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TITLE PAGE

Title

Prognostic factors for acute exacerbation of idiopathic pulmonary fibrosis: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Idiopathic pulmonary fibrosis (IPF) is chronic fibrosing interstitial pneumonia of unknown aetiology. Acute exacerbation of IPF is a phenomenon that demonstrates abrupt deterioration beyond its usually expected disease course without any apparent causes. This condition is noted to be a major cause of death of the disease with 30 days-mortality of 40%. However, there is still a variation in clinical course of this devastating condition. Although some previous studies investigated diverse clinical information that could be related to the prognosis of the disease, they have yet to be confirmed. Therefore, the aim of this systematic review is to clarify prognostic factors for acute exacerbation of IPF.

Methods and analysis

Acute exacerbation of IPF is eligible for the review. Prognostic factors are any clinical information that can be related to the prognosis of the disease. The primary outcomes are short-term all-cause and pulmonary-cause mortality. The secondary outcomes include the proportion of discharge from the hospital, long-term mortality and health-related quality of life. Primary studies of any type except for a case report or case series are included. Two reviewers search electronic databases such as Medline and

EMBASE from inception to the latest and extract data independently. A risk of bias in individual studies is assessed by the Quality in Prognostic Studies tool. Meta-analysis is sought to be conducted only for univariate data if at least three studies report the effect of a specific prognostic factor with the same statistics while multivariate results are reported qualitatively. Subgroup and sensitivity analyses are considered to identify the source of heterogeneity. The Grades of Recommendation, Assessment, Development and Evaluation method is applied to evaluate the evidence level of each prognostic factor.

Ethics and dissemination

There is no concerning ethical issue. The result will be reported in a peer-reviewed journal.

PROSPERO registration

CRD 42018106172

Strengths and limitations of this study

- The first systematic review addressing prognostic factors for acute exacerbation of idiopathic pulmonary fibrosis, which will be the foremost evidence for this unpredictable and critical condition as conducting a large-scale cohort study may be difficult.
- A focus on relevant clinical information that is commonly used in clinical practice and a presentation of the result of both univariate and multivariate analysis.
- A potential difficulty in combining the result due to a small number of studies and substantial heterogeneity.

INTRODUCTION

Rationale

Idiopathic pulmonary fibrosis (IPF) is chronic fibrosing interstitial pneumonia of unknown aetiology and the most common type among idiopathic interstitial pneumonias (IIPs).[1] It is a progressive disease and demonstrates poor prognosis with an average survival of two to three years after the diagnosis.[2] A previous study reported that most patients die of respiratory failure as a consequence of its progressive disease course or

other complications such as lung cancer, pneumonia, pulmonary embolism and cardiac failure.[3] However, after a rapid deterioration of the disease beyond its usually expected clinical course was recognized as an uncommon phenomenon,[4] this medical condition was termed as acute exacerbation of IPF and demonstrated to be a major cause of death of the disease.[5] In early reports it was diagnosed by excluding known causes of disease deterioration, in particular, eliminating potentially causative infectious agents was emphasized [6] whereas the latest international guideline proposed a new diagnostic criteria of acute exacerbation of IPF, which only focused on worsening symptoms and newly emerging bilateral radiological opacities rather than the aetiology of the exacerbation.[7] Regardless of the aetiology of this phenomenon, it is noted to be fatal with 30-days mortality of 40% [8] and 1-year mortality of over 80%,[9] which is mostly because there has been no effective treatment.[10] Nonetheless, there is still a variation in clinical course of the disease and some patients survive this devastating condition.[11] In addition, recent data suggested a promising preventive effect of some new therapeutic agents.[12] Therefore, it is important to elucidate prognostic factors of this intractable disease to inform anticipated consequences and plan the best therapeutic option tailored to an individual patient. Although several studies investigated diverse clinical information that could be related to the prognosis of acute exacerbation of IPF,

most reports were based on a small number of participants in a single institution and thus may be anecdotal.[13-14] In addition, it seems unfeasible to conduct a large-scale cohort study to compensate for this shortcoming of previous research because unpredictable and lethal clinical course might prevent a recruitment of a sufficient number of participants.[15] Therefore, this systematic review and meta-analysis was designed to clarify prognostic factors for acute exacerbation of IPF and the result of this study will be the best evidence currently available for this medical condition. As the aim of this article is to report the rationale and the methodology of a future systematic review of prognostic factors for acute exacerbation of IPF to ensure the transparency and the integrity of research, any result expected to be obtained from this study is not presented in this report.

Objective of the review

The aim of this systematic review is to clarify prognostic factors for acute exacerbation of IPF.

METHODS AND ANALYSIS

Patient and public involvement

There is no patient and public involvement in the whole process of conducting this research.

Registration

This protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews) [16] (CRD42018106172).

Timeline

This study has yet to be initiated except for a pilot search and constructing search terms. A full search is scheduled to be conducted on the 1st of February 2019 and may be updated depending on the date of publication of this protocol paper.

Eligibility criteria

Participants

Patients with acute exacerbation of IPF are eligible for this review. IPF will be diagnosed based on previously published international guidelines for diagnosis of the disease such as an official ATS/ERS/JRS/ALAT statement.[17] Acute exacerbation of IPF is diagnosed based on the latest international guideline, which consists of previous or concurrent diagnosis of IPF, acute worsening or development of dyspnoea typically

within less than one month, newly emerging bilateral ground glass opacity (GGO) and/or consolidation superimposed on a background radiological change consistent with usual interstitial pneumonia (UIP) on high resolution computed tomography (HRCT) scans.[7] Although it is necessary to rule out cardiac failure or fluid overload as a cause of deterioration, excluding infections or other potential triggers is no longer required, which allows this condition to be classified into triggered or idiopathic cases. Previously proposed diagnostic criteria, which emphasized the exclusion of pulmonary infection using endotracheal aspirate or bronchoalveolar lavage,[6] is considered as corresponding to idiopathic cases in this new definition.[7] Therefore, patients diagnosed by this previous criteria are also eligible. A rapid progressive form of interstitial pneumonia at the first presentation is also included if it is accompanied by radiological and/or pathological UIP without known causes such as connective tissue disease (CTD) [18] and drug toxicity.[19] Patients with multiple episodes of acute exacerbation are not excluded although only the first event will be considered for further analysis.

Exposure

Any clinical information including demographics, symptoms, pulmonary functions, radiological findings and laboratory tests is considered as potential prognostic factors if they are investigated for their association with the outcomes. 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]

Outcomes and prioritization

The primary outcomes are short-term all-cause and pulmonary-cause mortality, which are defined as in-hospital or 30 days-mortality. The secondary outcomes include the proportion of discharge from the hospital and long-term all-cause mortality, which are determined at 90 days, 6 months or 1 year after the diagnosis of the disease or start of treatment. Long-term health-related quality of life is also considered as the secondary outcome, which will be evaluated by a validated tool such as the 36-Item Short Form Health Survey (SF-36).[21]

Studies

Any type of primary studies excluding a case report or case series is included in the review if it describes the association of potential prognostic factors with pre-defined

outcomes and quantitative data is presented. If a study summarizes the result narratively without quantitative data, it is ineligible. Editorials, letters and review articles are excluded. Conference proceedings and reports with only abstracts are also excluded due to concerns of insufficient information. Only English articles are eligible and publication before 2002 is excluded as it is the year when the original form of current classification system of IIPs was first reported.[1]

Information sources

Medline (via Ovid 1946-)

EMBASE (via Ovid 1974-)

Science Citation Index Expanded (via Web of Science 1900-)

Google Scholar

Search strategy

Two reviewers (H.K. and O.M.P.) search the Medline and the EMBASE using subject headings and text words of study population, and their synonyms such as ‘idiopathic pulmonary fibrosis’ and ‘acute exacerbation’, which are determined referring to reviews of a similar subject identified in the Cochrane Database of Systematic Reviews (CDSR).

They are combined with the methodology filter of prognosis, which is modified to be fitted with each electronic database (e-Appendix).[22-23] The Science Citation Index Expanded is also searched using terms adapted from the search of the Medline and the EMBASE. These electronic databases are searched from inception through the date of publication of this protocol paper. Reference lists of eligible studies and relevant review articles are also hand-searched. Grey literature is sought to be identified through Google Scholar.[24]

Study records

Data management

All retrieved articles are processed through EndNote X7 whereby duplicates are identified and removed. All extracted data are stored in a Microsoft Excel spreadsheet.

Study selection and data collection process

Two reviewers (H.K. and O.M.P.) independently examine titles and abstracts of all retrieved articles after removing duplicates and select eligible reports. If the same research group conducted multiple studies with the same outcome and the same prognostic factor, a report with the largest sample size is selected. Data are extracted by the same reviewers based on a data extraction form, which is modified from a sheet

included in a previously published protocol paper of prognostic factor review.[25] An uncertainty or disagreement encountered through all of these processes is resolved through discussion between the reviewers.

Data items

The following data is extracted: the first author name, publication year, study location, study design, the number of participants and their demographic features, follow-up lengths, potential prognostic factors, the outcomes, counts of the outcome, methods for statistical analysis, summary statistics and items associated with a risk of bias.

Candidate of prognostic factors

After collecting data from all eligible studies, the items reported by at least three studies proceed with further analysis as potential prognostic factors and the studies reporting those factors are designated as final articles/studies that constitute this review.

Risk of bias in individual studies

The Quality in Prognostic Studies (QUIPS) tool is applied to assess a risk of bias in individual studies. It consists of six domains. Each domain is rated as either high, moderate or low risk of bias and the overall risk of bias is based on a total rating of all

domains. For example, a study showing a low risk of bias in all domains is deemed as low risk of bias.[26]

Statistical analysis

Summary statistics

When the outcome is binary, the effect size will be presented as the hazard ratio (HR) by the Cox proportional hazards model [27] or the odds ratio (OR) by the logistic regression model.[28] If the outcome is only presented by the Kaplan-Meier survival curve or the log rank test, the HR is re-calculated as previously reported.[29] If both the HR and the log rank test are presented, the former result is prioritized. The OR or the risk ratio (RR) may be calculated manually based on counts of the outcome in two comparative groups if it is not available directly. Where the outcome or prognostic factors are continuous, the effect size may be presented as the absolute values such as the mean difference by the unpaired Student's t test and the difference of the median by the Wilcoxon rank sum test.

Data synthesis

The results are pooled if the association of a specific potential prognostic factor with an outcome is presented by the same summary statistics in three or more studies. The

binary outcome is summarized by the OR, RR or HR separately while the continuous outcome is combined by either the mean difference or the standardized mean difference, which is calculated as Hedge's g,[30] depending on whether the outcome is presented with the same unit. When the median and the range or interquartile range are presented for continuous variables, they are converted to the mean and the standard deviation, respectively, using a formula reported by a previous study.[31] Only unadjusted estimates of the effect of potential prognostic factors are combined while that estimated from multivariate models is described qualitatively as the adjustment in the model will be diverse and pooling these data can be misleading. If meta-analysis is feasible, it is conducted by a random-effects model with the DerSimonian and Laird method [32] using the statistical software, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The 95% prediction interval will be calculated if combined results are statistically significant and there is heterogeneity between studies.[33] Statistical significance is set at p-value <0.05. If combining data is inappropriate due to a small number of studies or substantial clinical or methodological variability between studies, the result is reported qualitatively.

Heterogeneity

Between-study variance is estimated as the Tau square and assessed by the Q statistics and the I square. Statistical significance is set at p-value <0.1 because of low power of the test and the magnitude of heterogeneity is interpreted as not important (0 to 30%), moderate (30 to 50%), substantial (50 to 70%) and considerable (70 to 100%).[30] To clarify the source of heterogeneity subgroup analysis is considered based on the definition of acute exacerbation of IPF (idiopathic or triggered), study location (Asia and non-Asia) and sample sizes (less than 50 and 50 or more). Sensitivity analysis will also be conducted focusing on studies with a low risk of bias alone.

Metabiases

Small study bias such as publication bias is examined by both graphical asymmetry of a funnel plot and the Egger's test [34] if ten or more studies are available that report the effect of a specific potential prognostic factor. Statistical significance is set at p-value <0.1 because of low power of the test. If publication bias is suspected, an adjusted summary effect is estimated by the trim and fill method considering the presumptive number of missing studies.[35]

Confirmation of prognostic factors

Prognostic factors are finally determined based on the consistency and statistical significance of the results. If the effect of a potential prognostic factor is in the same direction across all studies and statistically significant in the majority of studies (≥75%) using both univariate and multivariate analyses, it is deemed as a prognostic factor. Combined data in univariate analysis is regarded as one study in the determination of prognostic factors.

Confidence in cumulative evidence

The level of evidence obtained from this systematic review is assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system. It is applied to both univariate and multivariate results of finally determined prognostic factors.[36]

ETHICS AND DISSEMINATION

There is no concerning ethical issue in conducting this systematic review as it is based on published data with no access to any information that can identify an individual patient. The result of the review will be formatted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [37] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement.[38] A

Microsoft Excel spreadsheet containing all data, which is extracted from included studies and becomes the basis for the analysis, may be provided from the corresponding author on a reasonable request or stored in a digital repository such as Dryad after the result of the review is published in a journal so that the original data could be open accessed.

DISCUSSION

This article has reported the rational and the methodology of a future systematic review of prognostic factors for acute exacerbation of IPF. As a systematic review of prognostic factor studies is methodologically more complicated than that of intervention,[39] a detailed description of the methodology beforehand is important to ensure the integrity and transparency of research in this field although a number of studies are still conducted without it.[40]

There are a couple of methodological limitations that need attention to appropriately interpret the findings of this research. Firstly, prognostic factors are to be determined based on the result of multivariate analysis, which is summarized qualitatively in this review. This decision may dismiss the advantage of a systematic review that false negative results due to a small sample size will be resolved by statistical synthesis [41]

and thus some potential prognostic factors may possibly be misclassified as non-prognostic. However, pooling multivariate data can be misleading as adjusted variables and the final model will be diverse between studies [42] although it is important to consider the influence of confounders in prognostic studies since baseline characteristics of comparative groups will usually be different and the conclusion is likely to be confounded by these factors.[43] Therefore, we decided to describe the result of multivariate analysis qualitatively instead of seeking combined summary estimates. In addition, although the consistency and statistical significance of the results were adopted as the criteria to determine prognostic factors, they were arbitrary set and thus some potential prognostic factors may also be disregarded due to this decision. However, one of the major roles of a systematic review of prognostic factor studies would be exploring all clinical information possibly related to the prognosis of the disease rather than discovering a specific prognostic factor.[44] Therefore, we suggest that all potential prognostic factors should further be examined for their clinical significance in a well-designed future research even if they are deemed non-prognostic in this research. The findings of this review also need to be updated with additional reports in the future.

Secondly, eligible studies for this review may be clinically or methodologically diverse. They will be composed of a mixture of both idiopathic and triggered cases of acute exacerbation of IPF, which will be diagnosed using either previous (narrow) [6] or current (broad) diagnostic criteria.[7] In addition, the definition of an outcome may also be varied between studies. Mortality may be evaluated at a various point of time such as in-hospital, 30 days, 90 days and one year after the diagnosis of the disease or start of treatment. Furthermore, the effect of continuous factors may be summarized by dichotomization using a different cut-off point, which will be arbitrarily set by each research group.[45] These clinical and methodological variability together with likely a small number of eligible studies may interrupt statistical synthesis of data, which may undermine the value of a systematic review due to the same reason as mentioned above. However, meta-analysis is only one aspect of this type of research and qualitative analysis of the result is also valuable and meaningful.

Finally, we decided to focus on any clinical information reported by at least three studies to select potential prognostic factors for further analyses because they might represent clinically relevant factors commonly used in clinical practice and thus the applicability of the findings would be enhanced. However, some of the factors reported by only one or two studies might still be related to the prognosis of the disease and thus

this definition of potential prognostic factors might deprive the opportunity for those factors to be further investigated.

It is well recognized that meta-analysis of prognostic factor studies is challenging [39] and there are some potential methodological limitations in our research project. However, we believe that this systematic review would clarify current evidence of prognostic factors for acute exacerbation of IPF and the integrity and transparency of the research will be ensured with a support of this protocol paper.

CONCLUSIONS

The rationale and methodology of a future systematic review and meta-analysis of prognostic factors for acute exacerbation of IPF were described. This research may involve some potential methodological limitations that are often encountered in a systematic review of prognostic factor studies. However, the result of the review would present the best evidence currently available in this research area with a support of this protocol paper.

AUTHORS' CONTRIBUTIONS

Hiroyuki Kamiya (H.K) conceived this research project and planned the entire methods to undertake it. He also wrote the manuscript of this protocol. H.K will be the guarantor of the content of the review including data analysis.

Ogee Mer Panlaqui (O.M.P) made contributions in conceiving this research project and planning literature search strategy and data extraction. He also made additions and revisions to the draft of this manuscript.

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COMPETING INTERESTS

There is no conflict of interests to declare for all authors in this protocol paper of a future systematic review.

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e-Appendix: Search terms for Ovid Medline

1 exp Lung Diseases, Interstitial/

2 exp Idiopathic Pulmonary Fibrosis/

3 (interstitial adj3 lung adj3 disease$).mp.

4 (interstitial adj3 pneumoni$).mp.

5 (pulmonary adj3 fibros$).mp.

6 exp Disease Progression /

7 (acute exacerbation$).mp.

8 (disease progression$).mp.

9 (disease exacerbation$).mp.

10 incidence.sh.

11 exp Mortality/

12 follow-up studies.sh.

13 prognos$.tw.

14 predict$.tw.

15 course$.tw.

16 1 or 2 or 3 or 4 or 5

17 6 or 7 or 8 or 9

18 10 or 11 or 12 or 13 or 14 or 15

19 16 and 17 and 18

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No in the manuscript	Checklist item
		ADMINISTRATIVE INFORMATION	
Title:			
Identification	1a	Page 1	Identify the report as a protocol of a systematic review
Update	1b	Not applicable	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	Page 4, 8	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	Page 1-2	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Page 22	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	Not applicable	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	Page 22	Indicate sources of financial or other support for the review
Sponsor	5b	Page 22	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Page 22	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
		INTRODUCTION	
Rationale	6	Page 5-7	Describe the rationale for the review in the context of what is already known
Objectives	7	Page 7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
		METHODS	
Eligibility criteria	8	Page 8-11	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Page 11	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Page 11-12	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Study records:			
Data management	11a	Page 12	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	Page 12	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Page 12-13	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	Page 13	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	Page 10	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Page 13-14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Page 14-15	Describe criteria under which study data will be quantitatively synthesised
	15b	Page 14-15	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Page 16	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	Page 15	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Page 16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Page 17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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Prognostic factors for acute exacerbation of idiopathic pulmonary fibrosis: protocol for a systematic review and meta-analysis

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TITLE PAGE

Title

Prognostic factors for acute exacerbation of idiopathic pulmonary fibrosis: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Idiopathic pulmonary fibrosis (IPF) is a form of chronic fibrosing interstitial pneumonia with unknown disease aetiology. Acute exacerbation (AE) of IPF occurs when disease progression accelerates beyond its expected course. AE of IPF is responsible for 40% of IPF's 30-day-mortality. While death may occur, there is much variation in the clinical progression of this condition. Previous attempts have been made to investigate various possible prognostic factors for AE of IPF, however, they have yet to be confirmed. The aim of this systematic review is to clarify these prognostic factors.

Methods and analysis

In this review, AE of IPF is the condition of interest, which has been defined according to previously established diagnostic criteria. The primary outcomes of interest include short-term all-cause mortality and pulmonary-cause mortality. The secondary outcomes of interest include long-term mortality and hospital-separation for the disease. Primary studies investigating prognostic factors for AE of IPF are eligible for inclusion in this review. All study types are permitted except case reports. Two reviewers will search electronic databases; such as Medline and EMBASE, from 2002 to the 1st of April 2019 and extract data independently. Risk of bias in individual studies will be assessed using

the Quality in Prognostic Studies tool. Meta-analysis will be conducted for univariate data if at least three studies report the effect of a specific prognostic factor using similar statistical methods. Multivariate results will be reported qualitatively. Subgroup analysis and sensitivity analysis will be considered with the aim of generalising findings to the clinical settings and drawing more robust conclusions. The 'GRADE' method (Grades of Recommendation, Assessment, Development and Evaluation) will be applied to evaluate the quality of evidence for each prognostic factor.

Ethics and dissemination

Ethical approval will not be required. Results will be reported in a peer-reviewed scientific journal.

PROSPERO registration

CRD 42018106172

Strengths and limitations of this study

- This systematic review and meta-analysis will be the first addressing prognostic factors for AE of IPF and be the foremost evidence for this potentially fatal disease as large-scale cohort studies investigating this disease may prove difficult.
- This study will focus on relevant clinical information, commonly used in clinical practice, which may facilitate the application of the review's findings to the clinical setting.
- There may be difficulty in combining the result due to substantial heterogeneity between studies.

INTRODUCTION

Rationale

Idiopathic pulmonary fibrosis (IPF) is a form of chronic fibrosing interstitial pneumonia with unknown disease aetiology. IPF is the most common type of pneumonia amongst idiopathic interstitial pneumonias (IIPs).[1] IPF is a progressive disease which can result in death. A recent study in the U.S. found that patients over the age of 65 had a median survival time of 3.8 years.[2] Another study reported numerous complications resulting from IPF such as lung cancer, pneumonia, pulmonary embolism and heart

failure, with mortality often a consequence of respiratory failure due to IPF.[3] However, after a rapid deterioration of IPF beyond its usually expected clinical course was recognized as not uncommon phenomenon,[4] this condition was termed as acute exacerbation (AE) of IPF and demonstrated to be a major cause of death of the disease.[5] In early reports AE of IPF was diagnosed by excluding known causes of disease deterioration, in particular, eliminating potentially causative infectious agents.[6] However, the latest international guideline proposed a new diagnostic criteria for AE of IPF, which isolates worsening symptoms and newly-emerging bilateral radiological opacities, rather than focusing on the aetiology of the exacerbation.[7] Irrespective of the aetiology of this phenomenon, it can be fatal, with a 30-day mortality rate of 40%,[8] and a 1-year mortality of over 80%.[9] The absence of effective treatment may explain the high rate of mortality.[10]

The clinical course of AE of IPF can vary and does not always lead to immediate death in affected individuals.[11] Recently, some studies trialling anti-fibrotic agents suggested a promising preventive effect for disease progression from IPF.[12] To better prevent against the harmful effects of AE of IPF, prognostic factors for the disease must be determined. Identifying these factors may help in tailoring specific treatment options to affected patients and better anticipate the consequence of this disease. Several studies

have investigated diverse clinical information that could be related to the prognosis of AE of IPF. However, these studies have been limited by small sample sizes drawn from a single institution.[13-14] Furthermore, it seems unfeasible to conduct a large-scale cohort study to compensate for this shortcoming of previous research because unpredictable and lethal clinical course might prevent a recruitment of a sufficient number of participants.[15] Due to the disparity of existing evidence, the aim of the proposed systematic review and meta-analysis is to clarify prognostic factors for AE of IPF. The results from this study will be the leading evidence available for this condition. The aim of this article is to rationalise the need for a systematic review of prognostic factors for AE of IPF and outline a proposed methodology for research integrity and transparency. Expected results of this study will not be discussed in this article.

Research aims

The aim of the proposed systematic review is to clarify prognostic factors for AE of IPF.

METHODS AND ANALYSIS

Patient and public involvement

There is no patient and public involvement in the whole process of conducting this research.

Registration

This protocol has already been registered with PROSPERO (International Prospective Register of Systematic Reviews) [16] (CRD42018106172).

Eligibility criteria

Subjects

Patients with AE of IPF are eligible for this review. IPF will be diagnosed based on previously published international guidelines, such as an official American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) statement.[17] AE of IPF will be diagnosed based on the latest international guideline, which consists of a previous or concurrent diagnosis of IPF, acute worsening or development of dyspnoea (typically within less than one month), newly emerging bilateral ground glass opacity (GGO), and/or consolidation superimposed on a background radiological change consistent with usual interstitial pneumonia (UIP) on high resolution computed tomography (HRCT) scans.[7] Although it is necessary to rule out cardiac failure or fluid overload as a cause

of deterioration of IPF, infections or other potential triggers of AE of IPF do not need to be excluded, as per the latest diagnostic criteria, which accounts for both triggered and idiopathic cases. Accordingly, previously proposed diagnostic criteria, (which emphasized the exclusion of pulmonary infection using endotracheal aspirate or bronchoalveolar lavage),[6] can be used to justify the inclusion of idiopathic cases for the disease under the latest diagnostic criteria.[7] Subjects diagnosed with a rapid progressive form of interstitial pneumonia at their first presentation will also be included. However, their diagnosis must have been accompanied by radiological and/or pathological UIP, and known causes for the disease, such as connective tissue disease (CTD) [18] or drug toxicity must have been absent.[19] In cases where patients had multiple episodes of AE of IPF, only the first presentation of the disease will be considered for further analysis.

Exposures

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. These factors may include; age, sex, breathlessness,

percentage of predicted forced vital capacity (%FVC), percentage of predicted diffusion capacity of the lung for carbon monoxide (%DLCO), arterial oxygen pressure (PaO2), Krebs von den Lungen-6 (KL-6), ground glass opacity (GGO) and consolidation on high resolution computed tomography (HRCT).

Outcomes and prioritization

The primary outcomes of interest will be short-term all-cause mortality and pulmonary-cause mortality, defined as in-hospital mortality or 30-day mortality. The secondary outcomes of interest will include the proportion of patients discharged from the hospital and long-term all-cause mortality, determined at 90 days, 6 months or 1 year after the diagnosis of the disease or the start of treatment. Long-term health-related quality of life will also be considered, and will be evaluated according to a validated tool such as the 36-Item Short Form Health Survey (SF-36).[20]

Studies

All primary study types (excluding case reports) will be considered for review, provided quantitative data has been used and they describe an association between potential prognostic factors and pre-defined outcomes for AE of IPF. Furthermore, editorials, letters and review articles will not be considered. Conference proceedings and reports

containing abstracts only will not be considered to alleviate concerns of insufficient information. Research papers prior to 2002 will not be considered, as 2002 marked the first year when the current classification system of IIPs was first introduced.[1] Only articles published in English will be reviewed.

Information sources

Medline (via Ovid 2002-present)

EMBASE (via Ovid 2002-present)

Science Citation Index Expanded (via Web of Science 2002-present)

Google Scholar

Search strategy

Two reviewers (H.K. and O.M.P.) will search electronic databases, such as Medline and EMBASE using subject headings and text words related to study population such as 'idiopathic pulmonary fibrosis' and 'acute exacerbation'. The Cochrane Database of Systematic Reviews (CDSR) will guide the search process by finding reviews similar to this area of research. Search terms will be combined with methodology filters for prognosis, which can be modified to fit each electronic database (e-Appendix).[21-22]

The Science Citation Index Expanded will also be consulted using terms adapted from the previous search of Medline and EMBASE. The search period spans 2002 through to the 1st of April 2019. The reference list of each study eligible for inclusion in this review will also be hand-searched to consolidate the implemented search strategy. Grey literature for this subject area will be identified using Google Scholar.[23]

Study records

Data management

All retrieved articles will be processed through EndNote X7, where duplicates can be identified and removed. All extracted data will be stored in a Microsoft Excel spreadsheet.

Study selection and the data collection process

Two reviewers (H.K. and O.M.P.) will independently examine the titles and abstracts of all retrieved articles (after removing duplicates), to identify eligible reports. In cases where one research group conducted multiple studies with the same outcome of interest focusing on the same prognostic factor(s), only the study with the largest sample size will be considered. Data will be extracted based on a modified data extraction form used in a previously published protocol paper reviewing prognostic factors.[24] Any

uncertainty or disagreement between reviewers arising from these processes will be resolved by discussion.

Data items

The following data will be extracted from each eligible study: first author's name, year of publication, study location, study design, sample size (and their demographic features), outcomes of interest, potential prognostic factors for disease, potential aetiology of disease, length of follow-up, methods for statistical analysis, summary statistics and items associated with risk of bias.

Candidate prognostic factors

Any clinical information relevant to the pre-specified outcomes, reported by a minimum of three separate studies will be further investigated as potential prognostic factors for this review.

Risk of bias in individual studies

The Quality in Prognostic Studies (QUIPS) tool will be applied to assess risk of bias in individual studies. QUIPS consists of six domains. Each domain receives an individual bias rating (low, moderate or high), with overall risk of bias based on the combined

rating of each domain. For example, a study showing low risk of bias across all domains would be deemed as having low risk of bias overall.[25]

Statistical analysis

Summary statistics

Where binary outcomes are presented, effect sizes will be measured using either Hazard Ratios (HRs) derived from Cox Proportional Hazards models [26] or Odds Ratios (ORs) derived from Logistic Regression models.[27] Where an outcome is presented only using a Kaplan-Meier survival curve or log-rank test, HRs will be re-calculated, as previously reported.[28] Where both HRs and log-rank tests are presented, HRs will be prioritized. ORs or risk ratios (RRs) may be calculated manually based on absolute numbers of the outcome of interest across two groups under comparison. Where prognostic factors or the outcome of interest are measured as continuous variables, effect sizes may be presented as absolute values using mean difference (calculated by the unpaired Student's t test) or difference in medians (calculated by the Wilcoxon rank sum test).

Data synthesis

Where an association between one potential prognostic factor and an outcome of interest is presented using the same summary statistics in three or more studies, results will be pooled. Binary outcome will be summarized separately using ORs, RRs or HRs. Continuous outcomes will be combined using mean difference or standardized mean difference (calculated as Hedge's g),[29] based on whether outcomes are presented using the same unit(s). When the median, range or interquartile range are presented for continuous variables, they will be converted to a respective mean value with a standard deviation, using a formula reported by a previous study.[30] Only unadjusted effect estimates for potential prognostic factors will be combined. Effect estimates from multivariate models will be described qualitatively, as model-adjustments will likely vary significantly, such that pooling these data could be misleading. If meta-analysis is feasible from the collated data, it will be conducted using a random-effects model employing the DerSimonian and Laird method.[31] If possible, meta-analysis will be conducted using the statistical software package, Review Manager (RevMan) Version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The 95% prediction interval will be calculated if combined results are presented and heterogeneity between studies has been determined.[32] Statistical significance is considered with respect to a p-value of <0.05. If combining data is deemed

inappropriate (due to a small number of studies or substantial clinical or methodological variability between studies), results will be reported qualitatively.

Heterogeneity between studies

Between-study variance will be estimated with respect to the Tau square value, and assessed using both Q statistics and the I square value. For the assessment of heterogeneity between studies, statistical significance will be considered with respect to a p-value of <0.1 due to the low power of the test. Magnitude of heterogeneity can be categorised as low (0 to 30%), moderate (30 to 50%), considerable (50 to 70%) and substantial (70 to 100%).[29] To better interpret sources of heterogeneity, subgroup analysis will be conducted based on: the definition of AE of IPF (idiopathic or triggered), study location (Asia or non-Asia) and sample sizes (N<50 or N≥50). Sensitivity analysis will also be conducted focusing on studies with low risk of bias.

Reporting bias

Small study bias (such as publication bias) will be examined using graphical asymmetry of a funnel plot and Egger's test, if ten or more studies are available that report the effect of a specific potential prognostic factor for AE of IPF.[33] Statistical significance will be considered with respect to a p-value of <0.1 due to the low power of the test. If

publication bias is suspected, an adjusted summary effect will be estimated using the trim and fill method, which considers the presumptive number of missing studies.[34]

Confirmation of prognostic factors

Prognostic factors will be determined and judged based on statistically significant findings and the consistency of results. Prognostic factors will be confirmed if their effects are consistently in the same direction across all studies and statistically significant in at least 75% of the included studies. Effects from multivariate analyses will be considered for confirmation of prognostic factors.

Confidence in cumulative evidence

The credibility of evidence generated from this systematic review will be assessed by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system. The GRADE system will be applied to the final list of confirmed prognostic factors generated from both univariate and multivariate results.[35]

ETHICS AND DISSEMINATION

Extensive ethical consideration will not be required to conduct this systematic review as evidence will be generated from existing published data. Furthermore, patient-level or

potentially identifiable information will not be accessed. The results of the review will be reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [36] and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines.[37] A Microsoft Excel spreadsheet containing all data gathered for this review will be stored in a digital repository such as Dryad after publication and may be made available for open access upon reasonable request to the corresponding author.

DISCUSSION

This article has outlined the rationale for a methodologically sound systematic review of prognostic factors for AE of IPF. Due to the relative complexity of conducting systematic reviews of prognostic factors,[38] a detailed description of the proposed methodology was required to ensure transparency and research integrity for the proposed study.[39]

There are several methodological limitations that warrant discussion to appropriately interpret the findings of this proposed study. Firstly, prognostic factors will be determined based on the result of multivariate analysis, which will be summarized qualitatively in this review. This may result in the omission or misclassification of

potential prognostic factors due to the low power of individual studies with small sample sizes. Statistical synthesis is expected to solve this issue.[40] However, pooling multivariate data can be misleading as adjusted variables and the final model will be diverse between studies [41] Besides, prognostic factors will be determined based on statistically significant results and the consistency of findings. This is an arbitrary measure which may disregard other potentially viable prognostic factors for the disease. Therefore, even if some potential prognostic factors are not confirmed in this proposed study, we suggest that all identified factors be examined for their clinical significance in future research. Furthermore, the results of this proposed study should be updated to include future research.

Secondly, it is likely that studies identified for this review will be both clinically and methodologically heterogeneous. The included studies may contain a mix of patients with both idiopathic and triggered forms of AE of IPF, diagnosed using the previous (narrow) [6] or current (broad) diagnostic criteria.[7] Additionally, the definition of an outcome may also vary between studies. For example, mortality may be evaluated at different time-scales across studies, such as: in-hospital, 30 days, 90 days or one year after the diagnosis of the disease or the start of treatment. Comparison of outcomes may be further complicated for continuous factors, which could be categorized with arbitrary

cut-off points, imposed by each respective research group.[42] While these limitations may undermine some of the statistical capabilities of the proposed meta-analysis, a qualitative description of results may also provide meaningful insights into prognostic factors for AE of IPF.

Finally, potential prognostic factors will be selected for further analyses if they are reported in a minimum of three separate studies. Repeated mention of clinical information may suggest clinical relevance, which could serve to improve the applicability of our findings. By employing this inclusion criteria, potential prognostic factors reported by only one or two studies will be omitted. This will deprive these potential prognostic factors from further investigation in this study and may stifle their further research in other studies.

Despite the potential methodological limitations discussed in this protocol paper, we believe in the value of clarifying current evidence surrounding prognostic factors for AE of IPF through systematic review. Peer-review of this protocol paper will also serve to improve the integrity and transparency of our proposed research.

CONCLUSION

This protocol paper outlined the need for a methodologically sound systematic review of prognostic factors for AE of IPF. The methodological limitations of the proposed study are common to research examining prognostic factors and are largely unavoidable. Despite these limitations, this study would represent the leading body of evidence for this area of research.

ACKNOWLEDGEMENTS

We would like to thank Mr. Istvan T. Kabdebo of The School of Population and Global Health, University of Western Australia for his support in editing this manuscript.

AUTHORS' CONTRIBUTIONS

Hiroyuki Kamiya (H.K) conceptualised this research project and its associated methodology. H.K. also wrote the manuscript for this protocol. H.K will be the guarantor of the content of the review including data analysis.

Ogee Mer Panlaqui (O.M.P) contributed in the conceptualisation of this research project by planning the literature search strategy and data extraction methods. O.M.P. also made additions and revisions to the draft of this manuscript.

FUNDING

The proposed research has received no specific grant from a funding agency in the public, commercial or not-for-profit sectors.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare for all authors in this protocol paper of the proposed systematic review.

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e-Appendix: Search terms for Ovid Medline

1 exp Lung Diseases, Interstitial/

2 exp Idiopathic Pulmonary Fibrosis/

3 (interstitial adj3 lung adj3 disease$).mp.

4 (interstitial adj3 pneumoni$).mp.

5 (pulmonary adj3 fibros$).mp.

6 exp Disease Progression /

7 (acute exacerbation$).mp.

8 (disease progression$).mp.

9 (disease exacerbation$).mp.

10 incidence.sh.

11 exp Mortality/

12 follow-up studies.sh.

13 prognos$.tw.

14 predict$.tw.

15 course$.tw.

16 1 or 2 or 3 or 4 or 5

17 6 or 7 or 8 or 9

18 10 or 11 or 12 or 13 or 14 or 15

19 16 and 17 and 18

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Page No in the manuscript	Checklist item
		ADMINISTRATIVE INFORMATION	
Title:			
Identification	1a	Page 1	Identify the report as a protocol of a systematic review
Update	1b	Not applicable	If the protocol is for an update of a previous systematic review, identify as such
Registration	2	Page 4, 8	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	Page 1-2	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Page 21	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	Not applicable	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support:			
Sources	5a	Page 21	Indicate sources of financial or other support for the review
Sponsor	5b	Page 21	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Page 21	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
		INTRODUCTION	
Rationale	6	Page 5-7	Describe the rationale for the review in the context of what is already known
Objectives	7	Page 7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
		METHODS	
Eligibility criteria	8	Page 8-11	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources	9	Page 11	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy	10	Page 11-12	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated

Study records:			
Data management	11a	Page 12	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	Page 12	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process	11c	Page 12	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items	12	Page 13	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization	13	Page 10	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies	14	Page 13	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis	15a	Page 14-15	Describe criteria under which study data will be quantitatively synthesised
	15b	Page 14-15	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Page 16	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	Page 15	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Page 16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Page 17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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