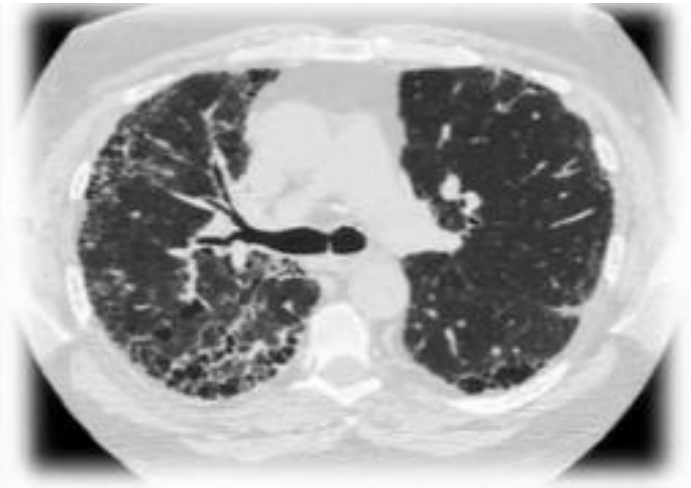
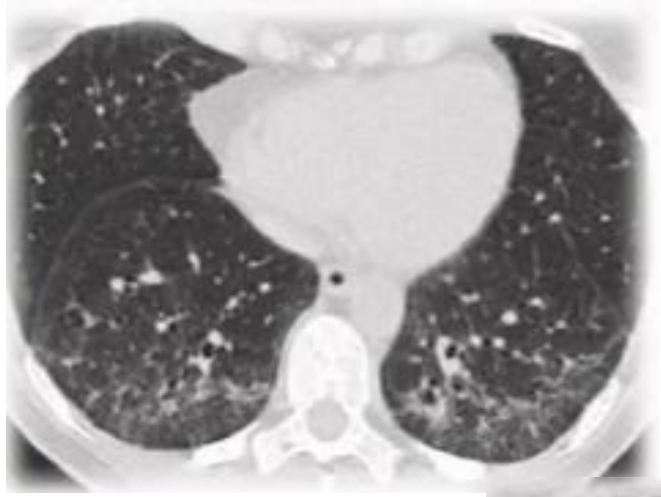
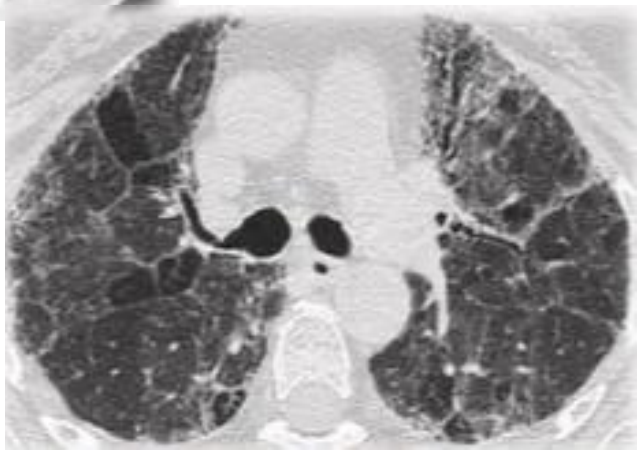






Bağ doku hastalıklarında interstisyel akciğer hastalığı

Dr.İlyas Ercan OKATAN

İç Hastalıkları Romatoloji Bilim Dalı

Karadeniz Teknik Üniveritesi Tıp Fakültesi Farabi Hastanesi

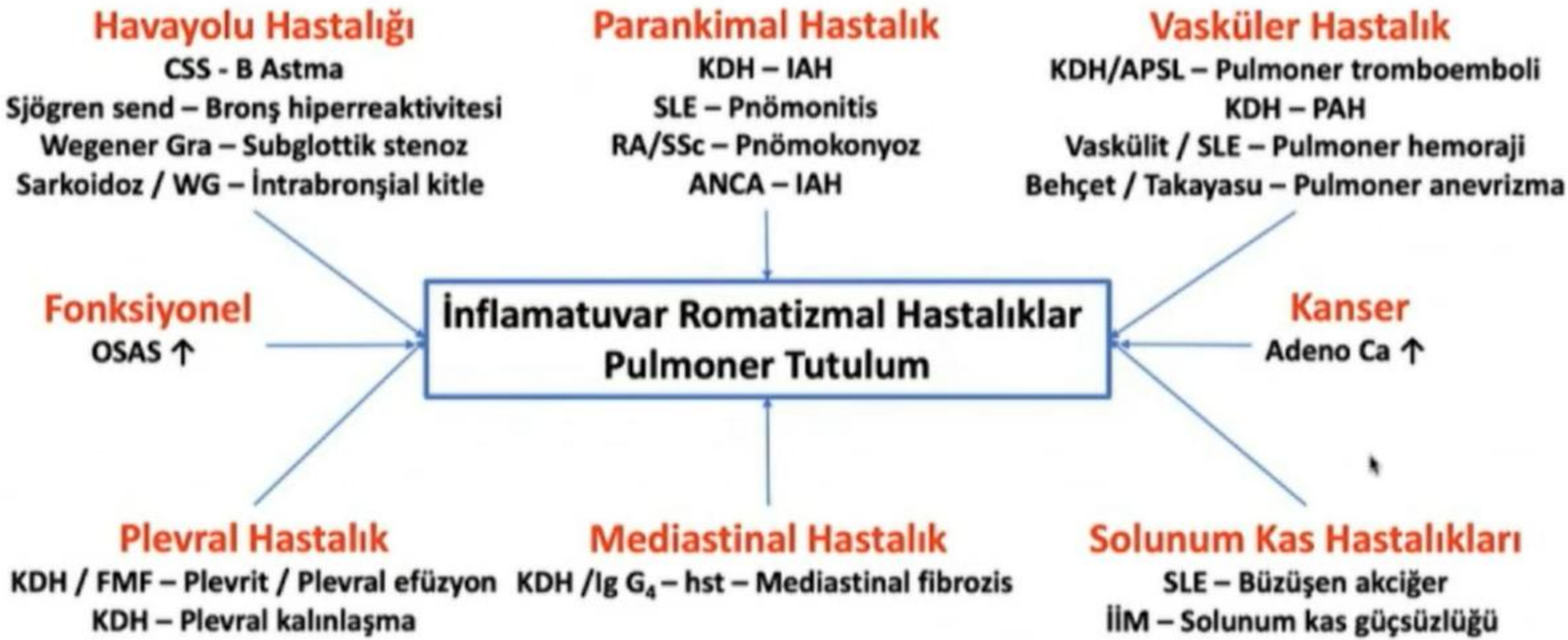
Sunum planı

1- Giriş

2- Patogenez

3- Bağ doku hastalıkları ile ilişkili interstisyel akciğer hastalığı

4- Tedavi


Havayolu Hastalığı
CSS - B Astma
Sjögren send – Bronş hiperreaktivitesi
Wegener Gra – Subglottik stenoz
Sarkoidoz / WG – İntrabronşial kitle
Parankimal Hastalık
KDH – IAH
SLE – Pnömonitis
RA/SSc – Pnömokonyoz
ANCA – IAH
Vasküler Hastalık
KDH/APSL – Pulmoner tromboemboli
KDH – PAH
Vaskülit / SLE – Pulmoner hemoraji
Behçet / Takayasu – Pulmoner anevrizma
Fonksiyonel
OSAS ↑
İnflamatuvar Romatizmal Hastalıklar
Pulmoner Tutulum
Kanser
Adeno Ca ↑
Plevral Hastalık
KDH / FMF – Plevrit / Plevral efüzyon
KDH – Plevral kalınlaşma
Mediastinal Hastalık
KDH /Ig G4 – hst – Mediastinal fibrozis
Solunum Kas Hastalıkları
SLE – Büzüşen akciğer
İİM – Solunum kas güçsüzlüğü

Bağ doku hastalıkları-İAH zamansal ilişki

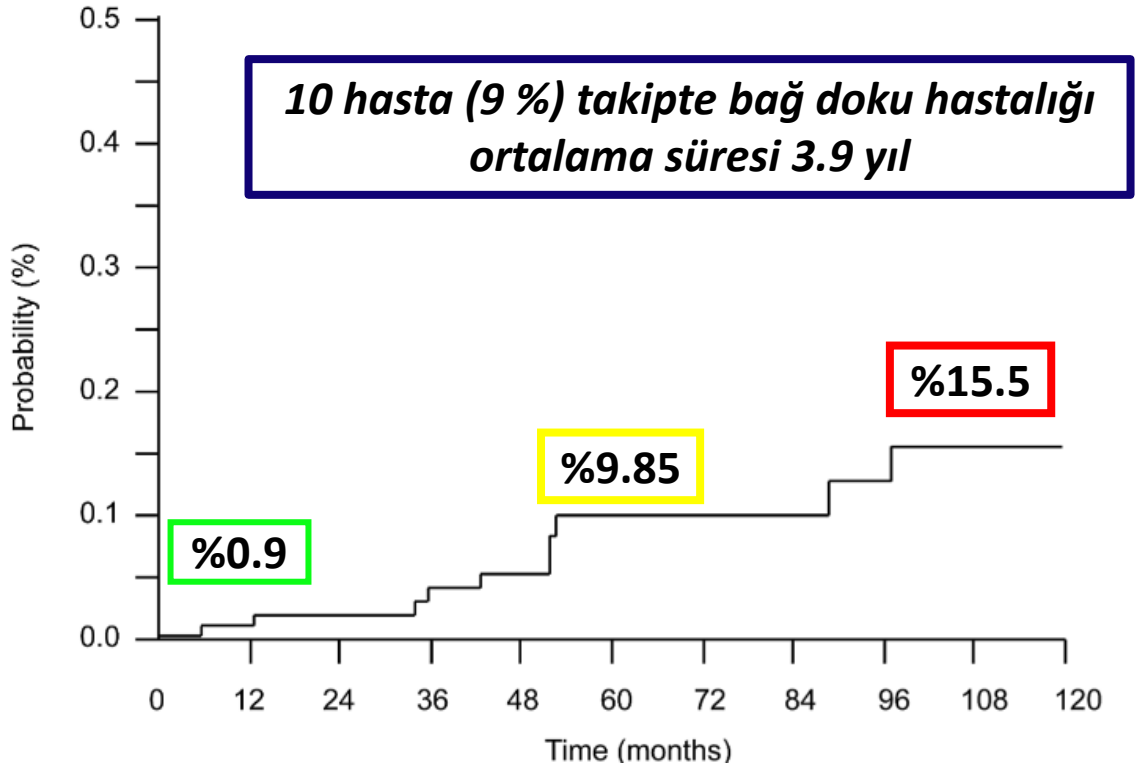
İlk bağ doku hastalığı % 70 (37 ay)

Eş zamanlı tanı % 18.5

İlk İAH % 11 (20 ay)

111 İPF hastası Retrospektif

10 hasta (9 %) takipte bağ doku hastalığı ortalama süresi 3.9 yıl



Walker et al. Medicine 47(6):501-20,1968 Kono et al, Plos ONE 2014

Bağ doku hastalıkları-İAH riski

SLE 1-15 %

RA 6.5-33 %

PM/DM 19.9-86 %

Anti-jo-1 pozitif hastalar 19.9-86 %

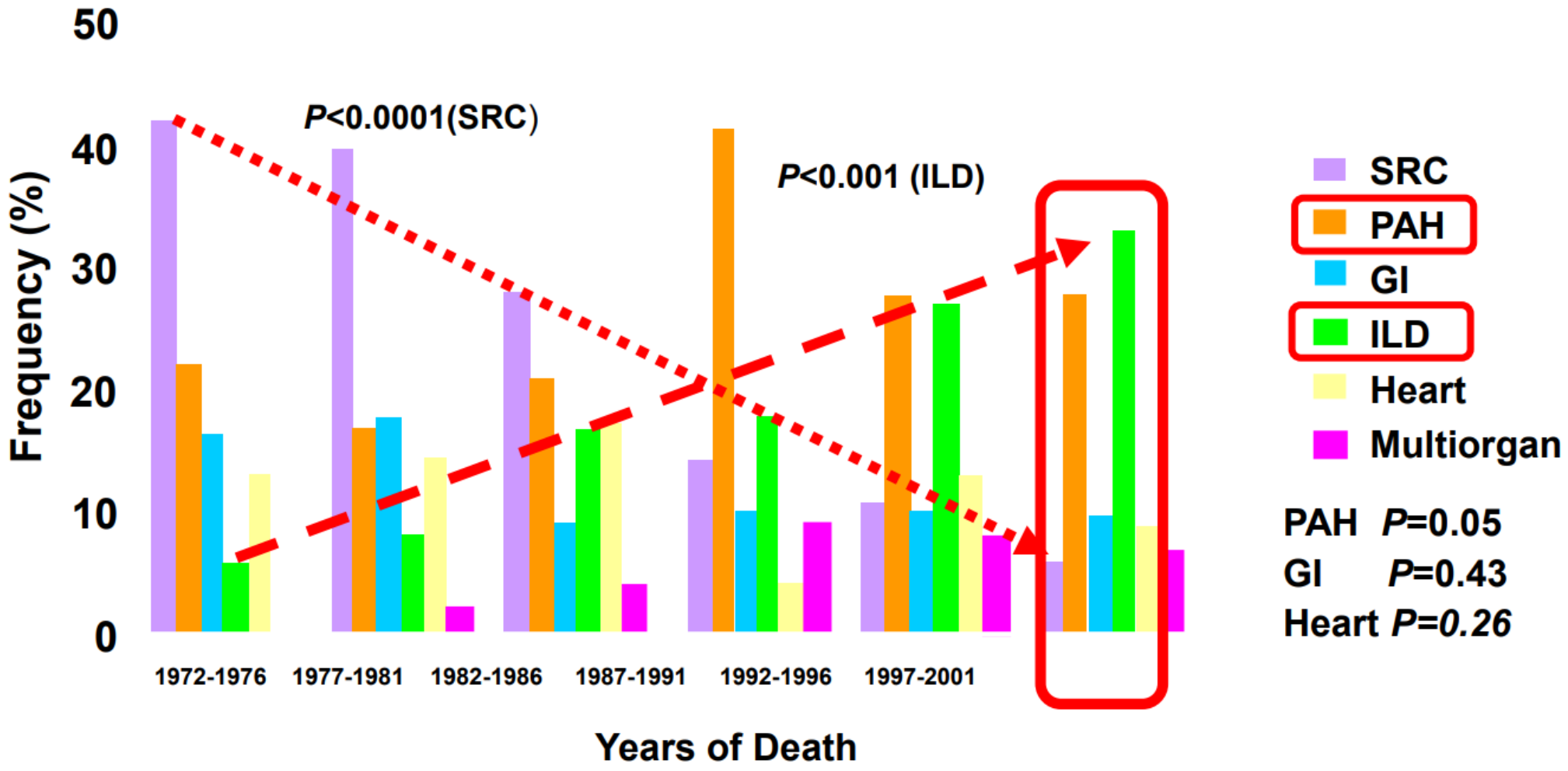
SSc 40-91 %

MBDH 47-90 %

PSS

Front. Immunol., 07 June 2021 interstitial Lung Disease in Connective Tissue Disease: A Common Lesion With Heterogeneous Mechanisms and Treatment Considerations Tihong Shao[1,2†], Xiaodong Shi[3†]

No Longer Changing Patterns of Mortality in Scleroderma



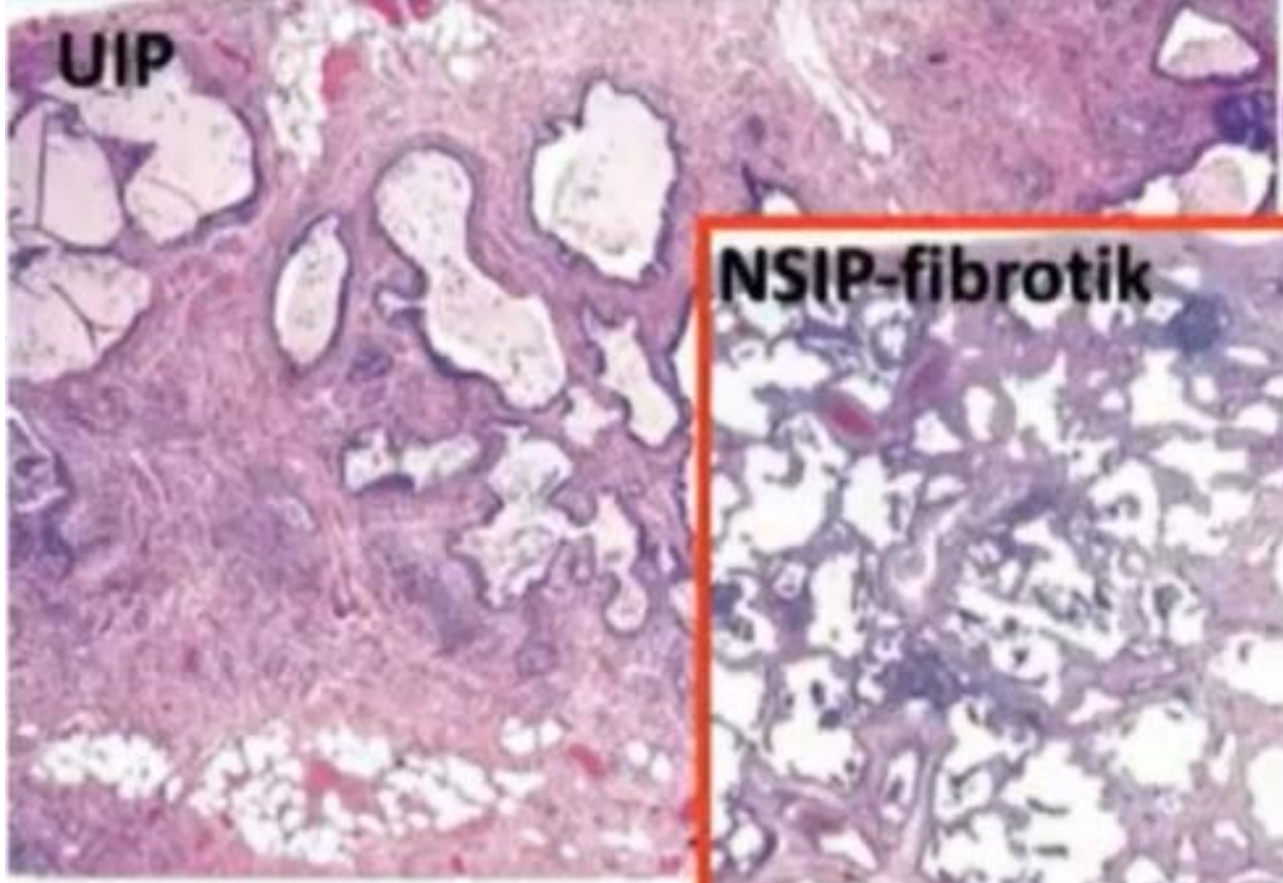
Ann Rheum Dis . 2007;66:940-944.

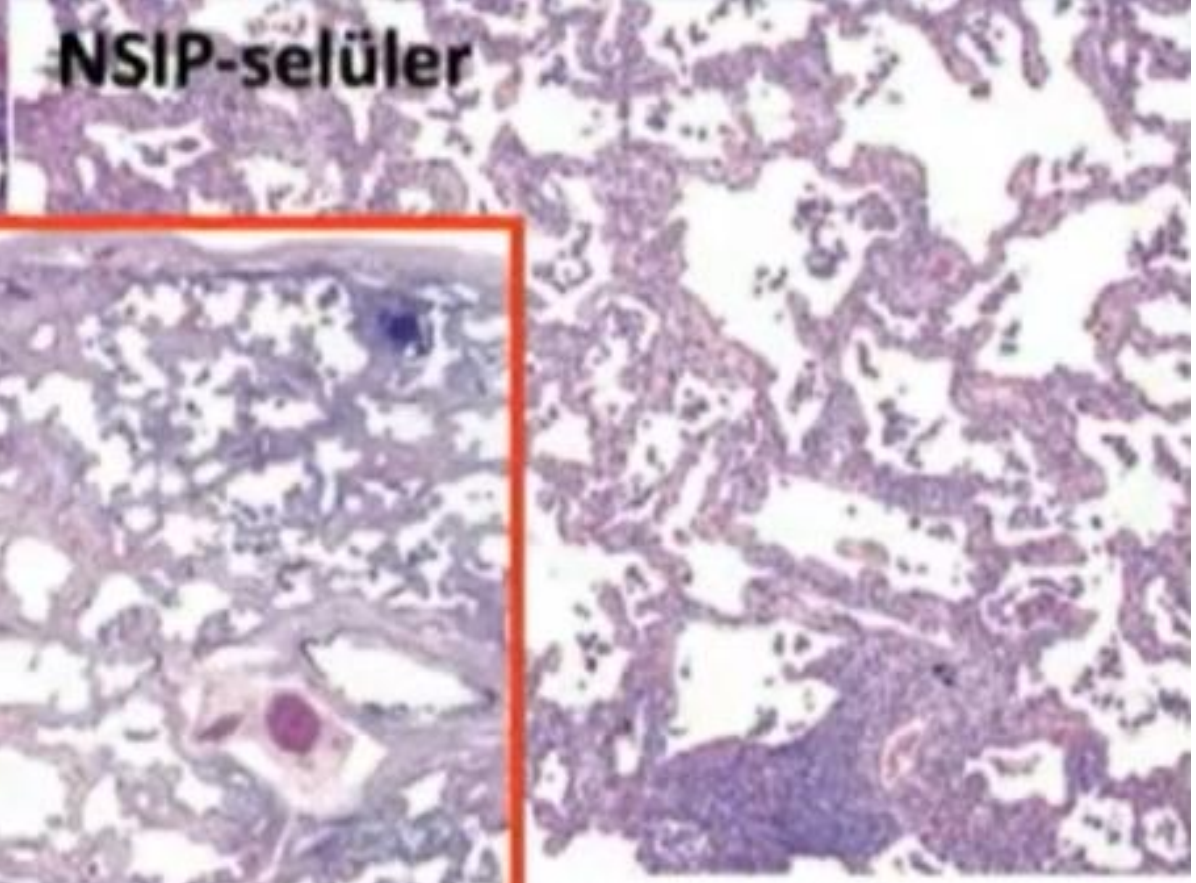
SSc interstisyel akciğer hastalıkları-mortalite

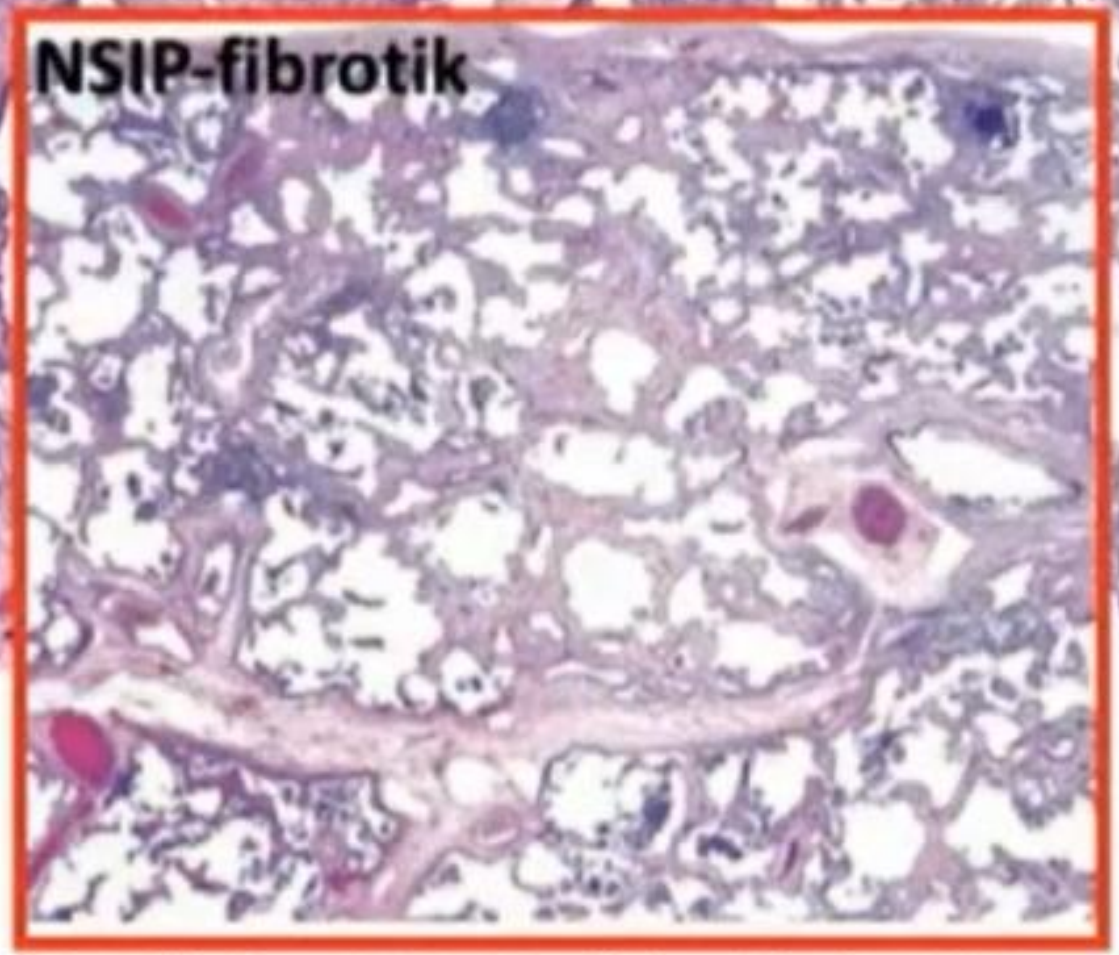
	Sağkalım şansı (%) 1 yıl	Sağ kalım şansı (%) 5 yıl	Sağkalım şansı (%) 10 yıl
SSc	85	64	45
SSc-İAH	77	44	22

Kanada, 3111 SSc olgusu, 10 yıllık dönem
SSc prevalansı: 100.000'de 19 Ort. Yaş 57 %84 Kadın
SSc-İAH oranı %18 Ort. Yaş 58 %80 Kadın

Pope J, et al. Prevalence and Survival of Systemic Sclerosis and Associated Interstitial Lung Disease in Ontario, Canada over 10 years. Arthritis Rheumotol 2020,72







5 yıllık sağkalım %43
10 yıllık sağkalım %15

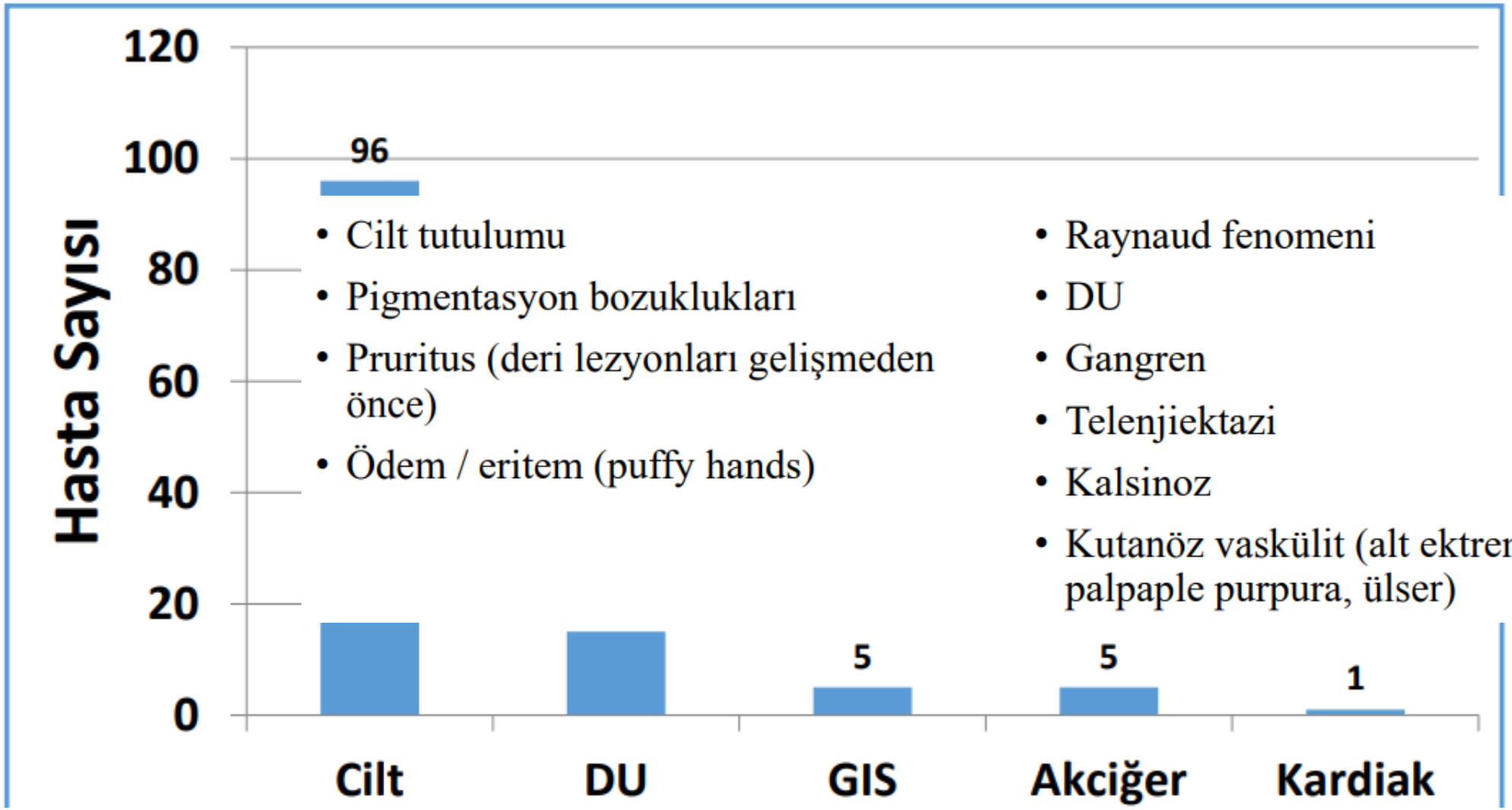
5 yıllık sağkalım %100

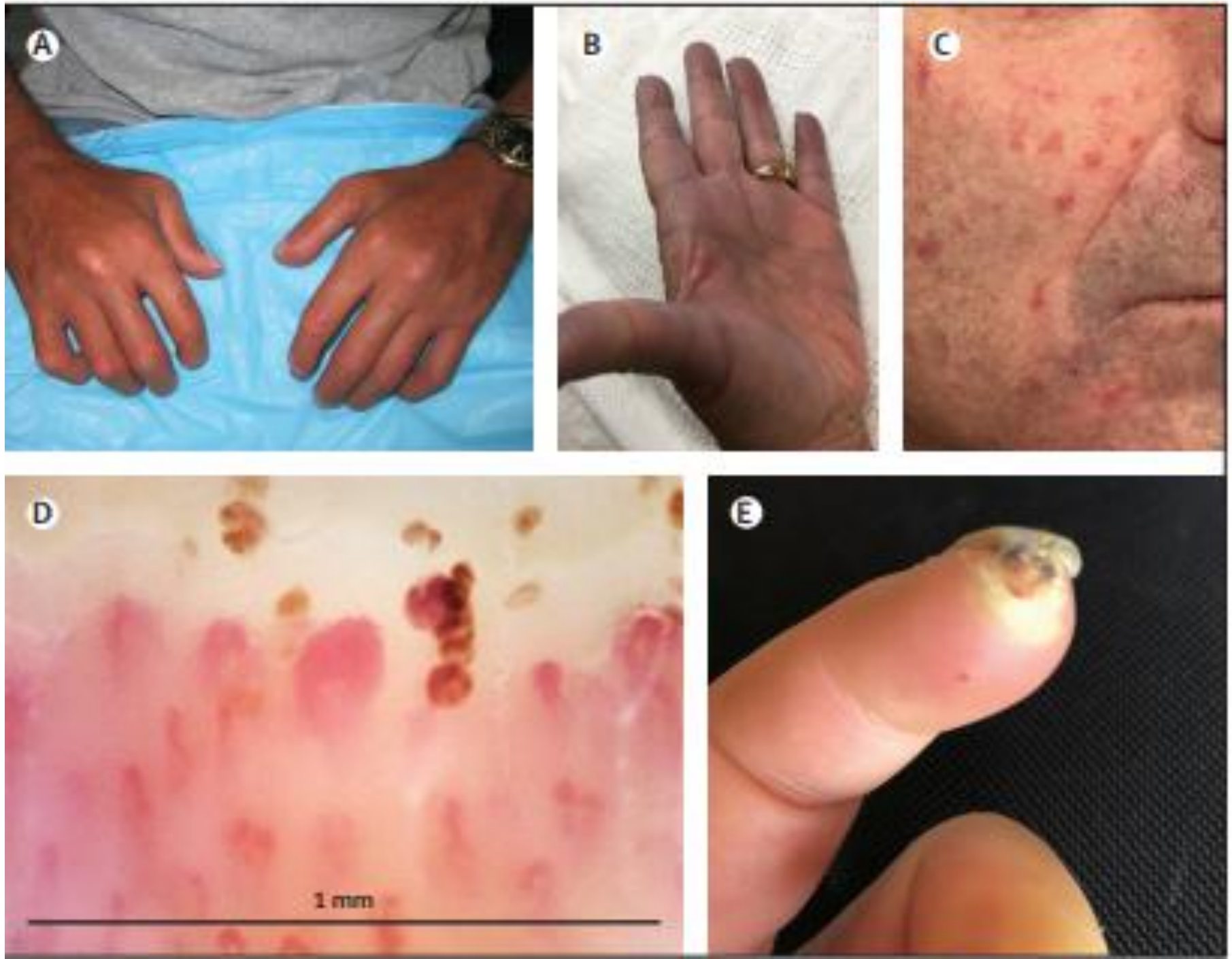
5 yıllık sağkalım %90, 10 yıllık sağkalım %35

Travis WD ve ark. Am J Surg Pathol 2000; 24: 19–33.
Myers JL ve Katzenstein A . Histopathology 2009, 54, 90–103
Travis WD ce ark Am J Respir Crit Care Med 2008; 1338-47


Sistemik skleroz
Sınırlı SSK
Yaygın SSk
RF
Preskleroderma
Çok erken skleroderma
Vasküler bazlı tedaviler
Vasküler bazlı tedaviler
İmmünsupresifler
Anti-fibrotikler
?
Komplikasyonların tedavisi

SSk hastalarının hastane başvurularında RF dışı ilk semptom veya bulguların dağılımı (122 hasta)




A
B
C
D
1 mm
E

Pre-skleroderma;

- RF
- Puffy finger
- ANA +

RF + iskemik değişiklikler ve sistemik skleroz spesifik antikorlar ve/veya kapilleroskopik değişiklikler

LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001

RF → Preskleroderma → **Çok erken SSk** → Erken SSk → SSk

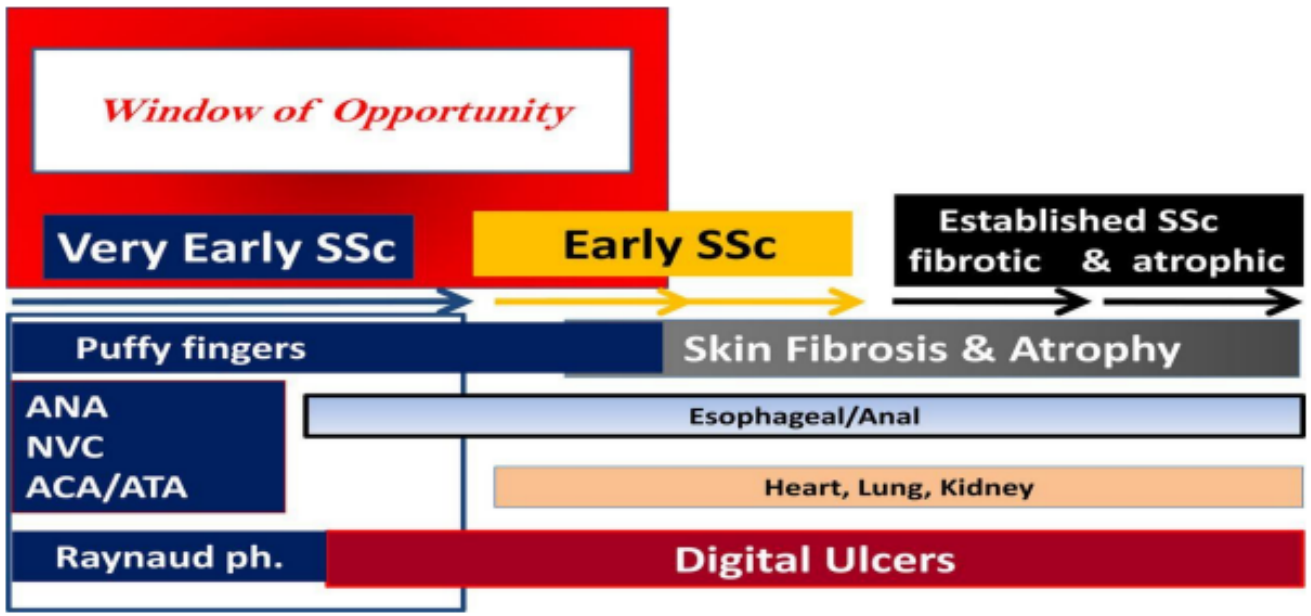
Çok erken SSk;

- Pre-skleroderma +
- Kapilleroskobik bulgular veya
- SSk'ye özgü otoantikor pozitifliği

Minier T, et al. ARD. 2014

- 316 RF hastası → 110 VEDOSS
- Bu aşamada hastaların %80'inde DÜ, pulmoner ve/veya GİS tutulumu var

Bruni C, et al. Rheumatology 2015



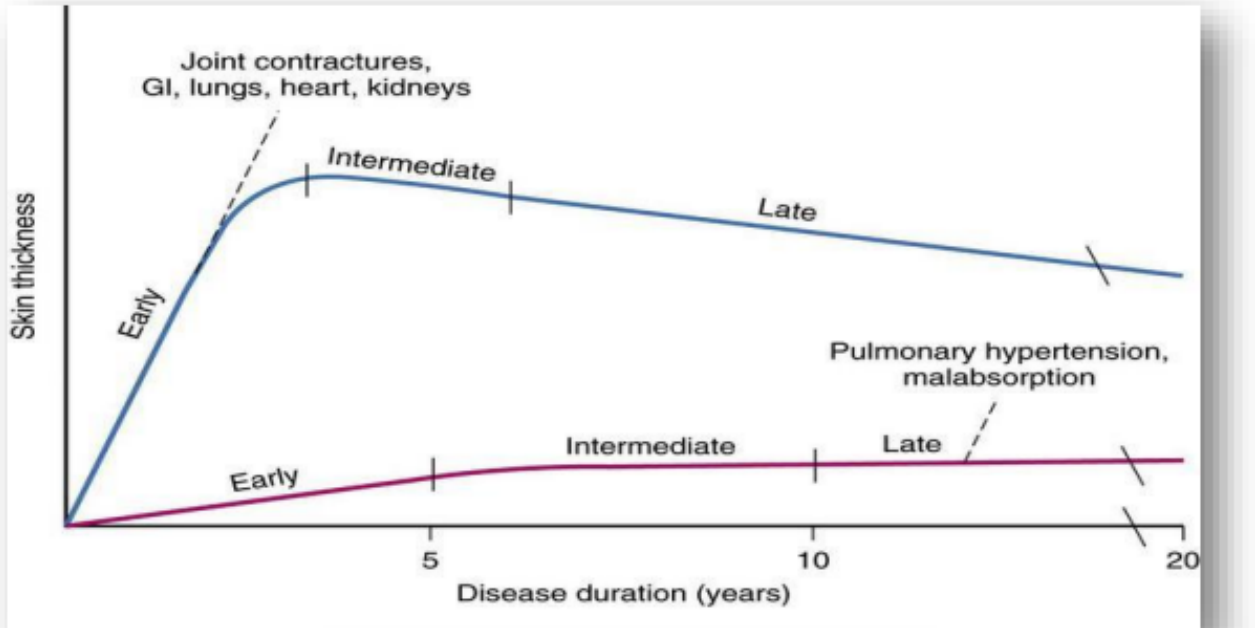
Matucci-Cerinic M et al. Ann Rheum Dis 2013;72:319-321

SSk – klinik süreç

RF → Preskleroderma → Çok erken SSk → Erken SSk → SSk

Erken SSk;

- Deri sertliği başladıktan sonraki ilk 3 (5??) yıl



LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001

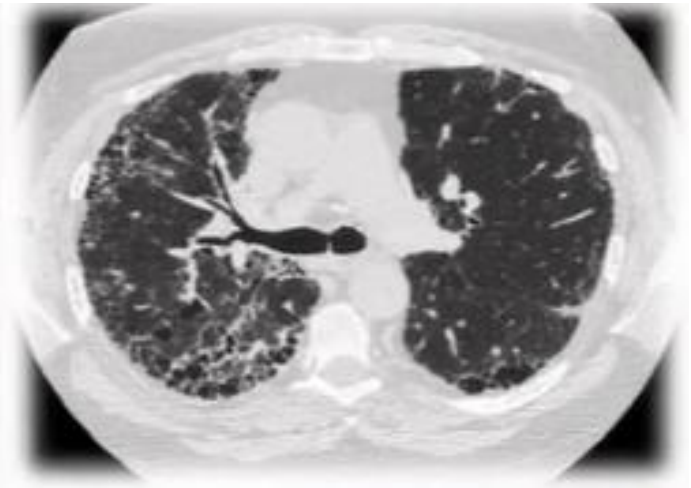
ACR/EULAR 2013

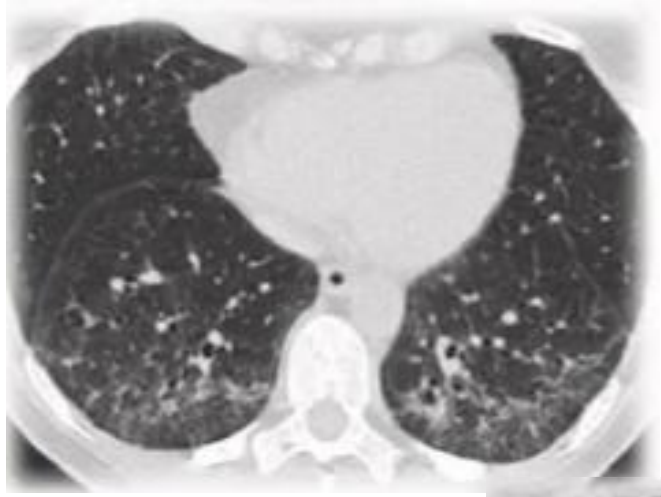
SSc Tanı Total skor ≥ 9

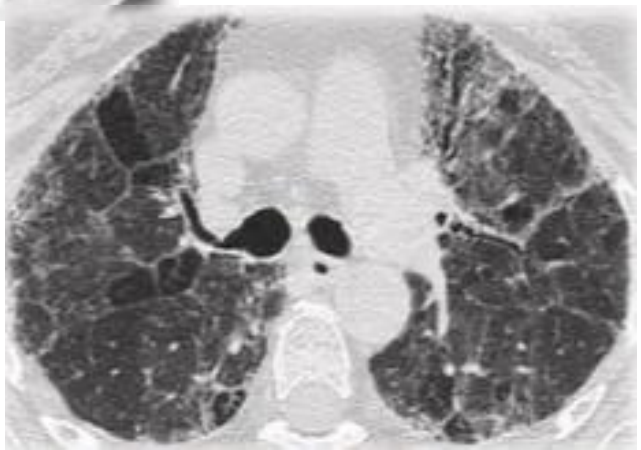
ITEM	SUB-ITEM	SCORE
Skin thickening proximal to MCP		9
Skin thickening of the fingers (highest score)	Puffy fingers Sclerodactyly	2 4
Fingertip lesions (highest score)	Digital tip ulcers Fingertip pitting scars	2 3
Telangiectasia		2
Lung involvement (max 2 points)	Pulmonary hypertension Interstitial lung disease	2 2
Raynaud phenomenon		3
Abnormal nailfold capillaries		2
SSc-related auto-antibodies (max 3 points)	Anticentromere Anti-topoisomerase I Anti-RNA polymerase III	3 3 3

91% sensitivite
92% spesifite

van den Hoogen F et al. Ann Rheum Dis 2013;72:1747-55







Pulmoner fibrozis patogenez

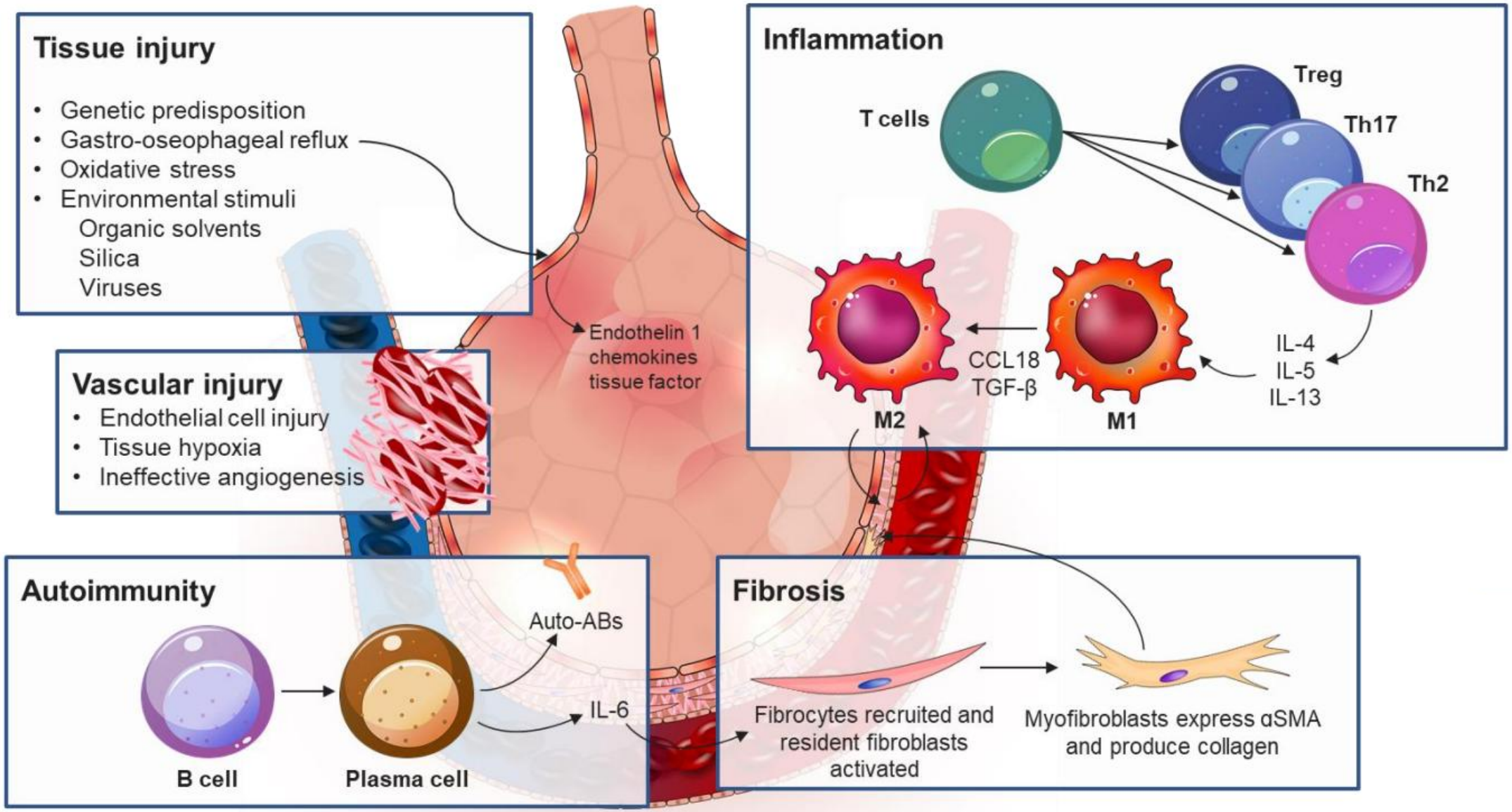
IPF ve SSc-İAH

Dr.İlyas Ercan OKATAN

İç Hastalıkları Romatoloji Bilim Dalı

Kanuni Eğitim ve Araştırma Hastanesi

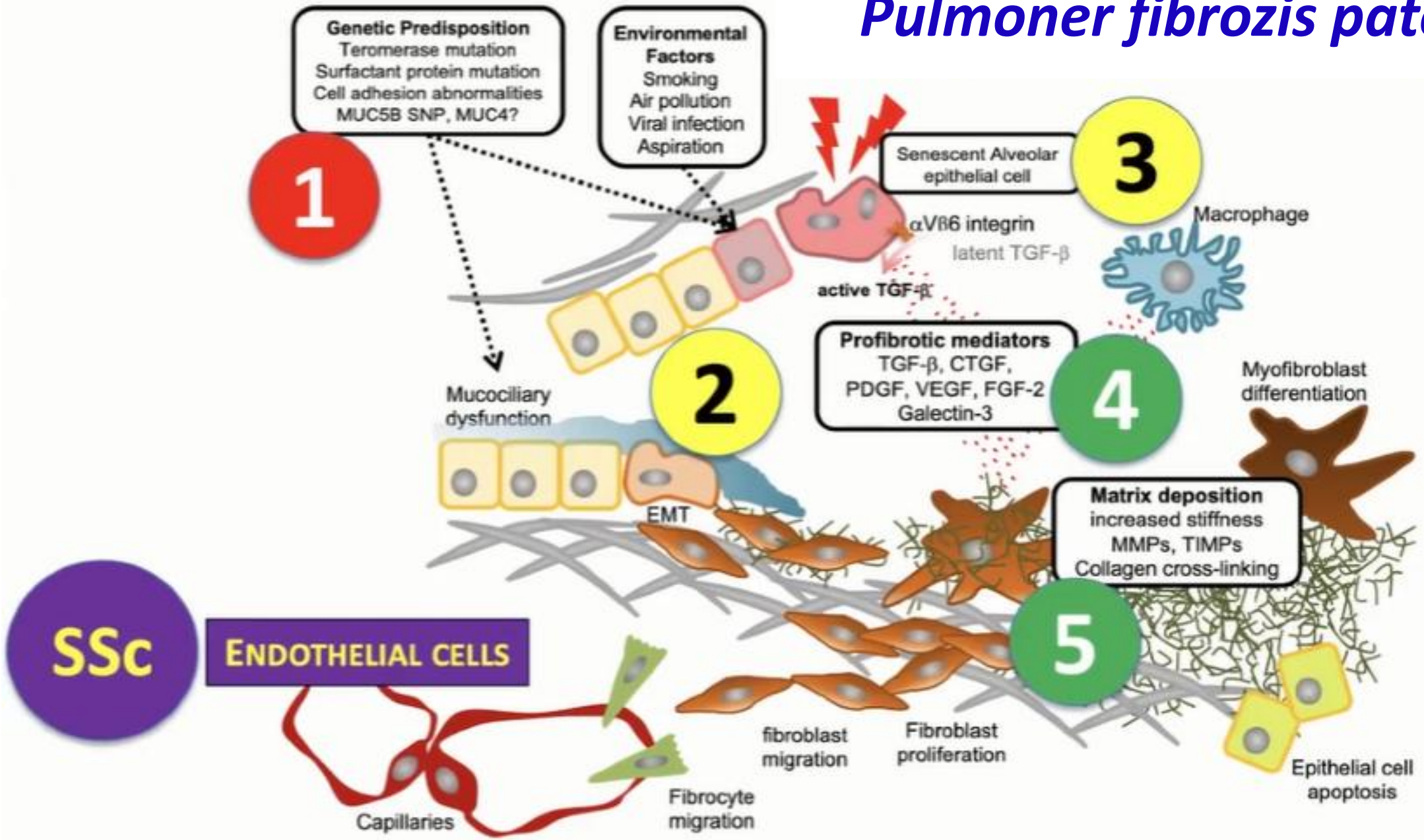
Pathogenez SSc-IAH



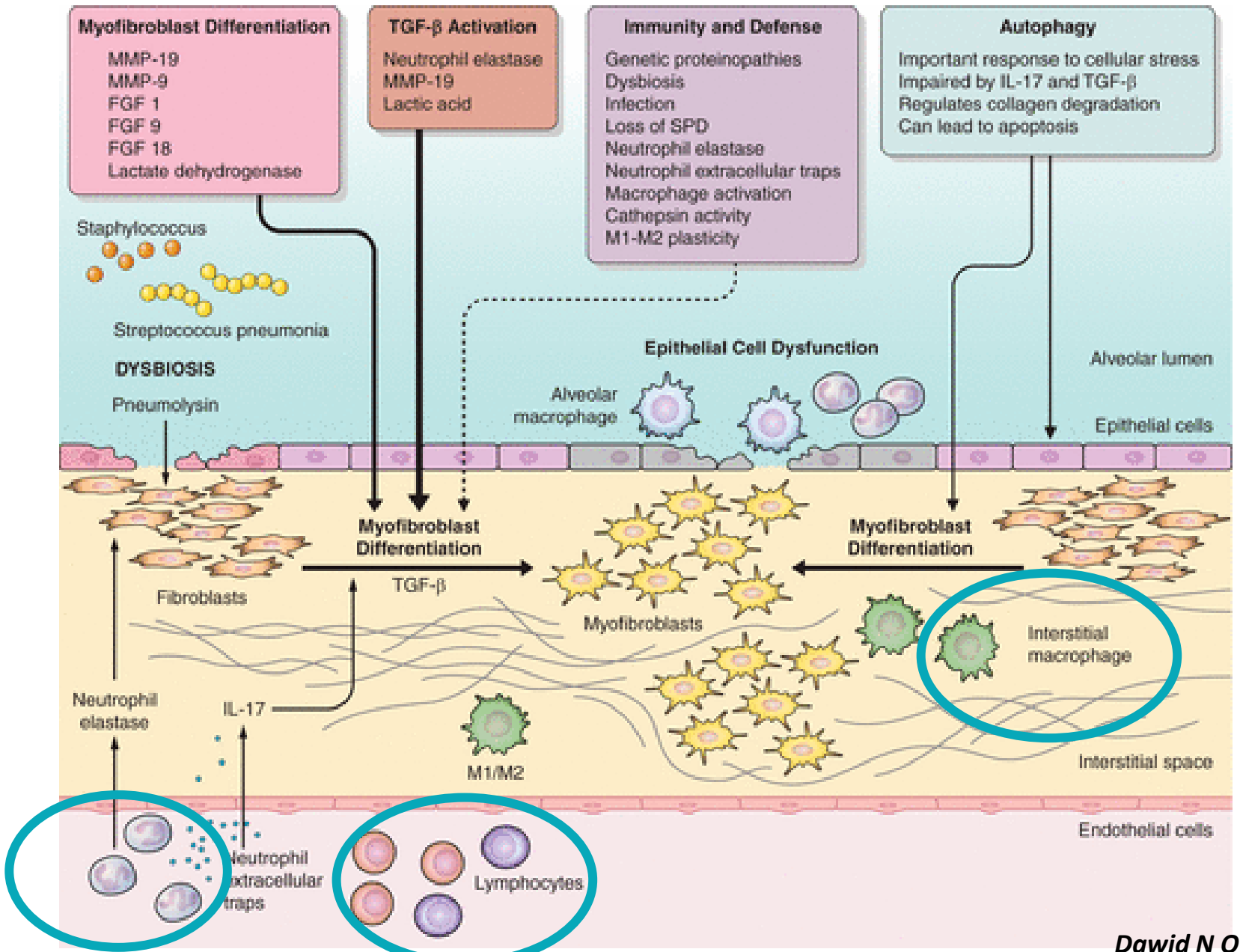
Perelas A, Silver RM, Arossi AV, Highland KB. Lancet Respir Med. 2020;8:304–20.

7661 SİSTEMİK SKLEROZ PANELİ:
7662 -ANTI CENP A
7663 -ANTI CENP B
7664 -ANTI FİBRİLLARİN
4203 -ANTI SS-A ANTİKOR(Anti-Ro)(52 kDa)
7665 -ANTI NOR 90
7666 -ANTI Th/To
4206 -ANTI Scl-70 ANTİKOR
7667 -ANTI PDGFR
4207 -ANTI PM/Scl100 ANTİKOR
3173 -ANTİ Ku ANTİKOR
3924 -ANTI PM/Scl75 ANTİKOR
7668 ANTI RNA POLİMERAZ III
7669 -ANTI RP11
7670 -ANTI RP155

Pulmoner fibrozis patogenez



İMMÜN AKTİVASYON IPF



LENFOSİTLER

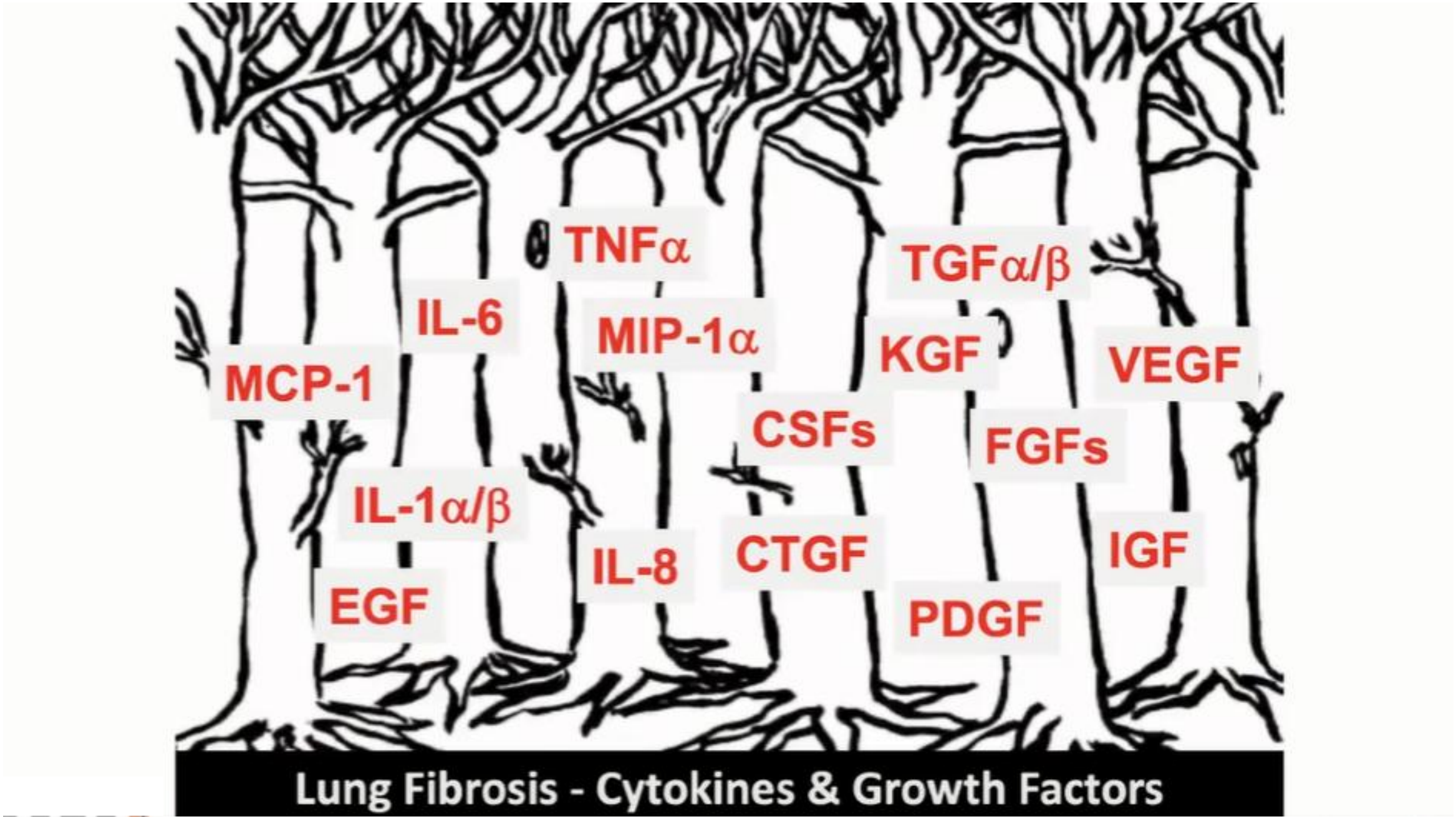
T effektör hücre
Treg
B hücreler
NK

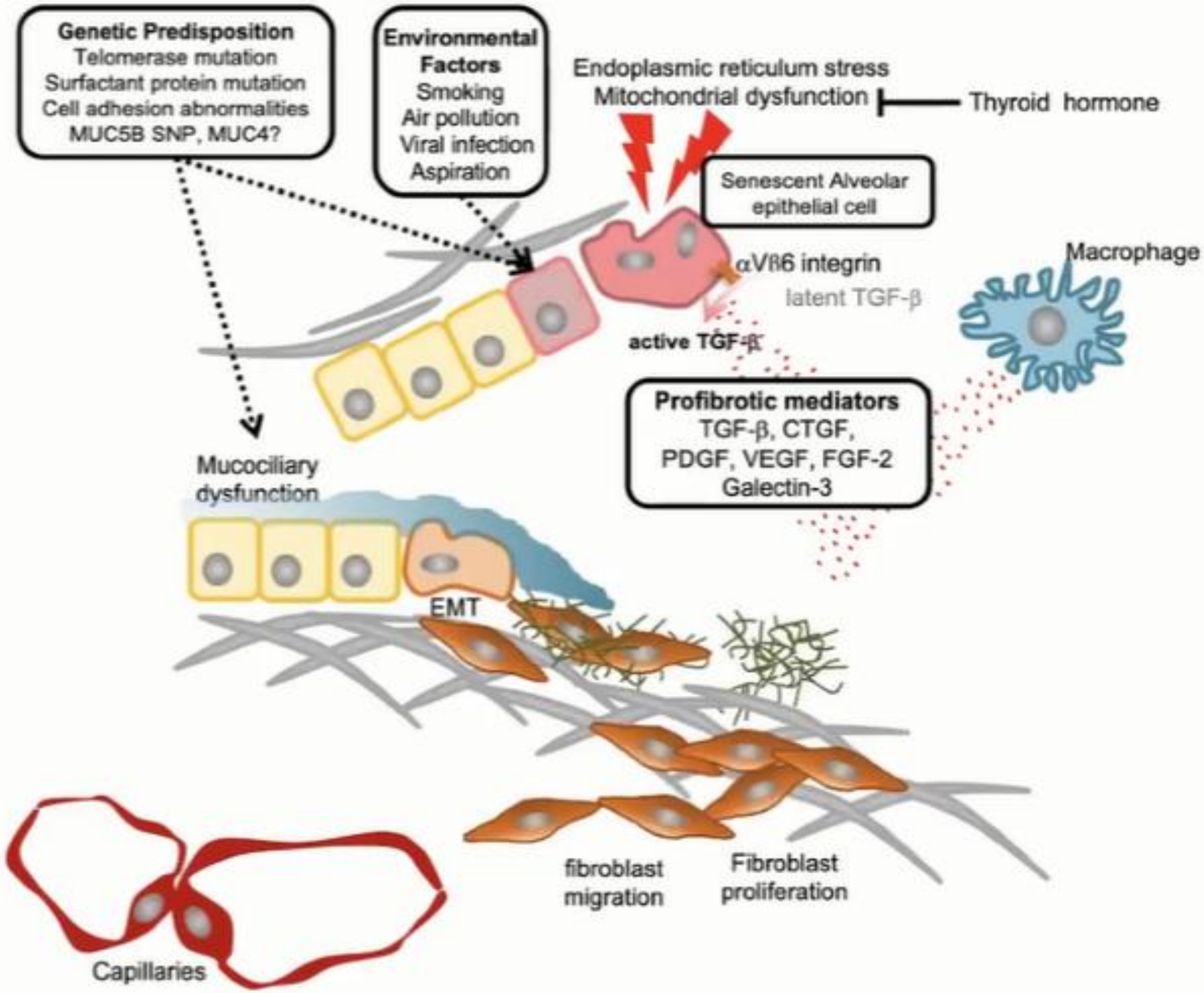
SSc-İAH immün aktivasyon

Otoantikorlar

Anti-scl 70
Anti-RNP
Anti-fibrillarin
Anti-topoizomeraz 2
Anti-endotelial hücre antikorları

Dawid N O Dwyer et al. Am J physiol Lung Cell Mol Physiol 2016


TNFα
TGFα/β
IL-6
MIP-1α
KGF
VEGF
MCP-1
CSFs
FGFs
IL-1α/β
IL-8
CTGF
IGF
EGF
PDGF
Lung Fibrosis - Cytokines & Growth Factors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Telomerase mutation
Surfactant protein mutation
Cell adhesion abnormalities
MUC5B SNP, MUC4?
Environmental Factors
Smoking
Air pollution
Viral infection
Aspiration
Endoplasmic reticulum stress
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Thyroid hormone
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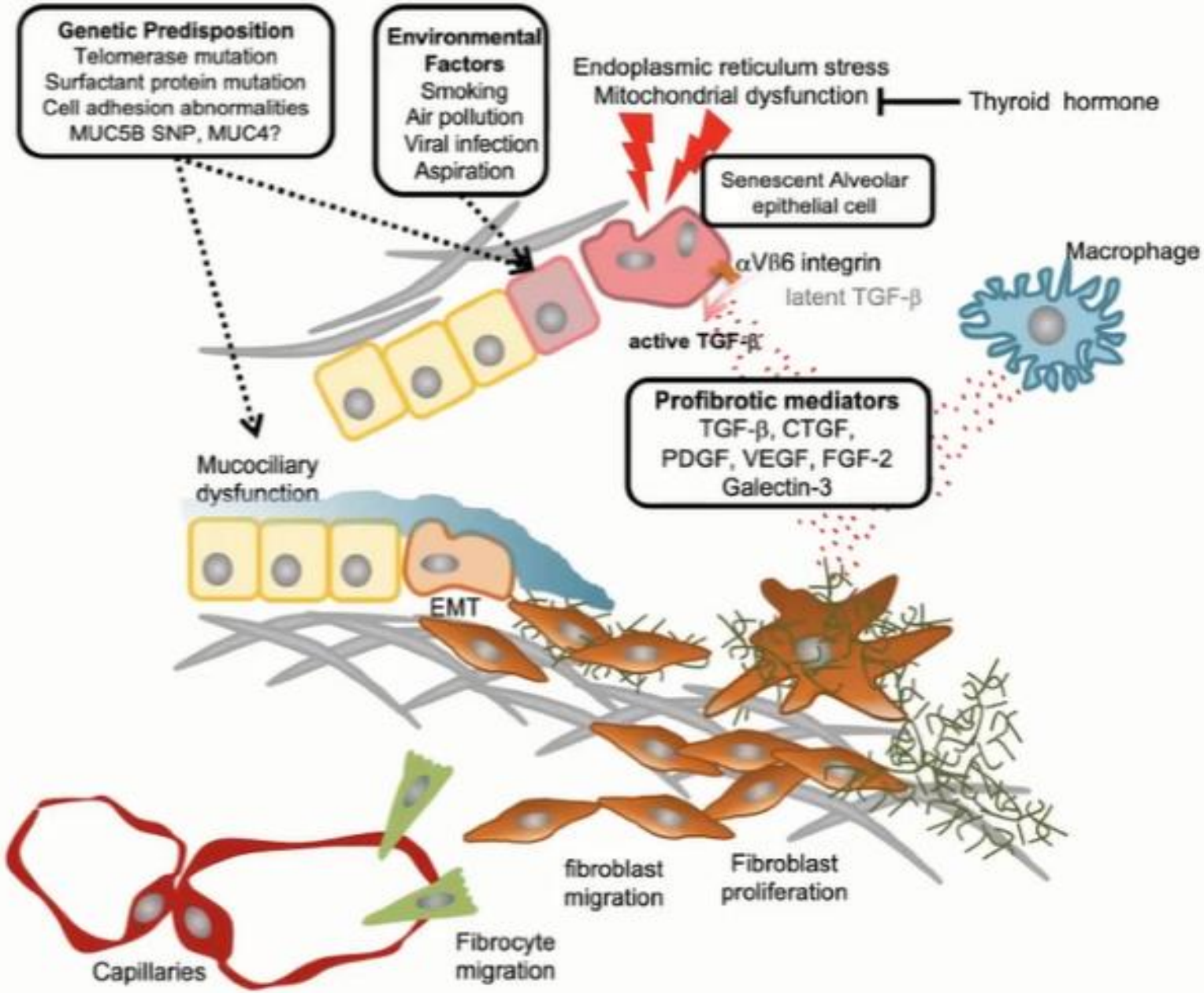
αVß6 integrin
latent TGF-β
active TGF-β
Macrophage
Profibrotic mediators
TGF-β, CTGF,
PDGF, VEGF, FGF-2
Galectin-3
Mucociliary dysfunction
EMT
fibroblast migration
Fibroblast proliferation
Capillaries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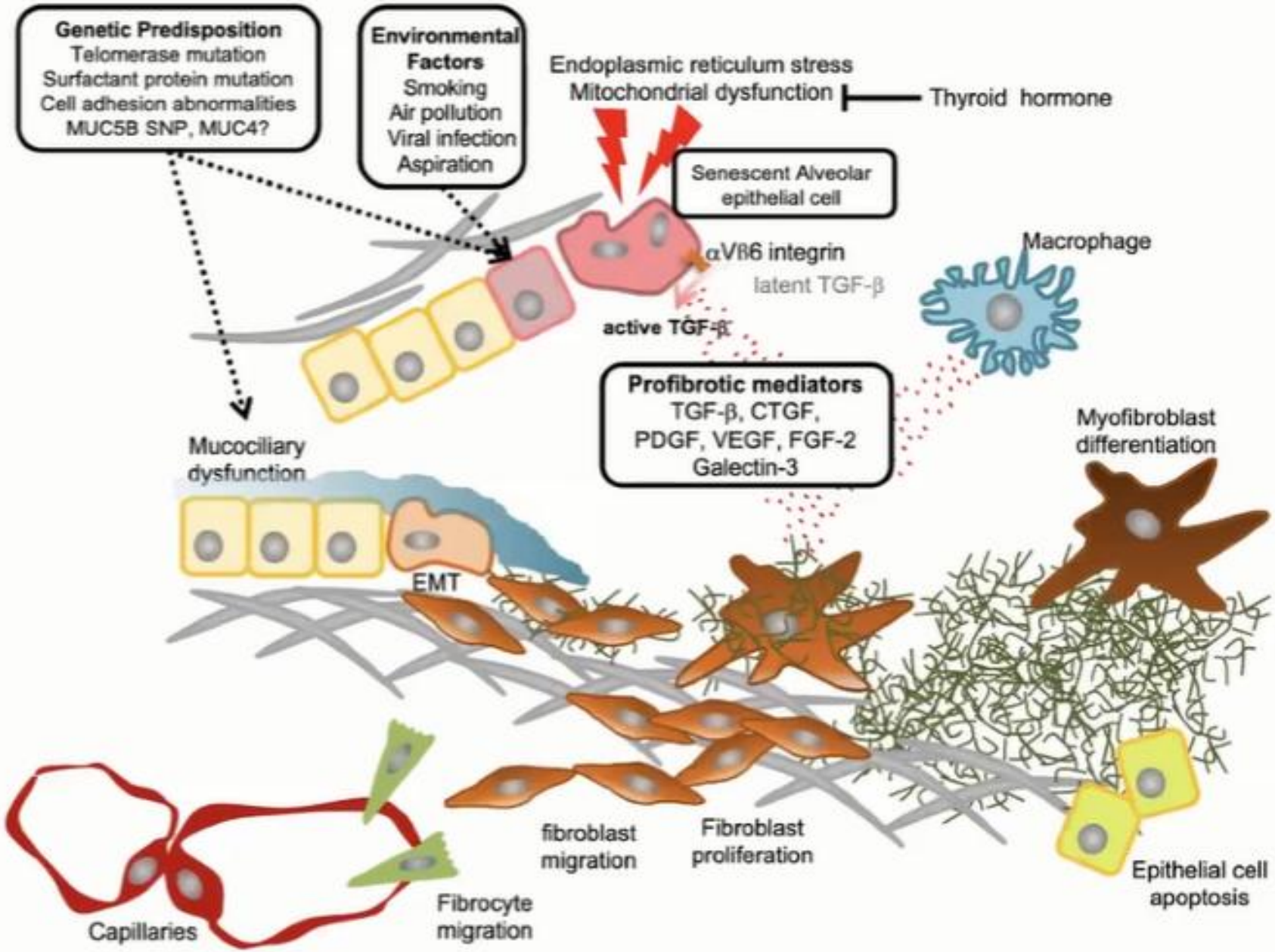
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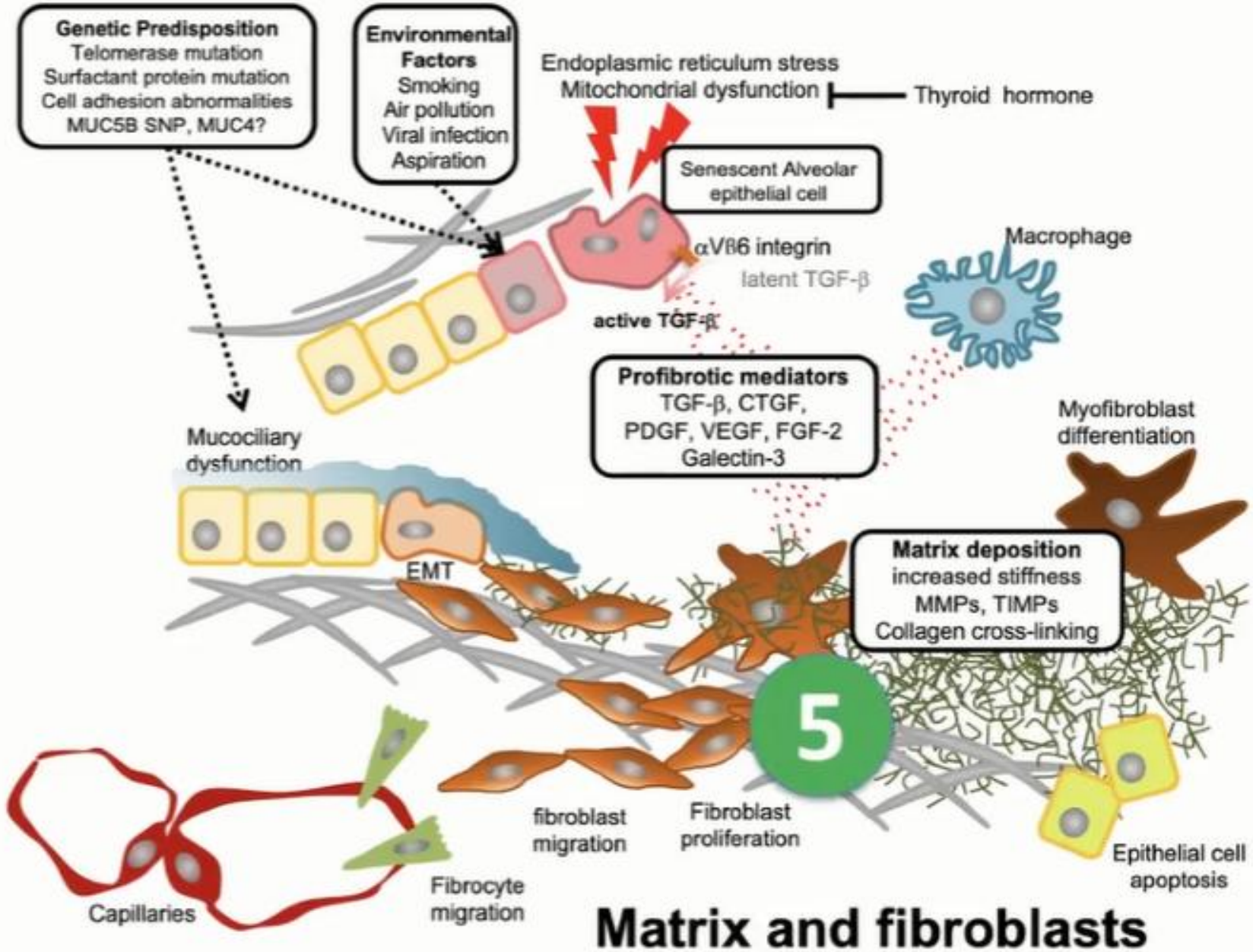
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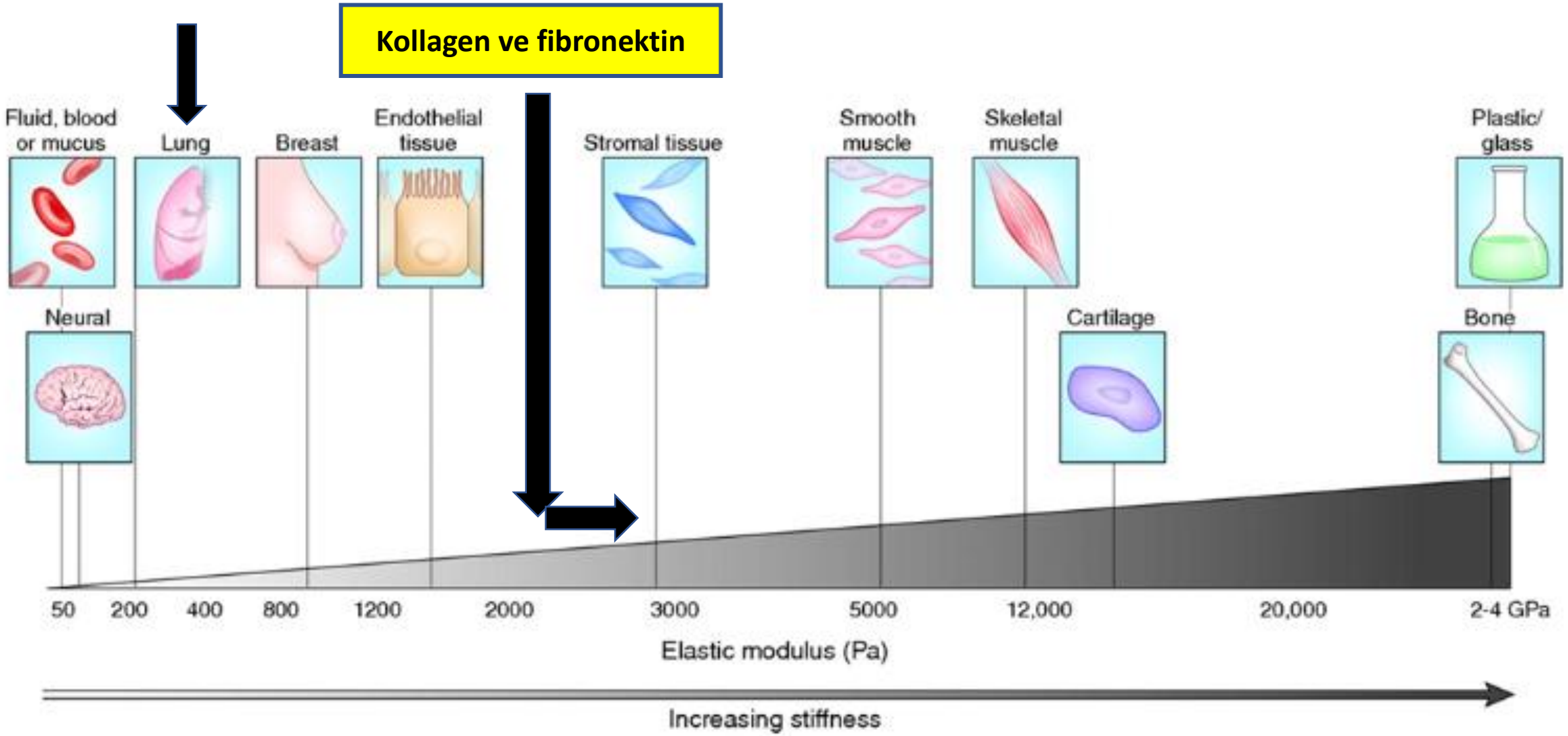
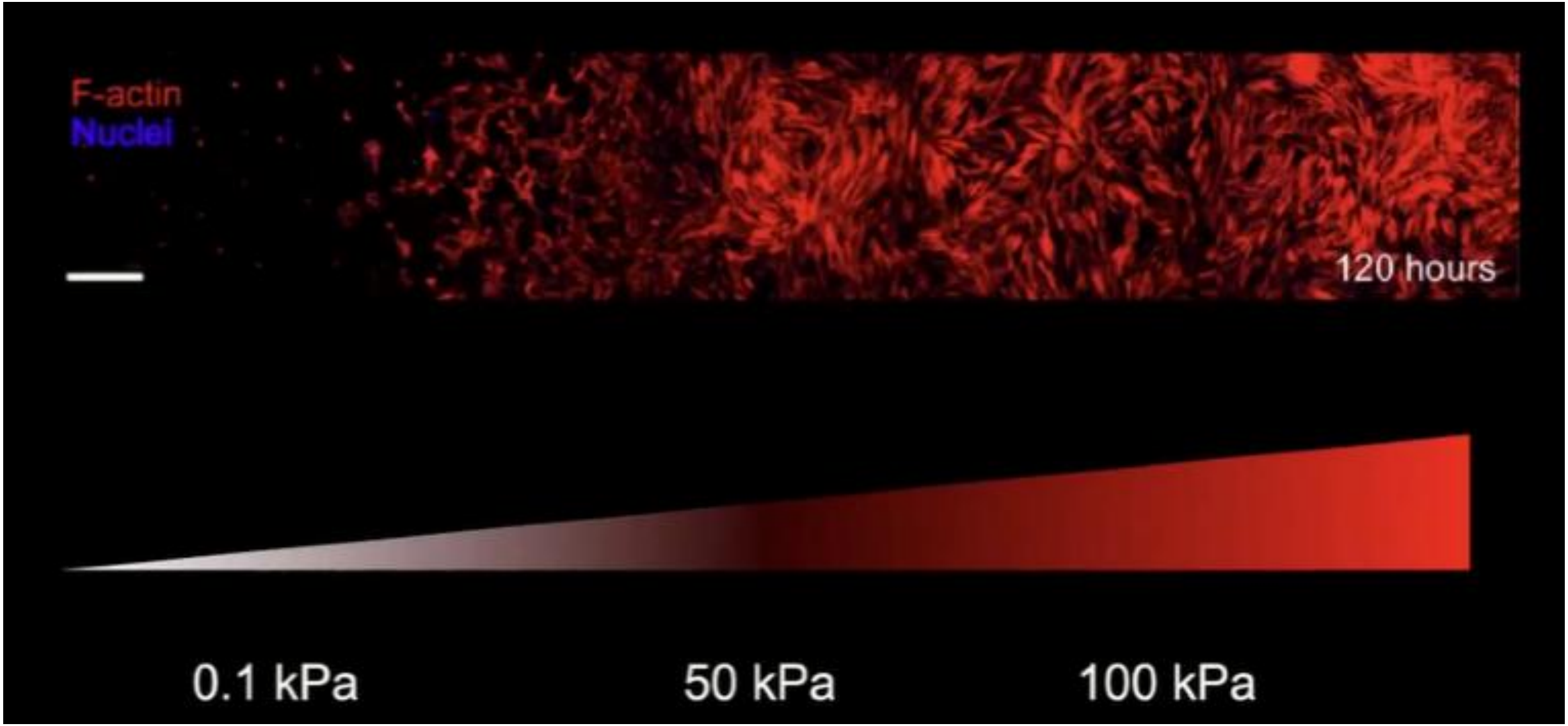
Mucociliary dysfunction
Myofibroblast differentiation
EMT
Matrix deposition
increased stiffness
MMPs, TIMPs
Collagen cross-linking
5
fibroblast migration
Fibroblast proliferation
Epithelial cell apoptosis
Capillaries
Fibrocyte migration
Matrix and fibroblasts



Cox T R and Erler J T Dis.Model.Mech.2011

Matris sertliği, fibroblast büyümesini ve aktivasyonunu artırır

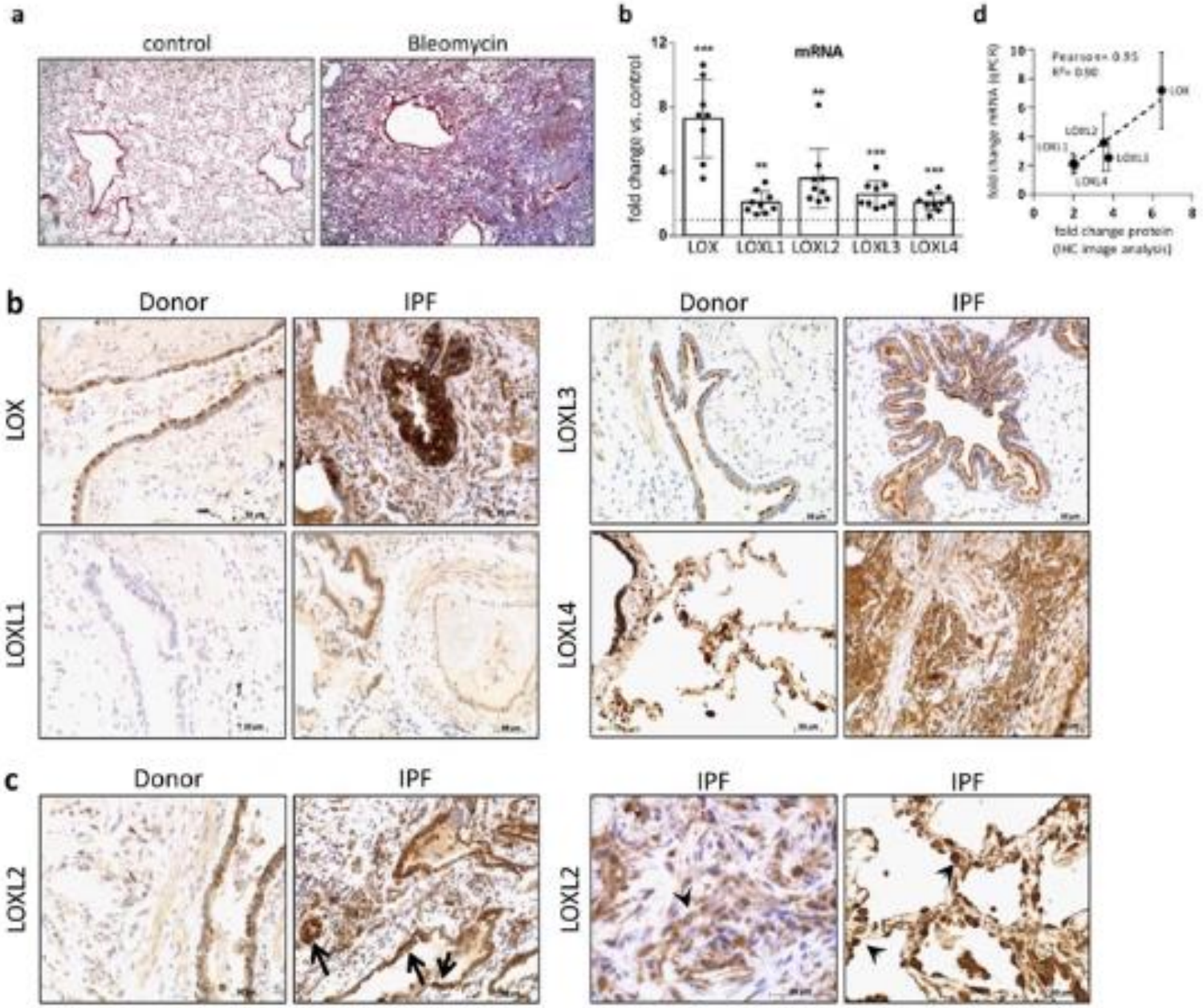


Liu F Tschumperlin D. J Cell Biol 2011

Doku sertliği sadece matris bileşenleri meselesi değildir

cross-linking of polymers

LOXL expression in fibrotic lungs



Aumiller V et al Sci Rep 2017

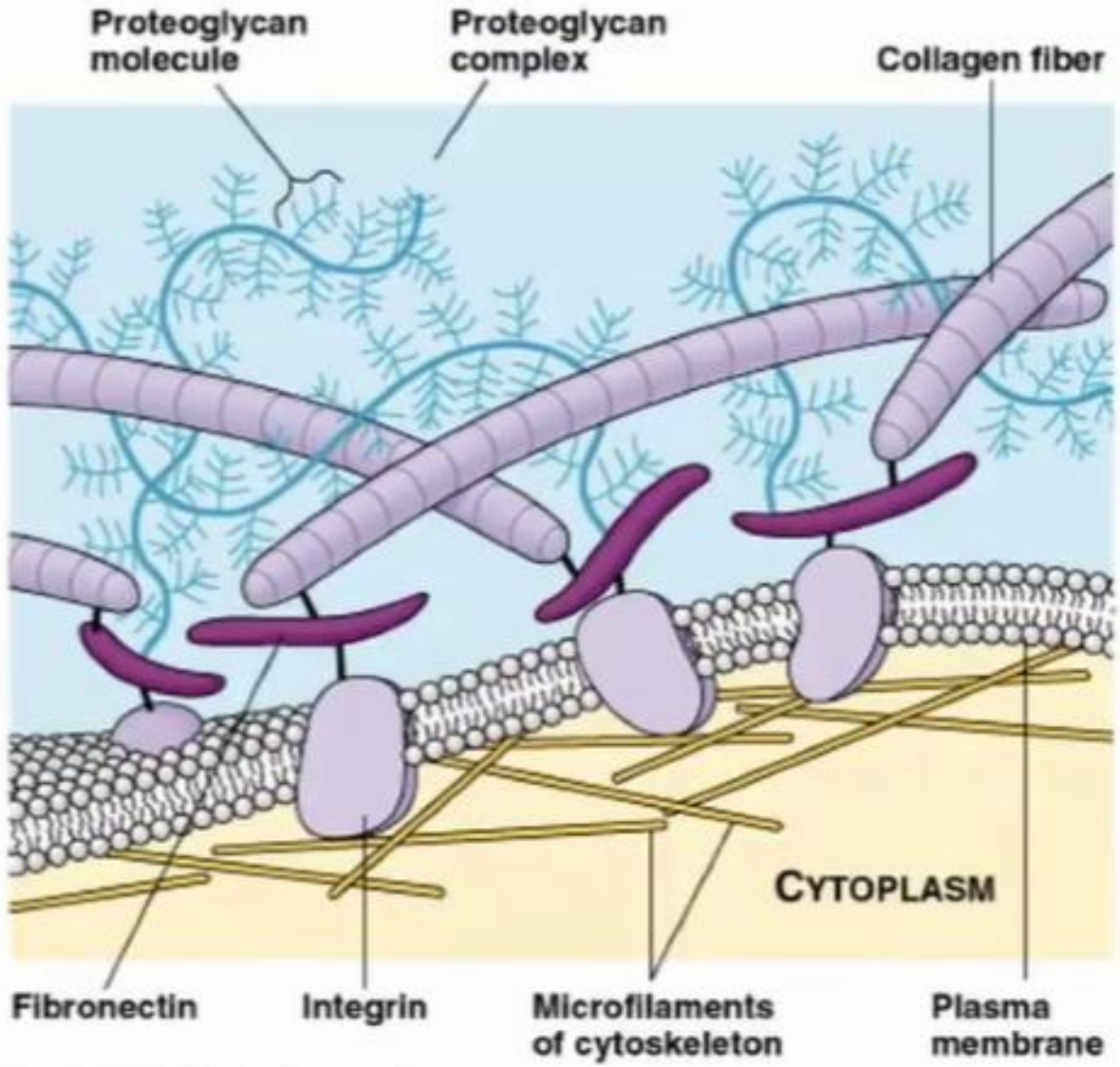
MESENCHYMAL CELLS

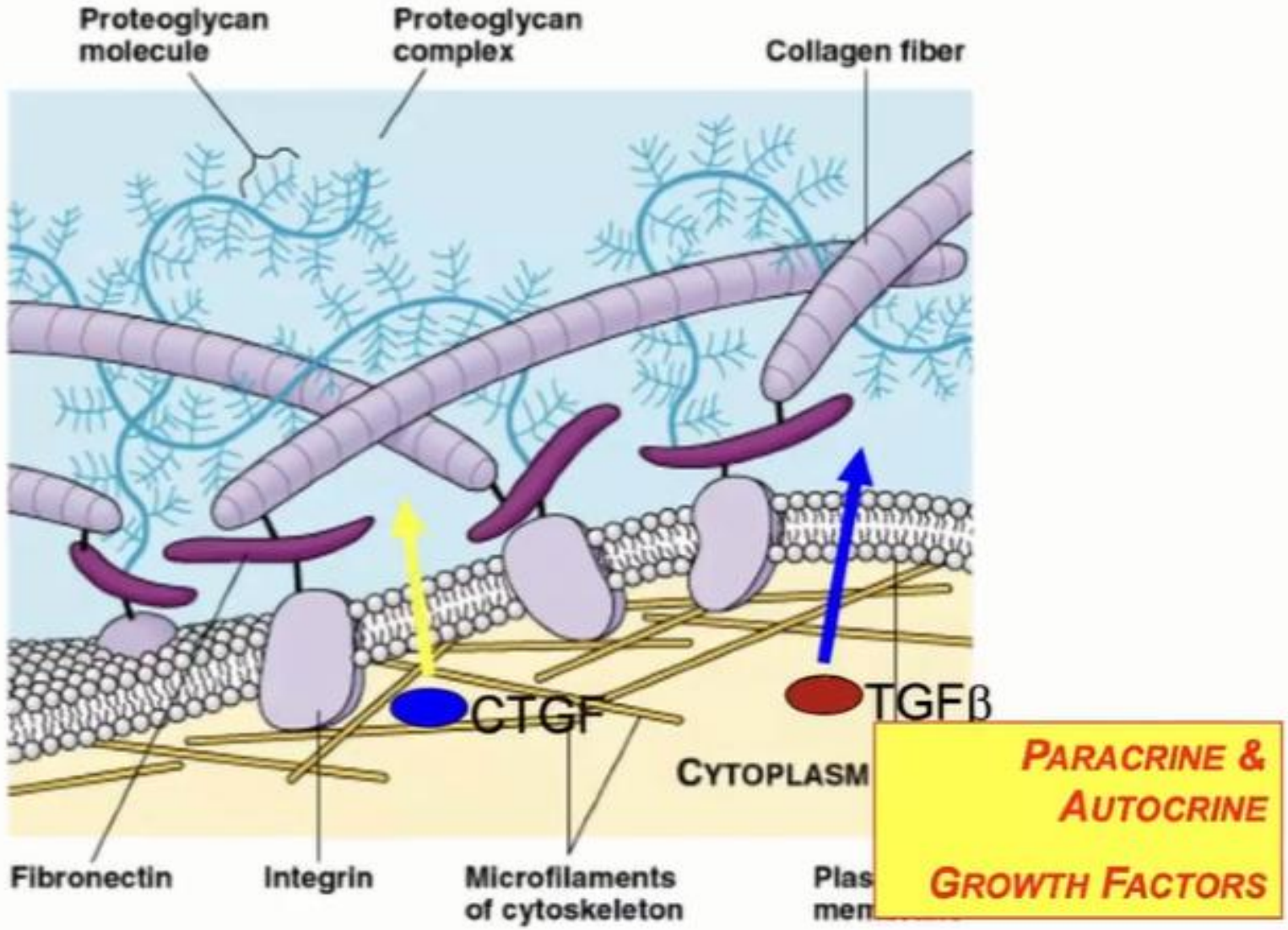
-

MEDIATORS

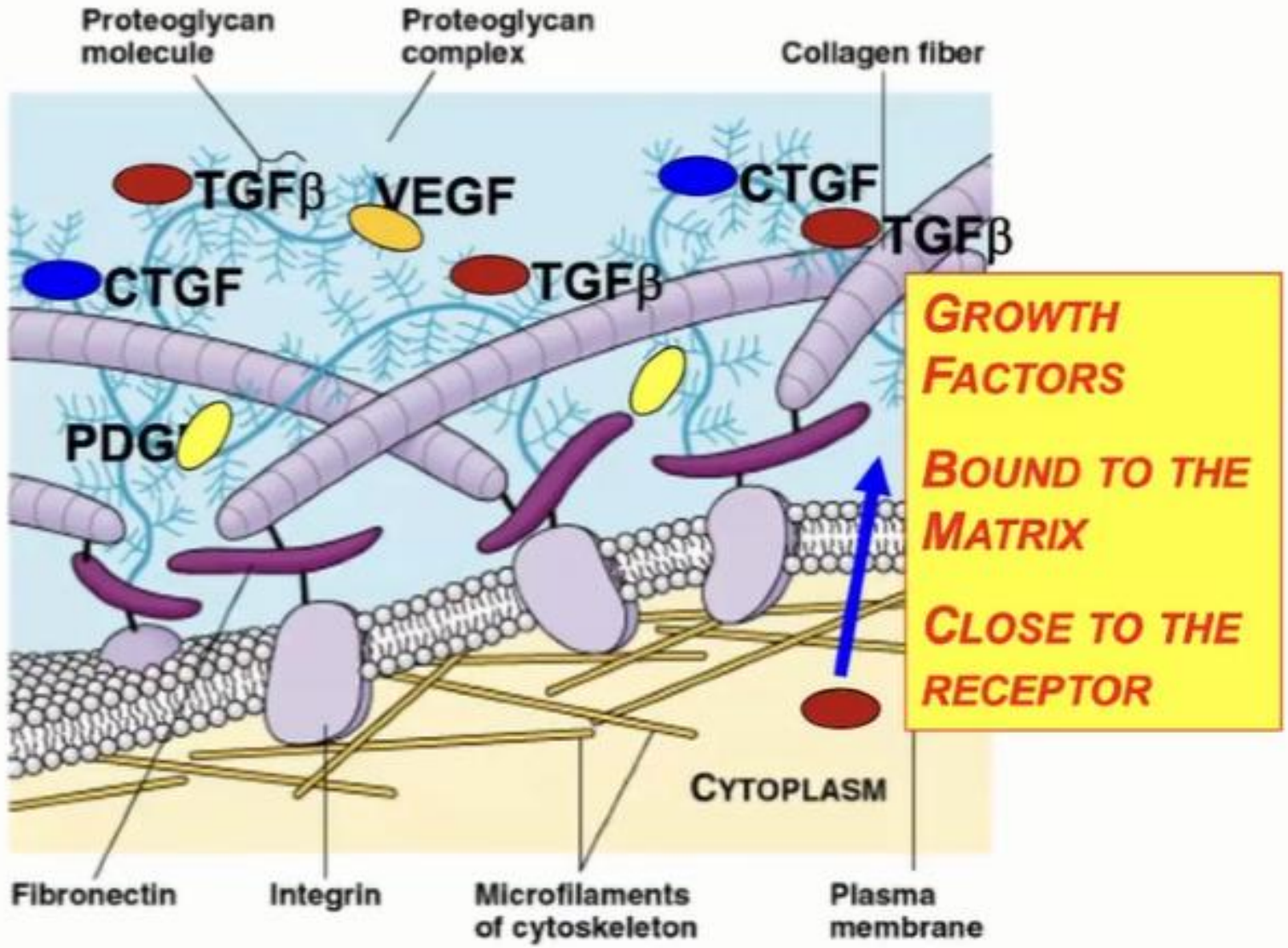
-

MATRIX



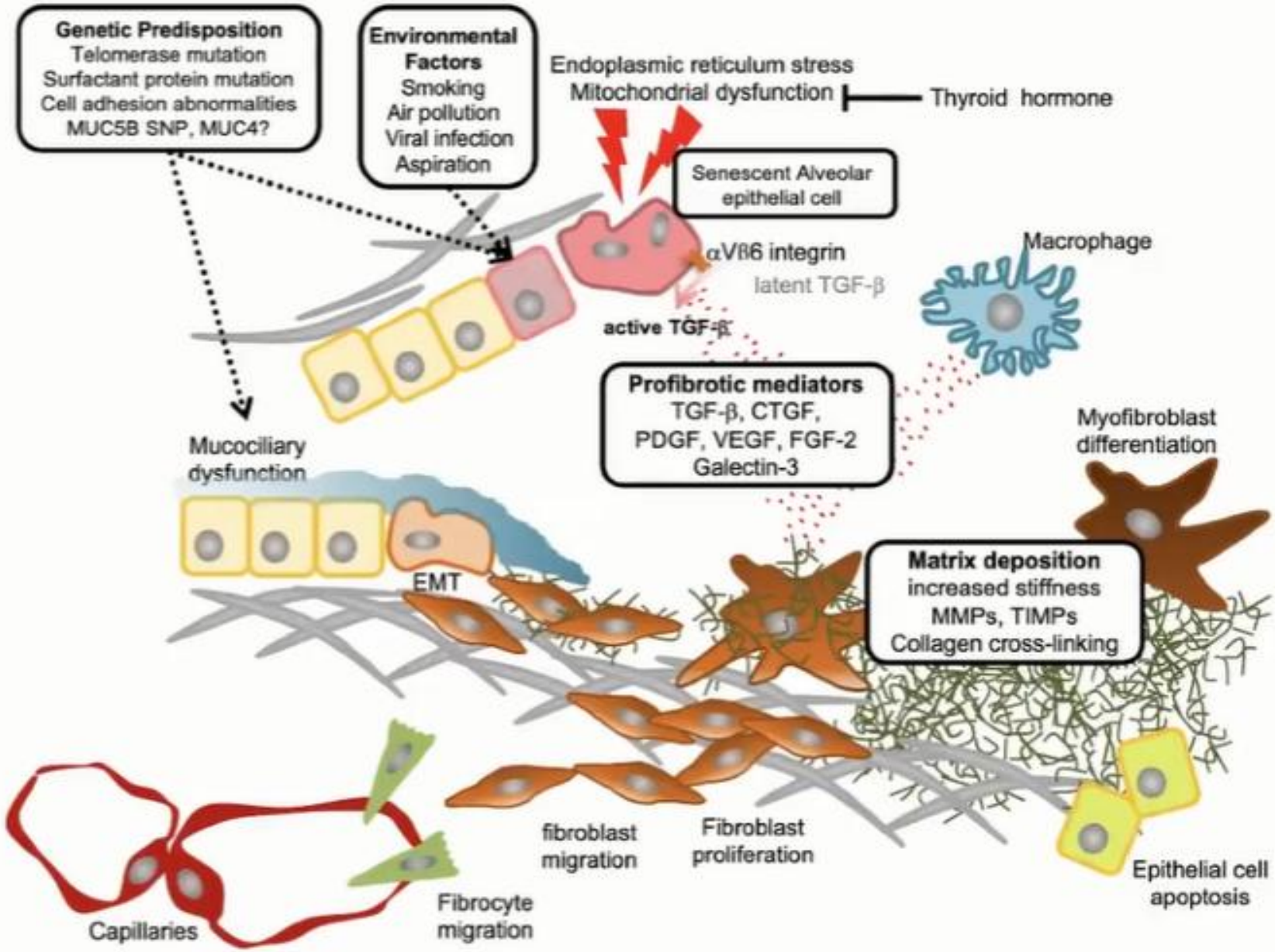


Fibrogenic growth factors released- TGFβ CTGF VEGF



Fibrogenic microenvironment

SSc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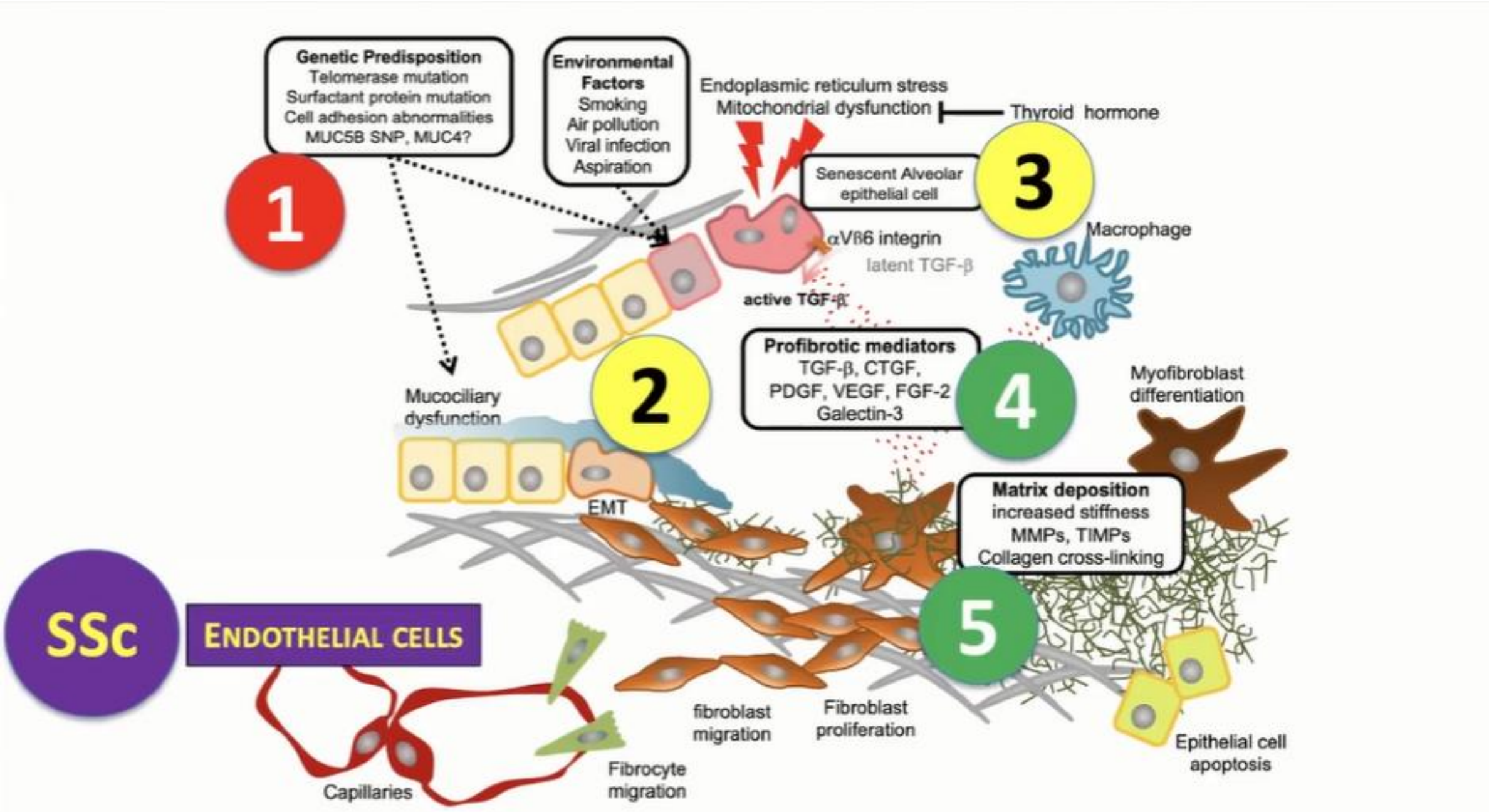
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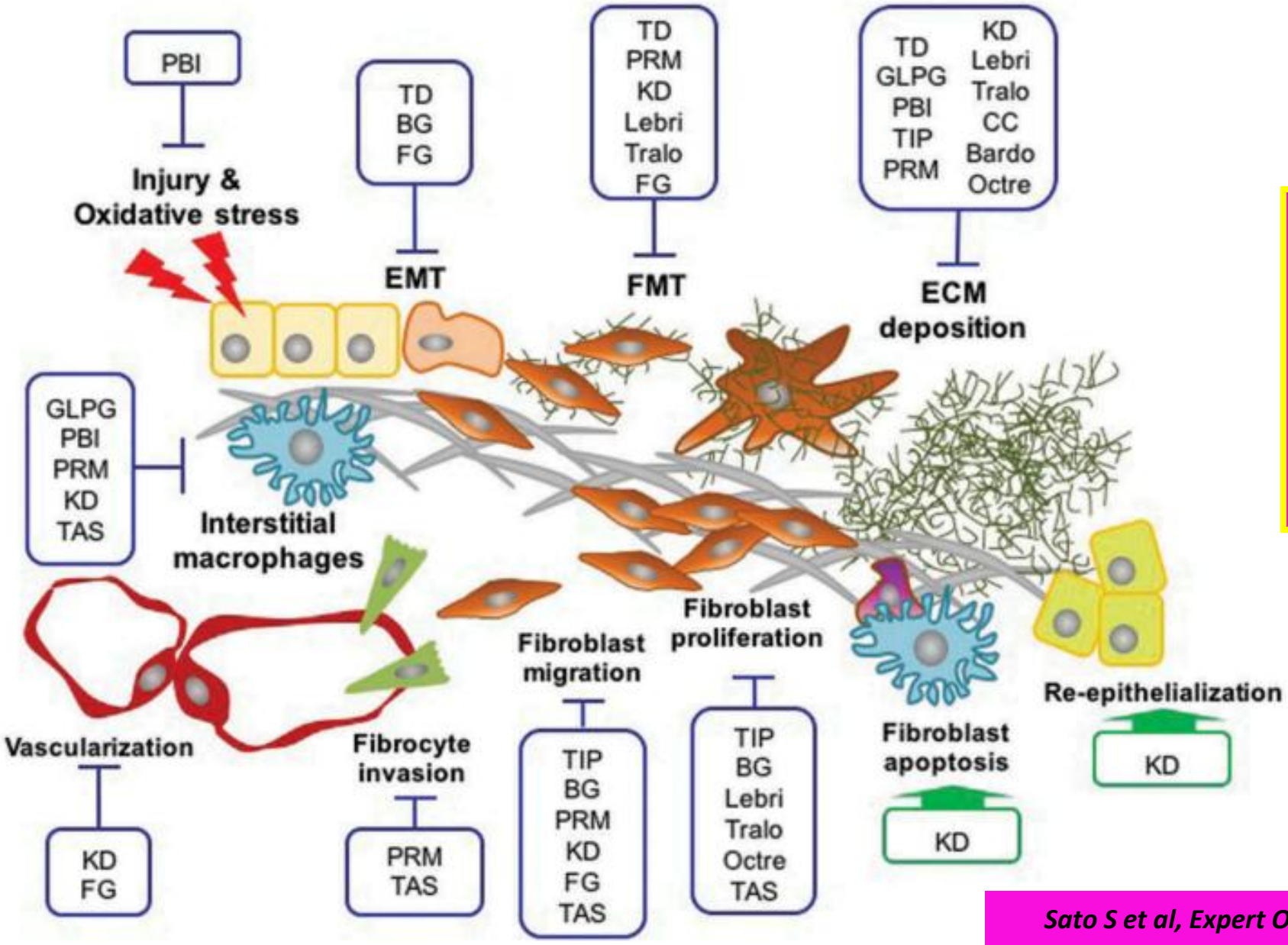
SSc
ENDOTHELIAL CELLS
fibroblast migration
Fibroblast proliferation
Epithelial cell apoptosis
Capillaries
Fibrocyte migration

Therapeutic targets and early stage clinical trials for pulmonary fibrosis
Seidai Sato, Toyoshi Yanagihara & Martin R. J. Kolb



Tipelukast
Lebrikizumab
Tralokinumab
Bardoksolon
Oktreotid

Sato S et al, Expert Opinion Invest Drugs 2019

BDH-İAH: Bazı karakteristik özellikleri

Sistemik Skleroz	- NSIP (2/3) ≫ UIP - Nükleolar ANA paterni ilişkili; anti-SCL70, anti-U3RNP, anti-PM-SCL - Tanı sırasında tüm hastalara SFT ve HRCT rutin
Otoimmün İnflamatuvar Miyopati	- NSIP ≫ UIP - Dermatomiyozit > polimiyozit - Anti-sentetaz antikoru olanlarda ⇑
Romatoid Artrit	- UIP > NSIP > OP - Rutin tarama önerisi olmadığından prevalansı ? - Genellikle seropozitif olup, şiddetli, uzun süreli eklem hastalığı (+) - Sigara, erkek cinsiyet ilişkili
MBDH	- NSIP ≫ UIP - Genellikle SSk tipi klinik bulgular ve antikorlarla ilişkili
Sjögren sendromu	- NSIP en sık, ancak LIP, OP veya UIP de görülür - Pulmoner lenfoma da akılda tutulmalı !!!
SLE	- NSIP ≫ LIP ve OP⋙UIP (çok nadir) - Lupus pnömonisi (%1-10) ve alveolar hemoraji (nadir) dışlanmalıdır

Table 1. Risk factors for the development of ILD that may indicate the need for screening*

Disease	Risk factors
Systemic sclerosis	• Anti–Scl-70 positivity, antinuclear antibody with nucleolar pattern[13] • Diffuse cutaneous subtype, male sex, African American race[14,15] • Early disease (first 5–7 y after onset) • Elevated acute phase reactants[13,16]
Rheumatoid arthritis	• High-titer rheumatoid factor, high-titer anti-CCP[17–19] • Cigarette smoking,[20,21] older age at rheumatoid arthritis onset,[22,23] high disease activity • Male sex,[22] higher body mass index
Idiopathic inflammatory myopathies	• Anti-synthetase (Jo-1, PL7, PL12, EJ, OJ, KS, Ha, Zo), anti–MDA-5, anti-Ku, anti-Pm/Scl, anti-Ro52 antibody positivity • Mechanic's hands, arthritis/arthralgia, ulcerating lesions[24]
Mixed connective tissue disease	• Dysphagia, Raynaud phenomenon • Other systemic sclerosis clinical or laboratory features
Sjögren disease	• Anti-Ro52 antibody, antinuclear antibody[25,26] • Raynaud phenomenon • Older age • Lymphopenia • Severe dental caries

Interstitial lung disease in systemic autoimmune rheumatic diseases: a comprehensive review Fabiola Atzeni 2017

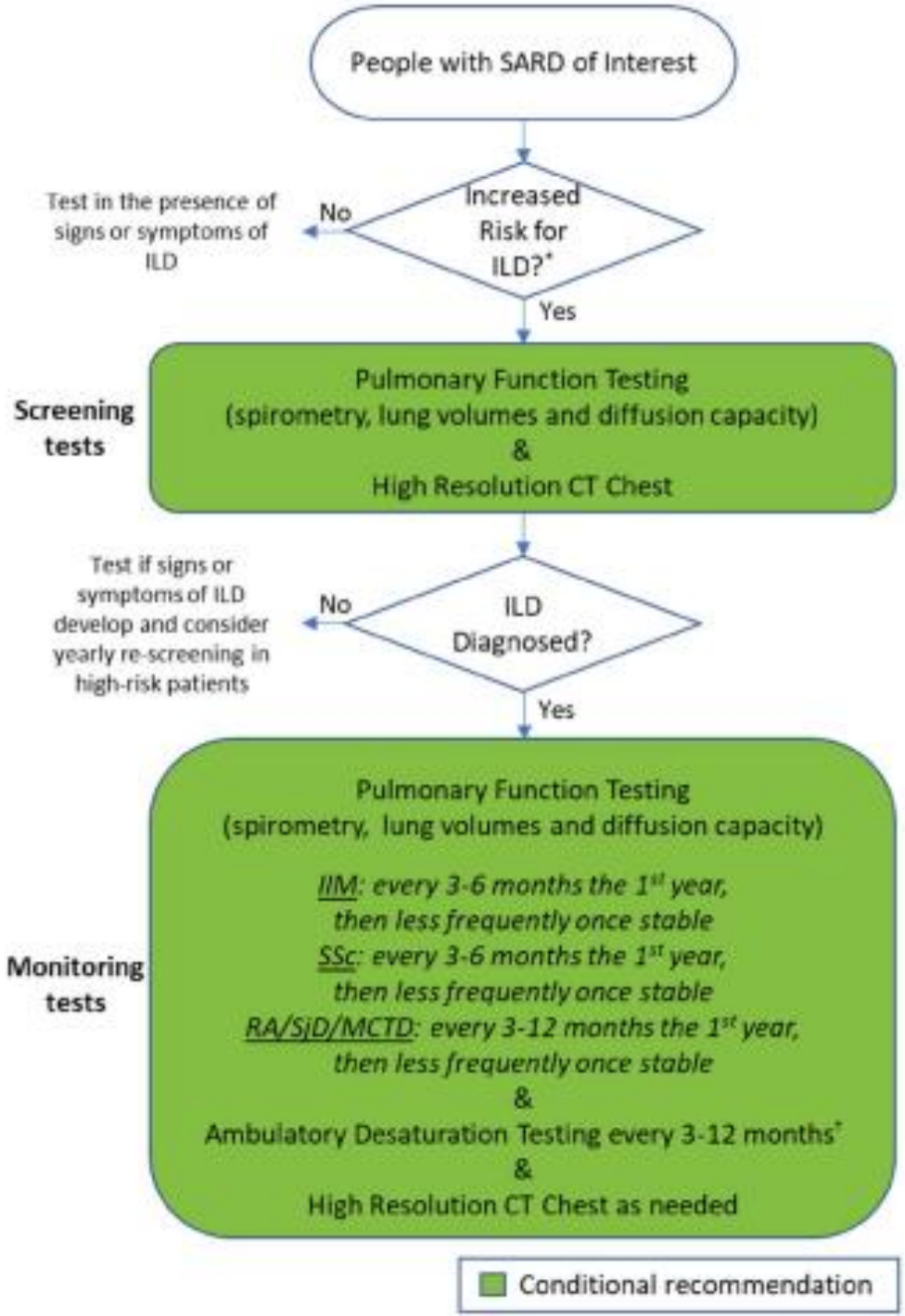


Figure 1: Recommendations for ILD Screening and Monitoring

* See Table 1 for risk factors for interstitial lung disease

† Ambulatory desaturation can be done during a routine office visit or as part of 6-minute walk testing

SARD = systemic autoimmune rheumatic disease; ILD = interstitial lung disease; CT = computed tomography; IIM = idiopathic inflammatory myopathy; SSc = systemic sclerosis; RA = rheumatoid arthritis; SjS = Sjögren's disease, MCTD = mixed connective tissue disease

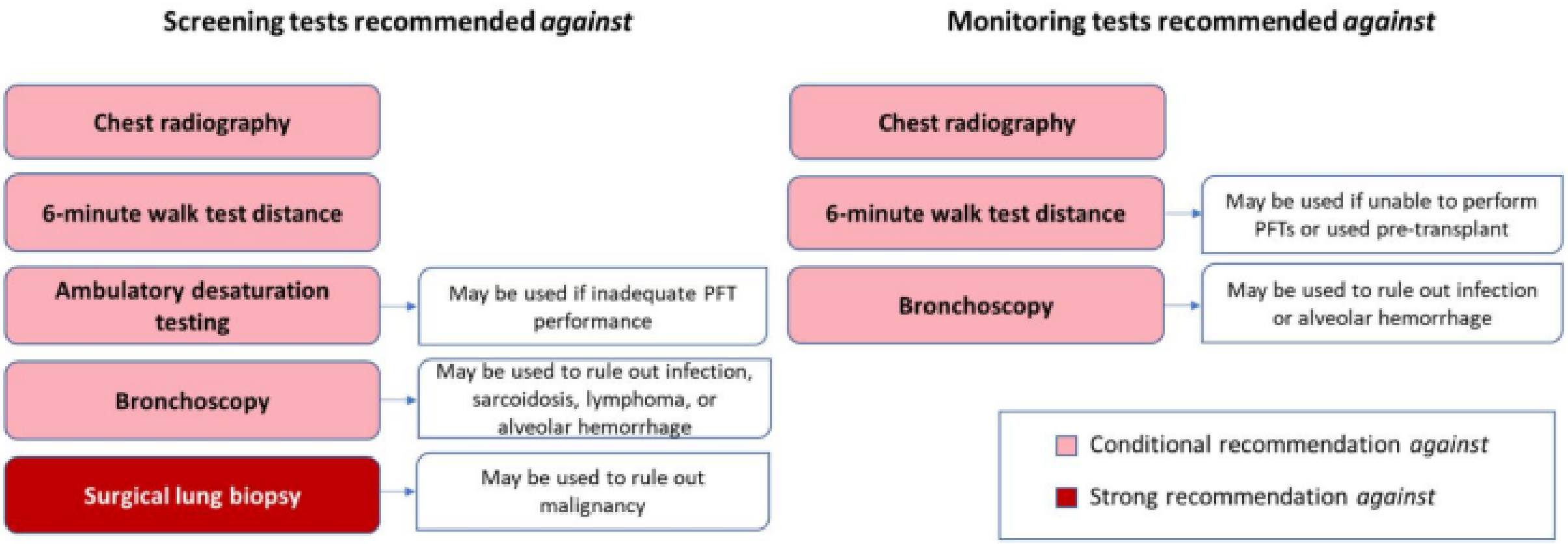


Figure 2: Interstitial lung disease screening and monitoring tests recommended *against*. Tests shown are recommended against for routine use, although examples are provided when these tests may have utility for assessing patients or ruling out other conditions.
PFT = pulmonary function test

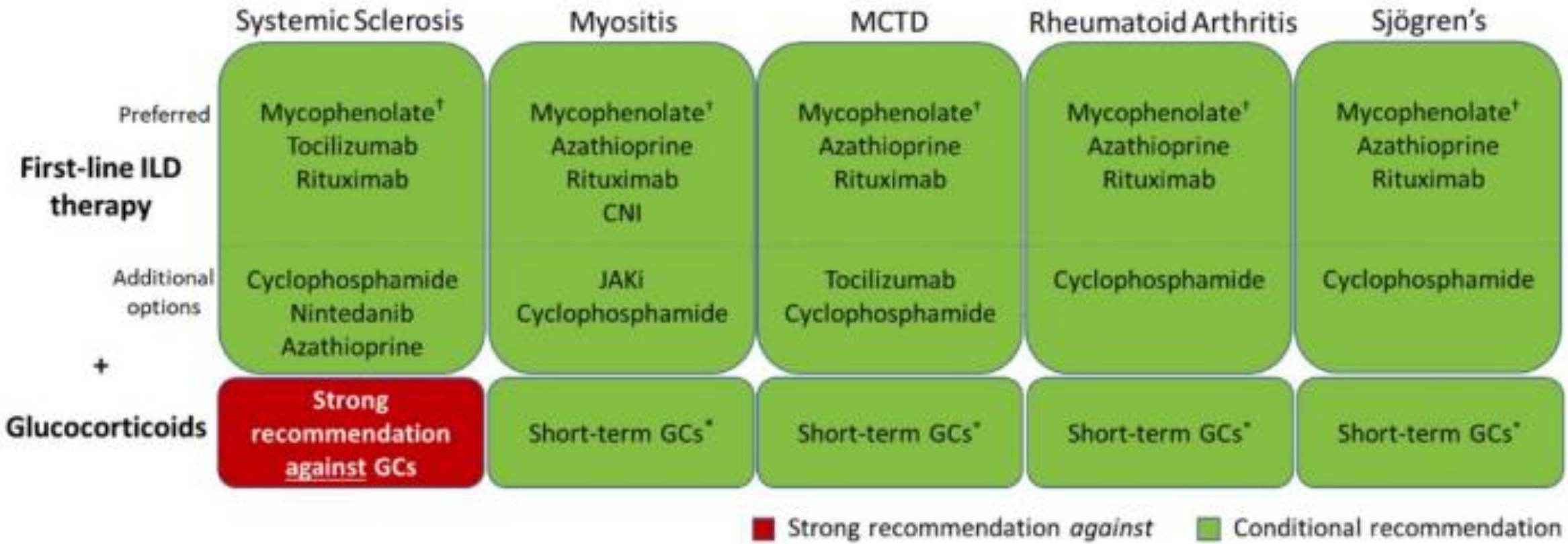


Figure 1: Initial treatment options for the treatment of interstitial lung disease associated with systemic autoimmune rheumatic diseases of interest.

* Decisions on GC dose and use of oral versus intravenous therapy depend on severity of disease. GCs should be used cautiously in patients with MCTD with a systemic sclerosis phenotype who may be at increased risk of renal crisis.

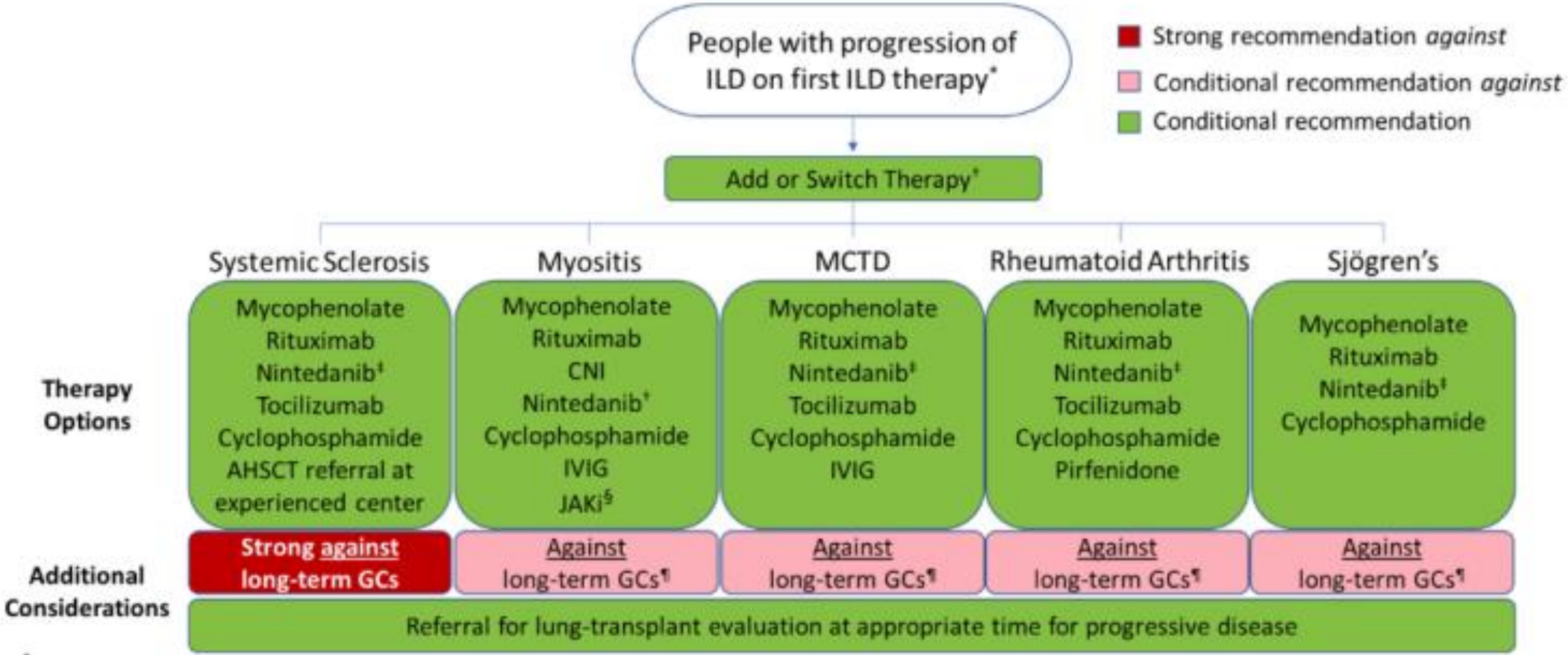
† Treatments are listed in order based on a hierarchy established by head-to-head votes, although the panel noted that decisions on which first-line therapy to use were dependent on specific situations and patient factors. In all diseases, mycophenolate was conditionally recommended over the other listed therapies. Therapies here are divided into "preferred" options and "additional options" based on the rank-order hierarchy.

MCTD = mixed connective tissue disease; GCs = glucocorticoids; CNI = calcineurin inhibitor; JAKi = janus kinase inhibitor

Inclusion criteria re: progressive phenotype

- Patients were required to meet ≥1 of the following criteria for ILD progression in the 24 months before screening, despite management:
  - Relative decline in FVC ≥10% predicted
  - Relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms
  - Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.



* If intolerance leads to suboptimal dosing of first-line therapy consider switch to an alternative first-line therapy.

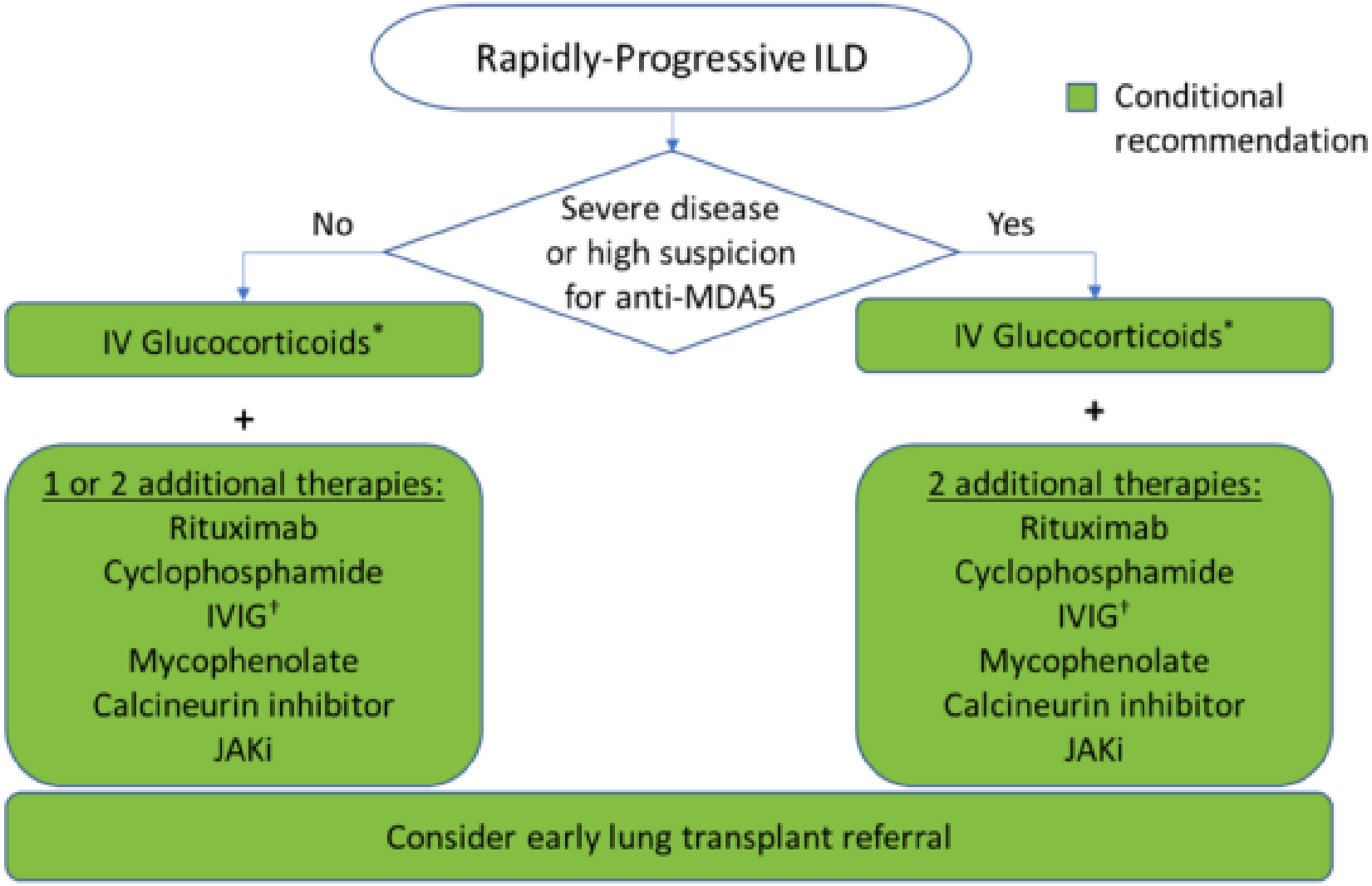
† Therapies are generally listed in order based on a hierarchy established by head-to-head votes, but decisions depend on specific clinical situations. Decision on whether to switch therapy or add to current therapy depends on current therapy and on which therapy is being initiated. Cyclophosphamide is not typically used in combination with other therapies, while others may be used individually or in combination.

‡ Decision on use of nintedanib vs immunosuppression depends on pace of progression and amount of fibrotic disease or presence of a usual interstitial pneumonia pattern on CT chest.

§ JAKi conditionally recommended as an option particularly in patients with anti-MDA-5.

¶ Short-term glucocorticoids may be of use in some patients with disease flares or as a bridge when switching therapy

MCTD = mixed connective tissue disease; CNI = calcineurin inhibitor; AHSCT = autologous hematopoetic stem cell transplant; GCs = glucocorticoids



* In rare patients with systemic sclerosis with rapidly progressive ILD, there was no consensus on whether or not to use glucocorticoids – if used, patients should be monitored closely for evidence of renal crisis.

† Rituximab and cyclophosphamide recommended over IVIG, but IVIG may be preferred if there is high concern for infection.

ILD = interstitial lung disease; IV = intravenous; IVIG = intravenous immune globulin; JAKi = janus kinase inhibitor

50 yaş erkek hasta SSc
2 yıllık hastalık süresi
scl 70 pozitif
Mrss 5/51
FVC %86 DLCO %88
6 dk yürüme testi 550m
NYHA dispne Class 2
GİS tutulumu reflü
Dijital ülser
Crp 4 mg/dl ESH: 20 mm/

Bu hasta için hangi tedaviyi seçersiniz?

MMF

Nintedanib

MMF + Nintedanib

İzlem kötüleşirse tedavi

SSc-İAH progresyonu nasıl ölçersiniz?

Inclusion criteria re: progressive phenotype

- Patients were required to meet ≥1 of the following criteria for ILD progression in the 24 months before screening, despite management:
  - Relative decline in FVC ≥10% predicted
  - Relative decline in FVC ≥5–<10% predicted and worsened respiratory symptoms
  - Relative decline in FVC ≥5–<10% predicted and increased extent of fibrosis on HRCT
  - Worsened respiratory symptoms and increased extent of fibrosis on HRCT

Flaherty KR, et al. N Engl J Med 2019; doi: 10.1056/NEJMoa1908681.

KDH – İAH progresyon sıklığı nasıl?

SSc – İAH 231 hastada FVC de azalma PF-İAH ve PPF kriterlerine göre hastalık davranışı

FVC >5% = 31%
FVC >10%= 17%
PF-ILD = 39%
PPF = 19%

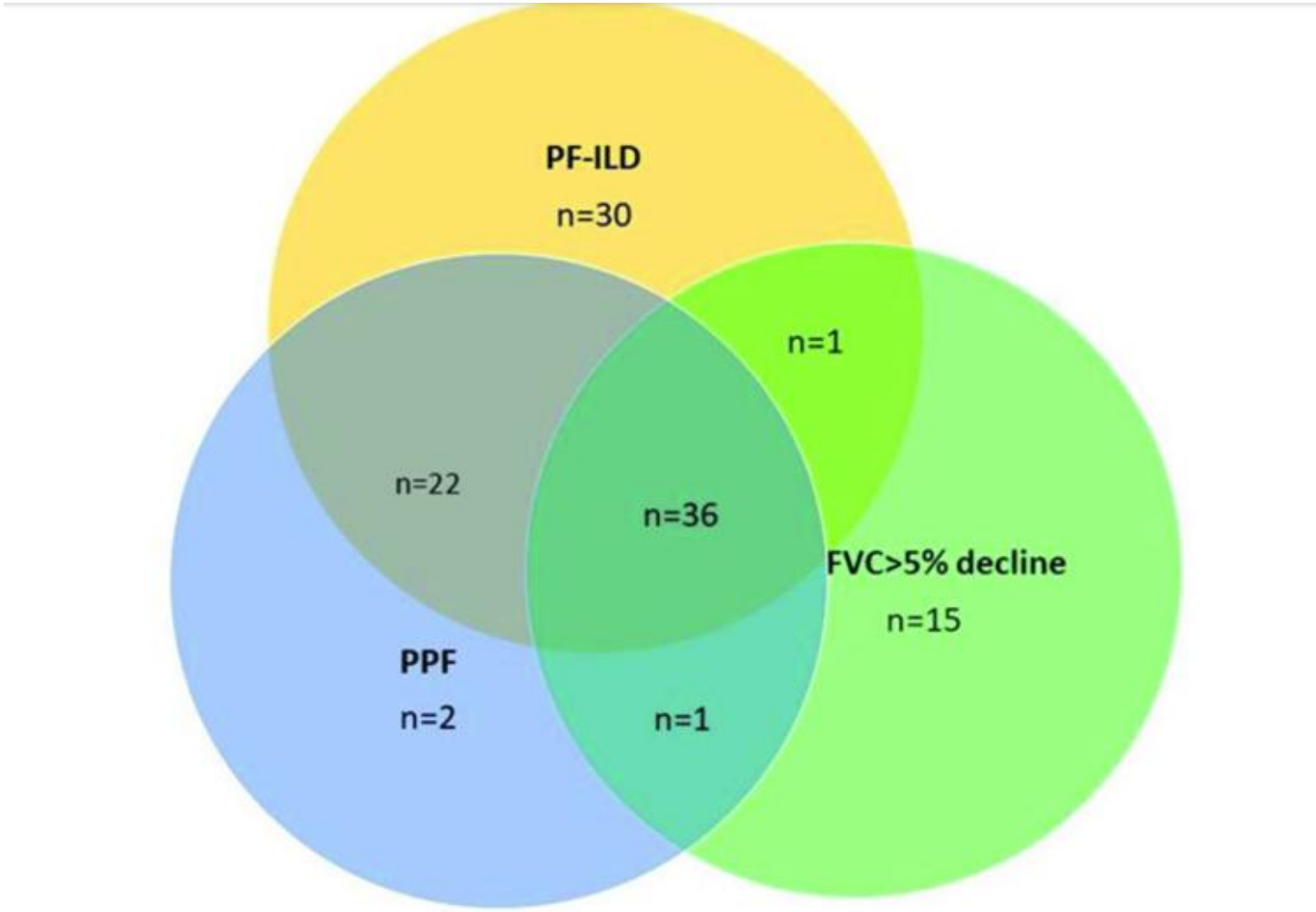


Figure 1: Venn diagram of patients fulfilling the different definitions of ILD progression

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CLINICAL SCIENCE

Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database

Anna-Maria Hoffmann-Vold ,[1] Yannick Allanore ,[2] Margarida Alves,[3] Cathrine Brunborg,[4] Paolo Airó,[5] Lidia P Ananieva,[6] László Czirják,[7] Serena Guiducci,[8] Eric Hachulla ,[9] Mengtao Li ,[10] Carina Mihai,[11] Gabriela Riemekasten,[12] Petros P Sfikakis ,[13] Otylia Kowal-Bielecka,[14] Antonella Riccardi,[15] Oliver Distler ,[11] on behalf of EUSTAR collaborators

Seçilmemiş SSc-İAH
826 hasta

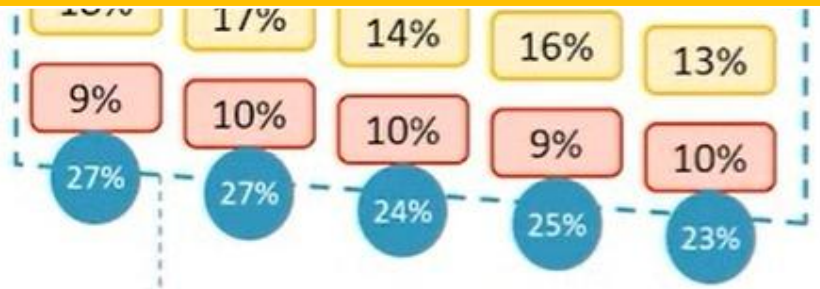
Tedavi altındaki SSc-İAH olanların yaklaşık %30'u 1 yıl içinde progrese oluyor

Hastaların çoğu ilk 12 aylık dönemde stabil kaldı veya iyileşti

Disease progression occurs in the majority of patients with SSc-ILD over time

5 yıl boyunca SSc-İAH olan hastaların %70'i progresyon gösterdi.

Toplamda, %67 hasta beş yıl içinde en az bir kez progrese oluyor.



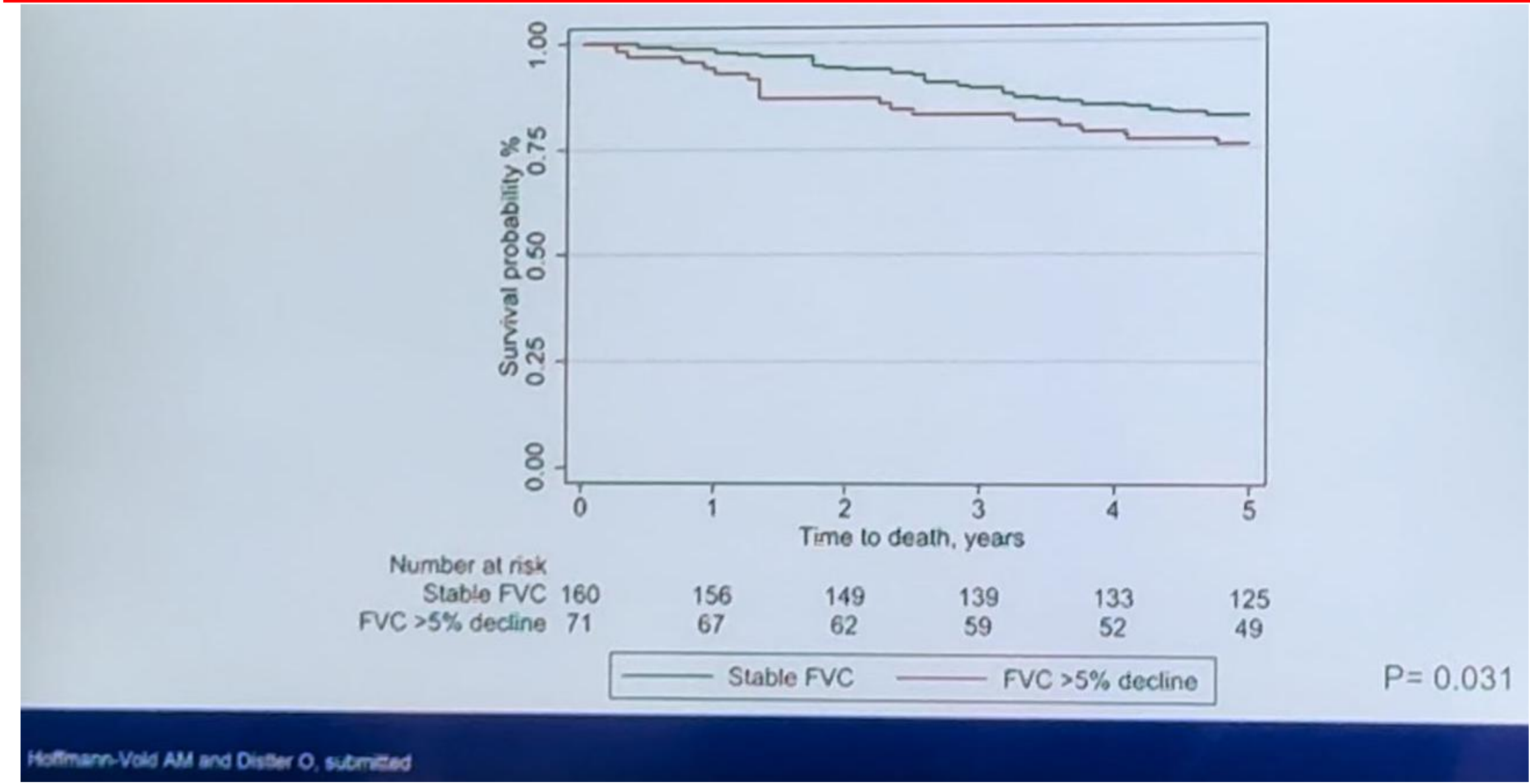
In total, **67%** of patients are affected at least once in 5 years by a period of progression

Only a minority of patients progress in sequential periods

SSc-ILD, systemic sclerosis-associated interstitial lung disease
Hoffmann-Vold AM *et al. Ann Rheum Dis* 2020;80:219–27

İAH’nın progrese olmasının uzun dönemdeki sonuçlarının anlamlı nedir?

FVC’de %5’in üzerindeki azalmalar SSc-İAH da mortaliteyi belirliyor



HRCT'de İAH açısından saptanan minör progresyon mortalite ile ilişkilidir.

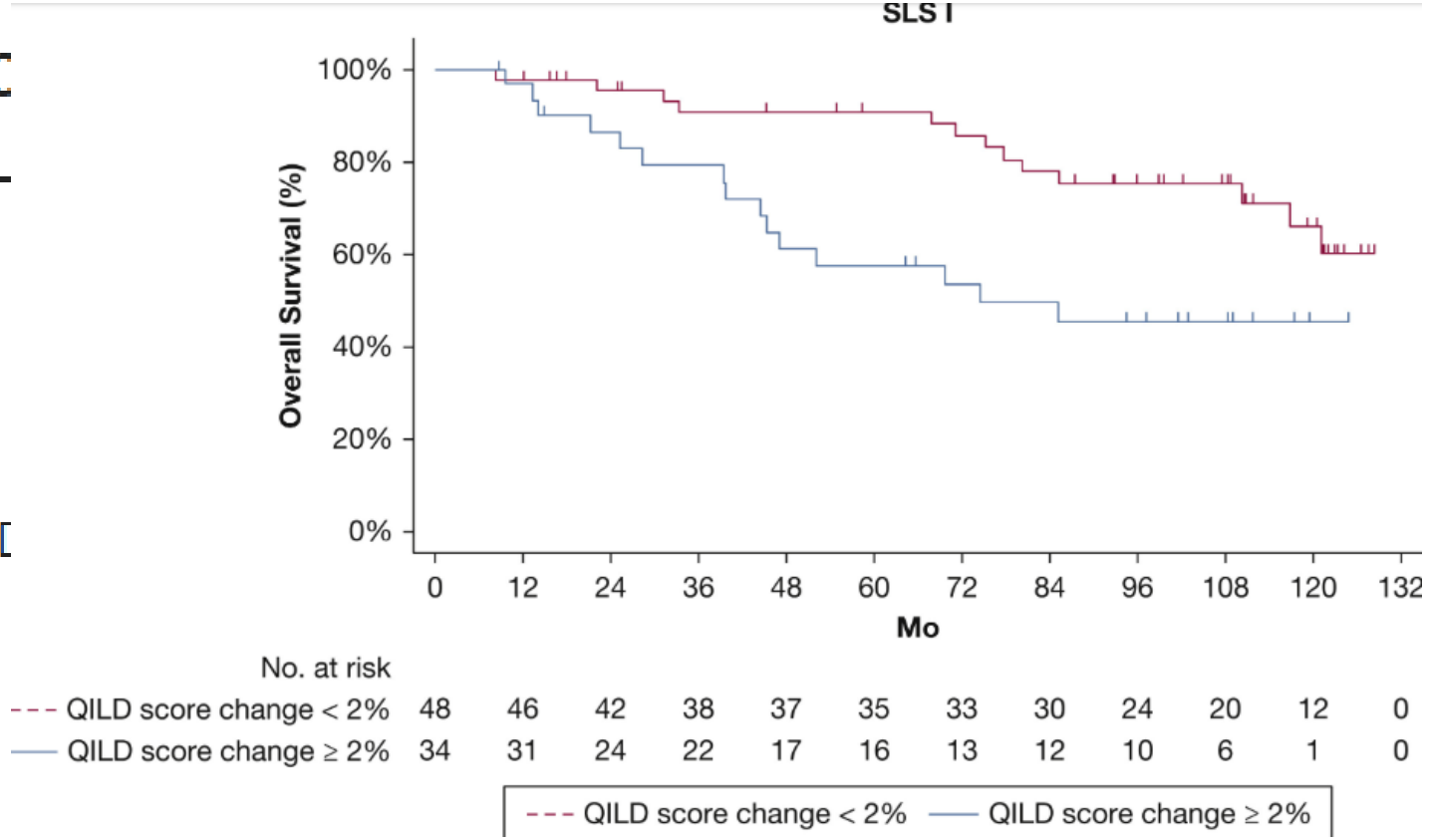
Chest. 2022 May;161(5):1310-1319. doi: 10.1016/j.chest.2021.11.033. Epub 2021 Dec 8.

Early Radiographic Prc
Disease Predicts Long-

Elizabeth R Volkmann [1], Donald P Tashkin

Affiliations + expand

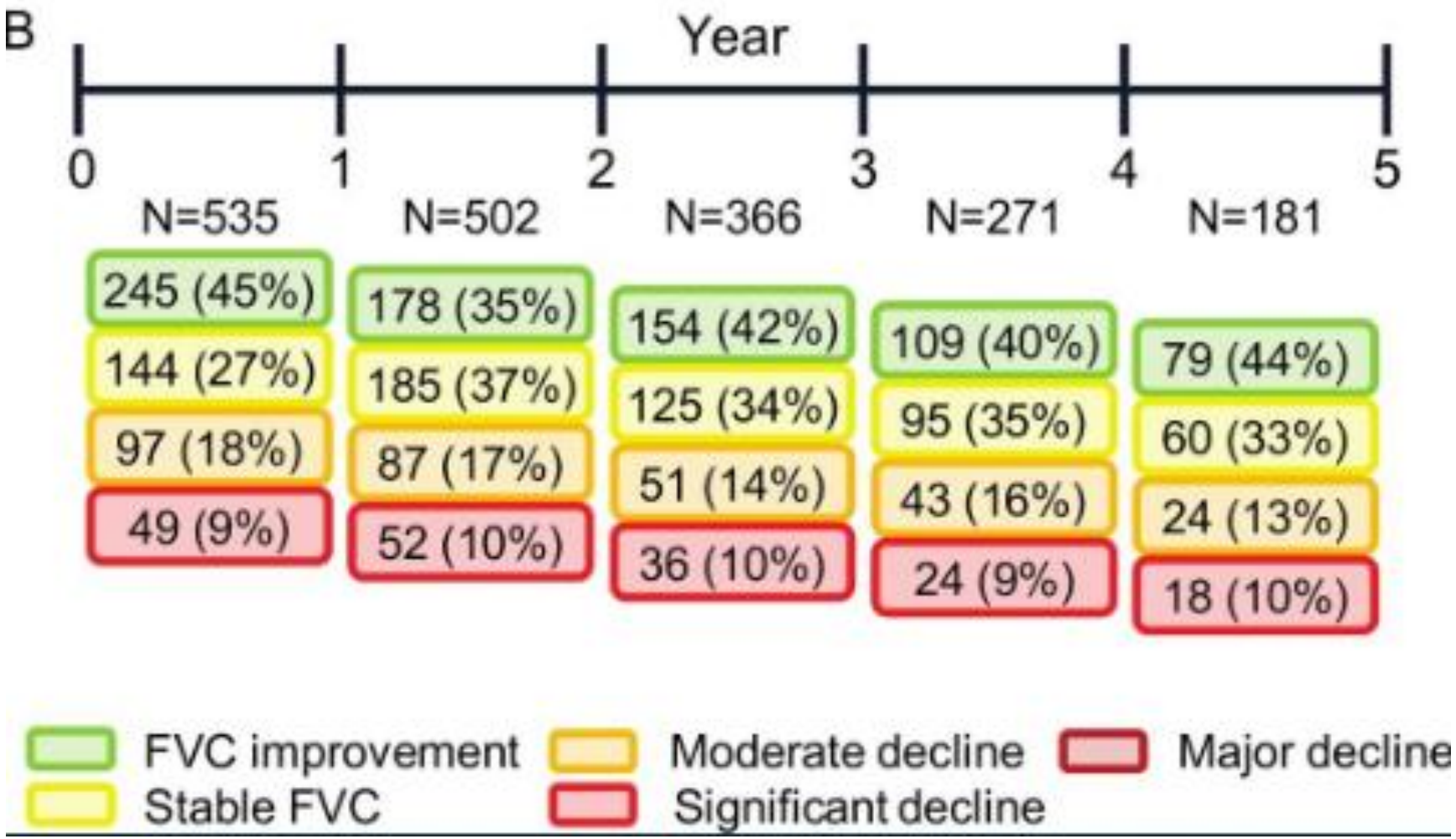
PMID: 34896093 PMCID: PMC9131045 [



AKCİĞERDE progresyon/hasar kötü sonuçlar ile ilişkili olması nedeniyle istenmez

Güvenli tarafta olmak için tüm hastaları tedavi mi edelim?

SSc-İAH olan hastaların %30'undan fazlasında 5 yıl boyunca progresyon olmadı.



Progresyonu beklemek yerine tüm hastaları tedavi etmek

OVERTREATMENT

Seçim gerekli

Progresif hastaları tedavi edelim. NEDEN?

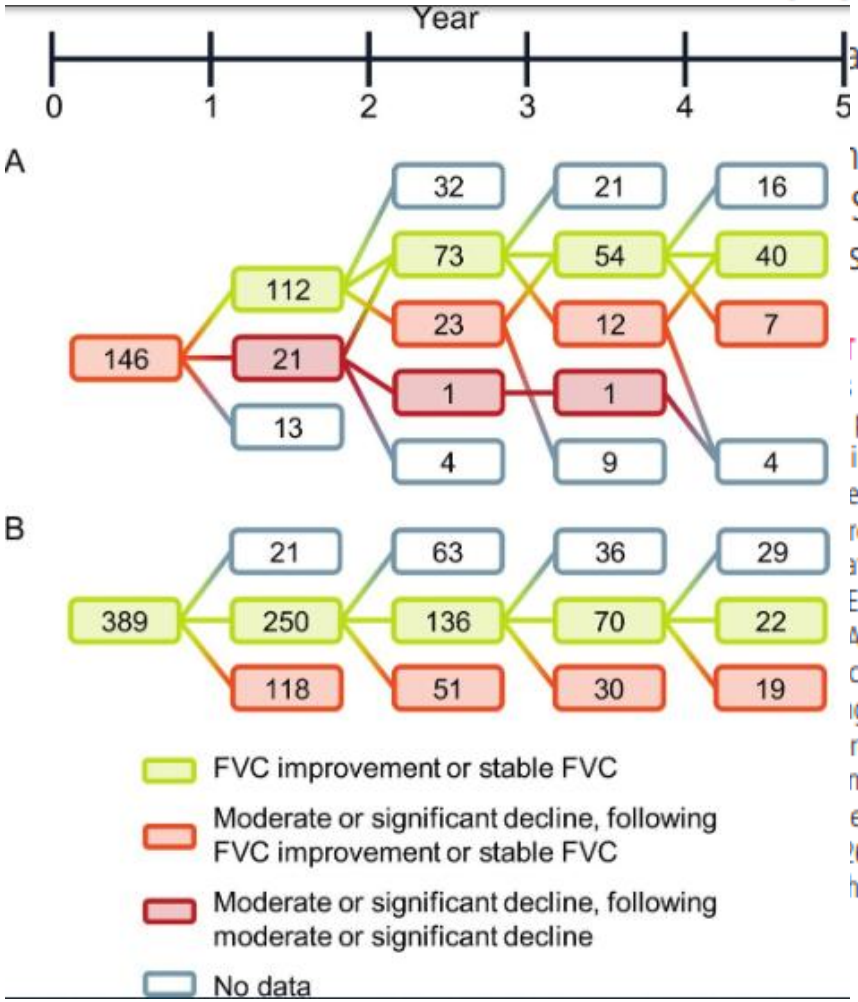
Bir kez progrese olurlarsa daha fazla progrese olacaklar

OPEN ACCESS

CLINICAL SCIENCE

Progressive interstitial lung disease in patients with systemic sclerosis-associated interstitial lung disease in the EUSTAR database

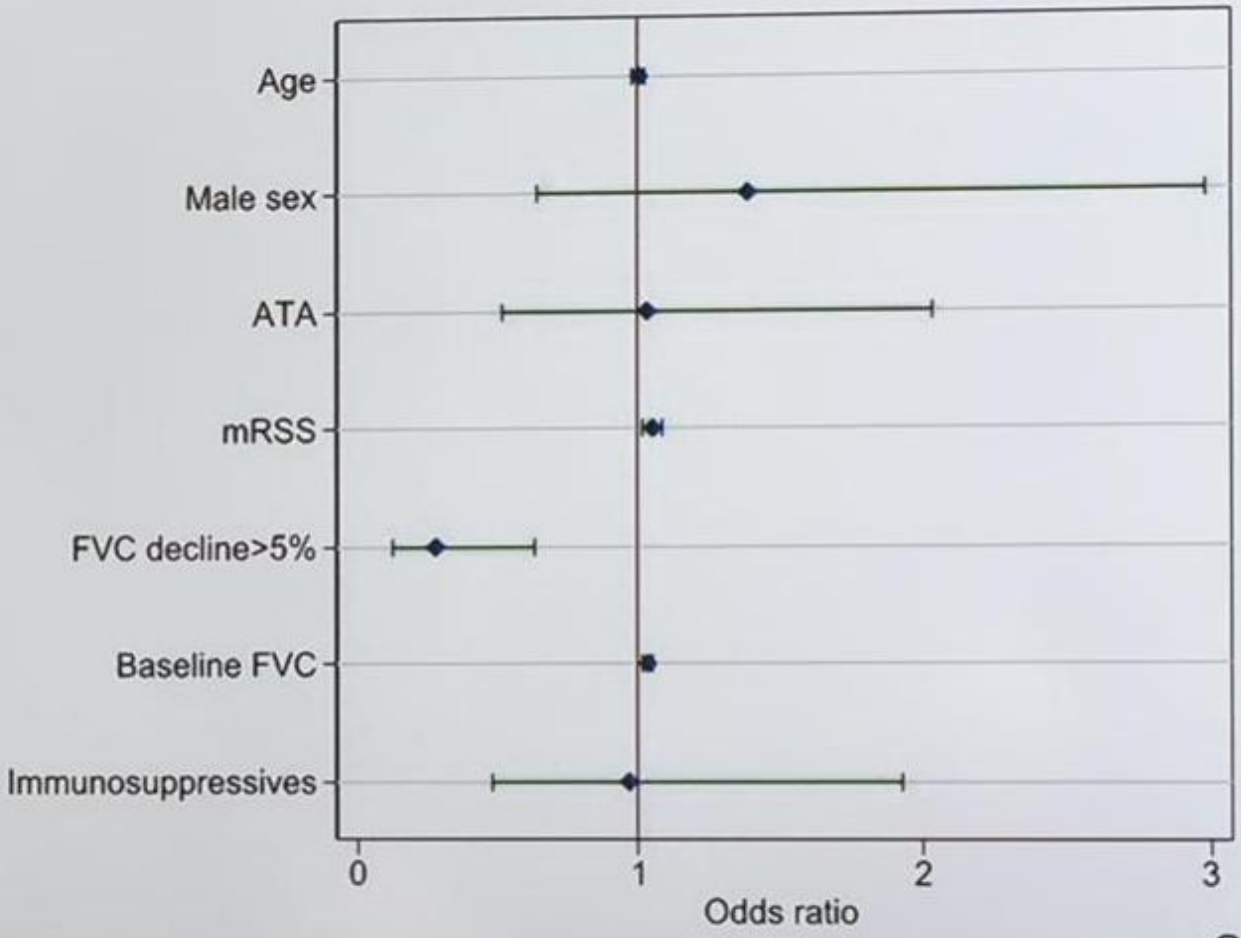
aria Hoffmann-Vold ,[1] Yannick Allanore ,[2] Margarida Alves,[3] Brunborg,[4] Paolo Airó,[5] Lidia P Ananieva,[6] László Czirják,[7] Serena Guiducci,[8] ulla ,[9] Mengtao Li ,[10] Carina Mihai,[11] Gabriela Riemekasten,[12] Sfikal stler



Önemli ilerlemeler (significant progression) süreç devam ediyorsa gerçekleşir

Standart tedavi altında önemli derecede progresyonlar nadirdir

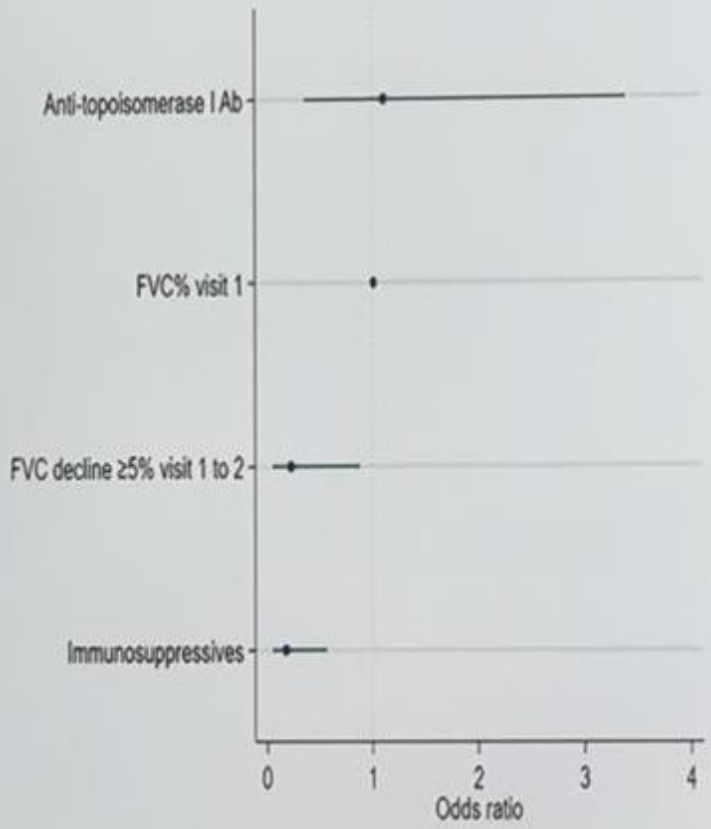
5% FVC decline predicts FVC stabilization independent of treatment in SSc-ILD



Oslo and Zurich cohort, N=231

Hoffmann-Vold and Distler O et al. submitted

5% FVC decline predicts FVC stabilization independent of treatment in SSc-ILD



	OR (95% CI)	p
Anti-topoisomerase I Ab	1·11 (0·36-3·38)	0·857
FVC% visit 1	1·01 (0·99-1·04)	0·346
FVC decline ≥5% visit 1 to 2	0·22 (0·06-0·87)	0·031
Immunosuppressives	0·18 (0·06-0·56)	0·003

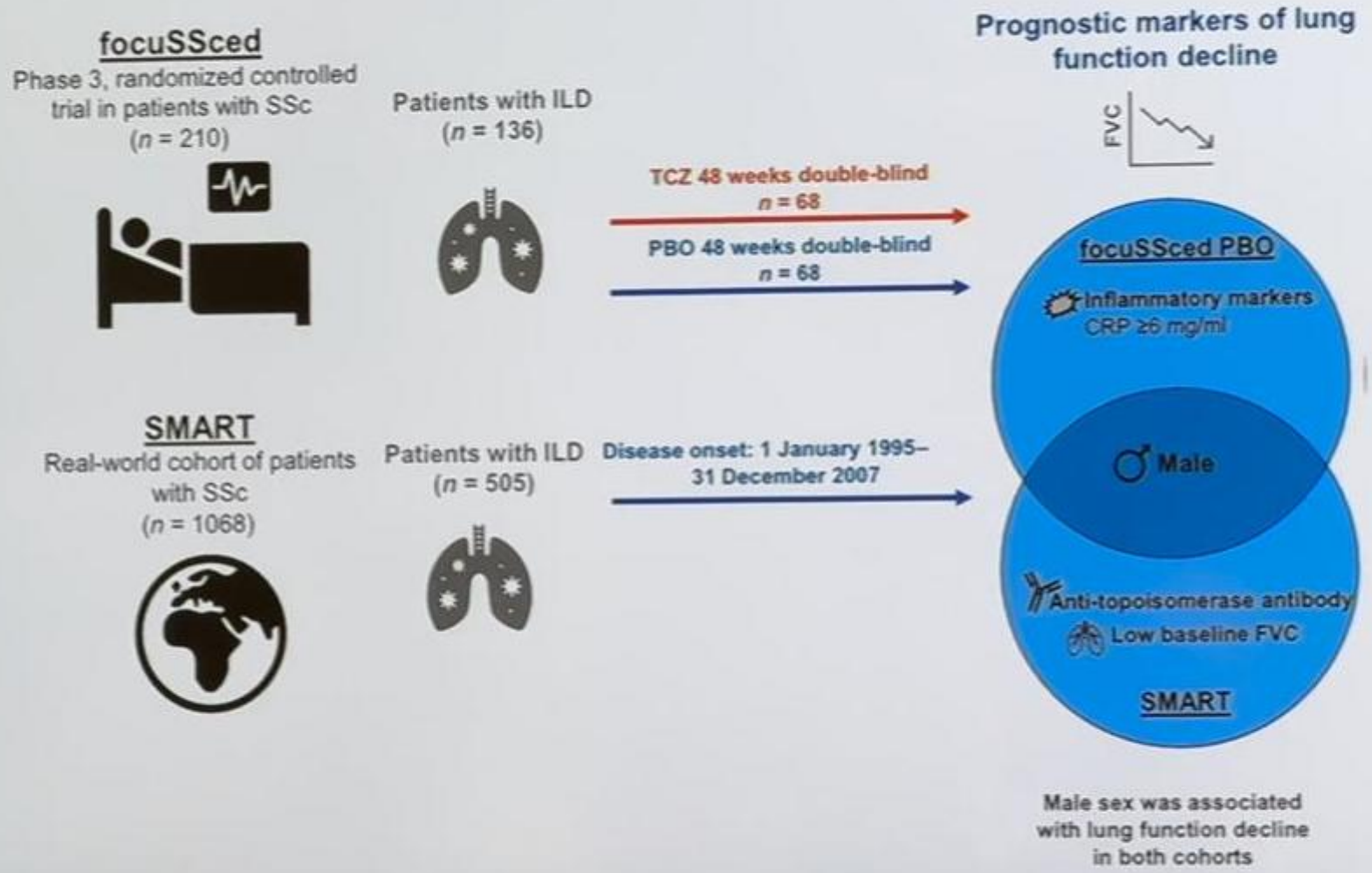
Michigan cohort, N=53

Hoffmann-Vold and Distler O et al. submitted

SSc-İAH da PROGRESYON OLMASI progresyonun daha da ilerleyeceğini BELİRLEMEZ

Daha kötü sonuçlarla ilişkilendirilen ilerlemenin gerçekleşmesini beklemek İSTEMİYORUZ

What do we know about risk factors for progression?



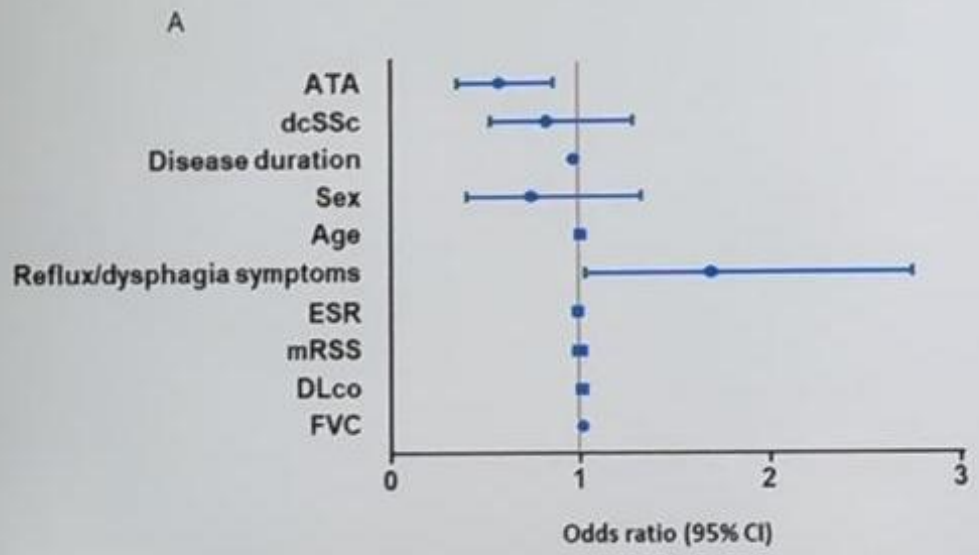
Ghuman et al, Rheumatology (Oxford) 2023 May 25, Online ahead of print.

What do we know about risk factors for progression?

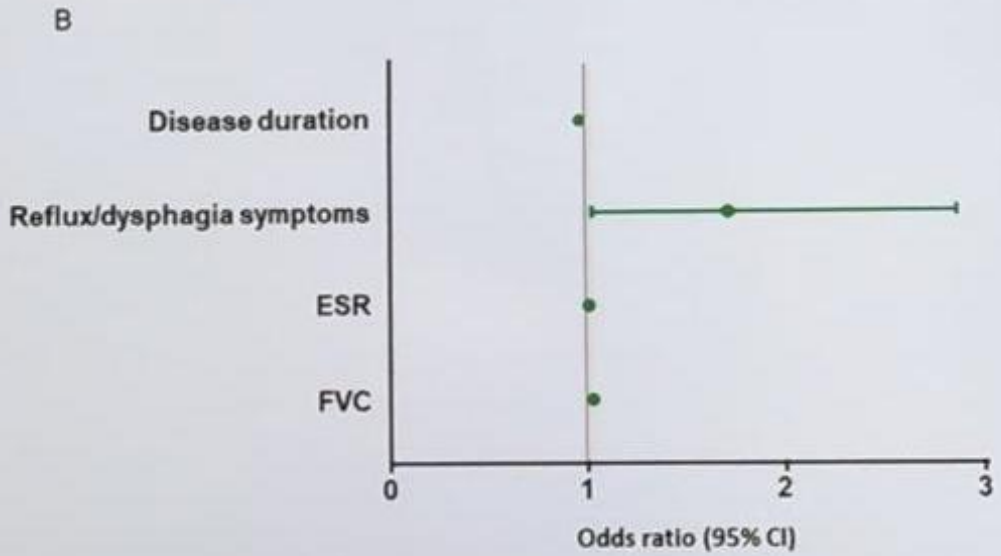
FVC decline of >10%, or FVC decline of 5–10% with DLCO decline of ≥15%

12±3 months follow-up in EUSTAR database

univariable



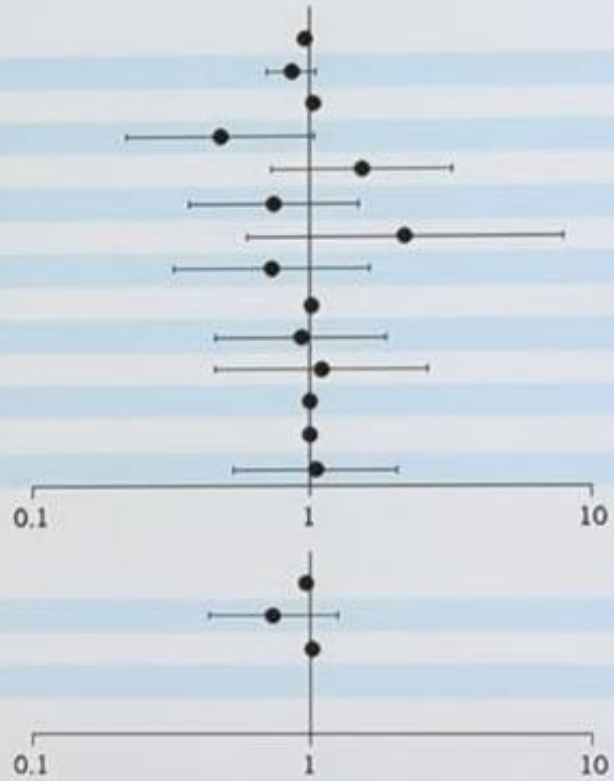
multivariable



Hoffmann-Vold AM et al. Ann Rheum Dis 2021;80:219-227

Different SSc-ILD phenotypes might require different risk assessments

Risk of decline in FVC % predicted >5% or death over 52 weeks in patients in the placebo group with pre-defined risk factors for rapid FVC decline at baseline (n=155)



Univariable models	OR (95% CI)*	p-value	AUC
DLco % predicted	0.96 (0.94, 0.99)	<0.01	0.66
Years since first non-Raynaud symptom	0.86 (0.71, 1.04)	0.12	0.59
mRSS	1.03 (1.00, 1.07)	0.06	0.59
Sex, female vs male	0.48 (0.22, 1.03)	0.06	0.57
ATA positive vs ATA negative	1.53 (0.73, 3.20)	0.26	0.55
Mycophenolate use, yes vs no	0.74 (0.37, 1.49)	0.41	0.54
Ground glass opacities on HRCT, yes vs no	2.18 (0.60, 7.94)	0.24	0.54
History of GERD, yes vs no	0.73 (0.33, 1.63)	0.44	0.53
Age, years	1.01 (0.98, 1.03)	0.66	0.52
Diffuse cutaneous SSc vs limited cutaneous SSc	0.93 (0.46, 1.88)	0.83	0.51
Honeycombing on HRCT, yes vs no	1.10 (0.46, 2.63)	0.84	0.51
Extent of fibrotic ILD on HRCT, %	1.00 (0.99, 1.02)	0.57	0.50
FVC % predicted	1.00 (0.98, 1.02)	0.99	0.50
High-sensitivity CRP, mg/L (log_{10} scale)	1.04 (0.53, 2.03)	0.91	0.50

Multivariable model	OR (95% CI)*	p-value	AUC
DLco % predicted	0.95 (0.92, 0.98)	<0.01	
Years since first non-Raynaud symptom	0.74 (0.58, 0.93)	0.01	
mRSS	1.06 (1.02, 1.10)	0.01	0.75
ATA positive vs ATA negative	1.63 (0.71, 3.75)	0.25	
Mycophenolate use, yes vs no	0.71 (0.33, 1.55)	0.39	

SENSCIS placebo group population enriched for risk of progression (early, inflammatory, diffuse SSc)

SSc-İAH tedavi şeması DEĞİŞTİ
KANIT

1- Siklofosfamid Oxford level 1

2- Nintedanib Oxford level 1

3- Mikofenolat mofetil Oxford level 2

4-Tosiluzumab Oxford level ½

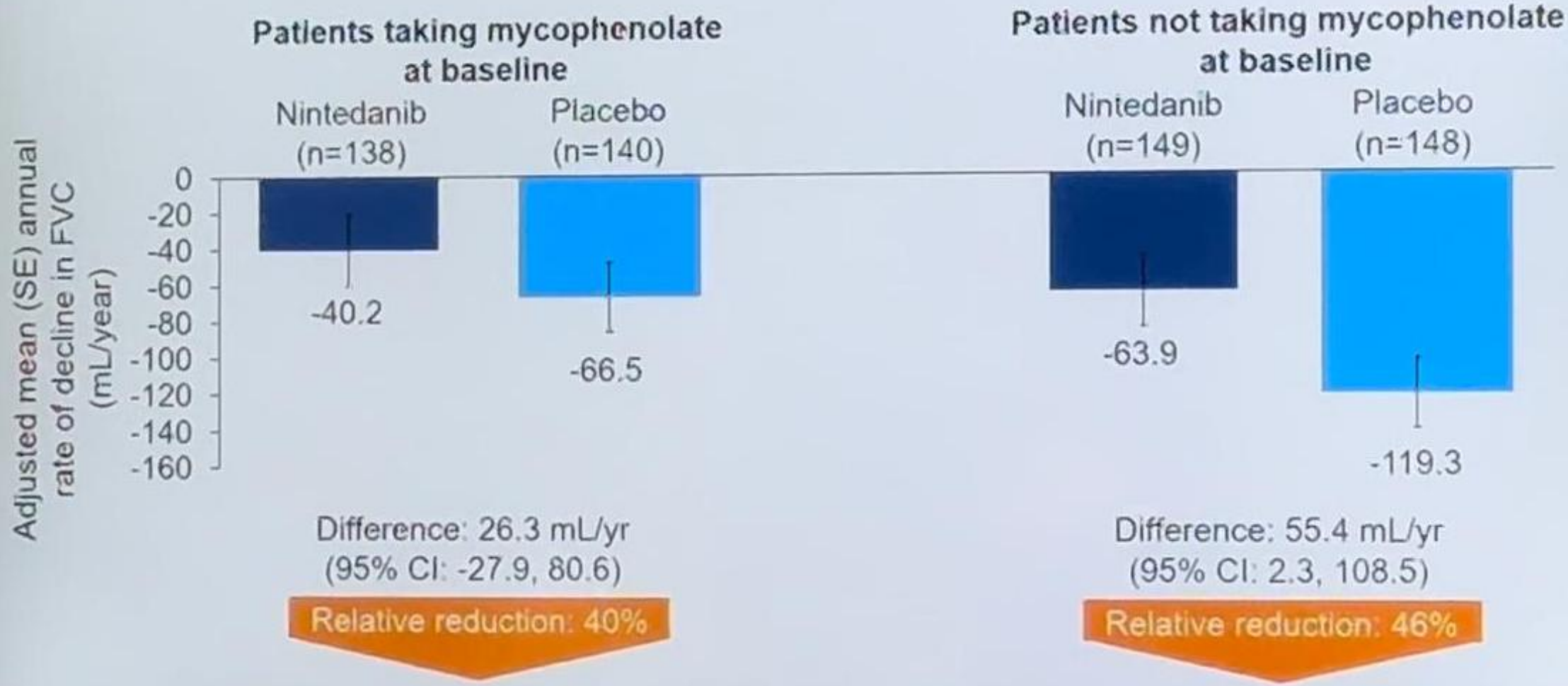
5- Rituximab Oxford level 2

Progresyon riski taşıyan hastaları belirlemek henüz optimum değil, ancak gelişmekte

Risk faktörleri ne kadar fazlaysa, progresyonu önlemek için advers olayları ve maliyetleri kabul etmeyi o kadar uygun görürüz

Tabiki ilaçlar etkiliyse

Clinical evidence for immunosuppressives versus "anti-fibrotics"



Treatment-by-time-by-subgroup interaction p=0.45.

Highland KB et al. Lancet Respir Med 2021;9:96–106.

Clinical Trial > N Engl J Med. 2025 Jun 12;392(22):2203-2214. doi: 10.1056/NEJMoa2503643. Epub 2025 May 19.

Nerandomilast in Patients with Progressive Pulmonary Fibrosis

Toby M Maher [1 2], Shervin Assassi [3], Arata Azuma [4 5], Vincent Cottin [6], Anna-Maria Hoffmann-Vold [7 8], Michael Kreuter [9 10], Justin M Oldham [11], Luca Richeldi [12], Claudia Valenzuela [13], Marlies S Wijsenbeek [14], Emmanuelle Clerisme-Beaty [15], Carl Coeck [16], Hui Gu [17], Ivana Ritter [15], Arno Schlosser [18], Susanne Stowasser [15], Florian Voss [19], Gerrit Weimann [15], Donald F Zoz [20], Fernando J Martinez [21]; FIBRONEER-ILD Trial Investigators

Collaborators, Affiliations + expand

PMID: 40388329 DOI: 10.1056/NEJMoa2503643

Abstract

Background: Nerandomilast (BI 1015550) is an orally administered preferential inhibitor of phosphodiesterase 4B with antifibrotic and immunomodulatory properties. Nerandomilast has been shown to slow the progression of idiopathic pulmonary fibrosis, but an assessment of its effects in

Results: A total of 1176 patients received at least one dose of nerandomilast or placebo, of whom 43.5% were taking background nintedanib therapy at baseline. The adjusted mean change in the FVC at week 52 was -98.6 ml (95% confidence interval [CI], -123.7 to -73.4) in the nerandomilast 18-mg group, -84.6 ml (95% CI, -109.6 to -59.7) in the nerandomilast 9-mg group, and -165.8 ml (95% CI, -190.5 to -141.0) in the placebo group. The adjusted difference between the nerandomilast 18-mg group and the placebo group was 67.2 ml (95% CI, 31.9 to 102.5; P<0.001), and the adjusted difference between the nerandomilast 9-mg group and the placebo group was 81.1 ml (95% CI, 46.0 to 116.3; P<0.001). The most frequent adverse event was diarrhea, reported in 36.6% of the patients in the nerandomilast 18-mg group, 29.5% of those in the nerandomilast 9-mg group, and 24.7% of those in the placebo group. Serious adverse events occurred in similar percentages of patients in the trial groups.

Conclusions: In patients with progressive pulmonary fibrosis, treatment with nerandomilast led to a smaller decline in the FVC than placebo over a period of 52 weeks. (Funded by Boehringer Ingelheim; FIBRONEER-ILD ClinicalTrials.gov number, NCT05321082.).

Nerandomilast Slows Progression of PPF: Changes in FVC From Baseline to Week 52 in FIBRONEER-ILD

Table 4. Additional integrative and pharmacologic interventions that may be considered in the care of people with SARD-ILD*

Interventions	Examples
Integrative	
Exercise	Aerobic, resistance training, yoga, tai chi
Palliative care	Symptom treatment (eg, cough, pain, air hunger), end of life planning[17,18]
Physiotherapy	Chest physiotherapy, airway clearance, incentive spirometry
Pulmonary rehabilitation	Cardiopulmonary rehabilitation, resistance training[19]
Smoking cessation	Smoking cessation program
Supplemental oxygen	Oxygen administration by nasal prongs
Pharmacologic	
Gastroesophageal reflux management	Proton pump inhibitors, H2 blockers[20,21]
PJP prophylaxis	Trimethoprim sulfamethoxazole
Promotility agents	Domperidone
Vaccines	MMR, influenza, COVID-19, pneumococcus, varicella zoster, RSV[22,23]

* ILD, interstitial lung disease; MMR, measle, mumps, rubella; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; SARD, systemic autoimmune rheumatic disease.

Progresyon kötü bir durumdur, tedavi etmekten ziyade önlenmelidir.

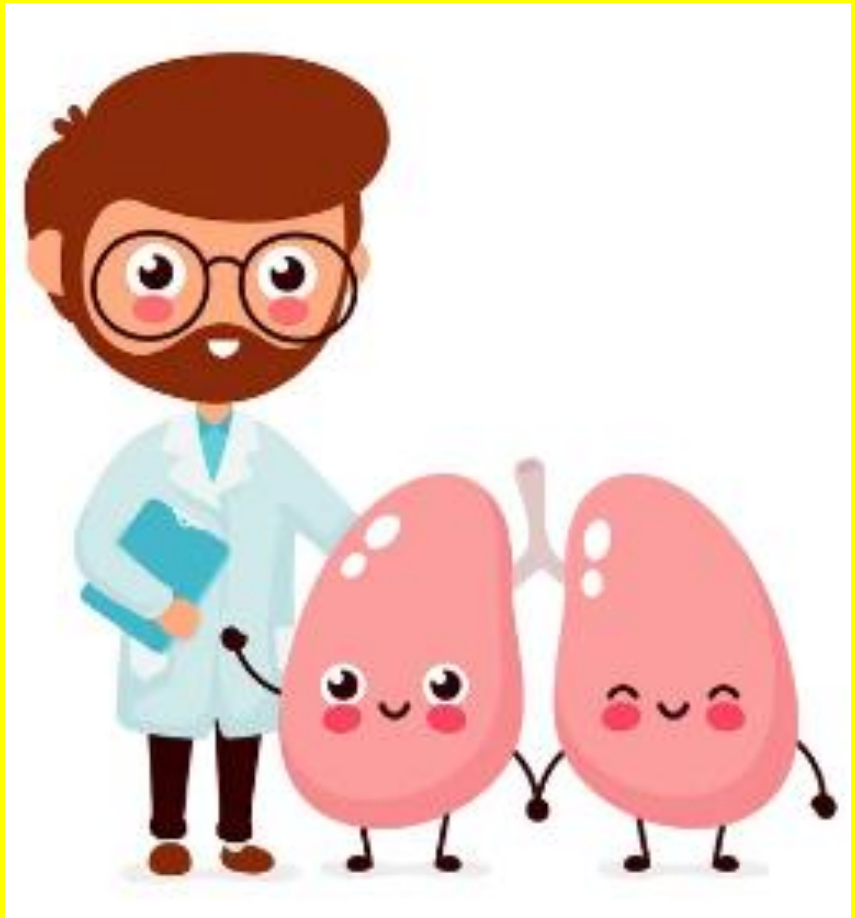
Progresyon riski taşıyan hastaların belirlenmesi henüz zor

Antifibrotik ve immünsupresif ilaçlar tedavi için seçeneklerdir.

Muhtemelen kombinasyonu daha etkili, ama strateji deneyiminden yoksun kalıyoruz.

Her yaşam birinci sınıf bakımı hak eder

Pulmonolog



İç Hastalıkları Romatolog

Radyolog