Author's response to reviews

Title: Perioperative blood transfusion adversely affects prognosis after resection of lung cancer: A systematic review and a meta-analysis

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Author's response to reviews:

Dear Mr. Eden Nonato:

Thank you for your kindness to have reviewed our manuscript (MS: 4054059611229612) and given so many constructive comments and suggestions. We have revised our paper carefully by following the criticisms from you and the reviewers earnestly.

With best wishes

Dr. Yanming Zhou

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Reviewer 1: Yixin Zhang

Reviewer's report:

The authors conducted a meta-analysis on the association between blood transfusion and the prognosis of lung cancer. The topic is important and interesting, but more input will be needed. And the suggestion was "Major Compulsory Revisions".

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Answer: We have invited a professor who is expert in both medicine and the English language to go over and revise the manuscript throughout.

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: I have no competing interests.

Reviewer 2: Reviewer: Juan Cata
Reviewer’s report:

Dear Editor

I had the great opportunity of reviewing the manuscript entitled "Perioperative blood transfusion adversely affects prognosis after resection of lung cancer: A meta-analysis". I had to congratulate the authors for their work. They conducted a meta-analysis of retrospective studies that looked at the association between BT and RFS and/or OS after cancer surgery. The authors concluded that such association might be real although they also recognize the limitations of the study.

I have some few comments and concerns regarding the current version of the manuscript.

Overall comments.
1- This is an article whose findings are important to those with closely related research interests

2- Statistical analysis is sound but I do not feel adequately qualified to assess the statistics.

Major concerns and comments.

1- The authors have analyzed data from studies in which staging was not taken into consideration. In fact they recognize this as a significant limitation. However, I would suggest to add an analysis of the data by staging of the disease.

Answer: We have performed sensitivity analysis of patients with stage I disease (see Table 2). No subgroup analysis of patients with stage II or stage III disease could be carried out, given the absence of adequate information in individual studies.

2- The authors mentioned that a RCT would never be conducted because of potential ethical issues. I disagree with them a RCT study can be done if appropriate triggers for transfusions are used and then stratification based on number of units is done. Please clarify because the reader might conclude that a RCT would be not ethical.

Answer: We have deleted the sentence (However, it is difficult to design a randomized trial from an ethical perspective, simply as it would be unacceptable to administer a transfusion without a clinical indication or to withhold transfusion from a patient who needed blood.)

3- Please also clarify the issue between single vs multiple units transfused since there might be an association between the number of units and worse outcomes.

Answer: We have added comments in the Discussion section as “With respect to colorectal liver metastasis, Stephenson et al. [29] reported that patients who received more than 11 units of blood had significantly shorter disease-free intervals and worse survival than those who received 3-10 units of blood after surgery. Of the included studies in the current analysis, Pastorino, Keller, Little, Nosotti and their colleagues noted that the number of units transfused did not affect the survival or recurrence-free survival [5-7,14]. In contrast, Cata et al. [23]
found that the number of units transfused was a factor associated with worse RFS and OS. We were unable to examine whether there was a dose-dependent effect of transfusion on survival because the stratification for the amount of transfused blood was not always the same between these studies.”

4- Please also clarify whether autologous BT were included in the analysis. 

Answer: We have added the following information to the part of Inclusion and exclusion criteria; “Inclusion criteria for primary studies were as follows: (i) the correlation between perioperative allogeneic blood transfusion and prognosis in patients undergoing lung cancer resection; and (ii) data available on overall survival (OS) or recurrence-free survival (RFS) with a median follow-up of at least 24 months.”

5- Please comment on the timing of BT. Were all given intraop, postop or perioperative. If possible subanalyze the data based on this.

Answer: In part of Discussion, we have added comments as “Finally, it has been suggested that pre-, intra-, and postoperative administration of blood would increase the likelihood of colorectal cancer recurrences by 50, 74 and 36%, respectively [30]. Unfortunately, no study available has reported the effect of the timing of transfusion on long-term survival or tumor recurrence after lung cancer resection.”

5- Figs and tables are very well done and clear.

Minor concerns

1- The manuscript would benefit from editorial assistance in terms of grammar and orthography.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Answer: We have invited a professor who is expert in both medicine and the English language to go over and revise the manuscript throughout.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests

Reviewer 3: Reviewer:Morgan LE GUEN

Reviewer's report:

This meta-analysis is the first about outcome of patients undergoing a lung resection and transfusion. This is a current interrogation with the theory of immunomodulation and even immunodepression during surgery, anaesthesia with opioids or with transfusion. For this concern, your study has caught my reviewer’s attention. Authors conclude to the negative impact of transfusion on postoperative mortality but they omit some interactions between patients ‘disability (ASA, preoperative low haemoglobin...) and risk of transfusion.
1. Is the question posed by the authors well defined?
The primary end-point is well defined in the introduction of the manuscript with a
devoted paragraph in the result and in the discussion section.

2. Are the methods appropriate and well described?
This is a meta-analysis as indicated in the title. This method is probably the only
one to answer to the question because a randomized study would not be ethical
as suggested in the manuscript.

The authors follow the current international guidelines. Nevertheless, as required
in the PRISMA methodology, it would be appreciable that authors mentioned in
methodology section the need to contact some original writers to complete
datasheet. In the opposite, just suggest it was not the case.

Major Compulsory Revisions
Authors should mention in methodology section the need to contact some
original writers to complete datasheet. In the opposite, just suggest it was not the
case.

Answer: In the methodology section, we have added the content as “If additional
data were needed, the authors were contacted to provide full details.”

About data extraction, some additional information is interesting in this specific
population undergoing major non cardiac surgery. First, ASA (American Society
of Anesthesiology) score is required because it is known to be directly and
independently correlated to the postoperative outcome of patients. If there is a
great unbalance with severe illness patients (ASA III or IV) in the group of
transfusion, this leads to a confusing factor with an expected poor outcome. In
the same way, the oncologic status may be interesting especially with
preoperative chemotherapy which could modulate the immune system and may
enhance immunodepression.

Answer: As only one study provided data of ASA, we did not add the relevant
data in Table 1. Similarly, there is a lack of data of preoperative or postperative
chemotherapy in individual studies. Although we sought to obtain additional
information from the corresponding author of each report by e-mail, source data
were unavailable. We have added data of preoperative hemoglobin in Table 1.

Minor Essential Revisions
As suggested in PRISMA guidelines, please mention “Systematic Review and
Meta-analysis” in the title as followed: “Perioperative blood transfusion adversely
affects prognosis after resection of lung cancer: A Systematic review and a
Meta-analysis.”

Answer: we have revised the title as “Perioperative blood transfusion adversely
affects the prognosis after lung cancer resection: a systematic review and
meta-analysis”

3. Are the data sound?
The article is short and precise with a huge sample. The choice of a clear primary
end-point with specific tables helps the reader to make his self-opinion.
Minor essential revisions:

It is surprising not to have included any Chinese studies. Is it really the case or is it a choice of the authors after the first selection of studies? Depending your answer, revision of method section may be required.

Answer: We have searched China National Knowledge Infrastructure and identified one study that was eligible for inclusion (reference 19).

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?

Yes it is except for the point detailed in the second point, mainly about communication with original authors of selected articles.

Major Compulsory Revisions

Authors did not describe the number of patients lost during the follow-up, neither the number of censured data especially for the secondary outcome as recurrence-free interval.

Answer: a) We have added the number of patients lost to follow-up in Table 1; b) none of the included studies provided the data regarding the number of censured data especially for the secondary outcome as recurrence-free interval.

5. Are the discussion and conclusions well balanced and adequately supported by the data?

In my opinion, discussion needs some further revision. Many confounding factors are not discussed as the medical history (neoadjuvant chemotherapy, preoperative cardiac status as ischemic cardiopathy, preoperative haemoglobin, anticoagulant…). Moreover, the extended period of analysis make comparison between study really hard because surgery, anaesthesia and threshold for erythrocyte prescription have notably changed!

Answer: We have revised the comments as “Several weaknesses of the present study should be taken into consideration in interpreting our results. First, all the included studies were retrospective and are therefore subject to inherent biases, although the results of pooled data of multivariate RRs are similar to the findings from overall analysis. Second, funnel plot analysis revealed the sign of publication bias, which may relate to only published studies included. Third, moderate to high level heterogeneity was detected within primay outcomes. There are considerable disparities between the studies that might introduce heterogeneity, including variation in the preoperative status (such as the American Society of Anesthesiologist physical status, body mass index, comorbidities and hemoglobin level), disease stage, the extent of resection and transfusion policies. In addition, some patients received preoperative or postoperative chemotherapy, which might have influenced the outcome. Also, it should be noted that these studies were conducted over a 20-year period, improvements in operative techniques and anesthesiological management as well as perioperative care are strongly linked to the outcome after lung cancer surgery. In order to minimize this effect, the RR was calculated by a random-effects model. Finally, it has been suggested that pre-, intra-, and postoperative administration of blood would increase the likelihood of colorectal...
cancer recurrences by 50, 74 and 36%, respectively. Unfortunately, no study available has reported the effect of the timing of transfusion on long-term survival or tumor recurrence after lung cancer resection.

6. Are limitations of the work clearly stated?
Limit section is correct but insufficient in regard to the superficial analysis of this question. Some confounding factors are not analysed and this should be discussed in this section.

Major Compulsory Revisions

Authors did not discuss some critical point as the extended period of inclusion with changes in surgical, anesthesiology practice and in the trigger of transfusion. Moreover, less invasive surgery (video-thoracoscopy…) has probably changed the risk of bleeding but in the other side more patients receive now antiagregant or anticoagulant with a higher risk of exposure to transfusion for a similar disease many years before.

Answer: we have revised the comments as “…significantly heterogeneity heterogeneity was detected within primay outcomes. There are considerable disparities between the studies that might introduce heterogeneity, including variation in the preoperative status (such as the American Society of Anesthesiologist physical status, body mass index, comorbidities and hemoglobin level), disease stage, the extent of resection and transfusion policies. In addition, some patients received preoperative or postoperative chemotherapy, which might have influenced the outcome…..”.

The authors should better define the primary outcome (the overall survival) in term of median follow-up with a detailed description of the follow-up duration for every study.

Answer: a) We have revised Inclusion criteria for primary studies as follows: (1) the correlation between perioperative allogenic blood transfusion and prognosis in patients undergoing lung cancer resection; and (2) data available on overall survival (OS) or recurrence-free survival (RFS) with a median follow-up of at least 24 months. b) We have added the data about the follow-up duration for every study in Table 1.

We are not sure of the homogeneity in the demographic data (rate of pneumonectomy varies from 1/30 patients to 1/1.5; ischemic cardiopathy is not given; histology of cancer…)

Answer: none of included studies provided these informations.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
This article is a meta-analysis and by essence, it is based on previously published article according to their power (number of patients, quality of the study: randomised controlled trial in comparison to observational cohort….)

8. Do the title and abstract accurately convey what has been found? Title and abstract follows current guidelines.
Yes they follow current guidelines: PRISMA method for Preferred Reporting
Items for Systematic Reviews and Meta-Analysis.

Minor Essential Revisions

As suggested in PRISMA guidelines, please mention “Systematic Review and Meta-analysis” in the title as followed: “Perioperative blood transfusion adversely affects prognosis after resection of lung cancer: A Systematic review and a Meta-analysis.”

Answer: we have revised the title as “Perioperative blood transfusion adversely affects the prognosis after lung cancer resection: a systematic review and meta-analysis”

9. Is the writing acceptable? Yes it is.

Minor essential revisions:

Background section: replace “Inspite of” by “Despite improvements”, “need” by “needs” or “requires”. Add “postoperative outcome” in the following sentences.

Statistical analysis: you should define “SEs” before giving abbreviation.

Eligible studies: in the second sentence, a word is lacking: inclusion “criteria” miss.

Answer: We have made corrections accordingly.

Many references included more than 6 authors. Indicate into brackets the number of journals from the start of the year.

There is probably a mistake in the 25th reference with a double and consecutive author “Zhou Y“

Answer: It has been confirmed to be correct.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests.