Pulmonary artery enlargement and mortality risk in moderate to severe COPD: results from COPDGene

To the Editor:

COPD is one of the leading causes of mortality worldwide [1]. Pulmonary hypertension has been associated with reduced survival among individuals with COPD [2] and is an independent risk factor for mortality following acute exacerbations of COPD (AECOPD) [3]. Measurement of the pulmonary artery to aorta (PA:A) ratio by computed tomography (CT) and assessment of pulmonary artery enlargement (PA:A >1) outperforms echocardiography in identifying pulmonary hypertension in severe COPD [4], and pulmonary artery enlargement has been independently associated with risk for total and severe AECOPD in two large prospective COPD cohorts [5]. Studies of population-based [6] and non-COPD [7] cohorts have indicated an association between pulmonary artery enlargement on CT and mortality. However, these studies did not include adjustment for other factors associated with COPD severity, known risk factors for COPD mortality and risk factors for atherosclerotic cardiovascular disease (ASCVD), which is a major cause of mortality in COPD.

We analysed CT imaging and clinical data from the COPDGene study and hypothesised that pulmonary artery enlargement is associated with all-cause mortality, even after adjustment for other known predictors of mortality in COPD and risk factors for ASCVD. We analysed data from 3464 COPDGene participants with Global Initiative for Chronic Obstructive Lung Disease spirometry grades 2–4 COPD [5] who had CT imaging, and vital status assessment ~6 years later. This cohort underwent detailed baseline assessment [8], volumetric non-contrast CT scans of the chest with measurement of pulmonary artery and aorta at the level of the pulmonary artery bifurcation [5], and long-term longitudinal clinical follow-up [9], as described previously. All-cause mortality was determined *via* longitudinal follow-up, contact with next-of-kin, clinical records, death certificates and information from the Social Security Death Index [10].

Participants had a median follow-up period of 6.3 years (interquartile range 1.7 years, range 8.4 years). Mean $\pm$ SD age was 63 $\pm$ 9 years; 44% were female and 78% were white. The mean forced expiratory volume in 1 s (FEV₁) was 50 $\pm$ 18% predicted, and 28% of participants used supplemental oxygen. Mean PA:A was 0.90 $\pm$ 0.14 and 810 (23.4%) participants had PA:A >1. During the follow-up period, 755 (21.8%) participants died. In Kaplan–Meier analysis (SPSS, IBM, Armonk, NY, USA), participants with PA:A >1 had shorter mean estimated survival (6.7 (95% CI 6.50–6.89) years *versus* 7.4 (95% CI 7.35–7.53) years; $p<0.001$ (log-rank); figure 1).

Cox proportional hazards (CPH) models were used to investigate for potential association between pulmonary artery enlargement (PA:A >1) and mortality. The multivariable CPH model included covariates that adjusted for other known factors associated with mortality and disease severity in COPD, as well as ASCVD. These included demographics (age, sex, race), body mass index (BMI), use of supplemental oxygen, 6-min walk distance (6MWD), modified Medical Research Council (mMRC) dyspnoea score, FEV₁ (% predicted), history of severe AECOPD within the preceding 12 months (self-reported using questions modified from standardised questionnaires), percentage emphysema on CT (Slicer software; www.slicer.org), current smoking and self-reported histories of coronary artery disease, diabetes mellitus, hypertension and hyperlipidaemia. In the unadjusted CPH model, pulmonary artery enlargement was associated with hazard ratio (HR) for mortality of 1.75 (95% CI 1.50–2.04; $p<0.001$). In

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Pulmonary artery enlargement on chest CT imaging is independently associated with all-cause mortality in moderate-severe COPD, after adjustment for other known risk factors for COPD mortality and cardiovascular disease <http://bit.ly/2rdYOR1>

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FIGURE 1 Association between pulmonary artery enlargement and all-cause mortality in COPD. Kaplan-Meier survival curves stratified by the presence or absence of pulmonary artery enlargement ($p < 0.001$, log-rank test). PA:A: pulmonary artery to aorta ratio.

the multivariable CPH model, pulmonary artery enlargement was associated with a 42% increase in mortality risk (HR 1.42, 95% CI 1.17–1.72; $p < 0.001$). Older age, male sex, lower BMI, lower FEV₁ (% pred), shorter 6MWD, supplemental oxygen use, higher mMRC dyspnoea scores and current smoking were also associated with increased mortality risk in the adjusted CPH model. ASCVD-specific factors were not associated with risk for mortality in this cohort.

Our results are the first to demonstrate an association between pulmonary artery enlargement on CT and mortality in moderate to severe COPD, even when adjusted for factors including AECOPD, components of the BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) index and ASCVD. Several studies have previously reported associations between CT-based PA:A ratio and mortality. Using coronary CT angiography from patients with suspected coronary artery disease, NAKANISHI *et al.* [7] demonstrated an association between pulmonary artery enlargement (defined as PA:A > 0.9 in that study) and mortality after adjustment for cardiovascular risk factors and left ventricular function. However, this study neither reported the prevalence of chronic lung disease nor performed adjustment for factors associated with it. ASCVD is a major cause of mortality in COPD, and several factors such as age, sex and smoking are related to both ASCVD risk and COPD severity/mortality. However, the results of our adjusted model suggest that the increased risk is unlikely to be attributable to ASCVD.

SHIN *et al.* [11] found an association between PA:A ≥ 1 and mortality over a shorter follow-up interval, in a smaller cohort of COPD patients referred for lung transplant/lung volume reduction evaluation, after adjustment for age, BMI and FEV₁ (% pred). Additionally, TERZIKHAN *et al.* [6] reported an independent association between PA:A ratio and mortality among participants with COPD in a large, predominantly white population in the Netherlands. However, only 5% of the study population had moderate-severe COPD, and 17 out of the total 2197 participants had PA:A ≥ 1 . In contrast to prior studies, COPDGene is a multicentre, disease-specific study that included larger numbers of African-American participants (approximately one-third of total enrolment) [8] as well large numbers of subjects with moderate to severe disease. In addition, our results indicate a high prevalence of pulmonary artery enlargement in the study cohort, with pulmonary artery enlargement in nearly a quarter of participants. Our findings add to the mounting body of evidence to indicate an association between PA:A ratio and adverse outcomes in COPD including severe acute exacerbations [5], reduced exercise tolerance [12] and risk of development of resting hypoxaemia [13] as well as cardiac injury and more complicated hospital course during severe acute exacerbations [14].

Our results demonstrate increased mortality risk after adjustment for supplemental oxygen use, FEV₁ and percentage emphysema. This suggests that COPD severity cannot completely account for the observed associations, and supports the importance of mechanisms other than chronic hypoxia and capillary dropout due to emphysema in the pathophysiology of pulmonary vascular disease in COPD. Direct pulmonary vascular injury as a result of cigarette smoke exposure could also contribute to the development of pulmonary hypertension in early or mild disease, in the absence of emphysema or hypoxaemia [15]. Genetic variants in *IREB2* and *GALC* that were identified through a genome-wide association study of COPDGene and ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points) participants with PA:A > 1 [16] might also account for earlier onset of pulmonary hypertension in certain individuals.

The strengths of our study include use of a well-defined cohort, length of follow-up and adjustment for other known predictors of mortality. PA:A ratio measurement represents a reproducible, practical method for evaluation of patients with COPD for pulmonary vascular disease. Our study has several limitations. First, our results should not be used to imply a direct causal relationship between pulmonary artery enlargement and mortality. Since we evaluated all-cause mortality, there is insufficient evidence to reach conclusions regarding specific causes of death among individuals with concurrent COPD and pulmonary artery enlargement. Measurement of disease-specific outcomes and study of PA:A ratio in common comorbid conditions such as obesity, obstructive sleep apnoea and congestive heart failure would be valuable in elucidating the nature of the associations observed in this study. Furthermore, our conclusions are based on a single cohort with moderate to severe disease, using non-contrast, non-gated CT imaging, though others have reached similar conclusions using different study populations and CT imaging protocols [6, 7, 17].

These findings extend the known utility of pulmonary artery enlargement on CT scan as an imaging-based biomarker for morbidity and mortality in COPD. The increased use of CT imaging for clinical indications (*i.e.* lung cancer screening) coupled with the relative ease in ascertaining pulmonary artery enlargement make this a practical metric for aiding in COPD prognosis.

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