

Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease

Celli BR et al.

Am J Respir Crit Care Med. 15;185(10):1065-72. (May 2012)

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- currently fourth highest cause of death worldwide¹
- abnormal inflammatory reaction as cause of obstruction²
- caused by particles, gases and cigarette smoke (80-90%)²
- therapy: smoking cessation, bronchodilators, oxygen, lung transplantation²

GOLD scale^{2,3}

- 0** normal spirometry, chronic symptoms (cough, sputum)
- I** $FEV_1/FVC < 70\%$, $FEV_1 \geq 80\%$ (with/without chronic symptoms)
- II** $FEV_1/FVC < 70\%$, $50\% \leq FEV_1 < 80\%$ (with/without chronic symptoms)
- III** $FEV_1/FVC < 70\%$, $30\% \leq FEV_1 < 50\%$ (with/without chronic symptoms)
- IV** $FEV_1/FVC < 70\%$, $FEV_1 < 30\%$ (with/without chronic symptoms)

¹ CELLI BR et al. (2012). *Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease*

² LORENZ J (2009). *Checkliste XXL Pneumologie*

³ http://www.goldcopd.org/uploads/users/files/GOLD_Pocket_May2512.pdf



How to Predict Mortality in Patients with COPD?



- severity of airflow limitation (FEV_1)
- arterial hypoxemia/hypercapnia
- exercise performance
- degree of breathlessness
- low BMI
- BODE: BMI, FEV_1 , dyspnea, 6-minute walk distance
- ADO: age, dyspnea, FEV_1

**Biomarkers reflecting pathobiological pathways which
may be altered in COPD?**

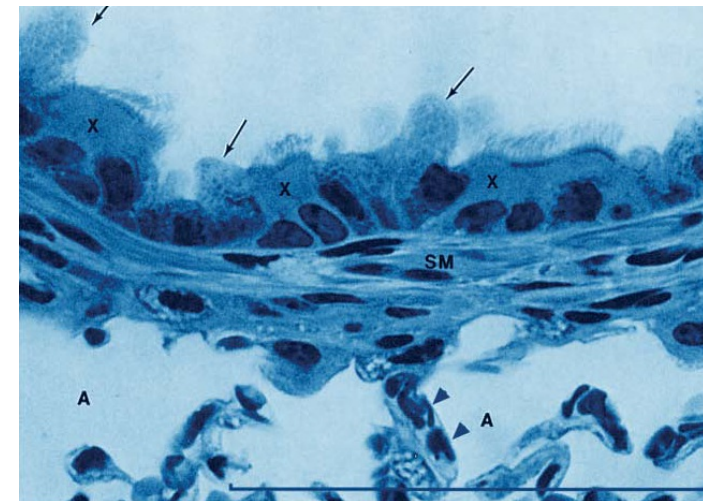


Biomarkers

Clara cell-16



- secreted by Clara cells¹
- expressed in airways, epithelial cells of the nose and urogenital tract¹
- acts as an immunosuppressant and provides protection against oxidative stress and carcinogenesis¹
- serum levels reduced in COPD, asthma, smokers and related to decline of FEV₁^{1,2}



¹ LOMAS DA et al. (2008). Evaluation of serum CC-16 as a biomarker for COPD in the ECLIPSE cohort

² CELLI BR et al. (2012). Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease

JUNQUEIRA LCU et al. (2005). Histologie



Biomarkers

CCL-18/PARC



- constitutively expressed in human lung¹
- expressed by PBMCs (constitutively or induced by bacterial toxins)¹
- induces tolerogenic immune responses → immunosuppressive¹
- increased serum levels in pathological conditions of the lung¹
- associated with increased risk of death in respiratory disease²

¹ CHANG CY et al. (2010). CC-chemokine ligand 18/pulmonary activation-regulated chemokine expression in the CNS with special reference to traumatic brain injuries and neoplastic disorders

² CELLI BR et al. (2012). Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease



Biomarkers

C-reactive protein



- produced in the liver (IL-6 induced)¹
- acute phase protein¹
- opsonisation of microbes → inflammatory marker^{1,2}
- associated with increased risk of death in patients with COPD²
- elevated in COPD patients compared to (non)smokers²
- associated with increased hospitalisation in COPD?²

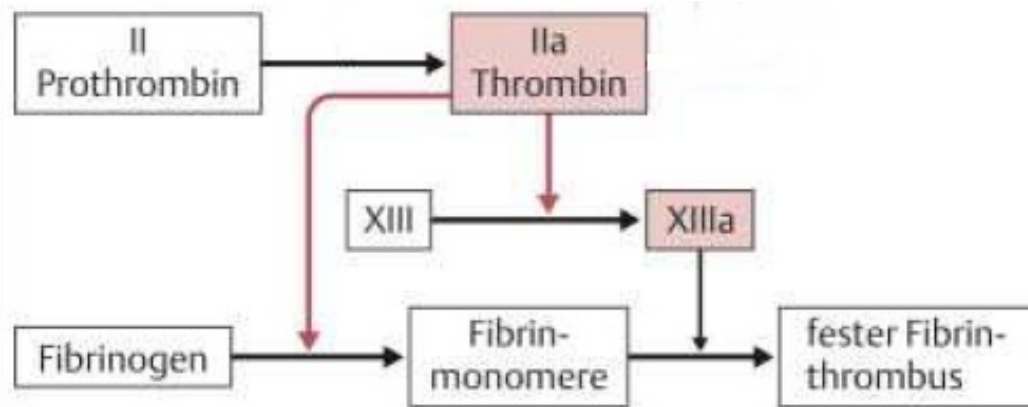
¹ MURPHY K et al. (2009). *Janeway Immunologie*

² CELLI BR et al. (2012). *Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease*

Biomarkers

Fibrinogen

- synthesizes by hepatocytes¹
- acute phase protein¹
- increased levels after injury, diseases associated with vascular disruption, infection & inflammation¹
- activates immune cells¹



¹ DAVALOS D et al. (2012). Fibrinogen as a key regulator of inflammation in disease
HUPPELSBERG J et al. (2009). Kurzlehrbuch Physiologie



Biomarkers

IL-6



- produced in macrophages and dendritic cells¹
- enhances immune response of lymphocytes and induces acute phase protein production in the liver¹
- endogenous pyrogen¹
- induces development of T_H17-cells¹
- associated with increased risk of death in respiratory disease²

¹ MURPHY K et al. (2009). *Janeway Immunologie*

² CELLI BR et al. (2012). *Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease*



Biomarkers

IL-8



- produced in macrophages, fibroblasts, keratinocytes, endothelial cells and dendritic cells¹
- chemotactic factor for T-cells, neutrophil and basophil granulocytes¹
- involved in angiogenesis¹
- increased levels in sputum COPD patients²
- association of elevated levels in other pulmonary diseases, such as: ARDS, reperfusion injury, asthma, idiopathic pulmonary fibrosis²

¹ MURPHY K et al. (2009). *Janeway Immunologie*

² MUKAIDA M (2003). *Pathophysiological roles of interleukin-8/CXCL8 in pulmonary diseases*



Biomarkers

Surfactant Protein-D



- involved in innate host defence & regulation of inflammatory processes in the lung¹
- expressed/secreted by alveolar type II pneumocytes & bronchiolar Clara cells¹
- present in: lung, mucosal epithelia, vascular epithelial cells, serum²
- related to pulmonary inflammation → elevated in smokers³
- associated with increased risk of death in respiratory disease³

¹ HU F et al. (2012). Surfactant protein D inhibits lipopolysaccharide-induced monocyte chemoattractant protein-1 expression in human renal tubular epithelial cells: implication for tubulointerstitial fibrosis

² SØRENSEN GL et al. (2005). Genetic and environmental influences of surfactant protein D serum levels.

³ CELLI BR et al. (2012). Inflammatory Biomarkers Improve Clinical Prediction of Mortality in Chronic Obstructive Pulmonary Disease



Methods



- Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE)
- evaluation at 3 & 6 months after baseline and every 6 months for 3 years
- no determination of cause of death

Functional measurements

- 6-minute walk distance
- Spirometry

Emphysema

- low-dose CT



Methods

Inflammatory Biomarkers

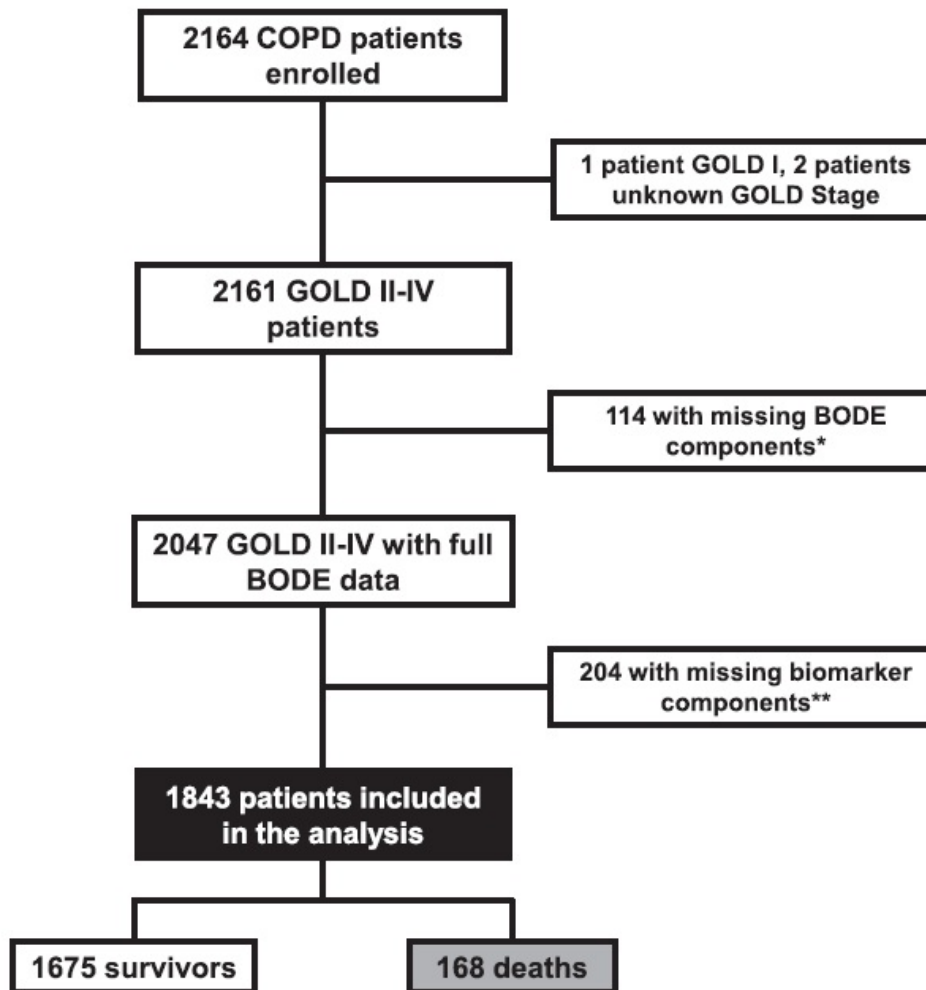


- Serum:
 - CC-16
 - CCL-18/PARC
 - SP-D
 - IL-8
 - TNF- α
- Plasma:
 - fibrinogen
 - CRP
- Whole blood:
 - white blood cells
 - neutrophils

→ Immunoassays



Methods





Methods



TABLE 1. BASELINE CLINICAL CHARACTERISTICS AND BIOMARKERS LEVELS OF THE PATIENTS WITH COPD WHO SURVIVED OR DIED DURING THE 3-YEAR FOLLOW-UP

	Alive at 3 Years* (n = 1,675)	Dead at 3 Years (n = 168)	P Value
Demographics			
Age, yr	63 (7)	66 (7)	<0.001
Females, %	35	30	0.232
Current smoker, %	37	35	0.558
Body mass index, kg/m ²	27 (5)	27 (6)	0.964
Clinical variables			
FEV ₁ , L [†]	1.37 (0.51)	1.14 (0.47)	<0.001
FEV ₁ , %predicted [†]	49 (15)	43 (15)	<0.001
FEV ₁ /FVC, % [†]	45 (11)	42 (12)	0.002
6-min walk distance, m	377 (117)	304 (129)	<0.001
Emphysema LAA, % (-950HU)	18 (12)	20 (12)	0.047
mMRC dyspnea score, 2+, %	51	68	<0.001
SGRQ-C total score	49 (20)	55 (20)	<0.001
BODE Index	3 (2)	4.3 (2.2)	<0.001
Percentage blood oxygen	94.7 (2.9)	93.5 (3.5)	<0.001
Comorbidities			
Hypertension, %	41	45	0.285
Cardiovascular history [‡] , %	32	49	<0.001
Diabetes	10	19	<0.001
Gastroesophageal reflux	26	21	0.228

Definition of abbreviations: CC16 = Clara cell secretory protein-16; CCL18/PARC = chemokine ligand 18/pulmonary and activation-regulated chemokine; COPD = chronic obstructive pulmonary disease; CRP = C-reactive protein; HU = Hounsfield units; LAA = low-attenuation area; mMRC = modified Medical Research Council; SGRQ-C = St. George's Respiratory Questionnaire, COPD-specific version; SP-D = surfactant protein D.

Continuous data are shown as means (SD) and categorical variables are shown as percentages. Biomarkers data are shown as median [interquartile range].

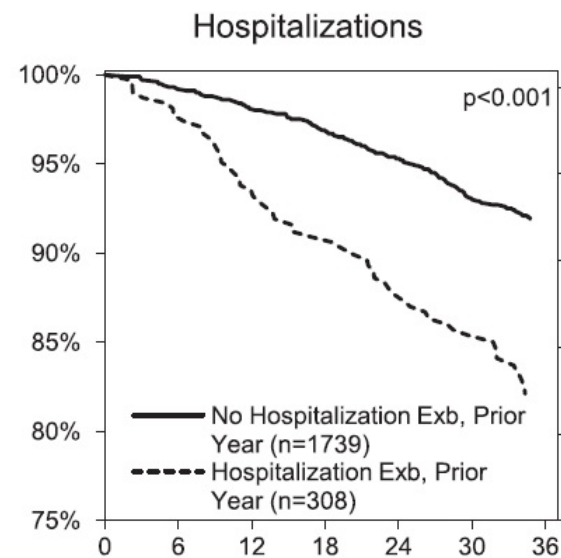
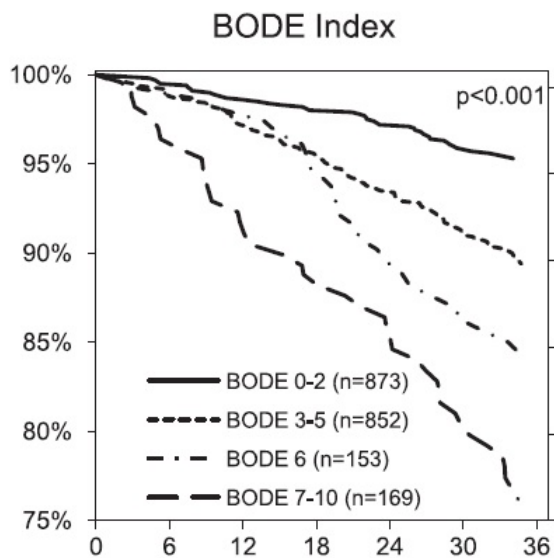
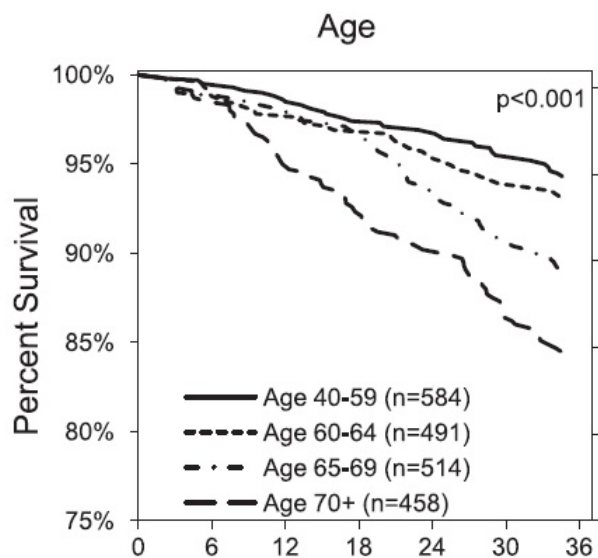
*Three years defined as survival status on Day 1,060.

[†] Post-bronchodilator values.

[‡] Cardiovascular history as defined with the American Thoracic Society–Division of Lung Diseases 78 Questionnaire.



Methods





Results

Biomarkers

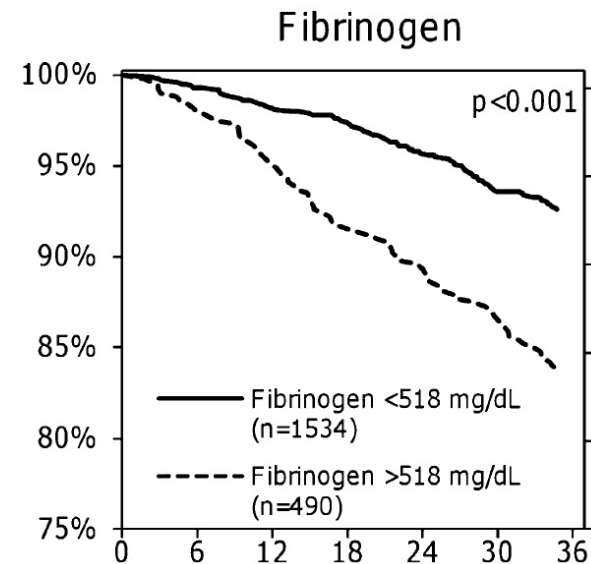
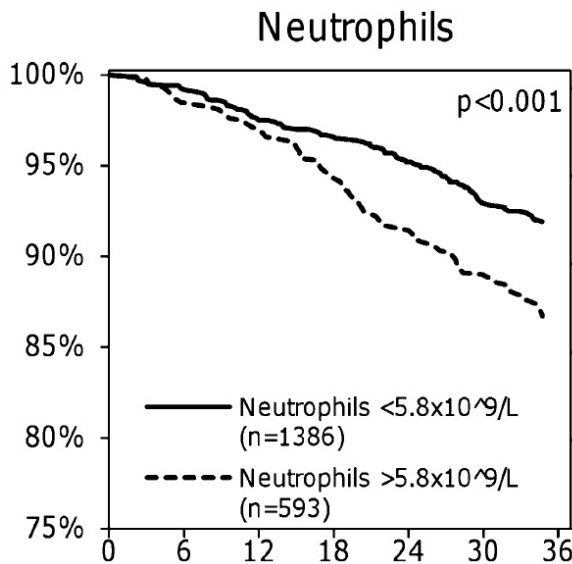
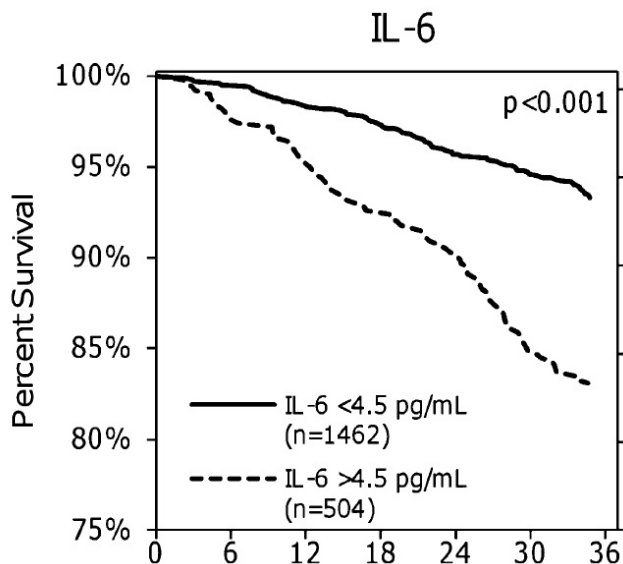


Baseline levels

	Alive at 3 Years* (n = 1,675)	Dead at 3 Years (n = 168)	P Value
Biomarkers			
White blood cells, 10 ⁹ /L	7.8 (2.2)	8.7 (3.4)	<0.001
Neutrophil count, 10 ⁹ /L	5.1 (1.9)	6 (3.2)	<0.001
IL-6, pg/ml	2 [0.6–4.3]	4.1 [1.3–8.6]	<0.001
Fibrinogen, mg/dl	444 [385–511]	504 [425–575]	<0.001
CRP, mg/L	3.1 [1.5–6.9]	4.6 [2.3–11.8]	<0.001
CCL-18/PARC, ng/ml	105 [81–135]	123 [92–164]	<0.001
SP-D, ng/ml	119 [84–168]	131 [93–188]	0.006
IL-8, pg/ml	6.9 [3.3–12.8]	9.5 [3.3–17]	0.038
CC-16, ng/ml	4.9 [3.4–6.9]	5.3 [3.6–7.7]	0.048



Results



Time Observed (Months)

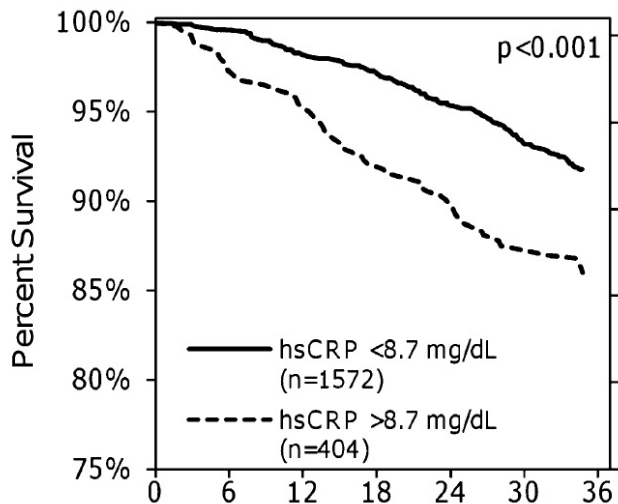
Parameter	Increment	Hazard Ratio	95% Confidence Interval	P Value
IL-6	1 log SD increase	1.47	(1.25–1.72)	<0.001
Neutrophils	1 SD increase	1.26	(1.14–1.40)	<0.001
White blood cells	1 SD increase	1.26	(1.13–1.42)	<0.001
Fibrinogen	1 log SD increase	1.33	(1.13–1.56)	<0.001



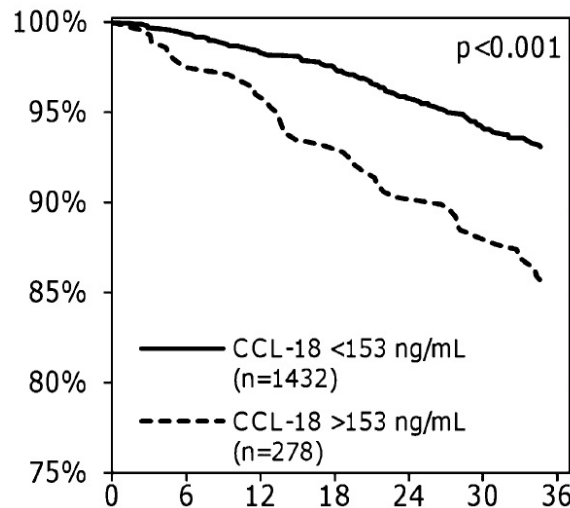
Results



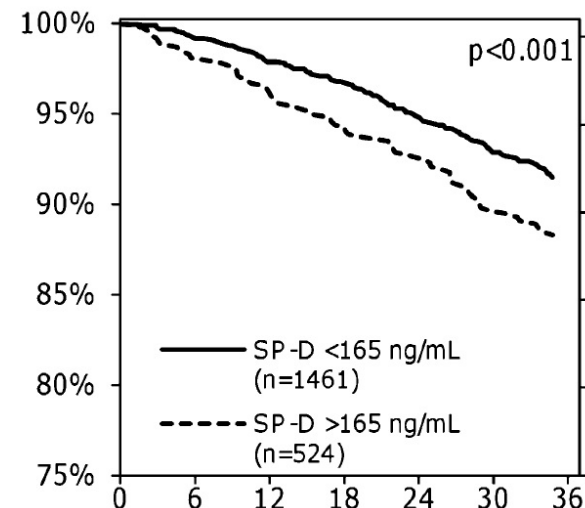
hsCRP



CCL-18/PARC



SP-D

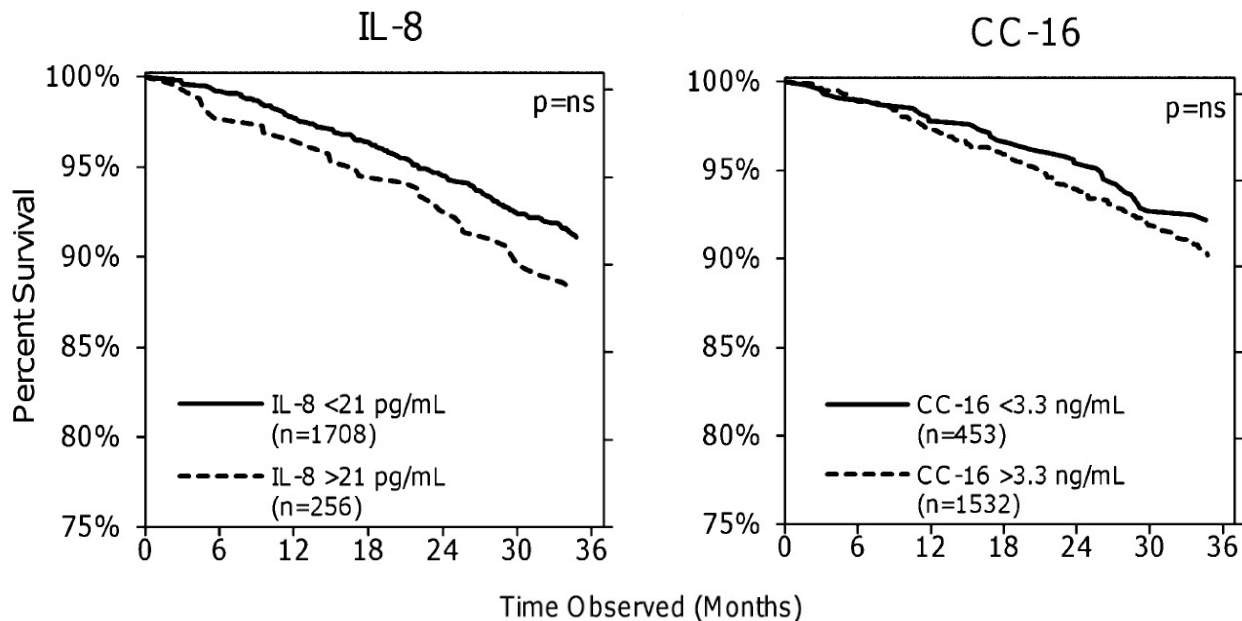


Time Observed (Months)

Parameter	Increment	Hazard Ratio	95% Confidence Interval	P Value
CRP	1 log SD increase	1.27	(1.09–1.48)	0.002
CCL-18/PARC*	1 log SD increase	1.3	(1.08–1.56)	0.005
SP-D	1 log SD increase	1.22	(1.04–1.43)	0.016



Results



Parameter	Increment	Hazard Ratio	95% Confidence Interval	P Value
IL-8	1 log SD increase	1.17	(1.00–1.36)	0.045
CC-16	1 log SD increase	1.04	(0.88–1.23)	0.674



Results



Model	C Statistic	Difference from Base	95% Confidence Interval for Difference from Base Model	P Value Versus Reference
Age + BODE + COPD Hosp	0.686			
+ IL-6	0.708	0.023	(0.003 to 0.043)	0.027
+ Neutrophils	0.699	0.013	(-0.001 to 0.028)	0.078
+ White blood cells	0.698	0.012	(-0.003 to 0.028)	0.119
+ CRP	0.697	0.012	(-0.005 to 0.028)	0.168
+ Fibrinogen	0.698	0.012	(-0.007 to 0.031)	0.207
+ SP-D	0.692	0.006	(-0.006 to 0.018)	0.309
+ IL-8	0.690	0.005	(-0.005 to 0.013)	0.371
+ All biomarkers	0.726	0.041	(0.014 to 0.067)	0.003
Sensitivity Model (n = 1,579)				
Age + BODE + COPD Hosp	0.697			
+ CCL-18/PARC	0.706	0.009	(-0.008 to 0.026)	0.294
+ All biomarkers	0.742	0.045	(0.010 to 0.079)	0.011



Discussion



- inflammatory biomarkers + well established clinical markers improve prediction of mortality
- no determination of correct cause of death
- missing biomarkers thought to be important in the pathobiology of COPD: e.g. MMPs, growth factors
- significant differences in age, clinical variables and comorbidities
- sponsored by GlaxoSmithKline