Peer Review File

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Review Comments

I believe that it would be better to completely rewrite the article based on the data the authors have.

First of all, the FEV1/FVC ratio of less than 0.7 is an absolutely essential in the diagnostic criteria for COPD.

That is true for the 2024-year version of GOLD and of course for the earlier versions. This 0.7 number has physiological significance, at the same time, there is clinical significance for this number. The recent JAMA article mentioned lower ratio less than 0.7 was accompanied with increase the number of hospitalizations and mortality (Surya P Bhatt et al. Discriminative Accuracy of FEV1: FVC Thresholds for COPD-Related Hospitalization and Mortality JAMA 321(24):2438-2447).

And in recent years, GOLD has focused on biomass-related COPD outside to tobacco-related COPD. However, this type of COPD is rare in other countries such as Europe, the U.S. and there are few opportunities to come into contact with such cases, and many chest physicians want information.

Response: indeed GOLD 2024 defines COPD, based on FEV1/FVC < 0.7 post-BD. Though in the paper of JAMA 2019, COPD was defined by FEV1/FVC < 0.7 pre-BD (and not post-BD). This criterion was a predictor of severity but not of mild COPD. Moreover, the population was from US, mainly associated with smoking habits (22.7 p-y). A recent paper (Celli B, et al (AJRCCM 2022; 206: 1317-25) on Definition and Nomenclature of COPD, highlighted that the definition of COPD should not be limited to one disease caused by one single agent because what we know today is derived from studies centered almost exclusively on COPD due to cigarette smoking while other causes of COPD are not included in any guidelines developed around the world.. This is particularly true in LMIC, such as Vietnam.

How about changing as the followings:

1) COPD cases should be restricted to patients with FEV1/FVC < 0.7.

Response: we have defined COPD based on post-BD FEV1/FVC < 0.7. By doing so, 93 patients were defined as COPD.

2) COPD patients are then classified into two groups as never smoker-COPD group and ex-smoker/ current-smoker (tobacco-related) COPD group.

The nonsmoking COPD patients (even small number of size) are defined as the biomass-related COPD group. However, it should be said in the discussion that it is unclear whether lung development disorders such as airway dysanapsis or other conditions are not included.

Response: all the 93 COPD were ex/currents smokers, while only 3/49 (i.e. %) asthmatics were smokers. Among the 93 ACO patients they were 22 (24%) smokers. The smokers and non-smokers (biomass-related) ACO were compared in an additional table (table 3).

The possible development disorders such as airway dysanapsis was included in the discussion (lines 551).

3) It is better to analyzed whether this biomass-related COPD is a phenotype similar to tobacco-related COPD.

Response: all the COPD (based on post-BD FEV1/FVC < 0.7) were smokers. Though, we did the requested analysis for the ACO patients (table 3).

4) Table 1 can use this format, although number of patients and results will be changed.

Response: done.

5) Table 2 is necessary to reanalyze by changing into three groups as the asthma group, the biomass-related COPD group and the tobacco-related COPD group.

Response: the revised table 2 compared COPD - ACO and asthmatics.

6) In Figure 1, A can be used as is, but B, C, and D are changed to asthma group, biomass-related COPD group, and tobacco-related COPD group for analysis.
Response: done.

7) ACO-A and ACO-B analysis is necessary to perform for biomass-related COPD and tobacco-related COPD, noting whether there is a difference between the two group (interesting whether there is a difference or not).
Response: in the revised paper the ACO were considered as a whole group. However, as asked by the reviewer, we compared the non-smoker (biomass-related) ACO and the tobacco-related ACO in table 3.

8) I think it would be better to stop using "airway obstruction" and use "airflow limitation" instead.
Response: done.

9) It would be interesting to know if the biomass-related COPD group and the tobacco-related COPD group have the similar patient characteristics or the similar positive rates for FENO and skin prick tests.
Response: in table 3 we showed that, compared to the smoker ACO, the non-smoker ACO were associated with a type-2 inflammation (history of allergy and positive skin prick tests), but not with the FeNO.