

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A systematic review and meta-analysis of prognostic factors of acute exacerbation of idiopathic pulmonary fibrosis
AUTHORS	Kamiya, Hiroyuki; Panlaqui, Ogee

VERSION 1 – REVIEW

REVIEWER	Tzouveleakis Argyrios First Academic Department of Pneumonology, Hospital for Diseases of the Chest, "Sotiria", Medical School, National and Kapodistrian University of Athens, Athens, Greece
REVIEW RETURNED	16-Nov-2019

GENERAL COMMENTS	<p>This is a well written systematic review and meta-analysis. The statistical analysis is proper and the results are well presented. However, i think that references are limited and should be expanded as there are key subjects that are missing or in need of more extensive presentation.</p> <p>1) I would suggest you to highlight the presence of pulmonary hypertension as a risk factor for acute exacerbation and add the following references</p> <p>Karampitsakos et al Pulm Pharmacol Ther. 2018 Pulmonary hypertension in patients with interstitial lung disease.</p> <p>Judge et al ERJ 2012 Acute exacerbations and pulmonary hypertension in advanced idiopathic pulmonary fibrosis</p> <p>2) I would suggest you to address the role of surgery (especially in patients with IPF and lung cancer) as a risk factor for exacerbation. I provided some refences that you should add to show the role of surgery and radiation(for patients with IPF and lung cancer) as a risk factor for acute exacerbation. In the discussion section, you may provide safety precautions in such procedures.</p> <p>Karampitsakos et al Pulm Pharmacol Ther 2017 Lung cancer in patients with idiopathic pulmonary fibrosis Sato et al J Thorac Cardiovasc Surg 2015 Long-term results and predictors of survival after surgical resection of patients with lung cancer and interstitial lung diseases. Fujimoto et al Ann Thorac Surg 2003 Operation for Lung Cancer in Patients With Idiopathic Pulmonary Fibrosis: Surgical Contraindication?</p>
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	<p>3) I would suggest just adding in your concluding remarks (where you mention the need for further research) the role of monocytes. Increased monocyte count has been recently presented as a cellular biomarker for poor outcomes. You should mention that future studies should investigate their role in acute exacerbation.</p> <p>Scott et al The Lancet Respiratory Medicine 2019 Increased monocyte count as a cellular biomarker for poor outcomes in fibrotic diseases: a retrospective, multicentre cohort study</p>
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REVIEWER	Qiao Ye Beijing Chao-Yang Hospital, Capital Medical University, China
REVIEW RETURNED	07-Dec-2019

GENERAL COMMENTS	<p>This article provides a systematic review and meta-analysis of prognostic factors of acute exacerbation of idiopathic pulmonary fibrosis (IPF). Thirty articles with potential prognostic factors for all-cause mortality out of a total of 6763 articles were analyzed. The main limitation is that the quality of evidence of this review is low or very low for all prognostic factors by the GRADE system. The majority of articles enrolled were case-control or retrospective study. Therefore, the findings should be interpreted cautiously due to the low evidence level. The limitations should be discussed fully in the article.</p>
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REVIEWER	Masanori Nojima The University of Tokyo
REVIEW RETURNED	20-Jan-2020

GENERAL COMMENTS	<p>Comment to the authors.</p> <ol style="list-style-type: none"> 1. In the e-Table 1, study design for several publications seemed to be incorrect, especially in studies annotated with case-control study. For example, Abe 2012, Kataoka 2015, Song 2011, and Tsushima 2014 seem not to be case-control studies. These are basically cohort studies and some of them might have a historical control group (Kataoka 2015). Nikaido 2018 is based on a case-control study, but the part of the risk assessment of death event was considered based on cohort design. Please re-review study design of all studies included. 2. Please describe why overall quality of most studies is very low, and how the poor quality of the studies affects the interpretation of the review. 3. Since this meta-analysis is based on univariate analysis of observational studies, an influence of confounding is basically critical. Please discuss the influence of confounding for each outcome-factor association. If the authors consider the risk factors just as biological marker, the influence of confounding is not so critical. However, since the oxygen therapy is an intervention (Figure 8) and the result can be critically biased by confounding, meta-analysis based on univariate analysis is not acceptable. Meta-regression is possible option for this type of study (meta-analysis for observational studies). In addition, the results can be combined even if the different statistics, 4. Please describe covariates for each multivariate analysis (e-Table 5), and the results of multivariate analysis should be more focused on. It is more important for assessment of the risk (especially for interventions) compared to the results without
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	<p>adjustment. If these were adjusted for the same confounders or if adjustment is considered enough across the studies, the results (HR, OR, or difference) can be combined. As described above, meta-regression is an alternative of multivariate analysis.</p> <p>5. In the abstract, the authors repeatedly describe about the quality problem. However, if potential influence of confounding was not critical for some outcome-factor associations, those results could be more reliable than authors considered. The reliability of the results should be evaluated separately for each factor. The description should not be too negative than necessary.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1 The reviewer commented, “I would suggest you to highlight the presence of pulmonary hypertension as a risk factor for acute exacerbation and add the following references.”

2 The reviewer commented, “I would suggest you to address the role of surgery as a risk factor for exacerbation. I provided some references that you should add to show the role of surgery and radiation as a risk factor for acute exacerbation. In the discussion section, you may provide safety precautions in such procedures.”

As the reviewer pointed out, mechanical procedures such as surgery and radiation can be a risk factor for acute exacerbation (AE) of IPF and strongly affect the prognosis of IPF. However, they will not be a prognostic factor for AE of IPF because no patients will undergo those procedures after they developed AE of IPF. This was confirmed in this review where mechanical procedures were not identified as a prognostic factor for AE of IPF.

Similarly, as the reviewer pointed out, pulmonary hypertension (PH) can be a risk factor for AE of IPF and strongly affect the prognosis of IPF. However, it was not identified as a prognostic factor for AE of IPF in this review. This may be because PH at baseline is not necessarily related to the severity of the insult causing AE, which seems to be directly associated with the prognosis of AE of IPF.

Following the reviewer’s comment, all of these issues were additionally described in the discussion section with references that were suggested by the reviewer (from the last 5th line on page 14 (in the latter one third of the 3rd paragraph in the discussion section)).

3 The reviewer commented, “I would suggest just adding in your concluding remarks (where you mention the need for further research) the role of monocytes. Increased monocyte count has been recently presented as a cellular biomarker for poor outcomes. You should mention that future studies should investigate their role in acute exacerbation.”

Following the comment, it was mentioned in the last two sentences in the discussion section on page 16.

Reviewer 2

The reviewer commented, “Therefore, the findings should be interpreted cautiously due to the low level evidence. The limitations should be discussed fully in the article.”

Following the comment, the limitations of this study were more extensively described in the 4th and 5th paragraph in the discussion section on page 15-16. Almost the entire of the 4th paragraph and the one third of the 5th paragraph were additionally described.

Reviewer 3

1 The reviewer commented, "In the e-Table 1, study design for several publications seemed to be incorrect. Please re-review study design of all studies included."

Following the comment, study design of all studies were reviewed and made amendments to some studies (e-Table 1).

2 The reviewer commented, "Please describe why overall quality of most studies is very low and how the poor quality of the studies affects the interpretation of the review."

Following the comment, risk of bias assessment in individual studies was fully explained in the "risk of bias" section on page 9. In the "Quality of evidence" section on page 13, it was explained in more details how these study limitations (risk of bias) led to low or very low level of evidence generated in this study. In addition, the issue caused by this low evidence level was discussed as the 3rd limitation in the last paragraph of the discussion section on page 16.

3 The reviewer commented, "Since this meta-analysis is based on univariate analysis of observational studies, an influence of confounding is basically critical. Please discuss the influence of confounding for each outcome-factor association."

Following the comment, the influence of confounders for each outcome-factor association was additionally described from the 8th line in the 4th paragraph in the discussion section on page 15.

The reviewer also commented, "If the authors consider the risk factors just as biological marker, the influence of confounding is not so critical. However, since the oxygen therapy is an intervention (figure 8) and the result can be critically biased by confounding, meta-analysis based on univariate analysis is not acceptable."

As the reviewer pointed out, the intervention will be affected by lots of confounders and thus it is desirable to seek the effect of treatment in a randomized controlled trial rather than observational studies. However, "treatment before AE" such as "oxygen therapy before AE" in this review is not an intervention to treat the disease (AE of IPF) but considered as a baseline feature. Accordingly, it could not be confounded by other clinical information that was collected at the time of the development of the disease or later. It is, of course, possible that "treatment before AE" was affected by other baseline features such as baseline pulmonary function because it can be reasonably assumed that subjects with lower pulmonary function were more likely to have needed oxygen therapy. However, this baseline pulmonary function does not necessarily affect the mortality of AE because the outcome of the disease may be more closely related to the severity of the insult when it developed rather than baseline pulmonary state. In this context "treatment before AE" may not be confounded by baseline pulmonary function either. Therefore, we believe that it is not unacceptable to combine the univariate results of "treatment before AE". Furthermore, there was no heterogeneity in the result of meta-analysis for "oxygen therapy before AE" (Figure 8). This indicates that the effect of this factor seemed to be uniform between studies regardless of their differences in subjects or methodologies (meaning that confounding effect, if any, was similar for all studies) although its true effect should have been sought in a further statistical analysis such as meta-regression, which was difficult due to the small number of studies in this review.

The reviewer commented, "Meta-regression is possible option for this type of study."

We agree with this suggestion but found that it was difficult due to the small number of studies. Therefore, it was explained as such (from the 8th line in the 4th paragraph in the discussion section on page 15).

4 The reviewer commented, “Please describe covariates for each multivariate analysis (e-Table 5)”

Following the comment, the new heading “Adjusted factors in multivariate analysis” was created to explain adjusted factors in the result section on page 12. “Adjusted factors” were also described in a new column in e-Table 5.

The reviewer also commented, “the results of multivariate analysis should be more focused on.”

Following the comment, univariate results that were previously described in the Abstract were replaced by the results of multivariate analysis. In addition, a comparative description between univariate and multivariate results was added at the last sentence regarding the effect estimates of each prognostic factor in the result section on page 10-12. Furthermore, it was mentioned that the effect estimates generated from pooled analysis of univariate results were reliable because they were consistent with that of multivariate results (from the 4th line in the 1st paragraph in the discussion section on page 13 and from the last 10th line in the 4th paragraph in the discussion section on page 15). Finally, a limitation of multivariate results in this review was also discussed (from the last 6th line in the 4th paragraph in the discussion section on page 15).

5 The reviewer commented, “In the abstract, the authors repeatedly describe about the quality problem. However, if potential influence of confounding was not critical for some outcome-factor associations, those results could be more reliable than authors considered. The description should not be too negative than necessary.

Following the comment and given the speculation that the influence of confounders for each outcome-factor association was not serious (this was also additionally discussed following the reviewer’s suggestion in the 4th paragraph on page 15), the conclusion of the abstract and the main text was changed a bit so that it would not be too negative.

VERSION 2 – REVIEW

REVIEWER	Argyrios Tzouvelekis University of Athens
REVIEW RETURNED	29-Mar-2020

GENERAL COMMENTS	Authors succinctly addressed all my concerns. I have no further comments to add
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REVIEWER	Qiao Ye Department of Occupational Medicine and Toxicology, Clinical Center for Interstitial Lung Diseases, Beijing Chaoyang Hospital, Capital Medical University, Beijing 100020, China
REVIEW RETURNED	06-Mar-2020

GENERAL COMMENTS	The authors replied the comments and surely improved the manuscript.
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REVIEWER	Masanori Nojima The Institute of Medical Science, The University of Tokyo.
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REVIEW RETURNED	15-Mar-2020
GENERAL COMMENTS	The author's responses are sufficient as answers to my comments, and the manuscript has been modified appropriately enough. There is no further comment.