*Supplementary Table S1.* Definitions of organ involvement*.*

|  |  |
| --- | --- |
|  | Criteria for diagnosis |
| Pulmonary fibrosis | Basal fibrosis on high resolution computed tomography (HRCT) scan with a forced vital capacity (FVC) of less than 70% predicted. If an HRCT scan was not performed, which was the case for 88 (27%) patients at baseline, one of the following criteria was sufficient to diagnose pulmonary fibrosis: chest X-ray confirmed bibasal shadowing, FVC<55% predicted or DLCO (carbon monoxide diffusing capacity) <55% predicted. |
| Pulmonary hypertension | Raised mean pulmonary artery pressure at right heart catheterisation (greater than 25mmHg) or an estimated systolic pulmonary artery pressure (sPAP)/right ventricular systolic pressure (RVSP) of > 40mmg Hg on echocardiography (or > 45 mmHg including right atrial pressure [RAP] if the measure included RAP, but the value of this was not stated). |
| Cardiac involvement | Haemodynamically significant cardiac arrhythmia, pericardial effusion or congestive cardiac failure requiring hospitalisation or specific drug treatment, diastolic dysfunction (diagnosed usually on echocardiogram), ejection fraction less than 50%, or other cardiac manifestation felt to be clinically significant as judged by the investigators. |
| Renal crisis | Defined on the basis of clinician opinion and at least one of: decrease in estimated glomerular filtration rate (eGFR) by 30%, new onset blood pressure > 150/90 mmHg, microangiopathic haemolytic anaemia, retinopathy or renal biopsy findings. |
| Renal impairment | Defined as mild (eGFR 60-89 ml/min), moderate (30-59ml/min) and severe (< 29ml/min). Furthermore, a separate classification labelled “Renal involvement” was categorized as the presence of renal crisis and/or moderate-to-severe renal impairment. |
| Gastrointestinal involvement | Present if any of the following: weight loss more than 10% in the preceding 6 months, oesophageal dysmotility (on barium swallow or manometry), malabsorption, severe constipation, faecal incontinence, or rectal prolapse. If a patient had had more than 3 episodes of intestinal pseudo-obstruction, or more than 6 weeks’ nutritional support, then a diagnosis of ‘advanced gastrointestinal involvement’ was made. A category labelled “Any gastrointestinal involvement” included patients with any kind of gastrointestinal involvement cited above. |
| Muscle involvement | One or more of the following: creatine kinase (CK) more than 4 times normal, abnormal muscle biopsy, abnormal electromyography, or proximal muscle weakness combined with investigator opinion. |

For each patient, the presence of organ involvement of any type was carried forward from the time of diagnosis until the time of study exit. That is, organ involvement (such as pulmonary fibrosis) was not assumed to be reversed once it was detected using the criteria outlined above. Conversely, for each category above, if the outlined criteria ruled out organ involvement and previous investigations during past visits were inconclusive, it was assumed that the patient never had this type of manifestation (the absence of organ involvement was carried backwards).

*Supplementary Table S2. Primary and secondary outcome measures.*

|  |  |  |
| --- | --- | --- |
| Clinical variables | Frequency of recording | Outcome variable |
| Modified Rodnan skin score (mRSS) | 3 monthly | mRSS (primary) |
| Haemoglobin  Erythrocyte sedimentation rate (ESR)  Plasma creatinine  Estimated glomerular filtration rate (eGFR)  C-Reactive protein (CRP) | 3 monthly | Outcomes assessed in a preliminary analysis but not included as secondary outcomes. |
| High-resolution computed tomography (HRCT) findings  Forced vital capacity (FVC - % predicted)  Carbon monoxide diffusing capacity (DLCO - % predicted)  Estimated systolic pulmonary arterial pressure (sPAP) / right ventricular systolic pressure (RVSP) | 12 monthly (except HRCT) | FVC (secondary)  DLCO (secondary) |
| Scleroderma Specific Health Assessment Questionnaire [sHAQ], including HAQ-DI disability index  FACIT fatigue score  Short Form 36 Health Survey (SF36)  Cochin Hand Function Scale | 12 monthly | HAQ-DI (secondary)  Cochin Hand Function Scale (secondary) |
| Side effects from primary disease-modifying treatment | 3 monthly | Side effects (secondary) |
| Survival | Date and cause of death recorded | Survival (secondary) |

*Supplementary Table S3. Doses by protocol.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  | Baseline | | 12 months | | 24 months | |
|  |  | Frequency | n | Median dose in mg (IQR) | n | Median dose in mg (IQR) | n | Median dose in mg (IQR) |
| Methotrexate |  |  |  |  |  |  |  |  |
| Oral |  | Weekly | 44 | 15 (10-20) | 20 | 17 (15-20) | 15 | 15 (13-20) |
| Subcutaneous |  | Weekly | 13 | 15 (15-20) | 7 | 15 (10-20) | 6 | 15 (10-15) |
| Intramuscular |  | Weekly | 8 | 10 (10-15) | 7 | 10 (10-15) | 7 | 10 (10-15) |
| Mycophenolate mofetil |  |  |  |  |  |  |  |  |
| Oral |  | Daily | 118 | 1000 (1000-2000) | 92 | 2000 (1000-2000) | 55 | 2000 (1000-2000) |
| Cyclophosphamide |  |  |  |  |  |  |  |  |
| Oral |  | Daily | 4 | 100 (100-1050) | 2 | 100 (100-100) | 2 | 100 (100-100) |
| Intravenous |  | Approx.  monthly | 82 | 1000 (750-1221) | 23 | 1200 (1000-1353) | 3 | 400 (267-1000) |

At 12 and 24 months, doses are shown for patients who remained on the same drug and route combination as baseline

*Supplementary Table S4. Use of concomitant medications, no. (% of drug family)*

|  |  |  |  |
| --- | --- | --- | --- |
|  | At baseline |  | During study |
| Endothelin receptor antagonists | 12 (3.7\*) |  | 35 (10.7\*) |
| Bosentan | 11 (91.7) |  | 32 (91.4) |
| Other | 1 (8.3) |  | 5 (14.2) |
|  |  |  |  |
| Calcium channel blockers | 128 (39.5\*) |  | 185 (56.8\*) |
|  |  |  |  |
| Musculoskeletal | 73 (22.5\*) |  | 130 (39.9\*) |
| NSAIDs | 42 (57.5) |  | 69 (53.1) |
| Analgesics | 4 (5.5) |  | 7 (5.4) |
| Hydroxychloroquine | 25 (34.2) |  | 49 (37.7) |
| Methotrexate (not as main treatment protocol) | 0 (0) |  | 2 (1.5) |
| Tocilizumab for inflammatory arthritis | 0 (0) |  | 1 (0.8) |
| Other | 3 (4.1) |  | 28 (21.5) |
|  |  |  |  |
| Renal | 51 (15.9\*) |  | 88 (27.1\*) |
| ACE inhibitors | 46 (90.2) |  | 79 (89.8) |
| Other | 12 (23.5) |  | 28 (31.8) |
|  |  |  |  |
| Gastrointestinal | 224 (70\*) |  | 289 (88.7\*) |
| Proton pump inhibitors | 216 (96.4) |  | 285 (98.6) |
| H2 blockers | 10 (4.5) |  | 40 (13.8) |
| Antacid | 12 (5.4) |  | 41 (14.2) |
| Broad spectrum antibiotics for bacterial overgrowth | 4 (1.8) |  | 14 (4.8) |
| Prokinetic drugs | 21 (9.4) |  | 69 (23.9) |
| Other | 10 (4.5) |  | 34 (11.8) |
|  |  |  |  |
| Anti-platelet agents | 58 (18.2\*) |  | 98 (30.1\*) |
| Aspirin | 55 (94.8) |  | 84 (85.7) |
| Other | 5 (8.6) |  | 18 (18.4) |
|  |  |  |  |
| Angiotensin II receptor antagonists | 27 (8.3\*) |  | 52 (16\*) |
| IV-prostanoids (a) | 53 (17.2\*) |  | 108 (33.1\*) |

\* As a % of entire cohort (326 patients)

(a) IV prostanoids prior to study entry

*Supplementary Table S5. Confounders included in each analysis.*

|  |  |
| --- | --- |
| Outcome | Potential confounders (for treatment allocation and censoring) |
| mRSS | Age, Months since onset of skin thickening, cCurrent or previous steroid use, Anti-topoisomerase (anti-Scl70), Anti-RNA polymerase III, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Renal involvement, Muscle involvement, HAQ-DI, FACIT fatigue score, Cochin Hand Function Score |
| FVC | Age, Female, Previous immunosuppressant use, Current or previous steroid use, mRSS, Anti-topoisomerase (anti-Scl70), Anti-RNA polymerase III, Anticentromere, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Renal involvement, Muscle involvement, HAQ-DI, FACIT fatigue score, Cochin Hand Function Score |
| FVC (subset with pulmonary fibrosis on HRCT scan at baseline) | Age, Female, Current or previous steroid use, mRSS, Pulmonary fibrosis, Pulmonary hypertension, Renal involvement, HAQ-DI, FACIT fatigue score |
| DLCO | Age, Female, Current or previous steroid use, Anti-topoisomerase (anti-Scl70), Anti-RNA polymerase III, Anticentromere, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Renal involvement, HAQ-DI, FACIT fatigue score, Cochin Hand Function Score |
| DLCO (subset with pulmonary fibrosis on HRCT scan at baseline) | Current or previous steroid use, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Renal involvement, HAQ-DI, FACIT fatigue score |
| HAQ-DI | Previous immunosuppressant use, Current or previous steroid use, mRSS, Anticentromere, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Muscle involvement, FACIT fatigue score, Cochin Hand Function Score |
| Cochin Hand Function Scale | Current or previous steroid use, mRSS, Pulmonary fibrosis, Muscle involvement, HAQ-DI, FACIT fatigue score |
| Survival | Age, mRSS, Pulmonary fibrosis, Pulmonary hypertension, Cardiac involvement, Renal involvement, HAQ-DI, FACIT fatigue score, Cochin Hand Function Score |
| Event-free survival (protocol change due to adverse effects) | None |

The criterion for inclusion as a potential confounder was association with the outcome variable, as detailed in Supplementary Tables 6 to 13 for the different models.

DLCO: Carbon monoxide diffusing capacity  
FVC: Forced vital capacity  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
HRCT: High resolution computed tomography  
mRSS: modified Rodnan skin score (17 sites)  
RVSP: Right ventricular systolic pressure   
sPAP: Systolic pulmonary artery pressure

*Supplementary Table S6. Confounder selection for skin score(mRSS).*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| mRSS | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 0.1 (0 to 0.2) | 0.004 | -1.8 | 0 (-0.1 to 0) | 0.007 | 0.324 | Y | Y |
| Female, no. | -1.8 (-3.7 to 0.2) | 0.072 | -3.5 | 0.1 (-0.5 to 0.8) | 0.680 | 0.003 |  |  |
| Months since onset of skin thickening | -0.1 (-0.2 to 0) | 0.156 | -4.3 | 0.1 (0 to 0.1) | 0.002 | 0.001 | Y | Y |
| Previous immunosuppressant use | -2.1 (-5.3 to 1.2) | 0.205 | -3.5 | 0.1 (-1 to 1.3) | 0.808 | 0.007 |  |  |
| Current or previous steroid use | 1.2 (-0.6 to 3) | 0.191 | -2.9 | -1.2 (-1.8 to -0.6) | <0.0005 | 0.001 | Y | Y |
| mRSS |  |  | 0.9 | -0.2 (-0.2 to -0.2) | <0.0001 | 0.306 |  |  |
| Haemoglobin g/l \* | -0.1 (-0.1 to 0) | 0.003 | -5.8 | 0 (0 to 0) | 0.074 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | 0.5 (0.2 to 0.8) | 0.002 | -2.2 | -0.1 (-0.3 to 0) | 0.014 | 0.029 | Y |  |
| Platelets x109/l \* | 0 (0 to 0) | 0.001 | -3.1 | 0 (0 to 0) | 0.546 | 0.459 | Y |  |
| ESR mm/hr \* | 0.1 (0 to 0.1) | 0.003 | -4 | 0 (0 to 0) | 0.079 | 0.341 | Y |  |
| CRP mg/l \* | 0.1 (0 to 0.2) | 0.003 | -4.4 | 0.1 (0 to 0.1) | 0.001 | 0.026 | Y |  |
| Anti-topoisomerase (anti-Scl70) | -2.6 (-4.4 to -0.8) | 0.005 | -4.3 | 2.2 (1.6 to 2.8) | <0.0001 | 0.228 | Y | Y |
| Anti-RNA polymerase III | 4.5 (2.1 to 6.9) | <0.0005 | -3 | -2.1 (-2.9 to -1.2) | <0.0001 | 0.433 | Y | Y |
| Anticentromere | -0.4 (-3.9 to 3.1) | 0.816 | -3.4 | 0.5 (-0.8 to 1.9) | 0.456 | 0.147 |  |  |
| Pulmonary fibrosis | 2.9 (0.4 to 5.4) | 0.021 | -3.5 | 0.3 (-0.6 to 1.2) | 0.534 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | -0.1 (-0.1 to 0) | 0.013 | -5.5 | 0 (0 to 0) | 0.005 | 0.026 | Y |  |
| DLCO (% predicted) \*\* | 0 (-0.1 to 0) | 0.105 | -3.2 | 0 (0 to 0) | 0.689 | <0.0005 |  |  |
| Pulmonary hypertension | 2.5 (-0.7 to 5.8) | 0.128 | -3.3 | -2.1 (-3.3 to -0.8) | 0.001 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | 0.1 (0 to 0.2) | 0.151 | -2.2 | 0 (-0.1 to 0) | 0.018 | 0.472 | Y |  |
| Cardiac involvement | 2.5 (-0.2 to 5.2) | 0.075 | -3.5 | 0 (-1 to 0.9) | 0.929 | 0.009 |  | Y |
| Renal involvement | 2.2 (-0.7 to 5.2) | 0.140 | -3.3 | -1.6 (-2.6 to -0.5) | 0.004 | 0.039 | Y | Y |
| eGFR ml/min \*\* | 0 (-0.1 to 0) | 0.383 | -5.4 | 0 (0 to 0) | 0.007 | 0.339 | Y |  |
| Renal crisis \*\* | 0.5 (-3.6 to 4.6) | 0.799 | -3.4 | -1.5 (-3.1 to 0.1) | 0.062 | 0.110 |  |  |
| Plasma creatinine  in μmol/l \* | 0 (0 to 0) | 0.882 | -3.5 | 0 (0 to 0) | 0.687 | 0.422 |  |  |
| Any GI involvement \* | 2.2 (0.3 to 4) | 0.021 | -3.4 | -0.1 (-0.8 to 0.5) | 0.664 | 0.078 | Y |  |
| Muscle involvement | 1.2 (-1.8 to 4.2) | 0.425 | -3.2 | -2 (-2.9 to -1) | <0.0005 | 0.002 | Y | Y |
| Current  digital ulcers \* | 2.5 (0.1 to 4.8) | 0.038 | -3.3 | -0.9 (-1.8 to 0) | 0.047 | 0.705 | Y |  |
| HAQ-DI Disability index (0-3) | 3.5 (2.5 to 4.6) | <0.0001 | -3 | -0.4 (-0.8 to 0) | 0.039 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | -0.1 (-0.2 to -0.1) | <0.0005 | -3.1 | 0 (0 to 0) | 0.484 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | 0.1 (0.1 to 0.2) | <0.0001 | -3.7 | 0 (0 to 0) | 0.979 | 0.025 | Y | Y |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S7. Confounder selection for FVC.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FVC | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 0.1  (-0.1 to 0.2) | 0.509 | -4.8 | 0.1  (0.1 to 0.2) | <0.0001 | 0.324 | Y | Y |
| Female, no. | 6  (1.1 to 10.9) | 0.017 | 1.9 | -1.5  (-3.2 to 0.2) | 0.077 | 0.003 | Y | Y |
| Months since onset of skin thickening | -0.2  (-0.5 to 0) | 0.067 | 0.8 | 0  (-0.1 to 0.1) | 0.824 | 0.001 |  |  |
| Previous immunosuppressant use | -3  (-11.2 to 5.1) | 0.462 | 1 | -3.1  (-5.8 to -0.4) | 0.024 | 0.007 | Y | Y |
| Current or previous steroid use | -6.1  (-10.7 to -1.5) | 0.009 | 0.5 | 0.8  (-0.7 to 2.4) | 0.299 | 0.001 | Y | Y |
| mRSS | -0.4  (-0.6 to -0.1) | 0.013 | 0.4 | 0  (-0.1 to 0.1) | 0.712 | 0.306 | Y | Y |
| Haemoglobin g/l \* | 0.1  (-0.1 to 0.2) | 0.231 | 8.1 | -0.1  (-0.1 to 0) | 0.025 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | -1.1  (-1.9 to -0.3) | 0.009 | -2.2 | 0.4  (0.1 to 0.6) | 0.008 | 0.029 | Y |  |
| Platelets x109/l \* | 0  (0 to 0) | 0.593 | -0.7 | 0  (0 to 0) | 0.239 | 0.459 |  |  |
| ESR mm/hr \* | -0.2  (-0.3 to -0.1) | 0.005 | -0.1 | 0  (0 to 0.1) | 0.051 | 0.341 | Y |  |
| CRP mg/l \* | -0.1  (-0.2 to 0.1) | 0.352 | 2 | -0.1  (-0.1 to 0) | 0.160 | 0.026 |  |  |
| Anti-topoisomerase (anti-Scl70) | -4.8  (-9.5 to -0.2) | 0.043 | 1.6 | -1.6  (-3.1 to -0.1) | 0.042 | 0.228 | Y | Y |
| Anti-RNA polymerase III | 9.4  (3.2 to 15.7) | 0.003 | 0.6 | -0.5  (-2.5 to 1.5) | 0.615 | 0.433 | Y | Y |
| Anticentromere | 12.9  (3.8 to 22.1) | 0.006 | 1 | -2.5  (-6 to 0.9) | 0.152 | 0.147 | Y | Y |
| Pulmonary fibrosis | -31.2  (-36.4 to -26) | <0.0001 | 0.2 | 4.6  (2.4 to 6.8) | <0.0001 | 0.036 | Y | Y |
| FVC (% predicted) \*\* |  |  |  | -0.1  (-0.2 to -0.1) | <0.0001 | 0.026 |  |  |
| DLCO (% predicted) \*\* | 0.6  (0.5 to 0.7) | <0.0001 | 6.4 | -0.1  (-0.1 to 0) | <0.0001 | <0.0005 | Y |  |
| Pulmonary hypertension | -16.8  (-24.8 to -8.7) | <0.0001 | 0.5 | 3.8  (0.8 to 6.8) | 0.014 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | -0.4  (-0.6 to -0.2) | 0.001 | -2.1 | 0.1  (0 to 0.2) | 0.005 | 0.472 | Y |  |
| Cardiac involvement | -11.7  (-18.5 to -4.8) | 0.001 | 0.5 | 2.2  (-0.1 to 4.6) | 0.059 | 0.009 | Y | Y |
| Renal involvement | -2.2  (-10 to 5.5) | 0.572 | 0.3 | 5.4  (2.8 to 8.1) | <0.0001 | 0.039 | Y | Y |
| eGFR ml/min \*\* | 0  (-0.1 to 0.1) | 0.609 | 7.3 | -0.1  (-0.1 to 0) | <0.0001 | 0.339 | Y |  |
| Renal crisis \*\* | 0.4  (-10.8 to 11.7) | 0.940 | 0.6 | 6.6  (2.2 to 11) | 0.003 | 0.11 | Y |  |
| Plasma creatinine  in μmol/l \* | 0  (-0.1 to 0) | 0.300 | 0.1 | 0  (0 to 0) | 0.010 | 0.422 | Y |  |
| Any GI involvement \* | -4.1  (-8.8 to 0.7) | 0.094 | 0.2 | 1.6  (0 to 3.1) | 0.051 | 0.078 | Y |  |
| Muscle involvement | -8.2  (-15.8 to -0.6) | 0.034 | 0.6 | 1.5  (-0.8 to 3.9) | 0.204 | 0.002 | Y | Y |
| Current digital ulcers \* | -3.6  (-9.8 to 2.6) | 0.255 | 1.1 | -2.2  (-4.4 to -0.1) | 0.041 | 0.705 | Y |  |
| HAQ-DI Disability index (0-3) | -6  (-8.7 to -3.2) | <0.0001 | 0.8 | -0.1  (-1 to 0.9) | 0.897 | 0.4 | Y | Y |
| FACIT fatigue score (0-52) | 0.4  (0.2 to 0.5) | <0.0001 | 0.2 | 0  (0 to 0.1) | 0.638 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | -0.2  (-0.3 to 0) | 0.009 | 1.2 | 0  (-0.1 to 0) | 0.724 | 0.025 | Y | Y |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S8. Confounder selection for FVC, subset.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| FVC, subset with pulmonary fibrosis on HRCT scan | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 0.1  (-0.2 to 0.3) | 0.587 | -5.3 | 0.1  (0 to 0.2) | 0.013 | 0.324 | Y | Y |
| Female, no. | 3.8  (-3.3 to 11) | 0.287 | 3.8 | -3.6  (-6.1 to -1) | 0.006 | 0.003 | Y | Y |
| Months since onset of skin thickening | 0  (-0.3 to 0.4) | 0.839 | 2.4 | -0.1  (-0.2 to 0.1) | 0.444 | 0.001 |  |  |
| Previous immunosuppressant use | -2.7  (-14 to 8.5) | 0.633 | 1.6 | -2.6  (-6.7 to 1.4) | 0.198 | 0.007 |  |  |
| Current or previous steroid use | -6.8  (-13.5 to 0) | 0.048 | 0.7 | 1.2  (-1.2 to 3.6) | 0.331 | 0.001 | Y | Y |
| mRSS | -0.5  (-0.9 to -0.2) | 0.006 | 0.2 | 0.1  (-0.1 to 0.2) | 0.513 | 0.306 | Y | Y |
| Haemoglobin g/l \* | 0.2  (0 to 0.4) | 0.104 | 4.5 | 0  (-0.1 to 0.1) | 0.529 | 0.721 |  |  |
| White blood count (WBC) x109/l \* | -1.3  (-2.3 to -0.2) | 0.021 | -6.2 | 0.9  (0.5 to 1.2) | <0.0001 | 0.029 | Y |  |
| Platelets x109/l \* | 0  (-0.1 to 0) | 0.094 | -5 | 0  (0 to 0) | 0.001 | 0.459 | Y |  |
| ESR mm/hr \* | -0.3  (-0.4 to -0.1) | 0.005 | -1.3 | 0.1  (0 to 0.2) | 0.017 | 0.341 | Y |  |
| CRP mg/l \* | -0.1  (-0.3 to 0.1) | 0.250 | 2.4 | 0  (-0.2 to 0.1) | 0.602 | 0.026 |  |  |
| Anti-topoisomerase (anti-Scl70) | -0.9  (-7.9 to 6) | 0.792 | 2.3 | -1.5  (-3.9 to 0.9) | 0.224 | 0.228 |  |  |
| Anti-RNA polymerase III | 11.3  (-2.6 to 25.1) | 0.109 | 1.1 | -0.9  (-5 to 3.1) | 0.651 | 0.433 |  |  |
| Anticentromere | 4.5  (-13.3 to 22.4) | 0.616 | 1.6 | -3.1  (-9.3 to 3.2) | 0.334 | 0.147 |  |  |
| Pulmonary fibrosis | -27.8  (-32.8 to -22.7) | <0.0001 | -0.3 | 5.2  (2.6 to 7.7) | <0.0001 | 0.036 | Y | Y |
| FVC (% predicted) \*\* |  |  | 12.9 | -0.1  (-0.2 to -0.1) | <0.0001 | 0.026 |  |  |
| DLCO (% predicted) \*\* | 0.5  (0.4 to 0.7) | <0.0001 | 5.2 | -0.1  (-0.1 to 0) | 0.070 | <0.0005 | Y |  |
| Pulmonary hypertension | -13  (-22.1 to -4) | 0.005 | 1.1 | 1.9  (-1.6 to 5.4) | 0.297 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | -0.2  (-0.5 to 0) | 0.097 | -1 | 0.1  (0 to 0.2) | 0.089 | 0.472 |  |  |
| Cardiac involvement | -6.8  (-15.1 to 1.4) | 0.103 | 0.9 | 2  (-0.9 to 5) | 0.176 | 0.009 |  |  |
| Renal involvement | -0.4  (-11.3 to 10.5) | 0.944 | 0.6 | 6.8  (3 to 10.7) | <0.0005 | 0.039 | Y | Y |
| eGFR ml/min \*\* | 0  (-0.2 to 0.1) | 0.650 | 8.4 | -0.1  (-0.1 to 0) | 0.007 | 0.339 | Y |  |
| Renal crisis \*\* | -2.6  (-20.1 to 15) | 0.771 | 1 | 12.3  (5.2 to 19.5) | 0.001 | 0.110 | Y |  |
| Plasma creatinine  in μmol/l \* | 0  (-0.1 to 0) | 0.271 | -0.1 | 0  (0 to 0) | 0.009 | 0.422 | Y |  |
| Any GI involvement \* | -2.5  (-9.3 to 4.3) | 0.462 | 0.6 | 1.6  (-0.8 to 4) | 0.188 | 0.078 |  |  |
| Muscle involvement | -3.4  (-13.7 to 6.9) | 0.514 | 0.9 | 2.9  (-0.6 to 6.3) | 0.102 | 0.002 |  |  |
| Current digital ulcers \* | -6.9  (-16.1 to 2.4) | 0.146 | 1.5 | -1.9  (-5.8 to 2.1) | 0.357 | 0.705 |  |  |
| HAQ-DI Disability index (0-3) | -6.9  (-10.7 to -3.1) | 0.001 | 1.6 | -0.5  (-2 to 1) | 0.521 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | 0.5  (0.2 to 0.7) | <0.0005 | 0.6 | 0  (-0.1 to 0.1) | 0.740 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | -0.2  (-0.4 to 0) | 0.106 | 2 | 0  (-0.1 to 0.1) | 0.623 | 0.025 |  |  |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S9. Confounder selection for DLCO.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| DLCO | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | -0.2  (-0.3 to 0) | 0.034 | -3.3 | 0.1  (0 to 0.1) | 0.068 | 0.324 | Y | Y |
| Female, no. | 6.4  (1.7 to 11.1) | 0.008 | 0 | -0.5  (-2.3 to 1.4) | 0.619 | 0.003 | Y | Y |
| Months since onset of skin thickening | -0.2  (-0.5 to 0) | 0.068 | -0.7 | 0  (-0.1 to 0.1) | 0.389 | 0.001 |  |  |
| Previous immunosuppressant use | -5.9  (-13.5 to 1.8) | 0.133 | -0.3 | -0.5  (-3.4 to 2.4) | 0.748 | 0.007 |  |  |
| Current or previous steroid use | -6  (-10.4 to -1.6) | 0.008 | -1.2 | 1.8  (0.1 to 3.5) | 0.033 | 0.001 | Y | Y |
| mRSS | -0.2  (-0.5 to 0) | 0.105 | -0.5 | 0  (-0.1 to 0.1) | 0.863 | 0.306 |  |  |
| Haemoglobin g/l \* | 0.2  (0 to 0.3) | 0.027 | 7 | -0.1  (-0.1 to 0) | 0.040 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | -1.4  (-2.2 to -0.6) | 0.001 | -1.4 | 0.1  (-0.2 to 0.4) | 0.418 | 0.029 | Y |  |
| Platelets x109/l \* | 0  (0 to 0) | 0.035 | -0.1 | 0  (0 to 0) | 0.887 | 0.459 | Y |  |
| ESR mm/hr \* | -0.2  (-0.3 to -0.1) | 0.002 | -0.5 | 0  (-0.1 to 0.1) | 0.941 | 0.341 | Y |  |
| CRP mg/l \* | -0.3  (-0.4 to -0.1) | 0.003 | 0 | 0  (-0.2 to 0.1) | 0.348 | 0.026 | Y |  |
| Anti-topoisomerase (anti-Scl70) | -5.9  (-10.4 to -1.5) | 0.009 | 0.2 | -1.4  (-3.1 to 0.3) | 0.106 | 0.228 | Y | Y |
| Anti-RNA polymerase III | 6.5  (0.6 to 12.4) | 0.031 | -0.6 | 0.7  (-1.5 to 2.9) | 0.520 | 0.433 | Y | Y |
| Anticentromere | 8.6  (-0.2 to 17.3) | 0.054 | -0.4 | -1.1  (-5 to 2.8) | 0.582 | 0.147 |  | Y |
| Pulmonary fibrosis | -21  (-27.2 to -14.8) | <0.0001 | -0.6 | 2.1  (-0.5 to 4.8) | 0.116 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | 0.6  (0.5 to 0.7) | <0.0001 | 5.4 | -0.1  (-0.1 to 0) | 0.007 | 0.026 | Y |  |
| DLCO (% predicted) \*\* |  |  | 9.6 | -0.2  (-0.2 to -0.1) | <0.0001 | <0.0005 |  |  |
| Pulmonary hypertension | -16  (-24.9 to -7.1) | <0.0005 | -0.5 | 3.2  (-0.6 to 6.9) | 0.097 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | -0.5  (-0.7 to -0.3) | <0.0001 | -2.9 | 0.1  (0 to 0.1) | 0.039 | 0.472 | Y |  |
| Cardiac involvement | -8.2  (-15.1 to -1.2) | 0.021 | -0.6 | 2.6  (-0.1 to 5.2) | 0.058 | 0.009 | Y | Y |
| Renal involvement | -7.4  (-14.8 to 0) | 0.049 | -0.6 | 3.4  (0.5 to 6.4) | 0.021 | 0.039 | Y | Y |
| eGFR ml/min \*\* | 0  (-0.1 to 0.1) | 0.337 | 2.8 | 0  (-0.1 to 0) | 0.044 | 0.339 | Y |  |
| Renal crisis \*\* | -11.6  (-22.1 to -1.1) | 0.031 | -0.6 | 8.2  (3.7 to 12.7) | <0.0005 | 0.110 | Y |  |
| Plasma creatinine  in μmol/l \* | 0  (-0.1 to 0) | 0.008 | -1.2 | 0  (0 to 0) | 0.013 | 0.422 | Y |  |
| Any GI involvement \* | -1.6  (-6.3 to 3.1) | 0.498 | -0.7 | 1.1  (-0.6 to 2.9) | 0.195 | 0.078 |  |  |
| Muscle involvement | -3.8  (-11.7 to 4.2) | 0.351 | -0.5 | 1.3  (-1.4 to 4) | 0.358 | 0.002 |  |  |
| Current digital ulcers \* | -3.8  (-9.9 to 2.3) | 0.218 | -0.3 | -0.4  (-2.8 to 2) | 0.759 | 0.705 |  |  |
| HAQ-DI Disability index (0-3) | -5.4  (-8.1 to -2.7) | <0.0005 | 0 | -0.4  (-1.5 to 0.6) | 0.410 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | 0.3  (0.2 to 0.5) | <0.0005 | -2.1 | 0.1  (0 to 0.1) | 0.130 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | -0.2  (-0.3 to -0.1) | 0.006 | 0.2 | 0  (-0.1 to 0) | 0.617 | 0.025 | Y | Y |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S10. Confounder selection for DLCO, subset.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| DLCO, subset with pulmonary fibrosis on HRCT scan | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | -0.1  (-0.3 to 0.2) | 0.542 | -0.9 | 0  (-0.1 to 0.1) | 0.496 | 0.324 |  |  |
| Female, no. | 4.3  (-2.6 to 11.3) | 0.221 | 0.6 | 0.5  (-2.1 to 3) | 0.712 | 0.003 |  |  |
| Months since onset of skin thickening | -0.3  (-0.6 to 0.1) | 0.132 | 1.8 | 0  (-0.2 to 0.1) | 0.644 | 0.001 |  |  |
| Previous immunosuppressant use | -1.1  (-11.7 to 9.4) | 0.832 | 0.8 | 1.2  (-2.5 to 5.0) | 0.520 | 0.007 |  |  |
| Current or previous steroid use | -5.2  (-11.9 to 1.4) | 0.123 | -0.3 | 2.3  (0 to 4.7) | 0.050 | 0.001 | Y | Y |
| mRSS | -0.3  (-0.7 to 0.1) | 0.118 | 1.3 | 0  (-0.2 to 0.1) | 0.815 | 0.306 |  |  |
| Haemoglobin g/l \* | 0.1  (-0.1 to 0.3) | 0.147 | 7.2 | 0  (-0.1 to 0) | 0.188 | 0.721 |  |  |
| White blood count (WBC) x109/l \* | -0.9  (-2 to 0.2) | 0.108 | 1.7 | -0.1  (-0.4 to 0.3) | 0.686 | 0.029 |  |  |
| Platelets x109/l \* | 0  (-0.1 to 0) | 0.018 | -0.2 | 0  (0 to 0) | 0.509 | 0.459 | Y |  |
| ESR mm/hr \* | -0.1  (-0.3 to 0) | 0.128 | -1.1 | 0  (0 to 0.1) | 0.335 | 0.341 |  |  |
| CRP mg/l \* | -0.2  (-0.4 to 0) | 0.077 | 0.5 | 0  (-0.1 to 0.1) | 0.901 | 0.026 |  |  |
| Anti-topoisomerase (anti-Scl70) | -3  (-9.8 to 3.7) | 0.376 | 1.4 | -1  (-3.4 to 1.4) | 0.403 | 0.228 |  |  |
| Anti-RNA polymerase III | 9.3  (-2.7 to 21.3) | 0.126 | 0.5 | 3.3  (-0.7 to 7.4) | 0.104 | 0.433 |  |  |
| Anticentromere | 2.9  (-15.4 to 21.2) | 0.751 | 0.8 | 0.6  (-5.9 to 7.2) | 0.851 | 0.147 |  |  |
| Pulmonary fibrosis | -12.6  (-19.4 to -5.8) | <0.0005 | 0.7 | 0.7  (-2 to 3.3) | 0.610 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | 0.5  (0.4 to 0.7) | <0.0001 | 1.3 | 0  (-0.1 to 0.1) | 0.934 | 0.026 | Y |  |
| DLCO (% predicted) \*\* |  |  | 7.2 | -0.1  (-0.2 to 0) | 0.001 | 0.000 |  |  |
| Pulmonary hypertension | -15.4  (-25.2 to -5.6) | 0.002 | 0.6 | 2.9  (-0.7 to 6.6) | 0.117 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | -0.4  (-0.7 to -0.2) | 0.002 | -1.5 | 0.1  (0 to 0.1) | 0.144 | 0.472 | Y |  |
| Cardiac involvement | -1.5  (-10 to 6.9) | 0.721 | 0.3 | 3.5  (0.5 to 6.4) | 0.023 | <0.0005 | Y | Y |
| Renal involvement | 2  (-9 to 12.9) | 0.723 | 0.5 | 4.0  (0.1 to 8.0) | 0.045 | 0.039 | Y | Y |
| eGFR ml/min \*\* | 0  (-0.2 to 0.1) | 0.680 | 6.1 | -0.1  (-0.1 to 0) | 0.023 | 0.339 | Y |  |
| Renal crisis \*\* | -3.2  (-21.4 to 15) | 0.730 | 0.6 | 9.1  (2.5 to 15.7) | 0.007 | 0.110 | Y |  |
| Plasma creatinine  in μmol/l \* | 0  (-0.1 to 0) | 0.197 | 0.6 | 0  (0 to 0) | 0.057 | 0.422 |  |  |
| Any GI involvement \* | 1.5  (-5.3 to 8.2) | 0.667 | 0.5 | 1.1  (-1.3 to 3.4) | 0.377 | 0.078 |  |  |
| Muscle involvement | 7.2  (-3.3 to 17.6) | 0.176 | 1.2 | -2.3  (-5.8 to 1.2) | 0.198 | 0.002 |  |  |
| Current digital ulcers \* | -4.1  (-13.7 to 5.6) | 0.405 | 0.9 | 0.4  (-3.7 to 4.5) | 0.852 | 0.705 |  |  |
| HAQ-DI Disability index (0-3) | -4.6  (-8.5 to -0.7) | 0.020 | 1.2 | -0.6  (-2.2 to 0.9) | 0.422 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | 0.3  (0.1 to 0.6) | 0.009 | -0.1 | 0  (-0.1 to 0.1) | 0.555 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | -0.1  (-0.3 to 0.1) | 0.232 | 1.3 | 0  (-0.1 to 0.1) | 0.972 | 0.025 |  |  |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S11. Confounder selection for HAQ-DI.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| HAQ-DI | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 0  (-0.01 to 0) | 0.568 | -0.12 | 0  (0 to 0) | 0.182 | 0.324 |  |  |
| Female, no. | 0.18  (-0.03 to 0.38) | 0.090 | -0.02 | 0  (-0.09 to 0.09) | 0.963 | 0.003 |  |  |
| Months since onset of skin thickening | 0  (-0.01 to 0.01) | 0.874 | -0.04 | 0  (0 to 0.01) | 0.561 | 0.001 |  |  |
| Previous immunosuppressant use | 0.09  (-0.26 to 0.44) | 0.619 | -0.01 | -0.19  (-0.34 to -0.03) | 0.016 | 0.007 | Y | Y |
| Current or previous steroid use | 0.31  (0.13 to 0.5) | 0.001 | 0.02 | -0.09  (-0.17 to -0.02) | 0.020 | 0.001 | Y | Y |
| mRSS | 0.04  (0.03 to 0.05) | <0.0001 | 0.03 | 0  (-0.01 to 0) | 0.427 | 0.306 | Y | Y |
| Haemoglobin g/l \* | -0.02  (-0.02 to -0.01) | <0.0005 | -0.25 | 0  (0 to 0) | 0.179 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | 0.03  (-0.01 to 0.06) | 0.098 | -0.02 | 0  (-0.01 to 0.01) | 0.947 | 0.029 |  |  |
| Platelets x109/l \* | 0  (0 to 0) | <0.0005 | -0.03 | 0  (0 to 0) | 0.887 | 0.459 | Y |  |
| ESR mm/hr \* | 0.01  (0.01 to 0.02) | <0.0001 | 0 | 0  (0 to 0) | 0.949 | 0.341 | Y |  |
| CRP mg/l \* | 0.02  (0.01 to 0.02) | <0.0001 | -0.03 | 0  (0 to 0) | 0.731 | 0.026 | Y |  |
| Anti-topoisomerase (anti-Scl70) | -0.08  (-0.28 to 0.11) | 0.400 | -0.03 | 0.03  (-0.05 to 0.11) | 0.475 | 0.228 |  |  |
| Anti-RNA polymerase III | 0.18  (-0.08 to 0.44) | 0.183 | -0.03 | 0.02  (-0.09 to 0.12) | 0.747 | 0.433 |  |  |
| Anticentromere | -0.27  (-0.63 to 0.09) | 0.137 | -0.03 | 0.19  (0.02 to 0.35) | 0.025 | 0.147 | Y | Y |
| Pulmonary fibrosis | 0.42  (0.14 to 0.7) | 0.004 | -0.03 | 0.09  (-0.03 to 0.21) | 0.133 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | -0.01  (-0.01 to -0.01) | <0.0001 | -0.03 | 0  (0 to 0) | 0.799 | 0.026 | Y |  |
| DLCO (% predicted) \*\* | -0.01  (-0.01 to 0) | <0.0005 | -0.04 | 0  (0 to 0) | 0.625 | <0.0005 | Y |  |
| Pulmonary hypertension | 0.33  (-0.02 to 0.67) | 0.063 | -0.01 | -0.15  (-0.32 to 0.02) | 0.076 | 0.488 |  | Y |
| sPAP or RVSP mmHg \*\* | 0.01  (0 to 0.01) | 0.302 | -0.01 | 0  (-0.01 to 0) | 0.570 | 0.472 |  |  |
| Cardiac involvement | 0.41  (0.13 to 0.69) | 0.004 | -0.01 | -0.07  (-0.19 to 0.06) | 0.321 | 0.009 | Y | Y |
| Renal involvement | 0.27  (-0.04 to 0.59) | 0.087 | -0.01 | -0.11  (-0.25 to 0.03) | 0.111 | 0.039 |  |  |
| eGFR ml/min \*\* | 0  (0 to 0) | 0.891 | -0.04 | 0  (0 to 0) | 0.787 | 0.339 |  |  |
| Renal crisis \*\* | -0.04  (-0.49 to 0.4) | 0.849 | -0.01 | -0.15  (-0.38 to 0.08) | 0.192 | 0.110 |  |  |
| Plasma creatinine  in μmol/l \* | 0  (0 to 0) | 0.477 | -0.05 | 0  (0 to 0) | 0.749 | 0.422 |  |  |
| Any GI involvement \* | 0.28  (0.09 to 0.48) | 0.004 | -0.01 | -0.02  (-0.1 to 0.07) | 0.677 | 0.078 | Y |  |
| Muscle involvement | 0.54  (0.22 to 0.85) | 0.001 | 0.01 | -0.27  (-0.39 to -0.14) | <0.0001 | 0.002 | Y | Y |
| Current digital ulcers \* | 0.39  (0.15 to 0.64) | 0.002 | 0 | -0.1  (-0.21 to 0.01) | 0.078 | 0.705 | Y |  |
| HAQ-DI Disability index (0-3) |  |  | 0.18 | -0.19  (-0.23 to -0.14) | <0.0001 | 0.400 |  |  |
| FACIT fatigue score (0-52) | -0.04  (-0.05 to -0.04) | <0.0001 | -0.15 | 0  (0 to 0.01) | 0.011 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | 0.03 (0.03 to 0.04) | <0.0001 | 0.02 | 0 (-0.01 to 0) | 0.002 | 0.025 | Y | Y |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test

*Supplementary Table S12. Confounder selection for Cochin Hand Function Scale.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Log(Cochin score+1) | 1. Association with outcome at baseline | | 1. Effect on outcome through time | | |  |  |  |
|  | Baseline predictor, coefficient  (95% CI) | p(1) | Time slope (12 months) | Time-predictor interaction, coefficient  (95% CI) | p(2) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 0  (-0.02 to 0.01) | 0.627 | 0.1 | 0  (-0.01 to 0) | 0.187 | 0.324 |  |  |
| Female, no. | 0.06  (-0.33 to 0.46) | 0.755 | 0 | 0.03  (-0.13 to 0.18) | 0.753 | 0.003 |  |  |
| Months since onset of skin thickening | 0  (-0.02 to 0.02) | 0.889 | -0.1 | 0  (-0.01 to 0.01) | 0.502 | 0.001 |  |  |
| Previous immunosuppressant use | 0.13  (-0.56 to 0.81) | 0.719 | 0 | -0.11  (-0.4 to 0.17) | 0.426 | 0.007 |  |  |
| Current or previous steroid use | 0.43  (0.09 to 0.76) | 0.014 | 0 | -0.07  (-0.2 to 0.07) | 0.337 | 0.001 | Y | Y |
| mRSS | 0.05  (0.04 to 0.07) | <0.0001 | 0 | 0  (-0.01 to 0.01) | 0.879 | 0.306 | Y | Y |
| Haemoglobin g/l \* | -0.01  (-0.02 to 0) | 0.019 | -0.5 | 0  (0 to 0.01) | 0.097 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | 0.03  (-0.03 to 0.09) | 0.308 | 0 | 0  (-0.02 to 0.02) | 0.982 | 0.029 |  |  |
| Platelets x109/l \* | 0  (0 to 0) | 0.001 | -0.1 | 0  (0 to 0) | 0.590 | 0.459 | Y |  |
| ESR mm/hr \* | 0.01  (0 to 0.02) | 0.003 | 0 | 0  (0 to 0) | 0.456 | 0.341 | Y |  |
| CRP mg/l \* | 0.02  (0.01 to 0.04) | 0.000 | -0.1 | 0  (-0.01 to 0.01) | 0.943 | 0.026 | Y |  |
| Anti-topoisomerase (anti-Scl70) | 0.09  (-0.27 to 0.45) | 0.608 | 0 | 0.09  (-0.05 to 0.23) | 0.209 | 0.228 |  |  |
| Anti-RNA polymerase III | 0.32  (-0.13 to 0.77) | 0.160 | 0 | 0.02  (-0.16 to 0.19) | 0.856 | 0.433 |  |  |
| Anticentromere | -0.41  (-1.04 to 0.21) | 0.196 | 0 | 0.24  (-0.02 to 0.51) | 0.073 | 0.147 |  |  |
| Pulmonary fibrosis | 0.58  (0.05 to 1.12) | 0.031 | 0 | -0.01  (-0.24 to 0.22) | 0.945 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | -0.01  (-0.02 to 0) | 0.004 | 0 | 0  (0 to 0) | 0.725 | 0.026 | Y |  |
| DLCO (% predicted) \*\* | -0.01  (-0.02 to 0) | 0.014 | -0.1 | 0  (0 to 0) | 0.686 | <0.0005 | Y |  |
| Pulmonary hypertension | -0.19  (-0.88 to 0.5) | 0.585 | 0 | -0.32  (-0.66 to 0.03) | 0.070 | 0.488 |  |  |
| sPAP or RVSP mmHg \*\* | 0  (-0.02 to 0.01) | 0.674 | 0.2 | -0.01  (-0.02 to 0) | 0.017 | 0.472 | Y |  |
| Cardiac involvement | 0.32  (-0.27 to 0.91) | 0.286 | 0 | 0.11  (-0.15 to 0.36) | 0.409 | 0.009 |  |  |
| Renal involvement | 0.33  (-0.25 to 0.9) | 0.268 | 0 | 0.04  (-0.21 to 0.29) | 0.739 | 0.039 |  |  |
| eGFR ml/min \*\* | 0  (-0.01 to 0.01) | 0.683 | 0.1 | 0  (0 to 0) | 0.540 | 0.339 |  |  |
| Renal crisis \*\* | -0.15  (-0.91 to 0.62) | 0.702 | 0 | 0.09  (-0.33 to 0.51) | 0.681 | 0.110 |  |  |
| Plasma creatinine  in μmol/l \* | 0  (0 to 0) | 0.198 | -0.1 | 0  (0 to 0) | 0.088 | 0.422 |  |  |
| Any GI involvement \* | 0.18  (-0.2 to 0.56) | 0.347 | 0 | -0.04  (-0.2 to 0.11) | 0.572 | 0.078 |  |  |
| Muscle involvement | 0.52  (-0.1 to 1.13) | 0.097 | 0 | -0.36  (-0.59 to -0.13) | 0.002 | 0.002 | Y | Y |
| Current digital ulcers \* | 0.52  (0.06 to 0.99) | 0.027 | 0 | -0.01  (-0.2 to 0.19) | 0.946 | 0.705 | Y |  |
| HAQ-DI Disability index (0-3) | 1.24  (1.13 to 1.36) | <0.0001 | 0.1 | -0.15  (-0.23 to -0.07) | <0.0005 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | -0.06  (-0.07 to -0.05) | <0.0001 | -0.1 | 0  (0 to 0.01) | 0.168 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) |  |  | 0.1 | -0.01  (-0.01 to 0) | <0.0001 | 0.025 |  |  |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)

p(1): significance p-value for characteristic coefficient in linear regression of baseline outcome on baseline predictor  
p(2): significance p-value for interaction coefficient between time and baseline characteristic in a longitudinal regression model  
p(3): p-value from Fisher’s or Kruskal-Wallis test  
*Supplementary Table S13. Confounder selection for survival analysis.*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Survival | Odds Ratio  (95% CI) | p(1) | Between group difference, p(3) | Potential confounder | Retained |
| Age, years | 1 (1 to 1.1) | 0.003 | 0.324 | Y | Y |
| Female, no. | 1.2 (0.5 to 2.6) | 0.697 | 0.003 |  |  |
| Months since onset of skin thickening | 1 (0.9 to 1.0) | 0.288 | 0.001 |  |  |
| Previous immunosuppressant use | 1.6 (0.5 to 4.9) | 0.428 | 0.007 |  |  |
| Current or previous steroid use | 1.3 (0.6 to 2.7) | 0.441 | 0.001 |  |  |
| mRSS | 1.1 (1.0 to 1.1) | <0.0005 | 0.306 | Y | Y |
| Haemoglobin g/l \* | 1 (0.9 to 1.0) | 0.001 | 0.721 | Y |  |
| White blood count (WBC) x109/l \* | 1 (0.9 to 1.1) | 0.882 | 0.029 |  |  |
| Platelets x109/l \* | 1 (1.0 to 1.0) | 0.055 | 0.459 |  |  |
| ESR mm/hr \* | 1 (1.0 to 1.0) | 0.012 | 0.341 | Y |  |
| CRP mg/l \* | 1 (1.0 to 1.1) | 0.002 | 0.026 | Y |  |
| Anti-topoisomerase (anti-Scl70) | 0.6 (0.3 to 1.3) | 0.207 | 0.228 |  |  |
| Anti-RNA polymerase III | 1.2 (0.5 to 3.3) | 0.662 | 0.433 |  |  |
| Anticentromere | 1.4 (0.4 to 4.9) | 0.621 | 0.147 |  |  |
| Pulmonary fibrosis | 2.7 (1.2 to 6.2) | 0.015 | 0.036 | Y | Y |
| FVC (% predicted) \*\* | 1.0 (1.0 to 1.0) | 0.005 | 0.026 | Y |  |
| DLCO (% predicted) \*\* | 1.0 (1.0 to 1.0) | 0.005 | <0.0005 | Y |  |
| Pulmonary hypertension | 4.5 (1.8 to 11.3) | 0.001 | 0.488 | Y | Y |
| sPAP or RVSP mmHg \*\* | 1.0 (1.0 to 1.1) | 0.079 | 0.472 |  |  |
| Cardiac involvement | 4.3 (1.9 to 9.6) | 0.000 | 0.009 | Y | Y |
| Renal involvement | 1.6 (0.6 to 4.5) | 0.351 | 0.039 |  | Y |
| eGFR ml/min \*\* | 1.0 (1.0 to 1.0) | 0.659 | 0.339 |  |  |
| Renal crisis \*\* | 1.2 (0.3 to 5.5) | 0.815 | 0.110 |  |  |
| Plasma creatinine  in μmol/l \* | 1.0 (1.0 to 1.0) | 0.441 | 0.422 |  |  |
| Any GI involvement \* | 1.5 (0.7 to 3.0) | 0.283 | 0.078 |  |  |
| Muscle involvement | 1.3 (0.4 to 3.8) | 0.683 | 0.002 |  |  |
| Current digital ulcers \* | 2.6 (1.2 to 5.6) | 0.018 | 0.705 | Y |  |
| HAQ-DI Disability index (0-3) | 2.4 (1.6 to 3.8) | <0.0001 | 0.400 | Y | Y |
| FACIT fatigue score (0-52) | 0.9 (0.9 to 1.0) | <0.0001 | 0.165 | Y | Y |
| Cochin Hand Function Score (0-90) | 1.0 (1.0 to 1.0) | 0.032 | 0.025 | Y | Y |

\* Variable not considered as confounder due to lack of clinical significance or concerns about data completeness.  
\*\* Variable not considered as confounder because it was already an input in another aggregate variable (e.g. FVC in pulmonary fibrosis)

CRP: C-reactive protein  
DLCO: Carbon monoxide diffusing capacity  
ESR: Erythrocyte sedimentation rate  
FVC: Forced vital capacity  
GI: Gastrointestinal  
HAQ-DI: Health Assessment Questionnaire - Disability Index  
mRSS: modified Rodnan skin score (17 sites)  
p(1): significance p-value for odds ratio