

Peer Review File

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Reviewer comments-Reviewer A

1) First of all, my major concern regarding this paper is the questionnaire data on the clinicians' knowledge on severe lung cancer, which seems to be an independent study and cannot be reported with the real-world data on severe lung cancer.

Reply 1: Thank you for your professional comments. Our team had carefully considered the same concerns as you when we constructed the framework of the article. Finally, we think that this is the first real-world research on severe lung cancer, a novel medical concept. In addition to the statistical analysis of clinical epidemiology for severe lung cancer patients, clinicians' views on the concept of severe lung cancer are also indispensable. Therefore, we decide to set clinicians as another research object in the study, and the questionnaire is a crucial method to obtain clinicians' opinions. Consequently, we put the questionnaire here as part of the article.

Change in the text: None.

2) Second, the title is problematic and did not accurately describe the focus and clinical research design of this study. Please indicate the prevalence of severe lung cancer in advanced lung cancer and its associated clinical characteristics and the clinical research design should be correctly described as a real-world cross-sectional study.

Reply 2: Thank you for your professional comments. In this article, two study cohorts were designed for lung cancer patients in our study; One is a cross-sectional study of severe lung cancer among all advanced lung cancers (n=1725) from January to June 2022; the other one is severe lung cancer in fatal lung cancer cases (n=268) from January 2019 to June 2022. Therefore, in our opinion, it may be incomplete if we define this article as a real-world cross-sectional study. Meanwhile, considering the brevity and generality of the title, it may be appropriate to set it as a multicenter retrospective study. And If you have other better comments about the title, please do not hesitate to contact us.

As for your comment about the prevalence of severe lung cancer in advanced lung cancer, we have already described the incidence of severe lung cancer in the result section of the article. (see Page 2, line 48; Page 7, line 215).

In addition, we added the clinical characteristics of patients with severe lung cancer in the cross-sectional study in the article.

Change in the text: We have modified our text as advised (see Page 7, line 216 to Page 8, line 225; Page 19, line 543, table 1)

3) Third, the abstract needs further revisions. The background did not indicate the clinical significance of the focus on severe lung cancer and what the knowledge gaps on the clinical characteristics of severe lung cancer. The methods need to describe the inclusion of subjects, the sampling method, the assessment of clinical factors, and the diagnosis of severe lung cancer. The results need to use detailed data to describe the clinical characteristics of cases with severe lung cancer. The conclusion needs comments for the clinical implications of the findings on severe lung cancer.

Reply 3: Thank you for your professional comments. For your comments on the methodology in the abstract: as mentioned in reply 2, we set up two research cohorts with patients as the research objects and one cohort with doctors as the research objects; Besides, due to the limitation of the number of

words and highlight more critical content of the result, we can only give a general description of the methodology; For the revision of the background, results, and conclusion of the abstract, we have made revisions according to your comments.

Change in the text: We have modified our text as advised(see Page 2, line 38 to 40, line 48 to 51, line 60 to 61;)

- 4) Fourth, the introduction of the main text needs to have an extensive review on what has been known on severe lung cancer including its definition, development of this conception, clinical usefulness, incidence rates, diagnostic criteria, and its clinical characteristics, as well as what the knowledge gap is on its clinical characteristics. The authors emphasized “real-world data” but did not explain the clinical needs for and the strengths of real-world data. Insights are needed for the clinical significance of this study.

Reply 4: Thank you for your professional comments. 1. For your comments about the definition and development of severe lung cancer, we have already described it in the introduction(see Page 4, lines 110-112); 2. For your professional comment on the clinical usefulness, incidence rates, diagnostic criteria, and clinical characteristics of severe lung cancer: Our team first proposed the concept of severe lung cancer in 2017 and formulated the first version of the international expert consensus one year ago (PMID: 34295668), besides this, there is no other previous research. Before we proposed the concept of severe lung cancer, severe lung cancer patients were often divided into lung cancer patients with poor PS scores (2-4). For the reasons above, we mainly reviewed a series of studies on lung cancer patients with poor PS scores (2-4) in the introduction. Therefore, your comments about the clinical usefulness, incidence rates, diagnostic criteria, and clinical features of severe lung cancer are currently unanswerable. But these unanswerable questions about severe lung cancer are the purpose of why we conducted this study.

Change in the text: None.

- 5) Fifth, in the methodology of the main text, please clearly describe the clinical research design, operational diagnostic criteria for severe lung cancer, not the definition, and the ethics approval of this study. In statistics, please specify what “observation and control groups” are and details of multiple Cox regression analysis.

Reply 5: Thank you for your professional comments. The design of our study has been shown in flowchart (Figure S1 and Figure S3), and we have modified our text as advised.

Change in the text: We have modified our text as advised (see Page 5, lines 131-135; Page 6, lines 156-161; Page 7, lines 196-198).

Reviewer comments-Reviewer B

This article describes a study on the incidence of moderate to severe lung cancer and the factors leading to severe lung cancer. This is a very interesting research topic, because there is not much experience and research data in this field, so clinicians often need to refer to a large amount of data when facing such patients. The data retrieved in this paper provides a good reference for us. After reading this paper, I would like to make the following suggestions or modifications based on my own understanding and experience, so as to facilitate the author to better improve the paper.

1. Although the inclusion criteria of severe lung cancer are provided in this paper, the definition of severe lung cancer is not provided. I believe that the definition of severe lung cancer can be explained in detail in this paper to increase readers' understanding.

Reply: Thank you for your professional comments. We have already provided the concept of severe lung cancer with citations in the methods section (see Page 7, line 193 to 199), and we consider this concept to be the same definition of severe lung cancer.

Change in the text: None.

2. The definition of some pictures is fuzzy. You can also adjust the format and color of the table appropriately.

Reply: Thank you for your professional comments. We rechecked the figures in the manuscript and found a lack of clarity in Figure 1 and Figure 2. Therefore, to avoid the same confusion for readers, we have modified Figures 1 and 2 in the manuscript, and the correTLCR-23-4-Reporting Checklist-有+号 ail.

Change in the text: see Page 17, line 531 to 532; Page 18, line 540 to 541; Figure 1-revised; Figure 2-revised.

3. It can be seen that the article does not talk about the relevant treatment plans of immunotherapy, so the immunotherapy plans involved in these patients can be introduced.

Reply: Thank you for your professional comments. The primary objective of this study was real-world epidemiological data from patients with severe lung cancer, and we focused more on whether the cause of the patients' worse PS scores was immunotherapy-related adverse reactions rather than patients' immunotherapy plans. Therefore, we think that the detailed immunotherapy plans of the patients are not highly relevant to the main study objectives of this study. Moreover, patient immunotherapy regimens are not currently collected and documented at any of the three participating centers, and it may take time to re-collect the relevant information. At the same time, the journal has set a tight time frame for this revision. Therefore, we decided not to present patients' immunotherapy plans in the manuscript after considering various factors. But, if you would like to learn more about that, we can discuss and collaborate on this issue via email, and we appreciate your valuable comments.

Change in the text: None.

4. What is the definition of mutation death? Please explain in detail.

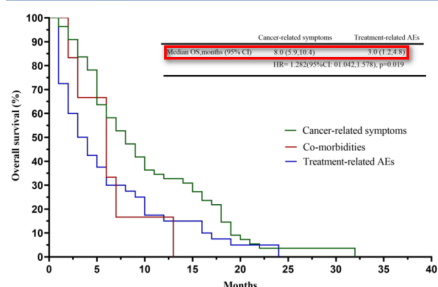
Reply: Thank you for your professional comments. We have a little confused because we did not find the word "mutation death" in the manuscript, even with the help of the software's search function. So we think maybe our writing errors have caused you confusion, and you can provide us with the exact location of "mutation death" in the manuscript so we can better solve your confusion.

Change in the text: None.

5. Confidence intervals can be added to the survival graph.

Reply: Thank you for your professional comments. We are unsure whether the graph you currently see containing the survival curve is the latest version because we have previously provided confidence intervals in graph. (see Page 19, line 555 to 556; Page 26, line 615 to 619; Or see the screenshot of the graph below). Please get in touch with us if our reply does not solve your confusion.

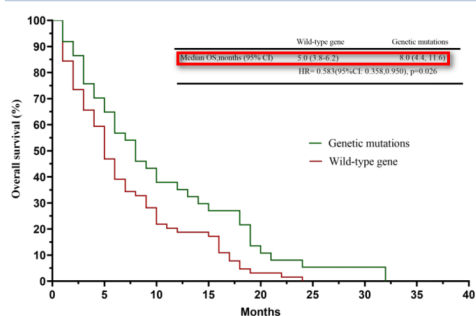
555



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557 Figure 4 Survival curves among deceased patients who developed severe lung cancer
 558 caused by different causes. Due to the small number of patients (n=6), we omitted
 559 patients with severe lung cancer caused by comorbidities. AEs, adverse events; HR,
 560 hazard ratio; CI, confidence interval.

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617 Figure S5 Survival curves between patients with genetic mutations and those with
 618 wild-type genes in fatal cases of severe lung cancer. OS, overall survival; CI,
 619 confidence interval.

Change in the text: None.

Review comments-Reviewer C

1. Reporting Checklist

Your study is a Cross-sectional study, N/A should be filled in the Case-control study and Cohort study in item 15.

| | | | |
|-----|------------------------------------------------------------------------------------------------------|----------------|----------------|
| 15* | Cohort study —Report numbers of outcome events or summary measures over time | 25/Line608-610 | gure4 |
| | Case-control study —Report numbers in each exposure category, or summary measures of exposure | Not Applicable | Not Applicable |
| | Cross-sectional study —Report numbers of outcome events or summary measures | 23/Line571-574 | gure2 |

Reply: Thank you for your professional comments.

Change in the text: We have modified Reporting Checklist as advised (see Reporting Checklist on the attached document).

2. Figure 3

Please explain NSCLC and AEs in the legend.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 18, line 543).

3. Figure 4

Please explain AEs, HR, and CI in the legend.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 19, line 551-552).

4. Table 1

Please explain SD and NSCLC in the table footnote.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 20, line 557).

5. Table 2

Please explain HR, CI, AEs and NSCLC in the table footnote.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 20, line 560).

6. Table S1

Please explain NSCLC in the table footnote.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 22, line 579).

7. Figure S1

Please explain PS in the legend.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 23, line 586).

8. Figure S2

Please provide the description of the y-axis.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 24, line 590; Figure S2-revised), beside we modified Figure S4 in the same way (see Page 26, line 600; Figure S4-revised).

9. Figure S3

Please explain PS in the legend.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 25, line 597-598).

10. Figure S5

Please explain OS and CI.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 26, line 608-609).

11. Figure S7

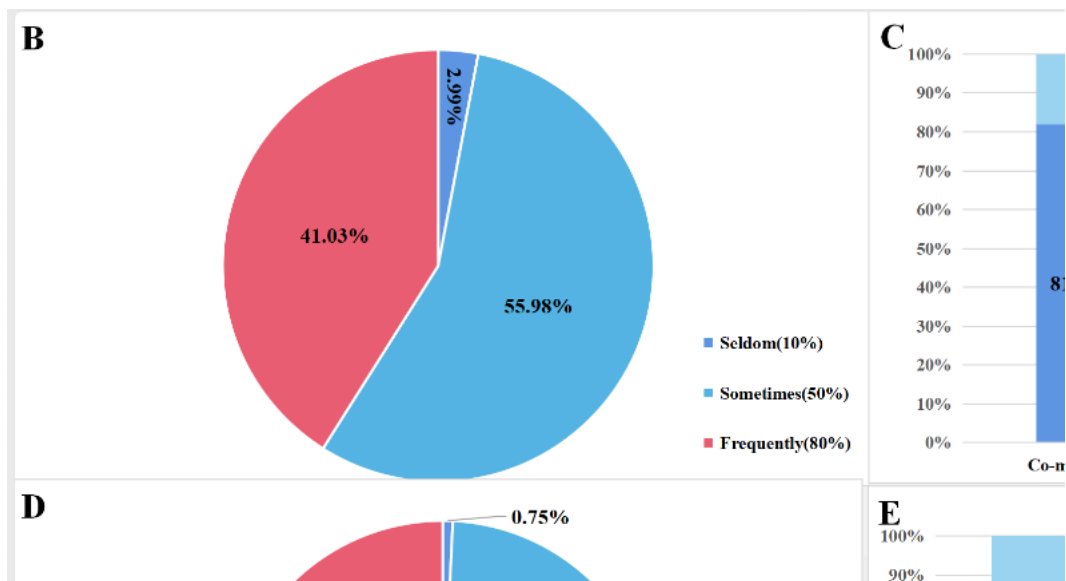
a) Please explain PS in the legend.

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 28, line 627-628).

b) Please revise the figure as A-D, NOT B-E.

340 indicated cancer-related symptoms (Figure S7A,S7B). When asked about treating
 346 treatment-related AEs were one of the primary causes (Figure S7C, S7D). As for the

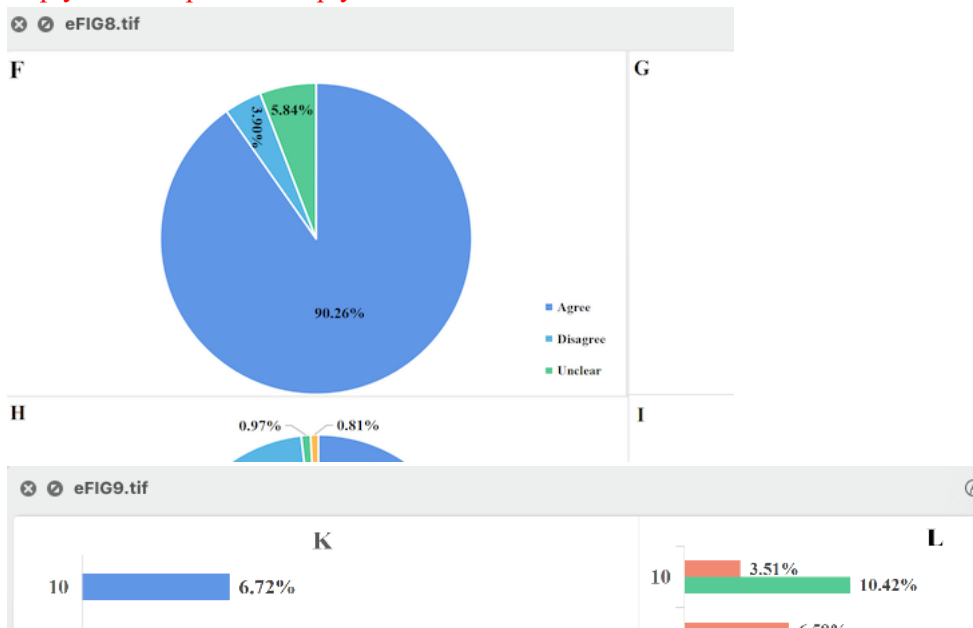


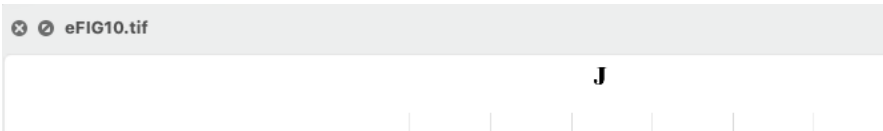
Reply: Thank you for your professional comments. Based on your comments, we think it is possible that Figure S7-10 you viewed is not the final version (without any adjustments this time, Pages 27-29, lines 620-648) because of our mistake in uploading the file last time. Again, we apologize for any inconvenience this may have caused you, and we have re-uploaded the relevant figure in the attachment. Change in the text: We have re-uploaded the relevant figure in the attachment (Figure S7-10-revised).

12. Figure 8-9

The same mistake as figure S7, please revise the figures.

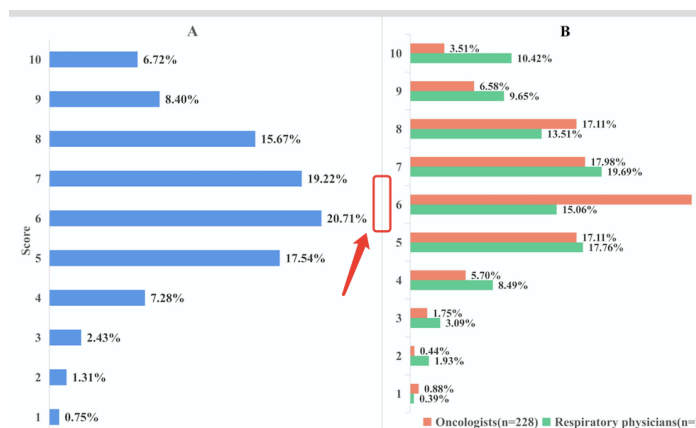
Reply: See the previous reply.





13. Figure S9B

Please provide the description of the y-axis, and send the updated figure S9 to us a separate file in jpg or tiff format.



Reply: Thank you for your professional comments. We have modified Figure S9B as advised.
 Change in the text: see Figure S9-revised.

14. References/Citations

Please double-check if more studies should be cited as you mentioned “studies”. OR use “study” rather than “studies”.

414 treatment of comorbidities in the patients with lung cancer. For example, **previous**
 415 **studies** have pointed out that oncologists may be neglectful in diagnosing and treating
 416 COPD in patients with lung cancer and COPD (31). However, comorbidity is not only

Reply: Thank you for your professional comments.

Change in the text: We have modified our text as advised (see Page 11, line 354).