**Supplement**

# Prediction of Improvement in Skin Fibrosis in Diffuse Cutaneous Systemic Sclerosis – a EUSTAR Analysis

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## Supplementary Methods

### Patients and study design

The longitudinally-followed EUSTAR cohort was analysed for this observational study. The whole EUSTAR dataset, consisting of 12,274 patients at the time of the first data export (20.02.2015), was considered.

The following inclusion criteria were used for cohort selection: diagnosis of dcSSc, fulfilment of ACR1980 criteria, mRSS ≥7 at the first visit (baseline) and available data for mRSS at 12±2 months follow-up.

Patients with dcSSc were identified according to LeRoy et al [1] or, in case of missing values for the LeRoy criteria, by the extent of skin involvement at any visit. The minimum

mRSS ≥7 was chosen because it reflects the lowest value classifiable as dcSSc, thus allowing the inclusion of dcSSc patients with less severe to extensive skin fibrosis. The 1 year follow-up has been shown adequate for capturing significant changes in mRSS and is often used in clinical trials in skin fibrosis in SSc.[2]

The clinical data in EUSTAR are prospectively collected in a multicentre approach following a standardized protocol.[3] Regular training courses in skin scoring are organized by EUSTAR and all centres are advised to have the same examiner assessing the skin score in individual patients at follow-up visits.[4] All laboratory investigations including immunological tests are performed according to the local practices of each contributing center, in accordance to international quality standards. Quality indicators for data from the registry include regular external monitoring of large centres, and plausibility checks on key items with written requests to centres for clarification. Ethics approval has been obtained from the respective local ethics committees by all participating EUSTAR centres.

**Statistical analysis**

The statistical analysis was performed by the biostatistician (NG) using R Version 3.1.0 (packages Hmsic, rms and mice).[5-8]

**Definition of variables**

The primary endpoint, improvement of skin fibrosis, was defined as a decrease in mRSS of >5 points AND ≥25 % within 1 year. The reduction of >5 points AND ≥25% was chosen in order to capture the minimally clinically important difference.[9] Similarly, progression of skin fibrosis was defined as an increase in mRSS of >5 points AND ≥25 % within one year as used previously.[10]

All standard EUSTAR parameters are described elsewhere.[11,12] The specific variables used for this study are explained below.

Immunosuppressive treatment was defined as explicit documentation of treatment with cyclophosphamide, methotrexate, azathioprine, mycophenolate, d-penicillamine, rituximab, imatinib, TNF inhibitors, and/or prednisone >10mg/day, either at baseline or at follow up visit. This set of medications was chosen because it covers the most relevant and also consistently-reported immunosuppressive agents in the EUSTAR database. Information about immunosuppressive drugs was collected systematically only after 2009, after data collection changed from paper case report forms (CRFs) to electronic CRFs. Patients with mention of receiving at least one of these agents at either baseline or 12-months' follow-up were classified as being treated with immunosuppressives, whereas those with negative inputs for all agents were classified as not having received immunosuppression.

Lung fibrosis was defined as fibrosis on HRCT and, additionally, as fibrosis on chest X-ray.

**Selection of parameters for multivariable analysis**

Parameters for multivariable analysis were selected exclusively based on expert opinion. Scleroderma experts (CM, OK, OD, YA, RD) were asked to suggest parameters that could be important for skin improvement, taking into account face validity, clinical and scientific reasoning. All suggestions were gathered as received, adding to a total of 19 parameters. Out of these, to allow a trustworthy imputation, only the parameters with >50% valid values were further considered for the analysis. This was acknowledged as a limitation. Regressors were no more likely than non-regressors to have missing values on any of the variables. An overview on all the suggested parameters is presented in Table S1, whereas the ones finally selected for the analysis are also shown in Table 2, main manuscript.

**Table S1. Overview on missing data for the candidate predictors of skin improvement suggested by the scleroderma experts**

| Variable | Missing | |
|---|---|---|
| | N | % |
| Baseline mRSS | 0 | 0.0 |
| Disease duration | 65 | 7.1 |
| ANA positive | 11 | 1.2 |
| Anti Scl70 positive | 33 | 3.6 |
| Joint contractures | 3 | 0.3 |
| Tendon friction rubs | 5 | 0.5 |
| Proteinuria | 32 | 3.5 |
| Conduction blocks | 42 | 4.6 |
| Abnormal diastolic function | 55 | 6.0 |
| Fibrosis on chest X-ray | 70 | 7.6 |
| DLCO≥70% | 298 | 32.4 |
| Immunosuppression | 483 | 52.6 |
| Active digital ulcers | 525 | 57.1 |
| Scleredema (puffy fingers) | 529 | 57.6 |
| CRP elevation | 545 | 59.3 |
| ESR<25mm/1h | 551 | 60.0 |
| LVEF <45% | 601 | 65.4 |
| Lung fibrosis on HRCT | 632 | 68.8 |
| Anti-RNA polymerase III positive | 704 | 76.6 |

Abbreviations: mRSS: modified Rodnan skin score; ANA: antinuclear antibodies; X-ray: radiography; DLCO: diffusion capacity of the lung for carbon monoxide; CRP: C-reactive

protein; ESR: erythrocyte sedimentation rate; LVEF: left ventricular ejection fraction; HRCT: high resolution computed tomography of the chest.

A comparison of the selected candidate variables between the patients who met all inclusion criteria (diagnosis of dcSSc, fulfilment of ACR1980 criteria, mRSS ≥7 at the first visit and available data for mRSS at 12±2 months follow-up) and were, therefore, included into the analysis ("selected") and those patients who could not be analyzed because they did not have a second follow-up visit within the required timeframe ("not selected") did not reveal significant differences between these two groups (Table S2).

**Table S2. Frequencies of the candidate predictors of skin improvement in the selected cohort (patients with both baseline and 1-year follow up visits), compared to the non-selected patients with dcSSc but not meeting the two required consecutive visits.**

| Parameters | Selected (n=919) | Not selected (n=2310) |
|---|---|---|
| ANA positive | 94.6% | 93.3% |
| Scl70 positive | 59.1% | 58.3% |
| Tendon friction rubs | 20.2% | 18.2% |
| Proteinuria | 8.3% | 8.0% |
| Conductions blocks | 12.4% | 13.4% |
| Abnormal diastolic function | 19.1% | 18.7% |
| Lung fibrosis on X-ray | 45.8% | 49.2% |
| DLCO≥70% | 42.5% | 38.4% |
| Disease duration (months) | Median:42.5 | Median:49 |
| Baseline mRSS | Median:16 | Median:18 |

Abbreviations: mRSS: modified Rodnan skin score; ANA: antinuclear antibodies; X-ray:

radiography; DLCO: diffusion capacity of the lung for carbon monoxide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LVEF: left ventricular ejection fraction; HRCT: high resolution computed tomography of the chest.

**Imputation of missing data and predictive modelling**

***Single conditional mean imputation and validation through Bootstrap***

A logistic regression model was fit after single conditional mean imputation of missing values. Multiple imputation is clearly superior to single conditional mean imputation, however, it is not possible to validate models with multiply imputed data. Therefore, the models were validated after single conditional mean imputation using the Bootstrap methods with 100 repetitions.

The method of single conditional mean imputation fills in missings with predicted values from using the multivariable imputation model based on non-missing data. Subsequently, a model was run with all potential predictors. Baseline mRSS was centered at 7 points as all included patients had mRSS ≥7. The linearity assumption was relaxed for baseline mRSS and disease duration by including restricted spline functions with 4 knots. The interaction between disease duration and baseline mRSS was also tested, but proved to be insignificant, meaning that the effect of baseline mRSS on regression of dSSc did not depend on values of disease duration.

***Multiple imputation***

Multiple imputation was used to fit the full und reduced model and to get standard errors. Missing values were multiply imputed with help of the R package mice. For the imputation model, all variables from the full model were included, i.e., all 11 variables as well as the dependent variable "regression of mRSS". Moreover, the time of the first visit (before 2009 vs. 2009 or later) was also included as it was strongly related to nonresponse: data collection was changed to an online version between 2008 and 2009 and some of the items were not

collected until after 2009. In addition, variables with an absolute correlation with the target variables of at least 0.2 were included. Only variables with a proportion of usable cases (cases with missing data on the target variable that had observed values on the predictor) of at least 25% were retained in the imputation model as to many missing cases on the same cases for both the target and the predictor variable would not contain much information to impute the target variable. The order in which variables should be imputed was defined according to their number of missing cases. Depending on the scale of the target variable, multiple imputation was performed using either predictive mean matching (pmm) or logistic regression (logreg). Ten imputed data sets were generated. Imputation was assessed via density plots for plausibility, i.e. whether imputed data were possible and close to the observed data.

**Supplementary results**

**Single mean imputation, development and validation of the prediction model**

A model was run with all the selected potential predictors (Table 2). The Wald statistics indicated that disease duration could be modelled linearly (Table S3). Baseline mRSS, however, did not behave linearly. Therefore, a quadratic term was included for baseline mRSS. As the effects were clearly insignificant (P>0.7) for joint contractures and DLCO≥70%, these effects were excluded from any future models (Table S3 and S4).

**Table S3. Wald statistics for the regression model for skin improvement at one year after single conditional mean imputation**

| Factor | Chi-square | Degrees of freedom | P-value |
|---|---|---|---|
| ANA positive | 1.28 | 1 | 0.259 |
| Anti Scl70 positive | 3.96 | 1 | 0.047 |
| Joint contractures | 0.01 | 1 | 0.919 |
| Tendon friction rubs | 7.74 | 1 | 0.030 |
| Proteinuria | 0.62 | 1 | 0.430 |
| Conduction blocks | 1.01 | 1 | 0.316 |
| Abnormal diastolic function | 0.96 | 1 | 0.323 |
| Fibrosis on chest X-ray | 1.19 | 1 | 0.276 |
| DLCO≥70% | 0.14 | 1 | 0.701 |
| Baseline mRSS | 70.08 | 3 | <0.001 |
| nonlinear | 9.30 | 2 | 0.001 |
| Disease duration | 1.21 | 3 | 0.752 |

| | | | |
|---|---|---|---|
| nonlinear | 0.45 | 2 | 0.799 |
| Total nonlinear | 9.55 | 4 | 0.049 |
| Total | 89.38 | 15 | <0.0001 |

Abbreviations: mRSS: modified Rodnan skin score; ANA: antinuclear antibodies; X-ray: radiography; DLCO: diffusion capacity of the lung for carbon monoxide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LVEF: left ventricular ejection fraction; HRCT: high resolution computed tomography of the chest.

The full regression model for prediction of skin improvement is shown in **Error! Reference source not found.**.

**Table S4. Full prediction model for skin improvement after single conditional mean imputation**

| Variable | Coefficient | Standard error | Odds ratio | P-value |
|---|---|---|---|---|
| ANA positive | -0.400 | 0.34 | 0.67 | 0.229 |
| **Anti Scl70 positive** | **-0.358** | **0.18** | **0.70** | **0.044** |
| **Tendon friction rubs** | **-0.480** | **0.22** | **0.62** | **0.026** |
| Proteinuria | 0.227 | 0.29 | 1.25 | 0.431 |
| Conduction blocks | 0.220 | 0.24 | 1.25 | 0.365 |
| Abnormal diastolic function | 0.214 | 0.21 | 1.24 | 0.317 |
| Fibrosis on chest X-ray | 0.181 | 0.18 | 1.20 | 0.304 |
| **Baseline mRSS** | **0.202** | **0.04** | **1.22** | **<0.0001** |
| **Baseline mRSS$^2$** | **-0.003** | **0.00** | **1.00** | **0.006** |
| Disease duration | -0.001 | 0.00 | 1.00 | 0.369 |
| Intercept | -3.373 | 0.57 | 0.03 | <0.0001 |

Abbreviations: mRSS: modified Rodnan skin score; ANA: antinuclear antibodies; X-ray:

radiography; DLCO: diffusion capacity of the lung for carbon monoxide; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LVEF: left ventricular ejection fraction; HRCT: high resolution computed tomography of the chest.

For the validation, the Bootstrap method was used. Table S5 shows the performance of the model. Discrimination refers to the ability of the model to separate subjects with and without the outcome. The C-index as a measure to estimate discrimination was 0.7231 for the full model, which was reduced to 0.7071 at validation. Calibration refers to the agreement between actual and predicted probabilities. The slope shrinkage factor was 0.9117 and the maximum absolute error in predicted probability was 0.0347. Thus, there was some overfitting present. Moreover, the model could only explain 13.4% of the variation at validation.

**Table S5. Performance of the prediction model for skin improvement before and at validation**

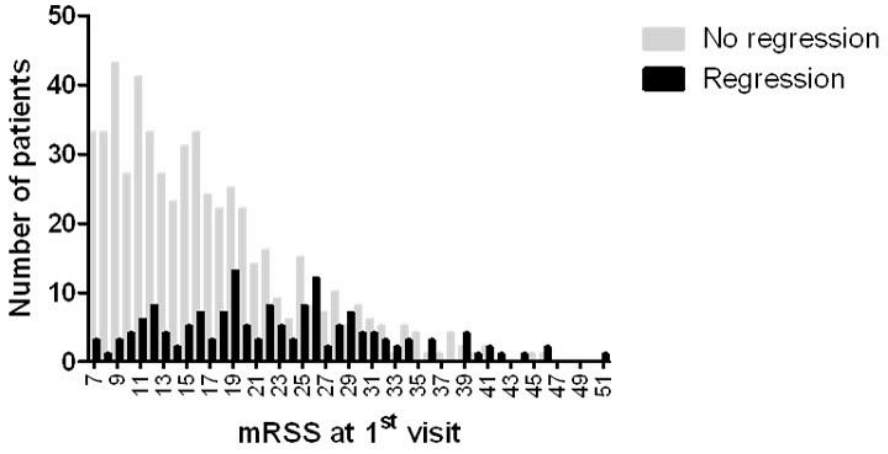
| **Performance measure** | **Full model** | **Validation full model** |
|---|---|---|
| $R^2$ | 0.1615 | 0.1342 |
| C-index (AUC) | 0.7231 | 0.7071 |
| Calibration slope | 1.0000 | 0.9117 |
| $E_{max}$ | 0.0000 | 0.0347 |

$R^2$: R-squared, the percentage of the response variable variation that is explained by a linear model. AUC: Area under the curve; $E_{max}$: maximum absolute error.

**Baseline mRSS as a predictor of the change in skin score at one year**

In the current cohort, 95/919 (10%) dcSSc patients who showed skin progression within one year had lower baseline mRSS ($p<0.001$). Baseline mRSS is thus a predictor of change in skin score after 1 year, patients with lower skin scores being prone to progress and those with higher skin scores to improve within the next 12 months (Figure S1).

**Figure S1. Baseline mRSS in patients with and without skin regression.** Patients with skin regression (black bars) have higher baseline mRSS values relative to patients without skin regression (grey bars).

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