Original Research

AN OBSERVATIONAL STUDY TO ASSESS NT-PRO BNP LEVELS AND CARDIOPULMONARY FUNCTION AS ASSESSED BY ECHOCARDIOGRAPHY IN CHILDREN WITH SICKLE CELL DISEASE ADMITTED IN A TERTIARY CARE CENTRE IN JHARKHAND

Katyayani Rai[1], Niraj Kumar[2], Anand Kumar[3], Rajeeva Mishra[4], Prativa Gari[5*], Fauzia Zarrin[6]

[1,2,3,5*,6]Junior Resident Academic (JRA-3), Department of Paediatrics, RIMS, Ranchi, Jharkhand, India.

[4]Professor and Head, Department of Paediatrics, RIMS, Ranchi, Jharkhand, India.

Corresponding Author: Dr. Prativa Gari

Junior Resident Academic JRA-3, Department of Paediatrics, RIMS Ranchi, Jharkhand, India.

Email: dr.prativagari@gmail.com

ABSTRACT

Background: Sickle cell disease (SCD) is among the most common single-gene disorders globally, classified as an autosomal recessive condition causing chronic anemia, painful vaso-occlusive crises, progressive multi-organ damage, and reduced lifespan. Cardiopulmonary complications are leading causes of morbidity and mortality.

Objective: To evaluate cardiopulmonary risk using serum NT-proBNP levels and transthoracic echocardiography in children with sickle cell disease at a tertiary care center in Jharkhand.

Methods: A hospital-based cross-sectional study was conducted on 73 children (aged 5–18 years) with confirmed SCD. Detailed clinical, laboratory, and standardized echocardiographic evaluations were performed, alongside quantitative measurements of serum NT-proBNP levels.

Results: Elevated NT-proBNP levels (>100 pg/mL) were found in 63% of participants, with a mean level of 142.6 ± 98.4 pg/mL. Echocardiography revealed left ventricular hypertrophy (LVH) in 35.6%, diastolic dysfunction in 42.5%, and pulmonary hypertension (elevated tricuspid regurgitant velocity, TRV >= 2.5 m/s) in 38.4% of patients. Left ventricular systolic function remained largely preserved (mean EF 64.2% ± 5.8%). NT-proBNP levels correlated significantly with lower hemoglobin ($r = -0.486$, $p < 0.001$), reticulocytosis ($r = +0.396$, $p = 0.001$), elevated TRV ($r = +0.642$, $p < 0.001$), and high E/e' ratio ($r = +0.568$, $p < 0.001$). Multivariate analysis identified TRV >= 2.5 m/s (OR 5.26), hemoglobin < 7 g/dL (OR 3.84), and diastolic dysfunction (OR 2.98) as independent predictors of elevated NT-proBNP levels.

Conclusion: Subclinical cardiopulmonary involvement is highly prevalent in pediatric sickle cell disease in Jharkhand. Routine screening with echocardiography and NT-proBNP can aid in early risk stratification and target timely therapeutic interventions.

Keywords: NT-proBNP, Cardiopulmonary Function, Echocardiography, Sickle Cell Disease, Diastolic Dysfunction, Pulmonary Hypertension.

INTRODUCTION

The global burden of sickle cell disease (SCD) is substantial, with an estimated 300,000 to 400,000 affected infants born annually worldwide. While sub-Saharan Africa, the Mediterranean, and the Middle East represent regions of high prevalence, India also exhibits a unique and dense epidemiological pattern [1].

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The disease is particularly prevalent among tribal populations in the central, western, and southern states. Recently, a carrier prevalence of 3.3% has been reported in Jharkhand, an eastern Indian state with a large tribal population where hemoglobinopathies are highly endemic [1].

Patients with SCD undergo unique and progressive cardiovascular changes throughout their lives. These changes begin with chronic intravascular and extravascular destruction of defective red blood cells (hemolysis). Ongoing hemolysis leads to persistent anemia and a dramatic reduction in oxygen-carrying capacity, with baseline hemoglobin levels typically ranging from 6 to 9 g/dL. To compensate for systemic tissue hypoxia, the body establishes a hyperdynamic circulatory

state characterized by increased stroke volume, resting tachycardia, and elevated cardiac output.

In this clinical context, N-terminal pro-brain natriuretic peptide (NT-proBNP) has emerged as an invaluable diagnostic and prognostic biomarker of cardiovascular involvement. NT-proBNP is synthesized and secreted by ventricular myocytes in response to increased wall stress or pressure overload. Compared to active BNP, NT-proBNP offers distinct clinical advantages, including a longer circulating half-life (~120 minutes), superior in-vitro stability, and lower analytical variability, making it highly suitable for routine clinical application [2].

Transthoracic Doppler echocardiography remains the primary non-invasive imaging modality for evaluating structural and functional cardiac abnormalities in SCD [3]. It enables accurate chamber quantification, measurement of left ventricular mass, and estimation of pulmonary artery systolic pressure (PASP) using the tricuspid regurgitant jet velocity (TRV). Doppler and tissue Doppler imaging (TDI) further facilitate the evaluation of diastolic function by assessing mitral inflow patterns and calculating E/A and E/e′ ratios [3,4]. This study aims to evaluate the cardiopulmonary function of children with SCD in Jharkhand using both NT-proBNP levels and comprehensive echocardiography to identify early subclinical cardiovascular impairment.

MATERIAL AND METHODS

Study Design and Setting

This hospital-based cross-sectional observational study was carried out in the Department of Pediatrics, Rajendra Institute of Medical Sciences (RIMS), Ranchi, Jharkhand, in collaboration with the Department of Cardiology. The study spanned an 18-month period from 2023 to 2026.

Sample Size and Sampling Technique

The calculated minimum sample size was 73 patients. A consecutive sampling method was adopted. All eligible children presenting during the study period were enrolled after obtaining informed consent, until the desired sample size was achieved.

Inclusion and Exclusion Criteria

Inclusion Criteria: Children aged 5 to 18 years with confirmed sickle cell disease (homozygous HbSS or HbS-beta thalassemia) diagnosed by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), attending pediatric outpatient clinics or admitted to inpatient wards.

Exclusion Criteria: Children under 5 years of age (to avoid age-related baseline variations in NT-proBNP); children with sickle cell trait (heterozygous HbAS) or other non-sickle hemoglobinopathies; patients presenting with obesity, diabetes mellitus, or known congenital, structural, or rheumatic heart disease.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of RIMS, Ranchi. Prior to enrollment, written informed consent was obtained from parents or legal guardians, and assent was taken from older children where applicable. Patient data were strictly anonymized to preserve confidentiality.

Data Collection and Laboratory Evaluation

Clinical history, physical examination (focusing on pallor, jaundice, hepatosplenomegaly, and respiratory distress), and anthropometrics (height, weight, BMI, body surface area) were systematically recorded. Complete blood counts, reticulocyte counts, and automated hematology parameters were evaluated. Serum NT-proBNP levels were quantified from 2 ml venous blood samples using standard immunoassay methods and categorized into three risk tiers based on established clinical literature: <100 pg/mL, 100–160 pg/mL, and >160 pg/mL.

Echocardiographic Assessment

All participants underwent 2D transthoracic Doppler echocardiography by an experienced cardiologist. Left ventricular end-diastolic (LVEDD) and end-systolic (LVESD) diameters were obtained using M-mode. Left ventricular mass index (LVMI) was calculated and indexed to body surface area, defining left ventricular hypertrophy (LVH) based on ASE pediatric reference guidelines. Diastolic function was graded (Grades I-III) using mitral inflow velocities (E and A waves) and tissue Doppler velocities (septal and lateral e'). Pulmonary pressures were evaluated using TRV and estimated PASP.

Statistical Analysis

Data were analyzed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t-test or Mann-Whitney U test. Categorical variables were expressed as frequencies and percentages. Correlations were evaluated using Pearson or Spearman correlation coefficients. Multivariate logistic regression was performed to identify independent predictors of elevated NT-proBNP (>160 pg/mL). A p-value <= 0.05 was considered statistically significant.

RESULTS

A total of 73 children with confirmed SCD were enrolled. The mean age of the participants was 10.2 ± 3.6 years, with the majority (42.5%) belonging to the 9–12 years age group. The sample included 41 males (56.2%) and 32 females (43.8%), representing a male-to-female ratio of 1.28:1. Geographical distribution indicated that patients primarily

originated from Ranchi (37.0%), Gumla (20.5%), and Simdega (16.4%) districts, aligning with the endemic tribal belt of Jharkhand.

Table 1: Anthropometric Parameters of Study Participants (n=73)

Parameter	Mean ± SD
Height (cm)	132.4 ± 18.6
Weight (kg)	28.8 ± 10.2
Body Mass Index (kg/m²)	16.2 ± 2.8
Body Surface Area (m²)	1.02 ± 0.26

Anthropometric metrics demonstrated mild to moderate growth retardation across the cohort, consistent with nutritional and chronic hypoxemic changes in SCD. The mean age at diagnosis was 4.8 ± 2.4 years. Pallor was present in 100% of participants, jaundice in 69.9%, hepatomegaly in 56.2%, splenomegaly in 50.7%, digital clubbing in 24.7%, and respiratory distress in 16.4%. Acute chest syndrome (ACS) was documented in 28.8%, and 76.7% had a history of blood transfusion. Moderate anemia (Hb 6–7.9 g/dL) was present in 50.7%, and severe anemia (Hb <6 g/dL) in 16.4%.

NT-proBNP and Echocardiographic Parameters

Serum NT-proBNP ranged from 28 to 486 pg/mL with a mean of 142.6 ± 98.4 pg/mL (median 118 pg/mL). Normal levels (<100 pg/mL) were observed in only 37.0% of patients, while 35.6% had borderline levels (100–160 pg/mL) and 27.4% had highly elevated levels (>160 pg/mL). Left ventricular hypertrophy (LVH) was present in 35.6%, while left ventricular diastolic dysfunction (LVDD) was detected in 42.5% (Grade I in 31.5%, Grade II in 11.0%). Left ventricular systolic function was well-preserved across the study population (mean ejection fraction 64.2% ± 5.8%).

Table 2: Pulmonary Artery Systolic Pressure and Velocities (n=73)

Parameter	Range	Mean ± SD
Tricuspid Regurgitant Velocity (TRV) (m/s)	1.8 – 3.6	2.38 ± 0.42
Pulmonary Artery Systolic Pressure (PASP) (mmHg)	18 – 62	32.6 ± 12.4

Table 3: Prevalence of Pulmonary Hypertension Categories (n=73)

TRV Category	Number (n)	Percentage (%)
Normal (TRV < 2.5 m/s)	45	61.6%
Borderline (TRV 2.5–2.9 m/s)	17	23.3%
Elevated (TRV >= 3.0 m/s)	11	15.1%

Table 4: Correlation between NT-proBNP and Hematological Parameters

Parameter	Correlation Coefficient (r)	p-value	Interpretation
Hemoglobin	-0.486	<0.001	Moderate negative
Total Leukocyte Count	+0.328	0.004	Weak positive
Platelet Count	+0.142	0.224	No correlation
Reticulocyte Count	+0.396	0.001	Moderate positive

Table 5: Correlation between NT-proBNP and Echocardiographic Parameters

Parameter	Correlation Coefficient (r)	p-value	Interpretation
LVEDD	+0.412	<0.001	Moderate positive
LVMI	+0.524	<0.001	Moderate positive
Ejection Fraction	-0.186	0.108	No correlation
E/e' ratio	+0.568	<0.001	Moderate positive
TRV	+0.642	<0.001	Strong positive
PASP	+0.618	<0.001	Strong positive

Table 6: Independent Predictors of Elevated NT-proBNP (>160 pg/mL) - Multivariate Logistic Regression Analysis

Variable	Odds Ratio (OR)	95% CI	p-value
Hemoglobin < 7 g/dL	3.84	1.52 – 9.68	0.004
TRV >= 2.5 m/s	5.26	2.14 – 12.94	<0.001
Diastolic Dysfunction	2.98	1.18 – 7.52	0.021
LVMI > 95 g/m²	2.42	0.96 – 6.12	0.062
Age > 12 years	2.18	0.84 – 5.64	0.108
Crisis Frequency > 5/year	1.86	0.74 – 4.68	0.186

DISCUSSION

Our study documented a remarkably high rate of cardiovascular abnormalities in children with sickle cell disease. Specifically, 42.5% of participants exhibited diastolic dysfunction, 38.4% had elevated tricuspid regurgitant velocity (suggestive of pulmonary hypertension), 35.6% demonstrated left ventricular hypertrophy (increased LVMI), and 27.4% had NT-proBNP levels exceeding 160 pg/mL. These findings underscore the substantial burden of subclinical cardiac involvement even in pediatric patients, many of whom were asymptomatic from a cardiovascular standpoint at the time of evaluation [5,6].

The high prevalence of diastolic dysfunction observed in our cohort aligns with emerging evidence suggesting that impaired ventricular relaxation represents one of the earliest and most frequent cardiac abnormalities in sickle cell disease [7]. Unlike systolic dysfunction, which typically manifests later in the disease course, diastolic impairment begins insidiously during childhood and progresses silently over years [8]. The pathophysiological mechanisms underlying diastolic dysfunction in sickle cell disease are multifactorial and include chronic volume overload from compensatory high cardiac output states, myocardial fibrosis from recurrent microvascular ischemic injury, iron deposition in chronically transfused patients, and structural remodeling characterized by eccentric left ventricular hypertrophy [9].

These correlations validate NT-proBNP as an integrated biomarker that reflects multiple dimensions of cardiovascular stress in sickle cell disease [10]. The peptide's elevation in response to increased ventricular wall stress makes it particularly valuable for detecting subclinical cardiac involvement before overt heart failure symptoms develop [11]. Unlike imaging modalities that require specialized equipment and expertise, NT-proBNP measurement is relatively straightforward and can be performed in most clinical laboratories, making it an attractive screening tool, especially in resource-limited settings [12,13].

The inverse relationship between hemoglobin concentration and NT-proBNP levels observed in our study provides important mechanistic insights [14]. Children with severe anemia (hemoglobin < 7 g/dL) had significantly higher NT-proBNP levels compared to those with milder anemia. This finding underscores the central role of chronic anemia in driving cardiovascular stress in sickle cell disease [15]. Our observation of progressively increasing NT-proBNP levels with advancing age provides compelling evidence for the cumulative nature of cardiovascular injury in sickle cell disease [4]. This progressive pattern has important implications for screening and intervention strategies [16]. The detection of elevated biomarkers and echocardiographic abnormalities in younger children indicates that pathological processes are initiated early in life, potentially during infancy [17].

The pathogenesis of pulmonary hypertension in sickle cell disease differs fundamentally from idiopathic pulmonary arterial hypertension and involves multiple overlapping mechanisms [18]. Chronic intravascular hemolysis releases free hemoglobin into the plasma, where it scavenges nitric oxide—a critical vasodilator and inhibitor of smooth muscle proliferation [19]. This nitric oxide depletion creates a state of endothelial dysfunction, vasoconstriction, and pulmonary vascular remodeling [20]. The strong correlation between NT-proBNP levels and TRV in our study suggests that these parameters reflect overlapping pathophysiological processes [21]. Elevated pulmonary pressures increase right ventricular afterload, leading to right ventricular hypertrophy and eventual right heart dysfunction with consequent NT-proBNP elevation [22].

Multivariate logistic regression analysis identified TRV >= 2.5 m/s (OR = 5.26), severe anemia with hemoglobin < 7 g/dL (OR = 3.84), and diastolic dysfunction (OR = 2.98) as independent predictors of elevated NT-proBNP levels [23]. Children exhibiting these risk factors warrant particularly close cardiovascular monitoring and may benefit from more aggressive therapeutic interventions [24]. Optimization of hemoglobin levels through either hydroxyurea therapy or chronic transfusion

programs represents another important strategy for reducing cardiovascular stress [25]. By improving oxygen-carrying capacity, these interventions can reduce the compensatory high cardiac output state and alleviate chronic volume overload [26].

Our findings regarding the prevalence of diastolic dysfunction (42.5%) fall within the wide range reported in previous studies, which have documented prevalences ranging from 11% to 77% depending on diagnostic criteria, methodology, and population characteristics [27]. The mean NT-proBNP level in our study population (~140 pg/mL overall) is comparable to that reported in other pediatric cohorts with sickle cell disease, though direct comparisons are complicated by differences in age distributions, disease severity, and laboratory assay methods [28]. The high burden of cardiovascular involvement documented in our study has important public health implications, particularly for regions with substantial sickle cell disease populations such as Jharkhand and other states in central and eastern India.

Advanced imaging techniques, including cardiac magnetic resonance with T2* quantification for iron assessment, late gadolinium enhancement for fibrosis detection, and parametric mapping sequences (T1, T2, extracellular volume) for tissue characterization could provide deeper insights into the pathophysiology of sickle cell cardiomyopathy. Speckle-tracking echocardiography for assessment of myocardial strain represents another promising tool for detecting subtle contractile abnormalities before conventional parameters become abnormal [30].

CONCLUSION

This study reinforces the importance of routine cardiopulmonary screening in children with sickle cell disease. Early recognition of cardiac involvement using NT-proBNP and echocardiography may allow for targeted interventions that can potentially reduce long-term complications, improve quality of life, and enhance survival outcomes.

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