Reviewer’s report

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

Version: 3 Date: 21 Feb 2019

Reviewer: Reviewer 2

Reviewer's report:

PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses a testable research question(s) (brief or other article types: is there a clear objective)?
Yes - there is a clear objective

DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
No - there are minor issues

EXECUTION - Are the experiments and analyses performed with technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately

Statistics - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
No - there are minor issues

OVERALL MANUSCRIPT POTENTIAL - Is the current version of this work technically sound? If not, can revisions be made to make the work technically sound?
Maybe - with major revisions

PEER REVIEWER COMMENTS:

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.

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

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.
2. Page 2, line 13: …and disease prognosis have been reported up to now.
3. Page 2, line 20: were searched for full-text literature citations.
4. Page 2, line 34: (I²=14.2%, P=0.319).
5. Page 2, line 38: All the results revealed that a significantly high TGF-β expression in patients…
6. Page 2, line 44: The present evidence indicates…
7. The discoveries from our meta-analysis may be confirmed using additional updated review pooling and more relevant investigations in the future.
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.
9. Page 3, line 15:… many concerned researchers are exploring new biomarkers that can be used as prognostic factors for lung cancer targeted therapy.
10. Page 3, line 22: It appears to play a dual role in cancer (provide references).
12. Page 3, line 32: However, fewer studies have examined the association between TGF-β expression and prognosis of patients with lung cancer.
13. Page 3, line 47: published from XXXX up to July 2018. The key words used were as follows:
14. Page 4, line 7: The HR value could not be obtained from the provided data.
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.
16. Page 4, line 17: The assessment tool including the star system, a maximum of 9 stars, was used in this research.
17. Page 4, line 27: Any matters that were unclear or disagreement was dealt with by means of discussion.
18. Page 4, line 28: Excel was used to collect the following details:
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.
20. Page 4, line 50: chosen by the heterogeneity…
21. Page 5, line 7: There were 288 articles by screening of titles and abstracts and excluding duplicate literature entries.
22. Page 5, line 11: There were 268 papers excluded due to unqualified document types,…
23. Page 5, line 22: eight qualified literature sources are recorded in Table 1.
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.
26. Page 6, line 7: The fixed-effect model was then considered for this part (I²=0.0%, P=0.434).
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).
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).
29. Page 6, line 23: We measured the association between..
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).
31. Page 6, line 29: and combination therapy, it was statistically meaningful..
32. Page 6, line 50: Both the Begg's funnel plot and Egger's test..
33. Page 7, line 15: TGF-β appears to be involved in the tumorigenesis of the patients in these studies.
34. Page 7, line 18: The higher the expression of TGF-β protein, the more advanced tumor stage for the patients.
35. 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].
36. 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.
38. Page 7, line 51: cancer cells lose cell-cell adhesion junctions and change into fibroblast-like…
40. 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..
41. Page 8, line 27: and some errors may have occurred during the rebuilding of HR calculated via Kaplan-Meier survival curves.
42. Page 8, line 31: might be an ethnic bias.
43. Page 8, line 33: heterogeneity in this study.
44. Page 8, line 45: The small numbers of studies examined may influence the validity of this conclusion.
45. Page 8, line 49: should be better confirmed with additional relevant research in the future using updated analyses.

Note: This reviewer report can be downloaded - see attached pdf file.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

No
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

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