# Post-infectious sequelae in chronic lung disease

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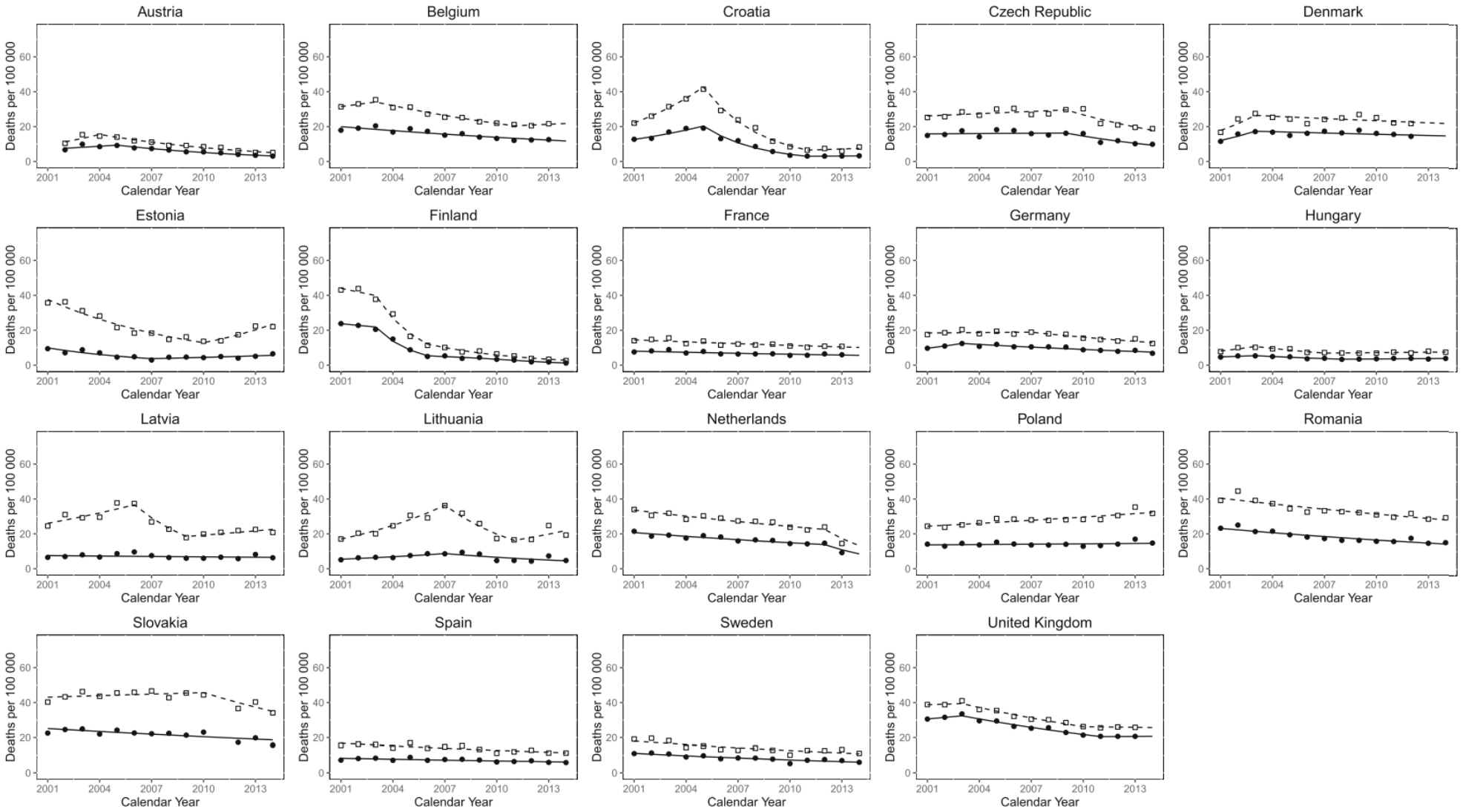
# Pneumonia mortality trends




19 European countries

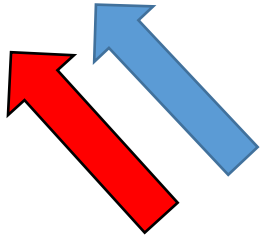
*Marshall et al. Respiratory Research (2018) 19:81*

# Survivors of low respiratory infection

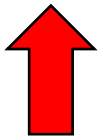
- Chronic respiratory symptoms
- Secondary pulmonary infections
- Death

# Infection-related lung injury

**Pathogen-mediated tissue destruction**



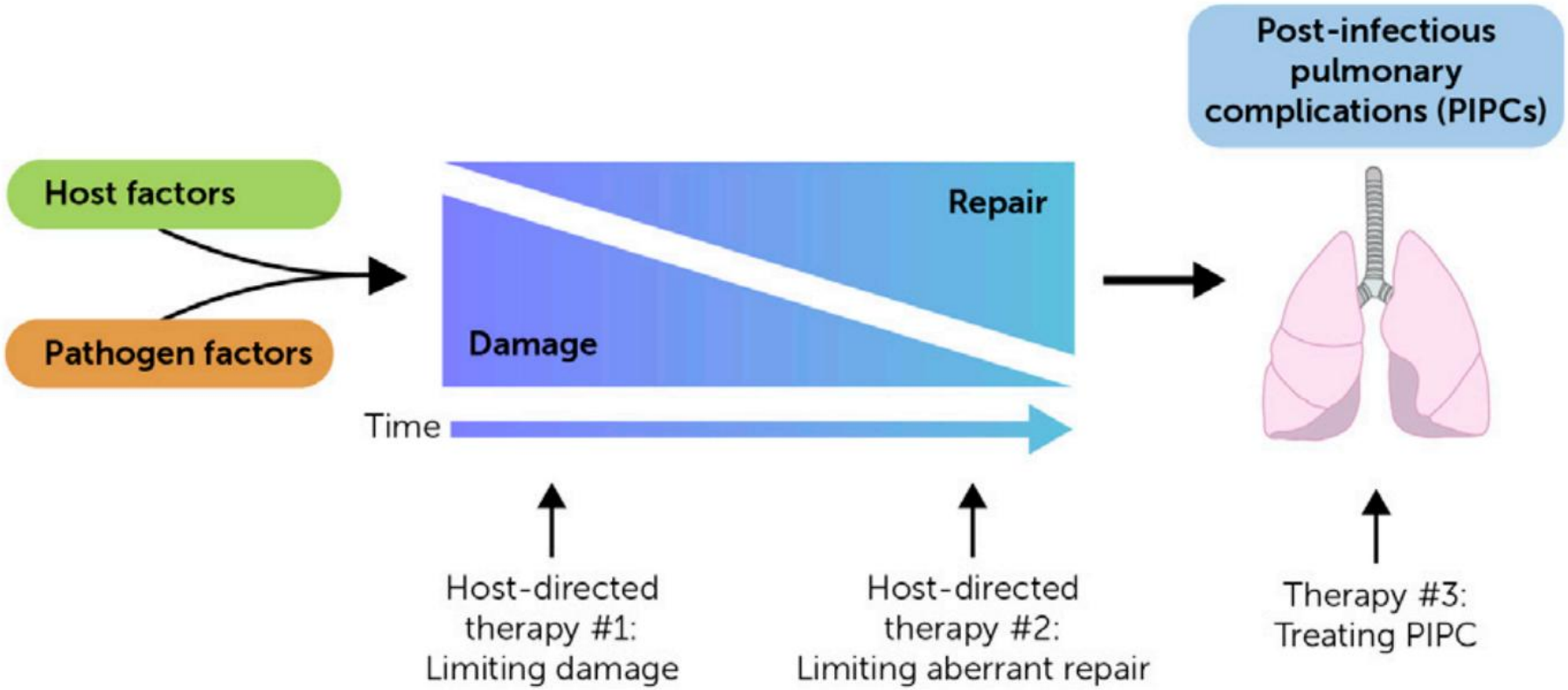
**Accompanying host response**



**Host immune response**

- **Local tissue destruction**
- **Chronic inflammation**
- **Aberrant remodeling and fibrosis**

# Post-infectious pulmonary complications (PIPCs)

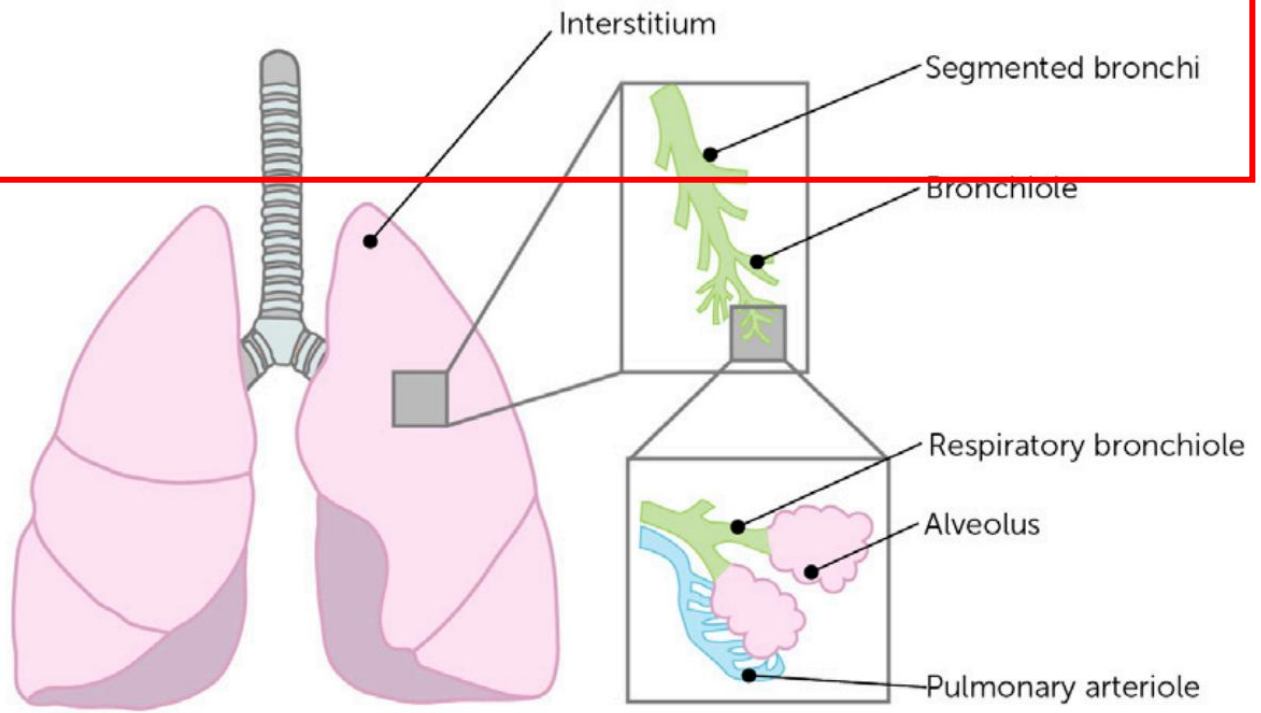



## Potential therapeutic interventions

Ann Am Thorac Soc 2024, 21:9. 1219–1237

# Anatomic locations of postinfectious pulmonary complications

| ANATOMIC DISTRIBUTION | CLINICAL SEQUELAE |
|---|---|
| **Parenchyma** | |
| • Alveoli<br>• Interstitium | • Fibrosis, cavities, nodules |
| **Airways** | |
| • Bronchi<br>• Bronchiole<br>• Respiratory bronchioles | • Bronchiectasis, bronchiolectasis |
| **Vasculature** | |
| • Pulmonary arteries<br>• Pulmonary veins<br>• Pulmonary vasculature | • Thrombosis, immunothrombosis |
| **Pleura** | |
| • Visceral pleura<br>• Parietal pleura | • Pleural thickening and scarring |




Ann Am Thorac Soc 2024, 21:9. 1219–1237

# COVID-19 patients surviving ARDS increased fibrotic changes compared to non-COVID pneumonia ARDS patients

scientific reports

OPEN Post-intensive care syndrome and pulmonary fibrosis in patients surviving ARDS-pneumonia of COVID-19 and non-COVID-19 etiologies

- Demographics

| Parameter | COVID-19 n = 64 | Non-COVID n = 30 | T-test or Chi-square, p = 0.05 |
|---|---|---|---|
| Age, years, mean ± SD | 54 ± 13 | 50 ± 13 | p = 0.14 |
| Male, n (%) | 32 (50) | 16 (53) | p = 0.77 |
| Race/ethnicity | | | |
| Caucasian/White, n (%) | 48 (75) | 30 (100) | p = 0.002[A] |
| African America/Black, n (%) | 9 (14) | 0 (0) | |
| Other, n (%) | 7 (11) | 0 (0) | |
| Tobacco use | | | |
| Chronic lung disease, n (%) | 10(16) | 11 (37) | p = 0.033 |
| MV duration, mean ± SD | 17.3 ± 12.4 | 15.1 ± 11.2 | p = 0.33 |
| Oxygenation (HFNC + MV) days, mean ± SD | 20.8 ± 12.6 | 16.2 ± 11.4 | p = 0.048 |
| FiO2 (peak 72 h), mean ± SD | 90.9 ± 14.3 | 78.8 ± 22.5 | p = 0.009 |
| PEEP (peek 72 h), mean ± SD | 13.6 ± 3.2 | 11.5 ± 4.4 | p = 0.030 |
| Steroids, n (%) | 58 (91) | 16 (53) | p < 0.001 |
| Tracheostomy, n (%) | 24 (38) | 14 (47) | p = 0.40 |
| ECMO, n (%) | 9 (14) | 4 (13) | p = 0.92 |
| CRRT, n (%) | 9 (14) | 4 (13) | p = 0.92 |
| Steroids, n (%) | 58 (91) | 16 (53) | p < 0.001 |
| Vasopressor/inotropes, n (%) | 45 (70) | 19 (63) | p = 0.50 |
| NMB, n (%) | 24(38) | 9 (30) | p = 0.48 |
| RASS (mean 72 h), mean ± SD | −3.4 ± 1.2 | −2.9 ± 1.5 | p = 0.16 |

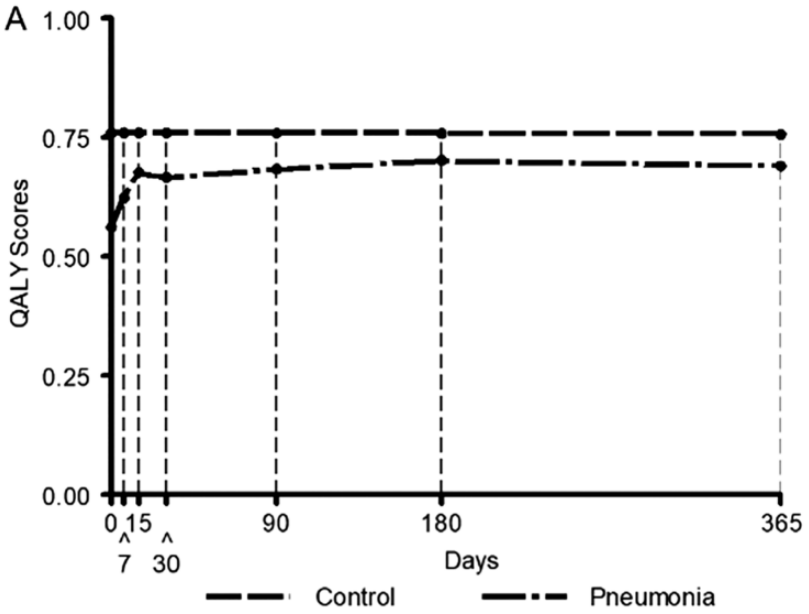
- Outcomes

| Parameter | COVID-19 n = 64 | Non-COVID n = 30 | T-test or Chi-square p = 0.05 |
|---|---|---|---|
| 90-day negative composite | 15 (23) | 7 (23) | p = 0.99 |
| CT findings | | | |
| Fibrotic changes, n (%) | 45 (70) | 13 (43) | p = 0.022 |
| Ground-glass opacity, n (%) | 52 (81) | 12 (40) | p < 0.001 |
| | 89 ± 38 | 117 ± 55 | p = 0.023 |
| | n = 55 | n = 24 | |
| | 2.2 ± 0.7 | 2.1 ± 0.7 | p = 0.84 |
| | 67 ± 17 | 66 ± 20 | p = 0.83 |
| | 2.6 ± 0.9 | 2.9 ± 0.9 | p = 0.081 |
| | 63.9 ± 19 | 71 ± 20 | p = 0.157 |
| 6 MW T (n) | n = 51 | n = 8 | |
| Distance, meters, mean ± SD | 229 ± 131 | 260 ± 169 | p = 0.63 |
| 6 MWD % | 44 ± 26 | 46 ± 32 | p = 0.87 |
| HADS-depression, mean ± SD | 5.9 ± 4.1 | 8.1 ± 5.5 | t = 1.78, p = 0.083 |
| HADS-depression cutoff > 8, yes, n (%) | 13 (25) | 12 (48) | p = 0.069 |

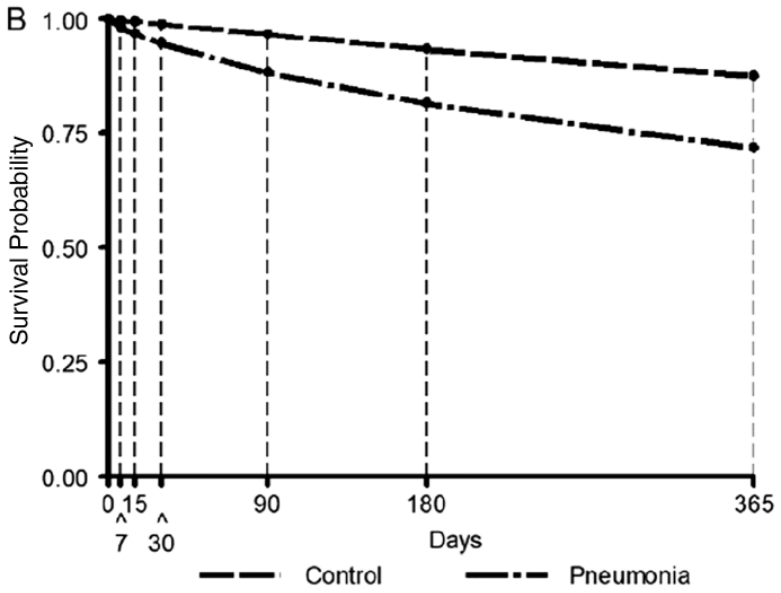
*Scientific Reports (2023) 13:6554*

# One-year quality of life post-pneumonia diagnosis

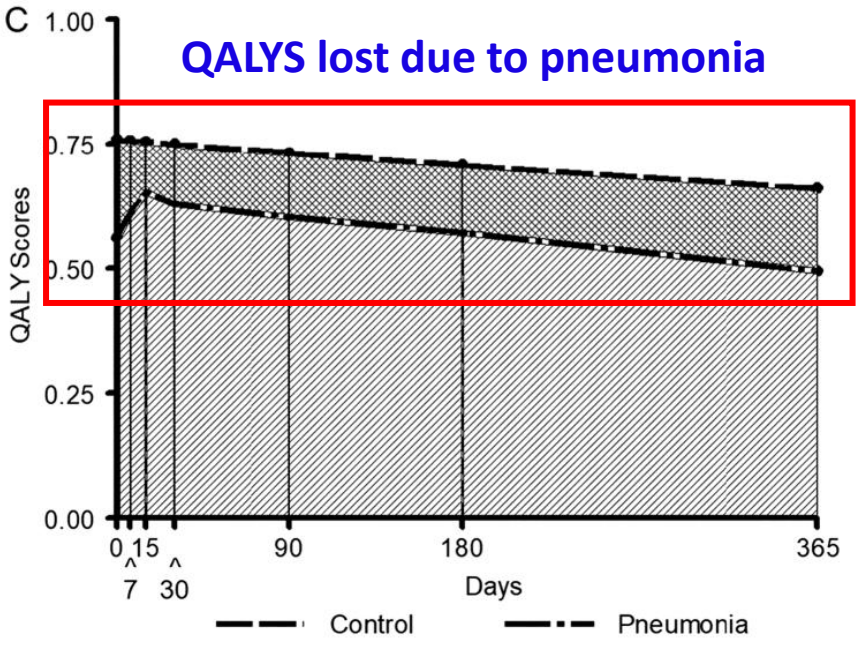
**Average adjusted QALY**




**Average adjusted survival curves**




**Average adjusted survival weighted QALY score curves**

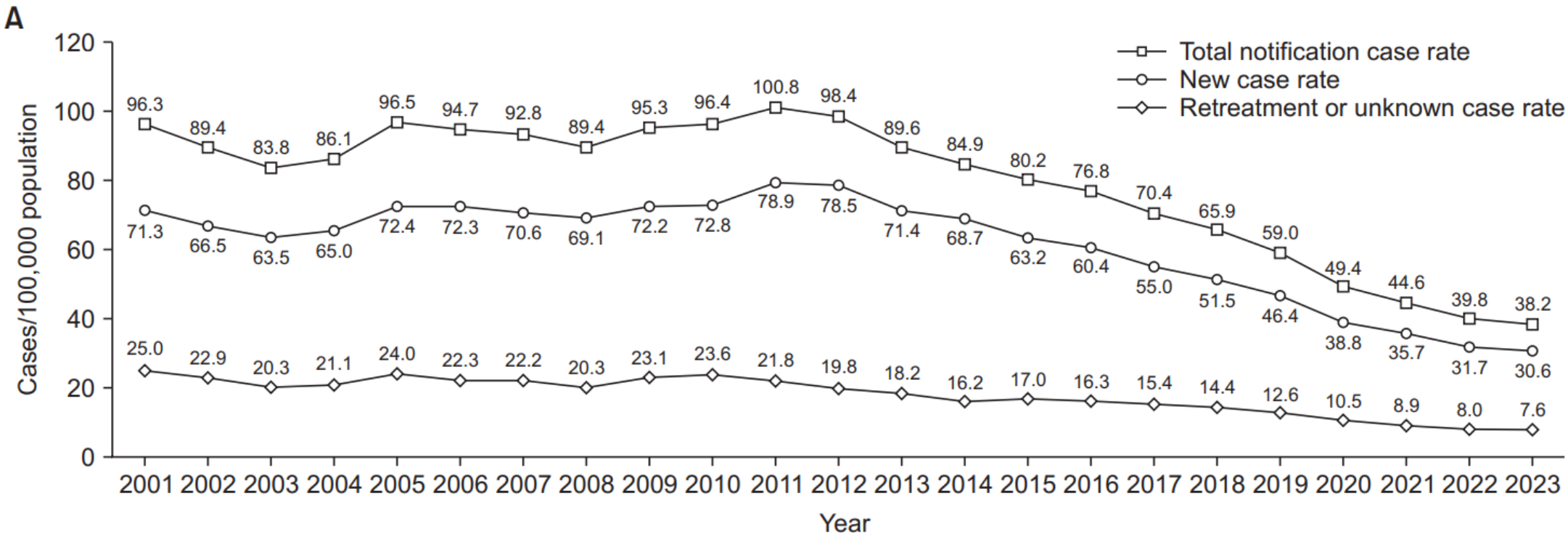



in Japanese adults

**QALY, 삶의 질 보정 생존연수(quality-adjusted life-year)**

*Clin Infect Dis 2021;73:283–290.*

# Tuberculosis Notification and Incidence: Republic of Korea, 2023




*Min J et al. Tuberc Respir Dis. 2025;88(3):606-609.*

# Residual respiratory disability after successful Tx for TB

| Meta-analysis | Number of study populations | Proportion of participants (n/N) | Pooled estimate (95% CI) | Prediction intervals | $I^2$ |
|---|---|---|---|---|---|
| ***All TB patients*** | | | | | |
| Abnormal | 42 | 4082/9864 | 59.1% (48.8%–68.7%) | 8.4%–95.8% | 98.3% |
| Obstruction | 41 | 1882/9803 | 17.8% (13.4%–23.1%) | 2.5%–64.5% | 96.6% |
| Restriction | 35 | 1339/5822 | 21.3% (15.3%–28.9%) | 2.3%–75.7% | 95.4% |
| Mixed pattern | 30 | 861/5095 | 12.7% (8.2%–19.2%) | 1.0%–68.9% | 93.2% |
| ***Controls*** | | | | | |
| Abnormal | 4 | 794/21,804 | 5.4% (2.6%–10.8%) | 0.2%–67.7% | 97.4% |
| Obstruction | 4 | 794/21,804 | 5.4% (2.6%–10.8%) | 0.2%–67.7% | 97.4% |
| Restriction/Mixed | 0 | – | – | – | – |

*J Taylor et atl., eClinicalMedicine 2023;59: 101979*

# One year after mild influenza A subtype H1N1

**Table 1. Change in pulmonary function at one year post-hospital discharge.**

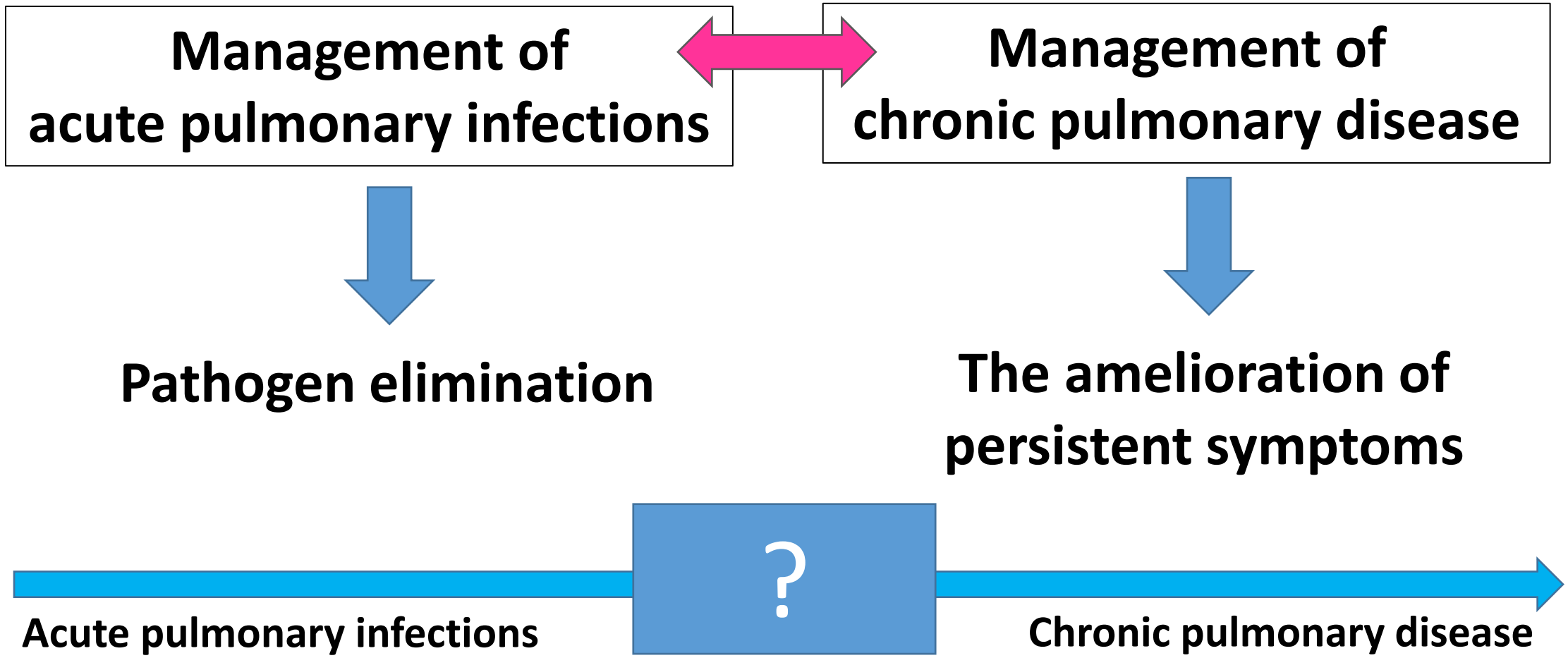
| Change in pulmonary function | Incidence rate; n(%) |
|---|---|
| **Gas exchange function** | |
| Diffusion disorder (DLCO↓) | 16/48 (33.3) |
| **Pulmonary ventilation** | |
| Small airway function disorder (FEF50↓, FEF75↓, MMEF75/25↓) | 16/48 (33.3) |
| Simple limitation (TLC-He↓) | 0 (0) |
| Mixed (small airway function disorder + simple limitation) | 6/48 (12.5) |
| Weakened storing function (MVV↓) | 14/48 (29.2) |

**Table 2. Correlation between pulmonary function one year post-hospital discharge and clinical manifestations of patients infected with influenza A virus subtype H1N1.**

| Clinical manifestations, n (%) | Normal pulmonary function (n = 22) | Abnormal pulmonary function (n = 26) | P value |
|---|---|---|---|
| Cough, expectoration or gasping | 2 (9.1) | 12 (46.2) | < 0.05 |
| Influence on general physical activities | 6 (27.3) | 14 (53.8) | |

*W. Liu et al., PLoS ONE 10(7): e0133698.*

# Is our current management right ?



# Parenchymal injury and repair after pulmonary infection

- Parenchymal fibroproliferative response to acute insults
  : ARDS → fibroproliferative (FP) ARDS

- Severity of ARDS – degree of fibroproliferation
  : Extent of fibroproliferation - poor prognosis

ORIGINAL ARTICLE
INFECTION AND LUNG FUNCTION

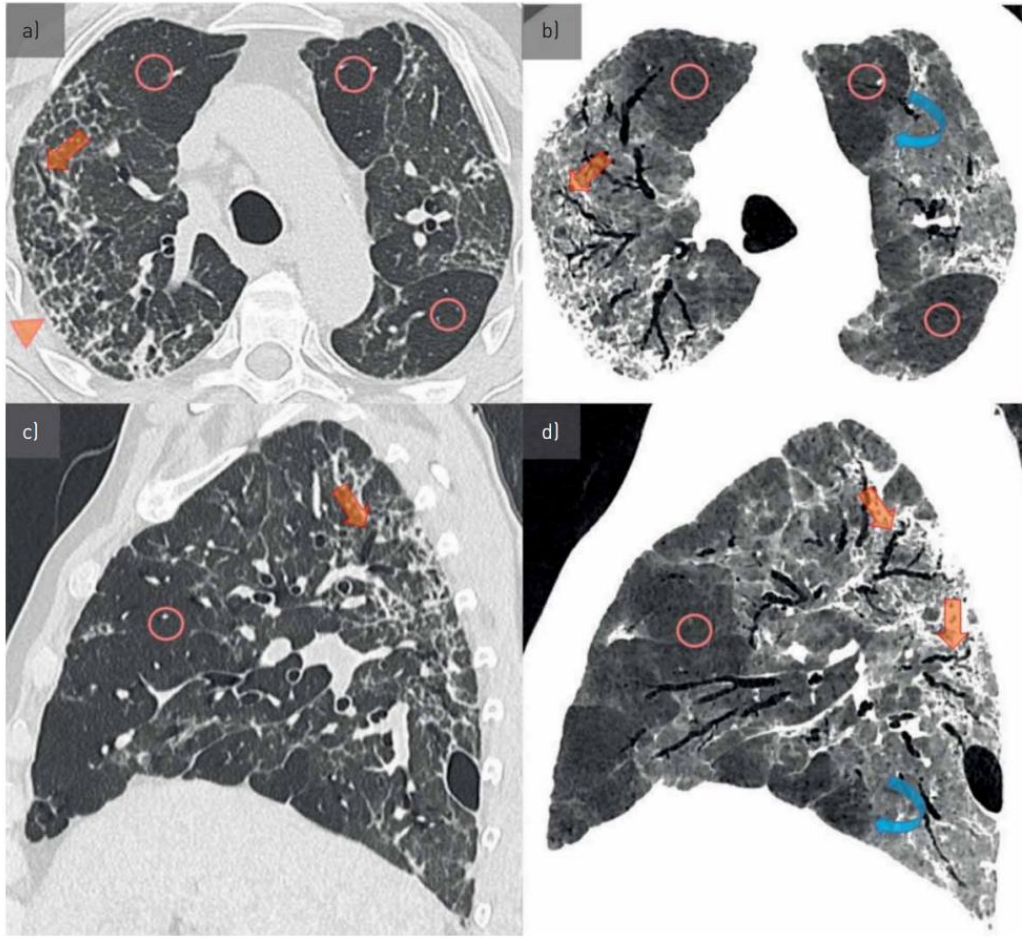
# Pulmonary function and radiological features 4 months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study

| | Severe/critical disease | Mild/moderate disease | p-value# |
|---|---|---|---|
| **Patients n** | 66 | 47 | |
| **Baseline characteristics** | | | |
| Male/female n/n | 40/26 | 27/20 | 0.89 |
| Age years | 60.3±12.0 | 52.9±10.9 | <0.001 |
| Ever-smokers¶ % | 56 | 37 | 0.16 |
| BMI kg·m$^{-2}$ | 29.8±5.7 | 25.5±4.7 | 0.02 |
| D-dimer+ µg·L$^{-1}$ | 1011 (366–1989) | 387 (1–658) | 0.26 |
| Mechanical ventilation§ % | 71 | | |
| Duration of mechanical ventilation§ days | 11.9 (9.5–18) | | |
| **Comorbidities %** | | | |
| Interstitial lung disease | 6 | 3 | 0.58 |
| COPD | 12 | 3 | 0.18 |
| Asthma | 9 | 19 | 0.32 |
| Arterial hypertension | 55 | 8 | 0.003 |
| | 35 | 0 | 0.04 |
| | 10 | 9 | 1.00 |
| | 16 | 3 | 0.09 |
| | 10 | 9 | 1.00 |
| | 19 | 0 | 0.009 |
| | 6 | 5 | 1.00 |
| | 12 | 7 | 0.66 |
| **Pulmonary function at follow-up**f | | | |
| $FEV_1$/FVC % | 94.7±13.7 | 84.2±14.3 | <0.001 |
| TLC L | 5.22±1.5 | 6.5±1.6 | 0.050 |
| TLC % pred | 86.0±20.0 | 102.0±19.3 | 0.047 |
| FVC L | 3.28±1.01 | 4.12±1.2 | <0.001 |
| FVC % pred | 86.6±20.1 | 95.6±17.9 | 0.02 |
| $FEV_1$ L | 2.64±0.8 | 3.34±1.1 | <0.001 |
| $FEV_1$ % pred | 89.4±20.7 | 94.0±15.6 | 0.19 |
| $D_{LCO}$ % pred | 73.2±18.4 | 95.3±20.6 | 0.003 |
| $P_{Imax}$ kPa | 10.3±8.8 | 8.1±2.6 | 0.14 |
| $P_{Emax}$ kPa | 8.7±3.3 | 10.3±4.1 | 0.20 |
| **Oxygenation at follow-up**f | | | |
| $P_{aO_2}$ mmHg | 79.0±12.2 | 87.5±9.0 | 0.0002 |
| 6MWD m | 456±105 | 576±78 | 0.001 |
| $O_2$ nadir on 6MWT | 90±4.5 | 93±3.1 | 0.001 |
| $O_2$ desaturation on 6MWT | 5.6±3.8 | 2.6±3.1 | 0.02 |
| | 94.7±13.7 | 84.2±14.3 | <0.001 |
| | 5.22±1.5 | 6.5±1.6 | 0.050 |
| | 86.0±20.0 | 102.0±19.3 | 0.047 |
| | 3.28±1.01 | 4.12±1.2 | <0.001 |
| | 86.6±20.1 | 95.6±17.9 | 0.02 |
| | 2.64±0.8 | 3.34±1.1 | <0.001 |
| | 89.4±20.7 | 94.0±15.6 | 0.19 |
| | 73.2±18.4 | 95.3±20.6 | 0.003 |
| | 10.3±8.8 | 8.1±2.6 | 0.14 |
| | 8.7±3.3 | 10.3±4.1 | 0.20 |
| | 79.0±12.2 | 87.5±9.0 | 0.0002 |
| | 456±105 | 576±78 | 0.001 |
| | 90±4.5 | 93±3.1 | 0.001 |
| $O_2$ desaturation on 6MWT | 5.6±3.8 | 2.6±3.1 | 0.02 |

*Eur Respir J 2021;57: 2003690*

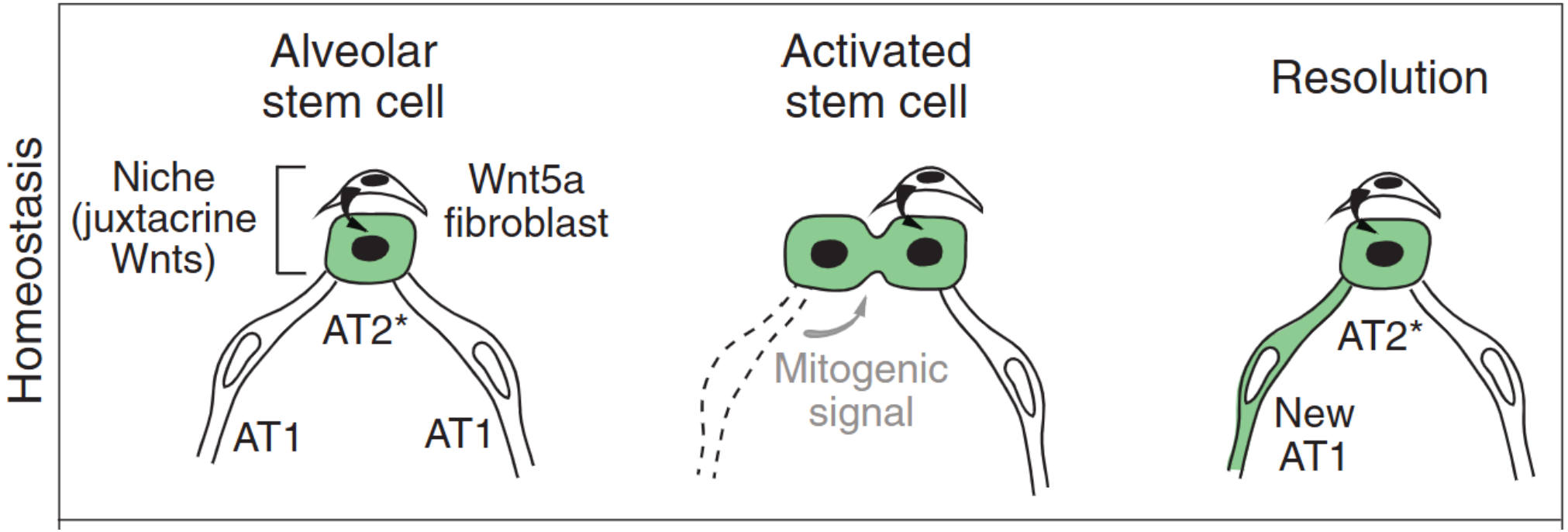
# Radiological changes of a patient with severe sequelae (3 month after COVID-19 pneumonia)

- **Classic feature of lung fibrosis**
  - Architectural distortion
  - Reticulations
  - Honeycombing
  - Traction bronchiectasis




*Eur Respir J 2021;57: 2003690*

# Repair of the alveolar epithelium occurs when AT2 cells proliferate and differentiate into AT1 cells




*Nabhan et al., Science 359, 1118–1123 (2018)*

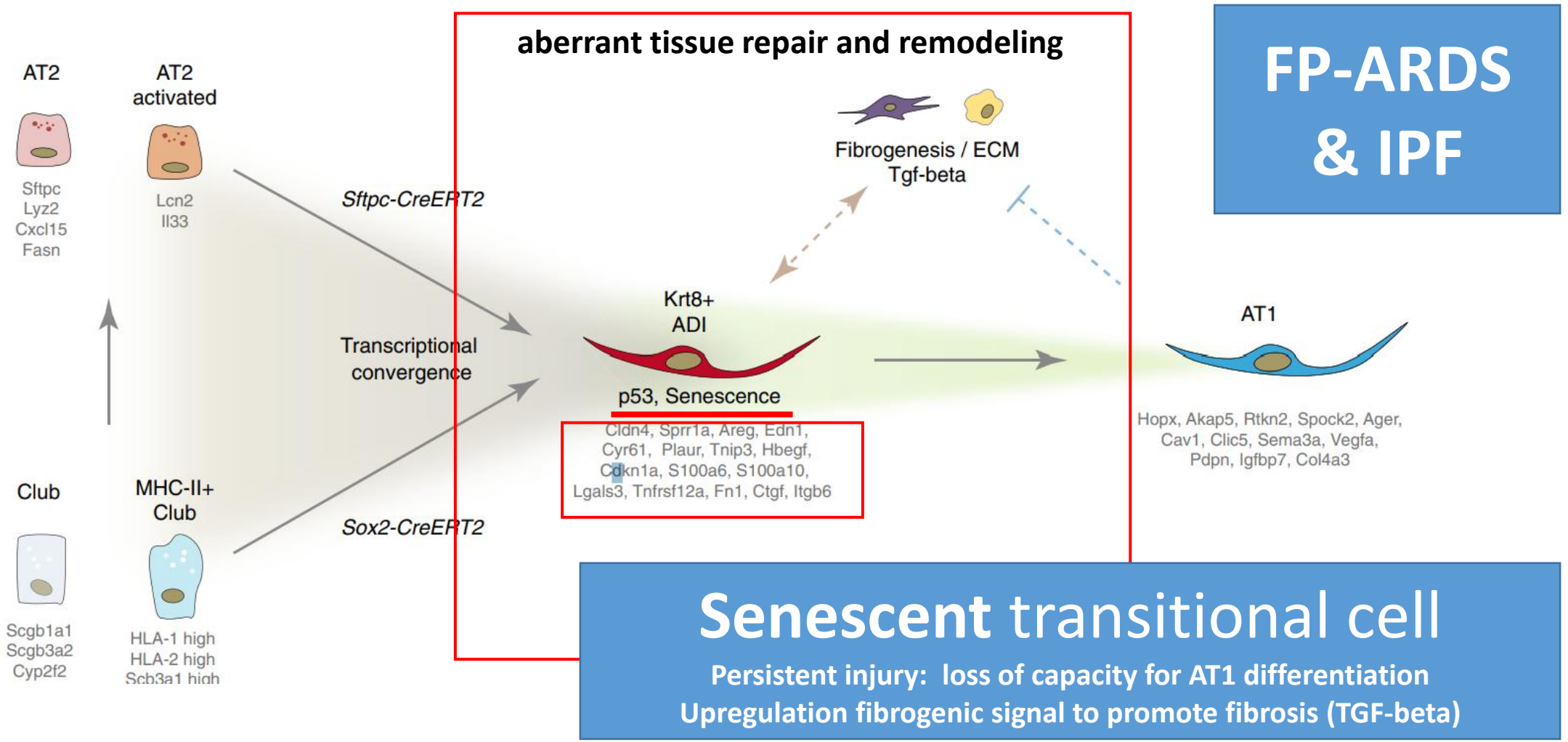
**Repeated injured alveolar epithelial cells**

**Accumulated DNA damage / endoplasmic reticulum stress**

**Alveolar type 2 (AT2) cells ↛ AT1 cells**

**Transitional-state cells ↑ (aberrant tissue repair and remodeling)**

# A model of alveolar regeneration

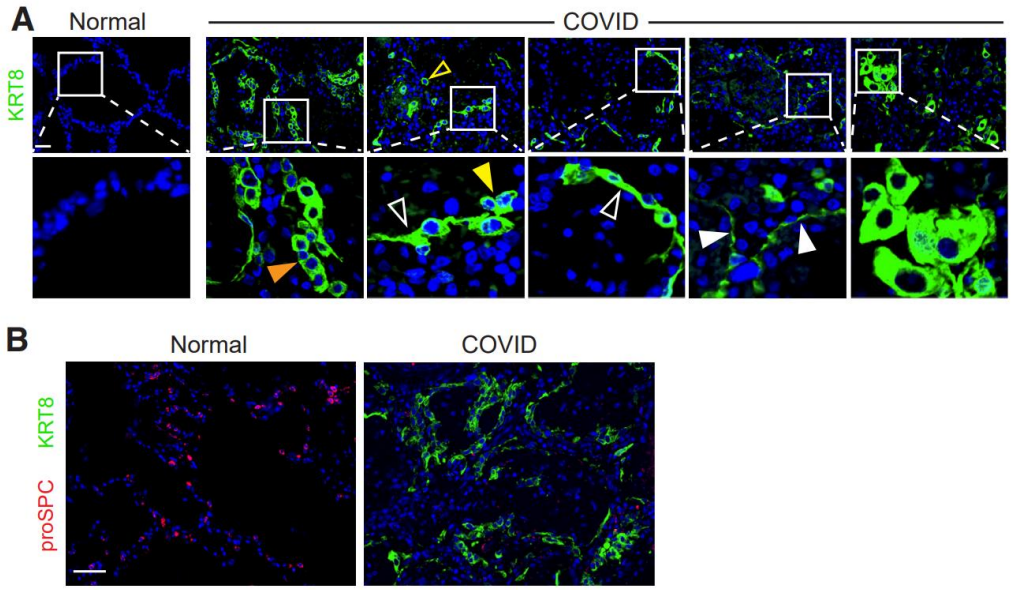



*NATURE COMMUNICATIONS | (2020) 11:3559*

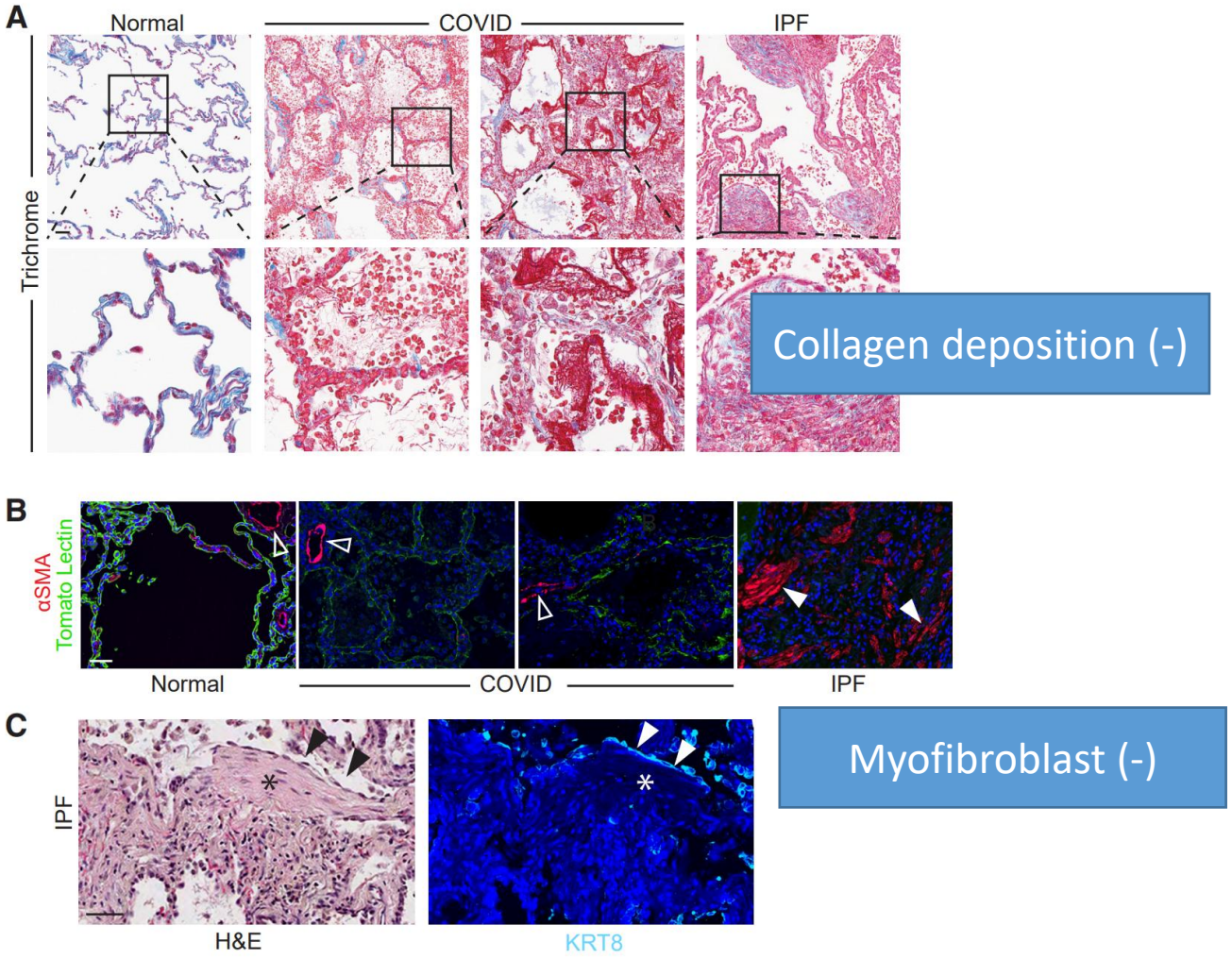
# Severe, but non-fibrotic ARDS

**Fatal COVID-19 and Non—COVID-19 Acute Respiratory Distress Syndrome Is Associated with Incomplete Alveolar Type 1 Epithelial Cell Differentiation from the Transitional State without Fibrosis**

Christopher Ting,* Mohit Aspal,† Neil Vaishampayan,† Steven K. Huang,* Kent A. Riemondy,† Fa Wang,* Carol Farver,‡ and Rachel L. Zemans*¶



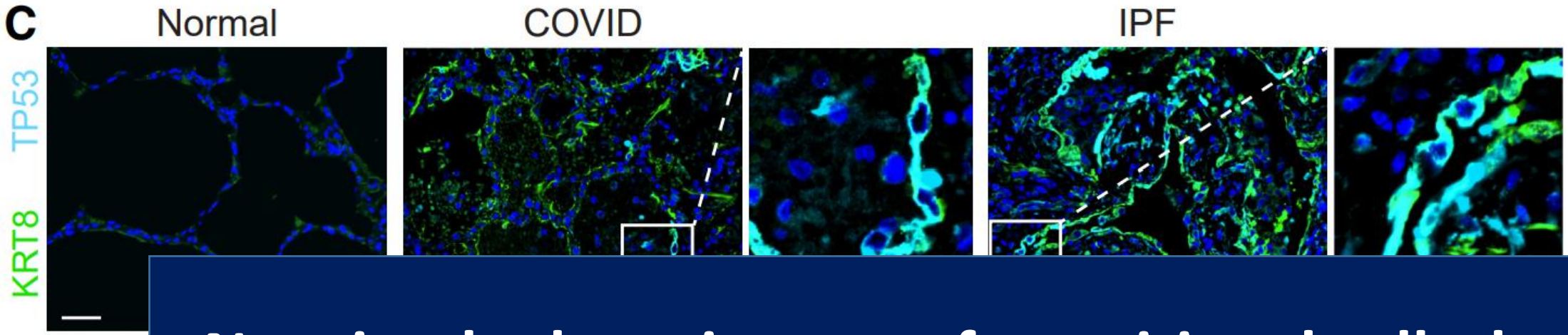

KRT8+ transitional cell



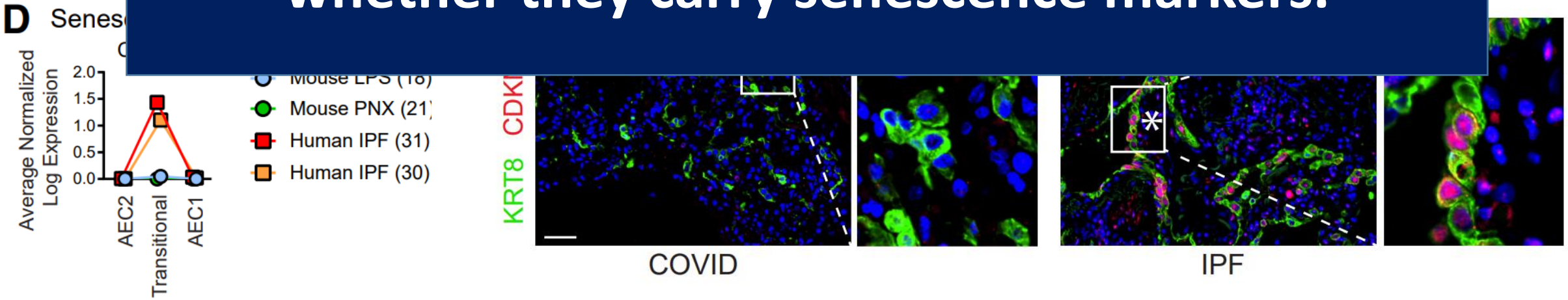

Collagen deposition (-)

Myofibroblast (-)

*Am J Pathol 2022 Mar;192(3):454-467*

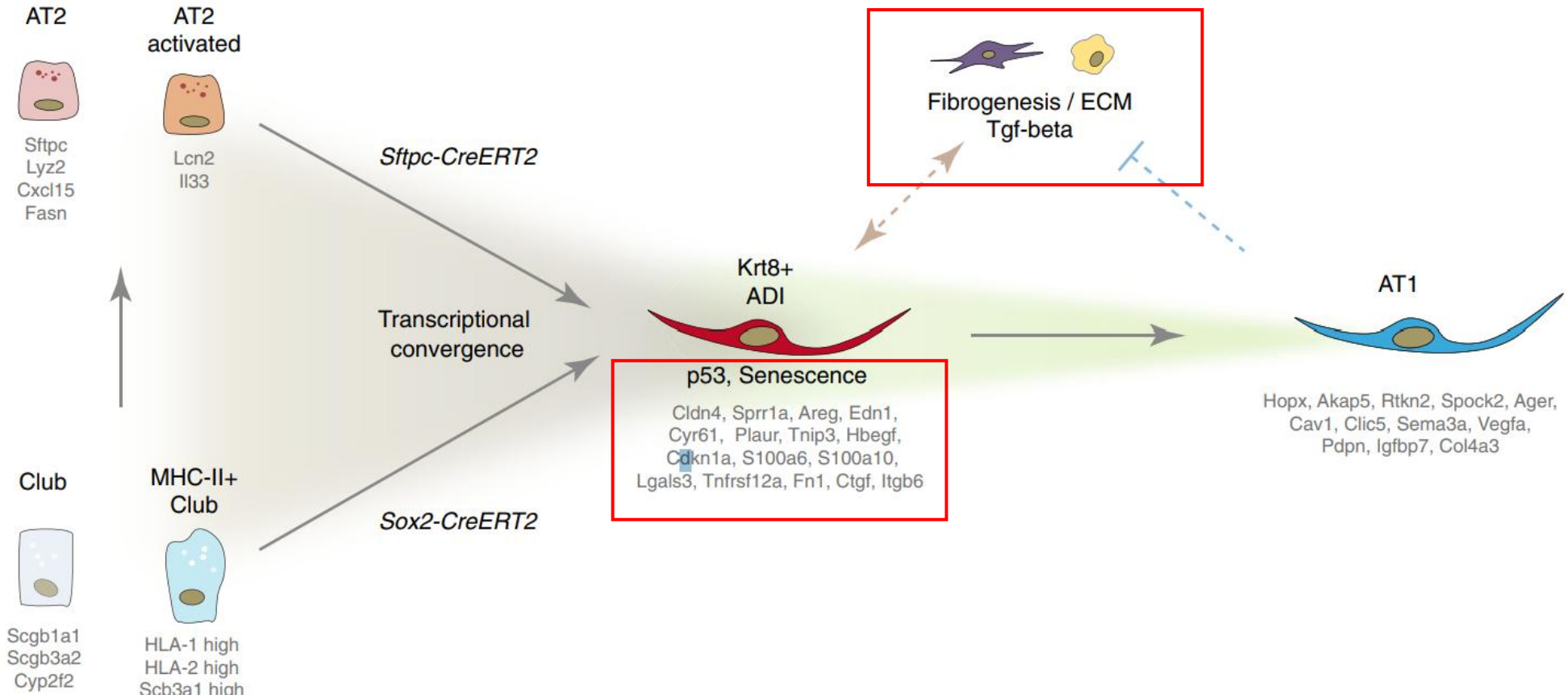



**Not simply the existence of transitional cells, but whether they carry senescence markers.**




*Am J Pathol 2022 Mar;192(3):454-467*

# A model of alveolar regeneration




*NATURE COMMUNICATIONS | (2020) 11:3559*

**Lung injury**

↓

**Monocyte-derived interstitial macrophages ↑**
**Monocyte-derived alveolar macrophages (MoAMs) ↑**

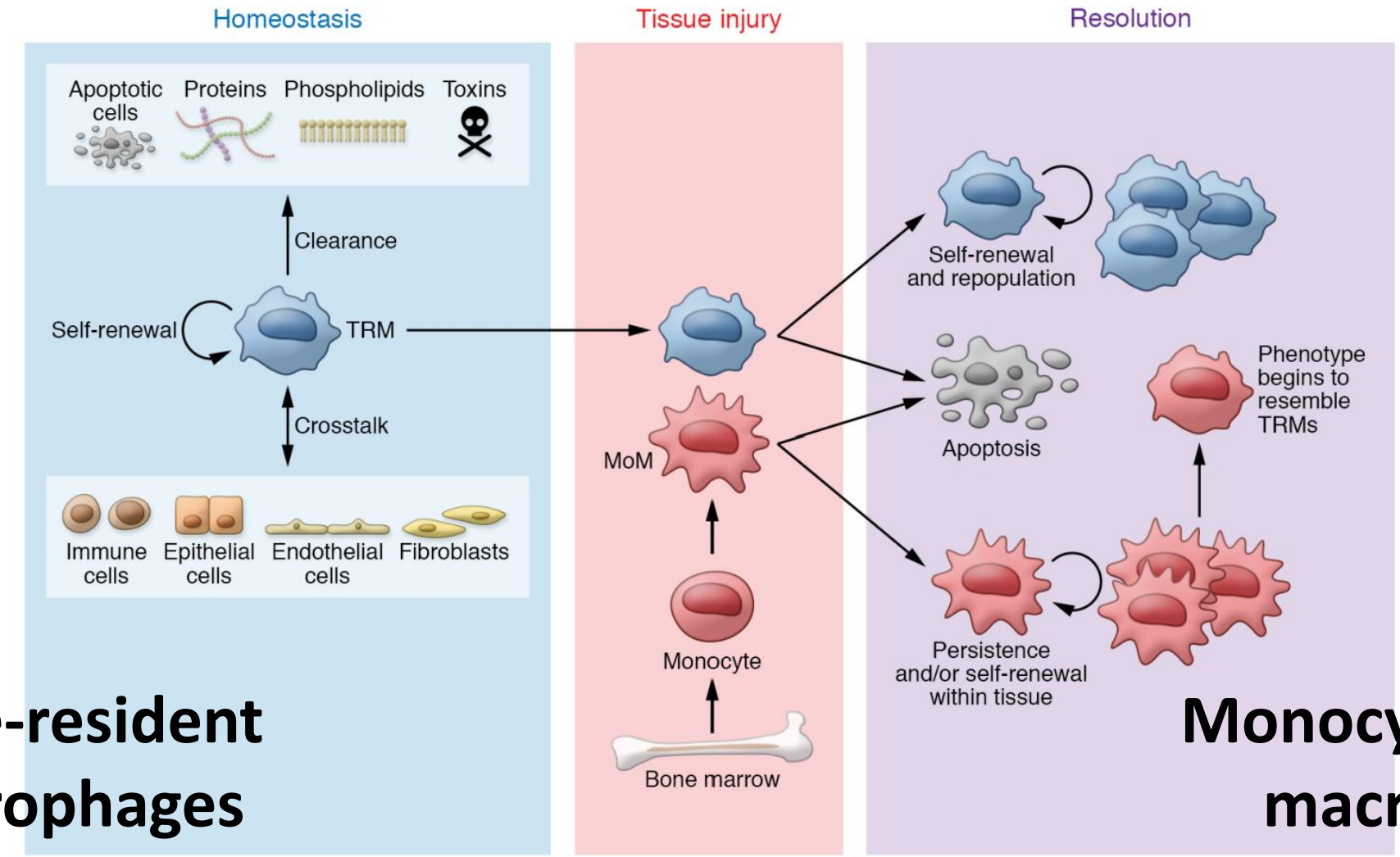
↓

**Fibroblast proliferation and differentiation ↑**

↓

**Development of fibrosis**

# Distinct roles of macrophages

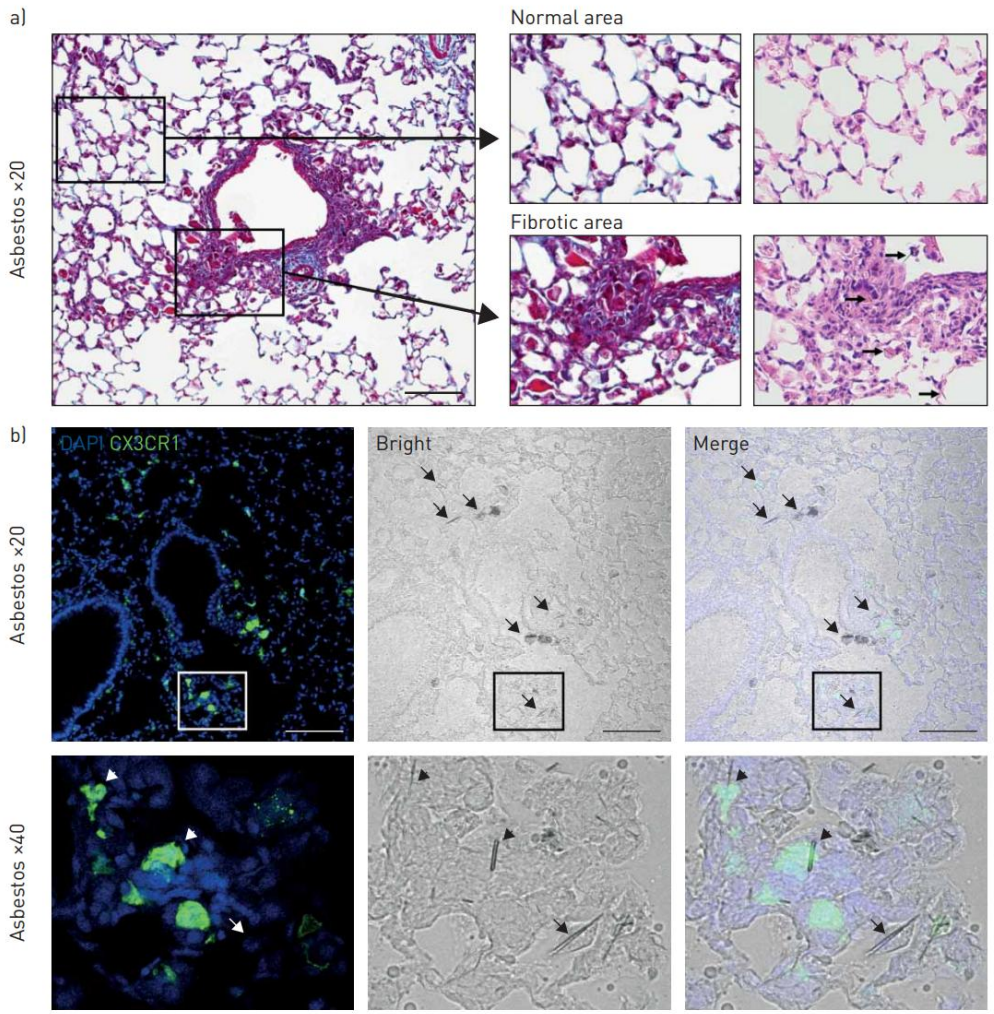



**Tissue-resident macrophages**

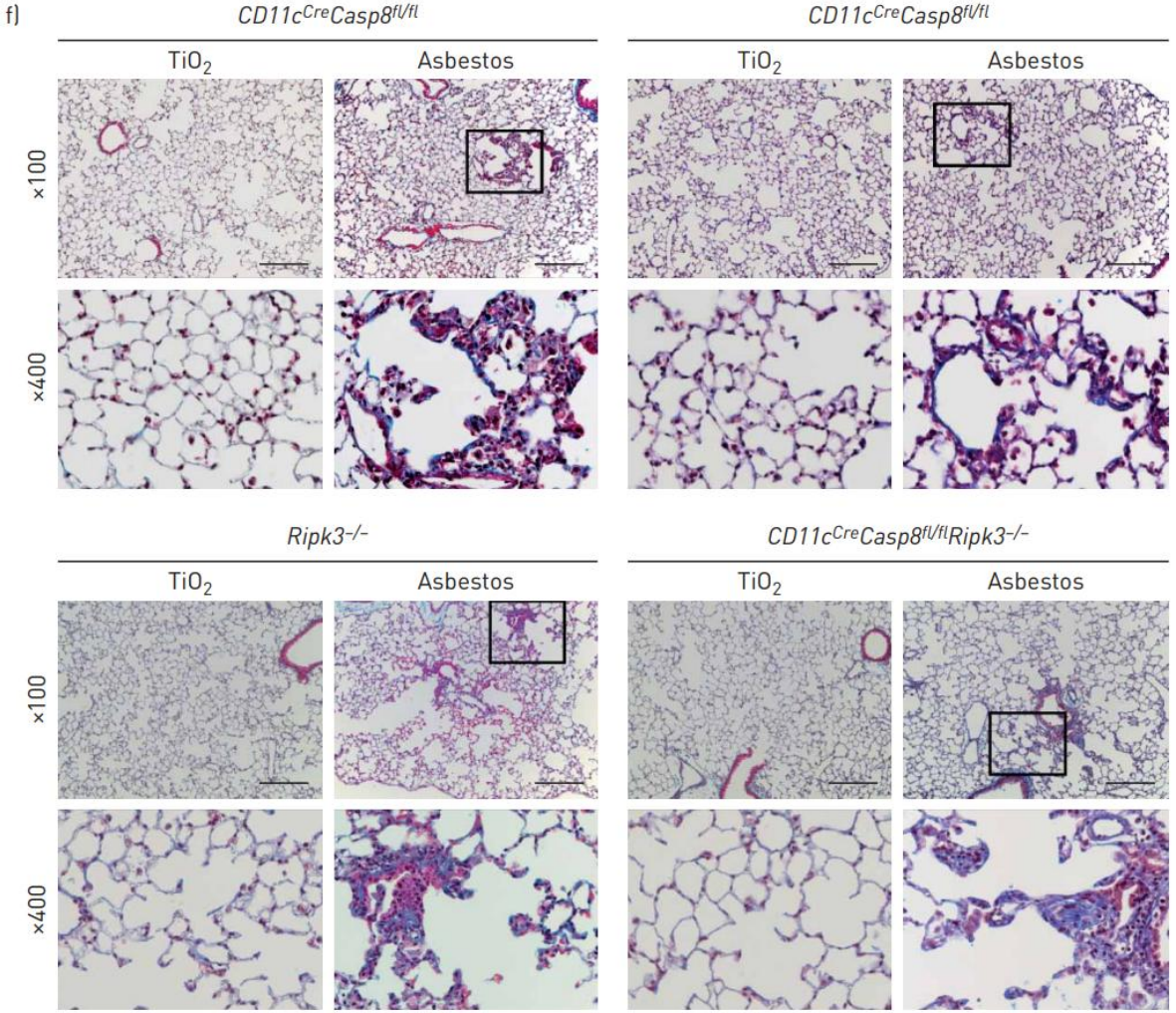
**Monocyte-derived macrophages**

*J Clin Invest. 2019;129(7):2619-2628*

# Monocyte-derived AMs in asbestosis-induced pulmonary fibrosis



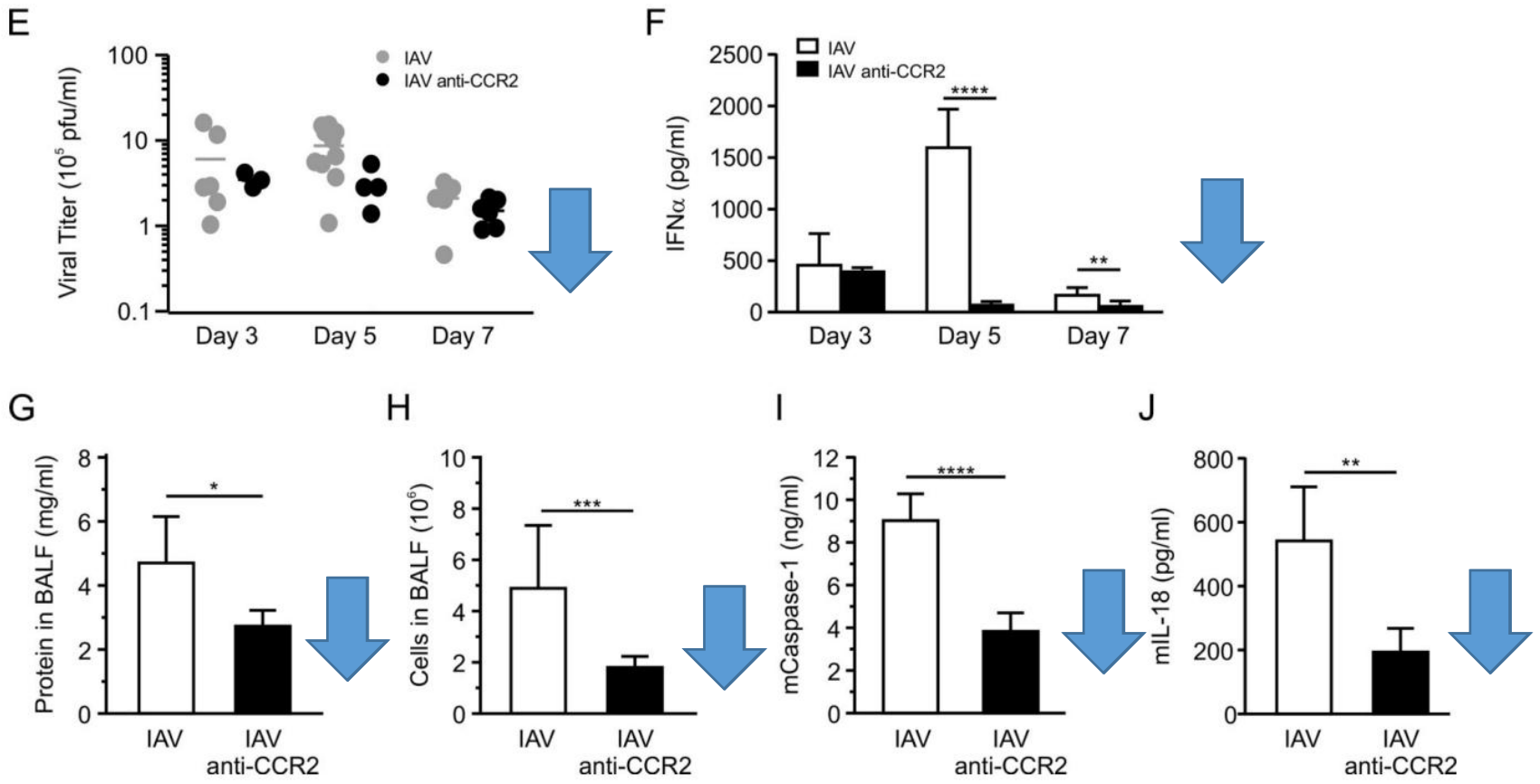

**Recruitment of monocyte-derived alveolar macrophages (MoAMs)**




**Deletion of MoAMs attenuates asbestos-induced PF**

*Eur Respir J 2020; 55: 1900646*

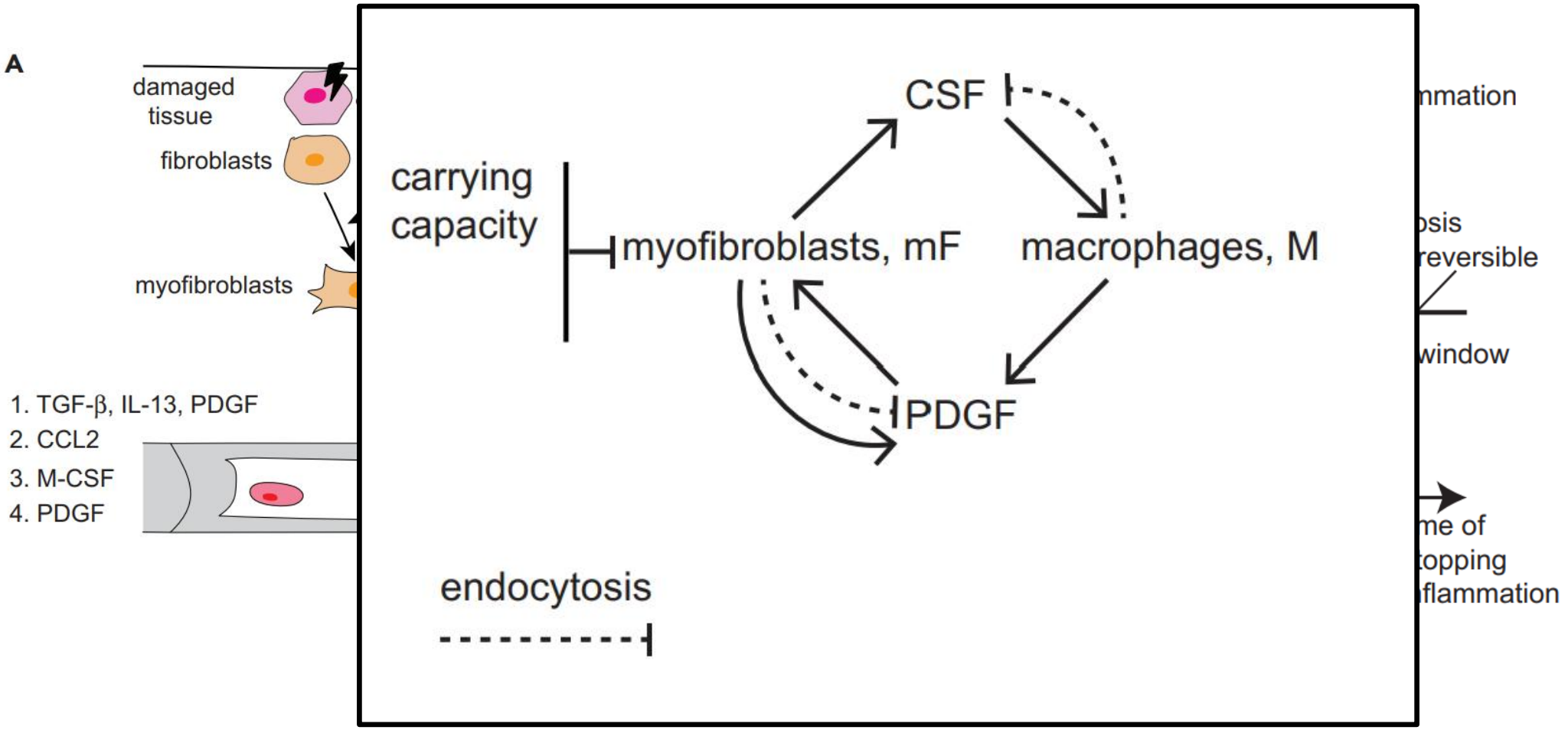
# Inhibition of monocyte recruitment with anti-CCR2




**Inflammatory monocytes drive influenza A virus-mediated lung injury in juvenile mice**

*J Immunol 2018;200:2391–2404*

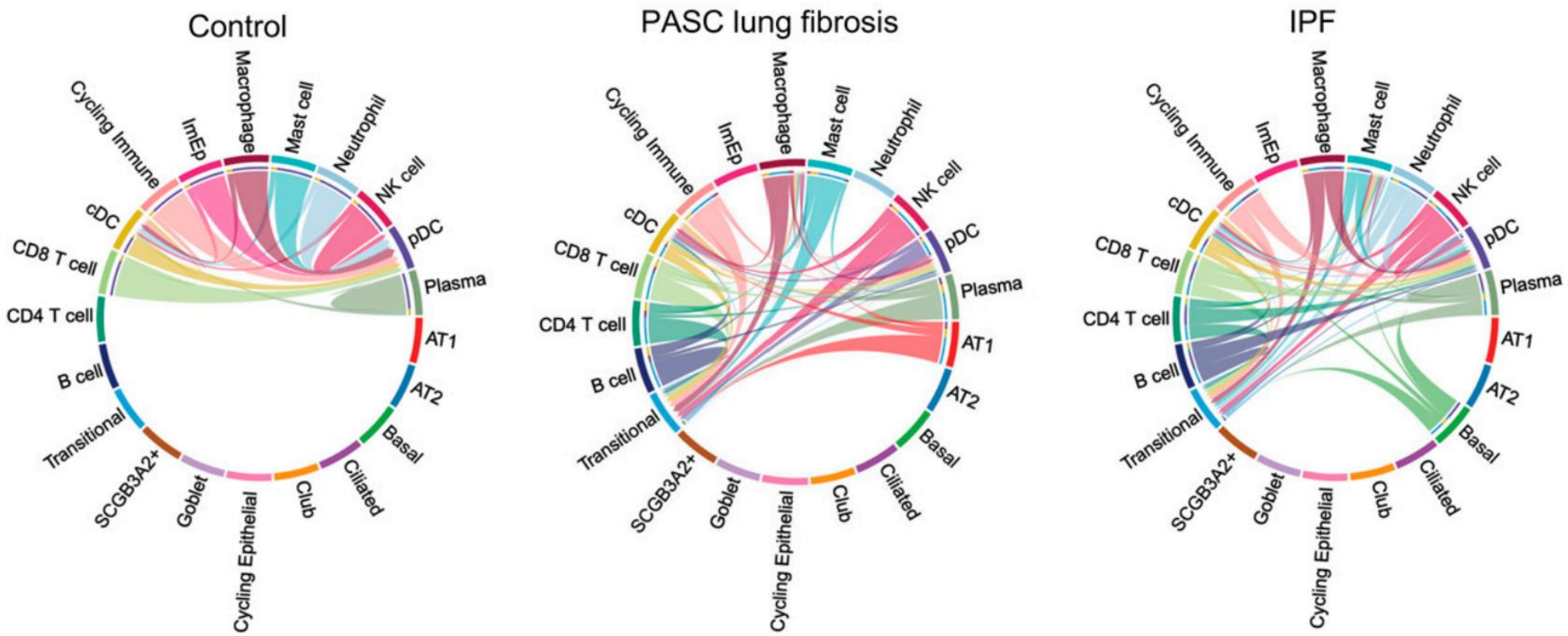
# Cell-cell interactions following tissue injury




*iScience 2020:23, 100841*

# Maladaptive TGF-β Signals to the Alveolar Epithelium Drive Fibrosis after COVID-19 Infection

## Cell–cell communication network of the TGF-b pathway




**PASC:** Post-acute sequelae of severe acute respiratory syndrome coronavirus 2

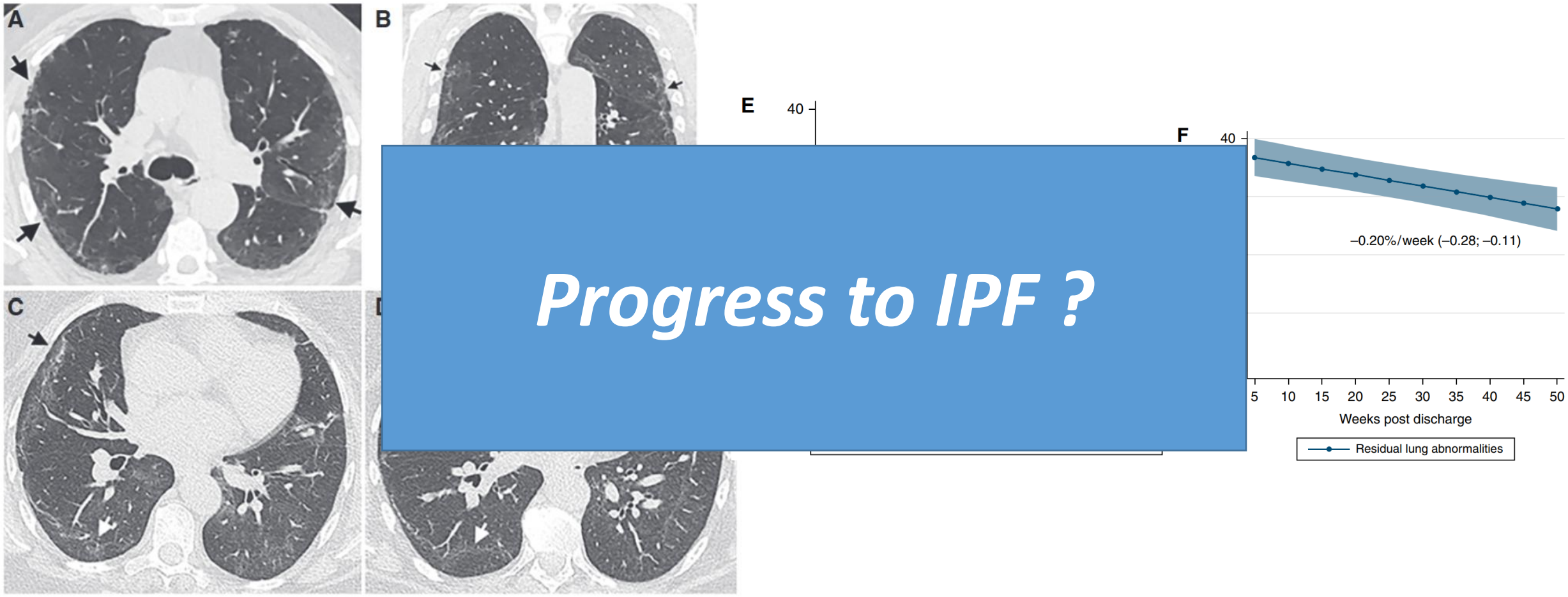
*C. Yao et at., AJRCCM 2023: 208: 2*

# Proposed concept for a continuum of lung fibrosis

| Clinical Phenotype | Normal → | ARDS → | PASC lung fibrosis → | IPF |
|---|---|---|---|---|
| **Histology** | Normal | DAD | NSIP-like | UIP |
| **Fibrosis Continuum** | Normal | Post-inflammatory fibroproliferation | Accelerated Fibrosis | Protracted Fibrosis |
| **Time After Injury** | n/a | Weeks | Months | Years |
| **Cellular Senescence** | - | - | ++ | +++ |
| **TGF-β Signaling** | - | + | ++++ | ++ |
| **Transitional Cells** | - | + | +++ | ++++ |

*C. Yao et at., AJRCCM 2023: 208: 2*

# Residual Lung Abnormalities after COVID-19 Hospitalization




***Progress to IPF ?***

UKILD post-COVID-19 study

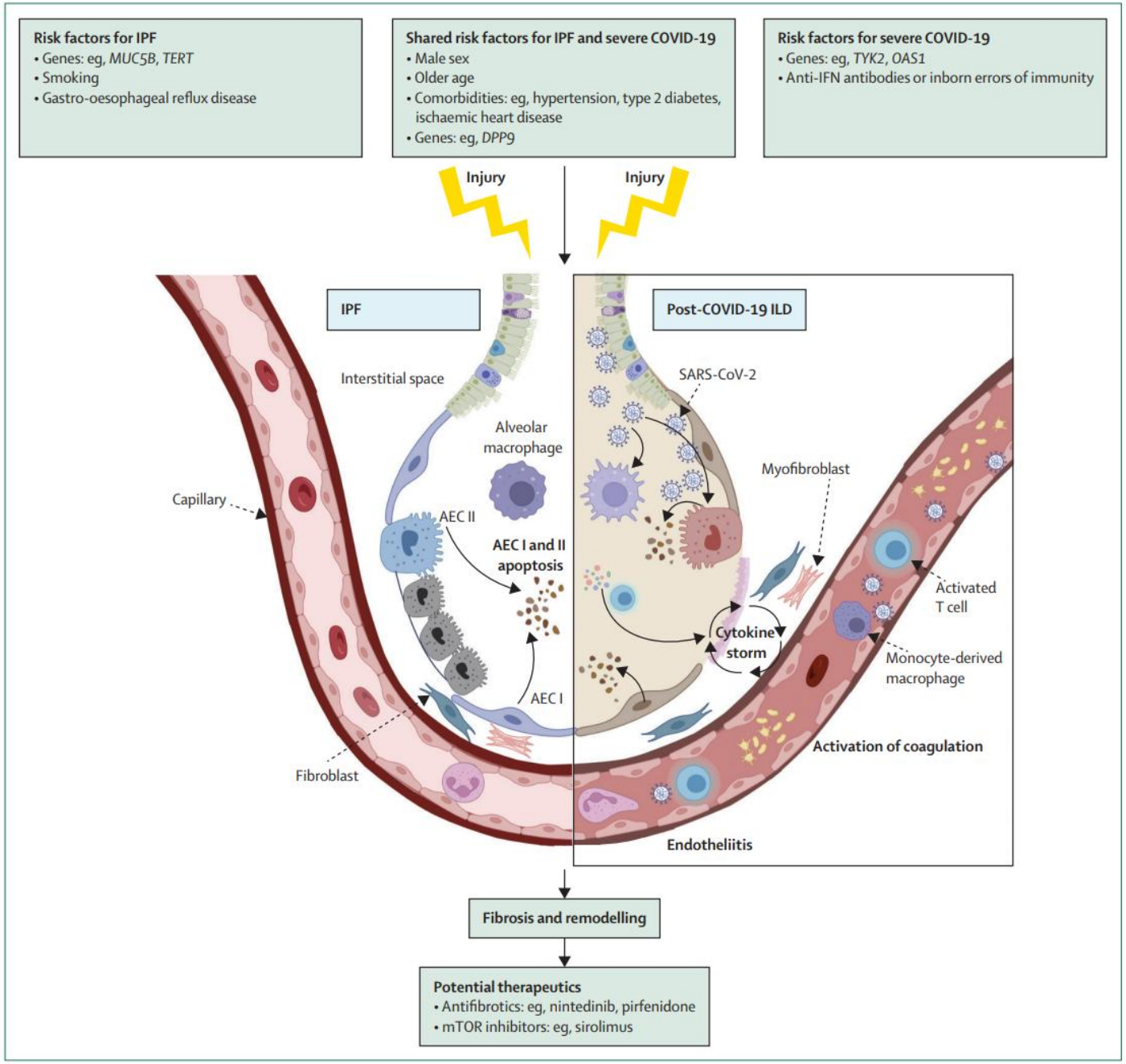
*AJRCCM (2023) 207: 6: 693–703*

# Fibroproliferative ARDS vs. IPF

- Similarities and differences
- Biomarkers
- Therapeutic strategies to stop or reverse fibroproliferation
- Time points (before/after)

# Post-COVID-19 ILD

**Shared risk factors for IPF and severe COVID-19**
- Male sex
- Older age
- Comorbidities: eg, hypertension, type 2 diabetes, ischaemic heart disease
- Genes: eg, *DPP9*

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# Summary

- **Infection-related lung injury**
  - Pathogen-mediated tissue destruction
  - Host immune response

- **Post-infectious pulmonary complications**

- **Parenchymal injury and repair after pulmonary infection**
  - Fibroproliferative ARDS – IPF
  - Senescent transitional cells
  - Aberrant macrophage-fibroblast circuit

- **New approaches needed in managing pulmonary infection**

***Thank you for your attention***