


CLINICAL SCIENCE

# Novel endotypes of antisynthetase syndrome identified independent of anti-aminoacyl transfer RNA synthetase antibody specificity that improve prognostic stratification

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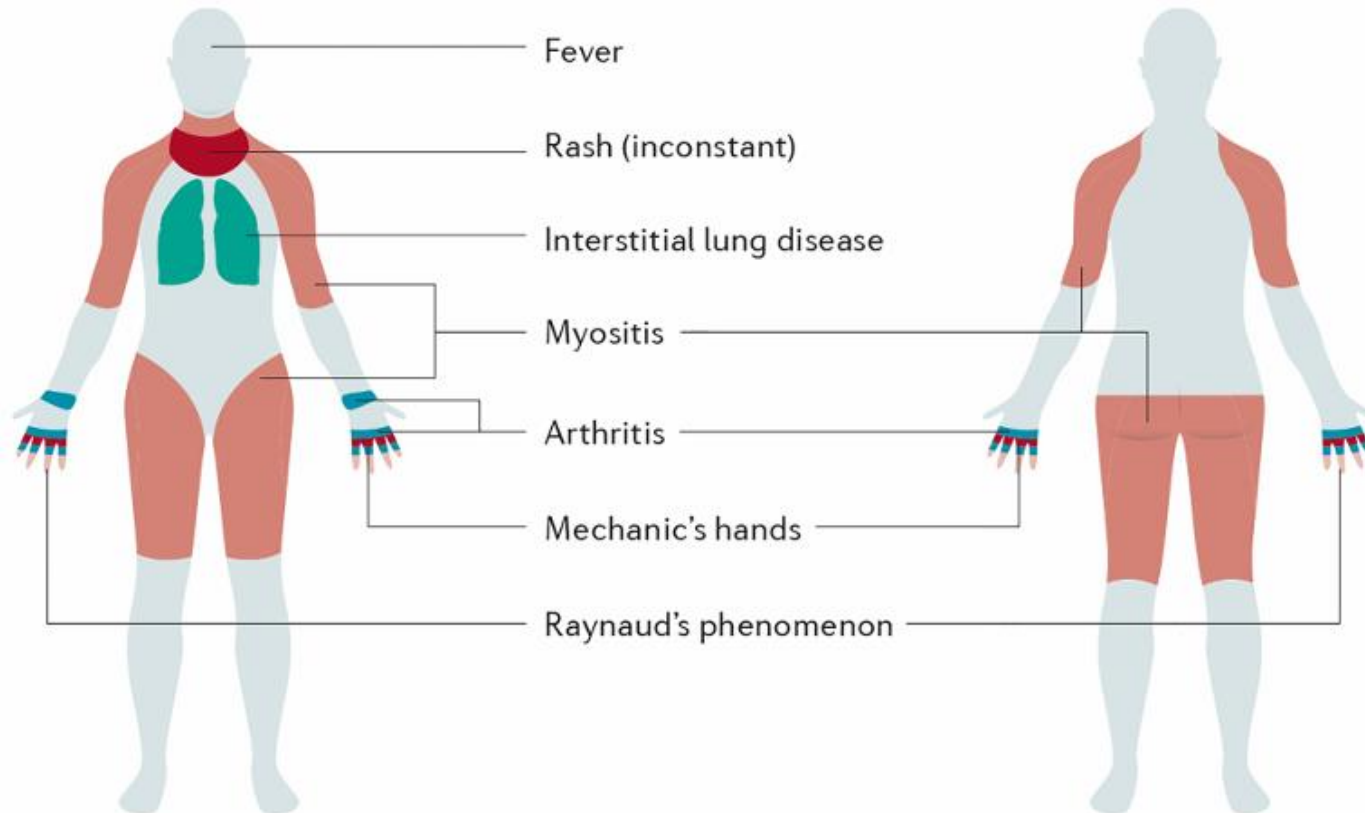
Ann Rheum Dis; 2024; 83: 775-786.

膠原病・リウマチ内科  
竹内 遼



### Idiopathic Inflammatory Myopathies

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## • 抗ARS抗体陽性の臨床的特徴

- 発熱
- 皮疹
- 間質性肺炎(ILD)
- 筋炎
- 関節炎
- Mechanic hand
- レイノー現象



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Review

Comparison of long-term outcome between anti-Jo1- and anti-PL7/PL12 positive patients with antisynthetase syndrome

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	Presence of anti-Jo antibody (n = 75)	Presence of anti-PL7/PL12 antibody (n = 20)	p
<b>General characteristics</b>			
Age (years)	53 [range: 18–75]	59 [range: 18–79]	0.10
Sex: male/female	37.3%/62.7%	40%/60%	1
DM subset*	38.7% DM	11.1% DM	0.01
<b>Clinical characteristics</b>			
Myalgia	81.3%	50%	0.007
Muscle weakness	69.3%	40%	0.02
Raynaud's phenomenon	46.7%	40%	0.62
Mechanic's hands	29.3%	30%	1
Esophageal involvement	22.7%	20%	1
Gastrointestinal signs	1.3%	17.6%	0.02
Joint manifestations	63.3%	40%	0.02
ILD*	68%	90%	0.05
Ventilatory insufficiency related to striated muscle weakness	13.3%	0%	0.11
Aspiration pneumonia	13.3%	15%	1
Cardiac impairment	4.1%	0%	0.59
Malignancy	13.3%	5%	0.44

\* ASS: antisynthetase syndrome; ILD: interstitial lung disease; DM: dermatomyositis. Except where indicated, values are median; p values were obtained with chi-square or Fisher's exact tests.

## • 関節症状

- 抗Jo-1抗体 63.3%、抗PL-7/12抗体 40.0%

## • ILD

- 抗Jo-1抗体 68.0%、抗PL-7/12抗体 90.0%

抗Jo-1抗体は関節症状が多く、抗PL-7/12抗体はILDが多い傾向にある

Original article

**A longitudinal cohort study of the anti-synthetase syndrome: increased severity of interstitial lung disease in black patients and patients with anti-PL7 and anti-PL12 autoantibodies**

Iago Pinal-Fernandez<sup>1,\*</sup>, Maria Casal-Dominguez<sup>2,\*</sup>, Julio A. Huapaya<sup>2,\*</sup>, Jemima Albayda<sup>2</sup>, Julie J. Paik<sup>2</sup>, Cheilonda Johnson<sup>2</sup>, Leann Silhan<sup>2</sup>, Lisa Christopher-Stine<sup>2,†</sup>, Andrew L. Mammen<sup>1,†</sup> and Sonye K. Danoff<sup>2,†</sup>



標準化死亡率

抗ARS抗体すべて、抗PL-7抗体  
抗PL-12抗体、抗Jo-1抗体  
標準化死亡率の増加はなし

## 目的:

- 異なる抗ARS抗体ごと(抗Jo-1抗体、抗PL-7抗体、抗PL-12抗体、抗EJ抗体)の臨床的特徴および予後の違いを明らかにする
- 抗ARS抗体症候群患者を臨床症状、予後、そして基礎となる病態生理学においてより相同性の高い病型に分類する

- 2004年4月から2023年2月までに中日友好医院で抗ARS抗体症候群と診断された733例を後ろ向きにenroll  
抗OJ抗体11例は除外
- 抗体はEuroline、ELISAで測定
- RNA sequence  
抗ARS抗体症候群: 23例、Healthy Control: 10例  
PBMCで実施
- 抗ARS抗体症候群患者を臨床症状、予後、そして基礎となる病態生理学においてより相同性の高い病型に分類するために教師なしクラスタリングを施行した



CHEST

Special Features

### Interstitial Lung Disease Associated With the Idiopathic Inflammatory Myopathies

What Progress Has Been Made in the Past 35 Years?

*Geoffrey R. Connors, MD; Lisa Christopher-Stine, MD; Chester V. Oddis, MD;  
and Sonye K. Danoff, MD, PhD, FCCP*

米国胸部学会の間質性肺炎の診断基準  
HRCTあるいは肺生検で診断  
HRCT: NSIP、OP、NSIP+OP、LIPパターン  
肺生検:  
NSIP、OP、NSIP+OP、LIPパターン  
胚中心を持つ間質性リンパ球集合体  
びまん性リンパ形質細胞浸潤

Eur Respir J 2015; 46: 976–987

## • 抗ARS抗体症候群の診断基準

- 抗ARS抗体(抗アミノアシルtRNA合成酵素に対する抗体)陽性

- 以下のうち少なくともひとつを満たす

- Peter and Bohanの多発筋炎/皮膚筋炎の診断基準を満たす
- 米国胸部学会の間質性肺炎(ILD)の診断基準をみたす
- 関節炎
- 他では説明できない持続する発熱
- レイノー現象
- Mechanic hand

Chest 2010; 138: 1464-74.

- **ILDの診断**

- 呼吸器症状、画像検査、肺機能検査を総合的に判断

- **画像検査**

- NSIP pattern
- OP pattern
- NSIP+ OP pattern
- UIP pattern

- **急速進行性間質性肺炎(RP-ILD)の診断**

- 呼吸困難の急性増悪
- HRCTにおける間質性陰影の増悪
- FVCの10%以上の低下
- PaO<sub>2</sub>の10mmHg以上の低下

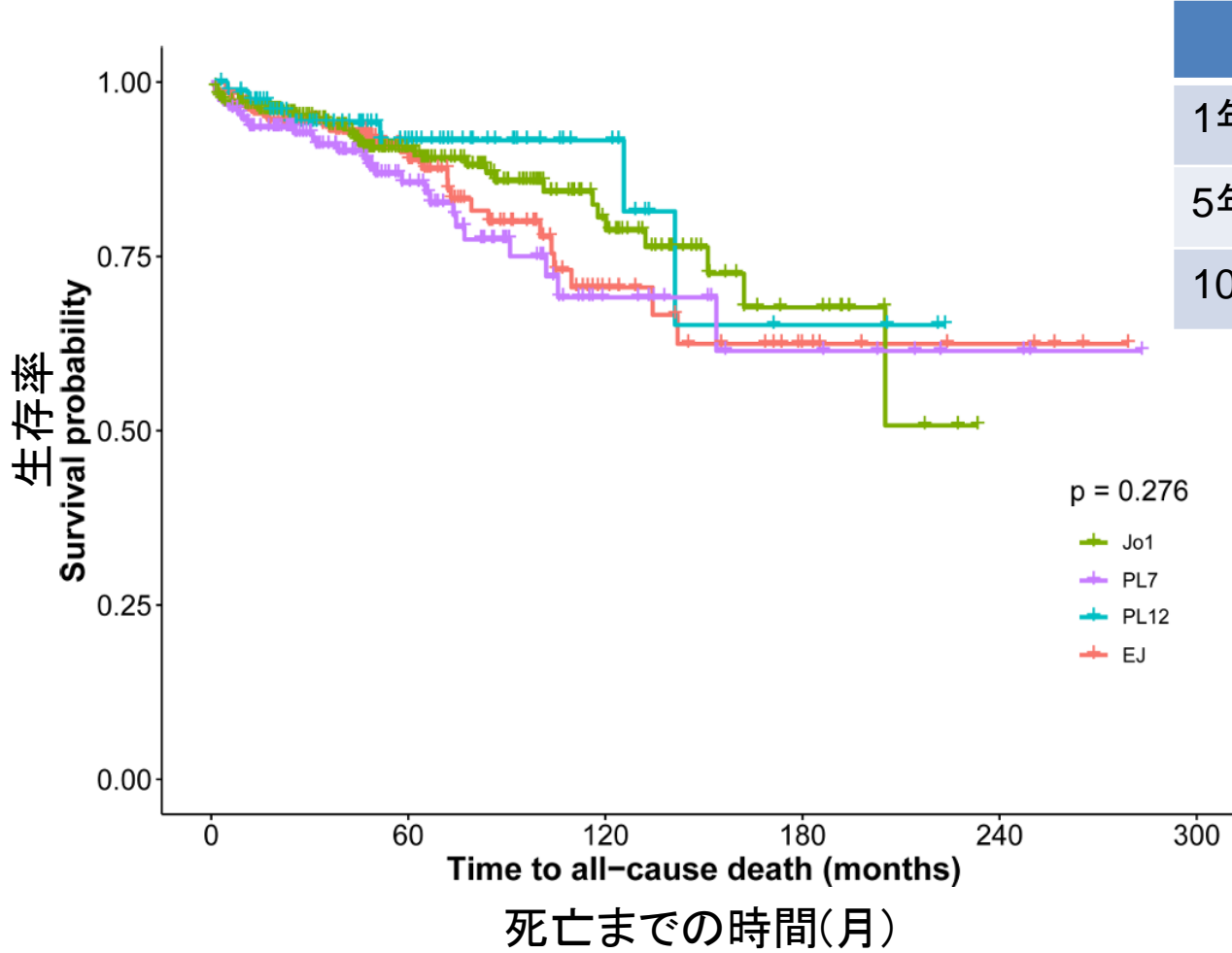


# 自己抗体ごとのprofile

Variables	Total (N=701)	Jo1 (n=276)	PL7 (n=155)	PL12 (n=78)	EJ (n=192)	p value
General						
Fever*, n/N (%)	287/701 (40.9%)	99/276 (35.9%)	68/155 (43.9%)	41/78 (52.6%)	79/192 (41.1%)	0.049
Mucocutaneous						
Heliotrope rash*, n/N (%)	108/701 (15.4%)	37/276 (13.4%)	37/155 (23.9%)	13/78 (16.7%)	21/192 (10.9%)	0.006
Gottron's sign*, n/N (%)	216/701 (30.8%)	69/276 (25.0%)	68/155 (43.9%)	38/78 (48.7%)	41/192 (21.4)	<0.001
V sign*, n/N (%)	90/701 (12.8%)	24/276 (8.7%)	33/155 (21.3%)	13/78 (16.7%)	20/192 (10.4%)	0.001
Shawl sign*, n/N (%)	75/701 (10.7%)	18/276 (6.5%)	26/155 (16.8%)	12/78 (15.4%)	19/192 (9.9%)	0.005
Mechanic's hands*, n/N (%)	342/701 (48.8%)	141/276 (51.4%)	82/155 (52.9%)	35/78 (44.9%)	84/192 (43.8%)	0.254
Raynaud phenomenon*, n/N (%)	61/701 (8.7%)	23/276 (8.3%)	19/155 (12.3%)	6/78 (7.7%)	13/192 (6.8%)	0.319
Skin ulcer, n/N (%)	12/701 (1.7%)	3/276 (1.1%)	3/155 (1.9%)	3/78 (3.8%)	3/192 (1.6%)	0.374
Periungual erythema, n/N (%)	25/701 (3.6%)	10/276 (3.6%)	10/155 (6.5%)	3/78 (3.8%)	2/192 (1.0%)	0.046
Alopecia, n/N (%)	26/701 (3.7%)	11/276 (4.0%)	8/155 (5.2%)	5/78 (6.4%)	2/192 (1.0%)	0.052
Musculoskeletal						
Muscle weakness*, n/N (%)	252/701 (35.9%)	122/276 (44.2%)	53/155 (34.2%)	27/78 (34.6%)	50/192 (26.0%)	0.001
Arthritis/arthritis*, n/N (%)	270/701 (38.5%)	143/276 (51.8%)	55/155 (35.5%)	23/78 (29.5%)	49/192 (25.5%)	<0.001
Pulmonary						
Dyspnoea, * n/N (%)	488/701 (69.6%)	179/276 (64.9%)	104/155 (67.1%)	51/78 (65.4%)	154/192 (80.2%)	0.003
ILD, n/N (%)	679/701 (96.9%)	270/276 (97.8%)	145/155 (93.5%)	74/78 (94.9%)	190/192 (99.0%)	0.015
RPILD*, n/N (%)	258/701 (36.8%)	92/276 (33.3%)	59/155 (38.1%)	25/78 (32.1%)	82/192 (42.7%)	0.160
Respiratory failure*, n/N (%)	123/701 (17.5%)	50/276 (18.1%)	27/155 (17.4%)	11/78 (14.1%)	35/192 (18.2%)	0.859
Pulmonary hypertension, n/N (%)	51/701 (7.3%)	18/276 (6.5%)	7/155 (4.5%)	5/78 (6.4%)	21/192 (10.9%)	0.116
Anti-Ro52\$, n/N (%)	435/668 (65.1%)	154/266 (57.9%)	90/149 (60.4%)	56/71 (78.9%)	135/182 (74.2%)	<0.001
CK, U/L*	81.0 (40.0, 297.0)	99.5 (40.0, 424.8)	74.0 (41.0, 308.0)	54.5 (31.0, 88.0)	84.5 (41.0, 285.0)	0.001
LDH, U/L*	263.0 (204.5, 351.5)	280.5 (208.3, 384.8)	258.0 (195.0, 376.0)	268.0 (200.8, 319.0)	252.0 (207.3, 334.8)	0.276
Lymphocytes count, cells/ $\mu$ l†††	1350.0 (950.0, 1917.5)	1500.0 (1045.0, 2085.0)	1325.0 (950.0, 1930.0)	1120.0 (850.0, 1477.5)	1240.0 (890.0, 1750.0)	<0.001
CRP elevate*, n/N(%)	327/701 (46.6%)	115/276 (41.7%)	70/155 (45.2%)	58/78 (74.4%)	84/192 (43.8%)	<0.001
CRP, ng/ml	0.69 (0.26, 2.21)	0.56 (0.25, 1.85)	0.67 (0.26, 2.16)	1.53 (0.59, 3.25)	0.66 (0.26, 2.21)	<0.001
ESR, mm/h***	21.0 (10.0, 38.0)	15.0 (7.0, 31.3)	21.0 (10.0, 38.5)	32.0 (18.3, 55.3)	23.0 (13.0, 38.0)	<0.001
Ferritin, ng/mL†††	21.0 (10.0, 38.0)	15.0 (7.0, 31.3)	21.0 (10.0, 38.5)	32.0 (18.3, 55.3)	23.0 (13.0, 38.0)	<0.001

	抗Jo-1抗体	抗PL-7抗体	抗PL-12抗体	抗EJ抗体
Heliotrope疹	13.4%	23.9%	16.7%	10.9%
V sign	8.7%	21.3%	16.7%	10.4%
Shawl sign	6.5%	16.8%	15.4%	9.9%
筋力低下	44.2%	34.2%	34.6%	26.0%
関節炎	51.8%	35.5%	29.5%	25.5%
ILD	97.8%	93.5%	94.9%	99.0%
RP-ILD	33.3%	38.1%	32.1%	42.7%
抗Ro-52抗体	57.9%	60.4%	78.9%	74.2%
リンパ球数(/ $\mu$ L)	1,500	1,325	1,120	1,240
CRP (ng/mL)	0.56	0.67	1.53	0.66

# 自己抗体ごとの生存率

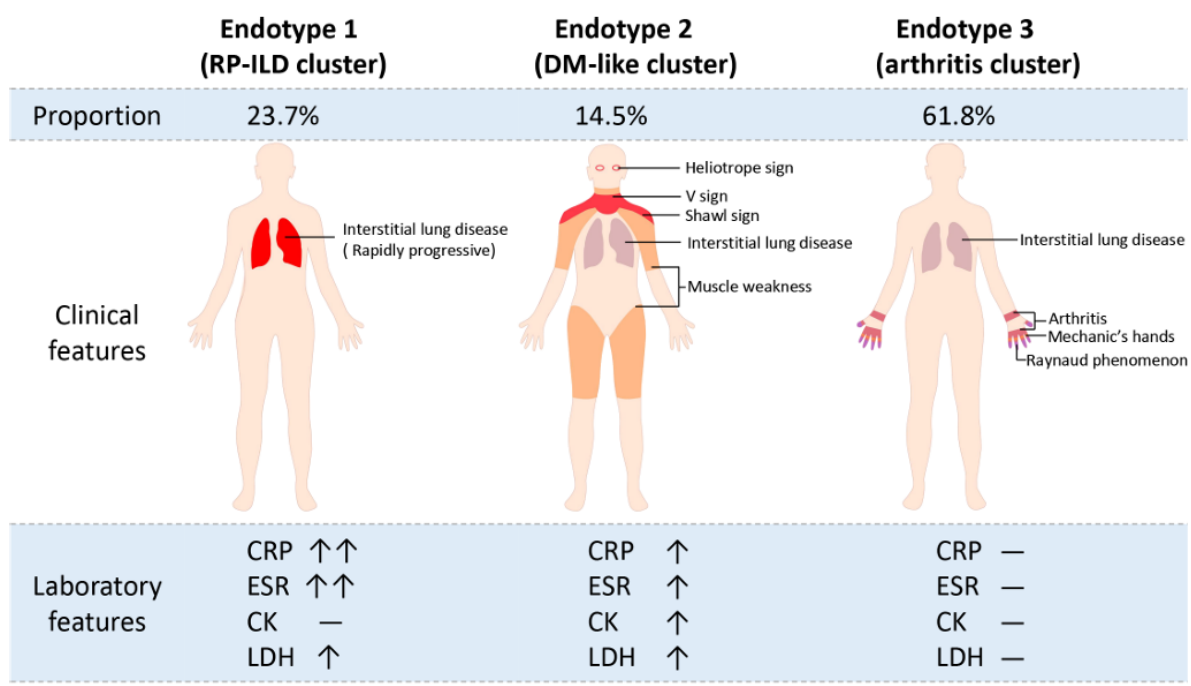


	抗Jo-1抗体	抗PL-7抗体	抗PL-12抗体	抗EJ抗体
1年生存率(%)	96.7	93.5	97.3	96.3
5年生存率(%)	90.5	85.5	91.7	88.8
10年生存率(%)	78.7	69.1	91.7	70.6

抗Jo-1抗体、抗PL-7抗体、抗PL-12抗体、抗EJ抗体で予後に差はなかった

# 教師なしクラスタリング

	Total (N=701)	Cluster 1 (n=166)	Cluster 2 (n=102)	Cluster 3 (n=433)
Onset age, year (N=701)	52.7 (12.5)	60.6 (11.4) <sup>ab</sup>	50.5 (12.8)	50.2 (11.6)
Fever (N=701)	40.9% (287/701)	59.6% (99/166) <sup>b</sup>	49.0% (50/102) <sup>c</sup>	31.9% (138/433)
Dyspnoea (N=701)	69.6% (488/701)	95.2% (158/166) <sup>ab</sup>	59.8% (61/102)	62.1% (269/433)
ILD (N=701)	96.9% (679/701)	100.0% (166/166) <sup>a</sup>	95.1% (97/102)	96.1% (416/433)
RPILD (N=701)	36.8% (258/701)	92.8% (154/166) <sup>ab</sup>	25.5% (26/102)	18.0% (78/433)
Respiratory failure (N=701)	17.5% (123/701)	69.9% (116/166) <sup>ab</sup>	5.9% (6/102) <sup>c</sup>	0.2% (1/433)
Pulmonary hypertension (N=701)	7.3% (51/701)	13.3% (22/166) <sup>b</sup>	6.9% (7/102)	5.1% (22/433)
Muscle weakness (N=701)	35.9% (252/701)	20.5% (34/166) <sup>ab</sup>	58.8% (60/102) <sup>c</sup>	36.5% (158/433)
Arthritis (N=701)	38.5% (270/701)	19.9% (33/166) <sup>ab</sup>	43.1% (44/102)	44.6% (193/433)
Mechanic's hands (N=701)	48.8% (342/701)	32.5% (54/166) <sup>ab</sup>	52.0% (53/102)	54.3% (235/433)
Raynaud phenomenon (N=701)	8.7% (61/701)	1.8% (3/166) <sup>ab</sup>	10.8% (11/102)	10.9% (47/433)
Heliotrope rash (N=701)	15.4% (108/701)	9.0% (15/166) <sup>a</sup>	51.0% (52/102) <sup>c</sup>	9.5% (41/433)
Gottron's sign (N=701)	30.8% (216/701)	19.3% (32/166) <sup>a</sup>	57.8% (59/102) <sup>c</sup>	28.9% (125/433)
V sign (N=701)	12.8% (90/701)	4.2% (7/166) <sup>a</sup>	74.5% (76/102) <sup>c</sup>	1.6% (7/433)
Shawl sign (N=701)	10.7% (75/701)	1.8% (3/166) <sup>a</sup>	65.7% (67/102) <sup>c</sup>	1.2% (5/433)
Holster sign (N=701)	3.3% (23/701)	1.2% (2/166) <sup>a</sup>	8.8% (9/102) <sup>c</sup>	2.8% (12/433)
Periungual erythema (N=701)	3.6% (25/701)	1.8% (3/166)	5.9% (6/102)	3.7% (16/433)
CK, U/L (N=701)	81.0 (40.0, 297.0)	68.5 (34.0, 196.8) <sup>a</sup>	204.0 (62.5, 866.0) <sup>c</sup>	75.0 (39.0, 249.5)
LDH, U/L (N=701)	263.0 (204.5, 351.5)	323.5 (261.0, 428.3) <sup>b</sup>	310.5 (237.8, 434.3) <sup>c</sup>	232.0 (188.5, 299.0)
Lymphocytes count, cells/μl (N=696)	1350.0 (950.0, 1917.5)	1135.0 (790.0, 1550.0) <sup>b</sup>	1255.0 (820.0, 1715.0) <sup>c</sup>	1475.0 (1020.0, 2052.5)
CRP elevate (N=701)	46.6% (327/701)	75.3% (125/166) <sup>ab</sup>	57.8% (59/102) <sup>c</sup>	33.0% (143/433)
CRP, ng/ml (N=701)	0.69 (0.26, 2.21)	2.43 (0.73, 6.57) <sup>ab</sup>	1.08 (0.31, 2.39) <sup>c</sup>	0.46 (0.25, 1.21)
ESR, mm/h (N=657)	21.0 (10.0, 38.0)	36.0 (19.0, 60.0) <sup>ab</sup>	22.0 (11.0, 37.5)	16.0 (8.0, 30.0)
Ferritin, ng/ml (N=456)	144.4 (65.8, 287.8)	214.9 (116.7, 452.8) <sup>b</sup>	167.6 (87.0, 357.7) <sup>c</sup>	110.5 (51.6, 236.3)
Jo1 (N=701)	39.4% (276/701)	34.3% (57/166)	30.4% (31/102)	43.4% (188/433)
PL7 (N=701)	22.1% (155/701)	22.1% (35/166)	33.3% (34/102) <sup>c</sup>	19.9% (86/433)
PL12 (N=701)	11.1% (78/701)	10.2% (17/166)	14.7% (15/102)	10.6% (46/433)
EJ (N=701)	27.4% (192/701)	34.3% (57/166)	21.6% (22/102)	26.1% (113/433)
Anti-Ro52 (N=668)	65.1% (435/668)	71.0% (115/162)	61.7% (58/94)	63.6% (262/412)
FVC, % (N=460)	71.9 (59.6, 86.0)	60.2 (49.2, 76.7) <sup>ab</sup>	73.9 (60.7, 85.3)	74.5 (62.3, 88.5)
FEV1, % (N=462)	70.0 (57.9, 82.5)	57.9 (50.3, 72.2) <sup>ab</sup>	72.5 (58.3, 81.6)	72.1 (59.9, 86.4)
FEV1/FVC (N=457)	86.8 (80.2, 96.0)	88.3 (82.3, 94.9)	85.8 (80.2, 96.7)	86.6 (79.8, 96.0)
DLco, % (N=448)	56.2 (43.6, 68.0)	42.0 (32.2, 56.7) <sup>ab</sup>	51.9 (42.3, 63.0) <sup>c</sup>	59.0 (47.9, 70.8)

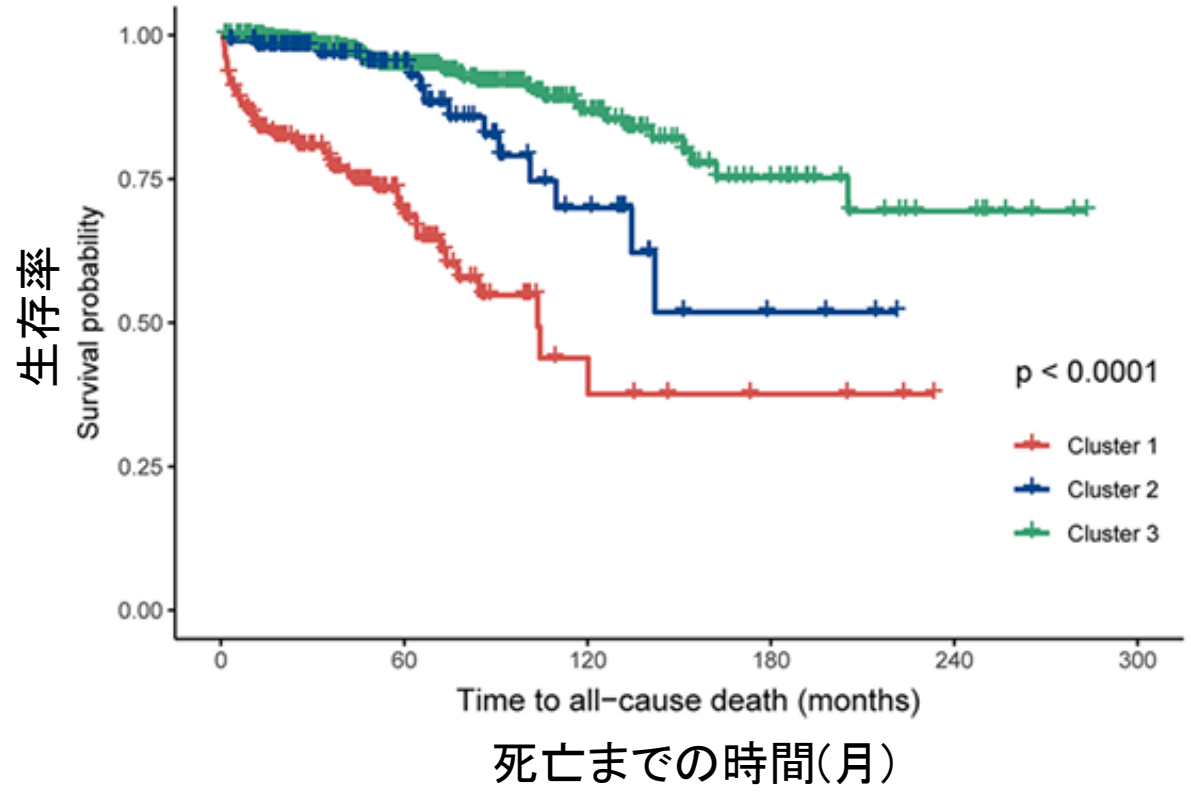


RP-ILD、発熱  
CRP高値

V sign  
Shawl sign  
Heliotrope疹  
筋力低下、ILD

関節炎  
Mechanic hand  
Raunaud現象

# Clusterごとの生存率



	Cluster1	Cluster2	Cluster3
1年生存率(%)	84.7	98.0	99.8
5年生存率(%)	66.8	95.1	95.4
10年生存率(%)	37.0	69.5	87.4

- Cluster2、3の5年生存率はほぼ同じだが、10年生存率はCluster2の方が悪い

- Cluster2、3でILD、RP-ILD、肺高血圧の発症率に差はなし

→%DLCOがCluster2の方が悪いのが影響している可能性(51.9% vs 59.0%)

# 決定木

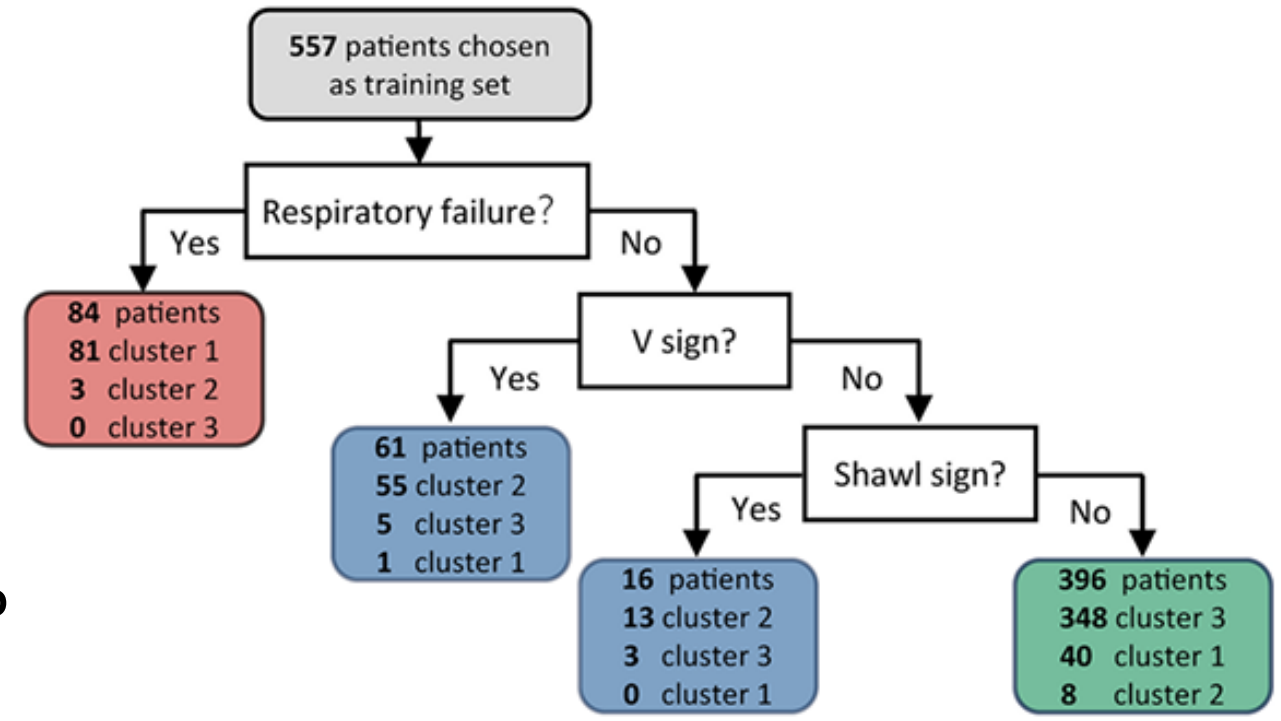
- CART algorithmで作成
- RP-ILDは予後と密接に関連するので、CART分析の際には除外

- **決定木の3項目**

- 呼吸不全
- V sign
- Shawl sign

- Training cohort → 精度 89.2%
- Validation cohort → 精度 88.2%

B

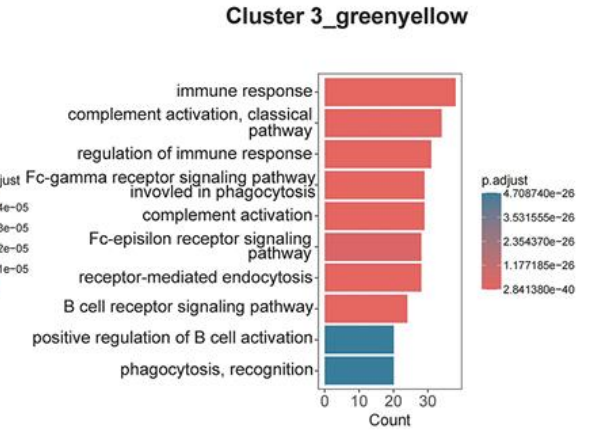
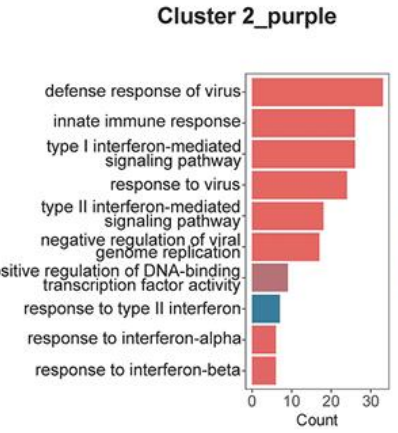
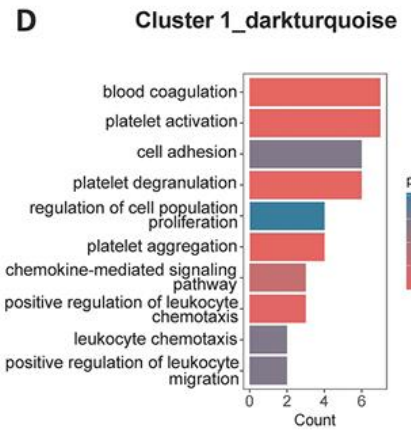
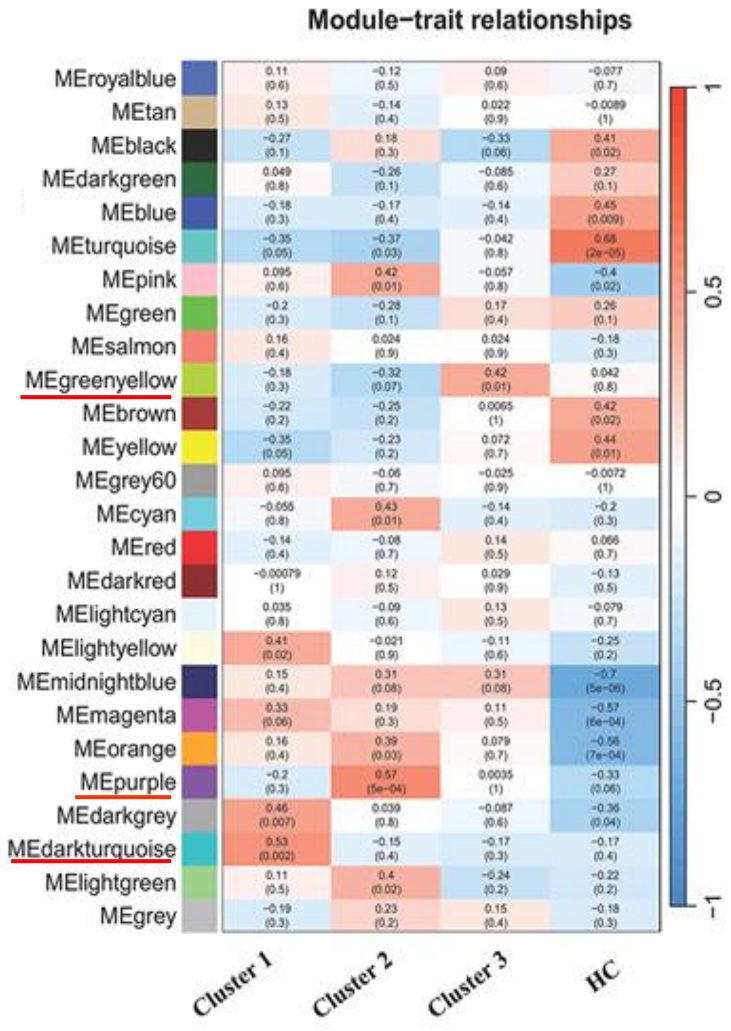


# 各Clusterと最も関連したモジュール・遺伝子

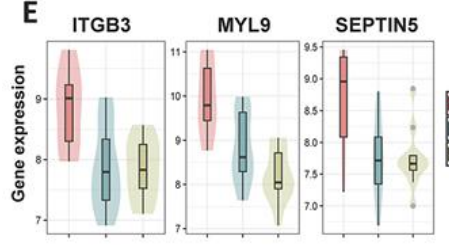
血液凝固  
 血小板活性化  
 炎症反応の活性化  
 ケモカインを介したシグナル伝達経路

ウイルスに対する防御反応  
 自然免疫反応  
 IFNを介したシグナル伝達経路

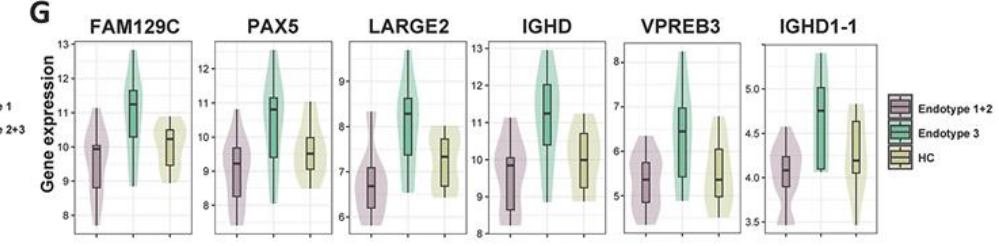
免疫反応  
 補体活性化  
 B細胞受容体 (BCR) シグナル伝達経路



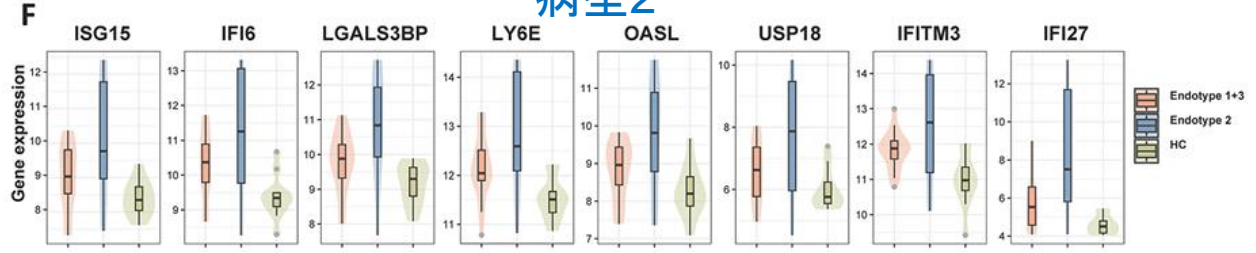
## 病型1



## 病型3



## 病型2



# Discussion

- **抗ARS抗体の中(抗Jo-1抗体、抗PL-7抗体、抗PL-12抗体、抗EJ抗体)で予後に差は認めなかった**
- **教師なしクラスタリングで臨床的に3群に分類することができた**
  - Cluster1: RP-ILD型、予後悪い
  - Cluster2: DM-like型
  - Cluster3: 関節炎型、予後良好
- **本研究の新規性はClusterを病因と関連づけられたこと**
  - Cluster1: 血液凝固、血小板、炎症反応の活性化→ARDSに近いメカニズム
  - Cluster2: 生体免疫反応、ウイルス感染やIFN関連のpathwayの活性化
  - Cluster3: B cellの活性化

# Limitation

- 後ろ向き研究である
- 単一の三次病院からenrollしており、recruitment biasが発生している可能性
- 抗体はラインブロットアッセイで測定しており、免疫沈降法で測定していない
- トランスクリプトームのデータサイズが十分でない