Disease progression in systemic sclerosis-overlap syndrome is significantly different from limited and diffuse cutaneous systemic sclerosis

Pia Moinzadeh,1 Elisabeth Aberer,2 Keihan Ahmadi-Simab,3 Norbert Blank,4 Joerg H W Distler,5 Gerhard Fierlbeck,6 Ekkehard Genth,7 Claudia Guenther,8 Ruediger Hein,9 Joerg Henes,10 Lena Herich,11 Ilka Herrgott,12 Ina Koetter,13 Alexander Kreuter,14 Thomas Krieg,1 Kathrin Kuhr,1 Hanns-Martin Lorenz,15 Florian Meier,16 Inga Melchers,17 Hartwig Mensing,18 Ulf Mueller-Ladner,16 Christiane Pfeiffer,19 Gabriela Riemekasten,20 Miklós Sáradi,21 Marc Schmalzing,10 Cord Sunderkoetter,12 Laura Susok,22 Ingo H Tanne,16 Peter Vaith,23 Margitta Worm,24 Gottfried Wozel,8 Gabriele Zeidler,25 Nicolas Hunzelmann,1 and all participating DNSS centers

ABSTRACT
Background Systemic sclerosis (SSc)-overlap syndromes are a very heterogeneous and remarkable subgroup of SSc-patients, who present at least two connective tissue diseases (CTD) at the same time, usually with a specific autoantibody status.

Objectives To determine whether patients, classified as overlap syndromes, show a disease course different from patients with limited SSc (lcSSc) or diffuse cutaneous SSc (dcSSc).

Methods The data of 3240 prospectively included patients, registered in the database of the German Network for Systemic Scleroderma and followed between 2003 and 2013, were analysed.

Results Among 3240 registered patients, 10% were diagnosed as SSc-overlap syndrome. Of these, 82.5% were female. SSc-overlap patients had a mean age of 48 ± 1.2 years and carried significantly more often ‘other antibodies’ (68.0%; p < 0.0001), including anti-U1RNP, -PmScl, -Rn, -La, as well as anti-Jo-1 and -Ku antibodies.

These patients developed musculoskeletal involvement earlier and more frequently (62.5%) than patients diagnosed as lcSSc (32.2%) or dcSSc (43.3%) (p < 0.0001). The onset of lung fibrosis and heart involvement in SSc-overlap patients was significantly earlier than in patients with lcSSc and occurred later than in patients with dcSSc. Oesophagus, kidney and PH progression was similar to lcSSc patients, whereas dcSSc patients had a significantly earlier onset.

Conclusions These data support the concept that SSc-overlap syndromes should be regarded as a separate SSc subset, distinct from lcSSc and dcSSc, due to a different progression of the disease, different proportional distribution of specific autoantibodies, and of different organ involvement.

INTRODUCTION
Systemic sclerosis (SSc) is a heterogeneous, multisystem, chronic disorder, leading to fibrosis of the skin and many internal organs. To classify patients with established disease, the American College of Rheumatology published in 1980 preliminary criteria.1 Currently a subclassification developed by LeRoy et al, this is the most widely used classification system for limited and diffuse SSc in clinical practice,2 and is the basis for many registries worldwide.3 In these registries, it became apparent that in a sizeable number of patients, symptoms of SSc occur in combination with those of other connective tissue diseases (CTD).4–10 also described by some authors as SSc-overlap syndrome.4 11–13 Up to now, no firm classification criteria for SSc-overlap syndromes are established, but it is generally considered when musculoskeletal involvement (myositis, arthritis) or clinical signs of other rheumatic diseases are substantially greater than usually found in SSc patients.12

Clinical features of overlap syndrome patients are very heterogeneous, and epidemiological studies report divergent frequencies of overlap subgroups as well as of organ manifestations.11 14 15

Musculoskeletal involvement, including joints, tendons and muscles, is the most frequent clinical feature, highlighting the difference to other SSc forms. Inflammatory joint involvement is reported to be the second most frequent manifestation in patients with musculoskeletal involvement and overlap syndromes. These patients are often identified by typical clinical symptoms (usually limited skin involvement) together with high titres of anticyclic citrullinated peptides (CCP/ACPA) and/or higher rheumatoid factors (RF).16 17

All known classification criteria for overlap syndromes include autoantibodies, which are helpful to separate them from other subsets.18–20 PmScl- and anti-U1RNP-antibodies are known to be the most common autoantibodies in patients with overlap syndromes.21–24

Pakozdi et al reported recently, that 20% of the patients attending the Centre for Rheumatology at...
the Royal Free Hospital had overlapping features with other rheumatologic diseases, such as polymyositis/dermatomyositis (43%), systemic lupus erythematosus (SLE) (8%), Sjögren’s syndrome (17%), and rheumatoid arthritis (32%).

It has been always debated whether patients suffering from overlap syndromes should be regarded as a separate entity, or should be included, depending on their skin involvement, in the two main groups of limited (lcSSc) and diffuse SSc (dcSSc) patients.

In this prospective study, it could be shown for the first time that SSc-overlap syndromes should be viewed as a distinct SSc subset.

**MATERIALS AND METHODS**

This study involves 3240 patients, registered in the database of the German Network for Systemic Sclerosis (DNSS). The network combines different subspecialties consisting of rheumatologists, dermatologists, pulmonologists and nephrologists from altogether more than 40 clinical centres. The Ethics Committee of the coordinating centre, that is, the Cologne University Hospital, gave a positive vote on the patient information and consent form for the registry. On the basis of this document, all participating centres received the approval of their local ethics committees prior to registering patients.

Patient data, including information about gender, age, autoantibodies, SSc subsets, symptoms and signs, organ involvement, modified Rodnan Skin Score (mRSSS) as well as treatments, were recorded on a prospective basis in a database started in 2003 with a mean follow-up time of 9.5 ± 0.2 years (from the time of SSc onset till the last follow-up visit). A significant number of these patients were classified according to the criteria of LeRoy et al. as having lcSSc or dcSSc. Additionally, a smaller but still considerable number of patients, did not fulfil these criteria, but were registered to follow-up their course of disease. Data of the first Raynaud phenomenon (RP) onset, as well as data of non-RP onset of skin and organ involvement were recorded. Due to the lack of satisfying classification criteria for patients with different forms of overlap syndromes, all patients with more than one CTD were classified as SSc-overlap syndrome in general, including symptoms and signs, autoantibodies and organ manifestations in detail. This information was used to characterise patients with SSc-overlap syndromes.

**SSc subsets**

Patients with overlap syndromes were defined as a disease, occurring with clinical features of SSc, according to the ACR criteria, or main SSc-associated symptoms, simultaneously with those typical for other rheumatic diseases. These patients were often positive for anti-PmScl, -U1RNP, -Jo1, -Ku, -Ro or -La autoantibodies. Patients with a mixed connective tissue disease (MCTD) were also included in SSc-overlap syndromes, as MCTD combines features of SLE, SSc and myositis, together with the presence of anti-U1RNP-antibodies.

Patients suffering from dcSSc were characterised by a progressive course of disease with an early onset of RP, usually within 1 year of onset of skin changes. They were defined by rapid skin involvement of the trunk, face, proximal and distal extremities and being frequently associated with antitoxopoisometerase (ATA) antibodies.

lcSSc was defined by skin thickening of the extremities distal to the knee and elbow joints, facial skin and occurrence of RP which usually appeared many years prior to skin involvement. These patients are often positive for antitoxopoisometerase (ATA) antibodies.

Patients with undifferentiated SSc were defined as positive RP together with at least one further feature of SSc (typical nailfold capillary alterations, puffy fingers, pulmonary hypertension (PH) and/or detectable SSc-specific autoantibodies without fulfilling the ACR criteria for SSc.

Patients with sclerosis sine scleroderma were defined as positive RP, no skin alterations, PAH, cardiac, pulmonary and gastrointestinal involvement.

Within this study, we focused on patients suffering from lcSSc, dcSSc and SSc-overlap syndromes.

**Antinuclear autoantibodies (ANAs)**

The antibody measurement was performed in respective laboratories of the participating centres. Serum was routinely analysed in all registered SSc patients at the first visit and repeated as needed. Autoantibodies were subdivided into SSc-specific (ACA, ATA, anti-PmScl, -U1RNP -Jo1, -Ku antibodies) and SSc non-specific autoantibodies (anti-Ro and -La antibodies). Missing data were less than 10%.

**Organ involvement**

**RP** was defined by recurrent vasospasms of small digital arteries/arterioles at fingers and/or toes, usually triggered by cold environment. We defined the age of RP onset as the age, at which the RP first appeared.

The first non-RP onset of organ involvement has been considered as the timepoint of first skin or organ manifestation. The onset of skin involvement has been set as onset of SSc.

Skin involvement was evaluated using the modified Rodnan Skin Score (mRSSS), which assesses the skin hardening/thickness by manual palpation of 17 body areas on a scale of 0 to 3.

**Pulmonary manifestation** includes pulmonary interstitial fibrosis and/or isolated PH. Isolated pulmonary hypertension was defined as clinical evidence of right-heart failure and/or increased mean pulmonary arterial pressure (PAP>25 mm Hg at rest or PAP>30 mm Hg during exercise), determined by right-heart catheterisation. Echocardiography was used to identify likely PAH (estimated RVSP>40 mm Hg).

**Pulmonary interstitial fibrosis** was established when bilateral basal fibrosis occurred, confirmed by chest X-ray and/or high-resolution CT scan together with restrictive pulmonary abnormalities on pulmonary function tests (TLC <80%), were found. We defined a normal diffusing capacity of lung for carbon monoxide (DLCO) level, when it was >75%, and a low level, when it was less than 75%.

**Gastrointestinal involvement** was defined as gastrointestinal motility disturbance, dysphagia, nausea, malabsorption, oesophageal stenosis, gastro-oesophageal reflux or intestinal pseudo-obstruction.

**Kidney involvement** was defined as the presence of renal insufficiency encompassing renal insufficiency due to acute renal crisis (creatinine clearance age-related less than 80 mL/min). The diagnosis of proteinuria was fulfilled in cases of albuminuria >=30 mg/24 h or >=20 mg/L; proteinuria >=300 mg/24 h or >=200 mg/L.

**Cardiac disease** was defined by heart palpitation, conduction disturbance and/or diastolic dysfunction.

**Skeletal muscle disease** was defined as proximal muscle weakness and/or atrophy associated with elevated serum muscle enzyme (creatine phosphokinase, CK) levels and/or articulal involvement. The articulal involvement included synovitis with swelling, with or without tenderness to palpation in one or more than one joint. The questionnaire also asked for any kind of joint contractures or tendon friction rubs.
**RESULTS**

**Patient characteristics of all SSc subsets**

Between the years 2003 and 2012, a total of 3240 patients with SSc had been registered in the DNSS database. Among all registered patients, 49.3% were diagnosed as lcSSc and 30.8% with dcSSc, 10.0% with an overlap syndrome, 7.7% with undifferentiated scleroderma, 0.7% with sclerosis sine scleroderma, and 1.4% patients were categorised as others. Within all registered patients, 81.5% were female; 87.5% were positive for ANA, 33.7% had anticentromere antibodies, and 26.4% were antitopoiso- merase antibody (ATA) positive, while the remaining patients had other antibody specificities (32.5%).

Of all registered patients (first visit), 13.3% had PH, 36.5% lung fibrosis, 55.1% suffered from gastrointestinal involvement, 9.9% had kidney involvement, 12.5% suffered from heart involvement, 39.1% from musculoskeletal involvement and 37.5% from sicca symptoms.

The mean time between the onset of SSc and the first visit/registration within our database was for all SSc patients (n=2522) 7.6±0.2 years (SSc diagnosis to first visit), for lcSSc patients (n=1236) 8.3±0.2 years (SSc diagnosis to first visit), against type I error inflation due to multiple testing, only p values below 0.001 were considered statistically significant. Statistical analysis was done with PASW Statistics V18.0 (Chicago: SPSS). Missing data were less than 15% for organ manifestations and clinical signs. Missing data for autoantibodies are included within table 2 (less than 10%).

**Table 1** Frequencies and p values ($\chi^2$ test) of organ manifestations and current symptoms in patients with overlap syndromes, compared to patients with limited systemic sclerosis/diffuse cutaneous SSc (lcSSc/dcSSc)

<table>
<thead>
<tr>
<th>SSc subsets</th>
<th>Overlap s. (n=325)</th>
<th>lcSSc (n=1598)</th>
<th>dcSSc (n=997)</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>82.5</td>
<td>85.9</td>
<td>73.1</td>
<td>0.122</td>
</tr>
<tr>
<td>Male</td>
<td>17.5</td>
<td>14.1</td>
<td>26.8</td>
<td>0.039</td>
</tr>
<tr>
<td>Positive family history</td>
<td>23.1</td>
<td>15.9</td>
<td>15.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>48±1.2</td>
<td>52.8±0.5</td>
<td>48±0.6</td>
<td>0.064</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mean±SD)</td>
<td>20.2±1.2</td>
<td>17.9±0.4</td>
<td>22.4±0.7</td>
<td>0.001</td>
</tr>
<tr>
<td>DLCO (mean±SD)</td>
<td>70.5±1.5</td>
<td>73.5±0.7</td>
<td>65.3±0.9</td>
<td>0.091</td>
</tr>
<tr>
<td>Modified Rodnan Skin Score (mean±SD)</td>
<td>6.8±0.4</td>
<td>7.4±0.2</td>
<td>15.8±0.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Organ involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary hypertension</td>
<td>10.8</td>
<td>12.3</td>
<td>18.2</td>
<td>0.402</td>
</tr>
<tr>
<td>Lung fibrosis</td>
<td>35.7</td>
<td>24.9</td>
<td>61.2</td>
<td>0.0001</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>52.0</td>
<td>56.2</td>
<td>60.8</td>
<td>0.031</td>
</tr>
<tr>
<td>Kidney</td>
<td>6.8</td>
<td>8.3</td>
<td>14.3</td>
<td>0.046</td>
</tr>
<tr>
<td>Heart</td>
<td>13.8</td>
<td>9.6</td>
<td>18.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>62.5</td>
<td>32.2</td>
<td>43.3</td>
<td>0.001</td>
</tr>
<tr>
<td>Sicca symptoms</td>
<td>40.0</td>
<td>39.5</td>
<td>33.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Current clinical signs at first visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digital ulcers</td>
<td>18.2</td>
<td>23.3</td>
<td>33.3</td>
<td>0.034</td>
</tr>
<tr>
<td>Synovitis</td>
<td>22.8</td>
<td>11.8</td>
<td>14.7</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dermatogenous contractures</td>
<td>20.6</td>
<td>19.5</td>
<td>35.2</td>
<td>0.818</td>
</tr>
<tr>
<td>Tendon friction rubs</td>
<td>8.0</td>
<td>5.4</td>
<td>10.4</td>
<td>0.090</td>
</tr>
<tr>
<td>Elevated creatine phosphokinase levels</td>
<td>17.8</td>
<td>6.3</td>
<td>10.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>36.9</td>
<td>20.5</td>
<td>29.7</td>
<td>0.001</td>
</tr>
<tr>
<td>Muscle atrophy</td>
<td>19.7</td>
<td>9.3</td>
<td>17.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>51.4</td>
<td>56.9</td>
<td>60.3</td>
<td>0.308</td>
</tr>
<tr>
<td>Renal failure</td>
<td>8.3</td>
<td>10.1</td>
<td>13.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>8.0</td>
<td>6.4</td>
<td>11.0</td>
<td>0.330</td>
</tr>
</tbody>
</table>

DLCO, diffusing capacity of lung for carbon monoxide; SD, standard deviation.
for dcSSc patients (n=857) 7.3±0.3 years (SSc diagnosis to first visit), and for overlap patients (n=238) 7.1±0.5 years (SSc diagnosis to first visit).

The mean follow-up time between the SSc diagnosis and the last follow-up visit registered in the DNSS was 9.5±0.2 years for all SSc patients (n=2539), 10.1±0.2 years for lcSSc patients (n=1244), 9.2±0.3 years for dcSSc patients (n=862) and 9.6±0.6 years for SSc-overlap syndromes (n=241).

**Overlap syndromes**

Within the group of patients with overlap syndromes (n=325), 82.5% (268/325) were women and had a mean age at time of SSc onset of 48±1.2 years (n=323) (table 1); 15.4% of these patients were ACA positive, 13.2% ATA positive and 68.0% ACA positive, 15.4% ATA positive and 68.0% ANAs positive, 92.0% ANAs positive. These other antibodies consisted of anti-U1RNP (33.0%), -Ro (24.4%), -PmScl (16.7%), -La (10.9%), -Ku (3.6%), -Jo1 antibodies (4.1%) and others (6.3%) (table 2).

During follow-up, of all 325 patients, more than 92.0% maintained their initial diagnosis. Patients with SSc-overlap syndromes tended to have more often a positive family history for rheumatological disorders compared to lcSSc and dcSSc patients, and were significantly more frequently treated with corticosteroids (60.6% vs 27.3% (lcSSc) and 44.3% (dcSSc); p<0.0001) and immunosuppressive agents (58.8% vs 21.0% (lcSSc) and 41.6% (dcSSc); p<0.0001) than other SSc subsets, as published in 2009.36,37 Additionally, this specific subset also had a significantly lower mRSS compared to dcSSc patients (6.8 ±0.4 vs 15.8±0.3; p<0.0001), but a very similar mean mRSS to lcSSc patients (7.4±0.2) (table 1). Following the criteria of LeRoy for limited and diffuse extension of skin thickening, we had 76.0% of patients with a limited extension and 14.8% with a diffuse form of skin thickening. Significantly more female SSc-overlap patients had a limited skin involvement (87.8% vs 63.3%; p<0.0001), while significant more male patients suffered from a diffuse skin involvement (36.7% vs 12.2%; p<0.0001). No significant abnormalities for organ manifestations/clinical signs or antibody distribution have been found.

Interestingly, significantly less patients with overlap syndromes suffered from digital ulcers (18.2% vs 33.3%; p<0.0001) (see online supplementary table S1).

### Table 2  Detailed autoantibody status of patients with overlap syndromes, compared to patients with lcSSc/dcSSc

<table>
<thead>
<tr>
<th>Autoantibodies</th>
<th>SSc subsets</th>
<th>p Values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overlap s.</td>
<td>lcSSc (n=1598)</td>
</tr>
<tr>
<td></td>
<td>(n=325)</td>
<td>% md</td>
</tr>
<tr>
<td>ANAs positive</td>
<td>92.0 3.1</td>
<td>87.9 4.1</td>
</tr>
<tr>
<td>ACA positive</td>
<td>15.4 5.2</td>
<td>53.8 7.6</td>
</tr>
<tr>
<td>ATA positive</td>
<td>13.2 4.9</td>
<td>16.0 7.9</td>
</tr>
<tr>
<td>Other Abs</td>
<td>68.0 4.3</td>
<td>26.7 6.9</td>
</tr>
<tr>
<td>Other Abs than ACA &amp; ATA, including</td>
<td>(n=221)</td>
<td>(n=426)</td>
</tr>
<tr>
<td>PmScl</td>
<td>16.7 5.9</td>
<td>2.6 3.9</td>
</tr>
<tr>
<td>anti-U1RNP</td>
<td>33.0 5.4</td>
<td>1.9 2.3</td>
</tr>
<tr>
<td>Jo-1</td>
<td>4.1 0.5</td>
<td>23.5 7.7</td>
</tr>
<tr>
<td>Ku</td>
<td>3.6 0.5</td>
<td>14.0 4.2</td>
</tr>
<tr>
<td>Ro</td>
<td>24.4 3.5</td>
<td>27.7 4.0</td>
</tr>
<tr>
<td>La</td>
<td>10.9 1.0</td>
<td>14.2 4.3</td>
</tr>
</tbody>
</table>
| md, missing data; missing data were less than 10%. Abs, antibodies; ACA, anticentromer antibodies; ATA, antitopoisomerase antibodies; ANAs, antinuclear autoantibodies.

**Musculoskeletal involvement**

Patients with overlap syndrome developed significantly earlier and more often musculoskeletal involvement, followed by patients with diffuse and limited SSc (data shown in table 1 and figure 1A). Musculoskeletal manifestation included muscle weakness (36.9%), synovitis (22.8%), contractures (2.6%), muscle atrophy (19.7%) and elevated CK levels (17.8%).

Logistic regression analysis revealed, that overlap patients had threefold the risk of developing musculoskeletal involvement, compared to patients with lcSSc (OR 3.2; p<0.001; 95%-CI 2.5 to 4.2), and double the risk compared to dcSSc patients (OR 2.2; p<0.001; 95%-CI 1.6 to 2.9).

We also found that the course of initially elevated CK serum levels decreased substantially over time, especially in overlap and dcSSc patients (figure 3A).

In a subgroup of patients classified as overlap syndrome with myositis and CK elevation (44/325), we determined the frequency of gender distribution (70.5% women, 29.5% men), as well as clinical features; 59.1% had oesophageal involvement, 38.6% of patients had lung fibrosis, and 34.1% suffered from cardiac involvement, while less than 15.0% had kidney failure or signs for PH. Most of the patients selected for myositis and CK elevation were PmScl positive (22.7%) followed by 9.1% anti-U1RNP antibodies, 6.8% ATA antibodies and 4.5% ACA, Ku- and Jo1-antibodies.

**Cardiopulmonary involvement**

Lung fibrosis and heart involvement was diagnosed earliest in patients with dcSSc, followed by SSc-overlap and lcSSc patients (log rank test p<0.0001); patients with SSc-overlap syndromes resulted in a clear intermediate position between patients suffering from lcSSc and dcSSc (figures 1B and 2A).

Logistic regression analysis revealed that patients with overlap syndromes had a higher risk of developing lung fibrosis compared to lcSSc patients (OR 1.6; p<0.001; 95%-CI 1.2 to 2.1), and a reduced risk compared to dcSSc patients (OR 0.4; p<0.001; 95%-CI 0.3 to 0.5). They also had a lower risk of developing lung fibrosis when they had a high DLCO-level (OR 0.9; p<0.001; 95%-CI 0.9 to 1.0). The analysis of DLCO within regular follow-up visits showed no significant interaction, for example, the decrease in DLCO over time does not differ between group memberships. However, there was an overall
significant difference in DLCO between groups (p<0.001) and between the years since SSc onset (p<0.001). A posthoc test revealed additionally a significant difference between years 1 and 5, again the course of the curve of overlap patients was running between dcSSc and lcSSc patients (figure 3B).

Other organ manifestations
Disease progression, as determined by the onset of PH, oesophagus and kidney involvement of SSc-overlap patients, was similar to lcSSc patients. There was also no significant difference in patients developing gastrointestinal involvement,
depending on their subset, gender and autoantibody status (table 1 and online supplementary table S1, figure 2B).

Autoantibody status

Detailed characterisation of overlap patients depending on their autoantibody status revealed that patients with anti-U1RNP-antibodies were significantly younger at RP onset, compared with PmScl-positive patients (36.2±1.8 years vs 44.6 ±2.3 years; p<0.008) and tended to be younger at onset of skin manifestations (39.3±2.0 years vs 53.5±2.4 years). The interval between RP onset and skin onset was shortest for patients with Ku antibodies (0.7±0.7 years), followed by Jo1 (1.6±0.9 years), PmScl (2.0±0.6 years), ATA (2.1±0.8 years), Ro (5.0 ±1.3 years), La (5.2±2.5 years), anti-U1RNP (6.7±1.4 years), followed by ACA-positive patients with 11.2±2.4 years.

DISCUSSION

SSc is a heterogeneous disease and includes subsets which are characterised by the extension of skin involvement and circulating autoantibodies. For many years it has been observed, that not all SSc patients fit into the categories defined by LeRoy et al. A considerable number of patients present with symptoms and signs of SSc together with clinical features of other CTDs.5

Of the 3240 patients registered in the DNSS, 10.0% were categorised as overlap syndrome. This frequency is in agreement with other reported data, ranging between 10.0% and 38.0%.41 43 0 Our study presents one of the largest studies, characterising patients with overlap syndromes in direct comparison with the two main SSc subsets, and our data indicate that overlap patients clearly differ from lcSSc and dcSSc.

Totally, 62.5% of the overlap patients in this study had musculoskeletal manifestations, which confirms previously published data of Balbir–Gurman et al, who reported myositis in 47.5% of their 40 overlap patients, and Troyanov et al, who reported SSc-myositis overlaps in 42.6% of their cases.33 In this registry, patients with SSc/myositis, who suffered from muscle weakness together with elevated CK serum levels, 59.1% had oesophageal involvement, 38.6% of patients had lung fibrosis, 34.1% suffered from cardiac involvement, while less than 15.0% had kidney failure or signs for PH. These frequencies are lower than in the study of Balbir–Gurman who reported higher frequencies of occurrence, but the same trend in the order of frequencies; 84.2% of patients with SSc-myositis had gastrointestinal involvement, 66.4% interstitial lung disease, and 26.3% cardiomyopathy or PH. Most of the patients showing myositis and CK elevation were PmScl positive (22.7%), followed by 9.1% anti-U1RNP antibodies, 7.0% ATA antibodies and 4.5% ACA, anti-Ku and -Jo1 antibodies. Compared to these data, other groups reported a higher frequency of ATA antibodies.4 The frequency of elevated CK serum levels decreased within the course of follow-up visits over a period of 9 years, which could indicate that myositis responds to treatment.34 As expected, significantly more SSc-overlap patients have been put on immunosuppressive treatment compared to lcSSc and/or dcSSc patients, confirming previously published data.26

We found significantly more overlap patients with joint involvement compared to lcSSc and dcSSc patients (p<0.0001), but with no significant difference in the frequency of RF positivity, although the presence of RF and the association with rheumatoid arthritis of SSc patients have been previously discussed controversially.35

Regarding the onset of lung fibrosis and heart involvement, patients with SSc-overlap syndromes had an intermediate rate of disease progression in between lcSSc and dcSSc. This observation is further supported by the DLCO levels following a similar course. Overlap patients, in general, had significantly less frequent PH and kidney involvement than dcSSc patients. The direct comparison between the three major SSc subsets, using Kaplan–Meier curves, visualised that the trend of the SSc-overlap curve was clearly between the curves standing for lcSSc and dcSSc patients (figures 1 and 2).
Additionally, patients with SSc-overlap syndromes were significantly younger (48±1.2 years) than patients with lcSSc, confirming the data of Garamaschi et al (48.5±13.3 years) and developed less frequently digital ulcers, resulting in significant differences, when compared with dcSSc patients.

Furthermore, the data of this study are in good agreement with Mierau et al and Hasegawa et al, who found that anti-U1RNP antibodies were associated with a younger age of disease onset when using a multiple regression analysis. However, Koschik et al reported that in their patient cohort, patients with PmScl-antibodies were significantly younger than those without PmScl-antibodies.2,3 These patients developed most frequently musculoskeletal involvement, including muscle weakness and synovitis, but in contrast with other studies, less lung fibrosis.3,4 Our study, however, did not allow analysing, whether symptoms and signs of other rheumatic diseases appeared prior or after first SSc features, but Caramaschi et al reported, that 40.5% of their patients were diagnosed with an additional autoimmune disease prior and 38.1% after SSc diagnosis.5

In summary, we could demonstrate that patients with overlap syndromes differ from lcSSc and dcSSc regarding lung fibrosis and heart involvement, and that musculoskeletal involvement is clearly the most frequent organ manifestation in overlap patients. Although these patients appear to have a milder course of the disease with a mean mRSS similar to lcSSc patients, but less lung fibrosis and heart involvement, when compared to dcSSc patients, they progressed more rapidly with earlier and more widespread significant organ involvement than patients with lcSSc. This study demonstrates that patients with SSc-overlap, on average, carry a higher disease burden than patients with the limited form.

Based on a large cohort, this study strongly supports the idea that patients with SSc-overlap syndromes should be regarded as a separate subset of patients with SSc.

Author affiliations
1Department of Dermatology, Cologne University Hospital, Cologne, Germany
2Department of Dermatology, Medical University of Graz, Graz, Graz, Germany
3Department of Rheumatology, Asklepios Clinic Altona, Hamburg, Germany
4Department of Internal Medicine, Division of Rheumatology, University of Heidelberg, Heidelberg, Germany
5Department of Rheumatology, University of Erlangen, Erlangen, Germany
6Department of Rheumatology, University of Tuebingen, Aachen, Germany
7Department of Rheumatology, Clinic of Rheumatology Aachen, Aachen, Germany
8Department of Dermatology, University-Hospital Carl Gustav Carus, Dresden, Germany
9Department of Dermatology, Medical University of Graz, Graz, Graz, Germany
10Department of Rheumatology, University of Tuebingen, Tuebingen, Germany
11Institute of Medical Statistics, Informatics and Epidemiology, University of Cologne, Cologne, Germany
12Department of Dermatology and Venereology, University of Muenster, Muenster, Germany
13Department of Internal Medicine and Nephrology (Centre for interdisciplinary Rheumatology), Robert-Bosch-Hospital, Stuttgart, Germany
14Department of Dermatology, Helios Clinic Oberhausen, Oberhausen, Germany
15Department of Haemat-Oncology and Rheumatology, University of Heidelberg, Heidelberg, Germany
16Department of Rheumatology and Clinical Immunology, Kerckhoff Clinic, Bad Nauheim, Germany
17Clinical Research Unit for Rheumatology, University Medical Center Freiburg, Freiburg, Germany
18Department of Dermatology, Hamburg Alstertal, Hamburg, Germany
19Department of Dermatology, Ulm University Hospital, Ulm, Germany
20Department of Rheumatology and Clinical Immunology, University of Berlin, Charité, Germany
21Department of Dermatology and Allergology, Ludwig Maximilian University, Munich, Germany
22Department of Dermatology and Venereology, Ruhr University Bochum, Bochum, Germany
23Department of Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Germany
24Department of Dermatology and Venerology, University of Berlin, Charité, Berlin, Germany
25Department of Rheumatology, Johanniter-Hospital, Treuenbrietzen, Germany

Acknowledgements The work of Ebru Keser, Patricia Scholz and Gabriele Browne at the central office in keeping the Network going is gratefully acknowledged.

Collaborators Nil Mona Ahrazouglu, Department of Dermatology, Cologne University Hospital; Mike Oliver Becker, Department of Rheumatology and Clinical Immunology, University of Berlin, Charité; Rudolf Mierau, Department of Rheumatology, Clinic of Rheumatology Aachen; Gunther Neek, Medical Center for Rheumatology Bad Doberan; Christoph Fehn, Medical Center for Rheumatology, Baden-Baden; Aaron Juche, Department of Rheumatology, Immanuel Hospital Berlin-Buch; Andrea Rubbert, Department of Rheumatology, University of Cologne; Manfred Weber, Department of Internal Medicine, Hospital Cologne Merheim; Rebecca Fischer-Betz, Department of Nephrology and Rheumatology, University of Duesseldorf; Michael Sticherling, Department of Dermatology and Venereology, University of Erlangen; Harald Burkhardt, Michaels Koehm, Med. Clinic II, Department of Rheumatology, University of Frankfurt; Comelia S Selz, Claudia Henrik, Department of Dermatology, Venerology and Allergology, University of Göttingen; Ivan Foeldvari, Department of Rheumatology, Schoen Clinic, Hamburg-Eilbek; Johannes Norgauer, Department of Dermatology and Venereology, University of Jena; Dieter Schoeffel, Clinic for Rheumatology, Mannheim; Regina Renner, Mirjana Ziemer, Department of Dermatology and Venereology, University of Leipzig; Kerstin Steinbrink, Department of Dermatology and Venerology, University of Mainz; Rudolf Studler, Verena Müller, Department of Dermatology and Venerology, Johannes Welzing Hospital, Minden; Mahzad Ziai, Department of Dermatology, Munich University of Technology; Sigrid Karrer, Michael Landthalter, Department of Dermatology and Venereology, University of Regensburg; Rotraud Meyringer, Department of Internal Medicine, University of Regensburg; Michael Buslau, Clinic for Rehabilitation Rheinfeld (CH); Dirk Tomsitz; Hae- Hyuk Lee, Department of Dermatology and Venereology, University of Berlin, Charité; Percy Lehmann, Noemi Gabriel-Wissing, Helios Clinic, Department of Dermatology, Wuppertal; Marieke Wagner, Department of Rheumatology, University of Tuebingen; Joachim Ebel, Department of Rheumatology, Asklepios Clinic Altona; Christian Beyer, Department of Rheumatology, University of Erlangen; Rita Varga, Department of Dermatology and Allergology, Ludwig Maximilian University, Munich; Agnes Bretterklieber, Department of Dermatology, Medical University of Graz; Frank Reichenberger, Department of Pneumology, Asklepios Clinic Gauting, Muenchen-Gauting; Andrea Himsel, Clinic for Internal Medicine and Rheumatology, GPR MVZ Russelsheim.

Contributors PM, NH and TK have conceived and designed the study. All authors and coauthors (excluding LH and KK) were involved in data acquisition. LH and KK have made particular contribution to statistical analyses and interpretation of data. All authors contributed to the interpretation of the data and jointly approved the final manuscript.

Funding This study was supported by a grant of the German Federal Ministry of Education and Research (BMBF) (01GM0310) and a grant of the Edith-Busch-Stiftung. The work of Ebru Keser was supported by a german ‘Koeln Fortune’ and ‘Deutsche Stiftung Sklerodermie’ grant.

Competing interests None.

Patient consent Obtained.

Ethics approval Ethics Committee University of Cologne.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES