



Reply to Polverino: Clearing the Air: Innovations in Imaging for Early Detection and Management of Chronic Obstructive Pulmonary Disease

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From the Authors:

In the letter “Clearing the Air: Innovations in Imaging for Early Detection and Management of Chronic Obstructive Pulmonary Disease,” Polverino postulates the existence of two different spans in the pathophysiology of chronic obstructive pulmonary disease (COPD): one going from pre-COPD to Global Initiative for Chronic Obstructive Lung Disease (GOLD) II and a second leading to the final phases of COPD. Although the pathophysiology of pre-COPD remains elusive at the moment, we indeed demonstrated in our paper in the recent issue of the *Journal* that small airway loss and alveolar destruction were equally present in patients with pre-COPD and early-stage COPD, whereas an additional decline was seen in patients with GOLD III/IV only (1), corroborating this hypothesis. However, three different spans seems more realistic, in which the initial step is emphysema development and small airway loss moving from “healthy smoker” to pre-COPD. A second step is the development of an obstructive pulmonary function defect moving from pre-COPD to COPD GOLD I/II. A final progression to GOLD III/IV is then associated with more alveolar and small airway destruction. Further investigation of the immune responses in pre-COPD in relation to established COPD GOLD I/II forms another crucial aspect next to this parenchymal and small airway destruction. This is crucial to unravel whether (lymphoid) inflammation is equally present in pre-COPD compared with patients with established COPD and to assess which stepwise pattern can be observed in the underlying immune responses. Based on existing data, the stepwise pattern to GOLD I/II

and to GOLD III/IV seems a plausible hypothesis, as only small differences in inflammatory and remodeling markers are found on histology in COPD GOLD I and II and much more pronounced differences in GOLD III and IV (2) compared with never-smokers and smoking control subjects, although no data currently exist on pre-COPD.

Questions were raised regarding the representability of *ex vivo* measures compared with *in vivo* computed tomography, especially regarding the inflation and fixation of the lung. Although a certain effect of manipulation cannot be excluded, the main findings derived from the *ex vivo* CT (i.e., the degree of emphysema) showed strong correlation among the two radiologic observers. In addition, our standardized approach rules out effects of inadequate inspiration, motion artifacts, and confounding rib cage, leading to a better resolution of the lung. The workup is uniform in all cases, so if there would be an impact of inflation and manipulation on our results, this is expected to be uniform across the different groups.

We did not find evidence for an increase in mucus plugging on *ex vivo* CT, in contrast to a recent study demonstrating a disease severity stage-dependent increase in mucus plugging in COPD (3). However, a few things are worth considering. This study was based on 4,363 participants and used a scoring system based on 18 lung segments. For most patients, we only had a single lobe available for analysis, and the section of the lung bearing the tumor for which surgery was indicated was removed before analysis. Because of these differences in protocol and n-value, we believe our study was not powered to detect differences regarding mucus plugging. In addition, the radiologists had poor correlations between their assessment of mucus plugging, indicating that more focused studies with dedicated scoring systems are warranted to further investigate mucus plugging in (pre-)COPD, which was outside the scope of the current study. The fact that mucus plugging was present in some of our patients with pre-COPD further corroborates that more detailed studies are needed. It was also speculated that there could be a different nature of the mucus plugs, which definitely sounds like an appealing hypothesis. However, one might also speculate that there is a spatial difference in mucus plugging, in which in the early stages the smaller airways are filled with mucus, and with increasing COPD severity more proximal airways are obstructed with mucus as there are a very limited number of small airways left, making these airways more visible with conventional chest CT scanning.

Ultimately, we completely concur that the advent of novel imaging and image analysis tools will spur novel insights into the pathophysiology and management of (pre-)COPD. We are convinced that also investigating the mechanisms of pre-COPD will be of utmost importance, because decades of research did not prove to be sufficient to cure COPD. We hope that finding novel ways to identify the patients at risk early (i.e., patients with pre-COPD) will lead to markers either on imaging or on physiology that can predict disease onset and progression. In addition, a better understanding of the pathophysiological mechanisms will significantly improve our knowledge of early COPD, which is crucial for improved therapeutic modulation. An important step to achieve this is the first definition of pre-COPD, as has been proposed in the recent GOLD guidelines (4). This can drive clinical trials specifically targeting this population designed to prevent COPD development (5). ■

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Erratum: A Polygenic Risk Score for Idiopathic Pulmonary Fibrosis and Interstitial Lung Abnormalities



It has recently come to the authors' attention that sex had been incorrectly assigned to a small proportion of subjects in the Denver, Colorado cohort that was a part of the article by Moll and colleagues, published in the October 1, 2023, issue of the *Journal* (1). Specifically, the corrected data resulted in a change of the sex variable for 66 out of 1,694 cases included in the data from Denver. Since some of the analyses adjusted for sex, this change resulted in minimal changes to some of the statistics reported in Tables 1 and 2. The authors state that there have been no changes in the data included from the other cohorts, the figures, or the conclusions of the article. In the interest of full transparency, they have recalculated statistics for the two tables. For the convenience of our readers, the *Journal* is replacing the online version of the article with a corrected version. ■

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