

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)	Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review
AUTHORS	Chen, Haisheng; Shi, Jing; Shi, Wenna; Xu, Hengwei; Duan, Cunxian; Fan, Qing; Wang, Yanhong; Li, Hui

VERSION 1 – REVIEW

REVIEWER	Antonio Passaro, MD PhD European Institute of Oncology, IRCCS, Milan, Italy
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	<p>Dear Authors,</p> <p>the proposed manuscript in an interesting report, discussing the role of COVID-19 in cancer patients, in particular lung cancer patients.</p> <p>The protocol is interesting, but the argumentations should be improved updating references that appeared not focused on the important topic.</p> <p>Please, consider to cite in the text the following manuscript focused on lung cancer and COVID-19</p> <p>Please, cite the following manuscript: Testing for COVID-19 in lung cancer patients DOI: 10.1016/j.annonc.2020.04.002. You can use this high cited manuscript instead of your Reference N5: Banna et al.</p> <p>It is highly recommended to add the most important guideline discussing the management of COVID-19 and lung cancer, published by ESMO KOLs on ESMO Open journal: Passaro et al, ESMO Open, doi: 10.1136/esmoopen-2020-000820.</p> <p>Data about TERA-VOLT trial, just published on Lancet Oncology doi: 10.1016/S1470-2045(20)30314-4. Epub 2020 Jun 12. are missing. Highly requested to be added.</p> <p>Professional Language editing is required.</p> <p>Please check all the manuscript for COVID-19, Coronavirus disease and similars words.</p> <p>Pag. 10, line 19. Discussion. The disease caused by COVID-19 is called "novel coronavirus pneumonia" is wrong. COVID-19 = the disease Sars-CoV-2 = virus --> the disease caused by Sars-CoV-2 infection is called COVID-19!!!</p>
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REVIEWER	Ilias I. Siempos National and Kapodistrian University of Athens Medical School, Greece
REVIEW RETURNED	07-Aug-2020

GENERAL COMMENTS	<p>Chen and colleagues report a protocol for a systematic review of studies examining differences between patients with cancer of lung as opposed to other solid organs after infection with COVID-19 in terms of presentation and outcomes. The following points may be helpful to the authors:</p> <p>General comments:</p> <ol style="list-style-type: none"> 1. The manuscript needs extensive editing to improve language and correct typos, such as "...a systematic review examing differences..." (sic) in the title. 2. The Title and the Abstract may need rewording so that it becomes clear that the systematic review will explore differences between patients with lung cancer as opposed to other solid organs cancer after infection with COVID-19 in terms of presentation and outcomes. A suggestion for a revised title is mentioned in my specific comments below. Abstract could be revised accordingly. <p>Specific comments:</p> <ol style="list-style-type: none"> 3. Page 3, Title, "COVID-19 in lung cancer patients and other solid cancer patients: protocol for a systematic review examing differences in outcome and presentation" (sic): A more informative title could be "Differences between patients with lung cancer as opposed to other solid organs cancer after infection with COVID-19 in terms of presentation and outcomes: protocol for a systematic review". 4. Page 4, Abstract, page 4, "We will use fixed-effect, random-effect or mixed-effect models to estimate the relative risk": Please replace "random-effect" with the correct "random-effects" model. The same correction should be done throughout the manuscript, e.g. page 9. 5. Page 4, Strengths and limitations, "This systematic review will be the first to systematically review studies that have investigated outcome and presentation of COVID-19 in lung cancer patients and other solid cancer patients": In the light of general comment#2, the authors may wish to rephrase to "This systematic review will be the first to systematically review studies that have investigated differences in presentation and outcome of COVID-19 in lung cancer patients as opposed to other solid cancer patients". 6. Page 5, Introduction, "Scholars such as Wenhua Liang found that patients with cancer might have a higher risk of COVID-19 than individuals without cancer, and COVID-19 can be particularly lethal in patients with cancer." A recent meta-analysis of 32 studies involving 46,499 patients (1,776 patients with cancer) showed that all-cause mortality was higher in patients with versus those without cancer (relative risk 1.66; 95% confidence intervals, 1.33 to 2.0) (Giannakoulis VG et al. JCO Glob Oncol 2020). The authors may wish to mention the findings of the above meta-analysis on the effect of cancer on clinical outcomes of patients with COVID-19. 7. Page 5, Introduction: The Introduction could be more concise and coherent than currently. Current Introduction contains sentences that seem loosely connected with each other. 8. Page 6, Objective and Review questions are clearly stated. 9. Page 9, Data synthesis, analysis and assessment of heterogeneity, "The inconsistency index (I²) will be used as
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	<p>quantified measure of heterogeneity”: The authors may wish to clarify that they refer to statistical heterogeneity.</p> <p>10. Page 9, Analysis of subgroups or subsets, “Analyses will be performed for subgroups stratified by patient age, sex, smoking status, comorbidities, country, and study risk of bias (low versus high)”: The authors may wish to acknowledge that the more the subgroup analyses the higher the risk of false positive finding (type I error).</p> <p>11. Page 10, Discussion, “And in my workplace...”: The authors may wish to rephrase to “our workplaces”.</p>
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VERSION 1 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1

1. Response to comment: the argumentations should be improved updating references that appeared not focused on the important topic. The reviewer suggested that the following three manuscripts be cited: "Testing for COVID-19 in lung cancer patients", "ESMO Management and treatment adapted recommendations in the COVID-19 era: Lung cancer", and "COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study".

Response: We have updated references, cited the above three manuscripts, and removed references that were not relevant to important topics such as Reference N5: Banna et al.

It is really true as the reviewer suggested that the references should be updated, and the three manuscripts recommended by the reviewers can improve the argument.

2. Response to comment: Professional Language editing is required.

Response: we have carefully checked the paper and corrected some typographical and grammatical errors. We changed the title to “Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review”. The abstract has been extensively revised. We rewrote the introduction section. We replaced "take appropriate measure" with "take appropriate measures". We also made other modifications, as shown in the text.

3. Response to comment: check all the manuscript for COVID-19, Coronavirus disease and similar words. Pag. 10, line 19. Discussion. The disease caused by COVID-19 is called "novel coronavirus pneumonia" is wrong.

Response: we are aware that the disease caused by Sars-CoV-2 infection is called COVID-19.

COVID-19 = the disease ,

Sars-CoV-2 = virus

We are very sorry for our incorrect writing. We checked all the manuscript for COVID-19, Coronavirus disease and similar words. There was a mistake in the discussion section. As we deleted the discussion part from the original manuscript according to the editor's suggestion, we did not edit the discussion part.

Responses to the comments of Reviewer #2

1. Response to comment: the manuscript needs extensive editing to improve language and correct typos

Response: we have carefully checked the paper and corrected some typographical and grammatical errors. We changed the title to “Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review”. The abstract has been extensively revised. We rewrote the introduction section.

We replaced "take appropriate measure" with "take appropriate measures". We also made other modifications, as shown in the text.

2. Response to comment: The Title and the Abstract may need rewording

Response: The Title was corrected to "Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review" as the reviewer's suggestion. The abstract has been extensively revised.

3. Response to comment: A more informative title could be "Differences between patients with lung cancer as opposed to other solid organs cancer after infection with COVID-19 in terms of presentation and outcomes: protocol for a systematic review".

Response: The Title was corrected to "Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review".

4. Response to comment: Abstract, page 4, "We will use fixed-effect, random-effect or mixed-effect models to estimate the relative risk": Please replace "random-effect" with the correct "random-effects" model. The same correction should be done throughout the manuscript, e.g. page 9.

Response: we have replaced "random-effect" with the correct "random-effects" throughout the manuscript.

5. Response to comment: Page 4, Strengths and limitations, "This systematic review will be the first to systematically review studies that have investigated outcome and presentation of COVID-19 in lung cancer patients and other solid cancer patients": In the light of general comment#2, the authors may wish to rephrase to "This systematic review will be the first to systematically review studies that have investigated differences in presentation and outcome of COVID-19 in lung cancer patients as opposed to other solid cancer patients".

Response: the Strengths and limitations section was rephrased as the reviewer's suggestion.

6. Response to comment: The authors may wish to mention the findings of a meta-analysis on the effect of cancer on clinical outcomes of patients with COVID-19.

Response: The reviewer recommended the manuscript entitled with "Effect of Cancer on Clinical Outcomes of Patients With COVID-19: A Meta-Analysis of Patient Data", and we cited it as reference.

7. Response to comment: The Introduction could be more concise and coherent than currently.

Response: we rewrote the introduction section and updated the references.

8. Response to comment: Objective and Review questions are clearly stated.

Response: Thanks.

9. Response to comment: Page 9, Data synthesis, analysis and assessment of heterogeneity, "The inconsistency index (I^2) will be used as quantified measure of heterogeneity": The authors may wish to clarify that they refer to statistical heterogeneity.

Response: we replaced "of heterogeneity" with "of statistical heterogeneity".

10. Response to comment: Page 9, Analysis of subgroups or subsets, "Analyses will be performed for subgroups stratified by patient age, sex, smoking status, comorbidities, country, and study risk of bias (low versus high)": The authors may wish to acknowledge that the more the subgroup analyses the higher the risk of false positive finding (type I error).

Response: the two types of errors are mainly affected by the sample size. Therefore, we can increase the sample size to make our sample as close to the population as possible and have better

representativeness, so as to reduce the probability of occurrence of the two types of errors. So this sentence was changed to "Analyses will be performed for subgroups stratified by patient age, sex, smoking status, comorbidities, country, and study risk of bias (low versus high) if the sample volume is enough".

11. Response to comment: Page 10, Discussion, "And in my workplace...": The authors may wish to rephrase to "our workplaces".

Response: thanks for the reviewer's correction. As we deleted the discussion part from the original manuscript according to the editor's suggestion, we did not edit the discussion part.

FORMATTING AMENDMENTS (if any)

Required amendments will be listed here; please include these changes in your revised version:

- Please re-upload your supplementary files in PDF format.

Response: we re-uploaded the supplementary files in PDF format.

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And here we list the main changes.

1. Title was changed to "Differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2: protocol for a systematic review".
2. Abstract was revised. In this section, the sentences of introduction was rewritten. The phrase "random-effect" and "fixed-effect" was changed to "random-effects" and "fixed-effects".
3. In the section of Strengths and limitation of this study, the first sentence and the second sentence were revised according to the suggestion of reviewer #2.
4. Introduction part was rewritten and the references was updated.
5. Objective part was corrected in line with the revised title.
6. In the Review questions part, "IS the mortality rate and ICU admission rate" was changed to "Are the mortality rate and ICU admission rate".
7. In the Protocol registration and review reporting part, the sentence "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist will be used as a guide to assess the reporting methodology of each observational study" was removed.
8. In the Inclusion criteria part, the sentence of comparator was corrected to "patients with a laboratory-confirmed SARS-CoV-2 infection and confirmed solid organs cancer other than lung cancer".
9. In the Ethics and dissemination part, the second sentence "The results of this systematic review will provide the most up to date literature synthesis on differences of COVID-19 outcome and presentation between lung cancer patients and other solid cancer patients" was changed to "The results of this systematic review will provide the most up to date literature synthesis on differences in terms of presentation and outcomes between patients with lung cancer as opposed to other solid organs cancer after infection with Sars-CoV-2".
10. the Discussion section was removed.

And there are some other subtle changes that we did not list here but marked in revised paper.

VERSION 2 – REVIEW

REVIEWER	Antonio Passaro, MD PhD European Institute of Oncology, Milan, Italy
REVIEW RETURNED	02-Sep-2020

GENERAL COMMENTS	Accepted in the present form
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REVIEWER	Ilias Siempos National and Kapodistrian University of Athens Medical School, Evangelismos Hospital, Athens, Greece
REVIEW RETURNED	17-Sep-2020

GENERAL COMMENTS	<p>Chen and colleagues made a good work in revising their protocol for a systematic review of studies examining differences between patients with cancer of lung as opposed to other solid organs after infection with COVID-19 in terms of presentation and outcomes. The following points may help them further improving their protocol:</p> <ol style="list-style-type: none"> 1. Abstract, page 3, line 7: The authors should explain the abbreviation "ICU" the first time it appears in the manuscript. 2. Abstract, page 3, line 17: The authors should explain the abbreviations "NSCLC" and "SCLC" the first time they appear in the manuscript. 3. Introduction, page 4, line 13: The sentence "3200 patients who died of SARS-CoV-2 has related mortality to elderly age and other active comorbidities including cancer" does not seem to make sense (what does "related mortality" mean?) and it may need rephrasing. 4. Introduction, page 4, lines 45-46, "Covid-19 appears to be more lethal in lung cancer patients than in other cancer patients": This statement should be supported by citations or, better, removed from the Introduction. If this is already known (i.e., that "Covid-19 appears to be more lethal in lung cancer patients than in other cancer patients"), then there is no need to perform the systematic review. 5. Methods, page 7, line 39: What does "a non-biased third investigator mean"? The authors may want to rephrase it.
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VERSION 2 – AUTHOR RESPONSE

Responses to the comments of Reviewer #1

1.Response to comment: Accepted in the present form

Response: Thanks very much.

Responses to the comments of Reviewer #2

1.Response to comment: Abstract, page 3, line 7: The authors should explain the abbreviation "ICU" the first time it appears in the manuscript.

Response: We are very sorry for our negligence. We wrote "intensive care unit" completely in the abstract. When it first appeared in the manuscript, we added the abbreviation after the full name.

2.Response to comment: Abstract, page 3, line 17: The authors should explain the abbreviations “NSCLC” and “SCLC” the first time they appear in the manuscript.

Response: The words appeared twice in the whole text, and we have written down their full names.

3.Response to comment: Introduction, page 4, line 13: The sentence “3200 patients who died of SARS-CoV-2 has related mortality to elderly age and other active comorbidities including cancer” does not seem to make sense (what does “related mortality” mean?) and it may need rephrasing.

Response: It is really true as Reviewer#2 suggested that the sentence does not make sense, and we removed it.

4.Response to comment: Introduction, page 4, lines 45-46, “Covid-19 appears to be more lethal in lung cancer patients than in other cancer patients”: This statement should be supported by citations or, better, removed from the Introduction. If this is already known (i.e., that “Covid-19 appears to be more lethal in lung cancer patients than in other cancer patients”), then there is no need to perform the systematic review.

Response: we removed the sentence. Special thanks to you for your good comments.

5.Response to comment: Methods, page 7, line 39: What does “a non-biased third investigator mean”? The authors may want to rephrase it.

Response: We are very sorry for our incorrect writing and we changed the phrase to “an impartial third investigator”.