Author’s response to reviews

Title: Acute exacerbations of fibrosing interstitial lung disease associated with connective tissue diseases: a population-based study

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Version: 2 Date: 23 Aug 2019

Author’s response to reviews:

Dear Editor,

Thank you for your review and comments on our manuscript " PULM-D-18-00700R1: Acute Exacerbations of Fibrosing Interstitial Lung Disease associated with Connective Tissue Diseases- A Population-Based Study" by Mengshu Cao et al.

We addressed the comments of editor and reviewers (see below) and revised the manuscript according to your comments. We appreciate the constructive criticisms of the reviewers and believe that our revisions have clarified and strengthened the manuscript. Specifically, we have made the following revisions in response to the reviewers’ comments point-by-point below.

If you have any questions regarding our manuscript, please don’t hesitate to contact us.

With Best Regards!
Mengshu Cao on behalf the authors.

Point-by-point reply:

PULM-D-18-00700R1

Acute exacerbations of fibrosing interstitial lung disease associated with connective tissue diseases: a population-based study

Mengshu Cao; Jian Sheng; Xiaohua Qiu; Dandan Wang; Dongmei Wang; Yang Wang; Yonglong Xiao; Hourong Cai

BMC Pulmonary Medicine

Reviewer reports:

Shinichiro Ohshimo, M.D., Ph.D. (Reviewer 1): Journal: BMC Pulmonary Medicine

Manuscript Number: PULM-D-18-00700R1

Title: Acute exacerbations of fibrosing interstitial lung disease associated with connective tissue diseases: a population-based study

Authors: Mengshu Cao

1. General Comments

The author investigated the prevalence, clinical characteristics and prognosis in patients with connective tissue disease-associated interstitial lung diseases (CTD-ILD) who developed acute exacerbation (AE) and identified risk and predictive factors of AE.

Authors revised the manuscript, according to the reviewers' recommendations. However, there still seem to be some drawbacks prohibiting publication in the current form.

2. Major Comments

1) Inappropriate statistical methods: Authors added the univariate analysis for the risk factors of AE in Table 2, according to my previous comment. However, one of the covariates was changed from DLCO %pred to TLC %pred without any explanation. In addition, the selection procedure of covariates seems still inappropriate; i.e. too many non-significant covariates have been incorporated in the analysis.
Reply: Thank you for your comments. Yes, we have used the inappropriate statistical methods in the previous manuscript. However, we corrected the statistical methods in this revised manuscript. Published reports showed that low FVC, DLCO and baseline oxygenation are known risk factors for AE in IPF patients, we found that only TLC% pred was associated with the occurrences of AE among CTD-ILD patients after ILD diagnosis for 1 year. After considering the clinical significance and adjusting other clinical variables, prior corticosteroids and immunosuppressant use, FVC, TLC% pred, PAH and BMI were included in the multivariate Cox analysis for AE occurrence. We pay more attention to the clinical significances of these covariates, and take into account of the results by univariate analysis. We included TLC in the multivariate Cox model because TLC% pred differed between the two groups and DLCO was an instable variate when conducted the pulmonary function tests. Please see the Table 2 and revised manuscript.

2) Unclear prognostic significance of the variables: Authors added the univariate analysis for the prognostic factors in Tables 4 and 5, according to my previous comment. However, the selection procedure of covariates is still inappropriate, and too many inappropriate covariates have been incorporated in the analysis. The statistical procedure is incorrect.

Reply: Thank you for your comments. We corrected the statistical methods in this revised manuscript. We analyzed the prognostic factors in all 177 cases, AE-CTD-fILD group and AE-IPF group, respectively. As we mentioned above, the clinical significances of these covariates, the results of univariate Cox analysis and whole 177 cases cohort were considered, we included WBC counts, PaO2/FiO2, CT scores and maximal dosage of methylprednisolone in multivariate Cox model. The findings showed that WBC counts and PaO2/FiO2 were the independent prognostic factors for survival by multivariate Cox analysis in the AE-CTD-fILD group. WBC counts, PaO2/FiO2, CT scores were the significant variates by univariate Cox models in the two groups. Maximal dosage of methylprednisolone was also a significant variate in AE-IPF group by univariate analysis, and it was very important clinical variate for AE patients. Please see the Table 4, 5 and revised manuscript.

3. Minor Comments

3) Nothing.

Reviewer 2 (Reviewer 3): "PEER REVIEWER ASSESSMENTS:

OBJECTIVE - Full research articles: is there a clear objective that addresses one or several testable research questions? (Brief or other article types: is there a clear objective?)

Yes - there is a clear objective

Reply: Thank you for your comments.
DESIGN - Is the current approach (including controls and analysis protocols) appropriate for the objective?
Yes - the approach is appropriate
Reply: Thank you for your comments.

EXECUTION - Are the experiments and analyses performed with sufficient technical rigor to allow confidence in the results?
Yes - experiments and analyses were performed appropriately
Reply: Thank you for your comments.

STATISTICS - Is the use of statistics in the manuscript appropriate?
Yes - appropriate statistical analyses have been used in the study
Reply: Thank you for your comments.

INTERPRETATION - Is the current interpretation/discussion of the results reasonable and not overstated?
Yes - the author's interpretation is reasonable
Reply: Thank you for your comments.

OVERALL MANUSCRIPT POTENTIAL - Has the author addressed your concerns sufficiently for you to now recommend the work as a technically sound contribution? If not, can further revisions be made to make the work technically sound?
Probably - with minor revisions
Reply: Thank you for your comments.

PEER REVIEWER COMMENTS:

GENERAL COMMENTS: The authors have adequately responded to reviewers comments. Please see specific comments below.
ADDITIONAL REQUESTS/SUGGESTIONS:

Given the low correlation coefficients and hazard ratios, the authors should mention the weak association with the covariates. In addition, the 4th page of discussion mentions ""In our relatively large cohort"" and a few paragraphs below ""...due to the small sample in our study"". I suggest the authors adhere to a more realistic approach and clearly acknowledge the sample size limitations, which have already been pointed out by other reviewers."

Reply: Thank you for your comments. We corrected our manuscript according to your comments.