Author’s response to reviews

Title: Malignant pleural mesothelioma: diagnostic value of medical thoracoscopy and long-term prognostic analysis

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Malignant pleural mesothelioma: diagnostic value of medical thoracoscopy and long-term prognostic analysis” (PULM-D-18-00048). Those comments are all valuable and are also very helpful for revising and improving our paper, as well as the important guiding significance to our future researches. We have studied comments carefully and have made corrections which we hope meet with approval. Revised corrections are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as follows:

Sincerely yours,

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Responses to the reviewer’s comments:
Reviewer 1:

Comment 1: The language of the manuscript needs to be reexamined especially in the areas where there are long sentences and multiple pieces of data combined together.

Response 1: Thank you for your comment. We tried our best to improve English and made some changes in the manuscript. These changes will not influence the content and framework of the paper. And all changes were marked in red in revised paper.

Comment 2: Expressing statistics by positive or negative predictive values will make more sense to the readers. For example: Page 11 line 31:

'The specificity of chest CT for identifying pleural tumors is about 88–95%, while the sensitivity is about 36–45%'

Response 2: We agree with you opinion. Positive and negative predictive values will make more sense than sensitivity and specificity. But the describe on Page 11 line 31: 'The specificity of chest CT for identifying pleural tumors is about 88–95%, while the sensitivity is about 36–45%" is cited from the reference. It is only expressed by sensitivity and specificity.

Comment 3: The manuscript mentions in many areas the phrase "prognostic factors". It is much more helpful for the readers if the phrase is more definitive for example: poor or good prognostic factor & positive of negative prognostic factor

Response 3: Thank you for your advise, it is our mistake not describing it clearly. We have changed the "prognostic factors" in page 2, Result; page 14, paragraph 2 and page 16, paragraph 1 to "poor prognostic factors" marked in red.

Comment 4: In the methods section, many elements were defined under the result section and in my opinion it should be mentioned under the method section. For example:

Page 5 Line 23: The suspected areas of the pleura were biopsied during medical throacoscopy. What kind of areas? These areas should be described in the methods section.

Page 5 Line 50: What type of pleural radiographic assessments? CT scan? CXR? Others? These was mentioned in the result and Table 1 but also it should be defined in the methods section

How you define small, moderate or large pleural effusion?

Response 4: For Page 5 Line 50, pleural biopsy was taken under direct visual control in the suspected areas such as pleural plaques and nodules. We have changed it in page 6, Methods, Patients, paragraph 2 mark in red.
For Page 5 Line 50, the pleural radiographic assessment was CT scan. We have changed it in page 7, paragraph 1 marked in red.

For pleural effusion, the effusion size of 300 ml - 500 ml was identified as small pleural effusion, the effusion size of 500 ml – 800 ml was identified as moderate pleural effusion, and the effusion size ≥ 800 ml was identified as large pleural effusion. This was mentioned in page 6, line 5 marked in red.

Comment 5: Finally, what is the reason for the delay in diagnosing 5 patients with mesothelioma? What happened to then? was the medical thoracoscopy inconclusive or limited? Operatory issues?

Response 5: The remaining 5 MPE patients could not obtain the correct diagnose after MT for the first time and the pleural biopsy only gave the result of nonspecific pleurisy. The reason was analysed in Discussion, paragraph 3 as follow: “The reason that MT has lower diagnostic efficiency for MPM may be multiple. Except the sampling error, this may, in part, be explained by the rapidly growing incidence of MPM, which can demonstrate various, misleading, histopathologic pitfalls, and the pleura is a common site for metastatic disease [22]. In addition, because neoplastic invasion of MPM occurs submesothelialy, it may be difficult for a thoracoscopist to detect these areas on grossly normal appearing pleura [15].”

After 8 mo follow-up, 2 of the 5 patients was diagnosed as MPE by second MT, one was diagnosed by percutaneous needle lung biopsy, one was diagnosed by open-long biopsy and one was diagnosed by liver-biopsy. We have made this clear in page 5, line 13 marked in red.

Reviewer 2

Comment 1: Abstract; Results; Line 1. Change "diagnosed" to diagnosis.

Response 1: Thank you for your comment. We have changed "diagnosed" to "diagnosis" in Abstract; Results; Line 1 marked in red.

Comment 2: Characteristics of patients with MPM. Paragraph 1; Line 5

Why do you think that 5 patients did not receive the correct diagnosis the first time? Was there a sampling or pathology technique that might avoid this in the future?

Response 2: It is our mistake not explainning this clear. The remaining 5 MPE patients could not obtain the correct diagnose after MT for the first time and the pleural biopsy only gave the result of nonspecific pleurisy. Except the sampling error, this may, in part, be explained by the rapidly growing incidence of MPM, which can demonstrate various, misleading, histopathologic pitfalls, and the pleura is a common site for metastatic disease. In addition, because neoplastic invasion of MPM occurs submesothelialy, it may be difficult for a thoracoscopist to detect these areas on grossly normal appearing pleura. This was mentioned in Discussion, paragraph 3. To avoid this, biopsies should be taken as much as possible under the premise of no other side effects,
especially in suspected areas such as pleural plaques and nodules. We have made this clear in page 12, line 8 marked in red.

Comment 3: Please spell check through document the for correct spelling of "pleural."

Response 3: We are sorry for these mistakes. We have changed "plural" to "pleural" on page 2, Result, line 6; page 5, line 1; page 6, Methods, Patients, paragraph 2, line 7; page 8, paragraph 2, line 7; page 10, the last line and page 16, line 5, all marked in red.

Comment 4: Methods; Patients; Paragraph 2; Line 7;

Reference 12 - Please clarify in the text if used the 7th or 8th edition of the staging system in your work as you reference is from 2012.

Response 4: We used the 7th edition of the staging system in our work as our patients were collected from 2005 to 2014. We have clarified this in Methods, Patients, Paragraph 2, Line 8 marked in red.

Reviewer 3:

Introduction

Comment 1: Page 4- you should state the accuracy of cytology and cite it (line 28).

Response 1: Thank you for your comments and these comments are very helpful for improving our article. The sensitivity of cytologic examination for a diagnosis of MPM was only 32% - 51.3% . We have made this clear and cite the appropriate articles in Introduction, Paragraph 2, line 5 and marked in red.

Comment 2: Page 4- In line 39 you state that MT is highly sensitive and safe, you should also provide the data to go along with this.

Response 2: Medical thoracoscopy refers to the examination of the pleural space, and this procedure has been well documented to be highly sensitive of 87%-92.6% for diagnosing exudative pleural effusions with few complications which reported rates of between 2% and 6%. We have made this clear in Introduction, Paragraph 2, line 7 and marked in red.

Methods

Comment 3: You need to state that this was a retrospective study. This is not stated until the limitations section of the discussion.
Response 3: Thank you for your advise and we have made this clear in Methods, Patients, the beginning of paragraph 2 marked in red.

Comment 4: Page 5 your misspelled pleural effusion as "plural"

Response 4: We are sorry for these mistakes. We have changed "plural" to "pleural" on page 2, Result, line 6; page 5, line 1; page 6, Methods, Patients, paragraph 2, line 7; page 8, paragraph 2, line 7; page 10, the last line and page 16, line 5, all marked in red.

Comment 5: You state that MT diagnosed 35 and the other 5 were diagnosed 8 months later, but you never state how they were diagnosed.

Response 5: The remaining 5 MPE patients could not obtain the correct diagnose after MT for the first time and the pleural biopsy only gave the result of nonspecific pleurisy. After 8 mo follow-up, 2 of the 5 patients was diagnosed as MPE by second MT, one was diagnosed by percutaneous needle lung biopsy, one was diagnosed by open-long biopsy and one was diagnosed by liver-biopsy. This was mentioned in page 6, last paragraph marked in red.

Comment 6: Table 1 should be in the results only, not the methods

Response 6: Thank you for your advise. We have deleted the description “The characteristics of the study population are presented in Table 1” from Methods, Patients, the end of paragraph 2. The content of Table 1 was described in Result, Characteristics of patients with MPM, paragraph 1.

Comment 7: On page 7 you write "various factors," when you should list out the variables.

Response 7: We stratified patients by various factors including age, gender, smoking history, MT findings, histological type, staging, therapeutic regimen, TP of pleural fluid, LDH of pleural fluid and CT imagings. We have made this clear in page 8, Methods, Statistical analysis, paragraph 2 marked in red.

Comment 8: You also performed cox regression and never mention whether they meet proportional hazards assumption. If you are conducting survival analysis, this is crucial especially given the small n.

Response 8: We are not sure if we realized what you mean. Associations between possible prognostic variables and survival were estimated using Cox proportional hazards regression. The effects of P values were considered significant if P < 0.05. P values were recorded in Table 2 and Table 3. The result was described and analysed in Result, Assessment of prognostic factors for MPM and Discussion. We agree with you that using a small sample increases the chance of
assuming as true a false premise. More prospective studies with a larger cohort of subjects are needed in the future to find the accurate prognostic factors for MPM and we will try to do our best for this.

Results

Comment 9: You cite your previous papers during this, and your results should be about the results to this study only. Especially since one paper cites the original 35 and another paper cites the other 5? Its confusing.

Response 9: Reference 6 is an article about the Efficacy and safety of diagnostic thoracoscopy in undiagnosed pleural effusions. All 833 patients were analysed in reference 6 and we chose the patients with definite diagnosis of MPM for this study, yielding 40 cases. In these 40 cases, 5 of them could not obtain the correct diagnose after MT for the first time and the pleural biopsy only gave the result of nonspecific pleurisy. After 8 mo follow-up, these 5 patients got the accurate diagnose and reference 15 discribe the detailed information about these 5 patients. As it is confusing, we delete the cite of reference 6 in page 9, Result, Characteristics of patients with MPM, paragraph 1.

Comment 10: 33/40 had complete data, what happened to the other 7?

Response 10: The other 7 patients lost of follow-up. We have made this clear in page 10, Result, Follow-up data of patients with MPM, paragraph 1 marked in red.

Comment 11: You use p-values rather than 95% CI in multiple areas, and 95% CI when you should use range. In general, for regression analysis I would favor using 95% CI. A small p-value is of little use when the confidence intervals are extremely wide. Likewise, when you use medians, you should state the range.

Response 11: Thank you for your advise. We agree with your opinion that HR and 95% CI should be used to explain the results. We have added the HR and 95% CI in Results marked in red. We also state the range when we use medians marked in red.

Comment 12: You conducted univariate analysis, but never mention if you looked for co-linearity, effect modification, etc. You need to conduct multivariable analysis to assess whether any of these variables are controlled for one another.

Response 12: Before multivariable, correlation analysis was needed to check the correlations between variables. We conduct the multivariable analysis in the first time, but before that, we conduct a correlation analysis about all these variables using SPSS. Significant correlations were observed between many variables. Therefor, we deleted the results of multivariable analysis.
Comment 13: You need to mention whether the proportional hazards assumption was met prior to showing cox regression statistics.

Response 13: Just like the comment 8, we are not sure if we realized what you mean. Associations between possible prognostic variables and survival were estimated using Cox proportional hazards regression. The effects of P values were considered significant if P < 0.05. P values were recorded in Table 2 and Table 3. The result was described and analysed in Result, Assessment of prognostic factors for MPM and Discussion. We agree with you that using a small sample increases the chance of assuming as true a false premise. More prospective studies with a larger cohort of subjects are needed in the future to find the accurate prognostic factors for MPM and we will try to do our best for this.

Discussion

Comment 14: p. 11 "Status of the lymph node" is odd wording

Response 14: Thank you for your advise. We have deleted the "Status of". This sentence is "Chest CT is commonly used in the preferred examination, which can display the surface of the whole pleura, the diaphragm and the lymph node " now.

Comment 15: p.12 and 13 have numerous grammatical errors

Response 15: We tried our best to improve English and made some changes in the manuscript. Many long sentences were separated into short sentences. These changes will not influence the content and framework of the paper. And all changes were marked in red in revised paper.

Comment 16: p.12 states MT as an imaging technique, which is incorrect- it is an invasive procedure.

Response 16: We have change the "imaging technique" to "invasive procedure" in page 13, paragraph 1 marked in red.

Comment 17: p.13 "Our data revealed longer survival for MPM patients with the epithelioid type and this result is in line with many previous studies"- you need citations of the studies you are referring to.

Response 17: We have added the citation of studies about this result in page 14, paragraph 3 marked in red.

Comment 18: You need to elaborate on why having such a small n is a limitation. You call it a limitation and do not mention why.
Response 18: Using a small sample increases the chance of assuming as true a false premise. Thus, chances are that the patients with proposed poor prognostic factors have no shorter lifetime compared to patients without these factors. We have made this clear in the last paragraph of Discussion marked in red.

Comment 19: This is a retrospective study- that is a huge limitation which you do not mention.

Response 19: Thank you for your advise. There is a potential selection bias to this retrospective study. Therefore, more prospective studies with a larger cohort of subjects are needed to support the present findings. We have mentioned this in the last paragraph of Discussion marked in red.

Conclusions

Comment 20: These need to be drastically toned down. You identified some variables that are associated by univariate analysis, but you stopped there. I think you need more statistical analysis before you can deem any of these "predictors" and even after that, with such a small n and the fact that this is retrospective you can not draw any major conclusions. These may be prognostic factors, but we dont know. I would address what you think can be done to further explore this?

Response 20: Indeed, with such small n of this retrospective study, no major conclusions can be made in this situation. We have toned down the conclusions and mentioned that more prospective studies with a larger cohort of subjects are needed in the future to find the accurate prognostic factors for MPM. We have made this clear in the part of Conclusions.

Tables

Comment 21: Table 1. looks good, maybe change means and sd's to medians and ranges

Response 21: We have change the mean and sd of age to median and range marked in red.

Comment 22: Table 2. Add a column of multivariable analysis- with such a small n you can only control for a couple things, but your results could significantly change.

Response 22: As we responded in comment 12, significant correlations were observed between many variables. Therefor, we deleted the results of multivariable analysis.

Comment 23: Table 3. see table 2

Response 23: As we responded in comment 12, significant correlations were observed between many variables. Therefor, we deleted the results of multivariable analysis.
Figures

Comment 24: I'm not clear as to how helpful a lot of these graphs are. You showed the cox regression data on a lot of this already. Especially since each group is maybe 15/15, there isn't a lot to gain from these graphs (in my opinion).

Response 24: We agree with your opinion. The figures partially restate the result in tables. But in our opinion, the Kaplan-Meier curve is relatively straightforward to describe the change of survival rate over time. Readers can realize the difference of the survival between different groups. Besides, Log Rank test was used in Kaplan-Meier survival analysis to get a further validation of the result of Cox proportional hazards regression. So, we considered to retain the figures.

We appreciate for Editors and Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.