Prevalence of Electrocardiographic Changes and Risk Factors For QTc Prolongation Among Steady State Sickle Cell Disease Patients: Cooperative Study of Sickle Cell Disease (CSSCD)

Mohammed B. Nawaiseh[1]*, Rund R. Haddadin[2], Yara B. Nawaiseh[3], Mohammad Z. Salameh[4], Abdallah A. Shurman[5], Osama W. Abu-Shawer[6], Asma I. Aljesrawi[7], Ibrahim A. Abuelbeh[8], Allaa Roto[9], Hadil Zureigat[6], Lana Mango[7], Munir Q. Zaqqa[10], Hanna K. Al-Makhamreh[11] and Nakhleh Abu-Yaghi[12]

[1]Department of Ophthalmology, Jordanian Royal Medical services, Amman, Jordan

[2]Department of Internal Medicine, Marshall University Joan C. Edwards School of Medicine, Huntington, West Virginia

[3]School of Medicine, Jordan University of Science & Technology (JUST), Irbid, Jordan

[4]Department of Internal Medicine, Hamad Medical Corporation, Doha, Qatar

[5]Insight Research Institute, Michigan, USA.

[6]Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio

[7]School of Medicine, The University of Jordan, Amman, Jordan

[8]Department of General Surgery, Manchester University NHS Foundation Trust, Manchester, UK

[9]Department of Internal Medicine, DMC/Wayne State University Sinai Grace Hospital, Michigan, USA.

[10]Department of Internal Medicine, Khaldi Medical Center, Amman, Jordan.

[11]Department of Internal Medicine, Cardiology Division, School of Medicine, The University of Jordan, Amman, Jordan

[12]Department of Special Surgery, Ophthalmology Division, School of Medicine, The University of Jordan, Amman, Jordan

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*Corresponding author: Mohammednawaiseh.md@gmail.com

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Abstract

Objective: 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 Sickle Cell Disease (CSSCD) Cardiac Ancillary Study. QT intervals were corrected using the Bazett formula (QTc), and prolongation was defined using gender-specific thresholds. The study population included African American steady state SCD patients in four clinical centers, located in both urban and rural settings.

Results: The study included 238 participants (92 males (38.7%) and 146 females (61.3%), with a median age of 19.0 (Interquartile Range = 14.0) years. Of those, more than two thirds of the studied sample (58.8%) had at least one abnormal ECG finding; being more common in males (72.8%) as compared to females (50%). In terms of ECG changes, almost half of the studied 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 gender (odds ratio [OR]=3.68, 95% confidence interval [CI]: 1.67-8.11, *P*=.001), history of heart disease (OR=3.53, 95% CI: 1.38-9.01, *P*=.008), pericardial effusion (OR=3.45, 95% CI: 1.10-10.86, *P*=.034), and lower levels of hemoglobin (OR=0.63, 95% CI: 0.43-0.93, *P*=.018).

Conclusions: Routine ECG screening would be recommended among SCD patients, particularly for those with increased risk for prolonged QTc, in addition to avoidance of concomitant factors that prolong QTc interval. Moreover, regularly monitoring hemoglobin levels is paramount, as it represents a modifiable factor influencing QTc prolongation risk.

Keywords: Sickle cell disease, ECG changes, QT prolongation, risk factors

Introduction

Sickle cell disease (SCD) is an autosomal recessive inherited disorder characterized by the presence of abnormal hemoglobin within erythrocytes, known as hemoglobin S (HbS), which 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. Affected individuals also frequently experience pain crises and are more susceptible to infections, which put 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 (PAH) 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. Most importantly, SCD patients are exposed to many potential QTc prolonging medications, including but not limited to: 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. Abnormal levels of electrolytes such as potassium, calcium, and magnesium can affect 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, which induces myocardial injury and fibrosis that triggers degenerative abnormalities in the cardiac conduction system, leading to electrophysiological changes (such as QTc prolongation), in addition to 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 history of recurrent vaso-occlusive crises (VOC), acute chest syndrome, or cardiopulmonary complications of SCD. Therefore, early detection and management of a prolonged QTc interval are essential in patients with SCD as there is a well-established relationship 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 (LFA-1), a member of the integrin family, is expressed on the surface of T lymphocytes, B lymphocytes, macrophages, neutrophils, and monocytes. LFA-1 plays a major role in mediating the adhesion of SCD eosinophils to fibronectin (FN), leading to vaso-occlusive process. Neutrophil-to lymphocyte (NLR) is considered reliable and surrogate marker for polymorphonuclear leukocytes (PMNL). Elevated NLR increases the likelihood of VOC and end-organ damage in SCD patients. Similarly, mean platelet volume (MPV), which describes the average platelet size reported in femtoliters and measures the heterogeneity in platelet size, is a simple way to measure platelet activation, resulting in vaso-occlusion and platelet aggregation. Additionally, interleukin-10 (IL-10) is 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. We aim in this study to assess the pattern of ECG changes in this population and more specifically, risk factors associated with increased odds for developing QTc interval prolongation.

This study aims to identify the prevalence of various ECG changes in steady state SCD patients, as well as identifying 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 3,800 patients. Approval to access the CSSCD study data was obtained from the BioLINCC (Biologic Specimen and Data Repository Information Coordinating Center; https://biolincc.nhlbi.nih.gov/home/), which is an open access data repository. [38]

The Cardiac Ancillary Study involved patients from four clinical centers, with equal representation of both rural and urban areas. All patients were of African American race (n = 238, 100%) with a wide age range (2-58 years). Informed consent was obtained from all subjects, and the study was approved by the Committee on Human Assurance at each of the centers involved. Cardiac function assessment was done in steady state SCD patients; all subjects were crisis-free for two weeks prior to the study and had not been transfused in the preceding three months.

Data collection took place between 1982 and 1983. Past medical history, 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 diseases), rheumatic heart disease (with or without carditis and valvular lesions), hypertension, myocardial infarction, cardiomyopathy or pericarditis were obtained. Physical examination, echocardiography, and ECG were also performed. The Echocardiogram scans and ECG strips were sent to cardiologists at Yale New Haven Hospital for interpretation. All those included in the study had to be enrolled at older than two years of age. Echocardiograms were performed using a standardized method in all four centers. Interpretation was then conducted by one investigator who was blinded to patient data. Systolic and diastolic left ventricle (LV) function in addition to wall thickness, were assessed.

The QT interval represents the duration of 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]. The formula involves dividing the measured QT interval by the square root of the RR interval, resulting in a corrected QT interval (QTc) that is independent of heart rate. QTc prolongation was defined as longer than 440ms for males and longer than 460ms for females. We specifically analyzed the QRS duration 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 could be contributing to observed QTc prolongation. Prolonged QRS interval was defined as QRS interval $\geq$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 (PVCs), right bundle branch block (RBBB), left axis deviation, or any abnormal rhythm types. This classification was selected because it encompassed all the changes that were reported in the dataset.

We conducted a comprehensive statistical analysis of the data collected using Statistical Package for the Social Sciences (SPSS) v.25. 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 standard deviations (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 gender. The age groups are divided into four categories: <10 years, [10-20) years, [20-30) years, and $\geq$30 years.

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

	Category	Frequency (%) or Mean (SD)	Total
Gender	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%)	
Hg 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 (3.6)	238
Systolic BP (mmHg)		112.8 (13.8)	236
Diastolic BP (mmHg)		68.6 (11.7)	231
Blood tests			
Hg (g/dl)		8.5 (1.1)	238
RBC ($*10^{12}/l$)		2.7 (0.5)	238
WBC ($*10^{9}/l$)		11.5 (2.6)	238
MCV (femtoliter)		91.8 (8.5)	238
Creatinine (mg/dl)		0.7 (0.4)	237
Hg F (%)		7.1 (5.1)	209
LDH (mg/dl)		462.1 (178.6)	222
Total protein (g/dl)		7.7 (0.5)	228
Albumin (g/dl)		4.4 (0.4)	228

† Including SB, SC, SS alpha, and other variants. Sickle cell disease (SCD), SD; standard deviation, Hg; Hemoglobin, BP; Blood pressure, BMI; Body mass index, RBC; Red blood cells, WBC; White blood cells, MCV; Mean corpuscular volume, LDH; Lactate dehydrogenase.

Table 2: ECG characteristics among the study participants.

ECG characteristics	Category	Frequency (%) or Mean (SD)	Total
Abnormal ECG	Total	140 (58.8%)	238

	Female	73 (50.0%)	
	Male	67 (72.8%)	
HR (beats per minute)		74.4 (12.9)	238
RR interval (second)		0.831 (0.141)	238
PR interval (second)		0.157 (0.027)	237
QRS duration (second) †		0.059 (0.018)	238
	Normal	235 (98.7%)	
	Prolonged	3 (1.3%)	
QT interval (second)		0.385 (0.040)	238
QTc ‡ interval		0.425 (0.037)	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 > 440ms for males and >460ms 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.

Age (years)	**Gender**	**<10**	**[10-20)**	**[20-30)**	**≥30**	***P*-value**

Abnormal ECG	Total	26/42 (61.9%)	49/87 (56.3%)	44/74 (59.5%)	21/35 (60.0%)	.936
	Male	9/15 (60.0%)	25/34 (73.5%)	24/30 (80.0%)	9/13 (69.2%)	.548
	Female	17/27 (63.0%)	24/53 (45.3%)	20/44 (45.5%)	12/22 (54.5%)	.418
Prolonged QTc	Total	10/42 (23.8%)	18/87 (20.7%)	16/74 (21.6%)	5/35 (14.3%)	.761
	Male	5/15 (33.3%)	11/34 (32.4%)	9/30 (30.0%)	1/13 (7.7%)	.358
	Female	5/27 (18.5%)	7/53 (13.2%)	7/44 (15.9%)	4/22 (18.2%)	.916

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 frequency (%)**	**Total**	***P*-value**
Gender	Male	26 (28.3%)	92	.020
	Female	23 (15.8%)	146	
Entry visit age group (years)	<=18 (Pediatric)	28 (24.1%)	116	.187
	>18 (Adults)	21 (17.2%)	122	
Hg genotype	SS	39 (22.8%)	171	.176
	Other genotypes †	10 (14.9%)	67	
Smoking	No	23 (22.3%)	103	.712
	Yes	20 (20.2%)	99	
Presence of pericardial effusion on Echocardiogram	No	38 (19.4%(	196	.074
	Yes	7 (36.8%)	19	
Previous history of				
Heart disease	No	35 (17.8%)	197	.018
	Yes	14 (34.1%)	41	
Eye disease	No	46 (20.6%)	223	.845
	Yes	2 (18.2%)	11	
Kidney diseases ‡	No	42 (20.7%)	203	.878
	Yes	7 (21.9%)	32	
SCD related bone diseases §	No	28 (21.1%)	133	.931
	Yes	21 (20.6%)	102	
Hearing loss	No	47 (21.2%)	222	.283
	Yes	1 (8.3%)	12	

Painful episodes	No	7 (15.9%)	44	.355
	Yes	42 (22.2%)	189	
Spleen sequestration	No	44 (20.9%)	211	.485
	Yes	2 (13.3%)	15	
Hepatitis	No	42 (20.3%)	207	.870
	Yes	5 (21.7%)	23	
Pneumonia	No	17 (17.7%)	96	.370
	Yes	30 (22.6%)	133	
Leg ulcers	No	40 (20.6%)	194	.849
	Yes	9 (22.0%)	41	
Liver sequestration	No	42 (21.0%)	200	.770
	Yes	6 (18.8%)	32	

Hg; Hemoglobin, QTc; corrected QT interval
† This includes SB, SC, SS alpha, and other variants genotypes. ‡ This includes renal insufficiency or nephrotic syndrome or hematuria. § This includes aseptic necrosis, handfoot syndrome, and osteomyltis.

To assess the differences between those with and without QTc prolongation, a Chi-square test was utilized for categorical variables (Table 5), and an independent samples t-test was employed for continuous variables (Table 6). The threshold for statistical significance was set at a p-value of less than 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. While 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.

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

	QTc	**N**	**Mean (SD)**	***P*-value**	**MD**
Systolic BP (mmHg)	Normal	187	112.67 (14.04)	.719	-0.80
	Prolonged	49	113.47 (13.03)		
Diastolic BP (mmHg)	Normal	182	68.84 (11.92)	.575	1.06
	Prolonged	49	67.78 (10.96)		
BMI (kg/m^2)	Normal	189	19.29 (3.60)	.706	0.22
	Prolonged	49	19.08 (3.46)		
Age at entry visit (years)	Normal	189	19.63 (10.57)	.349	1.55
	Prolonged	49	18.08 (9.34)		

Echocardiography					
LV end diastolic dimension (cm)	Normal	170	5.03 (0.77)	.198	-0.16
	Prolonged	48	5.19 (0.60)		
LV end systolic dimension (cm)	Normal	168	3.26 (0.56)	.070	-0.17
	Prolonged	48	3.43 (0.49)		
LV wall and septum thickness (cm)	Normal	171	1.23 (0.25)	.078	-0.07
	Prolonged	48	1.31 (0.30)		
Blood tests					
Hg (g/dl)	Normal	189	8.59 (1.11)	.003	0.53
	Prolonged	49	8.06 (0.95)		
RBC (* 10^{12}/l)	Normal	189	2.76 (0.51)	.005	0.22
	Prolonged	49	2.55 (0.36)		
WBC (* 10^{9}/l)	Normal	189	11.48 (2.63)	.611	-0.21
	Prolonged	49	11.69 (2.65)		
MCV (femtoliter)	Normal	189	91.82 (8.69)	.989	-0.02
	Prolonged	49	91.84 (7.88)		
Creatinine (mg/dl)	Normal	189	0.74 (0.41)	.733	-0.02
	Prolonged	48	0.76 (0.57)		
Hg F (%)	Normal	165	7.66 (5.34)	.005	2.46
	Prolonged	44	5.20 (3.78)		
LDH (mg/dl)	Normal	175	453.71 (177.71)	.176	-39.74
	Prolonged	47	493.45 (180.43)		
Total protein (g/dl)	Normal	181	7.66 (0.50)	.185	-0.11
	Prolonged	47	7.77 (0.54)		
Albumin (g/dl)	Normal	181	4.37 (0.45)	.738	0.02
	Prolonged	47	4.35 (0.45)		

QTc; Corrected QT interval, SD; standard deviation, MD; Mean difference, BP; Blood pressure, BMI; Body mass index, LV; Left ventricle, Hg; Hemoglobin, RBC; Red blood cells, WBC; White blood cells, MCV; Mean corpuscular volume, LDH; Lactate dehydrogenase.

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

Variable	*P*- value	Odds ratio	95% C.I. for odds ratio	
			Lower	Upper
Previous history of heart disease	.008	3.53	1.38	9.01
Gender (Male)	.001	3.68	1.67	8.11
Hg (g/dl)	.018	0.63	0.43	0.93
Pericardial Effusion	.034	3.45	1.10	10.86

QTc; Corrected QT interval, Hg; Hemoglobin.

Variables that demonstrated significant associations (*P*< .10) 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 a large number of potential predictors. However, it is important to note that 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% confidence intervals (CIs) and p-values for each risk factor identified (Table 7). A p-value of less than .05 was considered statistically significant in the final model. Age group at entry visit as a continuous variable was not significantly associated with QTc prolongation. Thus, it was not included in the multivariate analysis.

Results

The study included a total of 238 participants, consisting of 92 males (38.7%) and 146 females (61.3%). 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 of the cohort was 19.0 (Interquartile Range = 14.0) years. The majority of participants (71.8%) had SS hemoglobin, 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 only 41 (17.2%) of the participants. The study also showed a nearly even split between non-smokers (51.0%) and smokers (49.0%). The average BMI was 19.2 (3.6) kg/m^2.

The participants' mean hemoglobin level was 8.5 (1.1) g/dL, red blood cells (RBC) count 2.7 (±0.5) x 10^12 per liter, white blood cells (WBC) count 11.5 (2.6) x 10^9 per liter, and mean corpuscular volume (MCV) 91.8 (8.5) fL. The mean systolic blood pressure (BP) was 112.8 (13.8) mmHg, and diastolic BP was 68.6 (11.7) mmHg. The mean creatinine level was 0.7 (0.4) mg/dL, hemoglobin F (Hg F) 7.1% (5.1), lactate dehydrogenase (LDH) 462.1 (178.6) mg/dL, total protein 7.7 (0.5) g/dL, and albumin 4.4 (0.4) g/dL.

The results showed that among the included patients, 58.8% (140 out of 238) had abnormal ECG findings (at least one abnormal ECG finding). Among females, 73 (50.0%) had abnormal ECGs, while among males, 67 (72.8%) had abnormal ECGs. The mean heart rate, R-R interval, P-R interval, QRS duration, QT interval, and QTc were 74.4 beats per minute (12.9), 0.831 (0.141) seconds, 0.157 (0.027) seconds, 0.059 (0.018) seconds, 0.385 (0.040) seconds, and 0.425 (0.037) seconds, respectively. The QTc interval was found to be prolonged in 49 participants (20.6%). If the definition of prolonged QTc was more than 440 ms both among 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*= .583). Notably, only one patient (2%, 1 out of 49) exhibited both prolonged QRS and QTc. In terms of chamber hypertrophy, 97 (41.1%) patients had left ventricular (LV) hypertrophy, 10 (4.2%) had left atrial (LA) hypertrophy, and 100 (42.4%) showed LV or LA hypertrophy. 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 out of 237), 3.8% (9 out of 238), 4.2% (10 out of 237), and 11.8% (28 out of 238) of patients, respectively. Premature ventricular contractions (PVCS), right bundle branch block (RBBB), left axis deviation, and junctional or ventricular rhythm types were present in 1.7% (4 out of 237), 2.1% (5 out of 237), 0.8% (2 out of 237), and 0.8% (2 out of 237) of patients, respectively. Most patients (99.2%, 235 out of 237) 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 regarding the presence of abnormal ECG (p = .936) or prolonged QTc intervals (*P*= .761), even after stratifying the data by gender. The prevalence of abnormal ECG findings was observed to be relatively high in all age groups, with rates ranging from 56.3% to 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 various categorical variables, with a p-value less than 0.10 considered statistically significant. Results are presented in the table 4. Gender 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=.020). Age (pediatric vs. adults) did not show a significant association 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=.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*= .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, osteomyelitis), hearing loss, painful episodes, spleen sequestration, hepatitis, pneumonia, leg ulcers, and liver sequestration did not show significant associations with prolonged QTc interval.

The study analyzed the differences in prolonged QTc interval between various continuous variables using independent samples T-test (Table 5). A p-value less than 0.10 was considered statistically significant. Systolic BP pressure (*P*= .719, mean difference (MD) = -0.80 mmHg), diastolic BP (*P*= .575, MD = 1.06 mmHg), BMI (*P*= .706, MD = 0.22 kg/m2), and age (*P*= .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 (LVED, *P*= .198, MD = -0.16), however, it was associated with increased left ventricular end systolic dimension (LVES, *P*= .070, MD = -0.17) and increased left ventricular wall and septum thickness (*P*= .078, MD = -0.07). Several blood tests revealed significant findings. Hg levels (*P*= .003, MD = 0.53), RBC count (*P*= .005, MD = 0.22), and Hg F percentage (*P*= .005, MD = 2.46) were lower in patients with prolonged QTc intervals. Other blood parameters, including WBC count, MCV, 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 a significantly higher odds of experiencing QTc prolongation compared to those without such history (odds ratio [OR] = 3.53, 95% confidence interval [CI]: 1.38-9.01, *P*= .008). Males had a significantly higher odds of QT prolongation compared to females (OR = 3.68, 95% CI: 1.67-8.11, *P*= .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*= .034). Moreover, lower levels of hemoglobin (Hg) were significantly associated with higher odds of QT prolongation (OR = 0.63, 95% CI: 0.43-0.93, *P*= .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 gender, history of heart disease, pericardial effusion and lower Hg 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 but not limited to opioids and anti-emetics. [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 an important prognostic implication given its relatively acceptable specificity compared to 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%). This high prevalence in the latter study was contributed to more frequent nonspecific ST-T changes (53%), compared to only 5% in our analysis. [44] In another study conducted in Nigeria, a higher prevalence of first degree heart block, RBBB and LVH on ECG was appreciated. [45] This analysis found a 20.6% prevalence of QTc prolongation, lower than those reported in previous studies by Liem et al. (41%), Upadhya et al. (38%), and Oguanobi et al. (61.7%). The higher prevalence in Liem's study might be due to less stringent criteria that did not account for gender differences in defining QT prolongation. Our study included both pediatric and adult patients, with children under 10 years showing the highest rate of QT prolongation at 23.8%. In contrast, Muller et al. reported a lower prevalence (8.4%) among pediatric patients. [18,20,24,45]

Prolonged QTc was more prevalent in males than in females, supporting findings from previous studies. [19,24] Sickle cell pain crises have 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]

Hg level showed an inverse relation to QTc prolongation. This finding was also highlighted in a study conducted by Goel et al. [48] Persistently low Hg levels leads to compensatory long standing tachycardia and high output heart failure. [49] Another complication of chronic low Hg is elevated pulmonary arterial systolic pressure with subsequent right sided heart failure. [50,51] This continuous increased demand on the heart leads to cardiac myo-fibrosis affecting impulse conduction and QTc prolongation. [52,53] Another proposed mechanism is inflammatory mediators that are released constantly from chronic hemolysis. During hemolysis, free Hg-induced NO scavenging causes vasoconstriction, oxidative stress, inflammatory response, and endothelial dysfunction, which can potentially cause cardiac muscle damage and remodeling, predisposing to QTc prolongation. [1,2] In fact, previous studies have found a relationship between prolonged QTc and increased hemolysis markers, including higher free heme, LDH and AST levels in addition to lower Hg levels. [18–20,24] The clinical importance of Hg levels monitoring and correction lies in the fact that it is a modifiable risk factor. Maintaining adequate Hg levels helps reverse free Hg-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 linked to 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 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 age of 20 years. Comparatively, Dosunmu et al. found out that 50% of adolescent with SCD have at least one ECG abnormality; including RVH, biventricular hypertrophy or most commonly LVH. Surprisingly, a previous analysis of this CSSCD data by Covitz et al. reported an age-dependent relationship linking LV diastolic dimension to Hg levels particularly observed in patients older than 30 years. [13,55] Cardiac electrophysiology can be affected by dynamic influence of pubertal changes and hormonal factors during the developmental stages of childhood and adolescence. These changes that are 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. Also, this study 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 expand upon these results, especially in light of advances in SCD management.

The study population consisted of African American patients, which may limit 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. Also, PAH, 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 lack of data. [57,58] Of note, medications associated with prolonged QTc, such as: Hydroxyurea or Methadone were not included on our analysis. However, previous studies found neither significant correlation between QTc interval and methadone dose nor 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. As blood transfusions are used to prevent or treat complications in SCD patients, it increases 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 any 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 in other conditions like thalassemia. This discrepancy may be attributed to two mechanisms in SCD: the elevated erythropoiesis levels facilitate iron recycling, and chronic inflammation traps iron within macrophages. Conversely, thalassemia is marked by ineffective erythropoiesis, leading to an inability to manage free iron. [59–62]

Finally, 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

In conclusion, our study demonstrates that QTc prolongation is more frequently observed in males and in SCD patients with low Hg levels. These findings highlight the significance of monitoring and correcting Hg levels, as it represents a modifiable risk factor that may potentially prevent prolonged QTc interval and its related cardiac complications among SCD patients. They also show the need for prospective studies to examine the efficacy of periodic ECG screenings to identify SCD patients with QTc prolongation, especially among males and those with severe anemia. Due to the high prevalence of prolonged QTc interval in SCD patients, we recommend ECG testing before the use of certain drugs that are associated with QTc prolongation.

Disclosure

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Ethical approval

Approval to access the CSSCD study data was obtained from the BIOLINCC (Biologic Specimen and Data Repository Information Coordinating Center) website: (https://biolincc.nhlbi.nih.gov/home/), which is an open access data repository. This study received an official ethical approval from the institutional review board (IRB) at Jordan University Hospital, Amman, Jordan.

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