

Reviewer 1 v.1

Comments to Author:

Authors have performed a systematic review and meta-analysis for correlation between TNF-alpha and COPD

1. Please mention how was COPD diagnosed in all the studies that were reviewed. How many used post BD spirometry and how many did not use bronchodilator reversibility testing
2. Please mention in how many of the studies included in the study, COPD patients were treated with a. inhaled steroids. b. oral steroids
3. Please present the PICOS as a table
4. Please mention where the protocol for systematic review and meta-analysis was registered in Prospero or others
5. How much of homogeneity observed is due to different kits used for estimating TNF-alpha. There is a huge variation in the levels observed among COPD patients and controls. How were these adjusted for
6. With so much of heterogeneity can a meta-analysis be done or should the review be limited to only systematic review. Please justify
7. Please enumerate as a table the characteristics of excluded studies and the reasons for the exclusion
8. Were there no studies before the year 2000? All the included studies are after 2000
9. Please mention how was the risk of bias evaluated in each of the studies included
10. How was bias in studies handled in the final analysis?
11. Spelling and grammatical errors need to be corrected throughout the manuscript
12. In discussion (page 7), authors have described COPD as having reversible but progressive airflow obstruction. The airflow obstruction in COPD is partially reversible at best and is mostly irreversible
13. Please mention all the reasons for exclusion of studies in more detail
14. Introduction - page 3, please use more recent references from the global burden of disease series from the lancet series for the burden of COPD in the world.
15. Please discuss reasons for the variations in levels of TNF-alpha in COPD from 1 to 205 in various studies (Figure 2)

16. Please explain in detail how the weightage was given for various studies in the analysis. Similar weightage seems to be given to studies with very large number of subjects and very small number of subjects.

17. Please mention in more detail the strengths and limitations of this study and future directions.

Reviewer 1 v.2

The authors have clarified most of the comments adequately. However, the discussion needs to be strengthened

For example,

Why is only TNF -alpha important in COPD, when there are so many other inflammatory mediators

What is the possibility in the future that TNF-alpha levels can be used as a biomarker for COPD severity, COPD exacerbations, COPD progression and mortality.

Is it likely that TNF-alpha antagonists may have value in the management of COPD, then it would be useful to study TNF-alpha levels

Whether tissue/BAL TNF-alpha levels have a stronger association with COPD, COPD AE than serum levels of TNF-alpha

Table 1

The PICOS table should also contain the search strategy terms used for each heading

Table 2

Table 2. Exclusion standered - meaning not clear

Please separate TNF-alpha levels from tissue and BAL studies and serum studies and present them separately. Both of these cannot be compared to each other and need to be analysed separately.

Reviewer 2 v.1

#### Comments to the Author

The authors have performed a a systematic review and meta-analysis to evaluate the correlation between TNF- $\alpha$  level and COPD. They found COPD patients have increased TNF- $\alpha$  level than the healthy controls.

#### Major comments:

1. The samples size in COPD patients and controls were not large enough in most included studies.

2. Dose-dependent analysis may be performed to analysis the levels of TNF- $\alpha$  and FEV1

3. The discussion is not well presentation. It is worth the authors presenting some discussion about the limitations of this study.

#### Minor comments:

1. English language needs to be updated. The title should be revised accroding to MS

2. Cases in enrolled studies were diagnosed based on whcih criteria - can the authors provide?