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## Peer Review File

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### Reviewer A

The paper titled “Bioinformatics analysis based on DNA methylation data identified in lung adenocarcinoma subgroups with different immune characteristics and clinical outcomes” is interesting. The results proposed a LUAD typing system based on DMS, which was closely related to the survival, clinical features, immune characteristics, and genomic variations of LUAD, and may contribute to the development of personalized therapy for new specific subtypes. However, there are several minor issues that if addressed would significantly improve the manuscript.

1) In the introduction of the manuscript, it is necessary to clearly indicate the correlation between DNA methylation clusters in LUAD and disease characteristics and gene expression patterns among immune pathways.

Reply: Thank you for your comments. In introduction part, we added the context in line94-99, page4.

2) What are the biggest advantages and disadvantages of the LUAD typing system based on DMS in this study? What are the directions for improvement and breakthroughs? Suggest adding relevant content to the discussion.

Reply: Thank you for your comments. In discussion part, we added the context in line387-389, page13.

3) Figures 3 and 6 are not clear enough. It is recommended to provide clearer figures again.

Reply: Thank you for your comments. We revised figure 3/6.

4) What are the characteristics of infiltrating immune cells in LUAD? How to carry out immunotherapy based on molecular subgroups of LUAD? It is recommended to add relevant content.

Reply: Thank you for your comments. Those infiltrating immune cells are commonly dysexpression on tumors. The molecular subtype of LUAD were not been treated with immunotherapy. We used some indicator of immunotherapy, such as immune checkpoint gene expression, to predict the response to immunotherapy of molecular subtype.

5) The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Bioinformatics analysis of immune infiltration in glioblastoma multiforme based on data using a methylation chip in the GEO database,

Transl Cancer Res, PMID: 35116473”. It is recommended to quote the articles.

Reply: Thank you for your comments. We added the reference in Introduction part.

6) What is the role of DNA methylation in solid tumor resistance? How to analyze the gene expression characteristics of methylation region specific DNA to predict the outcome of anti-cancer treatment? It is recommended to add relevant contents.

Reply: Thank you for your comments.

Cancer cells can acquire significant resistance to anticancer drugs and escape programmed cell death through major epigenetic changes, including DNA methylation. But we don't have that right now. We thank you your comment, we will consider it in future analysis. Thank you again.

7) This study is based on the analysis of the bioinformatic study. It is suggested to add in vivo and in vitro experimental studies, which may be more meaningful.

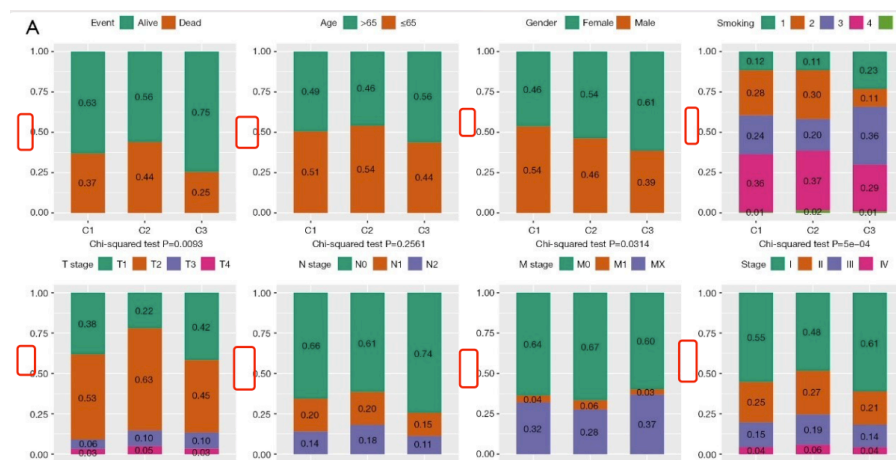
Reply: Thank you for your comments. Your comments are very meaningful. We will further add in vivo and in vitro experimental studies in LUAD through basic experiments in the future,

## Reviewer B

1. Figure 1: Please define “\*, \*\*\*” in figure legends.

Response: we added the mean of \*, \*\*\* in figure legend. Thank you.

2. Figure 2: Please provide the descriptions of Y-axis for below figures.



Response: we added Y: proportion

3. Figure 3: Please define “\*, \*\*, \*\*\*, \*\*\*\*, ns” in figure legends.

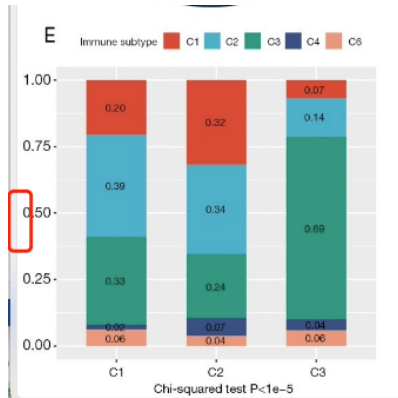
Response: we added the mean of \*, \*\*, \*\*\*, \*\*\*\*, ns in figure legend. Thank you.

4. Figure 4: Please define “\*, \*\*, \*\*\*, ns” in figure legends.

Response: we added the mean of \*, \*\*, \*\*\*, ns in figure legend. Thank you.

5. Figure 5:

a. Please provide the description of Y-axis for below figure.

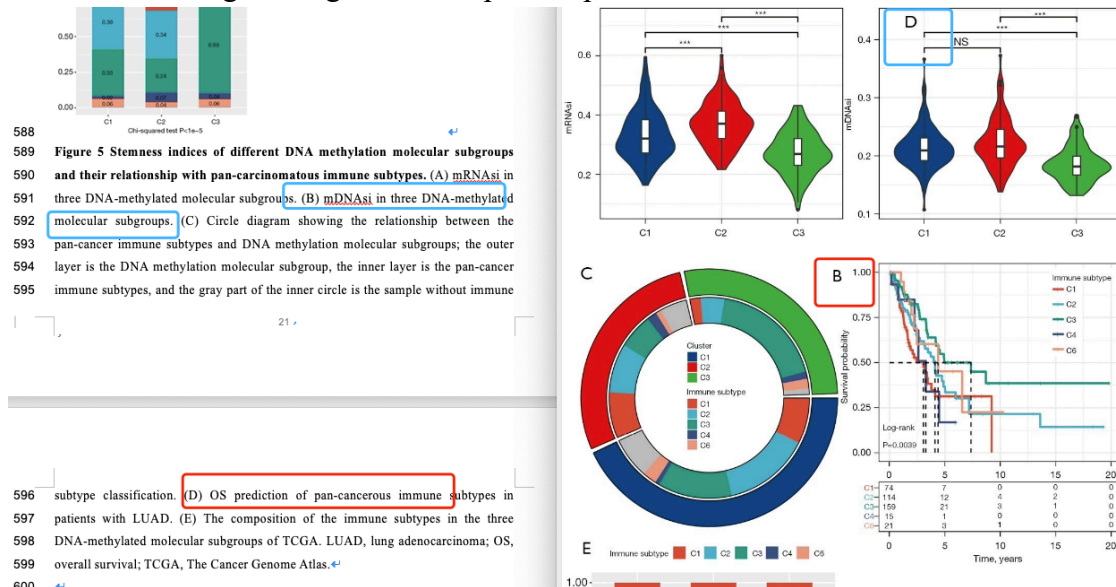


Response: we added Y axis.

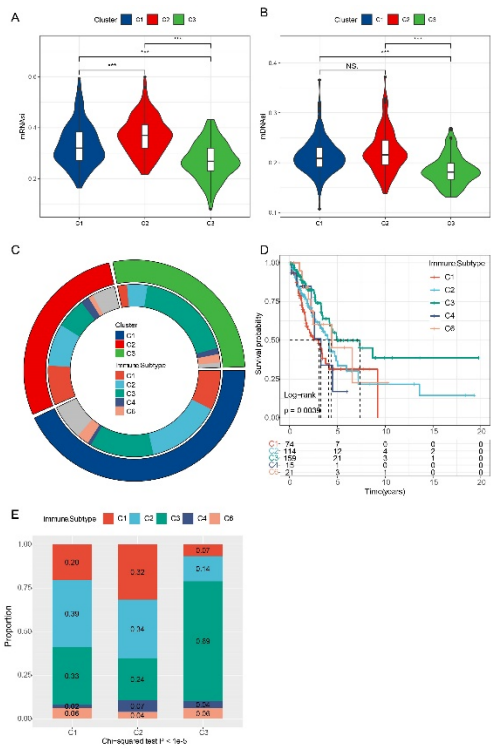
b. Please define “\*\*\*” in figure legends.

Response: we added the mean of \*\*\*\* in figure legend. Thank you.

c. It seems the legends/figure are misplaced, please check and revise.

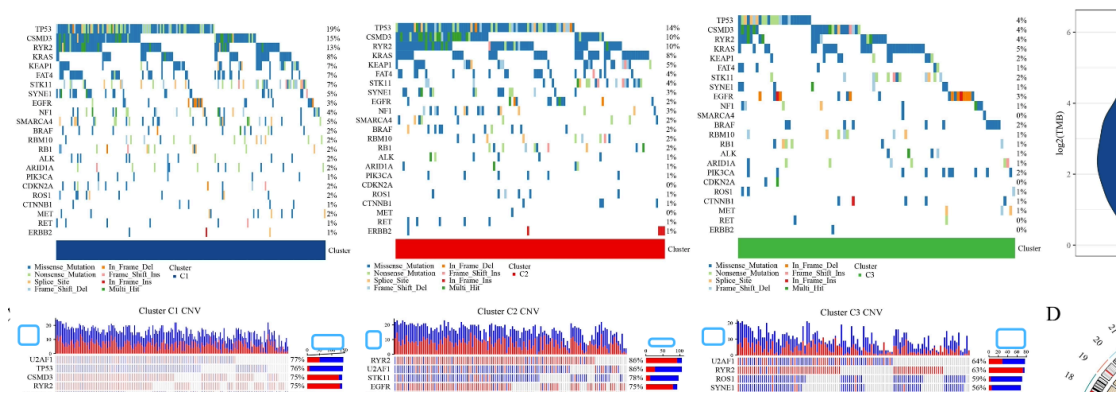


Response: we checked and the right was followed:



6. Figure 6

a. Please provide the descriptions of X- and Y-axis for below figures.



Response: we added X- and Y- axis in figure 6.

b. Please define “\*, \*\*\*” in figure legends.

Response: we added the mean of\*, \*\*\*, in figure legend. Thank you.

7. Table S1: Please check for the duplicated numbers in the table and revise.

Supplementary Table 1 Univariate Cox regression analysis of differential DMS

Genes	P.Value	HR	lower.95	upper.95
cg06607764	0.009924	10.78255	1.768977	65.72356
cg25117523	0.011508	12.56156	1.764315	89.4357
cg19797376	0.020934	4.739344	1.265286	17.75202
cg14112356	0.049252	7.413059	1.006579	54.59427
cg11679455	0.02633	5.914049	1.232585	28.37611
cg27566403	0.020984	9.968	1.414777	70.23086
cg12606911	0.000536	5.367317	2.073188	13.89555
cg27425784	0.047099	6.351988	1.023975	39.40305
cg16391678	0.015096	5.83702	1.40677	24.21916

Response: we deleted the one.

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