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Early View

Research letter

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Pulmonary vascular resistance predicts mortality in patients with pulmonary hypertension associated with interstitial lung disease: Results from the COMPERA registry

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Take home message: In patients with pulmonary hypertension associated with interstitial lung disease, pulmonary vascular resistance provides stronger prognostic information than mean pulmonary arterial pressure

Key words: pulmonary hypertension, interstitial lung disease, haemodynamics, pulmonary vascular resistance, survival, prognosis

Pulmonary hypertension (PH) is a common complication of many chronic lung diseases, especially chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD) [1]. In these conditions, the development of PH is associated with an aggravation of symptoms and an increase in mortality risk. In most patients with chronic lung disease, the haemodynamic severity of PH is mild to moderate, while some patients develop severe PH, which is presently defined by a mean pulmonary arterial pressure (mPAP) ≥35 mmHg or mPAP ≥25 mmHg in the presence of a cardiac index <2.0 l/min/m^2 [2]. These haemodynamic criteria were introduced per expert consensus but were not based on solid data.

In patients with PH associated with COPD, Zeder and co-workers showed recently that a pulmonary vascular resistance (PVR) >5 WU was the strongest haemodynamic predictor of mortality, and the authors suggested to use this threshold to define severe PH in this group of patients [3]. We wondered whether this threshold might also apply to patients suffering from PH associated with ILD (PH-ILD).

To address this question, we analysed data from the *Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension* (COMPERA). Details of COMPERA (www.COMPERA.org; Clinicaltrials.gov identifier NCT01347216) have been reported previously [4]. In brief, COMPERA is a large-scale ongoing web-based PH registry that prospectively collects detailed data on characteristics, treatment and outcomes of patients who receive therapies for PH. PH centres from various European countries participate (Austria, Belgium, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Netherlands, Slovakia, Switzerland, United Kingdom), with about 80% of the enrolled patients coming from Germany. COMPERA has been approved by the ethics committees of all participating centres, the data are pseudonymized, and all patients provide written informed consent prior to inclusion.

For the present analysis, patients were selected from the COMPERA database by the following criteria: (i) adult patients newly diagnosed with PH-ILD between June 13th, 2006, and January 21st, 2021, (ii) haemodynamics available at inclusion with mPAP ≥25 mmHg and PAWP ≤15 mmHg, and (iii) at least one documented follow-up visit. Continuous data were presented as median and first and third quartile (Q1, Q3), categorical data as number and percentage. Follow-up ended on April 30th, 2021. Group comparisons were done by Wilcoxon rank sum test for continuous variables and by Chi-squared test for binary variables. Survival was evaluated using Kaplan-Meier curves, log-rank tests and multivariable Cox

regression models with results shown as hazard ratio (HR) and 95% confidence intervals (CI). All statistical analyses were performed using R version 4.0.0.

At cut-off day (May 1st, 2021), 10,651 patients were registered in the COMPERA data base, of which 662 patients were classified as PH-ILD. Of these, 213 patients were excluded for the following reasons (more than one may apply): PH diagnosis >6 months prior to the baseline visit (n=73), age <18 years (n=2), lung transplantation at any time (n=29), no documented follow-up visit (n=55), failure to meet the haemodynamic inclusion criteria (no baseline PVR value, n=50; PAWP >15 mmHg or mPAP <25 mmHg, n=61). Finally, 449 patients were eligible for the present analysis.

The median (Q1, Q3) age of the included patients was 73 (67, 78) years; 65% were male. Usual interstitial pneumonia was the most common underlying disease (40%), followed by combined pulmonary fibrosis and emphysema (27%), non-specific interstitial pneumonia (15%) and others (18%). Pulmonary function tests at inclusion showed a total lung capacity (TLC) of 72 (60, 86) percent predicted, a forced vital capacity (FVC) of 67 (53, 84) percent predicted, a forced expiratory volume in 1 second (FEV_1) of 69 (55, 81) percent predicted and a diffusion capacity of carbon monoxide (DLCO) of 26 (20, 34) percent predicted. Haemodynamics at baseline were as follows: mPAP 39 (33, 46) mmHg, PAWP 8.0 (6.0, 11.0) mmHg, cardiac index 2.1 (1.7, 2.6) l/min/m^2, and PVR 7.6 (6.0, 10.6) WU.

A total of 321 (71.5%) patients died during follow-up; the estimated median survival time from inclusion was 1.8 (95% CI 1.6-2.0) years. Independent predictors of death by multivariable Cox regression analyses (based on 367 patients for whom all variables were available) were higher age (HR 1.02, 95% CI 1.01-1.04, p=0.004), male sex (HR 1.38, 95% CI 1.05-1.81, p=0.022), lower TLC (HR 0.99, 95% CI 0.98-1.00, p=0.012) and higher PVR (HR 1.09, 95% CI 1.02-1.17, p=0.014). Other haemodynamic variables including mPAP, cardiac index and pulmonary artery wedge pressure (PAWP) did not predict survival (HR 0.99, 95% CI 0.97-1.02, p=0.511; HR 1.08, 95% CI 0.79-1.48; p=0.614, and HR 1.02, 95% CI 0.98-1.06, p=0.419, respectively). Similarly, FVC and FEV_1 (HR 1.00, 95% CI 0.99-1.01, p=0.964 and HR 1.00, 95% CI 0.99-1.01, p=0.658, respectively) were not predictors in the model.

When looking at various PVR cut-off levels, PVR >5 WU was associated with a significantly worse survival compared to PVR ≤5 WU (Figure 1a). The corresponding Kaplan-Meier analysis visualizes the survival difference (p=0.03; Figure 1b). Patients with PVR ≤5 WU and

>5 WU did not differ in age, sex, BMI, TLC, FVC and FEV_1 at baseline (p for all group comparisons > 0.05; data not shown). However, patients with PVR >5 WU had lower 6 min walking distance (222 [144, 300] m versus 295 [222, 351] m) and lower DLCO (25 [20, 33] percent predicted versus 34 [21, 39] percent predicted) at inclusion.

A PVR cut-off level of 8 WU had the lowest p-value (Figure 1a) and provided the best discrimination in survival (Figure 1c). In contrast, the currently proposed haemodynamic definition of severe PH in chronic lung disease failed to distinguish between survivors and non-survivors (Figure 1d).

We acknowledge the limitations of the present study including retrospective design, incomplete follow-up data, limited patient numbers, especially in the non-severe PH group, and potential selection bias given that COMPERA enrols only patients who receive treatment with drugs approved for pulmonary arterial hypertension.

Despite these limitations, our data corroborates and extends previous observations by Zeder et al. [3] as well as Vizza et al. [5], both showing that in patients with PH-COPD, PVR provides stronger prognostic information than mPAP or other haemodynamic variables. In Zeder's analysis of patients with PH-COPD, PVR >5 WU was the best prognostic cut-off value, while in our analysis of patients with PVR-ILD, the best discrimination between survivors and non-survivors was seen at PVR >8 WU. However, our analysis also showed that mortality increased significantly with PVR >5 WU. At the same time, the current mPAP-based definition of severe PH in chronic lung disease was not found to be prognostic in the present analysis. Based on these findings, while bearing in mind the limitations of this and previous analyses, we believe that PVR >5 WU should be used to define the presence of severe PH in patients with chronic lung disease.

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Figure 1 Prognostic value of pulmonary haemodynamics in patients with pulmonary hypertension associated with interstitial lung disease

Fig 1a Scatterplot of different pulmonary vascular resistance (PVR) cut-off levels and the corresponding p-values of the log-rank test

Fig 1b Kaplan-Meier survival curve stratified by PVR ≤ 5 WU and PVR > 5 WU

Fig 1c Kaplan-Meier survival curve stratified by PVR ≤ 8 WU and PVR > 8 WU

Fig 1d Kaplan-Meier survival curve stratified by the current haemodynamic definition of severe PH in current lung disease (mPAP ≥35 mmHg or mPAP ≥25 mmHg with cardiac index <2.0 l/min/m^2)