Elevated pulmonary vascular resistance predicts mortality in COPD patients

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To the Editor:

COPD is frequently associated with mild to moderate pulmonary hypertension (PH). However, a small subset of patients develops severe PH, which is currently haemodynamically defined as mean pulmonary arterial pressure (mPAP) ⩾35 mmHg, or mPAP ⩾25 mmHg in combination with cardiac index <2.0 $L \cdot min^{-1} \cdot m^{-2}$ [1, 2]. These cut-offs are, however, arbitrary and mainly based on expert opinion. In this study we aimed to determine prognostically relevant haemodynamic thresholds for severe PH in COPD by using an unbiased approach.

We retrospectively analysed COPD patients with at least 1-year follow-up who underwent right heart catheterisation (RHC) and clinical evaluation at our clinic due to suspected PH between 2003 and 2018. RHC was performed in the supine position, with a mid-thoracic zero reference level, as previously described [3]. All data were included into a prospective local database (GRAPHIC (GRAz Pulmonary Hypertension In COPD) registry). Patients undergoing lung transplantation at any time (n=3) were excluded from this analysis. We performed Cox regression analysis, adjusting for age, sex and forced expiratory volume in 1 s (FEV_1) with the primary outcome all-cause mortality. For identification of the best prognostic cut-offs, we searched for the lowest p-values. Continuous baseline characteristics of the groups according to the best cut-off were compared using independent t-tests or Mann–Whitney U-test, as appropriate. Continuous variables are described as mean±SD or median (interquartile range), as appropriate. The study was approved by the institutional ethics board (EK: 32–180 ex 19/20) of the Medical University Graz.

We included 139 COPD patients (age 68 (62–73) years; 55.4% male; mPAP 35 (27–43) mmHg; pulmonary vascular resistance (PVR) 4.3 (2.9–7.3) WU; FEV_1 56±20% predicted). 72 patients (52%) died during a follow-up of 8.0 (3.8–11.7) years, with a median time to death of 3.0 (1.3–5.2) years. 61 (44%) patients received any PAH drug at any time-point.

Out of the examined haemodynamic parameters, after adjustment for age, sex and FEV_1, PVR (HR 1.09, 95% CI 1.02–1.16; p=0.007) and mPAP (HR 1.03, 95% CI 1.01–1.05; p=0.001) were associated with survival, while pulmonary arterial wedge pressure (PAWP) and cardiac index were not (p=0.696 and p=0.171). Among all haemodynamic parameters, PVR >5.0 WU was the best prognostic cut-off (HR 2.59, 95% CI 1.58–4.27; p<0.001) (figure 1a). Patients with PVR >5.0 WU were more frequently males (p<0.001) and had a lower 6-min walk distance (254±112 *versus* 333±117 m; p<0.001), lower peak oxygen uptake (41±13 *versus* 61±23% predicted; p<0.001) and higher N-terminal pro brain natriuretic peptide (2288 (694–3634) *versus* 442 (160–1126) $pg \cdot mL^{-1}$; p<0.001) as compared to patients with PVR ⩽5.0 WU.

For mPAP, the p-values for potential cut-off scores showed two equivalent minimal levels, the first at 33 mmHg (HR 2.26, 95% CI 1.37–3.71; p=0.001) (figure 1b) and the second at 45 mmHg (HR 2.44, 95% CI 1.43–4.16; p=0.001). Out of the patients with mPAP ⩾33 mmHg, n=28 (36%) and n=49 (64%) had PVR ⩽5.0 WU and >5.0 WU, respectively. A PVR >5.0 WU was associated with higher mPAP (46 (41–54) *versus* 36.5 (35–41.5); p<0.001), lower PAWP (10 (8–13) *versus* 13 (10–19); p=0.001) and higher FEV_1 (58±19 *versus* 47±15; p=0.016). PVR >5.0 WU appeared to better identify subjects with a poor prognosis as compared to mPAP ⩾33 mmHg (figure 1c). A PVR above 5.0 WU in the absence of mPAP ⩾33 mmHg was rare (n=6 out of 138; 4.3%).

Shareable abstract (@ERSpublications)
PVR >5 WU proved to be the strongest independent haemodynamic predictor of mortality in COPD patients. This threshold may best identify COPD patients with severe pulmonary vascular disease. https://bit.ly/3v4QE96

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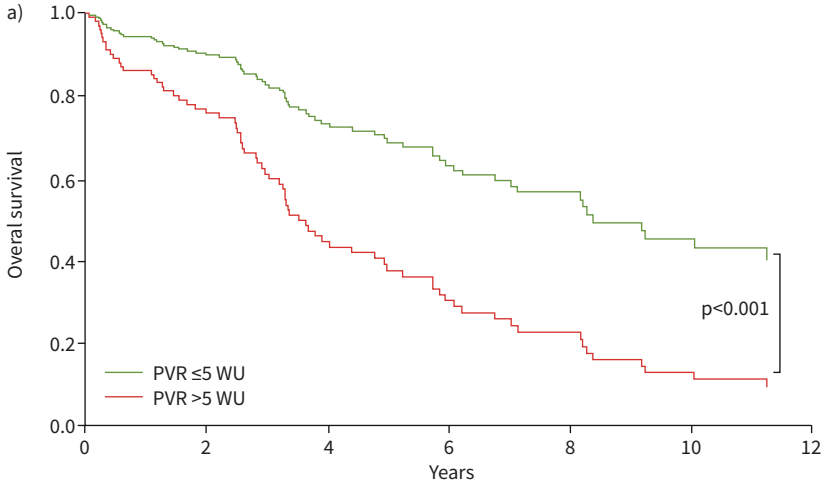
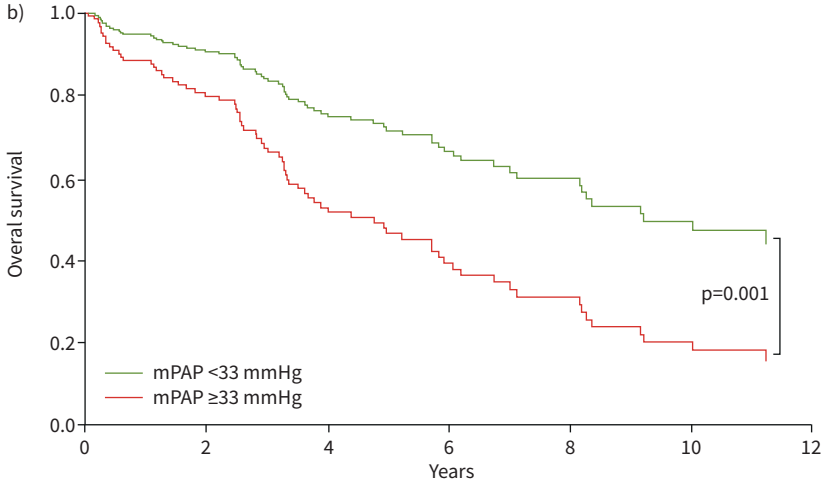
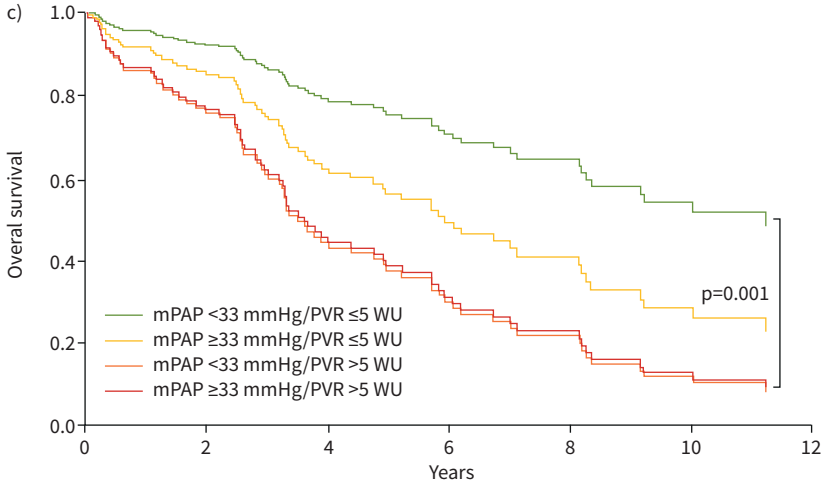


Number at risk						
PVR ≤5 WU	82	74	46	35	25	17
PVR >5 WU	56	35	14	9	6	3



Number at risk						
mPAP <33 mmHg	61	57	33	27	20	14
mPAP ≥33 mmHg	78	53	28	17	11	6



Number at risk						
mPAP <33 mmHg/PVR ≤5 WU	55	52	31	26	20	14
mPAP ≥33 mmHg/PVR ≤5 WU	28	23	15	9	5	3
mPAP <33 mmHg/PVR >5 WU	6	5	2	1		
mPAP ≥33 mmHg/PVR >5 WU	49	29	12	8	6	3

FIGURE 1 a) Multivariate Cox regression analysis by pulmonary vascular resistance (PVR) groups (cut-off: PVR >5.0 WU) accounting for age, sex and forced expiratory volume in 1 s (FEV_1) (n=138; HR 2.59, 95% CI 1.58–4.27; p<0.001). b) Multivariate Cox regression analysis by mean pulmonary arterial pressure (mPAP) groups (cut-off: mPAP ⩾33 mmHg) accounting for age, sex and FEV_1 (n=139; HR 2.26, 95% CI 1.37–3.71; p=0.001). c) Univariate Cox regression analysis by mPAP and PVR groups with mPAP cut-off ⩾33 mmHg and PVR cut-off >5.0 WU (n=138; p=0.001; reference category: mPAP <33 mmHg and PVR ⩽5.0 WU (green curve); *versus* mPAP ⩾33 mmHg and PVR ⩽5.0 WU (yellow curve): HR 2.02, 95% CI 1.04–3.93; *versus* mPAP <33 mmHg and PVR >5.0 WU (orange curve): HR 3.45, 95% CI 1.25–9.52; *versus* mPAP ⩾33 mmHg and PVR >5.0 WU (red curve): HR 3.35, 95% CI 1.95–6.06). For data in panels a and c, n=138 as pulmonary arterial wedge pressure and therefore PVR was not available in one patient.

Our study, using an unbiased approach, confirmed that an elevated mPAP has a significant impact on the age-, gender- and FEV_1-corrected prognosis of COPD patients. The identified threshold (⩾33 mmHg) was very near to the recommended threshold in the current PH guidelines at 35 mmHg. This is also in line with previous studies [4–8]. However, the strongest predictor of prognosis in our study was PVR, with the best prognostic cut-off at 5.0 WU. This was true for the whole cohort and the subgroup with classic group 3 PH. The prognostic relevance of PVR is supported by recently published data from the COMPERA registry, revealing PVR as an independent predictor of mortality in over 370 COPD patients with PH [9].

PVR >5.0 WU may be considered an appropriate threshold to define severe PH in COPD due to the following reasons. First, PVR elevation is considered as major hallmark of pulmonary vascular disease, better reflecting the severity of pulmonary vascular remodelling than mPAP. Second, the clinical and haemodynamic characteristics of our patients with mPAP ⩾33 mmHg and PVR >5.0 WU corresponded to the pulmonary vascular phenotype of COPD, with lower PAWP and less severe airway obstruction than other patients [10]. Third, patients presenting with mPAP ⩾33 mmHg and PVR ⩽5.0 WU rather represented a combination of pulmonary and left heart disease with some degree of pulmonary vasculopathy. Fourth, all currently available PAH drugs are strong pulmonary vasodilators, primarily acting on PVR. Therefore, it appears reasonable to consider severely elevated PVR as potential criterion for the indication of a PAH drug or at least as an inclusion criterion for future randomised controlled trials in group 3 PH [2].

It is often difficult to classify PH patients with COPD. The proceedings of the 6th World Symposium on PH [1] and the 2015 European Society of Cardiology/European Respiratory Society PH guidelines [2] provide some guidance regarding how to differentiate between patients with pulmonary arterial hypertension with COPD as comorbidity (group 1 PH) and patients with group 3 PH. Based on our data, PVR >5 WU may serve as a prognostic threshold independent of the PH classification, as long as the criteria for COPD are met.

As a limitation of our study, we included a relatively low number of patients; however, they were followed for a long time with a high number of events and sufficient statistical power. The single-centre retrospective design is another drawback. However, this may be compensated by the highly standardised clinical approach and the enrolment of all patients into a prospective registry. Nevertheless, further studies will be necessary to validate our findings in independent COPD cohorts.

In conclusion, by employing an unbiased approach, we identified PVR >5 WU as the strongest independent haemodynamic predictor of mortality in patients with COPD. A PVR >5 WU suggests the presence of severe pulmonary vascular disease and this was associated with less severe airflow obstruction and a relatively low pulmonary venous pressure, which is consistent with a pulmonary vascular phenotype of COPD.

Katarina Zeder[1,2], Alexander Avian[3], Gerhard Bachmaier[3], Philipp Douschan[1,2], Vasile Foris[1,2], Teresa Sassmann[1,2], Natascha Troester[2], Luka Brcic[4], Michael Fuchsjaeger[5], Leigh Matthew Marsh[1], Bradley A. Maron[6], Horst Olschewski[1,2] and Gabor Kovacs[1,2]

[1]Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria. [2]Division of Pulmonology, Dept of Internal Medicine, Medical University of Graz, Graz, Austria. [3]Institute for Medical Informatics, Statistics and Documentation, Medical University of Graz, Graz, Austria. [4]Dept of Pathology, Medical

University of Graz, Graz, Austria. [5]Dept of Radiology, Medical University of Graz, Graz, Austria. [6]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

Corresponding author: Horst Olschewski (horst.olschewski@medunigraz.at)

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