Predictors of Prognosis in Pulmonary Hypertension

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ABSTRACT

Background: Factors that may influence long term survival in PHT are not well established despite progress in its diagnosis and management.

Radiological findings of enlarged pulmonary artery size on Computed Tomography (CT) of chest may correlate with the presence of PHT but does not predict severity.

Our study evaluates severity parameters, CT chest findings and their correlation to survival.

Materials and Methods: 30 patients with established diagnosis of PHT were included in the study. Duration of study was 6 years; survival was calculated from the time of registry till either death of patient or end of the study.
9 variables were recorded. CT chest assessment of pulmonary artery diameter and its ratio to the ascending aorta (PA /AO ratio) were recorded. Pulmonary artery pressures were recorded by electrocardiogram and right heart catheterization.

Results: Most patients had 8/9 parameters positive, 8 patients (26·6%) died; they were labelled as high risk group. Worsening of 6 parameters was noticed in high risk group; RV size was increased to 25%, Average PVR was 29·4% higher, 6 min walk distance 21% less, pro BNP 96% higher, GGT and Alkaline phosphatase were 3 times higher and an increase in PA/AO ratio was noticed. Despite escalation of all standard therapeutic interventions, the average survival in high risk group was 2·3 years.

Conclusions: Worsening of 6 parameters observed in our study suggests poor prognosis. Such patients should be referred for early transplant.

INTRODUCTION

Pulmonary Hypertension is being recognized as a frequent medical problem as a primary idiopathic disorder or as secondary disorder associated with many systemic illnesses [1].

Factors that may influence long term survival in PHT are not well established despite progress in its diagnosis and management [2-10].
Patient with NYH Association functional class III and above, increase pro BNP, dilated right ventricle with increased right ventricular pressure has been reported as poor prognosis indicators [11].

Radiological findings of enlarged pulmonary artery size on Computed Tomography (CT) of chest may correlate with the presence of PHT but does not predict severity [1&12-17], no correlation has been established with CT findings in PHT and associated long term prognosis. With emerging new therapies the need for lung or heart lung transplant has significantly reduced. The impact of new evolving treatment on the subgroup of patients with aforementioned poor prognostic signs has not been look at.

Our is the first study that evaluates severity parameters, CT chest findings and their correlation to survival. Patients identified as high risk in our study these patients failed to respond to any treatment intervention and have shown continuous deterioration in their status with poor long-term survival. In our opinion, these patients should be considered for early referral for transplant.

PATIENTS AND METHODS

Patients were registered and were being treated at a tertiary care institution. 30 patients were involved in our review. It was one year enrollment period (2009-2010) then 6 years follow up (2010-2016).

The enrollment included every adult patient (>18 years old) underwent right heart catheter and was diagnosed with pulmonary hypertension regardless of the underlying cause. There was no exclusion criteria.

All patients received standard therapy for the treatment of pulmonary hypertension that included Sildenafil, bosentan or macitentan, systemic or inhaled prostanoids and anticoagulation, following the standard guidelines for management of PHT [1].

Their data was reviewed, 9 parameters were observed and their demographics were recorded (Tables 1-4).

The duration of our study was 6 years; survival was calculated from the time of registry till either death of the patient or end of the study. 6 patients died during follow up period, and those were labelled as high risk group.

Pulmonary artery diameter and the pulmonary and aortic diameter size ratio were recorded at the level of main pulmonary artery trunk (Figure 1). Right and left main bronchus and right and left pulmonary artery size and respective ratios were calcul-

-calculated, superior and inferior vena cava diameter were recorded, pulmonary artery systolic pressure by echocardiogram and right sided cardiac catheterization was recorded. Measured indices were looked at in correlation with pulmonary artery pressure total of 9 parameters; mean pulmonary artery pressure by right heart catheterization (mPAP), Pulmonary Vascular Resistance (PVR), Left Ventricular Ejection Fraction (Lt Vent. EF), Right ventricular size by echocardiogram (RT Vent. size), Systolic pulmonary artery pressure by echocardiogram (sPAP by echocardiogram), Radiological assessment by CT chest, to include Pulmonary artery diameter (PA diameter) and Ratio of pulmonary artery diameter to ascending aorta diameter (PA/AO ratio), 6 minute walk distance (6MWD), Pro-brain natriuretic peptide (Pro-BNP) and Liver function tests (LFTs) were recorded (Graph 2). Their association with mortality was assessed.

Statistical data analysis SAS institute Inc., Cary, NC, USA, SAS version 9.4 was used. Descriptive statistics for the continuous variable without are reported as mean + standard deviation and categorical variables are summarized as frequencies and percentages. Continuous variable are compared by general linear. Motel and Pearson correlation, the level of statistical significance is set at $P < 0.05$.

RESULTS

Most patients had significantly advance disease, majority of patients had 8/9 parameters positive, 8 patients out of 30 (26·6%) died; these patients were labelled as high risk group. This high risk group had significant worsening of 6 parameters (Table 1) the average PVR in this high risk group was 29·4% higher, average increase in RV size was 25%, 6 min walk distance was 21% less, pro BNP was 96% higher, GGT and Alkaline phosphatase were 3 times higher and an increase in PA/AO ratio was noticed in this high risk group. Left ventricular ejection fraction, sPAP, main pulmonary artery diameter, ALT, AST and bilirubin did not show correlation with poor outcome. The average survival in high risk group was 2·3 years despite escalation of all standard therapeutic interventions (Table 1).

DISCUSSION

Due to the rapid development of new treatment strategies for PHT, it has become very difficult to assess long term survival in these patients. Claims of performance and survival benefits are minimal with a huge cost to health care system and to the individual patients [17-20]. Timely interventions like, lung transplant decisions maybe delayed with false security of potential benefit [21-22].

In our study, we found a strong correlation of poor survival with the worsening of 6 parameters (Table 1), i.e., increase in PVR, an increase in RV size, a decrease in 6 MWD, an increase in pro BNP, GGT and Alkaline phosphatase and an increase in PA/AO ratio. (Table 1, Graph 1) while other parameters, i.e., Lt Vent EF, SPAP and PA size were abnormal in both groups (survivors and non survivors) without any impact on survival its self.
Average survival was less than 2.3 years in high risk group with positive worsening of 6 parameters while on maximum therapy (Table 1).

Parameters like pro BNP, Rt ventricular size, LFTs, 6 MWD all are variable with treatment interventions but all patients who developed worsening trend in 6 parameters (Table 1) in the high risk group required frequent hospitalizations and escalating treatment interventions but without significant benefit in long term survival10.

There was no correlation between the size of PA and the severity of PAP, but an increase in PA/OA ratio had a positive correlation with the severity of the disease and poor correlation with survival. This was probably due to a decrease in left ventricular end diastolic volume and stroke volume with increasing PAP that led to the decrease in the aortic diameter hence causing an increase in PA/OA ratio suggesting increased severity of the illness. High risk group also had an increased IVC diameter and an increased left main bronchus diameter to Lf main Pulmonary Artery (PA) branch diameter ratio.

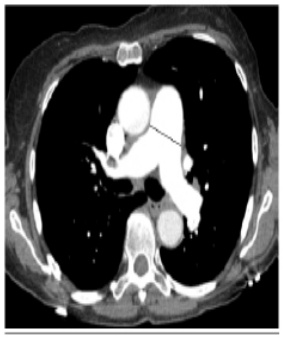
Most of the therapeutic interventions look for improvement in 6MWD which may show some variation or positive response but without an impact on patient survival [16,23-27].

Patients in the high risk group did not show any significant change in their clinical status and reversibility in their parameters despite escalating the standard therapy as mentioned above. We have a newly developed lung transplant program and most of our patients with pulmonary HTN are referred out of the Kingdom for lung transplantation where organ availability is sparse. The delay in referral for lung transplantation in high risk group may deny them a chance of timely lung transplantation which may decrease their survival as in our observation in the high risk group (Table 1).

In our opinion this sub group of patients should be referred for lung transplantation when the deteriorating trend is noticed; instead of escalating medical therapy and waiting for a possible beneficial outcome. Of course with a huge cost to the healthcare system and the patient but most likely with an unpredictable survival.

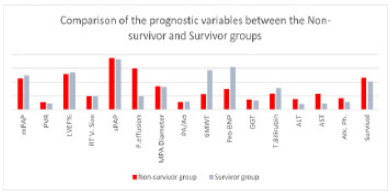
Our work needs to be further substantiated with a possible multicenter study.

FIGURE 1:



Measurements of main pulmonary artery and ascending aorta at the level of bifurcation. The main pulmonary artery (PA) size is typically taken at the level of the bifurcation of the main pulmonary artery perpendicular to the vessel wall. The aortic dimension of the ascending aorta is taken at the same level to calculate the PA to the aortic diameter (PA/Ao) ratio. The diameter is determined using the internal diameter in the contrast-enhanced image.

GRAPH 1



GRAPH 2: SHOWING RELATIONSHIP BETWEEN MEAN PULMONARY ARTERY PRESSURE (MEASURED BY RIGHT HEART CATHETER) (MPAP CATH) AND DIFFERENT VARIABLES

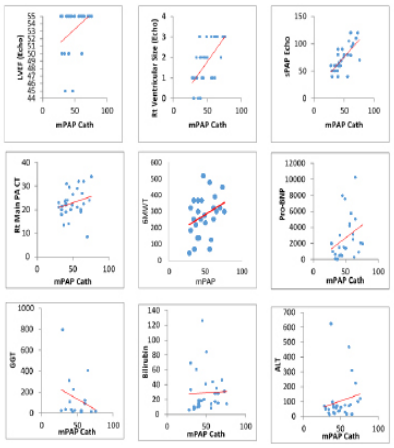


Table 1: Studied Variables of Pulmonary Hypertensions Assessment

Status	N Obs	Variable	N	Median	Mean	Std Dev	Lower 95% CL for Mean	Upper 95% CL for Mean	Minimum	Maximum
Alive	22	mPAP	22	46.0	49.4	14.8	42.8	55.9	28.0	76.0
		PVR	22	5.1	8.5	7.9	5.0	12.0	1.6	27.0
		LVEF	22	55.0	53.6	2.8	52.4	54.9	45.0	55.0
		Rt_Ventricular_size	22	1.5	1.6	1.0	1.2	2.1	0.0	3.0
		sPAP	22	64.4	73.1	25.9	61.6	84.6	40.0	120.0
		Main_PA_Diameter	22	32.0	32.5	7.0	29.4	35.6	14.5	45.0
		Distance	20	299.0	295.9	118.2	240.5	351.2	46.0	518.0
		Pro_BNP	20	1523.0	2495.8	2683.2	1240.0	3751.5	113.0	10257.0
		GGT	13	36.0	133.7	219.4	1.1	266.3	13.0	797.0
		Bilirubin	22	18.5	31.0	28.9	18.2	43.8	6.0	126.0
		ALT	22	60.0	82.3	97.3	39.2	125.5	15.3	467.0
		AST	22	63.2	87.7	81.3	51.7	123.8	11.2	359.0
		Alk_Phosphatase	22	62.0	115.5	141.6	52.7	178.2	19.3	664.0
Died	8	mPAP	8	40.5	45.4	10.5	36.6	54.1	35.0	65.0
		PVR	8	6.0	11.0	9.2	3.3	18.7	3.0	26.0
		LVEF	8	52.5	51.9	3.7	48.8	55.0	45.0	55.0
		Rt_Ventricular_size	7	2.0	2.0	1.2	0.9	3.1	0.0	3.0
		sPAP	8	77.5	75.0	16.3	61.4	88.6	50.0	100.0
		Main_PA_Diameter	8	34.5	33.7	4.8	29.7	37.7	23.5	38.5
		Distance	8	247.5	225.8	122.6	123.2	328.3	69.0	368.0
		Pro_BNP	7	3000.0	2956.4	2835.4	334.2	5578.7	33.0	7554.0
		GGT	3	110.0	175.3	206.9	-338.6	689.3	9.0	407.0
		Bilirubin	8	14.3	23.2	18.7	7.6	38.8	8.4	60.1
		ALT	8	64.0	152.0	212.8	-25.8	329.9	11.5	624.0
		AST	8	56.7	226.8	434.3	-136.3	589.9	12.0	1283.0
		Alk_Phosphatase	7	188.0	164.9	93.8	78.2	251.7	48.0	310.0
		Survival	8	2.3	8.3	13.4	-2.9	19.6	0.8	40.3

Table 2: Age and Standard Deviation of the Study Population

Gender	Frequency	percent	Mean of age	Standard deviation of age
All	30	100	40.4	12.3
Female	18	60	37.8	11.8
Male	12	40	44.25	12.4

Table 3: The Types and Percentage of Lung Diseases That Were Included In the Study

Group	Disease	Number	Percent
Pulmonary arterial hypertension	All	5	16.6
	Idiopathic pulmonary artery hypertension	3	10
	Congenital heart disease (ASD)	1	3.33
	Pulmonary capillary hemangiomatosis	1	3.33
Pulmonary hypertension due to left heart disease	All	0	0
Pulmonary hypertension due to lung diseases and/or hypoxia	All	18	60
	COPD (emphysema)	1	3.33
	Bronchiectasis	4	13.33
	Interstitial lung fibrosis	13	43.3
Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions	Chronic thromboembolic pulmonary hypertension	1	3.33
Pulmonary hypertension with unclear and/or multifactorial mechanisms	All	6	20
	Systemic disorders (Sarcoidosis)	4	13.3
	Haematological disorders (Beta thalassemia and Sickle cell disease)	2	6.66

Table 4: The Types and Percentage of Interstitial Lung Diseases That Were Included In the Study

Disease	Type	Number	Percent
	All	13	43.3
Interstitial lung fibrosis	Idiopathic pulmonary fibrosis	6	20
	Interstitial lung fibrosis 2nd to dermatomyositis	1	3.33
	Interstitial lung fibrosis 2nd to scleroderma	1	3.33
	Interstitial lung fibrosis 2nd to systemic lupus erythematosus	3	10
	Interstitial lung fibrosis 2nd Sjogren syndrome	1	3.33
	Interstitial lung fibrosis 2nd Mixed connective tissue disease	1	3.33

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