Peer Review File

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Reviewer #A

1. The authors reviewed 452 participants from the Chronic Obstructive Pulmonary Disease in Dusty Areas (CODA) cohort. They reside near a cement plant and include many cases with no history of smoking. Therefore, they are not a pure COPD group.

➔ Reviewer A-1. Thank you for your comment. In our study, patients with COPD were defined according to the chronic exposure to noxious agents, chronic respiratory symptoms, postbronchodilator ratio of FEV1/FVC < 0.7, and no serious structural change. Smoking is a significant factor that causes COPD, but various factors other than smoking cause COPD. Our study included patients with non-smoker COPD, so there may be limitation in generalizing smoker COPD. In addition, because they reside near a cement plant, other studies have shown that bronchial wall thickening tends to thicker than smoker COPD or non-COPD subjects. Therefore, further validation is needed. These were added to the limitation of discussion.

Limitation of discussion (page 9, 10): Fourth, in our study, COPD were defined according to the chronic exposure to noxious agents, chronic respiratory symptoms, postbronchodilator ratio of FEV1/FVC of < 0.7, and no serious structural change. Smoking is a significant factor that causes COPD, but various factors other than smoking cause COPD. Our study included patients with non-smoker COPD, so there may be limitation in generalizing smoker COPD. Therefore, further validation is needed.

2. The PSE group is defined as “subjects with substantital PSE regardless of other imaging characteristics”. PSE is often associated with centrilobular emphysema. Hence, this group may contain varying degrees of centrilobular emphysema mixed in. How many cases of pure PSE group were included in the study?

➔ Reviewer A-2. Thank you for your comment. As you mentioned, our study classified PSE subtypes in subjects with substantial PSE regardless of other characteristics, and the result of our study may not necessary reflect the characteristics of pure PSE. Our study included 17 participants with pure PSE (15 participants with mild PSE and 2 participants with substantial PSE). The number of patients with pure PSE was too small, so the analysis was conducted based on the criteria used by COPDgene (Park et al. chest 2020). We described these in the 3rd paragraph and limitation of discussion.

Discussion (page 7, 8): Our study classified PSE subtypes in subjects with substantial PSE regardless of other characteristics; most subjects with moderate to advanced destructive emphysema were included in the PSE subtype group. Therefore, this group may have slightly different physiological and functional characteristics to a pure PSE.

Discussion (page 9): Third, we classified PSE subtype if substantial PSE was present, regardless of other CT features, and thus our PSE subtype groups may not necessarily reflect the characteristics of pure PSE.

3. CT acquisition: CT reconstruction kernel should be described.

➔ Reviewer 1-3. Thank you for your comment. We have added a description of CT reconstruction kernel in CT acquisition

CT acquisition (page 2): CT images were reconstructed with B30f

Reviewer B

Reviewer B-1. Some important references are missing on PRM and the subject of this study. Please consider discussing / referencing these in the discussion section. It would enhance the discussion section.

➔ Reviewer 2-1. Thank you for your comment. We enhanced the discussion section based on the following reference, as you pointed out (Hoff BA et al Sci rep 2017, Pompe E et al Respir Med 2017, Am J Respir Crit Care Med 2015, Mohamed Hoesein FA et al COPD 2014)

Discussion (page 7): A study showed that emphysema associated with the FEV1/FVC, Pi10 did with the FEV1, and the ratio of mean lung density at expiration and inspiration (E/I-ratioMLD) did with the residual volume (Mohamed Hoesein FA et al. COPD 2014). PRM for COPD quantification is a voxel-based image analysis technique between inspiration and expiration scans after image registration (Pompe E et al. Am J Respir Crit Care Med 2015). Pompe E et al. (Pompe E et al. Respir Med 2017) showed that PRM^{emph} and PRM^{fSAD} strongly associated with presence and severity of COPD. in addition, the baseline model (age, BMI, smoking status and pack-years) with PRM had higher diagnostic value compared with other CT-derived biomarkers (Pi10, Perc 15, E/I-$ratio_{MLD}$) (Pompe E et al. Respir Med 2017). Therefore, in our study, PRM^{emph} and PRM^{fSAD} were used as the COPD quantification biomarkers.

Discussion (page 9): PRM is significant diagnostic value of CT quantification because of its ability to differentiation of emphysema from non-emphysematous air trapping (function small airway disease, PRM^{fSAD}) within lung parenhcyma (Pompe E et al. Am J Respir Crit Care Med 2015). Also, several studies have shown that PRM are valuable CT derived biomarker

assessment of small airway disease and COPD regardless of subtypes of COPD (Pompe E et al. Am J Respir Crit Care Med 2015, Pompe E et al. Respir Med 2017)