Assessment of Prognostic Factors and Natural History of Idiopathic Pulmonary Arterial Hypertension in Eastern India

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Abstract
Background and objectives: Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder of unknown aetiology associated with poor survival. Disease severity assessment by various prognostic factors play important role in management of these patients. The aim of our study was to assess various factors and their natural history and course of disease in Indian population.

Material and Methods: We followed 27 patients of IPAH after complete work up of exclusion of other causes of pulmonary hypertension and analysed various demographic, echocardiographic and haemodynamic parameters and their correlation with mortality.

Results: A total of 27 patients (14 new and 13 previously diagnosed) were followed for mean duration of 18 months. At time of data analysis, 11 patients were alive and 16 patients died with overall mortality rate of 59.25%. Among various factors, presence of pericardial effusion (p=0.005), pulmonary artery acceleration time (PAAT) (p = 0.005), tricuspid Annular Plane Systolic Excursion (TAPSE) (p = 0.0004), heart rate (p=0.031), mean blood pressure (p =0.017), right atrial pressure (p=0.045), mean pulmonary artery pressure (PAP) (p=0.039) and six minute walk distance (p=0.0002) were significantly associated with mortality. On multivariate cox proportional hazard analysis, PAAT (p =0.034), TAPSE (p=0.003) and six minute walk distance (p=0.002) remained significant predictors of mortality.

Conclusion: Idiopathic pulmonary arterial hypertension is associated with poor prognosis and survival despite advancements of disease specific therapies. Higher mortality in our study is due to delayed presentation and diagnosis. Also lack of availability of prostacyclins and lung transplantation in advanced stages of disease contribute to higher mortality in Indian setup. Non-invasive echocardiographic factors and six minute walk distance are important prognostic factors that help in disease severity stratification to identify patients in need of intensive medical management.

Introduction
Idiopathic pulmonary arterial hypertension (IPAH) is a rare disorder of unknown aetiology and poor survival. Pathophysiologically it is characterized by obliterative vasculopathy. Various invasive and non-invasive parameters (clinical, echocardiographic, cardiac catheterization) have been identified as markers of prognosis in previous studies. Also recent studies have shown improved survival with advancement of specific therapies and lung transplantation. Due to paucity of data in Indian population, this study was done to assess various prognostic factors and their impact on natural history and course of the disease in Indian population.

Methods
Patients
This study included 27 patients (14 newly diagnosed and 13 known prevalent cases of IPAH). The study had the approval of the ethics committee of our institution. All the patients were informed about the study in their vernacular language with written consent.

IPAH was diagnosed by a complete workup, including clinical history, physical examination, laboratory tests, chest radiography, electrocardiogram, pulmonary function tests, echocardiography, HRCT Chest, CT pulmonary angiography and cardiac catheterization. Criteria used to establish the diagnosis of IPAH included a mean pulmonary arterial pressure (mPAP) of more than 25 mmHg at rest with normal pulmonary capillary wedge pressure (PCWP) and absence of other disease known to cause or to be associated with secondary pulmonary hypertension.

Study Protocol
Following variables were assessed in our study protocol:
1. Demographic data: Age, Sex
2. Symptoms and Duration of symptoms
3. World Health Organization (WHO) Functional Class at presentation and during follow up (stable or worsening).
4. Echocardiography: Following echocardiographic variables were analysed using a predefined imaging protocol: Right ventricular end-diastolic area (RVEDA), Right ventricular systolic function as estimated by the right ventricular percent change in area, Right atrial area, Eccentricity index, presence of pericardial effusion, Severity of Tricuspid Regurgitation, Tricuspid regurgitation peak pressure gradient, Pulmonary Artery Acceleration Time (PAAT), Tricuspid Annular Plane Systolic Excursion (TAPSE), Inferior
Fig. 1: Kaplan-Meir Survival curve of the study population

Table 5: Univariate analysis of quantitative variables among survivors and non-survivors

<table>
<thead>
<tr>
<th>Label</th>
<th>Cohort = Survivors, N=11</th>
<th>Cohort = Non-Survivors, N=16</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGE</td>
<td>Median Lower Quartile Upper Quartile</td>
<td>Median Lower Quartile Upper Quartile</td>
<td>0.138</td>
</tr>
<tr>
<td>Symptom duration</td>
<td>29 18 45 41 30 53</td>
<td>22 10 29.1 15.5 0.45</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>13 12 14 13.6 12.55 15.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC%</td>
<td>84 77 87 82 78 86</td>
<td>86 80 88 88 45</td>
<td></td>
</tr>
<tr>
<td>FEV1%</td>
<td>88 81 89 86 80 88</td>
<td>88 88 88 88 45</td>
<td></td>
</tr>
<tr>
<td>RVEDA</td>
<td>19.2 18.1 26.8 23.2 17.65 29.4</td>
<td>45 35 60 50 60 70 0.67</td>
<td></td>
</tr>
<tr>
<td>RV area change %</td>
<td>23 20.98 28.4 20.35 17.9 23.6</td>
<td>0.068</td>
<td></td>
</tr>
<tr>
<td>RA area</td>
<td>18.5 15.6 24.3 17.6 15.4 21.5</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td>Systolic Eccentricity Index</td>
<td>1.72 1.6 2.07 1.735 1.54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Eccentricity Index</td>
<td>1.59 1.5 1.8 1.575 1.375 1.735</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>TR max pressure gradient</td>
<td>72 54 77 67 60 75</td>
<td>75 75 75 75 37</td>
<td></td>
</tr>
<tr>
<td>PAAT</td>
<td>68 64 90 54 39 67.5</td>
<td>67.5 67.5 67.5 67.5 0.005</td>
<td></td>
</tr>
<tr>
<td>TAPSE</td>
<td>19 17 21 9 6.5 11.5</td>
<td>11.5 11.5 11.5 11.5 0.0004</td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>68 59 74 66 61 72</td>
<td>72 72 72 72 0.76</td>
<td></td>
</tr>
<tr>
<td>Heart Rate</td>
<td>78 66 84 90 81.5 100</td>
<td>100 100 100 100 0.031</td>
<td></td>
</tr>
<tr>
<td>Mean BP</td>
<td>100 92 106 87 80 92</td>
<td>92 92 92 92 0.017</td>
<td></td>
</tr>
<tr>
<td>RA Pressure</td>
<td>7 4 11 14 7 18</td>
<td>18 18 18 18 0.045</td>
<td></td>
</tr>
<tr>
<td>Mean PAP</td>
<td>45 40 58 65 52 80</td>
<td>80 80 80 80 0.039</td>
<td></td>
</tr>
<tr>
<td>PCWP</td>
<td>4 4 5 5 4 6</td>
<td>6 6 6 6 0.0022</td>
<td></td>
</tr>
<tr>
<td>Six minute walk distance</td>
<td>966 832 1100 385 155 457</td>
<td>457 457 457 457 0.0002</td>
<td></td>
</tr>
</tbody>
</table>

vena cava (IVC) diameter and collapsibility, Left ventricular ejection fraction (LVEF).

5. Cardiac catheterization: Right heart catheterization was performed during the study after informed consents. Hemodynamic measurements included heart rate, mean arterial pressure, right atrial pressure, mean pulmonary artery pressure and mean pulmonary capillary wedge pressure. Pulmonary vasoreactivity testing was not done.

6. An unencouraged 6-min walk test was performed as an assessment of exercise capacity.

All patients were treated with vasodilators and oral anticoagulants; and therapy for heart failure as per guidelines directed was given to patients with clinical evidence of right heart failure. Long term follow up was done by regular 6 weekly outpatient clinic visits and by telephone contact.

**Statistical analysis**

Both descriptive and inferential statistical analysis were done. In descriptive statistical analysis results on continuous measurements were presented on Mean ± Standard deviation or Median (with interquartile range) depending on the distribution of data. The normality of the study variables was tested through Shapiro-Wilk and Anderson Darling test. The results on categorical measurements were presented in number (%). P value <0.05 was considered as statistically significant.

**Inferential statistical analysis**

Statistical analysis was performed...
Table 7: Multivariate Cox Proportional Hazard model for Identifying Predictors (continuous variables) of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>p</th>
<th>Hazard ratio for mortality</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAAT</td>
<td>-0.06881</td>
<td>0.0326</td>
<td>4.4567</td>
<td>0.034</td>
<td>0.93</td>
<td>0.89-0.96</td>
</tr>
<tr>
<td>TAPSE</td>
<td>-0.82066</td>
<td>0.28084</td>
<td>8.539</td>
<td>0.003</td>
<td>0.44</td>
<td>0.18-0.72</td>
</tr>
<tr>
<td>Heart rate</td>
<td>-0.10028</td>
<td>0.05087</td>
<td>4.0741</td>
<td>0.053</td>
<td>0.90</td>
<td>0.83-1.01</td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.08549</td>
<td>0.05477</td>
<td>2.4362</td>
<td>0.1186</td>
<td>0.91</td>
<td>0.36-1.44</td>
</tr>
<tr>
<td>RA pressure</td>
<td>-0.02893</td>
<td>0.07263</td>
<td>0.1586</td>
<td>0.690</td>
<td>0.97</td>
<td>0.33-1.62</td>
</tr>
<tr>
<td>Mean PAP</td>
<td>0.04143</td>
<td>0.03672</td>
<td>1.2727</td>
<td>0.259</td>
<td>1.042</td>
<td>0.064-1.076</td>
</tr>
<tr>
<td>Six minute walk distance</td>
<td>-0.175</td>
<td>.576</td>
<td>12.503</td>
<td>0.002</td>
<td>0.98</td>
<td>0.97-0.99</td>
</tr>
</tbody>
</table>

Objective parameters (p = 0.002) were significantly associated with mortality.

As illustrated in Table 7, PAAT, TAPSE and six minute walk distance were significant predictors of mortality in multivariate cox proportional hazard analysis.

**Discussion**

Pulmonary hypertension (PH) is defined as an increase in mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest as assessed by right heart catheterization (RHC). Pulmonary arterial hypertension (PAH) is defined as PH with normal left sided filling pressure (i.e., pulmonary capillary wedge pressure (PCWP) <15 mm Hg and an increased pulmonary vascular resistance (PVR).

Term IPAH corresponds to subgroup of PAH patients, without any familial history of PAH or known associated risk/triggering factor. Term ‘PH on exercise’ is no longer used due to insufficient data to define that which levels of exercise-induced changes in mPAP or PVR have prognostic implications.

IPAH is a progressive disease with a poor long term prognosis. Evaluation of disease severity and prognostic factors is important both for diagnosis and for therapeutic management. There is limited data and lack of consensus on prognostic factors. The reason behind this is that IPAH is fatal and a rare disease.

In our study of 27 patients, cumulative mortality rate was 59.25%. The mean survival duration of non-survivors was 3.76±3.63 months. Higher mortality and lower survival in our study was similar to as reported by Eysmann et al who reported mean survival rate of 4.8±8.0 months. However, the National Institutes of Health (NIH) registry reported estimated median survival rate of 2.8 years, with 1 year, 3 years and 5 years survival rates of 68%, 48% and 34% respectively. Lower survival rate in our study was probably due to higher functional class of patients during inclusion in study, lack of availability and use of prostacyclins and transplantation in WHO Class IV patients due to lower socioeconomic profile as compared to Western population.

At inclusion, the mean age of study population was 36.9±14.1 years with female predominance (female/male ratio: 2.3:1). Our findings are similar to as reported in literature and various previous registries, that women in third decade of life is the group with highest disease frequency.

The mean symptom duration of the patients included in the study was 24.7±26.2 months. This long symptom duration suggests that patient already have advanced disease when they presents because symptoms (fatigue, chest discomfort) in early stages are difficult to recognize and are often ignored.

Demographic characteristics i.e. age, sex distribution and symptom duration were statistically similar between survivors and non-survivors.

Among the presenting symptoms, exertional dyspnea was most common (100%) followed by palpitation (59.26%), chest pain (25.93%), peripheral edema (25.93%) and syncope (7.41%). Dyspnea occurs due to reduced oxygen delivery during physical activity as a result of an inability to increase cardiac output in response to increased demand.

On comparison among survivors and non survivors, Peripheral edema had statistically significant association with all-cause mortality on both univariate (p value 0.021) and multivariate analysis (p value 0.010), while there was no significant association with dyspnea, palpitation, chest pain and syncope. Peripheral edema is a sign of right ventricle failure and hence is more likely to be associated with advanced pulmonary vascular disease.

The functional status of patients during inclusion in the study according to WHO classification was as follows: 7.41% of the patients were in WHO Class I, 33.33% were in WHO Class II, 40.74% were in WHO Class III and 18.52% were in WHO Class IV. Most of the patients are in WHO Class II and III at the time of presentation. Relative
paucity of patients in WHO Class I may be due to difficulty in recognizing mild degree of symptoms and WHO Class IV due to higher mortality and poor survival in advanced disease. Although WHO functional class is a good indicator of disease severity, still it is a subjective measure and is confounded by other associated comorbidities such as obesity and age, coexisting diseases and exercise capacity.

Echocardiogram has been an important tool both in the term of diagnosis and prognosis. Among the above variables assessed, presence of pericardial effusion (p value=0.005), TAPSE (p value=0.0004), PAAT (p value=0.005), had a statistically significant association with mortality. On multivariate analysis, presence of pericardial effusion (p value=0.005), TAPSE (p value=0.003) and PAAT (p value=0.034) remained statistically significant.

Pericardial effusion occurs because of impaired lymphatic drainage because of raised right atrial pressure. Normally, myocardial lymph drains into right atrium, so raised atrial pressure will impair lymphatic drainage. Our study support the relation between severity of pericardial effusion and elevation of RA pressure, both of which are significantly associated with survival.

TAPSE was a prognostic factor for mortality on both univariate (p value 0.0004) and multivariate analysis (p value=0.003) in our study. TAPSE is a relatively simple assessment of the longitudinal movement of the lateral tricuspid annulus towards the right ventricle apex and has been shown to correlate with right ventricular systolic function. Forfia et al found cut-off value of 18 mm and TAPSE<18mm correlated with greater degrees of RV dysfunction.

Pulmonary artery acceleration time (PAAT) was associated with mortality on both univariate (p value 0.005) and multivariate analysis (p value 0.034) with a HR=0.93, 95% CI=0.89-0.96. Studies have shown strong association between PAAT and pulmonary pressures, because PAAT assess maximum acceleration of blood flow which occurs earlier with elevated right ventricle ejection impedance due to pulmonary vascular disease.

Right ventricular end diastolic area, Right ventricular % area change, Right atrial area were found not to be significantly associated with mortality. This could be because assessment of above variables are operator dependent and vary significantly dependent on patient’s body habitus. Also in diseased hearts, ventricular cavity shapes are distorted and getting true area on echocardiogram in sometimes difficult.

In our study, the eccentricity index, whether end diastolic or end systolic, did not appear to be a prognostic factor for mortality, which was statistically significant prognostic factor in analysis by Raymond et al. This may be due to difficulty of measurement of true diameters of distorted cavities, as qualitatively it is very easy to see an abnormal septal curve leading to D-shaped left ventricle cavity.

Severity of tricuspid regurgitation and Estimated Systolic PAP from maximum peak tricuspid regurgitation pressure gradient also did not correlate with mortality. This was in agreement in findings with earlier series by Yeo et al. This is because towards the advanced stages of disease, when right ventricle fails, severity and pressure gradient of tricuspid regurgitation starts decreasing. So assessment of pulmonary vascular disease based only on severity and pressure gradient of regurgitant jet may underestimate severity of the disease.

Among the cardiac catheterization parameters, heart rate (p value=0.031), mean blood pressure (p value=0.017), mean RA pressure (p value=0.045) and mean PA pressure (p value=0.039) correlated significantly with survival. Higher mean RA pressure and high mean PAP among non-survivors are predictive of more advanced pulmonary vascular disease. Higher heart rate and lower blood pressure among non-survivors also indicates right ventricle failure and fixed cardiac output.

There is large supportive data on haemodynamic and cardiac catheterization parameters. In NIH registry, three measured haemodynamic variables were associated with increased risk of death by univariate analysis: increased mPAP (odds ratio:1.16, CI=1.05-1.28); increased mRAP (odds ratio:1.99, CI=1.47-2.69); and decreased Cardiac Index (odds ratio:0.62, CI=0.46-0.82). In fact, a regression equation was formulated from data of NIH registry in which these three haemodynamic variables were used to estimate survival.

Exercise capacity of our patients was measured with six minute walk distance due to its ease of administration and reproducibility. The mean value of six minute walk distance in our study was 580±362 m; while REVEAL registry reported mean value of 370±127 m.

Six minute walk distance had a high statistically significant association with mortality on comparison among survivors and non-survivors with non-parametric Wilcoxon test (p value=0.0002). It remained statistically significant on multivariate analysis (p value=0.002). Our findings are supported by previous reported series that prognosticate six minute walk distance as predictive factor of mortality.

**Limitations**

It was a single centre study with small sample size of 27 patients (14 incident and 13 prevalent cases) with limited duration of follow up (mean follow up of 13.94±3.61 months). Small sample size could not be avoided because of rarity of disease and short mean survival due to advanced progressive nature of disease.

Genetic testing for identifying Heritable PAH which forms 6-10% of patients with PAH was not done in our set up due to lack of availability. As the term IPAH is reserved for patients without a family history and without an identified genetic abnormality.

Pulmonary vasoreactivity testing to detect patients responsive to high dose of calcium channel blockers was not done.

As all the patients were on anticoagulants, phosphodiesterase 5 inhibitors (PDE 5 inhibitors) and endothelin receptor antagonists, further sub group analysis to study the effect of treatment on mortality could not be done.

Lack of use of prostacyclins and lung transplantation in WHO FC IV patients because of poor affordability due to low socioeconomic profile and lack of easy availability of transplantation was the reason of high mortality rate (59.25%) seen in our study on Indian population as compared to previous data.

Further large multicenter study including large pool of patients with
increased duration of follow up with newer echocardiographic tools is necessary in Indian population.

**Conclusion**

Idiopathic pulmonary arterial hypertension is a rare disease with a short mean survival time. Females of third decade are most commonly affected. By the time of presentation, patients usually are in WHO functional class II or III. Various factors can be used to assess the disease prognosis so that early diagnosis and therapy escalation can be done. Among symptoms, presence of peripheral oedema is associated with worse survival suggestive of right ventricle failure. Echocardiography can be used as a tool to assess prognosis. Presence of pericardial effusion, lower TAPSE and PAAT are all indicators of advanced disease and poor survival. Hence, non-invasive methods like echocardiography may be used to evaluate prognosis when diagnosis of IPAH has been made and invasive testing is unavailable or risky. These characteristics may help identify patients appropriate for more intensive medical therapy.

Higher mortality in Indian population as compared to previous data indicates that further work needs to be done on both early diagnosis as well as therapeutic management (availability of prostacyclins and lung transplantation) of advanced disease.

**References**