Reviewer’s report

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

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Reviewer: Shinichiro Ohshimo

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

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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. The incidences of AEs were similar in CTD-ILD and idiopathic pulmonary fibrosis (IPF). The white blood cell (WBC) count, LDH, PO2/FIO2 ratio and the use of mechanical ventilation (MV) were the independent prognostic factors.

Because AE is a fatal condition, early predictors for survival are clinically important. From this point of view, this paper includes novel and useful findings. However, there seem to be some drawbacks prohibiting publication in the current form.

2. Major Comments

1) Inappropriate statistical methods: Authors showed the multivariate analysis for the risk factors of AE in Table 2. However, the univariate analysis seems lacking, and the statistical power is insufficient for these 7 variables with the authors' cohort. Authors should at first do the univariate analysis, and adequately select the potential covariates for the multivariate analysis.

2) Unclear prognostic significance of the variables: As pointed out in my comment 1), Table 4 also lacks the univariate analysis. The number of covariates also seems too many with the authors' cohort. Bivariate correlation analysis in Table 3 is insufficient for selecting adequate covariates. Authors should correct the statistical procedure.
3) Unclear difference in the prognoses between the cohorts: Authors mentioned that the overall survival in AE-CTD-ILD was better compared with that in AE-IPF. However, the baseline characteristics in the both cohorts were different, which could have affected the results. PaO2/FIO2 ratio and total lung capacity (TLC) were worse in the IPF cohort compared with the CTD-ILD cohort. Authors should evaluate the difference by using the multivariate analysis.

4) Unclear Kaplan-Meier analysis: Figure 2A showed the completely same prognosis between the cohort until around day 100. After that, the survival curves showed the apparently different prognoses, which seemed uncommon. Authors should discuss the reason for this finding.

5) Difficult clinical application of these markers: Authors demonstrated that WBC, LDH, PaO2/FIO2 ratio and the use of mechanical ventilation were the independent prognostic factors for the AE-CTD-ILD. However, WBC and LDH are the very non-specific markers. Low PaO2/FIO2 ratio and the use of mechanical ventilation could be the indicators of hypoxia, and their association with the survival seemed very common. Therefore, the clinical application of these parameters seemed difficult. Authors should discuss the desired clinical utility of these markers.

3. Minor Comments

6) Figure 1A, B, and C are just the yearly epidemiological data, which seemed less important for this manuscript.

7) Colors in Figure 2C disturbs the visibility of characters, which should be corrected.

8) English should be corrected by native speakers.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

No

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No
Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Not suitable for publication unless extensively edited

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