Peer Review File

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Reviewer Comments

Comment 1

The primary hypothesis of the study should be specified and provided in the final paragraph of the Introduction. Similarly, the study aim should be stated.

Reply: Thank you for the comment. Ohta et al (14) reported that serum M-PN level was strongly correlated serum fibrotic markers such as KL-6 and SP-D in IPF patients. A fibrotic marker is usually more elevated in AE-FIP than during the stable phase, and fibrosis of the lung parenchymal sometimes rapidly progresses after AE-FIP. Thus, we hypothesized that serum M-PN level would be elevated in patients with AE-FIP and might associated with AE-FIP outcome. This study evaluated serum M-PN level in patients with AE-FIP and its association with outcome. The relevant text has been added to the revised manuscript, as follows.

Revised text: page 5, lines 104–110

Serum fibrotic maker such as KL-6 or SP-D usually more elevated in AE-IPF than that of stable phase and the fibrosis of the lung parenchyma sometimes rapidly progress after AE-IPF. Thus, we hypothesized that the serum M-PN level elevated in the patients in AE-FIP and might associated with the prognosis of AE-FIP. The purpose of this study was to evaluate the serum M-PN level in patients with AE-FIP and its association of prognosis

Comment 2

The authors specified that this study only included patients with HRCT showing definite and possible UIP patterns, which are typical for IPF. How did the investigators define fibrotic NSIP? Was it based on histological patterns? Otherwise, how confident are the investigators in diagnosing patients with possible UIP radiological patterns as fibrotic NSIP? Was multidisciplinary discussion being used to achieve the diagnosis?

Reply: We understand the reviewer's concern. We re-evaluated HRCT findings in accordance with the 2018 IPF guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin-American Thoracic Association (ALAT). In this study, FIP comprises IPF and nonspecific interstitial pneumonia (NSIP). Usual interstitial pneumonia (UIP) or probable UIP patterns on high-resolution computed tomography (HRCT) images were diagnosed as IPF. Diagnosis of NSIP was based on histopathological patterns or HRCT patterns showing the presence of traction bronchiectasis with a peribronchovascular distribution and/or intralobular reticular opacity and, less frequently, peripheral distribution and/or ground-glass attenuation of wide extent. All diagnoses of interstitial pneumonia were made after multidisciplinary discussion. The relevant text has been added to the revised manuscript, as follows.

Revised text: pages 6–7, lines 129–143
Diagnosis of FIP was based on the 2013 update of the international multidisciplinary classification of the idiopathic interstitial pneumonias (15) and 2018 IPF guidelines of the American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin-American Thoracic Association (ALAT) (18). In this study, FIP comprises IPF and nonspecific interstitial pneumonia (NSIP). IPF was diagnosed on the basis of usual interstitial pneumonia (UIP) or probable UIP patterns on high-resolution computed tomography (HRCT) images. Diagnosis of NSIP was based on histopathogical patterns or HRCT patterns showing the presence of traction bronchiectasis with a peribronchovascular distribution and/or intralobular reticular opacity and, less frequently, peripheral distribution and/or a wide extent of ground-glass attenuation. All diagnoses of interstitial pneumonia were confirmed by multidiciplinary discussion.

Comment 3
Duration of survival for the non-survivors should be provided in the Clinical characteristics of survivors and non-survivors.

Reply: Thank you for the suggestion. We now describe the duration of survival for survivors and non-survivors. The relevant text has been added to the revised manuscript, as follows.

Revised text: page 10, lines 221–222
Duration of survival was significantly longer in survivors than in non-survivors (457.0 ± 478.0 days vs 27.8 ± 29.0 days, p=0.001).

Comment 4
The authors reported correlations between serum monomeric periostin levels at the onset of acute exacerbations and clinical characteristics. However, this evaluation was not specified in the statistical analysis. Data for the correlation of different variables would be better presented in a table format.
Reply: We performed statistical analysis using Spearman's rank correlation coefficients. The results are now shown in the new Table 2. The relevant text has been added to the revised manuscript, as follows.

Text revision: page 8, lines 184–185
Correlations between two variables were evaluated by using Spearman's rank correlation coefficients.

Comment 5
Change in serum M-PN levels in survivors and non-survivors, Page 10: The authors should include data of the change in serum M-PN levels at day 14 for non-survivors, even in the absence of statistical significance.
Reply: We have included data on change in serum M-PN levels at day 14 for non-survivors. The relevant text has been added to the revised manuscript, as follows.

Revised text: page 11, lines 242–246
However, there was no significant decrease in M-PN level from AE onset to day 7 in non-survivors (14.6±5.1 vs 13.2±5.1 ng/ml [onset to day 7; p=0.07]). There was a

significant decrease in M-PN from AE onset to day 14 in non-survivors (14.6±5.1 vs 9.8±3.1 ng/ml [onset to day 14; p=0.03]) (Fig. 2).

Comment 6

Another limitation in the evaluation of histological staining of periostin is the absence of baseline lung biopsy sample before the onset of acute exacerbation, acknowledging this could be challenging to obtain.

Reply: We agree. The relevant text has been added to the revised manuscript as a limitation, as follows.

Revised text: page 16, lines 367–369

In addition, we could not evaluate histological staining of periostin because we did not perform lung biopsies in all IPF patients before onset of AE-FIP.

Minor Comments

Comment 1

Nonsurvivors should be replaced by non-survivors.

Reply: We have made the suggested change.

Revised text: page 3 line 58, page 6 line 123, page 9 line 209, page 9 line 210, page 10 line 211, page 10 line 216, page 10 line 218, page 10 line 220, page 11 line 235, page 11 line 237, page 11 line 243, page 11 line 245, page 13 line 293, page 14 line 316, page 14 line 327, Table 1

Comment 2

Remove "chronic" before the term "idiopathic pulmonary fibrosis". This is unnecessary as there is no acute form of IPF.

Reply: We agree and have corrected the text in question.

Revised text: Page 4 line 83, Page 13 line 300

Comment 3

Line 85: Clarify the reference? (3)

Reply: We have corrected the text as advised.

Revised text: Page 4. line84

Comment 4

Line 198: GAP score should be replaced by ILD-GAP score.

Reply: We agree and have corrected the text as advised.

Revised text: Page 10, line 227; Page 10, line 228; Table 1; Table 2