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Prognostic significance of autoantibodies for idiopathic pulmonary fibrosis: protocol for a systematic review

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ABSTRACT

Introduction Idiopathic pulmonary fibrosis(IPF) is chronic fibrosing interstitial pneumonia of unknown aetiology. IPF is diagnosed based on the exclusion of known causes such as connective tissue diseases(CTDs). However, some patients fail to meet defined CTD criteria regardless of an implication of immunological involvement and these cases were described in a variety of terms. The classification criteria of this clinical entity consist of a combination of clinical, serological and morphological findings and it is reported to be distinct from IPF. However, the significance of the sole presence of autoantibodies complicated with IPF is still unknown. Therefore, this systematic review aims to clarify the significance of autoantibodies complicated with IPF.

Methods and analysis IPF with any autoantibody associated with CTDs is eligible for the review. Primary outcomes are all-cause mortality and pulmonary-cause mortality, while secondary outcomes include a progression of the disease, a deterioration of health-related quality of life and the development of a defined CTD. Primary studies of any type except a case report are included. Two reviewers search four electronic databases such as Medline, EMBASE, Science Citation Index Expanded and Google Scholar from each inception through 1 February 2018 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 if three or more studies report an outcome for a specific autoantibody with the same statistics. If it is inappropriate to combine data due to substantial heterogeneity, the result is 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 the result.

Ethics and dissemination There is no concerning ethical issue. The result will be sought for publication.

PROSPERO registration number CRD42017077336.

Strengths and limitations of this study

- The first systematic review addressing the significance of autoantibodies for idiopathic pulmonary fibrosis.
- The review based on all types of primary studies derived from comprehensive literature search.
- A potential difficulty in combining the result due to a small number of studies and substantial heterogeneity.

INTRODUCTION

Rationale

Interstitial lung disease (ILD) is a heterogeneous clinical entity characterised by common pathological findings of interstitial fibrosis and inflammation.[1] It is well recognised that ILD can be accompanied by a variety of connective tissue diseases (CTDs) and caused by certain drug or environmental exposure to some substances.[2 3] Accordingly, idiopathic interstitial pneumonia (IIP) can be diagnosed based on the exclusion of these known causes.[4] Idiopathic pulmonary fibrosis (IPF) is chronic fibrosing interstitial pneumonia and the most common type among IIPs.[1] As IPF is noted to follow a progressive and unfavourable clinical course,[5] it is important to make a correct diagnosis of IPF to decide a therapeutic plan and provide proper treatment. However, it is often difficult to detect or exclude underlying CTDs in the diagnosis of IIPs because interstitial pneumonia can be the sole presenting manifestation of certain CTD[6] or symptoms or signs of CTD are too subtle to be recognised as the underlying cause.[7] Possible involvement of autoimmunity in the development of interstitial pneumonia can be suspected by diverse clinical information such as demographics, physical exams, laboratory tests, radiology and pathological manifestations.[8] Nevertheless, some patients remain unclassified into a defined CTD under the current diagnostic criteria. These cases were termed as undifferentiated CTD (UCTD)[9] and ILD associated with UCTD has been described by different terminologies, including recently proposed interstitial pneumonia with autoimmune

features (IPAF).[10] The classification criteria of this disease group consist of a combination of clinical, serological and morphological domains. Some research group reported that patients meeting these criteria demonstrated a different clinical course from CTD-ILD or IPF and thus it might be a distinct disease entity.[11] However, the sole positivity of autoantibodies without any other symptoms or signs suggestive of CTDs fails to fit into the diagnostic criteria of a defined CTD as well as IPAF.[10] According to the current international guideline, IPF with autoantibodies in the absence of additional clinical findings is diagnosed as IPF,[5] which, however, seems to be lacking a sufficient explanation. Although some previous studies described that there was no significant difference of mortality between IPF with and without autoantibodies, they are mostly anecdotal reports due to a small number of participants in a single institution[12] and the significance of autoantibodies in patients with IPF is still uncertain. Therefore, we decided to undertake a systematic review of the literature to summarise previous evidence regarding this clinical question and clarify the prognostic significance of autoantibodies accompanied by IPF. As this article aims to report the rationale and the methodology of a future systematic review of IPF with autoantibodies to ensure the transparency and the integrity of the research, any result expected to be obtained from the review is not presented in this report.

Objective of the review

This systematic review aims to clarify the prognostic significance of autoantibodies complicated with IPF.

METHODS AND ANALYSIS

Registration

This protocol was registered with PROSPERO (International Prospective Register of Systematic Reviews)[13] (CRD42017077336).

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 1 February 2018 and may be extended depending on the date of publication of this protocol paper.

Eligibility criteria

Participants

Patients with IPF are eligible for the review. IPF is diagnosed based on the latest joint statement reported by four respiratory societies around the world.[5] Radiological and/or pathological usual interstitial pneumonia (UIP) without any extrapulmonary symptoms or signs may be reported as an equivalent to IPF. There is no limitation of follow-up lengths. All patients can be included at any point of time during the disease course and from any clinical setting such as outpatients and inpatients.

Exposure

Autoantibodies of interest in this study cover all antibodies specific to CTDs such as the ones listed in the serological domain of a recently proposed IPAF.[10] Non-specific markers such as antinuclear antibody and rheumatoid factor are also included and the positivity of these laboratory tests is based on the reference value of each institution. Antinuclear antibody is considered for inclusion regardless of immunofluorescence patterns. Antineutrophil cytoplasmic antibody (ANCA) targeted against myeloperoxidase or proteinase-3 also comprises autoantibodies in this study as ANCA-associated vasculitis is noted to be complicated with UIP,[14] which is a pathological feature of IPF. This study compares IPF with and without autoantibodies.

Outcomes and prioritisation

Primary outcomes are defined as all-cause mortality and pulmonary-cause mortality, while secondary outcomes are a progression of the disease and a deterioration of health-related quality of life. The disease progression is expected to be assessed by the established criteria, which include a combination of symptoms, radiology and physiology,[15] although it may be varied among studies. Health-related quality of life will be evaluated by a validated diagnostic tool such as the 36-Item Short Form Health Survey.[16] The development of a defined autoimmune disease over the follow-up period of time is also included in the secondary outcome. Although autoimmune disease of interest in this study contains any CTD, rheumatoid arthritis (RA) and ANCA-associated vasculitis may be reported most frequently as they are noted to manifest UIP as a pathological change of pulmonary parenchyma and often difficult to be differentiated from IPF.[14 17] Each disease will be diagnosed based on the established diagnostic criteria such as the American College of Rheumatology criteria for RA[18] and the classification of the ANCA-associated vasculitides proposed by Watts *et al*.[19]

Studies

Any type of primary study excluding a case report is included in the review. Case series are included if they describe a comparison between IPF with and without autoantibodies. Unavailability of relevant summary statistics does not exclude studies if they meet the inclusion criteria. Editorials, letters and review articles are excluded. Although there is no limitation regarding the number of participants, studies are limited to English literature and the publication year of 2002 or later as the original form of current classification system of IIPs was established in that year.[1] Conference proceedings and reports with only abstracts are also excluded due to concerns of insufficient information.

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 (HK/OMP) search the Medline and the EMBASE using subject headings and text words of study population and their synonyms such as 'idiopathic pulmonary fibrosis' and 'autoantibodies', which are determined referring to reviews of a similar subject identified in the Cochrane Database of Systematic Reviews or the Database of Abstracts of Reviews of Effects. They are combined with the methodology term of prognosis, which is modified for each electronic database (online supplementary appendix 1).[20 21] The Science Citation Index Expanded is also searched using terms adapted from the search of the Medline and the EMBASE. Reference lists of eligible studies and relevant review articles are also hand-searched. Grey literature is sought to be identified through Google Scholar.[22]

Study records

Data management

All retrieved articles are processed through EndNote X7, which can identify and remove duplicates. All extracted data are stored in a Microsoft Excel spreadsheet.

Study selection and data collection process

Two reviewers (HK/OMP) independently examine titles and abstracts of all retrieved articles after removing duplicates and select eligible studies. Multiple articles by the same research group are not excluded at this stage, although they may be eliminated from further analysis if the same outcome or prognostic factor is reported. Data are extracted by the same reviewers (HK/OMP) based on the predefined data extraction form, which was composed of relevant items for prognostic studies (online supplementary appendix 2). A disagreement is resolved through a discussion between the reviewers.

Data items

The following data are extracted: name of the first author, publication year, study location, study design, the number of participants and their demographic features such as age and gender, autoantibodies, follow-up lengths, clinical outcomes, counts of the outcome, methods for statistical analysis, summary statistics and items associated with a risk of bias.

Risk of bias in individual studies

The Quality in Prognostic Studies tool is applied to assess a risk of bias in individual studies. It consists of six domains. Each domain is rated as 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 designated as low risk of bias.[23]

Statistical analysis

Missing data

If summary statistics to report the effect of prognostic factors on the outcome are not obtained directly, they are sought to be estimated using other relevant data. If it is unfeasible, authors may be contacted and asked to provide these data.

Summary statistics

When the outcome is binary, the effect size is expected to be presented as the HR by the Cox proportional hazard model[24] or the OR by the logistic regression model.[25] If the outcome is only presented by the log-rank test or the Kaplan-Meier survival curve, the HR is recalculated as previously reported.[26] The OR or the risk ratio (RR) may be calculated manually based on counts of the outcome among two comparative groups if it is not available directly. Where the outcome or prognostic factors are continuous, the summary effect may be presented as the mean difference by the unpaired t-test or the adjusted mean difference by the linear regression model. The standardised mean difference will be calculated by the mean difference divided by the SD if needed when data are combined.

Data synthesis

The results are pooled if an outcome for IPF with a specific autoantibody is presented by the same summary statistics in three or more studies. The binary outcome is summarised by the OR, RR or HR separately, while the continuous outcome is combined by either the mean difference or the standardised mean difference depending on whether the outcome is presented with the same unit. When the median is presented for continuous variables, it is not sought to be combined and handled as it is.

Unadjusted and adjusted estimates of the effect size of prognostic factors are combined separately. If more than one multivariate model with adjustment are available, the model with the largest number of variables is selected. If the number of variables is the same in all models, the model with a factor of interest showing the most conservative result is selected.

If meta-analysis is appropriate, it will be conducted by a random-effect model with the DerSimonian and Laird method[27] using the statistical software, Review Manager (RevMan) V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). The 95% prediction interval will be calculated if there is heterogeneity among studies in addition to the 95% CI.[28] Statistical significance is set at the 5% level. If combining data is inappropriate due to a small number of studies or concerns of substantial variability, the result is reported qualitatively.

Heterogeneity

Between-study variance is estimated as the tau-squared and assessed by the Q-statistics and I^2. Statistical significance

is set at the 10% level because of low power of the test and the magnitude of heterogeneity is interpreted as not important (0–30%), moderate (30–50%), substantial (50–70%) and considerable (70–100%).[29] To clarify the source of heterogeneity, subgroup analysis is considered based on the same study design, follow-up lengths of time, that is, less than 1 year and 1 year or longer and sample sizes, that is, less than 50 and 50 or more. Sensitivity analysis will also be conducted focused on studies with a low risk of bias alone.

Metabiases

Small study bias, including publication bias, is examined graphically by a funnel plot and statistically by the Egger's test[30] if 10 or more studies are available. Statistical significance is set at the 10% level because of low power of the test. If publication bias is suspected, the trim and fill method is applied to estimate the number of missing studies and an adjusted summary effect.[31]

Confidence in cumulative evidence

The Grades of Recommendation, Assessment, Development and Evaluation method is applied to evaluate the level of evidence obtained from this systematic review.[32]

ETHICS AND DISSEMINATION

This systematic review is based on published data. Researchers will not access any information which can identify an individual patient even if authors of included studies are contacted for missing data. Therefore, no concerning ethical issue is involved in this research. The result of the review will be reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[33] and the Meta-analysis of Observational Studies in Epidemiology statement.[34] A Microsoft Excel spreadsheet containing all data extracted from included studies may be stored in a digital repository such as Dryad after the result of the review is published so that the original data could be open accessed.

DISCUSSION

This is a protocol paper describing in detail the methodology of a future systematic review regarding the significance of autoantibodies complicated with IPF. As a systematic review is inherently a retrospective study based on previously reported data, elaborating on the methodology before it commences is essential to ensure the transparency and the integrity of the research. Otherwise it may be manipulated so that the result would be matched with the preference of interested parties. Therefore, the significance of this report resides in the fact that it clarified all aspects concerning the conduct of the review.

This article described the analytical method assuming every possible situation encountered in prognostic studies. Potential individual studies in this review are expected to be clinically or methodologically diverse and thus subgroup analyses were planned to evaluate the consistency of the result. However, all the analyses may be possibly prevented due to a small number of studies. In particular, this review includes multiple autoantibodies as a prognostic factor of interest for IPF. Some studies may evaluate all of these autoantibodies as a whole while others may focus on a specific one. As a result, it may be difficult to combine the data and conduct subgroup analysis. Furthermore, sensitivity analysis focusing on studies with a low risk of bias alone may also be unfeasible as all included studies could contain some risk of bias. However, statistical analysis, including meta-analysis, should not be emphasised as a goal of a systematic review, although it must be a powerful tool to summarise the result. Descriptive analysis would be a vital and indispensable part of a systematic review.

We decided to include only studies published in 2002 or later, which may affect the comprehensiveness of selecting reports for the review. However, including reports before the publication of the current classification system of IIPs[1] will prevent focusing on a specific group of patients who are supposed to be categorised by the uniform terminology. Therefore, this decision will help conduct a focused review.

Some may also argue against excluding conference proceedings and reports with only abstracts because of a possible selection bias. However, these types of reports usually present insufficient data and thus their inclusion may possibly bias the result.

Overall, regardless of these potential methodological limitations, we believe that this protocol report of a future systematic review of IPF with autoantibodies has addressed every aspect of the research and will help ensure its integrity and transparency.

CONCLUSIONS

The rationale and methodology of a future systematic review of IPF with autoantibodies were described. Some potential methodological limitations involved in the conduct of the review will not be serious enough to undermine its significance. The result of the review would rather be the best evidence currently available and a distinguished guide in clinical practice under the support of this protocol paper.

Contributors HK conceived this research project and planned the entire methods to undertake it. He also wrote the manuscript of this protocol. HK will be the guarantor of the content of the review, including data analysis.OMP 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 the manuscript.

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