Author's response to reviews

Title: Ki-67 as a prognostic marker in early-stage non-small cell lung cancer in Asian patients: a meta-analysis of published studies involving 32 studies

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Responses to reviewers' comments

First of all, we would like to thank all the editors and reviewers for their valuable comments and suggestions. In reply to the Reviewer’s comments:

For Editors,

Q1. The title says "Asian patients", but the meta analysis seems to include Asian and non-Asian patients. A possible influence of race on Ki67 and its prognostic value should be discussed in more detail.

Reply: Thank you for the suggestion. Relevant detailed discussion were added. Please find the tracked changes in manuscript. We hope this addresses your concerns.

Q2. Literature review should be comprehensive. E.g. the large study of Warth et al., Br J Cancer 2014, 111(6) should be included.

Reply: Thanks for your comments. We have added Warth's study in the revised manuscript. Furthermore, all relevant data have been updated because of inclusion of Warth's study. More details please find tracks in the revised manuscript.

For Reviewer 1,

Q1. Method used for synthesizing the Ki-67 prognostic effect: Please specify method used for synthesizing the Ki-67 prognostic effect (and reference) over studies included in the analysis, although it could infer that random effect mete-regression model could be used.

Reply: Thanks for your advices. Although the method used in current study have been also used in many high-quality meta-analysis (1, 2), such as multiple subgroup analysis, random model analysis, it has some limitations. First, it was based on summary data rather than data from individual patients. Therefore, multivariate analyses for confounding factors such as histological subtypes, gender and smoking status were not performed. A meta-regression model that adjusted for those factors that were found to be correlated with high K-67 levels was also not performed, too.
we have added some relevant reference in the revised manuscript. We hope it may address your concern.

**Q2.** Variation of cutoff values for Ki-67 (range 5% to 50%) makes it difficult to get a precise estimate of the marker’s prognostic effect.  
**Reply:** Thank you for the suggestion. In the revised manuscript subgroup analysis have been added among three recommended cut-off values (10%, 25% and 50%) between high Ki67 and OS. Although the adverse effect of high Ki-67 expression on OS showed similar results using these three recommended cut-off values, a consensus for the optimal cut-off value for Ki-67 needs to be reached and validated in NSCLC patients in future studies. Moreover, we have demonstrated this limitation in the discussion. Thanks again for your kind point it out.

**Q3.** Lack of consideration of adjusting for confounders makes it difficult to judge the added value of Ki-67 as a potential prognostic factor (The analysis reveals that high Ki-67 is associated with a few poor prognostic factors of the population).  
**Reply:** Thanks for you suggestion. It is an important question for most meta-analysis, because it was based on summary data rather than data from individual patients. Meta-regression model could be performed to adjust those factors that were found correlated to high K-67 levels.  
**Reply:** Thanks for you suggestion. It is an important question for most meta-analysis, because it was based on summary data rather than data from individual patients. Meta-regression model could be performed to adjust those factors that were found correlated to high K-67 levels.

**Q4.** The overall conclusions and discussion are overly simplified and sweeping in their interpretation of the results without considering potential limitations inherent in such a project, limitation of the analysis should be discussed in the discussion section.  
**Reply:** Thanks very much for you kind suggestions. we have added relevant analysis and discussion sections in the revised manuscript. we hope this could address your concern. For more detailed changes in the manuscript, please see the tracked changes.
Reviewer 2,

Q1. The authors should show and highlight what the authors have provided interesting and new idea from those meta-analyses data. What is intriguing in this paper? Show the significant differences between the Authors’ paper and the previously published study.

Reply: Thanks for you suggestion. The present meta-analysis indicated that elevated Ki-67 expression was associated with a poorer outcome in NSCLC patients, particularly in early-stage Asian ADC patients. In addition, it was first reported that high Ki-67 expression in NSCLC patients was associated with a poor survival outcome for DFS. Moreover, subgroup analysis in this study showed that higher Ki-67 expression indicated a poorer outcome in Asian NSCLC patients compared with non-Asian patients. To our knowledge, this study is the most comprehensive and detailed meta-analysis to evaluate the association between Ki-67 expression and survival in NSCLC patients (nearly three-fold as many patients and double the number of studies when compared with previous meta-analysis published in 2004).

Q2. This is also a critical comment. The authors have used the method of subgroup analyses due to high heterogeneity between each study. Should discuss and explain this heterogeneity of 31 studies.

Reply: Thanks for your kind suggestion. We have added several sections for discuss and explain the heterogeneities. In addition, subgroup analysis, such as different cut-off value, were added in the revised manuscript. More details please find the tracks in the manuscript. We really hope these changes will address your concern.

Q3. Should explain the differences between studies for Asian and non-Asian patients.

Reply: Very thanks for your suggestion. Discussion about the differences between studies for Asian and non-Asian patients were added in the revised manuscript, please find the tracks of the manuscript.
Q4. It is strongly recommended to check the text from persons who have written many original research or case report papers. The manuscript has contained many careless mistakes. Very difficult to read it.

Reply: Thanks for you cordial advices. The manuscript have been checked by at least two professional editors, both native speakers of English. For a certificate, please see the website http://www.textcheck.com/certificate/rRzLS2. Thanks very much again.

Manuscripts with tracked changes please see the file “revised manuscript with tracks”. We hope that these changes address your concerns. Thanks again.

Reference