膠原病・リウマチ内科
Journal Club

Clinical science

Systemic sclerosis associated interstitial lung disease: a conceptual framework for subclinical, clinical and progressive disease

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Introduction

- 北米ではSScの50％以上でILDが合併しているが, 疾患全体への影響は不均一で, 重症度や進行の点でも様々.
- SSc-ILDでは, 同様の臨床経過をたどるsubpopulationも特定されている.
- conceptual frameworkを作成して, SSc-ILDの臨床試験でコホート登録時に使用され, 治療効果の恩恵を最も受ける集団を特定するのに役立つことを目的とする.

conceptual framework： Severity, risk of progression, progression

Methods

- **conceptual frameworkとpatient profile**

  2018年のACR/ARHP Annual Meetingで検討されたconceptual frameworkを39名の専門家(呼吸器 19名, リウマチ 13名, 放射線 7名)が協議して修正した.

  Conceptual frameworkの内容から, profileは, 実際のSSc-ILDを重症度、進行リスク、進行を特徴付けるために必要な情報を収集することを目的としている.

  対象患者：Scleroderma Lung Study II の53例とMichigan Scleroderma Program 27例

Profile: 年齢, 性別, 人種, 疾患因子(SSc皮膚分類, レイノー現象出現からの疾患期間, ANA, SSc特異抗体, mRSS, PRO(Mahler Baseline and Transition Dyspnea Index、Leicester Cough Questionnaire, PtGA, St. George‘s Respiratory Questionnaire, PFT(DLCo含む), 定量的HRCT(WLI %, WLF %)

Follow-up profile: mRSS, PRO, PFT, 定量的HRCTの経時的変化

Methods　評価の流れ

- 83名の専門家に, conceptual framework, baseline profile, follow-up profile(それぞれ5名)などをメール.
- 8グループにわけて, 80名のSSc-ILDを評価. 一致率75%と定義.
- Baseline profileは, severity (subclinical ILD, clinical ILD and unable to determine)と risk of progression (low risk, high risk and unable to determine)から選択.
- Follow-up profileは, progression(stable ILD, progressive ILD, improved ILD or unable to determine)から選択.
- 評価者間の信頼性はkappa 係数を使用.
  0.01-0.20:なし, 0.21-0.39:最小, 0.40-0.59:弱い, 0.60-0.79:普通,
  0.80-0.90:強い, 0.91:ほぼ完全に一致

Result　subclinical, clinical, progressionの定義

	SUBCLINICAL SSC-ILD	CLINICAL SSC-ILD	PROGRESSIVE SSC-ILD
Disease Features	*Should have all met*	*Must have ≥1 feature*	*Must have ≥1 feature*
Symptoms	None-to-mild	Present	Increasing respiratory symptoms
Spirometry with gas exchange	Normal-to-near normal	Deficits present	Decline on serial measurement
Desaturation on exercise	Normal-to-near normal	Deficits present	Decline on serial measurement
Quantitative HRCT	Minimal-to-mild	Moderate-to-severe	Increasingly severe
Disease Impact	*All features should be met*	*Must have ≥1 feature*	*Must have ≥1 feature*
Feel	None	Yes	Yes
Function	None	Yes	Yes
Survive	None	Yes	Yes
Treatment	*Based on current paradigm and data, although this may change with new data*		
Initiate	No	Yes	Yes
Escalate or switch	No	No	Yes

- subclinical ILD→無症候性ILD(ILDによる症状がない)のみに限定.
- SScのようなCTDが確定している場合は, Interstitial lung abnormalitiesには含めない.
- SSc-ILDの分類に応じて治療を選択する事は推奨しない.
- Progressionはsubclinical, clinicalの状態であり, 個別に分類されるものでない.

Result

Clinical features	Subclinical SSc-ILD All variables should be met but there may be exceptions	Clinical SSc-ILD Must have ≥1 feature
Demographics Age, sex, race	N/A	N/A
SSc disease factors SSc cutaneous classification Disease duration ANA status SSc specific autoantibody Modified Rodnan Skin Score	N/A	N/A
Respiratory symptoms Mahler Dyspnoea Index and Transitional Index Leicester Cough Questionnaire Patient Global Assessment St George's Respiratory Questionnaire	None	Present
Spirometry with gas exchange Forced vital capacity (% predicted) Diffusion capacity of carbon monoxide (% predicted)	Normal-to-near normal	Deficits present
Desaturation on exercise Oxygen desaturation during 6-min walk test	Normal-to-near normal	Deficits present
Quantitative HRCT Whole lung involvement (% of ground glass opacities, fibrotic reticulations and honeycombing) Whole lung fibrosis (% of only the fibrotic reticulations)	Minimal-to-mild	Mild-to-severe disease
Disease impact	All features should be met	Must have ≥1 feature
Feel	None	Yes
Function	None	Yes
Survive	N/A	Yes
Disease progression	Must have ≥1 feature for either category (attributable to ILD)	
Respiratory symptoms	New onset dyspnoea or cough	Advancing dyspnoea or cough
Spirometry with gas exchange	New decline	Advancing decline
Desaturation on exercise or exercise limitation	New desaturation and/or limitation	Advancing desaturation and/or limitation
Quantitative HRCT	New, larger extent of disease burden	Advancing extent of disease burden

Result

Patient Profile(Baseline)

- 6分間歩行や心エコーなどは含まれていない.
- 進行とはSSc-ILDに限定.

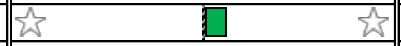
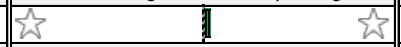
Demographics and Disease Features	Baseline
Age, years	44
Sex	Male
Race	Black
Type of SSc	Diffuse SSc
Disease duration, years (From 1st non-Raynaud's sign or symptom)	2
ANA status	ANA positive, nucleolar
Autoantibody status (Assessed for anti-centromere, anti-U1-RNP, anti-SCL-70, and anti-RNA Polymerase III antibodies)	Anti-SCL 70 Antibody

Assessment of Disease Severity	Baseline	Interpretation
Pulmonary Function Tests		
FVC Predicted, %	63	-
DLco Predicted, %	47	-
Patient Reported Outcome Measures		
Dyspnea		
Mahler Baseline Dyspnea Index, 0-12	9	Mild dyspnea
Transition Dyspnea Index, -9 to +9	-	-
Cough		
Leicester Cough Questionnaire, 3-21	18	Cough occuring occasionally
Health Related Quality of Life		
Patient Global Assessment, 0-100	51	Moderate impairment in overall QOL
St George Respiratory Questionnaire Total, 0-100	33	Mild impairment in respiratory QOL
Skin Involvement		
Modified Rodnan Skin Score (0-51)	13	Mild thickening
Computer Quantitation of ILD on HRCT		
Whole Lung Involvement, % (Defined as increased interstital markings, GGO, and HC, 0-100%)	29	-
Whole Lung Fibrosis, % (Defined as increased interstital markings, 0-100%)	9	-

Result

Follow-up Patient Profile

Demographics and Disease Features	Baseline
Age, years	44
Sex	Male
Race	Black
Type of SSc	Diffuse SSc
Disease duration, years (From 1st non-Raynaud's sign or symptom)	2
ANA status	ANA positive, nucleolar
Autoantibody status (Assessed for anti-centromere, anti-U1-RNP, anti-SCL-70, and anti-RNA Polymerase III antibodies)	Anti-SCL 70 Antibody

Assessment of Disease Severity	Baseline	12 Month Follow-up	Interpretation	Δ	Significance
Pulmonary Function Tests				*Worsening* *Improving*	Measurement Error
FVC Predicted, %	63	71	No change		10
DLco Predicted, %	47	54	No change		15
Patient Reported Outcome Measures				*Worsening* *Improving*	Minimal Important Difference
Dyspnea					
Mahler Baseline Dyspnea Index, 0-12	9	-	-		-
Transition Dyspnea Index, -9 to +9	-	0	Unchanged		2
Cough					
Leicester Cough Questionnaire, 3-21	18	20	No change		3
Health Related Quality of Life					
Patient Global Assessment, 0-100	51	35	No change		20
St George Respiratory Questionnaire Total, 0-100	33	22	Clinically meaningful improvement		4
Skin Involvement				*Worsening* *Improving*	Minimal Important Difference
Modified Rodnan Skin Score (0-51)	13	12	No change		3-5
Computer Quantitation of ILD on HRCT				*Worsening* *Improving*	Measurement Error
Whole Lung Involvement, % (Defined as increased interstital markings, GGO, and HC, 0-100%)	29	40	Decline > measurement error		2
Whole Lung Fibrosis, % (Defined as increased interstital markings, 0-100%)	9	15	Decline > measurement error		2

Result　専門家によるframeworkとprofileの評価

- 12ヶ国の83人中53%の44人(膠内 26名, 呼内 16名, 放射2名) で評価を完了.
- progressionに関しては合意に至った割合が少ない傾向(60%)
- コンセンサスを得たsubset
  severity：Clinical 55名(92%),
  risk of progression：Low 31名(54%),
  progression：stable 17名(71%)

	Severity		Risk of progression		Progression	
Number of profiles assessed	80		80		40	
Profiles achieving consensus, *n* (%)[a]	60 (75)		57 (71)		24 (60)	
Subset	Subclinical	3	High Risk	26	Improved	3
	Clinical	55	Low Risk	31	Progressive	4
					Stable	17
Cannot classify (based on the given information)		2		0		0
Profiles not achieving consensus, *n* (%)	20 (25)		23 (29)		16 (40)	

[a] A consensus was reached if ≥75% of experts in each group agreed.

Result　専門家によるframeworkとprofileの評価

・呼内-膠内間でのkappa係数はseverityでは「なし」であった.
・risk of progression, progressionは, 弱い～普通であった.

Table 3. Agreement of classification by discipline, along dimensions of severity, risk of progression and progression

A. Determined by Kappa statistic				
Kappa calculation	***n* (pair)[a]**	**Average *n* (profile)[b]**	**Mean**	**Bootstrapped mean (95% CI)[c]**
Severity				
Between rheumatologists and pulmonologists	66	7.6	0.13	0.13 (0.00, 0.25)
Among rheumatologists	44	8.7	0.17	0.17 (−0.01, 0.45)
Among pulmonologists	17	6.6	0.20	0.18 (0, 0.25)
Risk of progression				
Between rheumatologists and pulmonologists	66	6.6	0.61	0.59 (0.49, 0.69)
Among rheumatologists	44	8.3	0.70	0.66 (0.51, 0.86)
Among pulmonologists	17	5.9	0.48	0.4618 (0.26, 0.66)
Progression				
Between rheumatologists and pulmonologists	66	3.1	0.56	0.51 (0.18, 0.70)
Among rheumatologists	44	3.5	0.78	0.70 (0.36, 0.95)
Among pulmonologists	17	3.1	0.29	0.24 (−0.00, 0.50)

0.01-0.20:なし, 0.21-0.39:最小, 0.40-0.59:弱い, 0.60-0.79:普通, 0.80-0.90:強い, 0.91:ほぼ完全に一致

Result　専門家によるframeworkとprofileの評価

・severity, risk of progression, progressionは膠内と呼内で統計学的な有意差なし.

B. Determined by χ^2 analysis

χ^2 calculation	Rheumatology	Pulmonology	*P*-value
Severity[d]			
Clinical ILD	205 (93.2%)	114 (89.8%)	0.26
Subclinical ILD	15 (6.8%)	13 (10.2%)	
Risk of progression			
High risk	97 (45.3%)	55 (46.2%)	0.88
Low risk	117 (54.7%)	64 (53.8%)	
Progression			
Progressive	17 (18.9%)	11 (20.0%)	0.20
Stable	57 (63.3%)	40 (72.7%)	
Improved	16 (17.8%)	4 (7.3%)	

Result　専門家が重視した項目

・severity・progressionではPFT(FVC), quantitative HRCT(total lung involvement)

・risk of progressionでは, disease factor(duration)

Table 4. Importance based on percentage of items used in the classification of profiles along dimensions of severity, risk of progression, and progression

Domain with items used in classification	Severity		Risk of Progression		Progression	
	Rank between domains	Importance based on percentage selected	Rank between domains	Importance based on percentage selected	Rank between domains	Importance based on percentage selected
Demographics	5	Least influential	4	Less influential	—	Not ranked
Age, %		0		1		
Sex, %		0		1		
Race, %		0		1		
Disease factors	4	Less influential	1	Most influential	—	Not ranked
Systemic sclerosis subtype, %		3		7		
Disease duration, %		2		31		
ANA status, %		0		1		
Systemic sclerosis autoantibody status, %		2		11		
Modified Rodnan Skin Score, %		0		1		
Patient reported outcome measures	3	Influential	5	Least influential	3	Least influential
Baseline Dyspnoea Index/Transition Index, %		19		1		6
Leicester Cough Questionnaire, %		1		0		0
Patient global assessment, %		1		0		1
St George's Respiratory Questionnaire, %		3		1		2
Spirometry and gas exchange	1	Most influential	2	Very influential	1	Most influential
Forced vital capacity, %		29		17		48
Diffusion capacity of carbon monoxide, %		11		5		6
Quantitative high resolution chest CT	2	Very influential	3	Influential	2	Influential
Total lung involvement, %		25		15		29
Total lung fibrosis, %		5		6		8

Discussion

- SSc-ILDを3つの側面(severity, risk of progression, progression) に沿って特徴付けた評価基準を作成した.
- この枠組みは,
  (1)専門家が実際の患者プロファイルを分類することで検証,
  (2)3つの側面すべてにおいて合意に達し, 大多数のpatient profileでコンセンサスを得た,
  (3)SSc-ILD subsetの判断でどの項目が最も重要であるかを明らかになった.
- このframeworkには, 各サブセットの定義に特定の値やカットポイントは含まれていない.
- Severityではkappa係数が低い. Kappa係数は有病率に依存し, subclinical ILDが少ないため影響を受けた可能性がある.
- Progressionの合意が低いのは, Progressive SSc-ILDという概念がINBUILD試験以前は普及していなかった影響がある.

Discussion

- 一致度は, 分野間(呼内と膠内)で有意な差はなかった. 分野間の信頼性が高いということは, 参加者は同じ概念的枠組みを共有していたことを示唆している.
- グループごとの評価数が少なく, consensusの有無が共通のconsensusではなく, 偶然の結果であった可能性がある.
- social media platformを使い, 多くの地域から参加を呼びかけ, ILDに精通している専門家を選んだ.
- SLS II の患者などで検証したため重症群が多い可能性があり, 自施設のmild ILDの患者を組み入れた.
- PROはSSc-ILDと関連がない症状も測定する.
- 将来的なCTD-ILDのガイドライン作成や新しいSSc分類基準の作成のためにもこのframeworkは適宜改訂をしていくべきである.