

Early Detection of Pulmonary Hypertension in Pediatric Sickle Cell Anemia: A Non-invasive Diagnostic Approach

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What is known on this subject?

Pulmonary hypertension (PH) represents a progressive and often subclinical complication in pediatric sickle cell anemia (SCA), for which non-invasive modalities such as Doppler echocardiography and biomarker assessment provide valuable tools for early risk stratification and clinical surveillance.

What this study adds?

This study provides evidence supporting the implementation of non-invasive screening modalities, including echocardiographic parameters and laboratory biomarkers, for early identification of PH in children with SCA.

ABSTRACT

Objective: To evaluate early indicators of pulmonary hypertension (PH) in children and adolescents with sickle cell anemia (SCA) using non-invasive diagnostic methods.

Material and Methods: A total of 29 pediatric patients diagnosed with SCA (aged ≥10 years) and 23 age and sex matched healthy controls were enrolled. All participants underwent echocardiographic evaluation, pulmonary function tests, electrocardiography, and a six-minute walk test. Laboratory parameters including B-type natriuretic peptide (BNP), lactate dehydrogenase, bilirubin, and uric acid were analyzed. Cardiac systolic and diastolic functions were assessed using tissue Doppler imaging and myocardial performance index (MPI).

Results: SCA patients showed significantly higher tricuspid regurgitant velocity, systolic and mean pulmonary artery pressures, and MPI values for both ventricles compared to controls. Pulmonary acceleration time was lower, and BNP levels were significantly elevated, positively correlating with left ventricular end-diastolic diameter and right ventricular MPI. Pulmonary function tests suggested a restrictive pattern, and the six-minute walk distance was significantly reduced.

Conclusion: Although PH was not definitively diagnosed, early alterations in cardiac function and elevated BNP levels suggest a subclinical predisposition to PH in pediatric SCA patients. Non-invasive screening methods may be valuable for early detection.

Keywords: Pediatric cardiology, pediatric hematology, pediatric ventricular function, pulmonary hypertension, sickle cell anemia



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Introduction

Hemoglobin S (HbS) is an abnormal type of Hb that results from the substitution of valine for glutamic acid at the sixth position of the β -globin chain in normal Hb. Under low oxygen partial pressure, erythrocytes containing HbS assume a sickle shape. The severe form of sickling disorders is homozygous HbS disease, known as sickle cell anemia (SCA) (1,2).

Hemoglobinopathies can lead to intravascular hemolysis through a mechanism involving nitric oxide (NO) dysfunction, which may contribute to the development of pulmonary hypertension (PH). In addition, chronic hypoxia is among the key causes of secondary PH. PH is a serious complication in adult patients with SCA, associated with increasing mortality and morbidity (3). However, limited data are available in the pediatric population.

This study aims to assess the presence of PH in patients with SCA using non-invasive echocardiographic methods at earlier ages, to identify factors predisposing to PH, and to provide insights into treatment protocols. The study investigates the relationship between echocardiographic findings and respiratory function tests, six-minute walk test results, and clinical and laboratory parameters.

Material and Methods

Patients aged ≥ 10 years who were followed for a diagnosis of SCA at the Pediatric Hematology Outpatient Clinic of Çukurova University Department of Pediatrics between February 2015 and October 2015, and who consented to participate, were included in the study.

Patients experiencing painful or hemolytic crises, those with a history of such crises or infections within the past month, were patients who had received a blood transfusion in the past three months, and patients with mental retardation-who may not comply with respiratory function and six-minute walk tests-were excluded from the study.

Written informed consent was obtained from all participants (or their legal guardians) before their inclusion in the study.

The study commenced following approval by the Çukurova University Faculty of Medicine Ethics Committee (approval no: 3995, date: 06.03.2015).

The control group consisted of healthy children of similar age and gender, without any cardiopulmonary complaints, systemic diseases, anemia, or medication use, and with normal mental-motor development, followed in general pediatric outpatient clinics.

Blood and serum samples were obtained from both groups for complete blood count, Hb electrophoresis, B-type natriuretic peptide (BNP), total and direct bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, lactate dehydrogenase (LDH), uric acid, serum iron, total iron-binding capacity, ferritin, and transferrin levels.

Echocardiography, electrocardiography (ECG), six-minute walk test, and pulmonary function test were performed. Echocardiographic assessments were conducted using a Philips Epiq 7 system with variable-frequency transducers in supine or left lateral decubitus positions. Both patients and controls underwent parasternal long axis, apical four-chamber, short axis, subcostal, and suprasternal echocardiographic views.

Left ventricular (LV) systolic function was evaluated using M-mode echocardiography from the parasternal long axis view with the Teicholz method. The degree of pulmonary insufficiency (PI) was assessed with pulsed wave (PW) Doppler echocardiography using the left parasternal short axis view. Peak velocity and end-diastolic velocity of PI flow were used to calculate mean and diastolic, pulmonary artery pressure (PAP) via the Bernoulli equation. Tricuspid regurgitation (TR) severity was determined using color Doppler echocardiography based on Framingham Heart Study criteria in the apical four-chamber view. The area of the TR jet and right atrium was measured. A TR jet to right atrial area ratio of $<19\%$ was considered mild, $20-40\%$ was considered moderate, and $>41\%$ was considered severe (4).

Systolic pulmonary artery pressure (sPAP) was calculated using the TR jet peak velocity and estimated right atrial pressure with the Bernoulli equation. Diastolic function of both ventricles was assessed using PW Doppler to record ventricular inflow patterns at atrioventricular valve tips from the apical four-chamber view. Early (E wave) and late (A wave) diastolic velocities, E wave deceleration time (DT), and E/A ratios were calculated. The myocardial performance index (MPI) for each ventricle was measured using the pulsed tissue Doppler method, with early diastolic (E), late diastolic (A), and systolic (S) waves obtained from lateral mitral and tricuspid annuli.

Isovolumetric contraction time (IVCT) isovolumetric relaxation time (IVRT) and ejection time (ET) were measured. MPI was calculated as $MPI = (IVCT + IVRT) / ET$ (5). Doppler tracings were recorded at 100 mm/sec in all patients.

Statistical Analysis

Data were analyzed using SPSS version 17.0. Categorical variables were expressed as numbers and percentages, and

continuous variables as mean $\pm$ standard deviation or, when appropriate, as median (minimum-maximum). Normality of distribution was assessed before comparing groups. The Student's t-test was used for normally distributed variables, and the Mann-Whitney U test for non-normally distributed ones. A p value of <0.05 was considered statistically significant.

Results

A total of 29 patients diagnosed with SCA and 23 healthy children in the control group were included in the study. The demographic characteristics of the patients are presented in Table 1. The mean age of the patient group was 14.5 ± 2.6 years

(range 10-18), and that of the control group was 13.5 ± 2.3 years (range 10-17), ($p=0.060$). In the patient group, 69% ($n=20$) were male and 31% ($n=9$) were female; in the control group, 69.6% ($n=16$) were male and 30.4% ($n=7$) were female ($p=1.000$). Laboratory results of both groups are shown in Table 1.

Evaluation of pulmonary function test results revealed that the mean forced expiratory volume in one second (FEV_1) in the patient group was significantly lower ($81.3 \pm 16.1\%$) than in the control group ($96.1 \pm 14.2\%$) ($p=0.002$). Pulmonary function test results of both groups are presented in Table 2.

No conduction defects were detected in the ECG recordings of either group.

Table 1. Demographic characteristics and laboratory findings of patient and control groups

Parameter	Patient group (n=29)	Control group (n=23)	p value
Sex (F/M)	9/20 (30.4%/69.6%)	7/16 (30.4%/69.6%)	1.000
Age (years)	14.5 ± 2.6	13.5 ± 2.3	0.060
Height (cm)	154.4 ± 14.4	149.6 ± 16.4	0.274
Weight (kg)	47.1 ± 14.1	41.9 ± 13.1	0.177
BMI (kg/m^2)	19.4 ± 3.7	18.2 ± 2.7	0.201
WBC ($\times 10^3/\text{mm}^3$)	12.1 ± 4.8	8.6 ± 4.0	0.0001
Hb (g/dL)	8.9 ± 1.3	13.2 ± 0.9	0.0001
Hct (%)	24.9 ± 3.9	38.3 ± 2.8	0.0001
MCV (fL)	85.2 ± 9.8	81.6 ± 3.5	0.032
RDW (%)	19.7 ± 3.2	14.7 ± 0.9	0.0001
Platelet ($\times 10^3/\text{mm}^3$)	505.1 ± 215.8	259.3 ± 54.0	0.0001
HbF (%)	10.9 (4.8-40.99)	Not detected	-
HbA2 (%)	2.6 ± 0.9	1.7 ± 0.5	0.0001
HbA (%)	27.6 ± 17.6	98.3 ± 0.5	0.0001
HbS (%)	71.9 ± 14.9	Not detected	-
Total bilirubin (mg/dL)	3.7 ± 2.4	0.6 ± 0.2	0.0001
Direct bilirubin (mg/dL)	0.3 ± 0.1	0.1 ± 0.1	0.0001
AST (U/L)	43.9 ± 14.5	24.8 ± 5.2	0.0001
ALT (U/L)	24.5 ± 11.7	16.0 ± 3.8	0.001
LDH (U/L)	467 (164-946)	179 (112-268)	0.0001
Uric acid (mg/dL)	5.4 ± 1.4	4.3 ± 1.0	0.003
BUN (mg/dL)	7.1 ± 2.2	9.3 ± 2.6	0.002
Creatinine (mg/dL)	0.3 ± 0.1	0.5 ± 0.1	0.0001
GFR ($\text{mL}/\text{min}/1.73 \text{ m}^2$)	282.6 (175.6-904.4)	159.3 (118.5-232.4)	0.0001
Iron ($\mu\text{g}/\text{dL}$)	92.9 ± 38.0	87.2 ± 14.8	0.897
TIBC ($\mu\text{g}/\text{dL}$)	330.2 ± 47.6	382.7 ± 43.3	0.0001
Ferritin (ng/mL)	95.7 (34.1-1521)	21.5 (9.7-43.1)	0.0001
Transferrin (mg/dL)	251.0 ± 41.0	287.4 ± 63.2	0.0001

F: Female, M: Male, BMI: Body mass index, WBC: White blood cell, Hb: Hemoglobin, Hct: Hematocrit, MCV: Mean corpuscular volume, RDW: Red cell distribution width, HbF: Fetal hemoglobin, HbA2: Hemoglobin A2, HbA: Hemoglobin A, HbS: Hemoglobin S, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, BUN: Blood urea nitrogen, GFR: Glomerular filtration rate, TIBC: Total iron-binding capacity

In the echocardiographic evaluation of patients; LV systolic function measurements; such as interventricular septum thickness, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), and left ventricular posterior wall thickness (LVPW); were significantly higher in the patient group compared to controls. Although the ejection fraction (EF) and fractional shortening (FS) values were within normal ranges, they were found to be lower in the patient group (Table 3).

Assessment of right ventricular (RV) diastolic function showed no statistically significant differences between groups in tricuspid E wave, or RV DT. However, tricuspid A wave velocity was significantly higher in the patient group (53.7 ± 9.9 cm/s) compared to controls (45.4 ± 8.7 cm/s) ($p=0.004$). The tricuspid E/A ratio was significantly lower in the patient group

(1.319 ± 0.23) than in controls (1.470 ± 0.27) ($p=0.035$), though within normal limits in both groups.

LV diastolic parameters showed no significant differences in mitral E wave or DT. However, mitral A wave velocity was significantly higher in the patient group (68.9 ± 13.6 cm/s) than in the control group (60.0 ± 10.4 cm/s) ($p=0.015$), and mitral E/A ratio was significantly lower in the patient group (1.452 ± 0.27) than in the control group (1.628 ± 0.28) ($p=0.035$), though still within normal ranges (Table 4).

No significant differences were found between groups in LV IVCT or RV/LV ejection time. However, RV and LV IVRT, RV IVCT, and MPI values were significantly higher in the patient group. Tissue Doppler and MPI results by group are presented in Table 5. TR severity distribution was not statistically different between groups.

Table 2. Pulmonary function test results

Parameter	Patient group (n=29)	Control group (n=23)	p value
FEV ₁ (%)	80 (46-111)	95 (76-136)	0.002
FEV ₁ /FVC (%)	113 (103-117)	113 (98-118)	0.760
PEF (%)	76 (56-95)	84 (64-104)	0.010
MEF25-75 (%)	88 (61-137)	107 (62-146)	0.023

FEV₁: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak expiratory flow, MEF25-75: Maximal expiratory flow at 25-75% of the pulmonary volume

Table 3. Distribution of left ventricular systolic functions

Parameter	Patient group	Control group	p value
IVS (mm)	8.9 (7-11)	8.1 (6.1-9.6)	0.004
LVEDD (mm)	49.2 (35.6-62.0)	40.1 (35.6-51.1)	0.0001
LVESD (mm)	30.7 (7-42)	24.9 (21.8-31.1)	0.0001
LVPW (mm)	9 (6.5-30.0)	7.6 (6.0-9.2)	0.0001
EF (%)	66.7 (58.3-75.7)	69.8 (61.0-77.3)	0.001
FS (%)	36.8 (31.1-44.9)	39.1 (32.2-45.4)	0.010

IVS: Interventricular septum, LVDD: Left ventricular diastolic diameter, LVSD: Left ventricular systolic diameter, LVPW: Left ventricular posterior wall, EF: Ejection fraction, FS: Fractional shortening

Table 4. Distribution of right and left ventricular diastolic functions

Parameter	Patient group	Control group	p value
Mitral E (cm/s)	97.9 (70-135)	93.4 (78.3-117.0)	0.897
Mitral A (cm/s)	67.3 (40.1-91.3)	61.1 (44.7-84.7)	0.015
Mitral E/A	1.43 (0.9-2.0)	1.57 (1.2-2.1)	0.035
LVDT (ms)	144 (92-225)	155 (106-197)	0.632
Tricuspid E (cm/s)	70 (48.3-87.9)	64.3 (53.4-78.5)	0.052
Tricuspid A (cm/s)	51.8 (28.4-77.1)	45.3 (28-64.9)	0.004
Tricuspid E/A	1.22 (1.1-2.2)	1.40 (1.1-2.2)	0.031
RVDT (ms)	132 (88-211)	144 (99-173)	0.645

LVDT: Left ventricular deceleration time, RVDT: Right ventricular deceleration time

TR peak velocity was significantly higher in the patient group (2.4 ± 0.3 m/s) compared to controls (2.2 ± 0.2 m/s) ($p=0.001$). sPAP calculated from TR velocity was also significantly higher in the patient group (28.8 ± 6.6 mmHg), compared to the control group (22.7 ± 4.3 mmHg) ($p=0.0001$). Pulmonary artery acceleration time was significantly lower in the patient group (132.9 ± 20.1 ms) compared to controls (144.3 ± 14.9 ms), ($p=0.016$). Mean pulmonary artery pressure (mPAP) calculated from acceleration time was also significantly higher in the patient group ($p=0.017$). No significant difference in mPAP or pulmonary artery diastolic pressure, calculated from PI flow, was observed (PI present in 8 patients, 6 controls). No significant correlation was found between TR peak velocity and mPAP ($r=0.013$; $p=0.369$) (Table 6).

The average six-minute walking distance was significantly lower in the patient group (446.5 ± 50.8 m), compared to

the control group (500.0 ± 58.2 m) ($p=0.0001$) (Table 7). A significant correlation was found between the frequency of painful crises and HbS levels in the patient group ($p=0.028$).

No significant correlation was found between the frequency of painful crises or acute chest syndrome history and TR peak velocity or MPI values. RV MPI was significantly lower in patients receiving hydroxyurea ($p=0.014$). Patients with a history of priapism had significantly lower TR velocities ($p=0.003$).

A significant positive correlation was observed between BNP levels with both LVEDD, RV MPI values in the patient group ($r=0.28$, $p=0.042$ for both). No significant correlations were found between BNP and EF ($r=-0.18$, $p=0.188$), FS ($r=-0.14$, $p=0.306$), or LV MPI ($r=0.24$, $p=0.089$) (Table 8).

Table 5. Tissue Doppler measurements and myocardial performance index

Parameter	Patient group	Control group	p value
RV IVRT (ms)	42 (20-69)	35 (21-56)	0.011
RV IVCT (ms)	50 (30-77)	43 (28-56)	0.007
RV ET (ms)	280 (220-330)	278 (232-330)	0.810
RV MPI	0.34 (0.2-0.5)	0.30 (0.2-0.3)	0.001
LV IVRT (ms)	42 (25-85)	35 (22-53)	0.034
LV IVCT (ms)	53 (24-95)	46 (28-63)	0.076
LV ET (ms)	277 (218-324)	285 (211-317)	0.417
LV MPI	0.33 (0.2-0.6)	0.28 (0.2-0.4)	0.010

RV: Right ventricular, IVRT: Isovolumic relaxation time, IVCT: Isovolumic contraction time, ET: Ejection time, MPI: Myocardial performance index

Table 6. Distribution of pulmonary artery pressure findings by groups

Parameter	Patient group (n=29)		Control group (n=23)		p value
	n		n		
TR maximum flow velocity (m/s)	26	2.4 (1.8-3.2)	21	2.0 (1.7-2.5)	0.001
PA systolic pressure (mmHg)	26	28 (17-47)	21	21 (17-31)	0.0001
PA diastolic pressure (mmHg)	8	7 (6-15)	6	7 (6-9)	0.755
Estimated PA pressure (via PR) (mmHg)	8	9 (7-21)	6	11 (8-17)	0.573
PA acceleration time (ms)	29	130 (92-183)	23	148 (106-169)	0.016
Estimated PA pressure (via PA AT) (mmHg)	29	20.5 (2.9-37.6)	23	12.4 (2.9-31.3)	0.017

TR: Tricuspid regurgitation, PA: Pulmonary artery, PR: Pulmonary regurgitation, AT: Acceleration time

Table 7. Six-minute walk test results by groups

	Patient group	Control group	p value
Six-minute walking distance (m)	450 (322-540)	501 (350-635)	0.0001

Table 8. Correlation of BNP with systolic and diastolic parameters in the patient group

Parameter	r	p
LVEDd (mm)	0.28	0.042
EF%	-0.18	0.188
FS%	-0.14	0.306
RV MPI	0.34	0.014
LV MPI	0.24	0.089

LVEDd: Left ventricular diastolic diameter, EF: Ejection fraction, FS: Fractional shortening, RV MPI: Right ventricular myocardial performance index, LV: Left ventricular myocardial performance index

Discussion

This study aimed to investigate, using non-invasive diagnostic methods, the early detection of PH, a complication with significant prognostic implications, in children and adolescents aged 10 years and older with SCA. In the patient group, an increase of 9.1% was observed in the peak tricuspid regurgitation velocity (TRV), 26.9% in sPAP, and 37.6% in mPAP, calculated via pulmonary acceleration time, compared to the control group. Conversely, pulmonary acceleration time was found to be 7.9% lower. These findings suggest the presence of a subclinical predisposition to PH in SCA patients that can be identified through non-invasive methods, even at an early age. In this regard, our study contributes to the limited body of pediatric literature on the subject.

Sickle cell disease (SCD) is associated with varying degrees of hemolysis, with the most severe clinical and laboratory manifestations observed in individuals with homozygous HbSS genotype (6). Intravascular hemolysis in these patients leads to the release of Hb, arginase, and LDH from erythrocytes (7,8,9). Serum uric acid levels are indicative of oxidative metabolic stress in ischemic peripheral tissues (10). Studies by Kato et al. (8) demonstrated a correlation between hemolytic rate, defined by LDH levels, and both NO consumption and PH prevalence/severity in patients with SCD. Consistent with these findings, our study revealed significantly lower Hb and hematocrit (Hct) levels and significantly higher levels of mean corpuscular volume, red cell distribution width, total and direct bilirubin, uric acid, and LDH in the patient group. These findings support the presence of ongoing hemolysis.

BNP, a cardiac hormone secreted by the ventricles, serves as a useful biomarker in patients with PH, reflecting RV dysfunction. Elevated BNP levels at baseline have been associated with adverse outcomes and can guide both risk stratification and treatment monitoring. The primary cause of mortality in PH is RV failure, which is closely linked to elevated

BNP levels. Nagaya et al. (11) demonstrated that initial BNP values could be used to predict long-term prognosis, and persistently elevated levels were associated with poor clinical outcomes. Other studies have shown that BNP levels tend to be higher in conditions causing LV volume overload compared to right-sided pressure overload (12).

In our study, BNP levels were significantly elevated in the patient group compared to controls. Additionally, positive correlations were observed between BNP levels and both LVEDD and RV MPI, suggesting that systolic and diastolic functions are beginning to deteriorate, and that BNP elevation may be a consequence of this early dysfunction.

SCA is also associated with an increased prevalence of pulmonary fibrosis, chronic lung disease, interstitial lung disease, and asthma (13). Although the majority of SCA patients exhibit restrictive ventilatory patterns, some may show isolated reductions in diffusing capacity for carbon monoxide or present with normal findings. In PH, mild to moderate reductions in lung volumes are typically observed (14,15). In our study, pulmonary function testing showed significantly reduced FEV₁ and mid-expiratory flow rates (MEF25-75) in the patient group compared to controls. However, no significant difference was noted in FEV₁/FVC ratios, suggesting a predominantly restrictive pattern, although lower peak expiratory flow values may indicate the early onset of obstructive changes.

Transthoracic echocardiography remains the most valuable non-invasive screening tool for evaluating the likelihood of PH (16). Doppler echocardiography has demonstrated that systolic and diastolic dysfunction can occur in SCA patients at an early age. The presence of diastolic dysfunction and PH is associated with adverse outcomes in this population. Notably, some pediatric SCA patients may fall into New York Heart Association functional classes I and II, highlighting the need for early identification. Studies by Caldas et al. (17) and Arslankoylu et al. (18) reported increased interventricular septal thickness, LV diameters, posterior wall thickness, and MPI in patients with SCA compared to healthy controls, despite normal EF and shortening fraction values. Our findings align with those reports.

Normal reference values for RV MPI are approximately 0.28±0.04. In our study, right and LV MPI values were 0.345±0.06 and 0.337±0.09, respectively. MPI increases in the presence of both systolic and diastolic dysfunction. It is elevated due to prolonged IVCT and shortened ejection time in systolic dysfunction, and due to prolonged IVRT in diastolic dysfunction (17). In SCA patients, even when LVEF is within

normal limits, elevated MPI may indicate subtle systolic and/or diastolic impairment. These increases may also be influenced by elevated cardiac output due to chronic anemia, potentially confounding systolic indices.

Very few studies have evaluated ventricular diastolic function in SCA patients via echocardiography. Most studies report a decrease in mitral E/A ratio as an early marker of diastolic dysfunction before overt abnormalities are present (19). Consistently, our study also demonstrated significantly lower mitral E/A ratios in the patient group. Additionally, we observed reduced tricuspid E/A ratios, although all values remained within normal ranges. Pulmonary artery systolic pressure is known to inversely correlate with the tricuspid E/A ratio (19).

Although the precise etiology and severity of PH in SCA remain poorly understood, even mildly elevated PAP detected by Doppler echocardiography have been associated with poor outcomes (20). A study by Akgül et al. (20) found that not only patients with PH but also non-PH patients showed significantly elevated PAP compared to healthy controls.

In our study, mPAP values calculated from pulmonary acceleration time were significantly higher in the patient group, whereas those calculated from PI flow were not. Furthermore, no significant correlation was found between TRV and mPAP, likely due to the absence of detectable TR or PI in some patients, limiting the reliability of hemodynamic estimates in all cases. Differences in calculation methods and sample sizes may also have contributed to the observed variability.

Study Limitations

The main limitation of this study is the relatively small sample size and single-center design. The absence of confirmatory angiographic measurements, the gold standard for diagnosing PH, and the evolving diagnostic criteria over time also pose limitations.

Conclusion

Although PH was not definitively diagnosed in our patient group, early alterations in systolic and diastolic cardiac function were detected, accompanied by elevated BNP levels. Early identification of PH offers the opportunity for timely intervention before irreversible cardiovascular changes occur and has the potential to improve prognosis. Initiation of supportive therapies during the subclinical phase-such as hydroxyurea, oxygen supplementation, or optimized transfusion protocols-may help preserve RV function, limit pulmonary vascular damage, and enhance exercise capacity.

Given the potential for all subtypes of PH to develop in SCA, identifying predisposing factors and tailoring treatment protocols requires larger, multicenter longitudinal studies with long-term follow-up.

Ethics

Ethics Committee Approval: The study commenced following approval by the Çukurova University Faculty of Medicine Ethics Committee (approval no: 3995, date: 06.03.2015).

Informed Consent: Written informed consent was obtained from all participants (or their legal guardians) before their inclusion in the study.

Footnotes

Authorship Contributions

Concept: M.Ç., S.E., H.İ.Ş., Design: M.Ç., H.İ.Ş., Data Collection or Processing: M.Ç., Analysis or Interpretation: M.Ç., S.E., H.İ.Ş., Literature Search: M.Ç., Writing: M.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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