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Plasma interleukin-6 adds prognostic information in pulmonary arterial hypertension

To the Editor:

Noninvasive biomarkers are needed to aid in making challenging clinical decisions in pulmonary arterial hypertension (PAH). Several biomarkers have been described, but only the natriuretic peptides have gained clinical utility. A key question to answer is whether or not a new biomarker adds independent incremental information [1]. Novel PAH markers may be discovered from new pathobiological pathways, such as inflammation. In particular, interleukin (IL)-6 has been linked with the development of severe pulmonary hypertension in animal models, mimicking the pathology of human disease [2]. IL-6 is a major regulator of the production of C-reactive protein (CRP), a marker of cardiovascular risk [3]. We conducted this study to determine if these inflammatory biomarkers add incremental prognostic information in PAH.

This is a cohort study based on a prospective Biobank. We enrolled patients with idiopathic, heritable, connective tissue-associated and congenital heart disease-associated PAH, as defined by current guidelines [4], between March 2005 and June 2011. The study was approved by the Cleveland Clinic Institutional Review Board. We used ELISA (R&D Systems Inc., Minneapolis, MN, USA) to measure IL-6, the Abbott platform for highly-sensitive CRP (hsCRP) (Abbott Laboratories, Abbott Park, IL, USA) and a chemiluminescence immunoassay to measure B-type natriuretic peptide (BNP) (ADVIA Centaur XP; Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA) Peripheral plasma samples were kept at -80°C until retrieved for the measurement of the biomarkers (September 2011 for hsCRP and BNP, and February 2012 for IL-6). Investigators who performed the biomarker determination were blinded to the study participants' outcomes.

All-cause mortality since the date of study blood sampling was ascertained *via* manual and automated query of electronic medical records, as well as query of the Social Security Death Index. Lung transplantation was censored. The following data were collected on the same day as blood sampling: New York Heart Association (NYHA) functional classification, 6-min walking distance (6MWD), echocardiography, and per cent predicted diffusing capacity of the lung for carbon monoxide (*D*LCO % pred). Right heart catheterisation data obtained closest to the date of study blood sampling were recorded (median time 27 days, interquartile range 5–66 days). Analyses were performed using JMP Pro 9.0.0 (SAS Institute Inc., Cary, NC, USA) and R version 2.14.2 (The R Project for Statistical Computing, http://www.r-project.org/). We used receiver operating characteristic (ROC) curve analysis, Kaplan–Meier curves and Cox models to determine the associations between biomarkers and mortality. We also used recursive partitioning tree-based analysis, using the R function ''rpart'', to identify the group of biomarkers and baseline variables that had optimal discriminatory ability with regards to all-cause mortality. Each possible threshold of biomarker and baseline variable was evaluated to find the split that formed two groups with the greatest difference in

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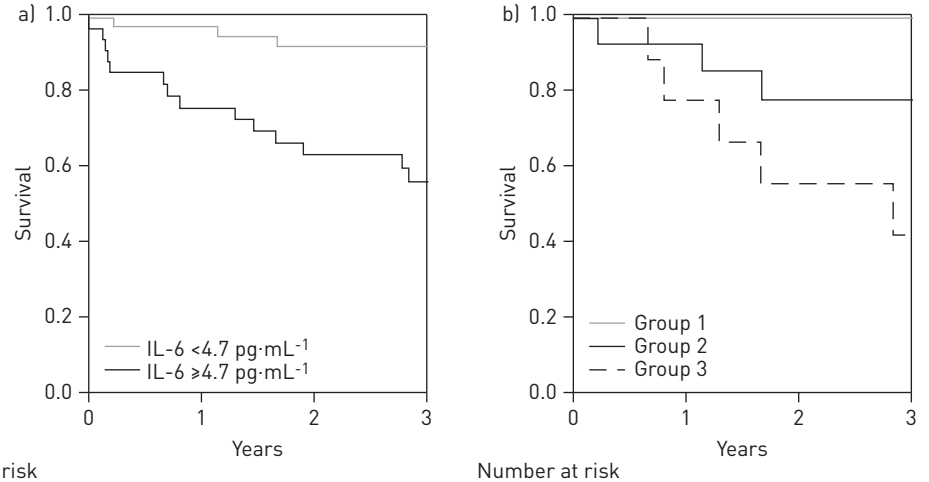
survival (alive *versus* dead). Survival was measured by estimated event rates after exponential scaling, which accounts for the time each subject was followed. Within the patient subsets defined by the first split, the process was repeated to identify optimal splits at a second level. This repeated splitting was stopped when the goodness-of-fit of the tree model could no longer be improved with further splits, or when resulting subgroups fell to a size of <20 patients.

We enrolled 76 patients, 62 of whom were female, with a mean±SD of 51±14 years. The types of PAH included 40 idiopathic, 10 heritable, 19 connective tissue disease-associated (13 scleroderma) and 7 congenital heart disease-associated. The cohort had a mean±SD 6MWD of 360±127 m, pulmonary arterial pressure of 51±13 mmHg, right atrial pressure (RAP) of 10±6 mmHg, cardiac index 2.4±0.8 $L \cdot min^{-1} \cdot m^{-2}$ and pulmonary vascular resistance of 11±7 Wood units. 63 patients were on PAH-targeted therapies, 32 of them were receiving parenteral prostacyclin.

The median (interquartile range) concentrations of the biomarkers were: IL-6 3.82 (1.79–9.87) $pg \cdot mL^{-1}$, hsCRP 5.7 (1.95–14.85) $mg \cdot L^{-1}$ and BNP 59 (19–132) $pg \cdot mL^{-1}$. Plasma IL-6 correlated with the 6MWD ($r=0.52$, $p<0.0001$) and RAP ($r=0.26$, $p=0.03$). hsCRP correlated with the 6MWD ($r=0.40$, $p=0.001$). During a median (interquartile range) follow-up of 2.8 (1.6–4.6) years, there were 22 deaths and five lung transplants. Both IL-6 and hsCRP were univariate predictors of mortality. On ROC curve analysis, IL-6 had better discriminant ability (IL-6 area under the curve 0.81, hsCRP area under the curve 0.68). IL-6 concentrations ⩾4.7 $pg \cdot mL^{-1}$ had a sensitivity of 86% and a specificity of 72%, and were associated with nine-fold increase in the risk of death (fig. 1a). A hsCRP level ⩾7.5 $mg \cdot L^{-1}$ was less strongly associated with mortality (hazard ratio (95% CI) 4.80 (1.77–13.1), $p<0.001$, sensitivity 77%, specificity 67%). Other univariate predictors of mortality included male sex, NYHA class, 6MWD, BNP, pericardial effusion, RAP and red cell distribution width. In a multivariable Cox model male sex, BNP and IL-6 were independently associated with mortality. When IL-6 was removed from the model, given its collinearity with hsCRP ($r=0.71$), then hsCRP entered the model. However, in the decision tree model only BNP, IL-6 and cardiac index were independent predictors.

In our cohort we confirmed that BNP levels above 180 $pg \cdot mL^{-1}$, as previously reported [5, 6], were associated with an extremely poor prognosis, with 3-year survival of only 16% (hazard ratio (95% CI) for death 13.01 (4.98–35.19), $p<0.0001$). Thus, we were interested in the prognostic utility of IL-6 and hsCRP in patients with BNP levels below 180 $pg \cdot mL^{-1}$ (n=60). In this subpopulation, IL-6 levels ⩾4.7 $pg \cdot mL^{-1}$, RAP and *D*LCO % pred were the only independent predictors of mortality in a forward stepwise Cox model



Number at risk

IL-6 <4.7 $pg \cdot mL^{-1}$	42	38	31	20
IL-6 ⩾4.7 $pg \cdot mL^{-1}$	34	24	20	15

Number at risk

Group 1	37	34	32	22
Group 2	14	13	9	7
Group 3	9	7	5	3

FIGURE 1 a) Transplant-free survival according to an interleukin (IL)-6 receiver operating characteristic curve identified cut-off of 4.7 $pg \cdot mL^{-1}$. Hazard ratio (95% CI) 9.26 (2.74–31.3); $p<0.0001$. b) Transplant-free survival of 60 pulmonary arterial hypertension patients with B-type natriuretic peptide levels <180 $pg \cdot mL^{-1}$ according to recursive partitioning tree-based analysis identified groups. Group 1 (n=37): 6-min walk distance (6MWD) ⩾450 m or 6MWD <450 m and right atrial pressure (RAP) <8 mmHg; 3-year survival 100%. Group 2 (n=14): 6MWD <450 m and RAP ⩾8 mmHg and IL-6 <5.6 $pg \cdot mL^{-1}$; 3-year survival 78%. Group 3 (n=9): 6MWD <450 m and RAP ⩾8 mmHg and IL-6 ⩾5.6 $pg \cdot mL^{-1}$; 3-year survival 42%.

(all $p<0.05$), while BNP was not. Recursive partitioning tree-based analysis showed that the combination of 6MWD (cut-off 450 m), RAP (cut-off 8 mmHg) and IL-6 (cut-off 5.6 pg·mL^{-1}) offered the highest ability to separate groups of patients with significantly different survival. BNP was not found to provide any predictive information in this model either. Figure 1b shows the survival curves for the tree-based analysis identified groups. The best prognosis was seen in patients with a good 6MWD or low RAP (group 1). Patients with more limited 6MWD and an elevated RAP, but with low plasma IL-6 levels had an intermediate prognosis (group 2). Those with limited 6MWD, high RAP and elevated plasma IL-6 had the worse outcome (group 3) (fig. 1b).

Plasma IL-6 levels were independent predictors of survival, both in a multivariable Cox proportional hazards model and in a recursive partitioning tree-based analysis. Importantly, plasma IL-6 level provided prognostic information, in conjunction with 6MWD and RAP, in patients with BNP levels below the established cut-off point of 180 pg·mL^{-1} [5, 6]. It is very clear that patients with elevated BNP levels have a poor prognosis; however, our study shows that below the established threshold, BNP does not provide any prognostic information. In this subset of patients plasma IL-6, in conjunction with 6MWD and RAP, allows for further risk stratification. By contrast, hsCRP did not add independent information in PAH. As 69 patients had blood drawn more than 2 years prior to IL-6 measurement, uncertainty about stability of IL-6 is a limitation of this study. However, our data are consistent with previous findings on IL-6 [7–10]. Another limitation is the lack of a validation cohort and the modest sample size, which also prevented us from entering other biomarkers into the models.

In conclusion, plasma IL-6 provides incremental prognostic information in PAH, especially in patients with low BNP levels.

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Plasma IL-6 provides prognostic information in pulmonary arterial hypertension, especially in patients with low BNP http://ow.ly/qzNkt

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