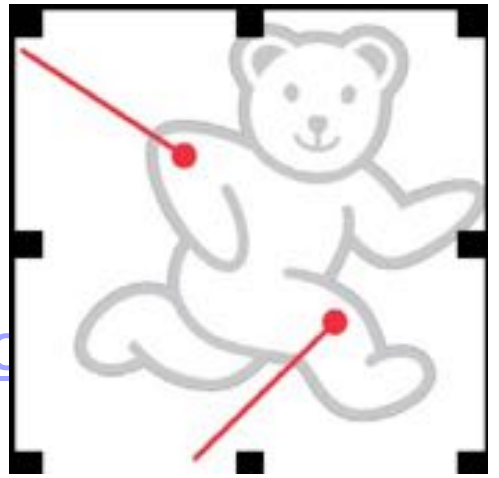
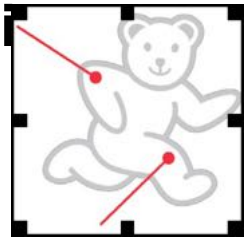
Presentation of juvenile systemic sclerosis and difference to adult patients

Ivan Foeldvari, MD
Hamburg Centre for Peadiatric and Adolescence Rheumatology, Germany
Centre for Treatment of Scleroderma and Uveitis in Childhood and Adolescence
Teaching Unit of the Asklepios Campus of the Semmelweis Medical School, Budapest, Hungary

www.kinderrheumatologie.de
www.sklerodermie.org
www.uveitis-kindesalter.de
www.orphan-diseases-in-pediatric-rheumatolo
de



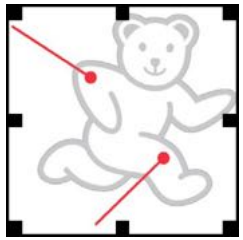
- Pediatric and Adolescent Rheumatologist
- Transtion programm with an associated adult rheumatologist
- Associated Occupationaltherapiest
- Associated Physiotherapiest
- Social worker
- Study nurses
- Assoziierted Team
  - Uveitis (Uveitis spesialised ophthalmologist)
  - Temporomandibular joint involvement (Orthodentist)
  - Pediatric orthopedic specialist
  - Pediatric dermatologist,....
  - **Outpatient „Painteam“**
    - **Paediatrician specialised on chronic pain and hi**
    - **Paediatric Psychiatrist**
    - **Occupational therapy team**



Cooperations/ Participation

- Hamburger Elterninitiative Rheumakranker Kinder e.V.
  www.kinderrheuma.de
- Deutsche Rheumaliga
- Lupus Erythematodes Selbsthilfegemeinschaft
- Scleroderma Foundation UK
- FEDERATION OF EUROPEAN SCLERODERMA ASSOCIATIONS (FESCA)
  - Advisor for pediatric issues
- Scleroderma Foundation – USA
- EMA /Enpra working group
- PRES Scleroderma working
- SCTC juvenile scleroderma working group

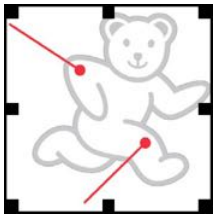
www.kinderrheumatologie.de



Topics of the talk

- Epidemiology of jSSc
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype

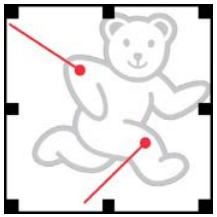
www.kinderrheumatologie.de



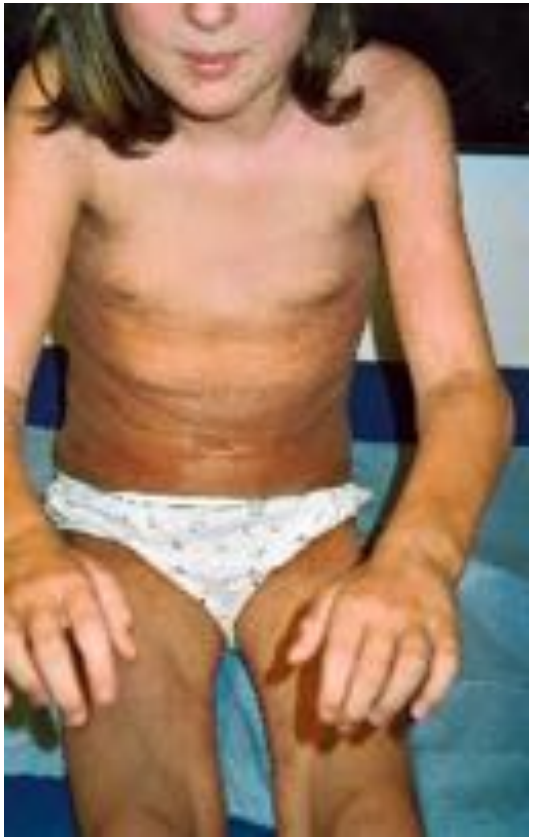
Topics of the talk

- Epidemiology of jSSc
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype

www.kinderrheumatologie.de



Epidemiology and demographic of jSSc



- **Data regarding incidence and prevalence is rare**
- **According a cross-sectional study by Herrick et al.**

(Arthritis Care 2010;62:213)

  - Incidence rate 0.27 (95% CI 0.1-0.5) per million children

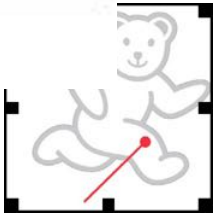
www.kinderrheumatologie.de

Estimated Prevalence of jSSc using the USA claims data

T. Beukelman, F. Xie, I. Foeldvari-
JSRD 2018, 3: 189-190

Year	N of Total Children	Diagnosis Code for Systemic Sclerosis	No Diagnosis Code for Localized Scleroderma	Use of Methotrexate, Mycophenolate Mofetil, or Cyclophosphamide	Estimated Prevalence per 1,000,000 Children [95% CI]
2010	5,888,868	254	186	23	3.9 [2.5-5.9]
2011	6,231,475	249	185	22	3.5 [2.2-5.3]
2012	6,278,116	217	170	26	4.1 [2.7-6.1]
2013	4,950,018	175	120	17	3.4 [2.0-5.5]
2014	4,933,522	138	91	14	2.8 [1.6-4.8]

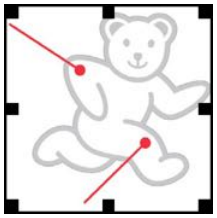
www.kinderrheumatologie.de



Topics of the talk

- Epidemiology of jSSc
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype

www.kinderrheumatologie.de



Proposed classification criteria for juvenile systemic scleroderma

Zulian et al. Arthritis Rheum 2007;57:203-12

First and Second International Workshop on Juvenile Scleroderma
June 2001 and 2004 Padua, Italy

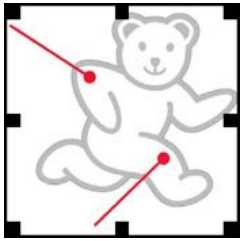
***Steering Committee*: F. Zulian (Padua), I. Foeldvari (Hamburg), J. Harper (London), A. Peserico (Padua), N. Ruperto (Pavia)**

- Major criteria
  - Sclerosis* / induration*
- Definite disease
  - 1 major and 2 minor criteria

- Minor criteria
  - Vascular changes*
  - Pulmonary involvement*
  - Gastrointestinal involvement*
  - Renal involvement*
  - Cardiovascular involvement*
  - Musculoskeletal involvement*
  - Neurologic involvement*
  - Serology*

www.kinderrheumatologie.de

* Per definition typical for SSc

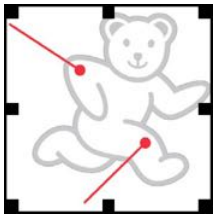


New Classifcation of Systemic Sclerosis

Arth Rheum 2013,65: 2737-47

- The maximum possible score is 19
- Patients with a score of ≥9 are classifed as having SSc.
- The defnitions of the items used in the criteria are defned in the publication.

www.kinderrheumatologie.de



New Classifcation of Systemic Sclerosis

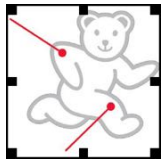
Arth Rheum 2013,65: 2737-47

Item	Sub-item(s)	Weight/score†
thickening of the fingers of both hands extending proximal the metacarpophalangeal joints *(sufficient criterion)*	–	9
thickening of the fingers *(only count the higher score)*	Puffy fingers	2
	Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints)	4
ertip lesions *(only count the higher score)*	Digital tip ulcers	2
	Fingertip pitting scars	3
ngiectasia	–	2
ermal nailfold capillaries	–	2
ionary arterial hypertension and/or interstitial lung disease	Pulmonary arterial hypertension	2
aximum score is 2)	Interstitial lung disease	2
aud's phenomenon	–	3
related autoantibodies (anticentromere,	Anticentromere	3
ti–topoisomerase I [anti–Scl-70], anti–RNA	Anti–topoisomerase I	
lymerase III) *(maximum score is 3)*	Anti–RNA polymerase III	

ese criteria are applicable to any patient considered for inclusion in an SSc study. The criteria are not applicable to patients with skin thickening ng the fingers or to patients who have a scleroderma-like disorder that better explains their manifestations (e.g., nephrogenic sclerosing fibrosis, ralized morphea, eosinophilic fasciitis, scleredema diabeticorum, scleromyxedema, erythromyalgia, porphyria, lichen sclerosis, graft-versus-host se, diabetic cheiroarthropathy).

e total score is determined by adding the maximum weight (score) in each category. Patients with a total score of ≥9 are classified as having ite SSc.

www.kinderrheumatologie.de

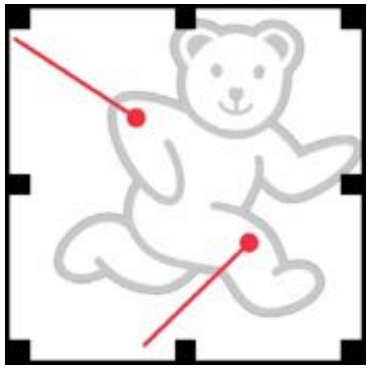


Performance of the adult Systemic Sclerosis classification in juvenile systemic sclerosis patients. Results from the juvenile systemic sclerosis inception cohorte – www.juvenile-scleroderma.com

I. Foeldvari [1], J. Klotsche[13], M. Katsicas[2], M. Teresa Terreri[3], R. Cimaz[4], M. Kostic[5], F. Sztajnbok[6], D. Nemcova[7], M. Moll[8], M. Jose Santos[9], T. Avcin[10], J. Brunner[11], S. Nielsen[12], T. Kallinich[13], K. Minden[13], J. Müller[14], M. Janarthanan[15], Y. Uziel[16], A. Giraldo[17], D. Eleftheriou[18], K. Torok[19], N.Helmus[1]

.

www.kinderrheumatologie.de



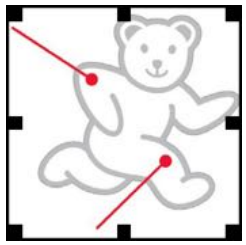
Inception Cohort for juvenile systemic Sclerosis (jsSc)

- **Data of juvenile systemic sclerosis patients are prospectively collected with a standardized assessment including quality of life**

- **The aim of collecting data in patients with recent onset jSSc is to learn more about the evolvement of organ involvement and the quality of life in these patients**

- **The project should help to improve the care of these patients throughout the world**

www.kinderrheumatologie.de



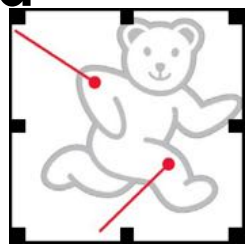
Inception Cohort for juvenile systemic Sclerosis (jsSc)

- **Inclusion criteria**

  - ⇨ **Patients diagnosed with juvenile systemic sclerosis (fulfilling the adult classification criteria)**
  - ⇨ **Developed the first non-Raynaud symptom before the age of 16 years**
  - ⇨ **Age at inclusion younger than 18 years of age**

- **Method**
  - ⇨ **Assessment every 6 months according to a standardized protocol**
  - ⇨ **Assessment of organ involvement and patient related outcomes**

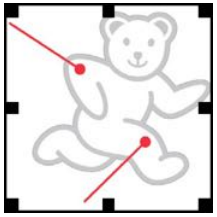
www.kinderrheumatologie.de



Results

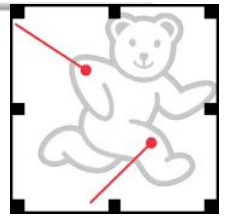
- All paediatric patients in the cohort fulfil the adult classification , as the main criteria of the paediatric classification, proximal skin sclerosis from MCP joint, already gives sufficient points to be classified as SSc.
- The pediatric patients had a mean score of:
  - 15.3 at ≤6 months (n=13)
  - 15.5 at ≤12 months(n=19)
  - 17.2 at ≤ 24 months (n=25)
  - 17.4 at ≤48 months (n=35).
- The cluster analysis showed 3 cluster of patients

www.kinderrheumatologie.de



	Padua Criteria	Class I n=17 %	Class II n=21 %	Class III n=48 %
ajor	Proximal skin sclerosis	100,0	100,0	100,0
itaneous	Sclerodacytly	100,0	100,0	100,0
ripheral vascular	Raynauds	100,0	0,0	95,8
	Nailfold changes	100,0	23,8	56,3
	Digital tip ulcers	87,5	0,0	2,1
astrointestinal	Dysphagia	0,0	0,0	0,0
	Reflux	58,8	33,3	22,9
rdiac	Arrythmias	29,4	14,3	8,3
	Heart failure	5,9	0,0	0,0
nal	Renal crisis	0,0	0,0	0,0
	New arterial hypertension	0,0	0,0	0,0
spiratory	Fibrosis	23,5	28,6	6,3
	Decreased DLCO	70,6	9,5	0,0
	PH	0,0	4,8	12,5
urologic	Neuropathy	0,0	0,0	0,0
	Carpal tunnel	0,0	0,0	0,0
usculoskeletal	Tendon friction	0,0	9,5	4,3
	Arthritis	17,7	47,6	2,1
	Myositis	0,0	0,0	0,0
rologic	ANA	100,0	57,9	85,4
	SSc AB	35,3	0,0	52,2

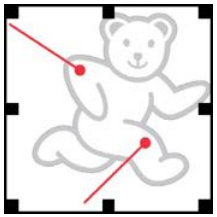
www.kinderrheumatologie.de



Topics of the talk

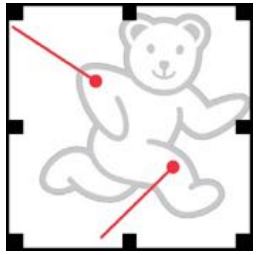
- Epidemiology of jSSc
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype

www.kinderrheumatologie.de

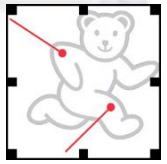


Are there clinical differences between male and female patients?

www.kinderrheumatologie.de

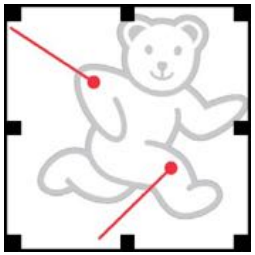


	Female N=66	Male N=14	P-Werte
Female to Male Ratio	(66/0)	(0/14)	
Diffuse subtype	48 (72.7%)	10 (71.4%)	0.982
Diffuse overlap	6	0	
Limited subtype	18 (27.3%)	4 (28.6%)	
Limited overlap	5	0	
Caucasian	59 (89.4%)	12 (85.7%)	0.834
African	4 (6.1%)	2 (14.3%)	
Indian	2 (3%)	0 (0%)	
Yemenite	1 (1.5%)	0 (0%)	
Mean Disease duration (years)	3.6 (± 3.1)	3.3 (± 2.9)	0.671
Mean age of onset of Raynaud's (years)	9.4 (± 4.1) 8 non-Raynaud	9.3 (± 3.9) 0 non-Raynaud	0.913
Mean age of onset of non-Raynaud's (years)	10.0 (± 4.1)	9.1 (± 3.9)	0.834
Disease modifying drugs	75.8% (50/66)	85.7% (12/14)	0.418



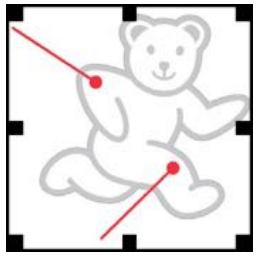
	Female N=66	Male N=14	P-Werte
6 Minute Walk Test (Mean, SD)	441.4m (±116.1) n=18	286.7m (±179.8) n=3	0.035
Musculoskeletal	55.4% (36/65)	92.9% (13/14)	0.009
Total contractures	38.1% (24/63)	78.6% (11/14)	0.006
Tendon Friction Rub	6.7% (4/60)	33.3% (3/9)	0.013
Patient global disease activity	41.9 (0-100) n=34	58.3 (30-80) n=6	0.041
Physician global disease activity	34.3 (0-90) n=38	58.3 (30-80) n=6	0.037
Physician global disease damage	26.2 (0-70) n=37	68.3 (40-80) n=6	0.001

www.kinderrheumatologie.de

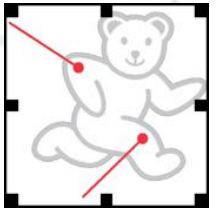


ARE THERE DIFFERENCES IN THE CLINICAL PRESENTATION ACCORDING ANTI-SCL70 POSITIVITY AND ANTI-SCL70 NEGATIVITY?

www.kinderrheumatologie.de

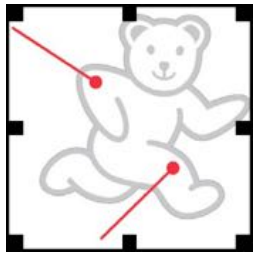


	Anti-Scl 70 negative N=53	Anti-Scl 70 positive N=24	P-value
male to Male Ratio	5.6:1 (45/8)	3:1 (18/6)	0.628
ffuse subtype	39 (73.6%)	17 (70.8%)	0.867
ffuse overlap	5	0	
nited subtype	14 (26.4%)	7 (29.2%)	
nited overlap	4	0	
ucasian	49 (92.4%)	20 (83.3%)	0.834
rican	4 (7.5%)	2 (8.3%)	
ian	0 (0%)	1 (4.2%)	
menite	0 (0%)	1 (4.2%)	
an Disease duration ears)	3.7 (± 3.1)	3.4 (± 3.0)	0.671
an age of onset of ynaud's (years)	9.5 (± 3.8) 6 non-Raynaud	9.7 (± 4.1) 1 non-Raynaud	
an age of onset of n-Raynaud's (years)	9.8 (± 4.0)	10.3 (± 4.0)	0.846



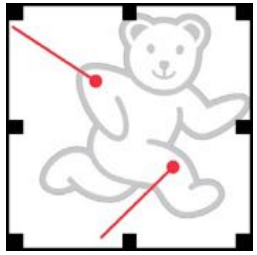
	Anti-Scl70 negative N=53	Anti-Scl 70 positive N=24	P-value
ease modifying drugs	71.7% (38/53)	87.5% (21/24)	0.129
A	75.5% (40/53)	86.4% (19/22)	0.294
i-scl 70	0% (0/53)	100% (24/24)	0.001
i-centromere	6.1% (2/33)	15.4% (2/13)	0.312
elevated mg/l)	8.5% (4/47)	35% (7/20)	0.007
normal findings in CT	58.1% (18/31)	23.1% (3/13)	0.034
nber of joints with reased range	57.7% (30/52)	29.2% (7/24)	0.021

www.kinderrheumatologie.de



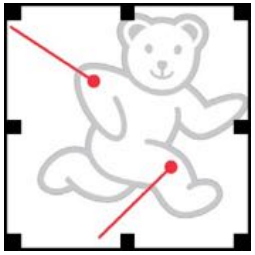
ARE THERE DIFFERENCES IN THE CLINICAL PRESENTATION ACCORDING THE AGE AT INCLUSION IN THE COHORT?

www.kinderrheumatologie.de



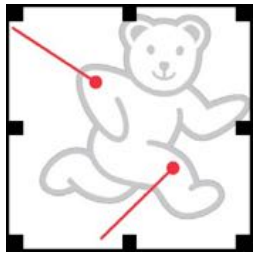
	< 10years at first visit N=16	> 10years at first visit N=64	P-value
emale to Male Ratio	3:1 (12/4)	5.4:1 (54/10)	0.688
iffuse subtype	14 (87.5%)	44 (68.7%)	0.574
iffuse overlap	0	6	
imited subtype	2 (12.5%)	20 (31.2%)	
imited overlap	1	4	
aucasian	14 (87.5%)	57 (89.1%)	0.972
frican	1 (6.25%)	5 (7.8%)	
ndian	0 (0%)	2 (3.1%)	
ermenite	1 (6.25%)	0 (0%)	

www.kinderrheumatologie.de



	< 10years at first visit N=16	> 10years at first visit N=64	P-value
ean Disease duration ears)	2.3 (± 1.8)	3.9 (± 3.2)	0.539
ean age of onset of ynaud´s (years)	4.3 (± 2.3) 0 non-Raynaud	11.0 (± 3.0) 8 non-Raynaud	0.027
ean age of onset of n-Raynaud´s (years)	4.8 (± 2.1)	11.2 (± 3.3)	0.074
sease modifying drugs	81.2% (13/16)	76.6% (49/64)	0.688
langiectasia	54.5% (6/11)	21% (8/38)	0.030
strointestinal beside sophageal	12.5% (2/16)	1.6% (1/64)	0.039
ysician global disease tivity	57.9 (10-90) n=7	33.7 (0-80) n=37	0.037

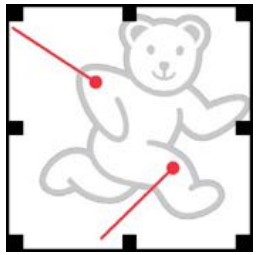
www.kinderrheumatologie.de



Is there a change in organ involvement pattern after 12 or 24 months ?

Results from the Juvenile Scleroderma Incpetion Cohort

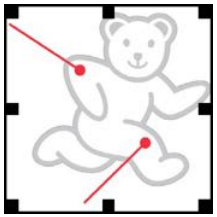
www.kinderrheumatologie.de



Topics of the talk

- Epidemiology of jSSc
- Classification issues
- Specific pediatric issues
- Comparison of the pediatric data to adult population with diffuse subtype

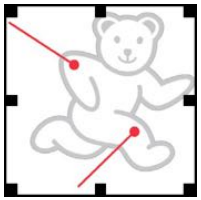
www.kinderrheumatologie.de



Publications selected for comparison

- 2. Scalapino K, Arkachaisri T, Lucas M, Fertig N, Helfrich DJ, Londino AV, Jr., et al. Childhood onset systemic sclerosis: classifcation, clinical and serologic features, and survival in comparison with adult onset disease. J Rheumatol. 2006;33(5):1004-13.
- 4. Martini G, Foeldvari I, Russo R, Cuttica R, Eberhard A, Ravelli A, et al. Systemic sclerosis in childhood: clinical and immunologic features of 153 patients in an international database. Arthritis Rheum. 2006;54(12):3971-8.
- 5. Foeldvari I, Zhavania M, Birdi N, Cuttica RJ, de Oliveira SH, Dent PB, et al. Favourable outcome in 135 children with juvenile systemic sclerosis: results of a multi-national survey. Rheumatology (Oxford). 2000;39(5):556-9.
- 24. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754-63.

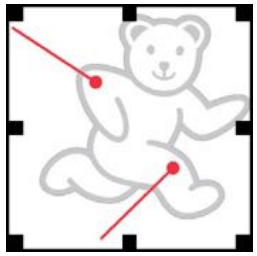
www.kinderrheumatologie.de



gan involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2)) n = 111	EUSTAR a55c (24) n=1349*
Age at onset in years	9.0** 9.4 ***	8.8	8.1	11.1	42.9*
Disease duration at diagnosis in years	3.7	ND	1.9	2.8	7.4*
Follow up in years	3.7*	5.0	3.9	14.4	ND
Subtype diffuse	72.5%	ND	91%	35%	100%
Subtype limited	22.5%	ND	9%	36%	-
Overlap feature	14%	ND	ND	29%	5.6%
Sex female /male	4.7:1	2.8:1	3.6:1	4.1:1	6.7:1
Ethnical background (% Caucasian)	91.1%*	Mostly caucasian	ND	92%	

iffuse; ** onset of Raynauds; *** onset of non Raynauds
) = not documented

www.kinderrheumatologie.de

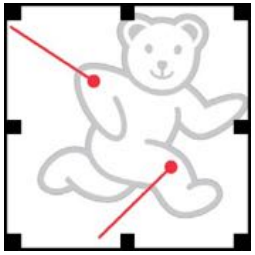


rgan involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2]) n = 111	EUSTAR aSSc (24) n=1349*
ANA positive	77%*	ND	80%	97%	92%*
nticentromere positive – diffuse*/limited	6%*	ND	7.1%	8%	6%*
Anti-scl 70 positive- diffuse* /limited	30.4%*	ND	34%	20%	60.8%*
Raynauds	100%*	72%	84%	97%	96%*
Capillary changes	62%*	ND	39.9%	ND	62%*
igital infarcts/ulceration	55%*	28.6%	29%	ND	42.7%*

diffuse; ** onset of Raynauds; *** onset of non Raynauds

ID = not documented

www.kinderrheumatologie.de

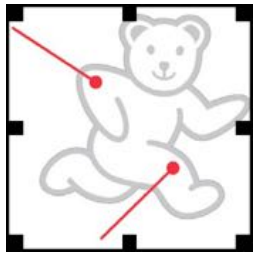


rgan Involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2)) n = 111	EUSTAR aSSc (24) n=1349*
Pulmonary	41.4%*	50%	42%	55%	67%*
ulmonary hypertension	7%*	ND	7.2%	7%	22%*
bnormal HRCT/fibrosis	31%*	ND	23.5%	ND	53.4%*
Reduced DLCO	17%*	ND	27.5%	ND	64%*
Reduced FVC	28%*	ND	41.8%	16% (severe FVC<50%)	ND
Cardiovascular	46.6%*	44%	29%	17%	27.3%*or more

diffuse; ** onset of Raynauds; *** onset of non Raynauds

D = not documented

www.kinderrheumatologie.de

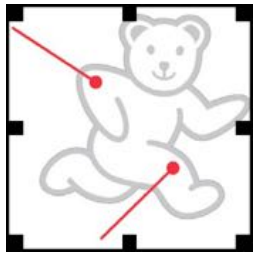


rgan involvement	Inception Cohort n=80	Foeldvari et.al. (5) n=135	Martini et.al (4) n=153	Scalapino et al (2)) n = 111	EUSTAR aSSc (24) n=1349*
CNS	0%*	16%	4 %	ND	0%
Renal	7%*	13%	10%	4%	9% or more
Raised creatinine/proteinuria	5%*	ND	4.6%	4%	9%*
hypertension	0%*	ND	2.6%	4%	19.3%*
Renal crisis	0%*	0.7%	0.7%	4%	4.2 %*

diffuse; ** onset of Raynauds; *** onset of non Raynauds

D = not documented

www.kinderrheumatologie.de



„Promotion for our project“

- I would like to invite you to participate on the

  Juvenile Inceptions Cohort Project

  www.juvenile-scleroderma.co

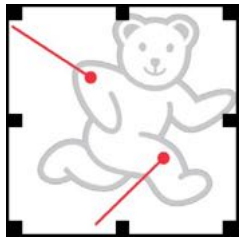
- If interested, please contact us:

  foeldvari@t-online.de or

  inceptioncohort

  @kinderrheumatologie.de

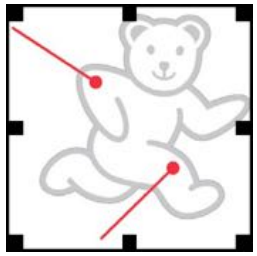
www.kinderrheumatologie.de



Conclusion

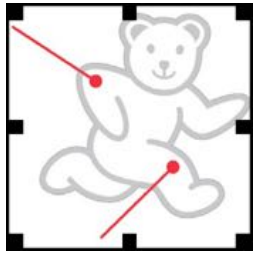
- Pediatric onset jSSc has a distinct feature with the around 75% diffuse subtype of patients
- 15 to 29% of patients with overlap features
- Rare occurence of renal crisis, less pulmonary hypertension
- The follow up in the inception cohort showes a stabilisation of the organ involvement pattern, with a significant improvement in patient related outcomes
- We need more patients with longer follow up with standardized assessment to answer lot of open questions

www.kinderrheumatologie.de



Thanks for Your interest
Looking forward to your questions ☺

www.kinderrheumatologie.de



New Classifcation of Systemic Sclerosis
Arth Rheum 2013,65: 2737-47

e 2 Definitions of items/sub-items in the American College of Rheumatology/European League Against Rheumatism criteria for the fication of systemic sclerosis

	Definition
ickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
ingers	Swollen digits–a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis.
ip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma. Digital pitting scars are depressed areas at digital tips as a result of ischaemia, rather than trauma or exogenous causes.
ectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels.
mal nailfold capillary pattern consistent ystemic sclerosis	Enlarged capillaries and/or capillary loss with or without pericapillary haemorrhages at the nailfold. May also be seen on the cuticle.
nary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterisation according to standard definitions.
itial lung disease	Pulmonary fibrosis seen on high-resolution CT or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of 'Velcro' crackles on auscultation, not due to another cause such as congestive heart failure.
ud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase colour change in finger(s) and often toe(s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor.
lated auto antibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti–topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti– RNA polymerase III antibody. Positive according to local laboratory standards.

ystemic sclerosis.

van den Hoogen F, *et al. Ann Rheum Dis* 2013;**72**:1747–1755. doi:10.1136/annrheumdis-2013-20442