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# Cellular sources of interleukin-6 and associations with clinical phenotypes and outcomes in pulmonary arterial hypertension

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**Circulating IL-6, a pro-inflammatory cytokine produced by pulmonary arterial smooth muscle cells, is significantly associated with clinical phenotypes and survival in pulmonary arterial hypertension, which may guide individualised disease management** <https://bit.ly/3awkkSz>

**Cite this article as:** Simpson CE, Chen JY, Damico RL, *et al.* Cellular sources of interleukin-6 and associations with clinical phenotypes and outcomes in pulmonary arterial hypertension. *Eur Respir J* 2020; 55: 1901761 [<https://doi.org/10.1183/13993003.01761-2019>].

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**ABSTRACT** The pro-inflammatory cytokine interleukin (IL)-6 has been associated with outcomes in small pulmonary arterial hypertension (PAH) cohorts composed largely of patients with severe idiopathic PAH (IPAH). It is unclear whether IL-6 is a marker of critical illness or a mechanistic biomarker of pulmonary vascular remodelling. We hypothesised that IL-6 is produced by pulmonary vascular cells and sought to explore IL-6 associations with phenotypes and outcomes across diverse subtypes in a large PAH cohort.

IL-6 protein and gene expression levels were measured in cultured pulmonary artery smooth muscle cells (PASMCs) and endothelial cells (PAECs) from PAH patients and healthy controls. Serum IL-6 was measured in 2017 well-characterised PAH subjects representing each PAH subgroup. Relationships between IL-6 levels, clinical variables, and mortality were analysed using regression models.

Significantly higher IL-6 protein and gene expression levels were produced by PASMCs than by PAECs in PAH ( $p < 0.001$ ), while there was no difference in IL-6 between cell types in controls. Serum IL-6 was highest in PAH related to portal hypertension and connective tissue diseases (CTD-PAH). In multivariable modelling, serum IL-6 was associated with survival in the overall cohort (hazard ratio 1.22, 95% CI 1.08–1.38;  $p < 0.01$ ) and in IPAH, but not in CTD-PAH. IL-6 remained associated with survival in low-risk subgroups of subjects with mild disease.

IL-6 is released from PASMCs, and circulating IL-6 is associated with specific clinical phenotypes and outcomes in various PAH subgroups, including subjects with less severe disease. IL-6 is a mechanistic biomarker, and thus a potential therapeutic target, in certain PAH subgroups.