PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema
AUTHORS	Tomoo Kishaba, Yousuke Shimaoka, Hajime Fukuyama, Kyoko Yoshida, Maki Noyama, Shin Yamashiro and Hitoshi Tamaki

VERSION 1 - REVIEW

REVIEWER	Matthew Jankowich, M.D. Assistant Professor of Medicine Alpert Medical School of Brown University Providence, RI, U.S.A. I have no competing interests.
REVIEW RETURNED	16/03/2012

THE STUDY	1. Regarding study population description, I think a simple flow diagram would be helpful to show how the patients with CPFE and IPF were identified from the pool of 319 patients, and how patients were classified into the IPF group versus the CPFE group. For example, I am assuming that presence of emphysema on HRCT was used to separate the CPFE patients from the IPF patients, but this should be clarified. Also, there is reference to a "multidisciplinary discussion" to identify CPFE patients, but who participated in this discussion? Was this a clinical multidisciplinary group or was this part of the research study? 2. I think there are a number of issues in the methods which need clarification. For example, in the methods, the definition of "acute exacerbation" used by the researchers for this study should be clearly stated. There is reference in the results to the 2002 ATS/ERS statement, but this statement really doesn't give a clear clinical definition of acute exacerbation of IPF, just a referenced statement that if an IPF patient has an "accelerated phase of illness" and no cause can be identified, this "may" represent an acute exacerbation of IPF. Since this is a retrospective study, it is unlikely that all CPFE patients had a systematic and standardized workup during acute clinical declines, so how did the researchers determine that an illness represented an "acute exacerbation"? Chart review, consensus, etc.? 3. Similarly, there is reference in the results to the prevalence of pulmonary arterial hypertension and the mean systolic PAP pressure in CPFE patients in this cohort. How was this determined? By echo? PA catheterization? A mean systolic PA pressure in the CPFE cohort is given as 62.76mmHg--unclear how results (to the hundredth of a mmHg) for this value were obtained, and what was the standard deviation? This should be clarified in the methods and results section. 4. Regarding survival, how was the length of survival determined?

	From the first clinic visit, from the time of the HRCT, etc. e.g. what was time 0? Again, the methods need clarification. 5. Similarly, what value of KL-6 was used to predict acute exacerbation? The first value available, the value obtained during hospitalization, etc.? Clarification needed in methods. 5. Regarding the standard of English, I found there was rather awkward phrasing throughout the manuscript e.g. "We investigated all available clinical and physiologic data with minimally invasive way"; "And we compared CPFE with IPF patients."; "Emphysema has been associated with heavy smoker's idiopathic pulmonary fibrosis (IPF)."; etc. These detract from the readibility of the paper.
RESULTS & CONCLUSIONS	1. Please see above regarding issues with definition of acute exacerbation, PA pressures, and how survival time was determined. 2. The HRCT results showing more honeycombing in the IPF-pattern group of CPFE patients and more ground glass and consolidation in the NSIP-pattern group are not meaningful, since presence and extent of honeycombing vs. ground glass are what is used to separate a UIP/IPF pattern from an NSIP pattern by imaging. So by definition, there will be more honeycombing in the IPF subgroup and more ground glass in the NSIP subgroup. 3. I think the focus on noninvasive determinants of survival in CPFE is interesting and important, but the methodology needs to be clarified to make the results more credible. 4. I think the final figure showing survival in IPF with FEV1%/FVC% of <1.5 vs. >1.5 is not helpful, as this is not the focus of the paper. Would stick with CPFE. 5. I don't feel qualified to comment on all the statistical methods used, such as the statistical validity of the survival curves in this retrospective study.

REVIEWER	Chang-Hoon Lee, M.D. Assisstant professor, Seoul National University Hospital Republic of Korea
REVIEW RETURNED	19/03/2012

THE STUDY	1. The primary outcome variable is 'acute exacerbation(AE) and mortality'. However, there is no description of AE definition in METHODS. How authors define the AE in the study?
RESULTS & CONCLUSIONS	1. The objective of the study is 'to determine the predictors of AE and mortality in CPFE patients using minimally invasive methods'. For this objective, enrolling IPF without emphysema patients is not required and the characteristics of IPF patients should be removed from Table 1 and RESULTS. 2. There are lack of AE predictors. Authors should inform readers the characteristics of cases with AE. 3. Authors should show the comparison between dead group and alive graoup OR HRs for the other clinical variables not seen in Table 3. Important possible predictors seems to be omitted: age, sex, radiologic findgins (emphysema index, IPF patterns), comorbidity (cancer, cardiovascular diseases), echoCG findings (ePASP, EF), and smoking status etc.
GENERAL COMMENTS	Thank you for reading this interesting articles. I think authors have sufficient data for revising the manuscript.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Matthew Jankowich
Thank you for your sincere comments about our article.
1. I will create simple flow diagram. In addition, I describe how HRCT separate CPFE patients from that of IPF. Multidisciplinary discussion was done by clinical multidisciplinary group.
2.I will describe definition of acute exacerbation more clearly.
3.PA pressure were measured by echo.
4.Survival was determined from the time of the HRCT.
5. Baseline KL-6 predict of acute exacerbation of CPFE patients.
6. Thank you for your comment about some phrases in our article.

1.I describe these issues including definition of acute exacerbation, PA pressures, and how survival time in methods section.
2.Among the CPFE patients, we divided two groups based on imaging pattern of fibrosis in lower lung field. First is more honeycombing in UIP/CPFE group. Second is NSIP/CPFE.
3. I will describe methodology about noninvasive determinants of survival in CPFE.
4.I Would stick with CPFE survival.
5. Thank you for your comments about statistical methods.

Dear Dr. Chang-Hoon Lee
1.I will describe about the definition of AE.
2.I remove characteristics of IPF patients.
3.I will inform characteristics of cases with AE.
4. I will show comparison between dead group and alive group.

Thank you for your all comments about our article.

VERSION 2 – REVIEW

REVIEWER	Matthew Jankowich, M.D. Pulmonary, Critical Care, and Sleep Medicine Providence VA Medical Center I have no competing interests to declare.
REVIEW RETURNED	02/04/2012

THE STUDY	I have reviewed the revised manuscript now titled "A cohort study of mortality predictors and characteristics of patients with combined pulmonary fibrosis and emphysema." I think the manuscript has been considerably improved in the revision, though with some minor revisions, the manuscript can be improved further. I think a major improvement is in the clarity of the data and results, with the elimination of the comparison between a CPFE cohort and an IPF cohort a major improvement, and with the manuscript now well focused on the CPFE alone. The data and results regarding clinical and physiologic predictors of survival in CPFE are intriguing. Regarding quality of English, I think some minor editing would be helpful: For example, under Key Messages: "Clinical point of view, finger

	clubbing is useful predictor of mortality in CPFE." should read, "From a clinical point of view, finger clubbing is a useful predictor of mortality in CPFE." Under Strengths and Limitations: "We evaluated clinical and physiological data...etc." should be modified to "This study's strength was the definition of noninvasive, easily obtainable clinical and physiological measures of prognosis in CPFE. The major limitation of the study is the single-center retrospective design." Under Abstract: Eliminate line under Participants: "Ninety-three patients had CPFE." The next sentence provides the same information with more detail. Under Abstract, Results: "Fourty-two" should be "Forty two". Under Article Summary: "The aim of the study is to investigate predictor of mortality in CPFE in less invasive way" should read "The study aim was to investigate non-invasive predictors of mortality in CPFE." Under the introduction on page 5/25: "Emphysema is sometimes associated with idiopathic pulmonary fibrosis (IPF) and usually occurs with elevated lung volume." should be "Emphysema is sometimes recognized in the setting of idiopathic pulmonary fibrosis (IPF), and patients with both emphysema and fibrosis (CPFE) usually have elevated lung volumes compared to patients with IPF alone." I would eliminate the next sentence "On the other hand, IPF is associated with a decline in lung volume..." In the last line of the introduction, I would change "minimally invasive methods" to "noninvasive methods". I don't think the repeated comments about the results of the study not being generalizable is necessarily true, otherwise why do the study? I would eliminate this, and as above just remark on the limitation being this is a retrospective single-center study. The methods section has been improved by a better description of the patient selection process, and by information on how pulmonary hypertension and survival were delineated. Also, the definition of an acute exacerbation is helpful. Under Results, second line page 7/25: "Ninety-three patients were (76 men, 17 women) were..." should read "Ninety three patients (76 men, 12 women) were..." Eliminate the double "were". I think the division of the patient group into survivors and nonsurvivors in Table 1 is helpful. The authors report in the text that 22 patients in the total cohort develop acute exacerbation. However, in the table, 0% of survivors are reported to develop acute exacerbation, but 31% of nonsurvivors--based on the n=22, I think 1 of the survivors must have had an acute exacerbation, as 31% of 67 survivors is only 21. It may be helpful in the table to list n (%) when reporting proportions. The abbreviation HOT in Table 1 should be defined. I believe this is "Home Oxygen Therapy"? The authors report a mean systolic pulmonary arterial pressure of 62mmHg in the results (page 8/25), however, in Table 1, the mean systolic PA pressure is 28.5 in survivors and 41 in non-survivors. How could the mean in the total group be 62mmHg? This should be reconciled. Again, I can't believe that by echo the PA systolic pressure can be

	estimated to the hundredth of a mmHg, I would round up or down and report the integer, not the two decimal points. The authors have eliminated the comparison to an IPF group, which I think is a major improvement, and aids the clarity of the manuscript. However, as a result, the Discussion section needs to be edited. For example, on page 11 "Regarding prognosis, CPFE patients showed poor survival similar to that of IPF patients in our cohort." Since the authors are not presenting data on comparison with IPF patients, I would eliminate this sentence/paragraph. Similarly, on page 12/25 "In conclusion, our CPFE patients showed poor survival compared to that of IPF patients." This needs to be edited in light of the other changes in the manuscript.
RESULTS & CONCLUSIONS	See above notes regarding elimination of text comparing CPFE with IPF patients in Discussion section, since the paper now just reports on CPFE patients.

VERSION 2 – AUTHOR RESPONSE

Dear Reviewer
Thank you for your kind and helpful advice for my manuscript.
Based on your advice, I changed my several sentences.
Regarding limitation, I changed appropriate sentence as you mentioned.
Result section, I changed correct word as you pointed out.
Regarding table 1 including abbreviation , I corrected as you mentioned.
In terms of systolic pulmonary artery pressure, I recalculated and described in table 1.
Regarding discussion part, I revised as you pointed out.
Thank you for your informative advice and taking much time for reading our manuscript.