PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A cohort study of mortality predictors in patients with acute exacerbation of chronic fibrosing interstitial pneumonia
AUTHORS	Usui, Yutaka; Kaga, Akiko; Sakai, Fumikazu; Shiono, Ayako; Komiyama, Ken-ichiro; Hagiwara, Koichi; Kanazawa, Minoru

VERSION 1 - REVIEW

REVIEWER	Osamu Nishiyama, M.D. Assistant proffesor Department of Respiratory Medicine and Allergology, Kinki University Faculty of Medicine Japan There are no competing interests to declare.
REVIEW RETURNED	09-Apr-2013

THE STUDY	1. The author excluded the patients who died from causes other than AE. However, it is quite interested and maybe important whether the same factors were selected as prognostic markers if patients with all-cause death were included in the analysis. At least, the author should note the results of this analysis because it is commonly recognized that patients with AE of CFIP usually die from cormorbid illnesses and/or other organ dysfunctions. 2. The author demonstrated that days from the onset to admission were correlated with prognosis in univariate analysis. However, it should be noted in the methods section that how the time of the disease onset was detected.
RESULTS & CONCLUSIONS	1. The author included patients with IPF and those with idiopathic interstitial pneumonia other than IPF together. Then, the author demonstrated that there was no difference in survival outcome between patients with IPF and with non-IPF. However, it was already reported that AE could occur in NSIP and prognosis was favorable (Park I. Chest 2007;132:214). In the study, some patients with IPF might be included in the non-IPF group, although the author noted this in the discussion section. The author also noted that no prognostic differences were seen among patients with definite UIP, possible UIP, and inconsistent with UIP pattern on TSCT, but these data should be showed. 2. Given that serum PCT was one of prognostic factors, I wonder if the possibility of infection might not be sufficiently excluded. How many patients underwent the BAL examination to exclude infection before the initiation of the therapy for AE, although no consensus is obtained in terms of BAL examination for AE.
REPORTING & ETHICS	1. A waiver of consent in a retrospective study should be granted by an ethics committee or Institutional Review Board.

REVIEWER	Dong Soon Kim, MD

	Professor, Dept. of Pulmoanry and Critical Care Medicine Ansan Medical Center, University of Ulsan Seoul, Korea I have no COI for this paper
REVIEW RETURNED	18-Apr-2013

THE STUDY	The aim of the study was clear and clinically very important, but the major problem of this study was the subjects (patients) definition was not clear both for CFIP and acute exacerbation, therefore the enrolled patients might not be representative cases. 1.1. Diagnosis of acute exacerbation (AEx): what kind of tests (microbial cultures of sputum, blood and BAL, serological or PCR for virus) were performed to rule out the possibility of infection? If not done in every patient, how many patients performed each tests? It is important because infection is the most difficult and important differential diagnosis. Especially in this study, it is more important to clearly exclude infection from AEx, because SIRS and procalcitonin level were concluded as major parameters. 2. Because this study included non-IPF, NSIP patients, it is important to know the prior medication, especially immediately before the AEx. Some patients, especially the patients with NSIP might have been treated with corticosteroid with or without immunosuppressants and in these patients the possibility of opportunistic infection such as pneumocystiis pneumonia is high. Therefore BAL examination is important for the diagnosis of AEx. These should be stated in detail. 3. Although there are no studies on SIRS specifically, most of AEx patients are quite sick and many of them had tachypnea (low PaCO2), mild fever, leukocytosis, and/or tachycardia. In this study, significant proportion of the patients (19/51=37%) did not have SIRS (none or only one of those parameters), meaning that these patients had only mild degree of AEx. It is not surprising that these mild patients had good prognosis. How many of them had definite diagnosis of IPF before the AEx and fulfilled the criteria of AEx. Then, it is important to know the extent of GGO increase and the degree of PaO2 decline, because slight increase in subpleural GGO around honeycombing can be seen in many patients with progressive IPF but no AEx. And how many of these mild cases did not have prior Dx of CFIP ? 4. About the underlying fibrotic disease: Although AEx can occur and also is clinically important in non-IPF like NSIP and connective tissue disease related pulmonary fibrosis, the mechanism, risk factor and subsequent outcome may be different from AEx of IPF. Actually previous report suggested better response to steroid in non-IPF AEx, although statistically not significant because of small number of the subject. In this study, underlying fibrotic lung disease was not clearly classified and mostly by the CT features. And the proportion of non-IPF (21:30) was higher compared to the proportion of idiopathic NSIP to that of IPF. 5. Furthermore, authors stated that the diagnosis of CFIP was made by review of previous CT in 40 patients and follow-up CT in 11 patients. How could the underlying CFIP be diagnosed by follow-up CT? It has been well known that the NSIP pattern is found in the survivors of ARDS. And these 11 patients did not have prior CT means that these 11 patients had not been diagnosed as CFIP before AEx and presented for the first time as AEx? Then, without definite honeycombing at initial CT (at the time of AEx), these

	patients cannot be diagnosed as CFIP-AEx even with follow-up CT and should not be included in the study. 6. The method of case selection should be described more in detail. During the study period, how many patients with CFIP(IPF and NSIP separately) were diagnosed at the same hospital (total cohort), among them how many patients were admitted due to acute respiratory problem, and how many patients were actually diagnosed as acute exacerbation (AEx) and how many were due to known cause like infection? How long was the interval between the diagnosis of CFIP and acute exacerbation? Was there any patient who presented for the first time as acute exacerbation without previous diagnosis of CFIP? Then how was the presence of CFIP diagnosed in these patients? 7. For the Dx of AEx, the patients should have done arterial blood gas analysis before AEx to show decline of more than 10 mmHg of PaO2 (or more than 5% O2 saturation). In this study, 11 patients did not perform CT before AEx for the differential diagnosis between IPF and NSIP but performed arterial blood gas analysis before and at the time of AEx, which seems to be very unusual (doing arterial blood gas analysis without HRCT in stable state). 8. What were the causes of death in 5 AEx patients who were excluded from the analysis because the death was due to other than respiratory failure secondary to AEx? It may not appropriate to exclude these patients. 9. There is increasing interest in the difference between IPF combined with emphysema (CPFE) and pure IPF, and it is important to verify the relative risk AEx and prognosis in CPFE. What was the definition of CLE, or PSE (threshold extent of emphysema) and what was the evedence? Was the extent of emphysema scored on all patients? Then, was there any correlation between emphysema score and prognosis? 10. The method of radiologic scoring was different from usual method (usually at 3 levels on HRCT (6 zones), the abnormalities were scored and summated or averaged), the authors stated that “the extent of GGO and honeycombing was scored to the nearest 10% at the 6 lung zones: right upper and middle lobes, left upper segment and lingula, bilateral lower lobes.” Then how they determined the extent of each zone? By calculating mean score on every level? For the more the radiologic score was determined by one radiologist and one pulmonologist, although they were experts in ILD. Then, kappa-value should be presented for each parameter. 11. It is necessary to state the statistical analysis method in detail rather than describing as “using the Mann-Whitney U test, c2 statistics, and Fisher’s exact test, as appropriate. For example, where c2 statistics was used? And multivariate analysis is usually performed among the parameters, which showed P< 0.1. In this study, BNP had no significance, but included in multivariate analysis. Because the result of multivariate analysis becomes different according to what parameters are included, even among the parameters, the parameters which have close correlation with other parameters are excluded. Authors need to state in detail. 12. In the discussion, authors stated that becuase proinflammatory cytokine (IL-6, IL-8) were reported to be increased in ARDS, AEx also can be mediated by certain circulating molecules and cause SIRS. However, in previous report reviewed also by authors showed that in AEx-IPF, proinflammatory cytokine, IL6 was not high in contrast to ARDS/ALI suggesting different mechanism. And this finding was also supported by other microarray study. Authors need to discuss more about this. 13. They used in-hospital mortality as the most important parameter,

	but no mention about the duration of hospitalization. 14. The total number of whole subjects in Figure 4 was 50 (not 51) and the total number of the patients with CLE was 17 (not 18 in Table 2). One patient with CLE was missed in grouping.

VERSION 1 – AUTHOR RESPONSE

Response to Dr. Nishiyama

Major comments
1. According to the reviewer's comments, causes of death of the excluded five patients and results of multivariate analysis including these five patients (total 56 patients) have been added in the text.
2. "The mean duration of symptoms before admission" in the 1st paragraph of the Results is a correct expression. We have replaced "onset" to "Duration of symptoms before admission, days" in the table 1 and 5.

Major comments
1. As the reviewer described, in the paper by Park et al. (reference #2), two of six (33%) idiopathic NSIP patients died of AE, on the other hand, the report by Silva et al. (reference #3) described three of four (75%) idiopathic NSIP died of AE. The total rate of death was 50% (five of 10). The description of "as high as 70%" in the 1st paragraph in the Discussion was incorrect and we replaced it to 50%, which still indicates high mortality rate. Survival curve for patients with definite UIP, possible UIP, and inconsistent with UIP pattern was added (new fig. 4) and the subsequent revision was done.
2. Bronchoalveolar lavage was performed in 17 patients studied and the BALFs disclosed any evidence of respiratory infection. Every patient was clinically diagnosed as free of overt respiratory infection by blood, serum, or urine exams as well as microbial culture of sputum or tracheobronchial aspirate (please refer the response to Dr. Kim in detail). We believe that we could carefully exclude a possibility of respiratory infection in this cohort. We added some description about it in the section of Diagnostic criteria in the Methods.

Minor comments
1. A waiver of consent of the present study has already been obtained by an Institutional review board of our institute. Please let me know how to prove it.

Response to Dr. Kim

1 and 2. In every 51 patient, we performed microbial cultures for common bacteria, mycobacteria fungi, using sputum or tracheal aspirates. BAL was done in 17 patients and the all the BALFs were examined in the same way. Those exams did not reveal any evidence of respiratory infection. 10 out of 17 patients underwent BAL, PCR exams for pneumocystis, aspergillus, and mycobacteria as well as that for common bacteria were performed and showed negative results. Furthermore, antigens for influenza A and B viruses (pharyngeal swab), antigens for pneumococcus and legionella (urine), aspergillus Ag, Ab, and beta-D glucan (serum), and cytomegalovirus antigenemia (blood) were examined in all subjects. All revealed negative results or within normal ranges. We added some description about it in the section of Diagnostic criteria in the Methods. According to the reviewer's comment, prior medication was added in the section of Subjects in the Methods.
3. As described in the text, previous CTs were not obtained or had not been performed in 11 patients. However, of those, previous plain chest radiographs had been obtained in six subjects and we could verify that there had been interstitial lung infiltrates but had not been marked GGOs in the past. In the remaining five subjects, honeycombing was clearly demonstrated by CTs on admission, indicating presence of previous CFIP. In addition, these five patients showed extensive GGO on admission, indicating that GGO was irrefutably a cause of acute onset of respiratory failure. In this cohort, GGO

was markedly extensive on TSCT, compared to reticulation and honeycombing in every patient.
4. We can agree the reviewer's comments in part, however, difference in pathogenesis between AE of IPF and AE of CFIP other than IPF requires future investigation. We suspect that some patients with IPF would be included in the non-IPF group, which may be a reason why the non-IPF group was consisted of 21 subjects in this cohort. Thus, we added the survival curves for patients with definite UIP, possible UIP, and inconsistent with UIP pattern (new fig. 4).
5. As described above, previous chest radiographs of six patients had been obtained and all of them revealed interstitial lung infiltrates. In the remaining five patients, honeycombing was evident on TSCT on admission. Follow-up CT was evaluated for the discrimination between honeycombing and emphysema with GGO and the sentence has been rewritten according to the fact.
6. According to the reviewer's comments, case selection has been described more in detail in the sections of Subjects and the section of Diagnostic criteria in the Methods. Figure 1 has been revised.
7. We did confirm the previous SpO2 of the patients in whom PaO2 had not been examined previously. Some description has been added about it.
8. Please refer to the response #1 to Dr. Nishiyama. Our aim is to know mortality predictors of patients with AE of CFIP who died of AE itself. Some description on it has been added in the 1st paragraph of the section of Subjects in the Methods and the result of multivariate analysis for 56 subjects, including five subjects died of a cause other than AE, has been added in the section of Univariate and multivariable analyses of survival in the Results.
9. According to the reviewer's comments, diagnostic definition of emphysema has been added in the CT imaging section of the Methods. In the present study, we did not set the threshold extent of emphysema. The presence or absence of CLE was simply evaluated and the data clearly demonstrated it to be associated with the outcome. Our point is that the background of CLE development may antagonize the ongoing disease process of AE, as described in the Discussion.
10. As described in the section of CT imaging in the Methods, the space occupying ratio was determined in each zone and the scores (%) at the six lung zones were finally averaged out to obtain a mean score. We have evaluated the correlation of the results obtained from two readers. The correlation was well and the data have been added in the section of CT imaging in the Methods.
11. According to the reviewer's comments, statistical methods have been added in the footnotes of the figures and tables. According to the reviewer's comment, BNP has been deleted from the multivariate analysis, then we re-evaluated the significance and the subsequent revision has been done.
12. According to the reviewer's comments, the part of circulating molecules in ALI/ARDS has been revised.
13. According to the reviewer's comments, description on the duration of hospitalization have been added in the 1st paragraph of the Results.
14. Table 2 is correct: the number of patients with CLE was 18 (7+11). Group 3 in the figure 4 was 11, not 10. We missed one patient in group 3, who has been added in the new figure 5. Numbers of subjects in group 2 (12 patients) and in group 4 (21 patients) were also miscounted and have been corrected. The subsequent revision has been done, including re-evaluation of the statistics..