Author’s response to reviews

Title: Prognostic value of TGF-β in lung cancer: systematic review and meta-analysis

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Author’s response to reviews:

Dear Editor,

Many thanks for your letter (April 2, 2019) about our manuscript “Prognostic value of TGF-β in lung cancer: systematic review and meta-analysis (BMC Cancer MS: BCAN-D-18-02436R3)” and thanks for the referees taking time to deal with the manuscript and giving our suggestions. These suggestions are all valuable and very helpful for improving our paper, as well as the important guiding significance to our researches. According to the referees’ suggestions, we have carefully amended and corrected the related contents in our paper. In addition to the referees’ suggestions, we also have made some small revisions in the manuscript. These revisions will not influence the content and framework of the paper. Revised parts have been highlighted using blue text in the paper. The main corrections in the paper and the responses to the referees’ comments are as following.

We changed the authors’ order of CHENG SHEN and JUE LI, and the Change of authorship request form has been attached in the mail.
Reviewer 1's report
I was asked to review a manuscript entitled, "Prognostic value of TGF-β in lung cancer: systematic review and meta-analysis". Overall, the paper was well analyzed, but the English is difficult. Although the author's main points are clear, the English needs to be greatly improved prior to publication. I have one small correction- The captions for figures 6 and 7 need to be reversed.

Thank you for your attention to our article. Review #1 has no suggested changes for the manuscript. We have carefully amended and corrected the related contents in our paper. In addition to the referees’ suggestions, we also have added and corrected the English in our manuscript. Revised parts have been highlighted using blue text in the paper.

Reviewer 2's report
GENERAL COMMENTS: The manuscript reviews the role of TGF-b in lung cancer using a literature review and a meta-analysis of eight Asian studies. The authors include studies that primarily examine TGF-b using ELISA-based analyses, however they do not discuss whether the specific method for how TGF-b is analyzed in lung cancer could influence whether TGF-b is prognostic for this disease in the text, and this should be defined better. They should also indicate whether by determining that TGF-b is prognostic in lung cancer, if this really will have any influence at all on the clinical management of this disease. Are there ways to inhibit this pathway for example and exactly how would this information be used.

Thank you for your attention to our article and valuable questions as well as suggestions. Transforming growth factor beta or TGF-β is a polypeptide member of the transforming growth factor beta superfamily of cytokines, while far fewer clinical studies addressing the association between TGF-β expression and the disease prognosis have been reported up to now. The findings of our meta-analysis may be confirmed in the future by the use of more updated review pooling and more relevant investigations. Studies have shown that many tumors evade immune system recognition by increasing the expression of TGF-β in the environment, thereby increasing the risk of tumor recurrence and metastasis[9-10]. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

REQUESTED REVISIONS:
The issue with examining studies that primarily used ELISA-based analysis raised above needs to be addressed.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. We also added new references in paper. Revised parts have been highlighted using blue text in the paper.

ADDITIONAL REQUESTS/SUGGESTIONS:
There are many places throughout the manuscript where the grammar needs improvement as indicated below:

1. Abstract, page 2 line 5: Lung cancer is the most important cause of cancer-related deaths worldwide and the overall survival of patients with non-small cell lung cancer has not improved.

   Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

2. Page 2, line 13: ...and disease prognosis have been reported up to now.

   Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been
highlighted using blue text in the paper.

3. Page 2, line 20: were searched for full-text literature citations.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

4. Page 2, line 34: (I2=14.2%, P=0.319).
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

5. Page 2, line 38: All the results revealed that a significantly high TGF-β expression in patients…
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

6. Page 2, line 44: The present evidence indicates…
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

7. The discoveries from our meta-analysis may be confirmed using additional updated review pooling and more relevant investigations in the future.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

8. Page 3, line 4: It is still difficult to improve the overall survival of patients with non-small cell lung cancer (NSCLC) for most patients their treatment is limited to chemotherapy or radiotherapy.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

9. Page 3, line 15:… many concerned researchers are exploring new biomarkers that can be used as prognostic factors for lung cancer targeted therapy.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

10. Page 3, line 22: It appears to play a dual role in cancer (provide references).
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

12. Page 3, line 32: However, fewer studies have examined the association between TGF-β expression and prognosis of patients with lung cancer.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

13. Page 3, line 47: published from XXXX up to July 2018. The key words used were as follows:
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
highlighted using blue text in the paper.
14. Page 4, line 7: The HR value could not be obtained from the provided data.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
15. Page 4, line 13: The guideline of Newcastle-Ottawa Scale (NOS) was used for evaluating this research including three perspectives of selection, comparability and exposure.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
16. Page 4, line 17: The assessment tool including the star system, a maximum of 9 stars, was used in this research.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
17. Page 4, line 27: Any matters that were unclear or disagreement was dealt with by means of discussion.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
18. Page 4, line 28: Excel was used to collect the following details:
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
19. Page 4, line 34: age, gender, tumor stage, tumor histology, the number of patients with positive expression and negative expression of TGF-β; treatment information, and survival analyses.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
20. Page 4, line 50: chosen by the heterogeneity…
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
21. Page 5, line 7: There were 288 articles by screening of titles and abstracts and excluding duplicate literature entries.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
22. Page 5, line 11: There were 268 papers excluded due to unqualified document types,…
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
23. Page 5, line 22: eight qualified literature sources are recorded in Table 1.
Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.
24. Page 5, line 26: Hasegawa et al.[13] enrolled a total of 53 NSCLC tissue samples (19 squamous cell carcinomas, 33 adenocarcinomas, and 1 adenosquamous cell carcinoma) in their study.
Thank you for your attention to our article and valuable questions as well as suggestions. We have
carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

25. Page 6, line 5: There were two studies reporting lung adenocarcinoma of patients and the defined HR based on this study was 2.14.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

26. Page 6, line 7: The fixed-effect model was then considered for this part (I²=0.0%, P=0.434).

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

27. Page 6, line 12: Another two studies that did not define the tumor pathology showed that TGF-β overexpression might be a strong predictor of poor survival for NSCLC patients (HR=2.04, 95% CI: 1.12-3.72) (Figure 3).

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

28. Page 6, line 15: From four of the included studies patients with other pathologies of lung cancer indicated that high TGF-β expression was a marker of poor survival (HR=2.23, 95% CI: 1.62-3.07) (Figure 3).

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

29. Page 6, line 23: We measured the association between.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

30. Page 6, line 23: In four studies examining surgery only, the summarized HR of analysis was 2.68 (95% CI: 1.91-3.75) (Figure 4).

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

31. Page 6, line 29: and combination therapy, it was statistically meaningful.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

32. Page 6, line 50: Both the Begg's funnel plot and Egger's test.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

33. Page 7, line 15: TGF-β appears to be involved in the tumorigenesis of the patients in these studies.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

34. Page 7, line 18: The higher the expression of TGF-β protein, the more advanced tumor stage for the patients.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been
Page 7, line 20: In addition, patients appear to be more likely to be diagnosed with lymph node metastasis if the TGF-β protein expression was drastically higher than normal levels [5, 16].

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 7, line 43: The interstitial cells of the lungs have no relative impact with an irregular manner. The meaning of this sentence is not clear.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 7, line 49: during EMT [19-21].

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 8: lung cancer patients without examining patient prognosis.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 11: Analyzing the prognostic value of TGF-β specifically in lung cancer using meta-analysis in our study, we further performed subgroup analysis including the...

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 27: and some errors may have occurred during the rebuilding of HR calculated via Kaplan-Meier survival curves.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 31: might be an ethnic bias.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 33: heterogeneity in this study.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 45: The small numbers of studies examined may influence the validity of this conclusion.

Thank you for your attention to our article and valuable questions as well as suggestions. We have carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.

Page 8, line 49: should be better confirmed with additional relevant research in the future using updated analyses.

Thank you for your attention to our article and valuable questions as well as suggestions. We have
carefully amended and corrected the related contents in our paper. Revised parts have been highlighted using blue text in the paper.