**Objective.** Systemic sclerosis (SSc) is a heterogeneous connective tissue disease that is typically subdivided into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) depending on the extent of skin involvement. This subclassification may not capture the entire variability of clinical phenotypes. The European Scleroderma Trials and Research (EUSTAR) database includes data on a prospective cohort of SSc patients from 122 European referral centers. This study was undertaken to perform a cluster analysis of EUSTAR data to distinguish and characterize homogeneous phenotypes without any a priori assumptions, and to examine survival among the clusters obtained.

**Methods.** A total of 11,318 patients were registered in the EUSTAR database, and 6,927 were included in the study. Twenty-four clinical and serologic variables were used for clustering.

**Results.** Clustering analyses provided a first delineation of 2 clusters showing moderate stability. In an exploratory attempt, we further characterized 6 homogeneous groups that differed with regard to their clinical features, autoantibody profile, and mortality. Some groups resembled usual dcSSc or lcSSc prototypes, but others exhibited unique features, such as a majority of lcSSc patients with a high rate of visceral damage and antitopoisoenserase antibodies. Prognosis varied among groups and the presence of organ damage markedly impacted survival regardless of cutaneous involvement.

**Conclusion.** Our findings suggest that restricting subsets of SSc patients to only those based on cutaneous involvement may not capture the complete heterogeneity of the disease. Organ damage and antibody profile should be taken into consideration when individuating homogeneous groups of patients with a distinct prognosis.
INTRODUCTION

Systemic sclerosis (SSc) is a chronic disease that affects connective tissue and is characterized by vascular damage, autoimmunity, and fibrosis. The European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) have recently developed new classification criteria for SSc (1). To date, the subclassification of SSc patients mainly relies on the cutaneous involvement subsets proposed by LeRoy et al in 1988 (2–4). It separates patients into 2 main groups: diffuse cutaneous SSc (dcSSc) associated with early skin changes affecting the trunk and proximal limbs, and limited cutaneous SSc (lcSSc), in which skin fibrosis is limited to the hands, face, feet, and forearms. Organ damage can vary between the 2 subsets, with an early and significant incidence of organ damage (lung fibrosis, gastrointestinal [GI] involvement, heart disease, and renal crisis) in dcSSc and pulmonary hypertension (PH) in lcSSc (4). The 2 subsets also differ in autoantibody profile, with a high prevalence (70–80%) of anticentromere antibodies (ACAs) in lcSSc, and a predominant presence of antibodies against topoisomerase I (anti–topo I) in dcSSc (30%) compared to lcSSc in the study by LeRoy et al (4). In addition, mortality is higher in patients with dcSSc than in patients with lcSSc (5,6). Overall, previous studies suggest that lcSSc and dcSSc are 2 clearly differentiated phenotypes with regard to clinical characteristics, serologic profiles, and prognosis (7).

Yet, past and recent studies of large cohorts have challenged this distinction by highlighting an often-neglected heterogeneity among clinical subsets (8–12), as suggested by, for example, lcSSc patients with anti–topo I antibodies and severe interstitial lung disease (ILD). One method of dealing with heterogeneity is to conduct a cluster analysis in order to organize data from a heterogeneous population into a fairly small number of homogeneous groups. Cluster analysis has been applied to various conditions, such as gout (13), chronic heart failure (14), asthma (15), mixed connective tissue diseases (16), and antineutrophil cytoplasmic antibody–associated vasculitis (17). Cluster analyses have also been carried out in 2 SSc studies, to our knowledge (18,19). One of them included patients from the EULAR European Scleroderma Trials and Research (EUSTAR) cohort but was centered on capillaroscopy patterns (18). Another recent study took into account a limited number of cluster variables and a limited number of patients (19). The aim of this study was to distinguish and characterize homogeneous groups of SSc patients using cluster analysis within the large EUSTAR cohort, and analyze survival between the clusters obtained.

PATIENTS AND METHODS

Patient population. SSc patients were included in the prospective, open, multinational SSc EUSTAR cohort beginning in June 2004 (20–22). For the present study, the EUSTAR database was locked in April 2014. Eligible patients were age ≥18 years, fulfilled the ACR criteria for SSc (23), and had a calculable SSc disease duration, i.e., a date of disease onset (defined as the onset of the first non–Raynaud’s phenomenon symptom) and at least one date of study visit.

All patients agreed to participate in the EUSTAR cohort by signing informed consent forms approved by the local ethics committees. The study was conducted in accordance with the principles of the Declaration of Helsinki, local laws, and Guidelines for Good Clinical Practice (21,22). See Appendix A for a list of the EUSTAR Collaborators.

Definition and selection of variables. The EUSTAR database contains data on demographic characteristics, disease features, organ damage, laboratory parameters, capillaroscopy, echocardiography, pulmonary function tests (PFTs), and medication. In order to harmonize clinical practices and ensure reliable evaluation of parameters among centers, EUSTAR arranges regular training courses and edits SSc management guidelines (24,25).

Autoantibodies were identified and characterized according to the local center’s guidelines (21,22). Clustering variables were selected in order to ensure a global phenotype of SSc patients by considering clinical relevance and representativeness of disease features, eliminating redundant variables providing analogous information, and dismissing variables with a high rate of missing values. We retained 24 variables, including symptoms or organ involvement observed at least once among visits (Raynaud’s phenomenon, esophageal, stomach, and intestinal symptoms, digital ulcers, joint synovitis, joint contractures, tendon friction rubs, muscle weakness, muscle atrophy, arterial hypertension, palpitations, and renal crisis), laboratory values (creatinine kinase elevation, proteinuria, antinuclear antibody, ACA, and anti–topo I antibody positivity), results of other tests (restrictive defect on PFTs, lung fibrosis on plain radiography, conduction blocks, abnormal diastolic function, suspected PH on cardiac echography), and the peak modified Rodnan skin thickness score (MRSS) observed during follow-up (Table 1 and Supplementary Figure 1, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract). Each variable included for symptoms or organ involvement, laboratory values, and results of other tests was considered positive for a specific patient if “yes” was recorded at least once for that variable at any of the visits included.

Statistical analysis. Cluster analysis. Cluster analysis determines the distances between individuals using the combined values of their measured features to obtain groups of individuals who have a greater resemblance to each other than to those in the other groups. Cluster analysis was carried out by ascendant hierarchical clustering of the 24 selected
Table 1. Characteristics of the EUSTAR patients analyzed and not analyzed and characteristics of the patients in the present study by cutaneous subset*

|                       | EUSTAR population | Study population |  |
|-----------------------|-------------------|------------------|---|
|                       | Patients analyzed (n = 6,927) | Patients not analyzed (n = 1,505) | P† | dcSSc | lcSSc | P† |
| % of patients         |                   |                   |   | 42    | 58    |   |
| Demographic           |                   |                   |   |       |       |   |
| characteristics       |                   |                   |   |       |       |   |
| Sex, female           | 86 (6,924)        | 83 (1,505)        | <0.001 | 80 | 91 | <0.001 |
| Ethnicity             |                   |                   | <0.001 | 92 | 97 | <0.001 |
| White                 | 95 (3,973)        | 87 (1,176)        |       | 5   | 2  | <0.001 |
| Asian                 | 3 (3,973)         | 11 (1,176)        |       | 3   | 1  |       |
| Black                 | 2 (3,973)         | 2 (1,176)         |       |     |    |       |
| Age, mean ± SD years (n) | 58.7 ± 13.2 (6,927) | 56.3 ± 13.9 (1,505) | <0.001 | 55.6 ± 13.0 | 60.9 ± 13.0 | <0.001 |
| Age at first non-Raynaud’s phenomenon symptom, mean ± SD years (n) | 47.3 ± 13.3 (6,927) | 47.6 ± 14.1 (1,505) | 0.474 | 45.6 ± 13.2 | 48.5 ± 13.3 | <0.001 |
| Disease duration, mean ± SD years (n)‡ | 11.4 ± 8.1 (6,927) | 8.7 ± 8.1 (1,505) | <0.001 | 10.0 ± 7.4 | 12.4 ± 8.5 | <0.001 |
| Time from onset of Raynaud’s phenomenon to first non-Raynaud’s phenomenon symptom, mean ± SD years (n) | 3.9 ± 8.0 (5,868) | 3.4 ± 8.1 (1,351) | <0.001 | 2.0 ± 5.6 | 5.2 ± 9.2 | <0.001 |
| Time from first non-Raynaud’s phenomenon symptom to EUSTAR enrollment, mean ± SD years (n) | 9.4 ± 7.8 (4,875) | 7.8 ± 7.8 (1,271) | <0.001 | 8.0 ± 7.3 | 10.3 ± 8.1 | <0.001 |
| Time from EUSTAR enrollment to last visit, mean ± SD years (n) | 2.6 ± 2.5 (4,875) | 0.8 ± 1.7 (1,271) | <0.001 | 2.7 ± 2.6 | 2.5 ± 2.5 | 0.031 |
| Body mass index, mean ± SD kg/m² (n) | 23.6 ± 4.3 (2,483) | 24.4 ± 4.8 (889) | <0.001 | 22.9 ± 4.0 | 24.1 ± 4.4 | <0.001 |
| SSc characteristics   |                   |                   |   |       |       |   |
| Autoantibody status   |                   |                   |   |       |       |   |
| Antinuclear antibody positive§ | 96 (6,927) | 94 (1,412) | <0.001 | 97 | 96 | 0.400 |
| Anticentromere antibody positive§ | 37 (6,927) | 36 (1,264) | 0.751 | 14 | 54 | <0.001 |
| Anti–topoisomerase I antibody positive§ | 39 (6,927) | 36 (1,270) | 0.028 | 61 | 23 | <0.001 |
| Anti–U1 RNP antibody positive | 5 (4,054) | 7 (807) | 0.006 | 5 | 5 | 0.770 |
| Anti–PM/Scl antibody positive | 3 (3,335) | 4 (648) | 0.278 | 5 | 2 | <0.001 |
| Anti–RNA polymerase III antibody positive | 4 (3,163) | 6 (563) | 0.025 | 6 | 3 | <0.001 |
| Cutaneous involvement |                   |                   |   |       |       |   |
| dcSSc                 | 42 (6,913)        | 38 (1,437)        | 0.011 |     |    |     |
| Peak MRSS value, mean ± SD (n)§ | 12.0 ± 9.2 (6,927) | 10.9 ± 9.7 (1,170) | <0.001 | 18.3 ± 9.8 | 7.5 ± 5.2 | <0.001 |

(Continued)
| Gastrointestinal involvement | Study population |     | P† | Study population |     | P† |
|-----------------------------|------------------|-----|----|------------------|-----|----|
| Esophageal symptoms§        | Patients analyzed | (n = 6,927) | 81 (6,927) | 69 (1,498) | <0.001 | 84 | 79 | <0.001 |
| Stomach symptoms§           | Patients not analyzed | (n = 1,505) | 42 (6,927) | 27 (1,491) | <0.001 | 47 | 38 | <0.001 |
| Intestinal symptoms§        |                  | (n = 6,927) | 43 (6,927) | 33 (1,497) | <0.001 | 44 | 42 | 0.027 |
| Joint involvement           | dcSSc             |     |     | lcSSc             |     |     |
| Joint contractures§         |                  |     |     | 48 (6,927) | 35 (1,492) | <0.001 | 64 | 36 | <0.001 |
| Joint synovitis§            |                  |     |     | 26 (6,927) | 18 (1,496) | <0.001 | 32 | 22 | <0.001 |
| Tendon friction rubs§       |                  |     |     | 17 (6,927) | 8 (1,477) | <0.001 | 28 | 9 | <0.001 |
| Vascular involvement        |                  |     |     | Raynaud's phenomenon§ |     |     | 98 | 97 | <0.001 |
| History of or current digital ulcers§ |     |     |     | 49 (6,927) | 35 (1,491) | <0.001 | 58 | 42 | <0.001 |
| Muscular involvement        |                  |     |     | Muscle weakness§ |     |     | 39 | 24 | <0.001 |
| Muscle atrophy§             |                  |     |     | 22 (6,927) | 12 (1,484) | <0.001 | 30 | 16 | <0.001 |
| CK elevation§               |                  |     |     | 13 (6,927) | 13 (1,231) | 0.711 | 18 | 9 | <0.001 |
| Cardiac involvement         |                  |     |     | Systemic arterial hypertension§ |     |     | 34 | 27 | <0.001 |
| Palpitations§               |                  |     |     | 39 (6,927) | 26 (1,483) | <0.001 | 41 | 38 | 0.014 |
| Conduction blocks§          |                  |     |     | 22 (6,927) | 14 (1,152) | <0.001 | 24 | 20 | <0.001 |
| LVEF <50%                   |                  |     |     | 5 (4,239) | 5 (879) | 0.799 | 6 | 4 | <0.001 |
| Abnormal diastolic function§ |                  |     |     | 33 (6,927) | 22 (1,116) | <0.001 | 34 | 33 | 0.588 |
| Pericardial effusion        |                  |     |     | 11 (4,442) | 8 (920) | 0.042 | 13 | 9 | <0.001 |
| Pulmonary hypertension      |                  |     |     | Pulmonary hypertension on echocardiography§ |     |     | 31 | 22 | <0.001 |
| Systolic PAP measured by echocardiography, mean ± SD mm Hg (n) |     |     |     | 34.5 ± 15.3 (3,983) | 34.2 ± 15.1 (727) | 0.041 | 34.8 ± 16.4 | 34.2 ± 14.5 | 0.013 |
| Interstitial lung disease   |                  |     |     | Lung fibrosis on plain radiography§ |     |     | 49 | 39 | <0.001 |
| Lung fibrosis on HRCT§      |                  |     |     | 57 (3,424) | 53 (816) | 0.023 | 68 | 48 | <0.001 |
| Restrictive defect on PFTs§ |                  |     |     | 43 (6,927) | 33 (1,083) | <0.001 | 57 | 32 | <0.001 |
| FVC, mean ± SD % predicted (n) |     |     |     | 89.3 ± 21.7 (4,349) | 90.0 ± 21.8 (903) | 0.437 | 81.4 ± 21.1 | 94.9 ± 20.3 | <0.001 |
| DLco, mean ± SD % predicted (n) |     |     |     | 61.8 ± 20.1 (6,196) | 66.1 ± 21.1 (1,026) | <0.001 | 57.4 ± 19.9 | 64.9 ± 19.7 | <0.001 |
| 6-minute walking distance, mean ± SD meters (n) |     |     |     | 392 ± 134 (1,179) | 411 ± 145 (338) | 0.007 | 394 ± 137 | 391 ± 131 | 0.872 |

(Continued)
variables using Ward’s minimum variance method. Results were graphically represented in a dendrogram. We estimated the number of clusters using the visual distance criterion of the horizontal intersection at the highest dissimilarity level on the dendrogram (i.e., where the vertical branches were the longest). In an exploratory approach, we increased the number of clusters considered in the suboptimal visual distance criterion by cutting the dendrogram horizontally at the second highest level of dissimilarity (26).

Evaluation of clusterwise stability and reproducibility is a major issue in cluster analysis (27). To assess stability and reproducibility, we conducted 100 iterations of the clustering process (with the number of clusters in the primary analysis) in randomly selected subsets of up to 50% of the original data set, and estimated the clusterwise stability by computing the Jaccard coefficient (which is a measure of similarity between data sets) between every cluster of the primary analysis and the most comparable cluster retrieved in each iteration (27). A Jaccard similarity index of ≤0.5 indicates a weakly stable and reproducible cluster (28).

The main cluster analysis was carried out in patients without missing data for the 24 selected variables. In order to estimate the impact of late complications on the cluster analysis, we performed a sensitivity analysis by adding in the clustering variables anti–RNA polymerase III, anti–PM/Scl, and anti–U1 RNP antibodies. Finally, a third sensitivity analysis was conducted to evaluate the potential survival bias, and was restricted to patients with a disease duration at the enrollment visit of <5 years. The descriptive words used to refer to disease features or severity in the Results section (low/mild/moderate/severe) were not used during the clustering process but were used to describe and interpret the groups of patients in accordance with established practice (13,14).

Survival analysis. Survival was assessed using disease duration (the time from disease onset to the most recent date data were obtained). We found that a high percentage (52%) of patients were lost to follow-up (i.e., data last obtained prior to January 2012), which was responsible for a significant overestimation of survival. Because we could not update data with actual vital status, we chose to exclude those patients from the survival analysis. A sensitivity analysis that included those patients was therefore performed. We also performed a sensitivity analysis using onset of Raynaud’s phenomenon as the definition of disease onset.

Survival rates were examined using several Cox proportional hazards models: unadjusted, adjusted for age at disease onset, adjusted for age at disease onset and sex, and adjusted for age at disease onset, sex, and immunosuppressive treatment. The proportional hazards assumption for Cox regression models was assessed by the graphical study of Schoenfeld’s residues.
and the log linearity assumption for quantitative predictors was assessed using cubic spline functions. Finally, we calculated the C-index for each Cox regression model (i.e., the estimation of the probability of concordance, which is equivalent to the area under the receiver operating characteristic curve for logistic regression models). Statistical analyses were carried out using

Figure 1. A, Dendrogram of the 6,927 patients with systemic sclerosis (SSc) included in the cluster analysis. The length of the vertical lines represents the degree of similarity between patients. Patients were divided into 2 clusters (cluster A and B) and into 6 clusters (clusters 1–6). B, Heatmap showing the clinical characteristics in each cluster. dcSSc = diffuse cutaneous SSc; CK = creatine kinase; PH = pulmonary hypertension; CRP = C-reactive protein; ACA = anticentromere antibody; anti–topo I = anti–topoisomerase I.
the “survival” and “fastcluster” packages in R software, version 2.14 (29). P values less than 0.05 were considered significant.

RESULTS

Patient characteristics. A total of 11,318 patients (from 122 centers) were registered in the EUSTAR database as of April 2014, and 34,066 visits were recorded. Of these patients, 2,886 were excluded and 1,505 were not analyzed (due to ≥1 missing value for the variables used for clustering). Therefore 6,927 patients (from 120 centers) were incorporated in the cluster analysis (Supplementary Figure 2, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract). Compared to patients who were not included in the analysis, patients who were included were slightly older (mean ± SD age 58.7 ± 13.2 versus 56.3 ± 13.9 years; P < 0.001), had a longer disease duration (mean ± SD 11.4 ± 8.1 versus 8.7 ± 8.1 years; P < 0.001), had a higher rate of dcSSc (42% versus 38%, P = 0.011), and had generally more severe disease as indicated by proportions of organ damage (Table 1). The median number of visits per patient was 3 (interquartile range 4).

Of the patients included, 42% had dcSSc and 58% had lcSSc. Patients with dcSSc were significantly younger than those with lcSSc, and had more severe disease. Of the patients with dcSSc, 14% had ACAs and 61% had anti–topo I antibodies, and of the patients with lcSSc, 54% had ACAs and 23% had anti–topo I antibodies (Table 1).

Primary cluster analysis. Clustering of individuals on the basis of the 24 selected variables yielded an optimal number of 2 clusters: cluster A and cluster B (Figure 1A). Jaccard indexes showed moderate stability: 0.64 for cluster A and 0.66 for cluster B. The characteristics of the 2 clusters are summarized in Table 2, Supplementary Table 1 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract), and Figures 1B and 2. Contingency tables (Supplementary Tables 2 and 3, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract) show the proportions of patients with ACAs and anti–topo I antibodies in the different subsets of SSC according to skin involvement (lcSSc or dcSSc).

Cluster A (n = 3,149; 45.5%). Cluster A contained principally patients with lcSSc (81%). Less than a third of the patients in this cluster had severe organ damage (digital ulcers, intestinal symptoms, or muscle, joint, cardiac, or lung involvement). ACAs were present in 54% of the patients, and anti–topo I antibodies were present in 21%.

Cluster B (n = 3,778; 54.5%). Patients in cluster B were a little younger than those in cluster A, with a younger age at disease onset. In cluster B, 61% of the patients had dcSSc. A majority of the patients presented with digital ulcers, joint contractures, intestinal involvement, and ILD. The autoantibody profile was the opposite of that seen in cluster A; 54% of the patients were positive for anti–topo I antibodies and 22% were positive for ACAs.

Exploratory cluster analysis. In an exploratory attempt to decipher the heterogeneity of the disease, we then increased the number of clusters. Graphical observation of the dendrogram determined that a suboptimal number of clusters was 6 (Figure 1A). As a consequence, we observed a decrease in Jaccard coefficients (ranging from 0.32 to 0.68). The characteristics of clusters 1–6 are summarized in Table 2, Figure 1B, and Figure 3.

Cluster 1 (n = 1,186; 17%). A majority of the patients in cluster 1 (89%) had lcSSc, and most were female. They were older at disease onset, had a high prevalence of GI involvement, and had a low proportion of patients with ILD. Most of the patients in cluster 1 (79%) were ACA positive.

Cluster 2 (n = 720; 10%). Cluster 2 was composed mainly of lcSSc patients (71%), with increased frequencies of suspected PH by echocardiography (39%), ILD (85%), and restrictive defect (61%). Anti–topo I antibodies were present in 35% of the patients, and ACAs were present in 24%.

Cluster 3 (n = 1,243; 18%). Cluster 3 included mainly patients with lcSSc (79%) characterized by low prevalence of GI involvement and ILD. ACAs were twice as frequent as anti–topo I antibodies (48% versus 24%, respectively).

Cluster 4 (n = 1,673; 24%). Patients in cluster 4 were mainly lcSSc patients (63%) with severe disease as demonstrated by high proportions of cardiac and lung, muscular, joint, and GI involvement and digital ulcers. Anti–topo I antibodies were present in 46% of the patients and ACAs in 29%.

Cluster 5 (n = 1,249; 18%). Cluster 5 consisted mainly of patients with dcSSc (72%), with a notable proportion of male patients (19%), and GI, joint, and cardiac disease and moderate lung involvement. Half of the patients in cluster 5 were anti–topo I antibody positive and 20% were ACA positive.

Cluster 6 (n = 856; 12%). Cluster 6 was characterized by the highest proportion of patients with dcSSc (92%) and men (21%), the highest mean peak MRSS (27.2), and severe disease as shown by high frequencies of GI, joint, muscular, renal, lung, and cardiac disease. Anti–topo I antibodies were present in 77% of the patients and ACAs in 12% of the patients.

Sensitivity cluster analyses. Three sensitivity cluster analyses were conducted. The first included only patients with a disease duration of >10 years (Supplementary Table 4, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract), the second included anti–U1 RNP, anti–RNA polymerase III, and anti–PM/Scl antibodies as clustering variables (Supplementary Table 5, available on the Arthritis & Rheumatology web site at
Table 2. Characteristics of the patients in the 2 and 6 clusters found in the cluster analysis (n = 6,927)*

|                         | 2 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters | 6 clusters |
|-------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|                         | Cluster A  | Cluster B  | Cluster 1  | Cluster 2  | Cluster 3  | Cluster 4  | Cluster 5  | Cluster 6  |            |            |
| Jaccard index           | 0.64       | 0.66       | 0.39       | 0.32       | 0.57       | 0.38       | 0.68       | 0.43       |            |            |
| No. of patients         | 3,149      | 3,778      | 1,186      | 720        | 1,243      | 1,673      | 1,249      | 856        |            |            |
| Demographic characteristics|           |            |            |            |            |            |            |            |            |            |
| Sex, female             | 90         | 84         | 94         | 88         | 88         | 88         | 81         | 79         |            |            |
| Ethnicity               |            |            |            |            |            |            |            |            |            |            |
| White                   | 94         | 96         | 97         | 88         | 94         | 96         | 94         | 96         |            |            |
| Asian                   | 5          | 2          | 2          | 10         | 4          | 2          | 3          | 2          |            |            |
| Black                   | 2          | 2          | 1          | 2          | 2          | 2          | 3          | 2          |            |            |
| Age, mean ± SD years   | 59.2 ± 13.3| 58.2 ± 13.2| 61.3 ± 12.9| 60 ± 12.8  | 56.6 ± 13.5| 61.2 ± 12.6| 55.8 ± 13.2| 55.9 ± 13.2|            |            |
| Age at first non-Raynaud's symptom, mean ± SD years | 47.9 ± 13.3| 46.7 ± 13.3| 48.9 ± 13.1| 48.3 ± 12.8| 46.7 ± 13.6| 48.1 ± 13.1| 46 ± 13.4  | 45.1 ± 13.4|            |            |
| Disease duration, mean ± SD years‡ | 11.3 ± 8.2 | 11.5 ± 8.1 | 12.4 ± 8.1 | 11.8 ± 8.3 | 9.9 ± 7.9  | 13.2 ± 8.4 | 9.8 ± 7.6  | 10.8 ± 7.5 |            |            |
| Time from onset of Raynaud's phenomenon to first non-Raynaud's symptom, mean ± SD years | 4.8 ± 8.7  | 3.1 ± 7.3  | 5.4 ± 8.7  | 4.4 ± 9.1  | 4.4 ± 8.5  | 3.9 ± 8.2  | 2.8 ± 6.6  | 2.2 ± 6.1  |            |            |
| Time from first non-Raynaud's phenomenon symptom to EUSTAR enrollment, mean ± SD years | 9.4 ± 7.9  | 9.3 ± 7.8  | 10.3 ± 7.9 | 9.8 ± 8.2  | 8.2 ± 7.4  | 10.5 ± 8.1 | 8.1 ± 7.4  | 8.6 ± 7.4  |            |            |
| Time from EUSTAR enrollment to last visit, mean ± SD years | 2.2 ± 2.3  | 2.8 ± 2.6  | 2.5 ± 2.3  | 2.3 ± 2.5  | 1.8 ± 2.2  | 3 ± 2.7   | 2.4 ± 2.5  | 2.9 ± 2.5  |            |            |
| Body mass index, mean ± SD kg/m² | 24.1 ± 4.3 | 23.2 ± 4.2 | 24.3 ± 4.4 | 24.5 ± 4.6 | 23.6 ± 4   | 23.6 ± 4.4 | 23.3 ± 3.9 | 22.1 ± 4.2 |            |            |
| SSc characteristics     |            |            |            |            |            |            |            |            |            |            |
| Autoantibody status     |            |            |            |            |            |            |            |            |            |            |
| Antinuclear antibody positive‡ | 96         | 97         | 98         | 94         | 95         | 97         | 95         | 98         |            |            |
| Anticentromere antibody positive‡ | 54         | 22         | 79         | 24         | 48         | 29         | 20         | 12         |            |            |
| Anti–topoisomerase I antibody positive‡ | 21         | 54         | 8          | 35         | 24         | 46         | 50         | 77         |            |            |
| Anti–U1 RNP antibody positive | 5          | 5          | 3          | 8          | 5          | 7          | 3          | 4          |            |            |
| Anti–PM/ScI antibody positive | 2          | 4          | 1          | 3          | 1          | 4          | 4          | 6          |            |            |
| Anti–RNA polymerase III antibody positive | 3          | 5          | 2          | 3          | 4          | 3          | 6          | 6          |            |            |

(Continued)
Table 2. (Cont’d)

|                          | 2 clusters | 6 clusters |
|--------------------------|------------|------------|
|                          | Cluster A  | Cluster B  | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
| Cutaneous involvement    |            |            |           |           |           |           |           |           |
| dcSSc                   | 19         | 61         | 11        | 29        | 21        | 37        | 72        | 92        |
| Peak MRSS, mean ± SD‡    | 6.6 ± 4.3  | 16.5 ± 9.8 | 6.6 ± 4.2 | 7.2 ± 4.6 | 6.3 ± 4.1 | 9.2 ± 5.3 | 19 ± 6.7  | 27.2 ± 8.7 |
| Gastrointestinal         |            |            |           |           |           |           |           |           |
| involvement§              | 73         | 88         | 88        | 76        | 58        | 91        | 79        | 95        |
| Esophageal symptoms‡     | 26         | 55         | 52        | 16        | 7         | 60        | 36        | 70        |
| Stomach symptoms‡        | 33         | 50         | 64        | 21        | 11        | 57        | 34        | 63        |
| Intestinal symptoms‡     |            |            |           |           |           |           |           |           |
| Joint involvement        |            |            |           |           |           |           |           |           |
| Joint contractures‡      | 24         | 67         | 29        | 17        | 23        | 65        | 55        | 91        |
| Joint synovitis‡         | 14         | 37         | 15        | 13        | 15        | 37        | 25        | 53        |
| Tendon friction rubs‡    | 4          | 28         | 6         | 3         | 4         | 19        | 19        | 57        |
| Vascular involvement     |            |            |           |           |           |           |           |           |
| Raynaud's phenomenon‡    | 98         | 99         | 99        | 98        | 97        | 99        | 98        | 99        |
| History of or current    | 32         | 63         | 35        | 24        | 33        | 62        | 50        | 85        |
| digital ulcers‡          |            |            |           |           |           |           |           |           |
| Muscular involvement     |            |            |           |           |           |           |           |           |
| Muscle weakness‡         | 16         | 59         | 27        | 8         | 10        | 69        | 33        | 77        |
| Muscle atrophy‡          | 6          | 35         | 9         | 3         | 6         | 38        | 17        | 57        |
| CK elevation‡            | 6          | 18         | 7         | 7         | 5         | 17        | 13        | 26        |
| Cardiac involvement      |            |            |           |           |           |           |           |           |
| Systemic arterial        | 31         | 37         | 38        | 28        | 26        | 44        | 26        | 38        |
| hypertension‡            |            |            |           |           |           |           |           |           |
| Palpitations‡            | 25         | 51         | 38        | 32        | 9         | 64        | 28        | 57        |
| Conduction blocks‡       | 12         | 30         | 16        | 14        | 6         | 39        | 16        | 34        |
| LVEF <50%                | 3          | 7          | 3         | 3         | 2         | 6         | 5         | 10        |
| Abnormal diastolic       | 24         | 42         | 27        | 33        | 15        | 54        | 24        | 43        |
| function‡                |            |            |           |           |           |           |           |           |
| Pericardial effusion     | 7          | 14         | 7         | 11        | 4         | 15        | 9         | 18        |
| Pulmonary hypertension   |            |            |           |           |           |           |           |           |
| Pulmonary hypertension   | 21         | 39         | 24        | 39        | 8         | 44        | 24        | 50        |
| on echocardiography‡     |            |            |           |           |           |           |           |           |
| Systolic PAP, measured   | 32.5 ± 13.7| 36 ± 16.2  | 33 ± 14.3 | 36.7 ± 14.1| 29.4 ± 12 | 37.2 ± 14.6| 32.4 ± 12 | 38.1 ± 22.1|
| by echocardiography,     |            |            |           |           |           |           |           |           |
| mean ± SD mm Hg          |            |            |           |           |           |           |           |           |

(Continued)
and the third included only patients with a disease duration of <5 years at the enrollment visit (Supplementary Table 6, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract). Results of the sensitivity analyses were similar to those of the main cluster analysis.

Survival analyses. Kaplan-Meier curves are shown in Figures 2 and 3 and Supplementary Figures 3 and 4 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract). Survival rates are presented in Supplementary Table 7 (available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract), and the results of Cox regression analyses are shown in Table 3.

The risk of death was increased for patients with dcSSc compared to patients with lcSSc, with a hazard ratio (HR) of 2.03 (95% confidence interval [95% CI] 1.61–2.56) in the most-adjusted model. An increased risk of death was also present in

### Table 2. (Cont’d)

| Clustering Variables | 2 clusters | 6 clusters |
|----------------------|------------|------------|
|                      | Cluster A  | Cluster B  | Cluster 1 | Cluster 2 | Cluster 3 | Cluster 4 | Cluster 5 | Cluster 6 |
| Interstitial lung disease | 29 | 65 | 8 | 85 | 17 | 72 | 46 | 80 |
| Lung fibrosis on plain radiography‡ | 38 | 70 | 22 | 78 | 29 | 73 | 56 | 82 |
| Lung fibrosis on HRCT | 24 | 58 | 13 | 61 | 14 | 60 | 42 | 77 |
| Restrictive defect on PFTs‡ | 97.8 ± 19.3 | 82.7 ± 21.1 | 101.2 ± 17.4 | 86.7 ± 21.9 | 99.9 ± 17.7 | 84.4 ± 20.8 | 87.5 ± 19.8 | 72.8 ± 20.3 |
| FVC, mean ± SD % predicted | 68 ± 18.9 | 56.6 ± 19.7 | 69.8 ± 17.2 | 57.7 ± 19.3 | 72.3 ± 18 | 55.2 ± 18.8 | 62.5 ± 20.3 | 50.6 ± 18.1 |
| DLCO, mean ± SD % predicted | 381 ± 136 | 400 ± 135 | 405 ± 130 | 427 ± 121 | 366 ± 133 | 418 ± 130 | 362 ± 138 |
| 6-minute walking distance, mean ± SD meters | 411 ± 129 | 418 ± 128 | 405 ± 127 | 593 ± 184 | 516 ± 189 | 495 ± 182 | 362 ± 138 |
| Renal involvement | 2 | 4 | 2 | 1 | 2 | 4 | 3 | 8 |
| History of renal crisis‡ | 7 | 16 | 6 | 8 | 7 | 15 | 11 | 26 |
| Proteinuria‡ | 24 | 45 | 25 | 29 | 20 | 43 | 36 | 62 |
| Blood tests | 10 | 13 | 13 | 7 | 8 | 14 | 10 | 12 |
| CRP elevation | 27 | 55 | 22 | 45 | 24 | 57 | 44 | 65 |
| Hypocomplementemia | 2.8 ± 6.4 | 5.7 ± 7.9 | 2 ± 4.9 | 5.5 ± 9.3 | 2.3 ± 5.6 | 5.6 ± 7.6 | 4.6 ± 7.6 | 7.3 ± 8.8 |
| Prednisone, mean ± SD mg/day | 27 | 54 | 17 | 44 | 27 | 48 | 54 | 66 |
| Past or current immunosuppressive drugs | Number of deaths per 1,000 patient-years | 10.3 | 22.6 | 7.5 | 17.3 | 9.7 | 19.1 | 20.8 | 31.9 |

* Except where indicated otherwise, values are the percent of patients. See Table 1 for definitions.
† Time between the first non-Raynaud’s phenomenon symptom and the last visit.
‡ Clustering variables.
§ Esophageal symptoms included dysphagia and/or reflux, stomach symptoms included early satiety and/or vomiting, and intestinal symptoms included diarrhea, bloating, and/or constipation.
cluster B compared to cluster A (HR 2.47 [95% CI 1.86–3.27]).

When analyzing 6 clusters, we noticed a continuous increasing mortality from cluster 1 to cluster 6 in the most-adjusted model. The risk of death had a magnitude superior to those noted in the 2 previous analyses (i.e., HR 6.14 [95% CI 3.81–9.89] for cluster 6 compared to cluster 1). C-indexes were similar for the most-adjusted models: lcSSc versus dcSSc, cluster A versus cluster B, and for the 6 clusters (mean ± SEM 0.78 ± 0.02, 0.78 ± 0.02, and 0.79 ± 0.02, respectively).

The sensitivity analysis taking into account patients who were lost to follow-up yielded comparable HRs when we examined survival in clusters A and B and clusters 1–6 (data not shown). We also performed a sensitivity analysis using the onset of Raynaud’s phenomenon as the date of disease onset (Supplementary Table 8, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract), which yielded similar results, albeit the number of patients with available data was lower.

DISCUSSION

This study aimed to distinguish homogeneous groups in a substantial population of ~7,000 SSc patients using a clus-
The study had 2 main findings. First, the optimal clustering divided patients into 2 distinct groups according to their clinical and serologic features and disease severity and prognosis; these 2 categories partially overlapped with the classifications dcSSc and lcSSc. Second, an exploratory analysis yielded 6 homogeneous subsets of individuals that broadly di-
CLUSTER ANALYSIS OF THE EUSTAR COHORT

The fact that 2 clusters were found could be considered a validation of the expected dichotomy between dcSSc and lcSSc. However, 19% of the patients in cluster A had dcSSc and 21% had anti–topo I antibodies. In cluster B, 39% of the patients had lcSSc and 22% had ACAs. No clear parallels between the severity of organ damage and the cutaneous extent of SSc were observed. This finding is consistent with the results of recent studies. For example, Nihtyanova et al demonstrated that the presence of significant organ involvement was a strong predictor of prognosis, in both lcSSc and dcSSc, in a study of nearly 400 consecutive patients followed up for up to 15 years. Notably, survival curves were close for the 2 cutaneous subsets when organ damage was present (30). Taken together, these results suggest that, while there is consensus on the relevance and practicality of subdividing SSC into lcSSc and dcSSc (31), this binary classification may be too restrictive as a separation within a continuous spectrum of varying severity primarily driven by organ damage and subsequent prognosis (12).

In an exploratory attempt to study the heterogeneity of SSc more in depth, we found 6 additional clusters. Some of the 6 clusters obtained were expected, since they were consistent with the historical descriptions of lcSSc and dcSSc. Indeed, cluster 1 included patients with the classic presentation of lcSSc, i.e., older female patients with a low rate of severe organ damage, a high frequency of ACA positivity, and a generally favorable prognosis. Cluster 6 resembled the classic description of dcSSc, with a high rate of male patients, the highest frequency of anti–topo I antibody–positive patients, and a high rate of severe organ damage and poor prognosis. Intriguingly, we observed clusters of patients that seemed to be grouped together based on characteristics other than the degree of skin involvement. Cluster 2 was composed principally of patients with lcSSc but with a rather high frequency of anti–topo I antibody–positivity and high rates of ILD and suspected PH. Of note, the prognosis for patients in cluster 2 was significantly worse than that for patients in cluster 1. Similarly, cluster 4 consisted of predominantly patients with lcSSc, often with visceral complication. Cluster 5 comprised, for the most

### Table 3. Cox regression analyses*

| Cutaneous involvement | Univariable analysis (n = 3,352) | Multivariable analysis | Adjusted for age at disease onset (n = 3,352) |
|-----------------------|---------------------------------|------------------------|-----------------------------------------------|
|                       | HR (95% CI) | P | HR (95% CI) | P |
| lcSSc                 | Reference  | 1.90 (1.64–2.19) | <0.001 | Reference  | 2.39 (2.07–2.77) | <0.001 | Reference  | 2.16 (1.80–2.64) | <0.001 |
| dcSSc                 | Reference  | 0.60 ± 0.01 | 0.73 ± 0.01 | 0.75 ± 0.01 | 0.78 ± 0.02 |
| C-index†              | 0.60 ± 0.01 | 0.73 ± 0.01 | 0.75 ± 0.01 | 0.78 ± 0.02 |
| 2 clusters            | Reference  | 2.23 (1.88–2.65) | <0.001 | Reference  | 2.40 (2.02–2.85) | <0.001 | Reference  | 2.26 (1.91–2.69) | <0.001 |
| Cluster A             | Reference  | 0.59 ± 0.01 | 0.72 ± 0.01 | 0.74 ± 0.01 | 0.78 ± 0.02 |
| Cluster B             | Reference  | 2.10 (1.46–3.00) | <0.001 | Reference  | 1.97 (1.38–2.82) | <0.001 | Reference  | 1.64 (0.88–3.03) | 0.119 |
| C-index†              | 2.10 (1.46–3.00) | 0.72 ± 0.01 | 0.74 ± 0.01 | 0.78 ± 0.02 |
| 6 clusters            | Reference  | 1.30 (0.89–1.91) | 0.172 | Reference  | 1.63 (1.11–2.38) | 0.12 | Reference  | 1.62 (1.11–2.37) | 0.13 | Reference  | 1.97 (1.10–3.54) | 0.023 |
| Cluster 2             | Reference  | 2.47 (1.88–3.30) | <0.001 | Reference  | 2.49 (1.88–3.30) | <0.001 | Reference  | 2.40 (1.81–3.19) | <0.001 | Reference  | 2.77 (1.74–4.39) | <0.001 |
| Cluster 3             | Reference  | 3.03 (2.23–4.11) | <0.001 | Reference  | 3.77 (2.77–5.12) | <0.001 | Reference  | 3.37 (2.47–4.58) | <0.001 | Reference  | 3.22 (1.93–5.36) | <0.001 |
| Cluster 4             | Reference  | 5.85 (4.38–7.81) | <0.001 | Reference  | 5.20 (3.89–6.95) | <0.001 | Reference  | 6.14 (3.81–9.89) | <0.001 |
| Cluster 5             | Reference  | 4.40 (3.30–5.87) | <0.001 | Reference  | 4.40 (3.30–5.87) | <0.001 | Reference  | 4.40 (3.30–5.87) | <0.001 |
| Cluster 6             | Reference  | 4.40 (3.30–5.87) | <0.001 | Reference  | 4.40 (3.30–5.87) | <0.001 | Reference  | 4.40 (3.30–5.87) | <0.001 |
| C-index†              | 0.63 ± 0.01 | 0.75 ± 0.01 | 0.76 ± 0.01 | 0.79 ± 0.02 |

* Disease onset was defined as the first non-Raynaud’s phenomenon symptom (see Supplementary Table 8, available on the Arthritis & Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.40906/abstract, for sensitivity analysis using the onset of Raynaud’s phenomenon as the definition of disease onset). HR = hazard ratio; 95% CI = 95% confidence interval; lcSSc = limited cutaneous systemic sclerosis; dcSSc = diffuse cutaneous systemic sclerosis.

† The C-index was calculated for each Cox regression model, and corresponds to the estimation of the probability of concordance, equivalent to the area under the receiver operating characteristic curve for logistic regression models. A value of 1 indicates perfect agreement and 0.5 indicates an agreement that is no better than chance. Values for the C-index are the mean ± SEM.
part, patients with dcSSc, but we noted lower frequencies of ILD and suspected PH in this group than in clusters 2, 4, or 6. These findings indicate that subclassifications established solely on the extent of skin involvement might not be entirely representative of the severity of organ damage and prognosis.

Furthermore, this work highlighted some groups of patients in which the classic relationships between lcSSc and ACAs and between dcSSc and anti–topo I antibodies were not obvious. For example, in cluster 2, 71% of the patients were classified as having lcSSc, although 85% had lung fibrosis. Moreover, we found a relatively small proportion of ACA-positive patients (24%) and a notable rate of anti–topo I antibody positivity (35%), which was unexpected in a group in which the majority of the patients had lcSSc. The prognosis for the patients in this group was worse than that for the patients in cluster 1, which included mainly patients with lcSSc and few with organ damage, which supports the findings of Nihntyana et al (30). Likewise, a Canadian Scleroderma Research Group study examined the clinical features and mortality of anti–topo I antibody–positive lcSSc and ACA-positive dcSSc patients. The autoantibody profile seemed to be more strongly associated with demographic characteristics and visceral damage than with the skin subgroup. Mortality was related to both skin and serologic profile (9). Kranenburg et al also demonstrated that lcSSc patients who were positive for anti–topo I antibodies contrasted with lcSSc patients who were negative for anti–topo I antibodies and dcSSc patients who were positive for anti–topo I antibodies in terms of survival and organ involvement (32). Taken together, those studies suggest that subclassification combining antibody profile and skin involvement might predict clinical outcomes more accurately than skin or serologic features alone (9,32).

The heterogeneity of SSc has been discussed over a long period, and many studies were published both before and after the work of LeRoy et al describing the limited and diffuse subsets (2–4,33,34). The significance of serologic profile has also been highlighted by Patterson et al, who characterized 5 groups of patients with homogeneous clinical and organ involvement (11,12). Significant efforts to classify patients into subsets on the basis of common clinical phenotypes, rather than through a predetermined decision process, have proposed to classify individuals using changes in MRSS over time (34,35), changes in the forced vital capacity percent predicted value (36,37), or gene expression patterns in the skin (38,39). Each of these attempts has resulted in a small number of subsets that define the range of phenotypes captured by the stratification characteristics (12). There is growing interest in a new subclassification of SSc that combines patterns of underlying pathogenesis, organ damage, and prognosis in order to personalize disease management and ameliorate outcomes (12,31).

This study has strengths and limitations. The principal strengths are the number of patients included in this large, prospective, multicenter cohort, and the lack of any a priori assumptions. The main weakness is that several clinically relevant variables were lacking or were disregarded due to the proportion of missing data being too high (e.g., autoantibodies other than ACAs/anti–topo I antibodies, extent of ILD on high-resolution computed tomography [HRCT] scan, detailed skin involvement, and overlap syndromes). In addition, 1,505 of 8,432 patients were excluded from the cluster analysis because of missing data for any of the selected clustering variables. Since those excluded patients had slightly less severe disease than the included ones, it could affect the extrapolation of our results. Imputation of missing data by model-based clustering was not performed because we could not assume that these data were missing at random (40,41). Moreover, several definitions of variables lacked precision (e.g., ILD was defined as lung fibrosis on radiography whereas HRCT scan is now widely used, and PH was defined as suspicion on echocardiography without invasive confirmation).

We also acknowledge that a thorough analysis of treatment regimens was not possible due to missing data. Nevertheless, for a majority of the patients we were able to determine whether or not they had been taking an immunosuppressive drug. To account for the potential effect of these drugs on survival, survival analyses were adjusted for immunosuppressive treatment. A potentially important bias is the influence of disease duration on the clustering process, since the frequency of organ damage tends to increase as the disorder progresses. Also, disease duration at the enrollment visit was relatively long, raising the possibility that study results were influenced by survival bias. Yet, the sensitivity analyses that included only patients with a long disease duration and those that included only patients with a short disease duration yielded similar results.

Another limitation is that a significant number of patients were excluded from the survival analysis because of loss to follow-up. Nevertheless, this exclusion did not alter the survival differences between clusters in a sensitivity analysis. The primary aim of our study was not to assess the prognosis factors for survival in SSc, but to decipher the heterogeneity of SSc by a cluster analysis and describe the survival rate in the clusters obtained, allowing us to validate this approach post hoc. In studies assessing the prognosis factors of survival, baseline data are most often used. In our study, we had to include follow-up data in order to identify the occurrence of organ involvement. Therefore, we considered an organ complication to be present if the corresponding variable was described as “positive” at least once among all the visits included for a specific patient. We did not describe the progression of organ involvement in the whole population or in the different clusters because the limited number of follow-up visits precluded us from performing a precise temporal description. In the end, the weak reproducibility of the exploratory analysis with 6 clusters precludes translating these results to a new subclassification (e.g., to allocate an individual to a designated group on the basis of their features). Moreover, previous studies have shown differences between distinct geographical
cohort (42). Of note, 95% of the patients included in this study were white. It is likely that inclusion of a higher proportion of Asian or black patients could have modified the results.

In conclusion, this study shows that SSC is a very heterogeneous condition. While there is consensus regarding the relevance and practicality of the subclassification of SSC into lcSSc and dcSSc, this binary system might omit a wider spectrum of clinical phenotypes characterized not only by skin involvement but also by organ damage, serologic profile, and subsequent prognosis. There is an increasing demand for a future SSC classification that combines these different patterns, in order to personalize approaches to diagnosis and clinical management.

**AUTHOR CONTRIBUTIONS**

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sobanski had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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**Analysis and interpretation of data.** Sobanski, Giovannelli, Allano, Distler, Matucci-Cerinic, Denton, Launay, Hachulla.

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APPENDIX A: THE EUSTAR COLLABORATORS

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CLUSTER ANALYSIS OF THE EUSTAR COHORT

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