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CLINICAL SCIENCE

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

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概要

- European Scleroderma Trials And Research (EUSTAR；ヨーロッパのSSc患者大規模データベース）のpost hoc後ろ向き解析
- SSc-ILDの臨床経過はHeterogeneous（不変/進行の混在）.
  本解析は最大規模の長期経過解析で，real worldのSSc-ILDの5年間の経過を明らかにすることが目的.
- 従来，増悪傾向にある患者を対象に治療強化をしていたが，それでは（既に線維化が進んでおり）遅い.
- SSc-ILD進行の因子を抽出することも目的.

背景

- SSc-ILD患者のうち一部は進行性であり死亡率が高い.
- progressive ILDの正確な頻度, 長期経過, ILDのパターンはまだ明らかになっていない(既報はNが少なすぎる).
- RCTでは12-24カ月しか経過観察しておらず短すぎる.
- Progressive ILD の患者に治療介入する重要性は分かっている.

目的

- EUSTARで下記を調査する:
  1. 初発12カ月のprogressive ILDの頻度
  2. 5年間でのILD進行パターン
  3. SSc-ILDがprogressive ILDになるリスク因子

結果：患者群

- SSc 6004人 (2010年～, >18yo)
  ↓
  SSc-ILD+ 2259人(38%)
  ↓
  1年間のPFTデータあり：826人
- lcSSc 50%, dcSSc 50%
- ATA 53%/ACA 18%/ARA 5%
- %FVC 87%, %Dlco 59%
- mRSS 10
- NYHA class: 1(44%), 2(38%), 3(13%), 4(2%)

Table 1 Overall baseline demographic and clinical characteristics of all patients with SSc-ILD and characteristics stratified by ILD progression over the 12±3-month observation period

Progression criteria: ΔFVC% predicted	Total (N=826)	Significant progression (n=100) <−10	Moderate progression (n=123) −10 to −5	Stable (n=396) >−5 to <5	Improvement (n=207) ≥5
Age, years (SD)*	56 (13.1)	59 (13.1)	56 (12.4)	55 (13.5)	58 (12.4)
Male, n (%)*	150 (18)	17 (17)	16 (13)	81 (20)	36 (17)
Disease characteristics at baseline					
Disease duration, years* (SD)	9.7 (8.3)	8.8 (7.7)	10.2 (8.2)	10.2 (8.5)	8.9 (8.3)
Disease duration <3 years*, n (%)	175 (21)	26 (26)	27 (22)	68 (17)	54 (26)
Diffuse cutaneous SSc, n (%)	365/732 (50)	44/96 (46)	55/106 (52)	182/357 (51)	84/173 (49)
Limited cutaneous SSc, n (%)	367/732 (50)	52/96 (54)	51/106 (48)	175/357 (49)	89/173 (51)
Anti-topoisomerase I Ab, n (%)	421/789 (53)	41/97 (42)	64/117 (55)	218/378 (58)	98/197 (50)
Anti-centromere Ab, n (%)	141/783 (18)	19/97 (20)	18/113 (16)	59/376 (16)	45/197 (23)
Anti-RNA polymerase III Ab, n (%)	23/451 (5)	3/54 (6)	3/60 (5)	10/217 (5)	7/117 (3)
Follow-up period, years*, mean (SD)	5.4 (2.0)	5.8 (1.4)	5.6 (2.0)	4.8 (3.2)	5.0 (3.2)
Lung characteristics					
FVC% predicted,* mean (SD)	87 (21.1)	95 (23.3)	90 (21.8)	85 (20.4)	85 (19.7)
DL_{CO}% predicted,* mean (SD)	59 (18.3)	61 (17.8)	60 (17.9)	58 (19.3)	60 (16.8)
ΔFVC% predicted,† mean (SD)	−0.1 (10.2)	−18 (7.9)	−7 (1.3)	0.3 (2.2)	12 (7.0)
ΔDL_{CO}% predicted,† mean (SD)	−0.7 (12.2)	−4 (15.4)	2 (12.8)	−0.3 (10.9)	0.9 (11.9)
NYHA class, n (%)	N=797	n=99	n=119	n=377	n=202
1	363 (44)	44 (44)	57 (46)	167 (42)	95 (46)
2	317 (38)	42 (42)	44 (36)	152 (38)	79 (38)
3	103 (13)	10 (10)	17 (14)	50 (13)	26 (13)
4	14 (2)	3 (3)	1 (1)	8 (2)	2 (1)
Other characteristics					
mRSS, mean (SD)	N=747 10 (8.1)	n=96 11 (7.6)	n=112 10 (8.5)	n=352 10 (7.6)	n=187 10 (8.8)
ΔmRSS,† mean (SD)	N=698 −0.4 (4.6)	n=88 0.5 (4.3)	n=103 −0.4 (3.1)	n=337 −0.3 (4.4)	n=170 −1.2 (5.6)
Reflux/dysphagia symptoms, n (%)	547/822 (67)	76/100 (76)	83/122 (68)	261/393 (66)	127/207 (61)
Digital ulcers, n (%)	266/808 (32)	35/100 (35)	38/118 (31)	141/386 (36)	5/2042 (25)
Tendon friction rubs, n (%)	73/804 (9)	7/99 (7)	10/119 (8)	35/383 (9)	21/203 (10)
Synovitis, n (%)	117/810 (14)	18/100 (18)	15/120 (13)	60/386 (16)	24/204 (12)
Muscle weakness, n (%)	182/814 (22)	25/100 (25)	31/120 (25)	78/388 (20)	48/206 (23)
Scleroderma renal crisis, n (%)	11/818 (1)	4/100 (4)	3/120 (2)	6/391 (2)	1/206 (0.5)
ESR, mean (SD)	766 (93) 26 (20.6)	98 (98) 29 (23.9)	115 (93) 25 (21.7)	361 (91) 26 (19.5)	192 (93) 25 (20.2)
Elevated CRP, n (%)	217/797 (27)	40/99 (30)	25/120 (33)	98/377 (26)	49/201 (24)
Immunosuppressant use, n (%)	89/244 (37)	8/20 (40)	8/31 (26)	51/121 (42)	22/72 (31)

Significant progression (FVC decline of >10%); moderate progression (FVC decline of 5% to 10%); stable ILD (FVC decline or improvement of <5%); moderate improvement (FVC improvement of 5% to 10%). Definitions of organ manifestations were described previously.[3 28] All characteristics were assessed before or on the index date. The following treatment options were received by the included patients at baseline, and for this study were defined as immunosuppressive: prednisone >10 mg/day, azathioprine, cyclophosphamide, mycophenolate, methotrexate or rituximab.

*Available for all 826 patients.

†Change from baseline to 12 months.

Ab, antibody; CRP, C-reactive protein; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; SSc, systemic sclerosis; SSc-ILD, systemic sclerosis-associated interstitial lung disease.

発症1年のFVC低下

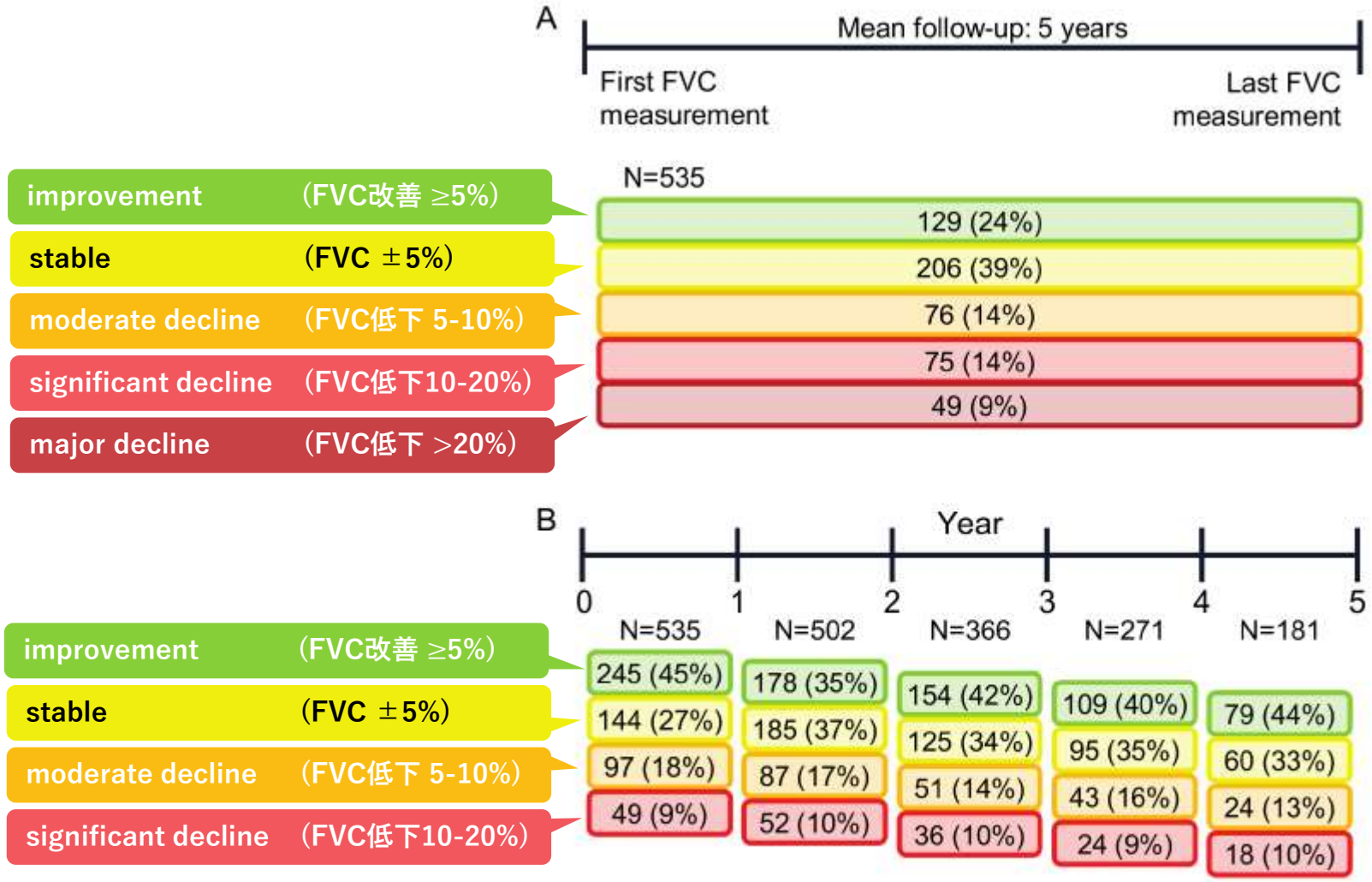
FVC変化	人数（%）
improvement (FVC改善 ≥5%)	N=207 (25%)
stable (FVC ±5%)	N=396 (48%)
moderate decline (FVC低下 5-10%)	N=123 (15%)
significant decline (FVC低下10-20%)	N=100 (12%)

Progressive ILD

- 発症1年（12±3カ月）のデータがある826人中，219人 (27%) が progressive ILD.
- Progressive ILD: FVC減少が moderate (5～10%) or significant (＞10%).
- Progressive ILDのリスク:
  1. FVC高値(OR 1.02)
  2. 逆流/嚥下障害症状 (OR 1.97)
  3. mRSS高値 (OR 1.06)

長期FVC観察

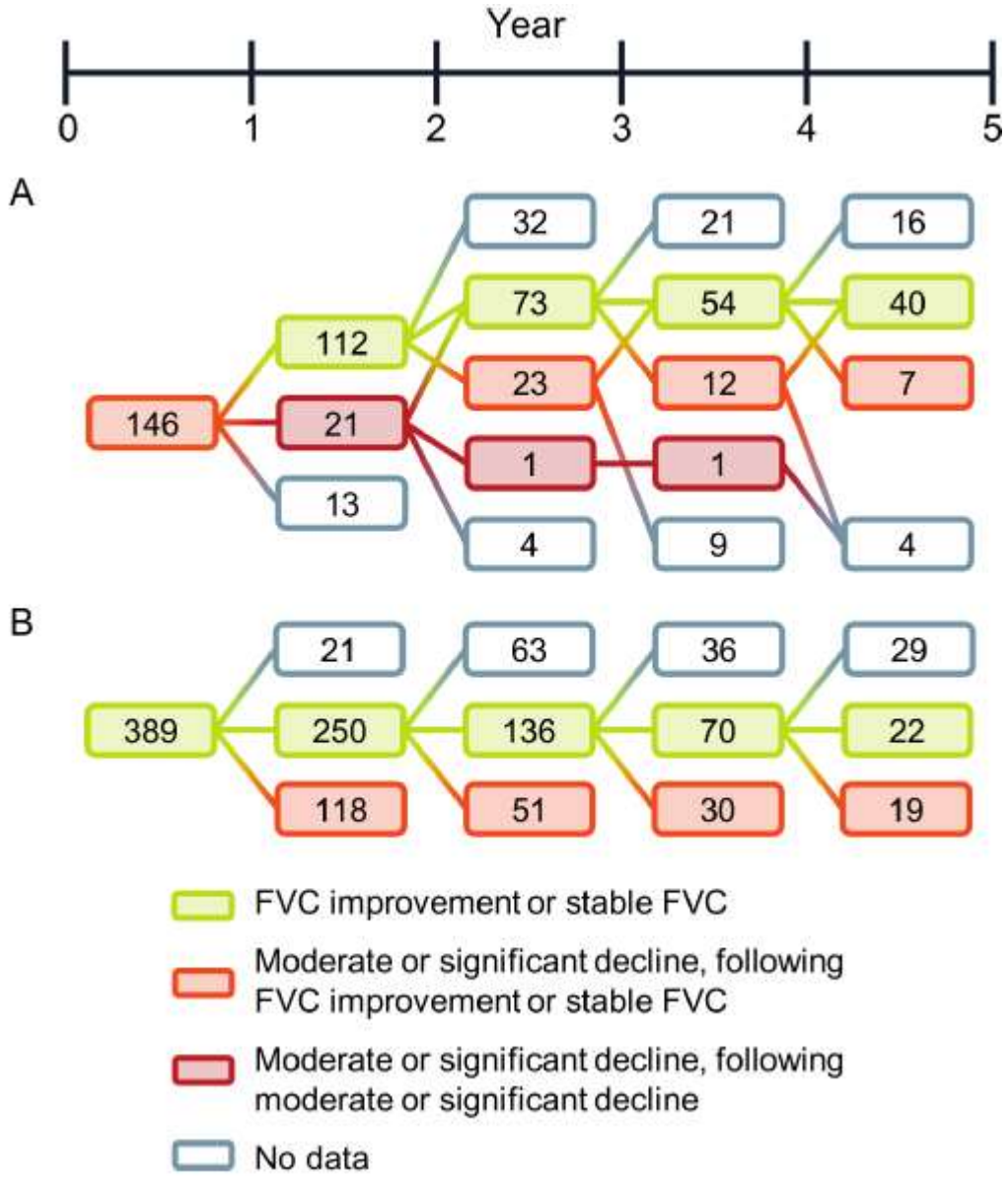
- 535人 (65%) が複数回FVCを測定 (平均5年follow-up).
- 毎年9～10%がsignificant decline.
- 12カ月ごとに23-27%の患者がprogressive ILDだが, 継続的進行はごく一部.



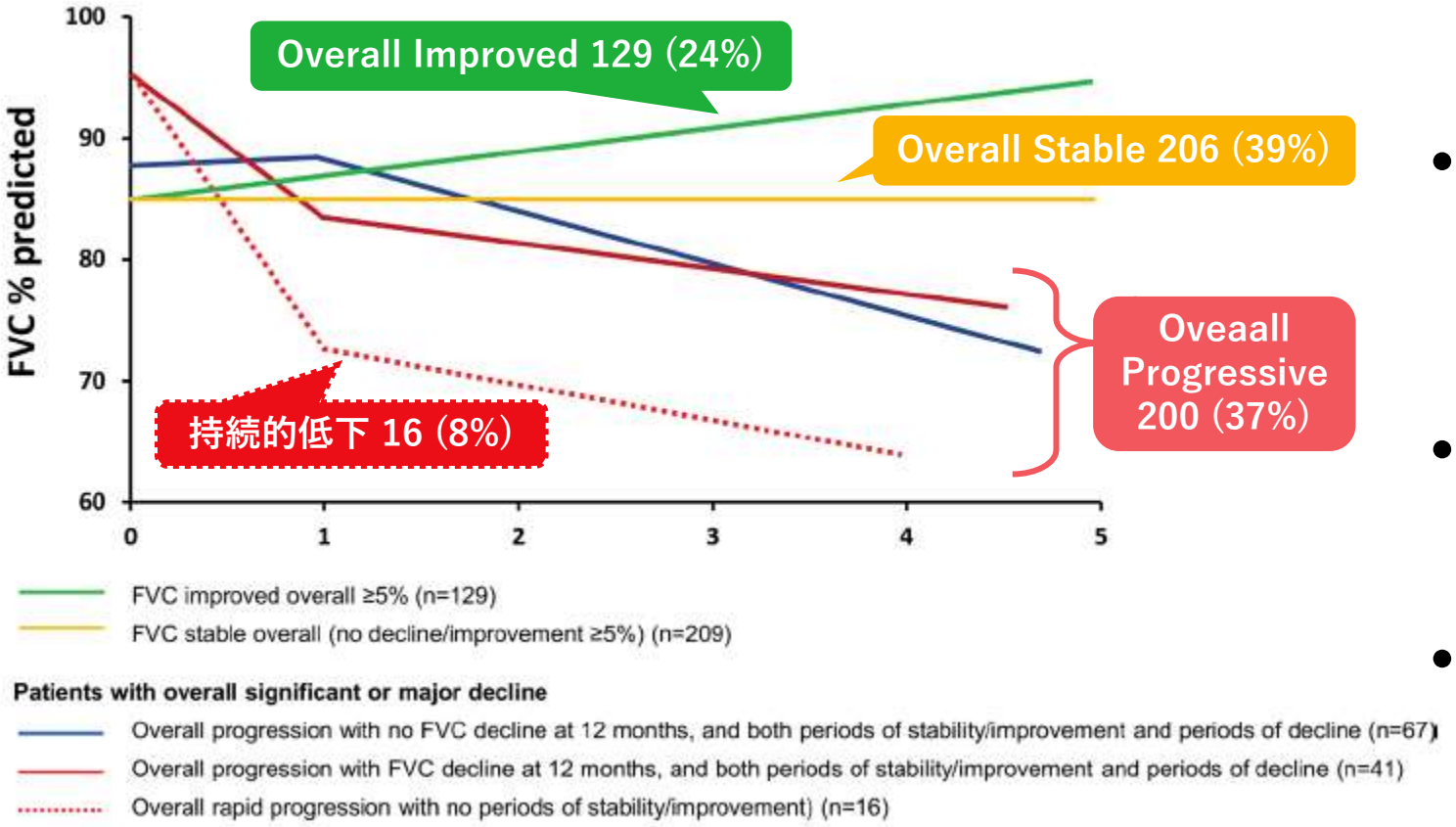
長期FVC観察

- Progressive ILDの次も連続減少する例はまれ
- 大部分がimprove/stableになる.

- improve/stableの後は30%程度がprogressiveになる.



SSc-ILDの進行パターン



- 長期 (5年間) でprogressive ILDは200人(37%)
- 大部分 (58%) ：slow progressive pattern (悪化<stable)
- 34%：progressive pattern (悪化>stable)
- 僅か(8%)：rapid progression pattern (悪化のみ, stableなし)

5年間でのFVC低下の予測因子

1. 男性
2. modified Rodman skin score高値
3. 逆流/嚥下障害症状があること.

Table 3 Risk factors for change in FVC over the 5-year follow-up in patients with ≥3 serial FVC measurements in univariable and multivariable linear mixed-effect regression analysis

	Univariable			Multivariable		
Predictor variable	Coefficient	95% CI	P value	Coefficient	95% CI	P value
Time	−0.45	−0.72 to −1.7	0.002	0.8	0.22 to 1.39	0.007
Reflux/dysphagia symptoms	−2.06	−5.06 to 0.94	0.180	0.58	−2.18 to 3.34	0.681
Time×reflux/dysphagia symptoms	−0.76	−1.34 to −0.17	0.011	−0.72	−1.34 to −0.10	0.024
mRSS	−0.51	−0.69 to −0.33	<0.001	−0.31	−0.47 to −0.15	<0.001
Time×mRSS	−0.05	−0.07 to −0.01	0.011	−0.06	−0.10 to −0.02	0.002
Sex	−5.25	−8.91 to −1.59	0.005	−3.90	−7.29 to −0.53	0.024
Time×sex	−0.97	−1.72 to −0.21	0.012	−1.30	−2.10 to −0.49	0.002
Age	0.42	0.31 to 1.53	<0.001	0.47	0.37 to 0.57	<0.001
DL_{CO}	0.55	0.47 to 0.62	<0.001	0.45	0.37 to 0.52	<0.001
ESR	−0.14	−0.21 to −0.01	0.001	−0.09	−0.15 to −0.03	0.005
NYHA class	−14.59	−18.7 to −10.49	<0.001	−4.76	−6.59 to −2.92	<0.001
ACA	11.42	7.65 to 15.19	<0.001			
ARA	10.95	1.62 to 20.27	0.021			
ATA	−5.01	−7.98 to −2.05	0.001			
CRP	−7.72	−11.01 to −4.43	<0.001			
dcSSc	−6.37	−7.43 to −3.32	<0.001			

ACA, anti-centromere antibody; ARA, anti-RNA polymerase III antibody; ATA, anti-topoisomerase I antibody; CRP, C-reactive protein; dcSSc, diffuse cutaneous systemic sclerosis; DL_{CO}, diffusion capacity of the lungs for carbon monoxide; ESR, erythrocyte sedimentation rate; FVC, forced vital capacity; mRSS, modified Rodnan skin score; NYHA, New York Heart Association.

結果のまとめ

- SSc-ILDの約30%で12カ月間でILD進行を認める(既報と一致)
- 5年間の観察期間のいずれかの時期で, 67%にILD進行を認める.
- 進行パターンはheteroで, 殆どの患者に進行と安定の時期がある.
- Slow progressive pattern (58%)は見逃しやすい．2回以上 5%低下に注意.
- Progressive ILDのごく僅か (8%) が急速進行性（安定/改善がなく継続的にFVC低下）.

Limitation

- 連続で呼吸機能検査をした患者数が多い（1433/2259人）
- 治療データ漏れ（244/826人しかない）
- 胸部CT検査結果がなく解析対象になっていない
- mRSSの一時データはあるが経過データがなくILD進行との関連がみられない

何がインパクトか

- 本研究では, 現時点での臨床practiceの弱点に焦点をあてている. SSc-ILDではFVCが低下してから治療介入することがしばしばであるが, その場合肺の障害は既に発生した後である.
- 肺障害を回避するために, 新たな治療conceptが必要である.
- 本研究では, SSc-ILDの増悪因子を同定した.
- また, SSc-ILDの臨床経過がheterogeneousであることを示し, SSc-ILD患者のモニタリングの必要性を明らかにした.

結論

- SSc-ILDはheterogeneousで多様な経過をたどる.
- 全患者の注意深いモニタリングが重要.
- 新しい治療コンセプト『FVCが低下する前の治療介入』は,
  不可逆的臓器障害を避けるために検討されるべき.

背景

- A subset of patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) develop progressive ILD, which is associated with higher mortality, but the prevalence of progressive ILD and the overall disease course and patterns of SSc-ILD are unknown.
- Current clinical practice emphasises treatment initiation of SSc-ILD patients with progressive ILD.

方法

- Eligible patients with SSc-ILD were registered in the EUSTAR database and had measurements of forced vital capacity (FVC) at baseline and after 12 ± 3 months.
- Long-term progressive ILD and progression patterns were assessed in patients with multiple FVC measurements. Potential predictors of ILD progression were analysed using multivariable mixed-effect models.

結果

- 826 patients with SSc-ILD were included.
- Over 12 ± 3 months, 219 (27%) showed progressive ILD: either moderate (FVC decline 5% to 10%) or significant (FVC decline >10%). A total of 535 (65%) patients had multiple FVC measurements available over mean 5-year follow-up.
- In each 12-month period, 23% to 27% of SSc-ILD patients showed progressive ILD, but only a minority of patients showed progression in consecutive periods.
- Most patients with progressive ILD (58%) had a pattern of slow lung function decline, with more periods of stability/improvement than decline, whereas only 8% showed rapid, continuously declining FVC; 178 (33%) experienced no episode of FVC decline.
- The strongest predictive factors for FVC decline over 5 years were male sex, higher modified Rodnan skin score and reflux/dysphagia symptoms.

結果のまとめ

- Around 30% of SSc-ILD patients experienced ILD progression during any 12-month period, and 67% of all SSc-ILD patients experienced progression at any time over the mean 5-year follow-up.
- ILD patterns in patients with SSc-ILD are very heterogeneous, with most patients showing both progressive and stable periods.
- Of all progressive SSc-ILDpatients, only a minority showed a pattern of rapid, continuously declining forced vital capacity (FVC) with several consecutive episodes of FVC decline and no periods of FVC stability or improvement.

結論

- SSc-ILD shows a heterogeneous and variable disease course, and thus monitoring all patients closely is important.
- Novel treatment concepts, with treatment initiation before FVC decline occurs, should aim for prevention of progression to avoid irreversible organ damage.

何がインパクトか

- These results highlight a pitfall in current clinical practice, where treatment is often initiated after FVC decline has happened, and thus when lung damage has already occurred.
- Novel treatment concepts are needed and should aim for prevention of progression to avoid irreversible organ damage.
- This study defines factors that can identify patients at risk for progression.
- The results also stress the heterogeneity and variability of the course of ILD in SSc, and highlight the need for close monitoring of all patients with SSc-ILD.

RCT

- Nintedanibのみが唯一FVC改善される薬剤（今の時点では）

Progressive ILDとは？

方法

- EUSTARに登録された症例のpost hoc 後ろ向き解析
- 2013 ACR/EULAR SSc criteriaを満たしXp/CTでILDを認め, FVC/DLcoデータのある18歳以上の患者を抽出（2010-登録）
- 1年間（SSc-ILD患者のベースラインと12±3か月後）のFVCを測定しProgressive ILDを分類する：Significant (<-10%), moderate (-5-10%), stable (±5%), improve (>+5%)
- 合計5年間毎年followして長期ILD進行パターンを評価, 5分類（↑に20％以上FVC低下Majorを追加）．5年間で有意なFVC低下（moderate/significant)が1回もない/1回のみ/複数回を調査.
- ILD悪化群のパターン分類：rapid progression (stable/improveがない), progression (低下の回数>stable/improveの回数), slow progression (低下の回数< stable/improveの回数)
- DLco 15%以上悪化+ significant/moderate FVC低下を線維化とする
- 多変量解析（mixed-effect models）によって潜在的なILD進行因子を解析する. 自己抗体3種(ATA, ACA, ARA), baseline FVC, DLco, disease duration, mRSS, ESR, CRP, Tx, dyspnea class, synovitis, muscle weakness

結果

- SSc-ILDの患者826人が解析対象となった.
- 12±3カ月で，219人 (27%) がprogressive ILDであった
- progressive ILD の定義: FVC減少が中程度 (5〜10%) か高度 (＞10%).
- 535人 (65%) が複数回FVCを測定した（平均5年follow-up).
- 12カ月ごとに23〜27%の患者がFVC低下するが, 継続的進行はごく一部.
- 大部分 (58%) が緩徐なprogressive ILDで, 悪化より安定/改善がみられる.
- ごくわずか (8%) が急速・持続的FVC低下を示す.
- 178人 (33%) がFVC低下を認めない.
- 5年間でのFVC低下の予測因子は, ①男性, ②modified Rodman skin score 高値, ③逆流/嚥下障害症状があること.