

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of the neutrophil to lymphocyte ratio and clinical outcomes in lung cancer patients receiving immunotherapy: a meta-analysis
AUTHORS	Jin, Jing; Yang, Lan; Liu, Dan; Li, Weimin

VERSION 1 – REVIEW

REVIEWER	Zhijun Dai Department of Breast Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University, China.
REVIEW RETURNED	12-Nov-2019

GENERAL COMMENTS	<p>Thank you for inviting me to evaluate the manuscript titled “Correlation of the neutrophil to lymphocyte ratio and clinical outcomes in lung cancer patients receiving immunotherapy: a meta-analysis”. The manuscript studied the relationship between neutrophil to lymphocyte ratio (NLR) and clinical outcomes via a meta-analysis. The study revealed that the higher level of NLR, as well as the pre-treatment NLR, were associated with poorer prognosis in lung cancer patients received immunotherapy. The study is well-designed and constructed. However, there are some recommendations before considering the publication:</p> <ol style="list-style-type: none">1. The language of this manuscript should be improved further. There are vague expression and grammar mistakes in this manuscript. For example, “The subgroup analysis stratified by ethnicity found that patients in Asia were significantly associated with a higher HR (HR=2.76; 95% CI: 1.88- 4.06) and smaller heterogeneity”.2. The expression of “Fig 6A and 6B” should be replaced by “Fig. 6A and 6B” or “Figure 6A and 6B”. Meanwhile, please check the similar expression, such as “Jiang, T”(line 40th on page 14th).3. Please check the reference format.4. There is no title for Table 2 which I am not sure if it is Table 2.5. The discussion is not deep enough. Please discuss more about your own results in depth.
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REVIEWER	Peter Baade Cancer Council Queensland
REVIEW RETURNED	09-Jan-2020

GENERAL COMMENTS	<ol style="list-style-type: none">1. Figure 1 – further clarification of the exclusions would be useful. For example, there were 1102 unique manuscripts initially considered. However only 690 records were screened. I assume this was using the title and abstract, but this is not specifically stated. What happened to the 412 records (1102-690) – how were these excluded? The close similarity between the number of full
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	<p>text manuscripts read (26) and the final number (23) increases the likelihood of false-negatives (ie. records were excluded based on title/abstract that would have been included with a full text search).</p> <p>2. Given all the included studies were published in 2017 and 2018, can the authors confirm there were no restrictions on earlier publication dates?</p> <p>3. Please keep a consistent number of decimal points. For percentages, 1 decimal point is sufficient (eg page 8 line 48 and page 9 line 4), and p-values to 3 decimal points are sufficient.</p> <p>4. Page 9. Lines 22-28. Please clarify this text, as it currently reads as though the text contradicts itself. Indeed the value of 5 was only used in 10 of the 23 included studies.</p> <p>5. Page 9. 46-48. This sentence needs rewording for clarity. Also the word “researches” is used several times throughout the manuscript, but should be changed to “studies”</p> <p>6. Page 10, lines 41-49. Please provide the HR and I2 values for Europe and America.</p> <p>7. Page 13, Lines 9-11. Please reword to “...had significantly higher HR than those in”</p> <p>8. Table 1 – it is not clear how the studies in the table are ordered. Some clear logical sequencing would be helpful.</p> <p>9. Table 1. What impact would the varying cut-off points have on the observed heterogeneity of the results? Lower cutoffs were associated with lower HRs in the supplementary figure 2.</p>
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VERSION 1 – AUTHOR RESPONSE

Response to reviewer 1

1. The language of this manuscript should be improved further. There are vague expression and grammar mistakes in this manuscript. For example, “The subgroup analysis stratified by ethnicity found that patients in Asia were significantly associated with a higher HR (HR=2.76; 95% CI: 1.88-4.06) and smaller heterogeneity”.

Response: Thank you for your suggestion. Our manuscript has been copyedited by American Journal Experts (AJE). The details of the professional service and a copy of the manuscript showing changes (by using track changes) are attached in supplementary information S4: Professional editing. We also made corrections to the text you mentioned above.

2. The expression of “Fig 6A and 6B” should be replaced by “Fig. 6A and 6B” or “Figure 6A and 6B”. Meanwhile, please check the similar expression, such as “Jiang, T”(line 40th on page 14th)

Response: Thank you for your suggestion. We have corrected these issues in the revised manuscript.

3. Please check the reference format.

Response: Thank you for your suggestion. We have confirmed that our reference format meets BMJ OPEN’s style requirements.

4. There is no title for Table 2 which I am not sure if it is Table 2.

Response: Thank you for reviewing our manuscript. There is no Table 2.

5. The discussion is not deep enough. Please discuss more about your own results in depth.

Response: Thank you for your suggestion. We have added explanations regarding our results to the Discussion (pages 14-15).

Response to reviewer 2

1. Figure 1 – further clarification of the exclusions would be useful. For example, there were 1102 unique manuscripts initially considered. However, only 690 records were screened. I assume this was using the title and abstract, but this is not specifically stated. What happened to the 412 records (1102-690) – how were these excluded? The close similarity between the number of full-text manuscripts read (26) and the final number (23) increases the likelihood of false-negatives (ie. records were excluded based on title/abstract that would have been included with a full-text search).

Response: Thank you for your advice on Figure 1 and the screening process. We apologize for the lack of detailed description for Figure 1. We rescreened all included studies (1102) and reconstructed Figure 1.

2. Given all the included studies were published in 2017 and 2018, can the authors confirm there were no restrictions on earlier publication dates?

Response: Thank you for reviewing our manuscript. We did not set a time limit when searching the literature (please see supplementary information S2: Search strategy). Among all studies that performed screening (1102), the earliest publication year was 2002. Therefore, we confirm that there were no restrictions on earlier publication dates. In addition, Begg's test presented no evidence of obvious publication bias in studies reporting the association between the NLR and OS ($P=0.673$) or in those reporting the association between the NLR and PFS ($P= 0.074$). In addition, trim and fill analysis on all studies confirmed that our results were robust.

3. Please keep a consistent number of decimal points. For percentages, 1 decimal point is sufficient (eg page 8 line 48 and page 9 line 4), and p-values to 3 decimal points are sufficient.

Response: Thank you for your advice on our manuscript. We have kept 1 decimal point for percentages and 3 decimal points for p-values in the revised manuscript.

4. Page 9. Lines 22-28. Please clarify this text, as it currently reads as though the text contradicts itself. Indeed the value of 5 was only used in 10 of the 23 included studies

Response: We apologize for our mistake. We have made corrections to the revised manuscript (page 9).

5. Page 9. 46-48. This sentence needs rewording for clarity. Also, the word “researches” is used several times throughout the manuscript but should be changed to “studies”.

Response: Thank you for your suggestion. We have made corrections to the revised manuscript and the word “researches” has been changed to “studies”.

6. Page 10, lines 41-49. Please provide the HR and I2 values for Europe and America.

Response: The HR and I2 values are provided in Figure 3. The HR and 95% CI for Europe and America were 1.63 and 1.22-2.16, respectively. The I2 value was 75.2%.

7. Page 13, Lines 9-11. Please reword to “...had significantly higher HR than those in”

Response: Thank you for your suggestion. We have corrected this text according to your suggestion.

8. Table 1 – it is not clear how the studies in the table are ordered. Some clear logical sequencing would be helpful.

Response: Thank you for your advice. We reconstructed Table 1, and all studies are now ordered according to the year of publication.

9. Table 1. What impact would the varying cut-off points have on the observed heterogeneity of the results? Lower cutoffs were associated with lower HRs in the supplementary figure 2.

Response: Thank you for reviewing our manuscript. I do not quite understand what you mean. Do you mean “What impact would the varying cutoff points have on the observed hazard ratios (HRs) of the results?”

As shown in Figure 3, lower cutoffs were indeed associated with lower HRs but also with high heterogeneity, and $P_{\text{interaction}}=0.095$, which is greater than 0.05; therefore, we cannot conclude that the cutoff value was significantly associated with the HRs. When the cutoff value is changed, the number of people in different groups will also change, and then HRs will be different. From the existing data, we cannot determine the impact of the cutoff value on the observed HRs.

We appreciate the editor/reviewers' earnest work and hope that the corrections will make the revised manuscript acceptable for publication. Once again, thank you very much for your comments and suggestions, and we look forward to hearing from you.

VERSION 2 – REVIEW

REVIEWER	Zhijun Dai Department of Breast Surgery, The First Affiliated Hospital, College of Medicine, Zhejiang University
REVIEW RETURNED	04-Mar-2020

GENERAL COMMENTS	Thank you for inviting me to evaluate the manuscript titled “Association of the neutrophil to lymphocyte ratio and clinical outcomes in lung cancer patients receiving immunotherapy: a meta-analysis”. The study revealed that NLR can be a prognostic factor in lung cancer patients receiving immunotherapy. This study is well-designed and the format is well-done, while there is one recommendation which I hope they could help to improve this paper: In “Discussion” part, some numeric results should be omitted because it had been showed in “Results”.
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REVIEWER	Peter Baade Cancer Council Queensland
REVIEW RETURNED	23-Feb-2020

GENERAL COMMENTS	Thank you to the authors for responding to the previous comments. My main concern remains with the impact of the varying cut off points on the reported associations. While the authors have assessed the impact of ≥ 5 and < 5 , this dichotomised variable is somewhat crude and arbitrary. It would be useful to provide some more information about how the cut points impact on the reported HR - even using a more detailed ordinal scale.
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VERSION 2 – AUTHOR RESPONSE

Response to reviewer 1

1. In the “Discussion” part, some numeric results should be omitted because it had been shown in “Results”.

Response: Thank you for your suggestion. We have omitted some data which has been shown in the result (pages 12)

Response to reviewer 2

1. My main concern remains with the impact of the varying cut off points on the reported associations. While the authors have assessed the impact of ≥ 5 and < 5 , this dichotomized variable is somewhat crude and arbitrary. It would be useful to provide some more information about how the cut points impact on the reported HR - even using a more detailed ordinal scale.

Response: Thank you for reviewing our response and revised manuscript. To better understand the relationship between the cutoff value and HR, we did correlation analysis on the original cut-off value and HR (both OS and PFS) provided in the article. we provided the detailed data in the following table. The P-values were also greater than 0.05. Therefore, we cannot conclude that the cutoff value was significantly associated with the HRs.

Pearson's

t P-value 95%CI Cor

OS 1.646 0.116 (-0.089,0.669) 0.345

PFS 0.989 0.335 (-0.239, 0.669) 0.227

We appreciate the editor/reviewers' earnest work and hope that the corrections will make the revised manuscript acceptable for publication. Once again, thank you very much for your comments and suggestions, and we look forward to hearing from you.