Research Square

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Echocardiogram Findings in Patients with Sickle Cell Disease at a Tertiary Care Center in Saudi Arabia

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Abstract

Background

Episodic vaso-occlusive (VOC) and chronic hemolytic anemia are the hallmarks of sickle cell disease (SCD), which progressively worsen end-organ complications, including cardiovascular manifestations, which can vary in severity. In Saudi Arabia, SCD was first identified in the Eastern Province, where rates continue to be high. This study aimed to investigate prevalence of echocardiographic parameters in patients with SCD at a single healthcare facility in the Eastern Province of Saudi Arabia.

Methods

A retrospective observational study was conducted in a tertiary hospital involving data of n = 225 adult patients with SCD with any phenotype between January 2022 and May 2024. A health informatics system (HIS) was used to collect demographic information, SCD course and medications, and echocardiography results.

Result

The mean age of study sample was 27 years, 54.2% were female and 86.7% had SS phenotype. Valve regurgitation was found to be the more common cardiac complication. Tricuspid regurgitation was the most common valvular disorder (20%) followed by mitral (7.5%), aortic (3.1%) and pulmonic regurgitation (2.2%) ($p = 0.0001$). Aortic and mitral stenosis accounted for 0.9% of cases while pulmonic stenosis accounted for 0.4% ($p = 0.0001$). In addition, SCD significantly affected ventricular size and function ($p = 0.0001$). Hydroxyurea use was significantly associated with TR ($p = 0.03$).

Conclusion

Shunt lesions such as PFO, valvular, and ventricular heart diseases were found to be strongly associated with SCD. The current findings illustrate the importance of early cardiac disease detection, by Echo screening in patients with SCD.

Introduction

Sickle cell disease (SCD) is an inherited disorder, an autosomal recessive mutation caused by single point mutations in the B-globin chain that alter the morphology of red blood cells (RBCs), giving them a crescent shape. This results in less oxygen reaching the tissues because RBCs have difficulty passing through the vascular system. As a result, end-organ damage occurs due to repeated hemolysis and tissue necrosis (1–3). In this process, the heart is one of the major organs that can be affected by the effects of sudden cardiac death, resulting in arrhythmia, sudden death, left ventricular diastolic heart

failure, elevated pulmonary artery pressure, pulmonary embolism, and pulmonary hypertension (2, 3). Dilated heart disease, hypertrophy, and cardiomegaly are other cardiac manifestations that lead to decreased oxygenation, increased cardiac output, and increased preload, resulting in high systolic volume and continued decrease in peripheral vascular resistance, which affects afterload (4, 5).

Additional evidence suggests that iron overload as a complication of repeated blood transfusion may lead to heart failure, arrhythmia, and dilation or hypertrophy (4–7). Thus, a case-control study by Cuervo et al. showed that restrictive ventilatory dysfunction was observed in all patients with sudden cardiac death (6). In turn, a retrospective study by Fitzhugh et al. showed that congestive heart failure, myocardial infarction, and arrhythmia are among the main causes of death in patients with sudden cardiac death (7). Moreover, left ventricular dysfunction has been found to predict mortality in patients with SCD, and the risk increases with age (8).

Pulmonary hypertension (PH) is one of the most common complications of SCD. It can be detected by transthoracic echocardiography (TTE) by measuring tricuspid regurgitation velocity (TRV) with diagnostic confirmation defined as TRV ≥ 2.5 m/s. However, due to the possibility of false-positive TTE when measuring TRV, right heart catheterization is the gold standard for diagnosing PH elevation (4, 9). However, using high-frequency sound waves during transthoracic echocardiography (TTE) cardiac manifestations can be checked. The life expectancy of patients with SCD increased when neonatal diagnosis, education, and premarital counseling were introduced, and new oral treatments other than blood transfusion were used (4, 10). The likelihood of developing cardiovascular symptoms increases as the life expectancy of a patient with SCD increases.

In Saudi Arabia, SCD was first identified in the Eastern Province in the 1960s (11). While cardiac manifestations in SCD are a serious condition, these manifestations have been less studied at the national level. A recent study conducted at King Abdulaziz University Hospital (KAUH) showed that PH and arrhythmia were among the most common cardiac manifestations in their institution, and the risk of PH increased with pre-existing cardiac disease, CKD, and liver cirrhosis (12). In addition, TTEcho was evaluated in about 65 patients at King Khalid University Hospital in Riyadh, and the result showed that PH was the most common cardiopulmonary manifestation (13). To the best of the authors' knowledge, no studies from the Eastern Province on the cardiac manifestations of SCD were conducted. This study aimed to investigate prevalence of echocardiographic parameters in patients with SCD at a single healthcare facility in the Eastern Province of Saudi Arabia.

Methods

Study design and setting

This study used a retrospective observational approach and was conducted at the King Fahd Military Medical Complex (KFMMC) in Dhahran, Saudi Arabia, between January 2022 and May 2024.

Study sample

Study sample was calculated based on the following formula:

Where: z is the z score, ε is the margin of error, N is the population size, and $\hat{p}$ is the population proportion (**14**).

At the time of data collection, there were n = 300 adult patients with SCD who were regularly seen in the hematology clinic at KFMMC . Based on the applied eligibility criteria and study sample calculation, n = 208 patients were recruited.

Eligibility criteria:
Inclusion criteria: Any adult patient aged ≥ 14 years (according to hospital policy, adult age starts from 14 years) who is eligible for treatment at KFMMC and diagnosed with sickle cell disease (HGB SS, HGB SB, HGB SC, HGB SD, HGB SE) was eligible to participate in the study. Exclusion criteria: cases of non-sickle cell disease, sickle cell trait and pediatric age group under 14 years, and those patients without Echo data were excluded from the study.

Data collection

Data collection from the health informatics system included age, gender, comorbidities,

$$\text{Unlimited population: } n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

$$\text{Finite population: } n' = \frac{n}{1+\frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2 N}}$$

smoking history, body mass index (BMI), medication use (hydroxyurea), hospitalization frequency (three or more hospitalizations per year versus less than three), phenotypes, and the presence of complications because of SCD. Data on hemoglobin level (HGB), platelet count (PLT), white blood cell (WBC), hemoglobin electrophoresis (HGBS%, HGBF%, HGBA%, HGBA2%), and other phenotypes such as HGBC%, HGBD%, HGBE%, or HGB O%, if present, were collected. In addition, evaluation of the results of transthoracic echocardiography (ventricles and atria, valves, signs of pulmonary hypertension (PH)) and the presence of any cardiac anomalies performed within the last 2 years was conducted.

Instrumentation

A Two-Dimensional and doppler echocardiogram studies including the measurements were performed in standard views (Parasternal, apical, subcostal and suprasternal notch) according to the American

Society of LV volume and ejection Fraction (LVEF) were calculated using Simpson's biplane method. LV EFs of < 52% for male and < 54% for female is suggestive of abnormal LV systolic function (16). LV diastolic function was assessed and determined according to the American society of echocardiography (ASE) and the European association of cardiovascular imaging (EACVI) (17).

Two-dimensional and Doppler echocardiogram studies, including measurements, were performed in standard projections (parasternal, apical, subcostal, and suprasternal notch). LV volume and ejection fraction (LVEF) were calculated using the biplane Simpson method. LVEF < 52% for men and < 54% for women indicate abnormal LV systolic function (16). LV diastolic function was assessed and defined according to the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) (17).

RV size and systolic function were assessed using several parameters, including tricuspid annular plane systolic excursion (TAPSE) (TAPSE < 17 mm is highly suggestive of RV systolic dysfunction) and tricuspid annular systolic motion velocity (s') (S' < 9.5 cm/sec suggests RV systolic dysfunction) as per ASE guidelines (15, 16). All patients underwent a comprehensive examination for valvular heart disease (stenosis and regurgitation) using appropriate methods and parameters to detect and classify the severity of lesions according to the latest published EAE/AS guidelines (18, 19).

Statistical analysis

Data entry, cleaning, and coding were done using an Excel worksheet. The data were analyzed using the Social Science Statistical Package (SPSS version 29, Armonk, NY: IBM Corp, USA). Quantitative data with a normal distribution are presented as mean (M) and standard deviation (SD). Skewed distribution is present by median and range. Qualitative data are presented though frequency (n) and percentage (%). The significance of demographic variables was tested using Student's t-test, analysis of variance (ANOVA), chi-square test, and Fisher's exact test. Binary logistic regression was used for multivariate analysis. Categorical data were compared using chi-square test and Fisher's Exact test (since some of the cell's frequency with less than 5). A $p \leq 0.05$ was considered to be statistically significant, at 95% confidence interval.

Procedures

The ethical approval for this study was obtained from the Eastern Province Armed Forces Hospital Institutional Review Board (AFTER-IRB-2024-036, August 26, 2024). No informed consent from patients was required as no patient tissue or samples were used. Data were collected retrospectively from an electronic record system extracted from clinical laboratory and echo records. No consent was required to create the current retrospective study with no patient tissue use. This research adheres to the Helsinki Declaration.

Results

Data from n = 225 patients with SCD who underwent echocardiography were analyzed. The average age of the study sample was 27 years, with a predominance of females n = 122 (54.2%) and males n = 103 (45.8%). The majority of patients had SS phenotype (86.7%), followed by SB (12.9%), and SD (0.4%). Obesity with BMI ≥ 30 accounted for 7.1%. In addition, 5.3% of patients had an association with rheumatological diseases, including systemic lupus erythematosus, antiphospholipid syndrome, mixed connective tissue disease, and rheumatoid arthritis. Other comorbidities that were less common included hypertension (4.4%), dyslipidemia (4%), chronic kidney disease (CKD) (3.6%), diabetes mellitus (DM) (3.6%), bronchial asthma (BA) (2.7%), and hypothyroidism (1.3%), as shown in Table 1.

Table 1
Socio-demographic data of study sample.

Demographic Characters			
Age /year	**Mean** = 27 years	Minimum = 14 years	Maximum = 69 years
	Frequency (n)	**Percentage (%)**	
Gender			
Male	103	45.8	
Female	122	54.2	
Phenotype			
SB	29	12.9	
SD	1	0.4	
SS	195	86.7	
Diabetes Mellitus			
Yes	8	3.6	
No	217	96.4	
HTN			
Yes	10	4.4	
No	215	95.6	
CKD			
Yes	8	3.6	
No	217	96.4	
Rheumatological			
Yes	12	5.3	
No	213	94.7	
Hypothyroidism			
Yes	3	1.3	
No	222	98.7	
Bronchial Asthma			
Yes	6	2.7	

Key words: **HTN** = hypertension, **CKD** = chronic kidney disease, **BMI** = body mass index.

Demographic Characters		
No	219	97.3
Dyslipidaemia		
Yes	9	4
No	216	96
Smoking		
Yes	0	0
No	225	100
High BMI (≥ 30)		
Yes	16	7.1
No	209	92.9
Key words: **HTN** = hypertension, **CKD** = chronic kidney disease, **BMI** = body mass index.		

Table 2 shows the clinical manifestations, course, and complications of SCD. The frequency of hospitalization is one of the clinical parameters reflecting the severity of SCD, and it was found that about 81.3% of cases required three hospitalizations per year or less. Moreover, 56% of cases were using hydroxyurea at the time of the study. The remaining 44% did not use hydroxyurea either due to the uneventful course of the disease or due to previous side effects, e.g., allergy or refusal to take it. In addition, the most common complications of SCD were found to be acute chest syndrome (ACS) (21.3%), followed by central nervous system (CNS) crisis (6.2%), thrombosis of any location except CNS (4%), and vascular necrosis (AVN) (3.6%).

Table 2
Clinical characteristic, medication and frequency of admissions.

Clinical Characters	Frequency(N)	Percentage (%)
Admission Frequency Past Year		
3 times or less times	183	81.3
More than 3 times	42	18.7
Hydroxyurea		
Yes	126	56
No	99	44
ACS		
Yes	48	21.3
No	177	78.7
AVN		
Yes	8	3.6
No	217	96.4
Hepatopathy		
Yes	2	0.9
No	223	99.1
CNS		
Yes	14	6.2
No	211	93.8
Iron Overload		
Yes	1	0.4
No	224	99.6
Thrombosis		
Yes	9	4
No	216	96
Priapism		

Keywords: ACS = acute chest syndrome, **CNS =** central nervus system crisis, **AVN** = A vascular necrosis.

Clinical Characters	Frequency(N)	Percentage (%)
Admission Frequency Past Year		
Yes	0	0
No	225	100
Spleen Sequestration		
Yes	1	0.4
No	224	99.6
Osteoporosis		
Yes	1	0.4
No	224	99.6
Keywords: ACS = acute chest syndrome, **CNS =** central nervus system crisis, **AVN** = A vascular necrosis.		

The echo result was expressed as an examination of the four main valves (aortic, mitral, tricuspid, and pulmonary) with a description of the abnormality (stenosis, regurgitation, or normal) and the degree of abnormality, if present (mild, moderate, severe). Of n = 225 patients, n = 45 (20%) cases had tricuspid regurgitation (TR) ($p \leq 0.0001$); among these, n = 37 (82.2%) were mild, and n = 8 (17.8%) were moderate (Table 3). The second most common valvular lesion was mitral regurgitation (MR) n = 17 (7.5%) ($p \leq 0.0001$), of which n = 15 (88.2%) were mild and n = 2 (11.8%) were moderate. In addition, aortic regurgitation (AR) n = 7 (3.1%) was also significantly expressed ($p \leq 0.0001$), with regurgitation being mild in n = 5 (71.4%), moderate in n = 1 (14.3%) and severe in n = 1 (14.3%). Pulmonary regurgitation (PR) was found in n = 5 (2.2%; $p \leq 0.0001$) cases, n = 4 (80%) had mild disease and n = 1 (20%) was in the moderate category. Valve stenosis was less common compared to valve regeneration. Both aortic (AS) and mitral stenosis (MS) were found in n = 2 (0.9%) cases, and pulmonary stenosis (PS) in 1 (0.4%), ($p \leq 0.0001$) (Table 3).

Table 3
Cardiac valves, pulmonary pressure and ventricles Echo findings.

Valve	Abnormal N (%)	Normal N (%)	Total (N)	P Value	Mild N (%)	Moderate N (%)	Severe N (%)
AS	2 (0.9)	223 (99.1)	225	0.0001	2 (100)	0 (0)	0 (0)
AR	7 (3.1)	218 (96.9)	225	0.0001	5 (71.4)	1(14.3)	1(14.3)
MS	2 (0.9)	223(99.1)	223	0.0001	1(50)	1(50)	0 (0)
MR	17 (7.5)	208(92.4)	225	0.0001	15 (88.2)	2 (11.8)	0 (0)
TS	0 (0)	225 (100)	225	Nil	0 (0)	0 (0)	0 (0)
TR	45 (20)	180 (80)	225	0.0001	37 (82.2)	8 (17.8)	0 (0)
PS	1 (0.4)	224 (99.6)	225	0.0001	1 (100)	0 (0)	0 (0)
PR	5 (2.2)	220 (97.8)	225	0.0001	4 (80)	1 (20)	0 (0)
Other							
PHTN	13 (5.7)	212(94.2)	225	0.0001	5 (38.5)	5 (38.5)	3 (23.1)
LV							
LVH	4 (1.7)	221(98.2)	225	0.0001	3 (75)	0 (0)	1 (25)
LV_DF	14 (6.2)	211(93.8)	225	0.0001	14 (100)	0 (0)	0 (0)
RV							

RV	Normal (N (%))	Abnormal Impaired / Dilated (N (%))	P value
RV Size	218 (96.9	7 (3.1)	0.0001*
RV Function	222 (98.7)	3 (1.3)	0.0001*
Atrium			
RA	222 (98.7)	3 (1.3)	0.0001*
LA	221(98.2)	4 (1.7)	0.0001*

Key words: AS = aortic stenosis, **AR** = aortic regurgitation, **MS**=mitral stenosis, **MR** = mitral regurgitation, **TS** =tricuspid stenosis, **TR** = tricuspid regurgitation, **PS**= pulmonary stenosis, **PR**=pulmonary regurgitation, **PHTN**= pulmonary hypertension. **LVH**=left ventricular hypertrophy, **RV**= right ventricular. **RA**= right atrium **LA**=left atrium. * Significant P < 0.05

Pulmonary hypertension (PHTN) was reported in n = 13 (5.7%) SCD cases ($p \leq 0.0001$). Among them, n = 5 (38.5%) had mild PHTN, n = 5 (38.5%) were in the moderate category, and severe was among n = 3 (23.1%) cases. Left ventricular hypertrophy (LVH) was also significantly reported among n = 4 (1.7%), and 75% of them had mild LVH ($p \leq 0.0001$). The right ventricle (RV) was significantly dilated in n = 7 (3.1%) and its function was impaired in n = 3 (1.3%) ($p \leq 0.0001$) (Table 3).

Shunt lesions were incidentally detected in n = 14 (6.2%) patients, among whom n = 13 (5.8%) had a patent foramen oval (PFO), and n = 1 (0.4%) had an atrial septal defect (ASD). This suggests a possible association of SCD with a rare congenital heart defect (Table 4).

Table 4
The frequency and percentage of shunt lesions:

Shunt Lesions	**Frequency (N)**	**Percentage (%)**
No	211	93.8
PFO	13	5.8
ASD	1	0.4
Total	225	100.0
Key words: **PFO** = patent foramen oval, **ASD** = atrio septal defect.		

Table 5 presents an analysis of the association of certain variables in relation to the frequency of hospitalizations. Fisher's exact test showed no significant correlation between the frequency of hospitalizations and specific valve lesions such as AS, AR, MS, and PS. Although n = 33 TR cases required three or fewer hospitalizations and n = 12 cases required more than three hospitalizations per year, the Chi-square test showed that the results were statistically insignificant. In addition, MR, PR, right atrial (RA) size, left atrial (LA) size, LVH, RV size and function, and PHTN also had a statistically insignificant correlation with the incidence of hospitalization for SCD (Table 5).

Table 5
Valves and ventricular in hydroxyurea use in relation to the frequency of admission.

Independent Factors	**Admission Frequency**		**P-value**
	3 times or Less (N = 183)	**More than three Times (N = 42)**	
	N (%)	N (%)	
LV_DF	11 (6.0)	3 (7.1)	0.73 [a]
RV Size	4 (2.2)	3 (7.1)	0.12 [a]
RV Function	3 (1.6)	0	1.000[a]
AS	2 (1.1)	0	1.000 [a]
AR	6 (3.3)	1 (2.4)	1.000 [a]
MS	2 (1.1)	0	1.000 [a]
MR	13 (7.1)	4 (9.5)	0.53 [a]
TR	33 (18)	12 (28.6)	0.14 []
PS	1 (0.5)	0	1.000 [a]
PR	3 (1.6)	2 (4.8)	0.24 [a]
RA size	1 (0.5)	2 (4.8)	0.09 [a]
LA Size	3 (1.6)	1 (2.4)	0.57 [a]
PHTN	8 (4.4)	5 (11.9)	0.07 []
LVH	3 (1.6)	1 (2.4)	0.57 [a]
Hydroxyurea	92 (50.3)	1- (81)	0.000 []*

Key words: AS = aortic stenosis, **AR** = aortic regurgitation, **MS**=mitral stenosis, **MR** = mitral regurgitation, **TS** =tricuspid stenosis, **TR** = tricuspid regurgitation, **PS**= pulmonary stenosis, **PR**=pulmonary regurgitation, **PHTN**= pulmonary hypertension. **LVH**=left ventricular hypertrophy, **RV**= right ventricular, **RA**=right atrium, **LA**= left atrium, **LV_DF**= left ventricular disfunction.

* Significant at 95%. [a] By Fisher Exact test. [] By Chi square test.

Hydroxyurea use was observed in n = 92 (50.3%) patients with SCD who required hospitalization three times or less and in n = 34 (81%) who required hospitalization more than three times per year ($p \leq 0.0001$). In addition, in patients with TR hydroxyurea was used in n = 32 (25.4%) patients and was not used in n = 13 (13.1%) ($p \leq 0.03$) (Table 6). PHTN was found in n = 10 (7.9%) patients receiving hydroxyurea and in n = 3 (3.0%) SCDs who did not, with no statistical significance. None of the other diseased valves or ventricles were significantly associated with hydroxyurea use (Table 6). The percentage association between hydroxyurea use and valvular heart disease is presented in Fig. 1.

Table 6
Association of valves, ventricular and atrium size and/or function with using hydroxyurea medication.

Independent Factors	**Hydroxyurea**		**P-value**
	Yes	**No**	
	(N = 126)	**(N = 98)**	
	N (%)	N (%)	
LV_DF	9 (7.1)	5 (5.1)	0.58 □
RV Size	3 (2.4)	4 (4)	0.70 ª
RV Function	2 (1.6)	1 (1)	1.000 ª
AS	2 (1.6)	0	0.51 ª
AR	3 (2.4)	4 (4.0)	0.70 ª
MS	2 (1.6)	0	0.51 ª
MR	8 (6.3)	9 (9.1)	0.46 ª
TR	32 (25.4)	13 (13.1)	0.03* □
PS	1 (0.8)	0	1.000 ª
PR	2 (1.6)	3 (3.0)	0.66 ª
RA size	3 (2.4)	0	0.26 ª
LA Size	4 (3.2)	0	0.13 ª
PHTN	10 (7.9)	3 (3.0)	0.15 ª
LVH	4 (3.2)	0	0.13 ª
Key words: AS = aortic stenosis, **AR** = aortic regurgitation, **MS**=mitral stenosis, **MR** = mitral regurgitation, **TS** =tricuspid stenosis, **TR** = tricuspid regurgitation, **PS**= pulmonary stenosis, **PR**=pulmonary regurgitation, **PHTN**= pulmonary hypertension. **LVH**=left ventricular hypertrophy, **RV**= right ventricular, **RA**=right atrium, **LA**= left atrium, **LV_DF**= left ventricular disfunction.			
* Significant at 95%. ª By Fisher Exact test. □ By Chi square test			

Finally, the complete blood count (CBC), hemoglobin electrophoresis, and BMI data are shown in Table 7. The mean BMI was 22.058 (SD 4.95696), the highest BMI was 41, and the lowest BMI was 13.30. This reflects the fact that there is a wide variation in BMI among SCD patients without standard BMI in such a population. The mean WBC was 9.3442 (SD 3.75703) and the mean platelet was 398.747 (SD 194.8044). The minimum HGB was 5.80 g/dL and the maximum was 13.9 g/dL with a mean of 9.5898 (SD 1.28268) (Table 7).

Table 7
Hematological laboratory values and BMI.

Parameters	N	Minimum	Maximum	Mean	Std. Deviation
BMI	225	13.30	41.00	22.0584	4.95696
WT	225	4.4	111.0	55.820	14.0005
HT	225	138.0	196.0	159.533	8.2561
WBC	225	3.06	31.10	9.3442	3.75703
PLT	225	76.0	1563.0	398.747	194.8044
HGB	225	5.80	13.90	9.5898	1.28268
HBS	225	11.6	88.7	64.886	16.8621
HBA	225	2.2	85.0	20.897	18.7658
HBA2	225	0.2	18.2	2.893	1.8523
HBF	225	0.0	35.5	10.928	7.5186

Discussion

This study investigated the prevalence of echocardiographic parameters in patients with SCD at a single healthcare facility in the Eastern Province of Saudi Arabia. Since cardiac manifestations have a significant impact on morbidity and mortality in patients with SCD, it is critical to diagnose potential cardiac problems early in Saudi Arabia, where SCD rates are rapidly increasing. Thus, to achieve the aim of the study, four main valves were studied: aortic, mitral, tricuspid, and pulmonary valves, with a description of the abnormality (stenosis, regurgitation, or normal) and the degree of abnormality, if present (mild, moderate, severe).

It was found that out of n = 225 patients, 20% had tricuspid regurgitation (TR), among which 82.2% were mild and 17.8% were moderate ($p \leq 0.0001$). Previous data in the literature have shown that elevated tricuspid regurgitant velocity (≥ 2.5 m/s) occurs in approximately 30% of adults with SCD and is an independent risk factor for death (20–23). However, the exact mechanism of the role of tricuspid regurgitant velocity and how disease-modifying therapies (DMTs) affect this biomarker are not fully understood and are the subject of ongoing research. In addition, tricuspid regurgitant velocity measured by echocardiography is an alternative marker for pulmonary hypertension. This study showed that pulmonary hypertension was observed in 5.7%, echoing the previous hypothesis of an association of increased tricuspid regurgitation velocity with pulmonary hypertension in patients with SCD in Saudi Arabia (22–24). The second most common valvular lesion found in this study was mitral regurgitation (MR) at 7.5% ($p \leq 0.0001$). This pattern is consistent with evidence showing that sickle cell disease appears to be associated with a spectrum of elastic tissue abnormalities, a feature that may predispose to mitral valve prolapse. However, it has also been suggested that the association of mitral valve

prolapse and sickle cell disease cannot be explained solely based on left ventricular size, systolic function, ischemic left ventricular or papillary muscle dysfunction, or chronic anemia. Thus, the association found in this study adds to the existing knowledge of mitral regurgitation and SCD but remains the subject of future case reports that may possibly show a definitive association (25–27).

Finally, although less common, still significant, aortic regurgitation (3.1%) and pulmonary regurgitation (2.2%) were found in patients with SCD in the current study ($p \leq 0.0001$), which is in line with international data (28–30).

It is well known that SCD is characterized by chronic hemolytic anemia leading to organ damage including atrial septal defects (ASDs) which in the absence of additional pathology lead to left-to-right shunt (31–33). Shunt lesions include a wide range of anatomical abnormalities leading to abnormal blood flow between cardiac chambers and great vessels. In this study, shunt lesions were incidentally discovered in n = 14 (6.2%) patients. Since intracardiac shunts are among the most common cardiac lesions observed in adult patients, future studies are recommended to understand the underlying association in SCD. This will allow for improved shunt management, ranging from simple clinical observation, medical therapy, and lifestyle modification to surgical intervention (32–34).

Analysis of the association between hydroxyurea use and valvular or ventricular diseases revealed no significant association except for tricuspid regurgitation with and without hydroxyurea. Although hydroxyurea is an available drug that reduces vaso-occlusive crises (VOC) and transfusion requirements in SCD, its effectiveness in preventing chronic organ damage is a subject of ongoing research (35–37). The most recent systematic review and meta-analysis by Khargekar et al. (2024) showed that tricuspid regurgitation was significantly reduced after hydroxyurea therapy with a mean dose of 22.66 mg/kg/day, and the mean HbF level after hydroxyurea therapy was 18.08%, suggesting that hydroxyurea therapy was beneficial in preventing cardiac dysfunction in patients with SCD (35). In addition, an earlier study by Dhar et al. (2021) on longitudinal analysis of cardiac events in children with SCD and the effect of hydroxyurea therapy found that although the association between TR and duration of HU treatment was not statistically significant, the prevalence of elevated TR readings decreased from 37% at baseline to 11% at the last visit (36). On the other hand, although hydroxyurea may have a positive effect on TR, the researchers suggest that its role in stroke prevention is inconclusive and requires further evidence. In addition, Khargekar et al. (2024) suggest that the beneficial effects of hydroxyurea on the liver, retina, pulmonary dysfunction, and avascular necrosis of the hip need to be further studied.

Lastly, in addition to echocardiographic parameters, other health conditions such as obesity, rheumatological diseases, hypertension, dyslipidemia, chronic kidney disease (CKD), diabetes mellitus (DM), bronchial asthma (BA), and hypothyroidism were also found in this study sample. These patterns support the existing evidence that SCD is a multi-organ disease of the blood and blood vessels with direct and indirect effects on the cardiovascular system, central nervous system, pulmonary complications, endocrine system, hematopoietic system, etc. (38–40) When considering endocrine complications, weight gain, metabolic syndrome, and obesity are increasingly recognized as

comorbidities in the SCD population, especially in individuals with compound heterozygous SC/SB+ genotypes. Regarding the hematopoietic system, there is a large body of evidence that links the severity of hemolysis with severe complications, including pulmonary hypertension and chronic kidney disease (CKD). Regarding pulmonary complications, this study is consistent with earlier data identifying patients with asthma, as asthma and airway hyperreactivity are significant comorbidities in SCD, particularly in children, and are associated with worse disease outcomes (38–40).

This study has thus confirmed that the complex pathophysiology of SCD is the subject of ongoing research and its treatment remains suboptimal, further research is needed to sufficiently understand the interactions between the pathophysiology of SCD, other health conditions, individual variability, pain perception, and SCD treatment. Finally, given the prevalence of SCD and cardiovascular disease in Saudi Arabia, a larger national study is needed to better understand the cardiac manifestations of SCD.

Limitation:

Several limitations were identified for this study. First, as a retrospective study, medical informatics can only provide a limited amount of data. The second limitation is that, as a military institution, the medical facility where the data were collected has access to patients with SCD who are only military personnel or their family members. Third, this is a single-center study with a small sample size. It is recommended that future studies be multicenter to confirm or refute these findings and generate new hypotheses.

Conclusion

The current study represents a significant cardiovascular finding in the SCD population through echocardiographic parameters. The results illustrate the importance of early detection of cardiac disease, leading to the recommendation of echo screening in patients with SCD. Promoting better screening of valvular and bypass lesions in young people reduces the likelihood of missing cardiac events between childhood and adulthood. Supportive guidelines are also needed to ensure adherence to a strategic checklist for transition between pediatric and adult SCD services. This study has thus confirmed that the complex pathophysiology of SCD is the subject of ongoing research and its treatment remains suboptimal, further research is needed to sufficiently understand the interactions between the pathophysiology of SCD, other health conditions, individual variability, pain perception, and SCD treatment.

Declarations

Acknowledgement:

Non to Acknowledge.

Ethics approval:

The study was conducted following ethical approval from the Eastern Province Armed Forces Hospital Institutional Review Board (AFTER-IRB-2024-036, August 26, 2024).

Financial Disclosure or Funding :

None to declare.

Informed Consent:

The consent was not required in a retrospective study with no human tissue use and no laboratory extraction were done for the sake of the study. The research was reviewed by local ethical and research . committee and IRB certificate provided with no consent requirement

Clinical Trial

Not applicable.

Data availability:

Data will be made available on reasonable request to the corresponded author.

Author Contributions:

All authors contributed equally to this research and manuscript development. R. Y. A and M.I.A: proposal of the study, ethical approval process and manuscript writing; R.I.A, and M. A.A, and A.F. A., and A.S.A: data collection; Z.J.A: statistic and data analysis; N.S, and M.F.A and N.B.E: writing and reviewing the results; F.S.A, and S.C., and A.W: critical review and editing and reviewing.

Conflict of Interest:

There are no conflicts of interest regarding the publication of this paper.

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Figures

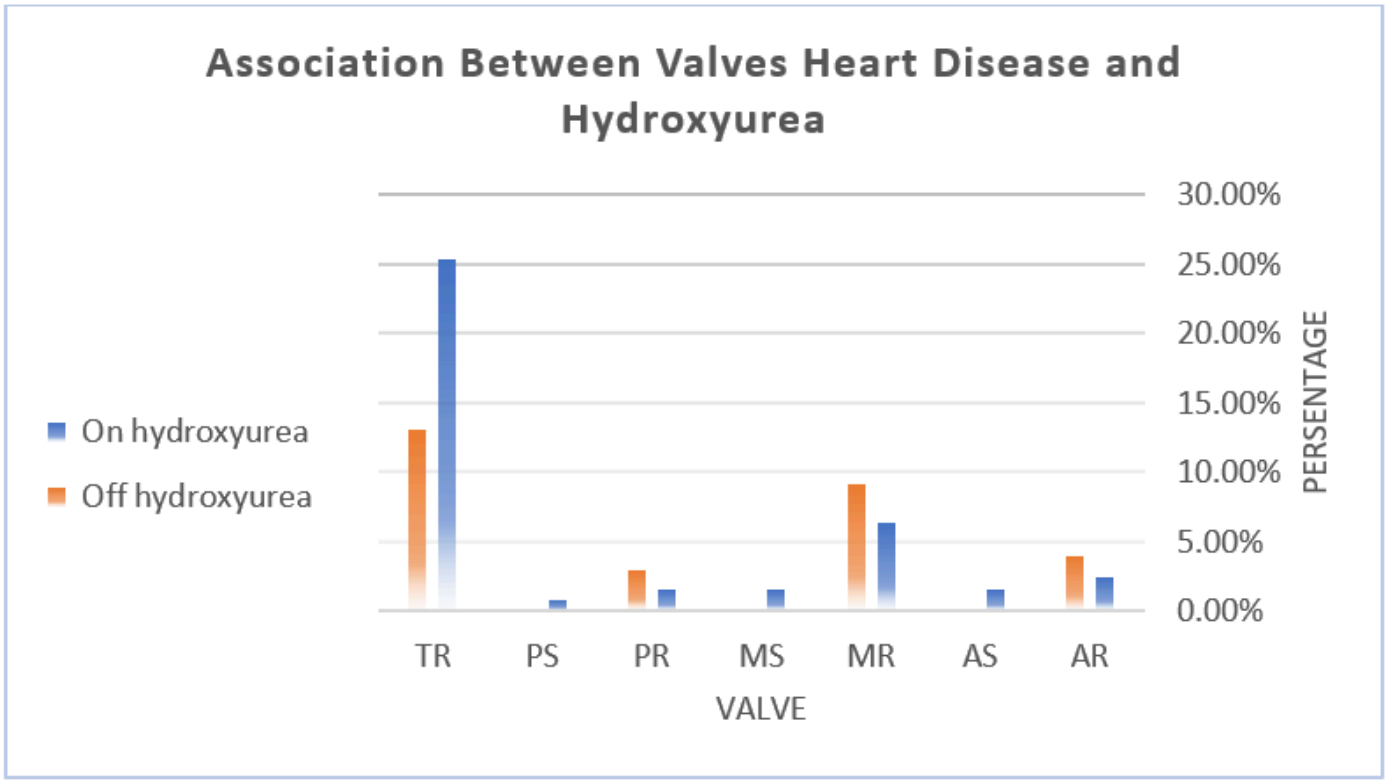


Figure 1

Association between valves heart disease and hydroxyurea use in SCD.