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Prevalence of pulmonary hypertension in Sickle cell Disease: A cross sectional observational study from Raipur, Chhattisgarh

Dr. Soumya Saxena[1] Dr.Proff D. P. Lakra(M.D.)[2],Dr R. K. Patel(M.D.)[3], Dr. C S Sharma(M.D)[4],Dr. S. Srivastava(M.D, D.M Cardio)[5]

[1]*Resident, Department of General Medicine, Dr. B.R.A.M Hospital, Raipur, Chhattisgarh*
[2]*Professor,* [3]*Associate Professor, Department of General Medicine, Dr. B.R.A.M Hospital, Raipur, Chhattisgarh*
[4]*Assistant Professor, Department of General Medicine, Dr. B.R.A.M Hospital, Raipur, Chhattisgarh*
[5]*Associate Professor, Department of Cardiology, Dr. B.R.A.M Hospital, Raipur, Chhattisgarh*

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I. INTRODUCTION

Pulmonary Hypertension is defined as a resting mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg. It occurs in 6 to 11% of patients with sickle cell disease and is classified in World Health Organization (WHO) PH group 5 because patients have variable hemodynamics (i.e., they may have precapillary, postcapillary, or both pre and postcapillary PH).[1]

The point mutation in position 6 of the beta-globin gene results in the replacement of hydrophilic glutamic acid by a hydrophobic valine. The consequence is haemoglobin S with reduced solubility in deoxygenated state and a low affinity for oxygen. Haemoglobin S polymerises in low oxygen tension in the capillaries and venules. As a result the RBC becomes more rigid and its membrane becomes more adherent to the endothelium and other blood elements.[2] The result is blockage of the microvasculature, reduction red cell life span (haemolysis) and release of inflammatory cytokines and mitogens. With haemolysis, there is release of haemoglobin and arginase. The haemoglobin mops up the constitutive nitric acid which reduces vasoconstriction, platelet activation, vascular fibrosis and vascular muscle proliferation while arginase mops up arginine which is a substrate for the production of nitric oxide.[2,3,4,5,6] Histopathology findings in pulmonary hypertension are medial and intimal thickening of the small pulmonary vessels.[7] This, in association with increased haemodynamic in sickle cell disease, contributes to the genesis of pulmonary hypertension in Sickle Cell Disease.

Objective: To assess the prevalence of pulmonary hypertension in sickle cell disease and to study profile of patients with sickle cell disease with pulmonary hypertension at Department of Medicine Dr.B.R.A.M.Hospital Raipur (C.G.)

II. MATERIALS AND METHODS

Study setting: OPD and casualty admissions of Department of Medicine Dr. B.R.A.M Hospital, Raipur, Chhattisgarh, along with patients from the Sickle Cell Institute, Raipur, Chhattisgarh

Design of the study: Cross sectional observational study

Sample Size: Faculty based time bound study

Ethical issues: Ethical clearance was obtained from institutional ethical committee and informed written consent was obtained from subjects.

Inclusion Criteria:

- Age > 18 years
- Known Sickle cell Disease patients (diagnosed by Hb Electrophoresis done at this institute)
- Patients willing to give informed consent

Exclusion Criteria:

- Clinically or hemodynamically unstable patients
- Patients in Vaso Occlusive Crisis
- Patients unwilling to give consent
- Known cases of Rheumatic or Congenital Heart Disease
- Known cases of COPD/ other pulmonary diseases
- Patients with Congestive Heart Failure

Outcome Variables:

- Presence/absence of pulmonary hypertension as determined by several markers on 2D ECHO
- Markers of hemolysis including Sr LDH (>190 IU/L), Reticulocyte count (>2.5%), indirect bilirubin levels (>0.4mg/dl)
- Severity of SCD as determined of no of vaso occlusive crises in the past year (>2) and requirement of blood transfusions (Y/N)

International Journal Dental and Medical Sciences Research
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Parameters used on 2D ECHO

- Tricuspid Annular Plane Systolic Excursion (A measure of RV ejection fraction, which is decreased in pulmonary hypertension) (<18)
- Tricuspid Regurgitation Velocity (> 2.5m/sec)
- Right Ventricular Wall thickness (>5mm)
- RVOT acceleration time (<130 msec)
- Diameter of Inferior Vena Cava (>1.7cm)

Estimation of Parameters

A Philips EPIC 7 two-dimensional transthoracic echocardiography was performed for all patients enrolled in this study. Transthoracic transducer selection was made for echocardiographic window as per every patient. Cardiac measurements were performed according to the guidelines of American Society of Echocardiography.

TRV was measured by pulsed-wave and continuous wave Doppler echocardiography wherever applicable. Multiple views (apical 4-chamber, parasternal short axis, parasternal long axis) were obtained to record optimal tricuspid Doppler flow signals. The right ventricular to right atrial systolic pressure gradient was calculated using the modified Bernoulli equation (4 × V2). Pulmonary artery systolic pressure was quantified by adding the Bernoulli-derived right ventricular systolic peak pressure to the estimated mean right atrial pressure (5 mm Hg). Pulmonary artery diastolic pressure was estimated by measurement of the end diastolic velocity of the pulmonary insufficiency jet by similar Doppler techniques.
Pulmonary hypertension was defined as a peak TRV of at least 2.5 m/second equating to a pulmonary artery pressure of at least 30 mm Hg.

Statistical Analysis

The data was coded and entered into Microsoft Excel spreadsheet. Analysis was done using SPSS version 20 (IBM SPSS Statistics Inc., Chicago, Illinois, USA) Windows software program. Descriptive statistics included computation of percentages, means and standard deviations. Chi-square test was used for qualitative data whenever two or more than two groups were used to compare. Level of significance was set at $P \leq 0.05$.

III. RESULTS

The prevalence of Pulmonary Hypertension in Sickle Cell Disease is 13.7%, determined according to ESC 2015 guidelines using 2D echocardiography (Table 5)

The occurrence of Pulmonary Hypertension in Sickle Cell Disease is associated with a significant increase in biochemical markers of hemolysis, such as LDH, indirect bilirubin and reticulocyte count. (Table 6). Pulmonary Hypertension is more common in SCD patients who suffer from repeated episodes of Vaso Occlusive Crises requiring frequent hospitalisations. (Table 4)

IV. DISCUSSION

Age and gender

In our study most patients were of an age group of <30 years (30 out of 51 patients) with a minimum age of 18, maximum age of 53 and mean age of 29.18 years (Std deviation 10.04).
In our study there were 20 female patients and 31 male patients with a gender ratio of 0.645.

Gosavi et al[16] in their study included 94 subjects with age group 12 to 54 years of age, out of which 54 had sickle cell disease. Maximum cases (44) were in the age group of 21 – 30 (46.8%). 46 males and 48 females were recruited in the study.
This study is most similar to our study for purposes of comparison

Florence et al[17] conducted a multicenter trial study in Franceon 398 SCD patients (mean age 34 +/- 10 years) with 60% female preponderance.
Fonseca et al[18]conducted a study in Brazil, on 80 SCD patients, with mean age of 33 +/- 10 years, with a 61% female preponderance
In all the above-mentioned studies, the prevalence of Pulmonary Hypertension was shown to increase with age.

Clinical Manifestations of Sickle Cell Disease patients

In our study, all patients were asymptomatic patients who had come for follow up in the medicine OPD of Dr.Bhim Rao Ambedkar Medical Hospital or in Sickle Cell Institute, Chhatisgarh. During history taking, the number of Vaso Occlusive crises (requiring hospitalization) and number of Blood Transfusions required in the previous year were recorded.

It was found that both the number of VOC's and the number of BT's required differed significantly between SCD patients who did have PH and SCD patients who did not have PH.

Out of 7 patients whose Echocardiography was suggestive of Pulmonary Hypertension, 4 did not have a VOC episode in the last 1 year; 2 had had one episode, and 1 had had 2 painful crises which required hospitalization in the last one year.

In the patients without Echocardiographic markers suggestive of Pulmonary Hypertension, 30 patients were symptom free for 1 year, 8 had

suffered from 1 episode, and 4 people had suffered from 2 or more than 2 episodes of VOC in the last 1 year.

In conclusion, in our study, 31.8% of people without pulmonary hypertension had suffered from a VOC in the last 1 year, while 42.9% of patients with pulmonary hypertension had suffered a VOC in the last 1 year.

In the study conducted by **Gosavi et al**[16], all 5 patients found to have pulmonary hypertension had been hospitalized for VOC at least once in the last one year; as compared to patients without Pulmonary Hypertension, out of which 65% patients had been hospitalized in the last one year. The differences in the results seen here may be because of different inclusion criteria and age distribution in both samples.

In the study conducted by **Fonseca et al**[17], 91% of patients without pulmonary hypertension gave a history of Vaso Occlusive Crises, as compared to 85% of patients with pulmonary hypertension.

In our study, only 1 patient with Pulmonary Hypertension had not had a blood transfusion in the last 1 year. The other 6 patients with PH had had 1 to 4 blood transfusions in the previous year

In patients without Pulmonary Hypertension, 61.4% of them had not required a Blood transfusion in the last one year, while around 37% of them required 1-2 BT last year, and 3 patients had required 3-4 BT's last year.

Gosavi et al[16] found that all 5 patients with pulmonary hypertension had received at least one BT in the last on year, while among the patients who were found not to have pulmonary hypertension, 42% had not required a BT in the last one year, 49% had required 1-2 BT's, while 8% had required more than 2 BT's last year.

In all other studies, requirement of Blood Transfusions had not been recorded.

Laboratory parameters of patients with Sickle Cell Disease

The various laboratory parameters recorded for our study were Hemoglobin levels, Hematocrit, WBC count, Platelet count, Total and direct bilirubin levels, Reticulocyte counts, SGOT/PT levels, FetalHemoglobin levels, and Lactate Dehydrogenase levels.

Out of all these parameters, levels of Hematocrit, Total bilirubin levels, Reticulocyte counts, and Lactate Dehydrogenase levels were found to vary significantly ($p<0.001$) between the PH and non PH groups.

Levels of Hemoglobin, FetalHemoglobin levels and levels of liver enzymes were not found to be significantly different among PH and non PH groups.

In the study done by **Gosavi et al**[16], The SS cases had significantly low mean Hb level and significantly high reticulocyte count and serum bilirubin vs. the AS cases, however no such differences were found in between the groups with and without Pulmonary Hypertension.

The study conducted by **Fonseca et al**[18] showed significant ($p<0.001$) differences between the Hematocrits, LDH levels and GGT levels of patients with and without Pulmonary hypertension. There was no significant difference in the FetalHemoglobin levels of patients with or without Pulmonary Hypertension. Total bilirubin levels and reticulocyte counts were not found to be different in between both groups of this study.

In the study done by **Florence et al**[17], 7 laboratory parameters were taken (Hemoglobin, LDH, Bilirubin, AST, ALT, ALP and creatinine levels) out of which only Hemoglobin and liver enzyme levels (SGOT/PT and ALP) were found to be significantly different in patients with or without pulmonary hypertension.

Despite the wide variability of results taken from different trials, both worldwide and in India, there are a few conclusions –

a) In all studies, at least one marker of Hemolysis (LDH, Bilirubin level, and Reticulocyte count) is raised in a patient of Pulmonary Hypertension as compared to a patient without Pulmonary hypertension, underlying hemolysis as one of the likely mechanisms in the development of pulmonary hypertension in SCD pateints.
b) In most studies, the average Hemoglobin and Hematocrit levels in patients with pulmonary hypertension are significantly lower than patients without pulmonary hypertension, a possible sequelae to the increased hemolysis in patients with PH
c) No significant differences between the levels of fetalhemoglobin were found between both groups; perhaps underlining the lack of protection provided by fetalhemoglobin in preventing chronic hemolysis in SCD patients and the sequelae arising from it.
d) Other, non-traditional markers (SGOT/PT levels, GGT and ALP levels) may also indicate an increased risk of Pulmonary Hypertension in cases of SCD. However, more research is required in this direction in order to reach a conclusion.

International Journal Dental and Medical Sciences Research
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Echocardiography results of patients with Sickle Cell Disease

A Philips EPIC 7 two-dimensional transthoracic echocardiography was performed for all patients enrolled in this study. Transthoracic transducer selection was made for echocardiographic window as per every patient. Cardiac measurements were performed according to the guidelines of American Society of Echocardiography.

The ESC Guidelines (2015) suggest the probability of PH based on TRV at rest and on the presence of additional pre specified echocardiographic variables suggestive of PH. Other variables suggested for this purpose are

- RVOT Acceleration Time < 105msec and/or midsystolic notching
- IVC diameter > 21mm with decreased inspiratory collapse (<50%)
- Right Ventricular free wall thickness > 5mm
- TAPSE < 18mm (Tricuspid Annular Plane Systolic Excursion)

In our study, the likelihood of the presence or absence of pulmonary hypertension has been determined during 2D transthoracic echocardiography on the basis of these guidelines.

The mean TRV of SCD patients with probable PH was found to be 3.17+/-0.59m/sec as compared to 1.64+/-0.5 m/sec in SCD patients without PH.

Out of 51 SCD patients, 10 patients were found to have TRV raised >=2.5 m/sec, out of which 7 were determined to have a high probability of having Pulmonary Hypertension in accordance to ESC guidelines of 2015

In the study done by **Florence et al**[17], 25% of SCD patients had TRV>2.5m/sec, as compared to 20% of patients in our study. Out of these, only 5% were found to have pulmonary hypertension on right heart catheterization.

Other studies could not be taken for analysis due to lack of comparability in data.

Prevalence of Pulmonary Hypertension in Sickle Cell Disease

In our study, 7 out of 51 SCD patients were suspected to have Pulmonary Hypertension on the basis of echocardiographic changes, and the prevalence of pulmonary hypertension was found to be 13.7%.

The study by **Gosavi et al**[16] calculated the prevalence of pulmonary hypertension in SCD to be 9.23%; using echocardiography determined indices.

A multicenter study conducted by **Florence et al**[17] in France used right heart catheterization to determine the prevalence of Pulmonary Hypertension in SCD; their results showed a prevalence of raised TRV > 2.5m/sec at 27%; however, the overall prevalence of PH on RHC was found to be 6%

A study conducted in America by **Mehari et al**[19] estimated the prevalence of pulmonary hypertension in SCD patients to be 10.5%, as determined by right heart catheterization.

Similar results were obtained in a trial conducted by **Fonseca et al**[18] in Brazil, where the prevalence of PH on right heart catheterization was found to be 10%.

The study conducted by **Mehari et al**[19] also calculated the 6-year mortality of patients after diagnosis of PH to be 37%, which was significantly higher than the non-PH group (13%). However, this parameter could not be included in our study design.

V. CONCLUSION

Prevalence of pulmonary hypertension was found to be 13.7%. All ECHO parameters in pulmonary HTN were significantly more compared to non PHTN patients.

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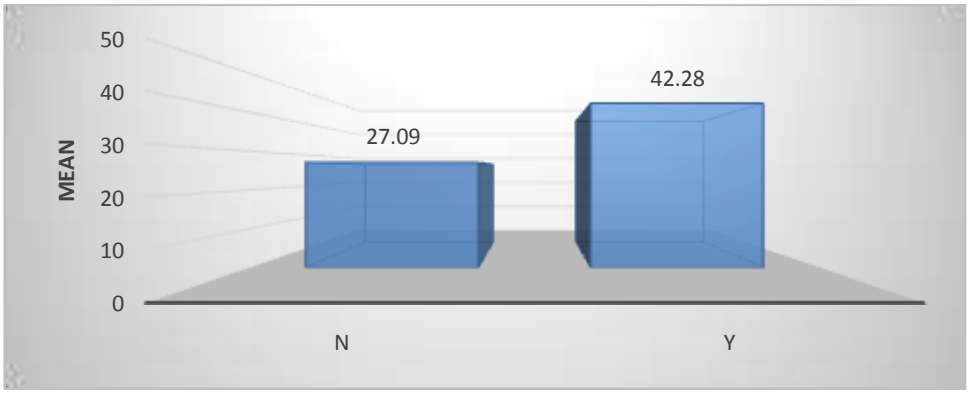
List of tables and figures

Table 1 : PH and age

	N	Mean	Std. Deviation	P value
N	44	27.09	8.56	0.001 (S)
Y	7	42.28	9.03	



International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 230-238 www.ijdmsrjournal.com ISSN: 2582-6018

This bar graph demonstrates the difference between the mean age of Sickle Cell Disease patients with and without Pulmonary Hypertension

Table 2 : PH and gender

			Gender		Total
			F	M	
PH	N	N	17	27	44
		%	38.6%	61.4%	100.0%
	Y	N	3	4	7
		%	42.9%	57.1%	100.0%
Total		N	20	31	51
		%	39.2%	60.8%	100.0%

P value=0.93

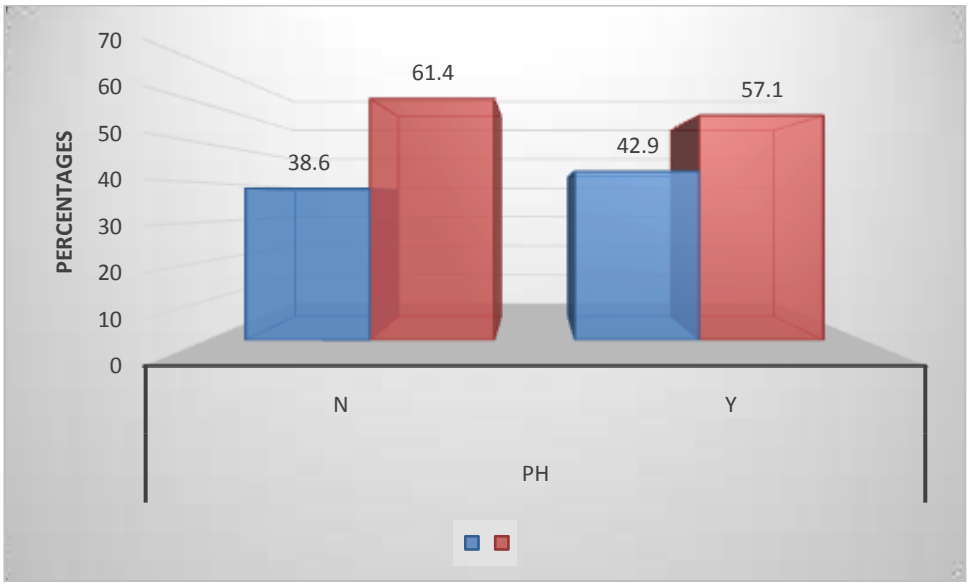


Table shows difference in gender distribution in patients with and without Pulmonary Hypertension in Sickle Cell Disease

International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 230-238 www.ijdmsrjournal.com ISSN: 2582-6018

Table 3 : PH and NO OF VOC EPISODES IN 1 YEAR

			NO OF VOC EPISODES			Total
			.00	1.00	2.00	
PH	N	N	30	8	6	44
		%	68.2%	18.2%	13.6%	100.0%
	Y	N	4	2	1	7
		%	57.1%	28.6%	14.3%	100.0%
Total		N	34	10	7	51
		%	66.7%	19.6%	13.7%	100.0%

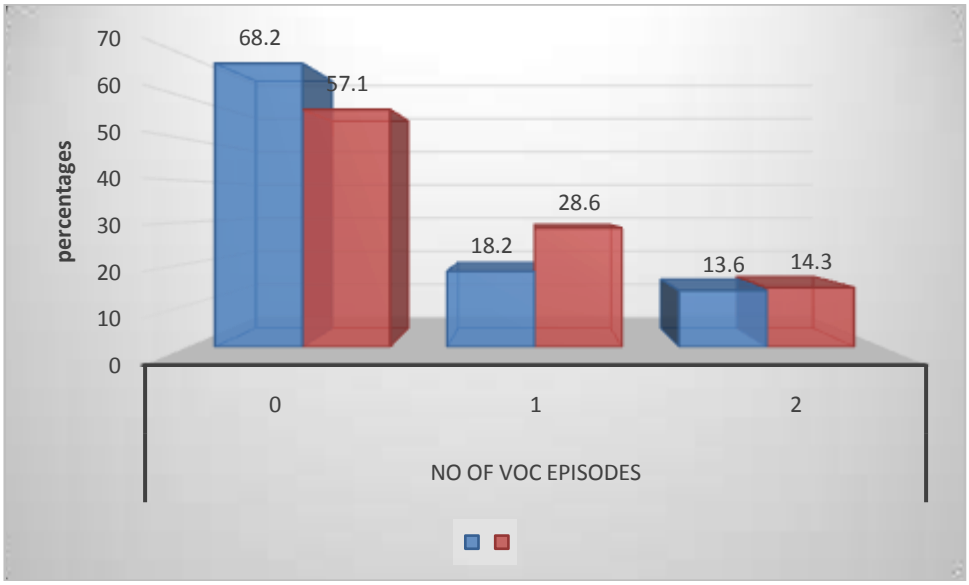


Table 4 : PH and NO OF BT IN 1 YEAR

			NO OF BT					Total
			.00	1.00	2.00	3.00	4.00	
PH	N	N	27	6	11	0	0	44
		%	61.4%	13.6%	25.0%	0.0%	0.0%	100.0%
	Y	N	1	0	3	2	1	7
		%	14.3%	0.0%	42.9%	28.6%	14.3%	100.0%
Total		N	28	6	14	2	1	51
		%	54.9%	11.8%	27.5%	3.9%	2.0%	100.0%

International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 230-238 www.ijdmsrjournal.com ISSN: 2582-6018

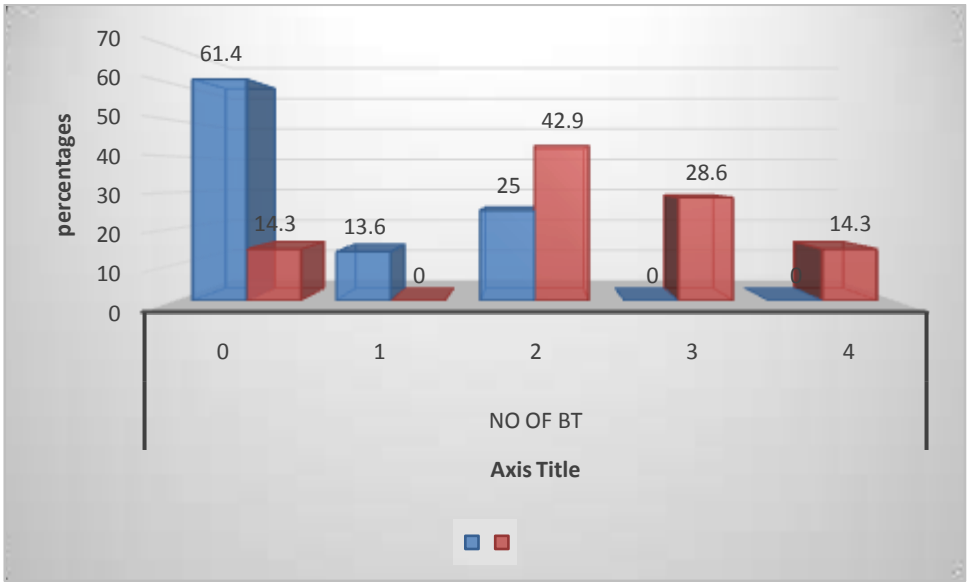


Table 5: Prevalence of pulmonary HTN

	Frequency	Percent
N	44	86.3
Y	7	13.7
Total	51	100.0

Out of 51 patients, 7 developed pulmonary hypertension. So, the prevalence of pulmonary HTN in our study was 13.7%

Table 6: ECHO parameter in pulmonary HTN

	Pulmonary HTN	N	Mean	Std. Deviation	P value
TRV	Yes	7	3.17	0.59	0.001 (S)
	No	44	1.64	0.48	
RV WALL THICKNESS	Yes	7	6.65	1.507	0.001 (S)
	No	44	2.92	0.52	
TAPSE	Yes	7	19.28	6.72	0.002 (S)
	No	44	24.79	3.52	
RVOT-AT	Yes	7	103	1.73	0.001 (S)
	No	44	118.02	8.57	
IVC DIAMETIER	Yes	7	2	0.58	0.001 (S)
	No	44	1.48	0.21	

International Journal Dental and Medical Sciences Research
Volume 3, Issue 3, May - June 2021 pp 230-238 www.ijdmsrjournal.com ISSN: 2582-6018

Table 7: Pulmonary Hypertension and blood reports

	PH	N	Mean	Std. Devi	P value
HCT	Y	7	28.213	6.73	0.005 (S)
	N	44	34.131	4.61	
HB	Y	7	9.11	2.33	0.19
	N	44	10.05	1.64	
WBC	Y	7	9.61	3.16	0.11
	N	44	7.37	2.65	
PLT	Y	7	245.14	67.32	0.48
	N	44	279.47	126.51	
Retic count	Y	7	3.37	.34	0.001 (S)
	N	44	2.45	.56	
Total bilirubin	Y	7	4.34	1.67	0.005 (S)
	N	44	1.97	.93	
Direct bilirubin	Y	7	.54	.207	0.16
	N	44	.402	.25	
SGOT	Y	7	66.14	32.23	0.98
	N	44	65.86	44.99	
SGPT	Y	7	45.85	23.66	0.98
	N	44	45.54	56.44	
LDH	Y	7	813.0	285.96	0.003 (S)
	N	44	322.45	183.19	
Fetal HB	Y	7	16.15	6.39	0.88
	N	44	16.64	8.504	