Circulating proteomic biomarkers to screen for PAH in systemic sclerosis

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Introduction

Pulmonary arterial hypertension (PAH) develops in 7-12% of patients with systemic sclerosis (SSc) and is associated with a very poor survival of 52% at 3-years. Screening for early identification of PAH is therefore recommended in SSc. The DETECT protocol uses a combination of biomarkers and clinical parameters that require multiple investigations. We hypothesised that a protein biomarker panel from a single blood draw could be used to screen for PAH in patients with SSc.

Methods

Serum from 58 treatment naïve patients with SSc-PAH, and 30 SSc controls were obtained from the Sheffield Pulmonary Hypertension biobank and analysed on the MYRIAD RBM DiscoveryMAP platform comprising more than 300 human protein assays. Proteins were excluded if >90% of values fell outside the limit of detection. Machine learning methods including LASSO and random forest were then used, along with univariate statistics for variable selection. The final predictive model was then compiled using only protein variables selected by these techniques, and optimized using logistic regression with backward step-Akaike Information Criterion (AIC). The protein panel was validated using ELISA on 78 samples obtained from Stanford and Vanderbilt University Pulmonary Hypertension services.

Results

The final model for classifying for PAH in patients with SSc consisted of 3 proteins: Tetranectin; Growth differentiation factor-15; and Protein DJ-1. From the derivation dataset this model predicts PAH in SSc with sensitivity 0.90, specificity 0.77, positive predictive value 0.88, negative predictive value 0.79 and an AUROC 0.87. External validation confirmed the potential of this work with an AUROC 0.79.

Discussion

Current screening for PAH in SSc involves a lengthy process of multiple investigations and clinical contact. Our work has demonstrated the utility of a novel protein biomarker panel to identify patients with high risk of PAH in SSc. This panel could potentially be rolled out to other PAH subtypes.