PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognosis of acute exacerbation in idiopathic pulmonary fibrosis with pulmonary emphysema: a retrospective cohort study in Japan
AUTHORS	Horio, Yukihiro; Takihara, Takahisa; Takahashi, Fuminari; Enokida, Keito; Nakamura, Noriko; Tanaka, Jun; Tomomatsu, Katsuyoshi; Niimi, Kyoko; Tajiri, Sakurako; Hayama, Naoki; Ito, Yoko; Oguma, Tsuyoshi; Asano, Koichiro

VERSION 1 – REVIEW

REVIEWER	Naito, Tateaki Shizuoka Cancer Center, Division of Thoracic Oncology
REVIEW RETURNED	17-Mar-2022

GENERAL COMMENTS	The authors reported the results of a retrospective cohort study that aimed to analyze the clinical characteristics and prognosis of acute exacerbation in patients with idiopathic pulmonary fibrosis with or without pulmonary emphysema. Patient data were obtained from two university hospitals in Japan from 2007 to 2018. The ethics committee approved the study. The topic is unique, and their hypothesis is reasonable. The results support their hypothesis and lead to a clear conclusion. Accordingly, I think this excellent manuscript needs a few revisions. Comments: 1. To minimize the selection biases, please show the patient flow diagram, which indicates each number of patients excluded and detailed reasons in each step of eliminating samples from all IPF-AE cohort to 62 patients. 2. Elderly patients were predominant in both groups. Therefore, please show the following pretreatment factors, which potentially affect the survival outcomes in acute care for IPF-AE: comorbidities (diabetes, cardiovascular disease, kidney disease, cancer, and chronic infection), nutritional status (BMI or serum albumin), premorbid performance status or disability, and do-not-resuscitation order (yes or no).

REVIEWER	Kishaba, Tomoo Okinawa Chubu Hospital, Respiratory Medicine
REVIEW RETURNED	28-Mar-2022

GENERAL COMMENTS	This is an interesting retrospective study. I proposed several questions for author. Major 1.Regarding IPF with emphysema, how did you define this group

	such as extent of emphysema in chest HRCT ? 2. In Table 1, baseline treatment of each group have very few antifibrotic agent. Could you explain why ? 3. Do you have any theory about elevation of serum KL-6 and SP-D in IPF with emphysema group ? 4. In terms of difference of survival for two groups, how about the effect of secondary infection of high dose prednisolone ?

VERSION 1 – AUTHOR RESPONSE

Response to the comments from Reviewer #1

General comment

The authors reported the results of a retrospective cohort study that aimed to analyze the clinical characteristics and prognosis of acute exacerbation in patients with idiopathic pulmonary fibrosis with or without pulmonary emphysema. Patient data were obtained from two university hospitals in Japan from 2007 to 2018. The ethics committee approved the study. The topic is unique, and their hypothesis is reasonable. The results support their hypothesis and lead to a clear conclusion. Accordingly, I think this excellent manuscript needs a few revisions.

Response to general comment

Thank you for the encouraging comments and valuable suggestions. We have corrected our manuscript as suggested by the reviewer.

Comment #1

To minimize the selection biases, please show the patient flow diagram, which indicates each number of patients excluded and detailed reasons in each step of eliminating samples from all IPF-AE cohort to 62 patients.

Response to comment #1

Thank you for the important suggestion.

There were 103 patients with idiopathic interstitial pneumonia admitted to two university hospitals due to its acute respiratory failure during the study period between January 2007 and August 2018. We excluded 31 cases who were diagnosed as unclassifiable interstitial lung disease (n = 28) or non-specific interstitial pneumonia (n = 3) based on multidisciplinary discussion. Another ten cases were excluded because the major cause of respiratory failure at admission was considered to be infection or heart failure, but not an AE-IPF, based on the the clinical course after treatments. We described this process in page 7, lines 148-149 in the Results section and added a flow diagram of patient selection as Supplemental Figure 1.

Comment #2

Elderly patients were predominant in both groups. Therefore, please show the following pretreatment factors, which potentially affect the survival outcomes in acute care for IPF-AE: comorbidities (diabetes, cardiovascular disease, kidney disease, cancer, and chronic infection), nutritional status (BMI or serum albumin), premorbid performance status or disability, and do-not-resuscitation order (yes or no).

Response to comment #2

According to the suggestion by the reviewer, we presented some additional baseline characteristics of the IPF patients with or without pulmonary emphysema in Tables 1 and 2. There were no significant differences between the groups in body mass index, co-morbidities (diabetes mellitus, chronic heart failure, chronic renal failure, and chronic respiratory infection, any type of cancer), serum albumin levels, or proportion of do-nt-resuscitation order.

Response to the comments from Reviewer #2

General comment
This is an interesting retrospective study. I proposed several questions for author.

Response to general comment
Thank you for the generous comments and valuable suggestions. We have corrected our manuscript as suggested by the reviewer.

Comment #1
Regarding IPF with emphysema, how did you define this group such as extent of emphysema in chest HRCT?

Response to comment #1
We analyzed low attenuation area (LAA) score in chest HRCT according to the method proposed by Goddard et al. (reference #12). The cases with LAA score > 0 was classified into the emphysema group; the mean and standard deviation of LAA score in the emphysema group was 6.2±3.8. We described the definition of pulmonary emphysema and LAA score in page 6, lines 125-127 of the Methods section and added data of LAA score in Table 1.

Comment #2
In Table 1, baseline treatment of each group have very few antifibrotic agent. Could you explain why?

Response to comment #2
Although pirfenidone has been available since 2008 in Japan, the number of IPF patients treated with antifibrotic drugs was limited in our institutes until 2015 when nintedanib became available. This retrospective study examined the patients who had AE-IPF between 2007 to 2018, when physicians were using anti-fibrotic agents less often than they are currently. Another possible factor contributing to the low rate of antifibrotic treatment in the patients with AE-IPF is that the patients using antifibrotic agents may have been less likely to experience acute exacerbation.

Comment #3
Do you have any theory about elevation of serum KL-6 and SP-D in IPF with emphysema group?

Response to comment #3
We do not have definite answer for this question. There have been some studies reporting that higher levels of serum KL-6 at AE-IPF were associated with poorer prognosis. It is, therefore, interesting that our study demonstrated that patients with IPF and emphysema had better short-term survival despite of their higher serum KL-6 levels than those with IPF alone.

Comment #4
In terms of difference of survival for two groups, how about the effect of secondary infection of high dose prednisolone?

Response to comment #4
Three patients with IPF and emphysema and none with IPF alone died due to pneumonia during the whole observation period. The patients with IPF and emphysema who survived acute phase of AE-IPF were more likely die due to pneumonia during the whole observation period, however, the difference was not statistically significant (p = 0.23, Table 5).
We must apologize about our miscalculation of the p values in Table 5 and total number of patients who died in the IPF alone group. We corrected Table 5 and a sentence in page 12, line 206.

VERSION 2 – REVIEW

REVIEWER	Naito, Tateaki Shizuoka Cancer Center, Division of Thoracic Oncology
REVIEW RETURNED	09-Jun-2022

GENERAL COMMENTS	Thank you for your revised manuscript. I think that all the comments are responded to and adequately reflected in the revised manuscript. The authors discussed all biases and weaknesses. I think this manuscript is now acceptable. Thank you for all your efforts.

REVIEWER	Kishaba, Tomoo Okinawa Chubu Hospital, Respiratory Medicine
REVIEW RETURNED	10-Jun-2022

GENERAL COMMENTS	Revised manuscript is well written.