

Major:

- I) You should include a description as to why early and mild COPD (mild according to the severity stage classified by GOLD) are not interchangeable concepts. COPD severity is indicative of the loss of lung function, whereas early relates to a timescale, and both may always not be coincident in the same individual. Ref: Agusti A, Celli B. Avoiding confusion in COPD: from risk factors to phenotypes to measures of disease characterization. *Eur Respir J* 2011;38(4):749-51. Thus, it is not possible to differentiate mild COPD of recent onset from earlier-onset COPD that has not progressed to a more severe disease stage. Ref: Soriano JB, Polverino F, Cosio BG. What is Early COPD and Why is it Important? *Eur Respir J* 2018.

The following reference may also be considered: Rossi A, Butorac-Petanjek B, Chilosi M, et al. Chronic obstructive pulmonary disease with mild airflow limitation: current knowledge and proposal for future research - a consensus document from six scientific societies [published correction appears in *Int J Chron Obstruct Pulmon Dis*. 2019 Jan 18;14:247]. *Int J Chron Obstruct Pulmon Dis*. 2017;12:2593-2610.

- II) The statement in the Abstract "it is recognized that disease progression is most rapid and pathology most active in early disease" seems not be based on robust evidence. Firstly, early COPD" has still to be defined (also stated in the 5th paragraph of your Introduction), and secondly, COPD is not a single disease; rather, it is a syndrome. Thus, there is no single COPD natural history. Reference: Agusti A and Celli B in the history of COPD: gaps and opportunities. *ERJ Open Res*. 2017;3(4):00117-2017. Published 2017 Dec 14. doi:10.1183/23120541.00117-2017.

Furthermore, under DISEASE TRAJECTORY AND PROGNOSIS IN COPD, page 6, row 11, you state that Tantucci et al. (14) demonstrated that the rate of FEV₁ decline is more rapid in *earlier stages* of COPD than in late disease. The statement seems to be correct, but the problem is that it is not telling the whole truth. Actually, the article by Tantucci C, Modena D, conclude that "the rate of FEV₁ decline in COPD patients strongly supports the concept that the faster progression of functional impairment in COPD occurs early, and it *particularly occurs in GOLD stage II.*" (Stage II = *moderate* COPD according to the GOLD classification). This is actually illustrated by Figure 2 in your manuscript (redrawn with permission from Tantucci C, Modena D), but you I recommend you describe this in the text as well. Furthermore, the article by Tantucci C, Modena C; emphasizes in the Discussion section that consistent information is still lacking regarding GOLD stage I. This could also be worthwhile to be mentioned in your manuscript.

- III) The Conclusion section should be improved. Surprisingly enough, the British Lung Foundation Early COPD Development Study in the UK is not described or referred to elsewhere in the manuscript, and it is difficult to understand why this particular study “will undoubtedly shed light into methods of early recognition, and facilitate design of novel treatments that have the ability to halt disease at this early and potentially reversible stage”. I would like to see a more logically constructed and clearer conclusion based on selected information, which you consider being of particular scientific interest in your review manuscript.

Minor:

1. Page 5, 3d paragraph after the sentence “Recent papers have proposed small airways disease as the earliest stage of COPD”.

Suggest adding a reference after the sentence, e.g.:

Singh D. Small Airway Disease in Patients with Chronic Obstructive Pulmonary Disease. *Tuberc Respir Dis (Seoul)*. 2017;80(4):317-324. doi:10.4046/trd.2017.0080

Section “Inhaled bronchodilator and steroid therapy”:

2. It would be more logical to put the paragraph describing the UPLIFT study directly after the one outlining the results of the Lung Health Study.
3. The paragraph below seems misplaced and should be moved either to the beginning or end of this section.

“The magnitude of clinical benefit of pharmacological treatment in early COPD is limited.

Although there is some evidence that inhaled therapy offers symptomatic benefit and reduction in exacerbation rates, long-term outcomes such as lung function decline and mortality appear not to be affected on the limited evidence available.”

4. A good overview of potential pharmacological interventions (pages 8-12) is provided by Singh D et al. and could be referred to. Singh D, D’Urzo AD, Donohue JF, Kerwin EM. Weighing the evidence for pharmacological treatment interventions in mild COPD; a narrative perspective. *Respir Res*. 2019;20(1):141. Published 2019 Jul 8. doi:10.1186/s12931-019-1108-9
5. Typo on in the heading on page 11: “NOVEL DIAGNOSTIC APPROACHES AND FUTURE RESEARCH AREAS – ROLE OF BIOMARKERS IN EARLY DETECTION OF COPD”

