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ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2025;14(1):55-60

Cardiomyopathy and elevated troponin in sickle cell disease

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Received 17 November 2024; Accepted 31 December 2024
Available online 28 February 2025 with doi: 10.5455/medscience.2024.11.146

Abstract

To highlight troponin elevation associated with non-coronary causes during hemolytic crises in patients with sickle cell disease (SCD), examine the impact of these crises on cardiac function, and determine the prevalence of cardiomyopathy and valvular abnormalities during stable periods. This retrospective study included 41 patients with SCD who presented to the emergency department with hemolytic crises between May 18, 2023, and July 30, 2024. Transthoracic echocardiography (TTE) was performed during the emergency visit and repeated at the 1-month outpatient follow-up. TTE assessments included left ventricular ejection fraction (EF), the presence of dilated cardiomyopathy (DCM), valvular pathologies, and cardiac chamber dimensions. DCM was defined as an EF <40% with left ventricular dilatation. Blood tests during hemolytic crises measured troponin T, creatine kinase-MB, and other laboratory markers. The median age of the patients was 32 years (range: 18–68), and 92.7% had positive troponin T levels. Tricuspid regurgitation was detected in 45% of patients, mitral regurgitation in 30%, aortic regurgitation in 2.5%, and left ventricular dilatation in 47.5%. DCM was identified in 6 patients (15%). Coronary computed tomography angiography performed in patients with DCM revealed no coronary obstruction. Among 5 patients with chest pain, invasive coronary angiography showed no evidence of coronary artery disease. Pulmonary hypertension was diagnosed in 61.1% of patients with tricuspid regurgitation. Cardiac changes observed during hemolytic crises in SCD patients are likely due to chronic processes. The development of left ventricular dilatation and DCM in this population necessitates investigation of non-SCD-related causes. Troponin positivity and valvular pathologies underscore the need for close monitoring and comprehensive management in these patients.

Keywords: Sickle cell disease, cardiovascular complications, troponin, dilated cardiomyopathy

Introduction

Sickle cell disease (SCD) is a hemoglobinopathy that affects multiple systems either acutely or chronically. Even among individuals with the same phenotype, the clinical course can vary significantly [1]. It is a disease caused by the substitution of glutamic acid with valine at the 6th position of the beta-globin chain, resulting in the formation of Hemoglobin S. This condition follows an autosomal recessive inheritance pattern [2]. The carrier rate ranges from 0.3% to 0.6% across Türkiye, while in some areas of the Cukurova region, it can reach up to 44% [3]. The most prominent clinical manifestation of SCD is acute, vaso-occlusive, and painful episodes. These events are the most common reasons for emergency treatment and hospitalization [4]. Vaso-occlusive crisis occurs when sickled erythrocytes block blood flow to the point where tissues are deprived of oxygen. This blockage leads to the development of inflammatory events throughout the body [5]. In SCD, Hemoglobin polymerization causes changes in the integrity of erythrocytes, leading to both extravascular and intravascular

CITATION
Faideci EM, Guzel S, Oztekin T, et al. Cardiomyopathy and elevated troponin in sickle cell disease. Med Science. 2025;14(1):55-60.

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DOI: 10.5455/medscience.2024.11.146

hemolysis. Chronic vaso-occlusion and hemolysis result in damage to multiple organ systems over the years [6]. Advancements in treatment methods have led to a reduction in infection rates and an extension of life expectancy. However, the incidence of cardiovascular complications has increased in parallel with the longer life expectancy [7]. Particularly, pulmonary hypertension (PHT) and left ventricular (LV) diastolic dysfunction are commonly observed conditions [8]. LV dilatation and diastolic dysfunction due to chronic anemia are common findings [9]. During hemolytic crises, chest pain and elevated troponin levels are frequently observed. Excluding myocardial infarction (MI) can be quite challenging [10]. In our study, we investigated the frequency of elevated troponin levels during hemolytic crises and the prevalence of cardiomyopathy and valvular pathologies during stable periods in patients diagnosed with SCD.

Differentiation between acute and chronic cardiac alterations during hemolytic crises presents significant diagnostic challenges. Furthermore, the identification of non-coronary etiologies underlying troponin elevation remains complex. The primary objective of this study is to delineate the prevalence of cardiomyopathy and other cardiac abnormalities through transthoracic echocardiography (TTE) in individuals with SCD. Additionally, it seeks to determine whether these abnormalities represent acute or chronic changes. Finally, the study aims to underscore the occurrence of troponin elevation attributable to non-coronary etiologies during hemolytic crises.

Material and Methods

Study Population

This retrospective study analyzed 41 patients with a confirmed prior diagnosis of SCD who presented to the emergency department due to hemolytic crisis between May 18, 2023, and July 30, 2024. The SCD diagnosis was verified through medical records and patient declarations and was established before the hemolytic crisis presentation. Hemolytic crisis was defined as a condition characterized by acute hemoglobin drop, reticulocytosis, elevated bilirubin, and LDH levels, accompanied by clinical signs such as jaundice, fatigue, and pallor. The diagnosis of hemolytic crisis was made by internal medicine or hematology specialists based on these criteria [11]. Patients were treated with the standard approach for hemolytic crisis management, including fluid replacement, pain management, and blood transfusion when necessary [12].

Patients underwent symptom evaluation and TTE in the emergency department, and an outpatient clinic follow-up was scheduled for the first month. During the follow-up, symptoms were reassessed, and TTE was repeated. This study does not aim to assess treatment processes or responses. Instead, it focuses on determining whether cardiomyopathy and other findings are associated with an acute or chronic process, as well as identifying and characterizing the frequency and nature of these abnormalities. Ejection fraction (EF) was calculated using the modified Simpson method [13].

Mitral, aortic, and tricuspid valve regurgitations were evaluated to determine the function, anatomical structure, and severity of the valvular insufficiency. The severity of regurgitation was classified based on the size, width, and intensity of the regurgitant jet into three categories: mild, moderate, and severe. All three degrees were considered as regurgitation, and thus were defined as mitral regurgitation (MR), tricuspid regurgitation (TR), and aortic regurgitation (AR). PHT was diagnosed if the tricuspid regurgitation jet velocity (TRJV) measured by Doppler was ≥2.5 m/s. The normal ranges for LV end-diastolic diameter were considered to be 42-58 mm for men and 38-52 mm for women. The left atrial diameter was generally considered normal between 30-40 mm, and the aortic root diameter was normal between 20-37 mm. Measurements exceeding these ranges were considered indicative of dilation of the respective structures [14]. Dilated cardiomyopathy (DCM) was defined as an LV end-diastolic diameter exceeding 58 mm in men and 52 mm in women, with an EF below 40% [15].

The presence of pleural effusion and cardiomegaly was assessed using thoracic computed tomography (CT). Pleural effusion was identified by the accumulation of free fluid in the pleural space on thoracic CT images. Cardiomegaly was evaluated based on heart and chest width measurements, with a diagnosis made when the cardiothoracic ratio exceeded 50% (0.5).

Blood tests conducted during hemolytic crises in all patients included measurements of troponin T, creatine kinase-MB, lactate dehydrogenase, renal function markers, complete blood count, and C-reactive protein levels. A troponin T level exceeding 14 ng/L was considered indicative of troponin positivity.

The study was conducted in compliance with the Helsinki Declaration and approved by the Mustafa Kemal University Ethics Committee (Approval No: 08/06/2024-46).

Statistical Analysis

The data were analyzed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were calculated for TTE and laboratory findings. The normality of continuous variables was assessed using the Shapiro-Wilk test. Variables with a normal distribution were summarized as mean and standard deviation, whereas non-normally distributed variables were presented as median, minimum, and maximum values. Categorical variables were expressed as frequencies and percentages.

Results

This retrospective study included 41 patients with SCD who presented to the emergency department during a hemolytic crisis. The median age of the patients was 32 years (range: 18–68), and 22 were male. Laboratory analyses conducted during

DOI: 10.5455/medscience.2024.11.146

hemolytic crises in 41 patients revealed that 38 (92.7%) had positive troponin T levels (Table 1). ST segment elevation was not observed in the electrocardiograms (ECG). Non-specific chronic ST depressions were present in 7 patients (17.1%). Sinus tachycardia was identified as a common finding in 33 patients (80.5%). Invasive coronary angiography (CAG) was performed in 5 patients with acute myocardial infarction-like symptoms, including typical retrosternal pressure-type chest pain and positive troponin levels. The CAG findings revealed no evidence of coronary artery atherosclerosis, ruling out ischemic coronary involvement. The remaining 36 patients without chest pain were evaluated as having type 2 myocardial infarction due to supply-demand imbalance, and CAG was not performed in these patients. None of the patients included in the study had diabetes mellitus, hypertension, a history of coronary artery disease, or hyperlipidemia. Thoracic CT revealed pleural effusion and cardiomegaly in 26 patients (63.4%). During hemolytic crises, positive blood cultures were identified in 34 patients (82.9%), with upper respiratory tract infections being the most common, followed by urinary tract infections. 40 patients were reevaluated in the stable period one month after the crisis. One patient had an in-hospital mortality and was not included in the 1-month follow-up.

Within one month after hospital discharge, 21 patients (52.5%) experienced dyspnea, and 8 patients (20%) reported palpitations. Dyspnea was attributed to heart failure, while palpitations were associated with anemia. The remaining 12 patients reported no symptoms.

Routine TTE was performed at the 1-month follow-up, and no differences were observed compared to the TTE performed during the emergency visit for the hemolytic crisis. TTE evaluations revealed LV dilatation in 19 patients. Among these, 6 had an EF of <40% and were diagnosed with DCM. The median EF of 40 patients was determined to be 55% (range: 20–60). No valve stenosis or severe valve insufficiency was detected. MR was detected in 30% (12/40) of the patients, AR in 2.5% (1/40) and TR in 45% (18/40). All cases of MR and TR were secondary valve pathologies associated with annular dilatation due to the enlargement of cardiac chambers. In the patient with AR, a concomitant bicuspid aortic valve was present. Grade 1 or higher diastolic dysfunction was present in 92.5% (37/40) of the patients and was identified as a common finding. Of the 18 patients with TR, 11 were diagnosed with PHT, indicating a potential association between TR and PHT (Table 2). No septal defects causing intracardiac shunting were observed in these patients. Pulmonary CT angiography was performed to rule out pulmonary embolism, and no embolic events were detected. In 6 patients diagnosed with DCM, coronary CT angiography was performed to investigate an ischemic origin, and no coronary obstruction was detected. Invasive CAG performed during the hemolytic crisis in five patients showed no evidence of DCM.

Table 1. Laboratory values during hemolytic crises

Test name (unit)	Median (Min-Max)/ Mean (standard deviation)
WBC (x10^9/L)	16.42 (2.39-23.13)
RBC (x10^{12}/L)	2.83 (1.32-5.01)
HGB (g/dL)	8.20 (4.99-9.12)
HCT (%)	23.00 (13.20-27.40)
MCV (fL)	85.70 (32.40-107.80)
MCH (pg)	28.63±6.93
MCHC (g/dL)	34.87±1.82
PLT (x10^9/L)	368.97 (12.30-530.23)
RDW-SD (fL)	60.91±22.89
RDW-CV (%)	13.92±7.06
NEUT (x10^9/L)	19.10 (6.10-66.40)
NEUT%	17.75±9.12
LYMPH (x10^9/L)	19.16±20.12
LYMPH%	0.55 (0.11-101.00)
MONO (x10^9/L)	11.87 (2.28-35.00)
MONO%	58.00 (0.03-80.70)
EOS (x10^9/L)	3.13 (0.01-45.10)
EOS%	15.70 (0.01-92.90)
BASO (x10^9/L)	1.64 (0.01-49.20)
BASO%	8.40 (0.01-35.50)
NRBC (x10^9/L)	0.20 (0.01-2.65)
NRBC%	0.60 (0.01-41.77)
BUN (mg/dL)	3.20 (0.10-45.40)
Creatinine (mg/dL)	1.92±1.63
Troponin T (ng/L)	86.71 (4.13-3685)
CK-MB (ng/mL)	46.50 (1.80-370.32)
LDH (U/L)	258.08 (46.44-1997)
CRP (mg/L)	82.50 (23.21-380.43)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, BASO: basophil count, BASO%: basophil percentage, BUN: blood urea nitrogen, CK-MB: creatine kinase-MB, CRP: C-reactive protein, EOS: eosinophil count, EOS%: eosinophil percentage, HCT: hematocrit, HGB: hemoglobin, LDH: lactate dehydrogenase, LYMPH: lymphocyte count, LYMPH%: lymphocyte percentage, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, MCV: mean corpuscular volume, MONO: monocyte count, MONO%: monocyte percentage, NEUT: neutrophil count, NEUT%: neutrophil percentage, NRBC: nucleated red blood cell count, NRBC%: nucleated red blood cell percentage, PLT: platelet count, RBC: red blood cell count, RDW-CV: red cell distribution width-coefficient of variation, RDW-SD: red cell distribution width-standard deviation, WBC: white blood cell count

DOI: 10.5455/medscience.2024.11.146

Table 2. Transthoracic echocardiography findings

Parameter	Median (Min-Max)
Left ventricular end-diastolic diameter (cm)	5.4 (4.1-7.2)
Left atrium diameter (cm)	3.4 (3.1-5.1)
Aortic root diameter (cm)	3.8 (3.2-4.4)
Ejection fraction (%)	35 (20-60)
Pulmonary artery pressure (mmHg)	25 (20-55)
	n, (%)
Mitral regurgitation	12/40, (40)
Aortic regurgitation	1/40, (2.5)
Tricuspid regurgitation	18/40, (45.00)
Left ventricular dilatation	19/40, (47.5)
Left atrial dilatation	6/40, (15.00)
Dilated cardiomyopathy	6/40, (15.00)

Discussion

In patients with SCD, TTE screening for PHT is recommended only for symptomatic individuals or those at risk of PHT. Routine TTE screening is not recommended in asymptomatic individuals due to treatment uncertainties, the lack of prognostic significance of the screening, and insufficient clinical studies. The recommendation level for screening diastolic functions in asymptomatic individuals is also uncertain [16]. TTE and clinical evaluations should be conducted or repeated during the stable period to facilitate differentiation between acute and chronic findings [17]. However, findings obtained during the acute phase cannot be definitively distinguished. In the presence of tricuspid regurgitation jet velocity (TRJV) ≥2.5 m/s, right heart catheterization is recommended only if high-risk findings, such as reduced six-minute walking distance or elevated NT-BNP, are present, while TRJV≥2.9 m/s or clinical findings suggestive of PHT necessitate catheterization [18].

In our study, the hemolytic crisis period cannot be considered asymptomatic. During this period, it is challenging to distinguish the underlying cause of symptoms such as elevated cardiac enzymes, palpitations, shortness of breath, and chest pain. Therefore, we identified the one-month follow-up as a reasonable time frame for stable-period evaluation in routine practice. Our study focused on the prevalence of abnormal TTE findings and elevated cardiac enzymes. As observed in the literature, treatment strategies in the presence of abnormal TTE findings remain uncertain. Ultimately, we concluded that TTE findings were chronic, whereas elevated cardiac enzymes were secondary to hemolytic crises.

Our findings align with reports in the literature, demonstrating that mitral annular dilatation leads to functional MR [19]. TR and PHT are common findings in SCD. Chronic hemolysis reduces nitric oxide bioavailability, contributing to secondary PHT [20]. Secondary PHT is characterized by lower pulmonary artery pressure and tricuspid velocity but higher cardiac output compared to primary PHT [21]. TR and PHT are associated with high mortality, and treatment approaches remain controversial [22]. Additionally, iron overload resulting from frequent blood transfusions contributes to cardiac complications such as left ventricular dilation and myocardial dysfunction [9]. These literature findings suggest that hemolytic crises and treatment-related factors may increase the risk of cardiomyopathy. Our study highlights this relationship and contributes to the existing literature on this important topic. Consequently, the risk of cardiomyopathy is associated with multifactorial causes. Further clinical studies are needed in this area. In our study, no cases of thromboembolism were observed, and PHT cases were attributed to vasculopathy and chronic hemolysis. However, the absence of right heart catheterization is a limitation of our study.

Diastolic dysfunction is a common finding in SCD and is recognized as an independent risk factor for mortality However, the relationship between systolic dysfunction and SCD remains controversial in the literature. Batra et al. reported that systolic function was normal [23]. In contrast, Lamers et al. observed a reduction in systolic function [24]. Differences in EF measurement methods may have contributed to this discrepancy. A meta-analysis demonstrated that systolic function in SCD patients was comparable to that of healthy individuals; however, cohort studies reported an incidence of systolic dysfunction ranging from 0% to 2.5% [25]. In our study, it is believed that factors other than SCD, which could not be identified, may have contributed to the diagnosis of DCM in some patients.

The development of MI in SCD has been reported in the literature. During acute crises, ECG abnormalities suggestive of MI and elevated troponin levels have been documented [26]. However, CAG findings in these cases have consistently shown normal coronary arteries [27]. ECG abnormalities and elevated troponin levels are thought to be associated with hemodynamic disturbances, sepsis, demand-supply imbalance due to low hemoglobin levels, acute and chronic microvascular occlusion, and systemic vasculopathy [28]. During crises, acute chest syndrome, which carries a high mortality rate, may develop and is characterized by chest pain, troponin positivity, and non-specific ECG changes. Excluding Type 1 MI caused by coronary occlusion can be challenging. Coronary occlusion is often overlooked in SCD patients due to their young age, absence of risk factors, and the low diagnostic value of non-specific ECG changes. In our study, troponin elevation was also a common finding. Coronary occlusion could not be ruled out in patients with chest pain, and these patients underwent CAG. There is a need for randomized clinical trials and guideline recommendations in this area. The lack of adequate guidelines to confirm or exclude coronary occlusion during acute crises creates a significant gap in the diagnosis and management of these patients.

DOI: 10.5455/medscience.2024.11.146

Conclusion

Our study highlights significant evidence gaps in SCD and emphasizes the need for a multidisciplinary approach. Further research is particularly required on the long-term management of cardiomyopathy and the treatment of troponin elevation.

Limitations

This study has several limitations. First, its retrospective design restricts the establishment of a causal relationship between hemolytic crises and the observed findings. The small sample size limits the generalizability of the results. Additionally, the absence of right heart catheterization to confirm pulmonary hypertension (PHT) in patients with elevated tricuspid regurgitation (TR) velocities represents a significant limitation. Coronary computed tomography (CT) angiography was used to rule out ischemic coronary artery disease in patients diagnosed with dilated cardiomyopathy (DCM); however, this method may not provide the diagnostic accuracy of invasive coronary angiography. Furthermore, the etiology of systolic dysfunction remains unclear, as comprehensive evaluations such as genetic analyses or advanced imaging techniques were not performed. The absence of advanced methods such as tissue Doppler imaging or strain analysis to evaluate diastolic function is another limitation; these approaches could have provided a more detailed assessment of cardiac dysfunction. The troponin T assay used in this study was not a high-sensitivity method, which might have led to an underestimation of the prevalence of minor myocardial injuries. Additionally, the frequency of hemolytic crises, the treatments applied, and the inability to establish a cause-effect relationship between these factors and cardiac findings represent limitations. The lack of advanced analyses to identify which patient groups are at a higher risk of developing cardiomyopathy is another significant limitation. Prospective studies with larger sample sizes and advanced diagnostic methods are needed to validate and expand upon these findings.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
The study was conducted in compliance with the Helsinki Declaration and approved by the Mustafa Kemal University Ethics Committee (Approval No: 08/06/2024-46).

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DOI: 10.5455/medscience.2024.11.146

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