Original Article

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Quick Response Code:

Website: https://journals.lww.com/ijhm

DOI: 10.4103/ijh.ijh_105_24

The risk of pulmonary hypertension in sickle cell disease in relation to the disease severity

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Abstract:

BACKGROUND: Sickle cell disease (SCD) is a heterogeneous disease which can induce fatal complications, especially cardiovascular complications. The development of a classification system to classify patients with SCD helps to identify those with high risk for further preventive measures and follow-up.

OBJECTIVES: This study evaluates the relationship between SCD severity and the risk of pulmonary hypertension (PH) development aiming to identify the group of SCD patients who are at high risk of PH development for further preventive measures.

PATIENTS AND METHODS: Retrospective analysis for SCD patients retrieved from records from 2009 to 2021. Five hundred and seventeen patients were selected; all patients were assessed for the risk of PH by following the guidelines of the European Society of Respiratory and European Society of Cardiology using echocardiography. Patients were then classified according to the Severity Classification System for SCD into three classes from the least severe to the most severe. This study was held at King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

RESULTS: Among participants, 93% have a low risk of PH. Fifty-eight (11.2%) patients have a severe SCD, and 458 (88.5%) patients have mild SCD. Twenty-nine (80.5%) of individuals with SCD who have a high or moderate risk of PH were found to have severe SCD (Class III).

CONCLUSION: SCD severity is strongly correlated with the risk of PH development. The severity classification system is easily applicable to identify those with a high risk of PH development to apply further preventive strategies.

Keywords:

Hemoglobinopathies, pulmonary hypertension, severity classification, sickle cell disease, vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is an inherited disease that affects the protein chain of the red blood cells, characterized by the substitution of the normal adult hemoglobin by hemoglobin S, causing distortion of the red blood cell and losing the flexibility of its membrane.[1-4] Under certain conditions, the distorted red blood cells will form a complex with the other circulating cells that subsequently becomes more adherent to the endothelium causing an occlusion of the blood vessels and decreasing the blood flow to the different vital organs, which will induce serious outcomes, such as pulmonary hypertension (PH).[5]

SCD is a heterogenous disease that has a broad range of disease severity, even with those SCD patients who have the same genotype.[6] The development of a widely accepted classification to characterize and classify SCD severity was a need to identify those with severe form of the disease and follow them up closely to

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Submission: 14-09-2024
Revised: 08-03-2025
Accepted: 14-03-2025
Published: 19-05-2025

How to cite this article: Bahashwan S. The risk of pulmonary hypertension in sickle cell disease in relation to the disease severity. Iraqi J Hematol 2025;14:123-6.

avoid serious complications that can be prevented by early detection.[7-10] A classification system has been developed which classify SCD patients into three categories according to the presence of certain clinical and pathological criteria. They were classified as Class I (least severe), Class II (moderate in severity), and Class III (most severe).[11]

PH is shown in multiple studies to be highly associated with adverse outcomes, especially in SCD patients.[12] The diagnosis of PH is confirmed by right heart catheterization, but this method has a lot of limitations that can ease the access to this diagnostic method for all suspected cases. Other acceptable noninvasive and less expensive methods can be used to screen and identify high-risk population, such as Doppler echocardiography (ECHO) and N-terminal pro-B-type natriuretic peptide.[13] Identification of the risk of PH development in SCD patient is crucial to monitor them up closely, to prevent complication and reduce associated morbidity and mortality.

In this study, we are evaluating the relationship between SCD severity and the risk of PH development aiming to identify the group of SCD patient who are at high risk of PH development for further preventive measures.

Patients and Methods

This study was conducted at a single center, using medical records to collect data in a retrospective manner. As the nature of this study was retrospective and noninterventional, ethical approval was obtained from the local ethical committee (Reference No 565-21), consent was not a requirement, and permission was given by the ethical committee to proceed without it. The collected data were anonymized and confidential in accordance with the Helsinki Declaration.

All included patients have a confirmed diagnosis at least by hemoglobin electrophoresis from 2009 to 2021. Exclusion criteria were either having sickle cell trait, abnormal hemoglobin other than hemoglobin S, having respiratory disorders like chronic obstructive pulmonary disease or interstitial lung disease, or younger than 18 years old. A total of 517 patients were included, all included patients' records were reviewed to assess and evaluate for two major points: SCD severity and risk of PH.

The severity assessment of SCD was done according to the Severity Classification System for SCD,[11] which evaluates and classifies SCD patients into three classes. The system defines patients as Class I (least severe disease) when they meet the following criteria: no organ damage, no chronic pain, having ≤4 vaso-occlusive crisis (VOC) that requires acute care visit in the last year. Patients with ≥5 VOC that requires acute care visit in the last year or having end-organ damage to one of the vital organs, such as kidney, bone, or heart, were considered as Class III. All other patients not meeting the criteria of Class I or III were classified as Class II.

Regarding the risk of PH, it was evaluated according to the guidelines of the European Society of Respiratory and the European Society of Cardiology.[14] The selected sickle cell patients were divided into three groups based on peak tricuspid valve regurgitation (TVR) measured in ECHO; low risk, when TVR is below or equal to 2.8, with no other signs of PH on ECHO. Moderate risk when peak TVR is between 2.9 and 3.4, with no other ECHO PH signs or peak TVR is ≤2.8, and other PH signs appear on ECHO. High risk was assigned to patients when peak TVR is between 2.9 and 3.4 in association with other PH signs on ECHO, or when peak TVR is >3.4.

Data were analyzed by IBM SPSS Statistics for Windows, Version 26.0 (IBM Corporation, Armonk, NY, USA) to test and assess for the relationship and association between different classes of severity to risk of PH development using the Chi-square test and multivariant logistic regression analysis. Statistically significant $P < 0.05$.

Results

A total of 517 patients with SCD were identified, and their records were reviewed. Demographic details are shown in Table 1.

Based on ECHO assessment to evaluate the risk of developing PH, 17 (3.9%) patients were identified to have high risk, and 19 (3.68%) patients were found to have intermediate risk for having PH.

Table 1: Patient demographics distribution (*n*=517)

Variables	n (%)
Demographics	517
Male	260 (50.3)
Female	257 (49.7)
Age (years), age±SD	35.5±9.3
Medical history	96
Preexisting cardiac condition	59 (11.4)
Chronic kidney disease	6 (1.2)
Liver cirrhosis	5 (1)
History of venous thromboembolism	26 (5)
PH risk	517
Low	481 (93)
Moderate	19 (3.7)
High	17 (3.3)
Severity of SCD	517
Class I	485 (88.5)
Class II	1 (0.19)
Class III	58 (11.2)

SD=Standard deviation, SCD=Sickle cell disease, PH=Pulmonary hypertension

When applying the system of severity classification, 58 (11.2%) patients have severe SCD (Class III), and 458 (88.5%) patients were classified as Class I, whereas only one patient was assigned to have a moderate SCD (Class II). Patients who were classified as Class II or Class II were on hydroxyurea.

Having high or intermediate risk of PH development was strongly correlated with the disease severity (Class III), 14 (82.35%) out of 17 patients, and 15 (78.9%) patients, in high-risk and intermediate-risk groups of PH development, respectively, were found to have Class III SCD with a spearman's rank correlation (rho) value of 0.866 (strong positive correlation), $P = 0.001$, and 95% confidence interval for both groups.

The distribution of patients according to the risk of PH in association with the disease severity is shown in Table 2.

Discussion

SCD is widely distributed inherited disorder,[15] manifested as a result of a mutation affecting the gene responsible for B globin synthesis, forming the unique long-branched polymers in the deoxygenated form.[16] The formation of these fragile and rigid polymers will lead to certain consequences and complications such as VOC, coagulopathy, and oxidative damage to different organs. These changes can explain the pathogenesis pf PH in SCD.[17] SCD is a widely variable disease in clinical manifestation and even in survival, which is usually difficult to explain and predict, especially cardiovascular complications.[18,19]

Individuals with SCD can develop many complications, whether in isolation, or combined with other complications.[20] Early prediction of these complications, and identification of individuals at high risk may prevent the progression of certain complications and improve morbidity and mortality. Following a validated model to assess the disease severity, individuals at risk for certain serious complications, such as PH, can be identified, and subsequently, outcome can be improved.[6]

PH is shown in multiple studies to be highly associated with adverse outcomes.[21] The risk of developing PH in individuals with SCD was shown to be significant in different studies.[22-25] Our study focused on evaluating the association between the severity of the disease to different risk groups for developing PH and showed a significant correlation between the severe form of SCD and individuals with moderate or high risk for developing PH. This result was expected as many studies highlighted the risk of having multiple complications in those individuals which was linked to the severity of the disease, but the risk of developing PH and its association with the disease severity was never studied as an individual risk factor.

Studying the correlation of SCD severity with this important cardiovascular complication in SCD individuals, which has an impact on their quality of life and even on survival, will help to identify individuals at high risk of developing PH to screen them and follow them up closely by frequent ECHO and cardiology follow-up, even in the absence of signs and symptoms as the risk of PH.[26] Early intervention by cardiologists in those with high risk will prevent progression and will have an impact on SCD patients' quality of life.

Table 2: Distribution of patients according to the risk of pulmonary hypertension in association with the disease severity (*n*=517)

Disease severity	Risk of PH		
	High risk	Intermediate risk	Low risk
Class I	2	4	452
Class II	1	0	0
Class III	14	15	29

PH=Pulmonary hypertension

Conclusion

Individuals with severe SCD (Class III) are at high risk of developing PH, which is a serious and life-threatening complication, that should be monitored and discovered in early stages to avoid consequences that can affect outcome and survival.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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