**STUDY HIGHLIGHTS**

**Background:** IPAH is characterized by precapillary PH of unknown origin. There is considerable variability in the clinical presentation.

**Objective:** Cluster analysis of large patient cohort from the COMPERA registry to identify clinical phenotypes of adult patients with IPAH.

**Design:** Prospective registry analysis (Clinicaltrials.gov identifier NCT01347216). 841 treatment naïve IPAH patients. Hierarchical agglomerative clustering analysis using baseline parameters of age, sex, DLCO, smoking status, and comorbidities/risk factors for left heart disease (obesity, hypertension, coronary heart disease, diabetes mellitus).

**Outcomes:** survival, treatment response (functional class, change in 6MWD and BNP/NT-proBNP).

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<table>
<thead>
<tr>
<th>Cluster</th>
<th>Number of Patients</th>
<th>Median Age</th>
<th>Sex</th>
<th>Smoking History</th>
<th>Comorbidities</th>
<th>DLCO &lt;45%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>106 (12.6%)</td>
<td>45 years</td>
<td>76%</td>
<td>31%</td>
<td>no</td>
<td>≥45%</td>
</tr>
<tr>
<td>2</td>
<td>301 (35.8%)</td>
<td>75 years</td>
<td>98%</td>
<td>0%</td>
<td>at least 1</td>
<td>&lt;45%</td>
</tr>
<tr>
<td>3</td>
<td>434 (51.6%)</td>
<td>72 years</td>
<td>72%</td>
<td>79%</td>
<td>at least 1</td>
<td>&lt;45%</td>
</tr>
</tbody>
</table>

Factors differentiating Cluster 3 from Cluster 2: increased frequency of male sex, smoking history and DLCO <45% (cardiopulmonary phenotype)

**Results:**
Cluster 1 had a better response to PAH treatment than the other clusters.
5 year survival was 84.6% in Cluster 1, 59.2% in Cluster 2, and 42.2% in Cluster 3 (p < 0.001).
Adjusted for age, the survival differences between Clusters 1 and 3 and Clusters 2 and 3 remained significant.

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**Limitations**

- Enrollment/selection bias
- Incomplete datasets
- Variables of interest selected in advance, necessitating a degree of assumption.
- The number of variables considered in this cluster analysis was relatively low.

**Reviewer comments:**
Whilst IPAH phenotypes may differ in clinical presentation, response to therapy, and survival, poor survival in cluster 2 and 3 may also reflect the impact of age and comorbidities, which are well established risk factors for poor survival in PAH.
Question: What is the relationship between age and hemodynamic and functional assessment in PAH?

Design: Retrospective analysis of PAH patients in the Pulmonary Hypertension Association Registry

Inclusion: 769 PAH patients age ≥18 were included. Patients with CTEPH, persistent PH of the newborn, and PH due to congenital heart disease were excluded.

Outcomes: Hemodynamic profile and functional risk assessment in different age groups

Results: Older patients had more CTD-PAH and less drug induced-PAH. Increased age was associated with reduced 6MWD and lower mPAP. Pulmonary arterial compliance (PAC), cardiac index, RV stroke work index, and % predicted 6MWD were unrelated to age. Relative to their PVR, older patients had lower PAC and worse RV performance.

In tracing the relationship between pulmonary arterial compliance and age, it is unclear which parameter in pulmonary arterial compliance calculation accounted for lack of variation with age.

Factors that affect the RV ability to condition to increased afterload need to be considered.

Relationship between functional measures and age is confounded by factors other than PAH.

Limitations:

- Important data on patients’ comorbid conditions and PAH therapy was not presented.
Yogeswaran A et al. Risk assessment in severe pulmonary hypertension due to interstitial lung disease.


**STUDY HIGHLIGHTS**

**Question:** What is the prognostic value of a truncated version of the European Society of Cardiology/European Respiratory Society (ESC/ERS) pulmonary hypertension (PH) risk stratification scheme in severe PH with interstitial lung disease (ILD)?

**Design:** Retrospective single center study

**Inclusion:** All ILD patients who were referred for invasive diagnostic workup of suspected severe PH

**Outcomes:** Transplant (Tx) free survival, stratified by risk grade

**Results:** 5-year Tx-free survival of low, intermediate and high-risk patients was 43%, 15%, 4% (P=0.01) respectively.

**CENTRAL FIGURES**

Risk stratification scheme is clinically relevant for prediction of Tx-free survival in patients with severe PH due to ILD

**REVIEWER’S COMMENTS**

- A major strength is the inclusion of all ILD patients (not just IPF, IIP)
- Mean (±SD) mPAP was 42 (±8)
- Tx was an infrequent outcome (only 5%)
- DLCO was not associated with increased mortality in severe PH with ILD, hence outcomes may have been driven primarily by RV function
- Role of PAH specific therapies remains unclear

**Limitations:**
- Retrospective single center analysis
- Possibility of selection and enrollment bias