Author Response 1

Response to Reviewers:
General answer to the reviewers: Thank you for the careful evaluation and valuable suggestions to our manuscript, “The correlation between Tumor necrosis factor-α and Chronic obstructive pulmonary disease: A Systematic Review and Meta-Analysis” (Manuscript ID TAR-19-034). We carefully read the review comments you have sent us. However, we could not find the reviewers’ comments in that letter. Time presses and we revised the manuscript according to the current content of the letter.

Reviewer: 1
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
Answer：We are very sorry for our negligence of COPD diagnosed criteria, We have added this in the inclusion and exclusion criteria parts. (Page 3) Considering the Reviewer’s suggestion we also have added reversibility testing for each study in table 3. 21 studies used bronchodilator reversibility testing. while 29 studies did not .
2. Please mention in how many of the studies included in the study, COPD patients were treated with a. inhaled steroids. b. oral steroids
Answer：In this revised version, the patients in nine studies were treated with steroids, while patients in the remaining 24 studies were not treated with steroids. We have add this parts in study selection part (page5) and Table 3.
3. Please present the PICOS as a table
Answer：We have added Table 1as PICOS framework.
4. Please mention where the protocol for systematic review and meta-analysis was registered in Prospero or others
Answer：Thanks for your suggestion, we have already registered this systematic review and meta-analysis in Cochrane recently and waiting for the result.
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?
Answer: Thanks for your suggestion, It is reported that TNF-a participates in metabolic changes associated with chronic wasting disease such as COPD [1,2]. Many research have also reported that TNF-A levels were higher in different biological specimens of COPD pateinst [3, 4]. In this meta-analysis, Compared with the control group, the higher TNF-a expression in COPD patients was due to inflammation in COPD patients. The difference level of TNF-a expression between studies is due to the different source of samples.
6. With so much of heterogeneity can a meta-analysis be done or should the review be limited to only systematic review. Please justify
Answer: Thanks for your suggestion, in this revise version, we have performed meta-analysis based on publication year, region, BMI, NOS, study sample size and smoking status as shown in Table 5.
7. Please enumerate as a table the characteristics of excluded studies and the reasons for the exclusion
Answer: We have add this parts in table 2
8. Were there no studies before the year 2000? All the included studies are after 2000
Answer: By retrieving the database again, we added three articles before 2000 years. (Ref 46-48)
9. Please mention how was the risk of bias evaluated in each of the studies included

Answer: To solve this question, we have performed a sensitivity analysis in the results part and Table 6. The result demonstrated that the stability of the overall treatment effect was good, indicating that our results were robust.
10. How was bias in studies handled in the final analysis?
Answer: We have performed sensitive analysis and the results showed that the overall treatment effect was good. Table 6
11. Spelling and grammatical errors need to be corrected throughout the manuscript
Answer: I'm sorry we have such a low-level mistake. In the revised version, we have carefully examined the spelling and grammar.
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
Answer: Thanks for your suggestion, we have revised this part as: Chronic obstructive pulmonary diseases induced by chronic bronchitis and emphysema are characterized by not fully reversible and progressive airflow limitation and represent one of the most serious public health concerns in the world.
13. Please mention all the reasons for exclusion of studies in more detail
Answer: We have added exclusion reasons in table 2 detailed.
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.
Answer: We have revised this section according to the Lancet. (Ref 1,2)
15. Please discuss reasons for the variations in levels of TNF-alpha in COPD from 1 to 205 in various studies (Figure 2)
Answer: Variable TNF concentrations are due to different sources of samples, some from blood and some from tissues.
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.
Answer: Weighttage was calculated by Revman5 software based on the sample size and outcome index of the COPD group and the control group.
17. Please mention in more detail the strengths and limitations of this study and future directions.
Answer:
Strengths Limitations Future directions
Large sample The significant heterogeneity The relationship between TNF-a and other inflammatory factors in COPD.
TNF-α might be a biomarker for COPD the methods for measuring TNF-α level were inconsistent The systemic inflammatory process and the risk of these complications in COPD
The stability of the overall treatment effect was good we limit the language of publication to English
The quality of include studies are high.
the association between TNF-α level and the quality of life (QOL) of patients was not evaluated
Explored the relationships of TNF-a and COPD in several specific suboioulations.

Reviewer: 2
Comments to the Author
The authors have performed a systematic review and meta-analysis to evaluate the correlation between TNF-α level and COPD. They found COPD patients have increased TNF-α level than the healthy controls.
Major comments:

1. The samples size in COPD patients and controls were not large enough in most included studies.
Answer: In the revise revision we added three studies before 2000. (Ref 46-48)
2. Dose-dependent analysis may be performed to analysis the levels of TNF-α and FEV1.
Answer: Thanks for your good suggestion. COPD is responsible for the systemic inflammation, there exists the possibility of reverse causation. The possibility that systemic inflammation causes injuries to the airways leading to COPD changes cannot be fully discounted [5]. And the aim of this meta-analysis is to evaluate the correlation between TNF-α level and COPD. However, the concentration range of TNF-A is relatively wide due to the sources of samples. It is difficult to perform dose-dependent analysis based on TNF-a. In addition, FEV1 is the volume of the maximum expiratory volume after the maximum deep inspiration and the maximum expiratory volume in the first second. FEV1% is the most commonly used spirometric measure for diagnosis and evaluation of treatment effect in COPD. Therefore, we perform an analysis based on FEV1% as shown in Fig 3.
3. The discussion is not well presented. It is worth the authors presenting some discussion about the limitations of this study.
Answer: The limitation of this study include: 1. The significant heterogeneity; 2 the methods for measuring TNF-α level were inconsistent; 3. we limit the language of publication to English;4. the association between TNF-α level and the quality of life (QOL) of patients was not evaluated
Minor comments:
1. English language needs to be updated. The title should be revised according to MS
Answer: Thanks for your suggestion, we have updated the grammar and spelling of full text by our Englilsh major colleagues. The title have revised as: Association between Tumor necrosis factor-α and Chronic obstructive pulmonary disease: A Systematic Review and Meta-Analysis.
2. Cases in enrolled studies were diagnosed based on which criteria - can the authors provide?
Answer: We are very sorry for our negligence of COPD diagnosed criteria, We have added this in the inclusion and exclusion criteria parts (Page 3).

Reference

1. Kosacka M, Porebska I, Korzeniewska A, et al. Serum levels of apoptosis-related markers (sFasL, TNF-a, p53 and bcl-2) in COPD patients. Pneumonol Alergol Pol.2016,84(1):11-15
2. Singh S, Verma SK, Kumar S, et al. Correlation of severity of chronic obstructive pulmonary disease with potential biomarkers. Immuol Lett.2018,196:1-10.
3. Kawayama T, Kinoshita T, Matsunaga K, et al. Responsiveness of blood and sputum inflammatory cells in Japanese COPD patients, non-COPD smoking controls, and non-COPD nonsmoking controls. Int J Chron Obstruct Pulmon Dis. 2016;10(11):295-303
4. Gaki E, Kontogianni K, Papaioannou AI, et al. Associations between BODE index and systemic inflammatory biomarkers in COPD.COPD. 2011;8(6):408-413.
5. Gan WQ, Man SFP, Senthilselvan A, et al. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. Thorax, 2004, 59(7): 574-580.

Author Response 2

Response to Reviewers

General answer to the reviewers: Thank you for the careful evaluation and valuable suggestions to our manuscript, “The correlation between Tumor necrosis factor-α and Chronic obstructive pulmonary disease: A Systematic Review and Meta-Analysis” (Manuscript ID TAR-19-034). We carefully read the review comments you have sent us. However, we could not find the reviewers’ comments in that letter. Time presses and we revised the manuscript according to the current content of the letter.

Reviewer: 1

Comments to the Author

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

For example,

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

Answer: TNF-a is one of the important inflammatory factors for COPD, and the importance of other inflammatory factors for COPD can not be ignored. We study TNF-a because it is a controversial factor, and the results of many studies are conflicting.

2. 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.

Answer: In mechanism, on the one hand, during inflammation processes, activated inflammatory cells and a variety of released inflammatory mediators such as IL-8, IL-6, and TNF-α can destroy lung structure and promote the inflammatory response of neutrophils [1]. On the other hand, the elevated blood inflammatory factors might be explained by several previously proposed mechanisms, such as local pulmonary inflammation due to smoking, oxidative stress and tissue hypoxia. Therefore, we can determine the relationship between TNF-α level and the severity of COPD by detecting the level of TNF-α in COPD patients. Some research have reported this [2]. 3. 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

Answer: Elevated TNF-a is a complication of COPD with infection, such as bacterial or viral infection. TNF-a antagonist also has some effect on COPD treatment, but does not affect TNF-a as a predictor of COPD. On the contrary, the close relationship between TNF-a and COPD is more evident.

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

Answer: Thank you for your advice. We have added subgroup analysis based on sample source. As shown in Fig.9 The TNF-a levels have a stronger association with COPD, COPD AE than control group in serum, sputum and BAL.

5. Table 1

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

Answer: We have added search strategy terms for each heading as shown in Table1.

Table 2

6. Table 2. Exclusion standed - meaning not clear

Answer: We have corrected this part in the revised version.

7. 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.
Answer: Thank you for your advice. We have added subgroup analysis based on sample source. As shown in Fig.9 The TNF-a levels have a stronger association with COPD, COPD AE than control group in serum, sputum and BAL.
Reference:
1. Emami Ardestani M, Zaerin O. Role of Serum Interleukin 6, Albumin and C-Reactive Protein in COPD Patients. Tanaffos. 2015; 14(2):134-140.
2. S Singh S, Verma SK, Kumar S, Ahmad MK, Nischal A, et al. Correlation of severity of chronic obstructive pulmonary disease with potential biomarkers. Immunol Lett. 2018,196,1-10.