

Prevalence of Electrocardiographic Changes and Risk Factors for QTc Prolongation Among Steady State Sick Cell Disease Patients: Cooperative Study of Sick Cell Disease

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ABSTRACT

Objectives: Sickle cell disease (SCD) is associated with several cardiovascular adverse events. Corrected QT (QTc) interval prolongation is one of the potential life-threatening complications that predispose patients to sudden cardiac death. This study aims to assess the prevalence of electrocardiogram (ECG) changes and to investigate risk factors associated with increased propensity of QTc prolongation. **Methods:** This study utilized data from the Cooperative Study of Sick Cell Disease Cardiac Ancillary Study. QT intervals were corrected using the Bazett formula, and prolongation was defined using sex-specific thresholds. The study population included African American patients with steady-state SCD across four clinical centers located in both urban and rural settings. **Results:** The study included 238 participants (92 (38.7%) males and 146 (61.3%) females), with a median age of 19.0 (IQR = 14.0 years). Of these, more than two-thirds of the sample (58.8%) had at least one abnormal ECG finding, which was more common in males (72.8%) compared to females (50.0%). In terms of ECG changes, almost half of the sample (41.1%, n = 97) had left ventricular hypertrophy, and 4.2% (n = 10) had left atrial hypertrophy. The prevalence of prolonged QTc was 20.6% (n = 49). Potential risk factors that showed higher odds of QTc prolongation included: male sex (odds ratio (OR) = 3.68, 95% CI: 1.67–8.11; p = 0.001), history of heart disease (OR = 3.53, 95% CI: 1.38–9.01, p = 0.008), pericardial effusion (OR = 3.45, 95% CI: 1.10–10.86, p = 0.034), and lower hemoglobin levels (OR = 0.63, 95% CI: 0.43–0.93; p = 0.018). **Conclusions:** Routine ECG screening is recommended among SCD patients, particularly for those at increased risk for prolonged QTc, in addition to avoidance of concomitant factors that prolong QTc intervals. Moreover, regular monitoring of hemoglobin levels is paramount, as it is a modifiable factor influencing QTc prolongation risk.

Sickle cell disease (SCD) is an autosomal recessive inherited disorder characterized by the presence of abnormal hemoglobin (Hb) within erythrocytes, known as hemoglobin S (HbS). This abnormality causes erythrocyte sickling and aggregation, rendering them less flexible and

more prone to premature hemolysis and clumping. Chronic hemolysis induces endothelial dysfunction, sterile inflammation, chronic anemia, and vaso-occlusive events, with subsequent chronic hypoxemia to tissues resulting in multi-organ damage. Individuals with SCD also frequently experience pain crises and

are more susceptible to infections, placing them at risk of recurrent hospital admissions with associated increased morbidity and mortality.¹⁻⁶

SCD may lead to potentially life-threatening adverse cardiovascular events, including atrial and ventricular arrhythmias, myocardial infarction, pulmonary arterial hypertension with subsequent right-sided heart failure, and high-output heart failure related to chronic anemia and hemolysis.⁷⁻¹⁷ One of the potential complications of SCD is corrected QT (QTc) interval prolongation, which can predispose to life-threatening arrhythmias and sudden cardiac death.^{9,18-20}

The exact mechanism of QTc interval prolongation is not completely understood. Factors that may contribute to QTc interval prolongation in SCD include chronic anemia and hemolysis, electrolyte imbalances, hemolysis-associated inflammatory mediators, and structural and functional cardiac changes secondary to chronic myocardial hypoxemia, inflammation, and oxidative stress. Importantly, SCD patients are exposed to many potential QTc prolonging medications, including hydroxyurea, antibiotics, opioids, and antiemetic medications.^{19,21-27}

Electrolyte imbalances are common in SCD patients, particularly during episodes of acute hemolysis or vaso-occlusive crises (VOC). Abnormal levels of electrolytes such as potassium, calcium, and magnesium can affect the conduction system of the cardiac muscle and resting membrane potential, contributing to QTc interval prolongation.^{23,28} Vaso-occlusive events, frequently encountered in the course of the disease, can cause microvascular ischemia from transient reduced blood flow and oxygen supply to the myocardium. This induces myocardial injury and fibrosis that triggers degenerative abnormalities in the cardiac conduction system, leading to electrophysiological changes (such as QTc prolongation), as well as diastolic dysfunction, heart failure, and cardiomyopathy.^{25,26,29}

Studies have shown that QTc interval prolongation is associated with an increased risk of sudden cardiac death in patients with SCD. This risk is particularly high in patients with a history of recurrent VOC, acute chest syndrome, or cardiopulmonary complications of SCD. Therefore, early detection and management of prolonged QTc interval are essential in patients with SCD, given the well-established association between QTc prolongation and overall mortality.^{19,24}

Vaso-occlusion, a hallmark of SCD, has an immunological basis that further contributes to

disease severity. Lymphocyte function-associated antigen-1, a member of the integrin family, is expressed on the surface of T lymphocytes, B lymphocytes, macrophages, neutrophils, and monocytes. It plays a major role in mediating the adhesion of SCD eosinophils to fibronectin, leading to vaso-occlusive process. The neutrophil to lymphocyte ratio is considered a reliable and surrogate marker for polymorphonuclear leukocytes. Elevated neutrophil to lymphocyte ratio increases the likelihood of VOC and end-organ damage in SCD patients. Similarly, mean platelet volume, which reflects the average platelet size and activation, resulting in vaso-occlusion and platelet aggregation. Additionally, interleukin-10, a key regulator of immune homeostasis, and its reduced level is associated with VOC pathogenesis.³⁰⁻³⁷

Studying the prevalence of electrocardiogram (ECG) changes and associated risk factors in SCD patients is crucial, as early detection of cardiac complications such as asymptomatic arrhythmias, allows for early intervention and prevention of life-threatening consequences. Moreover, this analysis provides valuable epidemiological data, which can help clinicians and researchers better understand the burden of cardiac adverse events in this population. In this study, we aim to assess the pattern of ECG changes in patients with SCD and the risk factors associated with increased odds of developing QTc interval prolongation.

This study aims to determine the prevalence of various ECG changes in steady state SCD patients and identify risk factors associated with QTc interval prolongation, by utilizing data from the Cooperative Study of Sickle Cell Disease (CSSCD) sub-study called the Cardiac Ancillary Study. The CSSCD was a multi-institutional investigation of the natural history of SCD from birth to adulthood and involved data collected from 23 institutions in a standardized manner on 3800 patients. Approval to access the CSSCD study data was obtained from the Biologic Specimen and Data Repository Information Coordinating Center; <https://biolincc.nhlbi.nih.gov/home/>, an open-access data repository.³⁸

METHODS

The Cardiac Ancillary Study involved patients from four clinical centers older than two years of age, with equal representation of both rural and urban areas between 1982 and 1983. All patients were of

African American race ($n = 238$) with a wide age range of 2–58 years. Informed consent was obtained from all subjects, and the study was approved by the Committee on Human Assurance at each involved center. Cardiac function was assessed in patients with steady-state SCD, as all subjects were crisis-free for two weeks prior to the study and had not been transfused in the preceding three months. Medical history was obtained, including complications/clinical events prior to enrollment, and cardiac history such as congenital heart disease (including ventricular septal defect, atrial septal defect, patent ductus arteriosus, coarctation of aorta, and cyanotic heart disease), rheumatic heart disease (with or without carditis and valvular lesions), hypertension, myocardial infarction, cardiomyopathy, or pericarditis. Physical examination, echocardiography, and ECG were also performed. The ECG scans and ECG strips were sent to cardiologists at Yale New Haven Hospital for interpretation. ECGs were performed using a standardized method in all four centers. Interpretation was then conducted by a blinded investigator. Systolic and diastolic left ventricle (LV) function, and wall thickness were assessed.

The QT interval represents the time between the start of the Q wave and the end of the T wave on an ECG. The QT interval can be influenced by the heart rate, making it necessary to correct for heart rate when interpreting QT intervals. QT prolongation was corrected using the Bazett formula ($QTc = QT / \sqrt{RR}$), which is a validated and commonly used method for QT interval correction.³⁹ QTc prolongation was defined as > 440 ms for males and > 460 ms for females. The QRS duration was analyzed alongside the QTc interval, given that the QTc interval encompasses the total time for both ventricular depolarization and repolarization. This approach allowed us to assess whether an extended QRS duration contributed to the observed QTc prolongation. Prolonged QRS interval was defined as QRS interval ≥ 120 ms.⁴⁰

An ECG was classified as abnormal if it presented any of the following findings: prolonged QTc interval, chamber hypertrophy, alterations in the ST-T waves, first-degree heart block, T-wave abnormalities, premature ventricular contractions, right bundle branch block (RBBB), left axis deviation, or any abnormal rhythm types. This classification was selected because it encompassed all reported changes in the dataset.

The data was analyzed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for

Windows, Version 25.0. Armonk, NY: IBM Corp.). Table 1 presents the baseline characteristics of all SCD patients included in the cardiac ancillary study. These characteristics encompass clinical variables and laboratory findings. The categorical variables were summarized using frequencies and percentages, while continuous variables were reported using means and SD. Table 2 shows the frequency of various ECG characteristics, and Table 3 presents the frequency of ECG characteristics categorized by age groups and stratified by sex. The age groups are divided into four categories: < 10 years, 10–20 years, 20–30 years, and ≥ 30 years.

A chi-square test was utilized for categorical variables to assess the differences between those with and without QTc prolongation [Table 4], and an independent samples *t*-test was employed for continuous variables [Table 5]. The threshold for statistical significance was set at a *p*-value of < 0.10 . This was adopted for the purposeful selection of covariates, as outlined by Bursac et al.⁴¹ This threshold was chosen to ensure that potentially significant variables were not prematurely excluded in the early stages of model development. Although more stringent *p*-values are typically recommended for multiple comparisons, our approach aims to preserve the comprehensiveness of the predictor set in models with numerous variables, thereby enhancing the model's explanatory power.

Variables that demonstrated significant associations with QTc prolongation in the univariate analysis were subsequently included in a binary logistic regression model to identify independent risk factors for QTc prolongation. A backward elimination approach was adopted to progressively remove variables that were not significantly contributing to the model. This process continued until only significant variables remained. Backward elimination was chosen to simplify the model by identifying the most important predictors and minimizing overfitting by excluding irrelevant variables, making the model easier to interpret while maintaining predictive power. This method is particularly useful when dealing with many potential predictors. However, this method may introduce bias by excluding clinically relevant variables that do not meet statistical significance.

The final model yielded adjusted odds ratios (ORs) with corresponding 95% CIs and *p*-values for each risk factor identified [Table 6]. A *p*-value < 0.05 was considered statistically significant in the final model. Age group at entry visit as a continuous variable was

Table 1: Baseline characteristics of all SCD patients included in the cardiac ancillary study.

Category	n (%) or Mean $\pm$ SD	Total
Sex		
Male	92 (38.7)	238
Female	146 (61.3)	
Age at entry visit, years		
≤ 18 (Pediatric)	116 (48.7)	238
> 18 (Adults)	122 (51.3)	
Hb genotypes		
SS genotype	171 (71.8)	238
Other genotypes [†]	67 (28.2)	
History of previous heart disease		
No	197 (82.8)	238
At least one previous heart disease	41 (17.2)	
Smoking status		
No	103 (51.0)	202
Yes	99 (49.0)	
BMI, kg/m ²	19.2 $\pm$ 3.6	238
Systolic BP, mmHg	112.8 $\pm$ 13.8	236
Diastolic BP, mmHg	68.6 $\pm$ 11.7	231
Blood tests		
Hb, g/dL	8.5 $\pm$ 1.1	238
RBC, $\times 10^{12}$ /L	2.7 $\pm$ 0.5	238
WBC, $\times 10^9$ /L	11.5 $\pm$ 2.6	238
MCV (femtoliter)	91.8 $\pm$ 8.5	238
Creatinine, mg/dL	0.7 $\pm$ 0.4	237
Hb F, %	7.1 $\pm$ 5.1	209
LDH, mg/dL	462.1 $\pm$ 178.6	222
Total protein, g/dL	7.7 $\pm$ 0.5	228
Albumin, g/dL	4.4 $\pm$ 0.4	228

[†]Including SB, SC, SS alpha, and other variants.

SCD: sickle cell disease; Hb: hemoglobin; BMI: body mass index; BP: blood pressure; RBC: red blood cell; WBC: white blood cells; MCV: mean corpuscular volume; LDH: lactate dehydrogenase.

Table 2: ECG characteristics among the study participants.

ECG characteristics	n (%) or Mean $\pm$ SD	Total
Abnormal ECG, sex	140 (58.8)	238
Female	73 (50.0)	
Male	67 (72.8)	
HR, bpm	74.4 $\pm$ 12.9	238
RR interval, second	0.83 $\pm$ 0.14	238
PR interval, second	0.15 $\pm$ 0.02	237
QRS duration, second [†]	0.059 $\pm$ 0.01	238
Normal	235 (98.7)	
Prolonged	3 (1.3)	
QT interval, second	0.38 $\pm$ 0.04	238
QTc interval [‡]	0.42 $\pm$ 0.03	238
Normal	189 (79.4)	
Prolonged	49 (20.6)	
Chamber hypertrophy		
LV	97 (41.1)	236
LA	10 (4.2)	
LV or LA	100 (42.4)	
None	136 (57.6)	
ST-T wave changes	12 (5.0)	237
First-degree heart block	9 (3.8)	238
T-wave changes [§]	28 (11.8)	238
PVCs	4 (1.7)	237
RBBB	5 (2.1)	237
Left axis deviation	2 (0.8)	237
Rhythm type		
Junctional	1 (0.4)	237
Ventricular	1 (0.4)	
Normal	235 (99.2)	

[†]Prolonged QRS interval was defined as QRS interval ≥ 120 ms. [‡]QTc corrected according to Bazett formula. QTc was considered prolonged if > 440 ms for males and > 460 ms for females. [§]Includes T wave inversion.

ECG: electrocardiography; HR: heart rate; QTc: corrected QT interval; LV: left ventricle; LA: left atrium; PVCs: premature ventricular contractions; RBBB: right bundle branch block.

Table 3: Frequency of ECG characteristics by age groups.

Sex	Age, years				p-value
	< 10	10–20	20–30	≥ 30	
Abnormal ECG					
Total	26/42 (61.9)	49/87 (56.3)	44/74 (59.5)	21/35 (60.0)	0.936
Male	9/15 (60.0)	25/34 (73.5)	24/30 (80.0)	9/13 (69.2)	0.548
Female	17/27 (63.0)	24/53 (45.3)	20/44 (45.5)	12/22 (54.5)	0.418
Prolonged QTc					
Total	10/42 (23.8)	18/87 (20.7)	16/74 (21.6)	5/35 (14.3)	0.761
Male	5/15 (33.3)	11/34 (32.4)	9/30 (30.0)	1/13 (7.7)	0.358
Female	5/27 (18.5)	7/53 (13.2)	7/44 (15.9)	4/22 (18.2)	0.916

Data given as n (%). ECG: electrocardiography; QTc: corrected QT interval.

Table 4: Chi-square test assessing the differences in prolonged QTc interval between different categorical variables.

Category	Prolonged QTc, n (%)	Total	p-value
Sex			
Male	26 (28.3)	92	0.020
Female	23 (15.8)	146	
Entry visit age group, years			
≤ 18 (Pediatric)	28 (24.1)	116	0.187
> 18 (Adults)	21 (17.2)	122	
Hb genotype			
SS	39 (22.8)	171	0.176
Other genotypes [†]	10 (14.9)	67	
Smoking			
No	23 (22.3)	103	0.712
Yes	20 (20.2)	99	
Presence of pericardial effusion on echocardiogram			
No	38 (19.4)	196	0.074
Yes	7 (36.8)	19	
Previous history of			
Heart disease			
No	35 (17.8)	197	0.018
Yes	14 (34.1)	41	
Eye disease			
No	46 (20.6)	223	0.845
Yes	2 (18.2)	11	
Kidney diseases [‡]			
No	42 (20.7)	203	0.878
Yes	7 (21.9)	32	
SCD related bone diseases [§]			
No	28 (21.1)	133	0.931
Yes	21 (20.6)	102	
Hearing loss			
No	47 (21.2)	222	0.283
Yes	1 (8.3)	12	
Painful episodes			
No	7 (15.9)	44	0.355
Yes	42 (22.2)	189	
Spleen sequestration			
No	44 (20.9)	211	0.485
Yes	2 (13.3)	15	
Hepatitis			
No	42 (20.3)	207	0.870
Yes	5 (21.7)	23	
Pneumonia			
No	17 (17.7)	96	0.370
Yes	30 (22.6)	133	
Leg ulcers			
No	40 (20.6)	194	0.849
Yes	9 (22.0)	41	

Table 4: Chi-square test assessing the differences in prolonged QTc interval between different categorical variables.

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Category	Prolonged QTc, n (%)	Total	p-value
Liver sequestration			
No	42 (21.0)	200	0.770
Yes	6 (18.8)	32	

QTc: corrected QT interval; Hb: hemoglobin; SCD: sickle cell disease. [†]This includes SB, SC, SS alpha, and other variants genotypes. [‡]This includes renal insufficiency or nephrotic syndrome or hematuria. [§]This includes aseptic necrosis, hand-foot syndrome, and osteomyelitis.

not significantly associated with QTc prolongation. Thus, it was not included in the multivariate analysis.

The study received an official ethical approval from the institutional review board at Jordan University Hospital, Amman, Jordan.

RESULTS

The study included 238 participants, consisting of 92 (38.7%) males and 146 (61.3%) females. The cohort was divided into pediatric (≤ 18 years) and adult (> 18 years) age groups, with 116 (48.7%) pediatric and 122 (51.3%) adult participants. The median age was 19.0 years (IQR = 14.0). The majority of participants (71.8%) had SS Hb, while the remaining 28.2% had other genotypes (including SB, SC, SS alpha, and other variants). A history of previous heart disease was reported in 41 (17.2%) participants. The study showed a nearly equal distribution between non-smokers (51.0%) and smokers (49.0%). The average body mass index was $19.2 \pm 3.6 \text{ kg/m}^2$.

The participants' mean Hb level was $8.5 \pm 1.1 \text{ g/dL}$, red and white blood cell counts were $2.7 \pm 0.5 \times 10^{12}/\text{L}$ and $11.5 \pm 2.6 \times 10^9/\text{L}$, respectively; and mean corpuscular volume was $91.8 \pm 8.5 \text{ fL}$. The mean systolic blood pressure (BP) was $112.8 \pm 13.8 \text{ mmHg}$, and diastolic BP was $68.6 \pm 11.7 \text{ mmHg}$. The mean creatinine level was $0.7 \pm 0.4 \text{ mg/dL}$, Hb F was $7.1 \pm 5.1\%$, lactate dehydrogenase (LDH) $462.1 \pm 178.6 \text{ mg/dL}$, total protein was $7.7 \pm 0.5 \text{ g/dL}$, and albumin was $4.4 \pm 0.4 \text{ g/dL}$.

Among the patients, 58.8% (140) had at least one abnormal ECG finding. Among females, 73 (50.0%) had abnormal ECGs, while this number was 72.8% among males ($n = 67$). The mean heart rate, R-R interval, P-R interval, QRS duration, QT interval, and

Table 5: Independent samples *t*-test assessing the differences between those with normal vs. prolonged QTc interval.

Variables	QTc	N	Mean (SD)	<i>p</i> -value	MD
Systolic BP, mmHg	Normal	187	112.6 (14.0)	0.719	-0.80
	Prolonged	49	113.4 (13.0)		
Diastolic BP, mmHg	Normal	182	68.8 (11.9)	0.575	1.06
	Prolonged	49	67.7 (10.9)		
BMI, kg/m ²	Normal	189	19.2 (3.6)	0.706	0.22
	Prolonged	49	19.0 (3.4)		
Age at entry visit, years	Normal	189	19.6 (10.5)	0.349	1.55
	Prolonged	49	18.0 (9.3)		
Echocardiography					
LV end diastolic dimension, cm	Normal	170	5.0 (0.7)	0.198	-0.16
	Prolonged	48	5.1 (0.6)		
LV end systolic dimension, cm	Normal	168	3.2 (0.5)	0.070	-0.17
	Prolonged	48	3.4 (0.4)		
LV wall and septum thickness, cm	Normal	171	1.2 (0.2)	0.078	-0.07
	Prolonged	48	1.3 (0.3)		
Blood tests					
Hb, g/dL	Normal	189	8.5 (1.1)	0.003	0.53
	Prolonged	49	8.0 (0.9)		
RBC, × 10 ¹² /L	Normal	189	2.7 (0.5)	0.005	0.22
	Prolonged	49	2.5 (0.3)		
WBC, × 10 ⁹ /L	Normal	189	11.4 (2.6)	0.611	-0.21
	Prolonged	49	11.6 (2.6)		
MCV (femtoliter)	Normal	189	91.8 (8.6)	0.989	-0.02
	Prolonged	49	91.8 (7.8)		
Creatinine, mg/dL	Normal	189	0.7 (0.4)	0.733	-0.02
	Prolonged	48	0.7 (0.5)		
Hb F, %	Normal	165	7.6 (5.3)	0.005	2.46
	Prolonged	44	5.2 (3.7)		
LDH, mg/dL	Normal	175	453.7 (177.7)	0.176	-39.74
	Prolonged	47	493.4 (180.4)		
Total protein, g/dL	Normal	181	7.6 (0.5)	0.185	-0.11
	Prolonged	47	7.7 (0.5)		
Albumin, g/dL	Normal	181	4.3 (0.4)	0.738	0.02
	Prolonged	47	4.3 (0.4)		

QTc: corrected QT interval; MD: mean difference; BP: blood pressure; BMI: body mass index; LV: left ventricle; Hb: hemoglobin; RBC: red blood cell; WBC: white blood cell; MCV: mean corpuscular volume; LDH: lactate dehydrogenase.

Table 6: Binary logistic regression that predicts the presence of prolonged QTc interval among the following variables.

Variable	<i>p</i> -value	Odds ratio	95% CI	
			Lower	Upper
Previous history of heart disease	0.008	3.53	1.38	9.01
Sex, male	0.001	3.68	1.67	8.11
Hb	0.018	0.63	0.43	0.93
Pericardial effusion	0.034	3.45	1.10	10.86

QTc: Corrected QT interval; Hb: Hemoglobin.

QTc were 74.4 ± 12.9 beats/min, 0.83 ± 0.14 seconds, 0.15 ± 0.02 seconds, 0.05 ± 0.01 seconds, 0.38 ± 0.04 seconds, and 0.42 ± 0.03 seconds, respectively. The QTc interval was prolonged in 49 (20.6%) participants. When prolonged QTc was defined as > 440 ms in both males and females, the QTc intervals will be prolonged in 75 (31.5%) patients. There was no significant association between QRS prolongation and QTc prolongation ($p = 0.583$). Notably, only one (2%) patient exhibited both prolonged QRS and QTc. In terms of chamber hypertrophy, 97 (41.1%) patients had left ventricular hypertrophy (LVH), 10 (4.2%) had left atrial hypertrophy (LAH), and 100 (42.4%) showed LVH or LAH. A total of 136 (57.6%) patients had no evidence of chamber hypertrophy. ST-T wave changes, first-degree heart block, and T-wave changes including T-wave inversion were observed in 5.0% (12/237), 3.8% (9/238), and 11.8% (28/238) of patients, respectively. Premature ventricular contractions RBBB, left axis deviation, and junctional or ventricular rhythm types were present in 1.7% (4/237), 2.1% (5/237), 0.8% (2/237), and 0.8% (2/237) of patients, respectively. Most patients (99.2%, 235) exhibited a normal rhythm.

The frequency of ECG changes was evaluated across different age groups. No statistically significant differences were found between the age groups in the presence of abnormal ECGs ($p = 0.936$) or prolonged QTc intervals ($p = 0.761$), even after stratifying by sex. The prevalence of abnormal ECG was high across all age groups, ranging from 56.3–61.9%. The occurrence of prolonged QTc interval changes was highest in the age group < 10 years (23.8%) and lowest in the age group ≥ 30 years (14.3%).

The study analyzed the differences in prolonged QTc interval changes between categorical variables, with a p -value < 0.10 considered statistically significant [Table 4]. Participant sex was found to be significantly associated with prolonged QTc interval, with males having a higher frequency of QTc prolongation compared to females (28.3% vs. 15.8%; $p = 0.020$). Age (pediatric vs. adult) was not significantly associated with prolonged QTc interval. Hb genotype (SS vs. other genotypes) and smoking status did not demonstrate a significant association with prolonged QTc interval. The presence of pericardial effusion on echocardiogram showed a marginal association with prolonged QTc interval ($p = 0.074$), where the frequency of prolonged QTc was higher in patients with a pericardial effusion (36.8%) compared to

those without (19.4%). A previous history of heart disease was significantly associated with prolonged QTc interval (34.1% vs. 17.8%; $p = 0.018$). Other variables such as previous history of kidney disease (including renal insufficiency, nephrotic syndrome, or hematuria), previous history of eye disease, SCD-related bone diseases (including aseptic necrosis, hand-foot syndrome, and osteomyelitis), hearing loss, painful episodes, spleen sequestration, hepatitis, pneumonia, leg ulcers, and liver sequestration did not show significant associations with prolonged QTc interval.

The differences in prolonged QTc interval between various continuous variables were analyzed using independent samples t -test [Table 5]. A p -value < 0.10 was considered statistically significant. Systolic BP ($p = 0.719$, mean difference (MD) = -0.80 mmHg), diastolic BP ($p = 0.575$, MD = 1.06 mmHg), body mass index ($p = 0.706$, MD = 0.22 kg/m²), and age ($p = 0.349$, MD = 1.55 years) did not show significant associations with prolonged QTc interval. On echocardiography, the presence of prolonged QTc intervals was not significantly associated with left ventricular end diastolic dimension ($p = 0.198$, MD = -0.16), however, it was associated with increased left ventricular end systolic dimension ($p = 0.070$, MD = -0.17) and increased left ventricular wall and septum thickness ($p = 0.078$, MD = -0.07). Several blood tests revealed significant findings. Hb levels ($p = 0.003$, MD = 0.53), red blood cell count ($p = 0.005$, MD = 0.22), and Hb F percentage ($p = 0.005$, MD = 2.46) were lower in patients with prolonged QTc intervals. Other blood parameters, including white blood cell count, mean corpuscular volume, creatinine, LDH, total protein, and albumin, did not exhibit significant association with prolonged QTc intervals.

In the binary logistic regression analysis, several variables were examined to assess their association with QTc prolongation. Individuals with a previous history of heart disease were found to have significantly higher odds of experiencing QTc prolongation compared to those without such history (OR = 3.53, 95% CI: 1.38–9.01; $p = 0.008$). Males had a significantly higher odds of QT prolongation compared to females (OR = 3.68, 95% CI: 1.67–8.11; $p = 0.001$). The presence of pericardial effusion was associated with an increased likelihood of QT prolongation (OR = 3.45, 95% CI: 1.10–10.86; $p = 0.034$). Moreover, lower levels of Hb were significantly associated with higher odds of QT prolongation (OR = 0.63, 95% CI: 0.43–0.93; $p = 0.018$).

DISCUSSION

This study showed 58.8% prevalence of at least one abnormal ECG finding. Of those, 20.6% and 41.1% showed prolonged QTc and LVH, respectively. Male sex, history of heart disease, pericardial effusion, and lower Hb levels were significantly associated with increased risk of QTc prolongation. Many mechanisms may contribute to these changes, including chronic anemia, chronic hemolysis, and related inflammatory products that induce endothelial injury, oxidative stress, and myocardial micro-ischemic events. Additionally, given the frequent pain crises, infections, and psychiatric complications these patients experience, they are more exposed to medication-induced QTc prolongation, including opioids and antiemetics.^{19,21–26}

ECG, an inexpensive, non-invasive, and widely available test, can help predict SCD cardiovascular complications. For instance, QTc prolongation and LVH can lead to fatal arrhythmias and heart failure. Thus, ECG may have important prognostic implications, given its relatively high specificity compared with echocardiography. However, it may not be suitable as a screening method given its low sensitivity. Additionally, ECG is a practical and time-efficient test in resource-limited centers.^{42,43}

Almost two-thirds (58.8%) had at least one ECG abnormality, which is lower than the prevalence reported by Holloman et al (72%).⁴⁴ This high prevalence in the latter study was contributed to more frequent nonspecific ST-T changes (53%), compared to only 5% in our study.⁴⁴ Another study conducted in Nigeria found a higher prevalence of first-degree heart block, RBBB, and LVH on ECG.⁴⁵ This analysis found a 20.6% prevalence of QTc prolongation, lower than those reported in previous studies by Liem et al (41%),¹⁸ Upadhy et al (38%),²⁴ and Oguanobi et al (61.7%).⁴⁵ The higher prevalence in Liem's study might be due to less stringent criteria that did not account for sex differences in the definition of QT prolongation.¹⁸ Our study included both pediatric and adult patients, with children < 10 years having the highest rate of QT prolongation (23.8%). In contrast, Mueller et al,²⁰ reported a lower prevalence (8.4%) among pediatric patients.

Prolonged QTc was more prevalent in males than in females, supporting findings from previous studies.^{19,24} Sickle cell pain crises have a higher incidence in males aged 14–20 years old, potentially associated with the pubertal surge in androgens.⁴⁶ On

the other hand, bioavailability of nitric oxide (NO) and endothelial response are higher in females, which may provide cardiovascular protection in females.⁴⁷

Hb level showed an inverse relation to QTc prolongation. This finding was also highlighted in a study conducted by Goel et al.⁴⁸ Persistently low Hb levels leads to compensatory long-standing tachycardia and high-output heart failure.⁴⁹ Another complication of chronic low Hb is elevated pulmonary arterial systolic pressure with subsequent right-sided heart failure.^{50,51} This continuous increased demand on the heart leads to myocardial fibrosis affecting impulse conduction and QTc prolongation.^{52,53} Another proposed mechanism is the inflammatory mediators that are released constantly from chronic hemolysis. During hemolysis, free Hb-induced NO scavenging causes vasoconstriction, oxidative stress, inflammatory response, and endothelial dysfunction, which can cause cardiac muscle damage and remodeling and predispose to QTc prolongation.^{1,2} Previous studies have found a relationship between prolonged QTc and increased hemolysis markers, including higher free heme, LDH, and aspartate aminotransferase levels in addition to lower Hb levels.^{18–20,24} The clinical importance of Hb levels monitoring and correction lies in their modifiable risk factor. Maintaining adequate Hb levels helps reverse free Hb-induced NO scavenging, which is crucial for preventing the adverse effects of hemolysis, thus maintaining vascular function, reducing vasoconstriction, and mitigating increased cardiac workload and potential damage. Using long-lived circulating NO-releasing nanoparticles has the potential to be used as a therapeutic agent.^{1,2}

Pre-existing heart disease and pericardial effusions are significantly associated with increased QTc prolongation risk. Cardiac fibrosis from ischemic or non-ischemic cardiomyopathy disrupts the heart's conduction system and increases the risk of QTc prolongation. In SCD, the persistent myocardium hypoxemia renders it at a higher risk of expanding areas of fibrosis and subsequent conduction abnormalities. Similarly, pericardial effusion causes diastolic dysfunction, which predisposes the myocardium to increase oxygen demand and secondary ischemia in the setting of hypoxemia from chronic anemia.⁵⁴

Generally, abnormal ECG findings were observed to be high in all age groups, yet half of SCD patients tend to have them early in life, usually before the age 20 years. Comparatively, Dosunmu et al,⁵⁵ found that 50% of adolescents with SCD have at least one

ECG abnormality, including RVH, biventricular hypertrophy, or most commonly LVH. A previous analysis of CSSCD data reported an age-dependent relationship linking LV diastolic dimension to Hb levels, particularly observed in patients > 30 years.¹³ Cardiac electrophysiology can be affected by the dynamic influence of pubertal changes and hormonal factors during the developmental stages of childhood and adolescence. These changes, triggered by hormonal shifts during puberty, might be responsible for the QTc shortening after puberty, decreasing the prevalence of QTc prolongation among adults.^{46,56}

The study uses data from 1982–1983, which may not reflect the current understanding of SCD and its cardiac complications. However, the findings remain valuable, especially in developing countries where advanced SCD treatment and up-to-date medical management are lacking. Thus, the study findings may closely resemble current disease presentations in these regions. This study also provides baseline insights into ECG abnormalities associated with SCD before the introduction of modern therapies, offering a historical perspective on untreated or minimally treated patients. More prospective studies with contemporary cohorts are needed to validate and extend these results, especially considering advances in SCD management.

The study population consisted of African American patients, which limits the generalizability of the findings to other racial or ethnic groups with SCD. Differences in genetic modifiers, comorbidities, and healthcare access among these groups may influence ECG findings. Future studies should aim to include more diverse populations to better capture variations in ECG patterns across racial and ethnic backgrounds. Additionally, they should investigate genetic differences, healthcare access, socioeconomic status, and environmental factors that may impact disease pathophysiology, ultimately improving the applicability of findings to a wider range of patients. Moreover, pulmonary arterial hypertension, which is common in SCD patients, is associated with increased QT dispersion. This was one of the study limitations, as we could not study this factor due to the lack of data.^{57,58} Of note, medications associated with prolonged QTc, such as hydroxyurea or methadone, were not included in our analysis. However, previous studies found no significant associations between QTc interval and methadone dose or hydroxyurea use.^{18,24} This secondary analysis of pre-existing data

lacked precise definitions for terms such as LVH, LAH, and ventricular or junctional rhythm, limiting comparability with other studies. Blood transfusions are commonly used to prevent or treat complications in SCD patients; however, they increase the risk of iron overload cardiomyopathy and subsequent ECG changes. Due to the lack of data on previous transfusions, we were unable to assess the association between blood transfusion and subsequent ECG changes. Despite the well-known risk of iron overload on the heart, some studies showed that iron deposition may spare the heart in SCD patients receiving blood transfusion, unlike other conditions such as thalassemia. This discrepancy may be attributed to two mechanisms in SCD. Elevated erythropoiesis levels facilitate iron recycling, and chronic inflammation traps iron within macrophages. In contrast, thalassemia is characterized by ineffective erythropoiesis, leading to an inability to manage free iron.^{59–62}

The use of a *p*-value threshold of < 0.10 in the selection of covariates during univariate analysis may increase the risk of type I error and the inclusion of variables with weaker associations. However, this threshold was chosen to ensure that potentially relevant variables were not prematurely excluded. As such, the findings should be interpreted with caution, and future studies with more stringent selection criteria or external validation are needed to confirm the validity of these results.

CONCLUSION

Our study demonstrates that QTc prolongation is more frequently observed in males and in SCD patients with low Hb levels. These findings highlight the significance of monitoring and correcting Hb levels, as they represent a modifiable risk factor that may potentially prevent prolonged QTc intervals and their related cardiac complications in this population. They also show the need for prospective studies to examine the efficacy of periodic ECG screenings to identify SCD patients with QTc prolongation, particularly among males and those with severe anemia. Given the high prevalence of prolonged QTc interval in SCD patients, ECG testing is recommended before the use of drugs associated with QTc prolongation.

Disclosure

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