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Original Research Article

Assessment of platelets in patients with pulmonary hypertension

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ABSTRACT

Background: Pulmonary hypertension (PH) occurs due to end result of multifactorial etiology causing significant morbidity and mortality. Platelets are observed to be activated during initiation and progression of disease, platelets indices used as surrogate markers for platelet activation was used in current study to investigate effect of PH on platelets and correlate it with severity of PH.
Methods: 104 patients with PH were grouped according to WHO classification depending upon etiology. Blood samples of patients from all groups were collected and investigated for platelet indices, peripheral smear, bleeding time, clotting time and echocardiography assessment to know the severity of pulmonary hypertension. Patients were reviewed after 2 months of appropriate treatment.
Results: Prevalence of PH due to chronic lung disease (48.1%) was the most common observation. Thrombocyte count was decreased significantly in all groups of PH with $p<0.01$. MPV, PDW, P-LCR (platelet-large cell ratio) were observed to be increased with increasing severity for PH. Significant correlation $p=0.01$ indicated that platelet indices were altered with treatment for PH.
Conclusions: Significant reduction was observed in platelet count with increase in platelet indices can be correlated with severity of PH. Hence in rural areas without echo cardiogram facilities, platelet indices can be considered as surrogate markers for early referral of patients to higher centers for further management of PH.

Keywords: Pulmonary hypertension, Platelet indices, Platelet count

INTRODUCTION

PH is a chronic, complex and progressive pathophysiologic state that is characterized by mean pulmonary artery pressure (PAP) equal to or greater than 25 mmHg.[1,2] PH can be associated with heterogeneous group of diseases not as a diagnostic parameter but rather as a hemodynamic state with elevated blood pressure in pulmonary circulation.[1-3] Dyspnea, weakness, decreased exercise tolerance and progression to right heart failure are some of the symptoms associated to PH.[3,4] Epidemiologically PH affects overall 1% of global population and the prevalence is PH is observed more (around 10%) amongst population over 65 years of age.[5] However, it is reported and observed that the incidence and prevalence of various forms of pulmonary hypertension differ considerably.[5,6] PH is classified into five varied groups by WHO mainly based on etiology.[7] The first group is pulmonary arterial hypertension (PAH), which can be idiopathic, heritable, caused due to drugs, toxins or due to other disorders like connective tissue diseases, congenital heart disease, portal hypertension. Second group is PH due to left heart disease. Third group is PH due to lung disease or hypoxia. Forth group is PH due to chronic thrombo-embolic diseases and the fifth group is PH due to miscellaneous multifactorial mechanisms.[7-9] Importance of distinguishing and classifying PH in different groups is to identify a more suitable and effective treatment strategy

that targets the molecular pathways leading to hypertension. Treatment goals in PH are aimed towards reducing the symptoms, reversing or slowing down the progression of PH and enhancing the functional capacity.[10] Treatment strategies for PH are broadly based on the class of PH to be treated and include supportive therapy like mild aerobic exercises, pulmonary rehabilitation, oxygen therapy, sodium restricted die, specific drug therapies like anticoagulants, diuretics, calcium channel blockers, prostanoids, endothelin receptor antagonists, phosphodiesterase inhibitors, guanylate cyclase stimulators and psychosocial support. Interventional therapies like atrial septostomy, balloon dilation and transplantation are also used in severe PH.[10-13]

Diagnosis of PH may be delayed as its symptoms overlap with other disease conditions like hypothyroidism, chronic obstructive pulmonary disease, congestive heart failure, pulmonary fibrosis, coronary artery disease to list a few.[13] However, some of the reported strategies widely used for diagnosis of PH are ECG abnormalities like prolongation of QRS and QTc, RV strain and hypertrophy, P pulmonale, right axis deviation and right bundle branch blockage are possible indicators of severe PH.[14,15] Echocardiography is preferred for diagnosing PH as it estimates systolic.

PAP and right as well as left ventricular dysfunctions.[16] According to ESC guidelines, peak tricuspid regurgitation velocity (m/s) of 2.8 or less assessed through electrocardiography indicates mild or intermediate PH whereas regurgitation velocity greater than 2.9 is an indicative of severe PH.[17] Cardiac MRI (CMR) can also be used in the diagnosis of PH as it accurately assess RV morphology, size, stroke volume, cardiac output and arterial distensibility. In addition, chest X-ray, ventilation perfusion scan, pulmonary function tests oxymetry and functional assessment as specified by WHO are some of the other techniques use to diagnose PH.[16-19]

Pathophysiology of PH mainly includes thrombosis, inflammation and vasoconstriction predominantly due to smooth muscles dysfunction and abnormal pulmonary artery endothelial cells (PAECs) proliferation.[20] Uncontrolled proliferation of both PAECs and pulmonary artery smooth muscles lead to formation of plexiform lesions and mucularization respectively leading to progressive pulmonary vascular obstruction.[21] It is revealed that pathophysiology of PH is mainly based on vasoconstriction, vascular remodeling and thrombotic pulmonary vascular lesions.[20-22] It is known and evident that platelets that are anucleate cytoplasmic fragments having functional mitochondria are related to all the above cited pathogenesis of PH.[23] Additionally, platelets would also escalate the pathogenesis of PH through platelet-endothelial cell interactions mediated by secretion of platelet- derived molecules, propagation of intravascular thrombosis and excess aggregation.[24] It is hypothesized that role of platelet is more prominent in PAH and types of PH caused due to inflammatory and infectious diseases, thromboembolism, cardiac surgery, thrombocythemia.[25]

Contribution of platelets towards development of PH can be attributed to factors like platelet aggregation, interaction with endothelial cells, production of eicosanoids, serotonins, von Willebrand factor, platelet activating factor, CD40 and its ligand, platelet-derived growth factor.[23-26] Also it was observed that pulmonary antihypertensive drugs have a negative effect on platelets.[27] Despite of all these strong clinical evidences, role of platelet in pathogenesis of PH was not actively investigated due to practical challenges and lack of adequate animal models.[25-27]

Aim and objectives

Aims and objectives of the current study were to study the prevalence of various groups of PH among patients attending Rajiv Gandhi government general hospital, to access the severity of pulmonary hypertension using echocardiogram, to study the platelet morphology, platelet indices and function in various groups of pulmonary hypertension and to study the effect of treatment on severity of pulmonary hypertension and its impact of the platelet indices.

METHODS

Study design

Study was an observational study performed on 104 patients admitted in Rajiv Gandhi government general hospital who were diagnosed to have PH using echocardiographic evidence. The study was performed for a period of six months.

Procedure

In current study, data of all newly diagnosed cases of PH admitted in our hospital were collected. Written consent was taken from patients after explaining the nature of study and investigations to be done. Patients willing to participate and accepted to come for follow up investigations were enrolled in the study. All the enrolled patients were subjected to clinical history investigations followed by general and systemic examinations. Functional class of enrolled patients was determined according to WHO grades used for PH. Blood samples were collected for CBC and peripheral smear and were processed within 1 hour of collection. Bleeding and clotting time was calculated. After taking ECG and chest X-ray, echocardiogram was done by cardiologist to access the PAP using tricuspid regurgitation jet velocity method. Thereby pulmonary systolic artery pressure and mean PAP were calculated. Right atrial and ventricular dimension were calculated. Tricuspid annular plane systolic excursion (TAPSE) value was calculated and thereby right ventricular dysfunction was assessed. Left ventricular systolic and diastolic functions were also accessed. Ejection fraction was calculated, condition of valves was observed and presence of pericardial effusion or clot was noted. The enrolled patients are given standardized

treatment and reviewed after two months. During the review, repeat detailed echocardiogram was done along with the blood investigations.

Inclusion criteria

Inclusion criteria for current study were all patients with echocardiographic evidence of PH of age more than 18 years and willing to participate in the study.

Exclusion criteria

Exclusion criteria for current study were patients already under treatment of anticoagulants, presence of liver disease, haematological malignancies, platelet function disorders, fevers causing thrombocytopenia, pregnant patients and renal failure patients on haemodialysis.

RESULTS

In current study, out of total 104 enrolled patients 37 (36.5%) belonged to the age group 41-50 years, least number of patients 8 (7.7%) patients were observed in the age group of 20-30 years (Table 1). In current study, it was observed that there was no significant difference in the incidence rate of PH between males and females. Incidence among males was observed to be slightly higher (Table 1). It was also observed from study investigations that idiopathic causes were common among PAH patients which were mostly females (Table 1). It was observed that most of the admitted patients 43 (41.3%) belonged to class 3 as per the WHO functional class category and pulmonary tuberculosis or chronic obstructive pulmonary disease was observed as the major cause of PH in majority 27 (25.96%) of admitted patients (Table 1 and 2). The above observation was supported by the fact that majority of admitted patients 50 (48.1%) belonged to group 3 of PH type, in which lung disease is the main cause of PH as categorized by WHO (Table 2). In our present study, according to severity grading of PH based on mPAP (mean pulmonary artery pressure), it was observed that 53 (51%) of the patients were graded to have moderate PH. Peripheral smear studies revealed that 52 (50%) patients had normal smear. Out of total 104 patients, mild TR was observed in 34 (32.7%) of the patients (Table 2).

Table 1: Age, gender and etiology based distribution of study population (N=104).

Variables	N	%
Age group (in years)		
20-30	8	7.7
31-40	22	21.2
41-50	37	35.6
51-60	23	22.1
>60	14	13.5
Total	104	100.0
Gender		
Male	56	53.8
Female	48	46.2
Total	104	100.0
Etiology		
ASD	2	1.92
Bronchiectasis	5	4.81
Chest deformities	3	2.88
CTEPH	4	3.85
ILD	5	4.81
LV systolic dysfunction	10	9.62
LV diastolic dysfunction	6	5.77
Old PT/COPD	27	25.96
OSA/morbid obesity	9	8.65
Others	2	1.92
PAH-CTD	6	5.77
PAH-HIV	3	2.88
PAH-idiopathic	5	4.81
PDA	1	0.96

ASD-atrial septal defect, CTEPH-chronic thromboembolic pulmonary hypertension, ILD-interstitial lung disease, LV-left ventricular, PT-pulmonary tuberculosis, COPD-chronic obstructive pulmonary disease, CTD-connective tissue disorders, PDA-patent ductus arteriosus, VSD-ventricular septal defect.

Table 2: Distribution of study population based on different variables (N=104).

Variables	N	%
WHO functional classification		
Class I	0	0
Class II	23	22.1
Class III	43	41.3
Class IV	38	36.5
Total	104	100.0
Type of PH		
Group I	13	12.5
Group II	35	33.7
Group III	50	48.1
Group IV	4	3.8
Group V	2	1.9
Total	104	100.0
Severity grade of PH		
Mild	18	17.3
Moderate	53	51.0
Severe	33	31.7
Total	104	100.0
Peripheral smear		
Large platelets	51	49.0
Normal	52	50.0
Thrombocytopenia	1	1.0
Total	104	100.0
Valves		
Mild MR	14	13.5
Mild TR	34	32.7
Moderate MR	9	8.7
MS moderate	5	4.8
MS/MR	2	1.9
Normal	28	30.8
Severe MS	5	1.0
TR moderate	1	1.0
VSD mild MR	2	1.9
VSD mild TR	3	2.9
Total	104	100.0

*MR-mitral regurgitation, TR-tricuspid regurgitation, MS-mitral stenosis.

Table 3: Patients review results after two months of treatment (N=104).

Variables	Initial assessment		After 2 months of treatment	
	N	%	N	%
Severity of pulmonary hypertension				
Mild	18	17.3	35	38
Moderate	53	51.0	34	37
Severe	33	31.7	24	26
Total	104	100.0	93	100
RA/RV dimension				
Dilated	90	86.5	79	84
Normal	11	10.6	11	12
Restricted	3	2.9	3	3
Total	104	100.0	93	100
WHO functional classification				
Class I	0	0	1	1.1

Continued.

Variables	Initial assessment		After 2 months of treatment	
	N	%	N	%
Class II	23	22.1	44	47.3
Class III	43	41.3	44	47.3
Class IV	38	36.5	4	4.3

Table 4: Statistical analysis of varied parameters before and after two months of treatment (N=93).

Variables	Initial assessment			After2 months of treatment			P value
	Mean	SD	Standard error	Mean	SD	Standard error	
TTCx10^3	1.9368	0.44116	0.04575	2.1276	0.4334	0.04494	<0.001
MPV_fL	10.5631	0.61704	0.06398	10.3742	0.55284	0.05733	<0.001
PDW	16.7978	1.73387	0.17979	16.9054	1.62256	0.16825	>0.05
PLCR	27.5108	3.68751	0.38238	26.8817	3.20614	0.33246	<0.001
mPAP	46.3376	9.84252	1.02062	43.7225	9.60185	0.99567	<0.001
TAPSE	15.5054	1.65256	0.17136	15.9355	1.64056	0.17012	<0.001
EF	56.6667	9.19396	0.95337	57.7957	6.75915	0.70089	<0.05

*PDW-platelet distribution width, TAPSE-tricuspid annular plane systolic excursion, EF-ejection fraction.

Table 5: Correlation analysis of different variables with echo parameters.

Variables	Pears on correlation coefficient	Significance (2-tailed test)
TTCx10^3		
PASP (N=104)	-0.621	0
mPAP (N=104)	-0.621	0
Systolic function (N=104)	0.263	0.007
Diastolic function (N=104)	-0.052	0.603
EF (N=104)	-0.176	0.704
Pericardial effusion clot (N=102)	-0.259	0.009
Severity (N=104)	-0.622	0
Mpv_fL		
PASP_4TRV2RA (N=104)	0.547	0
mpap_0#61xPSAP2 (N=104)	0.562	0
Systolic function (N=104)	-0.314	0.001
Diastolic function (N=104)	-0.027	0.786
EF (N=104)	-0.005	0.959
Severity (N=104)	0.547	0
P-LCR		
PASP_4TRV2RA (N=104)	0.311	0.001
mpap_0#61xPSAP2 (N=104)	0.312	0.001
Systolic function (N=104)	-0.190	0.053
Diastolic function (N=104)	-0.062	0.532
EF (N=104)	0.157	0.112
Pericardial effusion clot (N=102)	0.002	0.983
Severity (N=104)	0.282	0.004

Correlations were consideredsignificantat0.01 or at 0.05 levels (2-tailed).

Table 6: Wilcoxon Signed rank test results before and after treatment.

Results	Functional class	RARV dimensions	Pericardial effusion clot	Severity
Z value	-7.488	-1.414	-3.354	-4.914
P value	0.000	0.157	0.001	0.000

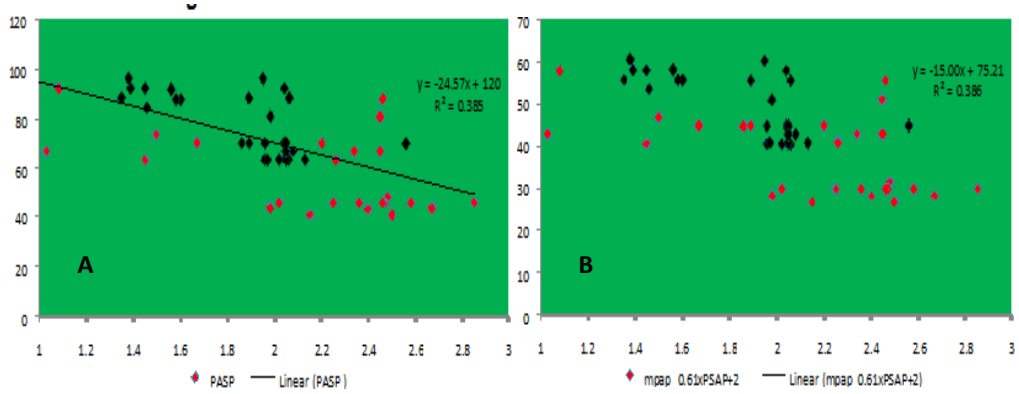

Figure 1: Scatter diagram of (A) TTCx103 versus PASP; (B) TTCx103 versus mPAP.

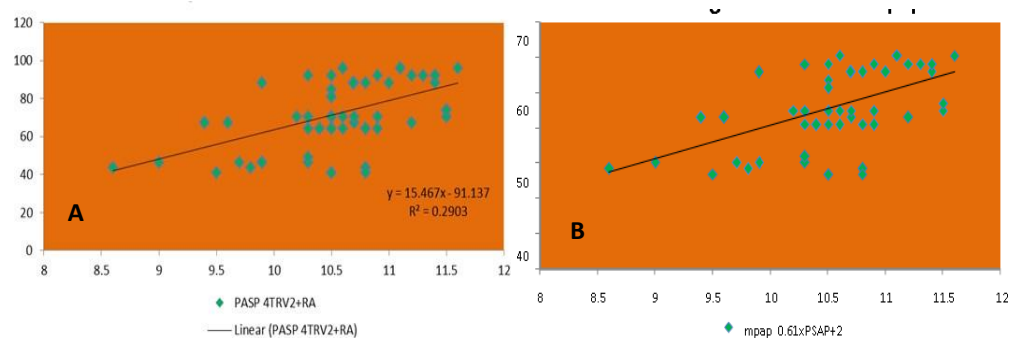

Figure 2: Scatter diagram of (A) MPV versus PASP_4TRV2RA; (B) MPV versus mPAP.

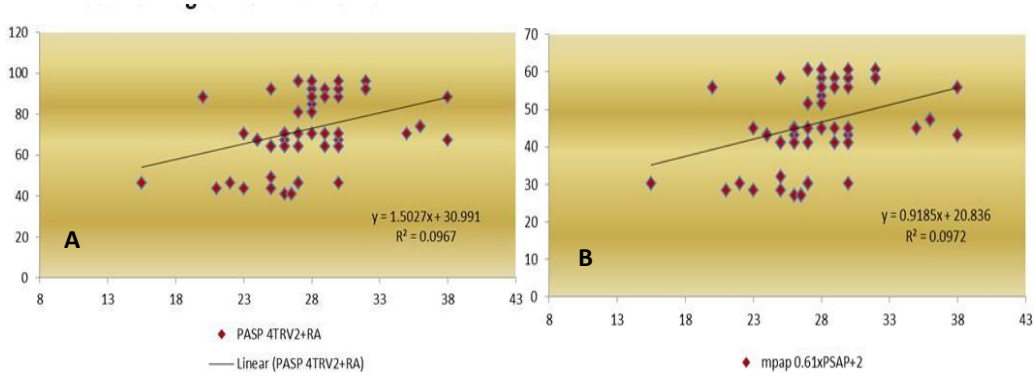

Figure 3: Scatter diagram of (A) P-LCR versus PASP_4TRV2RA; (B) P-LCR versus mPAP.

Review after 2 months of treatment

All enrolled given treatment according to the PH group which they belonged to and patients were reviewed after 2 months. The effect of treatment was assessed in terms of functional class, hemogram and echo. It was observed that after treatment, 51% patients with moderate PHT were reduced to 37%. It was observed from current investigation that after treatment, there was no significant change in dimensions of RA (right atrium) and RV (right ventricle). It was also observed that with treatment, the thrombocyte count and the platelet indices were altered as mPAP decreased with treatment. Thrombocyte count correlates with mPASP. It was seen that as mPASP increased, TTC (total thrombocyte count) decreased. MPV (mean platelet volume) was also observed to have a significant correlation with PASP (pulmonary artery systolic pressure), mPAP and severity of pulmonary hypertension and left ventricular systolic function. It was observed through study findings that P-LCR correlated with PASP, mPAP and severity of pulmonary hypertension. Study results revealed that after treatment, the functional severity of pulmonary hypertension and poor prognostic factors like pericardial effusion and clot improved without significant improvement in right atrial and ventricular dimensions.

DISCUSSION

Aetiology

In current study, PH due to chronic lung disease was found to be the commonest cause for PH in 50 (48%) patients. Cause of PH prevalence observed in current study is in accordance with the previous studies conducted on Indian population, while in western countries cardiac factors forms the most common cause of PH.[28,29] Amongst chronic lung diseases as causative factor for PH, COPD and old pulmonary tuberculosis were observed as the most common causes (20%), this may be due to increased prevalence of smoking and pulmonary tuberculosis in Indian population. The second most common cause of PH among five groups was found to be cardiac diseases which accounted for PH in 34% patients. Among cardiac diseases, valvular diseases emerged as the major cause followed by systolic dysfunction. It was also inferred from study findings that there could be significant overlap between group 2 and group 3 types of PH due to presence of similar risk factors and pathogenic mechanisms in both the types.

Age and sex

41 to 50 years was observed as the most common age group for PH occurrence as total 37 out of 104 patients in the mentioned age group were diagnosed with PH. Incidence of PH was observed to be very low in younger population where congenital and valvular heart disease predominated. In current study, prevalence of PH was more common in males 56 (53%), compared to females may be because more number of COPD cases occurred in males due to smoking. But the prevalence of PAH due to idiopathic causes and occurrence of connective tissue disorders leading to PH predominated in females.

Functional class and severity of PH

About 43 (41%) patients, admitted and diagnosed for PH belonged to WHO functional class 3, probable reason being patients with milder functional class of PH do not seek medical attention. Most of the diagnosed patients were having moderate degree of pulmonary hypertension with 53 patients had mPAP between 41 to 55 mmHg. This may be due to delay in early diagnosis of PH. A delay of 2 to 5 years in diagnosis has been documented in various PH registries.

Peripheral smear in PH

Almost 50% of the patients with PH had a normal peripheral smear and almost all patients with PAH showed large platelets as compared to other groups. Thrombocytopenia was not a regular association seen in pulmonary hypertension, but when present indicated poor prognosis as also evidenced and reported by Weaver et al.[30]

Valves in PH

Mild tricuspid regurgitation was commonly observed valvular lesion, seen in 34 cases. Mild TR was mostly observed with moderate pulmonary hypertension causing RA and RV dilatation. It was observed that most of the patients presented late after development of moderate hypertension.

Bleeding time and clotting time

There was no significant difference in bleeding or clotting time among the different groups of pulmonary hypertension patients. No correlation was observed between bleeding or clotting time and severity of PH.

TTC

TTC was observed to be lower than normal in all groups of PH ranging from 1.93×103 to 2.13×103. It was observed that patients with PAH had lower platelets than rest of the groups ranging from 1.67×103 to 1.84×103. There was no correlation observed between the platelet count and PASP, mPAP and the severity of PH. Results of current study were in accordance with study by Guvencetal.[31]

MPV

There was an inverse correlation observed between number of platelets with volume and distribution of platelets. In current study, MPV increased in all causes of PH especially with PAH ranging from 11.3 to 10.9 owing to the increased activation of platelets. This is seen in accordance with the study done by Guvencetal, comparing the MPV in different cause of pH.[31]

PDW

It was observed that as MPV, PDW correlated with the severity of PH, it also correlated with the presence of systolic function as also reported by Fajita et al in platelet indices and left ventricular function studies.

Presence of RA and RV dilation was observed to be associated with moderate to severe grades of PH. It was also observed that decreased TAPSE of less than 16 was associated with severe PH.

Review of patients two months after treatment

11 patients could not be reviewed as they lost follow up. Treatment for PH was given according to the functional class they presented, either with calcium channel blockers, endothelial receptor antagonists or prostanoids. Clinical assessment of pulmonary hypertension using WHO functional classification showed improvement post treatment in groups 1, 2 and 3. Groups 4 and 5 didn't show improvement and their condition worsened as surgery being the only treatment option in groups 4 and group 5.

Severity of PH post treatment

Total 51% of patients who were initially diagnosed with moderate PH, reduced to 37% after treatment. 32% of patients with severe PH reduced to 26% following treatment. The response to treatment was good with groups 2 and 3 compared to other groups. Response in patients with moderate hypertension was found to be better than severe groups may be due to onset of irreversible changes and progression of disease. It was observed that patients are needed to be diagnosed early and treatment is to be initiated early for better responses. The presence of right atrial and ventricular dilatation continued to be present after treatment, probable justification for this may be because functional improvement occurs earlier than the anatomical changes. Longer treatment and follow up studies are needed for the anatomical improvement investigations.

Limitations

Limitations of the current study were the small sample size of the study group was not adequate to make concrete recommendations. Longer treatment and follow up studies could have aided to establish more significant correlations between the results.

CONCLUSION

PH is the ultimate end result of alteration in pulmonary vasculature initiated and propagated by diverse pathologic mechanisms. Platelets are closely associated in both initiation and progression of disease. Platelet activation is associated with all groups of pulmonary hypertension. Platelet indices are found to be altered in all causes of PH. Thrombocytopenia is found to be an independent predictor of poor prognosis and mortality among patients with PH. Most of the cases of pulmonary hypertension are diagnosed only after development of moderate hypertension. PH should be suspected early whenever patients present with overlapping symptoms of cardiac and respiratory illness. Periodic screening with echocardiogram should be indicated especially in patients having high risk factors for PH like connective tissue diseases. Echocardiographic evidence of RA/RV dilation, TAPSE <16, pericardial effusion are associated with severe PH and indicate a poorer prognosis. Treatment of PH should be initiated after classification of patients to appropriate groups as the aetiology and treatment is different for each group. Earlier detection and early initiation of appropriate treatment is essential and advised in PH. Following treatment, functional improvement occurs earlier than the anatomical improvement which calls for a longer duration of treatment and follow up.

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