Kardiologisches Kolloquium St. Gallen 3.05.2023
Update Pulmonale Hypertonie

Kantonsspital St.Gallen

Diagnostische Strategie der PH im Spektrum der Autoimmunerkrankungen

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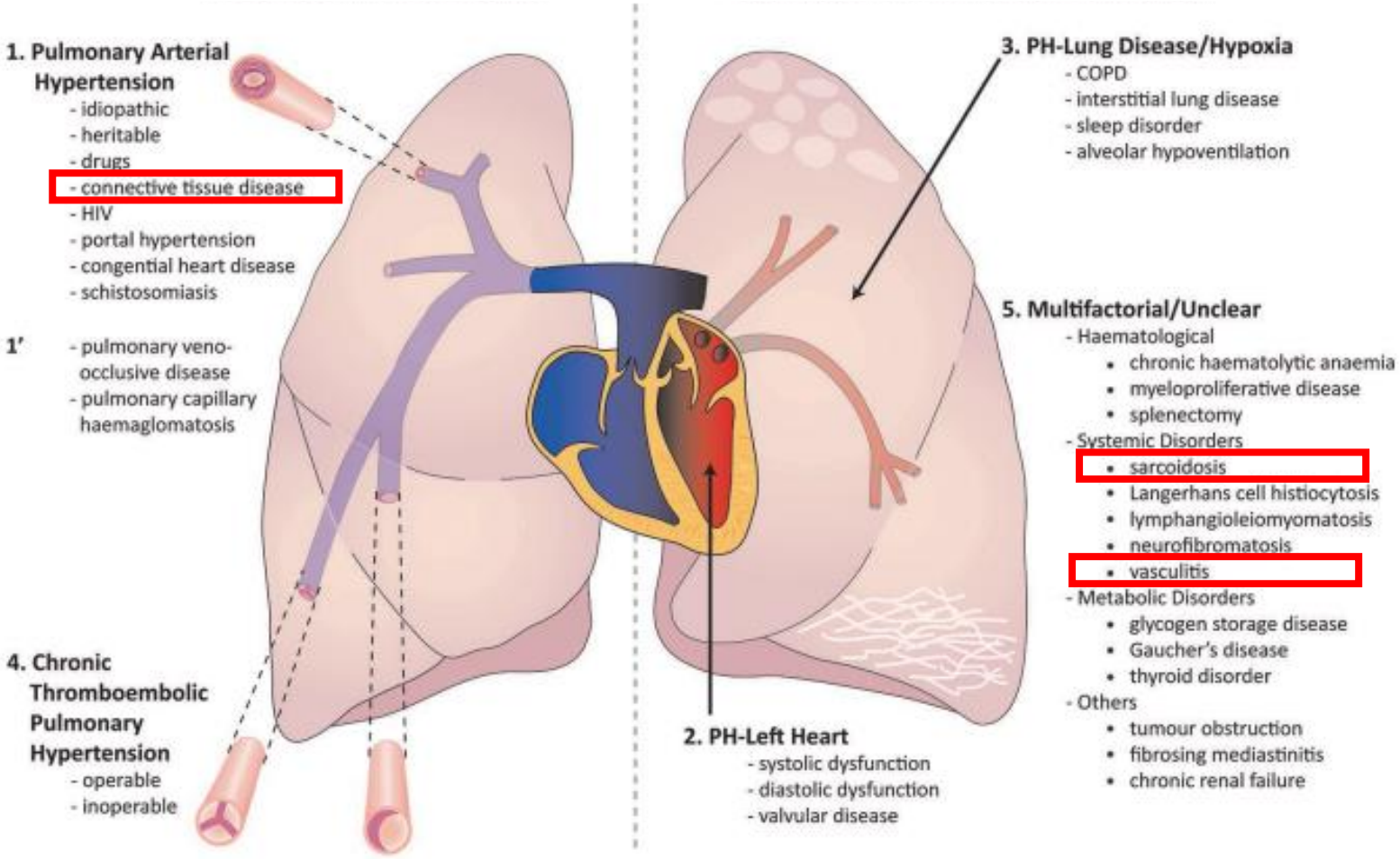
3. Mai 2023

Disclosures

Supports for clinical trials and projects:
AbbVie, BMS, Roche, Pfizer, UCB, Lilly, Sanofi, Novartis

Honoraria for consultation and lectures:
AbbVie, BMS, Gilead, Janssen, Lilly, MSD, Pfizer, Roche, UCB, Sanofi, Novartis, Rheuma Schweiz

Pulmonale Hypertonie: Klassifikation (Nizza 2013, 2018)



Kiely DG et al 2013

Warum ist die PH bei Autoimmunerkrankungen eine relevante Krankheits-Manifestation?

- PH bei Autoimmunerkrankungen (insb. Kollagenosen) ist mit schlechterer Prognose assoziiert, eine frühe Diagnose verbessert das Outcome

Kollagenose (CTD)-assoziierte pulmonale Hypertonie

Kobe University Hospital

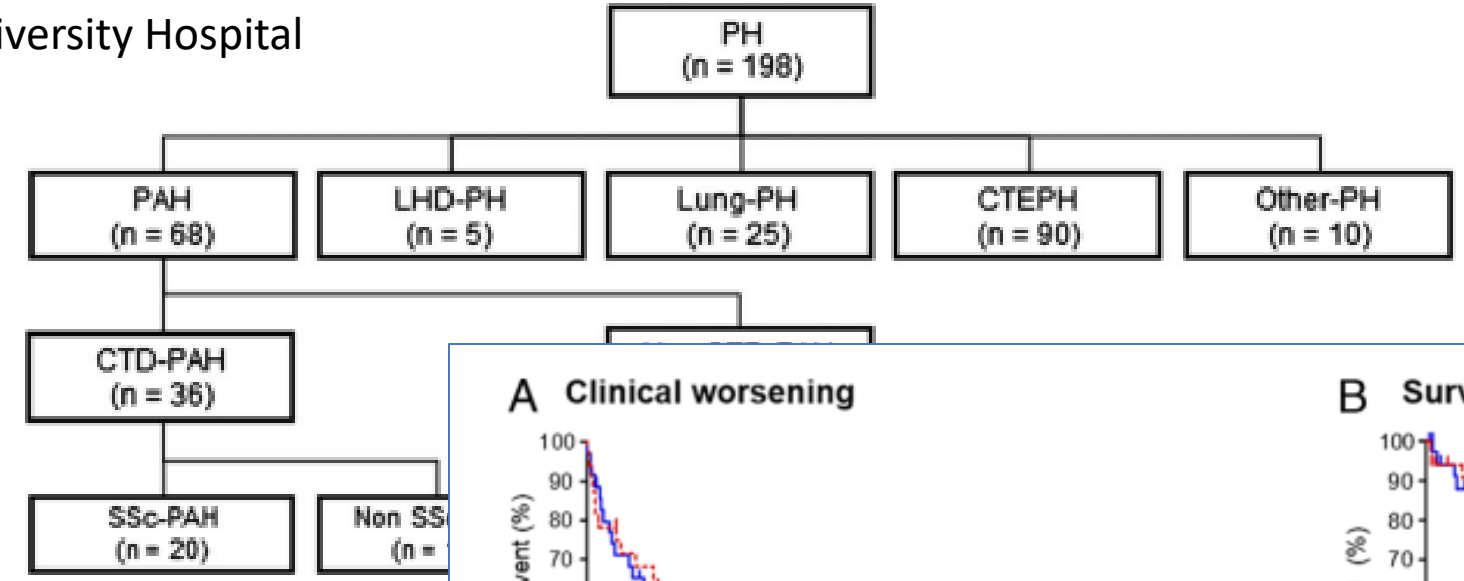
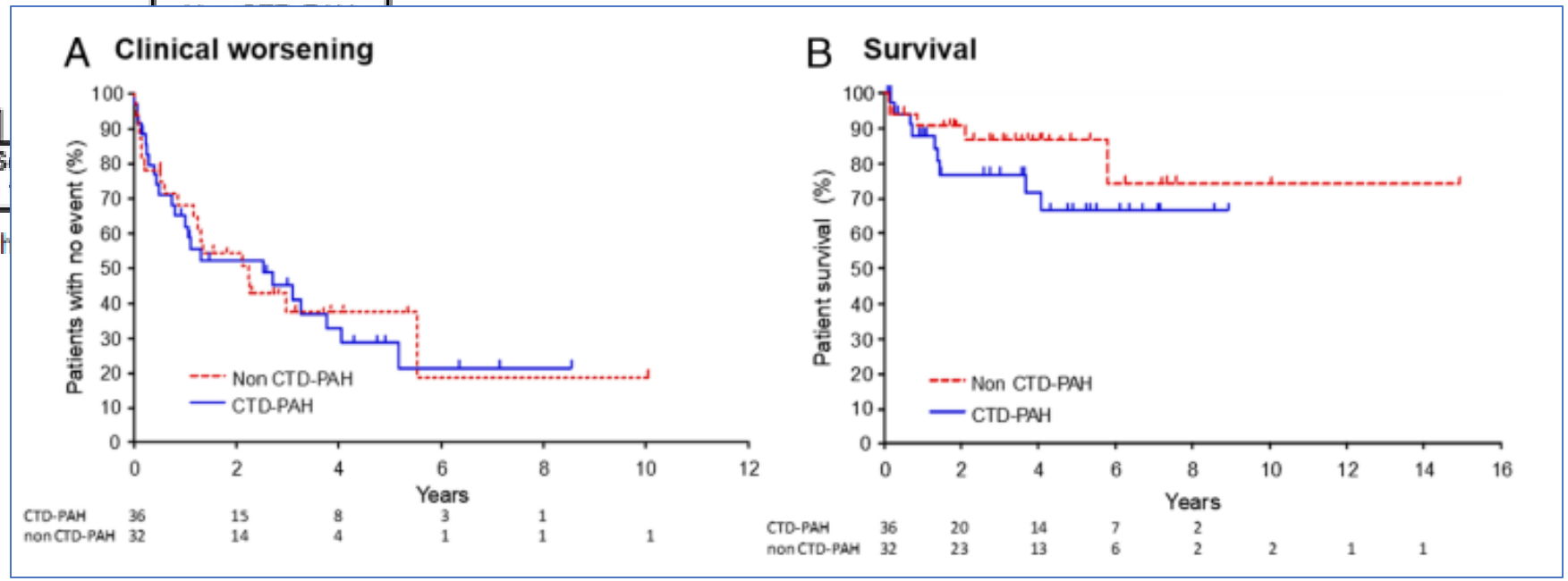


FIGURE 1. Patient composition. LHD-PH, left h



Nakayama K et al 2021

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SSc-assoziierte pulmonale Hypertonie

Cleveland Clinic Registry

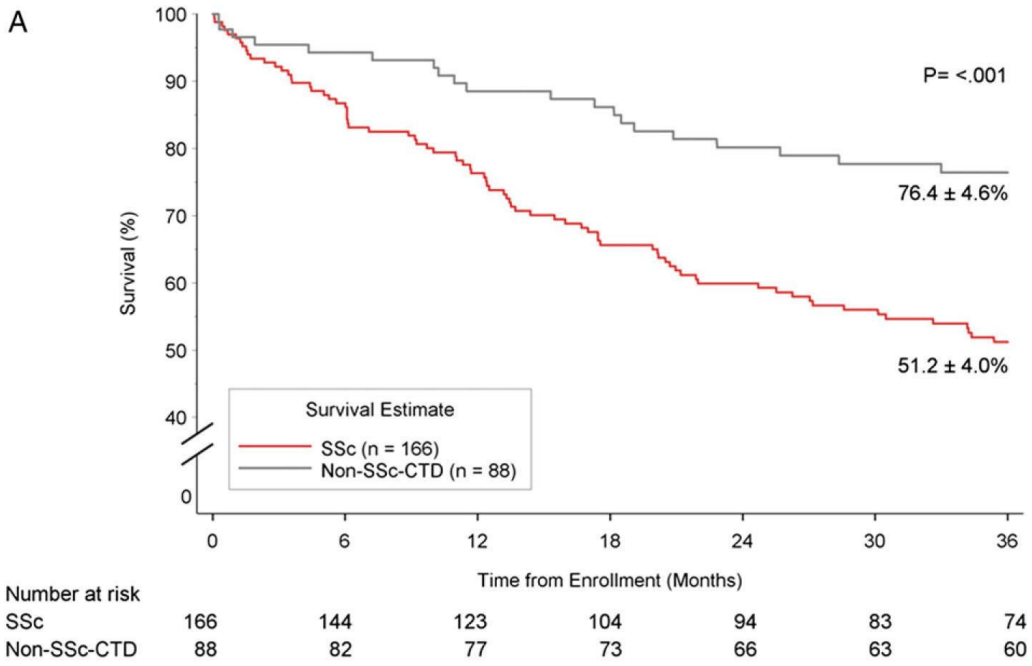
n = 2093 (Diagnose im RHK bestätigt)

11% Kollagenose assoziierte PH

- Systemische Sklerose 158 (68%)
- Systemischer Lupus erythematodes 27 (13%)
- Dermatomyositis 8 (3%)
- Polymyositis 8 (3%)
- Rheumatoide Arthritis 8 (3%)
- Mixed connective tissue disease 23 (10%)

Kristin B Highland et al. 2016

Überleben mit PAH bei SSc versus nonSSc CTD (REVEAL-Registry)



Chung L et al. Chest 2014

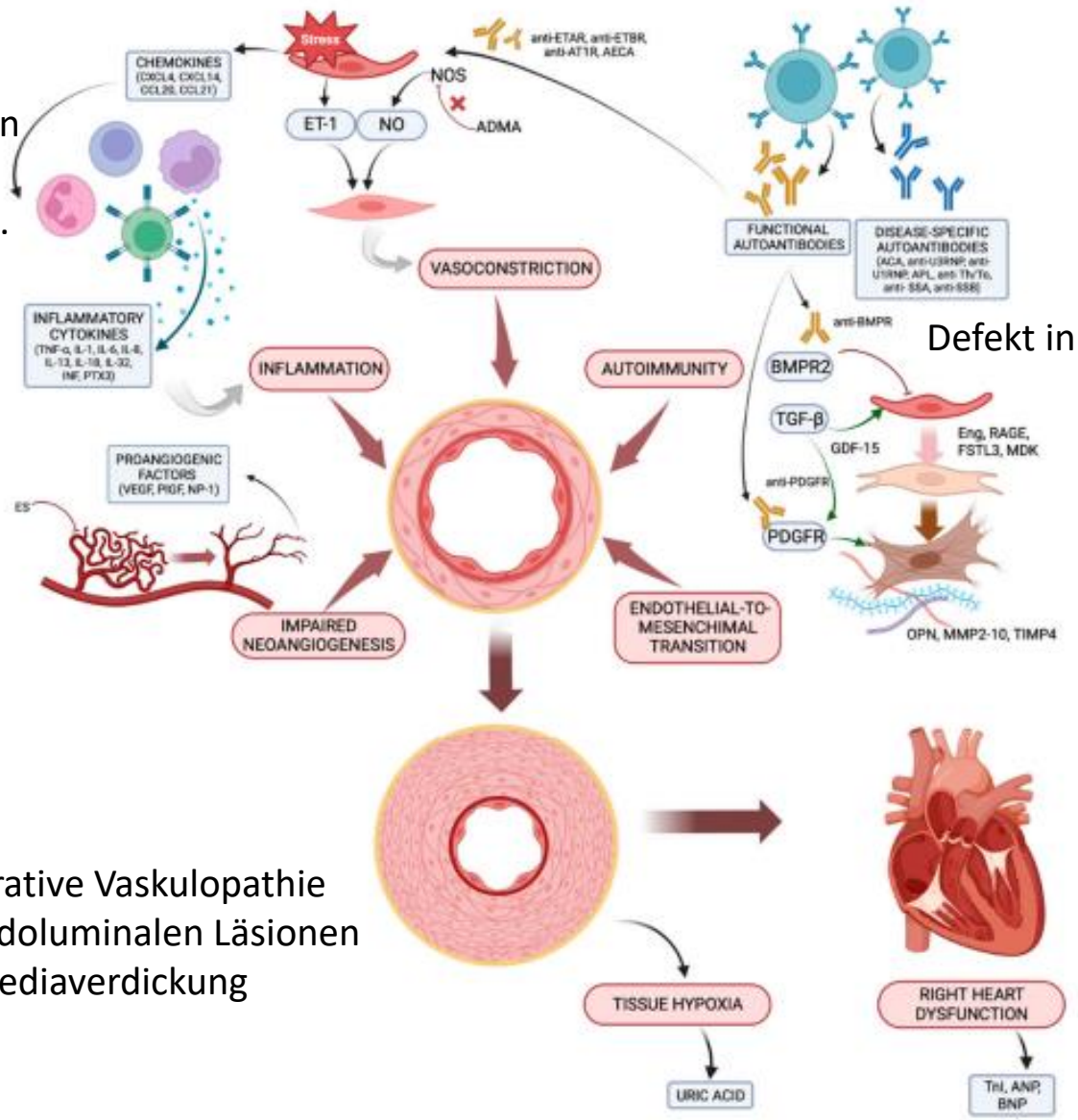
Mögliche Gründe für ein ungünstiges Outcome der SSc-PAH

- Mittleres Alter der SSc-PAH ca 10 Jahre höher als bei den IPAH Patienten
- Verminderte RV Pumpfunktion bei der SSc
- Hohe Prävalenz systolischer und diastolischer LV Dysfunktion bei der SSc
- Zusätzliche ILD (verschlechtert Ansprechen auf PH Therapie)
- Begleiterkrankungen: renovaskulär, gastrointestinal, Malnutrition etc bei der SSc
- Pathogene Autoantikörper (einschliessl. Autoantikörper gegen vaskuläre Rezeptoren)

Nach: Condliffe R et al 2015

Pathophysiologie der CTD-PAH und potentielle Biomarker

Genetik?
Endothelschaden
Inflammation
IL6, PDGF, CTGF..
Adipsin



Defekt in BMPR2?

Obliterative Vaskulopathie
mit endoluminalen Läsionen
und Mediaverdickung

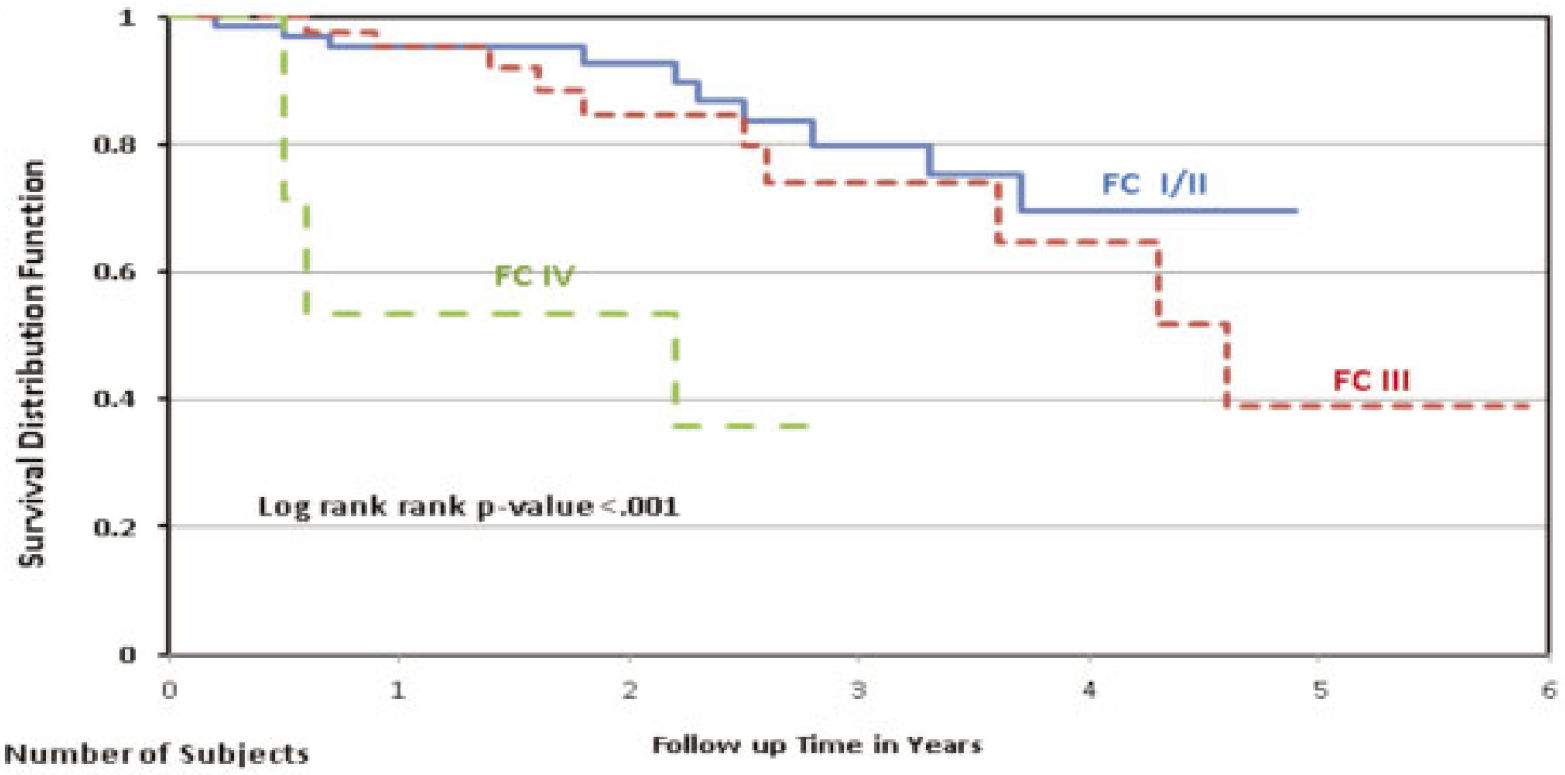
Table 2. Autoantibodies in CTD-PAH.

Autoimmunity in CTD-PAH		Autoantibodies
Disease-specific autoantibodies	SSc	ACA [23,92] anti-pc4.2 [94] Anti-U3RNP [92] Anti-Th/To [92] aPL [99,100]
	SLE	Anti-U1RNP [97,102] aPL [103,104,107,108] Anti-SSA, anti-SSB [102]
	Other CTDs	Anti-U1RNP [88,108]
Functional autoantibodies		Anti-ETAR and anti-AT1R [116,117] Anti-ETBR [31] AECA [88,127,128] Anti-PDGFR [136] Anti-BMPR [138]

ACA, anti-centromere antibodies; AECA, anti-endothelial cells antibodies; aPL, antiphospholipid antibodies; AT1R, angiotensin receptor type 1; BMPR, bone morphogenic protein receptor; ETAR, endothelin receptor type A; ETBR, endothelin receptor type B; pc4.2, phage clone expressing peptide 4.2; PDGFR, placental derived growth factor receptor; RNP, ribonucleoprotein.

Prognose der pulmonal arteriellen Hypertonie

- Mediane Zeitverzögerung zwischen SSc und SSc-PAH 4 Jahre, kein Unterschied zwischen limitierter und diffuser Skerodermie
- **Prognose abhängig von der Funktionsklasse**



PHAROS Register
22 US SSc Zentren

131 Pat mit SSc-PAH

Chung L et al. Arthritis Care Res 2014

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- Das Outcome der SSc-PAH ist schlechter im Vergleich zu anderen Kollagenosen

- SSc: Vaskulopathie, Inflammation und Fibrose

Pathogenese der Sklerodermie

Genetische Faktoren

Externe Faktoren

Externe Faktoren

Immunaktivierung

Vaskulopathie

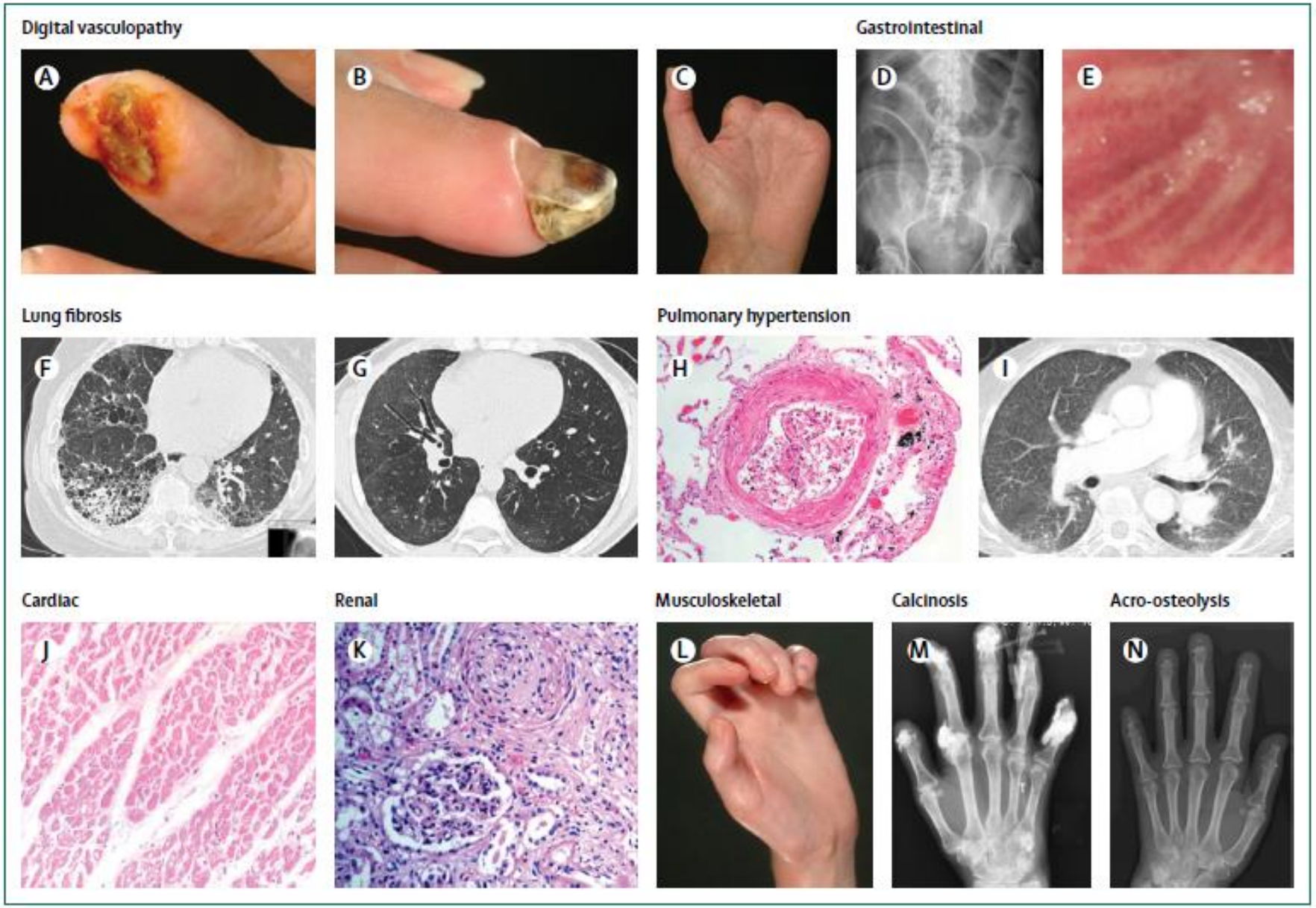
Inflammation

Fibrose

Aktivierung von Fibroblasten

Transformation in Myofibroblasten
Synthese und Akkumulation extrazellulärer Matrix

Typische Komplikationen der Sklerodermie



>50% der PH ist PAH

Inzidenz:

PH bei SSc – 1-2%/Jahr

Prävalenz:

5% nach 5 Jahren
10% nach 10 Jahren
15% nach 15 Jahren

Denton CP et al 2017

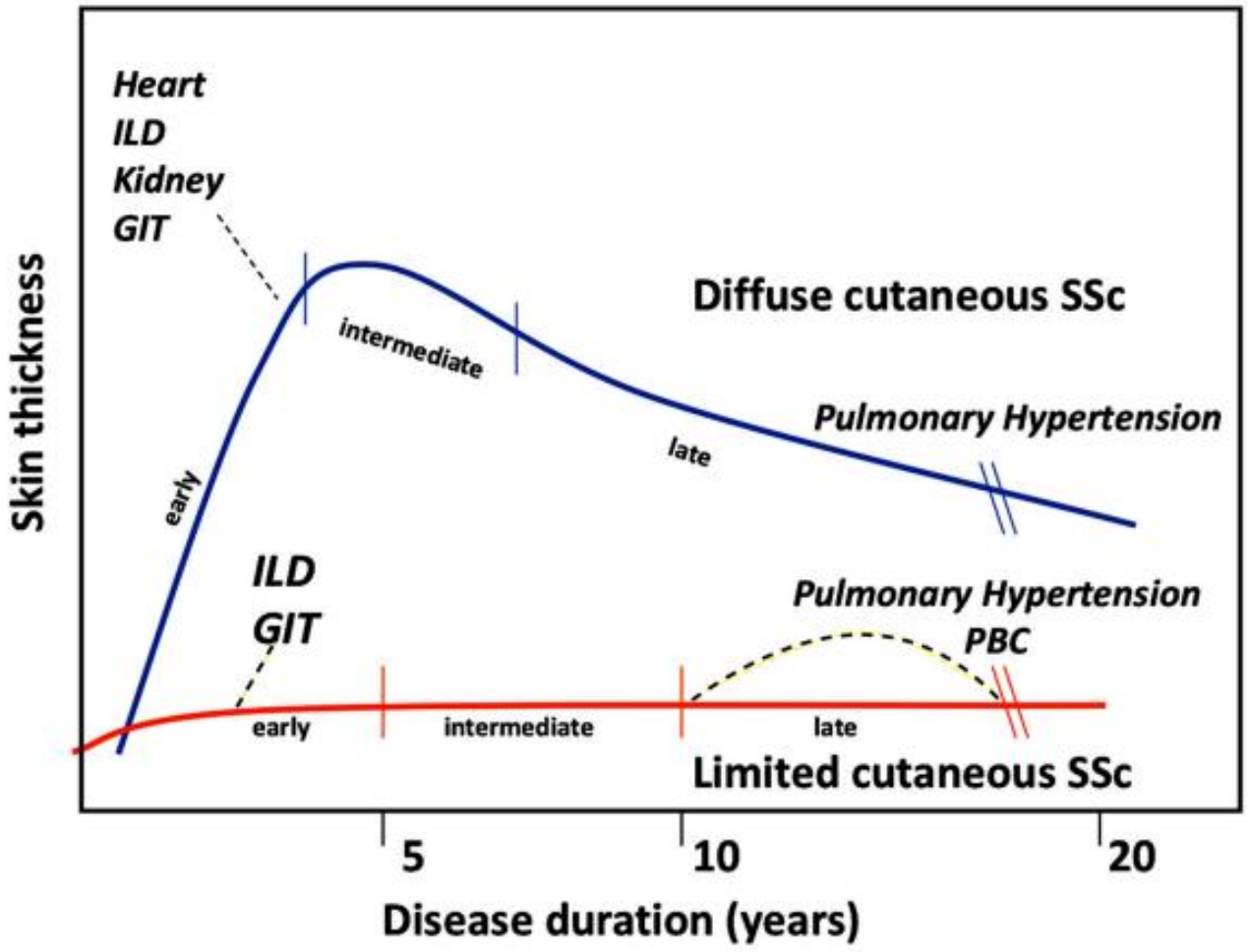
Sklerodermie – Klassifikationskriterien 2013

Kriterium	Subkriterium	Score
Sklerodaktylie und Sklerodermie beider Hände über die MCP-Gelenke hinausreichend nach proximal (ausreichendes Kriterium)	-	9
- Sklerodaktylie (nur der höhere Score zählt)	Puffy fingers (geschwollene Finger) Sklerodaktylie der Finger distal der MCP-Gelenke aber proximal der PIP-Gelenke	2 4
- Läsionen an der Fingerspitze (nur der höhere Score zählt)	Fingerspitzenulcerationen Fingerspitzen mit grübchenförmigen Narben	2 3
Teleangiektasien	-	2
Abnormale Kapillarmikroskopie	-	2
Pulmonal arterielle Hypertonie und / oder Interstitielle Lungenerkrankung (max. Score 2)	Pulmonal arterielle Hypertonie Interstitielle Lungenerkrankung	2 2
Raynaud-Phänomen	-	3
Sklerodermie assoziierte Autoantikörper (max. Score 3)	**Anti-Zentromer-Antikörper** **Anti-Topoisomerase I-Antikörper (antiScl-70)** Anti-RNA-Polymerase III	3

Der Gesamtscore wird bestimmt, indem der max. Score in jeder Kategorie addiert wird. **Pat. mit einem Score ≥ 9 werden klassifiziert als definitive Sklerodermie.**

Van den Hoogen et al 2013

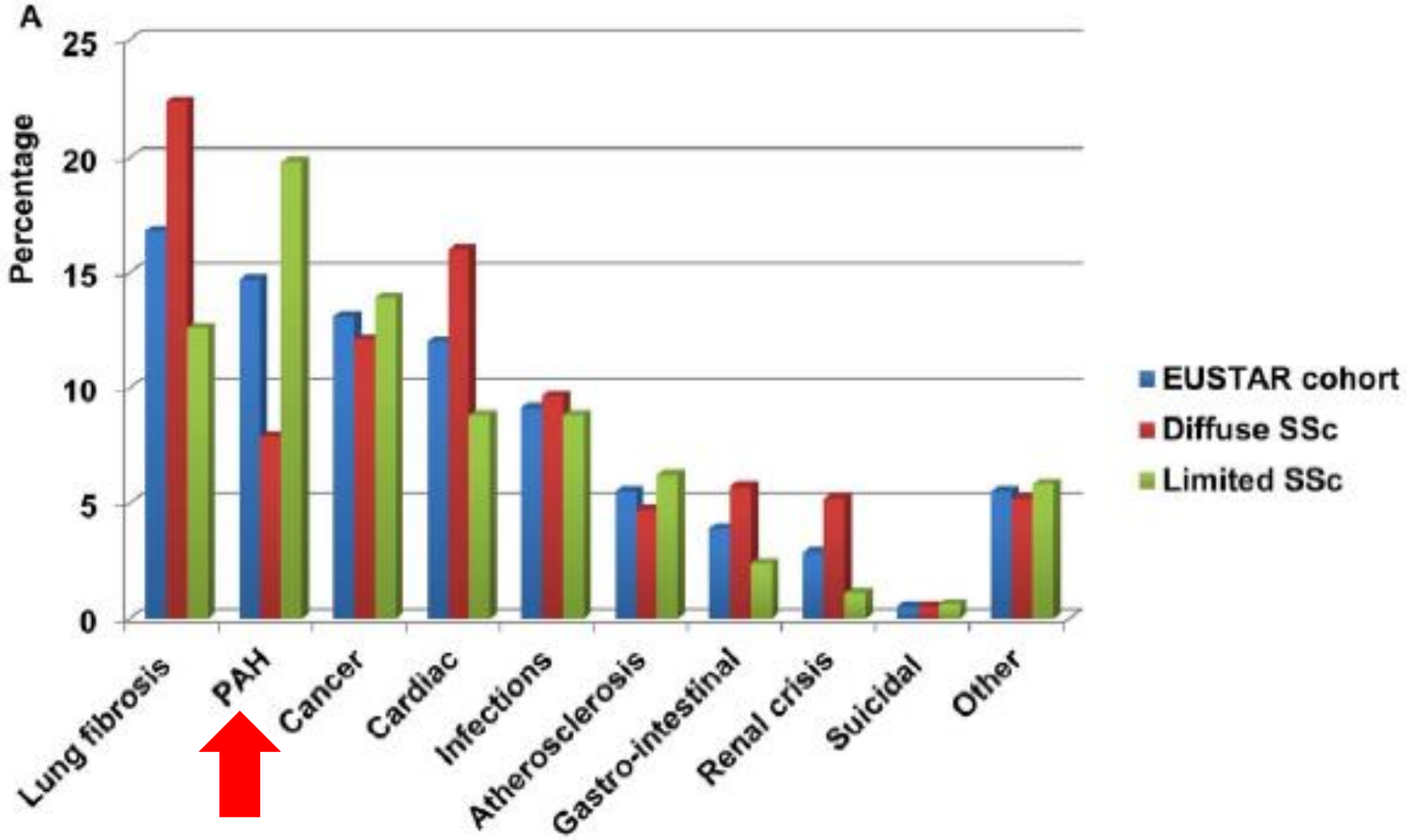
Entwicklung einer PH bei limitierter und diffuser Sklerodermie



Ca 50% PAH < 5 Jahre SSc Dauer
Kein Unterschied limit. und diffuse SSc

Nagaraja V et al Arthritis Rheumatol 2020

EUSTAR Kohorte: Todesursachen bei Patienten mit Sklerodermie



Elhai et al 2017

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- Das Outcome der SSc-PAH ist schlechter im Vergleich zu anderen Kollagenosen

- SSc: Vaskulopathie, Inflammation und Fibrose

- Strategien zur Frühdiagnose

Identifikation von Patienten mit PAH und Kollagenosen (CTD)

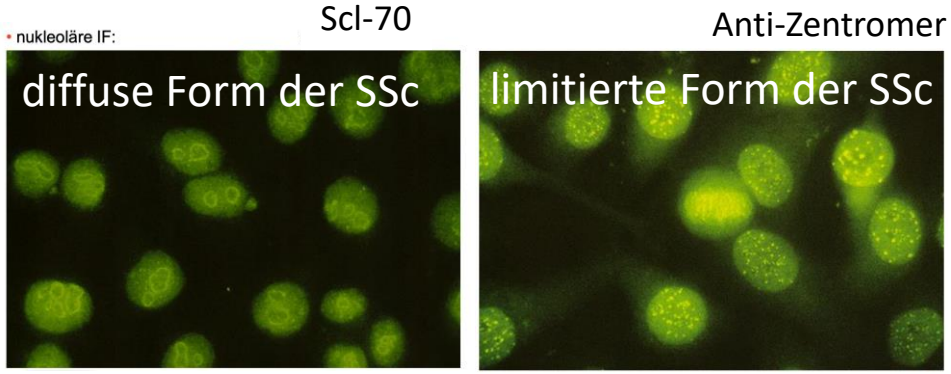
Scenario 1: V.a. Kollagenose bei PAH Patienten

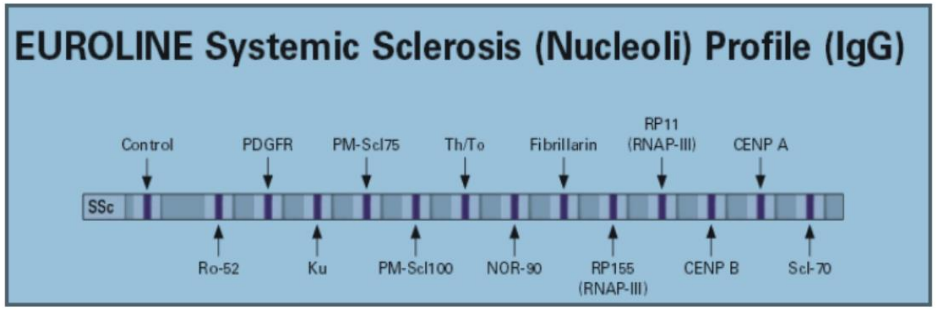
Klinik:

- Raynaudsymptomatik
- Siccasymptomatik
- Arthralgien/Arthritis
- Myalgien/Myositis
- Alopezie
- Photosensibilität
- Hautsklerose
- Dental-orale Probleme

Diagnostik

- Kapillarmikroskopie
- ANA/ENA Diagnostik





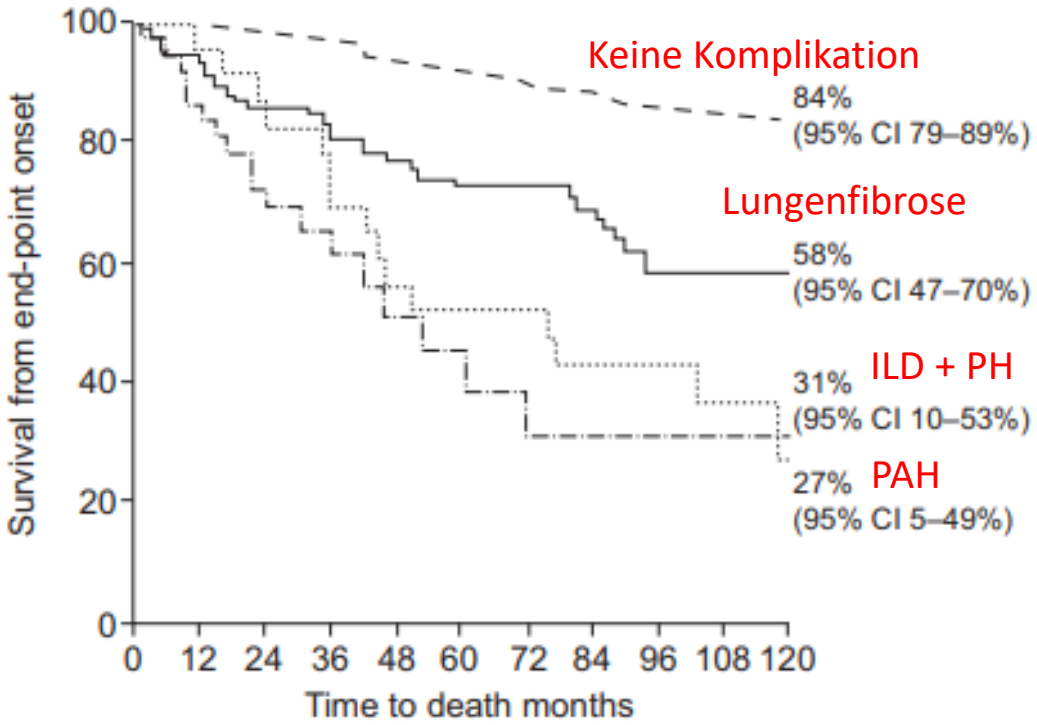
SSc Autoantikörper, Organkomplikationen und Outcome

	Cutaneous subtype	Clinical correlates
Anti-centromere	Limited cutaneous systemic sclerosis	Pulmonary arterial hypertension
Anti-topoisomerase 1 (anti-Scl 70)*	Diffuse cutaneous systemic sclerosis	Progressive interstitial lung disease
Anti-RNA polymerase 3	Diffuse cutaneous systemic sclerosis	Renal crisis and malignancy
Anti-U1 ribonucleoprotein (anti-ribonucleoprotein)	Limited cutaneous systemic sclerosis	Mixed connective tissue disease
Anti-U3 ribonucleoprotein (anti-fibrillarin)	Diffuse cutaneous systemic sclerosis	Pulmonary arterial hypertension and myositis
Anti-Pm-Scl	Limited cutaneous systemic sclerosis	Myositis
Anti-Th/To	Limited cutaneous systemic sclerosis	Interstitial lung disease and pulmonary arterial hypertension

Testing for systemic sclerosis-associated auto-antibodies is recommended early in the evaluation for systemic sclerosis because it can help establish a systemic sclerosis diagnosis and inform risk-stratification strategies. Patients will seldomly produce more than one systemic sclerosis-related auto-antibody concurrently. *Immunodiffusion is the preferred method for detecting anti-topoisomerase 1 antibodies, given that multibead assays are associated with high false-positive rates.

Table 1: **Autoantibodies associated with systemic sclerosis and their clinical correlates**

Volkmann ER et al, Lancet 2023



Subjects at risk n

No	247	222	175
PF	90	49	19
PAH	38	7	0
PF+PH	23	12	3

Denton CP et al 2011

Identifikation von Patienten mit PAH und Kollagenosen (CTD)

Scenario 2: V.a. PH bei SSc Patienten

Klinik:

- Belastungsdyspnoe
- Ruhedyspnoe
- Raynaud
- Anti-Zentromer, U1-RNP, Th/To

Diagnostik

- Herzecho
- Rechtsherzkatheter
- NT-proBNP
- HRCT Thorax
- 6MWT…

Table 2 Summary of Screening Models

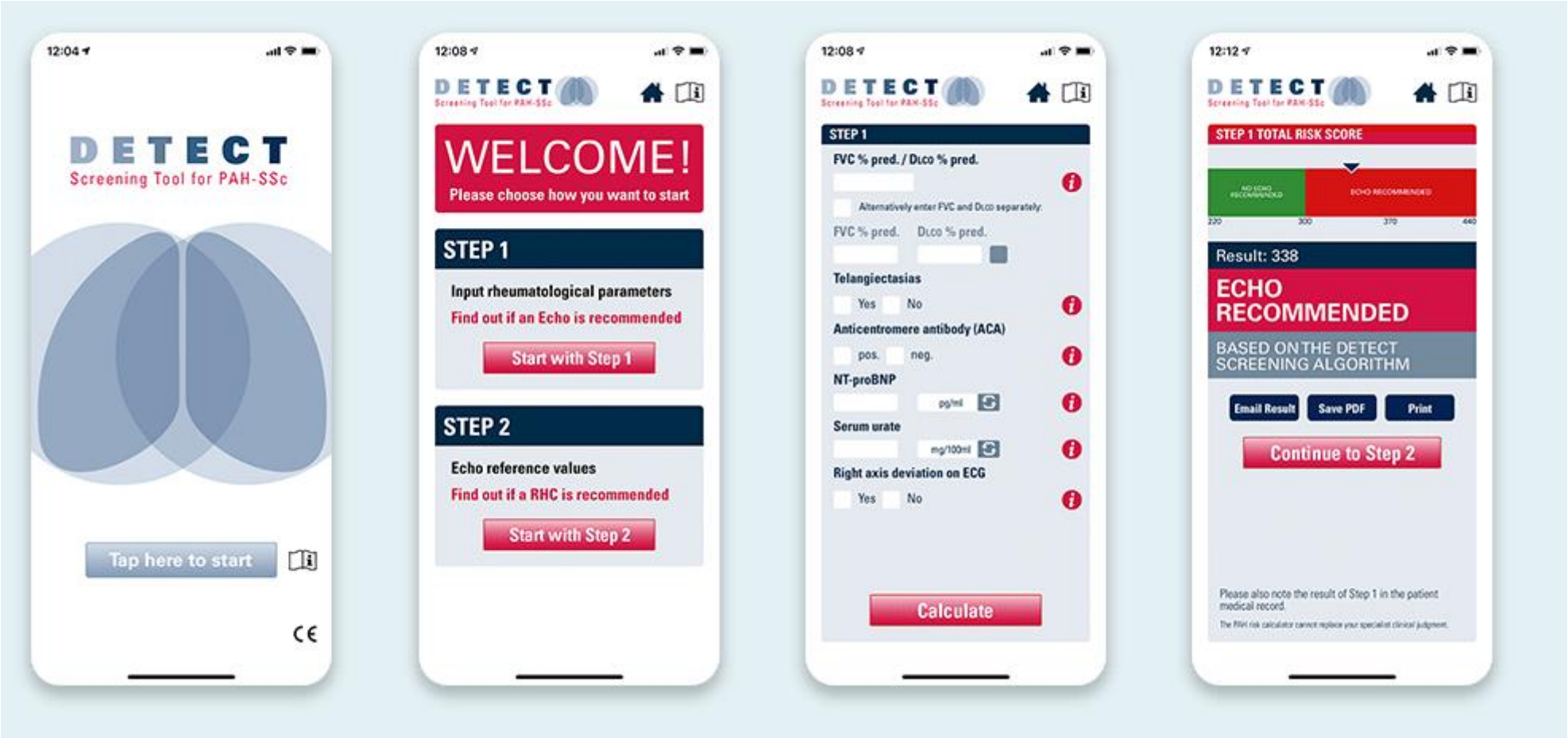
Screening Model	ESC/ERS[1]	DETECT[1]	ASIG[1]
Screening Criteria	High risk: • TRV > 3.4 m/s • TRV between 2.9 and ≤3.4 m/s and other echo findings suggestive of PH[a] Intermediate risk: • TRV between 2.9 and ≤3.4 m/s and no other echo findings • TRV ≤ 2.8 m/s and other echo findings suggestive of PH[a]	Step1 (non-echo): • FVC/DLCO (0–5) • Telangiectasias (0–1) • Anti-centromere Ab (0–1) • NT pro-BNP (0–10,000) • Serum urate (2–10) • Right axis deviation (0–1) If >300 points, move to step2 Step2 (echo): • Right atrium area (0–40) • TRV (0–5)	1. NT pro-BNP ≥ 210 pg/mL 2. DLCO < 70% predicted and FVC/DLCO ≥ 1.8
Referral for RHC	1. High risk 2. Intermediate risk with symptoms[b]	Score >35 points on step 2	Positive 1 and 2

Notes: [a]Findings include RV enlargement, flattening of the interventricular septum, RV outflow doppler acceleration <105 ms, early diastolic pulmonary regurgitation velocity >2.2 m/s, pulmonary artery diameter >2.5 cm, inferior vena cava enlargement, right atrial area in end-systole >18 cm^2. [b] Symptoms include ongoing dyspnea, syncope or near syncope, or presence of peripheral edema.

Abbreviations: Ab, antibody; ASIG, Australian Scleroderma Interest Group; DLCO, diffusing capacity for carbon monoxide; ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; echo, echocardiogram; PH, pulmonary hypertension, NT-proBNP, N-terminal-pro-brain natriuretic peptide; RHC, right heart catheterization; RV, right ventricle; TRV, tricuspid regurgitant velocity.

Almaaitah S et al 2020

Bsp: DETECT PAH online



Bsp: DETECT PAH online

DETECT
Screening Tool for PAH-SSc

STEP 2

Step 1 total risk score

points

Right atrium area

cm^2

TR velocity

m/s

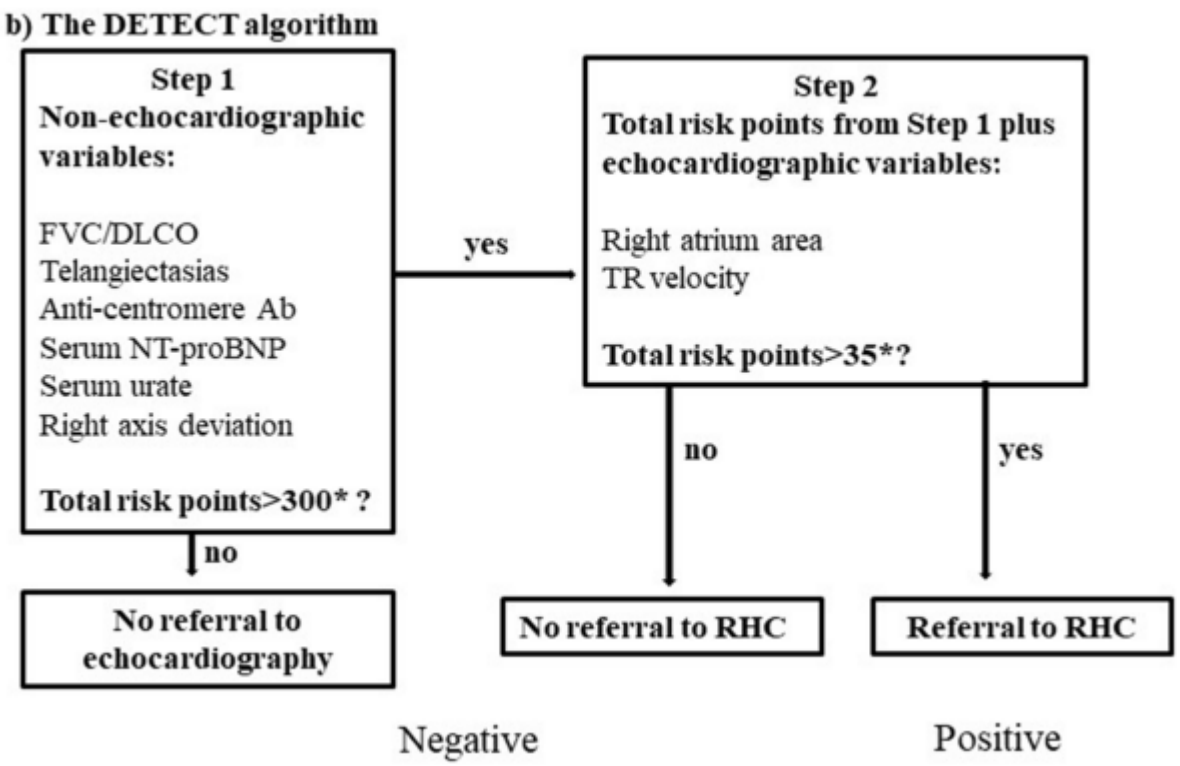
TR velocity not reported but RVSP is reported

RVSP(mmHg) **RAP(mmHg)**

No measurable TR

Calculate

DETECT und ASIG Algorithmus für das PAH Screening



Datenbasis: SSc > 3 Jahre, Dlco predicted < 60%

Coghlan et al 2014

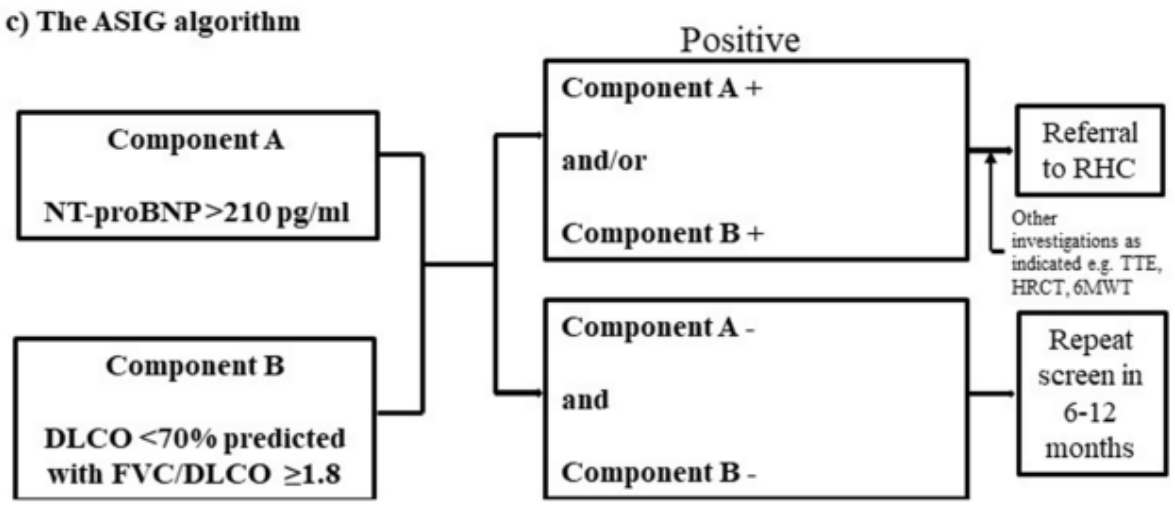


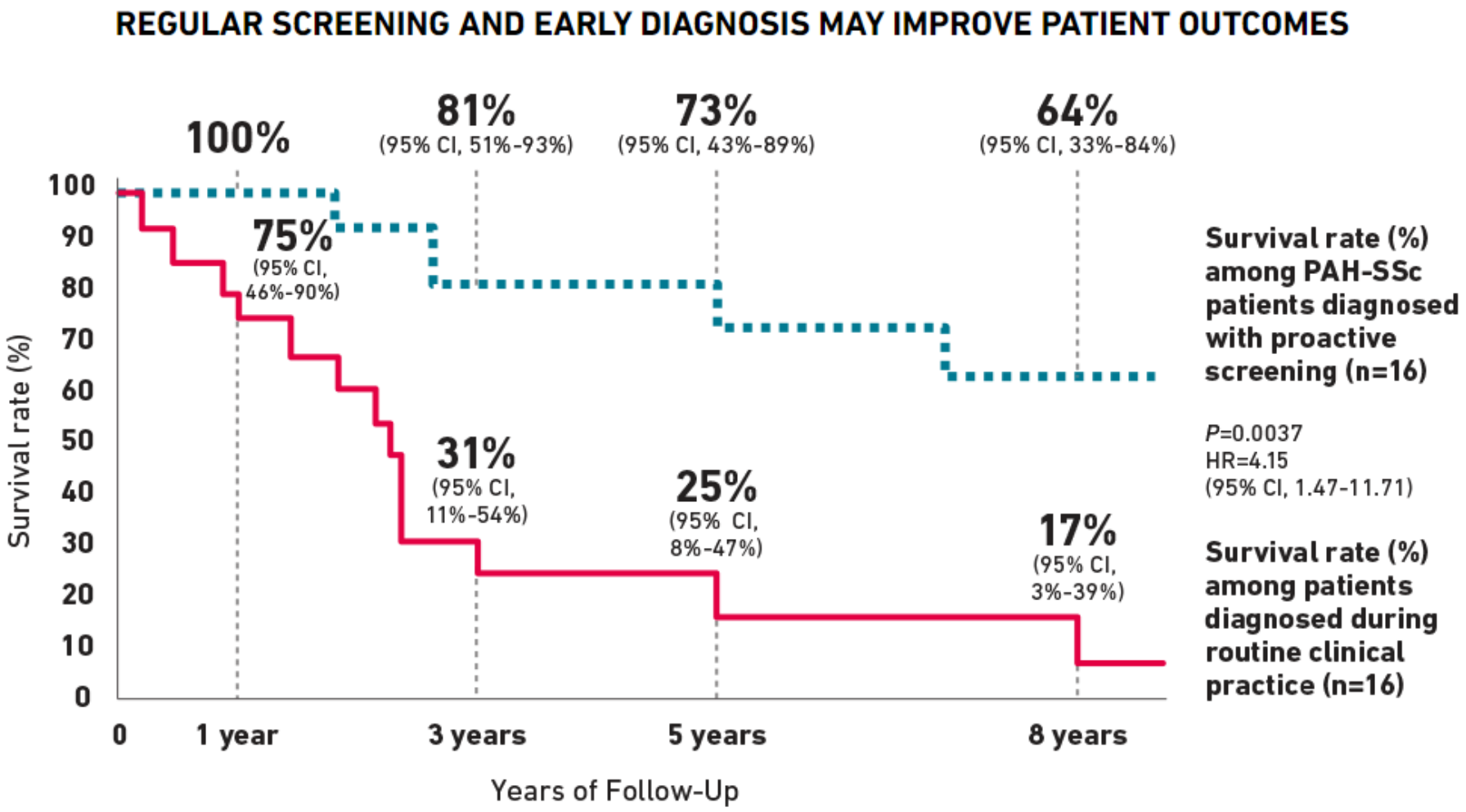
Table 3 Comparison of Reported Performance Characteristics of most commonly used Consensus Recommendations for Screening of Pulmonary Hypertension in Patients with Systemic Sclerosis

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
ESC/ERS guidelines	71.0%[34] 91.4%[36] 94.1%[37] 96.3%[35]	31.8%[37] 32.3%[35] 69.0%[34] 85.7%[36]	40.0%[34] 51.6%[37] 55.3%[35] 88.9%[36]	87.5%[37] 89.0%[34] 89.3%[36] 90.9%[35]
The ASIG algorithm	94.1%[37] 100%[35]	54.5%[35,37]	60.0%[35] 61.5%[37]	92.3%[37] 100%[35]
The DETECT algorithm	96.0%[34] 100%[35,36]	35.3%[35] 42.9%[36] 48.0%[34]	35.0%[34] 55.1%[35] 68.6%[36]	98.0%[34] 100%[35,36]

Abbreviations: ESC, European Society of Cardiology; ERS, European Respiratory Society; ASIG, Australian Scleroderma Interest Group.

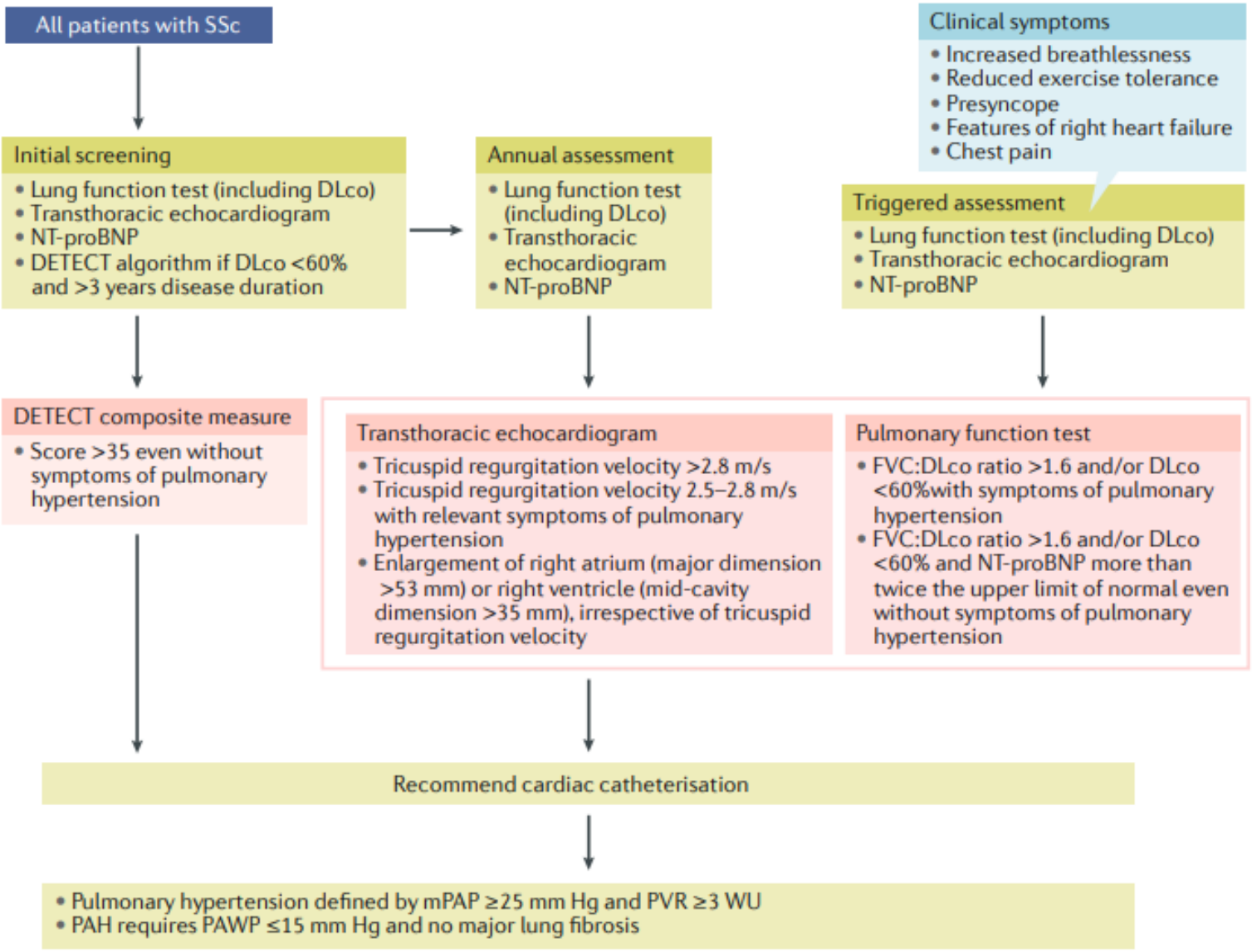
Saygin D et al 2019

Verbessertes Outcome bei regelmässigem Screening



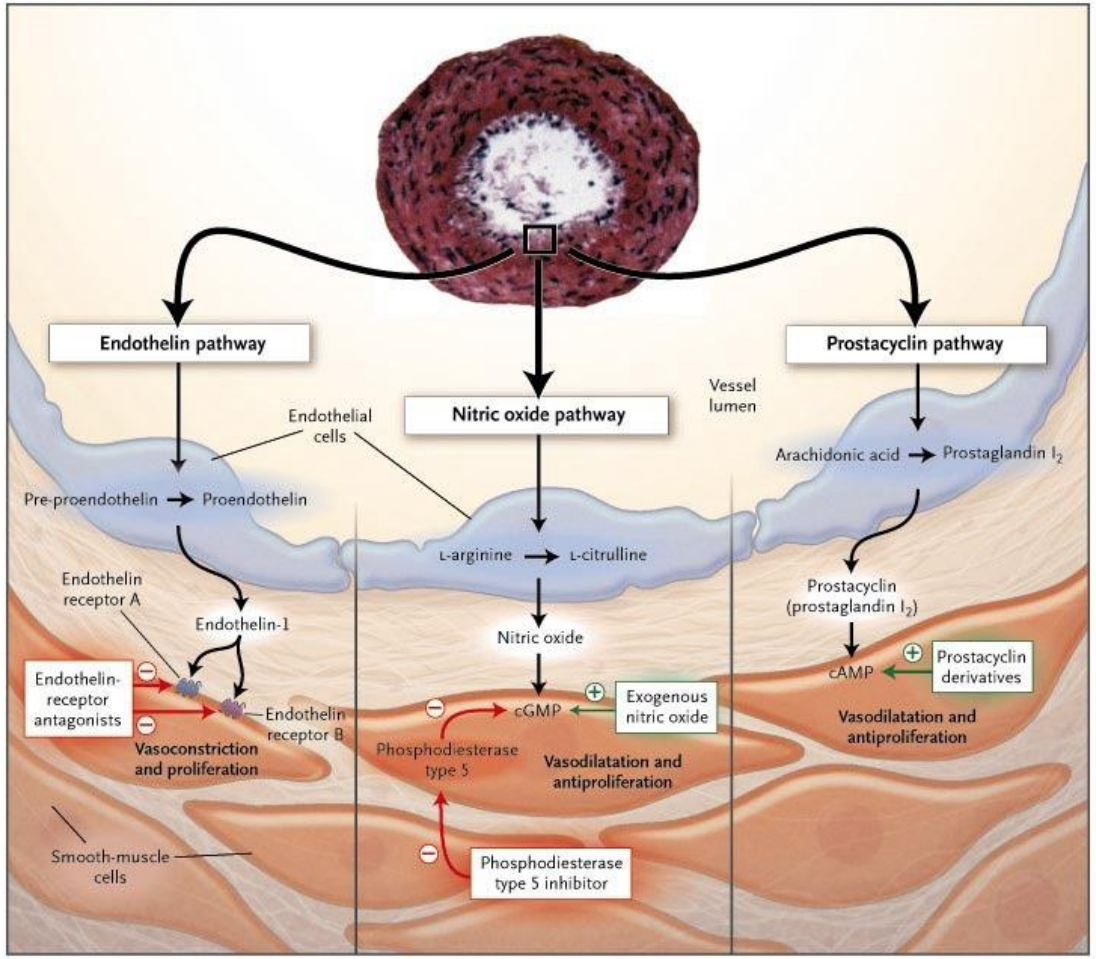
Zanatta E et al 2019

Jährliches PH Screening bei SSc Patienten

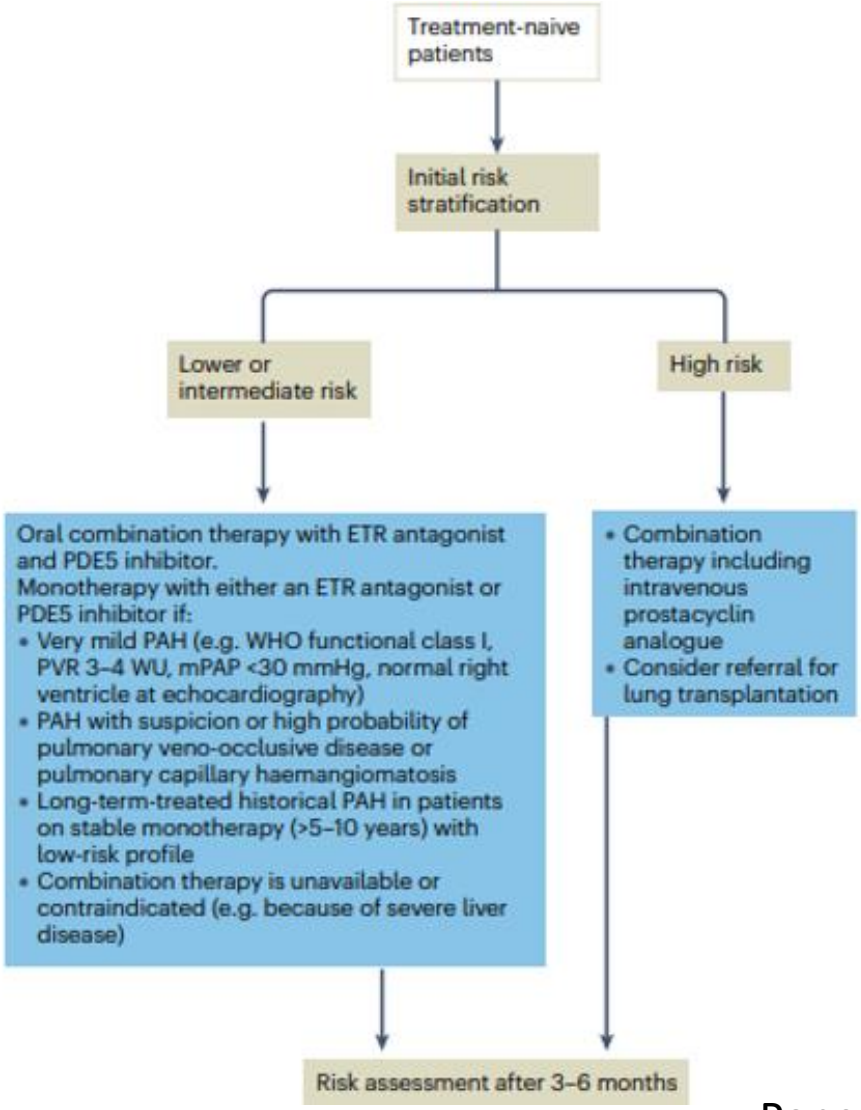


Denton CP et al 2018

Targets bei der pulmonal arteriellen Hypertonie (PAH)



Humbert M et al. NEJM 2004



Pope J et al 2023

Übersicht über vasoaktive Therapien bei Raynaud, digitalen Ulzera und SSc-PAH

	Mechanism of action	Benefit in systemic sclerosis	Safety issues
Pulmonary arterial hypertension: monotherapy or combination therapy with sildenafil and tadalafil and bosentan and ambrisentan are commonly used as first-line therapy for systemic sclerosis associated with pulmonary arterial hypertension. Selexipag, riociguat, and prostacyclin therapy are most often used as second-line therapies			
Sildenafil and tadalafil	Promote vasodilation via nitric oxide-cyclic guanosine monophosphate enhancement	Improved exercise capacity, haemodynamics, and functional class	Hypotension, particularly when used in combination with other vasodilator therapies
Bosentan and ambrisentan	Inhibit endothelin-A and endothelin-B receptor signalling	Improved exercise capacity, haemodynamics, and functional class	Lower extremity oedema and liver-function test abnormalities
Selexipag	Selective oral prostacyclin receptor agonist that results in vasodilation of the pulmonary vascular bed	Reduction in the number of hospitalisations and disease progression	Headache, diarrhoea, and nausea
Riociguat	Stimulates soluble guanylate cyclase, regardless of nitric oxide concentrations, to produce more cyclic guanosine monophosphate, resulting in vasodilation	Improved exercise capacity, haemodynamics, and functional class	Gastro-oesophageal reflux disease, diarrhoea, nausea, dizziness, and headache
Prostacyclin therapy (eg, reprostinil, epoprostenol, iloprost, and beraprost)	Prostacyclin agonist that promotes relaxation of smooth muscle, inhibition of platelet aggregation, and vasodilation of pulmonary arteries	Improved exercise capacity, haemodynamics, and functional class	Headache, diarrhoea, and nausea

Volkmann E et al Lancet 2023

Langzeitprognose der SSc-PAH (PHAROS)

- 160 Patienten aus PHAROS
- Survival bis zu 8 Jahren nach PAH Diagnose (8J: 49%)
- 52% aller Todesfälle wegen PAH
- 93% der PAH assoziierten Todesfälle < 4 Jahre nach Diagnose

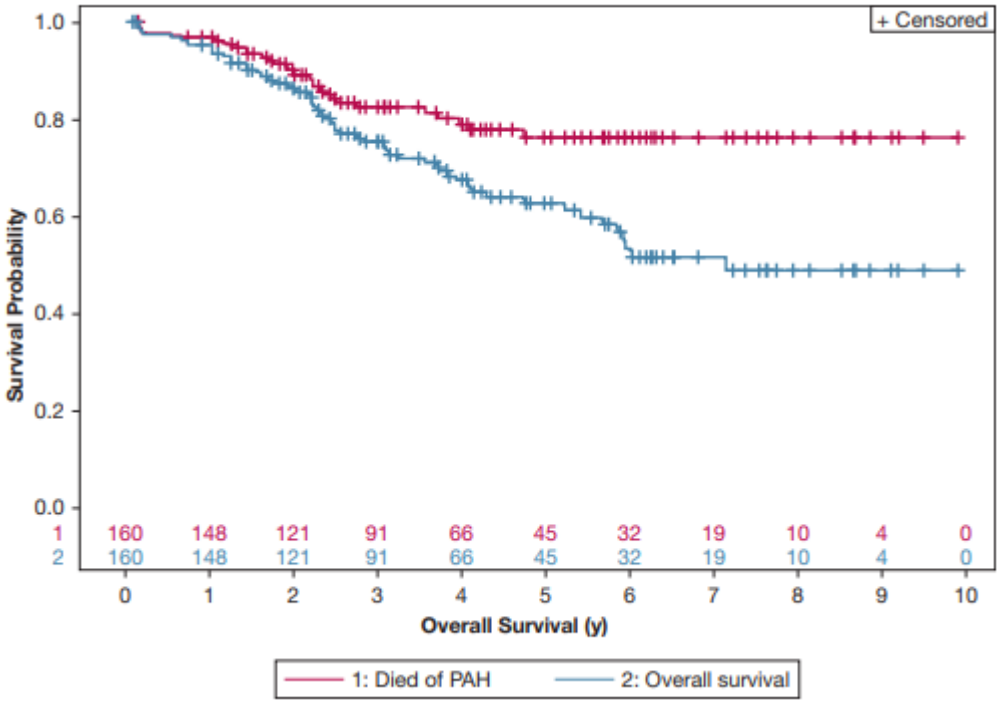


TABLE 2] Cause of Death by Survival Time

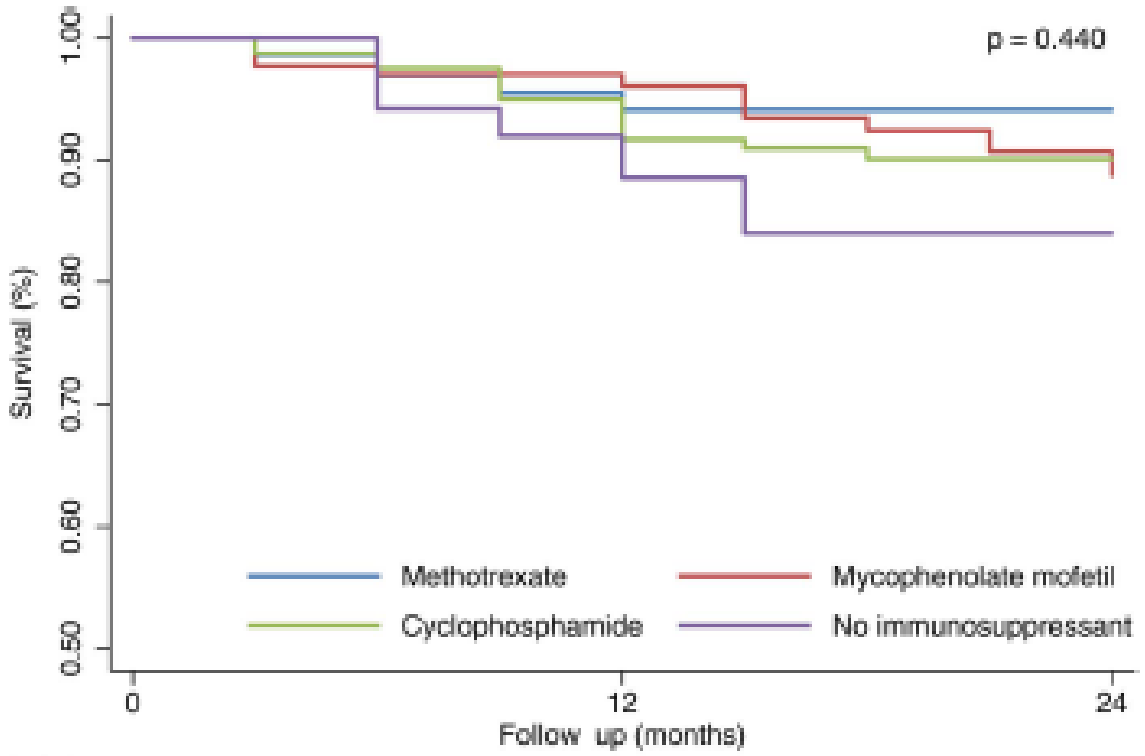
Cause of Death	Survival < 4 y (n = 44)	Survival ≥ 4 y (n = 12)
SSc related		
PAH	27 (61.4)	2 (16.7)
Pulmonary fibrosis	1 (2.3)	0
GI	0	1 (8.3)
Renal crisis	0	1 (8.3)
Multiorgan failure	4 (9.1)	2 (16.7)
SSc unrelated		
Cancer	4 (9.1)	2 (16.7)
Infection	4 (9.1)	1 (8.3)
Cerebrovascular disease	0 (0)	1 (8.3)
Sudden death	1 (2.3)	1 (8.3)
Unknown	3 (6.8)	1 (8.3)

Data are presented as No. (%) unless otherwise indicated. PAH = pulmonary artery hypertension. See Table 1 legend for expansion of other abbreviations.

Kolstadt KD et al 2018

Bringt eine immunsuppressive Therapie etwas? Schlechteres Überleben ohne Immunsuppression!

ILD/PAH 74.6%
kardial 71.6%



Number at risk			
Methotrexate	65	54	45
Mycophenolate mofetil	118	108	82
Cyclophosphamide	87	75	55
No immunosuppressant	56	50	32

Number of patients at risk displayed were derived from the unweighted model.

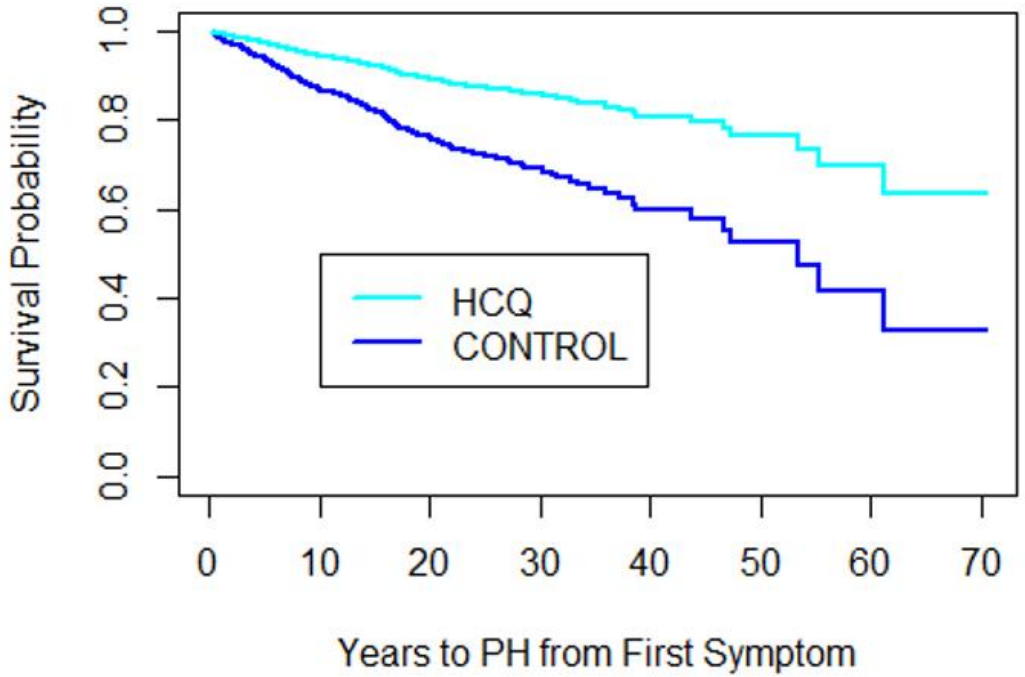
Herrick et al 2017

Hydroxychloroquin und PAH Risiko

Design: Prospektive Beobachtungstudie (Pittsburgh SSc-Zentrums) an 208 SSc-Pat. unter HCQ (≥ 3 Monate) und 976 SSc-Pat. ohne HCQ, Behandlungszeitraum 1990-2015

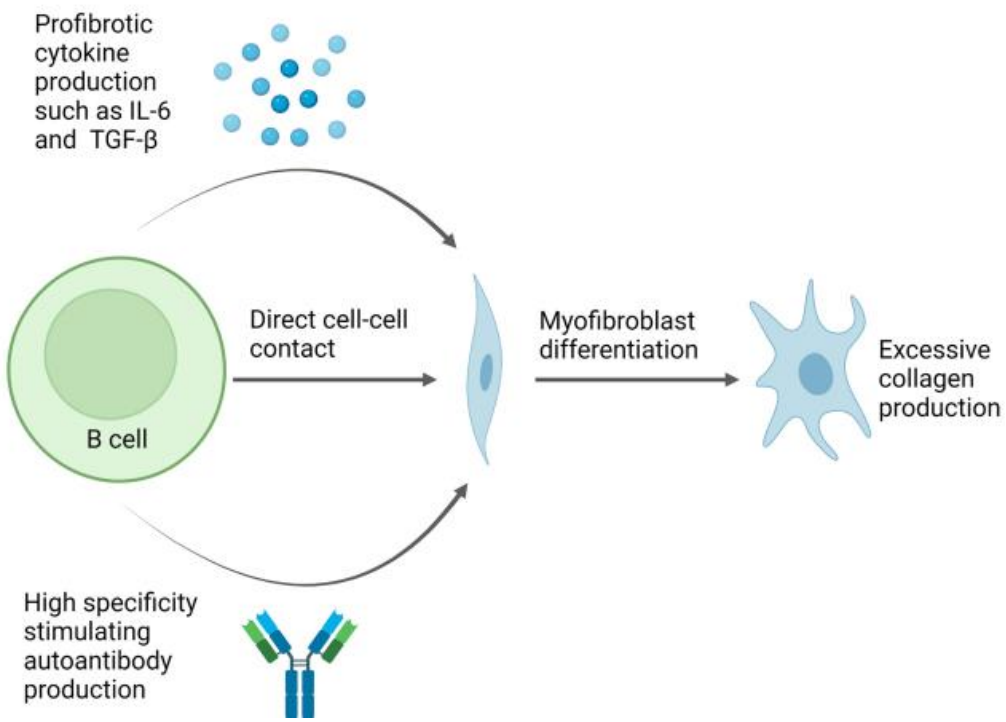
HCQ-Patienten hatten häufiger eine limitierte SSc und Anti-Centromer-Ak,

Kein Unterschied im Auftreten einer PAH in der Gesamtkohorte, aber signifikant seltener bei SSc-Patienten, die in den ersten 18 Monaten HCQ erhielten



A. Boucher et al. , Arthritis Rheumatol. 2020; 72 (suppl 10)

Hat eine gegen B-Zellen gerichtete Therapie einen Benefit?



NIH Studie
multizentrisch, doppelblind, randomisiert, plazebo-kontrolliert

57 Patienten mit SSc-PAH (2010-2018)

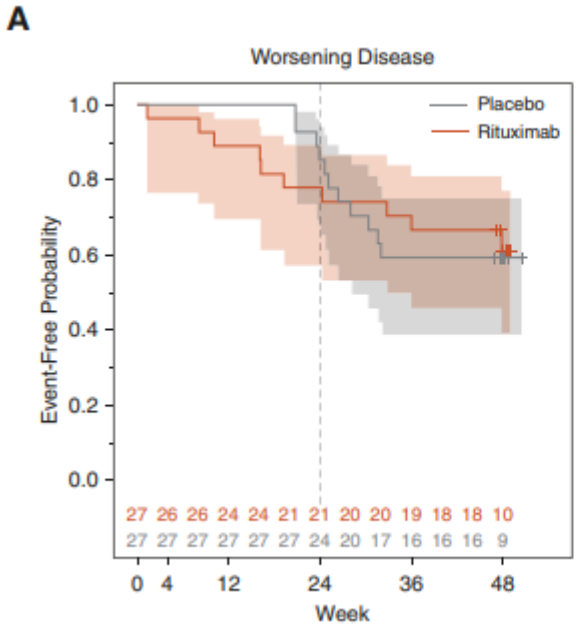
2 x RTX 1000mg (d0, d14) versus Plazebo

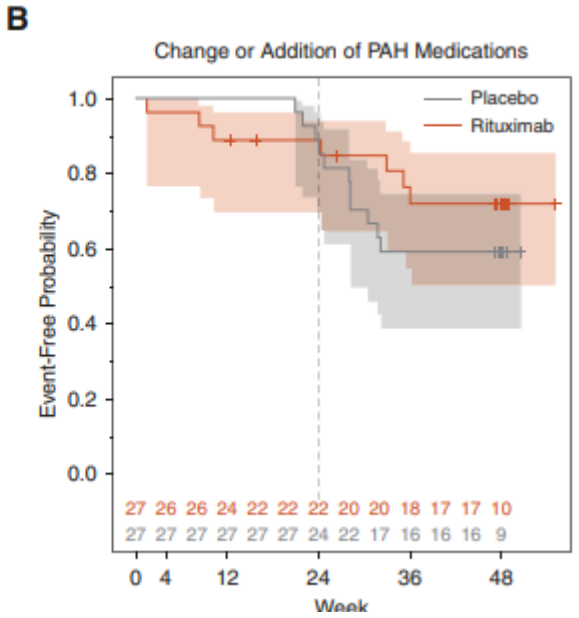
Primärer Endpunkt: Veränderung im 6MWD nach 24 Wochen

Beersley et al

Zamanian RT et al 2021

Rituximab bei der SSc-PAH

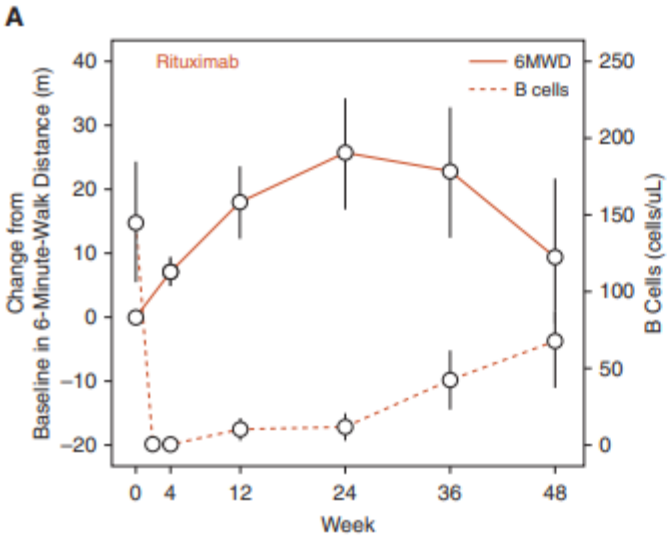


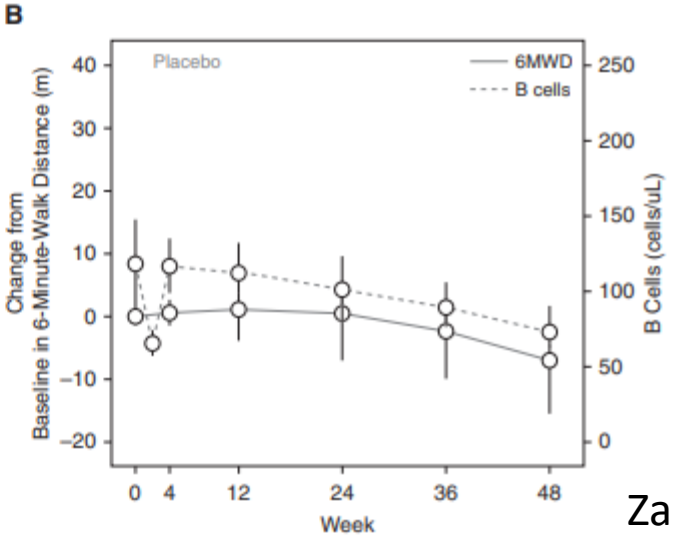


- Mittleres Alter 58.2 (9.1) J
- 43.9% Zentromer +, Th/T0 17.5%
- WHO Klasse 2/3/4: 42.1%, 56.1%, 1.8%
- PAH Medikation: PDE-I 73.7%, ERA 61.4%, Prostacyclin 52.6%
- Mittl 6MWD 331.2 m (99.7)
- Mittl NTproBNP 820.8 pg/ml (944.6)
- DLCO (% predicted) 45.3 (15.7)

6MWD nach 24 Wochen: NS
6MWD nach 48 Wochen:

RTX 25.5 ± 8.79
Plac 0.4 ± 7.43 p = 0.03





Zamanian RT et al 2021

SSc-Patienten mit vasoaktiven Therapien und PPI haben ein geringeres Malignomrisiko

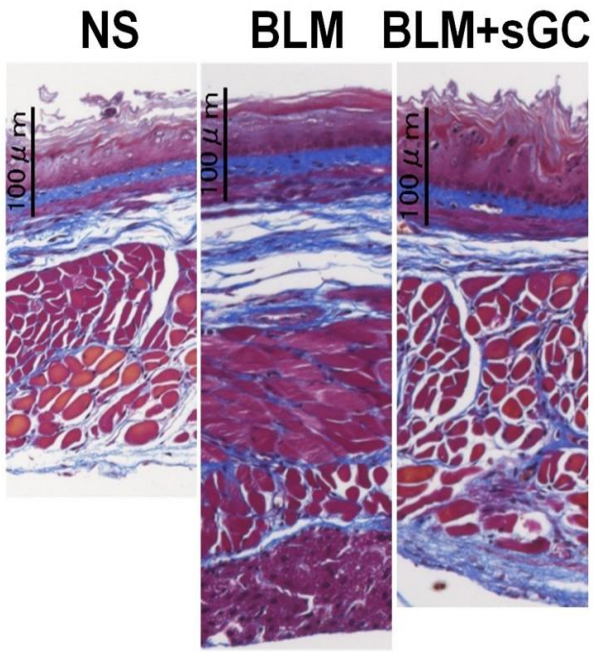
Analyse eines span.Registers, knapp 2000 Patienten, davon 1729 ohne und 206 mit Malignom

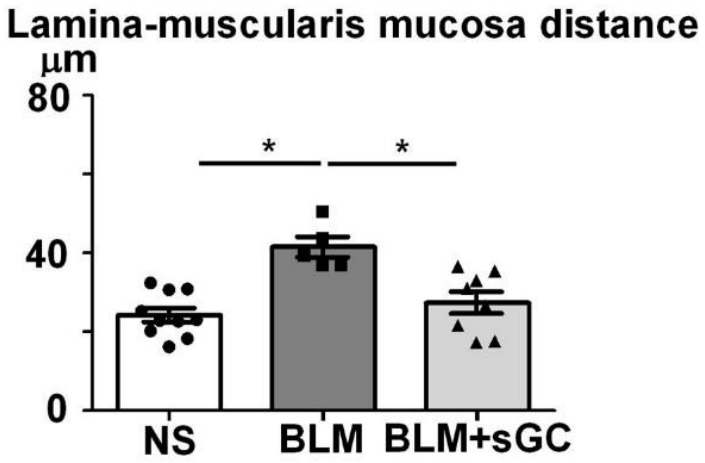
Risikofaktor	Odds ratio	95% CI	P-Wert
Erhöhtes Alter bei SSc-Beginn	**1,22**	**1,01-1,03**	**<0.001**
PBC	**2,35**	**1,16-4,68**	**0,015**
ILD mit FVC < 70%	**1,83**	**1,24-2,70**	**0,002**
Anti-Centromer-Ak	**0,66**	**0,45-0,97**	**0,036**
Calciumblocker	**0,54**	**0,37-0,79**	**0,002**
Spezifische Vasodilatoren wie ET-Blocker, PDE-V-Inhibitoren, Prostagl.	**0,46**	**0,26**	**0,006**

Auch ASS und PPI waren mit geringerem Auftreten von Malignomen assoziiert

Carbonellie C. et al., Autoimmunity Reviews 21 (2022), 103167

Riociguat und Ösophagusfibrose: Resultate aus dem Bleomycinmausmodell





Weibliche C56/Bl6 -Mäuse

Im Tiermodell gibt es Hinweise, dass die Bleomycin-induzierte Ösophagusfibrose durch Riociguat verbessert werden kann

Yamamoto-Y et al. Arthritis Rheumatol. 2020; 72 (suppl 10), Abstract # 1905

Der systemische Lupus erythematodes (SLE)

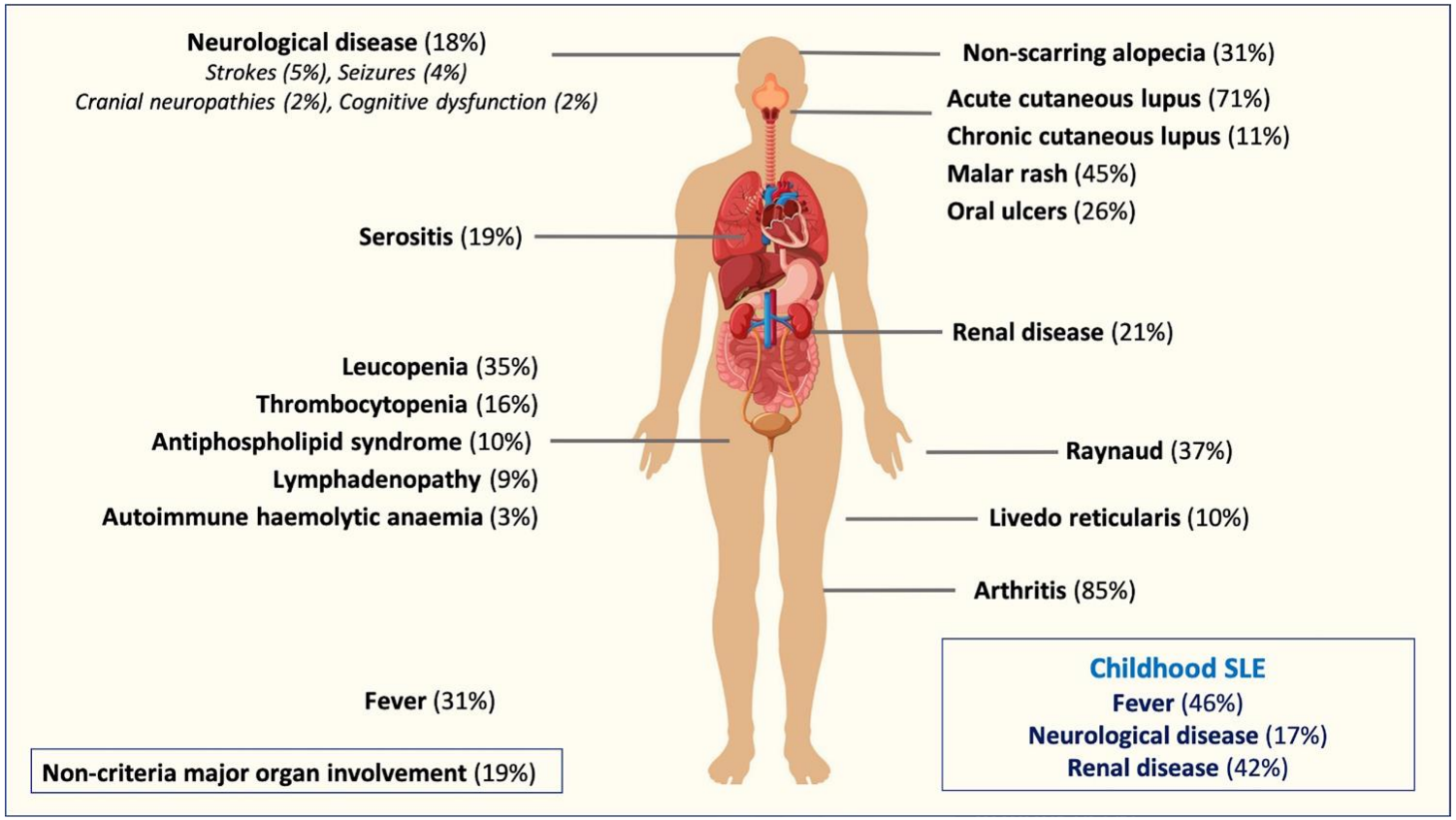


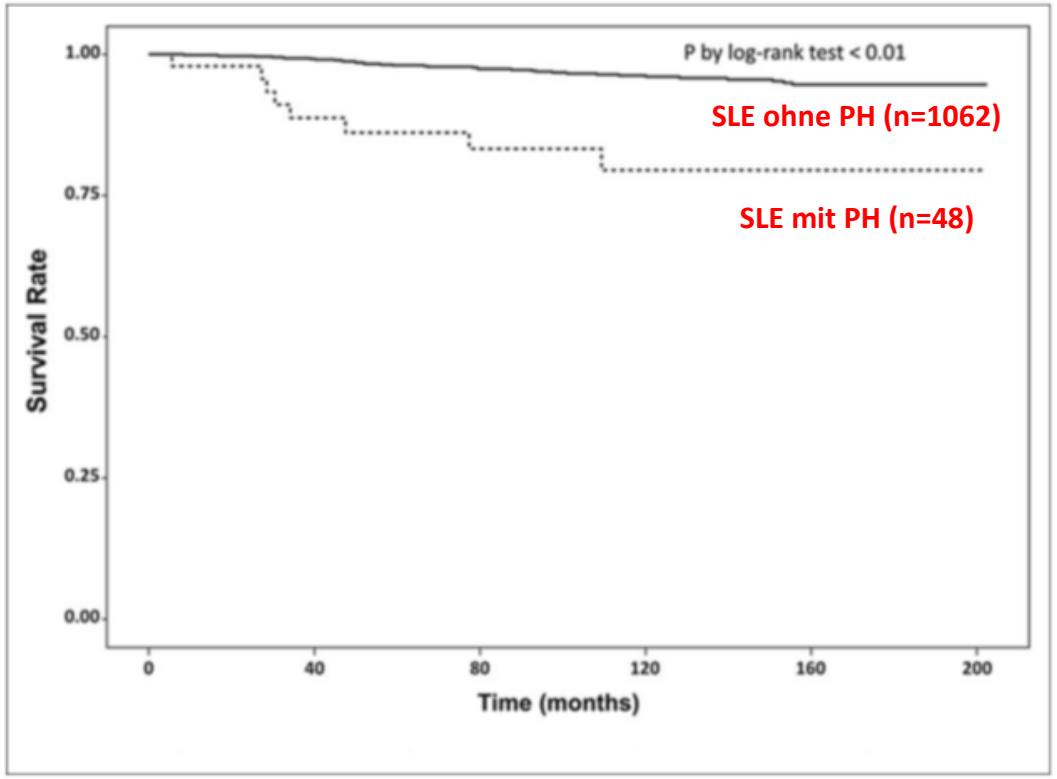
Figure 3 Key features and organs involved in SLE. Cumulative frequencies are depicted. Of note, the frequency of nephritis is not as common as previously reported, which may have been the result of referral biases in major lupus centres. Neuropsychiatric disease is an emerging frontier in lupus care. Childhood SLE has higher activity at presentation, is more likely to be severe and to receive more aggressive therapy, as well as accumulate damage. Data from Nikolopoulos *et al*.[18] SLE, systemic lupus erythematosus.

Pulmonale Hypertonie bei SLE: Risikofaktoren

1110 Patienten mit SLE (Einschluss 1998-2013)

PH: syst. Druck ≥30mmHg ECHO in Ruhe

48 Patienten mit PH + SLE



Risiko für PH bei SLE

- **Pleuritis/Perikarditis (OR 4,6)**
- **Anti-RNP-Ak (OR 2,4)**
- **ILD (OR 8,3)**
- **cerebro-kardiovask. Erkr. (OR 13,4)**
- **Raynaud-Syndrom**
- **kutane vaskulitische Läsionen**
- **Antiphospholipidantikörper**

Kim JS et al. Lupus 2018

Vergleich SSc-PAH und SLE-PAH

Table 1
Summary table of differences between SSc-PAH and SLE-PAH (with respect to the areas considered in this review).

	Systemic Sclerosis	Systemic Lupus Erythematosus
Estimated Prevalence in the United States (per 100,000)	20–30	20–200
Prevalence of PAH	7%–12% of SSc patients	1%–5% of SLE patients
% of CTD-PAH	60%–80%	15%–20%
Age of onset of CTD-PAH	60 - 65 years	40 - 45 years
% of CTD with positive anti-U1 RNP[b]	2%–14%	20%–40%
Association with CTD disease activity	No	Yes
Clinical course of CTD-PAH	Progressive	Variable and unpredictable
Response to immunosuppressants	No	Potentially Yes[a]
Prognosis, 3-year survival on PAH therapy	50%–60%	75%–85%
Clinical pulmonary & cardiovascular manifestations	• Pulmonary Arterial Hypertension • Interstitial Lung Disease • Recurrent aspiration • Pulmonary venoocclusive disease • Pulmonary capillary hemangiomatosis • Pulmonary Emboli • Diastolic LV dysfunction • Myocardial fibrosis • Increased lung cancer risk • Rarely LV systolic dysfunction • Pleural effusions are uncommon	• Pulmonary Arterial Hypertension • Interstitial Lung disease • Lupus Pneumonitis • Pulmonary Emboli • Alveolar Hemorrhage • Organizing Pneumonia • Pleuritis • Pleural effusion • Diastolic dysfunction • Valvular pathology • Shrinking Lung Syndrome

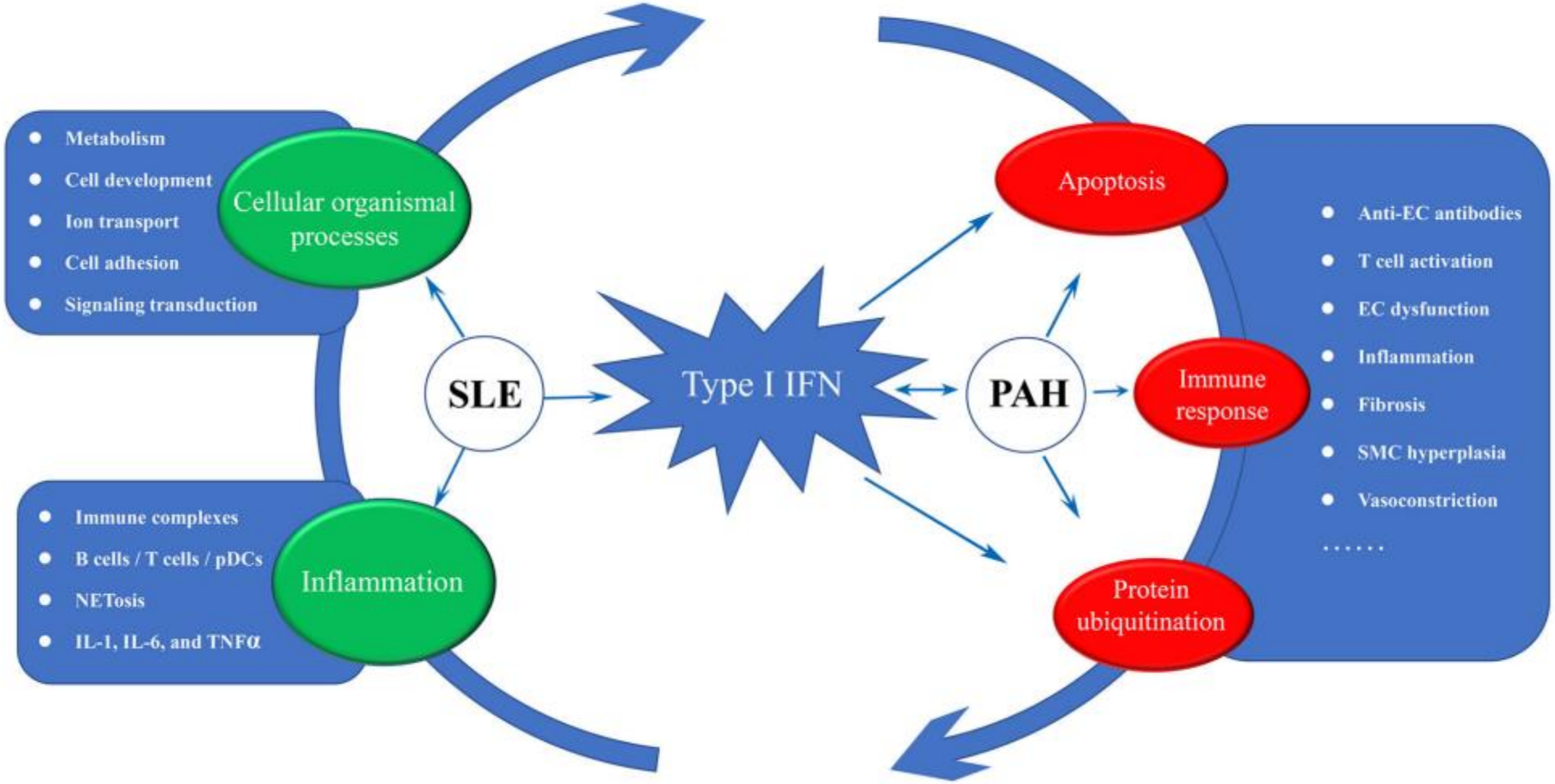
PAH: pulmonary arterial hypertension. SSc: Systemic Sclerosis (scleroderma). SLE: Systemic Lupus Erythematosus. CTD: Connective tissue disease.

[a] When/if responds to immunosuppressants, long-term response is not known, and likely only transient.

[b] anti-U1 RNP antibody is associated with PAH incidence, and with better survival in PAH.

Bazan IS et al 2018

Neue Daten zur Pathophysiologie: Erhöhte IFN alpha Signatur



Microarray Analyse von SLE und PAH Patienten in der Gene Expression Omnibus Database

Yao M et al Front Immunol 2021

Überlappende Genexpression bei SLE und PAH

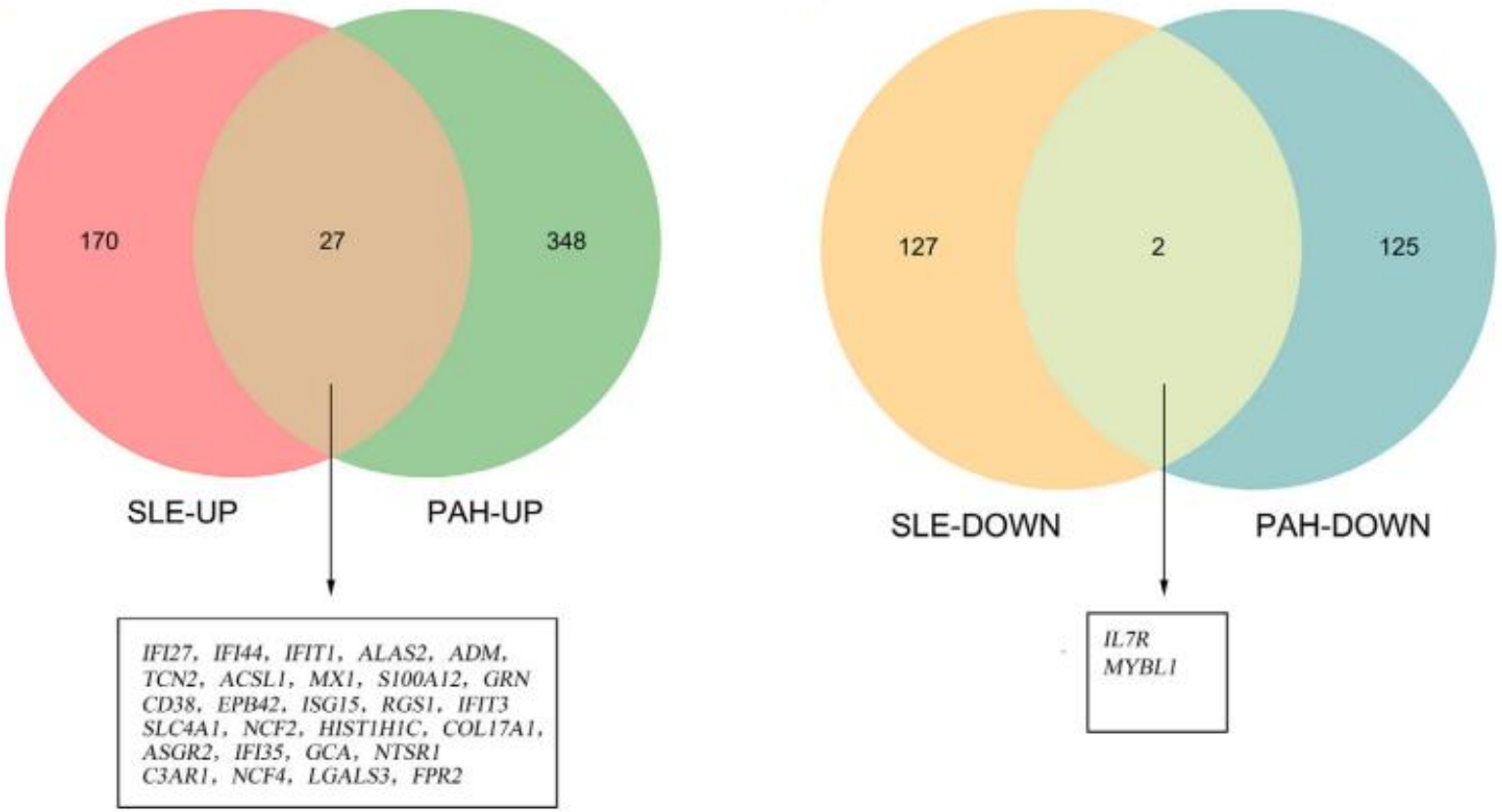


FIGURE 5 | Identification of the common DEGs. **(A)** The Venn diagram of the upregulated genes in GSE81622 and GSE703. **(B)** The Venn diagram of the downregulated genes in GSE81622 and GSE703. DEGs differentially expressed genes.

Yao M et al Front Immunol 2021

Zusammenfassung

- Die PH ist eine relevante Komplikation bei Autoimmunerkrankungen
- Die Klassifikation kann, bedingt durch andere Krankheitsmanifestationen, erschwert sein
- Survival CTD-PAH < iPAH (Pathophysiologische Besonderheiten)
- Regelmässiges Screening ist wichtig (Rheumatologen)
- Kollagenosen in der DD einbeziehen (Nicht-Rheumatologen)
- Unterschiede bei SSc-PAH und SLE-PAH
- Stellenwert der immunsuppressiven Therapie SLE, ggf auch SSc