Original Article

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Prevalence of high tricuspid regurgitation jet velocity in patients with sickle cell disease

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ABSTRACT

Background: Elevated tricuspid regurgitation jet velocity (TRV) is a key indicator of pulmonary hypertension (PHT) in sickle cell disease (SCD) patients, with SCD occurring frequently in both adults and children. **Aim**: This study aimed to estimate TRV through echocardiography and assess the presence of comorbidities in SCD patients at the Center of Hereditary Blood Diseases. It further aimed to determine the percentage of elevated TRV and its relationship to various SCD-related variables. **Methods**: A cross-sectional, descriptive study was conducted to assess TRV in children and adolescents with SCD registered at the Center of Hereditary Blood Diseases from October 1, 2021 to October 1, 2022. A specialized data collection form was designed to gather socio-demographic and disease-related variables, and echocardiography was performed on all patients. **Results**: A total of 142 SCD patients were included in the study. Their ages ranged from 10 months to 18 years, with a mean age of 8.48 ± 3.51 years and a male-to-female ratio of 1.36:1. Sickle cell anemia was the most common type of SCD (62.7%), followed by sickle/β-thalassemia. The study found that most patients (74.7%) had normal TRV values (< 250 cm/sec), while 25.3% exhibited elevated TRV (≥ 250 cm/sec), with a total mean of 209.50 ± 44.44 cm/sec. A significant difference was observed in the frequency of PHT symptoms between patients with elevated and normal TRV, with a p-value < 0.001. **Conclusion**: Elevated TRV is an alarming sign that necessitates early screening for PHT.

Keywords: Pulmonary hypertension, tricuspid regurgitation velocity, Sickle cell disease

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INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent severe monogenic disorders affecting millions globally, with approximately 300,000 infants born with SCD each year, primarily in Africa.[1,2]

SCD is frequently associated with high morbidity and mortality rates.[2] Pulmonary hypertension (PHT) is recognized as a common and severe complication of SCD in both adults and children.[3] In children, PHT is defined as a resting mean pulmonary artery pressure (mPAP) > 25 mmHg after 3 months of age.[4] Its reported prevalence in pediatric patients with SCD ranges from 8%–38%.[5-7]

In the pediatric population (up to 18 years old), PHT is linked to various cardiac, pulmonary, and systemic illnesses and is a major cause of morbidity and mortality.

Similar to adult PHT, pediatric PHT can be fatal and often negatively impacts treatment outcomes.[4] Anemia in SCD patients leads to significant left ventricular enlargement and dilation, ultimately resulting in eccentric hypertrophy and myofibers, which increase the left ventricle's bulk, elongate it, and causes diastolic dysfunction alongside PHT and right ventricular dysfunction.[8]

Measurement of the tricuspid regurgitate velocity (TRV) by Doppler echocardiography is the most accurate noninvasive and frequently used method for assessing PHT, allowing for the calculation of peak right ventricular systolic pressure (RVSP) and pulmonary artery systolic pressure (PASP).[9] TRV thus obtained is analyzed using the modified Bernoulli equation to estimate peak RVSP. In the absence of any blockage in the pulmonary blood flow, this derived RVSP is equivalent to the PASP.[(9)] TRV values of ≥ 2.5 m/s on Doppler echocardiography correlate with PASP of 30 mmHg or higher, as determined by the modified Bernoulli equation (4 multiplied by TRV^2).[10]

The current study was conducted to assess TRV through echocardiography in pediatric patients with SCD in Basra, Iraq.

MATERIALS AND METHODS

Study Design

A cross-sectional, descriptive study was conducted to evaluate TRV among individuals diagnosed with SCD enrolled at the Basra Center for Hereditary Blood Disorders (CHBD). A total of 142 patients with confirmed SCD, aged 10 months to 18 years, were recruited over 12 months, from October 1, 2021 to October 1, 2022. Patients were selected through a simple random sampling method to ensure diverse representation of the SCD population in Basra.

Data Collection

A specialized data collection form was designed to gather socio-demographic variables (date of birth, gender, and residence), SCD-related variables (age at diagnosis, type of SCD, disease-related complications, and echocardiographic [ECHO] findings), and hematological and biochemical investigations. Medical records were reviewed, and patients and their caregivers were interviewed personally for 30 minutes to gather information on the history of disease complications (vaso-occlusive crises, acute splenic sequestration [ASSC], acute chest syndrome [ACS], stroke, avascular necrosis [AVN], and splenectomy). Signs and symptoms suggestive of PHT (exertional dyspnea, syncope, fatigue, cyanosis, edema, hepatomegaly) were evaluated.

Inclusion and Exclusion Criteria

Inclusion criteria consisted of patients aged 10 months to 18 years with confirmed SCD registered at CHBD. Exclusion criteria included patients with acute painful episodes requiring hospitalization in the past four weeks from the echocardiography study, those with intercurrent illnesses or infections, and those receiving treatments such as antibiotics affecting blood counts within three weeks from the echocardiography study. This exclusion was necessary to ensure that only patients in a stable condition were included.

Imaging Study

Each patient underwent a uniform ECHO assessment conducted with a Philips CX50 series machine. The study was performed by a pediatric specialist and independently reviewed by a physician who was blinded to the clinical data. Tricuspid regurgitation (TR) was assessed using two-dimensional imaging, M-mode, and Doppler imaging. TRV was considered elevated if it was ≥ 2.5 m/s. At least five sequential complexes were recorded using continuous-wave Doppler.

Ethical Considerations

The research received approval from the Ethics Committee of the College of Medicine at the University of Basrah, the Basrah Health Directorate, and the Scientific Ethical Committee of the Arab Board for Health Specializations. Verbal consent was obtained from all patients or their guardians after explaining the study's significance.

Statistical Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 26. Descriptive statistics were calculated for all variables, and inferential statistics were employed to assess the association between TRV and demographic as well as SCD-related variables. Chi-square and Fisher's exact tests were used to determine statistical significance, with a p-value of < 0.05 considered significant.

RESULTS

Table 1 presents the demographic characteristics of the studied population, highlighting that most patients with SCD were aged between 5 and 10 years, with a male-to-female ratio of 1.36:1. This distribution suggests a higher prevalence of SCD among older children, consistent with previous findings indicating that the incidence of complications tends to increase with age in SCD patients

A significant relationship between age and TRV was observed, with older children (5–10 years) more likely to present with elevated TRV. The lack of a significant correlation between gender and TRV suggests that pulmonary complications in SCD may be more influenced by age-related factors than sex.

The data on residence indicates a relatively equal distribution between patients from urban and peripheral areas, which may provide insights into access to healthcare services and potential differences in disease management.

Table 2 presents the frequency of elevated TRV in the study population, categorized into Normal, Mild Elevation, and Severe Elevation. Most patients (74.7%) exhibited normal TRV values (≤ 2.5 m/s), indicating a lower risk of PHT. In contrast, a smaller proportion of patients demonstrated mild (16.9%) and severe (8.45%) elevation of TRV. The mean TRV values correspond to these categories, with normal TRV averaging 2.02 ± 0.39 m/s, while patients with mild and severe elevations had higher mean TRV values of 2.76 ± 0.11 m/s and 3.11 ± 0.10 m/s, respectively.

In Table 3, patients with either mild or severe TRV elevation were largely symptomatic, with 83.3% exhibiting clinical signs. Notably, dyspnea on exertion and fatigue were the most common symptoms observed, affecting 75% and 66.7% of patients with elevated TRV, respectively. In contrast, nearly all patients with normal TRV values (≤ 2.5 m/s) were asymptomatic, with only one patient (0.9%) reporting symptoms.

Patients with severe TRV elevation (> 3 m/s) demonstrated a slightly higher prevalence of serious symptoms, such as syncope, edema, hepatomegaly, and cyanosis, compared to those with mild elevation. However, these critical symptoms were relatively uncommon, with only 8.3% of patients in the severe TRV group exhibiting them. The absence of these symptoms in the normal TRV group emphasizes the correlation between elevated TRV and the presence of clinical symptoms, thus suggesting potential PHT or cardiovascular strain.

Table 4 categorizes patients with different TRV levels and compares the incidence of various complications. The correlation between ACS and elevated TRV becomes more evident as TRV increases, with 24% of the patients in the mild elevation group and 36.4% in the severe elevation group showing ACS compared to only 6.6% in the normal TRV group.

Likewise, the incidence of stroke significantly rises in patients with either mild or severe elevations in TRV. ASSC, however, shows a negative correlation with TRV, being more common in patients with normal TRV and decreasing with elevated TRV levels.

The correlation between elevated TRV and the need for hospitalization and blood transfusions is significant, particularly in the severe elevation group, where all patients had a history of hospitalization, and over 80% required blood transfusions. The incidence of splenectomy also rises as TRV increases, particularly in the severe elevation group.

Table 1: Demographic characteristics of the study population.

Characteristic	n (%)	Mean TRV ± SD (m/s)	p-value
Age Group			
10 months to 5 years	37 (26.1%)	2.04 ± 0.42	0.037
5–10 years	78 (54.9%)	2.15 ± 0.48	
10–18 years	27 (19.0%)	2.08 ± 0.41	
Gender			
Male	81 (57.0%)	2.11 ± 0.46	0.527
Female	61 (43.0%)	2.07 ± 0.43	
Residence			
Urban	69 (48.6%)	2.10 ± 0.45	0.271
Peripheral	73 (51.4%)	2.08 ± 0.43	

Table 2: Frequency of elevated TRV in the study population.

TRV Category	n (%)	Mean TRV ± SD (m/s)
Normal (≤ 2.5 m/s)	106 (74.7%)	2.02 ± 0.39
Mild Elevation (> 2.5–3 m/s)	24 (16.9%)	2.76 ± 0.11
Severe Elevation (> 3 m/s)	12 (8.45%)	3.11 ± 0.10

Table 3: Categorization of TRV values and corresponding symptoms in SCD patients.

Symptom	Severe Elevation (> 3 m/s)	Mild Elevation (> 2.5–3 m/s)	Normal (≤ 2.5 m/s)
Number of Patients	12	24	106
Symptomatic Patients (N, %)	10 (83.3%)	20 (83.3%)	1 (0.9%)
Unexplained Dyspnea (N, %)	2 (16.7%)	6 (25%)	0 (0%)
Dyspnea on Exertion (N, %)	9 (75%)	18 (75%)	1 (0.9%)
Fatigue (N, %)	8 (66.7%)	16 (66.7%)	0 (0%)
Syncope (N, %)	1 (8.3%)	1 (4.2%)	0 (0%)
Edema (N, %)	1 (8.3%)	1 (4.2%)	0 (0%)
Hepatomegaly (N, %)	1 (8.3%)	1 (4.2%)	0 (0%)
Cyanosis (N, %)	1 (8.3%)	1 (4.2%)	0 (0%)

Table 4: Pearson correlation between TRV values and different SCD complications.

Complication	TRV ≤ 2.5 m/s (n = 106)	Mild Elevation (> 2.5–3 m/s) (n = 24)	Severe Elevation (> 3 m/s) (n = 12)	Pearson Correlation (r)	p-value
ACS	7 (6.6%)	6 (25.0%)	4 (33.3%)	+0.32	0.002
Stroke	0 (0.0%)	3 (12.5%)	1 (8.3%)	+0.25	0.005
ASSC	43 (40.5%)	4 (16.7%)	3 (25.0%)	-0.29	0.004
AVN	4 (3.8%)	1 (4.2%)	0 (0.0%)	-0.03	0.892
Hospitalization (last year)	90 (84.9%)	24 (100%)	12 (100%)	+0.21	0.049
Blood Transfusion (last year)	22 (20.7%)	19 (79.2%)	9 (75.0%)	+0.62	< 0.001
Splenectomy	4 (3.8%)	3 (12.5%)	2 (16.7%)	+0.19	0.031

DISCUSSION

PHT is a severe complication of SCD and is associated with increased mortality.[11] The initial test of choice for screening for PHT is transthoracic echocardiography because it is a non-invasive, widely available, and reliable method for estimating pulmonary artery pressures and assessing cardiac function.[12]

In our study, 25.3% of the patients had elevated TRV, indicating a significant risk for PHT. This rate is comparable to other pediatric studies, such as those by Pashankar et al., Suell et al., and Gladwin et al.[9,11,13] However, another study by Minniti et al. reported a lower frequency (11%), which may reflect differences in patient selection, as the researchers adopted a criterion of 2.6 m/s or greater for high TRV.[14]

A significant relationship between age and elevated TRV was observed, aligning with findings by Agha et al., who noted that older SCD patients tend to have higher TRV

values. This could be attributed to prolonged disease duration and cumulative vascular damage in older patients.[15] However, Pashankar et al.'s study showed no correlation between age and TRV value.[9]

Complications such as ACS was strongly associated with elevated TRV in this study, contrasting with findings by Agha et al.,[15] which showed no significant difference between SCA patients with low or high TRV regarding their risk of developing ACS. However, autopsy investigations indicate that children with SCD may experience reversible histological alterations in the pulmonary vasculature.[11]

A history of stroke was also significantly associated with elevated TRV, consistent with study by Kato et al.,[16] who documented six patients with elevated TRV later developing cerebrovascular disease, suggesting a clinical link between the two disorders.[17] However, these findings contradict Pashankar et al.'s study, which showed no correlation between stroke and TRV value.[9]

Patients who underwent splenectomy exhibited a significant relationship with TRV value; however, Agha et al.[15] showed that splenectomy was common in SCD patients with elevated TRV, but the difference did not reach statistical significance.

Both ASSC and AVN showed an inverse correlation with TRV, indicating lower rates of these complications in SCA patients with high TRV values. These results contradict findings from Santiago et al.'s study.[12] However, there is a lack of polished data on this subject.

This study found a statistically significant relationship between symptoms of PHT and elevated TRV values, consistent with Agha et al.'s findings that patients with dyspnea had elevated TRV values.[15]

This study was limited by its single-center design and relatively small sample size, which may restrict the generalizability of the findings. Additionally, the lack of longitudinal data limits the ability to establish causal relationships between elevated TRV and complications. Future research should include larger, multi-center cohorts and longitudinal studies to confirm these findings and explore the underlying mechanisms. Regular monitoring of TRV is recommended for early detection of complications in sickle cell disease, along with targeted interventions to mitigate associated risks.

CONCLUSIONS

This study demonstrated that TRV is a significant indicator of increased risk for severe complications, such as PHT, ACS, and stroke, in children with SCD, approximately 25.3% of the patients had elevated TRV, correlating with the higher morbidity associated with these conditions. Age was identified as a key factor, with older children (5–10 years) more likely to exhibit elevated TRV, while gender showed no significant correlation. Interestingly, the study revealed an inverse correlation between elevated TRV and complications such as ASSC and AVN, suggesting that these conditions are less common in patients with higher TRV. Consequently, these findings emphasize the importance of monitoring TRV as a marker of disease severity and potential complications in SCD patients, thus reinforcing the need for early detection and targeted interventions.

REFERENCES

1. Sainati L, Montanaro M, Colombatti R. A Global Perspective on Milestones of Care for Children with Sickle Cell Disease. Sickle Cell Disease-Pain and Common Chronic Complications London, UK In Tech Publisher. 2016:17-35.
2. Tebbi CK. Sickle Cell Disease, a Review. Hemato. 2022;3(2):341-66.
3. Ballas SK, Lieff S, Benjamin LJ, Dampier CD, Heeney MM, Hoppe C, et al. Definitions of the phenotypic manifestations of sickle cell disease. American journal of hematology. 2010;85(1):6-13.
4. Abman SH, Hansmann G, Archer SL, Ivy DD, Adatia I, Chung WK, et al. Pediatric pulmonary hypertension: guidelines from the American heart association and American thoracic Society. Circulation. 2015;132(21):2037-99.
5. Lamina MO, Animasahun BA, Akinwumi IN, Njokanma OF. Doppler echocardiographic assessment of pulmonary artery pressure in children with sickle cell anaemia. Cardiovascular Diagnosis and Therapy. 2019;9(3):204.
6. Karthik L, Kumar G, Keswani T, Bhattacharyya A, Chandar SS, Bhaskara Rao K. Protease inhibitors from marine actinobacteria as a potential source for antimalarial compound. PloS one. 2014;9(3):e90972.
7. Patel PM, Sharma SM, Shah N, Manglani MV. Prevalence of pulmonary hypertension in children with sickle cell disease. International Journal of Contemporary Pediatrics. 2016;3(3):1076.
8. Chinawa JM, Chukwu BF, Chinawa AT, Ossai EN, Ikefuna AN, Aronu AE, et al. Right ventricular function among South East Nigeria children with sickle cell anaemia. BMC pediatrics. 2020;20:1-9.
9. Pashankar FD, Carbonella J, Bazzy-Asaad A, Friedman A. Prevalence and risk factors of elevated pulmonary artery pressures in children with sickle cell disease. Pediatrics. 2008;121(4):777-82.
10. Ambrusko SJ, Gunawardena S, Sakara A, Windsor B, Lanford L, Michelson P, et al. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. Pediatric blood & cancer. 2006;47(7):907-13.
11. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. New England Journal of Medicine. 2004;350(9):886-95.
12. Santiago MT, Feld L, Dhar A, Appiah-Kubi A, Mitchell E, Aygun B, et al. Cardiopulmonary Complications of Sickle Cell Disease in Children. 2024.
13. Suell MN, Bezold LI, Okcu MF, Mahoney Jr DH, Shardonofsky F, Mueller BU. Increased pulmonary artery pressures among adolescents with sickle cell disease. Journal of pediatric hematology/oncology. 2005;27(12):654-8.

14. Minniti CP, Sable C, Campbell A, Rana S, Ensing G, Dham N, et al. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: association with hemolysis and hemoglobin oxygen desaturation. haematologica. 2009;94(3):340.
15. Agha H, El Tagui M, El Ghamrawy M, Hady MA. The 6-min walk test: an independent correlate of elevated tricuspid regurgitant jet velocity in children and young adult sickle cell patients. Annals of hematology. 2014;93:1131-8.
16. Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: relevance to children. Pediatric hematology and oncology. 2007;24(3):159-70.
17. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood, The Journal of the American Society of Hematology. 1998;91(1):288-94.