Supplementary Material

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**Supplementary Figure S1** – MEDLINE search strategy (last search carried out on 12th November 2020). “OR” was used to combine search terms within each PICOS category, with “AND” used to combine search terms across PICOS categories.
Copy of email sent to authors

We would be very grateful for your assistance in undertaking a robust meta-analysis. The team at University of Nottingham (UK), led by Prof Gisli Jenkins, are conducting a systematic review and meta-analysis of blood biomarkers in IPF. The protocol for the study can be found on PROSPERO: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=120402

As part of the review, we will conduct a meta-analysis of the association of MMP-7 levels with mortality in IPF. We have chosen this biomarker because there is sufficient published data to make it feasible and useful.

To assist with this, we would be extremely grateful if you could kindly provide us with individual patient data from your highly relevant study entitled “…” published in ...

We also note significant heterogeneity in disease progression definitions across individual studies, and therefore hope to meta-analyse MMP-7 level associations with a shared definition based on FVC and mortality and would also appreciate data to assist with this. We appreciate the inconvenience such requests entail, and we would like to make the process as smooth as possible, we will of course acknowledge all support.

The attached excel spreadsheet highlights the anonymised data we are seeking for each patient, where available:

- MMP-7 level (baseline and 3-months)
- Assay method (type of assay used)
- Sample type (serum or plasma)
- Age
- Gender (M or F)
- Follow up time (days)
- Dead or alive at end
- Time to death (days)
- Baseline FVC (% predicted)
- 3-month FVC (% predicted)
- 12-month FVC (% predicted)
- Smoking (ever or never)

Thank you for your help, we look forward to communicating with you further.

Supplementary Figure S2 – copy of message sent to authors for individual participant data. A minimum of three reminders, 4 weeks apart were sent.
Supplementary Figure S3 – Funnel plots for outcomes evaluated in baseline MMP-7 IPD meta-analysis. A: overall mortality, B: 12-month mortality, C: Disease progression, D: Change in percent predicted FVC at 12 months. Publication bias assessed using Egger’s test for outcomes with at least ten studies, and p values presented next to funnel plot.
**Supplementary Figure S4** – Funnel plots for outcomes evaluated for three-month change in MMP-7 IPD meta-analysis. A: overall mortality, B: 12-month mortality, C: Disease progression, D: Change in percent predicted FVC at 12 months.
Supplementary Figure S5 - Pooled hazard ratios with 95% confidence intervals for risk of overall mortality, per percent relative increase in MMP-7 from baseline to three months. Study follow up time shown in months. \( n \) denotes the number of deaths, and \( N \) represents the total number of participants included per study.
**Supplementary Figure S6** - Pooled hazard ratios with 95% confidence intervals for risk of mortality at 12 months, per percent relative increase in MMP-7 from baseline to three months. n denotes the number of deaths, and N represents the total number of participants included per study.

| Study                        | Year | eHR (95% CI) | Weight | n/N       |
|------------------------------|------|--------------|--------|-----------|
| Rosas et al                  | 2018 | 1.05 (0.99, 1.10) 6.51 | 3/50   |
| Maher et al (Discovery)      | 2017 | 1.04 (0.97, 1.12) 3.37 | 9/56   |
| Maher et al (Validation)     | 2017 | 0.99 (0.98, 1.01)34.36 | 21/171 |
| Neighbors et al (Replication)| 2018 | 1.00 (0.99, 1.01)55.76 | 14/218 |
| Overall (I-squared = 37.4%) |      | 1.00 (0.99, 1.01)100.00 |        |

**NOTE:** Weights are from random-effects model
Supplementary Figure S7 – Pooled odds ratios with 95% confidence intervals for risk of disease progression, per standard deviation increase in baseline MMP-7. Separated by ELISA and non-ELISA measurements. n denotes the number of progressors, and N represents the total number of participants included in the analysis per study.

| Assay and Study         | Year | aOR (95% CI)      | Weight | n/N   |
|-------------------------|------|-------------------|--------|-------|
| ELISA                   |      |                   |        |       |
| Hamai et al             | 2016 | 1.27 (0.52, 3.11) | 2.28   | 12/33 |
| Rosas et al             | 2018 | 1.09 (0.61, 1.95) | 5.23   | 21/51 |
| Tzouvelekis et al       | 2017 | 1.61 (1.01, 2.57) | 8.06   | 31/97 |
| Raghu et al             | 2018 | 1.55 (1.03, 2.33) | 10.35  | 57/134|
| Maher et al (Validation)| 2017 | 1.66 (0.76, 3.66) | 2.89   | 106/196|
| Clynick et al           | 2020 | 1.82 (1.24, 2.68) | 11.46  | 67/205|
| Subgroup (I–squared = 0.0%) |     | 1.56 (1.26, 1.92) | 40.27  |       |

| Non-ELISA               |      |                   |        |       |
|-------------------------|------|-------------------|--------|-------|
| Maher et al (Discovery) | 2017 | 1.09 (0.72, 1.65) | 9.96   | 50/104|
| Oldham et al            | 2019 | 1.25 (0.86, 1.82) | 11.89  | 63/123|
| Neighbors et al (Test)  | 2018 | 1.18 (0.86, 1.61) | 17.14  | 72/213|
| Neighbors et al (Replication) | 2018 | 1.00 (0.76, 1.32) | 20.74  | 98/227|
| Subgroup (I–squared = 0.0%) |     | 1.11 (0.94, 1.31) | 59.73  |       |

Heterogeneity between groups: p = 0.013
Overall (I–squared = 5.9%) 1.27 (1.11, 1.46) 100.00

NOTE: Weights are from random-effects model.
Supplementary Figure S8 – Pooled odds ratios with 95% confidence intervals for risk of disease progression, per percent relative increase in baseline MMP-7 to three months. n denotes the number of progressors, and N represents the total number of participants included in the analysis per study.
Supplementary Figure S9 – Pooled effect size with 95% confidence intervals for relative change in FVC at 12 months, per percent relative increase in baseline MMP-7 to three months.

| Study                  | Year | Effect size (95% CI) | % Weight |
|------------------------|------|----------------------|----------|
| Maher et al (Discovery)| 2017 | 0.31 (0.04, 0.57)    | 6.61     |
| Maher et al (Validation)| 2017 | -0.06 (-0.14, 0.02)  | 29.99    |
| Neighbors et al (Replication) | 2018 | -0.00 (-0.01, 0.00)  | 47.72    |
| Rosas et al            | 2018 | 0.04 (-0.11, 0.19)   | 15.68    |
| Overall (I²=squared = 60.8%) |      | 0.01 (-0.07, 0.08)   | 100.00   |

NOTE: Weights are from random-effects model.
**Supplementary Figure S10** – Unadjusted analyses including pooled estimates with 95% confidence intervals for association of baseline MMP-7 per standard deviation increase and A. Mortality, B. Disease progression.
| Author and year of publication | Country of study | IPF Sample size | Study follow up, months | Age (years) | Sex – male (%) | Baseline FVC % predicted | Baseline DLco % predicted | Relevant Biomarkers evaluated | Relevant outcomes reported |
|-------------------------------|-----------------|----------------|------------------------|------------|---------------|-------------------------|---------------------------|-------------------------------|-----------------------------|
| Bauer, 2017<sup>1</sup>       | multi-national  | 211 (BUILD-3<sup>2</sup>) | NR                     | 63.1 (8.9) | 64            | 75.7 (10.7)             | 47.7 (10.7)                | collagen synthesis peptides | Disease progression (FVC%10% decline, DLco ≥ 15%, acute exacerbation or death) up to end of study, change in FVC at 4 months |
| Chien, 2014<sup>4</sup>       | USA multi-national | 69 (ARTEMIS)<sup>5</sup> | 24                     | 66.2 (7)   | 75            | 69.8 (12.1)             | 42.1 (11.1)                | LOXL2                        | Overall mortality, lung function decline at 24 months (FVC%10% with DLco ≥ 5%, or DLco ≥ 15% with FVC ≥ 5%), disease progression (mortality, hospitalisation or lung function decline) |
| Collard, 2010<sup>6</sup>     | South Korea single centre | 47 (AE-IPF) | NR                     | 66 (8)     | 77            | 75 (18)                 | 64 (20)                   | KL-6, SP-D                   | Overall mortality, acute exacerbation |
| Doubkova, 2016<sup>7</sup>    | Czech Republic single centre | 18 | NR                     | 68.5 (49-79) * | 56            | 68 (median)           | 52 (median)               | SP-A, SP-D                   | Overall mortality, change in FVC |
| Gui, 2020<sup>8</sup>         | China single centre | 126 | 60                     | NR         | 75.4          | 70.1 (17)              | 50.5 (12.6)               | KL-6, CXCL13                 | Overall mortality, change in FVC over 12 months |
| Hamai, 2016<sup>9</sup>       | Japan single centre | 65 | 31 (26.6-35.4) <sup>b</sup> | 69.3 (8.6) | 77            | 75.6 (21.9)            | 47.1 (15.8)               | SP-A, SP-D, CCL-18, KL-6    | 5-year mortality |
| Hoyer, 2020<sup>10</sup>      | Denmark multi-centre | 184 | 36                     | NR         | NR            | NR                      | NR                        | PRO-C3, PRO-C6               | Overall mortality, disease progression (FVC decline >10% and/or DLco decline >15% at any time) |
| Jiang, 2018<sup>11</sup>      | China single centre | 20 (85 ILD) | 12                     | 53.5 (10.5) | 59 *          | 71.1 (17.7)            | 49.4 (24.3) *              | KL-6                         | Disease progression (FVC decline ≥ 10% or DLco decline ≥ 15%, or death) at 12 months |
| Jenkins, 2015<sup>12</sup>    | UK multi-centre | 55 (Discovery) | 26 (1.6-35.2) <sup>a</sup> | 68.5 (9.5) | 78            | 75.9 (23.5)            | 44.4 (18.3)              | ECM-neoepitopes              | Overall mortality, disease progression at 12 months (all-cause mortality or >10% FVC decline) |
| Kennedy, 2015<sup>13</sup>    | Ireland single centre | 13 | 6                      | 72.6 (10.7) | 77            | 83.3 (26.9)           | 39.1 (16.1)              | SP-D                         | Change in FVC at 6 months |
| Kinder, 2009<sup>14</sup>     | USA single centre | 82 | 36 (16-72)<sup>3b</sup> | 62 (10) | 62            | 64 (18)                | 54 (16)                  | SP-A, SP-D                   | Death or transplantation at 1 year |
| Maher, 2017<sup>14</sup>      | UK multi-centre | 106 (Discovery) | 36                     | 70.8 (8.3) | 78            | 79 (18.9)              | 43.3 (14.8)              | SP-D, CA125, CA19-9, IGFBP-2, IL-8, ICAM-1 | Overall mortality, disease progression at 12 months (all-cause mortality or FVC decline ≥ 10%) |
| Naik, 2012<sup>14</sup>       | USA multi-centre | 54 (COMET<sup>15</sup>) | 18.5                   | 64.3 (8.2) | 72            | 68.5 (15.8)            | 40.8 (14.3)               | Periostin                    | Disease progression at 48 weeks (death, acute exacerbation, transplantation, relative FVC decline ≥ 10% or DLco > 15%) |
| Neighbors, 2018\(^{18}\) | multi-national | 221 CAPACITY \(^{19}\) | 12 | 66.9 (7.4) | 72 | 73.4 (13.4) | 46.5 (9.4) | CCL-18, CXCL13, YKL-40, Periostin | At 12 months: Disease progression (FVC \(\geq\)10% absolute decline or death), change in FVC, death |
|----------------------|-----------------|-----------------|-----|----------|----|----------|---------|----------------------|--------------------------------------------------|
| Ohshima, 2014\(^{21}\) | Germany single centre | 64 (without AE-IPF) | 36 (25.2) | 70 (8) | 73 | 68 (15) | 44 (14) | KL-6, CCL-18 | Acute exacerbation |
| Ohta, 2017\(^{22}\) | Japan multi-centre | 60 | 6.2 (5.8-8.5) \(^{a}\) | 69.2 (8.1) | 92 | 85.8 (20.1) | 59.7 (21.8) | Monomeric Periostin, Periostin, KL-6, SP-D | Change in FVC at 6-12 months |
| Okamoto, 2011\(^{23}\) | Japan multi-centre | 37 | NR | 66.3 (8.6) | 84 | 80.2 (20) | NR | Periostin | Overall months |
| Organ, 2019\(^{24}\) | UK multi-centre | 145 | 34.5 (median) | 71.7 (7.7) | 81 | 79.8 (20.4) | 48.2 (17.9) | ECM-neopepitopes, collagen synthesis peptides | Overall mortality, disease progression at 12 months (all-cause mortality or >10% FVC decline) |
| Papiris, 2018\(^{25}\) | Greece single centre | 23 (stable) | 12 | 71 (69-74) \(^{b}\) | 82 | 72 (60-93) \(^{b}\) | 56 (38-65) \(^{b}\) | IL-8 | Overall mortality at 12 months |
| Prasse, 2009\(^{26}\) | Germany and Italy | 72 | 24 | 67.2 (8.6) | NR | NR | NR | CCL-18 | Overall mortality, change in FVC at 6 months, disease progression at 24 months (>10% FVC decline or death) |
| Raghu, 2018\(^{27}\) | multi-national | 154 | 12 | 67.9 (8.4) | 64 | 71.5 (19.6) | 40.9 (15.9) | SP-A, SP-D, CCL-18, KL-6, ICAM-1, Periostin, YKL-40 | Disease progression at 52 weeks (FVC decrease \(\geq\)10% predicted or DL\(\text{CO}\) decrease > 15% or lung transplantation or death) |
| Richards, 2012\(^{28}\) | USA single centre | 140 (Derivation) | 22 (19) | 67.2 (8.3) | 72 | 62 (19.6) | 44.8 (17.1) | IL-8, ICAM-1 | Overall mortality, disease progression (FVC relative decline \(\geq\)10% within any 1 year of follow up) |
| Vuga, 2014\(^{29}\) | USA single centre | 95 | > 24 | 69 (9.7) | 74 | 66 (19.5) | 50 (19.5) | CXCL13 | Overall mortality |

**Supplementary Table S1** – Methodological characteristics of all included non-MMP7 studies with baseline participant characteristics and outcome data. Age, baseline FVC and baseline DL\(\text{CO}\) reported as mean (standard deviation) unless otherwise stated. DL\(\text{CO}\), gas transfer for carbon monoxide; FVC, forced vital capacity; \(^{a}\) = median and range; \(^{b}\) = median and IQR

\* = reported for all ILD
| Study                          | Study participation | Study attrition | Prognostic factor | Outcome | Confounding | Statistical analysis and reporting |
|-------------------------------|---------------------|----------------|------------------|---------|-------------|-----------------------------------|
| IPD studies                   |                     |                |                  |         |             |                                   |
| Hamai, 2016                   | Moderate            | Moderate       | Low              | Low     | Low         | Low                               |
| Maher, 2017                   | Low                 | Moderate       | Low              | Low     | Low         | Low                               |
| Navaratnam, 2014/Clynick, 2020| Low                 | Moderate       | Low              | Low     | Low         | Low                               |
| Neighbors, 2018               | Low                 | Low            | Low              | Low     | Low         | Low                               |
| Oldham, 2019                  | Low                 | High           | High             | Low     | High        | Moderate                           |
| Raghu, 2018                   | Low                 | Low            | Low              | Low     | Moderate    | Low                               |
| Richards, 2012                | Low                 | Low            | Low              | Low     | Moderate    | Low                               |
| Rosas, 2018                   | Low                 | Low            | Low              | Low     | High        | Moderate                           |
| Tzouvelekis, 2017             | Low                 | Low            | Low              | Low     | Low         | Low                               |
| Non-IPD studies               |                     |                |                  |         |             |                                   |
| Bauer, 2017                   | Low                 | Low            | Moderate         | Low     | High        | Low                               |
| Chien, 2014                   | Low                 | Low            | Low              | Low     | Moderate    | Low                               |
| Collard, 2010                 | Low                 | Low            | Low              | Low     | High        | Low                               |
| Doubkova, 2016                | Moderate            | High           | High             | High    | High        | High                               |
| Gui, 2020                     | Low                 | Low            | Low              | Moderate| High        | Low                               |
| Hoyer, 2020                   | High                | High           | High             | Low     | High        | High                               |
| Jiang, 2018                   | Low                 | Low            | Low              | Low     | High        | Low                               |
| Jenkins, 2015                 | Low                 | Moderate       | Low              | Low     | Low         | Low                               |
| Kennedy, 2015                 | Moderate            | Low            | Low              | Low     | High        | Moderate                           |
| Kinder, 2009                  | Low                 | Low            | Low              | Low     | Low         | Low                               |
| Naik, 2012                    | Low                 | Low            | Low              | Low     | Low         | Low                               |
| Ohshima, 2014                 | Low                 | Low            | Low              | Low     | Low         | Low                               |
| Ohta, 2017                    | Low                 | High           | Low              | Low     | High        | Low                               |
| Okamoto, 2011                 | Low                 | High           | Low              | Low     | Low         | Moderate                           |
| Organ, 2019                   | Low                 | Moderate       | Low              | Low     | Low         | Low                               |
| Papiris, 2018                 | Low                 | Low            | Low              | Low     | High        | Moderate                           |
| Peljto, 2013                  | Low                 | Low            | Moderate         | Low     | Low         | Low                               |
| Prasse, 2009                  | Moderate            | Low            | Low              | Low     | Low         | Low                               |
| Sokai, 2015                   | Low                 | Low            | Low              | Low     | High        | Low                               |
| Vuga, 2014                    | Moderate            | High           | Low              | High    | Low         | Low                               |

**Supplementary Table S2** – Risk of bias assessment for included studies. The risk of bias across studies was rated as low, moderate or high risk in six categories using the QUIPs tool.
| Baseline MMP-7 | Overall mortality (n=1492) | 12-month mortality (n=1492) | Disease progression (n=1383) | Change in FVC percent predicted over 12 months (n=891) |
|----------------|---------------------------|-----------------------------|----------------------------|---------------------------------|
| Variables      | R² (%) | P value | R² (%) | P value | R² (%) | P value | R² (%) | P value |
| Design (cohort vs. RCT) | 0.00 | 0.747 | 0.00 | 0.388 | 0.00 | 0.159 | 0.00 | 0.988 |
| Assay (ELISA vs. other) | 18.45 | 0.088 | 25.4 | 0.075 | 100 | 0.013 | 0.00 | 0.235 |
| Sample (Serum vs. plasma) | 0.00 | 0.98 | 0.00 | 0.483 | 71.35 | 0.1875 | 0.00 | 0.502 |
| IPF consensus (2011 vs. other) | 0.00 | 0.983 | 0.00 | 0.87 | 100 | 0.05 | N/A | N/A |
| Centre (single vs. multi) | 9.05 | 0.1995 | 0.00 | 0.293 | 6.23 | 0.418 | 91.14 | 0.195 |
| Publication type (peer reviewed) | 0.00 | 0.922 | 0.00 | 0.893 | 47.51 | 0.212 | 0.00 | 0.659 |

| Change in MMP-7 over 3 months | Overall mortality (n=498) | 12-month mortality (n=498) | Disease progression (n=481) | Change in FVC percent predicted over 12 months (n=481) |
|-----------------------------|---------------------------|-----------------------------|----------------------------|---------------------------------|
| Variables                   | R² (%) | P value | R² (%) | P value | R² (%) | P value | R² (%) | P value |
| Design (cohort vs. RCT)     | 0.00 | 0.916 | 0.00 | 0.78 | 82.84 | 0.62 | 0.00 | 0.716 |
| Assay (ELISA vs. other)     | 0.00 | 0.753 | 84.97 | 0.07 | 0.00 | 0.05 | 0.00 | 0.435 |
| Sample (Serum vs. plasma)   | 0.00 | 0.56 | 0.00 | 0.557 | 19.2 | 0.662 | 0.00 | 0.716 |
| IPF consensus (2011 vs. other) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Centre (single vs. multi)   | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |
| Publication type (peer reviewed) | N/A | N/A | N/A | N/A | N/A | N/A | N/A | N/A |

**Supplementary Table S3** - Results of meta-regression for variables assessed separated by study outcomes. Sample sizes for each outcome shown (n). R² and p values from meta-regression shown where applicable. N/A, not applicable.
| Outcome | The GRADE domains | Ratings for quality of evidence |
|---------|-------------------|---------------------------------|
| Baseline MMP-7 | Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| | Imprecision | Effect sizes in most studies favour MMP-7 as a marker of mortality. |
| | Inconsistency | Substantial heterogeneity not explained by variability in the factors assessed |
| | Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD. |
| | Publication bias | No publication bias as indicated by funnel plots and Egger’s tests |
| | Certainty of evidence | Moderate certainty of evidence |
| Overall mortality (10 studies; 1492 participants) | Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| | Imprecision | Imprecision present with wide confidence interval of 0.99-1.78. |
| | Inconsistency | Substantial heterogeneity not explained by variability in the factors assessed |
| | Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and 12-month mortality measured from IPD. |
| | Publication bias | No publication bias as indicated by funnel plots and Egger’s tests |
| 12-month mortality (10 studies; 1492 participants) | Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| | Imprecision | Imprecision present with wide confidence interval of 0.99-1.78. |
| | Inconsistency | Substantial heterogeneity not explained by variability in the factors assessed |
| | Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and 12-month mortality measured from IPD. |
| | Publication bias | No publication bias as indicated by funnel plots and Egger’s tests |
|                          | Disease progression (10 studies; 1383 participants) | Change in FVC at 12 months (8 studies; 891 participants) |
|--------------------------|-----------------------------------------------------|--------------------------------------------------------|
| Certainty of evidence    | Moderate certainty of evidence                       | High certainty of evidence                              |
| Risk of bias             | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure was measured objectively and consistently for all participants. Disease progression definition was standardised. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure was measured objectively and consistently for all participants. Change in FVC was measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| Imprecision              | Effect sizes consistently favour MMP-7 as a prognostic marker, although confidence intervals commonly cross 1. Overall estimate has appropriately narrow confidence interval supporting MMP-7 as a biomarker of disease progression. | The majority of the studies show MMP-7 to result in a negative change in FVC at 12 months, although confidence intervals cross 0 in all individual studies. Overall confidence interval does not cross 0. |
| Inconsistency            | No heterogeneity demonstrated.                       | No evidence of heterogeneity                            |
| Indirectness             | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and disease progression standardised using IPD. | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies and change in FVC standardised using IPD. |
| Publication bias         | No publication bias as indicated by funnel plots and Egger's tests | No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies |
| Certainty of evidence    | High certainty of evidence.                          | High certainty of evidence.                              |
### Three-month MMP-7 change

| Overall mortality (4 studies; 498 participants) | Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| --- | --- | --- |
| | Imprecision | Wide confidence intervals in individual studies but narrow confidence interval for overall effect size (no effect) |
| | Inconsistency | Substantial heterogeneity not explained by variability in the factors assessed |
| | Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD. |
| | Publication bias | No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies |
| | Certainty of evidence | Moderate certainty of evidence |

| 12-month mortality (4 studies; 498 participants) | Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
| --- | --- | --- |
| | Imprecision | Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect) |
| | Inconsistency | Heterogeneity not explained by variability in the factors assessed |
| | Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and 12-month mortality measured from IPD. |
| | Publication bias | No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies |
| | Certainty of evidence | Moderate certainty of evidence |
### Disease progression (4 studies; 481 participants)

| Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Exposure and outcomes were measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
|--------------|--------------------------------------------------------------------------------------------------------------------------|
| Imprecision  | Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect) |
| Inconsistency| No significant heterogeneity                                                                                                   |
| Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies, and overall mortality measured from IPD. |
| Publication bias | No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies |
| Certainty of evidence | High certainty of evidence |

### Change in FVC at 12 months (4 studies; 481 participants)

| Risk of bias | All studies included well-defined participants diagnosed according to international consensus guidelines. Change in FVC was measured objectively and consistently for all participants. Covariates were adjusted for using IPD. Follow up was sufficiently long to enable outcomes to occur. |
|--------------|--------------------------------------------------------------------------------------------------------------------------|
| Imprecision  | Wide confidence interval in individual studies but narrow confidence interval for overall effect size (no effect) |
| Inconsistency| Inconsistency present across results from studies                                                                 |
| Indirectness | No serious indirectness. All patients had IPF according to consensus criteria and were untreated. MMP-7 was measured at baseline in all studies and change in FVC standardised using IPD. |
| Publication bias | No obvious funnel plot asymmetry, although unable to assess statistically due to small number of studies |
| Certainty of evidence | Moderate certainty of evidence. |

**Supplementary Table S4** – GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach to rate the quality of evidence for the prognostic factor MMP-7
| Author (year) | Sample size | Follow up (months) | Effect size (Variance) | Level of adjustment | Effect size reported for |
|--------------|-------------|--------------------|------------------------|---------------------|--------------------------|
| **MMP-7 (IPD unavailable)** |
| Sokai (2015) | 57          | 15                 | Not significant (NR)   | NR                  | NR                       |
| Peljto (2013) | 438         | 19                 | 2.18 (95% CI 1.1-4.32) | b,d,e,h             | bio > or < 5.7ng/mL      |
| **SP-A** |
| Kinder (2009) | 82          | 36                 | HR 3.27 (95% CI 1.49-7.17) | a,b,c,d,e,g        | per bio SD               |
| Doubkova (2016) | 18         | NR                 | Not significant (NR)   | x                   | bio > or < median (98.1ng/mL) |
| Hamai (2016) | 65          | 31                 | HR 1.01 (95% CI 0.99-1.02) | x                   | continuous               |
| **SP-D** |
| Kinder (2009) | 82          | 36                 | HR 2.04 (95% CI 0.99-4.22) | a,b,c,d,e,g        | per bio SD               |
| Collard (2010) | 67          | NR                 | OR 1.23 (95% CI 0.36-4.21) | “Bivariate” - NR   | log change in bio        |
| Doubkova (2016) | 18         | NR                 | Not significant (NR)   | x                   | bio > or < median (623.1ng/mL) |
| Hamai (2016) | 65          | 31                 | HR 1.00 (95% CI 0.99-1.002) | x                   | continuous               |
| Maher (2017) - Validation | 206 | 36             | HR 2.72 (95% CI 1.65-4.48) | x                   | bio > or < 38.7ng/mL     |
| **CCL-18** |
| Prasse (2009) | 72          | 24                 | HR 7.98 (95% CI 2.49-25.51) | a,b,c,d,e           | bio > or < 150ng/mL      |
| Hamai (2016) | 65          | 31                 | HR 1.007 (95% CI 0.99-1.01) | X                   | continuous               |
| Neighbors (2018) – Test | 123 | 12             | OR 4.4 (95% CI 1.13-17.15) | X                   | bio ≥ or < median        |
| Neighbors (2018) – Replication | 237 | 12            | OR 3.37 (95% CI 1.17-9.67) | X                   | bio ≥ or < median        |
| **CXCL-13** |
| Guo (2020) | 126         | 60                 | HR 1.03 (95% CI 1.02-1.06) | a                   | bio > or < 62pg/mL       |
| Study                  | N   | C   | HR (95% CI)                  | Parameter         | Reference          |
|-----------------------|-----|-----|-----------------------------|-------------------|--------------------|
| **Vuga (2014)**       | 95  | >24 | HR 14.9 (95% CI 1.1-197.2)  | a,b,d,e           | bio > or < highest quartile |
| Neighbors (2018) – Test | 123 | 12  | OR 2.95 (95% CI 0.76-11.46) | x                 | bio ≥ or < median   |
| Neighbors (2018) – Replication | 237 | 12  | OR 6.17 (95% CI 1.75-21.8)  | x                 | bio ≥ or < median   |
| **KL-6**              |     |     |                             |                   |                    |
| Collard (2010)        | 67  | NR  | OR 0.41 (95% CI 0.06-2.93)  | “Bivariate” - NR  | bio log change     |
| Hamai (2016)          | 65  | 31  | HR 1.001 (95% CI 1.00-1.002)| a,b,c             | continuous         |
| Guo (2020)            | 126 | 60  | HR 1.83 (95% CI 1.01-3.69)  | a                 | bio > or < 800U/mL  |
| **IL-8**              |     |     |                             |                   |                    |
| Richards (2012) – Derivation | 140 | 22  | HR 2.4 (95% CI 1.2-4.79)    | a,b,d             | bio > or < 0.0029   |
| Richards (2012) – Validation | 101 | 17  | HR 2.3 (95% CI 0.94-5.64)   | a,b,d             | bio > or < 0.0097   |
| Papiris (2018)        | 41  | 12  | OR 1.067 (95% CI 1.01-1.12) | x                 | per increase of 1pg/mL |
| **CA19-9**            |     |     |                             |                   |                    |
| Maher (2017) – Validation | 206 | 36  | HR 2.95 (95% CI 1.82-4.78)  | x                 | bio > or < 22 U/mL  |
| **CA-125**            |     |     |                             |                   |                    |
| Maher (2017) – Validation | 206 | 36  | HR 3.01 (95% CI 1.64-5.54)  | x                 | bio > or < 12 U/mL  |
| **LOXL2**             |     |     |                             |                   |                    |
| Chien (2014) – ARTEMIS | 69  | 24  | HR 1.87 (95% CI 0.28-12.45) | d,e,f,h           | bio > or ≤ 800pg/mL |
| Chien (2014) – GAP    | 104 | 24  | HR 2.28 (95% CI 1.18-4.38)  | b                 | bio > or ≤ 700pg/mL |
| **Periostin**         |     |     |                             |                   |                    |
| Okamoto (2011)        | 77  | 36  | Not significant (NR)        | x                 | NR                |
| Neighbors (2018) - Test | 123 | 12  | OR 3.05 (95% CI 0.79-11.88) | x                 | bio ≥ or < median   |
| Neighbors (2018) – Replication | 237 | 12  | OR 1.91 (95% CI 0.72-5.05)  | x                 | bio ≥ or < median   |
| **YKL-40**            |     |     |                             |                   |                    |
| Study (Year) | Stage | Sample Size | Hazard Ratio (95% CI) | Sign | Bio Value Condition | Notes |
|-------------|-------|-------------|-----------------------|------|---------------------|-------|
| Neighbors (2018) – Test | | 123 | 12 | OR 1.77 (95% CI 0.53-5.92) | x | bio ≥ or < median |
| Neighbors (2018) – Replication | | 237 | 12 | OR 2.7 (95% CI 0.94-7.75) | x | bio ≥ or < median |
| **ICAM-1** | | | | | | |
| Richards (2012) - Derivation | | 140 | 22 | HR 2.6 (95% CI 1.43-4.73) | a,b,d | bio > or < 202.5ng/mL |
| Richards (2012) – Validation | | 101 | 17 | HR 2.8 (95% CI 1.36-5.76) | a,b,d | bio > or < 300ng/mL |
| **ECM neoepitopes** | | | | | | |
| Jenkins (2015) – Discovery **BGM** | | 55 | 26 | HR 1.17 (95% CI 0.53-2.58) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **BGM** | | 134 | 21 | HR 1.34 (95% CI 0.92-1.97) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **C1M** | | 55 | 26 | HR 1.21 (95% CI 0.66-2.22) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **C1M** | | 134 | 21 | HR 1.62 (95% CI 1.14-2.31) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **C3A** | | 55 | 26 | HR 1.34 (95% CI 0.95-1.88) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **C3A** | | 134 | 21 | HR 1.91 (95% CI 1.06-3.46) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **C3M** | | 55 | 26 | HR 2.18 (95% CI 0.95-5.00) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **C3M** | | 134 | 21 | HR 1.56 (95% CI 0.94-2.59) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **C5M** | | 55 | 26 | HR 1.66 (95% CI 0.95-2.91) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **C5M** | | 134 | 21 | HR 1.07 (95% CI 0.66-1.72) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **C6M** | | 55 | 26 | HR 1.49 (95% CI 0.86-2.56) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **C6M** | | 134 | 21 | HR 1.39 (95% CI 0.93-2.06) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **CRPM** | | 55 | 26 | HR 3.74 (95% CI 1.46-9.58) | x | two-fold increase in bio value |
| Jenkins (2015) – Validation **CRPM** | | 134 | 21 | HR 1.87 (95% CI 0.98-3.56) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **ELM** | | 55 | 26 | HR 0.96 (95% CI 0.48-1.92) | x | two-fold increase in bio value |
| Jenkins (2015) – Discovery **ELM2** | | 55 | 26 | HR 0.96 (95% CI 0.75-1.24) | x | two-fold increase in bio value |
| Study (Year) | Peptide | N  | Median | HR (95% CI) | Adjustments | Effect Size |
|-------------|---------|----|--------|-------------|-------------|------------|
| Jenkins (2015) – *Discovery* | **P3NP** | 55 | 26     | 1.48 (0.67-3.27) | x           | two-fold increase in bio value |
| Jenkins (2015) – *Discovery* | **VICM** | 55 | 26     | 1.11 (0.83-1.49) | x           | two-fold increase in bio value |
| **Collagen synthesis peptides** |         |    |        |             |             |            |
| Organ (2019) | **P1NP** | 145 | 34     | 0.81 (0.6-1.11) | d,e         | two-fold increase in bio value |
| Organ (2019) | **PRO-C3** | 145 | 34     | 1.2 (0.74-1.93) | d,e         | two-fold increase in bio value |
| Hoyer (2020) | **PRO-C3** | 184 | 36     | 2.32 (1.33-4.04) | a           | continuous |
| Organ (2019) | **PRO-C6** | 145 | 34     | 1.11 (0.57-2.16) | d,e         | two-fold increase in bio value |
| Hoyer (2020) | **PRO-C6** | 184 | 36     | 2.18 (0.74-4.35) | a           | continuous |
| Organ (2019) | **P1NP:C1M** | 145 | 34     | 0.77 (0.6-0.99) | d,e         | two-fold increase in bio value |
| Organ (2019) | **PRO-C3:C3M** | 145 | 34     | 1.17 (0.77-1.79) | d,e         | two-fold increase in bio value |
| Organ (2019) | **PRO-C6:C6M** | 145 | 34     | 0.86 (0.59-1.26) | d,e         | two-fold increase in bio value |
| Hoyer (2020) | **PRO-C6** | 184 | 36     | 1.8 (0.74-4.35) | a           | continuous |

**Supplementary Table S5** – Studies reporting mortality outcomes

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DLCO, f= 6MWT, g=race, h=medication

bio, biomarker; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio
| Author (year) | Sample size | Follow up (months) | Effect size (Variance) | Level of adjustment | Effect size reported for |
|---------------|-------------|--------------------|------------------------|---------------------|--------------------------|
| **SP-D**      |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.01 (95% CI 0.97-1.06) | x | rising vs stable bio over 3 months |
| Maher (2017) – Validation  | 206 | 36 | HR 0.99 (95% CI 0.59-1.67) | a,b,c,d | rising vs stable bio over 3 months |
| **CA19-9**    |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.02 (95% CI 1.00-1.05) | X | rising vs stable bio over 3 months |
| Maher (2017) – Validation  | 206 | 36 | HR 1.39 (95% CI 0.79-2.46) | a,b,c,d | rising vs stable bio over 3 months |
| **CA-125**    |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.77 (95% CI 1.39-2.26) | x | rising vs stable bio over 3 months |
| Maher (2017) – Validation  | 206 | 36 | HR 2.39 (95% CI 1.4-4.08) | a,b,c,d | rising vs stable bio over 3 months |
| **ICAM-1**    |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.002 (95% CI 0.99-1.01) | x | rising vs stable bio over 3 months |
| **IGFBP-2**   |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.02 (95% CI 1.002-1.03) | x | rising vs stable bio over 3 months |
| **IL-8**      |             |                    |                        |                     |                          |
| Maher (2017) - Discovery | 106 | 36 | HR 1.02 (95% CI 0.98-1.07) | x | rising vs stable bio over 3 months |
| **ECM neoepitopes** |                         |                    |                        |                     |                          |
| Jenkins (2015) – Validation BGM | 134 | 21 | HR 1.07 (95% Cl 1.00-1.15) | a,c,d,e | rising vs stable bio over 3 months |
| Organ (2019) BGM | 145 | 34 | HR 1.41 (95% Cl 0.8-2.47) | a,b,c | rising vs stable bio over 3 months |
| Jenkins (2015) – Validation C1M | 134 | 21 | HR 1.01 (95% Cl 1.00-1.02) | a,c,d,e | rising vs stable bio over 3 months |
| Organ (2019) C1M | 145 | 34 | HR 1.84 (95% Cl 1.03-3.27) | a,b,c | rising vs stable bio over 3 months |
| Study Details                                      | Sample Size | Follow-up | Hazard Ratio (95% CI) | Risk Factors | Description                                      |
|---------------------------------------------------|-------------|-----------|-----------------------|--------------|-------------------------------------------------|
| Jenkins (2015) – Validation C3A                    | 134         | 21        | HR 1.05 (1.01-1.1)    | a,c,d,e      | rising vs stable bio over 3 months              |
| Jenkins (2015) – Validation C3M                    | 134         | 21        | HR 1.1 (1.04-1.17)    | a,c,d,e      | rising vs stable bio over 3 months              |
| Organ (2019) C3M                                  | 145         | 34        | HR 2.44 (1.39-4.31)   | a,b,c        | rising vs stable bio over 3 months              |
| Jenkins (2015) – Validation C5M                    | 134         | 21        | HR 1.00 (1.00-1.00)   | a,c,d,e      | rising vs stable bio over 3 months              |
| Jenkins (2015) – Validation C6M                    | 134         | 21        | HR 1.04 (1.01-1.08)   | a,c,d,e      | rising vs stable bio over 3 months              |
| Organ (2019) C6M                                  | 145         | 34        | HR 2.19 (1.25-3.82)   | a,b,c        | rising vs stable bio over 3 months              |
| Jenkins (2015) – Validation CRPM                   | 134         | 21        | HR 1.33 (1.1-1.6)     | a,c,d,e      | rising vs stable bio over 3 months              |
| Organ (2019) CRPM                                 | 145         | 34        | HR 2.13 (1.21-3.75)   | a,b,c        | rising vs stable bio over 3 months              |
| Jenkins (2015) – Validation VICM                   | 55          | 26        | HR 1.01 (0.99-1.03)   | a,c,d,e      | rising vs stable bio over 3 months              |
| Collagen synthesis peptides                        |             |           |                       |              |                                                 |
| Organ (2019) P1NP                                 | 145         | 34        | HR 0.76 (0.44-1.3)    | a,b,c        | rising vs stable bio over 3 months              |
| Organ (2019) PRO-C3                               | 145         | 34        | HR 1.62 (0.95-2.79)   | a,b,c        | rising vs stable bio over 3 months              |
| Organ (2019) PRO-C6                               | 145         | 34        | HR 1.14 (0.67-1.93)   | a,b,c        | rising vs stable bio over 3 months              |
| Organ (2019) P1NP:C1M                             | 145         | 34        | HR 0.73 (0.41-1.29)   | a,b,c        | rising ratio levels                             |
| Organ (2019) PRO-C3:C3M                           | 145         | 34        | HR 0.83 (0.49-1.43)   | a,b,c        | rising ratio levels                             |
| Organ (2019) PRO-C6:C6M                           | 145         | 34        | HR 0.55 (0.32-0.95)   | a,b,c        | rising ratio levels                             |

**Supplementary Table S6** – Studies reporting short term biomarkers change and their association with mortality

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DLCO, f= 6MWT, g=race, h=medication
bio, biomarker; HR, hazard ratio.
| Author (year) | Sample size | Timepoint of outcome (months) | Disease progression definition | Effect size (Variance) | Level of adjustment | Effect size reported for |
|---------------|-------------|-------------------------------|--------------------------------|-----------------------|-------------------|------------------------|
| **MMP-7 (IPD unavailable)** | | | | | | |
| Sokai (2015) | 57 | 6 | FVC decline ≥10% or DL_{CO} ≥ 15% decline or respiratory failure or death | Not significant (NR) | NR | NR |
| Bauer (2017) | 211 | 19 | FVC decline ≥ 10% or DL_{CO} ≥ 15% decline or respiratory failure or death | HR 2.2 (95% CI 1.4-3.7) | NR | bio < or ≥ 3.8ng/mL |
| **SP-A** | | | | | | |
| Raghu (2018) | 130 | 12 | FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death | AUROC 0.61 (90% CI 0.52-0.7) | NR | NR |
| **SP-D** | | | | | | |
| Collard (2010) | 67 | NR | Acute exacerbation | 361ng/mL vs 294ng/mL (p=0.01) | x | median bio in event and non-event group |
| Maher (2017) *Discovery* | 104 | 12 | All-cause mortality or FVC decline ≥ 10% | GR 1.35 (95% CI 1.1-1.649) | x | bio level in progressive vs. stable group |
| Maher (2017) *Validation* | 204 | 12 | All-cause mortality or FVC decline ≥ 10% | GR 1.35 (95% CI 1.12-1.62) | x | bio level in progressive vs. stable group |
| Raghu (2018) | 130 | 12 | FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death | AUROC 0.62 (90% CI 0.53-0.7) | NR | NR |
| **CCL-18** | | | | | | |
| Prasse (2009) | 67 | 24 | FVC decline ≥ 10% predicted or death | OR 6.75 (95% CI 2.52-18.1) | x | bio < or > 150ng/mL |
| Ohshimo (2014) | 77 | 36 | Acute exacerbation | HR 2.92 (95% CI 0.76-11.4) | x | bio > or < 212ng/mL |
| Neighbors (2018) *Test* | 123 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 1.64 (95% CI 1.04-2.83) | x | ‘high’ vs ‘low’ bio |
| Neighbors (2018) *Replication* | 237 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 1.32 (95% CI 0.76-2.13) | x | ‘high’ vs ‘low’ bio |
| Raghu (2018) | 130 | 12 | FVC decrease ≥10% predicted or DL_{CO} decrease > 15% or lung transplantation or death | AUROC 0.62 (90% CI 0.54-0.71) | NR | bio > or < 150ng/mL |
| Study | Year | Sample Size | Event Definition | Hazard Ratio (95% CI) | Additional Information |
|-------|------|-------------|------------------|-----------------------|------------------------|
| Neighbors (2018) Test | 2018 | 123 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 1.23 (95% CI 0.89-1.69) | 'high' vs 'low' bio |
| Neighbors (2018) Replication | 2018 | 237 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | Not significant (NR) | 'high' vs 'low' bio |
| KL-6 | | | | | |
| Collard (2010) | 2010 | 67 | Acute exacerbation | 1791 U/mL vs 895 U/mL (p=0.003) | median bio in event and non-event group |
| Ohshimo (2014) | 2014 | 77 | Acute exacerbation | HR 11.8 (95% CI 1.43-97.8) | bio > or < 1300U/mL |
| Jiang (2018) | 2018 | 20 | FVC decline ≥ 10% or DLCO decline ≥ 15%, or death | OR 1.00 (95% CI 1.00-1.00) | continuous bio |
| Raghu (2018) | 2018 | 130 | FVC decrease ≥10% predicted or DLCO decrease > 15% or lung transplantation or death | AUROC 0.6 (90% CI 0.51-0.68) | NA |
| IL-8 | | | | | |
| Richards (2012) Derivation | 2012 | 140 | FVC relative decline ≥ 10% | HR 2.00 (95% CI 1.22-3.28) | bio > or < 0.0092ng/mL |
| Richards (2012) Validation | 2012 | 101 | FVC relative decline ≥ 10% | HR 1.2 (95% CI 0.5-2.85) | bio > or < 0.0092ng/mL |
| Maher (2017) Discovery | 2017 | 104 | All-cause mortality or FVC decline ≥ 10% | GR 1.51 (95% CI 1.12-2.023) | bio level in progressive vs. stable group |
| Maher (2017) Validation | 2017 | 204 | All-cause mortality or FVC decline ≥ 10% | GR 2.42 (95% CI 1.6-3.65) | bio level in progressive vs. stable group |
| CA19-9 | | | | | |
| Maher (2017) Discovery | 2017 | 104 | All-cause mortality or FVC decline ≥ 10% | GR 3.12 (95% CI 1.7-5.7) | bio level in progressive vs. stable group |
| Maher (2017) Validation | 2017 | 204 | All-cause mortality or FVC decline ≥ 10% | GR 2.42 (95% CI 1.6-3.65) | bio level in progressive vs. stable group |
| CA125 | | | | | |
| Maher (2017) Discovery | 2017 | 104 | All-cause mortality or FVC decline ≥ 10% | Not significant (NR) | bio level in progressive vs. stable group |
| Maher (2017) Validation | 2017 | 204 | All-cause mortality or FVC decline ≥ 10% | GR 1.26 (95% CI 1.05-1.51) | bio level in progressive vs. stable group |
| **LOXL2** |   |   |   |   |   |   |   |   |   |   |   |
|-----------|---|---|---|---|---|---|---|---|---|---|---|
| **Chien (2014) ARTEMIS** | 69 | 24 | Mortality, hospitalisation or lung function decline (FVC ≥ 10% & DLCO ≥ 5%, or DLCO ≥ 15% and FVC ≥5%) | HR 5.41 (95% CI 1.65-17.73) | d,e,f,h | bio > or ≤ 800pg/mL |
| **Chien (2014) GAP** | 70 | 24 | Mortality, hospitalisation or lung function decline (FVC ≥ 10% & DLCO ≥ 5%, or DLCO ≥ 15% and FVC ≥5%) | HR 1.78 (95% CI 1.01-3.11) | x | bio > or ≤ 700pg/mL |
| **Periostin** |   |   |   |   |   |   |   |   |   |   |   |
| **Naik (2012)** | 50 | 11 | Death, acute exacerbation, transplantation, relative FVC decline ≥ 10% or DLCO > 15% | HR 1.47 (95% CI 1.03-2.1) | a,b,c,d,e | per bio SD |
| **Neighbors (2018) Test** | 123 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 2.08 (95% CI 1.24-3.47) | x | ‘high’ vs ‘low’ bio |
| **Neighbors (2018) Replication** | 237 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 1.75 (95% CI 0.87-2.84) | x | ‘high’ vs ‘low’ bio |
| **Raghu (2018)** | 130 | 12 | FVC decrease ≥10% predicted or DLCO decrease > 15% or lung transplantation or death | AUROC 0.6 (90% CI 0.51-0.69) | NR | NR |
| **YKL-40** |   |   |   |   |   |   |   |   |   |   |   |
| **Neighbors (2018) Test** | 123 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | HR 1.39 (95% CI 0.79-2.41) | x | ‘high’ vs ‘low’ bio |
| **Neighbors (2018) Replication** | 237 | 12 | FVC ≥10% absolute decline, 50m decline in 6MWT or death | Not significant (NR) | x | ‘high’ vs ‘low’ bio |
| **Raghu (2018)** | 130 | 12 | FVC decrease ≥10% predicted or DLCO decrease > 15% or lung transplantation or death | AUROC 0.58 (90% CI 0.49-0.67) | NR | NR |
| **ICAM-1** |   |   |   |   |   |   |   |   |   |   |   |
| **Richards (2012) Derivation** | 140 | 12 | FVC relative decline ≥ 10% | HR 1.6 (95% CI 1.00-2.56) | a,b,d | bio > or < 202.5ng/mL |
| **Richards (2012) Validation** | 101 | 12 | FVC relative decline ≥ 10% | HR 2.2 (95% CI 1.21-4.01) | a,b,d | bio > or < 262ng/mL |
| **Maher (2017) Discovery** | 104 | 12 | All-cause mortality or FVC decline ≥ 10% | GR 1.29 (95% CI 1.02-1.65) | x | bio level in progressive vs. stable group |
| **Raghu 2018** | 130 | 12 | FVC decrease ≥10% predicted or DLCO decrease > 15% or lung transplantation or death | AUROC 0.65 (90% CI 0.56-0.73) | NR | NR |
| **ECM neoepitopes** |   |   |   |   |   |   |   |   |   |   |   |
| Study                                      | Cohort/Type | Sample Size | Disease Progression Outcome | Effect Size | Adjustments | Description                                      |
|--------------------------------------------|-------------|-------------|-----------------------------|-------------|-------------|--------------------------------------------------|
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | Not significant (NR) | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | Not significant (NR) | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.011 (NR)  | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | Not significant (NR) | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.013 (NR)  | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.014 (NR)  | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.033 (NR)  | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | D+V cohort  | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.003 (NR)  | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | Discovery only | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.63 (NR)   | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | Discovery only | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.55 (NR)   | x           | bio level in progressive vs. stable group        |
| Jenkins (2015)                             | Discovery only | 186         | All-cause mortality or FVC decline ≥ 10% | P=0.42 (NR)   | x           | bio level in progressive vs. stable group        |
| Hoyer (2020)                               | PROC3        | 184         | All-cause mortality or FVC decline ≥ 10% | P=0.005 (NR)  | NR          | NR                                               |
| Hoyer (2020)                               | PROC6        | 184         | All-cause mortality or FVC decline ≥ 10% | P=0.031 (NR)  | NR          | NR                                               |

**Supplementary Table S7** – Studies reporting disease progression outcomes including definition of disease progression outcome used and effect sizes reported.

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DL_{CO2}, f=6MWT, g=race, h=medication, NR=not reported

bio, biomarker; AUROC, area under the receiver operating characteristics; DL_{CO2}, gas transfer for carbon monoxide; FVC, forced vital capacity; GR, group ratio; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio; 6MWT, 6-minute walk test;
| Author (year) | Sample size | FVC change measured at (months) | Effect size (Variance) | Level of adjustment | Effect size reported for |
|---------------|-------------|-------------------------------|------------------------|---------------------|--------------------------|
| **MMP-7 (IPD unavailable)** | | | | | |
| Bauer (2017) | 195 | 4 | p=0.004 (NR) | x | baseline bio correlation with %pred FVC change |
| **SP-A** | | | | | |
| Doubkova (2016) | 18 | NR | 155.8 ng/mL vs 87.15 ng/mL; p=0.01 | x | baseline bio in PFT “improvement” vs “stabilisation” |
| **SP-D** | | | | | |
| Doubkova (2016) | 18 | NR | 861.4ng/mL vs. 802.8ng/mL; p=0.76 | x | baseline bio in PFT “improvement” vs “stabilisation” |
| Kennedy (2015) | 13 | 6 | r= -0.64 (95% CI -0.89 to -0.08) | x | baseline bio correlation with %pred FVC change |
| Ohta (2017) | 60 | 6-12 | r= 0.09 (p>0.05) | x | baseline bio correlation with %pred FVC change |
| **CCL-18** | | | | | |
| Neighbors (2018) – Test | 123 | 12 | -3.1% (p=0.03) | x | %pred FVC change in baseline bio ≥ or < median (411.5ng/mL) |
| Neighbors (2018) – Replication | 237 | 12 | -3.6% (p=0.004) | x | %pred FVC change in baseline bio ≥ or < median (458.6ng/mL) |
| Prasse (2009) | 67 | 6 | r=0.54 (p<0.0001) | x | baseline bio correlation with %pred FVC change |
| **CXCL-13** | | | | | |
| Guo (2020) | 126 | 12 | r= 0.56 (p<0.001) | x | baseline bio correlation with %pred FVC change |
| Neighbors (2018) – Test | 123 | 12 | -3.2% (p=0.06) | x | %pred FVC change in baseline bio ≥ or < median (87.9ng/mL) |
| Neighbors (2018) – Replication | 237 | 12 | -3.7% (p=0.05) | x | %pred FVC change in baseline bio ≥ or < median (88.7ng/mL) |
| **KL-6** | | | | | |
| Guo (2020) | 126 | 12 | r= 0.71 (p<0.001) | x | baseline bio correlation with %pred FVC change |
| Ohta (2017) | 60 | 6-12 | r= 0.09 (p>0.05) | x | baseline bio correlation with %pred FVC change |
| Okamoto (2011) | 26 | 6 | Not significant (NR) | x | baseline bio correlation with %pred FVC change |
Supplementary Table S8 – Studies reporting association with baseline biomarkers and change in forced vital capacity (FVC).

bio, biomarker; x = no adjustments

IPD, individual participant data.

| Periostin | Neighbors (2018) – Test | 123 | 12 | -3.6% (p<0.001) | x | %pred FVC change in baseline bio ≥ or < median (67.8ng/mL) |
|-----------|------------------------|-----|----|-----------------|---|----------------------------------------------------------|
|           | Neighbors (2018) – | 237 | 12 | -2.5% (p=0.19) | x | %pred FVC change in baseline bio ≥ or < median (65.4ng/mL) |
| Replication|                       |     |    |                 |   |                                                          |
|           | Ohta (2017)            | 60  | 6-12| r= -0.43 (p<0.01) | x | baseline bio correlation with %pred FVC change |
|           | Okamoto (2011)         | 26  | 6  | r= -0.50 (p<0.01) | x | baseline bio correlation with %pred FVC change |

| YKL-40    | Neighbors (2018) – Test | 123 | 12 | -2.4% (p=0.04) | x | %pred FVC change in baseline bio ≥ or < median (100.3ng/mL) |
|-----------|------------------------|-----|----|-----------------|---|----------------------------------------------------------|
|           | Neighbors (2018) –     | 237 | 12 | -1.5% (p=0.70) | x | %pred FVC change in baseline bio ≥ or < median (109.5ng/mL) |
| Replication|                       |     |    |                 |   |                                                          |
| Author (year)         | Sample size | Timepoint of outcome (months) | Disease progression definition | Effect size (Variance) | Level of adjustment | Effect size reported for |
|----------------------|-------------|------------------------------|--------------------------------|------------------------|---------------------|--------------------------|
| **MMP-7 (IPD unavailable)** |             |                              |                                |                        |                     |                          |
| Bauer et al (2017)   | 211         | “Study period”               | FVC ≥10% decline, DL\textsubscript{CO} ≥ 15%, acute exacerbation or death | OR 1.9 (95% CI 1.2-3.0) | NR                  | Two-fold change in bio over 4 months |
| **SP-D**             |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 106         | 12                           | All-cause mortality or FVC decline ≥ 10% | p=0.029                | x                   | rising vs stable bio over 3 months |
|                       |             |                              |                                |                        |                     |                          |
|                       |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 206         | 12                           | All-cause mortality or FVC decline ≥ 10% | Not significant (NR)   | x                   | rising vs stable bio over 3 months |
| **CXCL-13**          |             |                              |                                |                        |                     |                          |
| Vuga et al (2014)    | 95          | >24                          | Respiratory failure            | HR 7.2 (95% CI 1.3-40.0) | x                   | bio “increase greatest vs. less increased” (time not specified) |
| **CA19-9**           |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 106         | 12                           | All-cause mortality or FVC decline ≥ 10% | p<0.001                | x                   | rising vs stable bio over 3 months |
|                       |             |                              |                                |                        |                     |                          |
|                       |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 206         | 12                           | All-cause mortality or FVC decline ≥ 10% | Not significant (NR)   | x                   | rising vs stable bio over 3 months |
| **CA125**            |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 106         | 12                           | All-cause mortality or FVC decline ≥ 10% | p=0.041                | x                   | rising vs stable bio over 3 months |
|                       |             |                              |                                |                        |                     |                          |
|                       |             |                              |                                |                        |                     |                          |
| Maher et al (2017)   | 206         | 12                           | All-cause mortality or FVC decline ≥ 10% | p=0.0028               | x                   | rising vs stable bio over 3 months |
| **KL-6**             |             |                              |                                |                        |                     |                          |
| Jiang et al (2018)   | 20          | 12                           | FVC decline ≥ 10%, DL\textsubscript{CO} decline ≥ 15% or death | OR 3.61 (95% CI 1.05-6.22) | a,b,c,d,e         | Change in KL-6 (not otherwise specified) |

Supplementary Table S9 – Studies reporting short term biomarkers change and their association with disease progression

x=no adjustments, a=age, b=gender, c=smoking, d=FVC e=DL\textsubscript{CO}, f=6MWT, g=race, h=medication, NR=not reported
bio, biomarker; DL\textsubscript{CO}, gas transfer for carbon monoxide; FVC, forced vital capacity; GR, group ratio; HR, hazard ratio; IPD, individual participant data; NR, not reported; OR, odds ratio
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