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## The European Scleroderma Trials and Research group (EUSTAR) task force for the development of revised activity criteria for systemic sclerosis: derivation and validation of a preliminarily revised EUSTAR activity index

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1 **The European Scleroderma Trials and Research group (EUSTAR) Task Force for the**  
2 **Development of Revised Activity Criteria For Systemic Sclerosis: derivation and**  
3 **validation of a preliminarily revised EUSTAR activity index**

4  
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39  
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42 Abstract 250 words, Body 3597 words, 4 Tables, 1 Figure

43  
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70 **Abstract**

71 **Background** European Scleroderma Study Group (EScSG) activity index is currently used to  
72 assess disease activity in Systemic Sclerosis (SSc). Its validity has been criticized.

73 **Methods** Three investigators assigned an activity score on a 0-10 scale for 97 clinical charts. The  
74 median score served as gold standard. Two other investigators labelled the disease as  
75 inactive/moderately active or active/very active. Univariate-multivariate linear regression analyses  
76 were used to define variables predicting the “gold standard”, their weight and derive an activity  
77 index. The cut-off point of the index best separating active-very active from inactive/moderately  
78 active disease was identified by a Receiver Operating Curve analysis. The index was validated on  
79 a second set of 60 charts assessed by three different investigators on a 0-10 scale and defined as  
80 inactive/moderately active or active/very active by other 2 investigators. One hundred and twenty-  
81 three were investigated for changes over time in the index and their relationships with those in the  
82 summed Medsger severity score.

83 **Results** A weighted 10-point activity index was identified and validated:  $\Delta$ -skin=1.5 ( $\Delta$  =patient  
84 assessed worsening during the previous month), modified Rodnan skin score $>18=1.5$ ; digital  
85 ulcers=1.5; tendon friction rubs=2.25; C reactive protein $>1\text{mg/dl}=2.25$ ; diffusing capacity of the  
86 lung for CO  $<70\%=1.0$ . A cut-off  $\geq 2.5$  was found to identify patients with active disease. Changes  
87 of the index paralleled those of Medsger’s summed severity score ( $p= 0.0001$ ).

88 **Conclusions** A preliminarily revised SSc activity index has been developed and validated,  
89 providing a valuable tool for clinical practice and observational studies.

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98 **Introduction**

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100 The assessment of patients with systemic sclerosis (SSc) should address different disease  
101 aspects: diagnosis and fulfilment of classification criteria, extent of organ involvement, activity (the  
102 reversible part of the disease process), damage (the irreversible part of the disease process),  
103 prognosis prediction, outcome, and response to treatment.[1] Defining disease activity in SSc  
104 cannot be done using a single variable and it is challenging for a number of reasons: first, patients  
105 can present with an indolent course, irrespective of whether or not they belong to either of the two  
106 disease subsets, i.e., diffuse cutaneous SSc (dcSSc) and limited cutaneous SSc (lcSSc);[2-6]  
107 second, SSc flares can be difficult to separate from quiescent disease;[1]third, the two main  
108 morphological manifestations of the disease (interstitial fibrosis and vascular occlusion) may reflect  
109 both activity and damage and finally, validated biological markers reflecting disease activity are still  
110 lacking.[7]

111 In 2001, the European Scleroderma Study Group (EScSG) in an analysis of the clinical charts  
112 of 290 patients from 19 European SSc centres, identified 11 disease activity variables and  
113 developed a preliminary activity index.[8,9] The construct validity of the index was first verified by  
114 the jackknife technique (i.e., assessing the dispersion of the correlation coefficients calculated by  
115 removing out 1 patient at a time), [10] then confirmed by calculating the correlations between the  
116 index and the rank of disease activity assigned by 4 experts to 30 charts, selected to represent  
117 different degrees of disease activity.[11]

118 This index was subsequently endorsed by EUSTAR and has been used to assess disease  
119 activity in 149 studies.[12]Its criterion validity is supported by its correlation with the physician  
120 global assessment of activity of the Canadian Scleroderma Research group (CSRG), [13] its  
121 association with anti-topoisomerase1 titre,[14] and its role as the main predictor of the  
122 scleroderma phenotype (presenting a higher procollagen transcription) of skin fibroblasts from SSc  
123 patients.[15]

124 However, it has some limitations due to the procedure underlying its development. In fact, it  
125 most patients had a long disease duration and the number of missing values was high. Moreover,

126 the face validity of hypocomplementemia has been questioned since the complement fixation is  
127 not thought to be important in SSc. [16,17]. Finally, it was not validated on an independent cohort.  
128 Here, we present the results of a EUSTAR study devoted to revise the original activity index in  
129 order to improve and validate it.

130

## 131 **Material and Methods**

### 132 *Derivation study*

133 The Study Coordinator selected 97 clinical charts from patients included in the EUSTAR  
134 database.[5]The selection was carried out in order to identify patients fulfilling the 1980 ACR  
135 criteria for the classification of SSc;[18] followed in SSc referral centres in order to reduce the  
136 number of missing values; and representing one of the following disease subgroups: early dcSSc,  
137 late dcSSc, early lcSSc, and late lcSSc. Early disease was defined a disease duration  $\leq$  3 years  
138 from the onset of the first non-Raynaud symptom.[19]

139 Three clinical investigators (YA, CD and OK-B) from centres other than those from which the  
140 patients charts were derived, assigned a disease activity score on a 0-10 scale to each chart. The  
141 reliability of this scoring system was assessed by the evaluation of the Interclass Correlation  
142 Coefficient (ICC). The median disease activity score was used as the “gold standard” to identify  
143 items significantly associated to disease activity.

144 To this aim, the study coordinator selected from the items listed in the EUSTAR chart,[5]the  
145 following 18 thought to have face validity as activity variables 1) *anamnestic*:  $\Delta$ -skin,  $\Delta$ -vascular,  $\Delta$ -  
146 heart/lung worsening (i.e. worsening, as evaluated by the patient during the month before  
147 enrolment, of skin induration, Raynaud’s phenomenon and/or digital ischemic ulcers and dyspnea  
148 and/or palpitations, respectively); 2) *clinical*: active digital ulcers; modified Rodnan skin  
149 score(mRss); tendon friction rubs(TFR); muscle weakness; arthritis; 3) *laboratory*: C-Reactive  
150 Protein (CRP) elevation; erythrocyte sedimentation rate (ESR)/h value; hypocomplementemia;  
151 creatin-kinase(CK) elevation; proteinuria; 4) *functional and imaging* : systolic Pulmonary Arterial  
152 Pressure(sPAP) and pericardial effusion at echocardiography; ground glass and lung fibrosis at

153 lung High Resolution Computed Tomography (HRCT); Forced Vital Capacity(FVC); Diffusing Lung  
154 capacity for carbon monoxide-single breath (DLCO).

155 Subsequently, we performed an univariate linear regression analysis to search for significant  
156 associations between each of the selected items and the median disease activity score given by  
157 the 3 experts. Cut-off values for sPAP, FVC and DLCO were derived from literature.[20-22]

158 The items significantly associated with gold standard in univariate analysis, were all entered in a  
159 multivariate linear regression analysis to identify the set of variables independently associated with  
160 the “gold standard”. As far as the remaining 2 continuous variables (mRss and ESR) , we made a  
161 number of attempts devoted to both identify the cut off point most significantly associated with the  
162 gold standard (highest R2; lowest p)to construct a model with the highest sum of sensitivity and  
163 specificity .Each variable found to be significantly associated in multivariate analysis was assigned  
164 a weight corresponding to beta coefficient adjusted in order to construct a 10-point weighted  
165 activity index.

166 Two other investigators (LC and GV), who were unaware of the values assigned on the 0-10 scale,  
167 evaluated each of the 97 charts as inactive (corresponding to no need to change treatment and  
168 requiring a follow-up after six months- 1 year), or moderately active (corresponding to no need to  
169 change treatment and a three-six-monthly follow-up), or active (needing treatment intensification  
170 and one-three-monthly follow-up), or very active (requiring hospitalization for active disease).The  
171 reliability of this system was assessed by the evaluation of Cohen’s K. The charts that had  
172 received a discordant evaluation by the 2 investigators were resent to them for a reassessment  
173 devoted to find an agreement.

174 For each patient the overall disease activity was calculated summing the scores of the new index.  
175 The cut-off value presenting the highest sum of sensitivity and specificity in separating patients  
176 with active-very active disease from those with inactive-moderately active condition was identified  
177 by a receiver operating (ROC) curve.

178

179 *Validation study*

180 The new index was validated on 60 patients recruited from the same database and selected in  
181 order to satisfy the following aspects: 1) fulfilling 2013 ACR/EULAR criteria for the classification of  
182 SSc;<sup>[23]</sup>2) belonging to patients recruited at SSc centres with SSc expertise in whom  
183 capillaroscopy had been performed and the pattern defined according to Cutolo et al.;<sup>[24]</sup> 3) being  
184 representative of one of the following disease subgroups, as described above: early dcSSc, late  
185 dcSSc, early lcSSc, and late lcSSc. The 60 charts were assessed for disease activity on a 0-10  
186 scale by three different investigators (PC,AH, JP) and defined as inactive, moderately active,  
187 active, and very active by other two investigators (MB and EH), all of whom unaware of the derived  
188 index. The reliability of the two scoring systems was assessed by ICC and K statistics respectively.

#### 189 *Changes of the index over time and its relationships to summed Medsger severity score*

190 In order to furtherly validate the index, we assessed the changes in the activity index detected in  
191 patients from either derivation or validation cohorts in a follow-up visit at least 6 months apart and  
192 compared it with the changes in the summed Medsger severity score<sup>[25]</sup>, that is a validated  
193 measure of disease severity in observational studies.<sup>[26]</sup> We undertook this approach by  
194 considering that severity reflects both activity and damage and its change, being damage  
195 irreversible, can only depend on changes in the activity part of the disease process.

196

## 197 **Results**

198

### 199 *Derivation study*

200

201 Table 1 lists the main epidemiological, serological and clinical features of the 97 patients  
202 considered in the derivation part of this study. All of the patients also satisfied 2013 ACR/ EULAR  
203 criteria. The ICC among the activity scores given by the three clinical experts was 0.786 indicating  
204 that either the median or the mean value could be considered consistent measures of disease  
205 activity and supporting the use of one of them as a gold standard.

206



**TABLE 1**  
**Epidemiological, serological, capillaroscopic and clinical features of the 97 SSc patients**

<b>Patients</b>	<b>Whole cohort N=97</b>	<b>Early dcSSc N=25</b>	<b>Late dcSSc N=24</b>	<b>Early lcSSc N=23</b>	<b>Late lcSSc N=25</b>
Sex (F/M)	77/20	15/10	21/3	18/5	23/2
Age (years), median; range	55 (21-89)	54 (21-70)	55 (25-75)	52 (23-89)	58 (41-75)
Disease duration ( from the first non-Raynaud's manifestation):years (median; range)	3 (0.5-47)	1 (0.5-3)	6 (3.1-18)	2 (0.5-3)	9 (4-47)
Antinuclear antibodies positive <sup>o</sup>	95 (98)	24	24	23	24
Anti-Scl-70 antibody positive <sup>oo</sup>	50 (51%)	15	14	11	10
Anti-centromere antibody positive <sup>o</sup>	17 (17%)	0	2	5	10
Anti-RNA polymerase III antibody positive <sup>oo</sup>	6 (6%)	2	3	0	1
Anti-U1RNP antibody positive <sup>oo</sup>	1 (1%)	0	0	1	0
Raynaud's phenomenon	97 (100%)	25	24	23	25
Active Digital Ulcers*	16 (16%)	4	7	2	3
Arthritis**	15 (15%)	5	4	0	6
Proximal muscle weakness***	29 (30%)	9	6	6	8
Tendon Friction Rubs(TFR)****	14 (14%)	6	3	4	1
Skin sclerosis*****	92 (95%)	25	24	20	23
Esophageal, stomach and/or intestinal involvement <sup>^</sup>	66 (68%)	16	15	15	20
Interstitial lung disease (CT) <sup>^^</sup>	53/89 (59%)	13/25	17/24	10/18	13/22
FVC <sup>^^^</sup> , % of the predicted value (mean±SD)	87.5±18.9	89.4±17.3	78.7±20.0	90.8±12.8	91.0±22.3
DLCO <sup>^^^^</sup> , % of the predicted value(mean±SD)	65.7±21.5	65.9±20.1	56.5±19.9	69.9±16.4	70.6±26.3
Estimated systolic pulmonary artery pressure (sPAP)>30 mmHg <sup>^^^^</sup>	22 (23%)	4	5	6	7
Heart disease <sup>^^^^</sup>	45 (46%)	9	14	7	15
Scleroderma renal crisis (previous) <sup>o</sup>	3 (3%)	2	1	0	0

209  
210 <sup>o</sup> By IF on Hep-2 cells; <sup>oo</sup> By ELISA on ANA positive sera; \* ranging from small infarcts of the  
211 digital tips to digital gangrene; \*\* symmetric swelling and tenderness of the peripheral joints; \*\*\* as  
212 detected at physical examination; \*\*\*\* perception of leathery crepitus during motion of hands,  
213 wrists, elbows, shoulders, knees, ankles (both at anterior and posterior aspects) \*\*\*\*\* thickening and  
214 induration of the skin as detected by physical examination; <sup>^</sup>dysphagia and/or heartburn and/or  
215 bloating and/or vomiting and/or diarrhea and/or constipation; <sup>^^</sup>either ground glass or interstitial  
216 fibrosis as detected at lung high resolution computed tomography; <sup>^^^</sup> Forced vital capacity  
217 <sup>^^^^</sup>diffusing lung for Carbon monoxide (single breath), <sup>^^^^</sup>as assessed by B-MODE Doppler  
218 echocardiography; <sup>^^^^</sup> diastolic dysfunction and/or cardiac blocks and/or palpitations and/or left  
219 ventricular Ejection Fraction < 55% as assessed by EKG and B-MODE Doppler echocardiography,  
220 <sup>o</sup>rapidly deteriorating kidney failure with or without accelerated/malignant hypertension..  
221 -----

222 Table 2 lists the items, out of the 19 selected, that resulted to be associated to the median value of  
223 the three 0-10 scores, in univariate linear regression analysis.

224 **TABLE 2**

225  
226

**Associations between each potential activity parameter and the gold standard  
in Univariate Regression Analysis**

Item	R <sup>2*</sup>	P
ESR	0.441	<b>0.0001</b>
Digital ulcers	0.294	<b>0.0001</b>
CRP> 1 mg/dl	0.256	<b>0.0001</b>
mRss	0.238	<b>0.0001</b>
Δ-skin worsened	0.180	<b>0.0001</b>
Δ- vascular worsened	0.164	<b>0.0001</b>
Δ-heart/lung worsened	0.160	<b>0.0001</b>
CK elevation	0.127	<b>0.0003</b>
TFR	0.126	<b>0.0004</b>
FVC<80 % of predicted	0.114	<b>0.0007</b>
Muscle weakness	0.094	<b>0.002</b>
DLCO<70% of predicted	0.085	<b>0.003</b>
Dyspnea and/or palpitations	0.057	<b>0.017</b>
sPAP>30 mmHg	0.052	<b>0.023</b>
Arthritis	0.029	0.094
Lung fibrosis at lung HRCT	0.017	0.223
Hypocomplementemia	0.005	0.478
Ground glass at lung HRCT	0.0005	0.835

227 \*R-squared coefficient ;ESR. erythrocyte sedimentation rate;CRP. C-reactive protein; mRss.  
228 modified Rodnan skin score; CK. creatin kinase; TFR. tendon friction rubs; FVC. forced vital  
229 capacity; DLCO. diffusing lung for Carbon monoxide (single breath), HRCT. high resolution  
230 computed tomography;

231

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232 It is notable that no finding detected at high resolution computed tomography of the lung was  
233 associated to the gold standard. However, the extent of lung involvement is not defined in the  
234 EUSTAR chart.

235 With single exceptions (e.g. tendon friction rubs for lcSSc), the same items were also associated  
236 with the gold standard in each of the 2 subsets as well as in early and late disease (data not  
237 shown).After a number of attempts, we identified a mRss> 18 and a ESR > 50 mm/h as the cut off  
238 points most significantly associated with the gold standard (highest R2; lowest p), i.e. the value  
239 corresponding to the highest association of the variable in univariate analysis. These values were  
240 entered in multivariate analysis along with the other items resulted to be associated with the gold  
241 standard.

242 Table 3 lists the items resulted to be associated to the gold standard in multiple regression analysis  
 243 and the respective weight that was assigned depending on the  $\beta$  values of the regression model, in  
 244 order to construct a 10-point index.

245 **Table 3**  
 246 **Items found to be associated with the activity gold standard in multiple linear regression**  
 247 **analysis and the resulting 2016 preliminary activity index**

Items	beta regression coefficient (SE)	p	Weight
<b><math>\Delta</math>-skin</b>	1.00 (0.313)	0.001	1.5
<b>Digital ulcers</b>	1.078 (0.373)	0.004	1.5
<b>Modified Rodnan skin score &gt; 18</b>	1.040 (0.319)	0.001	1.5
<b>Tendon friction rubs</b>	1.408 (0.317)	0.0001	2.25
<b>C-reactive protein &gt; 1 mg/dl</b>	1.401 (0.285)	0.0001	2.25
<b>DLCO &lt; 70% of the predicted value</b>	0.527 (0.259)	0.044	1.0

248  
 249 **SE.** standard error; **DLCO.** Diffusing lung capacity for carbon monoxide  
 250

251 Since amRss lower than 18 can also reflect active disease, in the final index we considered a  
 252 formulain which the highest possible value that was associated with the cut off point found to be  
 253 most significantly associated with the gold standard. In detail, each mRss score lower than 18 can  
 254 contribute to the overall activity score according to the following formula: mRss score x 0.084.

255 **TABLE 4**  
 256 **REVISED EUSTAR INDEX**

ITEM	WEIGHT
<b><math>\Delta</math>-skin</b>	<b>1.5</b>
<b>Digital ulcers</b>	<b>1.5</b>
<b>Modified Rodnan skin score &gt; 18</b> <b>or for</b> <b>Modified Rodnan skin score up to 18</b>	<b>1.5</b>
<b>Tendon friction rubs</b>	<b>2.25</b>
<b>C-reactive protein &gt; 1 mg/dl</b>	<b>2.25</b>
<b>DLCO &lt; 70% of the predicted value</b>	<b>1.0</b>

257  
 258 The assessment of disease activity on the Likert scale was the same (i.e. either  
 259 inactive/moderately active or active/very active) in 91 patients; differed in 6 (Cohen's K=0.851). In

260 these 6 patients an agreement was reached after a re-evaluation of each chart that had given a  
261 discrepant evaluation. Out of the 97 SSc patients, 57 were considered to be inactive to moderately  
262 active; 40 active to very active.

263 Figure 1 shows the ROC curve exploring the best cut off value discriminating between  
264 inactive-moderately active disease (no treatment change needed) and active-very active disease.  
265 A value  $\geq 2.5$  resulted to have the maximal sum of sensitivity ( 80.0% ;95%CI 64.4-90.9) and  
266 specificity (91.2%;95%CI 80.7-97.1) and was used to validate the index in the validation cohort

### 267 *Validation*

268 Table 5 shows the epidemiological, serological, capillaroscopic and clinical features of the  
269 additional set of 60 patients selected for the validation cohort. Out of the 60 patients,47 also  
270 satisfied 1980 ACR criteria for the classification of the disease.

271 The scores given by the three raters were significantly correlated (ICC=0.749). Moreover, their  
272 median values were significantly correlated to the respective calculated indices (Rho=0.772,  
273 95%CI 0.644-0.857;  $p < 0.0001$ ).The early capillaroscopic pattern was associated with the gold  
274 standard ( $R^2=0.07$ ;  $p=0.029$ ). Nevertheless, adding it to the other items ( $\Delta$ -skin; digital ulcers;  
275 modified Rodnan skin score  $>18$ ; tendon friction rubs; C-reactive protein  $>1$  mg/dl; DLCO  $< 70\%$  of  
276 the predicted value) in multivariate regression analysis, did not improve the performance of the  
277 index

278 The evaluations on the Likert scale were consistent (i.e. either inactive/moderately active or  
279 active/very active) in 46 patients; differed in 14 (Cohen's K=0.525). In these 14 patients an  
280 agreement was reached. Out of the 60 patients, 37 were considered to be inactive to moderately  
281 active, 23 active to very active. An index  $\geq 2.5$  identified active/very active disease as defined by  
282 MB and EH with a 73.9% (95%CI 51.6-89.8) sensitivity and 78.3% (95%CI 61.8-90.2)  
283 specificity.Performing the validation process in the 47 patients also satisfying 1980 classification  
284 criteria, gave very similar results. In this cohort, a EScSG activity index  $\geq 3$  identified active disease  
285 with a 52.2% sensitivity and 89.1% specificity.

286

287  
288  
289

**TABLE 5**  
**Epidemiological, serological, capillaroscopic and clinical features of the 60SSc patients**  
**analyzed in the validation cohort**

<b>Patients</b>	<b>Whole series n=60</b>	<b>Early dcSSc n=16</b>	<b>Late dcSSc n=14</b>	<b>Early lcSSc n=16</b>	<b>Late lcSSc n=14</b>
Sex (F/M)	50/10	12/4	13/1	15/1	10/4
Age (years), median; range	56 (24-81)	51.5 (24-75)	59.5 (33-68)	56 (25-80)	58 (44-81)
Disease duration from 1 <sup>st</sup> non-Raynaud manifestation (years), median; range	2 (0-35)	1.5 (0-3)	13.5 (4-35)	1 (0-2)	8.5 (4-35)
Antinuclear antibodies positive	58 (97%)	15	13	16	14
Anti-Scl-70 antibody positive	24 (40%)	8	8	5	3
Anti-centromere antibody positive	15 (25%)	0	2	6	7
Anti-RNA polymerase I-III antibody positive	9/56 (16%)	3/13	3/13	2	1
Anti-U1RNP antibody positive	1/55 (2%)	0/13	0/12	0/16	1
Scleroderma pattern on nailfold capillaroscopy					
Early	13	1	1	6	5
Active	23	9	3	5	6
Late	19	3	8	5	3
Raynauds' phenomenon	59 (98%)	16	14	15	14
Active Digital Ulcers	14 (23%)	4	5	3	2
Arthritis	13 (21%)	3	2	4	4
Proximal muscle weakness	6 (10%)	1	3	1	1
Tendon Friction Rubs (TFR)	4 (7%)	2	1	1	0
Skin fibrosis	51 (85%)	16	13	11	11
Esophageal, stomach and/or intestinal involvement	40 (67%)	12	11	11	6
Interstitial lung disease ( CT)	38/55 (69%)	10/14	9/12	6	6/13
Estimated sPAP>30 mmHg	9/52 (17%)	3/12	1/13	4/13	1
Heart disease	26 (43%)	4	7	8	7
Scleroderma renal crisis (previous)	1 (2%)	0	0	0	1

290

291 *CT. computed tomography. sPAP. systolic pulmonary arterial pressure*

292

293 *Changes of the index over time and its relationships to summed Medsger severity score*

294 A follow-up visit made after 6-38 months (median 13) was available in 123 out of the 157 patients  
295 from either derivation and validation cohorts. The calculated index unchanged in 36 patients,  
296 decreased in 59, increased in 28. The changes in the activity index resulted to be significantly  
297 correlated to those in the Medsger severity score in the 123 patients with a follow-up visit (Rho=  
298 0.330; 95%CI 0.162-0.479, p=0.0002), pointing out a significant relationship between the index and

299 the course of disease severity. In particular, at baseline, 43 out of the 123 patients had an activity  
300 index  $\geq 2.5$ . Twenty-two resulted to have an activity index  $< 2.5$  at the end of follow-up; out of  
301 them, 18 experienced a decrease ( $\geq 1$  point), 4 a stable severity score. On the other hand, among  
302 the remaining 80 patients with a baseline activity index  $< 2.5$ , 8 resulted to develop an activity  
303 index  $\geq 2.5$  at the end of follow-up; out of them, 5 experienced an increase ( $\geq 1$  point), 3 a stable  
304 severity score.

305

## 306 **Discussion**

307 Using the multinational EUSTAR database, we have identified a preliminarily revised set of  
308 weighted items correlated to disease activity in patients with SSc. The 2001 EScSG study [8, 9]  
309 was based on the analysis of 290 patients, most of whom with longstanding disease and was  
310 affected by a high number of missing values ensuing in a low number of patients evaluable for  
311 most items. In order to overcome these limitations, we only relied on charts from centres with a  
312 large and scientifically supported expertise and included a high proportion of patients with early  
313 disease.

314 The 97 patients selected for the derivation cohort present some aspects that deserve to be  
315 discussed. First, 21 out the 48 patients with lcSSc were anti-Scl-70 positive. Differences in the  
316 prevalence of anti-Scl-70 positivity among patients from different geographical regions have long  
317 been known: 29% of French patients with lcSSc vs 15% of American patients. [27]. Since all our  
318 patients came from European centres, this is an expected result. Secondly, 2 dcSSc patients were  
319 anticentromere antibody positive. However, this figure does not differ from the 5% prevalence of  
320 ACA in dcSSc reported by Steen et al. [28]. Thirdly, 5 lcSSc patients presented tendon friction rubs.  
321 Again, tendon friction rubs have been detected in 5% of lcSSc patients supporting the absence of  
322 any derived generalizability issues. [29]

323 The revised EUSTAR activity index differs from the original EScSG index in several aspects.  
324 Hypocomplementemia and arthritis were not associated with disease activity in the present study,  
325 even in univariate analysis. The role of hypocomplementemia in assessing SSc activity has been

326 largely debated. [16,17] Hudson et al. [30] investigated 321 patients from the Canadian  
327 Scleroderma Research Group Registry, and found that hypocomplementemia was significantly  
328 associated with inflammatory myositis and vasculitis, and concluded that it may identify a subgroup  
329 of SSc patients who have overlap disease. These data suggest that some patients enrolled in the  
330 EScSG study [31] were affected by SSc (all of them satisfied the 1980 ACR criteria)[18] in overlap  
331 with other autoimmune systemic rheumatic diseases. This aspect might also justify the exclusion of  
332 arthritis.

333 The revised EUSTAR index contains tendon friction rubs and increased serum CRP. Tendon  
334 friction rubs were associated with diffuse and reduced survival in 1301 SSc patients.[32] This item  
335 was predictive of worsening of skin fibrosis and scleroderma renal crisis in the EUSTAR cohort.[32]  
336 CRP levels were increased in early disease and were associated with activity, skin, lung, kidney  
337 disease and poor survival in 1043 SSc patients from the CSRG Registry.[33]

338 Similarly to the EScSG activity index, the revised EUSTAR index contains mRSS, digital  
339 ulcers, and DLCO. mRSS reflects the degree of skin sclerosis and has long been considered a  
340 measure of disease activity in SSc. [34] One could argue that a decreasing mRss (e.g. from 24 to  
341 18) might represent a reduced disease activity. Nevertheless, the persistence of defined skin  
342 sclerosis is not consistent with inactive disease. Digital ulcers are clearly related to vascular  
343 disease activity and have been recently found to predict the occurrence of new digital ulcers during  
344 follow-up and to be associated with cardiovascular morbidity and decreased survival.[35] A  
345 decreased DLCO can depend on both vascular and interstitial lung disease. In the absence of  
346 pulmonary hypertension, however, it has been found to provide the best overall estimate of HRCT-  
347 measured lung fibrosis. [36]

348 Similarly to the EScSG activity index, the revised EUSTAR index contains  $\Delta$ -factors (namely  $\Delta$ -  
349 skin).  $\Delta$ -items had been criticized because they can fail to capture persistent activity and are  
350 influenced by depression.[16] Recently, however, patient assessment has been reported to be  
351 significantly correlated to mRSS, the Short Form 36 health survey physical component and skin  
352 involvement in the last month. [37] In any case, the present index is less influenced by  $\Delta$  items,  
353 which represented 45% of the 2001 index with respect to the 15% of the present one.

354 In the present study, three patients of the derivation cohort and 1 of the validation cohort had  
355 previously presented with scleroderma renal crisis, preventing the use of the revised EUSTAR  
356 activity index in that context.

357 Following the publication of the EScSG activity criteria, several attempts have been made to  
358 identify a set of criteria with an improved performance. Diaconu et al. [38] asked 6 SSc experts to  
359 evaluate 40 charts completed by clinical investigators from Nijmegen; 20 patients had early  
360 disease, not yet satisfying 1980 ACR classification criteria [18] and 20 had established disease.  
361 They derived an eight-unweighted item index (scleroderma, mRSS, fatigue, exertional dyspnoea,  
362 DLCO, musculoskeletal symptoms, ESR and digital ulcers), performing similarly to the EScSG  
363 activity index [9] in patients with either early or late disease. Furthermore, Minier et al. [39]  
364 identified two activity indexes (a 12-point extended index including  $\Delta$  variables and a simplified 8.5-  
365 point devoid of them) by investigating 131 consecutive patients at enrolment and 1 year later.  
366 These patients were assessed using a standardised protocol including high-resolution computed  
367 tomography of the lung and echocardiography. The authors confirmed the good construct validity  
368 of the original EScSG activity index and found a very good correlation both at baseline and after 1  
369 year between both the extended and the simplified score and the original EScSG activity.

370 The SSc activity reported herein represents a step forward with respect to the EScSG activity  
371 index.[9]. First of all, unlike the EScSG activity index, it was validated on an independent  
372 cohort..Moreover, , the lower number and value of  $\Delta$ -factors as well as the exclusion of disputable  
373 items like hypocomplementemia give it a greater face validity. In addition, , the greater sensitivity  
374 detected in the validation cohort make it valuable in better characterising the series investigated  
375 in observational studies.Finally, the revised EUSTAR activity index was found to parallel Medsger  
376 severity score over time.

377 Our study has some limitations.

378 First, the evaluation of predefined EUSTAR charts did not allow to capture either the extent of  
379 lung involvement, which has been found to be related to disease activity [40] or any change in  
380 laboratory, physical or physiologic or radiological parameter, preventing any consideration of the  
381 changes of parameters like FVC/DLCO,  $\Delta$ -fibrosis at lung HRCT or acute phase reactants. This



382 aspect can have prevented the inclusion of these items. In that regard, however, one should  
383 consider the possible unavailability of some previous values and the need to assess disease  
384 activity at the first patient visit. Secondly, no relevant biomarker was investigated. This limitation  
385 could be approached in the future by a collaborative multicentre study including the assessment of  
386 parameters not included in the EUSTAR chart..Finally, the lower specificity with respect to the  
387 EScSG activity index in the validation cohort requires a careful evaluation in the clinical setting e.g.  
388 the patient with a respiratory infection presenting high CRP and low DLCO, who would be  
389 considered active according to the index, but is suffering from an unrelated condition..

390 In conclusion, the revised EUSTAR activity index is feasible, presents face, construct and  
391 content validity and represents a step forward to the so far widely used EScSG activity  
392 index.Future collaborative, prospective studies are needed to further improve its performance.

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#### 400 **Contributors**

401 **Design of the study:** GV, YA; **Acquisition of data:** GV, MI, UW, VKJ, PC, LC, CD, OD, EH, AH,  
402 OKB, JP, UML, GR, JA, MF, SJ, TM, ES, VO, SV, YA. **Data interpretation and analysis:** GV, MI,  
403 UW, VKJ, MB, PC, LC, CD, OD, EH, AH, OKB, JP, UML, GR, YA. **Drafting and revisiting the**  
404 **manuscript:**GV, MI, UW, VKJ, PC, LC, CD, OD, EH, AH, OKB, JP, UML, GR, YA. **Final approval**  
405 **of the manuscript:** GV, MI, UW, VKJ, MB, PC, LC, CD, OD, EH, AH, OKB, JP, UML, GR, JA, MF,  
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#### 407 **Competing interests**

408 GVhas received research funding in the area of systemic sclerosis from Abbvie, Actelion, Bayer,  
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416 Pfizer, Serodapharm, Sinoxa, Ergonex, Pharmacyclics, Sanofi. In addition, OD has a patent mir-29  
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421

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**Figure Legends.**

**Figure 1.** Receiver Operating Curve showing the relation between the value of the calculated 2016 EUSTAR activity index and the presence of active disease in the derivation cohort.

To be deleted

**Figure 2.** Receiver Operating Curve showing the relation between a EScSG activity index  $\geq 3$  and the presence of active disease.