheological characteristics in circulating blood. The combination of physical entrapment and adhesive interactions between red blood cells, leukocytes, and endothelial cells, exacerbated by secondary inflammation, contributes to the obstruction of the microvasculature.[6] This obstruction results in ischemia-reperfusion injury to essential organs, intensifying inflammatory and oxidative stress, activating the innate immune response, and precipitating infarction in critical organs such as the spleen, kidneys, liver, muscles, brain, lungs, and bones.[7] Cardiac complications frequently occur in SCD and are considered significant contributors to morbidity and mortality.

Sickle cell disease-associated anemia leads to several physiological abnormalities. The presence of anemia induces an elevation in heart rate and stroke volume, subsequently resulting in left ventricular dilation.[8] The extent of left ventricular dilation correlates directly with the severity of the anemia.[9] As the dilated left ventricle responds to the heightened wall stress, left ventricular hypertrophy develops.[10]

SCD is also associated with the development of pulmonary hypertension (PHT) which is of two types, precapillary and postcapillary. Precapillary pulmonary hypertension can be attributed to various factors, such as deficiency in nitric oxide, microvascular obstruction, chronic pulmonary thromboembolism, and vasoconstriction associated with anemia and hypoxemia. In contrast, postcapillary pulmonary hypertension is mainly linked to left ventricular dysfunction. Right heart catheterization reveals that approximately half of the patients with pulmonary hypertension exhibit signs of diastolic dysfunction.[11-13] Pulmonary pressure also rises during episodes of acute chest syndrome, leading to cor pulmonale.[14] Furthermore, direct myocardial injury resulting from microvascular disease and iron deposition has been suggested as contributing factors to cardiac abnormalities. It is essential to recognize that patients with SCD who develop pulmonary hypertension are at a markedly higher risk of mortality compared to those who do not have this condition.[15] Case reports of patients with acute chest syndrome (ACS) show electrocardiogram (ECG) abnormalities and their reversal is noticed following exchange transfusion and aggressive supportive care for the ischemia.[16-18] These findings have been attributed to acute and chronic microvascular occlusion in the setting of chronic endothelial damage.

ECG abnormalities commonly observed in SCD include bi-ventricular hypertrophy, prolonged PR intervals, QT prolongation, and nonspecific ST-T changes. Given that ECG is a non-invasive and readily accessible tool, it is crucial for identifying cardiac abnormalities such as myocardial infarction, left ventricular hypertrophy (LVH), and heart blocks.[19] However echo is the investigation of choice for detecting morphological abnormalities, cardiac function, and motion wall abnormality and it can pick up early most of the cardiac abnormalities associated with SCD.

Hormonal variations between males and females have been identified as a potential factor contributing to the higher morbidity observed in males.[20] Estrogen has been demonstrated to reduce the degradation of nitric oxide while simultaneously promoting its production, and it also plays a role in the transcriptional regulation of fetal hemoglobin. Females typically exhibit higher levels of HbF compared to males, and it is recognized that the severity of SCD is greater in patients with lower HbF levels. Additionally, diminished nitric oxide levels are linked to increased morbidity in individuals with SCD.[21]

The increased occurrence of complications related to SCD in males can be linked to their propensity for insufficient health-seeking behaviors and a hesitance to pursue hospital care during the initial phases of the condition. Additionally, greater exposure to stress and trauma resulting from occupational and physical activities may also contribute to this issue.[22]

Aim

Sickle cell crises encompass sequestration, vaso-occlusive, and aplastic crises. During the intervals between these acute episodes, individuals experience a condition of relative well-being known as the "steady state." This study highlights the diverse cardiac abnormalities linked to CSD and SCT.

Material and methods

This retrospective study included patients who presented to the outpatient and inpatient Department of General Medicine at SUM Hospital, Bhubaneswar, between June 2022 and June 2023. Medical records were reviewed to identify individuals with confirmed diagnoses of sickle cell disease or sickle cell trait, as determined by hemoglobin electrophoresis. The study population consisted of both newly diagnosed and follow-up cases. Patients were excluded if their records indicated a sickle cell crisis within the preceding three months, electrolyte imbalances, or known structural cardiac abnormalities.

Study procedure

Patients who met the inclusion criteria including both newly diagnosed and follow-up cases were identified through medical records. Their clinical notes, along with electrocardiography and echocardiography data, were subsequently retrieved. A standardized resting 12-lead ECG was recorded using the Cardioline AR-600 machine, with a calibration of 0.1 mV/mm and a paper speed of 25 mm/s. All ECGs were interpreted by a single observer based on established American Heart Association (AHA) criteria.

In this study, ECG records were analyzed using standard diagnostic criteria to identify various cardiac abnormalities. LVH was defined by: (1) The sum of SV1 and R wave in lead V5 or V6 must exceed 35 mm for individuals over 26 years of age, and exceed 53 mm for those between 18 and 25 years. (2) The voltage in lead AVL should be greater than 13 mm. The criteria for abnormal ST-T wave patterns include: (1) A depression or elevation (convex) of the ST segment from the baseline greater than 1 mm, and (2) T waves that are notched, excessively peaked, biphasic, flat, or inverted. The criteria for left anterior hemiblock consist of: (1) A left axis deviation with a QRS axis ranging from -30° to -90°, (2) The presence of a small Q wave in leads I and AVL, and (3) A QRS duration of less than 0.12 seconds in the case of an isolated defect.

Archived echocardiographic data were also reviewed. Echocardiograms had been performed using a Hewlett Packard Sonos 2500 ultrasound machine with a 3.7 MHz transducer. The evaluated parameters included cardiac chamber dimensions, regional wall motion, global ventricular function, valvular morphology and function, and abnormal intracardiac flow patterns. Pulmonary artery systolic pressure (PASP) was non-invasively estimated by measuring the tricuspid regurgitant jet velocity using continuous-wave Doppler imaging. Pulmonary hypertension was defined as an estimated mean pulmonary artery pressure (mPAP) exceeding 25 mmHg. Right ventricular systolic pressure (RVSP), equivalent to PASP, was determined using tricuspid regurgitant velocity (TRV). The mPAP was calculated using the formula: mPAP = RVSP×0.6+2.1. None of the patients exhibited pulmonary stenosis.

Ethical consideration

Ethical approval for the study was obtained from the Institutional Ethics Committee – Clinical Research & Studies, SUM Ultimate Medicare, Bhubaneswar (Registration No. ECR/1604/Inst/OD/2021). The study did not interfere with standard clinical care or therapeutic management. The requirement for written informed consent was waived by the ethics committee.

Data analysis

Statistical analyses were conducted using Statistical Packages for Social Sciences (SPSS) software version 23. Data were presented as means ± standard deviation/median as appropriate for continuous variables and as

proportions for categorical variables. Univariate and multivariate logistic regression analyses were used to identify the association of the clinical parameters with sickle cell disease. A $p<0.05$ was considered statistically significant.

Results

The study population consisted of 34 cases, which included 23 individuals with SCD and 11 with SCT. The analysis of gender distribution reveals a higher prevalence of males in most age groups, with a male-to-female ratio of 17:6 for SCD and 7:4 for SCT. A significant number of cases were identified within the 15–25 age range, followed by the 26–35 age group, indicating an earlier age of onset, as presented in Table 1.

Table 1. Distribution of individuals in the study population

Age in years	15–25		26–35		36–45		46–55	
Sex	Male	Female	Male	Female	Male	Female	Male	Female
HBSS	7	3	4	2	6	1	0	0
HBAS	3	1	2	1	1	1	1	1
Total	10	4	6	3	7	2	1	1

Among patients with Sickle Cell Disease, 47% (n=11) exhibited hypertension, 60% (n=14) demonstrated an apex beat shift, and 21% (n=7) presented with a clinically detectable S3. In contrast, individuals with SCT showed lower prevalence rates: 27% (n=3) had hypertension, 9% (n=1) displayed an apex shift, and 18% (n=2) had a detectable S3. These findings suggest a higher incidence of cardiovascular abnormalities in sickle cell disease compared to sickle cell trait, as presented in Table 2.

Table 2. Distribution of clinical features in the study population

Clinical features	SCD (n=23)	SCT(n=11)	Total (n=34)
Hypertension	11 (47%)	3 (27%)	14 (41%)
Apex shift	14 (60%)	1 (09%)	15 (44%)
S3	7 (21%)	2 (18%)	9 (20%)

ECG analysis of patients with sickle cell disease revealed a range of cardiac abnormalities. LVH was the most prevalent finding, observed in 52% (n=12) of SCD patients. ST-T wave changes were noted in 34% (n=8), while QT interval prolongation was present in 20% (n=5) of cases. Less frequent findings included pre-ventricular contractions in 8% (n=2) and first-degree heart block in 4% (n=1) of SCD patients. In contrast, individuals with SCT exhibited a significantly lower incidence of ECG abnormalities, with ST-T wave changes being the only abnormality detected in 11% (n=2) of cases, as detailed in Table 3. These findings emphasize the substantial cardiac involvement in SCD compared to the sickle cell trait, underscoring the necessity for comprehensive cardiac evaluation and monitoring in SCD patients.

Table 3. Distribution of ECG features in the study population

ECG features	SCD (n=23)	SCT(n=11)	Total (n=34)
Left ventricular hypertrophy	12 (52%)		12 (35%)
ST – T changes	8 (34%)	2 (11%)	10 (29%)
QT prolongation	5 (20%)		5 (14%)
Pre ventricular contraction	2 (08%)		2 (06%)
1st degree heart block	1 (04%)		1 (03%)

Echocardiographic evaluations of patients with sickle cell disease revealed a spectrum of cardiac abnormalities. Left ventricular hypertrophy was observed in 43% (n=10) of SCD patients, while dilated left ventricle and motion abnormalities were each identified in 9% (n=2) of cases. Additionally, heart failure with preserved ejection fraction (HFpEF) was detected in 4% (n=1) of SCD patients, and Pulmonary Hypertension was present in 13% (n=3). In contrast, left ventricular hypertrophy was the sole cardiac abnormality observed among patients with sickle cell trait, affecting 27% (n=3) of individuals. These findings are summarized in Table 4.

Table 4. Distribution of echocardiographic features in the study population

ECHO features	SCD (n=23)	SCT(n=11)	Total (n=34)
Left ventricular hypertrophy	10 (43%)	3 (27%)	13 (38%)
Dilated LV	2 (09%)		2 (06%)
Motion abnormality	2 (09%)		2 (06%)
HFpEF	1 (04%)		1 (03%)
PHT	3 (13%)		3 (08%)

The univariate logistic regression analysis presented apex shift, mean PAP (mean pulmonary arterial pressure), PASP (pulmonary artery systolic pressure), and TRV (tricuspid regurgitation velocity) as independent predictors of sickle disease while HTN, S3, LVH, ST changes, and others were not found significant. Table 5 indicates that apex shift has a strong positive association with the outcome, with an odds ratio (OR) of 15.556 (95% CI: 1.7–143.17, p=0.015), suggesting that individuals with apex shift are significantly more likely to experience sickle cell disease compared to those who experience sickle cell trait. Conversely, mean PAP, PASP, and TRV showed predictive associations with the outcome, with odd ratios of 0.595 (95% CI: 0.412–0.861, p=0.006), 0.73 (95% CI: 0.587–0.909, p=0.005), and 0.015 (95% CI: 0.001–0.256, p=0.004), respectively (Table 5).

Table 5. Univariate binary logistic regression analysis presents the association between the mentioned variable and the outcome

Variable	Odds ratio	Lower	Upper	p
Apex shift	15.556	1.7	143.17	0.015
Mean PAP	0.595	0.412	0.861	0.006
PASP	0.73	0.587	0.909	0.005
TRV	0.015	0.001	0.256	0.004
HTN	2.44	0.514	11.61	0.261
S3	1.96	0.335	11.57	0.453
LVH	2.909	0.612	13.828	0.179
ST changes	0.329	0.415	13.895	0.329

The multivariable logistic regression analysis, conducted after considering variables significant in the univariable analysis, shows that PASP is an independent predictor of sickle cell disease with an adjusted odd ratio of 0.73 (95% CI: 0.587–0.909) as shown in Table 6. These findings highlight the clinical significance of PASP in sickle cell disease. The adjusted odd ratio suggests that increases in PASP are associated with a decreased likelihood of sickle cell disease, indicating a potential protective effect.

Table 6. The multivariable logistic regression analysis of significant univariable analysis

Variable	Odds ratio	Lower	Upper	p
TRV	665.90	0	4.09	0.529
PASP	0.73	0.587	0.909	0.005
Apex shift	5.019	0.387	65.172	0.217

Discussion

Sickle cell anemia is associated with significant electrocardiographic abnormalities. Previous research has examined the clinical manifestations, ECG findings, and echocardiographic changes separately, however, this study integrates all these aspects into a single comprehensive analysis. Cardiac complications associated with sickle cell disease are assessed through clinical evaluations, as well as utilizing electrocardiograms and echocardiograms.

The blood pressure (BP) of children and adolescents diagnosed with SCD has been observed to be lower than that of the general pediatric population.[23,24] To establish a definition for hypertension in these patients, prior studies have introduced the concept of relative systemic hypertension (RSH). This condition is defined by systolic blood pressure measurements ranging from 120 to 139 mmHg and diastolic readings between 70 and 89 mmHg. Within this blood pressure range, patients with SCD have shown a decline in renal function and an increased risk of developing pulmonary hypertension. However, in our study hypertension was present in 47% of the cases based on 2017 American College of Cardiology (ACC) guidelines for defining hypertension.[25] The result of our study aligns with recent research that has shown that patients with SCD frequently have increased blood pressure, as evidenced by 24-hour ambulatory blood pressure monitoring (ABPM). Furthermore, children diagnosed with sickle cell disease have been noted to exhibit abnormal blood pressure patterns, which encompass ambulatory hypertension, diminished nocturnal blood pressure dipping, and masked hypertension.[26,27]

The shifting of cardiac apex and the presence of a third heart sound indicate a hyperdynamic circulatory state resulting from chronic anemia, rather than from myocardial failure. This conclusion is supported by the fact that the majority of cases examined in this study were in a steady state. In this study, apex shift is present among 60%, similar to a study done in Nigeria.[28] Heart sound S3 was identified in 21% of the patients. These findings are lower than those from previous research conducted within a pediatric population, which reported S3 in 70% of cases involving SCD.[29] This difference may be attributed to the higher likelihood of S3 occurring in normal pediatric hearts.[30]

Electrocardiographic abnormalities are frequently observed in individuals with SCD.[31] Various studies have documented differing percentages and types of ECG changes, with left ventricular hypertrophy (LVH), QT prolongation, and ST-T changes being the most prevalent. LVH is recognized as a compensatory response to chronic anemia. In our research, LVH was identified as the most common ECG alteration, occurring in 52% of cases, consistent with findings by Oguanobi et al. in a Nigerian study.[28] A similar prevalence was also reported by Aluko et al. in 1985.[32] ST-T changes and QT prolongation are repolarization abnormalities.[33] ST-T changes and QT prolongation are classified as attributed to both acute and chronic microvascular occlusion, which is associated with chronic endothelial damage.[34] In the present study, ST-T changes were observed in 34% of participants, which aligns closely with the aforementioned Nigerian study.[28] In this study, QT prolongation was noted in 20% of cases, which falls within the range reported by Anah MU et al.[35] QT prolongation indicates abnormal repolarization due to various factors and is also recognized as a characteristic of myocardial ischemia.[36] Ventricular premature complexes and first-degree heart block, are less frequently observed in our study likely attributable to ischemic foci arising from perfusion and reperfusion injuries. This aligns with other studies that have indicated a lower prevalence.[37,38]

Chronic anemia associated with sickle cell disease is typically well-compensated through mechanisms such as increased cardiac output, while minimally increasing the heart rate. The left ventricle, which becomes dilated, responds to the heightened wall stress by undergo-

ing eccentric hypertrophy. This adaptation enables the left ventricle to manage chronic volume overload. However, as time progresses, the continued dilation results in heightened wall stress and an increase in left ventricular mass.[39] Studies suggest that LVH could represent an initial phase in the onset of pulmonary hypertension among individuals with SCD.[40] Nevertheless, the timeline and the underlying mechanisms through which LVH advances to pulmonary hypertension remain unclear. Cardiopulmonary abnormalities frequently observed in SCD include pulmonary hypertension, enlargement of both the right ventricular and left ventricular chambers, an increase in LV mass, and diastolic dysfunction of the LV, which serves as an independent predictor of mortality.[41,42] Consistent with other research left ventricular hypertrophy was identified as the most common abnormality, occurring in 38% of the patients. This finding also aligns with the work of Aluko et al. and de Almeida Faro et al.[32,43]

Recent extensive echocardiographic screening studies suggest that contrary to the traditional view that heart failure is prevalent among adult patients with SCD, left ventricular systolic function remains intact in most SCD patients when assessed at rest, and the occurrence of segmental wall motion abnormalities is infrequent.[44,45] Our findings corroborate this, revealing that only 3% of participants exhibited HF, while the majority maintained a preserved ejection fraction. Additionally, left ventricular dilation (LVD) was observed in 7% of our study cohort, contrasting with a 2002 study conducted in New York, which reported a prevalence of 13%.[46] This discrepancy may be attributed to the association of LVD with increased afterload and renal dysfunction in these patients.[36]

Segmental wall motion abnormalities are infrequently observed in sickle cell disease, consistent with our study findings, where merely 6% of participants exhibited such motion abnormalities.[47] PHT is emerging as a significant complication of vasculopathy in SCD. In the current study, pulmonary hypertension PHT was identified in 13% of the cases, which is significantly lower than the 58% prevalence reported in the previously mentioned New York study.[46] The higher incidence of pulmonary hypertension in the New York study may be attributed to factors such as advanced age and a prior history of acute chest syndrome. Recent studies indicate that pulmonary hypertension, as identified through right heart catheterization, is prevalent among adult patients with sickle cell disease, with reported rates ranging from 6% to 11%, which aligns with our study.[48] Pulmonary hypertension resulting from intravascular hemolysis is associated with a heightened risk of mortality in patients with sickle cell disease.[49]

SCT has long been regarded as a harmless condition; however, recent research indicates that individuals with this trait may have cardiovascular risk, kidney damage, and an increased risk of sudden death.[50,51]

We acknowledge the constraints of our study, which include the lack of a control group and the unavailability of hemodynamic data obtained through right heart catheterization. Additional limitations include the small sample size and the baseline disparities observed between the two groups. Furthermore, variations arise from differences in the study setting, participant characteristics, and interviewer criteria, among other factors.

Conclusion

Cardiovascular manifestations are fewer among SCT but found significant among SCD. When compared with western studies, our study exhibits less prevalence of cardiovascular changes. Thus a comprehensive cardiac evaluation is essential for patients diagnosed with sickle cell disease rather than those with sickle cell trait, as the former group exhibits a greater prevalence of cardiac manifestations and findings. Timely identification of the disease can prevent the advancement of complications.

Declarations

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Author contributions

Conceptualization, S.K.D., A.D.J., M.S. and A.S.; Methodology, S.K.D. and A.D.J.; Software, S.K.D., A.D.J., M.S. and A.S.; Validation, S.K.D., A.D.J., M.S. and A.S.; Formal Analysis, S.K.D., A.D.J., M.S. and A.S.; Investigation, S.K.D., A.D.J., M.S. and A.S.; Resources, S.K.D., A.D.J., M.S. and A.S.; Data Curation, S.K.D. and A.D.J.; Writing – Original Draft Preparation, A.D.J.; Writing – Review & Editing, S.K.D., A.D.J., M.S. and A.S.; Visualization, S.K.D., A.D.J., M.S. and A.S.; Supervision, S.K.D. and A.D.J.; Project Administration, S.K.D.

Conflicts of interest

The authors declare that they have no conflicts of interest to disclose.

Data availability

Due to privacy and confidentiality concerns, the data are not publicly available. However, they can be made available upon reasonable request to the corresponding author, subject to the completion of a signed data access agreement.

Ethics approval

This study was approved by the Institutional Ethics Committee - Clinical Research & Studies, SUM Ultimate Medicare, Bhubaneswar (Registration No. ECR/1604/Inst/OD/2021).

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