# Derivation and External Validation of a 5-year Mortality Prediction Rule for Patients with Early Diffuse Cutaneous Systemic Sclerosis

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The derivation and validation of a 5-year mortality rule for diffuse scleroderma

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**ABSTRACT**

**Objective:** Although diffuse systemic sclerosis (SSc) is associated with a reduction in life expectancy, there are no validated, prognostic models for 5-year mortality in diffuse SSc. The objective of this study was to derive and validate a 5-year mortality prediction rule for early diffuse SSc patients.

**Methods:** We used an inception cohort of 388 Caucasian US patients with early diffuse SSc (< 2 years from the first symptom). Predefined baseline variables were entered into a stepwise logistic regression model to identify factors independently associated with 5-year all-cause mortality. After rounding the beta-weights to the nearest integer, and summing them, we stratified patients into low (<0 points), moderate (1-2 points) and high-risk (≥ 3 points) groups. We then applied this rule to an external validation cohort of 110 Caucasian early diffuse SSc patients from the Royal Free Hospital cohort and compared stratum-specific 5-year mortality.

**Results:** Six independent predictors (rounded beta-weight) comprised the model: age at first visit (-1, 0, 1), male gender (0,1), tendon friction rubs (0,1), gastrointestinal involvement (0,1), RNA polymerase III antibody (0,1) and anemia (0,1). The 3-level risk stratification model performed well with no significant differences between the US derivation (AUC =0.73 (95% CI 0.69–0.78) ) and UK (AUC= 0.69 (95% CI 0.61–0.77)) validation cohorts.

**Conclusion:** We have derived and externally validated in US and UK cohorts an easy-to-use 6-variable prediction rule that assigns low, moderate and high risk categories for 5-year mortality in early diffuse SSc patients. Only history, exam and basic labs are required.

## INTRODUCTION

Systemic sclerosis (SSc) is a multisystem autoimmune disease with a heterogeneous clinical presentation and disease course, but the highest case specific mortality among the rheumatic diseases(1). Given this varied clinical course in SSc, it is important to identify patients at high risk for mortality from a clinical and research perspective. Risk assessment is of particular relevance in the context of new emerging therapies and recent advances in autologous hematopoietic stem cell transplantation, for which there may be substantial treatment-related mortality but improved long-term outcomes in subgroups of SSc patients.

Published estimates of 5-year mortality range from 5-65% in the medical literature (2-12), with a lower survival in the diffuse cutaneous SSc subtype consistently reported. Dissimilar survival is not surprising given the natural history of disease in the diffuse and limited cutaneous subtypes. Patients with diffuse cutaneous SSc tend to accumulate internal organ involvement very early in their disease, whereas those with limited cutaneous disease may develop new organ involvement even decades after onset (13). This distinction in natural history is important because it is likely that there are different significant contributors to mortality risk in limited and diffuse SSc patients. Thus, we feel that the cutaneous subtypes should be considered separately in SSc mortality modeling, particularly in early disease (9).

There have been two validated 5-year mortality models published in SSc. The first (14) is a 5-factor model derived and validated in 5 Italian centers. The second (15) used the

European (EUSTAR) population to validate a 5-factor model originally published by Bryan et al. in 1996, using a UK population(1). Both of these models combined limited and diffuse SSc patients. The first assessed 5-year mortality from first physician diagnosis, and the second from SSc onset (defined as first non-Raynaud symptom). These definitions introduce potential bias by including variable amounts of times prior to the observational period in the mortality model.

As advances have been made in SSc diagnosis, clinical care and treatments, there has been an emphasis on multi-center and international collaborative research. This is exemplified by reports published by the EUSTAR group and therapy trials in which the vast majority of patients came from centers participating in the Scleroderma Clinical Trials Consortium (SCTC). With this in mind it is important to test prognostic prediction models in novel populations where performance can decline. Therefore, we sought to validate our US model in a United Kingdom (UK) SSc population.

The objective of this study was to derive and validate a prediction rule for 5-year in patients with early diffuse SSc. We strove to develop a bedside-friendly risk stratification tool that could be used at the first rheumatology or SSc clinic visit. To address biases in prior mortality studies, we used a prospectively followed inception cohort of patients with early diffuse SSc to derive the model. We then performed an external validation in a prospectively followed cohort of early diffuse SSc patients from the UK.

## METHODS

### Patient Selection

*Derivation cohort (Pittsburgh):* We prospectively identified an inception cohort of adult early diffuse SSc patients seen for a first visit at the UPMC and University of Pittsburgh Scleroderma Center between January 1, 1980 and December 31, 2008. We defined early diffuse SSc at the first visit as: SSc presenting within two years from the first symptom attributable to SSc (including Raynaud phenomenon), and the presence of diffuse skin thickening at the first visit (i.e. skin thickening proximal to the elbows and knees). All patients had provided informed consent to participate in our institutional observational SSc prospective cohort study. To ensure accurate assessment of vital status, we excluded individuals who were not US citizens or did not reside in the United States.

To be included in the derivation cohort all diffuse SSc patients were required to have a complete history, physical examination, and sufficient clinical and laboratory objective testing to accurately assess organ involvement and severity. Since the overall percentage of non-Caucasians in our sample was < 7%, we restricted the derivation sample population to Caucasians to reduce model variability, and that we felt future genetic information could be added later to improve model performance.

*External validation cohort (Royal Free).* We used patients included the Royal Free Hospital scleroderma research database to externally validate our prognostic model. We applied the same inclusion criteria to identify a validation cohort of adults with early diffuse SSc seen at the Royal Free Hospital for an initial visit between January 1, 2000

and December 31, 2008. All of the Royal Free patients had previously provided informed consent to participate a longitudinal study of SSc outcome at their institution.

**Baseline data**

*Pittsburgh derivation cohort.* For all Pittsburgh patients, one of three rheumatologists (Drs. Medsger, Steen or Domsic) completed an initial visit data collection form, which included demographics, date of symptom onset, date of organ system involvement using objective criteria, other medical history, tobacco use, physical examination findings and the following objective test results: chest radiograph or high resolution chest computer tomography (HRCT), pulmonary function tests (PFTs), echocardiogram, EKG, cine esophagram or esophageal manometry, hemoglobin, erythrocyte sedimentation rate (ESR), serum creatine phosphokinase (CPK) and SSc-associated serum autoantibody.
*Royal Free validation cohort.* For all patients an initial visit data collection form had been previously completed at the time of visit. This included demographics, physical examination findings, objective GI and cardiopulmonary testing and laboratory results which included hemoglobin and SSc-associated serum antibody testing. Medical records were reviewed to minimize missing data.

**Candidate predictor variables**

We identified candidate predictor variables by reviewing the literature on SSc prognosis and included all variables that had been reported as significantly associated with mortality. Candidate predictor variables were then grouped into five categories: 1) patient demographics and referral characteristics (i.e., age, gender, referral area, decade

of presentation (1-5, 7, 8, 10, 12, 16-24); 2) medical history, i.e., disease duration, presence of another connective tissue disease (overlap syndrome), tobacco use, hypertension, diabetes mellitus, heart disease, obesity, medication use (12, 25); 3) physical examination findings i.e., the modified Rodnan skin score (mRss), mRss >20 (26), skin thickness progression rate (STPR) calculated by dividing the mRss by the time since onset of skin thickening in years (27), presence and number of tendon or bursal friction rubs, presence of digital ulcers (28); 4) laboratory findings (anti-RNA polymerase III antibody, anti-topoisomerase I antibody, hemoglobin, ESR (1, 4, 5, 10-12, 16, 17, 21, 29); and 5) organ involvement i.e. lung disease, renal crisis, cardiac, gastrointestinal, skeletal muscle, joint/tendon, pulmonary hypertension, peripheral vascular (2-5, 8, 16-19, 21, 23-25, 30, 31).

Organ involvement was quantitated using two classification methods: present or absent (27), and severity (21). The presence of organ system involvement presence was classified in the following manner: 1) lung (fibrosis on chest x-ray or high resolution chest CT or abnormal PFTs with FVC < 70% with a normal FEV1/FVC ratio); 2) renal (clinical evidence of renal crisis defined as the abrupt onset of accelerated arterial hypertension or rapidly progressive oliguric renal failure); 3) cardiac (pericarditis, myocarditis, arrhythmia requiring treatment or complete heart block); 4) gastrointestinal (distal esophageal dysmotility by esophagram or manometry, evidence of hypomotility of the duodenum or small intestine on imaging or manometry, small bowel bacterial overgrowth requiring antibiotics, gastric antral vascular ectasia, wide-mouthed colonic sacculations, pseudoobstruction, physician judgment of malabsorption syndrome, or

heartburn plus distal dysphagia for solid foods); 5) muscular (proximal muscle weakness on physical exam with elevated serum CPK > 2 times normal, myopathic changes on electromyogram or abnormal muscle biopsy); 6) articular (joint swelling or contractures, palpable tendon friction rubs or joint space narrowing or erosions on radiograph); 7) pulmonary arterial hypertension (PAH) defined as mean pulmonary artery pressure > 25 mmHg on cardiac catheterization and not attributable to ILD or cardiac involvement; and 8) vascular (Raynaud phenomenon or the presence of digital pitting scars, digital tip ulceration or digital gangrene).

We used the Medsger severity scale to quantify the severity of internal organ involvement, which uses a scale from 0 (no involvement) to 4 (end-stage) in 8 different organ systems. We used the SSc expert consensus "modified" version of this scale (21) in our analysis. Lung involvement was classified and analyzed separately as: 1) a fibrosis component using FVC and positive radiographic imaging, and 2) a pulmonary hypertension component for two reasons. First, the pathology of these complications is different, as one is primarily fibrotic and the other a vasculopathy. Secondly, the natural history of these complications is different, particularly in patients with early diffuse scleroderma (13). Renal disease was classified as no involvement/mild disease and moderate/severe disease as there was only one patient with mild severity. Given the low frequencies of high severity scores, we classified the remainder of organ severity as none, mild or moderate/severe/end-stage (3 stages combined) involvement. We did not use the cardiac severity index as a predictor variable due to low frequency of transthoracic echocardiogram ascertainment during the early years of this cohort.

**Outcomes**

We developed our prognostic model to predict 5-year, all-cause mortality from the time of the first Scleroderma Center visit. Vital status was determined as of December 31, 2013 using the U.S. Social Security Death Index for the Pittsburgh cohort. For the Royal Free cohort, vital status as of May 1, 2014, was determined using the UK National Care Record Service.

**Model derivation**

We first performed bivariate analysis of the predefined candidate predictor variables at the first visit using 5-year all-cause mortality as the dependent variable. All candidate predictor variables with a p-value $\leq 0.20$ on bivariate analysis were then placed into a stepwise multivariable logistic regression model with a p-value $\leq 0.05$ required to remain in the model. Regression diagnostics were performed and goodness of fit assessed. To generate a simple integer point score that would be easy to calculate, the logistic regression model coefficients were rounded to the nearest 1.0. A total point score for each patient was then calculated by summing the rounded beta-weights. Using the summed score, patients were assigned to one of three risk categories for two-year mortality based on distribution: low ($\leq 0$ points), moderate (1-2 points) or high ($\geq 3$ points). We performed the model derivation in accordance with previously published methodologic standards for clinical risk prediction model development (32).

**Model validation**

In the validation cohort we evaluated missing data. There were four areas in which there was some missing data and these included the recording of tendon friction rubs, objective GI testing, hemoglobin and RNA polymerase III antibody testing. We did not feel that the recording of tendon friction rubs and ordering objective GI testing was at random, as it was likely that they were not recorded or ordered because the symptoms or findings were absent. Thus, we evaluated missing data with two methods. First, we assumed that all missing elements were negative or not present. Second, multiple data imputations were performed for hemoglobin and antibody testing, as these were felt to be missing at random. All statistical analysis was completed using SAS version 9.3 software (SAS, Cary, NC).

We constructed a receiver operating characteristic (ROC) curve of the prediction rule with the area under the ROC (AUC) calculated as a measure of model discrimination (33). The model developed in the Pittsburgh cohort was then applied to the Royal Free cohort and an AUC calculated. The performance of the total integer score and associated three-level risk stratification was then evaluated using two methods. First, we compared stratum-specific mortality rates in the derivation and validation cohorts within each of the three risk classes using chi-square statistics. Next, we compared the exact AUC for predicting mortality using each of the three risk classes as cut-points in the derivation and validation cohorts. Stratum-specific chi-square analysis was then performed between the derivation and validation cohorts.

## RESULTS

*Pittsburgh Derivation cohort.* Of the 2879 SSc patients first evaluated at the University of Pittsburgh Scleroderma Center between 1980 and 2007, 1304 had diffuse disease, of which 805 presented within two years of symptom onset. Of the 688 Caucasian adults with early diffuse SSc who lived in the US, 388 (56%) had the laboratory and objective testing required to assess organ system involvement at or within 60 days of their initial visit and comprised our final study cohort (Figure 1). There was no difference in demographics, disease characteristics, laboratory findings or mortality between the 388 with complete objective testing and the 300 without. In the final population of 388, there was minimal missing data. Missing data included: ESR (20%), hemoglobin (3%), autoantibody (4%) and body mass index (38%). We categorized age at the first visit into five groups (<35, 35-44, 45-54, 55-64, >65 years) based upon prior SSc literature (18, 34, 35).

*Royal Free validation cohort.* Of 160 early diffuse SSc patients seen for an initial visit between the years 2000 and 2008, 144 were Caucasian and formed the external UK validation cohort.

### Baseline patient characteristics

The overall Pittsburgh cohort of 388 patients was 76% female, had a mean age of 50.4 (± 13.3) years were first evaluated a median of 0.93 (0.63, 1.33) years after the first SSc symptom. Sixty-one (16%) were current and 34% prior smokers. 141 (36%) lived within 100 miles of Pittsburgh (our typical referral area). At the first visit, 209 (53%) had

evidence of gastrointestinal involvement, 108 (28%), lung involvement, 79 (21%) cardiac involvement and 62 (16%) renal crisis. Overall, 209 (56%) were RNA polymerase III antibody positive, and 91 (24%) were anti-topoisomerase I antibody positive.

The only statistically significant differences in baseline demographics between the Pittsburgh and Royal Free cohorts (Table 1) was the median disease duration at first visit, which was slightly longer at 1.02 (0.78, 1.45) years in the Royal Free cohort, and may reflect the difference in referral patterns and operation in two different healthcare systems. There were no differences in baseline medical history and total skin score, but the distribution of STPR was different between the cohorts, with the Royal Free having more patients with a slow STPR. The Pittsburgh cohort also had more patients with tendon friction rubs and RNA polymerase III antibody, which may explain the lower percentage of slow STPR compared to the Royal Free cohort. There was no difference in baseline visit organ system involvement. BMI and cardiac involvement based on arrhythmia were not consistently available for the Royal Free cohort, and thus could not be assessed.

**Survival**

At five years of follow-up from the first visit, 110 (28%) of Pittsburgh patients had died. In the Royal Free cohort 29 (26%) had died at five years. There was no difference ($p=0.65$) in 5-year mortality between the cohorts.

**Derivation of the prediction rule**

In bivariate analyses, we identified 18 baseline variables significantly associated with 5-year mortality (Table 2), including two demographic factors (age, gender), two history variables (referral area, decade of presentation), four physical examination findings (mRss, STPR, presence and number of tendon friction rubs), three laboratory abnormalities (anti-topoisomerase I positivity, anti-RNA polymerase III positivity, anemia), and the presence or absence of involvement of four organ systems (lung, renal crisis, cardiac and GI), and severity of involvement of four organ systems (lung, GI, skeletal muscle and skin). The odds ratios for these variables ranged from 0.43 to 4.79.

In the multivariable analysis, six factors were independently associated with 5-year mortality including: (1) age at first visit; (2) male gender; (3) tendon friction rubs; (4) GI involvement; (5) anti-RNA polymerase III antibody; and (6) anemia (Table 3). The AUC for the derivation cohort was 0.79 (95% CI 0.74 – 0.84) using the original beta values of these six variables.

When the beta values were rounded to the nearest one (Table 3) in the Pittsburgh derivation cohort, 63 patients (25%) were low risk (≤0 points) and had a mortality rate of 1.6%; 108 (43%) were intermediate risk (1-2 points) with a mortality rate of 14.8%, and 81 (32%) were high risk (≥3 points) and had a mortality rate of 49.4% (Table 4). The AUC for this 3-level risk stratification tool is 0.73 (95% CI 0.69 – 0.78)

**Validation of the risk stratification model**

When the 6-variable points were summed in the Royal Free cohort, 50 patients (35%) were low risk, 78 patients (54%) moderate and 16 (11%) high risk. The mortality rates for patients in these risk stratification levels were 3%, 18% and 50%, respectively (Table 4). In the stratum-specific analysis comparing the derivation and validation cohorts, there were no differences in mortality in the low (p=0.72), moderate (p=0.47), or high risk classes (p=0.39). The area under the ROC curve for the Royal Free cohort was AUC =0.68 (95% CI 0.59 – 0.77), which was not different from the Pittsburgh cohort (p=0.19) using the three risk classes. When multiple data imputation for hemoglobin and anti-RNA polymerase III was performed the AUC was 0.69 (95% CI 0.61 – 0.77), which was not different from the Pittsburgh cohort (p=0.35, Figure 4)

**DISCUSSION**

We derived and internally and externally validated a prediction model to risk-stratify adult Caucasian patients with early diffuse SSc for 5-year mortality. To develop this model, we used an inception cohort of patients, and carefully applied methodologic standards for risk prediction rule development. The result is a simple, six-factor model that can be easily used to accurately risk stratify patients at the bedside, requiring only history, physical examination and standard available laboratory variables.

Only two prior studies have performed internal or external validation in 5-year mortality models in SSc. Beretta et al. (14) published a paper in which multiple regression modeling techniques and data mining based classifiers were used to develop a 5-year prognostic model in Italian patients with SSc from the time of diagnosis. An external

cross-validation was then performed on 356 patients from 5 different Italian centers. The final five-factor model seemed to perform well, although actual statistical comparisons between the original and validation samples were not reported, and the model is somewhat cumbersome to use at the bedside. Fransen et al. (15) externally validated a 5-year mortality model originally published by Bryan et al. in 1996 (1). The Bryan model was developed in 260 patients from a single UK center who were followed for five years after SSc disease onset. This was a five-factor model composed of age, gender, ESR, carbon monoxide diffusing capacity (DLCO) and presence of urine protein. The AUC was not reported in the Bryan paper, but showed good discriminatory ability in the Fransen external validation cohort (AUC = 0.78) when the original beta-estimate weights were used. When a clinically useful tool was created by adding the number of risk factors together as originally proposed by Bryan, performance appeared to diminish in the validation cohort, although true accuracy is unknown as the AUC was not reported. The poorer performance is likely related to the significantly lower mortality rate in the Fransen validation cohort (11%) compared to the Bryan derivation cohort (28%). Both the Beretta and Fransen reports combined limited and diffuse cutaneous SSc patients, and both used prevalent rather than inception cohorts, which introduces multiple left-censoring biases to be considered in applying the results. Our model is designed specifically for patients with clearly defined early diffuse SSc, and was developed in an inception cohort of SSc patients to reduce bias. Finally, the 5-year mortality prediction starts from the time of first SSc diagnosis in Beretta's manuscript, and from SSc onset (defined as first non-Raynaud symptom) in the Fransen and Bryan papers. Our model is

designed for the first SSc center visit, which we feel is easily defined and relevant to patient care.

Although we used all prospectively collected cohort data, and our derivation cohort contained complete data on demographics, history, examination and objective tests, there are potential limitations. First, the model was developed at a single, tertiary care scleroderma center, and validated at another single-center scleroderma referral center. This may somewhat limit generalizability, although we have sought to maximize generalizability by choosing a validation cohort from the European continent. Second, this model was developed in Caucasian SSc patients only, and will need to be evaluated in more racially diverse populations. Third, our final cohorts were modest in size. Although our initial comparisons showed that there was no difference between those with and without objective data available, it is possible that significant unmeasured differences exist in these two patient groups which could have affected model performance. Finally, we were not able to assess some of the newer biomarkers in this derivation cohort, such as CRP or genetic markers as these were not collected at the time these cohorts were enrolled. However, the effect size of these biomarkers could be tested in future prospectively-followed cohorts of early diffuse SSc patients.

**Conclusions**

We derived and validated in an American and European population a simple prediction rule to accurately risk stratify early diffuse adult SSc patients for 5-year mortality at their first visit to a scleroderma center. This rule can be used by clinicians at the first

evaluation to risk stratify patients for early mortality when they weigh therapy decisions, and by researchers to identify appropriate at-risk populations for inclusion or exclusion criteria for clinical trials.

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**Table 1: Baseline characteristics of the derivation and validation cohorts**

| Characteristics | | Pittsburgh derivation cohort (n=388) | Royal Free validation cohort (n=144) | p-value |
|---|---|---|---|---|
| **Demographics** | | | | |
| Mean age in years at the first visit (±SD) | | 50.4 ± 13.3 | 52.4 ± 12.3 | 0.31 |
| Gender (female) | | 294 (76%) | 103 (72%) | 0.37 |
| **Medical History** | | | | |
| Disease duration at first visit in years | | 0.93 | 1.02 | 0.03 |
| (IQR) | | (0.63, 1.33) | (0.78, 1.45) | |
| Hypertension | | 20 (5%) | 7 (5%) | 0.89 |
| Coronary artery disease | | 5 (1%) | 3 (2%) | 0.69 |
| Diabetes mellitus | | 14 (4%) | 1 (1%) | 0.08 |
| Tobacco use*: | none | 180/377 (48%) | 34/76 (45%) | 0.88 |
| | prior use | 134/377 (36%) | 29/76 (38%) | |
| | current use | 63/377 (17%) | 13/76 (17%) | |
| **Physical Examination Findings** | | | | |
| Mean modified Rodnan skin score (SD) | | 26.1 ± 11.7 | 25.6 ± 9.4 | 0.69 |
| Skin thickness progression rate slow (<25) | | 124 (32%) | 65 (45%) | 0.02 |
| | intermediate (25-45) | 125 (32%) | 40 (28%) | |
| | rapid (>45) | 139 (36%) | 39 (27%) | |
| Tendon friction rubs present | | 154 (59%) | 27(22%) | <0.001 |

| | | | | |
|---|---|---|---|---|
| Number of tendon friction rubs | 0 | 101 (39%) | 83 (79%) | 0.30 |
| | 1-3 | 79 (30%) | 19 (14%) | |
| | > 3 | 80 (31%) | 13 (6%) | |
| Median body mass index (IQR) | | 23.6 (21.2, 26.5) | ----◊ | ---- |
| **Internal Organ System Involvement** | | | | |
| Pulmonary | | 108 (28%) | 39 (28%) | 0.91 |
| Renal crisis | | 62 (16%) | 19 (14%) | 0.50 |
| Cardiac | | 79 (20%) | ---- | ---- |
| Gastrointestinal | | 209 (54%) | 66 (55%) | 0.12 |
| Skeletal muscle | | 27 (7%) | 6 (5%) | 0.31 |
| Pulmonary hypertension | | 4 (1%) | 0 | 0.34 |
| **Laboratory Findings** | | | | |
| Anti-topoisomerase I antibody | | 91/384 (24%) | 38/138 (27%) | 0.50 |
| Anti-RNA polymerase III antibody | | 209/375 (56%) | 53/123 (43%) | 0.001 |
| Elevated erythrocyte sedimentation rate‡ | | 172/311 (55%) | 106/135 (79%) | <0.001 |
| Anemia† | | 174/376 (46%) | 50/137 (37%) | 0.06 |

*overall 43% missing data for tobacco use

‡ defined as ESR > (age + 10)/2 for females; ESR > (age/2) for males

†defined as hemoglobin (hgb) <12 mg/dL

◊ not collected at first visit

**Table 2: Associations of baseline variables and 5-year mortality in the derivation cohort (bivariate analysis, n=388)**

| Characteristics | | Odds Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|---|
| **Demographic Features** | | | | |
| Age | | | | <0.0001 |
| | <35 | -0.63 | 0.76 | |
| | 35-44 | -0.73 | 0.69 | |
| | 45-54 | ---- | --- | |
| | 55-64 | 0.46 | 2.26 | |
| | > 65 | 1.26 | 5.01 | |
| Male | | 0.55 | 1.73 | 1.06 – 2.84 |
| **History** | | | | |
| Hypertension | | 1.39 | 0.54 – 3.57 | 0.50 |
| Coronary artery disease | | 1.70 | 0.28 – 10.30 | 0.56 |
| Diabetes mellitus | | 1.01 | 0.31 – 3.30 | 0.99 |
| Overlap with another connective tissue disease | | 0.84 | 0.22 – 3.16 | 0.79 |
| Tobacco use | | | | 0.18 |
| | prior vs none | 1.29 | 0.78 – 2.12 | |
| | current vs none | 1.75 | 0.95 – 3.21 | |
| Prednisone use | never | | | 0.85 |
| | prior to first visit | | | |

| | | | |
|---|---|---|---|
| prescribed at first visit | | | |
| Referral area (<100 miles from Pittsburgh) | 2.23 | 1.42 – 3.51 | 0.005 |
| Decade of diagnosis | | | 0.29 |
| 1990s vs 1980s | 0.69 | 0.42 – 1.11 | |
| 2000s vs 1980s | 0.76 | 0.39 – 1.49 | |
| **Physical Examination Findings** | | | |
| Modified Rodnan skin score | 1.02 | 1.003 – 1.04 | 0.02 |
| Skin score > 20 (yes/no) | 1.42 | 0.89 – 2.27 | 0.14 |
| Skin thickness progression rate slow | | | 0.34 |
| intermediate | 1.22 | 0.69 – 2.15 | |
| rapid | 1.50 | 0.87 – 2.58 | |
| Tendon friction rubs (present or absent) | 2.41 | 1.49 – 3.90 | 0.0003 |
| Number of tendon friction rubs | | | 0.002 |
| 1-3 vs 0 | 1.86 | 1.07 – 3.25 | |
| > 3 vs 0 | 3.17 | 1.82 – 5.53 | |
| Mean body mass index | 0.94 | 0.86 – 1.03 | 0.81 |
| **Laboratory Findings** | | | |
| Anti-topoisomerase I antibody | 2.18 | 1.33 – 3.59 | 0.002 |
| Anti-RNA polymerase III antibody | 0.42 | 0.26 – 0.67 | 0.0003 |
| Elevated sedimentation rate (ESR)* , | 0.65 | 0.40 – 1.08 | 0.10 |
| Anemia (present or absent) Hgb < 12 mg/dL | 2.49 | 1.58 – 3.92 | < 0.0001 |

| | | | | |
|---|---|---|---|---|
| Degree of anemia | | | | 0.0002 |
| | Hgb > 12 mg/dL | | | |
| | Hgb 10-12 mg/dL (mild) | 0.63 | 1.88 | |
| | Hgb < 10 mg/dL (severe) | 0.96 | 2.62 | |
| **Organ System Involvement (present/absent)** | | | | |
| Lung | | 2.10 | 1.31 – 3.38 | 0.002 |
| Renal crisis | | 1.92 | 1.09 – 3.37 | 0.02 |
| Cardiac | | 2.66 | 1.59 – 4.45 | 0.0002 |
| Gastrointestinal tract | | 2.44 | 1.53 – 3.89 | 0.0002 |
| Joint/tendon | | 4.41 | 1.02 – 19.15 | 0.05 |
| Skeletal muscle | | 2.15 | 0.97 – 4.75 | 0.06 |
| Pulmonary hypertension | | 2.55 | 0.36 – 18.4 | 0.35 |
| **Modified Medsger Severity Score** | | | | |
| Interstitial lung disease | none | | | 0.002 |
| | mild/moderate | 1.62 | 0.71 – 3.20 | |
| | severe/endstage | 3.58 | 2.17 – 13.61 | |
| Gastrointestinal tract | none | | | <0.001 |
| | mild/moderate | 2.53 | 1.56 – 4.01 | |
| | severe/endstage | 6.07 | 1.64 – 22.43 | |
| Joint/tendon | none | | | 0.16 |
| | mild/moderate | 0.61 | 0.35 – 1.06 | |
| | severe/endstage | 0.88 | 0.45 – 1.70 | |
| Skeletal muscle | none | | | < 0.0001 |

| | | | | |
|---|---|---|---|---|
| | mild/moderate | 1.81 | 1.08 – 3.04 | |
| | severe/endstage | 5.05 | 2.36 – 10.83 | |
| Peripheral vascular | none | | | 0.63 |
| | mild | 1.23 | 048 – 1.80 | |
| | moderate | 1.06 | 0.60 – 1.85 | |
| | severe/endstage | 1.51 | 0.78 – 2.92 | |

* ESR:greater than age/2 for males or greater than age + 10 years/2 for females

Hgb = hemoglobin in mg/dL

**Table 3: First visit multivariable associations with 5-year mortality in the derivation cohort (n=388).**

| Characteristics | β | Odds Ratio | 95% Confidence Interval | p-value | Points Assigned |
|---|---|---|---|---|---|
| **Age at the First Visit (years)** | | | | <0.0001 | |
| < 35 | -0.58 | 0.56 | 0.20 – 1.53 | | -1 |
| 35-44 | -0.37 | 0.69 | 0.31 – 1.54 | | 0 |
| 45-54 | -- | 1.00 | | | 0 |
| 55-64 | 0.67 | 1.96 | 0.94 – 4.10 | | 0 |
| >65 | 1.42 | 4.12 | 1.92 – 8.85 | | 1 |
| **Male** | 0.59 | 1.80 | 1.01 – 3.20 | 0.05 | 1 |
| **Tendon Friction Rubs** | | | | 0.002 | |
| none | -- | | | | 0 |
| 1-2 | 0.66 | 1.94 | 1.01 – 3.70 | | 1 |
| ≥ 3 | 1.21 | 3.36 | 1.71 – 6.59 | | 1 |
| **GI involvement** | 0.88 | 2.42 | 1.39 – 4.21 | 0.002 | 1 |
| **RNA Polymerase III Antibody Positive** | -0.89 | 0.41 | 0.23 – 0.72 | 0.002 | -1 |
| **Anemia (**<12 mg/dL) | 0.77 | 2.17 | 1.25 – 3.76 | 0.006 | 1 |

**Table 4: Comparison of risk class-specific 5-year mortality in the derivation and validation cohorts**

| Risk Class (sum of points) | Pittsburgh Derivation Cohort (n=388) | | Royal Free Validation Cohort (n=144) | | p-value |
|---|---|---|---|---|---|
| | Deceased | | Deceased | | |
| | n | (%) | n | (%) | |
| Low (≤ 0) | 106 | 5.7 | 50 | 8.0 | 0.73 |
| Moderate (1-2) | 216 | 28.7 | 78 | 33.3 | 0.47 |
| High (≥3) | 66 | 63.6 | 16 | 50.0 | 0.39 |

**Figure 1:** Patient population identification

**Figure 2:** Comparison of the area under the curve for the 3-level risk stratification for 5-year mortality between the Pittsburgh and Royal Free cohorts.

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