Research Paper

Prevalence and Correlation of Pulmonary Hypertension in Patients With Sickle Cell Disease: A Descriptive Study

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ABSTRACT

Background: One common outcome for people with chronic hemolytic disorders is the development of pulmonary hypertension (PHT). However, there is little knowledge about the correlation between vasculopathy, cardiopulmonary function, contributing variables, and the associated mortality in patients with sickle cell disease (SCD).

Objectives: The purpose of this investigation was to determine the prevalence of PHT among patients with sickle cell anemia in Bandar Abbas City during the years 2022 to 2023.

Methods: This research was a descriptive cross-sectional investigation carried out on individuals with sickle cell anemia in Bandar Abbas. The data underwent thorough assessment for reliability and validity using a researcher-developed checklist, which included input from respected professors. This checklist contains essential demographic data, including gender and age, as well as pertinent treatment information related to PHT, hemoglobin level, vascular occlusion crisis, high hematocrit level, α-thalassemia, hydroxyurea treatment, reduction of white blood cells, high creatinine level, genotype, and high ferritin level in affected individuals. Statistical analysis was performed using SPSS software, version 22.

Results: Participants had a mean age of 10.50±2.94 years. Among the 75 patients examined, 46.7% were female and 53.3% were male. The majority of the patients, specifically 58 individuals (77.3% of the subjects evaluated), did not exhibit PHT, whereas 17 individuals (22.7%) were found to have PHT. An analysis of platelet data revealed that individuals with PHT had lower platelet levels compared to those without PHT, and this disparity was statistically significant (P=0.04). There was also a significant correlation between PHT and α-thalassemia (P=0.01). In addition, there was no significant correlation between age, genotype, gender, hematocrit, white blood cell count, hemoglobin levels, creatinine levels, ferritin levels, usage of hydroxyurea medication, and the existence of PHT (P>0.05).

Conclusions: According to the study's findings, PHT was present in 22.7% of patients with SCD. PHT was significantly associated with α-thalassemia and platelet count. Additionally, the prevalence of the disease was higher in women than in men. Consequently, essential diagnostic and preventative treatments must be implemented for high-risk individuals, given the serious consequences of the disease and the elevated mortality risk among these patients.

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Introduction

Sickle cell disease (SCD) is an inherited disorder caused by an aberrant type of hemoglobin S (HbS), resulting from a single-point mutation in the *β-globin* gene [1, 2]. This condition is notably common in areas, including India, Sub-Saharan Africa, Saudi Arabia, and South America. Individuals affected by SCD inherit two copies of the *HbS* gene, leading to hemolytic anemia and complications such as acute chest syndrome and vaso-occlusive pain crises (VOC). Because HbS precipitates during deoxygenation, symptoms usually manifest within the first year of life, causing erythrocytes to assume a sickle shape. This deformation disrupts blood flow, leading to hemolysis and vaso-occlusive episodes [1-3]. SCD patients are susceptible to progressive vasculopathy, which is characterized by endothelial dysfunction, systemic issues, PHT, and structural alterations, such as smooth muscle remodeling and intimal proliferation in blood vessels [1].

PHT represents a serious and potentially fatal complication of SCD, impacting the pulmonary vessels and compromising the structure and function of the right ventricle. It is characterized by a resting mean pulmonary artery pressure of more than 25 mm Hg. Notwithstanding its clinical significance, there is a lack of clarity regarding the prevalence and risk factors of PHT in individuals with SCD, and differences have been noted between studies and groups [4, 5].

PHT in SCD is associated with a range of crippling consequences, such as a worse quality of life, decreased ability to exercise, trouble with day-to-day functioning, and noticeably lower survival rates [6]. Common clinical symptoms include fatigue, peripheral edema, dyspnea, and chest pain. During the physical examination, one might observe indicators of right ventricular dysfunction, including a pronounced second heart sound, evidence of right ventricular hypertrophy, right-sided fourth heart sound, and right parasternal heave. The findings provide valuable understanding into cardiovascular functional and structural changes, aiding in diagnosis and guiding targeted management strategies [2].

The diagnosis of PHT in SCD patients typically depends on invasive right cardiac catheterization, regarded as the gold standard for assessing pulmonary artery pressure. Noninvasive methods, especially Doppler echocardiography, are employed to evaluate right ventricular dimensions and performance while estimating pulmonary artery systolic pressure (PASP). As a valuable screening tool, Doppler echocardiography helps identify people susceptible to PHT, enabling additional assessment and action [7]. Acute complications of SCD, such as vaso-occlusive crises and acute chest syndrome, can exacerbate PHT, resulting in rapid clinical decline and potentially life-threatening consequences. Thus, early identification and prompt intervention in SCD patients with PHT are essential to enhance prognosis and optimize patient outcomes [8].

SCD is one of the most common hemoglobinopathies in Iran, particularly in the southern regions. It is associated with vascular occlusive crises, severe pain, and multisystem complications; thus, studying its complications is of significant importance. However, data on the prevalence, incidence, and associated factors of PHT in the Iranian population, especially among children and adolescents under 18 years of age, are limited. This study, utilizing echocardiography and analyzing data from hospitalized patients, aimed to determine the incidence of this complication and examine its association with demographic and treatment-related factors. Therefore, the study was conducted to investigate the incidence of PHT in patients with SCD in Bandar Abbas in 2022-2023. The findings of this research could play a crucial role in early diagnosis, effective therapeutic interventions, and the development of management strategies to improve patients' quality of life. Additionally, they can serve as a foundation for future studies on SCD in Iran.

Methods

Design and participants

This cross-sectional descriptive study was performed on individuals diagnosed with SCD who sought specialized and subspecialized care at clinics and were hospitalized in the wards of Bandar Abbas Children's Hospital during the years 2022 to 2023.

Eligibility and ineligibility criteria

Inclusion criteria

- Age below 18 years
- Referral to specialized and sub-specialized heart and blood clinics or admission to the Children's Hospital departments in Bandar Abbas City
- History of at least one episode of vascular occlusion crisis resulting in hospitalization

• Willingness to participate in the study

Exclusion criteria

• Non-native residents of the area

• Absence of prior hospitalization due to blood vessel obstruction

Sample selection

In this study, a census sampling method was used. Following the application of the inclusion and exclusion criteria, all eligible participants were enrolled.

Data collection

After obtaining informed consent and ethical clearance, eligible patients were assessed through a standardized checklist developed by the researcher. The checklist was validated by hematology and pediatric cardiology experts and included demographic data (age, gender) and the following clinical variables:

Pulmonary hypertension (PHT), hemoglobin levels, vascular occlusion crisis, high hematocrit levels, α-thalassemia , hydroxyurea treatment, white blood cell count reduction, high creatinine levels, genotype and high ferritin levels.

Data collection process

This checklist comprises crucial demographic information, encompassing gender and age, as well as pertinent treatment details, such as PHT, hemoglobin levels, vascular occlusion crisis, high hematocrit levels, α-thalassemia, hydroxyurea treatment, reduction of white blood cells, high creatinine levels, genotype, and high ferritin levels in affected individuals.

All participants underwent echocardiographic evaluation for PHT. Among individuals with sickle cell anemia, chronic anemia and the frequent development of cardiac complications contribute to PHT, which is considered one of the most severe complications associated with the disease. Relevant laboratory tests were conducted, and data were collected through interviews and a review of patient records.

Statistical analysis

Data were analyzed using SPSS software, version 22. Descriptive statistical methods, including Mean±SD, frequency, and percentage, were applied to describe the data. To assess the association between risk factors and the presence or absence of PHT, the chi-square test was employed.

Results

The research findings indicated that of the 75 patients assessed, 35 patients (46.7%) were female and 40 patients (53.3%) were male. The youngest age among the patients was 6 years, while the oldest age was 17 years. The mean age of the patients was determined to be 10.50±2.94 years.

Table 1 reveals that out of the individuals examined, 58 cases (77.3%) were determined to be free of PHT, whereas 17 cases (22.7%) were diagnosed with the condition.

The findings indicate that 23 individuals (30.7%) did not receive hydroxyurea treatment, whereas the majority, 52 individuals (69.3%), were treated with hydroxyurea. Furthermore, a significant proportion of patients (72%) had α-thalassemia.

Table 2 reveals a comparison of gender based on the existence of PHT. Among those without PHT, 29 were female and 29 were male. On the other hand, among those with PHT, there were 11 females and 6 males. There was no statistically significant disparity between males and females in both the control and treatment groups `significant correlation was found between genotype and PHT (P>0.05).

Based on the findings shown in Table 2, the majority of individuals (39 people) had used hydroxyurea but did not exhibit PHT. Conversely, a minority of individuals (4 people) had PHT but did not use hydroxyurea. There was no significant link between the usage of hydroxyurea and the occurrence of PHT (P>0.05). Additionally, a majority of individuals, specifically 12 individuals, did not exhibit α-thalassemia and PHT. Conversely, a minority of individuals, namely 8 individuals, exhibited α-thalassemia and PHT. There was a significant difference between α-thalassemia and the occurrence of PHT (P=0.01).

Table 3 presents a comparison of the correlation between age, hematocrit, platelets, WBC, hemoglobin levels, creatinine levels, ferritin levels, and the occurrence of PHT. Individuals with PHT had a greater mean age compared to the healthy individuals. However, this difference was not significant. The analysis of hematocrit data revealed that individuals with PHT had elevated

Table 1. The frequency of studied subjects according to the presence of PHT, α-thalassemia, and treatment with hydroxyurea

Groups	Yes/No	No. (%)
Pulmonary hypertension	No	58(77.3)
	Yes	17(22.7)
Treatment with hydroxyurea	No	23(30.7)
	Yes	52(69.3)
α-trait	No	21(28)
	Yes	54(72)

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hematocrit levels compared to those without disease, but this disparity was not significant (P>0.05).

A statistically significant difference (P<0.05) was observed in platelet counts between patients with PHT and those without. Specifically, those who had the disease exhibited lower platelet counts. Additionally, individuals with PHT had a reduced count of leukocytes compared to those without the disease, but this difference was not significant (P>0.05). The analysis of haemoglobin, creatinine, and ferritin data revealed that individuals with PHT had elevated levels of hemoglobin, creatinine, and ferritin compared to healthy individuals. However, the increase was not significant (P>0.05).

Discussion

PHT is a serious and progressive complication in 6–10% of adults with SCD. While traditional mechanisms, like hemolysis, nitric oxide deficiency, and thrombosis, have been studied, the disease's clinical variability remains unclear [9]. Due to its rapid global transmission, the World Health Organization (WHO) declared SARS-CoV-2, the virus responsible for acute respiratory syndrome, a pandemic in March 2020. Individuals with SCD have a

Table 2. Correlation between genotype, hydroxyurea medication, α-thalassemia, and the occurrence of PHT

Variables		No. (%)		P
		Pulmonary Hypertension		
		Yes	No	
Gender	Female	11(14.7)	29(38.7)	0.28
	Men	6(8)	29(38.7)	
Genotype	SB0	2(2.7)	10(13.3)	0.71
	SS	8(10.7)	27(36)	
	SC	3(4)	6(3)	
	SB+	4(5.3)	11(14.7)	
	SD	0(0)	4(5.3)	
Treatment with hydroxyurea	No	4(5.3)	19(25.3)	0.34
	Yes	13(17.3)	39(52)	
α-thalassemia	No	9(12)	12(16)	0.01
	Yes	8(10.7)	46(61.3)	

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Table 3. Correlation between age, platelets, WBC count, and hematocrit, hemoglobin, creatinine, ferritin levels, and the occurrence of PHT

Variables	Pulmonary Hypertension	Mean±SD	P
Age (y)	No	10.39±2.86	0.58
	Yes	10.88±3.25	
Hematocrit (%)	No	25.73±4.33	0.22
	Yes	27.8±4.22	
Platelet (10^3/uL)	No	368.13±126.06	0.04
	Yes	295.52±139.41	
WBC (10^3/uL)	No	10.36±3.22	0.08
	Yes	10.04±2.68	
Hemoglobin (g/dL)	No	9.41±4.02	0.16
	Yes	10.04±2.34	
Creatinine (mg/dL)	No	0.64±0.18	0.1
	Yes	0.68±0.21	
Ferritin (ng/dL)	No	97.6±34.4	0.31
	Yes	104.03±26.85	

WBC: White blood cell; PHT: Pulmonary hypertension.

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heightened risk of experiencing severe clinical problems if they are infected with COVID-19 due to the widespread damage to their blood vessels and endothelial cells [10, 11]. Given this potential danger, it is crucial to methodically assess individuals with PHT in order to detect the many clinical presentations and consequences observed in children with SCD.

The findings of our study indicated that PHT was present in 22.7% of the patients diagnosed with sickle cell anemia. The study by Amadi et al. reported an overall prevalence of Doppler-derived PH of 38% among individuals with sickle cell anemia [12]. According to the research conducted by Elfaki et al., PHT was observed in 29% of the studied population [2]. Ramsey et al. found that PHT was prevalent among patients diagnosed with sickle cell anemia, a finding that aligns with the results of our study [13]. Sokunbi et al. revealed that the occurrence of PHT in children diagnosed with sickle cell anemia was found to be 22.9%, which aligns with the findings of our study [14]. Dosunmu et al., in a study conducted in Lagos, Nigeria, reported a significantly lower prevalence of 3.6%. This lower rate may be attributed to the age group of the study population compared to that of the present study [15].

In this cross-sectional study involving 75 Children affected by SCD, no significant correlation was found between age and gender and the occurrence of PHT in patients with SCD (P>0.05). Eskandarian et al. found no significant differences in age or gender between patients with and without PHT [16]. Tarrass et al. conducted an evaluation of PAP through echocardiography in patients undergoing dialysis. Their findings indicated no correlation between PHT and factors, such as age, gender, duration of dialysis, vascular access location, biological parameters, or parathyroid hormone levels [17].

Our study revealed that female patients and those of older age had a higher likelihood of developing PHT. According to the findings of Mukhtar et al., PHT was reported to occur more commonly in women; however, there was no significant relationship between gender and PHT [18]. Furthermore, our findings align with those of Odeyemi et al.'s study on children diagnosed with SCD, indicating that being female and advancing in age contribute to a higher occurrence of PHT in these individuals. In contrast to our investigation, this study found a statistically significant association (P<0.05) between gender, age, and the occurrence of PHT [19].

In our study, the predominant genotype among most participants was HbSS (SCD), accounting for 46.7% of the group. Elfaki et al. found a similar result, with 90% of their subjects carrying the HbSS genotype [2]. Our study identified a notable correlation between the α-thalassemia trait and the prevalence of PHT observed in SCD populations (P<0.05), indicating that those with α-thalassemia are less likely to develop PHT. Similarly, Fonseca et al. utilized echocardiography to assess pulmonary complications by evaluating right ventricular function, and their findings also demonstrated a significant association between α-thalassemia and a lower incidence of PHT (P<0.05) [20].

Fraidenburg and Machado reported that PHT is a very rare complication in individuals with α-thalassemia [21]. Furthermore, in another study that assessed pulmonary hemodynamics using echocardiography in patients with α-thalassemia, only 80.3(4%) of those diagnosed with HbH or Bart's disease exhibited echocardiographic evidence of PHT, defined by a tricuspid regurgitant velocity exceeding 2.9 m/s [22]. Teawtrakul et al. indicated that patients with beta thalassemia had a significantly higher risk of developing PHT compared to those with α-thalassemia or combined α and β thalassemia (OR=9.47, P=0.036) [22]. The studies conducted by Dosunmu et al. and Aliyu et al. reported a significantly lower incidence of PHT in individuals with SCD who also possess the α-thalassemia (P<0.05), which is consistent with the findings of our research [4, 15].

The research findings demonstrated a significant correlation between PHTN and platelet counts (P<0.05), indicating that individuals with lower platelet counts had a higher likelihood of developing PHT. This conclusion is consistent with the findings of Sokunbi et al. [14]. The results of Liao and Wu indicated that red blood cell distribution width (RDW) and mean platelet volume (MPV) were significantly higher in patients with interstitial lung disease (ILD) and moderate-to-severe PHT (Ms-PH) compared to those with ILD without PHT and those with mild PHT (P<0.05). Furthermore, in patients with ILD, RDW, age, MPV, and serum IgG levels independently contributed to the risk of developing Ms-PH [23].

Hydroxyurea, which increases the generation of fetal hemoglobin (HbF), is a commonly used and successful therapy for SCD patients worldwide. An elevation in HbF expression helps reduce RBC sickling and decreases the vaso-occlusive crisis frequency [24, 25]. Consequently, the occurrence of vasculopathic consequences, such as PHT, is reduced, leading to a substantial increase in lifespan after a six-year course of therapy [26].

The findings revealed that the majority of individuals (39 people) had used hydroxyurea but did not show signs of PHT. In contrast, a smaller group (4 people) had PHT despite not using hydroxyurea. The data analysis revealed no significant correlation between the use of hydroxyurea and the existence of PHT. Elfaki et al. reported that, due to the high proportion of asymptomatic patients, initiating targeted treatment with hydroxyurea was not deemed warranted [2]. Consistent with our research, Sokunbi et al. and Klings et al. observed no significant correlation between hydroxyurea and PHT in their studies of individuals with SCD (P<0.05) [14, 25]. The lack of a significant correlation between PHTN and hydroxyurea administration in our research may be attributed to the delayed commencement or relatively short duration of this hydroxyurea therapy among our subjects. PHT was observed in a minority (17%) of the individuals who received hydroxyurea treatment.

The findings of the current study indicated no significant difference in mean hemoglobin levels between patients with and without PHT. Similarly, Sedighi et al., employing a 35 mm Hg threshold to diagnose PHT, reported no association between hemoglobin concentration and the occurrence of PHT [27]. In their study of pulmonary arterial pressure (PAP) in dialysis patients, Domenici et al. found that PHT was associated with longer dialysis durations, higher hemoglobin levels, and higher serum albumin levels compared to those with normal PAP [28]. Hemoglobin levels and the prevalence of PHT were shown to be highly associated in the study by Eskandarian et al. People with normal hemoglobin levels (≥11 g/dL) were approximately 70.2% less likely to develop PHT than those with low hemoglobin levels, according to the binary logistic regression analysis [16].

Conclusion

The study results showed that 22.7% of patients with SCD had PHT. PHT was significantly associated with α-thalassemia and platelet count. Additionally, the prevalence of the disease was higher in women than in men. Therefore, necessary diagnostic and preventive measures should be taken in high-risk individuals, considering the severe complications of the disease and the increased risk of mortality in these patients. It is advisable to conduct frequent screening for PHT in individuals with SCD, considering all pertinent criteria during the screening process.

Limitations of this research include the relatively small number of participants and its single-center design. Also, this study did not examine symptoms, such as

smoking or current symptoms of the disease. It is suggested that future studies should examine more demographic and laboratory variables that may be influential.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Hormozgan University of Medical Sciences, Bandar abbas, Iran (Code: IR.HUMS.REC.1400.258). All participants or their legal guardians gave written informed consent prior to enrollment. Confidentiality and anonymity were strictly maintained by assigning participants unique identification codes and securely storing data. Also, participation was voluntary, and patients had the right to withdraw at any time without any repercussions for their medical care. The study also complied with the national ethical charter for biomedical research and the institutional ethical guidelines.

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Authors contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflicts of interest

The authors declared no conflict of interest.

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