PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Prognostic factors for acute exacerbation of idiopathic pulmonary fibrosis: protocol for a systematic review and meta-analysis
AUTHORS	Kamiya, Hiroyuki; Panlaqui, Ogee

VERSION 1 - REVIEW

REVIEWER	Argyris Tzouvelekis First Academic Respiratory Department, National and Kapodistrian University of Athens, Greece
REVIEW RETURNED	26-Dec-2018

GENERAL COMMENTS	Thank you for allowing me to review the paper by. This is a systematic review that describes the rationale and the methodology of a future systematic review or metanalysis of prognostic factors in IPF. This is an article that adds limited knowledge to the current literature. The article is narrative with extending methodological details that are of limited clinical relevance. The topic related to the systematic review is prognostic factors of AEx-IPF. Authors decided to focus only on clinical indicators. I certainly do not agree with this approach as there have been some interesting studies (Collard et al 2010, Konishi et al. 2009) showing that plasma biomarkers including (RAGE, defensins, IL-6, coagulation proteins) can differentiate stable from progressive IPF. In addition, current definition of AEx is somewhat flawed as some of criteria used to define AEx cannot be easily applied in the clinical setting especially when it comes to confidently exclude infections (use of invasive microbiological assessment is often limited considering the severity of acutely deteriorating patients. Thus the incidence of acute exacerbations varies in many studies (ie STEP-IPF) if stringent adherence to the 2007 or 2016 criteria are applied. In addition in many studies there is no centralized adjudication and therefore major discrepancies regarding incidence of acute exacerbation are reported between cohort and registry studies. Furthermore, even current clinical definition cannot reliably differentiate between events of disease progression and exacerbation. To this end, a systematic review on prognostic factors for AEx based on old and recent studies using different definition criteria is somewhat outdated and can be misleading given the considerable heterogeneity of studies included in the analysis.

REVIEWER	Ferran Morell Vall d´Hebron Institut de recerca
REVIEW RETURNED	18-Jan-2019

GENERAL COMMENTS	When accepting the revision, I thought that it was a compilation of the studies already carried out and published, but I have verified that it is a bibliographic study project of the IPF exacerbations. It is a very methodological project that I as a clinical doctor can hardly judge. In any case, I make some recommendations to the authors This is a study project of bibliographic review of all published studies of IPF exacerbations. In my opinion the project is well written and complies with the conditions required for this type of revision. I only suggest to the authors that they write in a way easier to understand the second paragraph of page 6 (strengths and limitations) since I do not know if it is a strength or limitatioon. Reference number 2 seems very old and the authors could look for a more recent one. On page 13 in Data items, according to my criteria it would be very interesting to include a search for potential or proven etiologies.

REVIEWER	Paolo Eusebi University of Perugia
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	Revise Methods and Analysis section in the abstract. The sentence “Acute exacerbation of IPF is eligible for the review.” Is simplistic and without explanation. This section should mention only methodology: search strategy, definition of outcomes, statistical analysis and so on. Furthermore, “subgroup and sensitivity analyses” are expected to inform clinical practice and drawn robust conclusions, respectively, rather than just “identify source of heterogeneity”. The timeline section should be removed Prognostic factors should be detailed. Please, remove the following paragraph “Although therapeutic intervention can affect the prognosis of the disease, it is excluded from potential prognostic factors as the effect of treatment on prognosis will be confounded by a number of factors and thus difficult to be evaluated in prognostic studies.[20]” Planned activities in the protocol should be reported as future. For example, “Two reviewers (H.K. and O.M.P.) independently examine” should be replaced with “Two reviewers (H.K. and O.M.P.) will independently examine”. The section “Candidate of prognostic factors” should be entitled as “Candidate prognostic factors”. The section should be rewritten for increasing transparency. Are the authors sure that an unlimited screening of all the potential prognostic factors is an effective choice? Would it be preferable to restrict the space of candidate prognostic factors? The section “metabiases” should be entitled “reporting bias” Discussion should be shortened English should be considerably improved.

VERSION 1 – AUTHOR RESPONSE

Reply to reviewer1

1. “Authors decided to focus only on clinical indicators. I certainly do not agree with this approach as there have been interesting studies showing that plasma biomarkers can differentiate stable from progressive IPF.”

We totally agree with this opinion and thus it was stated that “Any clinical information related to demographics, symptoms, pulmonary functions, radiological findings and laboratory tests will be considered as potential prognostic factors for AE of IPF, provided they have been investigated for their association with the outcomes of the disease” (on the last paragraph on page9). Besides, an example of prognostic factors was described in the same section, which included a potential biomarker.

2. “Current definition of AEx is somewhat flawed as some of criteria used to define AEx cannot confidently exclude infections (use of invasive microbiological assessment is often limited considering the severity of acutely deteriorating patients). Thus the incidence of acute exacerbations varies in many studies”.

We totally agree with this opinion. We think that an updated international guideline 2016 was intended to address this issue and accordingly heterogeneity derived from the thoroughness of implementing diagnostic procedures to exclude infectious agents may be alleviated. However, as the reviewer pointed out, there may be a significant difference in the incidence or prognostic factors for AE of IPF depending on whether it was diagnosed based on the previous criteria or the current one although the outcome is reported to be similar. Therefore, we planned to conduct subgroup analysis to identify any difference between those two diagnostic criteria. (in “Heterogeneity between studies” section of page16)

3. “In many studies there is no centralized adjudication and therefore major discrepancies regarding incidence of acute exacerbation are reported between cohort and registry studies.”

We totally agree with the opinion that in many studies there is no centralized adjudication. We think centralized adjudication is beneficial in a multi-institutional study as it could reduce diagnostic variance between institutions. However, subjects in one study with centralized adjudication may be different from those of another study with centralized adjudication. This is because these two studies implement their own centralized adjudication system and it is usually the case. Therefore, we are not sure how important centralized adjudication will be when multiple studies with centralized adjudication are compared. By contrast, expertise may be more important to make a correct diagnosis and minimize diagnostic discrepancies. All these issues will be evaluated by risk of bias assessment in individual studies and clinical heterogeneity between studies was planned to be assessed by subgroup analysis and sensitivity analysis.

4. “Even current clinical definition cannot reliably differentiate between events of disease progression and exacerbation.”

We believe “acute exacerbation of IPF” is widely recognized as a unique phenomenon that is different from ordinary deterioration of the disease. This will be understood from the fact that diagnostic criteria of this condition was released by international societies and this phenomenon has also been employed as an important outcome in a major clinical trial of a new promising therapeutic agent (Eur Respir J 2017;49:1601339 (INPULSIS trial)).

5. “A systematic review on prognostic factors for AEx based on old and recent studies using different definition criteria is somewhat outdated and can be misleading given the considerable heterogeneity of studies included in the analysis.”

We agree with the opinion that heterogeneity can be caused by different diagnostic criteria. Ccases diagnosed based on the previous guideline in 2007 correspond to idiopathic cases by the new guideline in 2016. Therefore, we planned subgroup analysis by the aetiology of the disease (page16). Besides, a variation of the results between studies is one of the main motives for a systematic review to clarify current evidence. A recently published “risk factors for acute exacerbation of idiopathic pulmonary fibrosis: a systematic review and meta-analysis (Clin Respir J 2018;12:1084-92)” may indicate that this proposed systematic review is not out of date.

Reviewer2

1. “I only suggest to the authors that they write in a way easier to understand the second paragraph of page 6 (strengths and limitations).”

Following the comment, it was rephrased. (1st part on page5)

2. “Reference number 2 seems very old and the authors could look for a more recent one.”

Following the comment, it was replaced by a recent one.

3. “In Data items, it would be very interesting to include a search for potential or proven etiologies.”

Following the comment, “potential aetiology of disease” was included as a potential aetiology. (Data items section on page13)

Reviewer3

1. Revise Methods and Analysis section in the abstract.

“Acute exacerbation of IPF is eligible for the review” is simplistic and without explanation.

Following the comment, it was described in more details. (1st and 4th sentence in Methods and Analysis section in the abstract on Page3)

“This section should mention only methodology.

Following the comment, it was focused on only methodology. (Methods and Analysis section in the abstract on Page3)

“’Subgroup and sensitivity analyses’ are expected to inform clinical practice and draw robust conclusions, respectively, rather than just ‘identify source of heterogeneity’”.

Following the comment, it was rephrased as such. (line 3-5 in Methods and Analysis section in the abstract on Page4)

2. The timeline section should be removed.

Following the comment, it was removed. (Page8)

3. Prognostic factors should be detailed.

Following the comment, it was described in more details. (last sentence on Page9)

4. Remove the following paragraph, “Although therapeutic intervention can affect the prognosis of the disease…”

Following the comment, it was removed. (Page10)

5. Planned activities in the protocol should be reported as future.

Following the comment, it was revised as such throughout this manuscript.

6. The section “”Candidate of prognostic factors” should be entitled as “Candidate prognostic factors” and the section should be rewritten for increasing transparency.

Following the comment, it was rephrased as such and rewritten to increase transparency. (“Candidate prognostic factors” section on Page13)

7. “Are the authors sure that an unlimited screening of all the potential prognostic factors is an effective choice? Would it be preferable to restrict the space of candidate prognostic factors?”

We agree with this opinion. However, this is an explanatory study for prognostic factors of the disease, which should be the first step to establish a prediction model in future research. Besides, we believe through our previous experience that this type of study is feasible. (Kamiya H, et al. BMJ Open 2018;8:e023998)

8. The section “metabiases” should be entitled “reporting bias”.

Following the comment, it was rephrased as such. (on Page16)

9. English should be considerably improved.

Following the comment, we asked a native English speaker working in the same institution to edit English of this manuscript and it was acknowledged appropriately.

VERSION 2 – REVIEW

REVIEWER	Paolo Eusebi University of Perugia, Italy
REVIEW RETURNED	10-Apr-2019

GENERAL COMMENTS	The authors addressed all the issues and I have no further comments.