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TITLE

Prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease: protocol for a systematic review and meta-analysis

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Idiopathic inflammatory myopathy, interstitial lung disease, prognosis, systematic review, meta-analysis

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ABSTRACT

Introduction

Idiopathic inflammatory myopathies may be an overlapping disease complex. Although interstitial lung disease affects the mortality and morbidity of the disease, a clinical course and prognosis of the disease complicated with interstitial lung disease are diverse among individuals and prognostic factors have yet to be clarified. This study will be the first to systematically elucidate prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease and improve the daily clinical practice.

Methods and analysis

Participants are eligible if they are diagnosed as polymyositis/dermatomyositis, clinically amyopathic dermatomyositis or anti-synthetase syndrome complicated with interstitial lung disease. The primary outcomes are all-cause and pulmonary-cause mortality and the secondary outcomes include the progression-free survival and health-related quality of life. All primary studies of any study design aside from case reports or case series are included. Two reviewers search electronic databases such as the Ovid Medline, Ovid EMBASE and Science Citation Index Expanded and extract relevant data according to a piloted data extraction form independently. The risk of bias in individual studies is evaluated based on the Quality in Prognostic Studies (QUIPS) tool. Meta-analysis will be conducted if 3 or more studies are available for each outcome and pooled effects will be presented by the odds ratio. Where combing data is inappropriate due to a small number of studies or substantial heterogeneity, the results are reported qualitatively. The subgroup and sensitivity analysis are also considered based on clinical and methodological differences such as clinical manifestations, study designs, and quality of studies. Evidence level is assessed following the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method.

Ethics and dissemination

This study raises no ethical issues as it is based on the summary results of previously published articles. The results will be reported in a peer-reviewed medical journal.

PROSPERO registration number

CRD42016036999

ARTICLE SUMMARY

Strengths and limitations of this study

- Systematic review and meta-analysis of primary studies of any type of design excluding case reports or case series to address the clinical question of prognosis.
- First evidence based on a potentially large population derived from data synthesis for a rare disease.
- Potential difficulty in interpreting and applying the results due to a diversity and high risk of bias in included studies.

BACKGROUND

Rationale

Interstitial lung disease (ILD) has been drawing much attention for the last few decades.[1] It is partly because there is a growing number of patients with the disease due to the development of diagnostic tools [2] and it is often difficult to be treated and can follow a fatal clinical course.[3] ILD is a comprehensive disease entity that demonstrates common final findings of parenchymal fibrosis mixed with an inflammation despite a diversity of those mixtures among cases.[4] While external stimuli such as certain drug and occupational exposure are noted to cause ILD,[5-6] another notorious factor is connective tissue disease, which will manifest ILD as a pulmonary complication.[7]

Polymyositis/dermatomyositis is one of the classical connective tissue diseases and categorized into idiopathic inflammatory myopathies.[8-9] It is triggered by unknown causes and progressed by an accelerated autoimmune reaction.[10] Although polymyositis/dermatomyositis is characterized by proximal muscular weakness and unique cutaneous findings, ILD frequently complicates and is closely related to the morbidity and mortality of the disease.[11] Historically, anti-Jo-1 antibody, an autoantibody directed against histidyl-tRNA synthetase (one type of aminoacyl-tRNA synthetase (ARS)) in the cytoplasm, was identified in patients with polymyositis/dermatomyositis and helped in the diagnosis of the disease as it was highly specific and predictive of the disease.[12] The latest immunochemical development has discovered a large number of other autoantibodies that are also specific or associated with autoimmune myositis.[13] In particular, anti-ARS antibodies other than anti-Jo-1 antibody have been identified [14] and patients with those antibodies are noted to frequently present with cutaneous changes pathognomonic of dermatomyositis, arthralgia/arthritis and fever in addition to myositis and ILD. This led to the development of the new term called anti-synthetase syndrome [15] although manifestations of the disease could be diverse depending on the type of anti-ARS antibodies.[16] Furthermore, anti-melanoma differentiation-associated gene 5 (MDA5) antibody was identified in clinically amyopathic dermatomyositis,[17] which is considered as a subgroup of dermatomyositis featuring clinically no or less muscular

weakness and rapidly-progressive ILD.[18] It is recognized that the morbidity and mortality of anti-synthetase syndrome and clinically amyopathic dermatomyositis are also related to ILD.[19-20]

As polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome demonstrate common findings regardless of some clinical differences, they may be on the same disease spectrum that characterizes a complication of ILD, which will affect the prognosis of the disease.[21-22] However, it is generally believed that clinical courses are diverse and the prognosis varies among individuals although ILD is known to suggest a poor prognosis of the disease.[23-24] The identification of prognostic factors for patients with ILD will improve the management of this disease complex and provide great benefits with daily clinical practice as it will enable clinicians to predict the prognosis and implement medical resources sensibly. There has been little literature describing prognostic factors of this disease spectrum complicated with ILD and most currently available evidence is based on a small number of patients in a single or few medical institutions as this is a rare disease and thus could result in anecdotal reports.[25-26] Therefore, this systematic review has been planned to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and eventually to better the prognosis of the disease.

Hypothesis

The clinical course of idiopathic inflammatory myopathies complicated with ILD is diverse and there must be undefined factors related to the prognosis of the disease.

Research question

- What are prognostic factors of idiopathic inflammatory myopathies complicated with ILD?
- What is the most predictive clinical information of the mortality of idiopathic inflammatory myopathies complicated with ILD?
- Is there any difference of prognostic factors of idiopathic inflammatory myopathies complicated with ILD depending on the difference of clinical manifestations?

Objectives

This systematic review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and clarify what is the most predictive factor of the mortality of the disease.

METHODS

Registration and methodology

This protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews) at Centre for Review and Dissemination at University of York [27] (CRD42016036999) and reported following a guideline of PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols).[28]

Timeline

This study has yet to be initiated except for a pilot search and determining search terms and constructing a data extraction form. The full search is scheduled to be conducted on the first week of May, 2016 and extended to the latest depending on the publication of this protocol.

Eligibility criteria

Participants

Patients with polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome complicated with ILD of adult onset (over 16 years of age) are included. Polymyositis/dermatomyositis and clinically amyopathic dermatomyositis are diagnosed based on the criteria such as Bohan and Peter [8-9] and Sontheimer,[29] which combine clinical, physiological and pathological findings as previously proposed. Anti-synthetase syndrome is included if a complication of ILD is noted in addition to the positivity of anti-ARS antibody and another organ involvement such as myopathies and unique cutaneous manifestations. The diagnosis of ILD is made based on physical exams, pulmonary function tests and radiological abnormalities. Patients are required to be followed up for at least 6 months. All patients are included at any time point during

the disease course and from any clinical setting such as primary and secondary care. Juvenile myositis and overlap-myositis are excluded from the review.

Exposures or interventions

All clinical information such as demographic features and disease profiles are considered as potential prognostic factors. Therapeutic interventions can also be a prognostic factor of the disease. Although there is no limitation as to the type of therapeutic interventions, only the treatment with a duration of more than 6 months is a candidate for a factor of prognosis. Comparators are no presence or less values of these factors including demographic features, disease profiles and therapeutic interventions.

Outcomes and prioritization

All-cause and pulmonary-cause mortality are primary outcomes and secondary outcomes include a progression of the disease and a deterioration of health-related quality of life. The disease progression is defined based on combined findings of symptomatic, functional (pulmonary function tests) and radiological changes over the follow-up period of time after the diagnosis or the initiation of treatment. An individual component comprising the combined criteria can also define the clinical course of the disease. Health-related quality of life is expected to be evaluated based on questionnaires such as the 36-Item Short Form Health Survey (SF-36).[30] The unavailability of relevant statistics to describe the association of potential prognostic factors with the outcomes does not exclude studies if they meet the inclusion criteria otherwise.

Studies

Any type of primary studies excluding case reports or case series, whether prospective or retrospective, is included in the review if it describes the association of the predefined outcomes with potential prognostic factors of polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome with ILD. Where studies consisted of a composite of this disease category, they are eligible for inclusion unless other ineligible cases such as juvenile myositis and overlap-myositis are included. Editorials, letters and review articles are excluded. Although there is no limitation

regarding the date of studies and the number of participants, studies are limited to English literature. Conference proceedings with no further full reports and studies with only abstracts are also excluded due to concerns of lack of information.

Information sources

Medline (via Ovid 1946-)

EMBASE (via Ovid 1974-)

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

Search strategy

Two reviewers (HK/OMP) search the Ovid Medline, Ovid EMBASE using key terms of study population and methodology such as polymyositis, dermatomyositis, anti-synthetase syndrome, ILD and prognosis. Appropriate search filters for prognostic studies of the Ovid Medline and Ovid EMBASE are derived from previous reports.[31-32] They are combined with both subject headings and text words of content specific terms and their synonyms, which are determined referring to applicable reviews of the similar subject in the Cochrane Database of Systematic Reviews (Appendix). Search terms are finalized through an independent attempt of construction and a pilot search by two reviewers and examining the agreement of retrieved articles. Science Citation Index Expanded (via Web of Science) is also searched for citations, which are not covered by the Ovid Medline and Ovid EMBASE. In addition, review articles identified through the same searching process over the last 5 years are screened to identify potential primary articles and an expert in this field is consulted to collect additional reports such as grey literature. Reference lists of relevant articles are also hand-searched.

Study records

Data management

Relevant articles are managed through EndNote X7 and all extracted data are stored in a Microsoft Excel spreadsheet.

Selection of studies and data extraction

Two reviewers (HK/OMP) independently examine titles and abstracts of all retrieved articles and select studies following the inclusion and exclusion criteria. If a duplicate or updated report is revealed, the study with the largest dataset alone is included. However, multiple articles by the same research group are included if the outcomes are different. Data are also extracted by the same reviewers (HK/OMP) based on the data extraction form, which has been predefined, reviewed and finalized through a pilot test to a small sample of eligible studies and a discussion among reviewers. A disagreement is resolved through a consultation with another reviewer.

Data items

The following data are extracted: names of the first author, publication years, countries where research is conducted, study designs, follow-up periods, study population, pattern of ILD, number of participants, their demographic features such as age and gender, autoantibodies, comparators if applicable, clinical outcomes, counts of the outcomes, potential prognostic factors, methods for statistical analysis of the association of prognostic factors with the outcomes, summary statistics and items associated with risk of bias. Both unadjusted and adjusted measurements are drawn and adjusted factors are also extracted if available.

Assessment of risk of bias in individual studies

The risk of bias in individual studies is assessed based on the Quality in Prognostic Studies (QUIPS) tool.[33-34] Specifically, it contains 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Each domain is rated as having high, moderate or low risk of bias and the overall risk of bias of a study is evaluated by total ratings of all domains. For example, a study showing low risk of bias in all domains is defined as having low risk of bias.

Statistical analysis

Dealing with missing data

If summary statistics to address the association of potential prognostic factors with the outcomes are not obtained directly, they are estimated using other relevant data. If it is unfeasible, authors are contacted and asked to provide these data.

Measurements of the association

Two major study designs to address the question of prognosis are cohort and case-control studies. In general, the former is summarized with the hazard ratio (HR) using the Cox proportional hazard regression model where time-to-event data are fitted although the odds ratio (OR), risk ratio (RR) or risk difference (RD) may also be used to estimate the proportion of the event. The latter type of studies calculates the OR using the logistic regression model where only point estimates of the event are considered. Therefore, the common measurements of the association of potential prognostic factors with the outcomes will include the OR, RR, RD and HR.

If the HR is not directly provided, it is re-calculated from other information such as the log rank test and Kaplan-Meier survival curve.[35-36] The OR may also be unavailable directly through the logistic regression model and only the comparison of potential prognostic factors between two groups with and without the event may be presented. In this case the OR is calculated manually based on counts of the outcome.

The RD is affected by the baseline risk of the event, which can be varied among studies and thus unfavorable in pooling data. The RR has an advantage over the RD regarding this issue and therefore the latter is converted to the former if the proportion of the outcome in two comparative groups is available. The OR can be approximated to the RR if the outcome is rare [37] and the HR can also be approximated to the RR or OR if the follow-up duration is short and the ratio of the occurrence of the outcome in two comparative groups is small in addition to the condition that the outcome is rare.[38] As a result, the OR, RR and HR are assumed to be interchangeable and the OR will be used to summarize the association of potential prognostic factors with the outcomes. The association is reported following the convention that over one value indicates an increased risk of the outcome, i.e., the OR>1.0 indicates an increased chance of death.

Where potential prognostic factors are continuous variables, the mean difference may be presented from the comparison of groups with and without the event. The mean difference is divided by the standard deviation and converted to the standardized mean difference for further analysis of the association.

Data synthesis

The results across studies are pooled if the outcome data are available in 3 or more studies. Summary effects are sought to be presented as the OR with the assumption that the OR, RR and HR could be interchangeably approximated to each other under a specific condition. Accordingly, the OR and HR of continuous variables are assumed to be representing the same effect measurement and can be combined together as the OR while those of categorical variables are assumed similarly and can undergo the same data handling. The standardized mean difference, which may be presented as the effect measurement of continuous variables, is combined by itself. As the standardized mean difference may be estimated from the comparison of groups with and without the event, it is difficult to be combined with the OR, which will be estimated through the logistic regression model with binary outcomes. This presumable situation is different from a previously reported case where continuous and binary outcomes can be combined.[39]

Both unadjusted and adjusted estimates of the association are combined separately as it is reasonably expected that prognostic studies can be distorted by confounders and presenting summary statistics with adjustments in comparison with crude effects without adjustments are more likely to demonstrate meaningful results. If more than one multivariable models with adjustments are available, the model with the best fit or with the most variables is selected. If the number of variables is the same in all models, the model containing a factor of interest with the least significance is selected.

Meta-analysis is conducted by a random-effect model [40] considering that there should be certain extent of variability among studies due to clinical and methodological differences. Data such as the logarithmic scale of the OR or the standardized mean difference and their standard errors are combined by the inverse variance method using the statistical software, Review Manager (RevMan) Version 5.3 (Copenhagen: The

Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary effects of each prognostic factor are estimated as the OR or the standardized mean difference with 95% confidence interval and Tau square, which indicates between-study variances. 95% prediction interval will also be calculated.[41] The statistical significance is set at the 5% level. If meta-analysis is inappropriate due to few studies or a concern of substantial heterogeneity, the results are reported qualitatively.

Heterogeneity

Statistical heterogeneity is assessed by the chi-square test and I square. The 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 to 30%), moderate (30 to 50%), substantial (50 to 70%) and considerable (70 to 100%).[42] The clinical heterogeneity is assumed to be mainly derived from a different subset of diseases and types of ILD and autoantibodies among included studies while the methodological heterogeneity is caused by a variety of study designs such as prospective or retrospective studies and diverse follow-up lengths. In particular, clinically amyopathic dermatomyositis, which is characterized by high probability of a complication of rapidly progressive ILD and the presence of anti-MDA5 antibody, may be a different group of the same spectrum of the disease. Therefore, the subgroup analysis is considered if data are available according to the difference of clinical manifestations (polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome) and types of ILD (acute or rapidly progressive and chronic) and autoantibodies identified (anti-ARS antibody including anti-Jo-1 antibody and non-Jo-1 antibody and anti-MDA5 antibody). An analysis of studies with the same design such as a prospective cohort study and a case-control study is also explored. In addition, the influence of different follow-up lengths is analyzed based on two different time points; 1 and 5 years. The summary effects will also be presented as their original statistical forms, i.e, OR, RR and HR, to investigate the validity of considering these three statistics as interchangeable measurements. The sensitivity analysis is conducted focused on studies with low risk of bias alone.

Metabiases

The small study bias including publication bias is evaluated graphically examining the presence of asymmetry in a funnel plot and statistically by the Egger's test with the natural logarithmic scale of the OR being regressed against its standard error if a meta-analysis is based on 10 or more studies for an outcome.[43] The statistical significance for asymmetry is set at the 10% level because of low power of the test. Selective reporting is assessed examining the consistency of study findings with its protocol if available.

Confidence in cumulative evidence

It was reported that the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method could be useful in the assessment of prognostic reviews as in the case of assessing treatment effects.[44] Although the report focused on a question of prognosis in a specific population rather than prognostic factors, 5 domains described to rate down the quality of evidence (risk of bias, inconsistency, imprecision, indirectness and publication bias) and 2 domains to rate it up (large effect and dose response gradient) are also applicable for this review as the fundamental methodological process of evaluation is similar between these two types of prognosis studies.

ETHICAL CONSIDERATION AND REPORTING

This systematic review is based on the summary results of previously published articles and individual patient data will not be obtained or accessed. Even if authors of included studies are asked to provide relevant missing data, any clinical information connecting with an individual patient will not be revealed. Therefore, there is no concerning ethical issue in the conduct of this research. The result of the review will be reported in a peer-reviewed medical journal following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [45] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement.[46]

DISCUSSION

This review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and identify the most predictive factor of the mortality of this disease spectrum. Although some literature has addressed this clinical

question,[25-26] the reports are based on a small number of population in a few medical institutions. In addition, systematic reviews have yet to be conducted to solve the issue. Therefore, this will be the first comprehensive review to answer the question and be a valuable guide for clinicians to treat patients with this diverse disease spectrum.

FUNDING

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CONFLICT OF INTERESTS

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

REFERENCES

1. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015;192:e3-19.
2. King TE, Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268-79.
3. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431-40.
4. Leslie KO. Historical perspective: a pathologic approach to the classification of idiopathic interstitial pneumonias. *Chest* 2005;128:513s-9s.
5. Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig* 2013;51:260-77.
6. Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. *Curr Opin Pulm Med* 2015;21:193-200.
7. Fischer A, Lee JS, Cottin V. Interstitial lung disease evaluation: detecting connective tissue disease. *Respiration* 2015;90:177-84.
8. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344-7.
9. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975;292:403-7.
10. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med* 2005;201:591-601.
11. Marie I, Hatron PY, Dominique S, et al. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. *Arthritis Rheum* 2011;63:3439-47.
12. Yoshida S, Akizuki M, Mimori T, et al. The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. A marker for a subset of polymyositis with interstitial pulmonary fibrosis. *Arthritis Rheum* 1983;26:604-11.
13. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine* 1991;70:360-74.
14. Nakashima R, Imura Y, Hosono Y, et al. The multicenter study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. *PLoS One* 2014;9:e85062.

15. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med* 1990;77:1019-38.
16. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One* 2013;8:e60442.
17. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum* 2005;52:1571-6.
18. Gerami P, Schope JM, McDonald L, et al. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006;54:597-613.
19. Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. *Autoimmunity* 2006;39:233-41.
20. Ye S, Chen XX, Lu XY, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. *Clin Rheumatol* 2007;26:1647-54.
21. Yamasaki Y, Yamada H, Ohkubo M, et al. Longterm survival and associated risk factors in patients with adult-onset idiopathic inflammatory myopathies and amyopathic dermatomyositis: experience in a single institute in Japan. *J Rheumatol* 2011;38:1636-43.
22. Marie I, Josse S, Hatron PY, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. *Arthritis Care Res* 2013;65:800-8.
23. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep* 2013;15:349.
24. Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. *Autoimmun Rev* 2012;12:210-7.
25. Fujisawa T, Hozumi H, Kono M, et al. Prognostic factors for myositis-associated interstitial lung disease. *PLoS One* 2014;9:e98824.
26. Hozumi H, Enomoto N, Kono M, et al. Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. *PLoS One* 2015;10:e0120313.
27. Center for Review and Dissemination, University of York. PROSPERO:

International Prospective Register of Systematic Reviews. Available from: http://www.crd.york.ac.uk/prospero/. [Accessed 17 Apr 2016].

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

29. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? *J Am Acad Dermatol* 2002;46:626-36.

30. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.

31. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005;12:481-5.

32. Ware JE, Jr, Snow KK, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Center 1993.

33. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427-37.

34. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280-6.

35. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.

36. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.

37. Deeks JJ, Altman DG. Effect measures for meta-analysis of trials with binary outcomes. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care Meta-Analysis in Context*. 2nd ed. London: BMJ Publishing Groups 2001:313-35.

38. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55:893-9.

39. Whitehead A, Bailey AJ, Elbourne D. Combining summaries of binary outcomes with those of continuous outcomes in a meta-analysis. *J Biopharm Stat* 1999;9:1-16.

40. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*

1986;7:177-88.

41. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.

42. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration 2011. Available from: http://www. handbook.cochrane.org.

43. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

44. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.

45. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, w64.

46. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

AUTHORS' CONTRIBUTIONS

Hiroyuki Kamiya (HK) conceived this research project and planned the entire methods to undertake it. He also wrote the manuscript of this protocol.

Ogee Mer Panlaqui (OMP) made contributions in the conception of this research project and planning search strategy and data extraction.

Shinyu Izumi (SI) got involved in the process of determining the selection of the appropriate population and the outcomes targeted in this review.

Takashi Sozu (TS) made contributions in planning statistical analysis, in particular, determining the appropriate statistical methods to report summary effects and data synthesis.

COMPETING INTERESTS

No, there are no competing interests

Appendix: Searching strategies for prognostic studies with high sensitivity

Ovid Medline

1 exp Polymyositis/

2 exp Dermatomyositis/

3 exp Myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp Lung Diseases, Interstitial/

12 exp Pulmonary Fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 incidence.sh.

19 exp Mortality/

20 follow-up studies.sh.

21 prognos$.tw.

22 predict$.tw.

23 course$.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

Ovid EMBASE

1 exp polymyositis/

2 exp dermatomyositis/

3 exp myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp interstitial lung disease/

12 exp lung fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 exp disease course/

19 risk$.mp.

20 diagnos$.mp.

21 follow-up.mp.

22 ep.fs.

23 outcome.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

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	Checklist item
ADMINISTRATIVE INFORMATION		
✓ Title:		
Identification	1a	Identify the report as a protocol of a systematic review
Update	1b	If the protocol is for an update of a previous systematic review, identify as such
✓ Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
✓ Authors:		
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments	4	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	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
✓ Rationale	6	Describe the rationale for the review in the context of what is already known
✓ Objectives	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	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	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	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	Describe the mechanism(s) that will be used to manage records and data throughout the review

	Selection process	11b	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	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	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	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	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	Describe criteria under which study data will be quantitatively synthesised
		15b	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	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
		15d	If quantitative synthesis is not appropriate, describe the type of summary planned
√	Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
√	Confidence in cumulative evidence	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 of idiopathic inflammatory myopathies complicated with interstitial lung disease: protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
Keywords:	idiopathic inflammatory myopathy, Interstitial lung disease < THORACIC MEDICINE, prognosis, systematic review, meta-analysis

TITLE

Prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease: protocol for a systematic review and meta-analysis

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WORD COUNTS

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ABSTRACT

Introduction

Idiopathic inflammatory myopathies may be an overlapping disease complex. Although interstitial lung disease affects the mortality and morbidity of the disease, a clinical course and prognosis of the disease complicated with interstitial lung disease are diverse among individuals and prognostic factors have yet to be clarified. This article aims to report the rationale and methodology of a future intended systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease.

Methods and analysis

Participants are eligible if they are diagnosed as polymyositis/dermatomyositis, clinically amyopathic dermatomyositis or anti-synthetase syndrome complicated with interstitial lung disease. Primary outcomes are all-cause and pulmonary-cause mortality and secondary outcomes include a progression-free survival and a deterioration of health-related quality of life. All primary studies of any study design aside from case reports or case series are included. Two reviewers search electronic databases such as the Medline, EMBASE and Science Citation Index Expanded and extract relevant data according to a piloted data extraction form independently. The risk of bias in individual studies is evaluated based on the Quality in Prognostic Studies (QUIPS) tool. Meta-analysis will be conducted if 3 or more studies are available for each outcome and pooled effects will be presented by the odds ratio. Where combing data is inappropriate due to a small number of studies or substantial heterogeneity, the results are reported qualitatively. The subgroup and sensitivity analysis are also considered based on clinical and methodological differences such as clinical manifestations, study designs and quality of studies. Evidence level is assessed following the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method.

Ethics and dissemination

This study raises no ethical issues as it is based on the summary results of previously published articles. The results will be reported in a peer-reviewed medical journal.

PROSPERO registration number

CRD42016036999

ARTICLE SUMMARY

Strengths and limitations of this study

- Systematic review and meta-analysis of primary studies of any type of design excluding case reports or case series to address the clinical question of prognosis.
- First evidence based on a potentially large population derived from data synthesis for a rare disease.
- Potential difficulty in interpreting and applying the results due to a diversity and high risk of bias in included studies.

AIM

This article aims to report in details the rationale and methodology of an intended future systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease to ensure the rigorousness and transparency of the research. Any result expected to be derived from the review is not sought or presented in this report.

BACKGROUND

Rationale

Interstitial lung disease (ILD) has been drawing much attention for the last few decades.[1] It is partly because there is a growing number of patients with the disease due to the development of diagnostic tools [2] and it is often difficult to be treated and can follow a fatal clinical course.[3] ILD is a comprehensive disease entity that demonstrates common final findings of parenchymal fibrosis mixed with an inflammation despite a diversity of those mixtures among cases.[4] While external stimuli such as certain drug and occupational exposure are noted to cause ILD,[5-6] another notorious factor is connective tissue disease, which manifests ILD as a pulmonary complication.[7]

Polymyositis/dermatomyositis is one of the classic connective tissue diseases and categorized into idiopathic inflammatory myopathies.[8-9] It is triggered by unknown causes and progressed by an accelerated autoimmune reaction.[10] Although polymyositis/dermatomyositis is characterized by proximal muscular weakness and

unique cutaneous findings, ILD frequently complicates and is closely related to the morbidity and mortality of the disease.[11] Historically, anti-Jo-1 antibody, an autoantibody directed against histidyl-tRNA synthetase (one type of aminoacyl-tRNA synthetase (ARS)) in the cytoplasm, was identified in patients with polymyositis/dermatomyositis and helped in the diagnosis of the disease as it was highly specific and predictive of the disease.[12] The latest immunochemical development has discovered a large number of other autoantibodies that are also specific or associated with autoimmune myositis.[13] In particular, the identification of anti-ARS antibodies other than anti-Jo-1 antibody is clinically important [14] and patients with those antibodies are noted to frequently present with cutaneous changes pathognomonic of dermatomyositis, arthralgia/arthritis and fever in addition to myositis and ILD. This led to the development of the new term called anti-synthetase syndrome [15] although manifestations of the disease could be diverse depending on the type of anti-ARS antibodies.[16] Furthermore, anti-melanoma differentiation-associated gene 5 (MDA5) antibody was identified in clinically amyopathic dermatomyositis,[17] which is considered as a subgroup of dermatomyositis featuring clinically no or less muscular weakness and rapidly-progressive ILD.[18] It is recognized that the morbidity and mortality of anti-synthetase syndrome and clinically amyopathic dermatomyositis are also related to ILD.[19-20]

As polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome demonstrate common findings regardless of some clinical differences, they may be on the same disease spectrum that characterizes a complication of ILD, which will affect the prognosis of the disease.[21-22] However, it is generally believed that clinical courses are diverse and the prognosis varies among individuals although ILD is known to suggest a poor prognosis of the disease.[23-24] The identification of prognostic factors for patients with ILD will improve the management of this disease complex and provide great benefits with daily clinical practice as it will enable clinicians to predict the prognosis and implement medical resources efficiently. There has been little literature describing prognostic factors of this disease spectrum complicated with ILD and most currently available evidence is based on a small number of patients in a single or few medical institutions as this is a rare disease and thus could

result in anecdotal reports.[25-26] Therefore, this systematic review has been planned to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and eventually to improve the prognosis of the disease.

Hypothesis

The clinical course of idiopathic inflammatory myopathies complicated with ILD is diverse and there must be undefined factors related to the prognosis of the disease.

Research question

- What are prognostic factors of idiopathic inflammatory myopathies complicated with ILD?
- What is the most predictive clinical information of the mortality of idiopathic inflammatory myopathies complicated with ILD?
- Is there any difference of prognostic factors of idiopathic inflammatory myopathies complicated with ILD depending on the difference of clinical manifestations (i.e., polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome)?

Objectives of the review

This systematic review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and clarify what is the most predictive factor of the mortality of the disease.

METHODS

Registration and methodology

This protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews) at Centre for Review and Dissemination at University of York [27] (CRD42016036999) and reported following a guideline of PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols).[28]

Timeline

This study has yet to be initiated except for a pilot search and determining search terms and constructing a data extraction form. The full search is scheduled to be conducted on the first week of May 2016 and extended to the latest depending on the date of publication of this protocol.

Eligibility criteria

Participants

Patients with polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome complicated with ILD of adult onset (over 16 years of age) are included. Polymyositis/dermatomyositis and clinically amyopathic dermatomyositis are diagnosed based on the criteria such as Bohan and Peter [8-9] and Sontheimer,[29] which combine clinical, physiological and pathological findings as previously proposed. Anti-synthetase syndrome is included if a complication of ILD is noted in addition to the positivity of anti-ARS antibody and another organ involvement such as myopathies and unique cutaneous manifestations. The diagnosis of ILD is made based on physical exams, pulmonary function tests and radiological abnormalities. Patients are required to be followed up for at least 6 months. All patients are included at any time point during the disease course and from any clinical setting such as primary and secondary care. Juvenile myositis and overlap-myositis are excluded from the review.

Exposures or interventions (potential prognostic factors)

All clinical information such as demographic features and disease profiles are considered as potential prognostic factors. Therapeutic interventions can also be a prognostic factor of the disease. Although there is no limitation as to the type of therapeutic interventions, only the treatment with a duration of more than 6 months is a candidate for a factor of prognosis. Comparators are no presence or less values of these factors including demographic features, disease profiles and therapeutic interventions. Some studies may pre-specify a prognostic factor of interest while others may only describe demographic, laboratory or radiological data depending on the occurrence of the outcomes. Although the former case is obvious, all clinical information stated in the latter case is also sought to be analyzed as potential prognostic factors.

Outcomes and prioritization

All-cause and pulmonary-cause mortality are primary outcomes and secondary outcomes include a progression of the disease and a deterioration of health-related quality of life. The disease progression is defined based on combined findings of symptomatic, functional (pulmonary function tests) and radiological changes over the follow-up period of time after the diagnosis or the initiation of treatment. An individual component comprising the combined criteria can also define a clinical course of the disease. Health-related quality of life is expected to be evaluated based on questionnaires such as the 36-Item Short Form Health Survey (SF-36).[30]

Studies

Any type of primary studies excluding case reports or case series, whether prospective or retrospective, is included in the review if it describes the association of the predefined outcomes with potential prognostic factors of polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome with ILD. The unavailability of relevant statistics to describe the association does not exclude studies if they meet the inclusion criteria otherwise. Where studies consisted of a composite of this disease category, they are eligible for inclusion unless other ineligible cases such as juvenile myositis and overlap-myositis are included. Editorials, letters and review articles are excluded. Although there is no limitation regarding the date of studies and the number of participants, studies are limited to English literature. Conference proceedings with no further full reports and studies with only abstracts are also excluded due to concerns of lack of information unless a detailed data is offered by authors.

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 Ovid Medline and Ovid EMBASE using key terms of study population and methodology such as polymyositis, dermatomyositis, anti-synthetase syndrome, ILD and prognosis. Appropriate search filters for prognostic studies of the Medline and EMBASE are derived from previous reports.[31-32] They are combined with both subject headings and text words of content specific terms and their synonyms, which are determined referring to applicable reviews of the similar subject in the Cochrane Database of Systematic Reviews (Appendix). Search terms are finalized through an independent attempt of construction and a pilot search by two reviewers and examining the agreement of retrieved articles. Science Citation Index Expanded (via Web of Science) is also searched for citations, which are not covered by other electronic databases. In addition, review articles identified through the same search process over the last 5 years are screened and reference lists of relevant articles are also hand-searched to identify potential primary articles. Authors of conference proceedings with no further full reports and studies with only abstracts are asked to provide a relevant unpublished data. Grey literature is searched through Google Scholar following the previous report,[33] which focuses on article titles of the first 300 reports using the above-mentioned search terms. An expert in this field is also consulted to collect additional reports.

Study records

Data management

Relevant articles are managed through EndNote X7 and all extracted data are stored in a Microsoft Excel spreadsheet.

Selection of studies and data extraction

Two reviewers (HK/OMP) independently examine titles and abstracts of all retrieved articles and select studies following the inclusion and exclusion criteria. If a duplicate or updated report is revealed, the study with the largest dataset alone is included. However, multiple articles by the same research group are included if the outcomes are different. Data are also extracted by the same reviewers (HK/OMP) based on the data extraction

form, which has been predefined, reviewed and finalized through a pilot test to a small sample of eligible studies and a discussion among reviewers. A disagreement is resolved through a consultation with another reviewer.

Data items

The following data are extracted: names of the first author, publication year, study location, study design, follow-up periods, study population, pattern of ILD, number of participants, their demographic features such as age and gender, autoantibodies, comparators if applicable, clinical outcomes, counts of the outcomes, potential prognostic factors, methods for statistical analysis of the association of prognostic factors with the outcomes, summary statistics and items associated with risk of bias. Both unadjusted and adjusted measurements are drawn and adjusted factors are also extracted if available.

Assessment of risk of bias in individual studies

The risk of bias in individual studies is assessed based on the Quality in Prognostic Studies (QUIPS) tool.[34-35] Specifically, it contains 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain is rated as having high, moderate or low risk of bias and the overall risk of bias of a study is evaluated by a total rating of all domains. For example, a study showing low risk of bias in all domains is defined as having low risk of bias.

Statistical analysis

Dealing with missing data

If summary statistics to address the association of potential prognostic factors with the outcomes are not obtained directly, they are estimated using other relevant data. If it is unfeasible, authors are contacted and asked to provide these data.

Measurements of the association

Two major study designs to address the question of prognosis are cohort and case-control studies. In general, the former is summarized with the hazard ratio (HR)

using the Cox proportional hazard regression model where time-to-event data are fitted although the odds ratio (OR), risk ratio (RR) or risk difference (RD) may also be used to estimate the proportion of the event. The latter type of studies calculates the OR using the logistic regression model where only point estimates of the event are considered. Therefore, the common measurements of the association of potential prognostic factors with the outcomes will include the OR, RR, RD and HR.

If the HR is not directly provided, it is re-calculated from other information such as the log rank test and Kaplan-Meier survival curve.[36-37] The OR may also be unavailable directly through the logistic regression model and only the comparison of potential prognostic factors between two groups with and without the event may be presented. In this case the OR is calculated manually based on counts of the outcome.

The RD is affected by the baseline risk of the event, which can be varied among studies and thus unfavorable in pooling data. The RR has an advantage over the RD regarding this issue and therefore the latter is converted to the former if the proportion of the outcome in two comparative groups is available. The OR can be approximated to the RR if the outcome is rare [38] and the HR can also be approximated to the RR or OR if the follow-up duration is short and the ratio of the occurrence of the outcome in two comparative groups is small in addition to the condition that the outcome is rare.[39] In fact, a recent study with a large sample size demonstrated that the survival rates at 1 and 5 years were 97 and 91% in polymyositis/dermatomyositis with ILD while they were 99 and 95% in those without ILD.[40] As a result, the OR, RR and HR are assumed to be interchangeable and the OR will be used to summarize the association of potential prognostic factors with the outcomes. The association is reported following the convention that over one value indicates an increased risk of the outcome, i.e., the OR>1.0 indicates an increased chance of death.

Where potential prognostic factors are continuous variables, the mean difference may be presented from the comparison of groups with and without the event. The mean difference is divided by the standard deviation and converted to the standardized mean difference for further analysis of the association.

Data synthesis

The results across studies are pooled if the outcome data are available in 3 or more studies. Summary effects are sought to be presented as the OR with the assumption that the OR, RR and HR could be interchangeably approximated to each other under a specific condition. Accordingly, the OR and HR of continuous variables are assumed to be representing the same effect measurement and can be combined together as the OR while those of categorical variables are assumed similarly and can undergo the same data handling. The standardized mean difference, which may be presented as the effect measurement of continuous variables, is combined by itself. As the standardized mean difference may be estimated from the comparison of groups with and without the event, it is difficult to be combined with the OR of the same variable, which will be estimated through the logistic regression model with binary outcomes. This presumable situation is different from a previously reported case where continuous and binary outcomes can be combined.[41] When the median is presented for continuous variables instead of the mean, the latter is estimated from the former using the range and a sample size based on the previous report.[42] In short, for a smaller sample the mean is recalculated by a sum of the smallest and largest value, and twice the median, which is divided by four whereas it is approximated to the median if a sample size is larger than 25.

Unadjusted and adjusted estimates of the association are combined separately as it is reasonably expected that prognostic studies can be distorted by confounders and presenting summary statistics with adjustments in comparison with crude effects without adjustments are more likely to demonstrate meaningful results. If more than one multivariable models with adjustments are available, the model with the best fit or with the most 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.

Meta-analysis is conducted by a random-effect model [43] considering that there should be certain extent of variability among studies due to clinical and methodological differences. Data such as the logarithmic scale of the OR or the standardized mean difference and their standard errors are combined by the inverse variance method using the statistical software, Review Manager (RevMan) Version 5.3 (Copenhagen: The

Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary effects of each prognostic factor are estimated as the OR or the standardized mean difference with 95% confidence interval and Tau square, which indicates between-study variances. 95% prediction interval will also be calculated.[44] The statistical significance is set at the 5% level. If meta-analysis is inappropriate due to few studies or a concern of substantial heterogeneity, the results are reported qualitatively. However, in such a case that a study comprises a different subset of the disease, i.e., polymyositis and dermatomyositis, pooling data is sought by contacting authors and asking them to provide data in each subset.

Heterogeneity

The heterogeneity is assessed statistically by the chi-square test and I square. The 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 to 30%), moderate (30 to 50%), substantial (50 to 70%) and considerable (70 to 100%).[45] The clinical heterogeneity is assumed to be mainly derived from a different subset of diseases and types of ILD and autoantibodies among included studies while the methodological heterogeneity is caused by a variety of study designs such as prospective or retrospective studies, diverse follow-up lengths, a sample size and study location. In particular, clinically amyopathic dermatomyositis, which is characterized by high probability of a complication of rapidly progressive ILD and the presence of anti-MDA5 antibody, may be a different group of the same spectrum of the disease. Therefore, the subgroup analysis is considered if data are available according to the difference of clinical manifestations (polymyositis, dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome) and types of ILD (acute or rapidly progressive and chronic) and autoantibodies identified (anti-ARS antibody including anti-Jo-1 antibody and non-Jo-1 antibody and anti-MDA5 antibody). An analysis of studies with the same design such as a prospective cohort study and a case-control study is also explored. In addition, the influence of different follow-up lengths is analyzed based on two different time points; 1 and 5 years. The summary effects will also be presented as their original statistical forms, i.e., OR, RR and HR, to

investigate the validity of considering these three statistics as interchangeable measurements. The effect of a sample size and study location on the association between the outcomes and prognostic factors is sought to be revealed by dividing into a few arbitrary groups, i.e., less than 50, 50-100 or over 100 and Asia or non-Asia, respectively. The sensitivity analysis is conducted focused on studies with low risk of bias alone.

Metabiases

The small study bias including publication bias is evaluated graphically examining the presence of asymmetry in a funnel plot and statistically by the Egger's test with the natural logarithmic scale of the OR being regressed against its standard error if a meta-analysis is based on 10 or more studies for an outcome.[46] The statistical significance for asymmetry is set at the 10% level because of low power of the test. If publication bias is statistically suspected, the number of missing studies and adjusted summary effects are estimated by the method of trim and fill.[47] Selective reporting is assessed examining the consistency of study findings with its protocol if available.

Confidence in cumulative evidence

It was reported that the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method could be useful in the assessment of prognostic reviews as in the case of assessing treatment effects.[48] Although the report focused on a question of prognosis in a specific population rather than prognostic factors, 5 domains described to rate down the quality of evidence (risk of bias, inconsistency, imprecision, indirectness and publication bias) and 2 domains to rate it up (large effect and dose response gradient) are also applicable for this review as the fundamental methodological process of evaluation is similar between these two types of prognosis studies.

ETHICAL CONSIDERATION, REPORTING AND DISSEMINATION

This systematic review is based on the summary results of previously published articles and individual patient data will not be obtained or accessed. Even if authors of included studies are asked to provide relevant missing data, any clinical information connecting with an individual patient will not be revealed. Therefore, there is no concerning ethical

issue in the conduct of this research. The result of the review will be reported in a peer-reviewed medical journal following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [49] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement.[50] Any information, which is obtained or utilized in the process of conducting the review, will be offered individually on request. The Microsoft Excel spreadsheet, which stores all data extracted from included studies and is the basis of the analysis in this research, may become open to the public in a digital repository such as Dryad after the final result is published in a journal.

DISCUSSION

This review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and identify the most predictive factor of the mortality of this disease spectrum. Although some literature has addressed this clinical question,[25-26] the reports are based on a small number of population in a few medical institutions. In addition, systematic reviews have yet to be conducted to solve the issue. Therefore, this will be the first comprehensive review to answer the question and be a valuable guide for clinicians to treat patients with this diverse disease spectrum. Moreover, it will help patients benefit from the appropriate medical care based on higher evidence and decrease the improper implementation of medical resources, which may eventually contribute to reduce the burden of the society.

However, there are some methodological limitations in the conduct of this review. Firstly, conference proceedings and studies with only abstracts are excluded, which may lead to biased results although we believe that the influence of the issue can be reduced to the minimum by contacting authors and requesting them to offer relevant data. Secondly, our statistical assumption that the OR, RR and HR could be interchangeably approximated to each other may not necessarily be correct although this is partly supported by the finding of one of the largest studies that the mortality of idiopathic inflammatory myopathies complicated with ILD is not high.[40] However, we also believe that this will not affect the validity of the results because the summary effects are also presented as their original statistical forms. Finally, it may be difficult to

combine data from all eligible studies and estimate summary effects due to clinical and methodological diversity among studies, which may reduce the statistical power in the analysis and spoil the significance of the review. However, we also expect this issue to be solved at least to some extent by requesting authors to offer relevant data. In addition, as the importance of a systematic review is not necessarily placed on statistical data synthesis and a qualitative analysis of the results will remain meaningful, we believe that the value of the review will never be ruined by this issue.

CONCLUSIONS

The rationale and methodology of a systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with ILD were described. Although there are some methodological limitations in conducting the review, they will not be serious enough to ruin its value. The results of the review is expected to be a future guide for both clinicians and patients to treat the disease.

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CONFLICT OF INTERESTS

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

REFERENCES

1. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015;192:e3-19.
2. King TE, Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268-79.
3. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431-40.
4. Leslie KO. Historical perspective: a pathologic approach to the classification of idiopathic interstitial pneumonias. *Chest* 2005;128:513s-9s.
5. Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig* 2013;51:260-77.
6. Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. *Curr Opin Pulm Med* 2015;21:193-200.
7. Fischer A, Lee JS, Cottin V. Interstitial lung disease evaluation: detecting connective tissue disease. *Respiration* 2015;90:177-84.
8. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344-7.
9. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975;292:403-7.
10. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med* 2005;201:591-601.
11. Marie I, Hatron PY, Dominique S, et al. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. *Arthritis Rheum* 2011;63:3439-47.
12. Yoshida S, Akizuki M, Mimori T, et al. The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. A marker for a subset of polymyositis with interstitial pulmonary fibrosis. *Arthritis Rheum* 1983;26:604-11.
13. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine* 1991;70:360-74.
14. Nakashima R, Imura Y, Hosono Y, et al. The multicenter study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. *PLoS One* 2014;9:e85062.

15. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med* 1990;77:1019-38.
16. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One* 2013;8:e60442.
17. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum* 2005;52:1571-6.
18. Gerami P, Schope JM, McDonald L, et al. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006;54:597-613.
19. Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. *Autoimmunity* 2006;39:233-41.
20. Ye S, Chen XX, Lu XY, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. *Clin Rheumatol* 2007;26:1647-54.
21. Yamasaki Y, Yamada H, Ohkubo M, et al. Longterm survival and associated risk factors in patients with adult-onset idiopathic inflammatory myopathies and amyopathic dermatomyositis: experience in a single institute in Japan. *J Rheumatol* 2011;38:1636-43.
22. Marie I, Josse S, Hatron PY, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. *Arthritis Care Res* 2013;65:800-8.
23. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep* 2013;15:349.
24. Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. *Autoimmun Rev* 2012;12:210-7.
25. Fujisawa T, Hozumi H, Kono M, et al. Prognostic factors for myositis-associated interstitial lung disease. *PLoS One* 2014;9:e98824.
26. Hozumi H, Enomoto N, Kono M, et al. Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. *PLoS One* 2015;10:e0120313.
27. Center for Review and Dissemination, University of York. PROSPERO:

International Prospective Register of Systematic Reviews. Available from: http://www.crd.york.ac.uk/prospero/. [Accessed 17 Apr 2016].

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

29. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? *J Am Acad Dermatol* 2002;46:626-36.

30. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.

31. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005;12:481-5.

32. Ware JE, Jr, Snow KK, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide.* Boston, MA: The Health Institute, New England Medical Center 1993.

33. Haddaway NR, Collins AM, Coughlin D, et al. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. *PloS one.* 2015;10:e0138237.

34. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427-37.

35. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280-6.

36. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.

37. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.

38. Deeks JJ, Altman DG. Effect measures for meta-analysis of trials with binary outcomes. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care Meta-Analysis in Context*. 2nd ed. London: BMJ Publishing Groups 2001:313-35.

39. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55:893-9.

40. Johnson C, Pinal-Fernandez I, Parikh R, et al. Assessment of Mortality in

Autoimmune Myositis With and Without Associated Interstitial Lung Disease. *Lung* Published Online First: 11 May 2016. doi:10.1007/s00408-016-9896-x

41. Whitehead A, Bailey AJ, Elbourne D. Combining summaries of binary outcomes with those of continuous outcomes in a meta-analysis. *J Biopharm Stat* 1999;9:1-16.

42. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology.* 2005;5:13.

43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

44. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.

45. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration 2011. Available from: http://www. handbook.cochrane.org.

46. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

47. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56:455-63.

48. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.

49. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, w64.

50. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

AUTHORS' CONTRIBUTIONS

Hiroyuki Kamiya (HK) conceived this research project and planned the entire methods to undertake it. He also wrote the manuscript of this protocol.

Ogee Mer Panlaqui (OMP) made contributions in the conception of this research project and planning search strategy and data extraction.

Shinyu Izumi (SI) got involved in the process of determining the selection of the appropriate population and the outcomes targeted in this review.

Takashi Sozu (TS) made contributions in planning statistical analysis, in particular, determining the appropriate statistical methods to report summary effects and data synthesis.

Appendix: Searching strategies for prognostic studies with high sensitivity

Ovid Medline

1 exp Polymyositis/

2 exp Dermatomyositis/

3 exp Myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp Lung Diseases, Interstitial/

12 exp Pulmonary Fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 incidence.sh.

19 exp Mortality/

20 follow-up studies.sh.

21 prognos$.tw.

22 predict$.tw.

23 course$.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

Ovid EMBASE

1 exp polymyositis/

2 exp dermatomyositis/

3 exp myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp interstitial lung disease/

12 exp lung fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 exp disease course/

19 risk$.mp.

20 diagnos$.mp.

21 follow-up.mp.

22 ep.fs.

23 outcome.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

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 3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	Page 1	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 17	Indicate sources of financial or other support for the review
Sponsor	5b	Page 17	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Page 17	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
		INTRODUCTION	
Rationale	6	Page 4-6	Describe the rationale for the review in the context of what is already known
Objectives	7	Page 6	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 7-8	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 8	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 9	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 9	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	Page 9	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 9-10	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 10	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 8	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 10	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 12	Describe criteria under which study data will be quantitatively synthesised
	15b	Page 10-13	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 13-14	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	Page 13	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Page 14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Page 14	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 of idiopathic inflammatory myopathies complicated with interstitial lung disease: protocol for a systematic review and meta-analysis

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Primary Subject Heading:	Respiratory medicine
Secondary Subject Heading:	Evidence based practice
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TITLE

Prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction

Idiopathic inflammatory myopathies may be an overlapping disease complex. Although interstitial lung disease affects the mortality and the morbidity of the disease, a clinical course and the prognosis of the disease complicated with interstitial lung disease are diverse among individuals and prognostic factors have yet to be clarified. This article aims to report the rationale and the methodology of a future intended systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease.

Methods and analysis

Participants are eligible if they are diagnosed as polymyositis/dermatomyositis, clinically amyopathic dermatomyositis or anti-synthetase syndrome complicated with interstitial lung disease. Primary outcomes are all-cause and pulmonary-cause mortality and secondary outcomes include a progression of the disease and a deterioration of health-related quality of life. All primary studies of any design aside from case reports or case series are included. Two reviewers search electronic databases such as the Medline, the EMBASE and the Science Citation Index Expanded and extract relevant data independently. A risk of bias in individual studies is evaluated based on the Quality in Prognostic Studies tool. Meta-analysis will be conducted if 3 or more studies are available for each outcome and pooled effects will be presented by the odds ratio. Where combining data is inappropriate due to a small number of studies or substantial heterogeneity, the result is reported qualitatively. Subgroup and sensitivity analysis are also considered based on clinical and methodological differences such as clinical manifestations, study designs and the quality of studies. The evidence level is assessed following the Grades of Recommendation, Assessment, Development and Evaluation method.

Ethics and dissemination

This study raises no ethical issues as it is based on the findings of previously published articles. The result will be reported in a peer-reviewed medical journal.

PROSPERO registration number

CRD42016036999

ARTICLE SUMMARY

Strengths and limitations of this study

- A systematic review and meta-analysis of primary studies of any type of designs excluding case reports or case series to address a clinical question of prognosis.
- The first evidence based on a potentially large population derived from data synthesis for a rare disease.
- A potential difficulty in interpreting and applying the result due to diversity and a high risk of bias in included studies.

INTRODUCTION

Aim of the report

This article aims to report in detail the rationale and the methodology of an intended future systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with interstitial lung disease (ILD) to ensure rigorousness and transparency of the research. Any result expected to be derived from the review is not sought or presented in this report.

Rationale

ILD has been drawing much attention for the last few decades.[1] It is partly because there is a growing number of patients with the disease due to the development of diagnostic tools [2] and it is often difficult to be treated and can follow a fatal clinical course.[3] ILD is a comprehensive disease entity that demonstrates common final findings of parenchymal fibrosis mixed with inflammation despite a diversity of those mixtures among cases.[4] While external stimuli such as a certain drug and an occupational exposure are noted to cause ILD,[5-6] another notorious factor is connective tissue disease, which manifests ILD as a pulmonary complication.[7]

Polymyositis/dermatomyositis is one of the traditional connective tissue diseases and categorized into idiopathic inflammatory myopathies.[8-9] It is triggered by unknown causes and progressed by an accelerated autoimmune reaction.[10] Although polymyositis/dermatomyositis is characterized by proximal muscular weakness and unique cutaneous findings, ILD is frequently complicated and closely related to the morbidity and the mortality of the disease.[11] Historically, anti-Jo-1 antibody, an

autoantibody directed against histidyl-tRNA synthetase (one type of aminoacyl-tRNA synthetase (ARS)) in the cytoplasm, was identified in patients with polymyositis/dermatomyositis and helped in the diagnosis of the disease as it was highly specific and predictive of the disease.[12] The latest immunochemical development has discovered a large number of other autoantibodies that are also specific or associated with autoimmune myositis.[13] In particular, the identification of anti-ARS antibodies other than anti-Jo-1 antibody is clinically important [14] and patients with those antibodies are noted to frequently present with cutaneous changes pathognomonic of dermatomyositis, arthralgia/arthritis and fever in addition to myositis and ILD. This led to the development of a new term called anti-synthetase syndrome [15] although manifestations of the disease could be diverse depending on the type of anti-ARS antibodies.[16] Furthermore, anti-melanoma differentiation-associated gene 5 (MDA5) antibody was identified in clinically amyopathic dermatomyositis,[17] which is considered as a subgroup of dermatomyositis featuring clinically no or less muscular weakness and rapidly-progressive ILD.[18] It is recognized that the morbidity and the mortality of anti-synthetase syndrome and clinically amyopathic dermatomyositis are also related to ILD.[19-20]

As polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome demonstrate common findings regardless of some clinical differences, they may be on the same disease spectrum that characterizes a complication of ILD, which will affect the prognosis of the disease.[21-22] However, it is generally believed that a clinical course is diverse and the prognosis varies among individuals although ILD is known to suggest a poor prognosis of the disease.[23-24] The identification of prognostic factors for patients with ILD will improve the management of this disease complex and provide great benefits with daily clinical practice as it will enable clinicians to predict the prognosis and implement medical resources effectively. There has been little literature describing prognostic factors of this disease spectrum complicated with ILD and most currently available evidence is based on a small number of patients in a single or few medical institutions as this is a rare disease and thus could result in anecdotal reports.[25-26] Therefore, this systematic review has been planned to

elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and eventually to improve the prognosis of the disease.

Hypothesis

A clinical course of idiopathic inflammatory myopathies complicated with ILD is diverse and there must be undefined factors related to the prognosis of the disease.

Research question

- What are prognostic factors of idiopathic inflammatory myopathies complicated with ILD?
- What is the most predictive clinical information of the mortality of idiopathic inflammatory myopathies complicated with ILD?
- Is there any difference among prognostic factors of idiopathic inflammatory myopathies complicated with ILD depending on the difference of clinical manifestations (i.e., polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome)?

Objective of the review

This systematic review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and clarify what is the most predictive factor of the mortality of the disease.

METHODS AND ANALYSIS

Registration and methodology

This protocol is registered with PROSPERO (International Prospective Register of Systematic Reviews) at Centre for Review and Dissemination at University of York [27] (CRD42016036999) and reported following the guideline of PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols).[28]

Timeline

This study has yet to be initiated except for a pilot search and determining search terms and constructing a data extraction form. A full search is scheduled to be conducted on the first week of May 2016 and extended to the latest depending on the date of publication of this protocol.

Eligibility criteria

Participants

Patients with polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome complicated with ILD of adult onset (over 16 years of age) are included. Polymyositis/dermatomyositis and clinically amyopathic dermatomyositis are diagnosed based on the criteria such as Bohan and Peter [8-9] and Sontheimer,[29] which combine clinical, physiological and pathological findings as previously reported. Anti-synthetase syndrome is included if a complication of ILD is noted in addition to the positivity of anti-ARS antibody and another organ involvement such as myositis and unique cutaneous changes. The diagnosis of ILD is made based on physical exams, pulmonary function tests and radiological abnormalities. Patients are required to be followed up for at least 6 months. All patients are included at any time point during the disease course and from any clinical setting such as primary and secondary care. Juvenile myositis and overlap-myositis are excluded from the review.

Exposure or intervention (potential prognostic factors)

All clinical information such as demographic features and disease profiles are considered as potential prognostic factors. A therapeutic intervention can also be a prognostic factor of the disease. Although there is no limitation as to the type of therapeutic interventions, only treatment with a duration of more than 6 months is a candidate for the factor of prognosis. Comparators are no presence or less values of all of these information. Some studies may pre-specify a prognostic factor of interest while others may only describe demographic, laboratory or radiological data depending on the occurrence of the outcome. Although the former case is obvious, all clinical information stated in the latter case is also sought to be analyzed as potential prognostic factors.

Outcomes and prioritization

All-cause and pulmonary-cause mortality are primary outcomes and secondary outcomes include a progression of the disease and a deterioration of health-related quality of life. The disease progression is defined based on the combined findings of symptomatic, functional (pulmonary function tests) and radiological changes over the follow-up period of time after the diagnosis or the initiation of treatment. An individual component comprising the combined criteria can also define a clinical course of the disease. Health-related quality of life is expected to be evaluated based on a questionnaire such as the 36-Item Short Form Health Survey (SF-36).[30]

Studies

Any type of primary studies excluding case reports or case series, whether prospective or retrospective, is included in the review if it describes the association of the predefined outcome with potential prognostic factors of polymyositis/dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome with ILD. Unavailability of relevant statistics to describe the association does not exclude studies if they meet the inclusion criteria. If a study comprises a different subset of the disease complex, it is eligible for inclusion unless other ineligible cases such as juvenile myositis and overlap-myositis are included. Editorials, letters and review articles are excluded. Although there is no limitation regarding the date of studies and the number of participants, studies are limited to English literature. Conference proceedings with no further full reports and studies with only abstracts are also excluded due to concerns of lack of information unless detailed data are offered by authors.

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 Ovid Medline and the Ovid EMBASE using key terms of study population and the methodology such as polymyositis, dermatomyositis, anti-synthetase syndrome, ILD and prognosis. Appropriate search filters for prognostic studies of the Medline and the EMBASE are derived from previous reports.[31-32] They are combined with both subject headings and text words of content specific terms and their synonyms, which are determined referring to applicable reviews of the similar subject in the Cochrane Database of Systematic Reviews (Appendix). Search terms are finalized through an independent attempt of construction and a pilot search by two reviewers and examining the agreement of retrieved articles. The Science Citation Index Expanded (via Web of Science) is also searched for citations, which are not covered by other electronic databases. In addition, review articles identified through the same search process over the last 5 years are screened and reference lists of relevant articles are also hand-searched to identify potential primary articles. Authors of conference proceedings with no further full reports and studies with only abstracts are asked to provide relevant unpublished data. Grey literature is searched through Google Scholar following the previous report,[33] which focuses on article titles of the first 300 reports using the above-mentioned search terms. An expert in this field is also consulted to collect additional reports.

Study records

Data management

Relevant articles are managed through EndNote X7 and all extracted data are stored in a Microsoft Excel spreadsheet.

Selection of studies and data extraction

Two reviewers (HK/OMP) independently examine titles and abstracts of all retrieved articles and select studies following the inclusion and exclusion criteria. If a duplicate or updated report is revealed, the study with the largest dataset alone is included. However, multiple articles by the same research group are included if an outcome is different. Data are also extracted by the same reviewers (HK/OMP) based on the data extraction form, which has been predefined, reviewed and finalized through a pilot test to a small

sample of eligible studies and a discussion among reviewers. A disagreement is resolved through a consultation with another reviewer.

Data items

The following data are extracted: a name of the first author, the publication year, a study location, study designs, follow-up periods, study population, a pattern of ILD, the number of participants and their demographic features such as the age and the gender, autoantibodies, comparators if applicable, a clinical outcome, counts of the outcome, potential prognostic factors, methods for statistical analysis of the association of prognostic factors with the outcome, summary statistics and items associated with a risk of bias. Both unadjusted and adjusted measurement are drawn and adjusted factors are also extracted if available.

Assessment of a risk of bias in individual studies

A risk of bias in individual studies is assessed based on the Quality in Prognostic Studies (QUIPS) tool.[34-35] Specifically, it contains 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting. Each domain is rated as having a high, moderate or low risk of bias and the overall risk of bias of a study is evaluated by a total rating of all domains. For example, a study showing a low risk of bias in all domains is defined as having a low risk of bias.

Statistical analysis

Dealing with missing data

If summary statistics to address the association of potential prognostic factors with the outcome are not obtained directly, they are estimated using other relevant data. If it is unfeasible, authors are contacted and asked to provide these data.

Measurement of the association

Two major study designs to address a question of prognosis are cohort and case-control studies. In general, the former is summarized with the hazard ratio (HR) using the Cox proportional hazard regression model where time-to-event data are fitted although the

risk ratio (RR) or the risk difference (RD) may also be used to estimate the proportion of an event. The latter type of studies calculates the odds ratio (OR) using the logistic regression model where only point estimates of an event are considered. Therefore, the common measurement of the association of potential prognostic factors with an outcome will include the OR, the RR, the RD and the HR.

If the HR is not directly provided, it is re-calculated from other information such as the log rank test and the Kaplan-Meier survival curve.[36-37] The OR may also be unavailable directly through the logistic regression model and only the comparison of potential prognostic factors between two groups with and without an event may be presented. In this case the OR is calculated manually based on counts of the outcome.

The RD is affected by the baseline risk of an event, which can be varied among studies and thus unfavorable in pooling data. The RR has an advantage over the RD regarding this issue and therefore the latter is converted to the former if the proportion of an outcome in two comparative groups is available. The OR can be approximated to the RR if an outcome is rare [38] and the HR can also be approximated to the RR or the OR if the follow-up duration is short and the ratio of occurrence of an outcome in two comparative groups is small in addition to the condition that the outcome is rare.[39] In fact, a recent study with a large sample size demonstrated that the survival rates at 1 and 5 years were 97 and 91% in polymyositis/dermatomyositis with ILD while they were 99 and 95% in those without ILD.[40] As a result, the OR, the RR and the HR are assumed to be interchangeable and the OR will be used to summarize the association of potential prognostic factors with the outcome. The association is reported following the convention that the value of over one indicates an increased risk of the outcome, i.e., the OR>1.0 indicates an increased chance of death.

Where potential prognostic factors are continuous variables, the mean difference may be presented from the comparison of groups with and without an event. The mean difference is divided by the standard deviation and converted to the standardized mean difference for further analysis of the association.

Data synthesis

The result across studies are pooled if the outcome data are available in 3 or more studies. Summary effects are sought to be presented as the OR with the assumption that the OR, the RR and the HR could be interchangeably approximated to each other under a specific condition. Accordingly, the OR and the HR of continuous variables are assumed to be representing the same effect measurement and can be combined together as the OR while those of categorical variables are assumed similarly and can undergo the same data handling. The standardized mean difference, which may be presented as the effect measurement of continuous variables, is combined by itself. When the standardized mean difference is estimated from the comparison of groups with and without an event, it is difficult to be combined with the OR due to the same variable, which will be estimated through the logistic regression model with a binary outcome. This assumed situation is different from a previously reported case where a continuous and binary outcome can be combined.[41] When the median is presented for continuous variables instead of the mean, the latter is estimated from the former using the range and a sample size according to the previous report.[42] Briefly, for a smaller sample the mean is re-calculated by a sum of the smallest and largest value and twice the median, which is divided by four whereas it is approximated to the median if a sample size is larger than 25.

Unadjusted and adjusted estimates of the association are combined separately as it is reasonably expected that prognostic studies can be distorted by confounders and presenting summary statistics with adjustment in comparison with crude effects without adjustment are more likely to demonstrate meaningful result. If more than one multivariable models with adjustment are available, the model with the best fit or with the most 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.

Meta-analysis is conducted by a random-effect model [43] considering that there should be some extent of variability among studies due to clinical and methodological differences. Data such as the logarithmic scale of the OR or the standardized mean difference and their standard errors are combined by the inverse variance method using the statistical software, Review Manager (RevMan) Version 5.3 (Copenhagen: The

Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Summary effects of each prognostic factor are estimated as the OR or the standardized mean difference with the 95% confidence interval and Tau square, which indicates between-study variances. The 95% prediction interval will also be calculated.[44] Statistical significance is set at the 5% level. If meta-analysis is inappropriate due to few studies or concerns of substantial heterogeneity, the result is reported qualitatively. However, in a case where a study comprises a different subset of the disease, i.e., polymyositis and dermatomyositis, pooling data is sought by contacting authors and asking them to provide data in each subset.

Heterogeneity

Heterogeneity is assessed statistically by the chi-square test and I square. 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 to 30%), moderate (30 to 50%), substantial (50 to 70%) and considerable (70 to 100%).[45] Clinical heterogeneity is assumed to be mainly derived from a different subset of the disease and types of ILD and autoantibodies among included studies while methodological heterogeneity is caused by a variety of study designs such as prospective or retrospective studies and diverse follow-up lengths, sample sizes and study locations. In particular, clinically amyopathic dermatomyositis, which is characterized by high probability of a complication of rapidly progressive ILD and the presence of anti-MDA5 antibody, may be a different group of the same spectrum of the disease. Therefore, subgroup analysis is considered if data are available according to the difference of clinical manifestations (polymyositis, dermatomyositis, clinically amyopathic dermatomyositis and anti-synthetase syndrome) and types of ILD (acute or rapidly progressive and chronic) and autoantibodies identified (anti-ARS antibody including anti-Jo-1 antibody and non-Jo-1 antibody, and anti-MDA5 antibody). An analysis of studies with the same design such as a prospective cohort and a case-control study is also explored. In addition, the influence of different follow-up lengths is analyzed based on two different time points; 1 and 5 years. Summary effects will also be presented as their original statistical forms, i.e., the OR, the RR and the HR, to investigate the validity of

considering these three statistics as interchangeable. The effect of a sample size and a study location on the outcome is sought to be revealed by dividing them into a few arbitrary groups, i.e., less than 50, 50 to 100 or over 100 and Asia or non-Asia, respectively. Sensitivity analysis is conducted focused on studies with a low risk of bias alone.

Metabiases

Small study bias including publication bias is evaluated graphically examining the presence of asymmetry in a funnel plot and statistically by the Egger's test with the natural logarithmic scale of the OR being regressed against its standard error if meta-analysis is based on 10 or more studies for an outcome.[46] Statistical significance for asymmetry is set at the 10% level because of low power of the test. If publication bias is statistically suspected, the number of missing studies and an adjusted summary effect are estimated by the method of trim and fill.[47] Selective reporting is assessed examining the consistency of study findings with its protocol if available.

Confidence in cumulative evidence

It was reported that the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) method could be useful in the assessment of prognostic reviews as in the case of assessing treatment effects.[48] Although the report focused on a question of prognosis in a specific population rather than prognostic factors, 5 domains described to rate down the quality of evidence (risk of bias, inconsistency, imprecision, indirectness and publication bias) and 2 domains to rate it up (large effect and dose response gradient) are applicable for this review as the fundamental methodological process of evaluation is similar between these two types of prognosis studies.

ETHICS AND DISSEMINATION

This systematic review is based on the summary result of previously published articles and individual patient data will not be obtained or accessed. Even if authors of included studies are asked to provide relevant missing data, any clinical information connecting with an individual patient will not be revealed. Therefore, there is no concerning ethical issue in the conduct of this research. The result of the review will be reported in a

peer-reviewed medical journal following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [49] and the MOOSE (Meta-analysis of Observational Studies in Epidemiology) statement.[50] Any information, which is obtained or utilized in the process of conducting the review, will be offered individually on request. The Microsoft Excel spreadsheet, which stores all data extracted from included studies and is the basis of the analysis in this research, may become open to the public in a digital repository such as Dryad after the final result is published in a journal.

DISCUSSION

This review is intended to elucidate prognostic factors of idiopathic inflammatory myopathies complicated with ILD and identify the most predictive factor of the mortality of this disease complex. Although some literature has addressed this clinical question,[25-26] the reports are based on a small number of population in a few medical institutions. In addition, a systematic review has yet to be conducted to solve the issue. Therefore, this will be the first comprehensive review to answer the question and be a valuable guide for clinicians to treat patients with this diverse disease spectrum. Moreover, it will help patients benefit from the appropriate medical care based on higher evidence and decrease the improper implementation of medical resources, which may eventually contribute to reduce the burden of the society.

However, there are some methodological limitations in the conduct of this review. Firstly, conference proceedings and studies with only abstracts are excluded, which may lead to biased result although we believe that the influence of the issue can be reduced to the minimum by contacting authors and requesting them to offer relevant data. Secondly, our statistical assumption that the OR, the RR and the HR could be interchangeably approximated to each other may not necessarily be correct although this is partly supported by one of the largest studies, which reported that the mortality of idiopathic inflammatory myopathies complicated with ILD is not high.[40] However, we also believe that this will not affect the validity of result because summary effects are also presented as their original statistical forms. Finally, it may be difficult to combine data from all eligible studies and estimate summary effects due to clinical and

methodological diversity among studies, which may reduce statistical power in the analysis and spoil the significance of the review. However, we also expect this issue to be solved at least to some extent by requesting authors to offer relevant data. In addition, as the importance of a systematic review is not necessarily placed on statistical data synthesis and qualitative analysis of result will remain meaningful, we believe that the value of the review will never be ruined by this issue.

CONCLUSIONS

The rationale and the methodology of a systematic review and meta-analysis of prognostic factors of idiopathic inflammatory myopathies complicated with ILD were described. Although there are some methodological limitations in conducting the review, they will not be serious enough to ruin its value. The result of the review is expected to be a future guide for both clinicians and patients to treat the disease.

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COMPETING INTERESTS

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

REFERENCES

1. Raghu G, Rochwerg B, Zhang Y, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. *Am J Respir Crit Care Med* 2015;192:e3-19.
2. King TE, Jr. Clinical advances in the diagnosis and therapy of the interstitial lung diseases. *Am J Respir Crit Care Med* 2005;172:268-79.
3. Ley B, Collard HR, King TE, Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011;183:431-40.
4. Leslie KO. Historical perspective: a pathologic approach to the classification of idiopathic interstitial pneumonias. *Chest* 2005;128:513s-9s.
5. Kubo K, Azuma A, Kanazawa M, et al. Consensus statement for the diagnosis and treatment of drug-induced lung injuries. *Respir Investig* 2013;51:260-77.
6. Gulati M, Redlich CA. Asbestosis and environmental causes of usual interstitial pneumonia. *Curr Opin Pulm Med* 2015;21:193-200.
7. Fischer A, Lee JS, Cottin V. Interstitial lung disease evaluation: detecting connective tissue disease. *Respiration* 2015;90:177-84.
8. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975;292:344-7.
9. Bohan A, Peter JB. Polymyositis and dermatomyositis (second of two parts). *N Engl J Med* 1975;292:403-7.
10. Casciola-Rosen L, Nagaraju K, Plotz P, et al. Enhanced autoantigen expression in regenerating muscle cells in idiopathic inflammatory myopathy. *J Exp Med* 2005;201:591-601.
11. Marie I, Hatron PY, Dominique S, et al. Short-term and long-term outcomes of interstitial lung disease in polymyositis and dermatomyositis: a series of 107 patients. *Arthritis Rheum* 2011;63:3439-47.
12. Yoshida S, Akizuki M, Mimori T, et al. The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. A marker for a subset of polymyositis with interstitial pulmonary fibrosis. *Arthritis Rheum* 1983;26:604-11.
13. Love LA, Leff RL, Fraser DD, et al. A new approach to the classification of idiopathic inflammatory myopathy: myositis-specific autoantibodies define useful homogeneous patient groups. *Medicine* 1991;70:360-74.
14. Nakashima R, Imura Y, Hosono Y, et al. The multicenter study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. *PLoS One* 2014;9:e85062.

15. Marguerie C, Bunn CC, Beynon HL, et al. Polymyositis, pulmonary fibrosis and autoantibodies to aminoacyl-tRNA synthetase enzymes. *Q J Med* 1990;77:1019-38.
16. Hamaguchi Y, Fujimoto M, Matsushita T, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: heterogeneity within the syndrome. *PLoS One* 2013;8:e60442.
17. Sato S, Hirakata M, Kuwana M, et al. Autoantibodies to a 140-kd polypeptide, CADM-140, in Japanese patients with clinically amyopathic dermatomyositis. *Arthritis Rheum* 2005;52:1571-6.
18. Gerami P, Schope JM, McDonald L, et al. A systematic review of adult-onset clinically amyopathic dermatomyositis (dermatomyositis sine myositis): a missing link within the spectrum of the idiopathic inflammatory myopathies. *J Am Acad Dermatol* 2006;54:597-613.
19. Yoshifuji H, Fujii T, Kobayashi S, et al. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. *Autoimmunity* 2006;39:233-41.
20. Ye S, Chen XX, Lu XY, et al. Adult clinically amyopathic dermatomyositis with rapid progressive interstitial lung disease: a retrospective cohort study. *Clin Rheumatol* 2007;26:1647-54.
21. Yamasaki Y, Yamada H, Ohkubo M, et al. Longterm survival and associated risk factors in patients with adult-onset idiopathic inflammatory myopathies and amyopathic dermatomyositis: experience in a single institute in Japan. *J Rheumatol* 2011;38:1636-43.
22. Marie I, Josse S, Hatron PY, et al. Interstitial lung disease in anti-Jo-1 patients with antisynthetase syndrome. *Arthritis Care Res* 2013;65:800-8.
23. Hervier B, Benveniste O. Clinical heterogeneity and outcomes of antisynthetase syndrome. *Curr Rheumatol Rep* 2013;15:349.
24. Hervier B, Devilliers H, Stanciu R, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. *Autoimmun Rev* 2012;12:210-7.
25. Fujisawa T, Hozumi H, Kono M, et al. Prognostic factors for myositis-associated interstitial lung disease. *PLoS One* 2014;9:e98824.
26. Hozumi H, Enomoto N, Kono M, et al. Prognostic significance of anti-aminoacyl-tRNA synthetase antibodies in polymyositis/dermatomyositis-associated interstitial lung disease: a retrospective case control study. *PLoS One* 2015;10:e0120313.
27. Center for Review and Dissemination, University of York. PROSPERO:

International Prospective Register of Systematic Reviews. Available from: http://www.crd.york.ac.uk/prospero/. [Accessed 17 Apr 2016].

28. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;349:g7647.

29. Sontheimer RD. Would a new name hasten the acceptance of amyopathic dermatomyositis (dermatomyositis sine myositis) as a distinctive subset within the idiopathic inflammatory dermatomyopathies spectrum of clinical illness? *J Am Acad Dermatol* 2002;46:626-36.

30. Wilczynski NL, Haynes RB. Developing optimal search strategies for detecting clinically sound prognostic studies in MEDLINE: an analytic survey. *BMC Med* 2004;2:23.

31. Wilczynski NL, Haynes RB. Optimal search strategies for detecting clinically sound prognostic studies in EMBASE: an analytic survey. *J Am Med Inform Assoc* 2005;12:481-5.

32. Ware JE, Jr, Snow KK, Kosinski M, et al. *SF-36 Health Survey Manual and Interpretation Guide.* Boston, MA: The Health Institute, New England Medical Center 1993.

33. Haddaway NR, Collins AM, Coughlin D, et al. The Role of Google Scholar in Evidence Reviews and Its Applicability to Grey Literature Searching. *PloS one.* 2015;10:e0138237.

34. Hayden JA, Cote P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. *Ann Intern Med* 2006;144:427-37.

35. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280-6.

36. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.

37. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007;8:16.

38. Deeks JJ, Altman DG. Effect measures for meta-analysis of trials with binary outcomes. In: Egger M, Smith GD, Altman DG, eds. *Systematic Reviews in Health Care Meta-Analysis in Context*. 2nd ed. London: BMJ Publishing Groups 2001:313-35.

39. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. *J Clin Epidemiol* 2002;55:893-9.

40. Johnson C, Pinal-Fernandez I, Parikh R, et al. Assessment of Mortality in

Autoimmune Myositis With and Without Associated Interstitial Lung Disease. *Lung* Published Online First: 11 May 2016. doi:10.1007/s00408-016-9896-x

41. Whitehead A, Bailey AJ, Elbourne D. Combining summaries of binary outcomes with those of continuous outcomes in a meta-analysis. *J Biopharm Stat* 1999;9:1-16.

42. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC medical research methodology.* 2005;5:13.

43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.

44. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.

45. Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*. The Cochrane Collaboration 2011. Available from: http://www. handbook.cochrane.org.

46. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.

47. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56:455-63.

48. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *BMJ* 2015;350:h870.

49. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med* 2009;151:264-9, w64.

50. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-12.

AUTHORS' CONTRIBUTIONS

Hiroyuki Kamiya (HK) conceived this research project and planned the entire methods to undertake it. He also wrote the manuscript of this protocol.

Ogee Mer Panlaqui (OMP) made contributions in conceiving this research project and planning literature search strategy and data extraction.

Shinyu Izumi (SI) got involved in the process of selecting the appropriate population and the outcomes targeted in this review.

Takashi Sozu (TS) made contributions in planning statistical analysis, in particular, determining the appropriate statistical methods to report summary effects and data synthesis.

Appendix: Searching strategies for prognostic studies with high sensitivity

Ovid Medline

1 exp Polymyositis/

2 exp Dermatomyositis/

3 exp Myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp Lung Diseases, Interstitial/

12 exp Pulmonary Fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 incidence.sh.

19 exp Mortality/

20 follow-up studies.sh.

21 prognos$.tw.

22 predict$.tw.

23 course$.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

Ovid EMBASE

1 exp polymyositis/

2 exp dermatomyositis/

3 exp myositis/

4 polymyositis.mp.

5 dermatomyositis.mp.

6 myositis.mp.

7 myopath$.mp.

8 PM.mp.

9 DM.mp.

10 (anti$synthetase adj syndrome).mp.

11 exp interstitial lung disease/

12 exp lung fibrosis/

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

14 (interstitial adj3 pneumoni$).mp.

15 (interstitial adj3 pneumopath$).mp.

16 alveolitis.mp.

17 (pulmonary adj3 fibros$).mp.

18 exp disease course/

19 risk$.mp.

20 diagnos$.mp.

21 follow-up.mp.

22 ep.fs.

23 outcome.tw.

24 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

25 11 or 12 or 13 or 14 or 15 or 16 or 17

26 18 or 19 or 20 or 21 or 22 or 23

27 24 and 25 and 26

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 3	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors:			
Contact	3a	Page 1	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 17	Indicate sources of financial or other support for the review
Sponsor	5b	Page 17	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Page 17	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
		INTRODUCTION	
Rationale	6	Page 4-6	Describe the rationale for the review in the context of what is already known
Objectives	7	Page 6	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 7-8	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 8	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 9	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 9	Describe the mechanism(s) that will be used to manage records and data throughout the review
Selection process	11b	Page 9	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 9-10	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 10	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 8	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 10	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 12	Describe criteria under which study data will be quantitatively synthesised
	15b	Page 10-13	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 13-14	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	Page 13	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es)	16	Page 14	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence	17	Page 14	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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