A systematic review and individual patient data meta-analysis of physiological biomarkers in idiopathic pulmonary fibrosis

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Citation

Review question
Do baseline values or 3-month change in physiological (FVC, DLCO, 6MWD) biomarkers predict disease progression and mortality in untreated patients with idiopathic pulmonary fibrosis?

Searches
Electronic searches will be carried out in MEDLINE (1946 to latest), EMBASE (1974 to latest), 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”, “physiology” 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. Only manuscripts written in English language will be reviewed.

Two reviewers 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.

Types of study to be included
Inclusion: Placebo arms of randomised interventional clinical trials in adult (aged>18) patients with IPF.

Exclusion: Non-interventional studies, conference abstracts, letters, commentaries, correspondence, case reports, expert opinions, editorials, other non-original systematic reviews, retrospective studies and animal studies. Studies investigating non-IPF Interstitial Lung Diseases. Studies with sample size n<30 will be excluded to minimise heterogeneity and bias.

Condition or domain being studied
Idiopathic pulmonary fibrosis (IPF) is a chronic 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. Physiological biomarkers 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 meta-analysis of individual patient data (IPD), to critically appraise existing evidence and evaluate the usefulness of 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 untreated idiopathic pulmonary fibrosis diagnosed according to contemporaneous consensus guidelines.

Intervention(s), exposure(s)
Physiological biomarkers (Forced Vital Capacity, Gas transfer and 6-minute walk test) at the following time points:

1) Baseline
2) Change over 3 months.

**Comparator(s)/control**
Age, Gender, Smoking

**Context**

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

**Timing and effect measures**
All time periods.

**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

**Timing and effect measures**
12 months.

**Data extraction (selection and coding)**
Data from chosen articles will be extracted independently using a pre-defined data extraction form by two reviewers. 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 to be extracted will include:

- Author details and year of publication
- Study design and recruitment strategy
- Sample size
- Participant demographics
- IPF diagnostic criteria used
- Biomarkers measured

Corresponding authors of identified studies will be contacted for individual patient data including:

- Age
- Gender
- Smoking status (Current, Ex, Never)
- Baseline, 3 and 12 months FVC (% predicted)
- Baseline 3 and 12 months DLCO (% predicted)
- Baseline 3 and 12 months 6-min walk distance (m)

**Survival outcome measures**
Follow up duration

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.

Strategy for data synthesis
A narrative synthesis of the findings from the included studies will be presented according to the review question, with summary tables inclusive of study and participant characteristics. Derivation and validation cohorts from the same study will be treated as two individual cohorts.

Correlation of physiological performance over 3 months and twelve months from baseline will be assessed in a repeated measures design, relevant time-point meta-analysis. Individual patient data will be sought and a two-step meta-analysis performed adjusted for a priori confounders including age, sex and smoking status.

Hazard ratios for baseline and three month change of physiological parameters in predicting mortality will be calculated. Disease progression will be standardised as 10% relative decline in FVC or death within 12 months of baseline, and odds ratios for predicting disease progression calculated. Data will be graphically displayed using forest plots.

Heterogeneity will be assessed by Cochran's Q and I² using random effects. Synthesis criteria exclude sample sizes that are not conducive to random effect models (n<30). Where heterogeneity is high, sensitivity analyses will be performed using inverse variance heterogeneity models.

Analysis of subgroups or subsets
None.

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Organisational affiliation of the review
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Type and method of review
Individual patient data (IPD) meta-analysis, Prognostic, Systematic review

Anticipated or actual start date
13 January 2020

Anticipated completion date
04 January 2021

Funding sources/sponsors
National Institute of Health Research (NIHR) through the Nottingham Biomedical Research Centre

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

Date of registration in PROSPERO
10 January 2020

Date of publication of this version
10 January 2020

Revision note for this version
Typing error corrected (Cronbach changed to Cochran's Q). Study search criteria updated to include only randomised clinical trials. Search not yet commenced by authors.

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

Stage of review at time of this submission
The review has not started

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Versions
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PROSPERO
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