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Title: Pulmonary arterial enlargement and acute exacerbations of COPD

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Body: Background: Exacerbations of COPD (AECOPD) are associated with accelerated loss of lung function and mortality. Identification of patients at risk for these events, particularly those requiring hospitalization, is of major importance. Severe pulmonary hypertension is an important complication of advanced COPD and predicts AECOPD though pulmonary vascular abnormalities also occur early in the disease. We hypothesized that a computed tomography (CT) metric of pulmonary vascular disease (pulmonary artery (PA) enlargement as determined by a PA/Aorta (A) ratio > 1) would predict severe AECOPD. Methods: The COPDGene study is a multicenter, observational trial that enrolled current and former smokers with COPD. We determined the association between PA/A>1 and severe AECOPD requiring hospitalization as reported at enrolment and then examined its utility as a predictor of these events in longitudinal follow-up as well as in an external validation cohort [Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)] using logistic and zero-inflated negative binomial regression and adjusting for known risk factors for AECOPD. Results: Multivariate logistic regression demonstrated a significant association between PA/A>1 and severe AECOPD [OR 3.60 (95% CI, 2.49-5.22, p<0.001)] at enrolment in COPDGene. PA/A>1 also independently predicted the occurrence [OR 2.03 (95% CI, 1.17-3.49, p=0.01) in COPDGene and OR 2.80 (95% CI, 2.11-3.71, p<0.001) in ECLIPSE] and frequency of future severe AECOPD in both cohorts. In ECLIPSE, PA/A>1 was the strongest predictor of severe AECOPD over both 1 and 3 years of follow-up. Conclusions: CT detected pulmonary artery enlargement (PA/A>1) predicts severe COPD exacerbations.