

가톨릭대학교
의정부성모병원

보건복지부 의료기관평가 우수병원 전국4위
- 500이상 이상 대형병원(70개) 중 4위 · 종합병원 부문 1위 -



가톨릭대학교
의정부성모병원
경기북부
권역의료중심센터

주요 인점

BIOMARKERS IN COPD

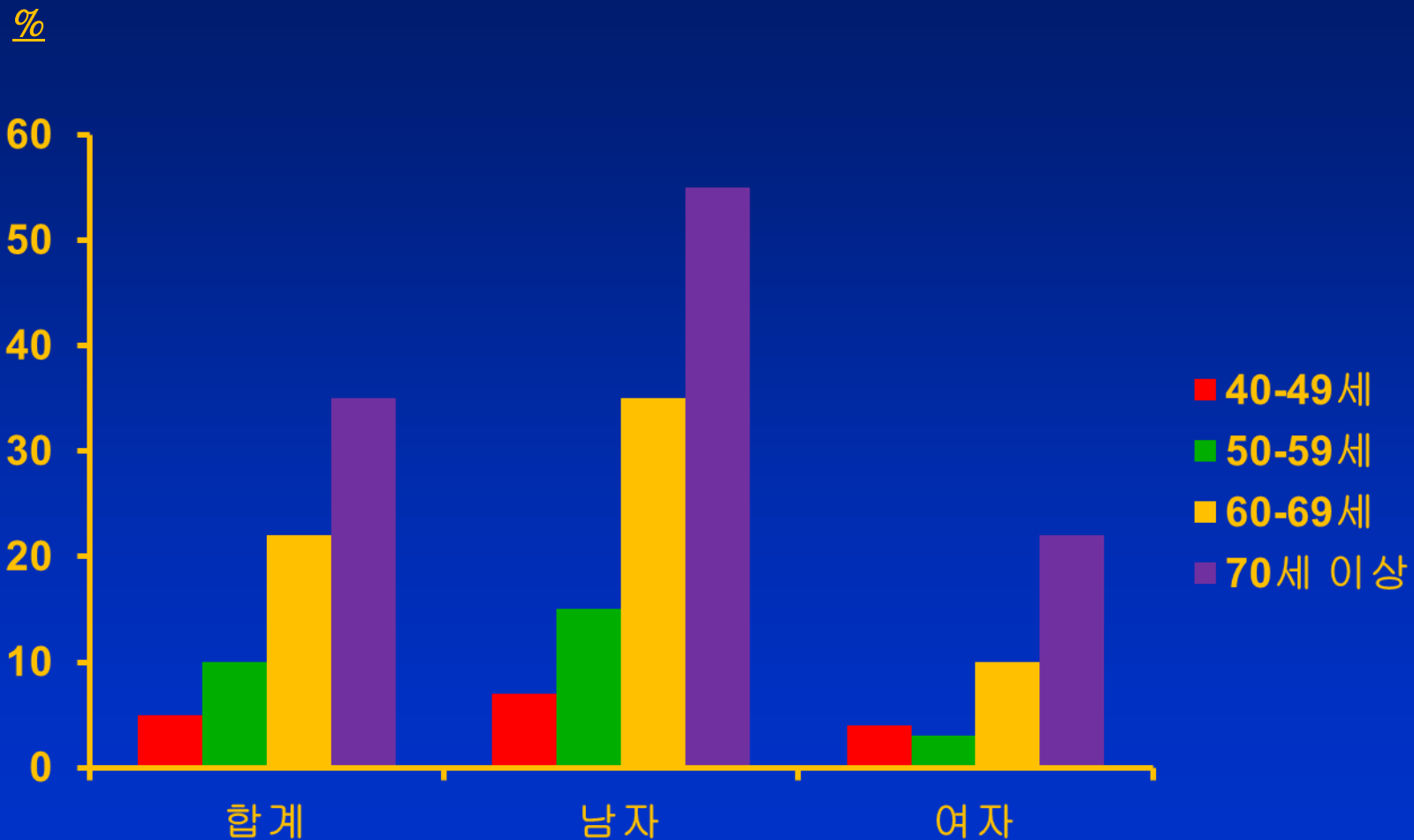
가톨릭의대
의정부 성모병원
호흡기 내과
김진우

COPD prevalence

Table 1 Prevalence of airflow obstruction stratified by place of residence, education and income

	Total population		Men		Women	
	Number of subjects	Prevalence %	Number of subjects	Prevalence %	Number of subjects	Prevalence %
Age						
≥19 years	3435	8.8	1478	11.6	1957	5.9
≥40 years	2501	13.4	1056	19.4	1445	7.9
Place of residence						
Rural	1741	12.2	730	17.4	1011	7.5
Urban	760	17.8	326	25.9	434	9.5
Education						
Elementary school or lower	957	21.2	275	38.6	682	12.7
Middle school	423	15.1	201	22.7	222	6.4
High school	712	7.0	318	11.4	394	2.6
College or higher	401	8.5	256	10.2	145	5.3
Income						
Low	561	14.6	221	20.6	340	9.2
Low ~ middle	596	13.2	257	19.7	339	7.0
Middle ~ high	629	11.8	281	17.7	348	5.8
High	642	10.7	267	15.6	375	6.6

COPD 유병률

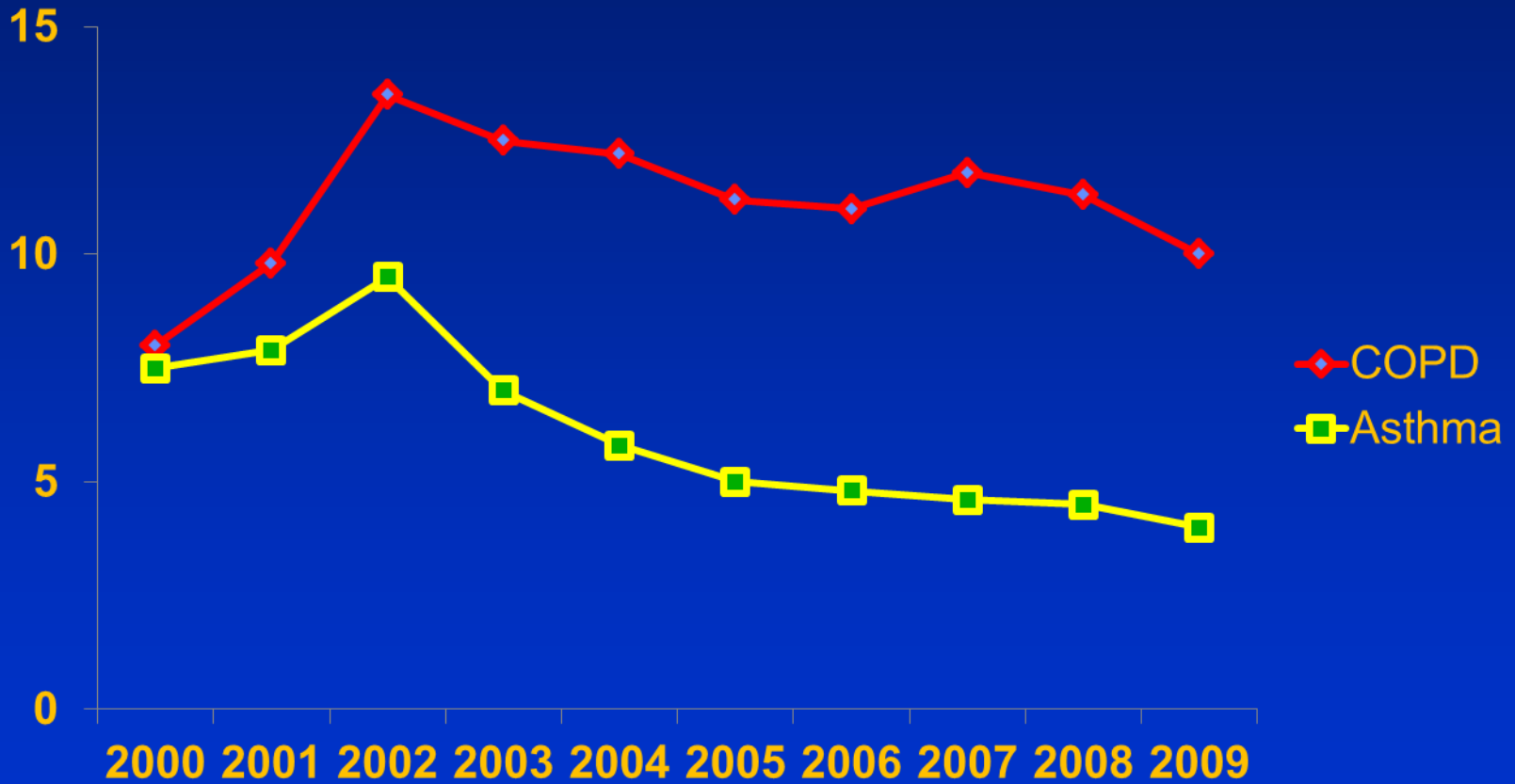


국민건강 영양조사 2008

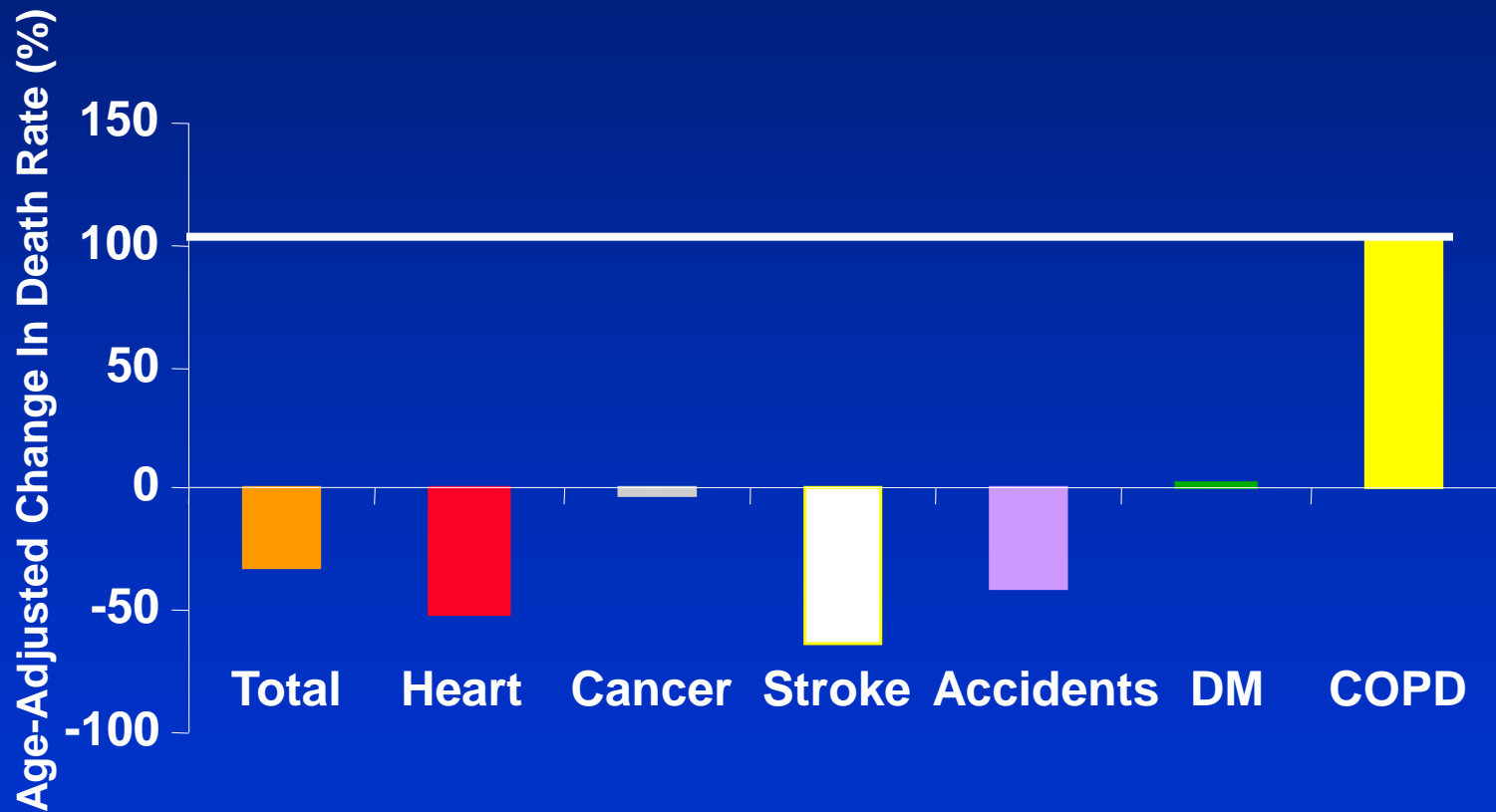
Yoo KH et al Respirology 2011 16, 659-665

COPD 사망률

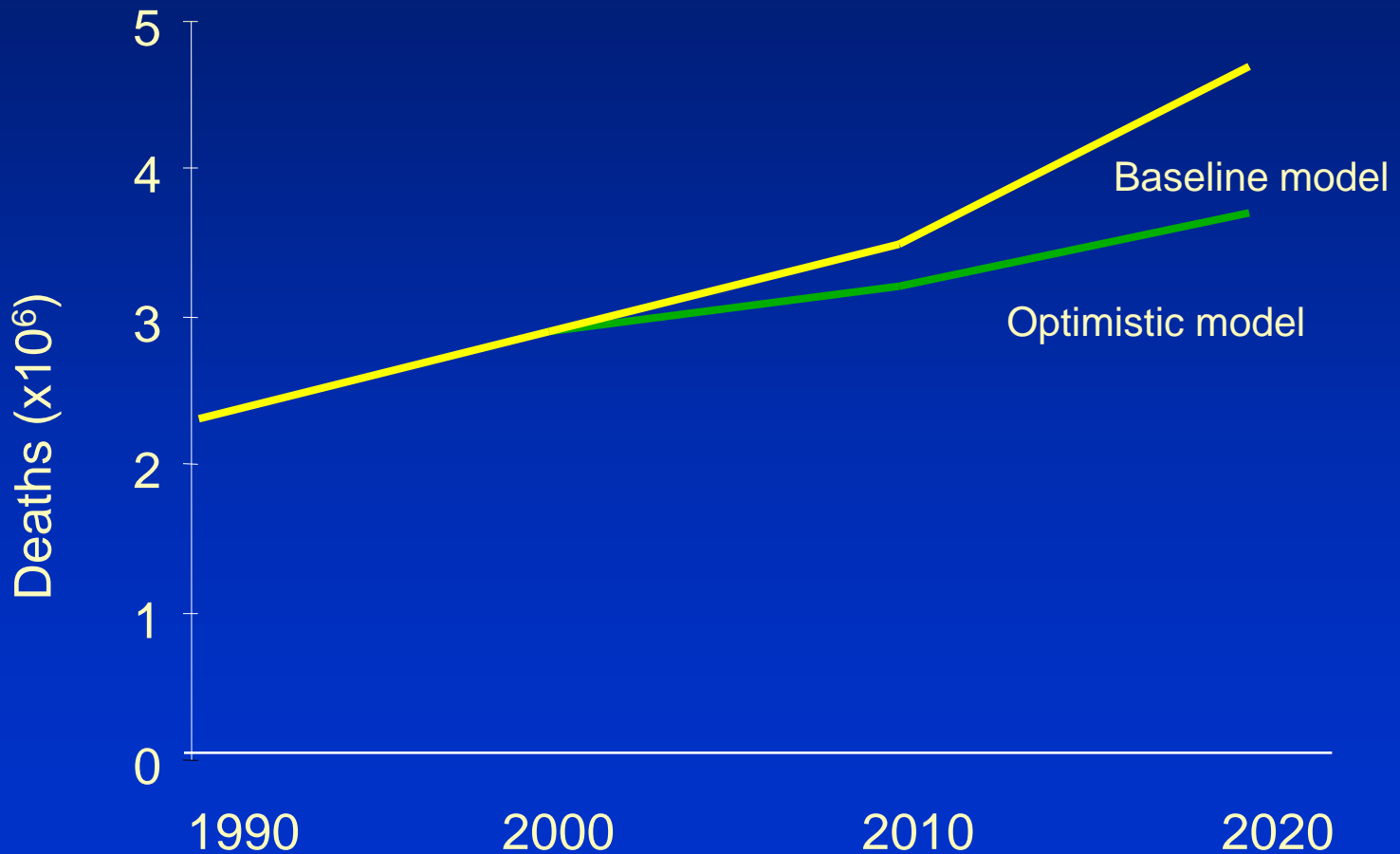
명/10만



Change in Death Rate Between 1970-2002



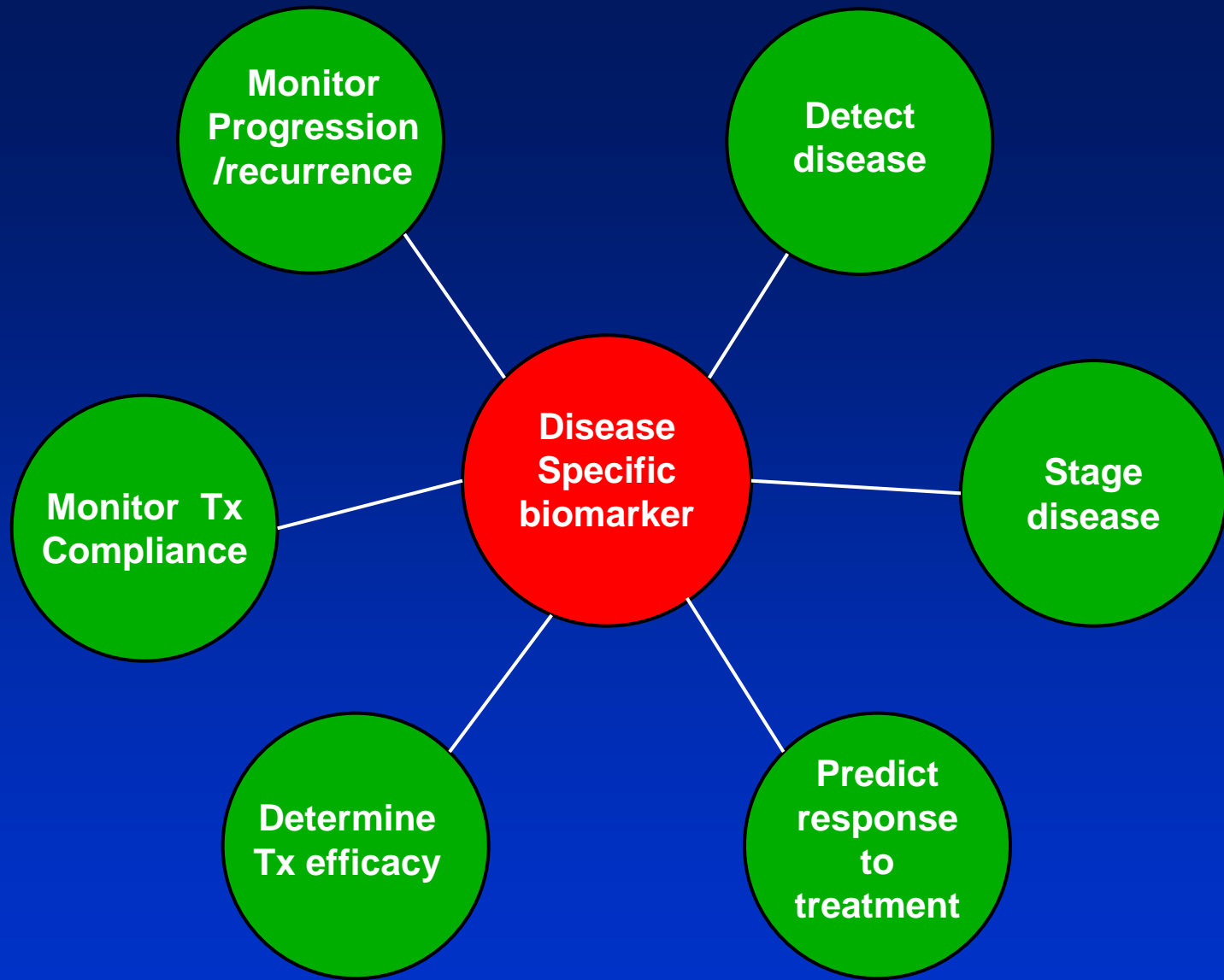
The Future?



What is Biomarker?

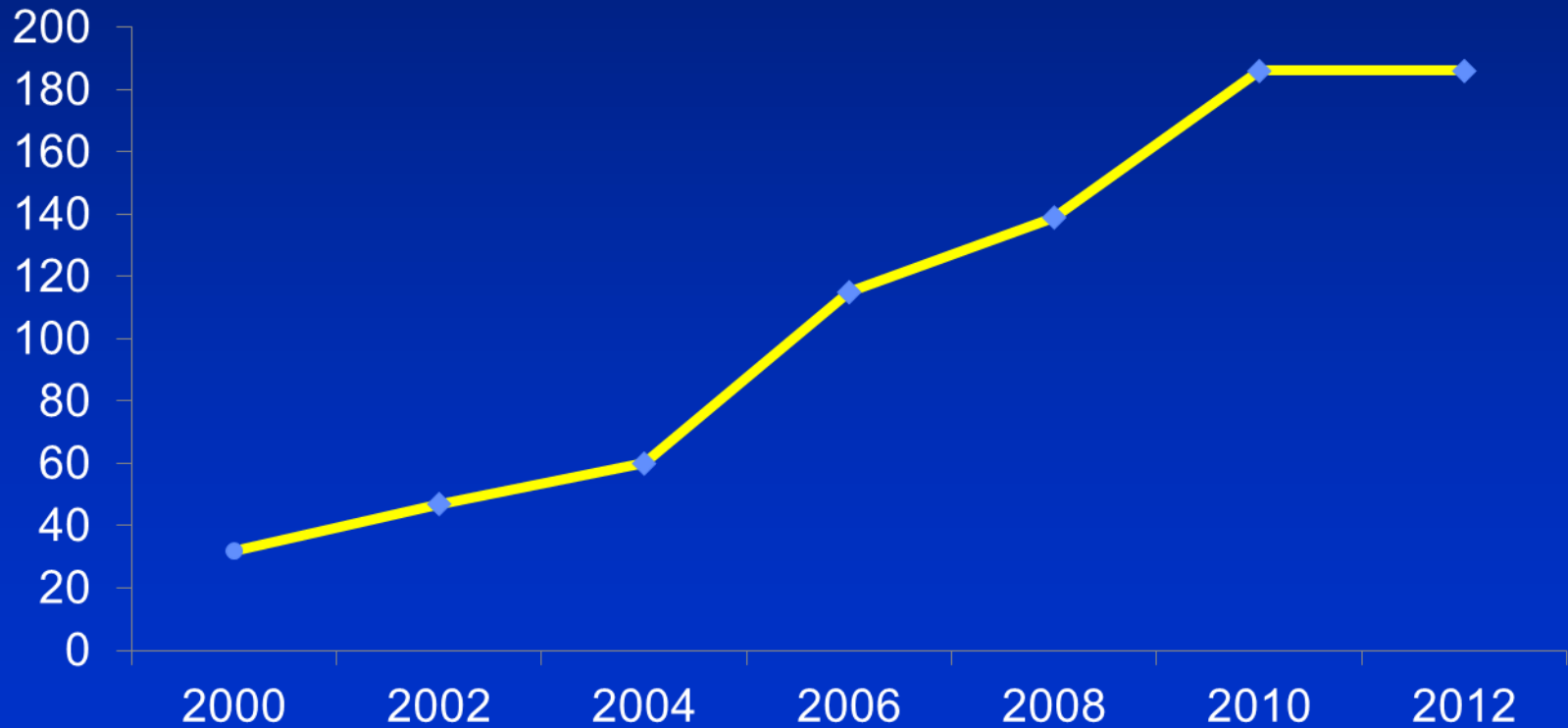
“a characteristic (or variable) that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.”

The National Institutes of Health (NIH)



The number of publications in PUBMED identified using search terms “biomarker” and “COPD” between 2000 and 2012

Publication number



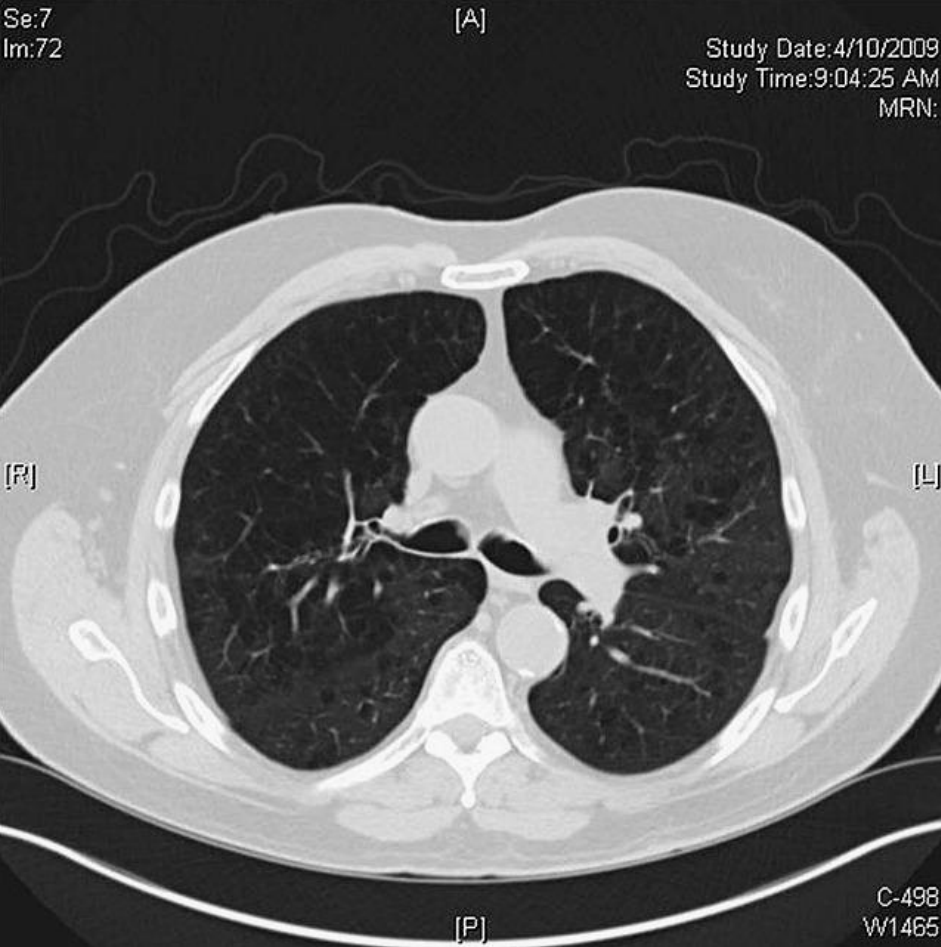
COPD Biomarker

“with exception of the lung function tests, there are no well-validated biomarkers or surrogate endpoints that can be used to establish efficacy of a drug for COPD.

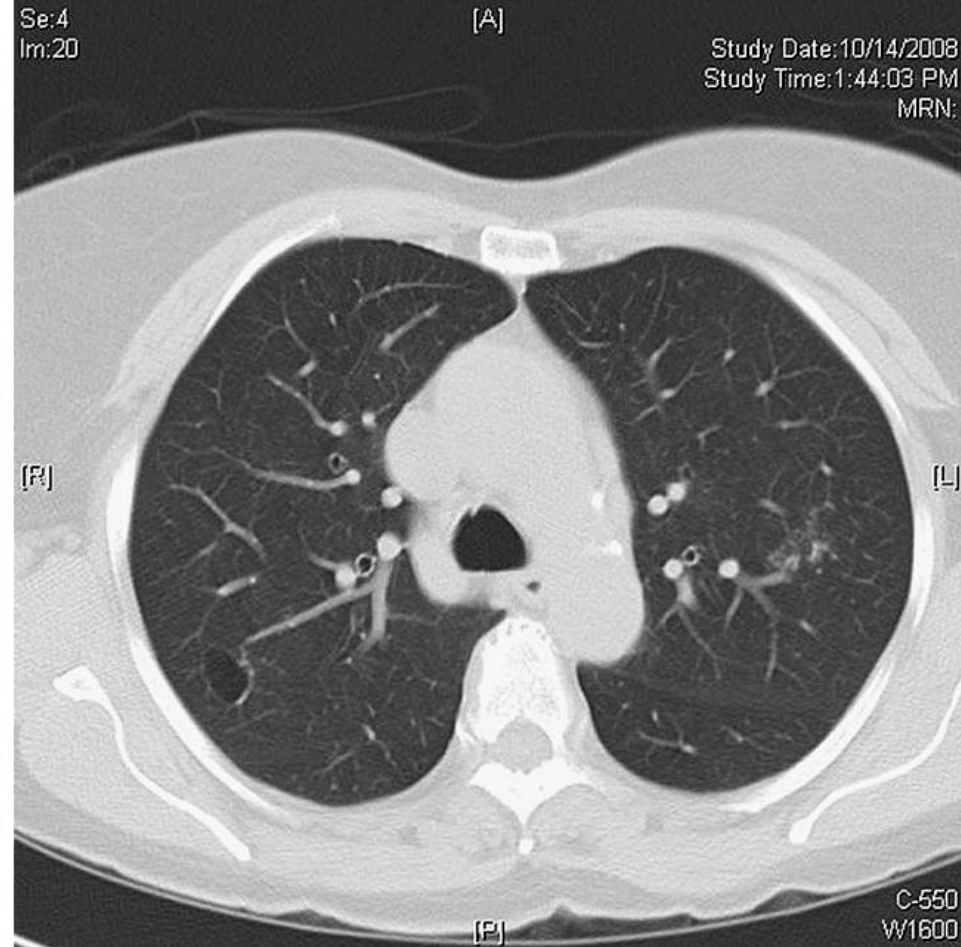
FDA(U.S.Food and Drug Administration)

FEV1

- Highly reproducible
- Tracks certain health outcomes in COPD,
- It is hard to modify with therapies, does not reflect disease activity
- correlates only loosely with clinically important health endpoints (mortality, hospitalization and QOL)



51세 남자 FEV1 51% predicted



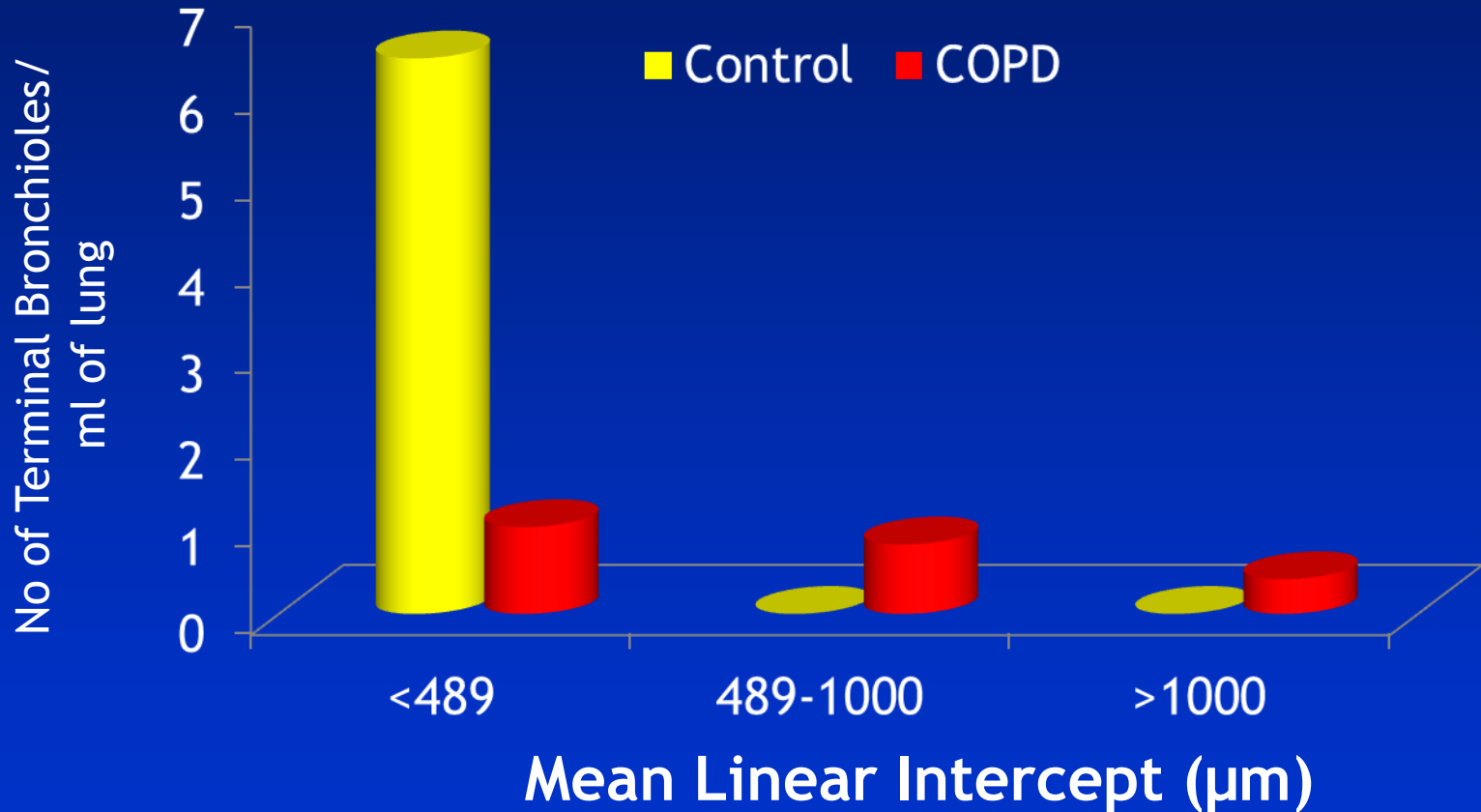
50세 여자 FEV1 49% predicted

Chest Imaging as Biomarkers in COPD

- Inspiratory and expiratory LDCT
 - diagnostic information regarding COPD
- Positive predictive value of 76%
- Negative predictive value of 79%

AIRWAYS DISAPPEAR!

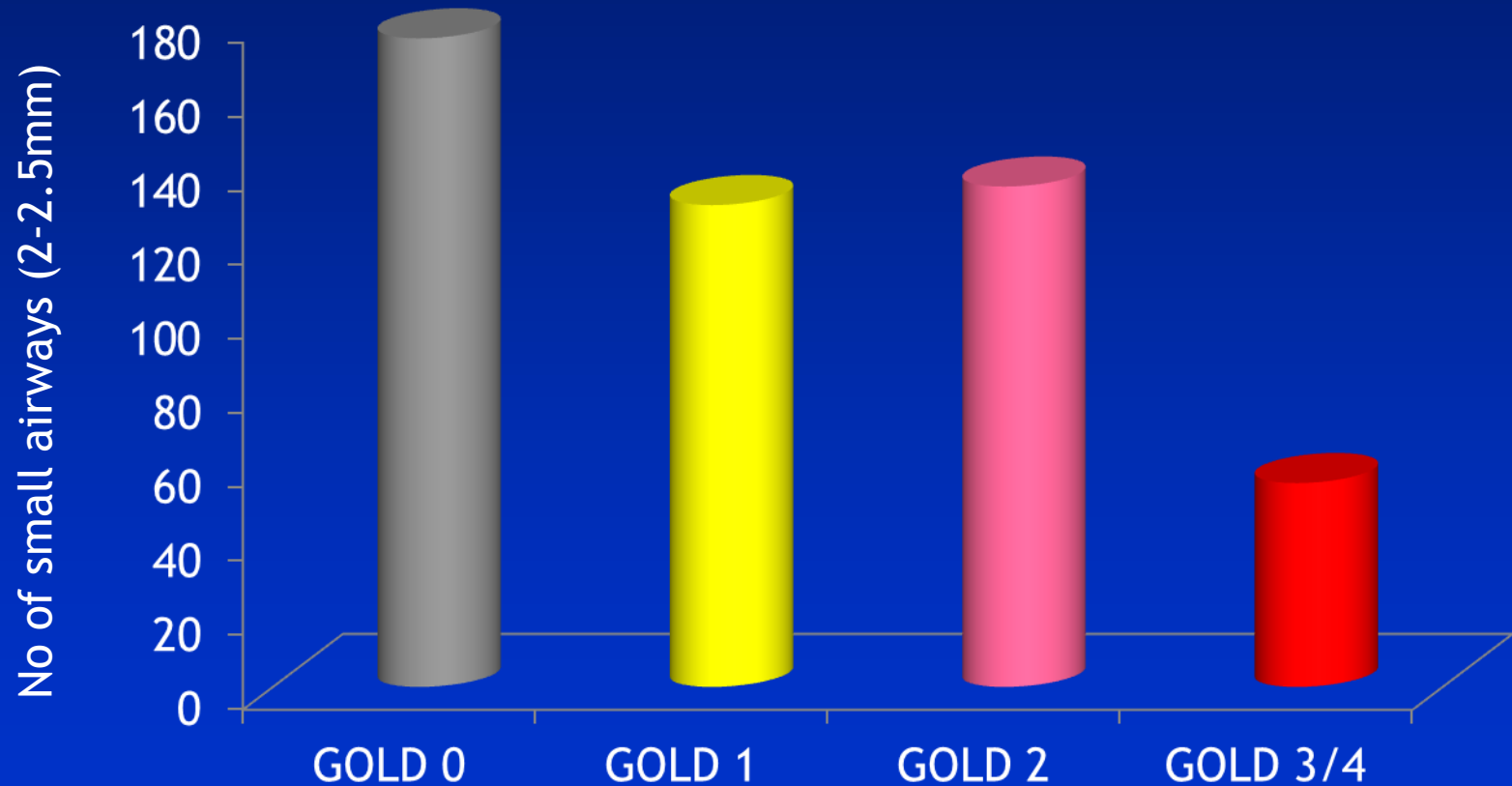
>80% reduction in number of small airways



Emphysema Progression

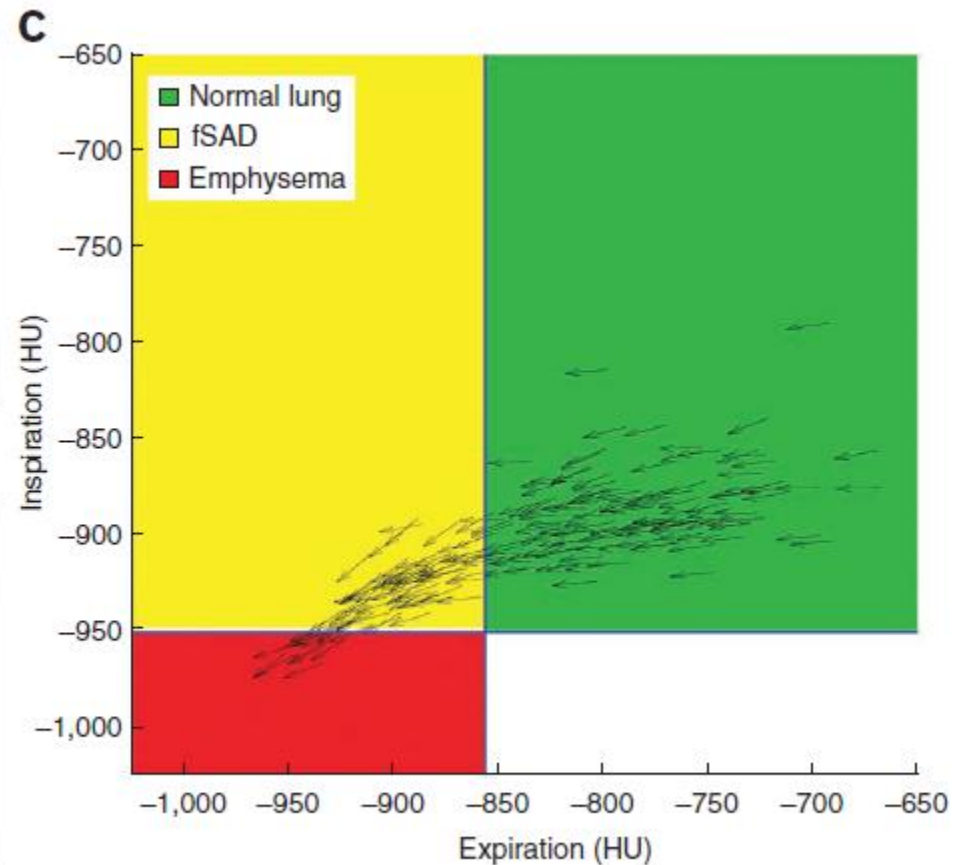
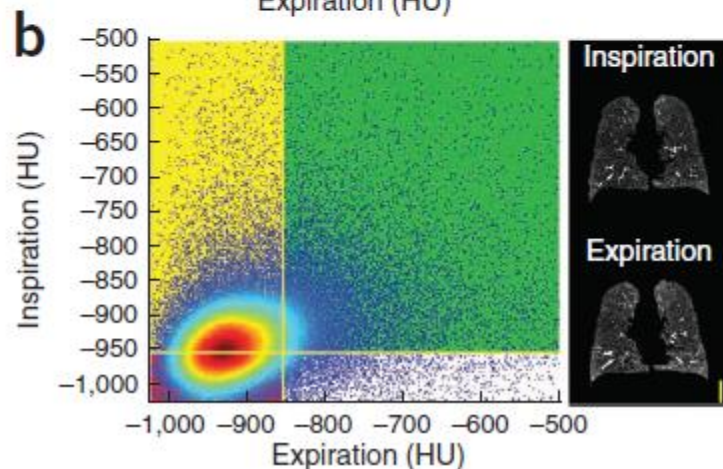
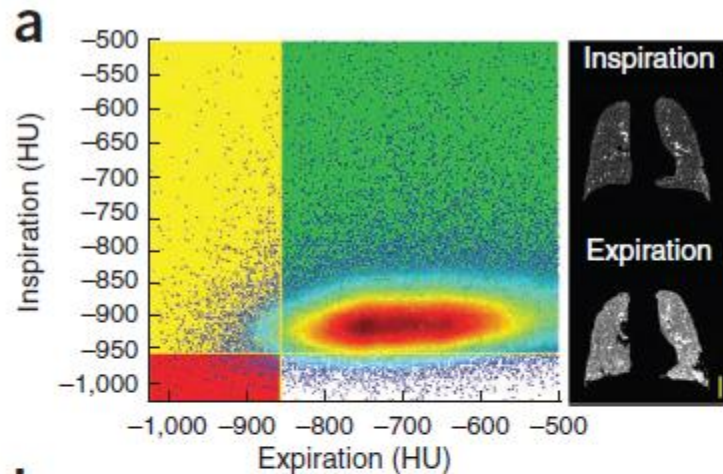
McDonough et al. N Engl J Med 2011;365:1567-75

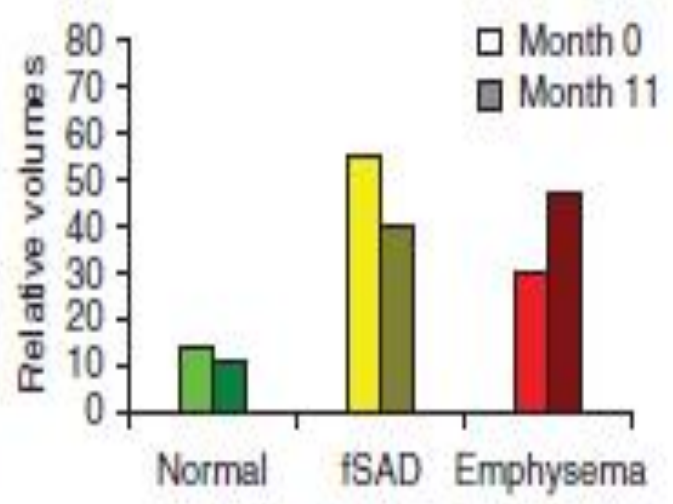
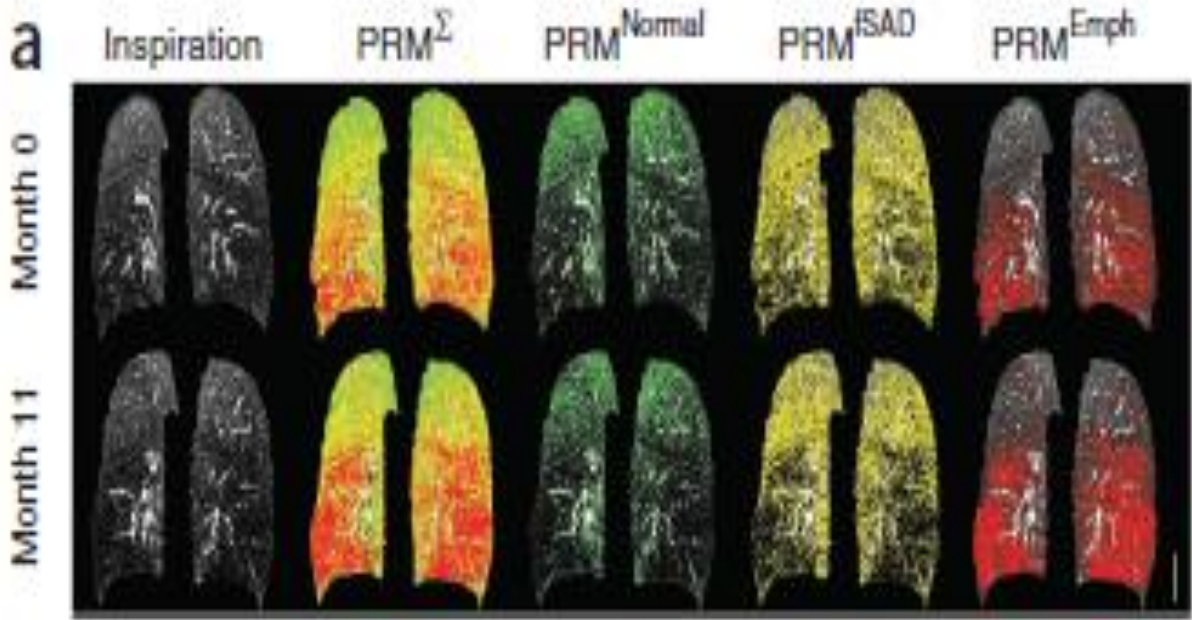
SMALL AIRWAY ATTRITION IN COPD



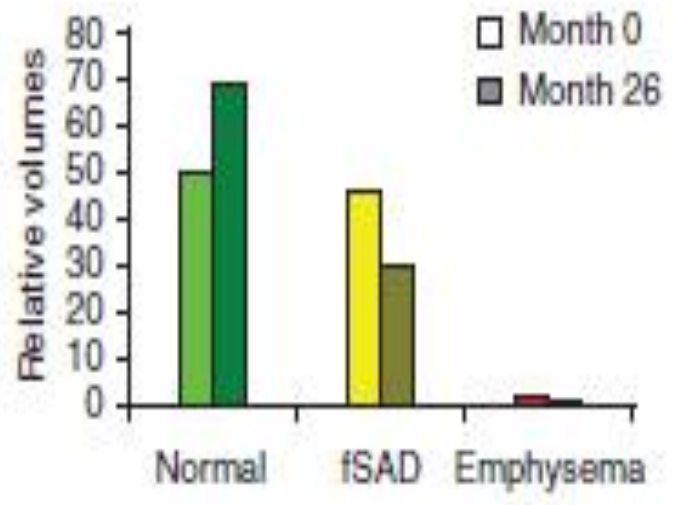
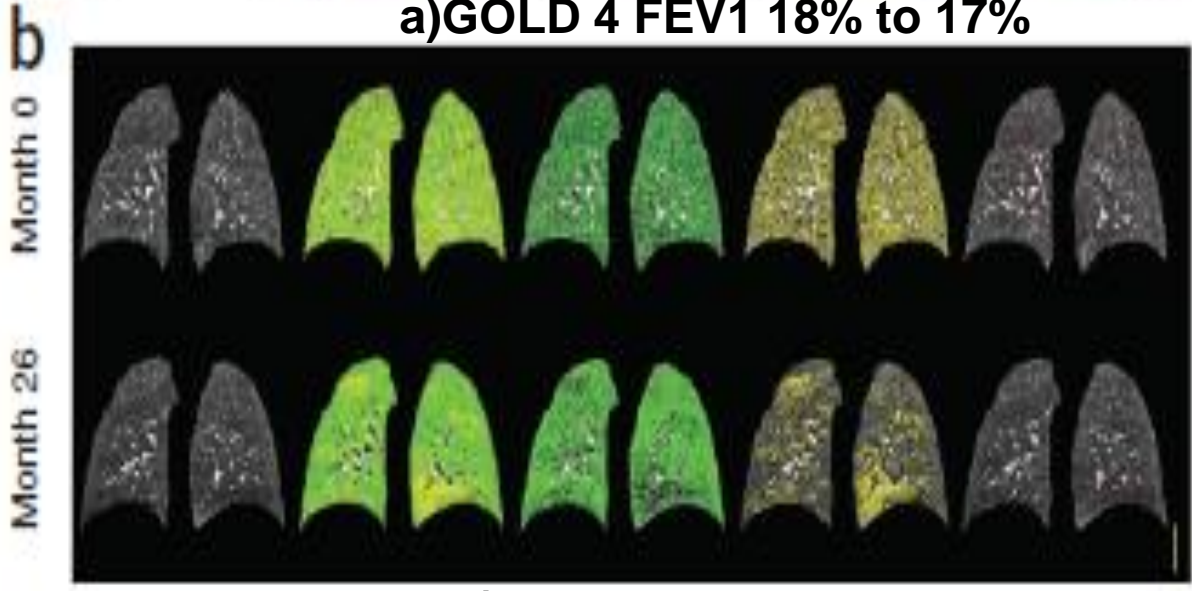
- This novel approach to imaging and its findings in terms of small airways number : biomarker for COPD risk, Px, response to Tx.

Computed tomography–based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression





a) GOLD 4 FEV1 18% to 17%



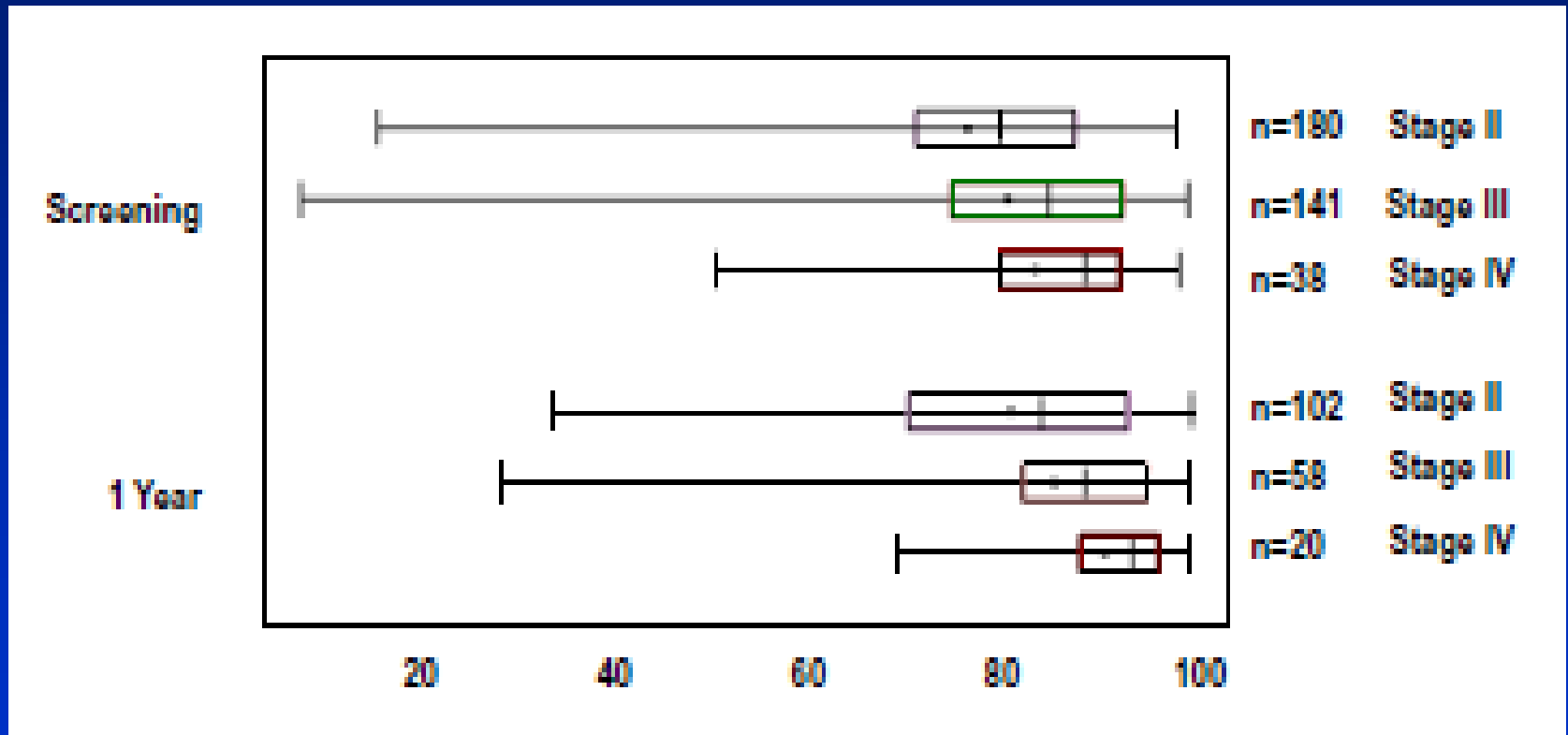
b) GOLD 2 FEV1 66 to 75%

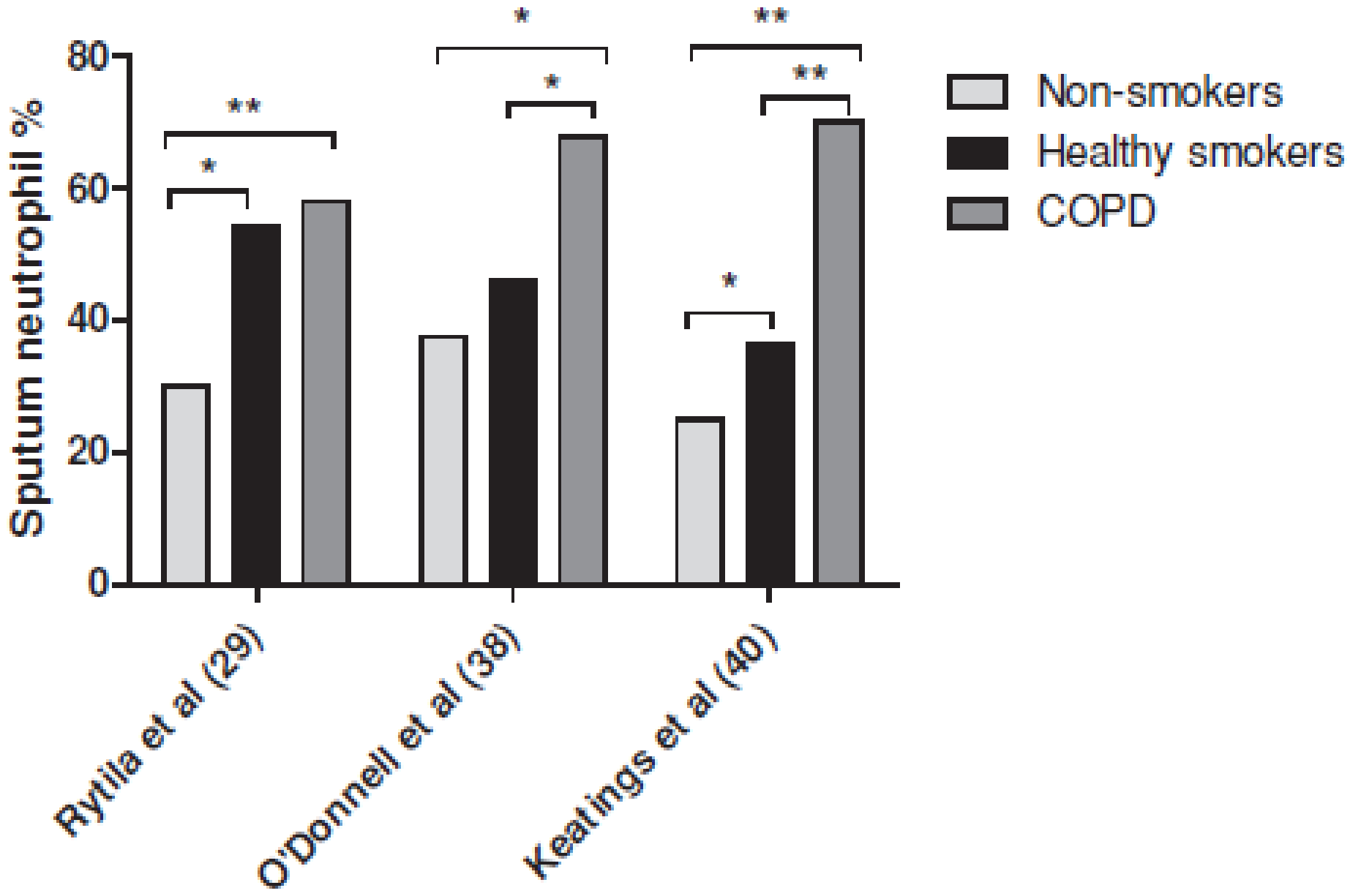
Sputum Parameters as Biomarkers in COPD

- Sputum: attractive source of biomarker
primary site of disease in COPD
- Sputum eosinophilia (Eosinophil counts 3% or greater)
 - affects about 25% of patients with COPD
 - increased clinical responsiveness to both inhaled and oral corticosteroids

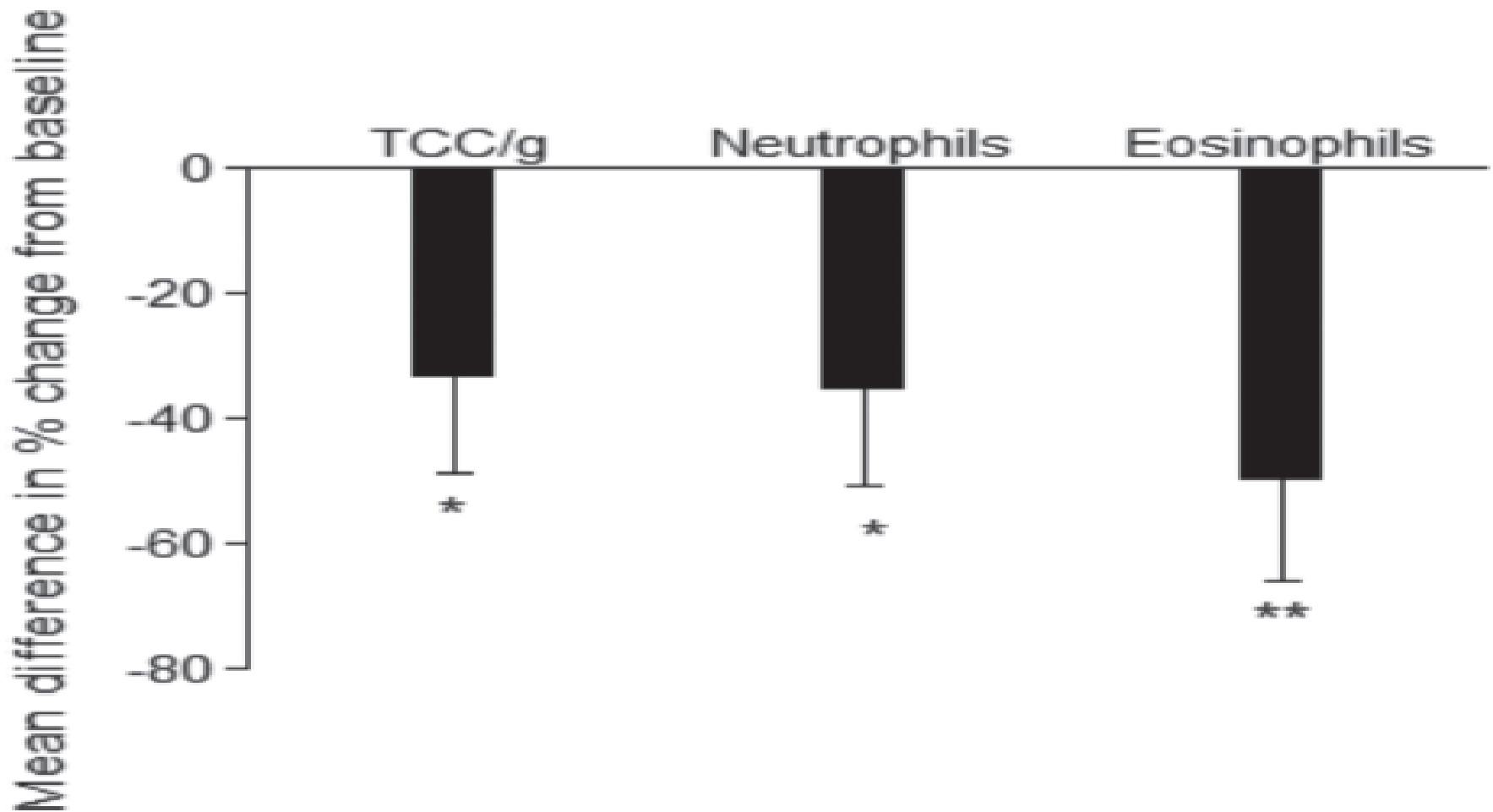
- Sputum neutrophilia, on the other hand, is associated with poor (or no) therapeutic responses to corticosteroids

Sputum neutrophil % according to GOLD stage





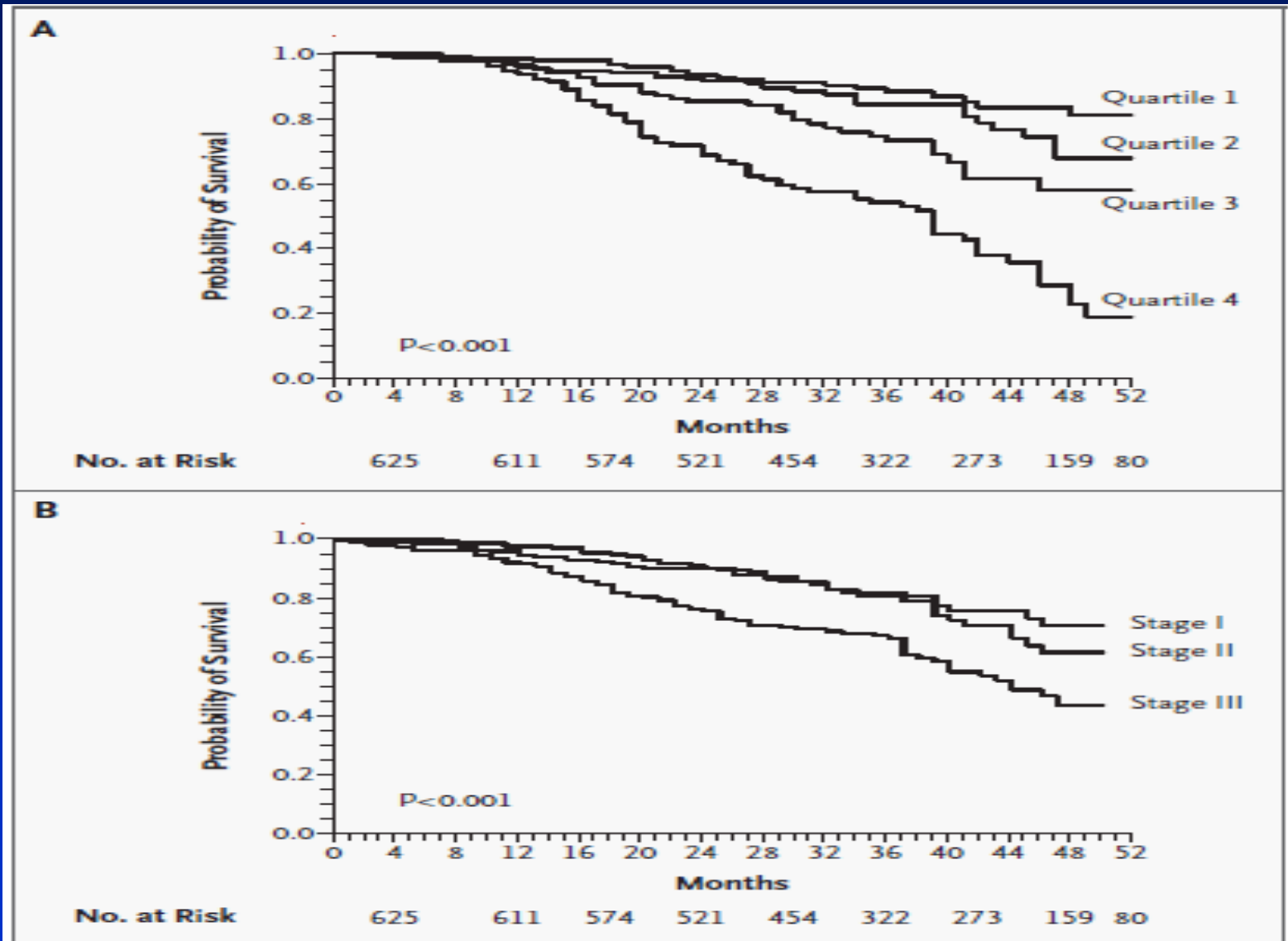
Sputum Biomarker as Treatment Efficacy (roflumilast and placebo Tx after 4 weeks)



Integrative severity indices as biomarker

- **BODE** index
body mass index,
degree of airflow obstruction measured
by FEV1,
dyspnea as determined by the medical
research council(MRC) dyspnea scale,
exercise capacity as determined by
distance walked in 6 min(6MWD)

BODE



BODE: Predictor of hospitalization

Variables	IRR for Hospital Admissions	95% CI	P Value
Risk of hospitalization			
BODE index	1.20	1.15-1.25	<0.001
Body mass index score	1.96	1.55-2.49	<0.001
Airflow obstruction score	1.50	1.32-1.69	<0.001
Dyspnea score	1.38	1.25-1.52	<0.001
Exercise capacity score	1.33	1.20-1.47	<0.001

ADO index

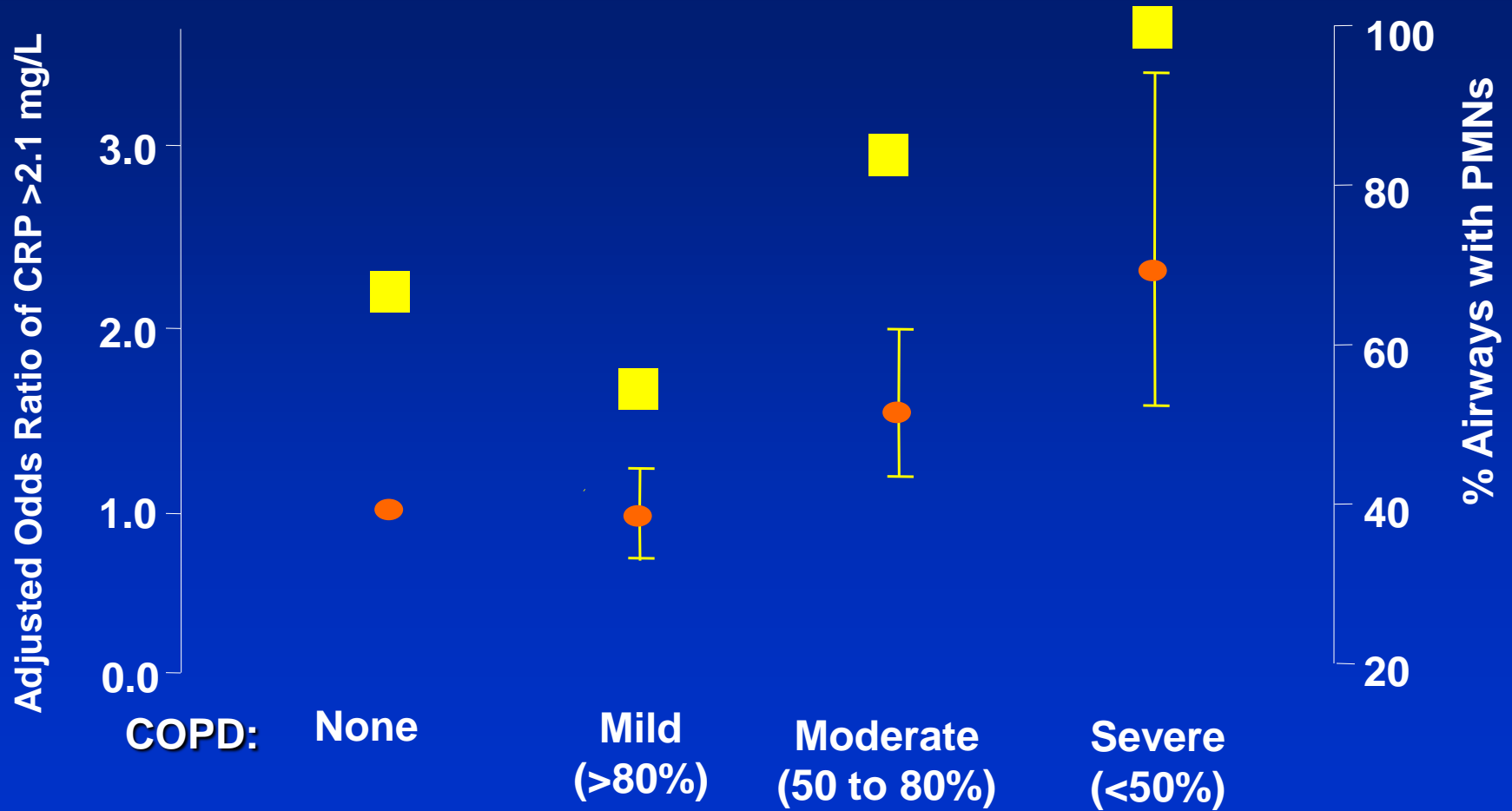
- Age
- Dyspnea(MRC scale)
- Severity of airflow obstruction(FEV1)

DOSE index

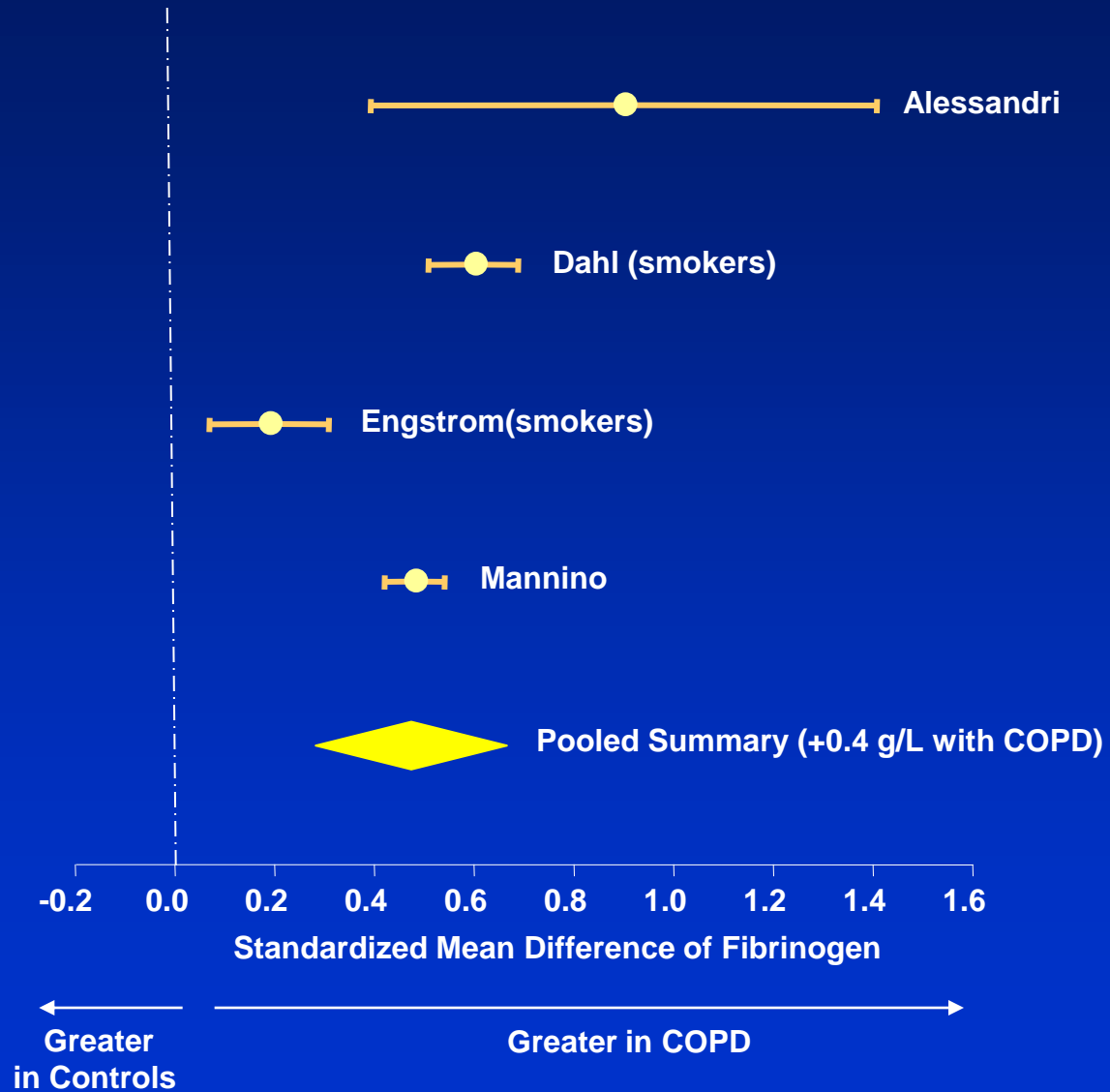
- Dyspnea(MRC scale)
- Obstruction (FEV1)
- Smoking status(Current or former)
- Exacerbation frequency

Biomarkers of COPD exacerbation

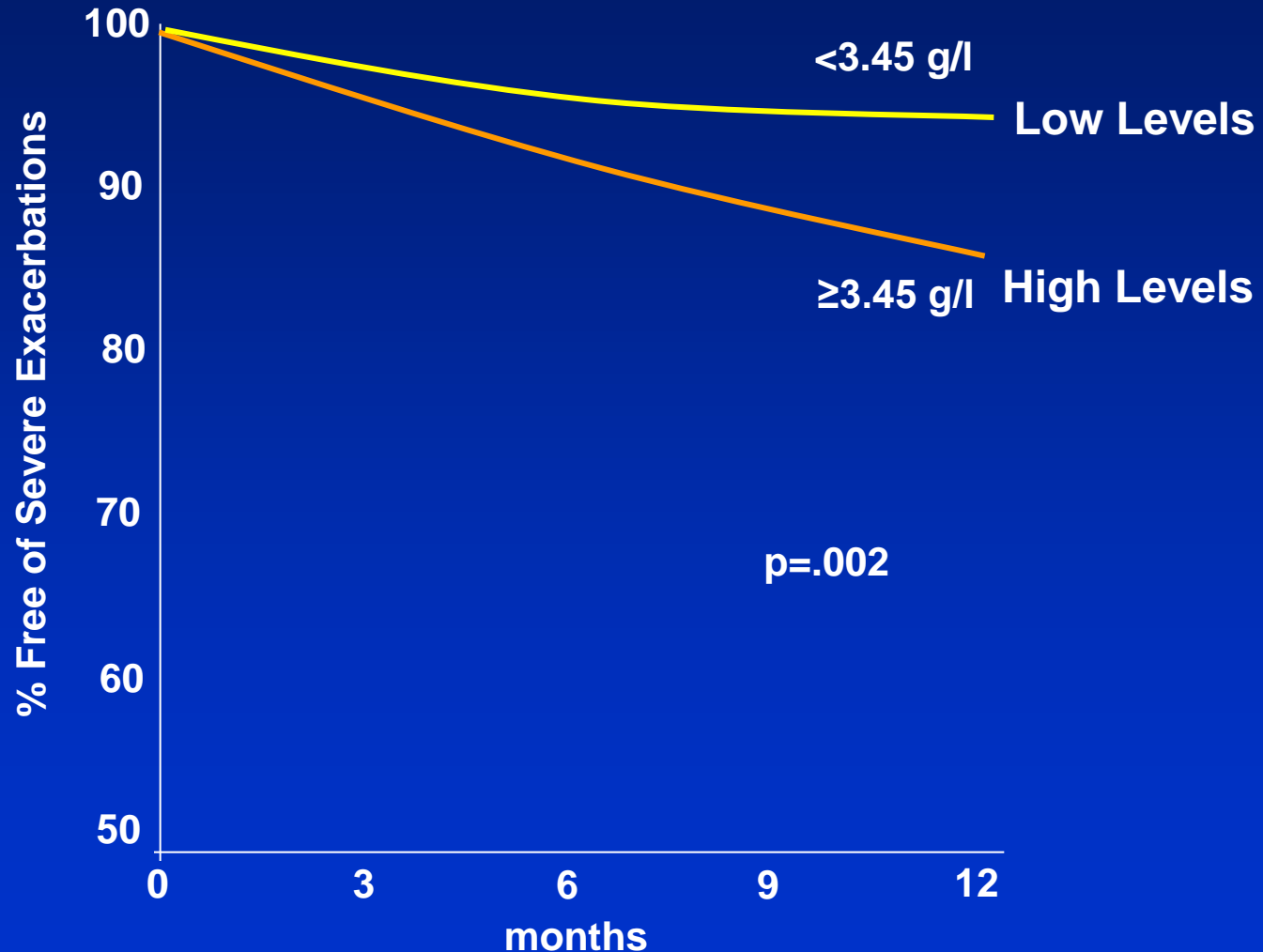
CRP and COPD



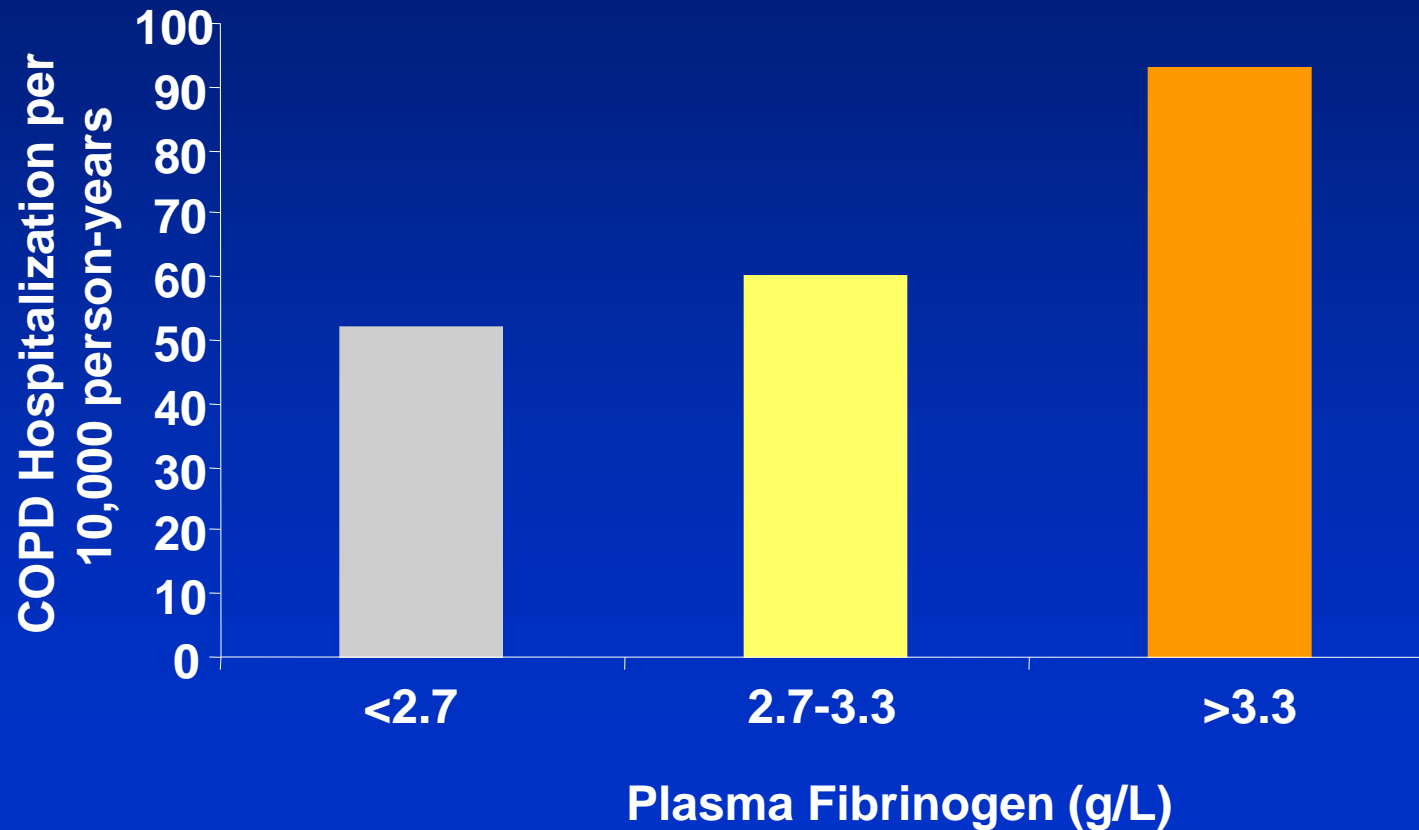
Fibrinogen and COPD



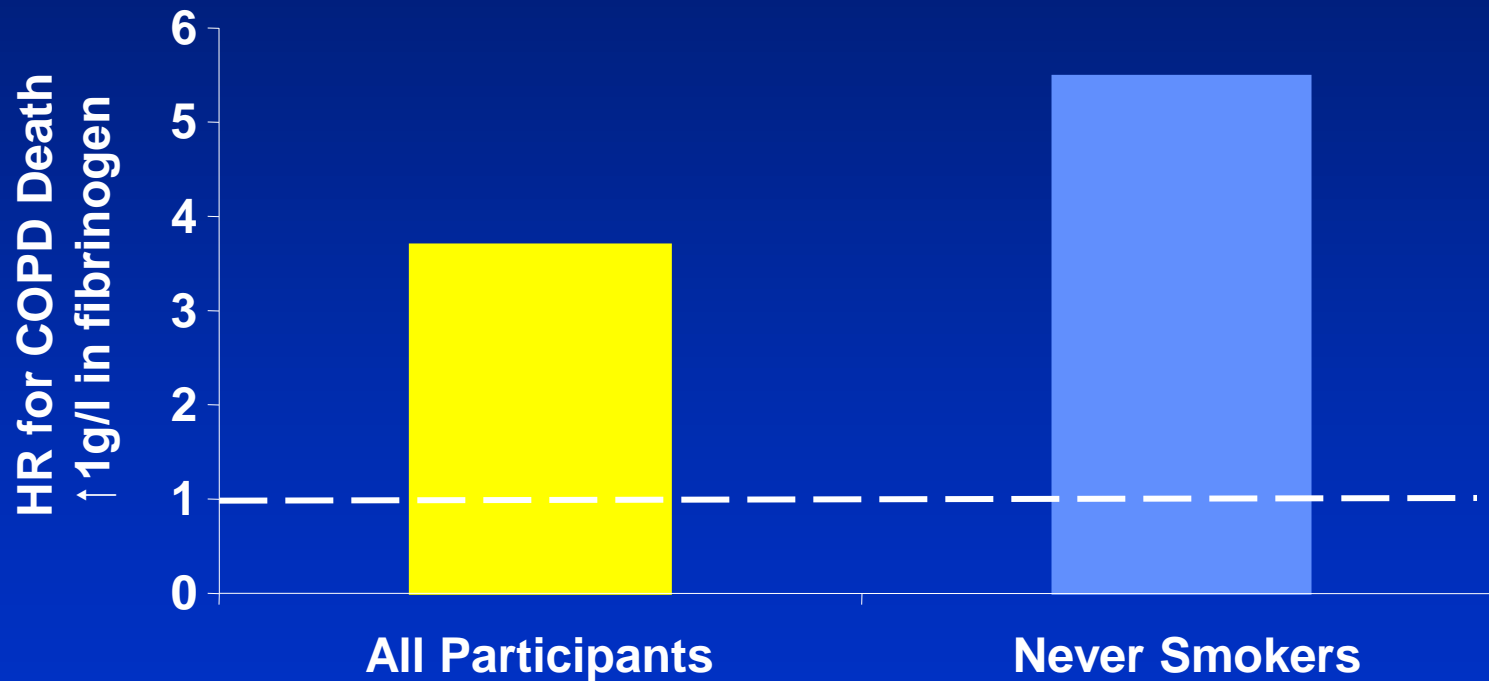
Fibrinogen is associated with Exacerbations



High Fibrinogen---More COPD Hospitalization



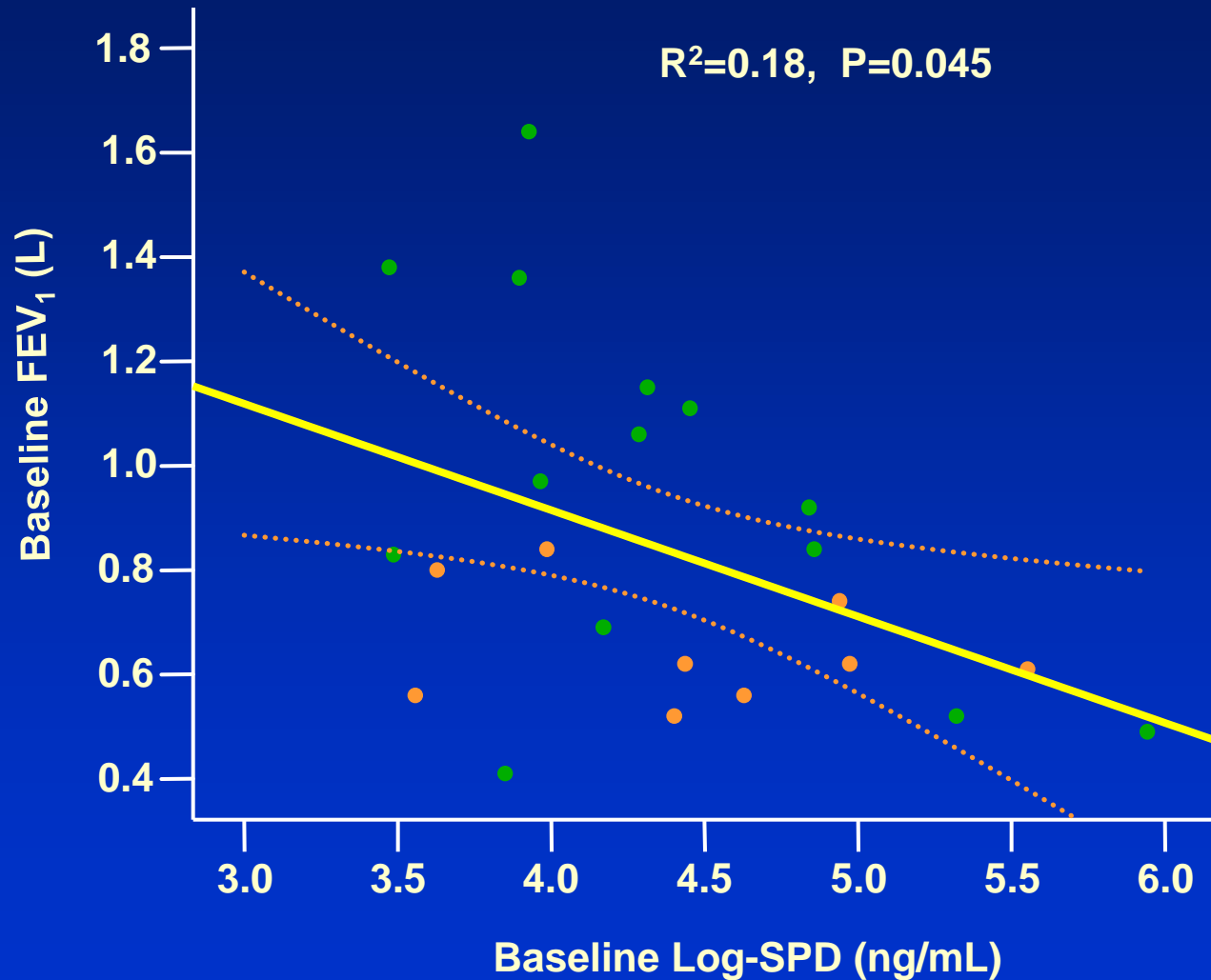
High Fibrinogen Levels Increase Risk of COPD Deaths



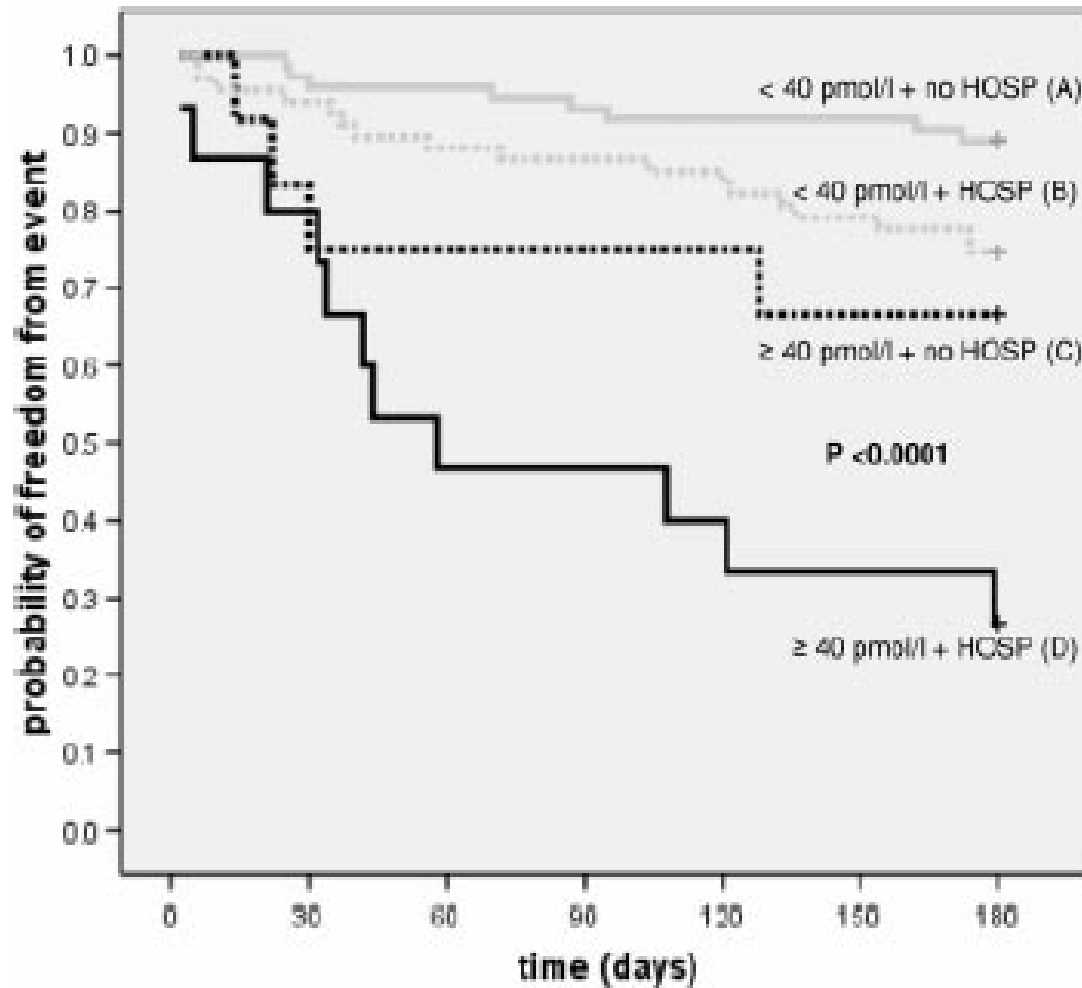
Plasma fibrinogen and IL-6 in COPD exacerbation

Biomarker	Exacerbation within 30 days		No or Resolved Exacerbations		P-value
	N	Median(IQR)	N	Median(IQR)	
Fibrinogen(mg/dl)	33	534.0(156.0)	157	464.0(115.0)	<0.001
Interleukin-6(pg/mL)	30	2.8(6.0)	151	0.6(2.6)	<0.001

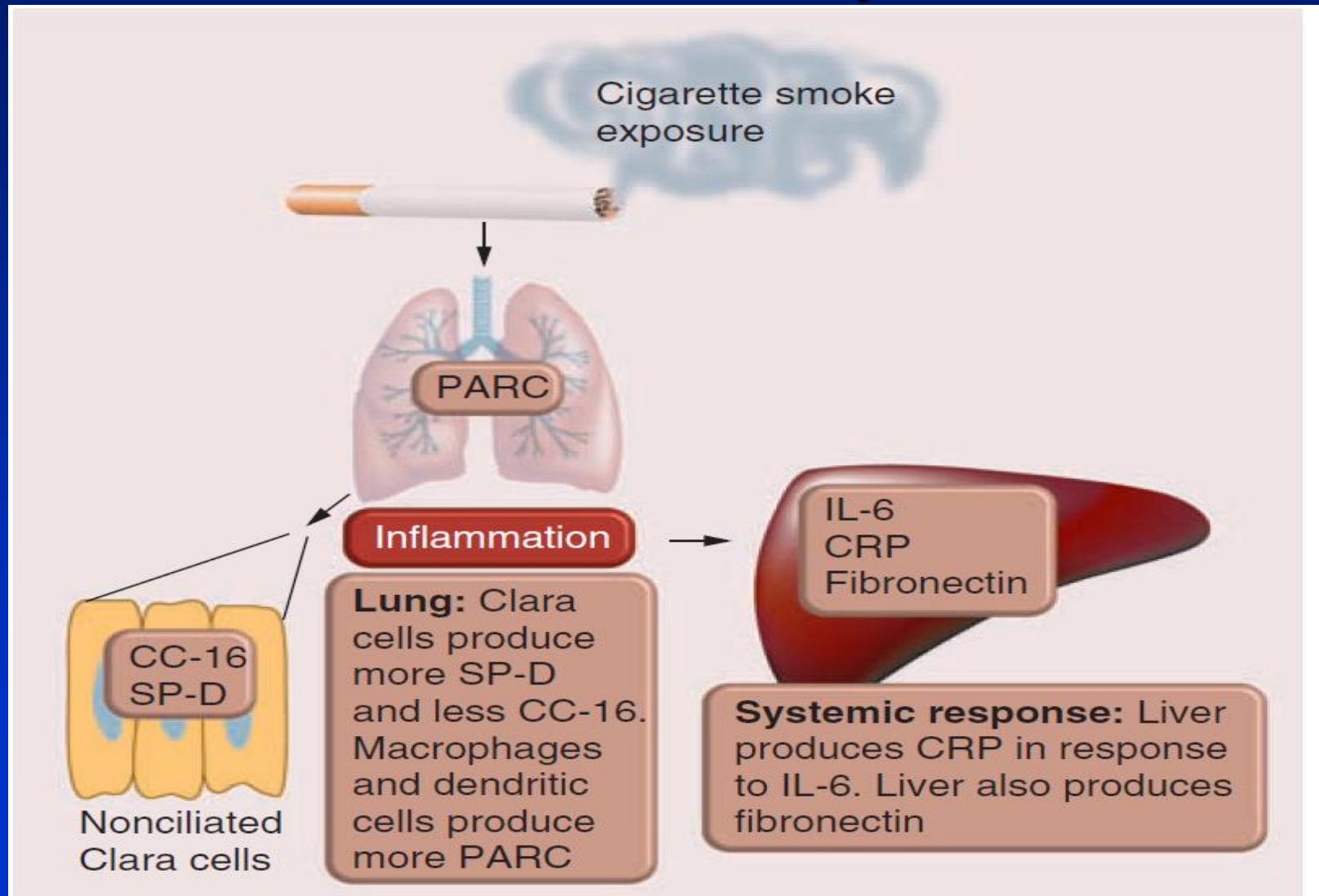
↑ Serum SPD Related to ↓ FEV₁



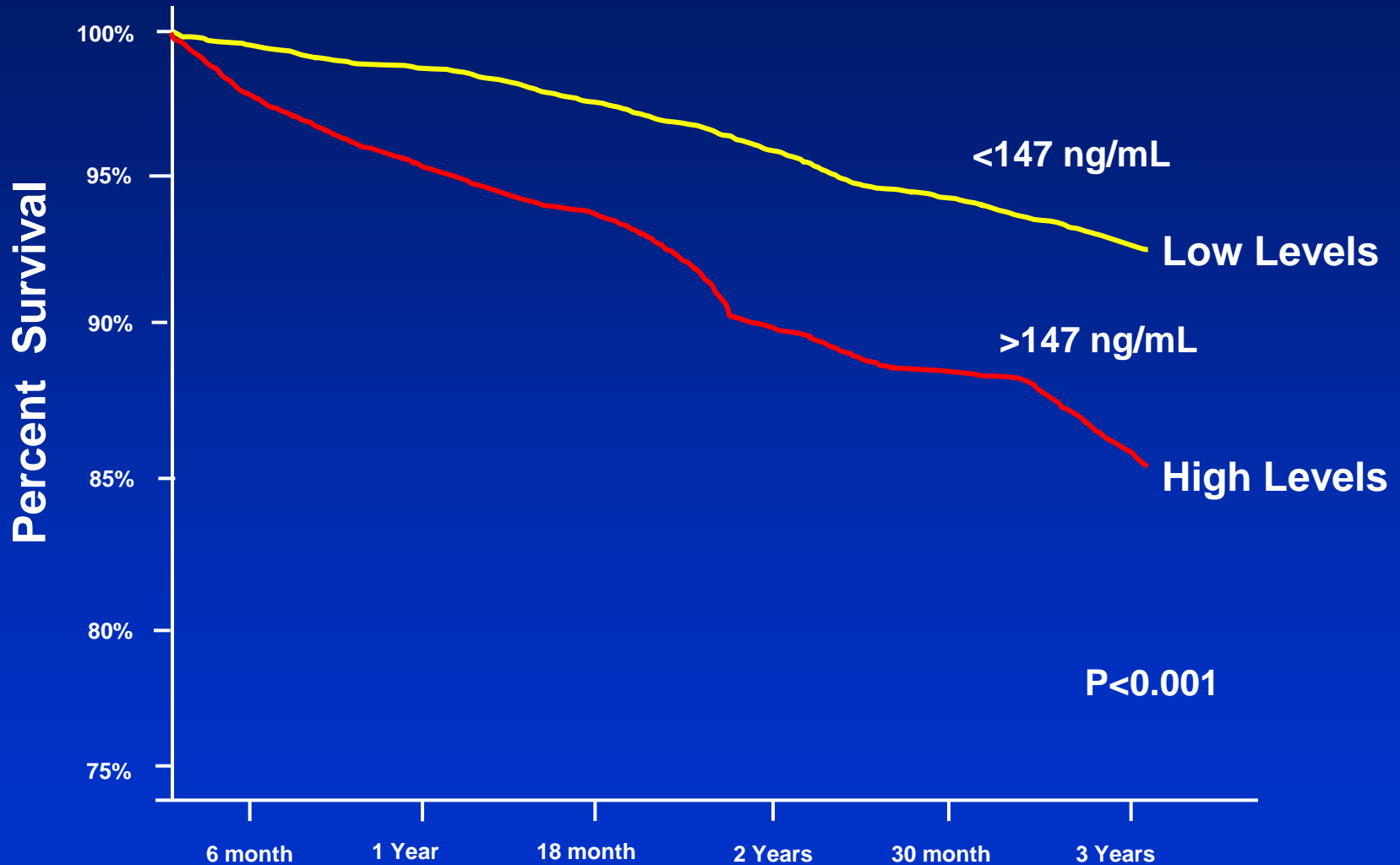
Copeptin



Inflammatory biomarkers predictive of COPD mortality



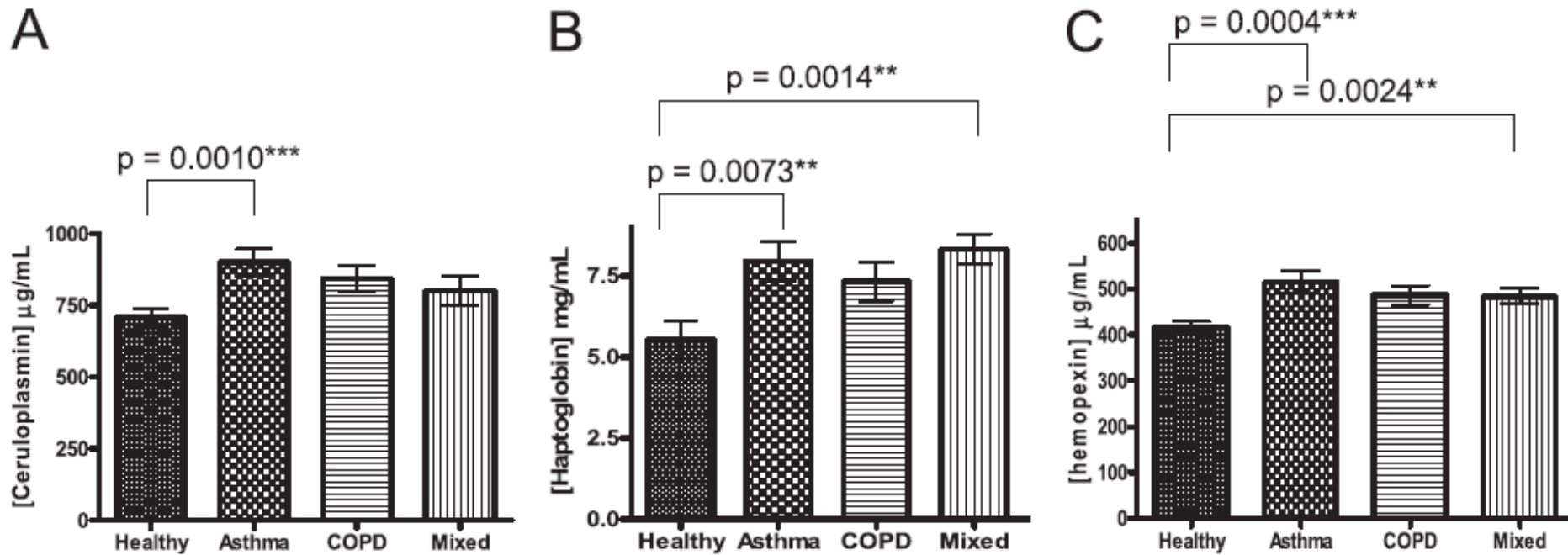
PARC/CCL-18 is associated with Mortality



Blood Parameters as Biomarkers in COPD

Biomarker	Mortality	Exacerbation	FEV1 decline
CRP	Yes	Yes	No
MMP9	No data	Yes	No data
PARC	Yes	Yes	No
Copeptin	No data	Yes	No data
Serum amyloid A	No data	Yes	No data
IP-10	No data	Yes	No data
IL-6	Yes	Yes	No
fibrinogen	Yes	Yes	No
Surfactant Protein D	Yes	Yes(high Con)	No
CC-16	Yes	No data	Possibly
TNF- α	No data	No data	No

Proteomics as novel diagnostic Biomarker



Genome-Wide Association Analysis of Blood Biomarkers in COPD


Protein	CHR	SNP	BP	Nearest Gene	Minor Allele	Test	OR	95% CI	<i>P</i> *
CC16	11	rs17157266	61956393	AHNAK	C	ADD	1.20	1.05 to 1.37	0.008
Surfactant protein D	16	rs8063863	82958351	ATP2C2	T	ADD	0.80	0.70 to 0.92	0.001
	16	rs8048576	82980535	ATP2C2	A	ADD	0.82	0.71 to 0.95	0.008
	10	rs7078012	81695413	SFTPD	T	ADD	0.84	0.73 to 0.97	0.017
	10	rs1885553	81701691	SFTPD	C	ADD	1.11	1.00 to 1.24	0.049
	10	rs1923539	81684930	RP11-479O17.4	A	ADD	1.13	1.00 to 1.27	0.043

Summary and Future direction

- Several promising biomarkers
 - **sputum**: eosinophilia
 - **Blood** :
 - CRP (for exacerbation, especially if the levels are >10 mg/L)
 - IL-6 (for predicting total mortality)
 - CC-16 (for predicting accelerated decline in lung function)
 - eosinophilia($>2\%$ of total cell count)

Summary and Future direction

- Evolving technology in gene sequencing, micro-RNA interrogation, high throughput proteomics, coupled with large scale cohort studies in COPD (e.g. ECLIPSE, SPIROMICS, COPDGene) :identification, validation and qualification of even better biomarkers in the near future for the diagnosis, prognosis and monitoring (of therapeutics) in COPD.



경청해 주셔서 감사합니다.