A systematic review of prognostic biomarkers in idiopathic pulmonary fibrosis
Fasihul Khan, Iain Stewart, Gavin Jones, Karen Robinson, Gauri Saini, Gisli Jenkins

Citation

Review question
Do baseline values or 3-month change in serum and physiological biomarkers predict disease progression and mortality in untreated patients with idiopathic pulmonary fibrosis?

Objective 1
To identify whether baseline physiological biomarkers or subsequent change over 3 months predict prognosis in untreated patients with idiopathic pulmonary fibrosis.

Objective 2
To identify whether baseline serum proteomic biomarkers or subsequent change over 3 months predict prognosis in untreated patients with idiopathic pulmonary fibrosis.

Searches
Electronic searches will be carried out in MEDLINE (1946 to latest), EMBASE (1974 to latest), Google Scholar, the Cochrane Central Register of Controlled Trials and ClinicalTrials.gov using keywords and controlled vocabulary terms (i.e. medical sub-heading (MeSH) terms, EMTREE terms) for “Idiopathic pulmonary fibrosis”, “biomarkers” and “prognosis”. Pre-print servers including medRxiv, bioRxiv and Wellcome Open Research will also be searched. Hand searches will be conducted of the reference lists of eligible primary studies, and relevant review articles and clinical guidelines. No language restrictions will be applied.

Two reviewers (FK and IS) will independently screen titles and/or abstracts of all identified citations. The full manuscript of all selected citations will be retrieved and independently assessed for inclusion in the systematic review. Conflict will be resolved through discussion, with unresolved conflicts resolved by a third reviewer (RGJ).

Types of study to be included
Inclusion: All original prospective observational studies that report outcomes from adult (aged > 18) patients with IPF stratified according to status of at least one biomarker. Conference abstracts and placebo arms of randomised interventional clinical trials will also be eligible for inclusion.

Exclusion: Letters, commentaries, correspondence, case reports, expert opinions, editorials, other non-original systematic reviews, retrospective studies, experimental studies and animal studies. Studies investigating non-IPF Interstitial Lung Diseases.

Condition or domain being studied
Idiopathic pulmonary fibrosis (IPF) is a devastating lung condition of unknown origin characterised by progressive and irreversible interstitial fibrosis. Although median survival is 3 years, IPF is manifest by variable and unpredictable disease trajectory amongst individual patients. Advances in the management of IPF are hampered by the absence of validated prognostic measures, especially biomarkers that change over short time periods. Biomarkers, both serum and physiological may be suitable as early predictive markers of disease behaviour enabling stratification of therapy and personalised medicine. We aim to conduct a systematic review and if possible, meta-analysis, to critically appraise existing evidence and evaluate the usefulness of serum and physiological biomarkers as prognostic factors for IPF. A scoping search of the
Database of Abstracts of Reviews of Effects (DARE) did not identify any current or past reviews regarding the research question.

**Participants/population**
Adult patients aged > 18 with idiopathic pulmonary fibrosis diagnosed according to contemporaneous consensus guidelines.

**Intervention(s), exposure(s)**
The following biomarkers used as prognostic factors will be considered:

1) Serum proteomic biomarkers (specifically KL-6, SP-A, SP-D, CA125, CA19-9, MMP-1, MMP-7, LOXL2, Periostin, ECM-neoepitopes, CCL-18, IL-8, YKL-40, IGFBP-2, ICAM-1, VEGF, HSP70, Leptin, CXCL13)

2) Physiological biomarkers (FVC, DLCO and 6-minute walk test)

at the following time points:

1) Baseline

2) Change over 3 months.

**Comparator(s)/control**
Change in FVC over 1 year.

**Context**

**Main outcome(s)**
Overall mortality.

**Additional outcome(s)**
1) Absolute or relative percentage change from baseline in FVC at 12 months

2) Disease progression at 12 months defined as:

a. >10% relative decline in FVC

b. Death

**Data extraction (selection and coding)**
Data from chosen articles will be extracted independently by two reviewers (FK and IS) for subsequent evaluation using a pre-defined data extraction form. For physiological biomarkers, corresponding authors will be contacted for missing data. Data extraction from studies reporting data from the same cohort will be limited to the study with the most complete outcome data, largest sample size and longest follow up. Data extracted will broadly consist of:

**Author details**

Year of publication

Study design and recruitment strategy

Sample size

Study objectives

Participant characteristics

Diagnostic criteria of IPF used
Characteristics of biomarker studied (biomarker, assay method, threshold, level, trend over study period)

Lung function measures

Survival outcome measures

Follow up duration

Overall conclusions

**Risk of bias (quality) assessment**
The risk of bias across studies will be assessed by two authors independently using the Quality in Prognostic Studies (QUIPS) tool. Disagreements will be resolved by consensus, or by involvement of a third author if necessary. The QUIPS tool assesses risk of bias in prognostic factor studies across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting. Each domain will be judged as having low, moderate or high risk of bias. Studies addressing both objectives (serum and physiological biomarkers), will be assessed using a modified version of the QUIPS tool. This will enable evaluation of the risk of bias separately for each objective.

**Strategy for data synthesis**
A narrative synthesis of the findings from the included studies will be presented with summary tables for study characteristics and quality assessment. Data will be aggregated, and meta-analysis conducted if there is adequate data for analysis. The I² test of heterogeneity and visual inspections of forest plots will be used to measure heterogeneity between studies. The thresholds for interpretation of I² will be in accordance with the definitions presented in the Cochrane Handbook for Systematic Reviews of Interventions.

Only studies that provide a survival estimate of the hazard ratio (HR) and associated 95% confidence interval (CI) for each biomarker, or sufficient information to enable calculation of these values using the inverse variance method will be used in the meta-analyses of overall survival. Adjusted HRs will be used where possible, and sensitivity analysis excluding unadjusted HRs carried out to confirm that findings are robust. Summary-estimates for the HR will be computed by the random-effects model.

Sample sizes, mean values and standard deviations of the biomarkers for individuals with and without disease progression will be extracted where possible to enable calculation of the standardised mean difference (SMD). Measurements of relative risk (including hazard ratios, odds ratios and risk ratios) will also be reported where appropriate.

Continuous outcome data (change in FVC at 12 months) will be combined using either correlation coefficients with meta-regression or standardised mean differences. Trend data will be analysed using ANOVA. Studies that report correlation coefficients for biomarker (baseline and trend) association with change in lung function will be reported in a narrative manner if there are insufficient data for meta-analysis. ROC analysis will be carried out to compare baseline values or three-month change with twelve-month change in predicting outcomes. Positive predictive values from the included samples will be calculated through contingency tables.

**Analysis of subgroups or subsets**
None.

**Contact details for further information**
Fasihul Khan
fasihul.khan@nottingham.ac.uk

**Organisational affiliation of the review**
University of Nottingham
https://www.nottingham.ac.uk

**Review team members and their organisational affiliations**
**Type and method of review**
Meta-analysis, Narrative synthesis, Prognostic, Systematic review

**Anticipated or actual start date**
07 January 2019

**Anticipated completion date**
06 January 2020

**Funding sources/sponsors**
National Institute of Health Research (NIHR) through the Nottingham Biomedical Research Centre and a NIHR Professorship (RGJ).

**Conflicts of interest**

**Language**
English

**Country**
England

**Stage of review**
Review Ongoing

**Subject index terms status**
Subject indexing assigned by CRD

**Subject index terms**
Biomarkers; Humans; Idiopathic Pulmonary Fibrosis; Prognosis

**Date of registration in PROSPERO**
03 January 2019

**Date of publication of this version**
28 February 2019

**Details of any existing review of the same topic by the same authors**

**Stage of review at time of this submission**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Started</th>
<th>Completed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preliminary searches</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Piloting of the study selection process</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Formal screening of search results against eligibility criteria</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Data extraction</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Risk of bias (quality) assessment</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Data analysis</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
This information has been provided by the named contact for this review. CRD has accepted this information in good faith and registered the review in PROSPERO. The registrant confirms that the information supplied for this submission is accurate and complete. CRD bears no responsibility or liability for the content of this registration record, any associated files or external websites.