간질성폐질환 코호트에서 미세먼지 건강영향 바이오마커

21th March 2026

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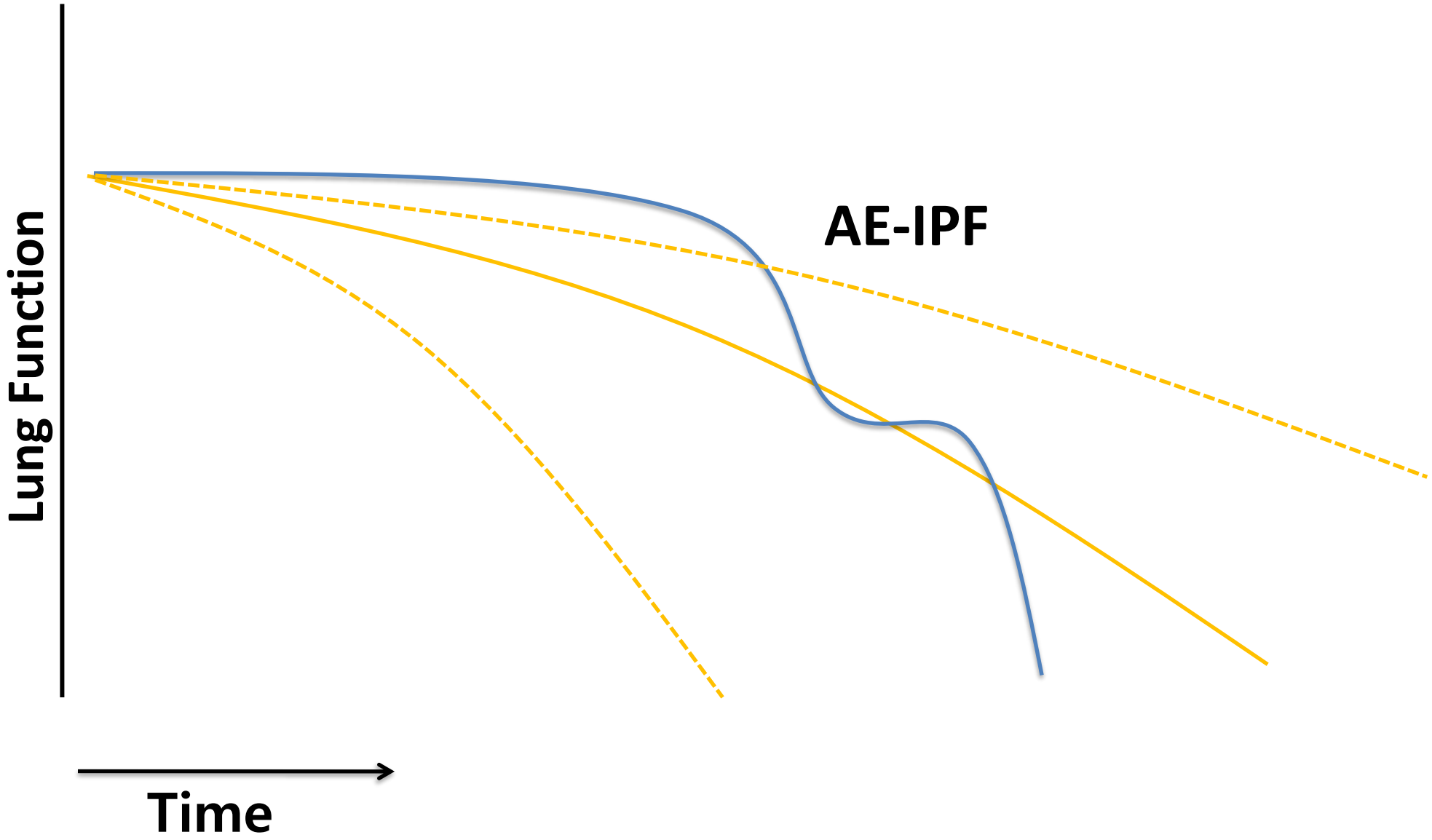
Contents

- Blood biomarkers in IPF
- Biomarker study for progression of IPF related to PM exposure

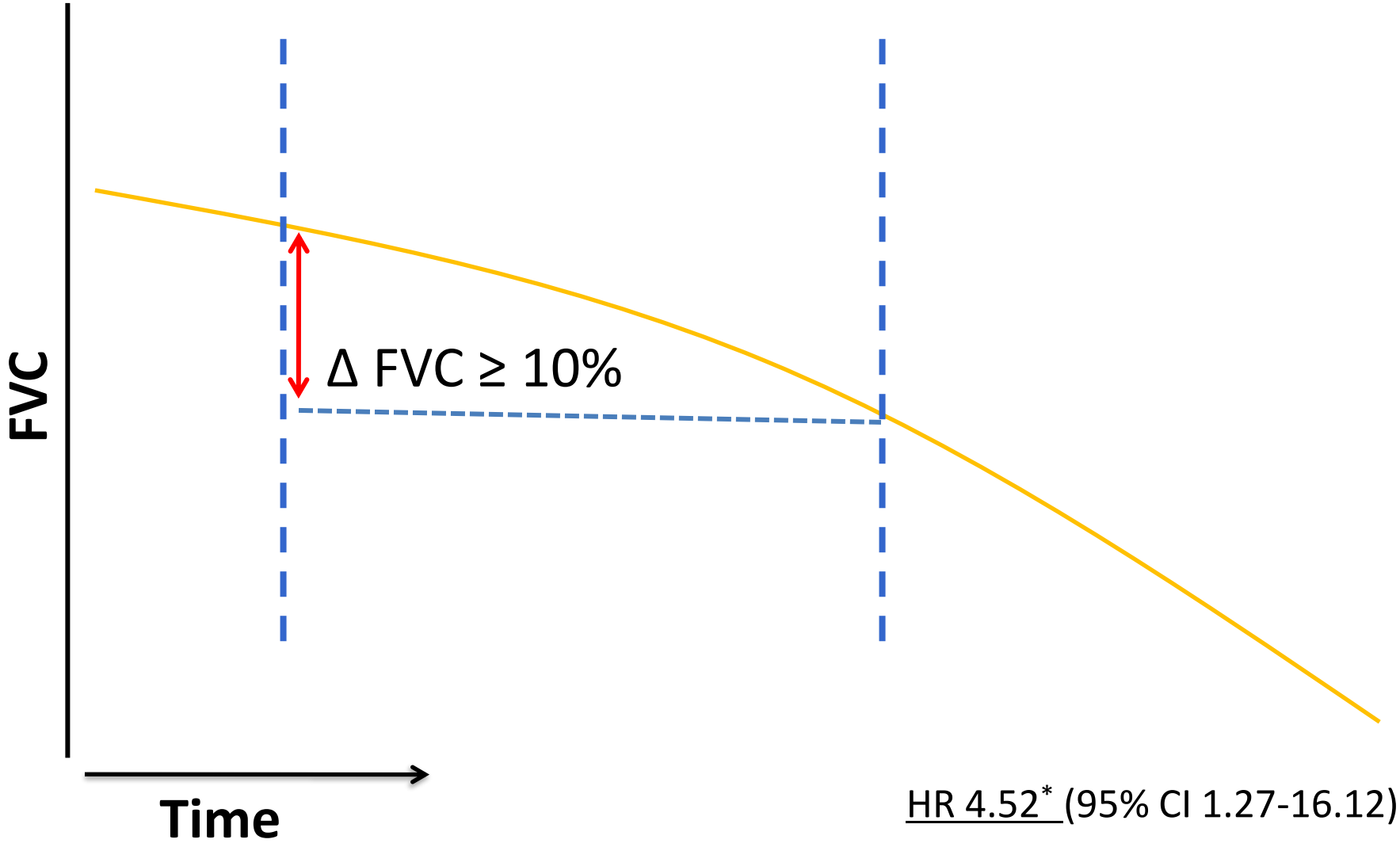
IPF is a progressive fibrosing ILD with a variable course



AE: acute exacerbation

Raghu G et al. *Am J Respir Crit Care Med*. 2011;183:788

Dynamic predictor: change in FVC predicts mortality



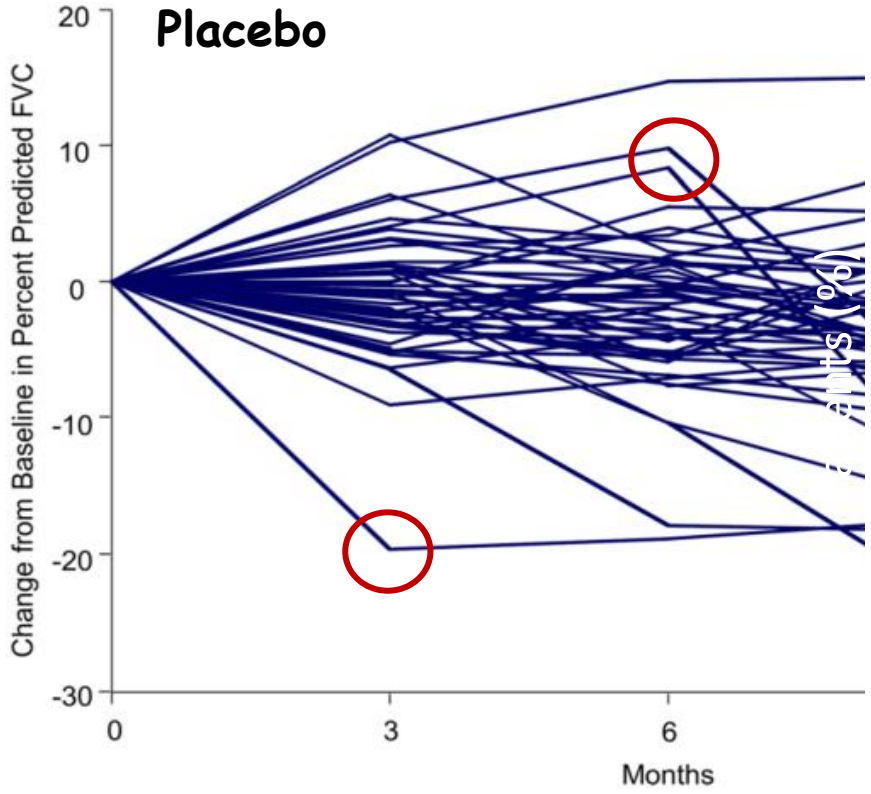
HR 4.52* (95% CI 1.27-16.12)

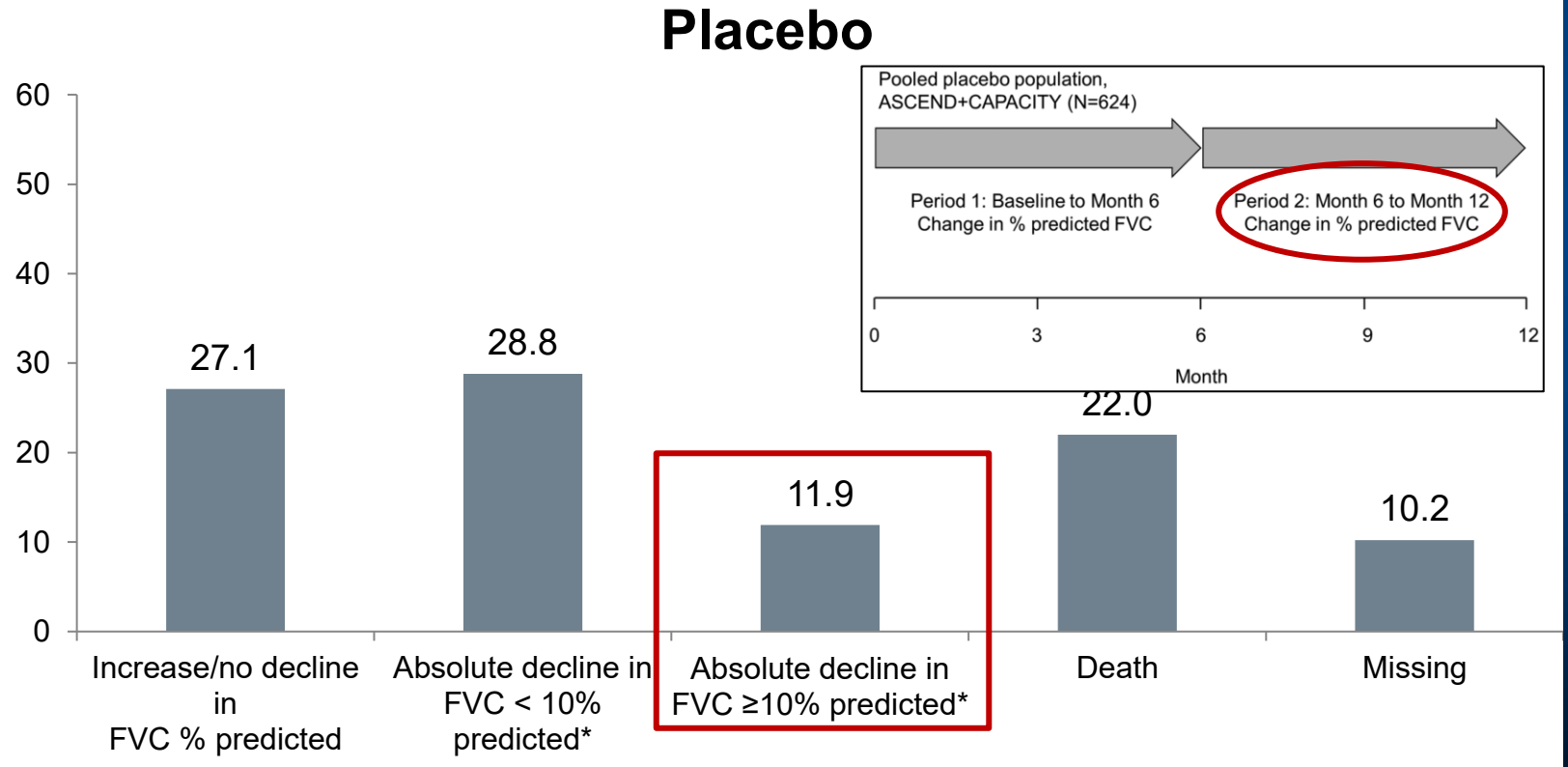
•A two prospective IPF cohorts (N=142), * adjusted for age, gender, oxygen use, FVC and DLCO

Richeldi L et al. *Thorax* 2012;67:407-11

Changes in FVC do not predict subsequent changes in FVC

- Change from baseline to one year in % predicted FVC
- Outcome for subsequent 6 mo. in patients with absolute decline in FVC predicted ≥10% for initial 6 mo.

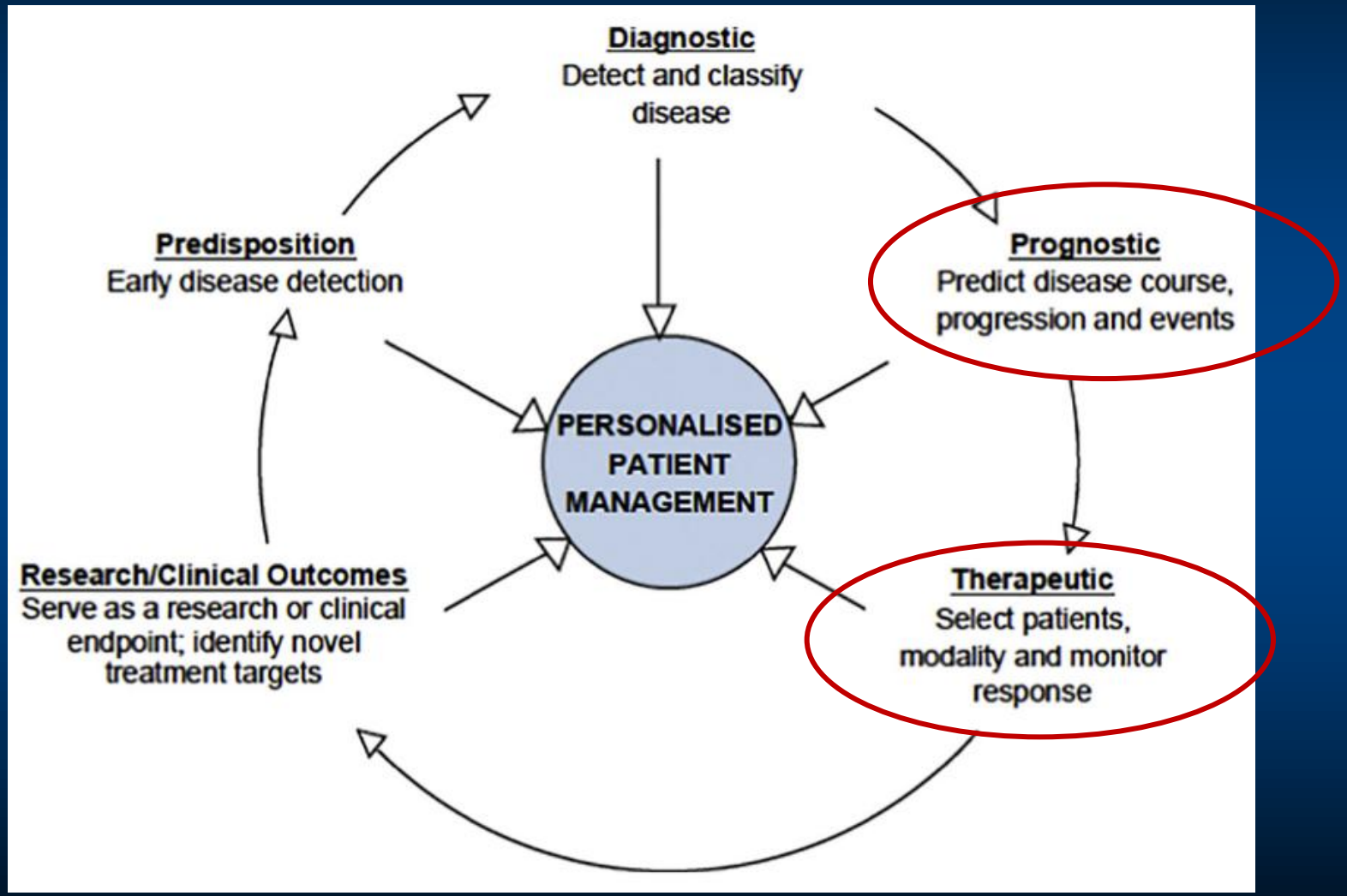




* ASCEND + CAPACITY (N=1247, 50 randomly selected)

Nathan SD et al. *Thorax*, 2016;71:429-435

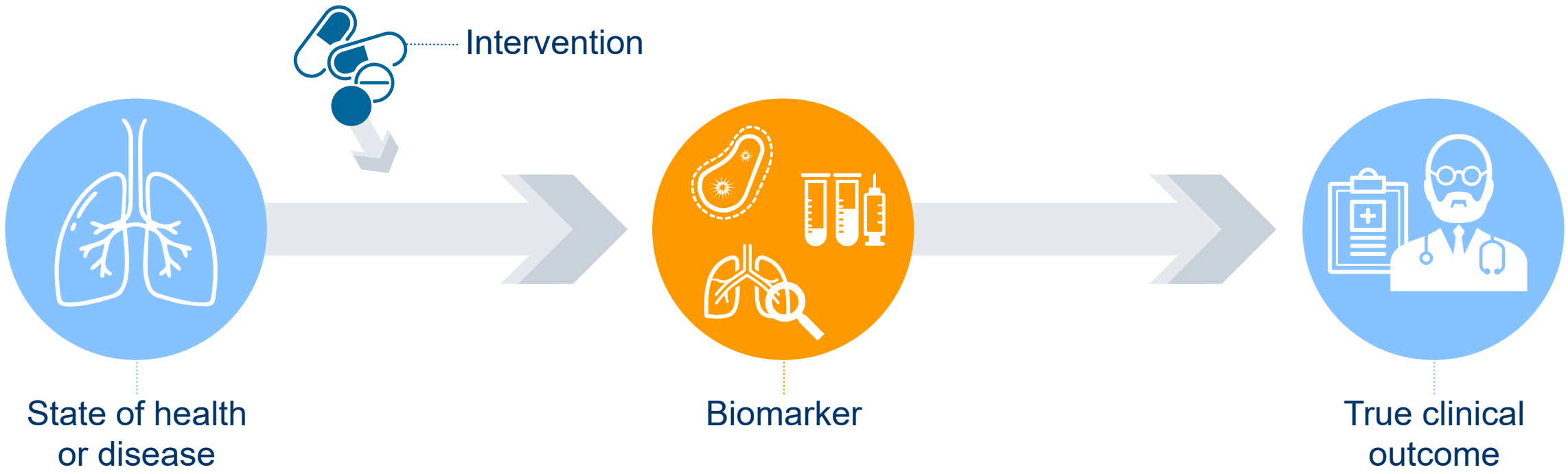
Roles of biomarkers in ILD



Jee AS et al. *Pharmacology & Therapeutics* 2019;202: 40-52

Biomarkers indicate health, disease, or response to therapy

‘A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or pharmacologic responses to a therapeutic intervention’



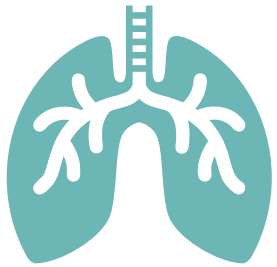
Biomarkers correlate with clinical outcomes; they do not represent the causal pathway of the disease process

Biomarkers Definitions Working Group. *Clin Pharmacol Ther.* 2001 Mar;69(3):89-95; Fleming T. *Health Aff (Millwood).* 2005 Jan-Feb;24(1):67-78.

Biomarkers can be classified by source

Physiologic biomarkers

Derived from imaging patterns or functional tests



Biomarker: UIP pattern on HRCT, or FVC decline ≥10%, indicating progressive lung fibrosis

Genetic biomarkers

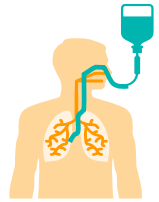
Derived from the mutational status of a gene

Biomarker: *MUC5B* promoter polymorphism indicates increased risk of developing IPF. *TOLLIP* polymorphism are associated with IPF susceptibility, mortality and treatment response to NAC.

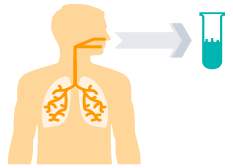
Molecular biomarkers

Molecular biomarkers, such as autoantibodies and other proteins, can be obtained from:

Peripheral blood



BAL fluid



Induced sputum

Devaraj A. *Eur Respir Rev* 2014;23:215–9; Collard H *et al. Am J Respir Crit Care Med* 2003;168:538–42; James C *et al. The Oncologist* 2007;12:142–50; Rekha V & Noth I. *Transl Res* 2012;159:218–27; Pesci A *et al. Respir Med* 2010;104:S70–3; Guiot J *et al. PLoS ONE* 2017;12:e0171344

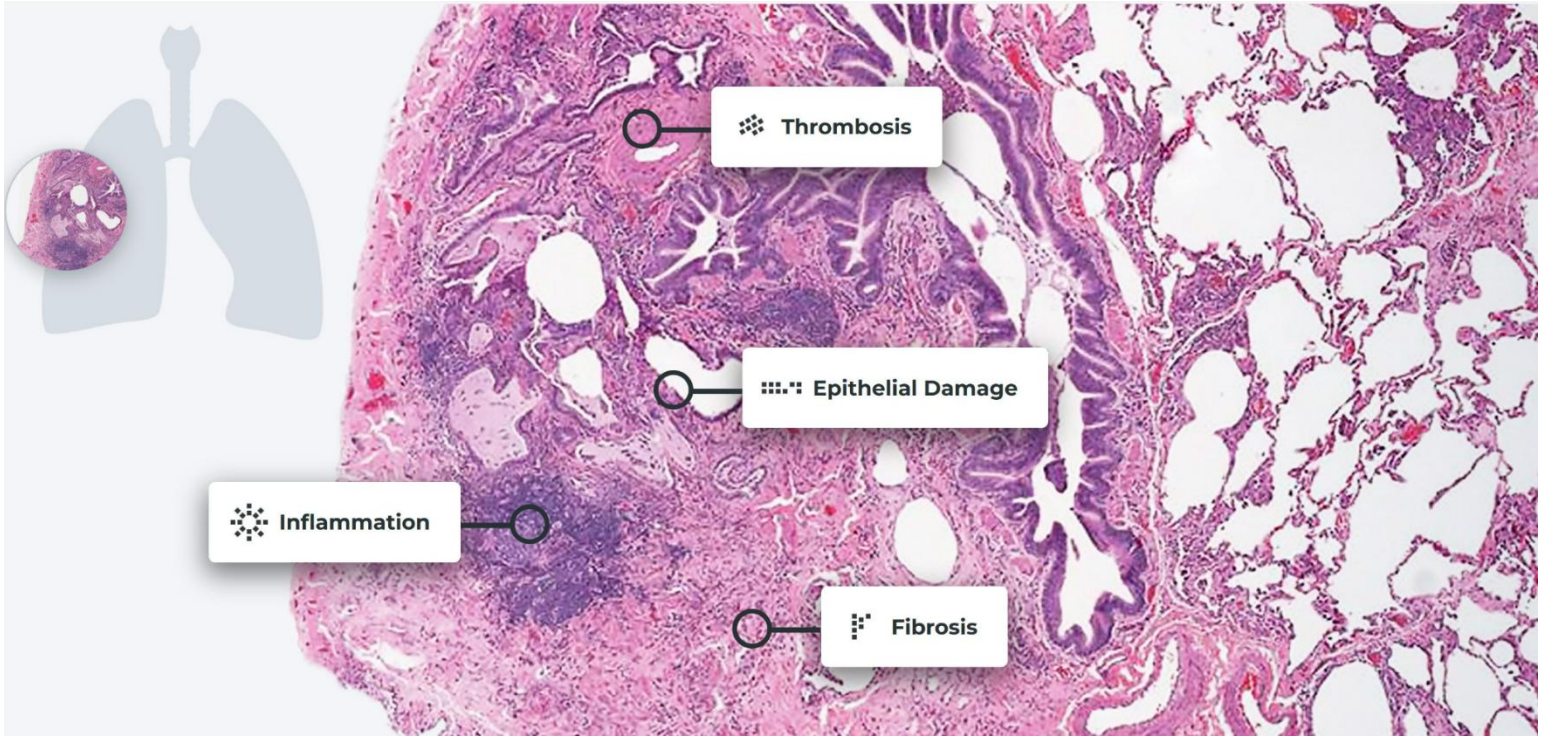
Molecular biomarkers studied in IPF and their potential clinical utility

	Biomarker	Diagnosis	Differential diagnosis	Prognosis	Treatment response
Alveolar epithelial dysfunction	KL-6	+	-	+	+/-
	SP-A	+	+	+	+/-
	SP-D	+	+	+	+/-
	CA 19-9	+	-	+	-
	CA-125	+	-	+	+/-
Fibroproliferation and ECM remodelling	MMP-7	+	+	+	-
	MMP-1	+	+	-	-
	LOXL2	+	-	+	-
	Fibrocytes	+	-	+	-
	Periostin	+	+	+	-
	Osteopontin	+	+	-	-
	ECM neoepitopes			+	
Immune dysfunction	CCL-18	+	-	+	-
	YKL-40	+	-	+	-
	Anti-HSP70	+	-	+	-
	a-defensin	+	-	+	-
	CXCL13	+	-	+	-

Drakopanagiotakis F et al. *Matrix Biol* 2018;68:404-421, Karampitsakos T et al. *eBioMedicine* 2023;95:104766

IPF molecular biomarkers originate from various sources

- PROLIFIC biomarker

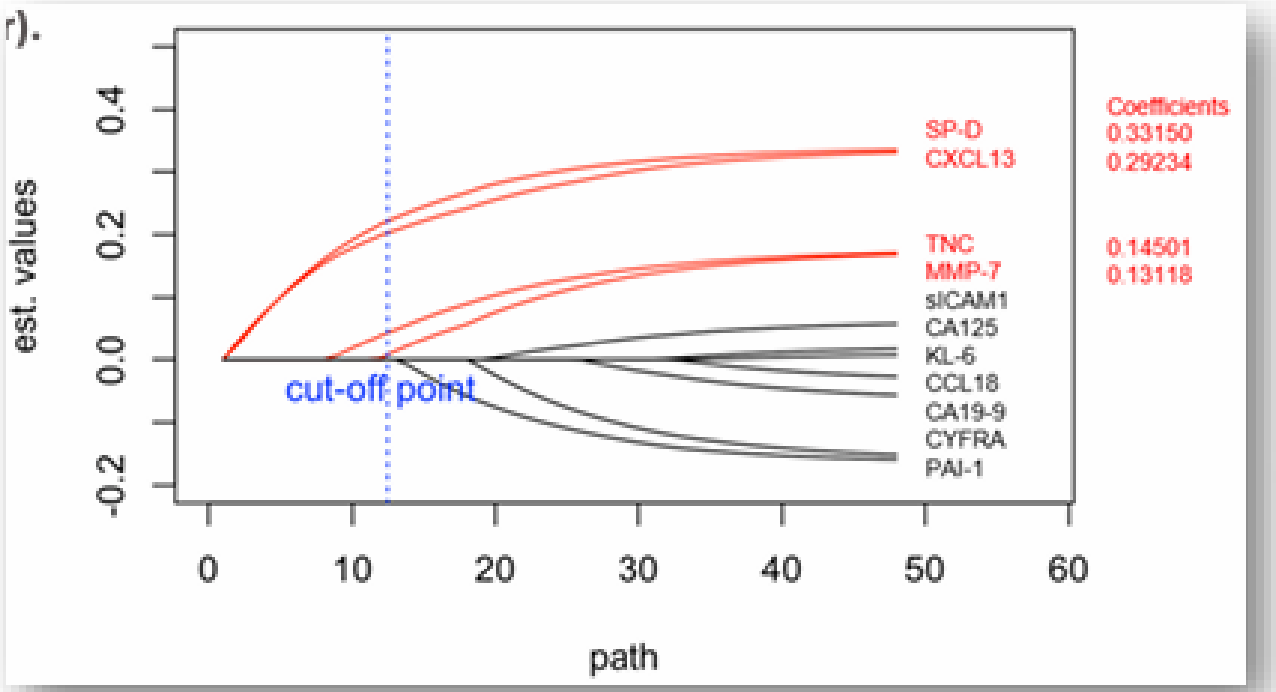


Alveolar epithelial dysfunction	CA-125, CA 19-9, CYFRA 21-1, SP-D, KL-6
Fibrosis	MMP-7, Tenascin C
Inflammation	CCL18, CXCL13, sICAM1
Thrombosis	PAI-1

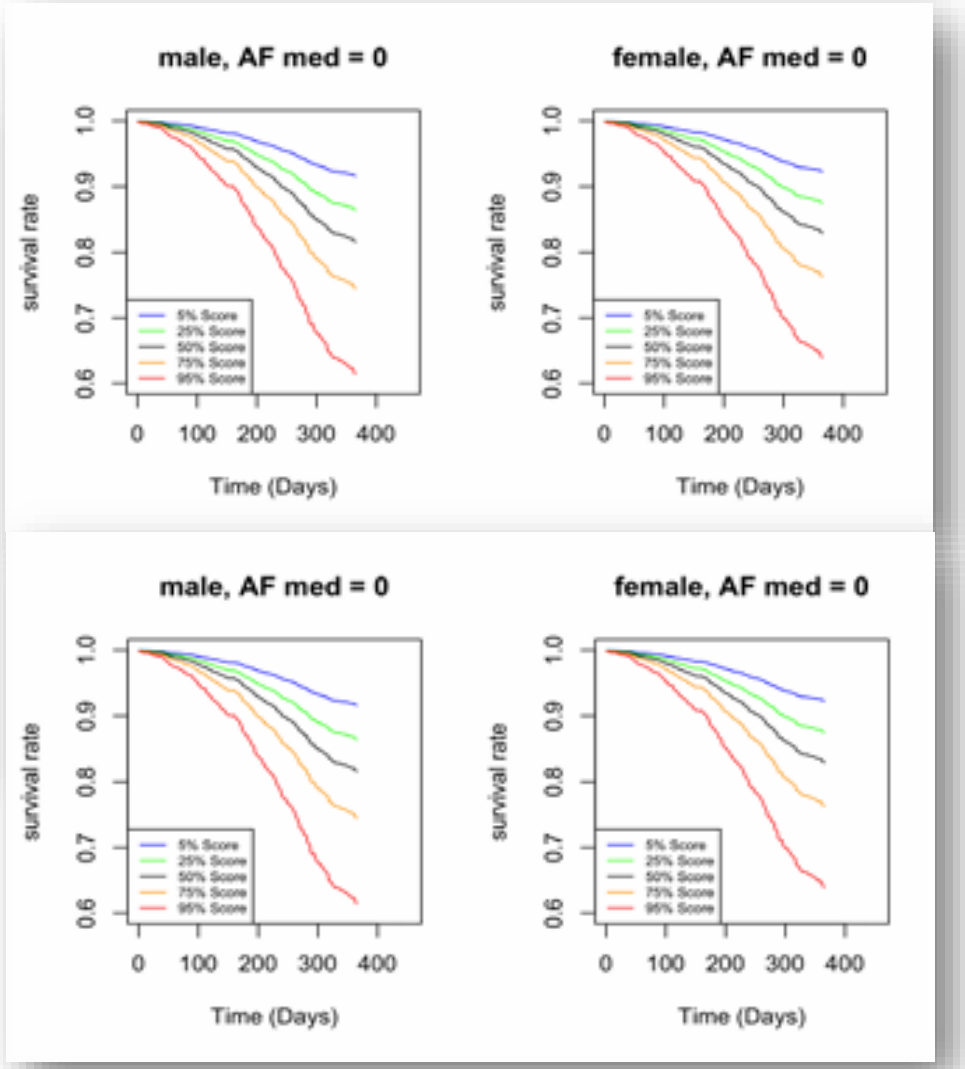
- Prognostic Lung Fibrosis Consortium (PLROLIFIC) risk score for prognosis was approved by FDA Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program

Multi-marker risk score predicts disease progression of IPF

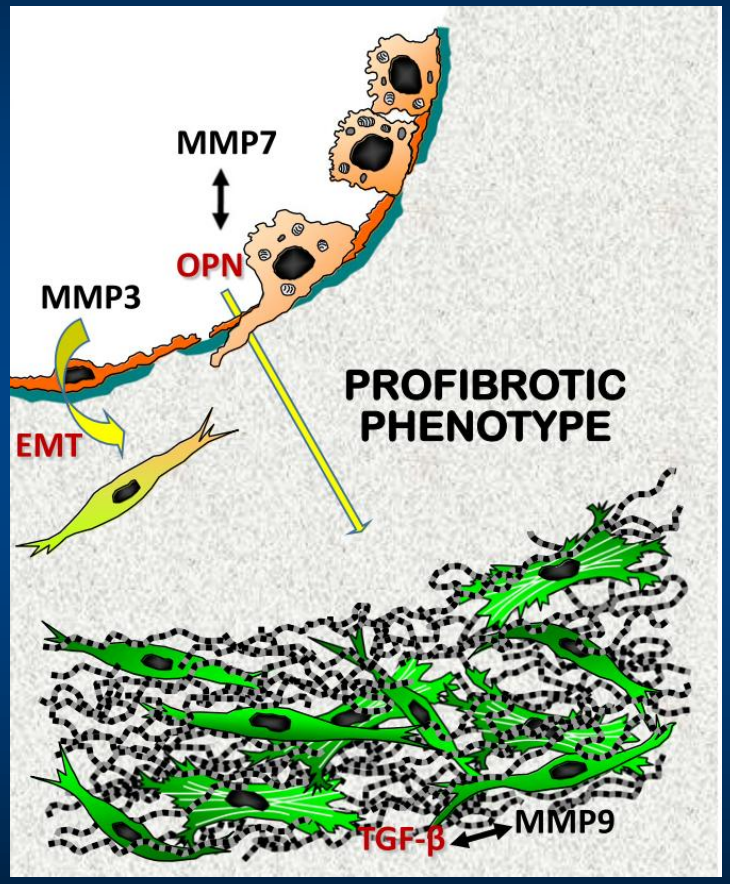
- LASSO logistic regression for <u>disease progression</u> (death, lung transplant, or ≥ 10% decline in % pred. FVC at one year)



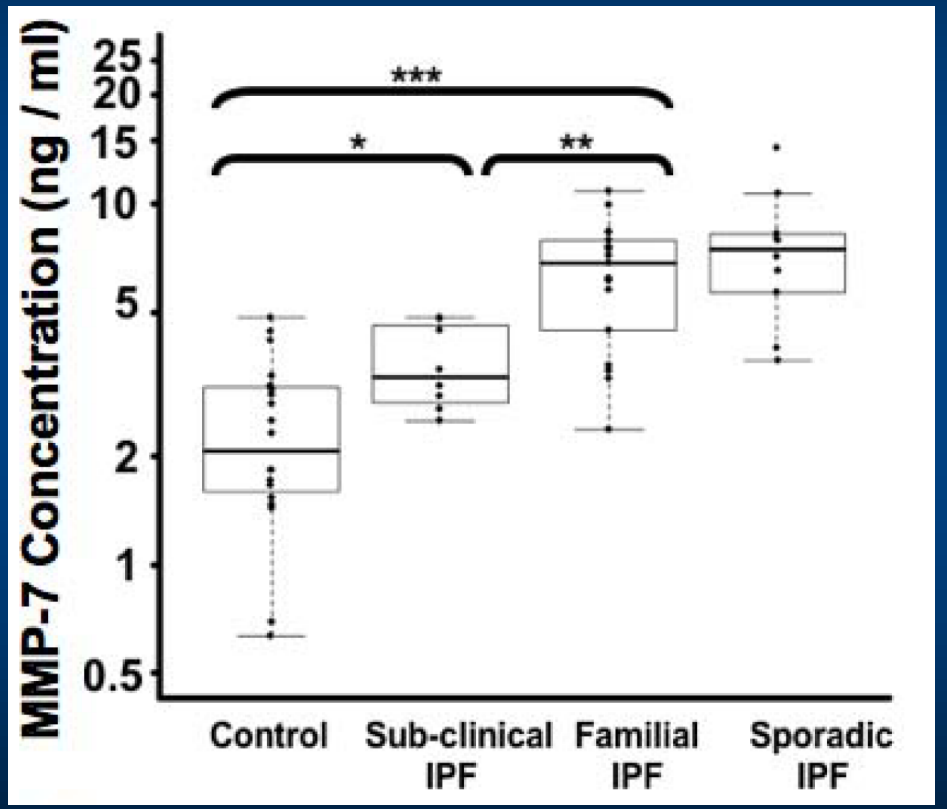
- AUC=0.796, sensitivity=0.752, specificity=0.699



Matrix metalloproteinase in IPF



- Comparison of MMP-7 levels

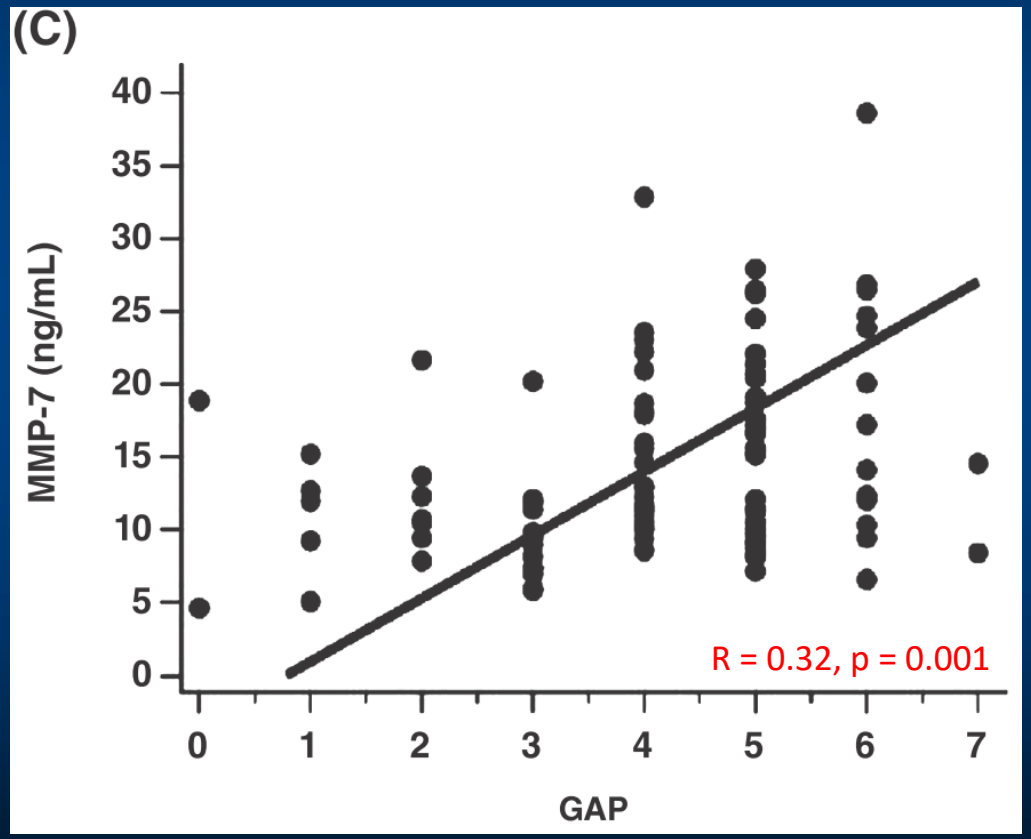


- ECM turnover regulation, activation and degradation of biological mediators
- Single center IPF cohort (n=74)

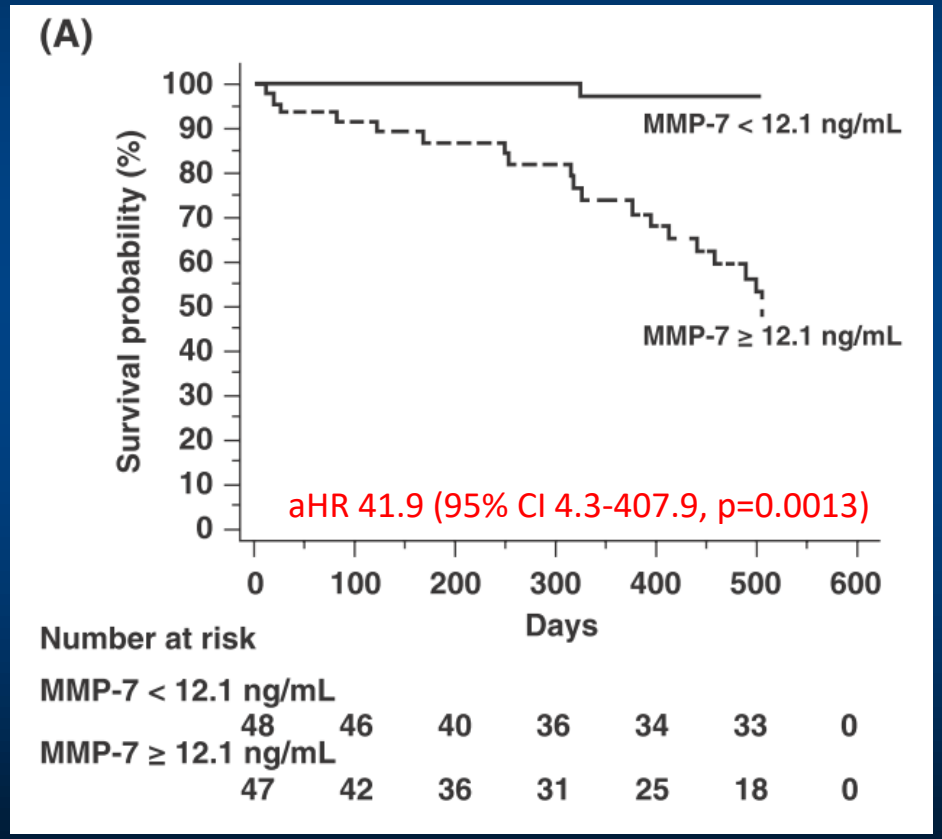
Pardo A et al. *Respir Res* 2016;17:23, Rosas IO et al. *Plos Med* 2008;5(4):e93

Matrix metalloproteinase in IPF

- Correlation with GAP score



- Overall survival

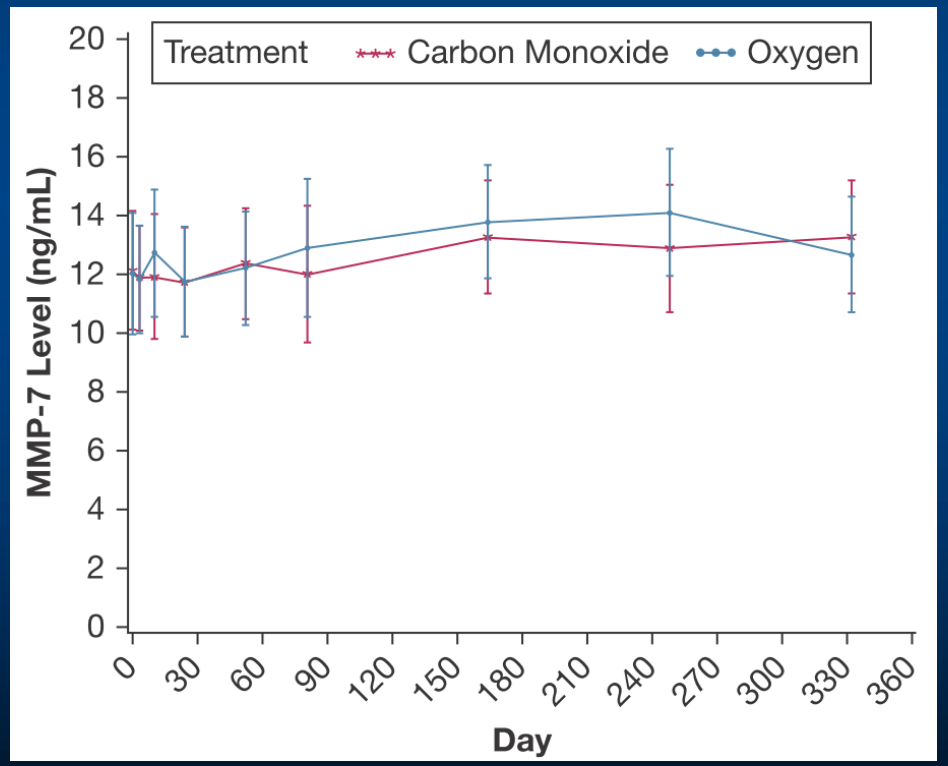


- A retrospective single center IPF cohort study (n = 97)

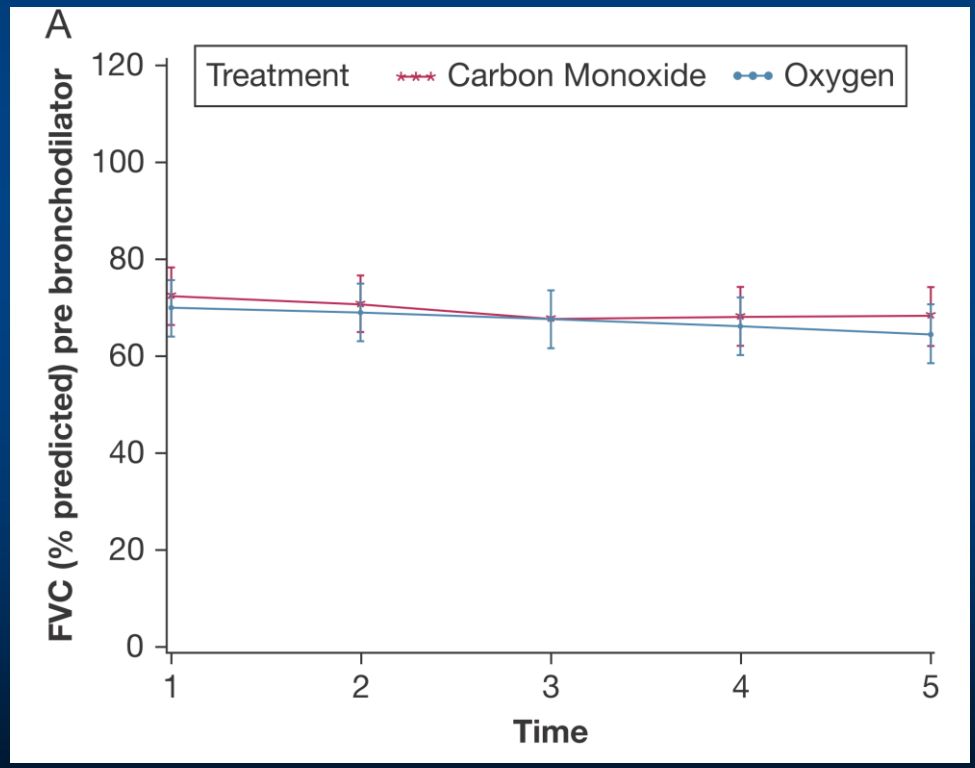
Tzouvelekis A et al. *Respirology* 2017;22:486-493

A Phase II Clinical Trial of Low-Dose Inhaled Carbon Monoxide in Idiopathic Pulmonary Fibrosis

- MMP-7 concentration



- FVC

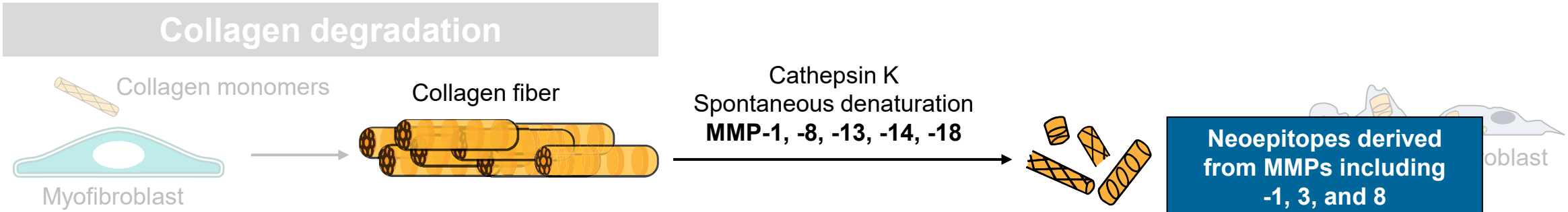


- Phase IIa for IPF (n=58)
- Diffrernce in change in MMP-7 serum concentration after 12 weeks

Rosas IO et al. *Chest* 2018;153(1):94-104

ECM degradation fragments are neoepitopes

MMP-generated protease-generated degradation fragments, known as neoepitopes, are released into the circulation during ECM turnover



Neoepitopes may better reflect <u>local inflammation</u> than their parent proteins and provide more accurate diagnostic and prognostic markers in fibrosing lung diseases

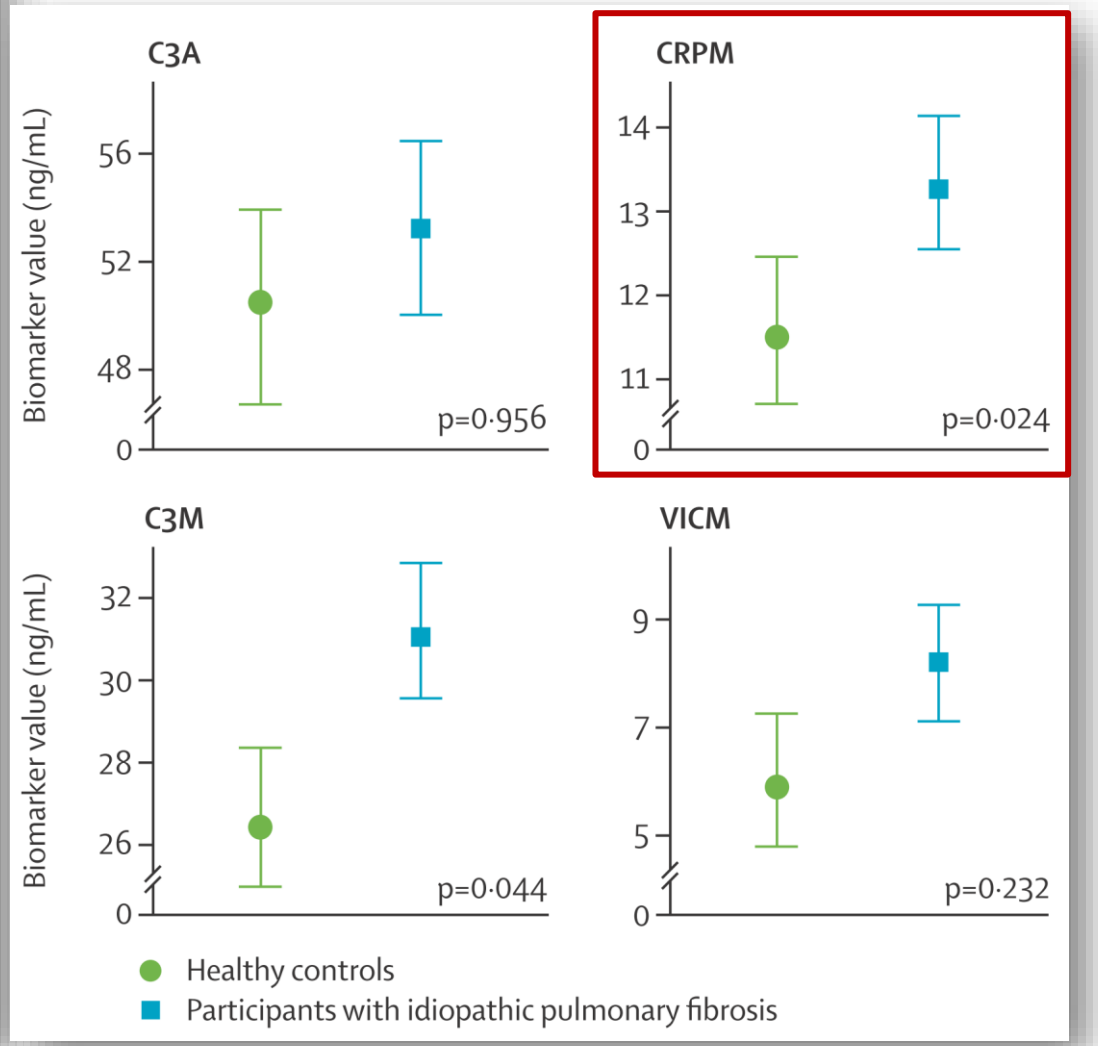
Jenkins R *et al. Lancet Respir Med* 2015;3:462–72; Karsdal M *et al. Biomarkers* 2009;14:181–202; Skjøt-Arkil H *et al. Clin Exper Rheumatol* 2012;30:371–9; McKleroy W *et al. Am J Physiol Lung Cell Mol Physiol* 2013;304:L709–21

PROFILE: baseline levels of neoepitopes

Collagen degradation biomarkers

Assay name	Assay description
C1M	Neo-epitope of MMP-2,9,13 mediated degradation of type I collagen
C2M	Neo-epitope of MMP mediated degradation of type II collagen
T2CM	Neo-epitope of MMP-1 and -13 mediated degradation of type II collagen
C3M	Neo-epitope of MMP-9 mediated degradation of type III collagen
urine C3M	Neo-epitope of MMP-9 mediated degradation of type III collagen
C3A	Neo-epitope of ADAMTS-4,5 mediated degradation of type III collagen
C3C	Neo-epitope of cathepsin-B,L,S mediated degradation of type III collagen
C4M	Neo-epitope of MMP-2,9,12 mediated degradation of type IV collagen alpha 1 chain
C4Ma3	Neo-epitope of MMP-2,9,12 mediated degradation of type IV collagen alpha 3 chain
TUM	MMP-9 mediated release of tumstatin from type IV collagen alpha 3 chain
urine C4M	Neo-epitope of MMP-2,9,12 mediated degradation of type IV collagen alpha 1 chain
C4G	Neo-epitope of granzyme B mediated degradation of type IV collagen
C5M	Neo-epitope of MMP-2,9 mediated degradation of type V collagen
C6M	Neo-epitope of MMP-2 mediated degradation of type VI collagen
C6Ma3	Neo-epitope of MMP-9 mediated degradation of type VI collagen
C7M	Neo-epitope of type MMP-13 mediated decradation of type VII collagen
C10C	Neo-epitope of cathepsin-K mediated decradation of type X collagen
Col10NC	Neo-epitope of the NC domain of type X collagen
CTX-I	Neo-epitope of cathepsin mediated degradation of type I collagen
CTX-II (Urine)	Neo-epitope of MMP mediated degradation of type II collagen
CTX-III	Cross-linked type III collagen C-terminal telopeptide

- Baseline comparison of neoepitope levels



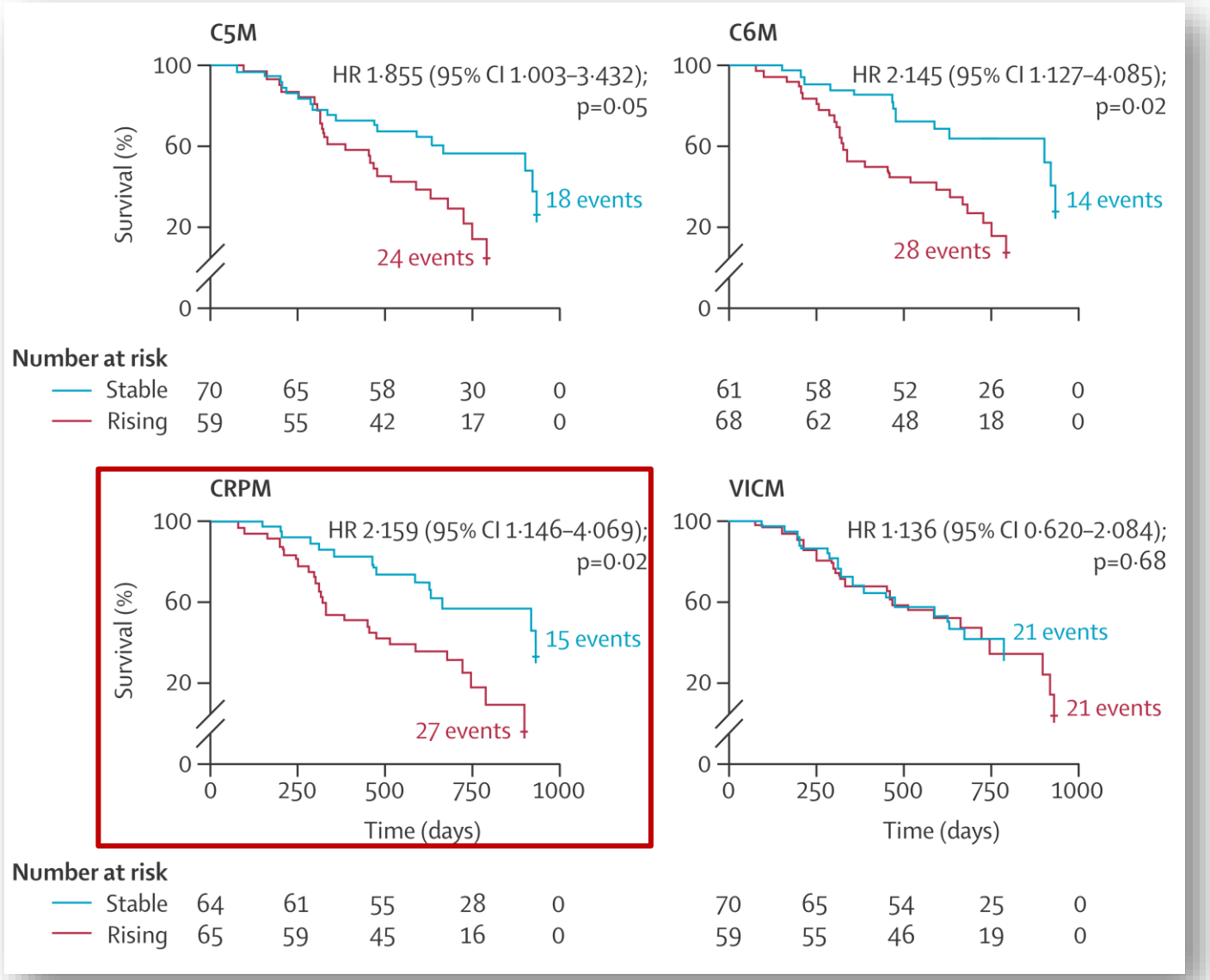
* CRPM: c-reactive protein degraded by MMP-1/8; C3M: collagen 3 degraded by MMP-9

•A prospective multicenter IPF cohort (n = 189)

Jenkins RG et al. *Lancet Repir Med* 2015;3:462-72

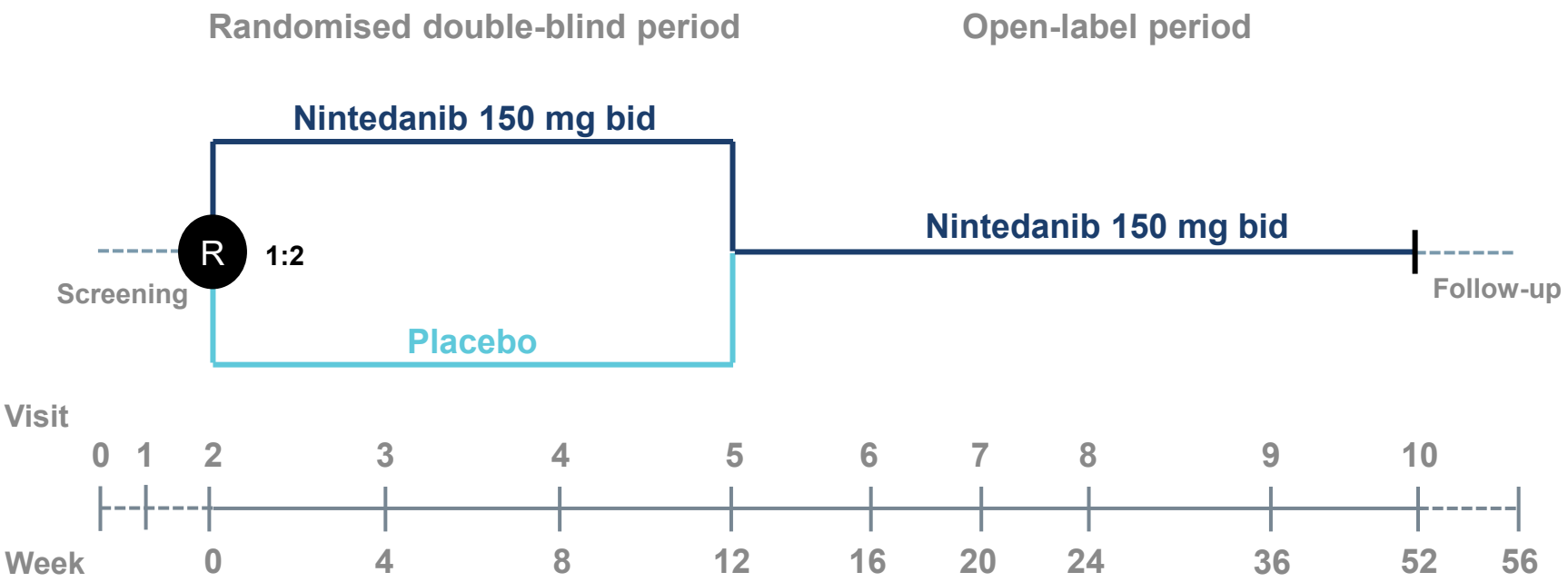
PROFILE: effect of 3M-change in neoepitopes levels on overall survival

- Overall survival



Jenkins RG et al. *Lancet Repir Med* 2015;3:462-72

INMARK trial - design



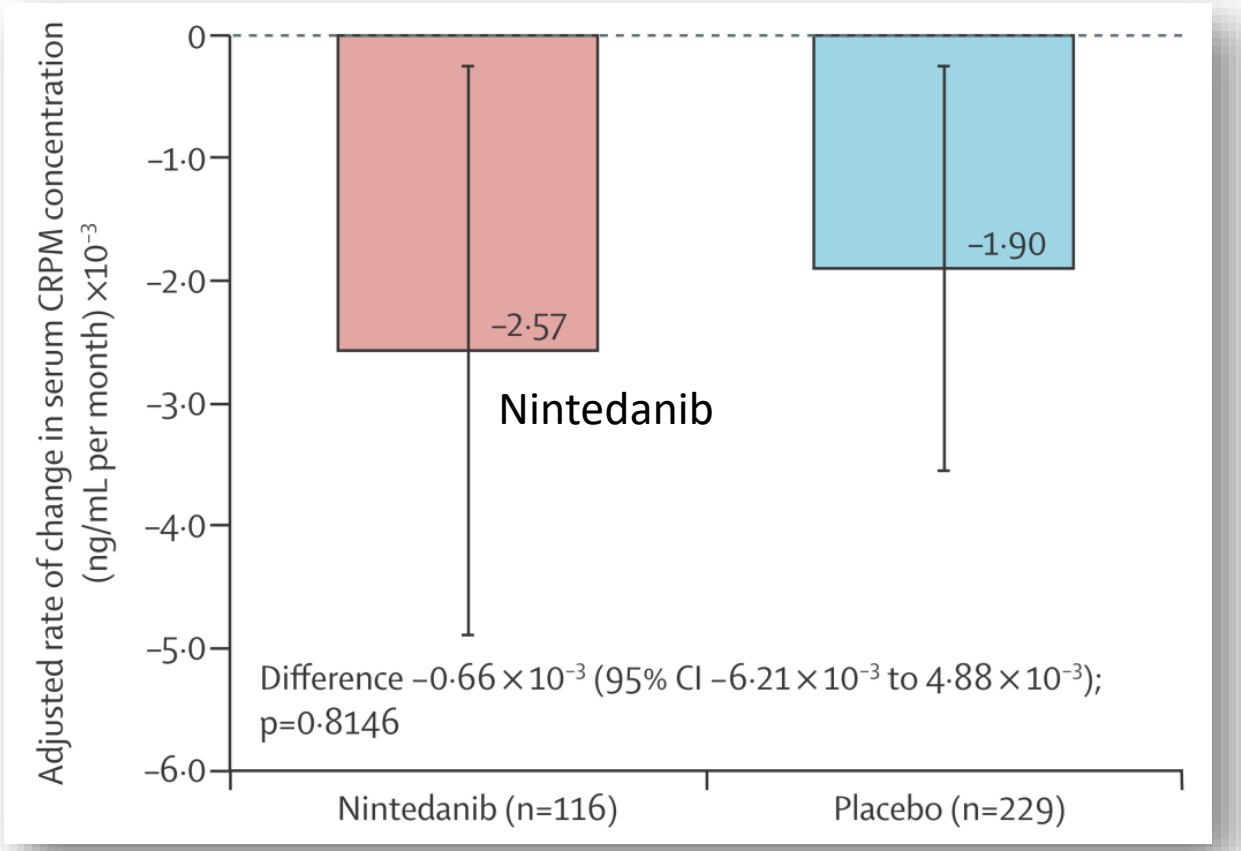
- Double <u>blinded for 12wks</u>, followed by open-label period for 40 wks (IPF, n=347)
- Rate of <u>change in serum CRPM</u> (ng/mL/month) from baseline to week 12

* CRPM: c-reactive protein degraded by MMP-1/8

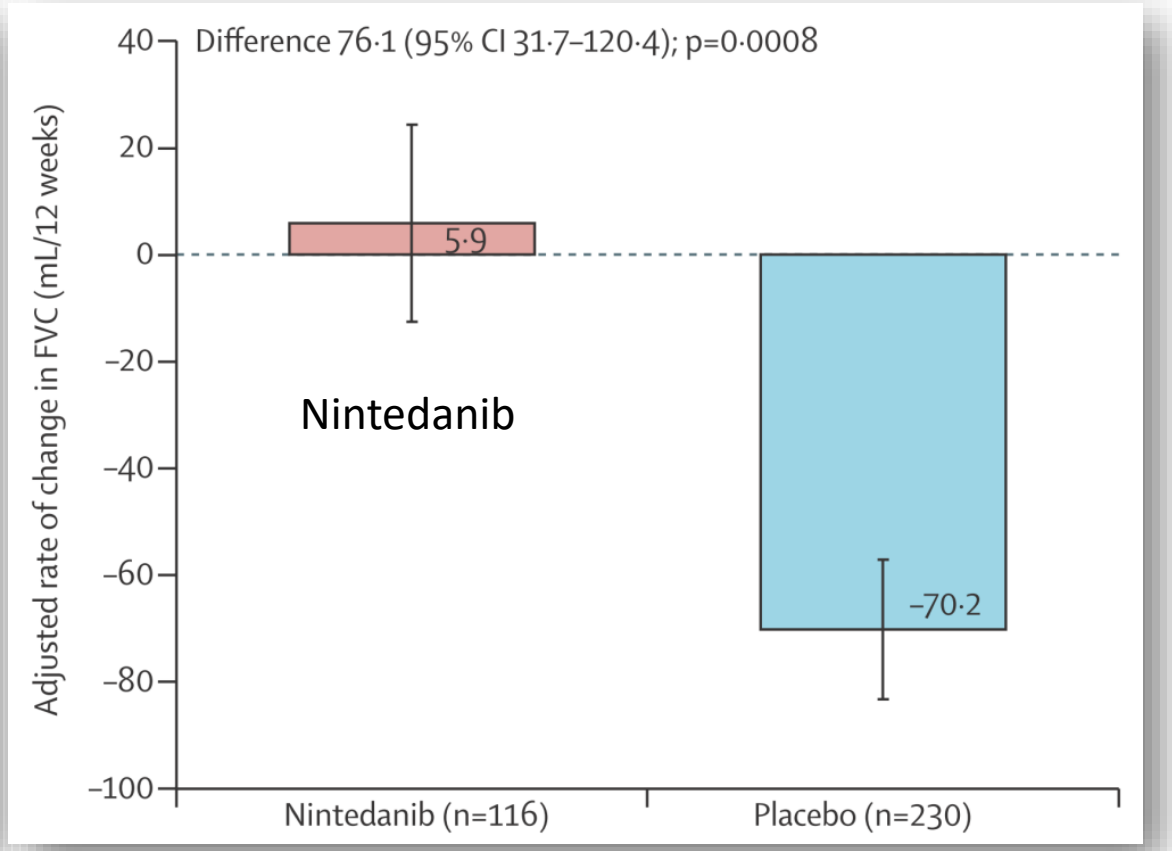
Maher TM et al. *Lancet Repir Med* 2019;7:771-79

INMARK trial - results

- Rate of change in serum CRPM over 12weeks



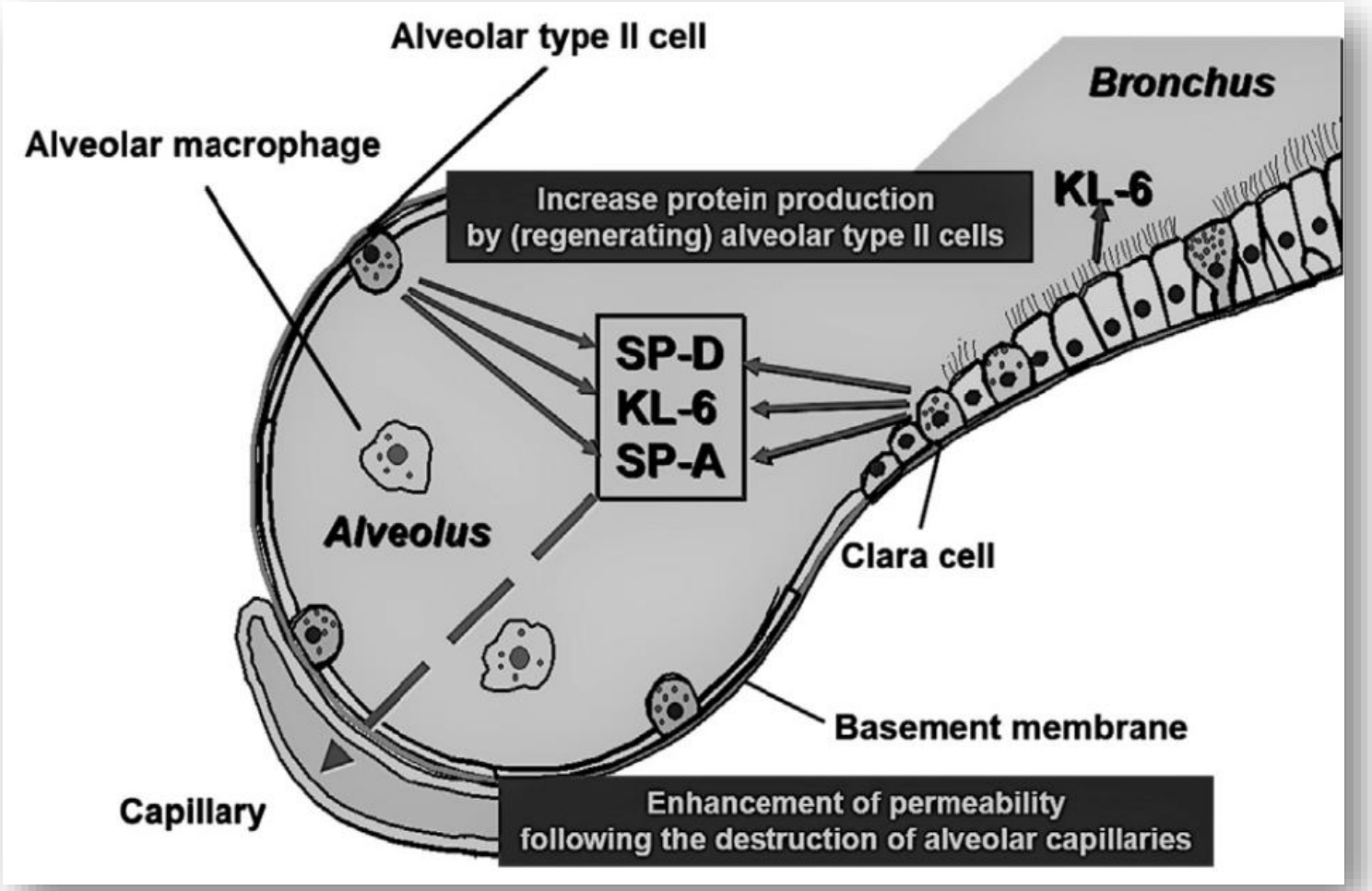
- Rate of change in FVC over 12 weeks



* CRPM: c-reactive protein degraded by MMP-1/8; C3M: collagen 3 degraded by MMP-9

Maher TM et al. *Lancet Repir Med* 2019;7:771-79

Marker of alveolar epithelial injury

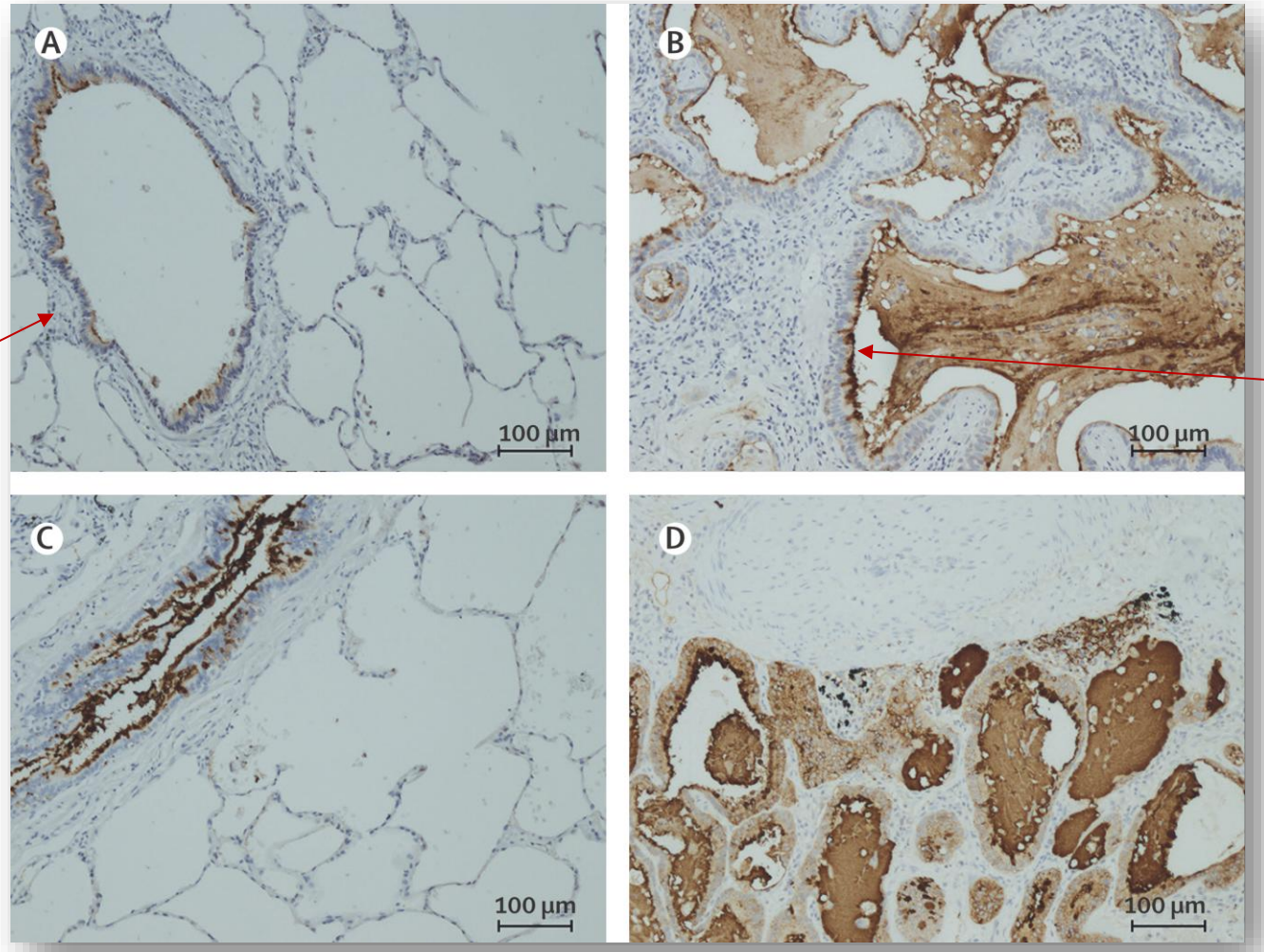


- KL-6: mucin-like, high molecular weight glycoprotein (MUC1) – profibrotic effect
- SP-A, SP-D: lipoprotein complexes– host defense

Chiba H et al. *Respiratory Investigation* 2018;56:384-391

CA-125, CA 19-9: marker of alveolar epithelial injury

- Control (non-IPF)
- IPF



CA-125

CA 19-9

bronchial epithelium

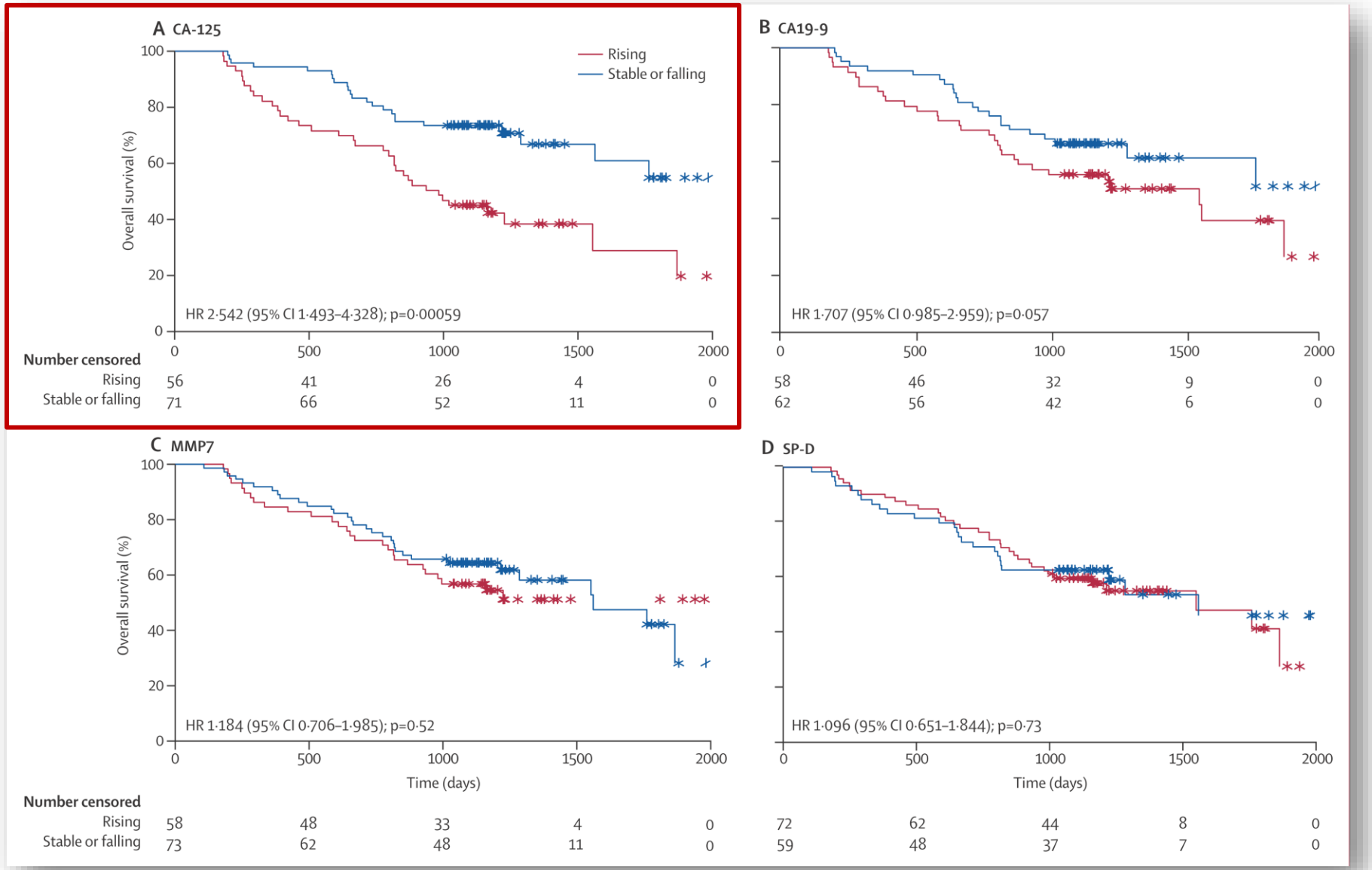
Metaplastic alveolar epithelium
Mucus secretion

• CA-125: cancer antigen 125, CA 19-9: cancer antigen 19-9

Maher TM et al. *Lancet Repir Med* 2017;5:946-55

Risk of overall mortality by biomarker concentration at 3M

- Overall survival

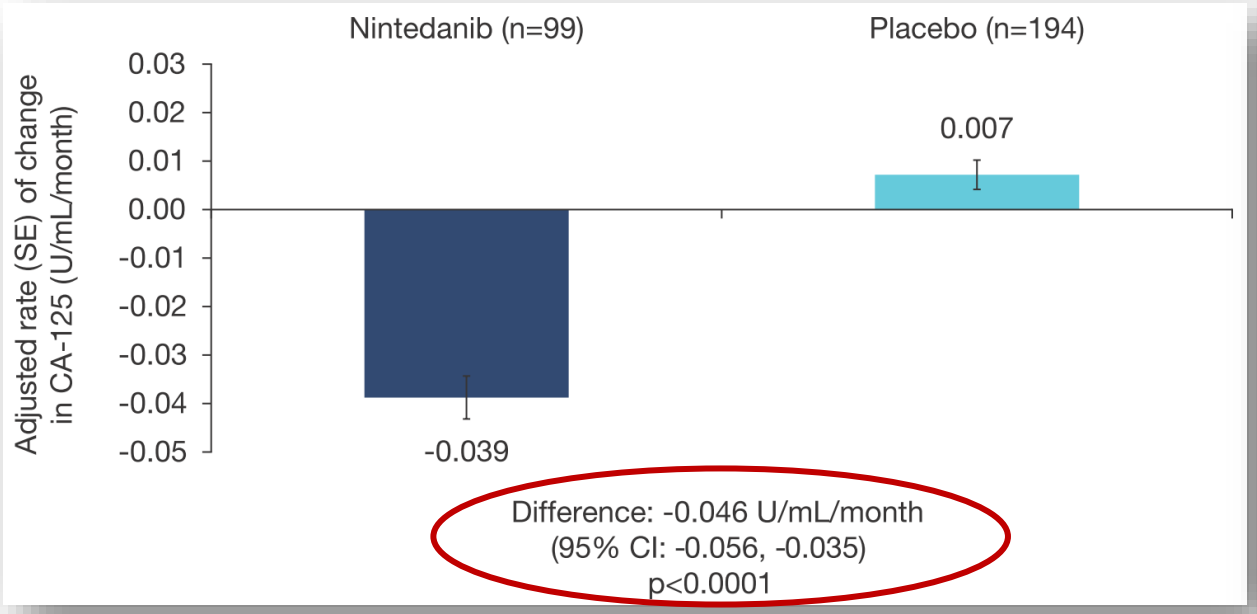


- Adjusted for age, sex, and smoking status

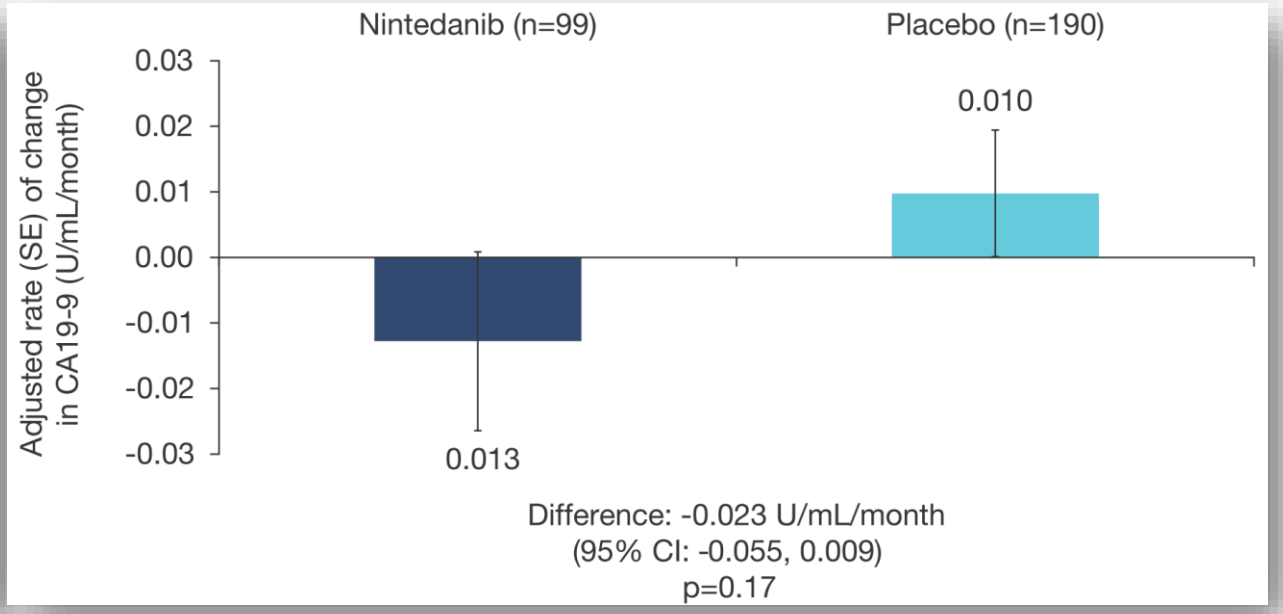
Maher TM et al. *Lancet Repir Med* 2017;5:946-55

INMARK: Effect of nintedanib on markers of epithelial damage in IPF

- Change in CA-125 over 12 weeks



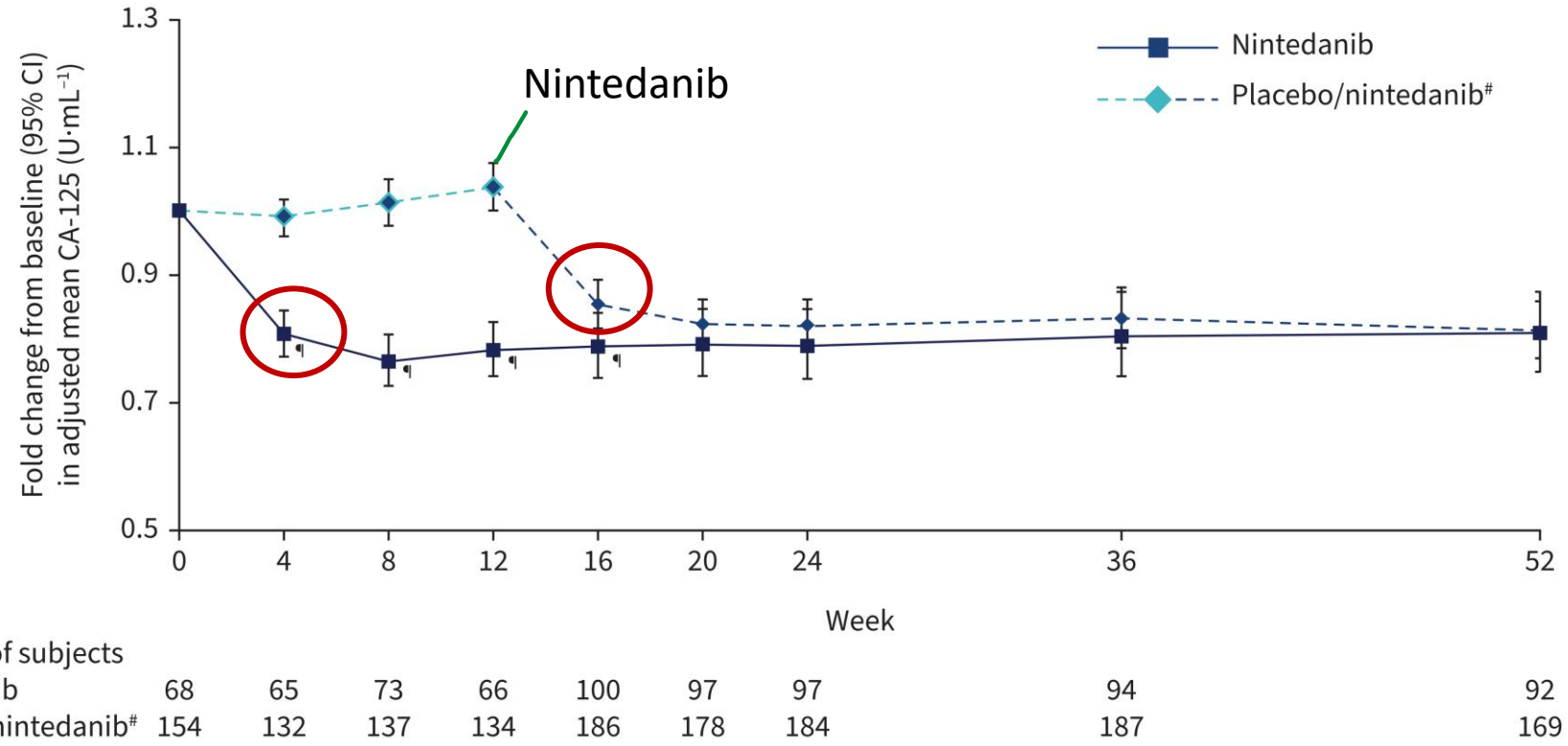
- Change in CA 19-9 over 12 weeks



Jenkins RG et al. *Eur Respir J* 2020;56:Suppl 64, 5187

Change of marker of epithelial injury: CA-125

- Fold changes from baseline in CA-125 over 52 weeks

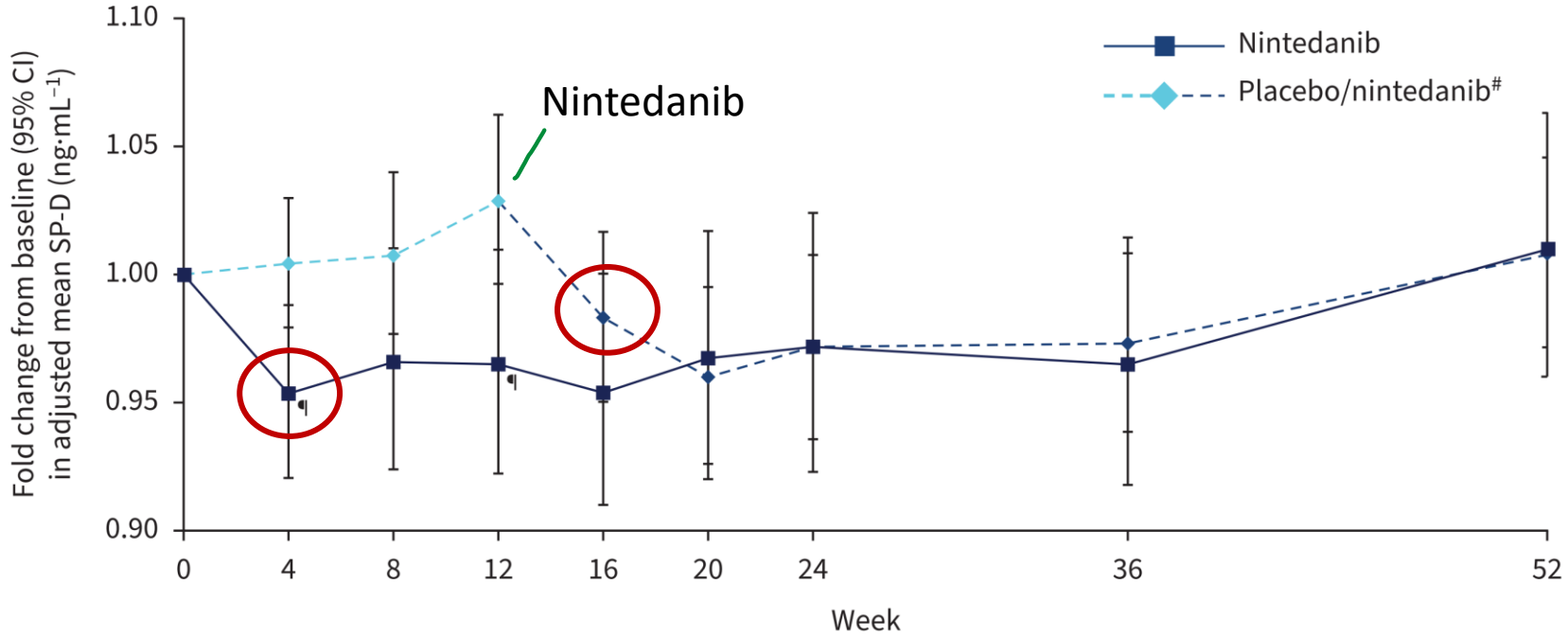


• CA-125: cancer antigen 125

Jenkins RG et al. *ERJ Open Res* 2024;10:00558-2023

Change of marker of epithelial injury: SP-D

- Fold changes from baseline in SP-D over 52 weeks



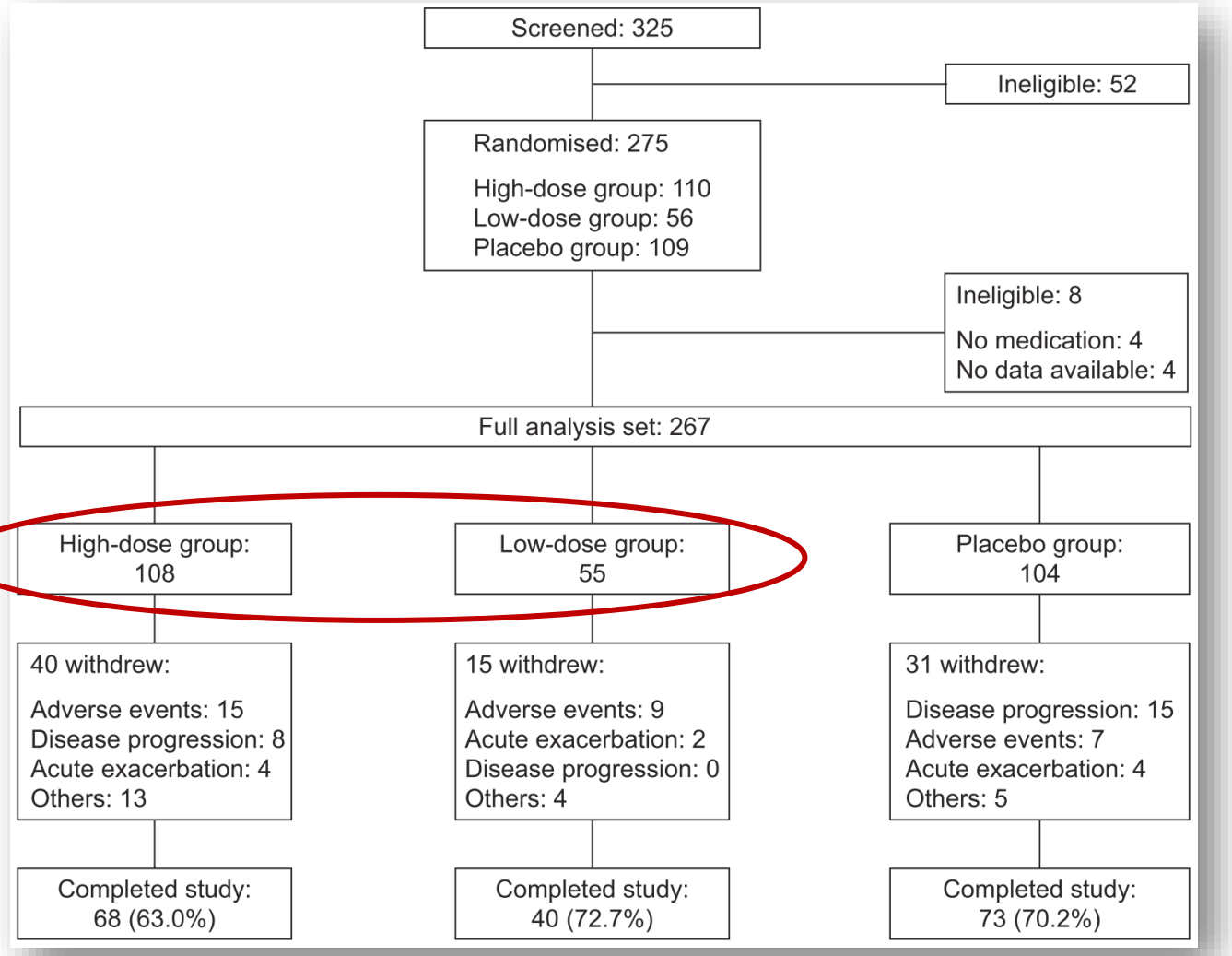
Number of subjects									
Nintedanib	115	114	112	109	111	107	105	103	98
Placebo/nintedanib#	228	227	223	221	211	204	206	199	185

• SP-D: surfactant protein D

Jenkins RG et al. *ERJ Open Res* 2024;10:00558-2023

Shionogi trial: SP-D as a theragnostic biomarker of pirfenidone in IPF

Pirfenidone



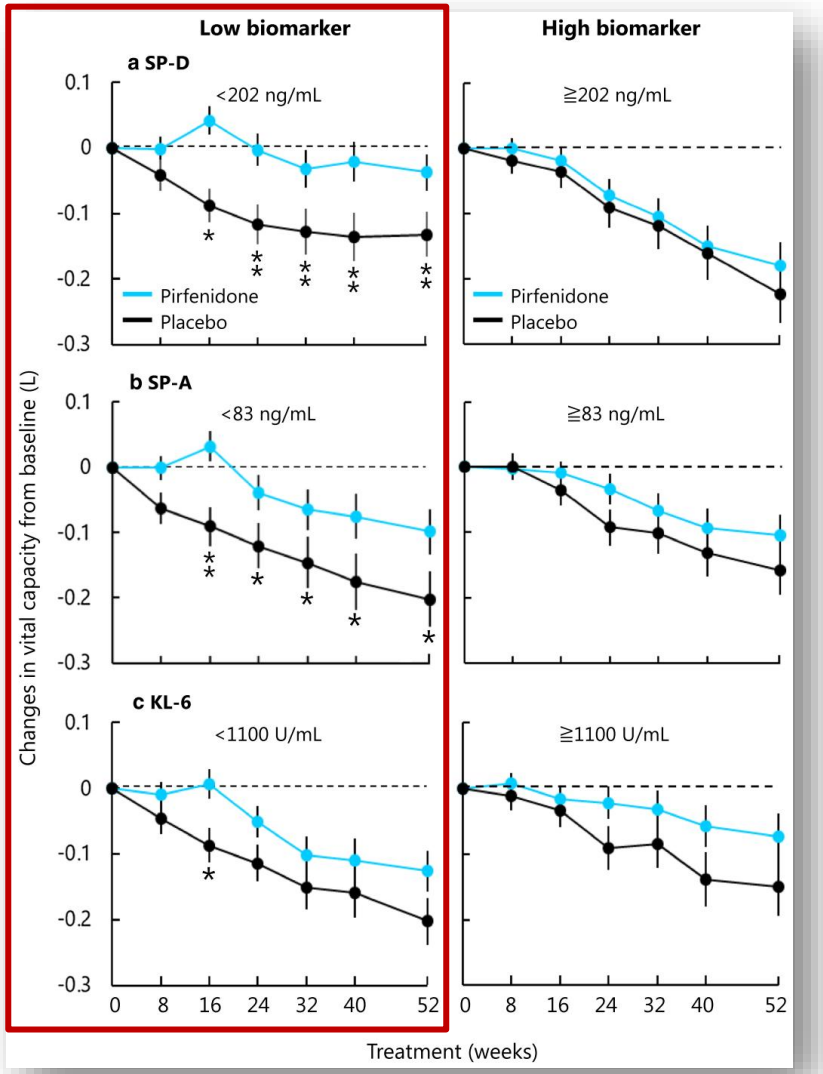
- To predict efficacy
- Pharmacodynamics

- A phase 3 trial of pirfenidone for IPF in Japan (n=275)

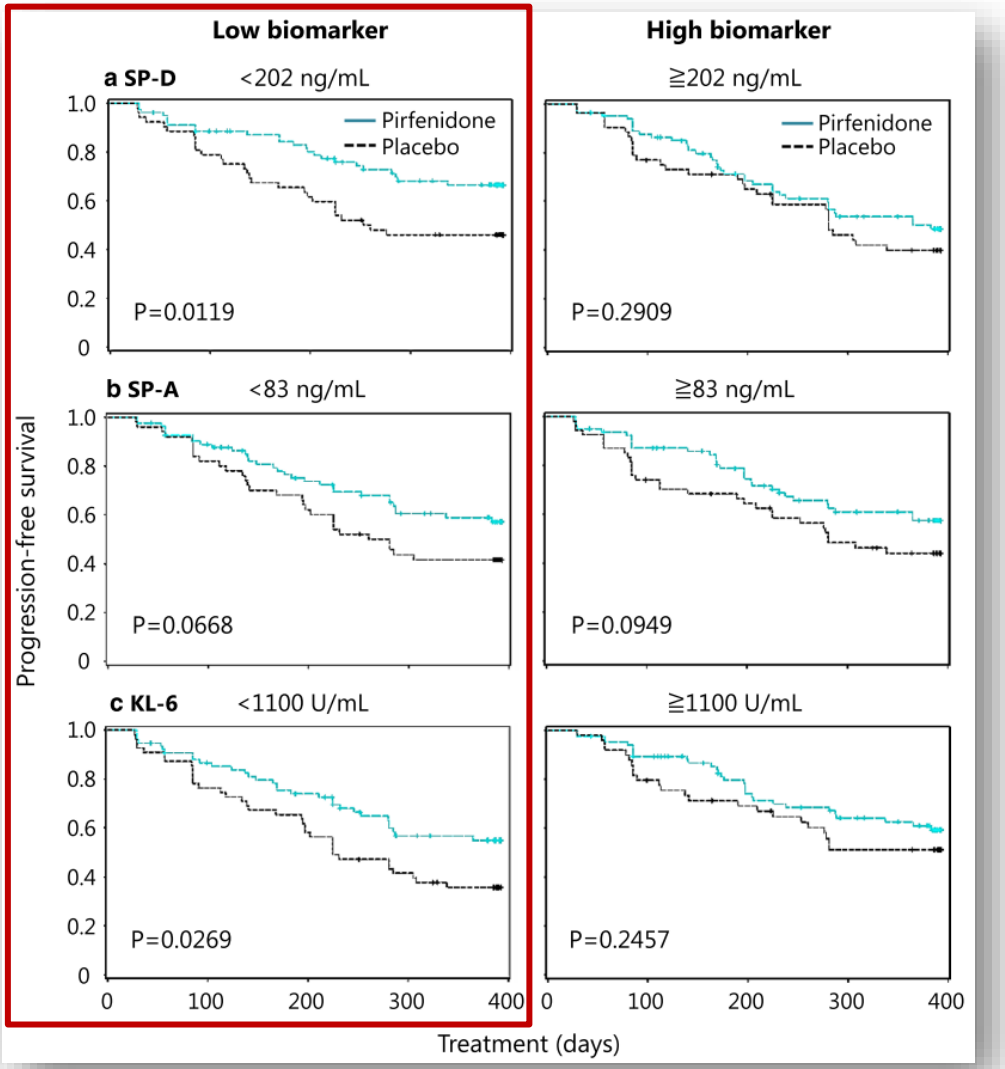
Ikeda K et al. *Respir Res* 2020;21:316

Relationship between biomarker levels at baseline and efficacy of pirfenidone

- Changes in FVC



- Progression-free survival

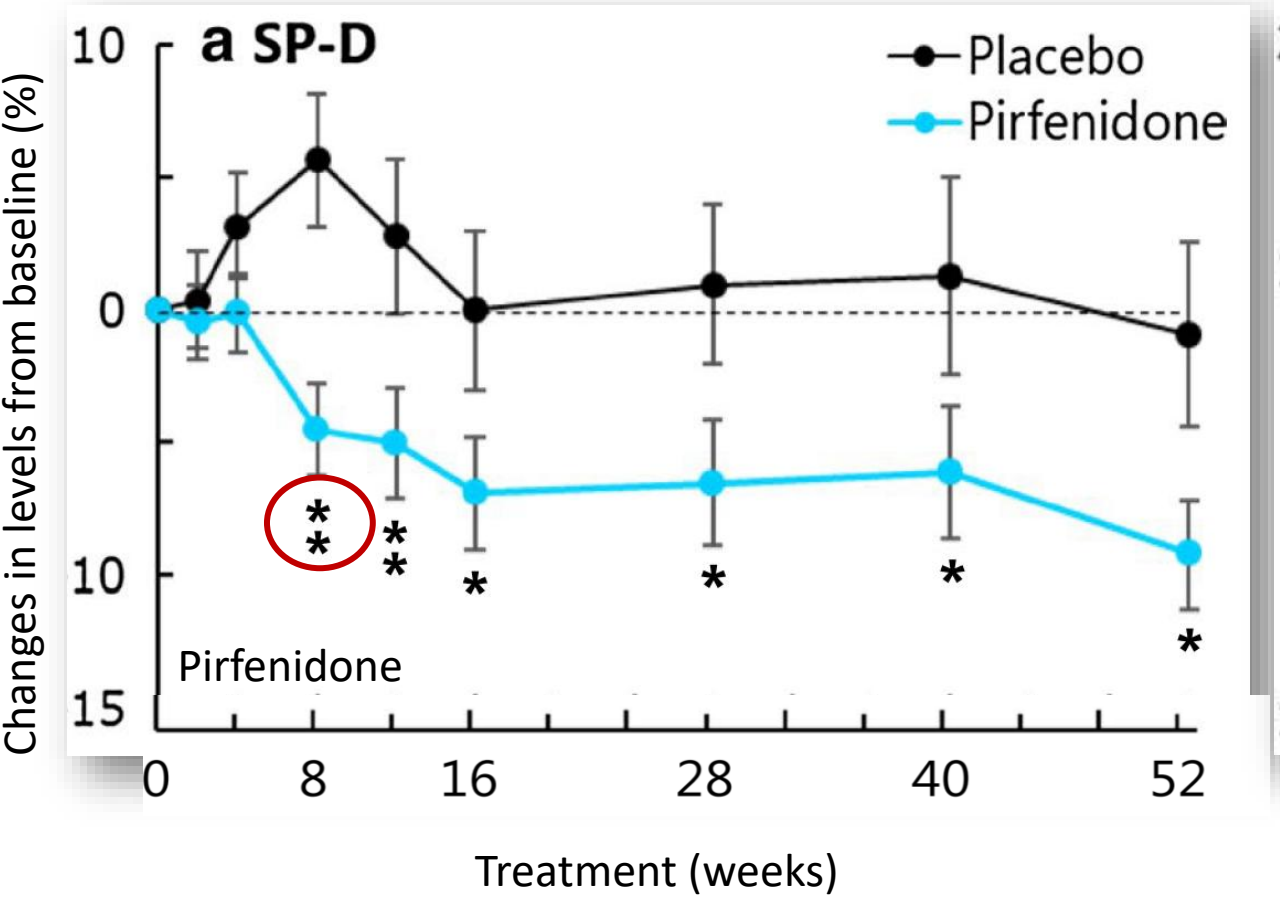


- Disease progression was defined by a ≥ 10% relative decline in VC from baseline and/or death.

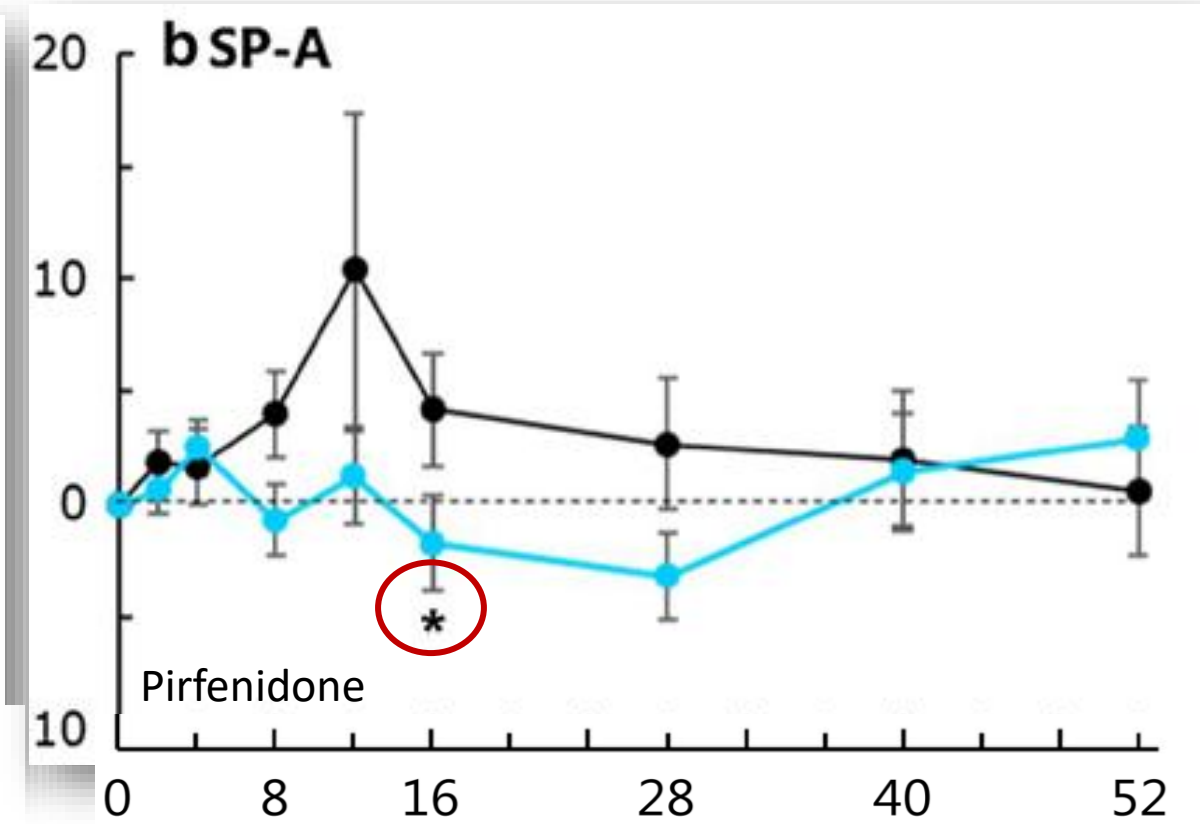
Ikeda K et al. *Respir Res* 2020;21:316

Effect of pirfenidone on relative changes in biomarker levels over 52 weeks

- Relative changes in SP-D levels



- Relative changes in SP-A levels



Ikeda K et al. *Respir Res* 2020;21:316

Summary - I

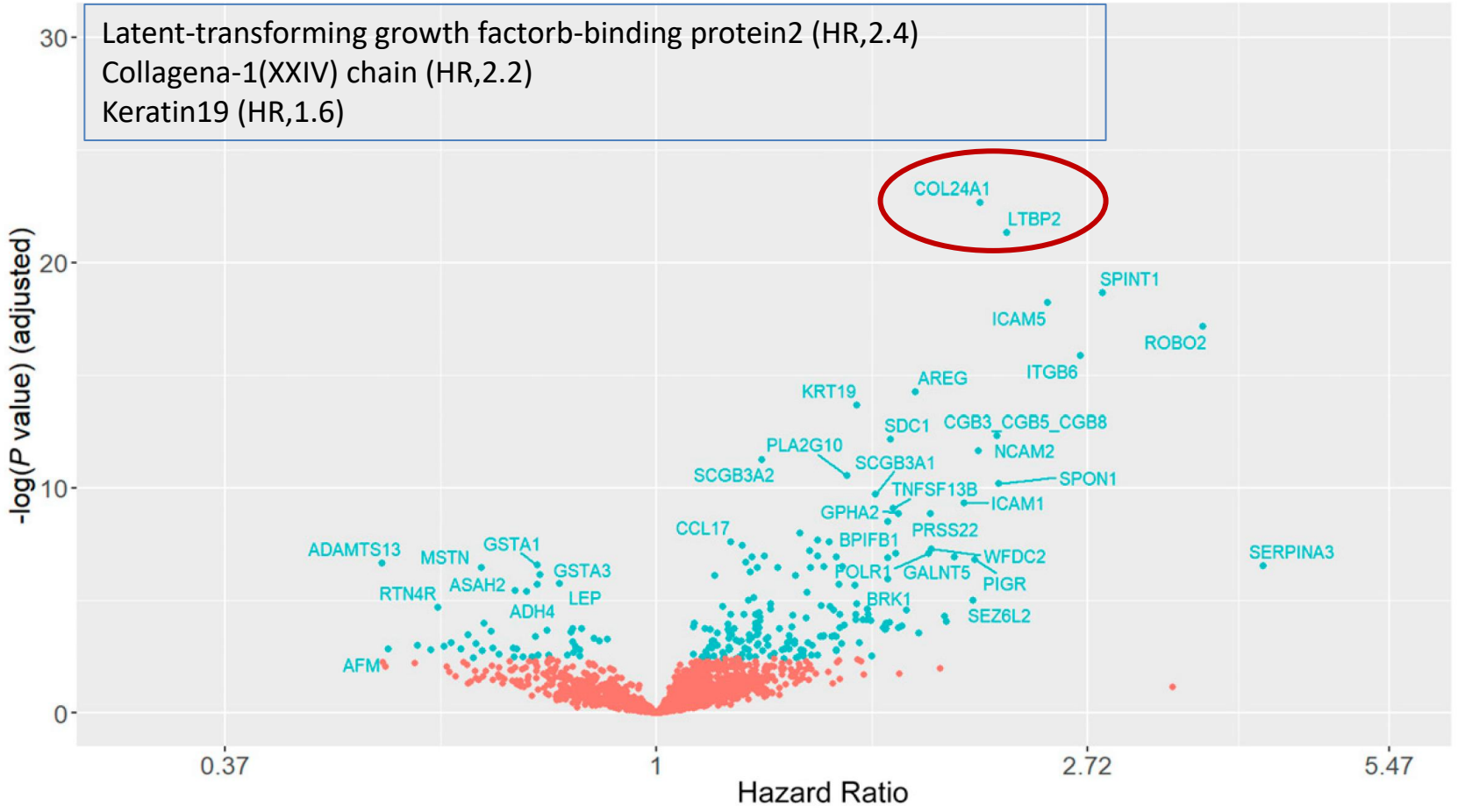
- MMP-7 and CRPM: prognostic, but needs to be evaluated more as a theragnostic marker

- Nintedanib:
  - CA-125, SP-D: theragnostic marker

- Pirfenidone
  - SP-D: predictive marker for treatment response, theragnostic marker

Proteomic biomarkers of survival in IPF

- Volcano plot displaying the association with transplantation free survival



•A prospective multicenter IPF cohort (discovery = 871, validation = 355), 140 protein marker for TFS

Oldham JM et al. *Am J Respir Crit Care Med 2024;209(9):1111-1120*

Fine Particulate Matter Exposure Alters Serum Protein Signatures in Human Serum Samples : An Olink 96-Target Panel Analysis of Inflammation and Developmental Markers

- Proximity Extension Assay (PEA)

실내 대기오염 건강영향 연구 다기관 전향 IPF 코호트

① 질병관리청 관찰 코호트

2021–2023

n = 127

② 환경부 관찰 코호트

2023–2024

n = 122

③ 질병관리청 중재 코호트

2024 – 2026 (ongoing)

n = 140

주요 등록 기준

진단
국제 가이드라인 기반 IPF 진단
(ATS/ERS/JRS/ALAT)

FVC
40–80% pred

DLCO
30–80% pred

3개월 간격 반복 추적 (0 · 3 · 6 · 9 · 12개월)

0M → 3M → 6M → 9M → 12M

폐기능 검사
On site PFT + Home spirometry

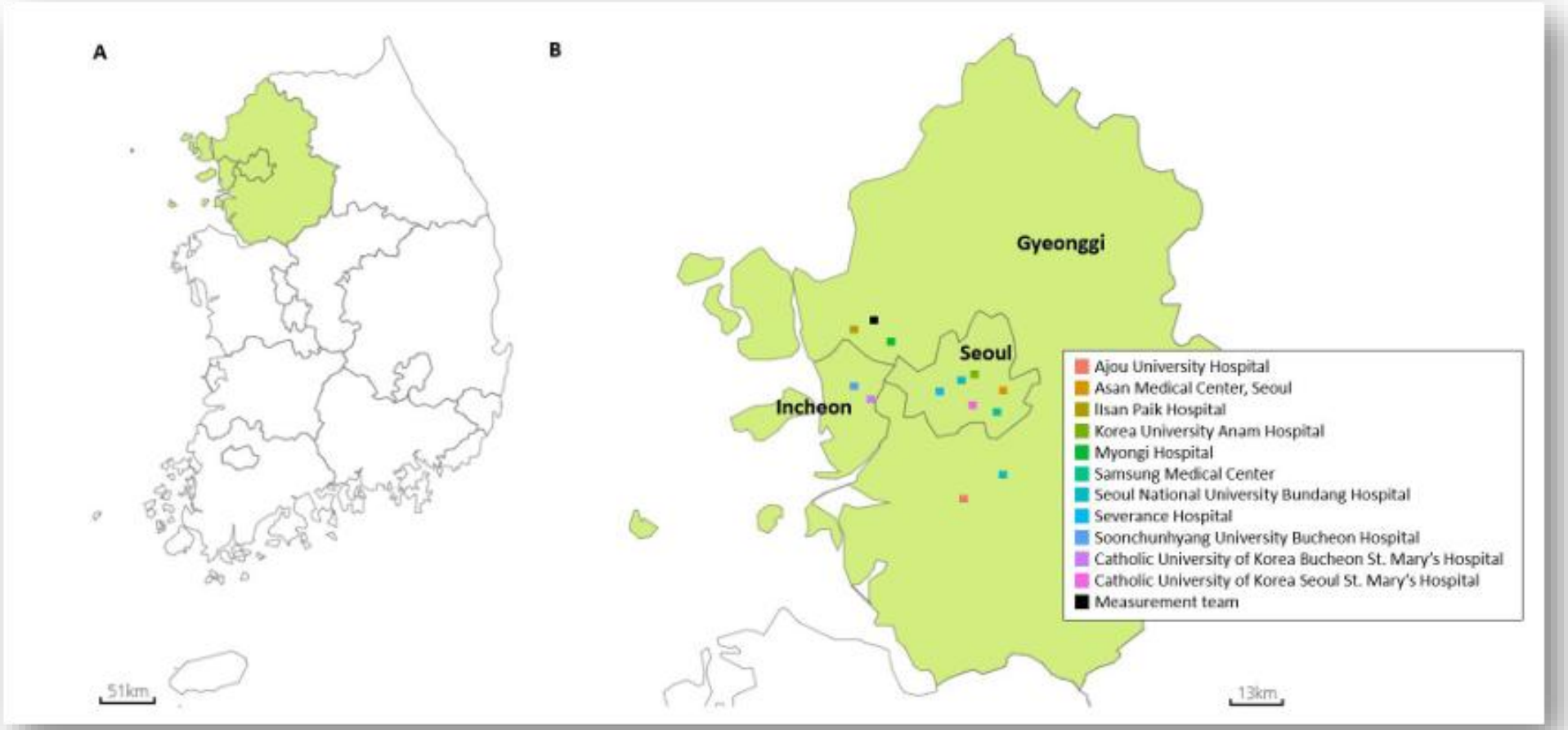
삶의 질 설문
K-BILD, EQ-5D, L-IPF, mMRC
HAD5, Cough VAS

생체 검체
혈액 및 호기 검체 수집
바이오마커 분석

예후 연관 사건
급성악화, 입원, 사망, 질병진행

실내 대기오염 건강영향 연구 다기관 전향 IPF 코호트

- 참여기관 (15개)



Yoon HY et al. *BMJ Open Respir Res 2024;11:e002053.*

가정내 실내 미세먼지 노출측정

- IAQ-CW(LTE) (**케이웨더**, 대한민국; **광산란법**)
- 연중 측정(1분), 결과 실시간 전송
- 일부 가구에서 MicroPEM 측정(계절별)

연구 목표

구분	내용
최종 목표	PM 노출에 의한 IPF 악화 연관 바이오마커 발굴 및 중재법 검증
세부 목표	1. 1차년도 목표: PM 노출에 의한 IPF 악화 기전 확립 및 바이오마커 발굴 2. 2차년도 목표: PM 노출에 의한 IPF 악화 중재요법 검증 코호트 구축 및 실험모델에서의 효과 검증 3. 3차년도 목표: PM 노출에 의한 IPF 악화 중재효과 분석 및 바이오마커 발굴

Baseline characteristics of IPF cohorts

	Total	High PM2.5 (≥ 8μg/m^3)	Low PM2.5 (< 8μg/m^3)	P-value
No.	237	156	81	
나이, years	68.9 ± 6.8	69.4 ± 6.6	67.8 ± 7.3	0.160
남성	195 (82.3%)	127 (81.4%)	68 (83.9%)	0.279
과거 흡연자	184 (77.6%)	121 (77.5%)	63 (77.8%)	0.582
흡연량, 갑년	31.2 ± 27.3	29.7 ± 22.8	34.3 ± 34.6	0.746
체질량지수, kg/m^2	25.2 ± 3.4	25.1 ± 3.4	25.6 ± 3.4	0.262
폐기능				
FVC, % predicted	68.5 ± 14.0	69.1 ± 13.5	67.3 ± 15.0	0.376
DLCO, % predicted	58.1 ± 18.0	59.0 ± 17.8	56.3 ± 18.3	0.258
TLC, % predicted (n=176)	44.7 ± 36.1	49.4 ± 34.2	37.0 ± 37.9	0.074
치료력				
항섬유화제	226 (95.4%)	150 (96.2%)	76 (93.8%)	0.756

Data are presented as mean ± standard deviation, number (percent) or median (interquartile range),

Clinical course of IPF cohorts

	Total	High PM2.5 (≥8μg/m^3)	Low PM2.5 (<8μg/m^3)	P-value
No.	237	156	81	
입원	8 (3.4%)	5 (3.2%)	3 (3.8%)	0.513
사망	11 (4.6%)	6 (3.8%)	5 (6.2%)	1.000

Data are presented as number (percent).

Definition of disease progression

예후	1년의 f/u기간동안 event
Composit_1	사망+입원
Composit_2	FVC 상대 10% 감소 + 사망 + 입원
Composit_3	FVC 절대 10% 감소 + 사망 + 입원
Composit_4	FVC 상대 10% 감소 혹은 DLCO 15%상대 감소
Composit_5	FVC 절대 10% 감소 혹은 DLCO 15%절대 감소
Composit_6	FVC 상대 10% 감소 혹은 DLCO 15%상대 감소+사망+입원
Composit_7	FVC 절대 10% 감소 혹은 DLCO 15%절대 감소+ 사망 + 입원

임상정보	Com1 0/1		Com2 0/1		Com3 0/1		Com4 0/1		Com5 0/1		Com6 0/1		Com7 0/1	
PM high 156	148	8	118	38	137	19	102	54	134	22	95	61	126	30
PM low 81	74	7	70	11	71	10	66	15	76	5	60	21	69	12
NA	9		9		9		9		9		9		9	
total	246		246		246		246		246		246		246	

- 고농도 노출 환경 에서 질환 악화를 예측하는 인자/모델 발굴

Data processing

- NPX Data 추출

↓

- Normalization (with adjustment)

↓

- Statistical Analysis (LIMMA model)

↓

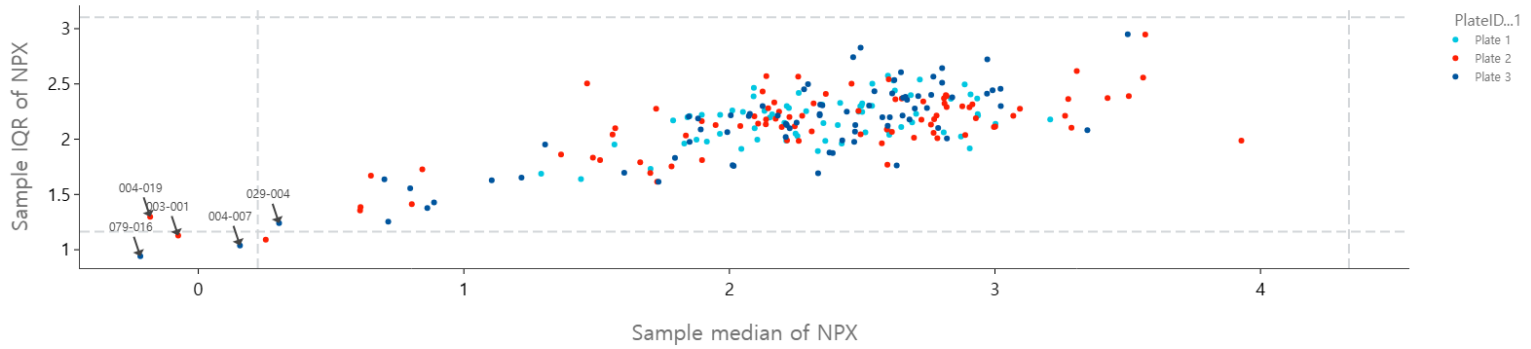
- Visualization

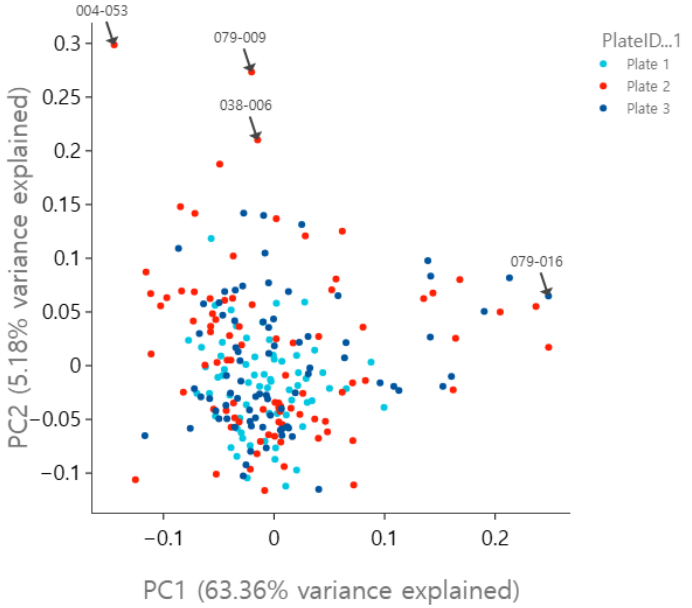
Sample QC (intensity normalization)

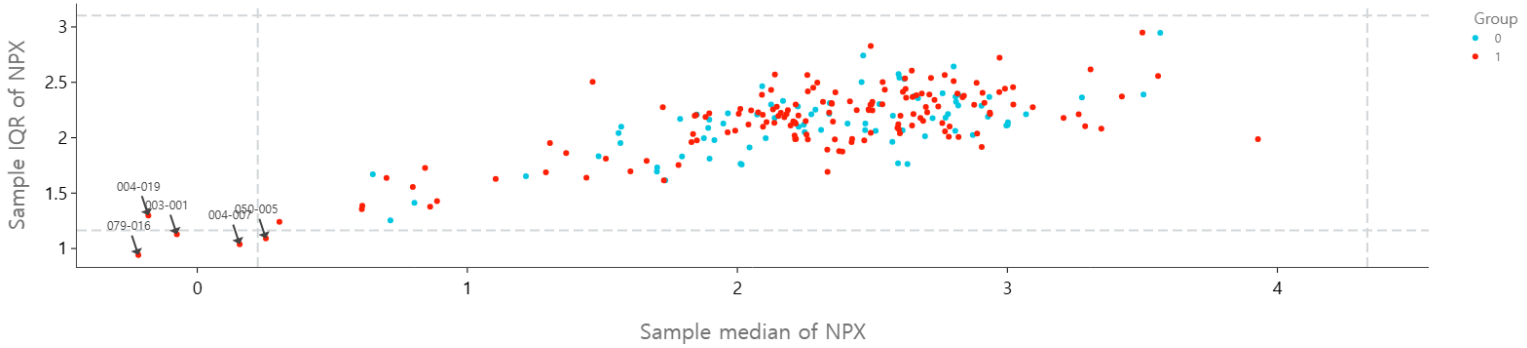
- **Panel 구성 (총 6판; visit 1 sample)**

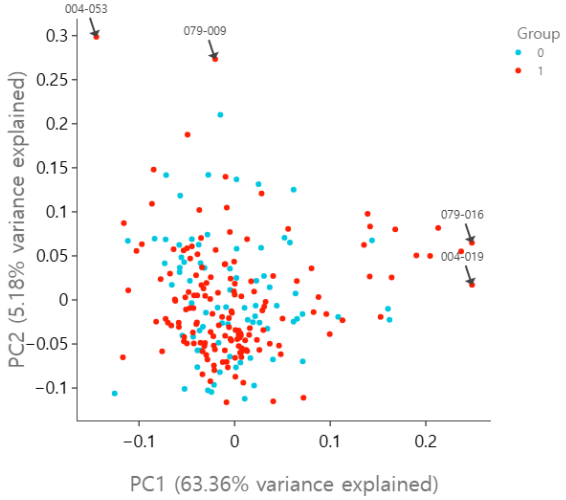
  ① Target 96 Inflammation → #76, #77, #78 (3판)

  ② Target 96 Development → #24, #25, #26 (3판)



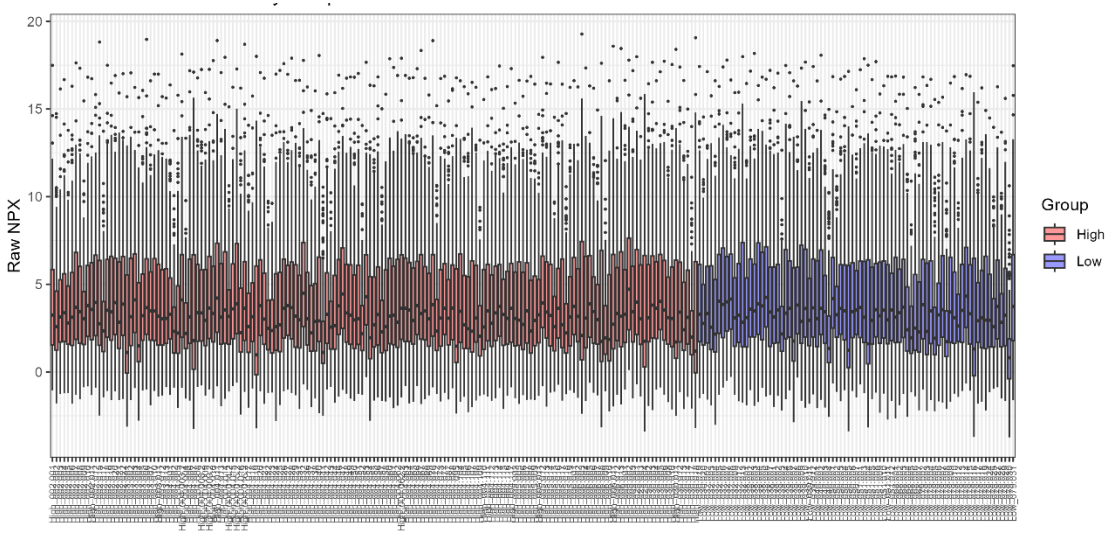




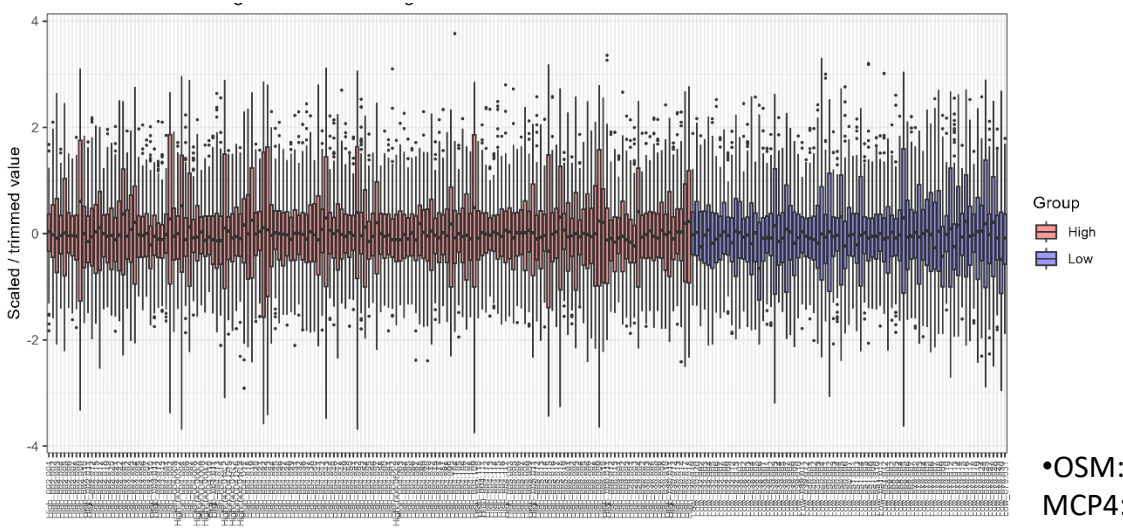


LIMMA model; PM High vs. PM Low

- **Before Normalization**

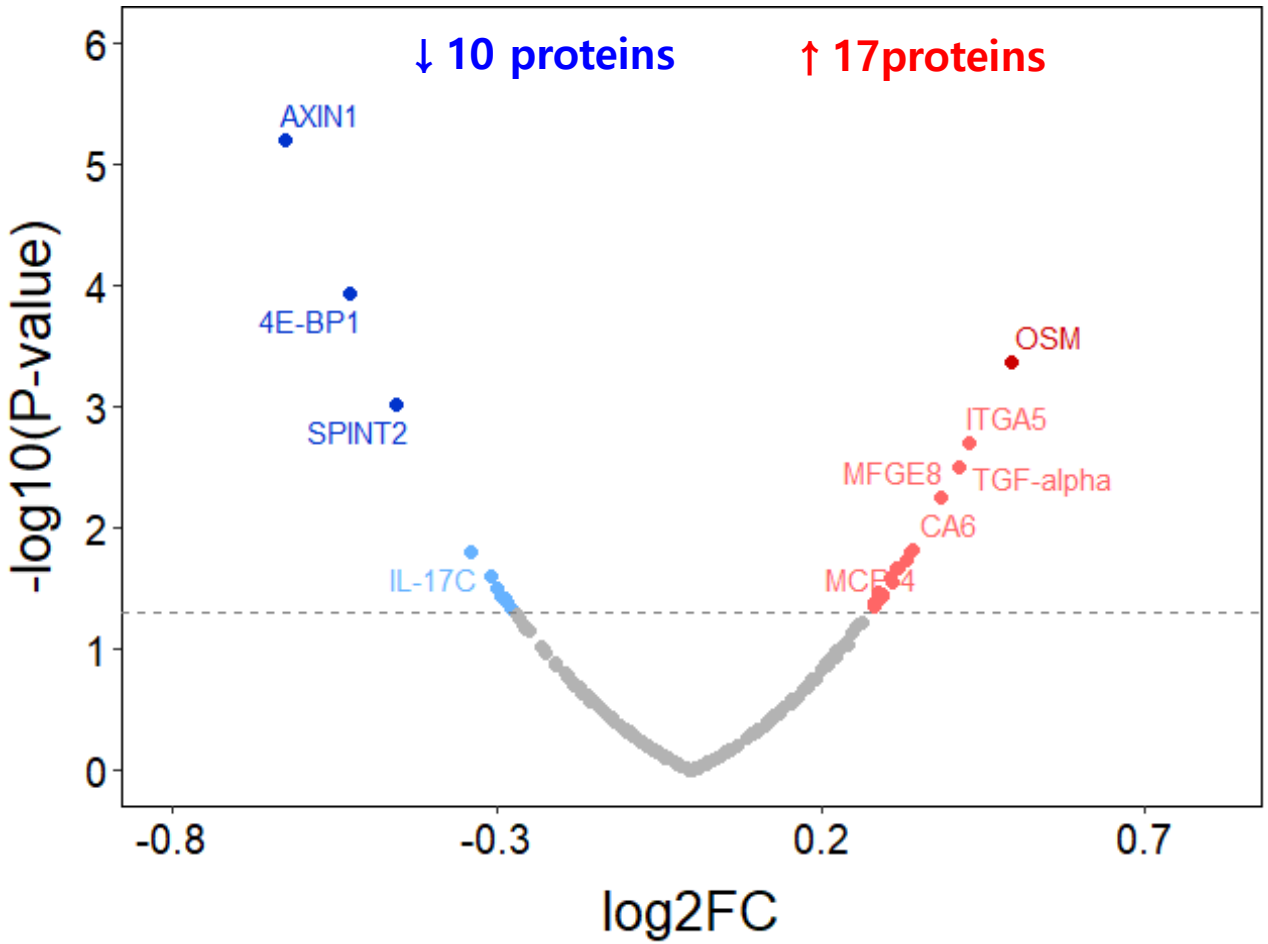


- **After Normalization**



•High: annual median levels of PM ≥ 8 ug/m^3

- High $PM_{2.5}$ exposure

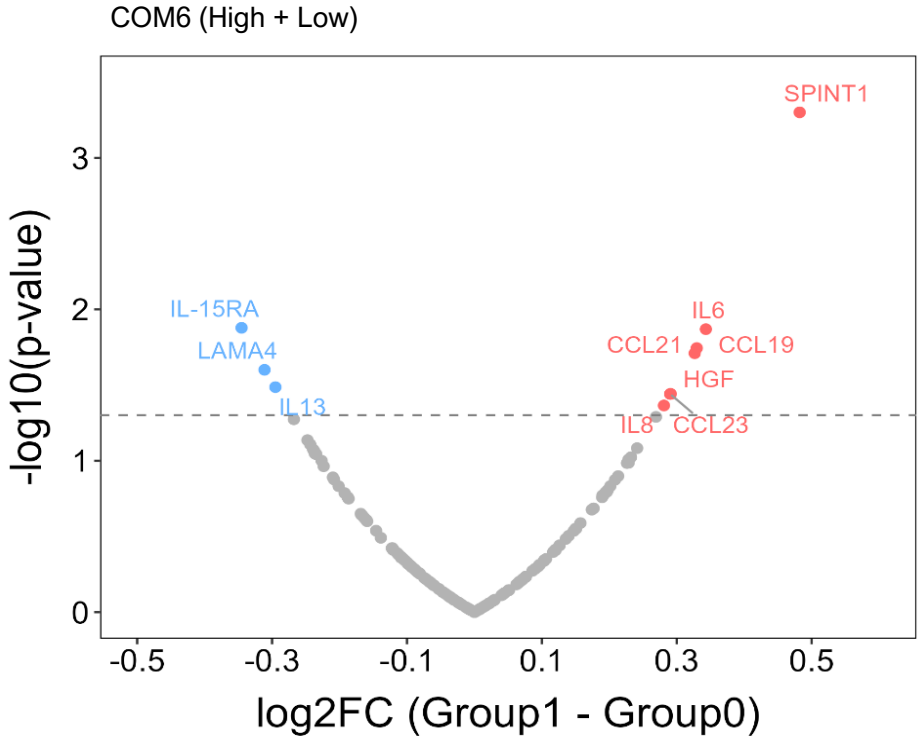


•OSM: oncostatin M, ITGA5: integrin α-5, MFGE8: milk fat globule-EGF factor 8, CA6: carbonic anhydrase 6, MCP4: monocyte chemoattractant protein-4 (CCL13), AXIN1: axis inhibition protein 1, 4E-BP1: Eukaryotic translation initiation factor 4E-binding protein 1, SPINT2: serine peptidase inhibitor Kunitz type 2

Composition 6: FVC 상대 10% 감소 혹은 DLCO 15% 상대 감소 + 사망 + 입원

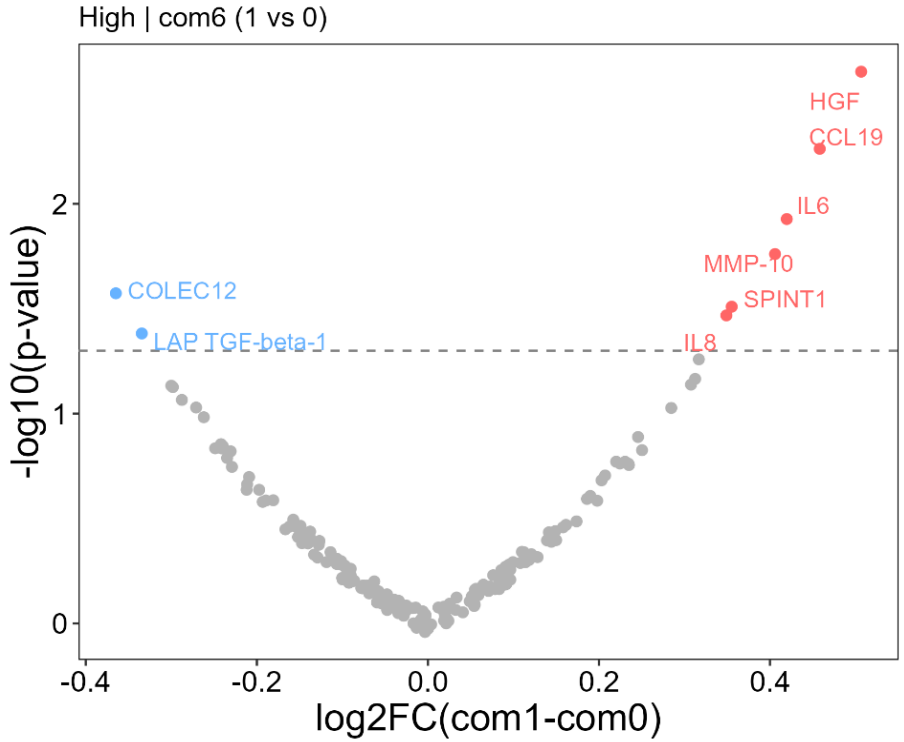
- Disease progression

↓ 3 proteins ↑ 7 proteins



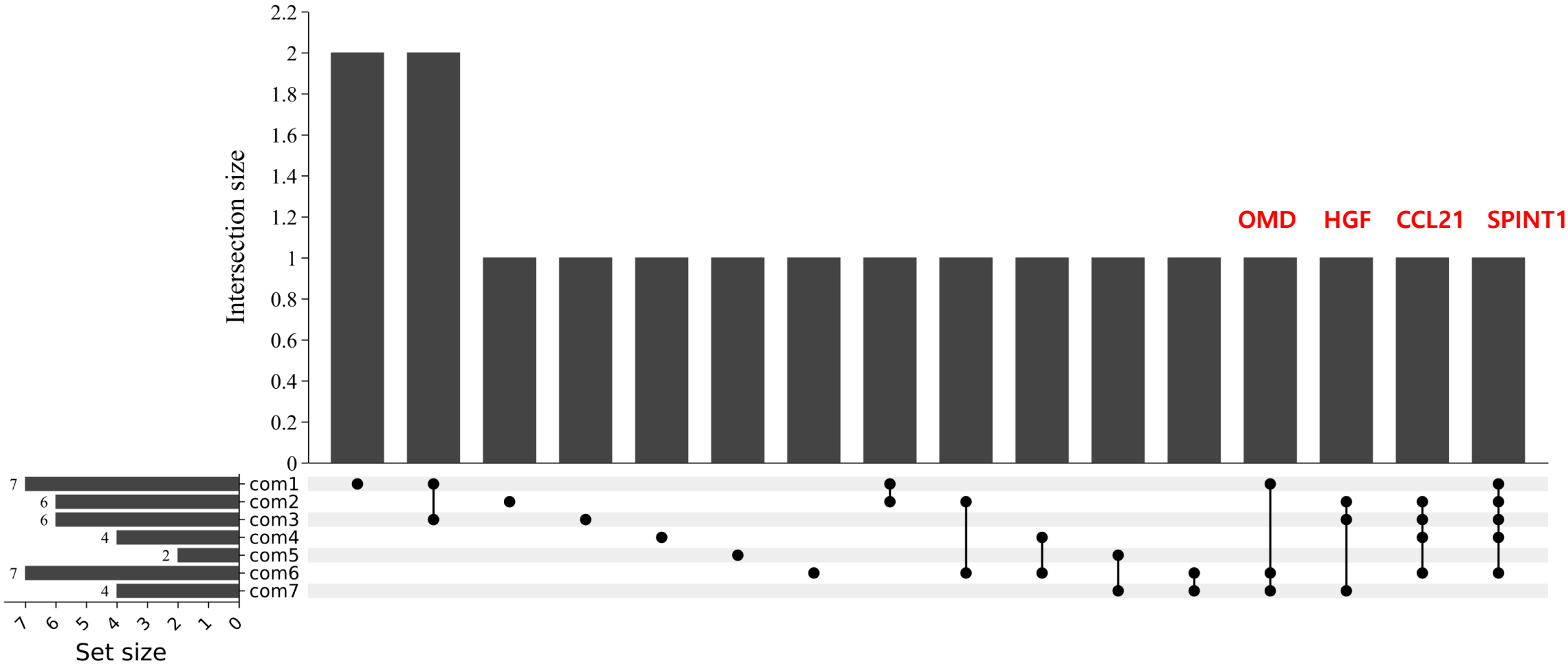
- Disease progression and high $PM_{2.5}$ exposure

↓ 2 proteins ↑ 6 proteins



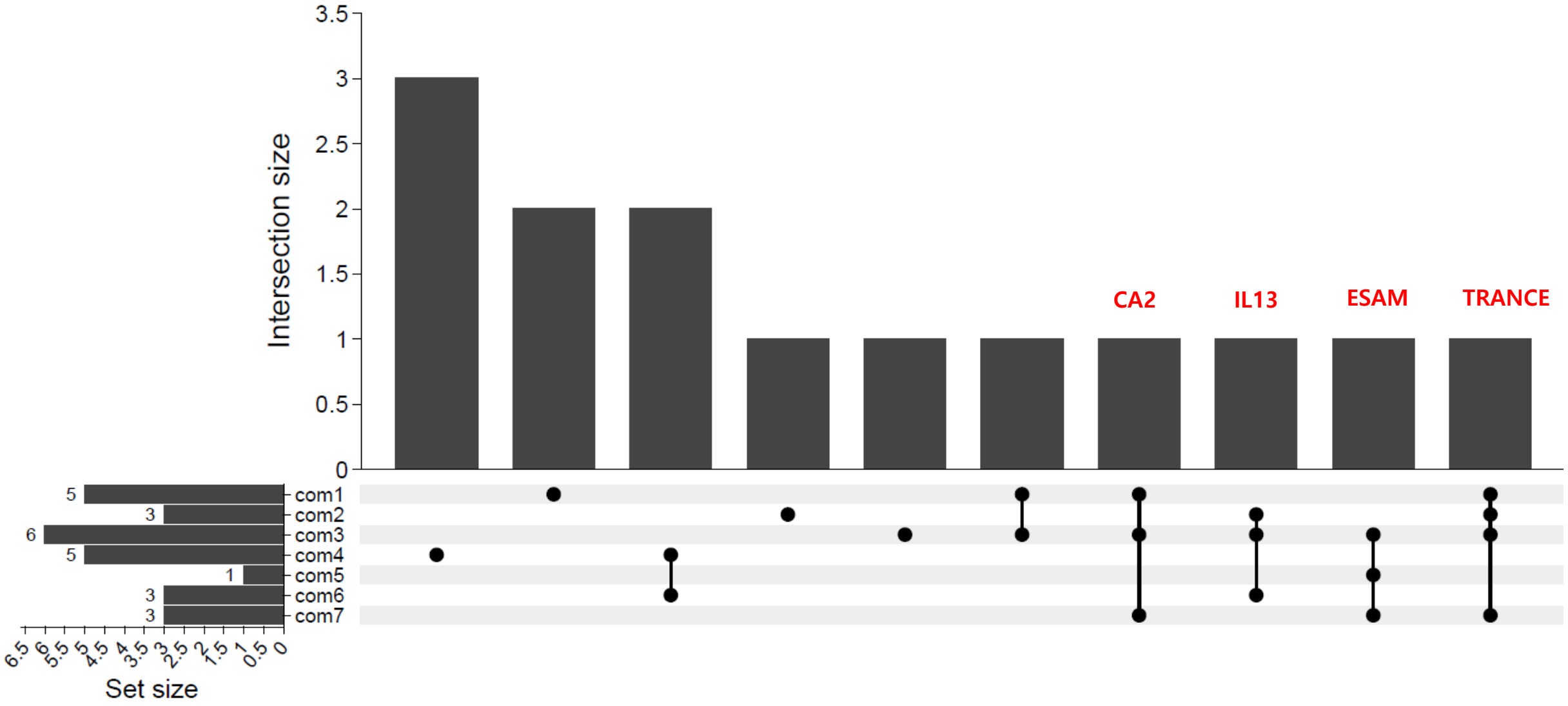
•HGF: hepatocyte growth factor, SPINT1: serine peptidase inhibitor Kunitz type 1, COLEC12: Collectin placenta 1

Upset plot: up-regulated DEPs for disease progression (total)



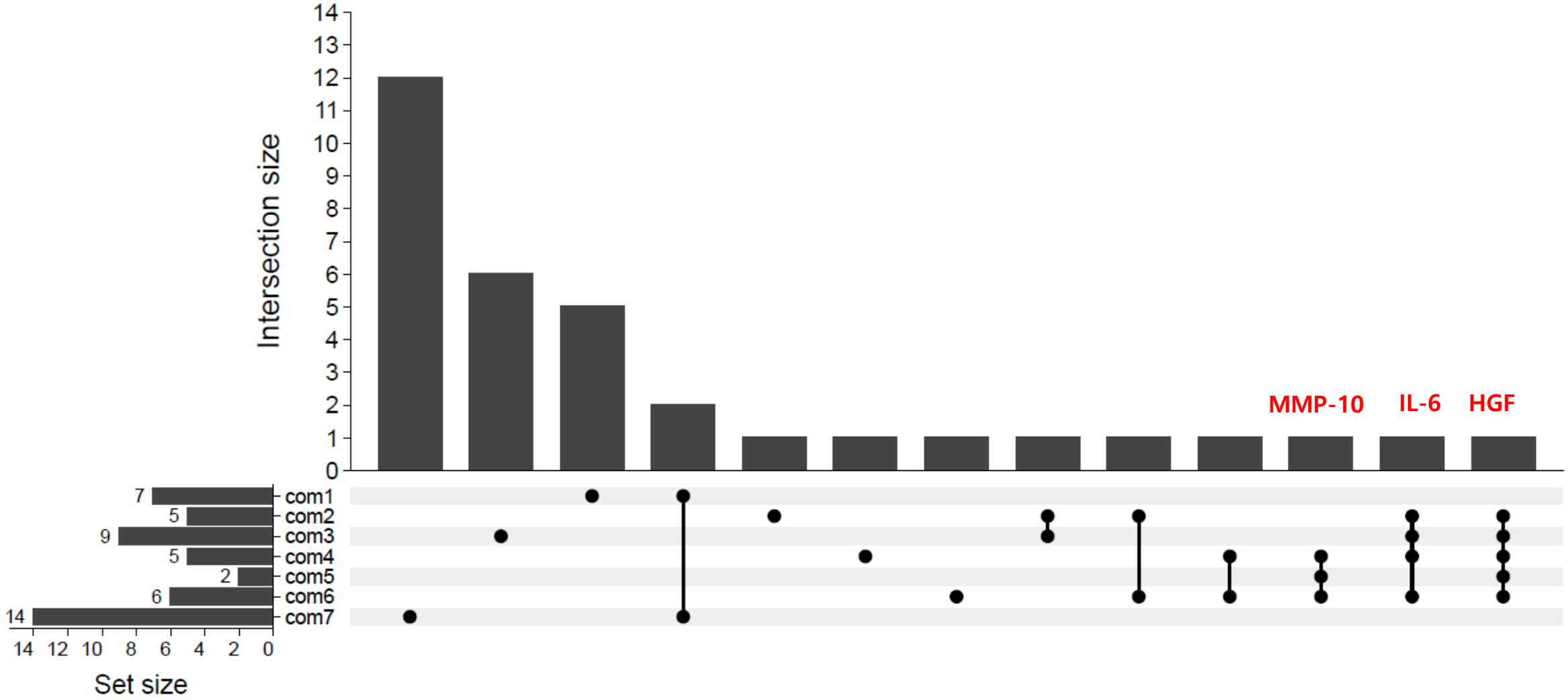
•DEP: differentially expressed proteins, OMD: osteomodulin, HGF: hepatocyte growth factor, SPINT1: serine peptidase inhibitor

Upset plot: down-regulated DEPs for disease progression (total)



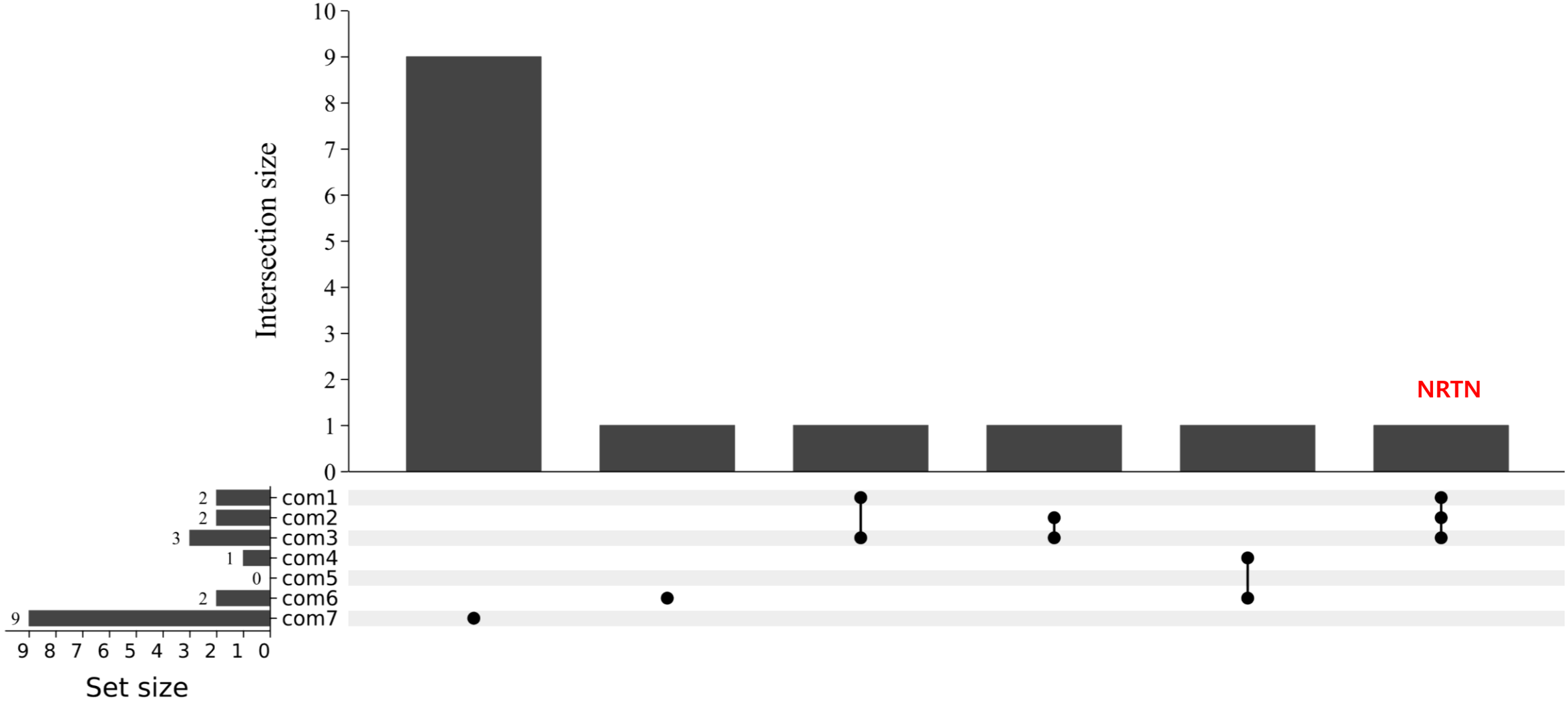
•CA2: carbonic anhydrase 2, ESAM: endothelial cell adhesion molecule, TRANCE: TNF-related activation induced cytokine (RANKL)

Upset plot: up-regulated DEPs for disease progression (High $PM_{2.5}$ exposure)



•HGF: hepatocyte growth factor

Upset plot: down-regulated DEPs for disease progression (High $PM_{2.5}$ exposure)



•NRTN: neurturin

Common DEPs among each composition (High $PM_{2.5}$ exposure)

- **MMP-10 (Matrix Metalloproteinase-10)**
- IPF 환자의 폐에서 bronchiolized alveolar epithelia 에서 강하게 발현
- EMT 촉진, ECM 재구성, 비정상복구/과도한 섬유화 반응관여
- IPF 환자의 혈청 및 BAL 에서 증가, FVC 감소 및 사망과 연관, 질병중증도 반영

- **IL-6 (Interleukin-6)**
- FMT, 섬유아세포 사멸성 저항, 폐포상피세포 노화관여
- 혈액내 농도는 폐기능저하 및 사망, 급성악화와 연관
- Toclizumab (anti IL6)

- **HGF (Hepatocyte Growth Factor)**
- 폐포상피세포 보호, TGFb 길항작용, EMT 저해, ECM 분해촉진 (보상적 상승)
- 혈중 수치가 높은 경우 중증도가 높거나 급성악화 연관

- **NRTN (Neurtrin)**
- 신경영양인자, 신경세포의 성장과 생존을 촉진하는 신호 전달 분자(리간드) 역할
- 폐포상피세포 생존촉진, 섬유화 신호억제
- IPF 환자 폐조직내 감소

Prediction model using DEPs from LIMMA

예후	1년의 f/u기간동안 event
Composit_1	사망+입원
Composit_2	FVC 상대 10% 감소 + 사망 + 입원
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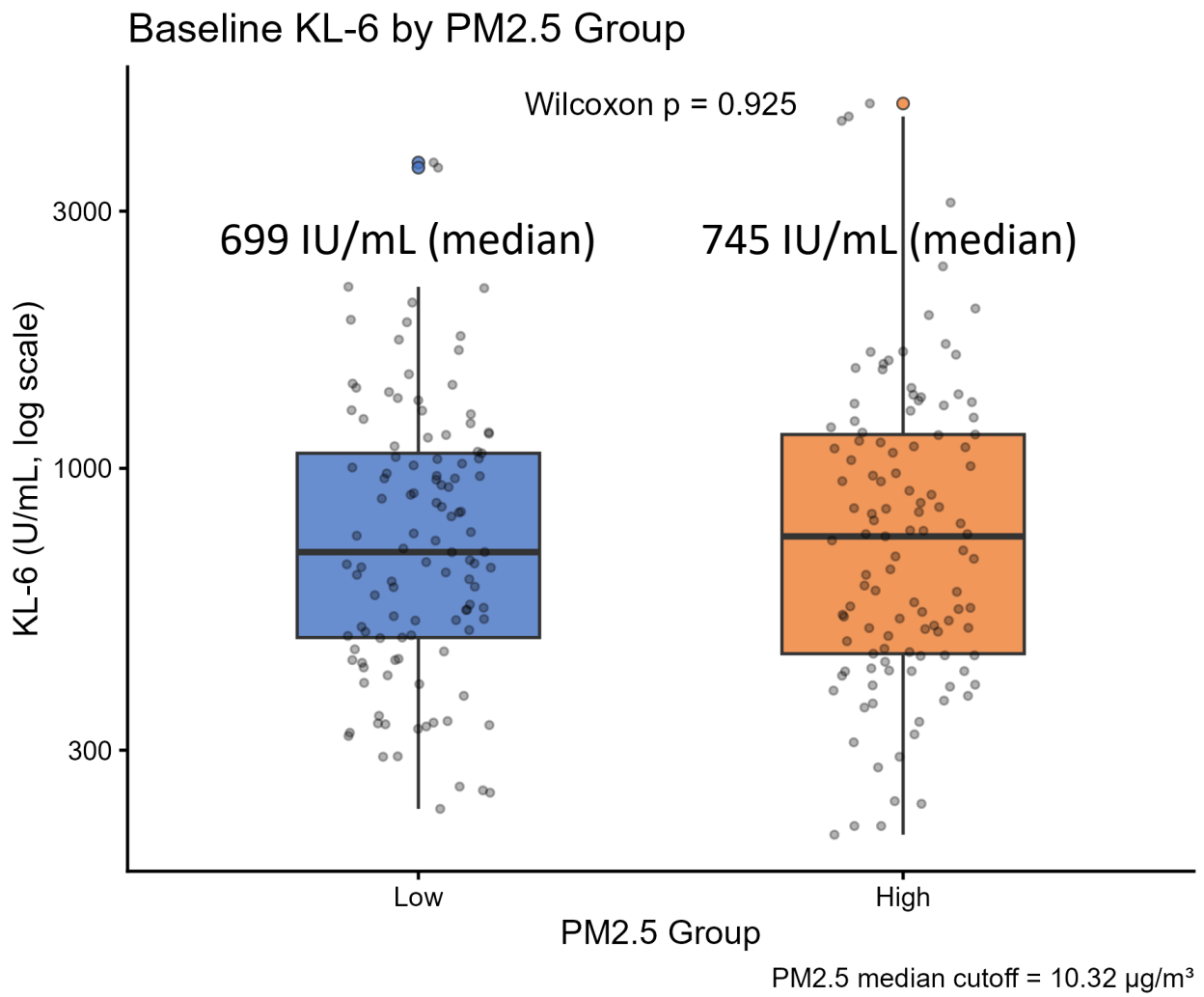
Composit_7	FVC 절대 10% 감소 혹은 DLCO 15%절대 감소+ 사망 + 입원

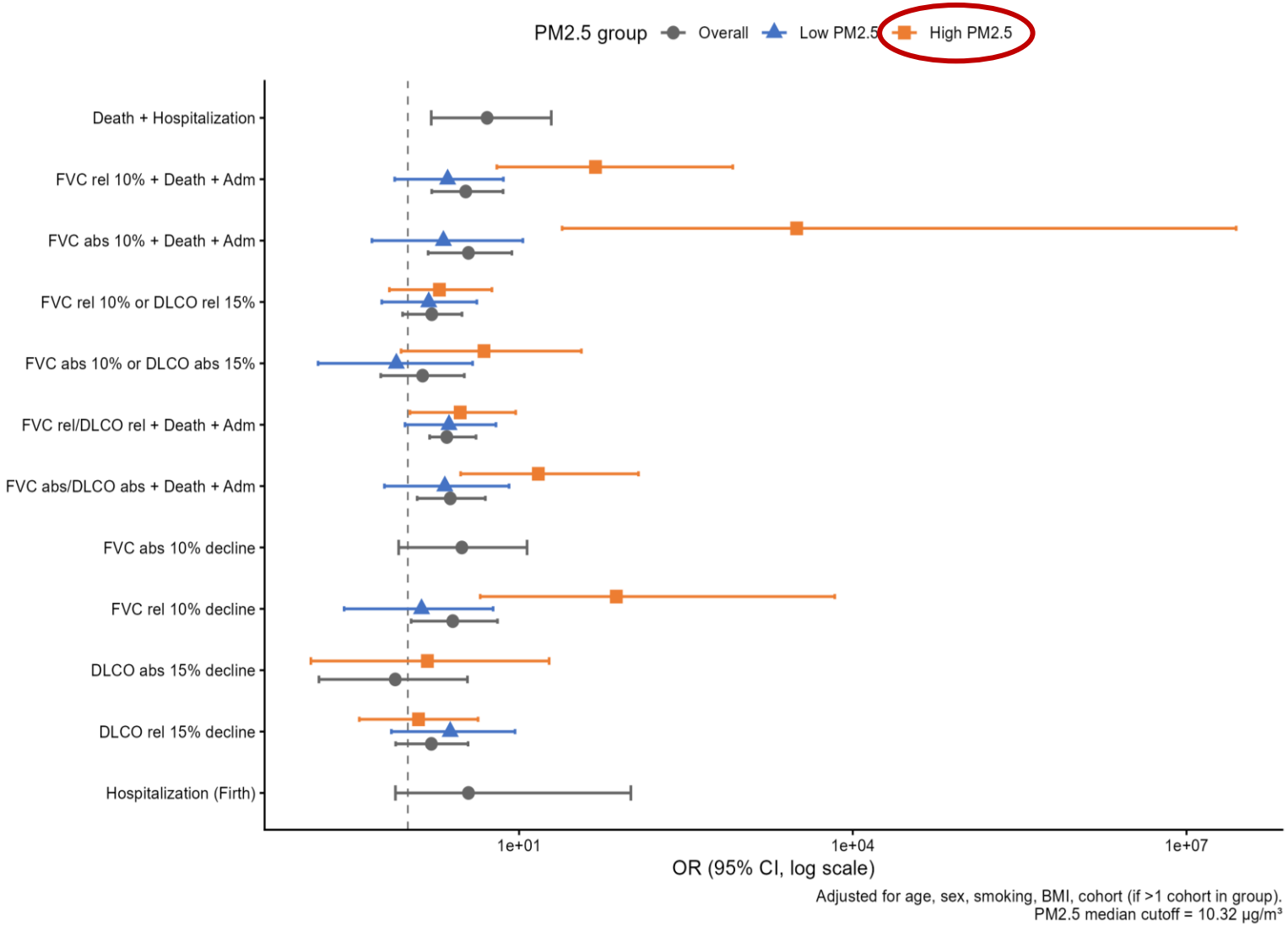
Dataset	N (1/0)	Model	ROC-AUC (OOF)	PR-AUC	Sens-focused Threshold	Sensitivity	Specificity	Youden Threshold	Sens (Y)	Spec (Y)
High_com2	156 (38/118)	Logistic Reg	**0.776***	0.488	0.42	0.816	**0.585**	~0.50	0.73	0.65
High_com6	156 (≈?)	Logistic Reg	0.714	0.638	0.37	0.803	0.474	~0.45	0.7	0.62
HighLow_com2	237 (49/188)	XGBoost	0.593	0.376	0.02	0.837	0.229	0.149	0.551	**0.633**
HighLow_com6	237 (82/155)	XGBoost	**0.639**	**0.525**	0.094	0.817	0.335	0.381	0.598	**0.658**

Baseline KL-6 levels according to $PM_{2.5}$ exposure



Prognostic role of KL-6 according to $PM_{2.5}$ exposure

- Association between baseline KL-6 levels and disease progression



Summary -Ⅱ

- Among 239 patients with IPF, different blood proteomics profiles were observed at baseline according to disease progression or exposure to $PM_{2.5}$.
- Patients who were exposed to high indoor $PM_{2.5}$ had increased levels of OSM, ITGA5, MFGE8, TGFα, CA6, and MCP4, and decreased levels of AXIN1, 4E-BP1, SPINT2, IL-17C in their baseline blood.
- Patients exposed to high indoor $PM_{2.5}$ who showed disease progression had increased levels of MMP-10, IL-6 and HGF, and decreased levels of neurturin in their baseline blood.
- KL-6 levels were associated with disease progression in patients exposed to high $PM_{2.5}$