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Original Article

The Relationship between Sickle Cell Disease and Pulmonary Hypertension in Adults

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Abstract *- Sickle cell disease (SCD) is an inherited hemoglobinopathy associated with high morbidity and mortality. Pulmonary hypertension (PH) is reported to play a significant role. There is very limited literature on PH in SCD in Syria. This study aimed to assess the prevalence of pulmonary hypertension and its relationship with clinical and laboratory parameters in sickle cell disease patients. This prospective case-control study included 50 patients with sickle cell disease and 50 controls matched for age and sex at Tishreen University Hospital at Lattakia between July 2019 – and July 2020. Both the patients and controls were subjected to echocardiography. Pulmonary hypertension was prospectively defined as a tricuspid regurgitant jet velocity of at least 2.5 m per second. Sickle cell disease patients had a greater mean TRV than controls. Doppler-defined pulmonary hypertension occurred in 32% of patients. Using the dichotomous variable of a TRV < 2.5 m/s or TRV ≥ 2.5 m/s, multiple logistic regression analysis identified an increased age, high LDH, and indirect bilirubin levels (markers of hemolysis) as significant correlates of pulmonary hypertension. The white-cell count, reticulocytes, sickle complications, clinical measures, or hydroxyurea therapy were unrelated to pulmonary hypertension. In this study of adults with sickle cell disease, the prevalence of pulmonary hypertension, as confirmed by echocardiographic evaluation, was 32%. It appears to be a complication of chronic hemolysis and is resistant to hydroxyurea therapy. Clinical assessment of adult patients with sickle cell disease should include echocardiography.*

Keywords *- Pulmonary hypertension, Sickle cell disease, Echocardiography.*

I. INTRODUCTION

Sickle cell disease (SCD) is a group of common genetic disorders. The term "*disease*" is applied to this condition because the inherited abnormality causes a pathological condition that can lead to death and severe complications [1][23]. SCD is one of the most common inherited life-threatening disorders in humans, and it predominantly affects people of African, Indiana, and Arab ancestry [2].

It is an inherited autosomal recessive disorder with the presence of hemoglobin S in blood. Not all inherited variants of hemoglobin are detrimental, a concept known as genetic polymorphism. This disease has significant morbidity and is a potentially fatal disease. Patients undergo painful crises and may have renal failure, heart failure, infections, and other complications. In addition to its impact on patient's health, it causes a huge financial burden because heavy expenses are required for frequent hospitalization, medication, and blood transfusion. Sickle cell has a profound impact, not just on the patient but on the whole family dynamic. Regular follow-up and care may improve a patient's ability to lead productive life and reduction in acute care costs [1][21][25].

Pulmonary hypertension (PH) is a relatively frequent and severe complication of SCD and an independent risk factor for mortality [3]. Echocardiographic screening studies have identified evidence of elevated pulmonary pressures, defined as a tricuspid regurgitant jet velocity (TRV) ≥2.5 m/sec (equivalent to a pulmonary artery systolic pressure of approximately 36 mmHg), in 30 to 40 percent of hemoglobin SS (HbSS) and 10 to 28 percent of hemoglobin SC (HbSC) adults [4][20]. Additionally, up to 22 percent of HbSS children and adolescents have this echocardiographic finding [5], including children as young as three years. However, echocardiographic estimates of pulmonary pressures are substantially less accurate than right heart catheterization. Three prospective studies utilizing right heart catheterization have defined the prevalence of PH in SCD to be between 6 and 10.5 percent [6] [7] [8]. The exact pathogenesis of PH in SCD is not known. Still, a number of potential contributing factors have been implicated, including endothelial injury from recurrent sickling, acute and chronic inflammation, hypercoagulability, chronic intravascular hemolysis, and altered bioavailability of the potent vasodilator nitric oxide (NO) [9]. Vascular remodeling caused by chronically elevated left heart pressures from diastolic dysfunction may also contribute, similar to PH group 2, which is purely due to left heart disease [10][22].

One theory is that hemolysis results in increased plasma levels of cell-free hemoglobin (Hgb) more than the binding capacity of the Hgb scavengers, haptoglobin, and hemopexin. This excess of cell-free Hgb may rapidly deplete circulating NO, although there is continuing disagreement over the impact of this process on NO bioavailability [9]. Additionally, hemolysis releases arginase

I from erythrocytes, limiting arginine availability for NO synthesis. In addition to these effects on endothelial regulation, increased cell-free Hgb may also contribute to endothelial and vascular smooth muscle dysfunction [11][24].

Doppler echocardiography estimates pulmonary artery and right ventricular systolic pressures via the TRV and assesses left and right ventricular size, thickness, and function. In addition, echocardiography can evaluate the right atrial size, left ventricular systolic and diastolic function, and valve function. Although much attention has been given to the association of a TRV of ≥2.5 m/sec with increased mortality risk in SCD [12], each echocardiogram helps inform the clinician of PH risk.

This study was designed to determine the prevalence of pulmonary hypertension in sickle cell disease patients in our sickle cell clinic and to correlate this with other clinical and laboratory parameters.

II. PATIENT AND METHODS

A. Study Design and Settings

The study was carried out in the department of Hematology of Tishreen University Hospital, Lattakia, Syria, between July 2019 and July 2020. Ethical Institutional ethical approval was obtained from the hospital research and ethics committee. Informed written and verbal consent was obtained from participants. This was a cross-sectional case-controlled study.

B. Participants

Fifty patients with sickle cell hemoglobinopathy documented by hemoglobin electrophoresis were eligible for the study. Only outpatients in stable condition were included; patients who had had a Vaso-Occlusive crisis, an episode of acute chest syndrome, or received transfusions within the previous two weeks were excluded.

In addition, 50 control subjects with age and sex distributions similar to those of the patients were evaluated for laboratory and echocardiographic data comparisons.

C. Clinical evaluation

Baseline, clinical and demographic characteristics were obtained from all the subjects. These include the date of birth, gender, medical history, and treatment history (hydroxyurea, blood transfusion).
Information about hemoglobin genotype was obtained from existing records.

All subjects' blood pressures were measured in the right arm with the subjects seated and rested for at least 5 minutes before the procedure. Measurements were taken using a mercury sphygmomanometer. Systolic and diastolic blood pressures were measured at Korotkoff sounds V and I. A physical examination was performed on each subject. The weight, height, Body mass index (BMI), heart rate, and pulse oxygen saturation were also recorded.

Alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, lactate dehydrogenase, creatinine, and complete blood count (CBC) tests were done.

D. Echocardiography

All Doppler Echocardiographic examinations were done by the same cardiologist, who was blinded to all other patient data except the diagnosis of SCD, using a Philips HD-11 Digital Ultrasound Machine and involved two-dimensional, M-mode, conventional Doppler (pulsed and continuous wave) and tissue Doppler studies to assess cardiac structure and function. All measurements were made as recommended by the American Society of Echocardiography [13]. Left ventricular wall and chamber dimensions, left atrial dimension, and ejection fraction (EF) were measured using 2D-guided M-mode echocardiography. Echocardiographic assessment of PH was obtained using two methods:

- Determination of peak TRV by continuous-wave Doppler by placing the cursor along the tricuspid regurgitant jet in the apical four-chamber view after obtaining a color Doppler display of the tricuspid regurgitation jet across the valve.
- Determination of the right ventricular acceleration time (AT) and the ratio of right ventricular acceleration time to right ventricular ejection time (AT/RVET) from the pulmonary ejection flow jet obtained by continuous-wave Doppler with sample volume just proximal to the pulmonary valve in the parasternal short-axis view. The acceleration time was taken as the time interval from the onset of right ventricular ejection to peak ejection velocity. In contrast, the ejection time was taken as the time interval from the onset to the end of the ejection.

Pulmonary hypertension (PH) was defined as a peak TRV of ≥2.5 m/s. Mean pulmonary arterial pressure (MPAP) was estimated using the regression equation developed by Dabestani et al [14]: MPAP (mmHg) = 90 - (0.62 × AT).

E. Statistical Analysis

Analysis was done using SPSS version 16.0 (Statistical Package for Social Sciences, Inc., Chicago, IL). All data generated were entered into a standard pro forma. Continuous variables were expressed as mean (standard deviation, SD), and categorical variables were expressed as percentages. Normality was assessed with the Shapiro-Wilks test. Differences in categorical variables were assessed by chi-square analysis. The student's t-test compared continuous variables between the two groups for independent groups. Where the assumption of normality was not satisfied, the Kruskal-Wallis test was used to compare continuous variables. The critical level of significance was set at $P < 0.05$.

III. RESULT

A. Patient Characteristics

Table 1. shows the baseline characteristics of all 100 participants recruited for the study. The mean age of the SCD subjects was 39 ± 10 years, while the mean age for the control group was 41 ± 10.5 years. The groups were of comparable age and sex distribution. There were 28 males and 22 females in the SCD group, while the control group had 25 males and 25 females. The BMI, systolic blood pressure, diastolic blood pressure, and oxygen saturation were lower in the subjects with SCD than in normal controls. There were no differences in the heart rates between the two groups.

Table 1. Clinical characteristics of sickle cell patients and controls

Variable	SCD	Normal controls	P-value
Age (years)	39 ± 10	41 ± 10.5	0.331
Age groups			
18 – 30 years	23 (46%)	18 (36%)	0.585
31 – 50 years	20 (40%)	23 (46%)	
> 50 years	7 (14%)	9 (18%)	
Gender			
Male	28 (56%)	25 (50%)	0.54
Female	22 (44%)	25 (50%)	
BMI (Kg/m^2)	22.4 ± 2.6	23.6 ± 2.5	0.02
Systolic blood pressure (mmHg)	122.5 ± 19	132 ± 18	0.008
Diastolic blood pressure (mmHg)	68 ± 15	75 ± 14	0.017
Heart rate	84 ± 12	82 ± 11	0.387
Oxygen saturation (%)	96 ± 3	99 ± 1	<0.001

Table 2 shows the baseline characteristics of SCD patients.

Table 2. Characteristics of the Patients at Baseline

Variable	Number of patients	Percent (%)
History of Vaso-Occlusive crisis	43	86%
History of acute chest syndrome	14	28%
History of leg ulcers	10	20%
History of priapism	8	16%
Hydroxyurea therapy	19	38%
>10 Blood transfusions during the lifetime	21	42%
Disease phenotype		
Hemoglobin SS	36	72%
Hemoglobin SC	10	20%
Sβ0 thalassemia	4	8%

Table 3 shows the laboratory features in SCD subjects and controls. The white blood cells count, reticulocytes count, LDH, total bilirubin, indirect bilirubin, and AST were significantly higher among the SCD subjects than in the controls. On the other hand, hemoglobin and hematocrit concentrations were significantly lower among the SCD subjects. There were no differences in creatinine and ALT levels between the SCD subjects and the control group.

Table 3 also shows the echocardiographic parameters in SCD subjects and controls. The left atrial area, right atrial area, and left ventricular (LV) systolic and diastolic diameters were significantly higher among the SCD subjects than in the controls. On the other hand, there was no difference in the left ventricular ejection fraction (EF) between the SCD subjects and the control group.
There were significantly higher mean pulmonary pressure and mean tricuspid regurgitant jet velocity (TRV) among SCD subjects.

As assessed by a TRV of ≥ 2.5 m/s in this study, the frequency of pulmonary hypertension was 32% among SCD subjects; none of the controls had pulmonary hypertension. In this study, the patients with pulmonary hypertension had mild pulmonary hypertension, as evidenced by the range of tricuspid regurgitant jet velocity of < 2.9 m/s. Only four (8%) subjects had a TRV ≥ 3 m/s.

Table 3. Laboratory and echocardiographic features of sickle cell patients and controls

Variable	SCD	Normal controls	P-value
White blood cells (10^3/mL)	10.2 ± 4	7.5 ± 3.9	<0.001
Reticulocyte count (%)	11 ± 6	1.5 ± 1.1	<0.001
Hemoglobin (g/dL)	8.6 ± 1.4	13.6 ± 1.5	<0.001
Hematocrit (%)	25 ± 5	33 ± 4.2	<0.001
Lactate dehydrogenase (U/L)	355 ± 160	183 ± 54	<0.001
Total bilirubin (mg/dL)	2.7 ± 1.4	0.9 ± 0.4	<0.001
Indirect bilirubin (mg/dL)	2 ± 1.6	0.6 ± 0.1	<0.001
Creatinine (mg/dL)	0.73 ± 0.2	0.8 ± 0.2	0.08
Aspartate aminotransferase (U/L)	41 ± 22	22 ± 7.8	<0.001
Alanine aminotransferase (U/L)	26.2 ± 15	25.5 ± 13	0.8
Tricuspid regurgitant jet velocity (m/sec)	2.3 ± 0.6	2 ± 0.3	0.002
Mean pulmonary arterial pressure (mmHg)	20.1 ± 10	14 ± 8	0.001
Ejection fraction (%)	65 ± 2	64 ± 3	0.052

Right atrial area (cm^2)	15.6 ± 3.3	13.8 ± 2.7	0.003
Left atrial area (cm^2)	18.1 ± 4.2	15.4 ± 4.3	0.002
LV systolic diameter (cm)	3 ± 0.5	2.7 ± 0.4	0.0013
LV diastolic diameter (cm)	4.8 ± 0.4	4.5 ± 0.35	0.0001
TRV (m/sec)			
< 2.5	34 (68%)	50 (100%)	<0.001
2.5 – 2.9	12 (24%)	0 (0%)	
≥ 3	4 (8%)	0 (0%)	

Table 4 shows the characteristics of patients with SCD according to the tricuspid regurgitant jet velocity (TRV). SCD patients with pulmonary hypertension (PH) were older, had significantly lower hemoglobin and hematocrit concentrations, and had higher levels of indirect bilirubin and creatinine than SCD patients without pulmonary hypertension.

Ten SCD patients (62.5%) with pulmonary hypertension (TRV ≥ 2.5 m/sec) had more than 10 Blood transfusions during lifetime compared to 11 SCD patients (32.4%) without pulmonary hypertension (TRV < 2.5 m/sec) (P=0.04).

Higher tricuspid regurgitant jet velocity (TRV ≥ 2.5 m/sec) increased left and right atrial sizes. There was a slight increase in the ejection fraction at higher levels of jet velocity (P=0.343).

There was no association between jet velocity and left ventricular systolic and diastolic diameters.

Table 4. According to the tricuspid regurgitant jet velocity, characteristics of patients with sickle cell disease.

Variable	**Jet Velocity < 2.5 m/sec (34 patients)**	**Jet Velocity ≥ 2.5 m/sec (16 patients)**	**P-value**
Age (years)	36 ± 9	42 ± 9.2	0.033
Disease phenotype			
Hemoglobin SS	25 (73.5%)	11 (68.7%)	0.81
Hemoglobin SC	6 (17.7%)	4 (25%)	
Sβ0 thalassemia	3 (8.8%)	1 (6.3%)	
Gender			
Male	18 (53%)	10 (62.5%)	0.52
Female	16 (47%)	6 (37.5%)	
BMI (Kg/m^2)	23.1 ± 2.6	22.1 ± 2.5	0.164
Systolic blood pressure (mmHg)	121 ± 19	124 ± 20	0.61
Diastolic blood pressure (mmHg)	65 ± 16	73 ± 14	0.093
Heart rate	83 ± 11	87 ± 12	0.249
Oxygen saturation (%)	95.8 ± 3	96.7 ± 3	0.32
Hemoglobin S (%)	60 ± 10	65 ± 9	0.095
White blood cells (10^3/mL)	10 ± 4.2	10.5 ± 4.1	0.68
Reticulocyte count (%)	10.8 ± 6	11.2 ± 6.3	0.829
Hemoglobin (g/dL)	8.9 ± 1.7	7.8 ± 2	0.049
Hematocrit (%)	26 ± 5.2	22.1 ± 4.8	0.014
Lactate dehydrogenase (U/L)	325 ± 161	432 ± 159	0.0326
Total bilirubin (mg/dL)	2.6 ± 1.5	2.8 ± 1.3	0.649
Indirect bilirubin (mg/dL)	1.8 ± 1.1	2.2 ± 1.5	<0.001
Creatinine (mg/dL)	0.6 ± 0.2	0.82 ± 0.19	0.0006
Aspartate aminotransferase (U/L)	40 ± 23	44 ± 21	0.55
Alanine aminotransferase (U/L)	25 ± 15	28 ± 16	0.52
History of Vaso-Occlusive crisis	29 (85.3%)	14 (87.5%)	0.833
History of acute chest syndrome	8 (23.5%)	6 (37.5%)	0.304
History of leg ulcers	6 (17.6%)	4 (25%)	0.544
History of priapism	6 (17.6%)	2 (12.5%)	0.643
Hydroxyurea therapy	12 (35.3%)	7 (43.7%)	0.565
>10 Blood transfusions during the lifetime	11 (32.4%)	10 (62.5%)	0.04
Ejection fraction (%)	64.6 ± 2.1	65.2 ± 2	0.343
Right atrial area (cm^2)	14.1 ± 3.3	16.4 ± 3.2	0.0246
Left atrial area (cm^2)	16.8 ± 4.1	19.5 ± 4	0.03
LV systolic diameter (cm)	2.9 ± 0.4	3.1 ± 0.5	0.134
LV diastolic diameter (cm)	4.8 ± 0.39	5 ± 0.4	0.08

IV. DISCUSSION

Sickle cell disease is a clinical condition characterized by hemoglobin's qualitative or quantitative disorder. Cardiopulmonary manifestations are prominent components of sickle cell hemoglobinopathy. Most patients show cardiac dysfunction manifested principally as fatigue, dyspnea on exertion, cardiomegaly, electrocardiographic and echocardiographic abnormalities. Some patients develop acute chest syndrome and sickle cell chronic lung disease. With better medical management, patients with SCD are living longer, and what was previously uncommon sequelae of sickle cell disease are now being seen, including pulmonary artery hypertension (PH), which is a prime contributor to mortality in young adult patients with sickle cell disease. This study aimed to determine the prevalence of pulmonary hypertension among sickle cell disease patients attending Tishreen University Hospital and determine the characteristics of patients with pulmonary hypertension.

The study included 50 patients with sickle cell disease and 50 healthy controls. The groups were of comparable age and sex distribution. The BMI, systolic blood pressure, diastolic blood pressure, and oxygen saturation were lower in the subjects with SCD than in normal controls. There were no differences in the heart rates between the two groups. Our results agree with Gladwin et al. [15] and Enakpene et al. [16].

In our study, SCD patients had lower hemoglobin and hematocrit than controls and higher leukocytes, reticulocytes, LDH, total bilirubin, direct bilirubin, and AST. Our results are in agreement with Gladwin et al. [15], Enakpene et al. [16], and Aliyu et al. [17].

We found that the prevalence of pulmonary hypertension, defined as TRV ≥ 2.5 m/s by transthoracic echocardiography among patients with sickle cell disease was 32%. Twenty-four percent of them had mild PH (TRV 2.5-2.9 m/s), and 8% had severe PH (TRV ≥ 3 m/s). None of the controls had pulmonary hypertension.

Previous studies have reported percentages as high as 12.5% to 40%. Defined as TRV ≥ 2.5 m/s in SCD patients by transthoracic echocardiography, Gladwin et al. [15] reported pulmonary hypertension in 32%, Enakpene et al. [16] in 12.2%, Aliyu et al. [17] in 25%, and Amadi et al. [18] found pulmonary hypertension in 23.9%.

Parent et al. [6] studied 398 patients with SCD who all underwent transthoracic echocardiography; pulmonary hypertension, defined as TRV ≥ 2.5 m/s, was found in 27% of patients. These patients (with TRV≥2.5 m/s) underwent right heart catheterization, and only 6% were diagnosed with right heart catheter-confirmed pulmonary hypertension. Fonseca et al. [8] studied 80 patients with SCD who all underwent transthoracic echocardiography; pulmonary hypertension, defined as TRV ≥ 2.5 m/s, was found in 40% of patients. These patients (with TRV≥2.5 m/s) underwent right heart catheterization, and only 10% were diagnosed with right heart catheter-confirmed pulmonary hypertension.

In our study, SCD patients with pulmonary hypertension (PH) were older than patients who did not have pulmonary hypertension (P = 0.033), with no difference according to gender. Gladwin et al. [15], Fonseca et al. [8], and Amadi et al. [18] showed similar results.

Enakpene et al. [16] found no statistically significant association with age, while they found that male gender is an independent determinant of pulmonary hypertension in SCD. They attributed the relatively lower frequency of elevated pulmonary pressure (12.2%) compared with some other studies and the absence of association between age and pulmonary hypertension to the age of patients used in their study (mean age 24 ± 9 years).

In our study, SCD patients with pulmonary hypertension (PH) had significantly lower hemoglobin and hematocrit concentrations and higher indirect bilirubin and creatinine levels compared to SCD patients without pulmonary hypertension. The observation that markers of hemolysis are associated with pulmonary hypertension provides a link between sickle cell disease and other chronic hemolytic disorders and suggests that there is a distinct syndrome of hemolysis-associated pulmonary hypertension. Thalassemia, for example, is another chronic hemolytic disease associated with secondary pulmonary hypertension; the prevalence of pulmonary hypertension among patients with thalassemia ranges from 10% to 93%, depending on the patient population studied [15]. Hemolysis results in increased plasma levels of cell-free hemoglobin (Hgb) in excess of the binding capacity of the Hgb scavengers, haptoglobin, and hemopexin. This excess of cell-free Hgb may rapidly deplete circulating NO, although there is continuing disagreement over the impact of this process on NO bioavailability [9].

Additionally, hemolysis releases arginase I from erythrocytes, limiting arginine availability for NO synthesis. In addition to these effects on endothelial regulation, increased cell-free Hgb may also contribute to endothelial and vascular smooth muscle dysfunction [11]. Our results agree with Gladwin et al. [15] and Fonseca et al. [8].

Parent et al. reported that data regarding biologic markers of hemolysis were discordant. Hemoglobin and indirect bilirubin levels were similar in patients with confirmed pulmonary hypertension and those without pulmonary hypertension. In contrast, they observed in patients with confirmed pulmonary hypertension significantly increased lactate dehydrogenase and aspartate aminotransferase levels, which may also be influenced by liver dysfunction. They concluded that the role of hemolysis in the pathogenesis of pulmonary hypertension in patients with sickle cell disease remains controversial and further studies are needed [6].

Our study found no association between treatment with hydroxyurea and the prevalence of pulmonary hypertension in SCD patients (P = 0.565). More SCD patients with pulmonary hypertension received > 10 Blood transfusions during their lifetime compared to SCD patients without pulmonary hypertension (P=0.04).

Gladwin et al. [15] found no association between treatment with hydroxyurea and pulmonary hypertension. Neither Fonseca et al. [8] nor Parent et al. [6] found an association between treatment with hydroxyurea and pulmonary hypertension.

Treatment with hydroxyurea may not reduce the incidence of pulmonary hypertension, but it may increase survival. Hydroxyurea may be beneficial by decreasing hemolysis and the frequency of painful episodes, acute chest syndrome, and mortality associated with sickle cell disease. Evidence favoring hydroxyurea comes from a longitudinal study of 299 SCD patients who were followed up for 17.5 years [19]. In that study, 24% of deaths were due to pulmonary complications; 87.1% occurred in patients who never took hydroxyurea or took it for <5 years.

Higher tricuspid regurgitant jet velocity (TRV ≥ 2.5 m/sec) was associated with our study's increased left and right atrial sizes. There was a slight increase in the ejection fraction at higher levels of jet velocity (P=0.343). No association was found between jet velocity and left ventricular systolic and diastolic diameters.

Our results are in agreement with Gladwin et al. [15]. Enakpene et al. [16] found no difference in left ventricular ejection fraction between SCD patients with pulmonary hypertension and patients without pulmonary hypertension. Amadi et al. [18] found that SCD patients with pulmonary hypertension had lower left ventricular ejection fractions than patients without pulmonary hypertension.

A. Study limitation

This present study had several limitations. First, right heart catheterization remains the gold standard for measuring pulmonary pressures, yet none of the subjects underwent the procedure due to its non-availability in this environment. Parent et al. [6] found a low positive predictive value of echocardiography for detecting pulmonary hypertension when compared with right heart catheterization (25%). Using a TRV of > 2.9 m/s increased the positive predictive value to 64% and increased the false-negative rate to 42%. This false-negative rate improved using a 6-minute walk test of fewer than 333 meters. Thus, in some of our subjects, elevated pulmonary artery pressures might be due to the high cardiac output accompanying SCD. Second, our patients did not assess the arginine, fibrinogen, ferritin, and fetal hemoglobin levels to identify if they could be possible predictors of pulmonary hypertension in our SCD subjects.

V. CONCLUSION

This study has shown that the pulmonary artery pressure is higher in SCD subjects than in normal controls. The prevalence of pulmonary hypertension, defined as TRV ≥ 2.5 m/s by transthoracic echocardiography among patients with SCD, was 32%. Elevated serum markers of hemolysis (LDH, indirect bilirubin) were associated with the prevalence of pulmonary hypertension.

VI. RECOMMENDATIONS

Further studies using right heart catheterization are recommended, as it is the gold standard for pulmonary hypertension evaluation. Follow-up studies with a larger number of patients would also be necessary to evaluate the contribution of elevated pulmonary pressure to morbidity and mortality in SCD subjects.

Future studies with further laboratory evaluation (arginine, fibrinogen, ferritin, fetal hemoglobin) and clinical evaluation (six-minute walk test) are recommended.

VII. AUTHOR'S CONTRIBUTIONS

MA, FH, and BM designed the study. MA collected the data, analyzed and interpreted the result, and drafted the manuscript. FH, BM revised the manuscript. All authors read and approved the final manuscript.

VIII. ETHICAL APPROVAL

Ethical approval to conduct the study was obtained before the commencement of the study. Informed consent was sought from each patient before being enrolled in the study.

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