

SUPPLEMENTARY DATA

Table S1. Overview on baseline characteristics and missing data of the EUSTAR database up to October 2017

Variable	Whole cohort n (%)	Whole cohort missing value n (%)	Included patients missing value n (%)
mRSS >14	640 (4)	2428 (16)	23 (4)
Anti Scl70 positive	4005 (27)	2667 (18)	20 (3)
Tendon friction rubs	924 (6)	383 (2)	1(0.1)
Proteinuria	690 (4)	1322 (8)	26 (4)
Anti-RNA polymerase III positive	238 (1)	9113 (61)	218 (39)
Hypocomplementemia	525 (3)	2628 (17)	22 (4)
DLCO<70%	5394 (36)	805 (5)	38 (6)
Digital ulcers	1746 (11)	1766 (11)	22 (4)
Scleredema	5386 (36)	4903 (33)	16 (2)
CRP elevation	679 (4)	4623 (31)	109 (19)
ESR>25mm/1h	2815 (19)	5491 (37)	116 (21)
LVEF <45%	122 (0.8)	6788 (46)	147 (26)
Lung fibrosis on x-ray	3419 (23)	2305 (15)	49 (8)

Abbreviations: mRSS: modified Rodnan skin score; DLCO: diffusion capacity of the lung for carbon monoxide; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate

Calculation of the adjusted mean European Scleroderma Group activity index (EScSG) and European Scleroderma Trials and Research Group Activity Index (EUSTAR)

The 'adjusted mean' is equivalent to the area under the curve of activity over time. In particular, we:

- (1) Calculate the area under the curve between each visits, that is the length of time between visits multiplied by the average of the two values;
- (2) add up all the calculated areas;
- (3) divide the result by the total length of the time period.

The formula is:

$$\frac{\sum_{i=2}^n \left(\frac{X_i + X_{i-1}}{2} \right) t_i}{\sum_{i=2}^n t_i}$$

X_i is the index value at Visit i , X the average activity index values in a given time interval, t_i is the length of time between visits i and $i-1$, i is the mean time, and n is the number of visits in the interval.

Table S2. Odds ratio and p-values for severity accrual over 2 years at univariable logistic regression analysis

Features	OR (IC 95%)	Organ/ system severity accrual	p- value
Adj mean EUSTAR- AI	1,43 (1,23-1,66)	Δ Medsger's severity score ≥ 1	<0,0001
Adj mean ESSCG -AI	1,41 (1,20-1,67)		<0,0001
Diffuse subset	1,46 (1,01-2,10)		0,04
Anti-Scl70 Ab positivity	1,72 (1,20-2,47)		0,003
ESR>25 mm/h	1,58 (1,01-2,51)		0,04
Age	1,01 (1,00-1,02)		0,01
Male gender	1,19 (0,77 - 1,83)		0,43
Tendon friction rubs	1,12 (0,60- 2,08)		0,70
Anti-RNA polymerase III Ab	2,25 (0,56- 8,92)		0,24
Presence of urine protein	0,58 (0,27-1,23)		0,15
Hb<12	1,30 (0,21- 7,88)		0,76
Baseline GI severity	0,75 (0,53 - 1,07)		0,12
Baseline vascular severity	0,94 (0,65-1,35)		0,74
Baseline skin severity	1,24 (0,78 -1,97)		0,34
Baseline joint severity	0,76 (0,49-1,17)		0,22
Baseline general severity	3,35 (0,68- 16,53)		0,13
Baseline heart severity	1,41 (0,78 - 2,56)		0,24
Baseline lung severity	1,01 (0,70-1,46)		0,94
Baseline muscle severity	0,77 (0,50-1,20)		0,26
Baseline renal severity	2,83 (0,74-10,76)		0,12
Adj mean EUSTAR-AI	1,12 (1,01- 1,25)	Δ Lung severity score ≥ 1	<0,0001
Adj mean ESSCG -AI	1,15(0,96-1,38)		0,11
Diffuse subset	0,63 (0,27-1,49)		0,30
Anti-Scl70 Ab positivity	1,30 (0,16-10,14)		0,79
ESR>25 mm/h	0,25 (0,01-3,58)		0,30
Age	0,98 (0,95-1,01)		0,24
Male gender	0,42 (0,12-1,51)		0,18
Tendon friction rubs	0,83 (0,16 - 4,14)		0,82
Anti-RNA polymerase III Ab	2,67 (0,58- 12,26)		0,20
Presence of urine protein	0,45 (0,13- 0,52)		0,20
Hb<12	3,32 (0,34-31,65)		0,29
Baseline GI severity	0,86 (0,15- 4,76)		0,86
Baseline heart severity	1,87 (0,99- 3,51)		0,05
Baseline vascular severity	1,88 (0,99 - 3,51)		0,48
Baseline skin severity	1,15 (0,76-1,75)		0,48
Baseline joint severity	1,20 (0,71 -2,03)		0,33
Baseline general severity	0,77 (0,45-1,30)		0,20
Baseline lung severity	2,42 (0,61- 9,52)		0,23
Baseline muscle severity	0,75 (0,48- 1,18)		0,43
Baseline renal severity	1,22 (0,73-2,01)		0,25
Adj mean EUSTAR -AI	1,38(1,15- 1,67)	Δ Heart severity score ≥ 1	0,0006
Adj mean ESSCG -AI	1,42 (1,11 - 1,83)		0,005
Age	1,02 (1,01-1,05)		0,02
Baseline lung severity	2,95 (1,27-6,83)		0,002
Diffuse subset	1,24 (0,60-2,57)		0,01
Anti-Scl70 Ab positivity	2,42 (0,97-5,98)		0,55
ESR>25 mm/h	8,06 (0,46-140,01)		0,15
Male gender	1,72 (0,11-25,02)		0,69
Tendon friction rubs	4,02 (0,94-17,18)		0,06
Anti-RNA polymerase III Ab	3,13 (0,55-17,64)		0,19
Presence of urine protein	0,90 (0,20-3,96)		0,86
Hb<12	0,76 (0,03-18,80)		0,86
Baseline GI severity	4,72 (0,23-94,48)		0,30
Baseline heart severity	0,19 (0,02-1,46)		0,11
Baseline vascular severity	2,13 (0,96-4,69)		0,05
Baseline skin severity	1,57 (0,57-4,34)		0,37
Baseline joint severity	2,13 (1,03-4,42)		0,04
Baseline general severity	1,51 (0,16-13,83)		0,71
Baseline muscle severity	1,91 (0,90-4,04)		0,08

Baseline renal severity	0,87 (0,10-7,23)		0,90
Adj mean EUSTAR-AI	1,44 (1,23-1,71)	Δ Skin severity score ≥ 1	0,0002
Adj mean ESSCG -AI	1,40 (1,08-1,80)		0,02
Age	0,97 (0,95- 0,99)		0,0002
Baseline skin severity	0,36 (0,18- 0, 73)		0,0004
Diffuse subset	-		0,99
Anti-Scl70 Ab positivity	2,03 (0,75-5,50)		0,15
ESR>25 mm/h	0,83 (0,34- 2,04)		0,69
Male gender	2,04 (0,93-4,47)		0,07
Tendon friction rubs	1,14 (0,31-4,10)		0,84
Anti-RNA polymerase III Ab	1,43 (0,17-12,01)		0,74
Presence of urine protein	0,90 (0,20-3,96)		0,89
Hb<12	12,46 (0,92-168,18)		0,05
Baseline GI severity	1,10 (0,55-2,20)		0,78
Baseline heart severity	0,46 (0,10-2,00)		0,30
Baseline vascular severity	1,86(0,88-3,91)		0,09
Baseline joint severity	1,18(0,53-2,64)		0,67
Baseline general severity	3,91 (0,77-19,84)		0,09
Baseline lung severity	0,98 (0,49-1,97)		0,97
Baseline muscle severity	0,70 (0,28-1,78)		0,46
Baseline renal severity	2,51 (0,32-19,72)		0,37
Adj mean EUSTAR-AI	1,32 (1,18- 1,47)	Δ Peripheral Vascular severity score ≥ 1	<0,0001
Adj mean ESSCG -AI	1,32 (1,09- 1,60)		0,004
AntiScl70 positivity	1,55 (1,07-2,25)		0,019
Diffuse subset	2,24 (1,54-3,25)		0,001
Age	0,99 (0,97-1,01)		0,51
ESR>25 mm/h	1,04(0,56-1,95)		0,88
Male gender	1,05 (0,55-2,00)		0,87
Tendon friction rubs	0,95 (0,35-2,60)		0,93
Anti-RNA polymerase III Ab	1,53 (0,31-7,60)		0,59
Presence of urine protein	0,18 (0,02-1,40)		0,10
Hb<12	-		0,99
Baseline GI severity	1,03 (0,14- 7,22)		0,97
Baseline skin severity	1,30 (0,62-2,71)		0,47
Baseline heart severity	1,30 (0,59-2,87)		0,50
Baseline vascular severity	0,30 (0,18-0,50)		<0,0001
Baseline joint severity	1,04 (0,57-1,90)		0,89
Baseline muscle severity	0,86 (0,46- 1,62)		0,64
Baseline general severity	-		0,99
Baseline lung severity	2,26 (1,30-3,95)		0,003
Baseline renal severity	2,45 (0,71-8,41)		0,15
Adj mean EUSTAR-AI	1,13 (0,78-1,64)	Δ Muscle severity score ≥ 1	0,50
Adj mean ESSCG -AI	1,18 (0,76-1,84)		0,44
AntiScl70 positivity	0,94 (0,40-2,18)		0,89
Diffuse subset	0,41 (0,14-1,14)		0,08
Age	1,00 (0,97-1,03)		0,57
ESR>25 mm/h	1,01 (0,41-2,49)		0,97
Male gender	0,29 (0,06-1,26)		0,10
Tendon friction rubs	1,08 (0,11-10,07)		0,94
Anti-RNA polymerase III Ab	7,67 (1,37-42,99)		0,02
Presence of urine protein	0,53 (0,07-4,04)		0,54
Hb<12	-		0,99
Baseline GI severity	1,28 (0,59-2,79)		0,52
Baseline skin severity	0,94 (0,35-2,49)		0,84
Baseline heart severity	0,62 (0,14-2,75)		0,55
Baseline vascular severity	1,25 (0,56-2,79)		0,41
Baseline joint severity	0,79 (0,28-2,20)		0,38
Baseline muscle severity	-		0,99
Baseline general severity	-		0,99
Baseline lung severity	1,27(0,58-2,76)		0,54
Baseline renal severity	-		0,99
Adj mean EUSTAR-AI	0,83 (0,14- 4,86)	Δ Kidney severity score ≥ 1	0,83
Adj mean ESSCG -AI	1,56(0,19-12,66)		0,67
AntiScl70 positivity	-		0,99
Diffuse subset	-		0,99
Age	1,02 (0,87-1,19)		0,76
ESR>25 mm/h	-		0,99

Male gender	-		0,99
Tendon friction rubs	-		0,99
Anti-RNA polymerase III Ab	-		0,99
Presence of urine protein	-		0,99
Hb<12	-		0,99
Baseline GI severity	-		0,99
Baseline skin severity	0,54 (0,10-2,90)		0,47
Baseline heart severity	3,89 (1,07-14,05)		0,03
Baseline vascular severity	0,72 (0,21-2,44)		0,59
Baseline joint severity	7,29 (2,01-26,33)		0,02
Baseline muscle severity	0,68 (0,14-3,21)		0,62
Baseline general severity	-		0,99
Baseline lung severity	6,43 (0,81-50,70)		0,07
Baseline renal severity	3,28 (0,38-28,32)		0,27
Adj mean EUSTAR-AI	1,11 (0,31-3,95)	Δ GI tract severity score ≥ 1	0,86
Adj mean ESSCG -AI	0,92 (0,17-4,75)		0,92
AntiScl70 positivity	-		0,99
Diffuse subset	-		0,99
Age	1,14 (0,92-1,42)		0,22
ESR>25 mm/h	3,58 (0,21-59,10)		0,37
Male gender	-		0,99
Tendon friction rubs	-		0,99
Anti-RNA polymerase III Ab	-		0,99
Presence of urine protein	-		0,99
Hb<12	-		0,99
Baseline GI severity	0,60 (0,03-9,94)		0,72
Baseline skin severity	-		0,99
Baseline heart severity	5,06 (1,46-17,47)		0,01
Baseline vascular severity	0,80 (0,24-2,59)		0,71
Baseline joint severity	-		0,99
Baseline muscle severity	-		0,99
Baseline general severity	15,13 (0,84-270,04)		0,06
Baseline lung severity	0,60 (0,03-10,71)		0,73
Baseline renal severity	-		0,99
Adj mean EUSTAR-AI	1,05 (0,81-1,37)	Δ Joint/tendon severity score ≥ 1	0,66
Adj mean ESSCG -AI	1,01 (0,72-1,42)		0,92
AntiScl70 positivity	1,99 (0,97-4,08)		0,05
Diffuse subset	2,44 (1,28-4,66)		0,006
Age	1,00 (0,98-1,03)		0,43
ESR>25 mm/h	0,55 (0,24-1,26)		0,16
Male gender	1,26 (0,43-3,66)		0,66
Tendon friction rubs	1,80 (0,45-7,21)		0,40
Anti-RNA polymerase III Ab	3,17 (0,73-13,68)		0,12
Presence of urine protein	-		0,99
Hb<12	0,87 (0,08-8,99)		0,90
Baseline GI severity	1,31 (0,20-8,29)		0,77
Baseline skin severity	3,72 (1,42-9,75)		0,007
Baseline heart severity	0,85 (0,31-2,35)		0,76
Baseline vascular severity	1,50 (0,82-2,74)		0,17
Baseline joint severity	-		0,99
Baseline muscle severity	1,50 (0,78-2,89)		0,22
Baseline general severity	0,97 (0,11-8,02)		0,98
Baseline lung severity	0,69 (0,39-1,22)		0,20
Baseline renal severity	0,81 (0,10-6,51)		0,84
Adj mean EUSTAR-AI	1,11(0,79-1,56)	Δ General severity score ≥ 1	0,51
Adj mean ESSCG -AI	1,04 (0,67-1,62)		0,84
AntiScl70 positivity	1,49 (0,62-3,56)		0,36
Diffuse subset	0,99 (0,42-2,33)		0,98
Age	1,05 (1,02-1,08)		0,0009
ESR>25 mm/h	0,97 (0,37-2,51)		0,95
Male gender	1,54 (0,62-3,80)		0,34
Tendon friction rubs	1,02 (0,22-4,57)		0,97
Anti-RNA polymerase III Ab	-		0,99
Presence of urine protein	-		0,99
Hb<12	16,00 (0,95- 267,04)		0,05
Baseline GI severity	0,99 (0,47-2,08)		0,98
Baseline skin severity	1,17 (0,42-3,23)		0,75

Baseline heart severity	1,36 (0,45- 4,10)		0,57
Baseline vascular severity	0,80 (0,38-1,67)		0,55
Baseline joint severity	0,95 (0,39-2,33)		0,92
Baseline muscle severity	0,94 (0,37-2,38)		0,89
Baseline general severity	8,90 (2,11- 37,55)		0,002
Baseline lung severity	1,15 (0,53-2,48)		0,71
Baseline renal severity	1,69 (0,20-13,82)		0,62

Abbreviations: OR: Odds ratio, IC: interval confidence, ESR: Erythrocyte Sedimentation Rate, Hb : hemoglobin, Ab : antibody, GI : gastrointestinal

Table S3: Correlation coefficients and Variance Inflation Factors (VIFs) at multivariable regression analysis for Δ Medsger's severity score ≥ 1 over 2 years

Variable	Δ Medsger's severity score ≥ 1	Adj mean ESScG	Adj mean EUSTAR	Subset diffuse	ESR>25	Anti Scl70 Ab	VIF
Adj mean ESScG	0,1634						2,171
Adj mean EUSTAR	0,2311	0,7024					2,296
Subset diffuse	0,08460	0,3283	0,4490				1,463
ESR>25	0,09539	0,4636	0,3852	0,1100			1,321
Anti Scl70 Ab	0,1479	0,2613	0,3669	0,4531	0,08924		1,327
age	0,04459	0,06690	0,003056	-0,1736	0,1593	-0,1454	1,080

Table S4. Separate models of multivariable variable logistic regression for the two activity indices and area under the curves

Features	OR (IC 95%)	Organ/ system severity accrual	p-value	AUC (IC 95%)
Adj mean EUSTAR- AI	1,40 (1,17 to 1,68)	Δ Medsger's severity score ≥ 1	0,002	0,65 (0,59 to 0,69)
age	1,00 (0,99 to 1,02)		0,33	
ESR>_25	1,00 (0,60 to 1,68)		0,97	
anti_Scl70 Ab	1,51 (0,94 to 2,44)		0,08	
subset_diffuse	0,79 (0,48 to 1,31)		0,37	
Adj mean ESScG- AI	1,25 (1,01 to 1,55)	Δ Medsger's severity score ≥ 1	0,03	0,61 (0,57 to 0,66)
age	1,00 (0,99 to 1,02)		0,30	
ESR>_25	1,11 (0,66 to 1,89)		0,67	
anti_Scl70 Ab	1,71 (1,07 to 2,72)		0,02	
subset_diffuse	0,98 (0,61 to 1,58)		0,94	