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Reviewer A

This study is a single-center retrospective analysis of 849 lung adenocarcinoma patients, divided into 180 patients with pleural effusion (PE) and 669 without PE, followed by PSM analysis comparing 180 patients with PE and 360 without PE. The interpretation of the obtained results is insufficient, and the following additional considerations are recommended.

#EGFR mutation analysis in Methods
The genetic testing method used and the name of the company were not listed.
Reply: Thank you very much for your valuable comments. The methods of genetic testing have been described in our manuscript, mainly using next-generation sequencing and ddPCR(see page 6, lines 170-172). Since the 849 patients were collected over different years, their genetic testing was not all performed by the same company. However, all genetic tests were conducted by accredited companies, such as Geneseeq Genetic Testing Co.
Changes in the text: We have revised our manuscript to add the name of the genetic testing company as you suggested, as detailed in Page 6, Line 172-173.

#Patients in Methods
There is no mention of "Stage", so it is unclear whether n=849 is a group of only Stage IV patients, or whether it also includes groups of Stages I to III. Similarly, it is unclear whether the N-MPE group includes groups of Stages I to III, so this should be stated.
The median follow-up duration is not described in the Results.
Reply: We sincerely appreciate your thorough review and constructive comments. Of the 849 patients, 180 in the MPE group were classified as Stage IV, as MPE to M1a, which is categorized under Stage IV. The remaining 669 patients in the non-MPE group contained Stages I to IV, but none of them developed MPE. The median follow-up duration was 61 months, which has now been added to the results section as you suggested.
Changes in the text: We have added a description of the stage (Page 5, Line 159-161) and median follow-up duration (Page 8, Line 247-248).

#Results

In the MPE group, univariate analysis showed that EGFR MT was associated with a longer OS, whereas multivariate analysis showed that EGFR MT was independently associated with a shorter OS. Figure 2B shows that the EGFR MT group had a significantly longer median OS, so the results of the multivariate analysis and their interpretation may be incorrect.

Reply: We sincerely appreciate your insightful feedback and for pointing out the errors in our manuscript. Upon re-examining the results of our univariate and multivariate analyses, we found that the population with EGFR mutations almost overlapped with those treated with EGFR-TKIs. We now consider this overlap to represent the same confounding factor in the multivariate analyses. Based on this, we revised our multivariate Cox regression model and discovered that EGFR mutation emerged as a protective factor for OS in patients, aligning with both the univariate analysis and the KM curve results in Figure 2B.

Changes in the text: We have updated Figures 3 and 4 (Pages 27-28) and revised the corresponding conclusions in the Results and Discussion sections (Pages 8-9, Lines 247-264; Page 12, Lines 381-389).

#Prognostic factor analysis

The study suggests that 1st generation EGFR-TKI alone has a significantly shorter OS than 3rd generation and sequential 1st and 3rd generation, but this is an existing fact, as it was proven in a pivotal study.

Reply: As you mentioned, this study confirmed that patients had significantly shorter overall survival (OS) with first-generation EGFR-TKI compared to third-generation and consecutive first- and third-generation EGFR-TKI. This result is consistent with previous studies. However, our study further reveals the impact of EGFR-TKIs on treatment efficacy and overall survival in selected patients with malignant pleural effusion (MPE). Additionally, we have modified the discussion to underscore the notable association between the T790M mutation and MPE, which represents an important and interesting discovery.

Changes in the text: Thank you very much for your valuable comments. We have revised the manuscript as detailed in Page 11, Line 334-357.

#Patients with MPE are divided into two groups, EGFR-TKI group and non-EGFR-TKI group, but these are almost all EGFR and non-EGFR groups, and it is a known fact that OS is longer in the EGFR group.

Given the above, the comparison populations in Figures 2B and 2C are almost the same, so Figure 2B alone is sufficient.

In addition, it will be easier to understand if patients are classified into EGFR MT and EGFR WT groups and Characteristics are created by classifying them rather than into EGFR-TKI and non-EGFR-TKI groups.

Reply: Thank you very much for your careful review and professional guidance, we have removed Figure 2C and retained only Figure 2B to simplify the presentation of results.

We have followed your suggestion to reclassify patients to create a table of patient characteristics based on EGFR mutation status

Changes in the text: In compliance with your comments, we have revised Figure 2 (Page 25-26) , and its associated description (Page 9, Line 269-272).

Patients are now categorized according to EGFR mutation (MT) and EGFR wild-type (WT), as detailed in Table 3 (Page 20-22)

Reviewer B

A propensity score-matched analysis of a single-center database

The authors studied the association between epidermal growth factor receptor (EGFR) mutations and the occurrence of malignant pleural effusions in patients with lung adenocarcinomas. In total, 849 patients were studied. The EGFR mutation rate was higher in patients with malignant pleural effusions compared to those without malignant pleural effusions (62.7% vs. 50.2%), mainly due to higher T790M mutations (8.3% versus 1.3%). EGFR-TKI therapy was associated with improved overall survival of patients. These findings are of clinical interest.

Reply: We are very grateful for your positive comments on our study. Your affirmation motivates us to further improve our research.

Reviewer C

I have reviewed the article titled "EGFR Mutations in Patients with Lung Adenocarcinoma and Malignant Pleural Effusion: A Propensity Score-Matched Analysis of a Single-Center Database." While the single-center analysis poses a limitation, the manuscript is well-written, and the content is novel, making it worthy of acceptance.

Reply: Thank you for your kind review of our study, and we hope to conduct larger-scale, multi-center studies to further validate our conclusions.

Reviewer D

A propensity score-matched analysis of a single-center database

①There are several reports that the level of PD-L1 expression is also associated with the prognosis of EGFR-TKI treatment. Wouldn't it be worthwhile to consider this as well?

Reply: Thank you for your important comments regarding PD-L1 expression levels. While it is true that several studies have shown that PD-L1 expression levels correlate with the prognosis of EGFR-TKI treatment, our patient cohort only had data on those who received immunotherapy, and detailed data on PD-L1 expression levels were lacking. We look forward to collecting more relevant data and obtaining more comprehensive and rigorous conclusions in the future.

②Were there any cases where ramucirumab was used as an anti-angiogenic agent?

I found it intriguing that the T790M mutation, unlike other EGFR mutations, is particularly associated with MPE, providing new insights.

Reply:Thank you for your thoughtful and detailed comments. It is very unfortunate that ramucirumab is not yet approved for the treatment of advanced first-line NSCLC in our country. However, we remain hopeful that more indications will be approved in the future, allowing us to offer patients with lung adenocarcinoma and MPE a wider range of therapeutic options, particularly with anti-angiogenic agents.

The association between the T790M mutation and MPE is an interesting finding that deserves further in-depth exploration. T790M mutation not only contributes to resistance against EGFR-TKI treatments, but also influences tumor biology and is associated with tumor metastasis, especially the formation of MPE. We plan to explore deeper into the specific mechanism by which the T790M mutation contributes to MPE formation in future studies.

Changes in the text: We briefly discuss the T790M mutation in the discussion section in the context of our findings, as detailed in Page 11, Line 334-357.

Reviewer E

I have several quetions in this paper. First, statistical methods are questionable. For example, despite the authors have performed PSM, there is some difference in the background factors of MPE and non-MPE. In addition, there is no indication in the statistical method which factors were used to perform PSM. Second, in the univariate analysis of survival, the positive EGFR gene mutation is a factor with a favorable prognosis, however in the multivariate analysis, the result is so opposite. If this is a true

result, the authors need to explain more clearly why in the discussion. Third, lung adenocarcinoma with non-common EGFR mutations has differences from lung adenocarcinoma with common EGFR mutations both in biological aspects and in effect on EGFR TKIs. Because the two groups are analyzed together in this paper, it does not appear to accurately characterize EGFR mutation-positive lung cancer with malignant pleural effusion.

Reply: Thank you for your advice and guidance on our statistical methods. We were unable to balance confounding factors that were not included in the model. When making between-group comparisons, we tried as much as possible to eliminate confounding factors between the MPE and non-MPE groups, so that the background factors between the two groups could be balanced as much as possible, and although the background factors between the paired cases between the two groups were not exactly the same after the PSM, the P-value was greater than 0.05, and it can be assumed that the difference in background factors between the two groups was not statistically significant. We added descriptions of the factors included in PSM to the statistical method.

We re-examined the multivariate COX regression model in our study, and the EGFR mutation population and the population treated with EGFR-TKI largely overlapped, and EGFR mutation and receiving EGFR-TKI treatment were strongly correlated, so it can be considered as the same confounding factor when included in the multivariate analysis. Based on this, we modified the multivariate COX regression model and found that EGFR mutation was a protective factor for OS in patients, which was consistent with the results of the univariate analysis and the K-M curves in Figure 2B.

We agree with the reviewer's point that lung adenocarcinoma with non-common EGFR mutations may exhibit different biological and clinical characteristics compared to those with common EGFR mutations. In response to this, we have revised our analysis to separately examine the impact of common versus non-common EGFR mutations on malignant pleural effusion. As a result, the results indicated that there was no significant difference, and we analyzed that this might be due to the sample size limitation. We will expand our sample size in the future, with a view to exploring the relationship between EGFR common and EGFR non-common mutations for OS in patients with lung adenocarcinoma, as well as between EGFR-TKI treatments.

Changes in the text: We included a detailed description of PSM in the Statistical Methods section, see Page 6, Lines 188-190.

We modified the Multivariate Regression Analysis model (Figure 3 and Figure 4, Page 27-28) and the description of its conclusion in the Results and Discussion section (Page 8-9, Line 247-264; Page 12, Line 381-389).

Reviewer F

This article examines the association between lung adenocarcinoma and malignant pleural effusions; the number of cases is large and the content is well considered.
As a result, it is interesting to note that EGFR-positive lung cancers (especially T790M) are more likely to develop malignant pleural effusions.

Although it does not require major revisions, the following points should be reconsidered.

1. About Figure 2
Figure 2C is divided into two groups according to whether the patients were treated with EGFR-TKI or not. However, since EGFR-TKI was used in almost 100% of EGFR-positive lung cancers in this study, this division into two groups is almost the same as EGFR MT vs. WT in Figure 2B. In fact, the KM curves in Figures 2B and 2C are almost the same. Please tell me why you need two figures that are almost the same in meaning.
Reply: Thank you very much for your positive feedback on our research. We appreciate your observation regarding the overlap between patients with EGFR mutations and those treated with EGFR-TKI. In response, we have removed Figure 2C and retained only Figure 2B to better address this overlap and clarify our findings.
Changes in the text: In compliance with your comments, we have revised Figure 2 (Page 25-26) , and its associated description (Page 9, Line 269-272).

2. About multivariate analysis
This is similar to the comment above, but EGFR-positive and treatment with EGFR-TKI are almost equivalent. Therefore, it could be considered to be a confounding factor when included in the multivariate analysis.
Reply: We appreciate the reviewer's insight regarding the potential confounding factor of EGFR-positive status and EGFR-TKI treatment. We acknowledge that these two variables are closely related, and their overlap could indeed introduce confounding effects in our multivariate analysis. To address this concern, we have re-evaluated our statistical approach and made the following adjustments:
We have revisited the multivariate analysis to account for the potential confounding effect of EGFR-TKI treatment. We conducted additional analyses without the EGFR-TKI treatment variable to assess its impact on our results. In addition, we have revised the interpretation of this result in the Reseults and Discussion section.

Changes in the text: We modified the multivariate regression analysis model (Figure 3 and Figure 4, Page 27-28) and the description of its conclusion in the Results and Discussion section (Page 8-9, Line 247-264; Page 12, Line 381-389).

Reviewer G

A propensity score-matched analysis of a single-center database
Although it was a single-center study, I would like to express my respect for conducting such a large-scale retrospective study using propensity score-matched analysis. I also found it very interesting that there are many cases of EGFR mutations in lung adenocarcinoma patients with malignant pleural effusion, and that the T790M mutation in particular contributes to this difference.
However, unfortunately, the idea that subsequent EGFR-TKI contributes to prognosis is already commonplace and does not seem to be of any particular value. And the more worthless aspects are highlighted, the less valuable this paper seems to be.
In my opinion, this would be a better paper if the already commonplace notion that the use of EGFR-TKIs improves prognosis was removed as much as possible from the introduction and discussion, and the focus was instead on the topics of malignant pleural effusion and EGFR gene mutations.
Reply: Thank you for your thoughtful and constructive feedback. We appreciate your recognition of our work and the insights you've provided. We understand your concern regarding the focus on EGFR-TKI and its impact on prognosis, which is indeed a well-established concept. To enhance the value of our paper and align with your suggestions, we have made the following revisions:
Refocused Content: We have revised the introduction and discussion sections to minimize the emphasis on the established notion that EGFR-TKIs improve prognosis. Instead, we have redirected our focus to highlight the novel aspects of our study, particularly the relationship between EGFR mutations and malignant pleural effusion.
Enhanced Discussion: The revised manuscript now places greater emphasis on the implications of the T790M mutation and its contribution to MPE. We have expanded the introduction and discussion to explore these aspects in more detail and to underscore the significance of our findings in this context. We hope these changes address your concerns and strengthen the focus of our manuscript.
Changes in the text: We have modified the Introduction and Discussion sections in response to your advice (Page 4, Line121-123; Page 4-5, Line 127-137; Page 11, Line 334-357) .