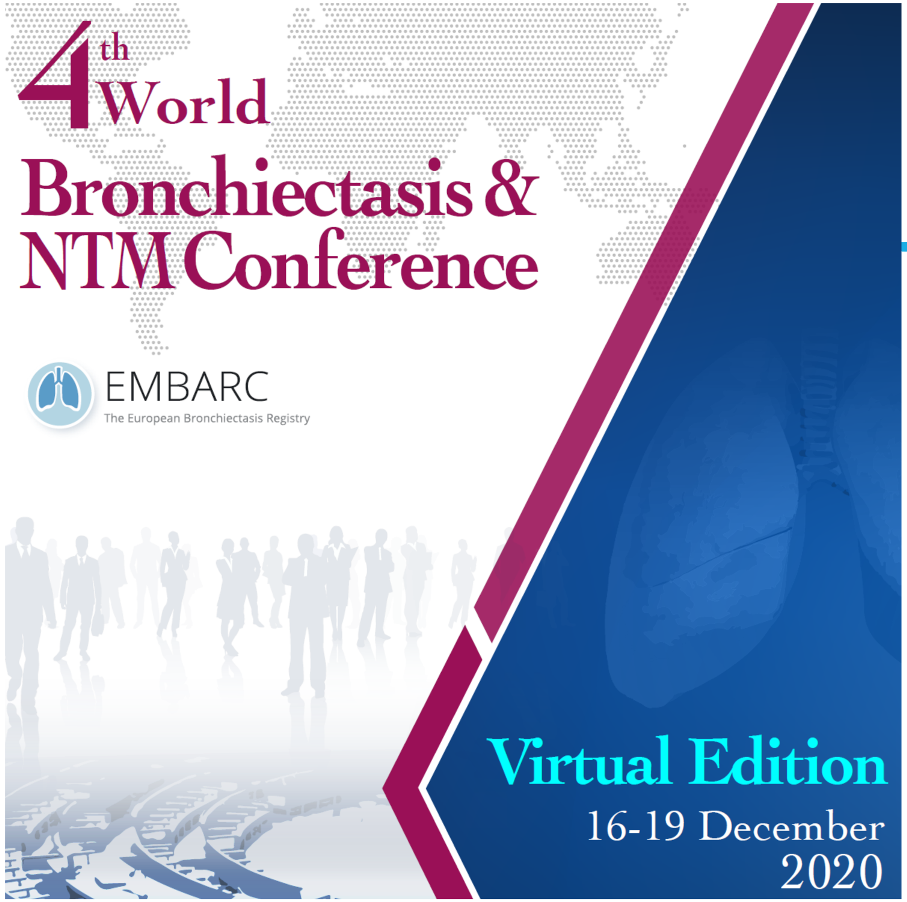
G y e o n g s a n g   N a t i o n a l   U n i v e r s i t y   H o s p i t a l

Introduction of Biomarkers in Bronchiectasis

경상대학교병원 **이 승 준**
부울경.호흡기지회
2021-2-24



13.55 – 15.30	**SESSION I: NOVEL DIAGNOSTICS AND ASSESSMENT METHODS**

Chairs: Felix Ringshausen, Hannover (Germany),
Michael Loebinger, London (UK)


14.15 – 14.35	**Biomarkers to assess severity & prognosis** *Stefano Aliberti, Milan, Italy*
14.55 – 15.15	**Genetics and Bronchiectasis** *Kenneth Olivier, Bethesda, USA*

EMBARC

The European Bronchiectasis Registry

A European Network for Non-CF Bronchiectasis

- Austria
- Belgium
- Bulgaria
- Croatia
- Czech Republic
- Denmark
- Finland
- France
- Germany
- Greece
- Ireland
- Israel
- Italy

BRONCHIECTASIS AND NTM INITIATIVE

US Bronchiectasis research registry

Definition of Biomarker

Definition [edit]

The term "biological marker" was introduced in 1950s.[23][24]

- In 1987, biological markers were defined as "indicators signaling events in biological systems or samples" that could be classified into three categories: exposure, effect and susc ... [25]
- In 1 ... habitats or i ... resp ...

A characteristics that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses

- In 1994, Depledge defined a biomarker as, "a biochemical, cellular, physiological or behavioral change which can be measured in body tissues or fluids or at the level of the whole organism that reveals the exposure at/or the effects of one or more chemical pollutants."[27]
- In 1996, Van Gestel and Van Brummelen attempted to redefine biomarkers to unambiguously differentiate a biomarker from a bioindicator. According to Van Gestel and Van Brummelen, a biomarker by definition should be used only to describe sublethal biochemical changes resulting from individual exposure to xenobiotics.[28]
- In 1998, the National Institutes of Health Biomarkers Definitions Working Group defined a biomarker as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[29][1]
- In 2000, De Lafontaine defined the term biomarker as a "biochemical and/or physiological change(s) in organisms exposed to contaminants, and thus represent initial responses to environmental perturbation and contamination".[30]

BEST (Biomarkers, EndpointS, and other Tools) Resource by FDA/NIH

- **Diagnostic biomarkers**: biomarker used to detect or confirm presence of a disease or condition of interest or to identify individuals with a subtype of the disease (blood glucose)
- **Monitoring biomarkers**: biomarker measured repeatedly for assessing status of a disease or medical condition or for evidence of exposure to (or effect of) a medical product or an environmental agent (PT-INR)
- **Pharmacodynamic/response biomarkers**: biomarker used to show that a biological response has occurred in an individual who has been exposed to a medical product or an environmental agent (HbA1c)
- **Predictive biomarkers**: biomarker used to identify individuals who are more likely than similar individuals without the biomarker to experience a favorable or unfavorable effect from exposure to a medical product or an environmental agent (Squamous NSCLC, avoid pemetrexed)
- **Prognostic biomarkers**: biomarker used to identify likelihood of a clinical event, disease recurrence or progression in patients who have the disease or medical condition of interest (Fibrinogen in COPD, association with exacerbation, mortality)
- Safety biomarkers, Susceptibility biomarkers

Experimental Biology and Medicine 2018; 243: 213–221

Criteria for novel biomarkers, ideal COPD

1. Is there a strong biological plausibility in terms of its role in the pathogenesis of disease?
2. Is there a strong, consistent and independent association between the biomarker and chronic obstructive pulmonary disease?
3. Is there a strong, independent association between the biomarker and hard clinical outcomes such as mortality and hospitalization?
4. Is there evidence from randomized controlled trials that the biomarker is modifiable by interventions?
5. Is there evidence from randomized controlled trials that changes in the biomarker status result in changes in an important (and accepted) clinical outcome (e.g. mortality, exacerbation, rate of decline in FEV_1, health status)?

Proc Am Thorac Soc Vol 6. pp 543–545, 2009

Biomarkers

Sputum

Neutrophil elastase
Cathepsin-G

MMP-8,9
IL-8,13

Blood

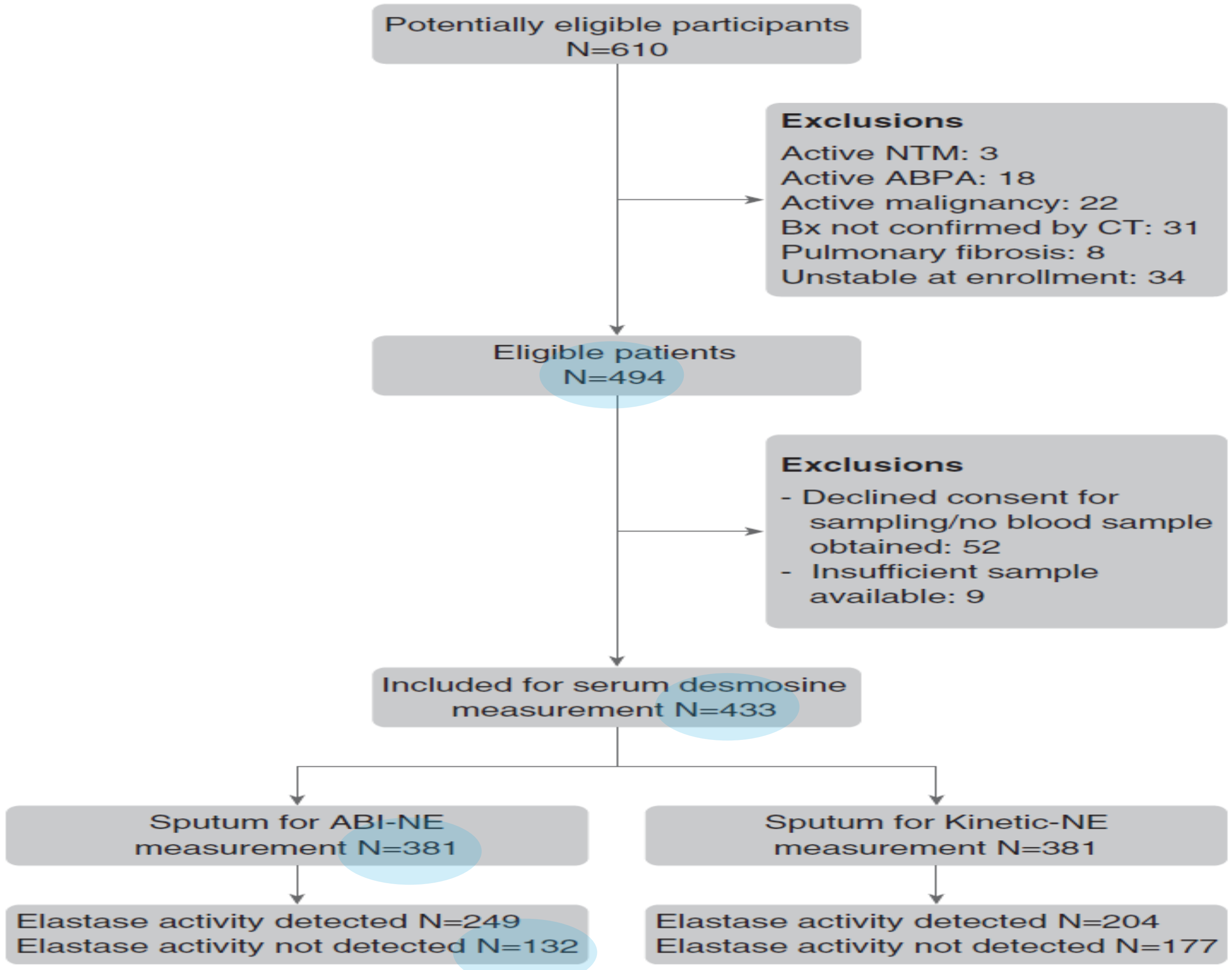
Desmosine
Fibrinogen
Platelet

NLR
Vitamin D
Albumin
Hepatocyte growth factor

Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis

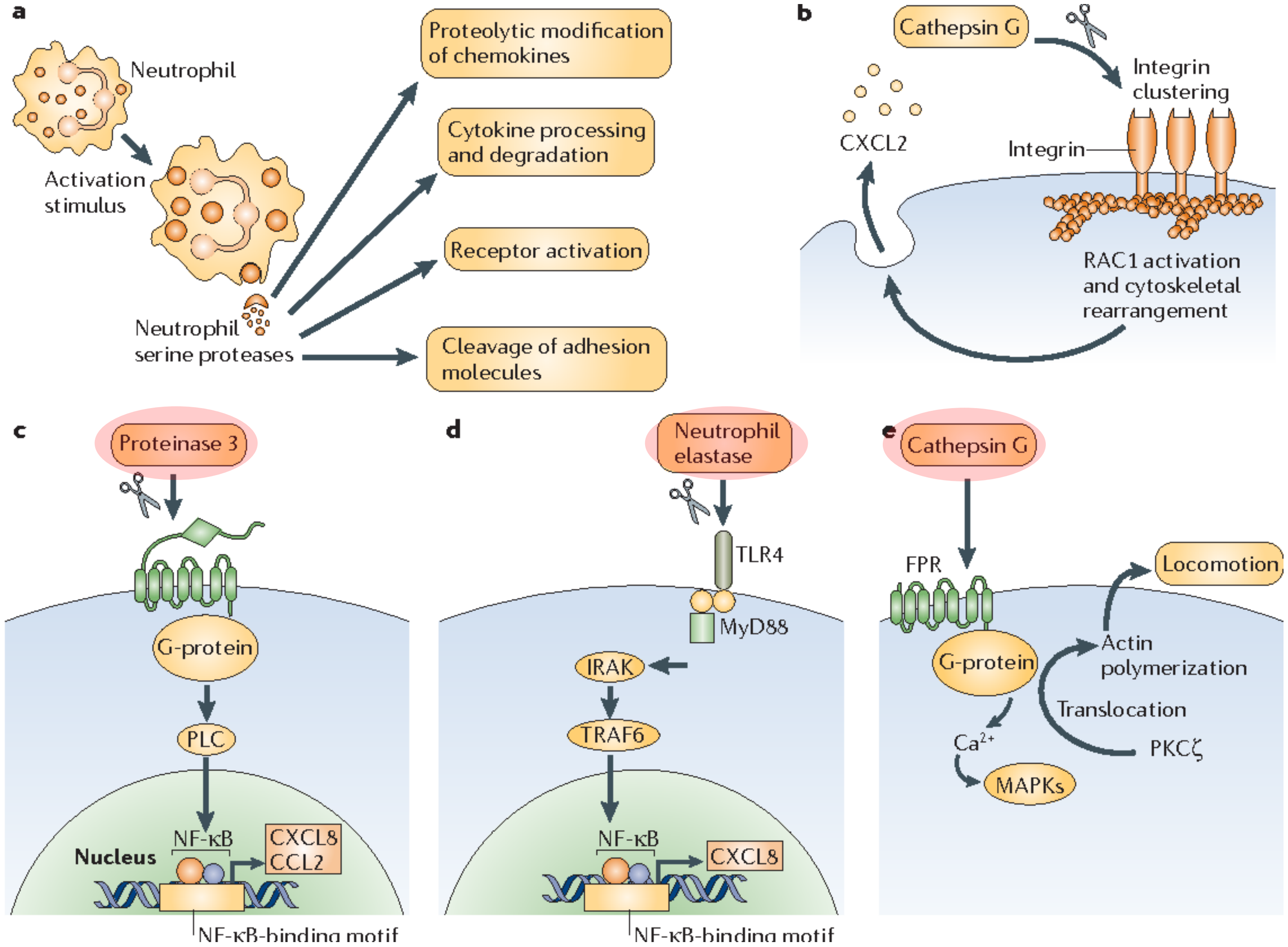
James D. Chalmers[1,2], Kelly L. Moffitt[3], Guillermo Suarez-Cuartin[4], Oriol Sibila[4], Simon Finch[1], Elizabeth Furrie[2], Alison Dicker[1,2], Karolina Wrobel[2], J. Stuart Elborn[5,6], Brian Walker[3], S. Lorraine Martin[3], Sara E. Marshall[2], Jeffrey T.-J. Huang[2*], and Thomas C. Fardon[1*]

- Single-center prospective cohort study
- TAYBRIDGE registry in Dundee, UK



AJRCCM 2017; 195 (10): 1384-1393

NE is one of Neutrophil serine proteases (NSP)



-Neutrophil: live 8hr in healthy condition, but following inflammatory activation live up to 5 days
=>prolonged life of neutrophil leads to damage host cells and tissues

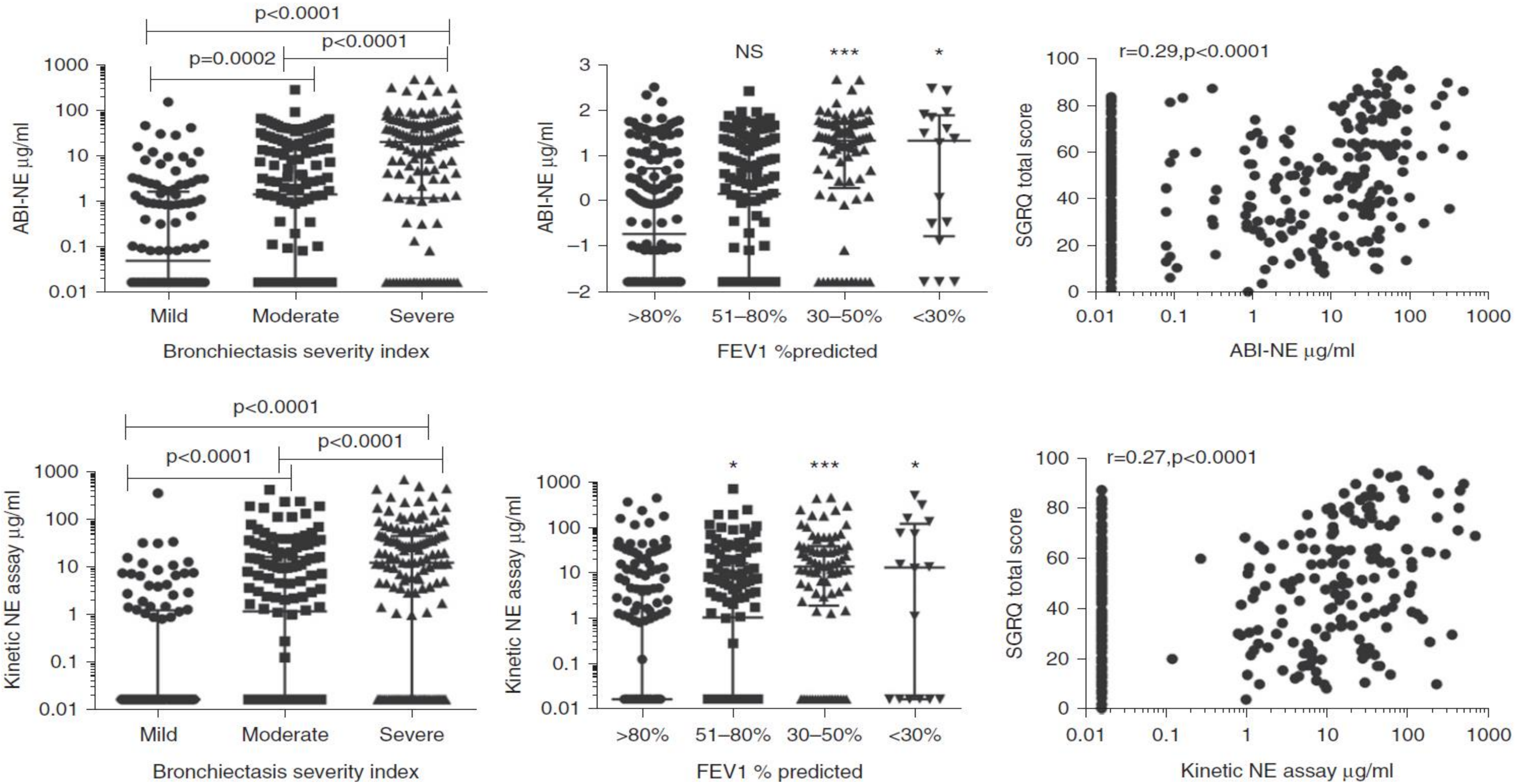
-Neutrophil degradation is responsible for NSP (NE, Cathepsin G, Proteinase 3)

-NE: mainly involved in bacterial response, but it can cause detrimental effects including extracellular matrix destruction, mucus gland hyperplasia, damage to airway epithelium

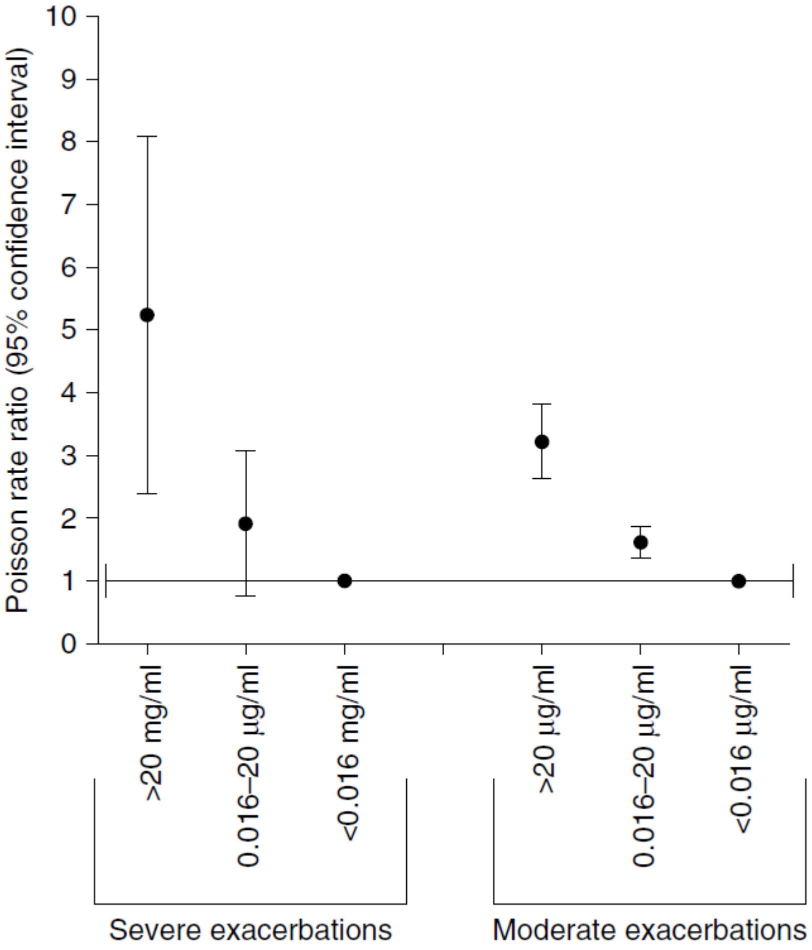
Table 1. Baseline Characteristics of the Cohort

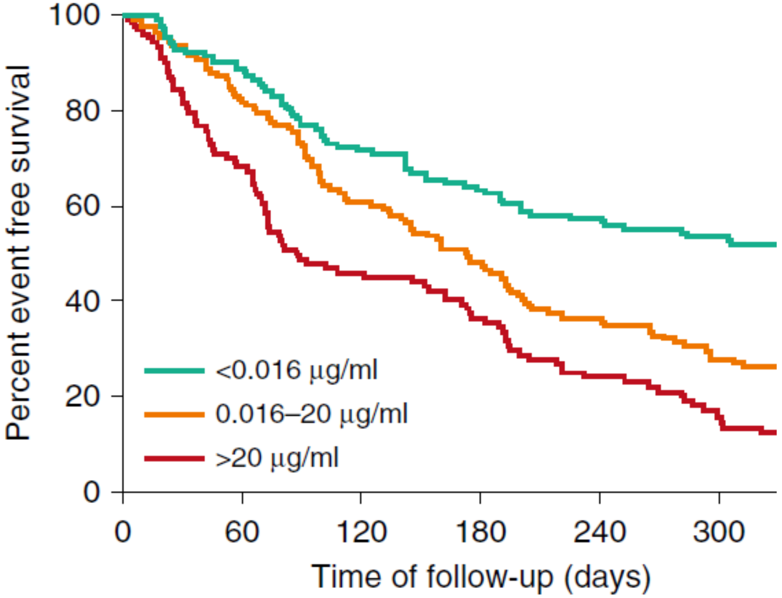
Baseline Characteristics	Full Cohort	Patients Providing Sputum
N	433	381
Age, yr	67 (58–74)	67 (58–74)
Sex, % female	263 (60.7)	225 (59.1)
Body mass index	25.0 (22.3–28.5)	25.1 (22.2–28.6)
Smoking status, never/ex/current	266 (61)/151 (34.9)/16 (3.7)	239 (62.7)/131 (34.4)/11 (2.9)
MRC dyspnea score	2 (1–3)	2 (1–3)
FEV_1, L	1.58 (1.10–2.20)	1.58 (1.10–2.23)
FEV_1% predicted	71.9 (50.0–91.0)	71.4 (49.4–90.9)
FVC, L	2.45 (1.84–3.21)	2.41 (1.85–3.19)
FVC, % predicted	83.9 (68.4–99.5)	83.2 (67.7–98.7)
Etiology of bronchiectasis		
Idiopathic	195 (45.0)	169 (44.4)
Postinfective	84 (19.4)	78 (20.5)
Previous ABPA	37 (8.5)	34 (8.9)
Asthma	15 (3.5)	14 (3.7)
COPD	22 (5.1)	19 (5.0)
Rheumatoid arthritis	21 (4.8)	17 (4.4)
Connective tissue disease	6 (1.4)	4 (1.0)
Inflammatory bowel disease	11 (2.5)	11 (2.9)
Primary immunodeficiency	18 (4.2)	17 (4.5)
Previous NTM infection	7 (1.6)	4 (1.0)
Primary ciliary dyskinesia	4 (0.9)	3 (0.8)
Alpha-1 antitrypsin deficiency	2 (0.5)	1 (0.3)
Others	11 (2.5)	10 (2.6)
Exacerbations per year	1 (0–3)	1 (0–3)
Previous hospitalization for severe exacerbations	107 (24.7)	101 (26.5)
St. George's Respiratory Questionnaire total score	44.3 (24.6–62.7)	46.1 (27.3–63.2)
Bronchiectatic on CT	3 (2–4)	3 (2–4)
Reiff score	3 (2–6)	3 (2–6)
Chronic colonization*	236 (54.5)	213 (55.9)
H. influenzae	129 (29.8)	116 (30.4)
P. aeruginosa	63 (14.5)	60 (15.7)
Moraxella catarrhalis	51 (11.8)	49 (12.9)
Streptococcus pneumoniae	25 (5.8)	23 (6.0)
Streptococcus aureus	34 (7.9)	30 (7.9)
Enterobacteriaceae	39 (9.0)	39 (10.2)
Bronchiectasis severity index	6 (4–10)	6 (4–11)
Mild	126 (29.1)	108 (28.3)
Moderate	170 (39.3)	144 (37.8)
Severe	137 (31.6)	129 (33.9)

Sputum NE activity is associated with Disease Severity

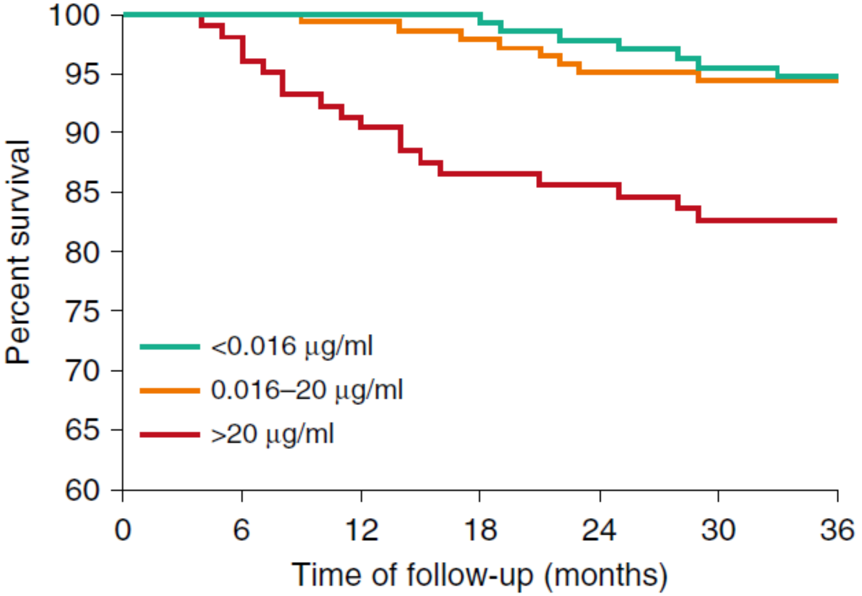


NE activity and longitudinal clinical outcomes





Time to next exacerbation, p<0.0001



All-cause mortality, p<0.001

Research letter

Sputum neutrophil elastase in bronchiectasis: a Southern European cohort study

Andrea Gramegna, Stefano Aliberti, Oriol Sibila, Carlotta Di Francesco, Giovanni Sotgiu, Lidia Perea, Leonardo Terranova, Martina Oriano, Tommaso Pilocane, Laura Saderi, James D. Chalmers, Paola Marchisio, Francesco Blasi

- An external validation of the Scottish data is needed in view of the heterogeneity of bronchiectasis (in terms of microbiology with chronic *Pseudomonas aeruginosa* infection been more prevalent in Southern vs. Northern Europe)
- Multicentric, prospective, observational study in two bronchiectasis referral centers in **Italy and Spain**.
- N=266

ERJ 2020 in press

NE and disease severity

Variables		Sputum neutrophil elastase level			p-value
Demographics		Low (0-6 ug/ml) (n= 91)	Medium (7-20 ug/ml) (n= 77)	High (>20 ug/ml) (n= 98)	
Male, n (%)		19 (27.9)	19 (25.0)	21 (25.3)	0.91
Median (IQR) age, years		65 (51-75)	63 (53-73)	64 (54-74)	0.83
Current/former smoker, n (%)		32 (47.1)	36 (47.4)	32 (38.6)	0.45
Median (IQR) BMI, kg/m^2		23.2 (20-26)	22 (18.9-25.0)	21 (19.4-24.5)	0.15
Disease severity					
Median (IQR) BSI		6 (4-9)	7 (4-10)	8 (5-12)	0.009(1)
BSI risk class, n (%)	Mild	28 (31.1)	23 (29.1)	17 (17.9)	0.09
	Moderate	39 (43.3)	28 (35.4)	35 (36.8)	0.52
	Severe	23 (25.6)	28 (35.4)	43 (45.3)	0.02(2)
Median (IQR) E-FACED		2 (1-3)	2 (1-3)	3 (1-4)	0.0006(3)
E-FACED risk class, n (%)	Mild	73 (84.9)	55 (76.4)	59 (64.8)	0.008(4)
	Moderate	12 (14.0)	12 (16.7)	25 (27.5)	
	Severe	1 (1.2)	5 (6.9)	7 (7.7)	
mMRC 3-4		6 (6.6)	8 (10.4)	14 (14.4)	0.22

-NE correlated with BSI (r =0.23; P=0.0002), E-FACED scores (r =0.26; P<0.0001)

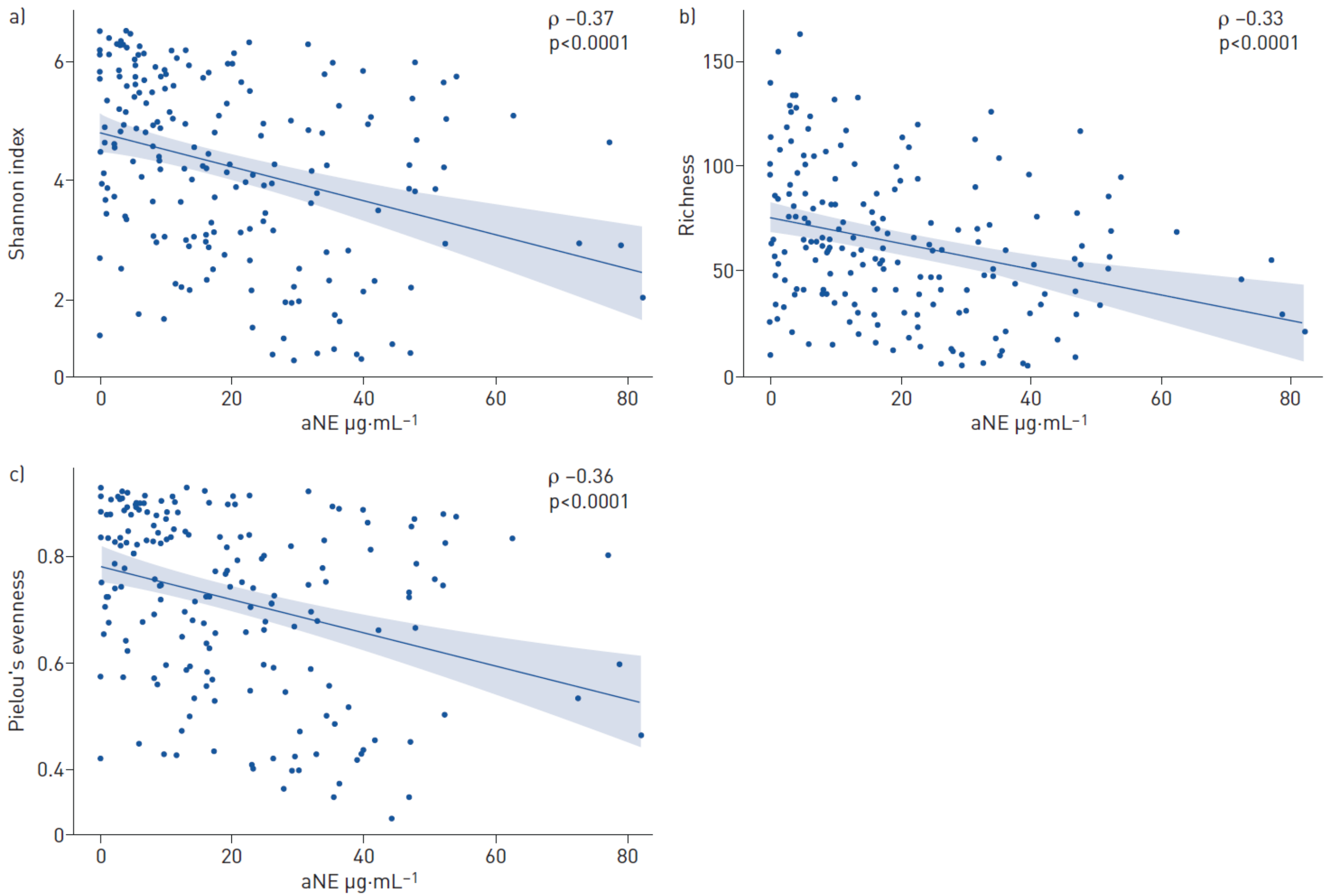
-Median levels [IQR] of aNE significantly increased across mild, moderate and severe BSI (8.7 [2.8-20.7] VS. 11.1 [4.7-29.3] VS. 18.2 [8.1-37.7], p=0.001) and E-FACED (10.0 [3.6-24.4] VS. 21.4 [8.2-34.4] VS. 31.5 [11.4-42.3], p=0.004) risk classes

-Median levels [IQR] of aNE were higher in patients with chronic *P. aeruginosa* infection (25.1 [11.3-40.5] VS. 9.2 [3.1-22.7] ug/ml, P<0.0001)

-QoL-B Respiratory Domain inversely correlated with increasing aNE concentrations in sputum (r=-0.25, p=0.009).

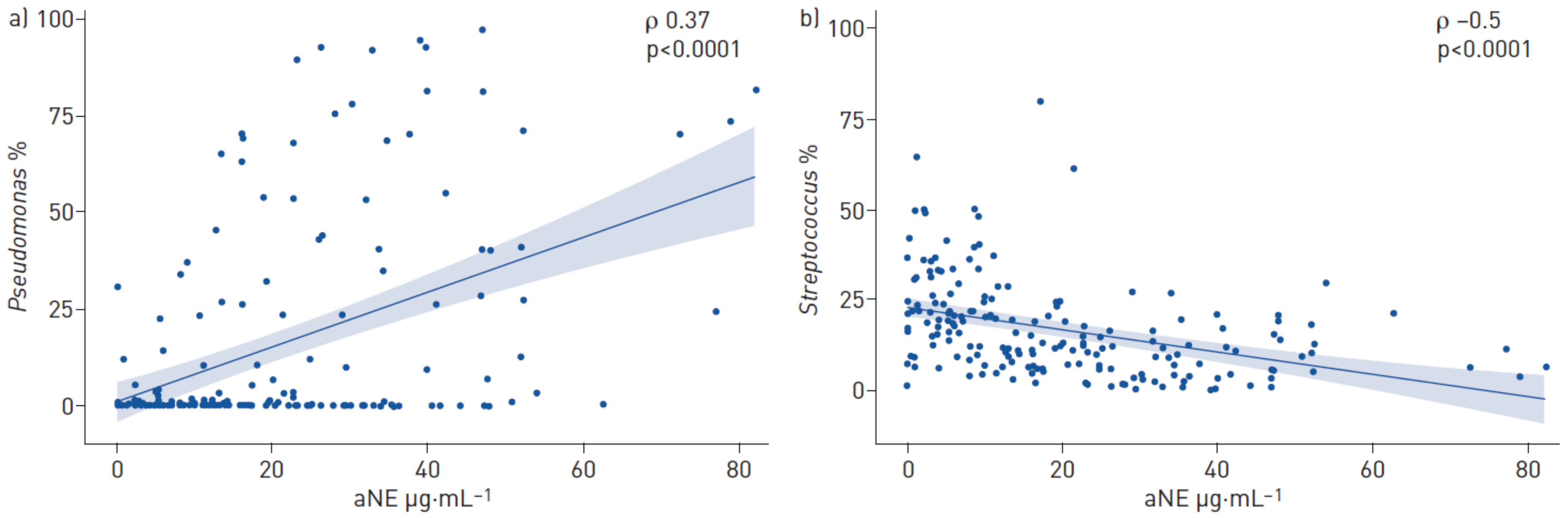
Sputum neutrophil elastase associates with microbiota and *Pseudomonas aeruginosa* in bronchiectasis

N=185



ERJ 2020; 56: 2000769

Correlation of NE and bacterial relative abundance



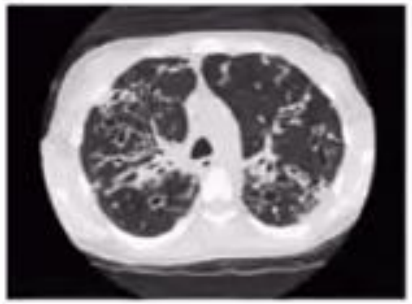
-Direct correlation between aNE and <u>Pseudomonas relative abundance</u>
-Inverse correlation is shown between Streptococcus and aNE levels

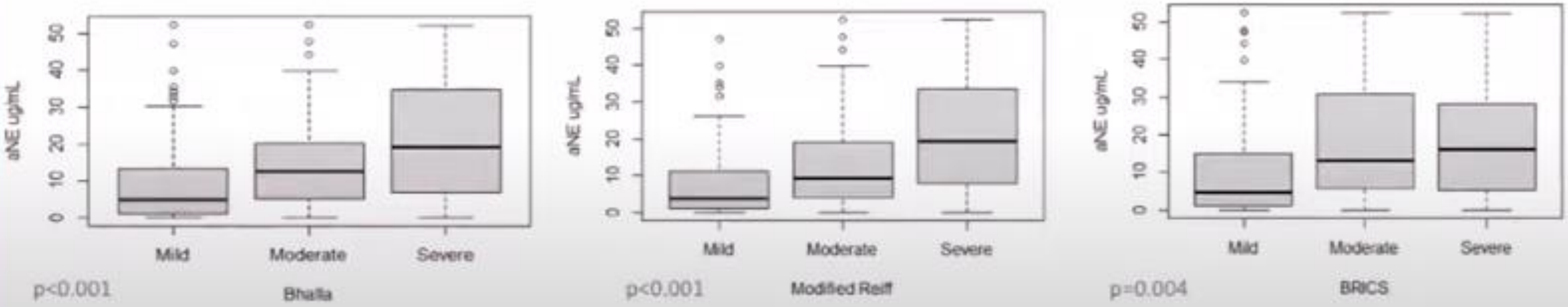
Sputum

Neutrophil elastase correlates with radiological severity

- 165 adults with bronchiectasis
- Milan and Barcelona
- Radiological evaluation (2 radiologist from Milan and 2 radiologists from Parma)
- Bhalla score, modified Reiff score, BRICS
- Sputum aNE

		Active neutrophil elastase
BRICS score	Rho	0.234
	p-value	0.002
Bhalla score	Rho	-0.411
	p-value	<0.001
Modified Reiff score	Rho	0.388
	p-value	<0.001

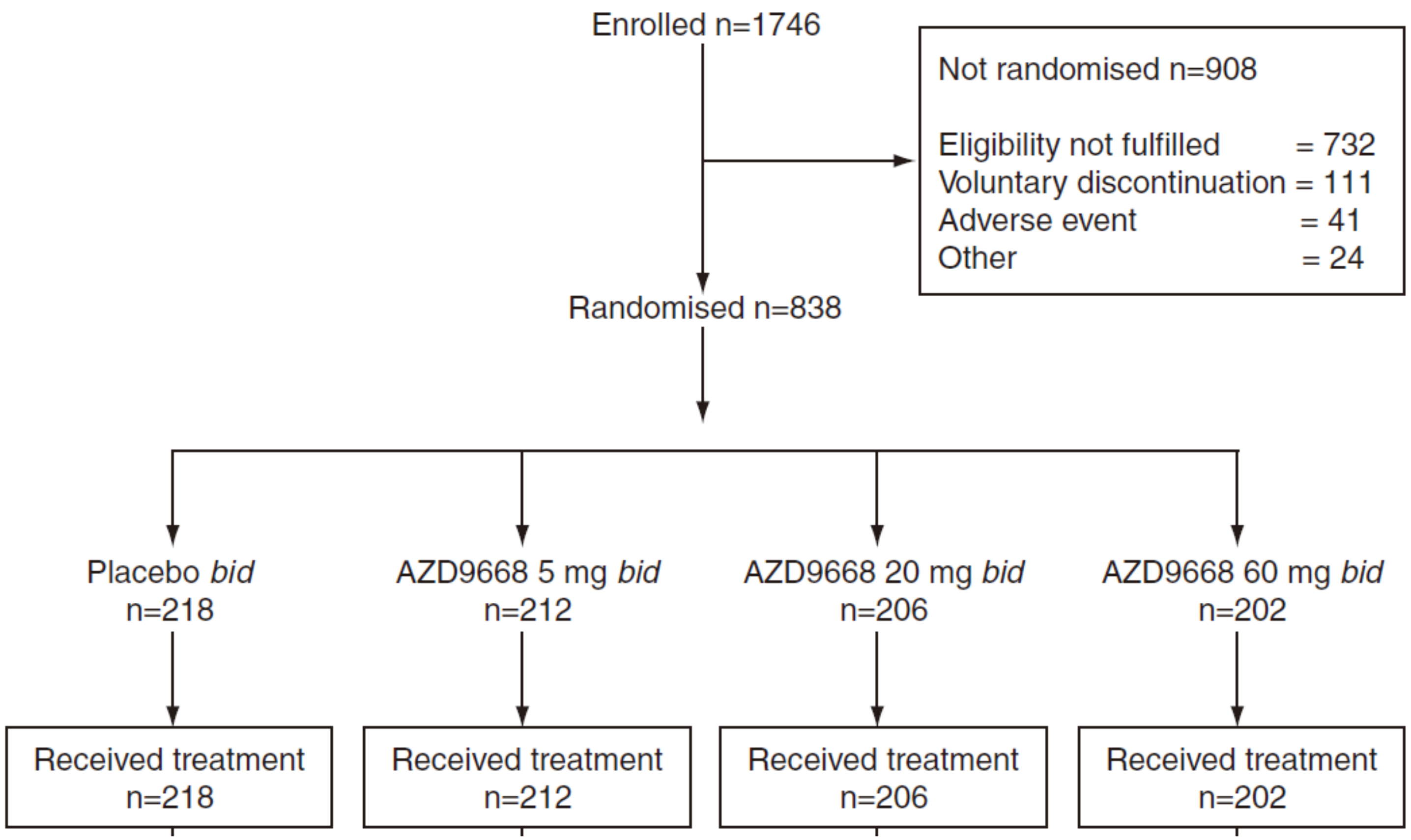




Personal Data

A Randomised, Placebo-Controlled, Dose-Finding Study Of AZD9668, An Oral Inhibitor of Neutrophil Elastase, in Patients with Chronic Obstructive Pulmonary Disease Treated with Tiotropium

NE as a treatment target



COPD 2012; 9: 111-120

Abstract

AZD9668 is a fully reversible, selective, oral inhibitor of neutrophil elastase, a protease implicated in chronic obstructive pulmonary disease (COPD). Efficacy, safety and tolerability of AZD9668 (5, 20 and 60 mg *bid*) were compared with placebo in a randomised, double-blind, placebo-controlled, 12-week, Phase IIb trial (NCT00949975: approved by an Investigational Review Board), in patients with symptomatic COPD receiving maintenance tiotropium. The primary endpoint was pre-bronchodilator forced expiratory volume in 1 second (FEV_1). Secondary endpoints included forced vital capacity and inspiratory capacity, peak expiratory flow, Breathlessness, Cough and Sputum Scale score, exercise capacity, quality of life (QoL), exacerbation assessments, safety and pharmacokinetics. Exploratory endpoints included inflammatory and tissue degradation biomarkers. A total of 838 patients were randomised to AZD9668 5 mg *bid* (212 patients), 20 mg *bid* (206 patients), 60 mg *bid* (202 patients) or placebo (218 patients). AZD9668 showed no effect on lung function, respiratory signs and symptoms, QoL or biomarkers. At end of treatment, the change in mean pre-bronchodilator FEV_1 for AZD9668 60 mg *bid* compared with placebo was 0.00L (95% confidence interval: –0.05, 0.04; $p = 0.873$). Overall, AZD9668 was well tolerated; the numbers of patients with adverse events (AEs), serious AEs and AEs leading to discontinuation were similar in each of the four study groups.

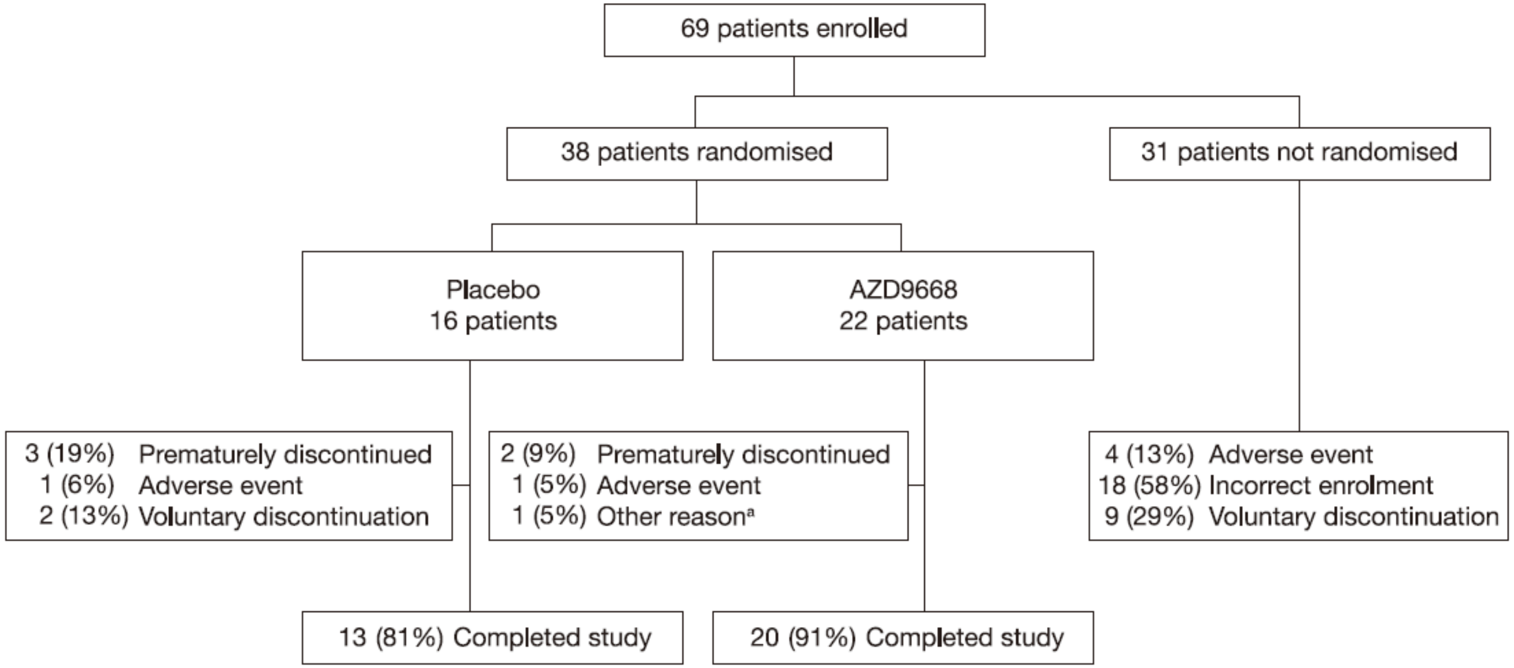
AZD9668 60 mg *bid* showed no clinical benefit and no effect on biomarkers of inflammation or tissue degradation when added to tiotropium in patients with COPD. These results raise important questions for future investigation of anti-inflammatory and disease-modifying agents in patients with COPD.

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis



Primary endpoint

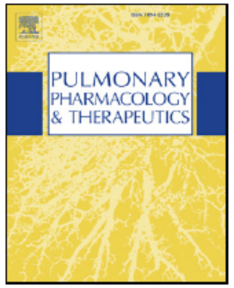
Table 2 Measurements for primary outcome variables and sputum NE activity (efficacy analysis set).

	Baseline measurements		End of treatment measurements		Comparison between AZD9668 and placebo at end of treatment (ANCOVA)		
	Placebo	AZD9668	Placebo	AZD9668			
Sputum neutrophils	$n = 11$ (waking) $n = 10$ (post-waking)	$n = 19$ (waking) $n = 18$ (post-waking)	$n = 11$ (waking) $n = 10$ (post-waking)	$n = 19$ (waking) $n = 18$ (post-waking)	Ratio	90% CI	*p*-value
Waking sample, 10^6/g geometric mean (CV, %)	5.63 (100.4)	6.57 (123.8)	5.34 (297.5)	6.5 (141.1)	1.06	0.59, 1.91	0.872
Post-waking sample, 10^6/g geometric mean (CV, %)	5.19 (368.1)	6.69 (284.4)	5.75 (270.8)	7.05 (224.9)	1.07	0.55, 2.07	0.862
24-h sputum weight, g mean (SD)	$n = 13$	$n = 20$	Change from baseline $n = 13$	Change from baseline $n = 20$	LSM difference (SEM)	90% CI	*p*-value
Weight, g mean (SD)	15.48 (9.663)	37.06 (39.61)	5.01 (18.37)	−8.27 (18.72)	−5.22 (5.693)	−14.9, 4.46	0.367
Lung function tests	$n = 13$	$n = 20$	Change from baseline $n = 13$	Change from baseline $n = 20$	LSM difference (SEM)	90% CI	*p*-value
FEV_1, L mean (SD)	1.77 (0.377)	2.07 (0.798)	−0.04 (0.082)	0.06 (0.100)	0.10 (0.034)	0.04, 0.16	0.006
SVC, L mean (SD)	2.74 (0.687)	3.38 (1.071)	−0.06 (0.173)	0.06 (0.200)	0.13 (0.074)	0.01, 0.26	0.079
FVC, L mean (SD)	2.67 (0.680)	3.37 (0.994)	−0.01 (0.174)	0.05 (0.227)	0.03 (0.080)	−0.10, 0.17	0.674
$FEF_{25-75\%}$, L/s mean (SD)	1.08 (0.416)	1.16 (0.939)	0.01 (0.165)	0.08 (0.134)	0.07 (0.049)	−0.01, 0.15	0.157
BronkoTest® diary card variables	$n = 16$	$n = 21$	Change from baseline $n = 16$	Change from baseline $n = 21$	LSM difference (SEM)	90% CI	*p*-value
PEF, L/min mean (SD)							
Morning	312.8 (74.92)	364.4 (124.6)	−2.06 (35.22)	2.11 (22.70)	9.05 (N/A)	−7.14, 25.23	0.351
Evening	311.0 (73.09)	372.4 (132.7)	0.99 (35.79)	2.24 (23.38)	5.71 (N/A)	−11.0, 22.46	0.568
Night time symptoms,[a] mean (SD)	0.76 (0.966)[b]	0.74 (1.035)	−0.28 (0.920)[b]	−0.15 (0.657)	0.11 (0.215)	−0.25, 0.48	0.598
Breathing,[a] mean (SD)	2.08 (0.299)	2.07 (0.301)	−0.01 (0.340)	−0.07 (0.518)	−0.05 (0.131)	−0.27, 0.17	0.700
Sputum colour,[a] mean (SD)	3.44 (1.939)	3.85 (1.454)	−0.13 (0.752)	−0.17 (1.285)	0.12 (0.330)	−0.44, 0.68	0.713
Sputum amount,[a] mean (SD)	2.17 (0.712)	2.57 (0.655)	−0.13 (0.488)	−0.12 (0.626)	0.09 (0.199)	−0.25, 0.42	0.666
How do you feel?,[a] mean (SD)	2.22 (0.225)	2.03 (0.305)	−0.17 (0.447)	0.04 (0.531)	0.05 (0.153)	−0.21, 0.31	0.731
How often do you cough?,[a] mean (SD)	1.57 (0.716)	1.30 (0.689)	−0.16 (0.520)	−0.02 (0.571)	0.11 (0.184)	−0.20, 0.42	0.549
Reliever medication use,[a] mean (SD)	0.96 (1.979)	1.94 (3.816)[c]	−0.04 (0.143)	0.16 (0.581)[c]	0.22 (0.152)	−0.04, 0.47	0.165
SGRQ-C score	$n = 13$	$n = 19$	Change from baseline $n = 13$	Change from baseline $n = 19$	LSM difference (SEM)	90% CI	*p*-value
Symptoms, mean percent (SD)	68.91 (13.80)	66.18 (16.13)	−1.8 (11.49)	−7.2 (18.60)	−6.02 (5.947)	−16.1, 4.10	0.320
Activity, mean percent (SD)	52.20 (29.96)	37.75 (24.63)	0.6 (13.31)	−3.5 (14.06)	−5.55 (5.278)	−14.5, 3.43	0.302
Impact, mean percent (SD)	38.17 (23.15)	31.22 (19.68)	−2.3 (13.87)	−6.3 (13.84)	−5.74 (5.001)	−14.2, 2.77	0.261
Overall, mean percent (SD)	47.93 (21.22)	39.42 (17.90)	−1.3 (11.04)	−5.6 (13.15)	−5.64 (4.651)	−13.5, 2.27	0.236

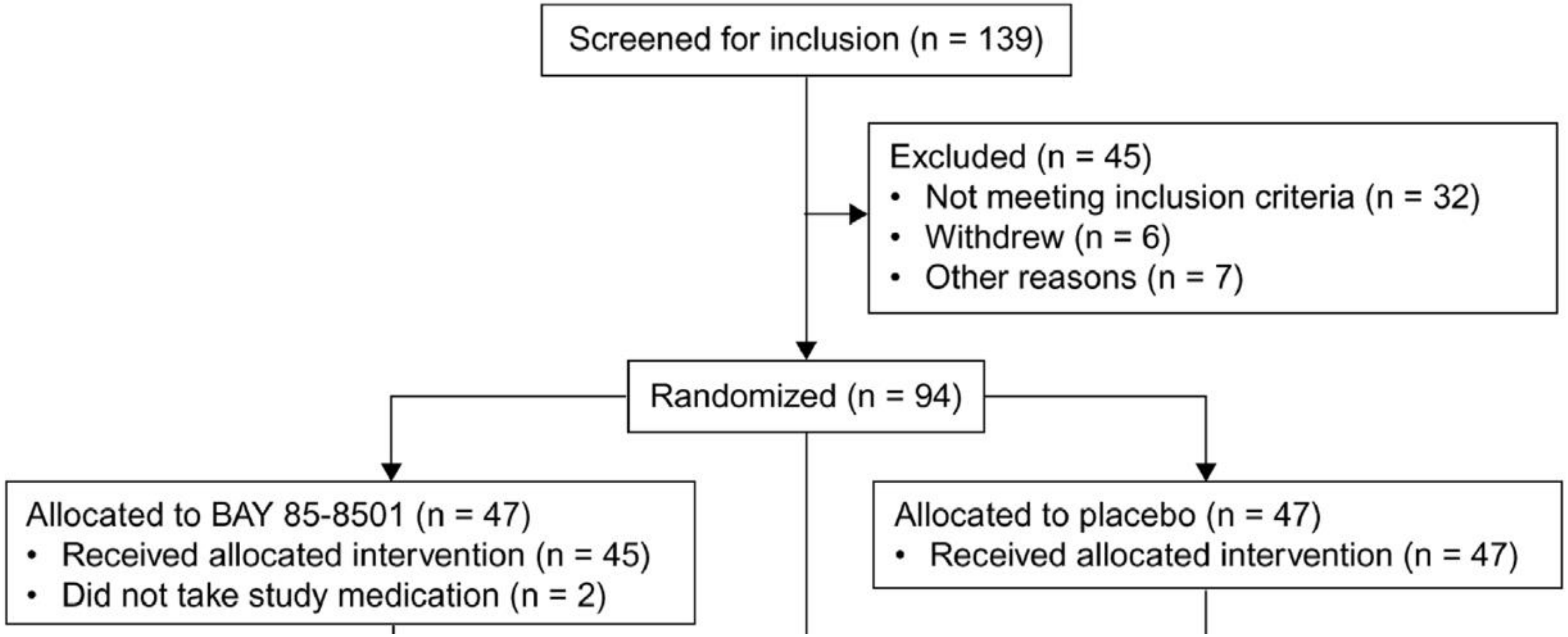
Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt



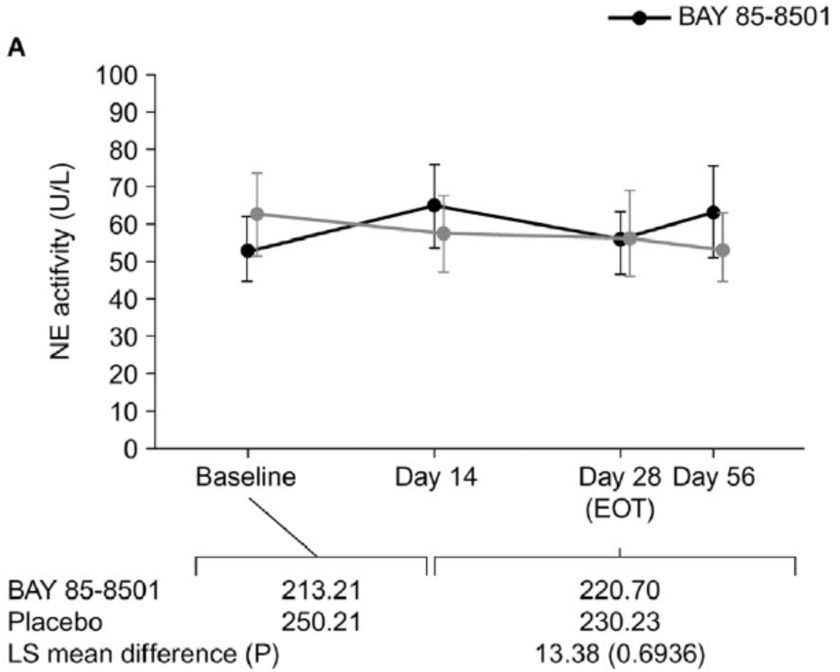
Safety and efficacy of the human neutrophil elastase inhibitor BAY 85-8501 for the treatment of non-cystic fibrosis bronchiectasis: A randomized controlled trial



Pulmonary Pharmacology & Therapeutics 56 (2019) 86–93

Adverse events (safety analysis set).

AE, n patients (%)	BAY 85-8501 N = 45	Placebo N = 47	Total N = 92
Any AE	32 (71.1)	38 (80.9)	70 (76.1)
Any TEAE	31 (68.9)	36 (76.6)	67 (2.8)
Serious	3 (6.7)	1 (2.1)	4 (4.3)
Leading to study drug discontinuation	4 (8.9)	1 (2.1)	5 (5.4)
Any study-drug related TEAE	11 (24.4)	12 (25.5)	23 (25.0)
Serious study-drug related TEAE	0	0	0
Death	0	0	0
TEAEs in > 5% of patients by system organ class			
Gastrointestinal	10 (22.2)	9 (19.1)	19 (20.7)
Diarrhoea	4 (8.9)	3 (6.4)	7 (7.6)
Nausea	1 (2.2)	3 (6.4)	4 (4.3)
Vomiting	3 (6.7)	0	3 (3.3)
Infections and infestations	9 (20.0)	15 (31.9)	24 (26.1)
Nasopharyngitis	2 (4.4)	6 (12.8)	8 (8.7)
Viral URT infection	3 (6.7)	1 (2.1)	4 (4.3)
Musculoskeletal and connective tissue disorders	7 (15.6)	7 (14.9)	14 (15.2)
Muscle spasms	3 (6.7)	0	3 (3.3)
Nervous system disorders	7 (15.6)	9 (19.1)	16 (17.4)
Headache	5 (11.1)	4 (8.5)	9 (9.8)
Respiratory, thoracic and mediastinal disorders	11 (24.4)	12 (25.5)	23 (25.0)
Cough	4 (8.9)	4 (8.5)	8 (8.7)
Sputum increased	3 (6.7)	3 (6.4)	6 (6.5)



Changes in pulmonary function and St George's Respiratory Questionnaire total score.

Mean (SD) change from baseline	BAY 85-8501 N = 47	Placebo N = 47	P value[a]
Pulmonary parameters (day 28; EOT)			
Pre-BD FEV_1, L	−0.004 (0.155)	−0.078 (0.199)	
Post-BD FEV_1, L	0.026 (0.192)	−0.051 (0.197)	0.0558
Pre-BD FVC, L	−0.009 (0.300)	−0.060 (0.250)	
Post-BD FVC, L	0.013 (0.340)	−0.029 (0.209)	0.3993
Health-related quality of life	43.36 (20.25)	39.58 (15.85)	
SGRQ total score (day 28; EOT)	0.36 (9.05)	0.18 (11.72)	0.7028
SGRQ total score (day 56)	−0.87 (6.85)	1.54 (10.87)	

ORIGINAL ARTICLE

Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis

James D. Chalmers, M.B., Ch.B., Ph.D., Charles S. Haworth, M.B., Ch.B., M.D., Mark L. Metersky, M.D., Michael R. Loebinger, B.M., B.Ch., Ph.D., Francesco Blasi, M.D., Ph.D., Oriol Sibila, M.D., Ph.D., Anne E. O'Donnell, M.D., Eugene J. Sullivan, M.D., Kevin C. Mange, M.D., M.S.C.E., Carlos Fernandez, M.D., M.P.H., Jun Zou, Ph.D., and Charles L. Daley, M.D., for the WILLOW Investigators*

- AZD7986 => INS1007
- Discovered in 2016
- First effective new drug for non-CF BE

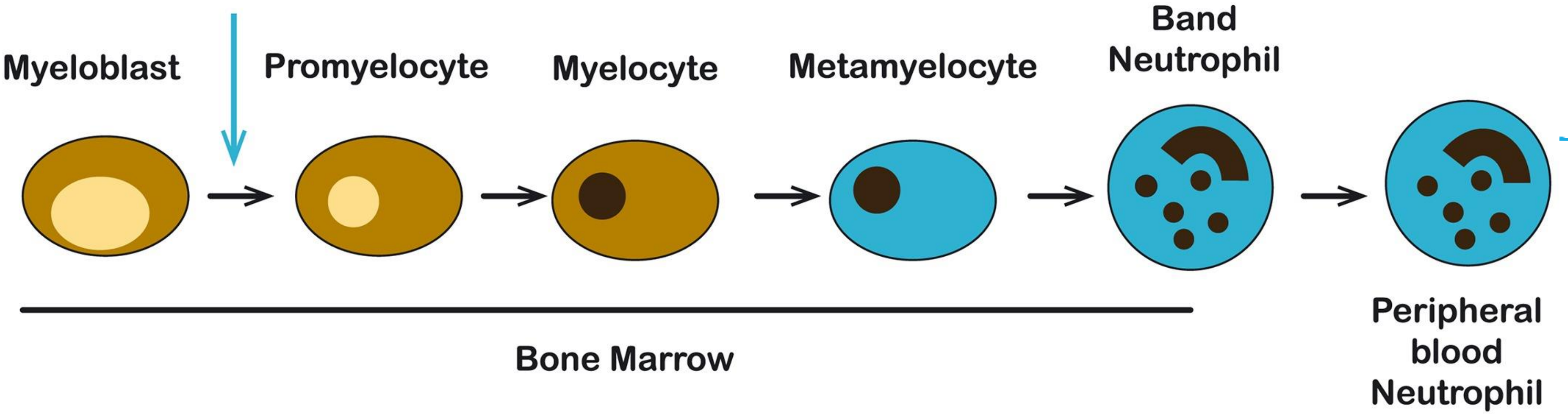
Phase 2 Trial of the DPP-1 Inhibitor **Brensocatib** in Bronchiectasis.
3 Cite Share
Chalmers JD, Haworth CS, Metersky ML, Loebinger MR, Blasi F, Sibila O, O'Donnell AE, Sullivan EJ, Mange KC, Fernandez C, Zou J, Daley CL; WILLOW Investigators.
N Engl J Med. 2020 Nov 26;383(22):2127-2137. doi: 10.1056/NEJMoa2021713. Epub 2020 Sep 7.
PMID: 32897034 Clinical Trial.
RESULTS: Of 256 patients, 87 were assigned to receive placebo, 82 to receive 10 mg of **brensocatib**, and 87 to receive 25 mg of **brensocatib**. The 25th percentile of the time to the first exacerbation was 67 days in the placebo group, 134 days in the 10-mg **brensocati** ...

Dipeptidyl Peptidase 1 Inhibitor **AZD7986** Induces a Sustained, Exposure-Dependent Reduction in Neutrophil Elastase Activity in Healthy Subjects.
5 Cite Share
Palmér R, Mäenpää J, Jauhiainen A, Larsson B, Mo J, Russell M, Root J, Prothon S, Chialda L, Forte P, Egelrud T, Stenvall K, Gardiner P.
Clin Pharmacol Ther. 2018 Dec;104(6):1155-1164. doi: 10.1002/cpt.1053. Epub 2018 Apr 16.
PMID: 29484635 Free PMC article. Clinical Trial.
We conducted a randomized, placebo-controlled, first-in-human study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple oral doses of the DPP1 inhibitor **AZD7986** in healthy subjects. Pharmacokinetic and pharmacodynamic data were ...

Discovery of Second Generation Reversible Covalent DPP1 Inhibitors Leading to an Oxazepane Amidoacetonitrile Based Clinical Candidate (**AZD7986**).
6 Cite Share
Doyle K, Lönn H, Käck H, Van de Poël A, Swallow S, Gardiner P, Connolly S, Root J, Wikell C, Dahl G, Stenvall K, Johannesson P.
J Med Chem. 2016 Oct 27;59(20):9457-9472. doi: 10.1021/acs.jmedchem.6b01127. Epub 2016 Oct 11.
PMID: 27690432
A novel series of second generation DPP1 inhibitors free from aorta binding liabilities found for earlier compound series was discovered. This work culminated in the identification of compound 30 (**AZD7986**) as a highly potent, reversible, and selective clinical candidate fo ...

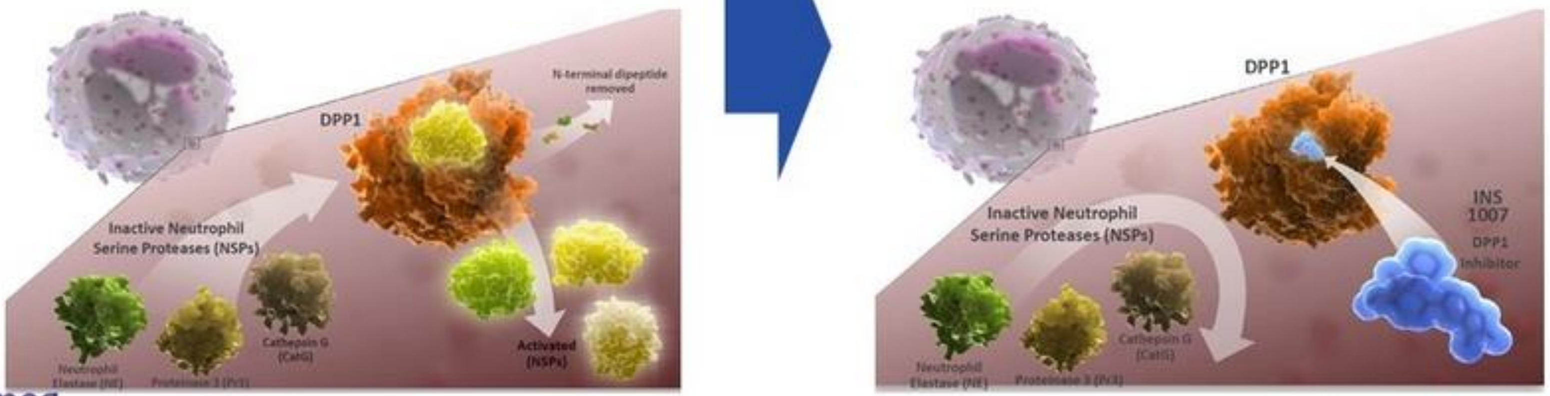
NEJM 2020 Nov 26;383(22):2127-2137

NSP processing occurs during initial stages of neutrophil maturation



Neutrophil serine proteases (NSPs) are activated by dipeptidyl peptidase 1 (DPP1) during neutrophil maturation in bone marrow

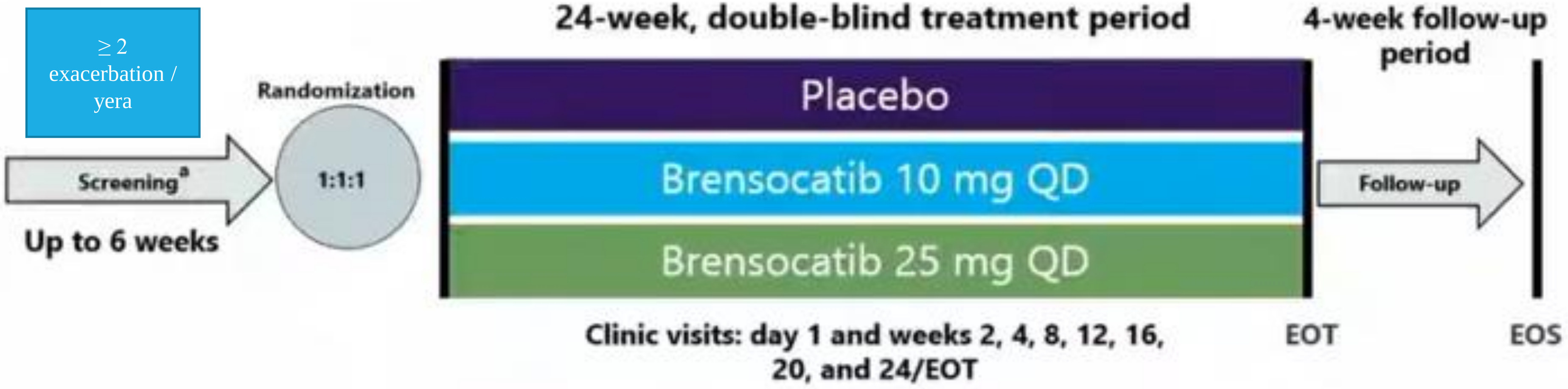
INS1007 inhibits DPP1, preventing activation of NSPs; neutrophils mature and are released without active NSPs



insmed

4th World Bronchiectasis & NTM Conference

WILLOW Study Design



- **Primary objective:** Evaluate the effect of brensocatib compared with placebo on time to first bronchiectasis exacerbation over 24 weeks in patients with non-CF bronchiectasis
- **Secondary objectives:** Evaluate the effect of brensocatib compared with placebo on:
  - Bronchiectasis exacerbation rate over 24 weeks
  - Change in QOL-B Respiratory Symptoms domain score over 24 weeks
  - Change in postbronchodilator FEV_1 over 24 weeks
  - Change in sputum NE activity from pretreatment to on treatment

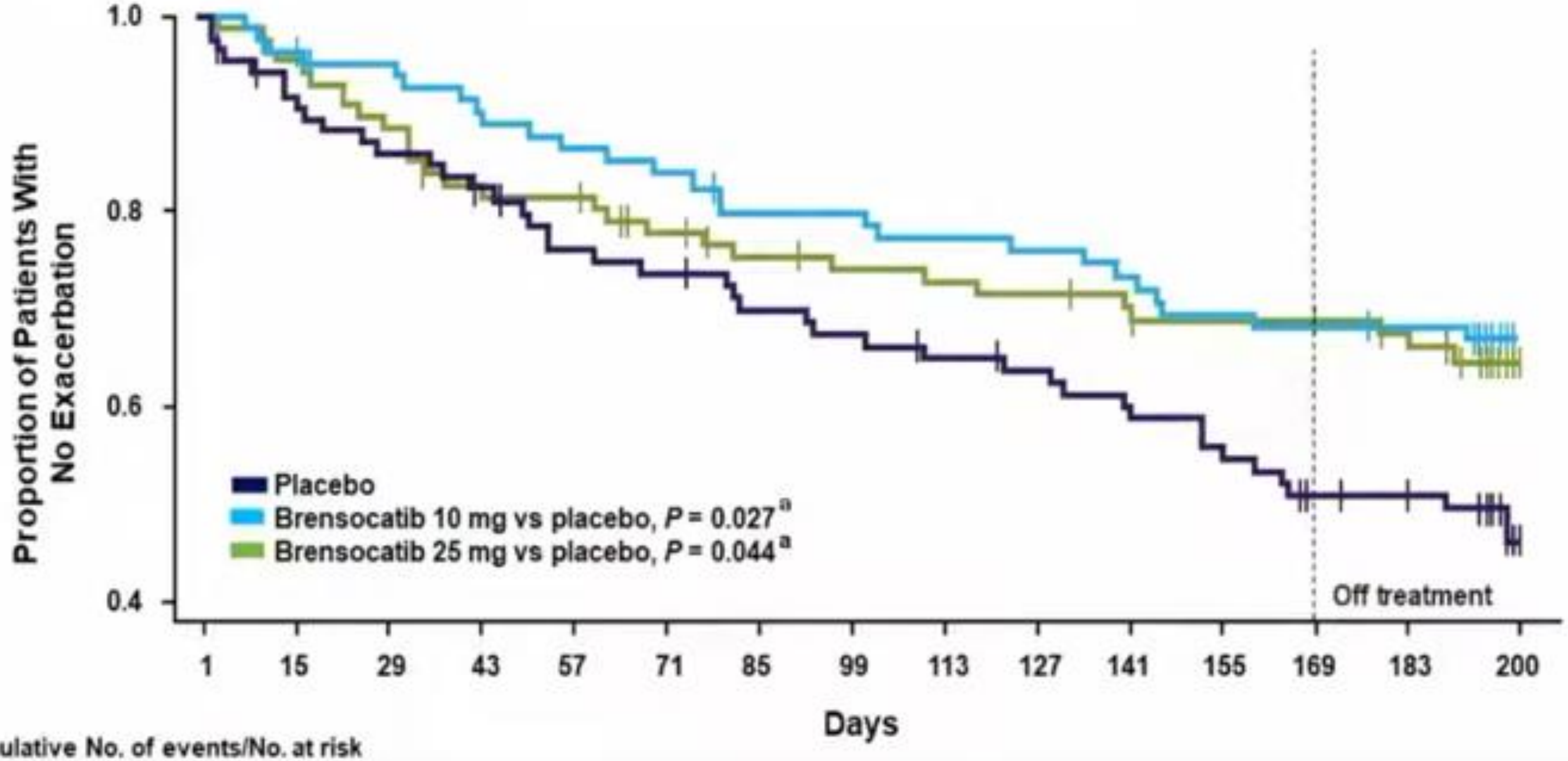
NEJM 2020 Nov 26;383(22):2127-2137

4th World Bronchiectasis & NTM Conference

Baseline Demographics and Characteristics

Characteristics	Placebo (n = 87)	Brensocatib 10 mg (n = 82)	Brensocatib 25 mg (n = 87)
Age, mean (SD), y	64.0 (11.86)	64.6 (12.42)	63.7 (12.67)
Female, n (%)	55 (63.2)	57 (69.5)	62 (71.3)
White, n (%)[a]	71 (81.6)	76 (92.7)	78 (89.7)
History of COPD, n (%)	17 (19.5)	12 (14.6)	13 (14.9)
History of asthma, n (%)	25 (28.7)	18 (22.0)	21 (24.1)
Pseudomonas aeruginosa positive, n (%)[b,c]	29 (33.3)	27 (32.9)	33 (37.9)
Chronic macrolide use, n (%)[b]	14 (16.1)	10 (12.2)	16 (18.4)
Hospitalized for exacerbation in prior 24 months, n (%)	30 (34.5)	31 (37.8)	31 (35.6)
Mean FEV_1, % predicted (SD)	67.3 (23.9)	65.9 (23.9)	70.0 (23.2)

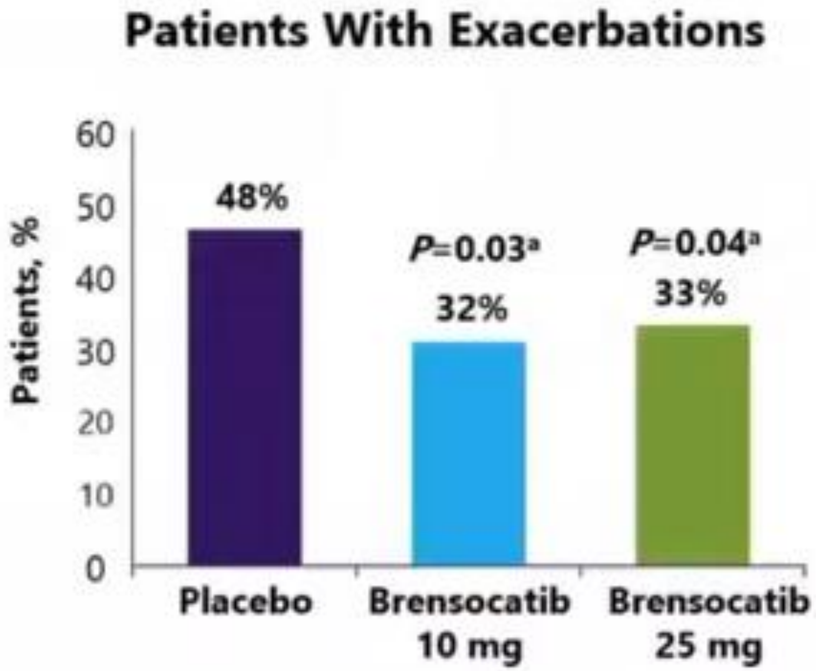
Primary Endpoint: Time to First Exacerbation

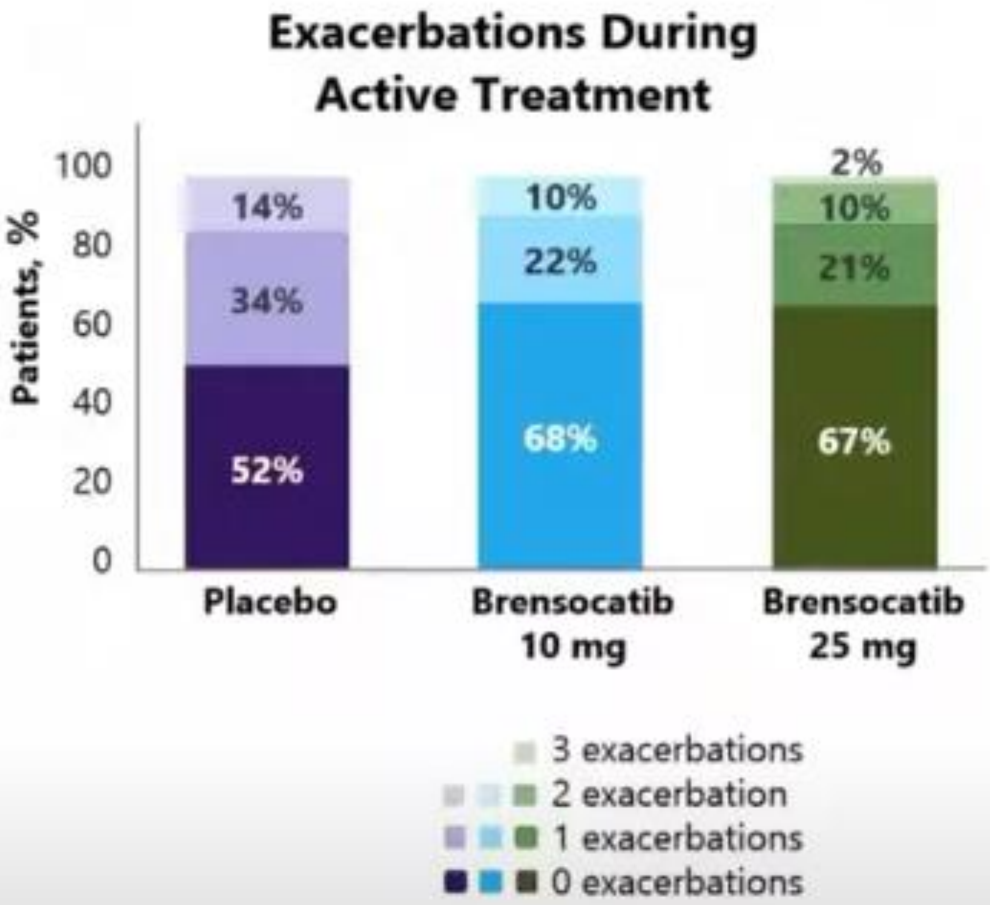


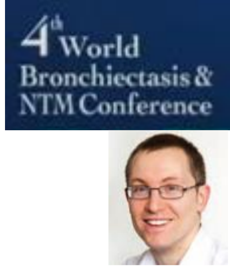
Cumulative No. of events/No. at risk

Placebo	0/87	8/78	12/73	15/69	20/63	22/61	25/57	27/55	29/52	30/50	34/47	37/44	40/38	40/37	42/5
10 mg Brensocatib	0/82	3/79	4/76	9/72	11/69	13/66	16/62	16/62	18/60	19/59	21/57	24/54	25/53	25/52	26/4
25 mg Brensocatib	0/87	4/83	10/77	16/71	16/70	19/64	21/60	22/58	23/57	24/56	26/54	26/52	26/52	28/49	29/10

Exacerbations During the Active Treatment Period

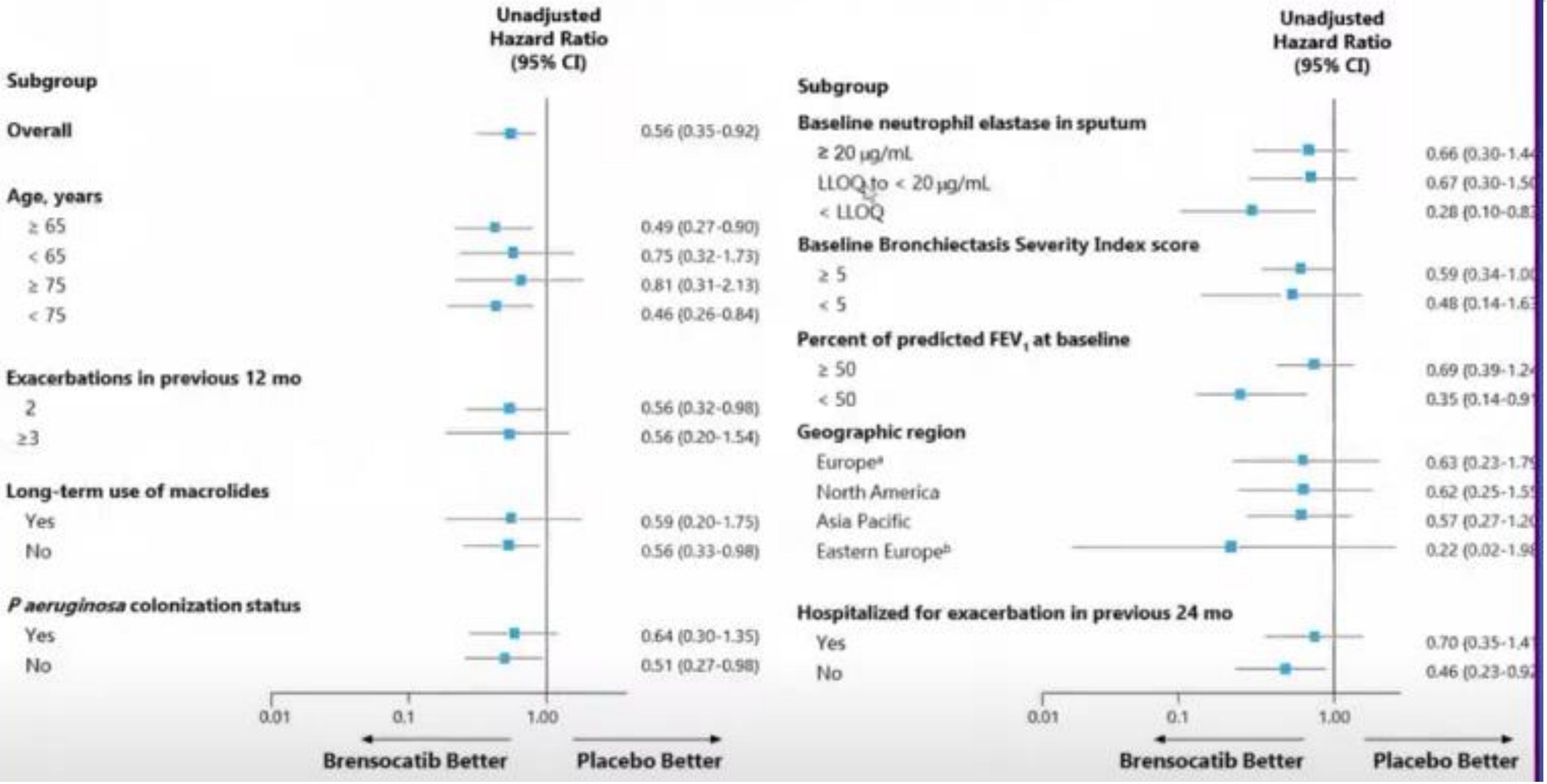






Time to First Exacerbation by Patient Subgroups

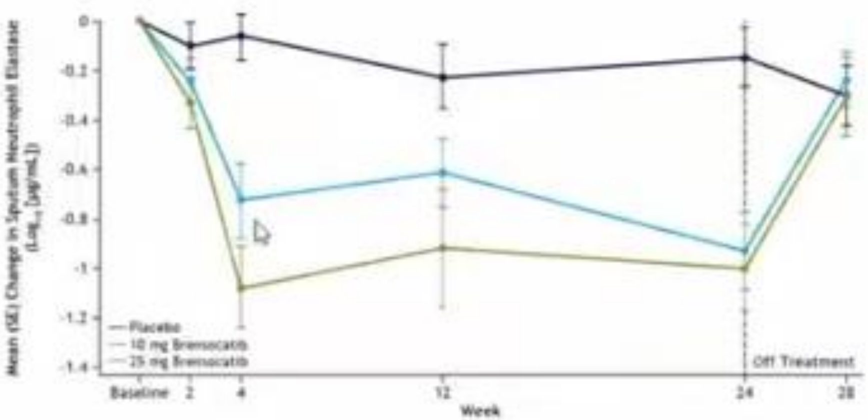
Brensocatib 10 mg vs Placebo



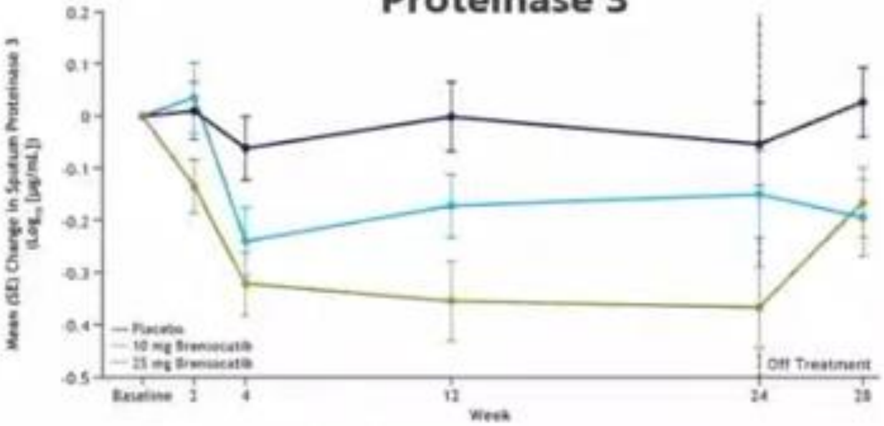
Pharmacodynamic Endpoints

- Brensocatib reduced sputum activity of neutrophil elastase, proteinase 3, and cathepsin G

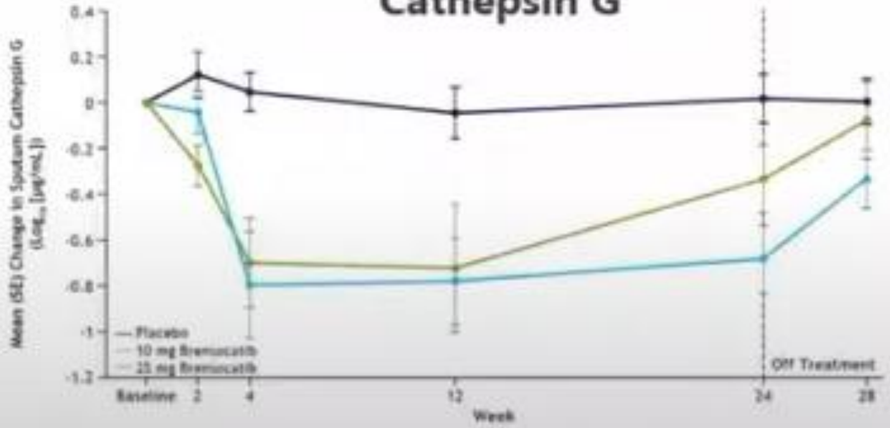
Neutrophil Elastase[1]



Proteinase 3

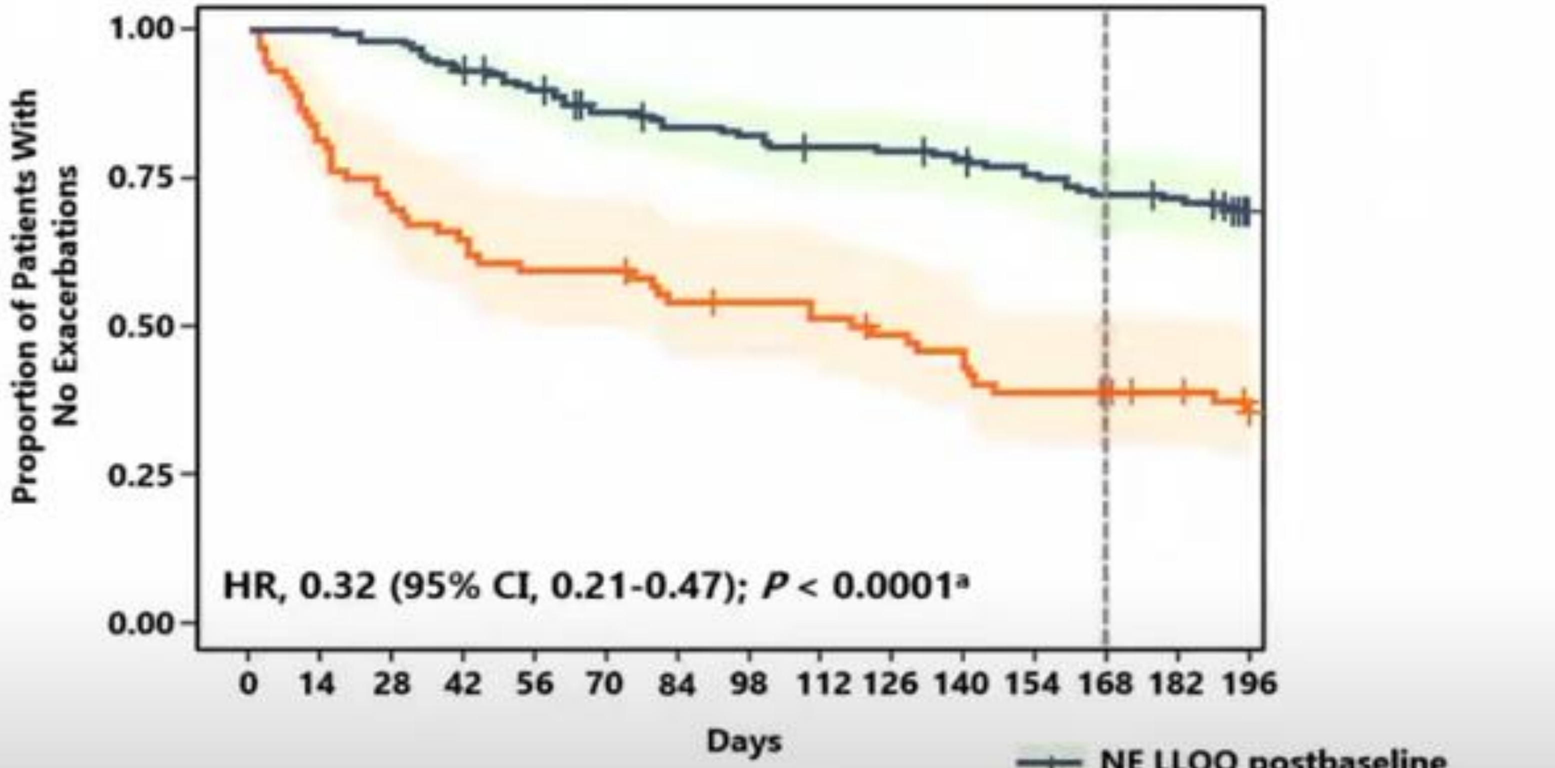


Cathepsin G



Association of Achievement of Sputum Neutrophil Elastase Levels Below the LLOQ and Time to First Exacerbation

- Patients who achieved sputum NE levels below the LLOQ postbaseline had a lower incidence of exacerbations

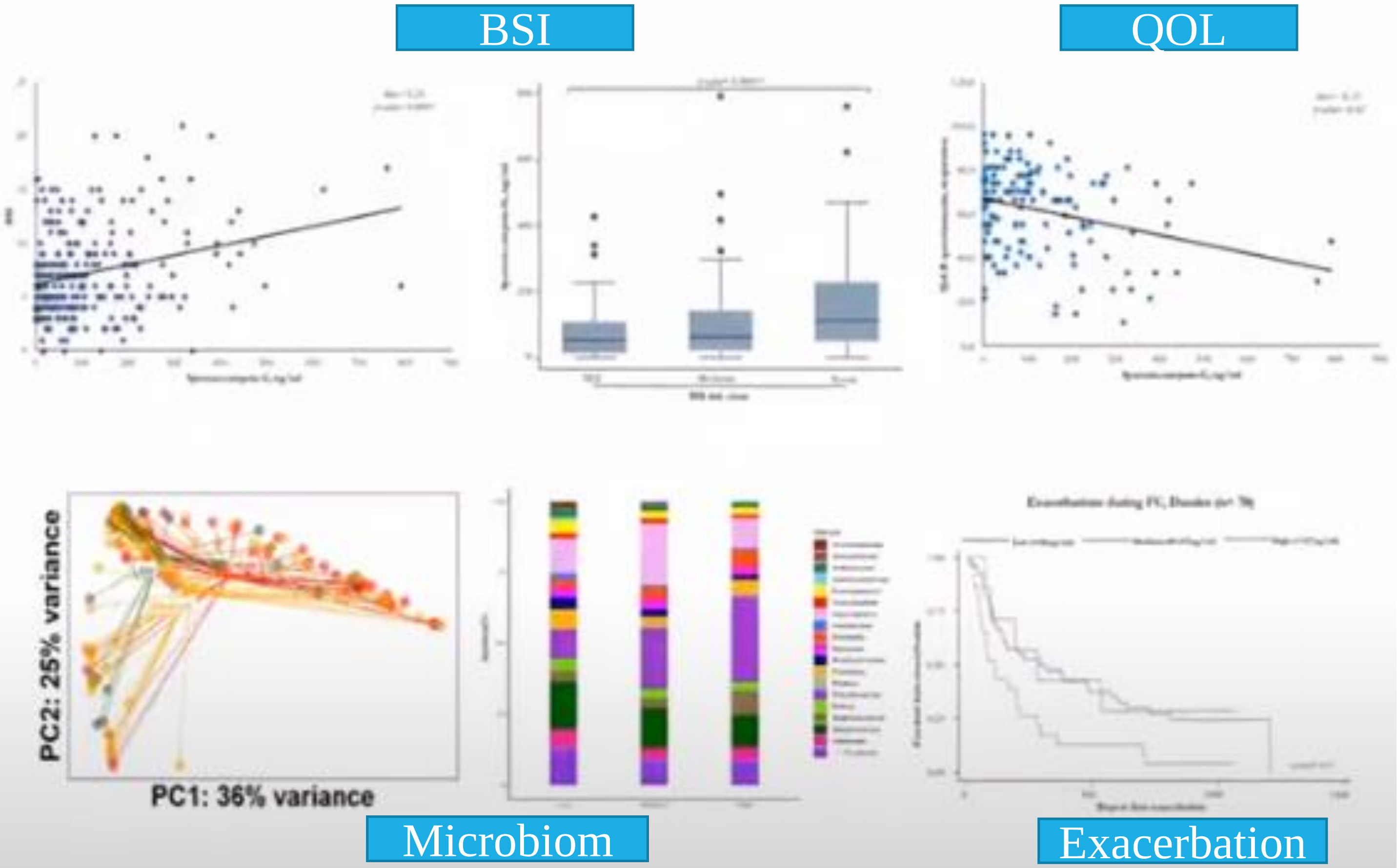


HR, hazard ratio; LLOQ, lower limit of quantification; NE, neutrophil elastase.
[a] Log-rank test applied post hoc to the time-to-event data.

4th World Bronchiectasis & NTM Conference

Cathepsin-G correlates with disease severity, QOL, microbiome diversity, and exacerbation

- Observational, cross-sectional study
- Milan, Barcelona, Dundee
- March 2017 and May 2019
- 320 patients
- 77% had detectable levels of Cat-G in the sputum
- Median (IQR) levels of 75.0 (23.4-163.0)

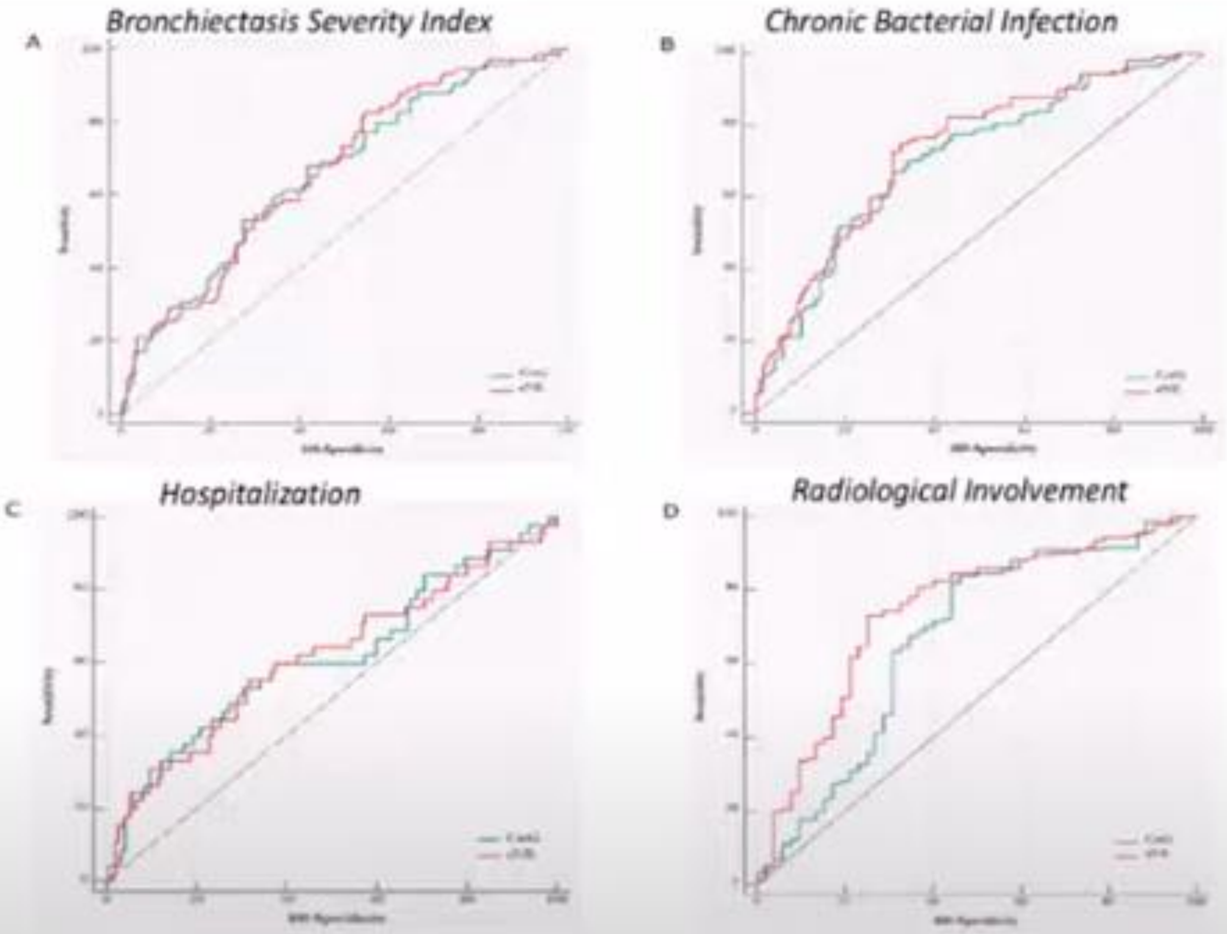


Sputum NE vs Cathepsin-G

- 242 patients

No statistically significance differences in ROC AUC in predicting

- Disease severity
- Chronic infection / Chronic *P. aeruginosa* infection
- Radiological involvement
- Exacerbation / Hospitalization
- FEV_1%



The role of non-invasive modalities for assessing inflammation in patients with non-cystic fibrosis bronchiectasis

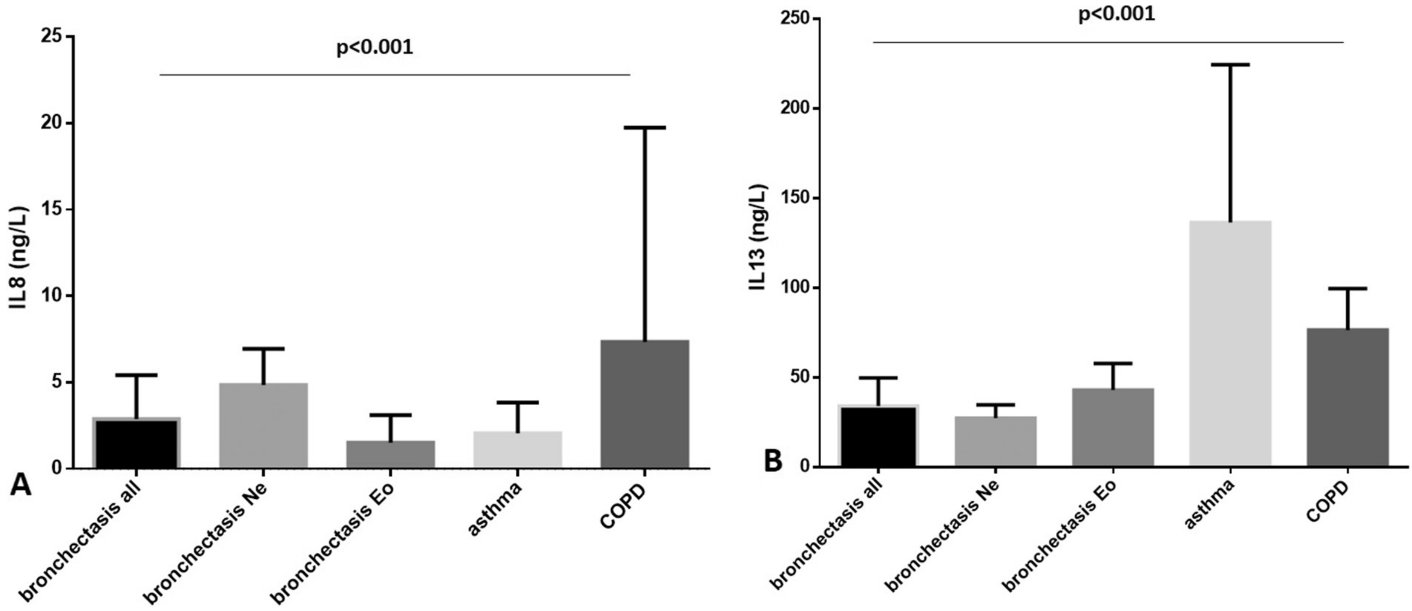
Stamatoula Tsikrika[a], Katerina Dimakou[b], Andriana I. Papaioannou[c], Georgios Hillas[d], Loukas Thanos[e], Kostantinos Kostikas[c], Stelios Loukides[c], Spyros Papiris[c], Nickolaos Koulouris[a], Petros Bakakos[a,*]

- N=40
- Cell counts in induced sputum, University of Athens

: 15 (37.5%) had a neutrophilic phenotype, 7 (17.5%) had an eosinophilic phenotype, 3 (12.5%) had a mixed neutrophilic-eosinophilic phenotype and 15 (37.5%) had a paucigranulocytic phenotype

Association of sputum cell count, pulmonary function testing, and severity of disease with IL-13 and IL-8 in sputum supernatant.

	IL-13	IL-8
Neutrophils	r = 0.068 p = 0.73	r = 0.798 p < 0.001
Eosinophils	r = 0.656 p < 0.001	r = −0.109 p = 0.50
Bronchiectasis score	r = 0.042 p = 0.84	r = 0.765 p < 0.001



Cytokine, 2017 Nov;99:281-286

Respirology

Sputum matrix metalloproteinase-8 and -9 and tissue inhibitor of metalloproteinase-1 in bronchiectasis: Clinical correlates and prognostic implications

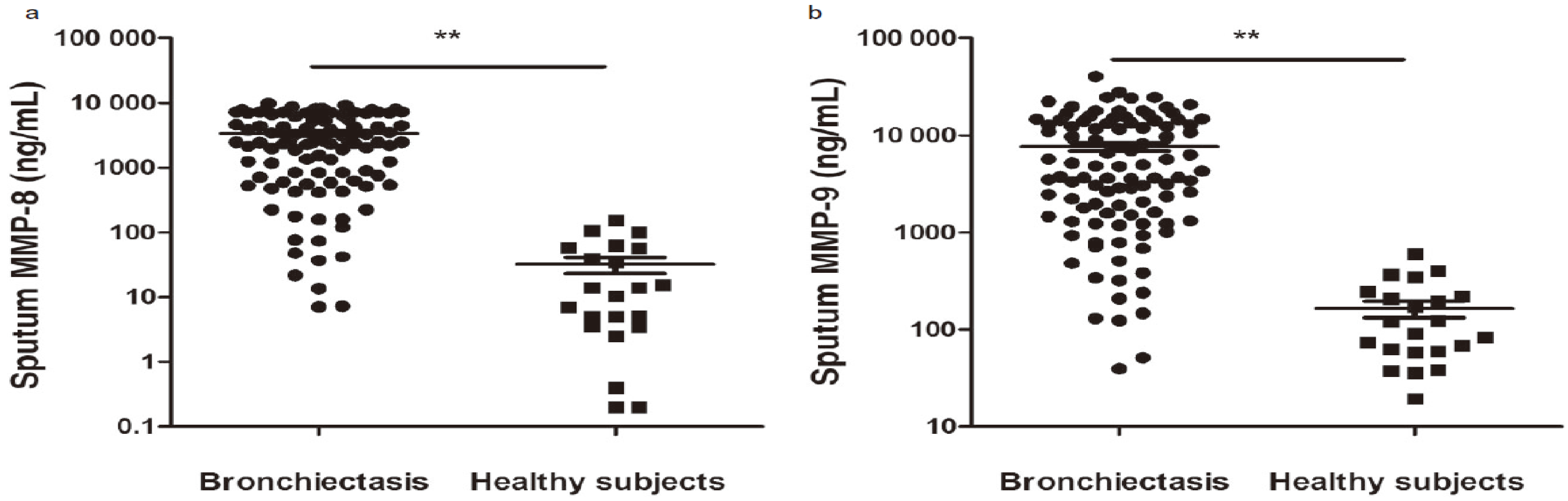
- N=102 BE pts and 22 controls
- Guangzhou Medical University Hospital

Table 2 Correlation between MMP levels and clinical parameters in clinically stable bronchiectasis

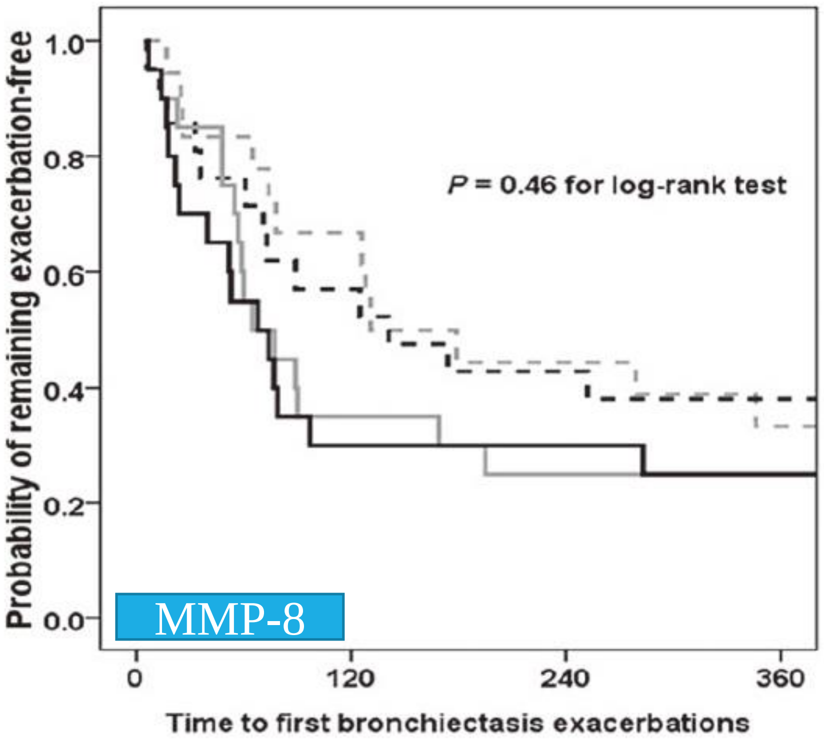
	MMP-8 (ng/mL)		MMP-9 (ng/mL)		TIMP-1 (ng/mL)		MMP-9/TIMP-1	
Clinical parameters	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Disease duration (years)	0.16	0.12	**0.20**	**0.04**	–0.08	0.46	0.14	0.18
No. of bronchiectatic lobes	**0.30**	**<0.01**	**0.22**	**0.03**	–0.18	0.07	0.16	0.12
HRCT score	**0.38**	**<0.01**	**0.33**	**<0.01**	**–0.25**	**0.01**	0.15	0.15
Sputum bacterial density (log_{10} cfu/mL)	**0.28**	**0.03**	0.21	0.10	0.01	0.99	0.10	0.42
Bronchiectasis Severity Index	**0.29**	**<0.01**	**0.31**	**<0.01**	–0.08	0.43	0.05	0.65
FVC pred (%)	**–0.48**	**<0.01**	**–0.44**	**<0.01**	0.09	0.38	**–0.25**	**0.01**
FEV_1 pred (%)	**–0.44**	**<0.01**	**–0.42**	**<0.01**	0.10	0.32	**–0.23**	**0.02**
FEV_1/FVC (%)	–0.17	0.09	–0.18	0.08	0.08	0.43	–0.15	0.14

Respirology (2015) **20**, 1073–1081

Higher levels in BE than healthy subjects

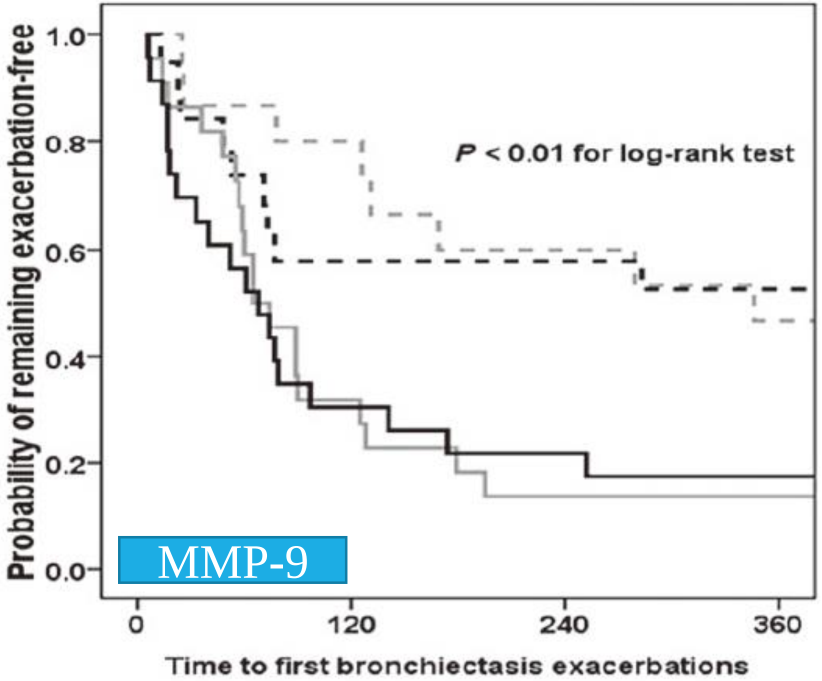


MMP-9 (not MMP-8, TIMP-1) for predicting time to first exacerbation within 1 year



No. of patients at risk

Quartile 1	18	12	8	6
Quartile 2	20	7	5	5
Quartile 3	21	12	9	8
Quartile 4	20	6	6	5



No. of patients at risk

Quartile 1	15	12	9	7
Quartile 2	22	7	3	3
Quartile 3	19	9	9	8
Quartile 4	23	7	5	4

Blood

The heterogeneity of systemic inflammation in bronchiectasis

Aarash D. Saleh [a], James D. Chalmers [b], Anthony De Soyza [c], Thomas C. Fardon [b], Spiro O. Koustas [c], Jonathan Scott [c], A. John Simpson [c], Jeremy S. Brown [a], John R. Hurst [a, *]

- N=90 (derivsation cohort)// 97 and 79 (validation cohort)
- Assayed blood concentration of 31 proteins
- Hypothesis: systemic inflammatory markers can distinguish aetiology and severity groups

(all logs)	n = above the lower limit of detection	Mean (SD)
CRP	90	2.8 (3.9)
Eotaxin	90	147.9 (1.9)
Eotaxin-3	73	14.1 (3.3)
Fibrinogen	90	3.5 (1.4)
GM-CSF	83	0.4 (2.3)
IFN-γ	84	9.1 (3.4)
IL-1α	41	0.4 (6.2)
IL-1β	53	0.1 (4.3)
IL-2	45	0.3 (4.3)
IL-4	37	0.1 (3.4)
IL-5	86	0.5 (2.6)
IL-6	86	1.3 (2.5)
IL-7	90	15.1 (1.6)
IL-8	90	13.5 (2.8)
IL-10	78	0.4 (3.2)
IL-12p40	90	107.2 (2.2)
IL-12p70	65	0.7 (2.3)
IL-13	63	6.9 (1.7)
IL-15	90	2.3 (1.4)
IL-16	90	257.0 (1.6)
IL-17	90	4.0 (2.6)
IP-10	90	309.0 (2.5)
MCP-1	90	263.0 (1.8)
MCP-4	90	81.3 (1.6)
MDC	90	831.8 (1.7)
MIP-1α	83	21.9 (1.6)
MIP-1β	90	112.2 (1.6)
TARC	90	275.4 (2.1)
TNF-α	90	1.8 (1.6)
TNF-β	79	0.2 (2.8)
VEGF	90	109.6 (1.9)

Respiratory Medicine 127 (2017) 33–39

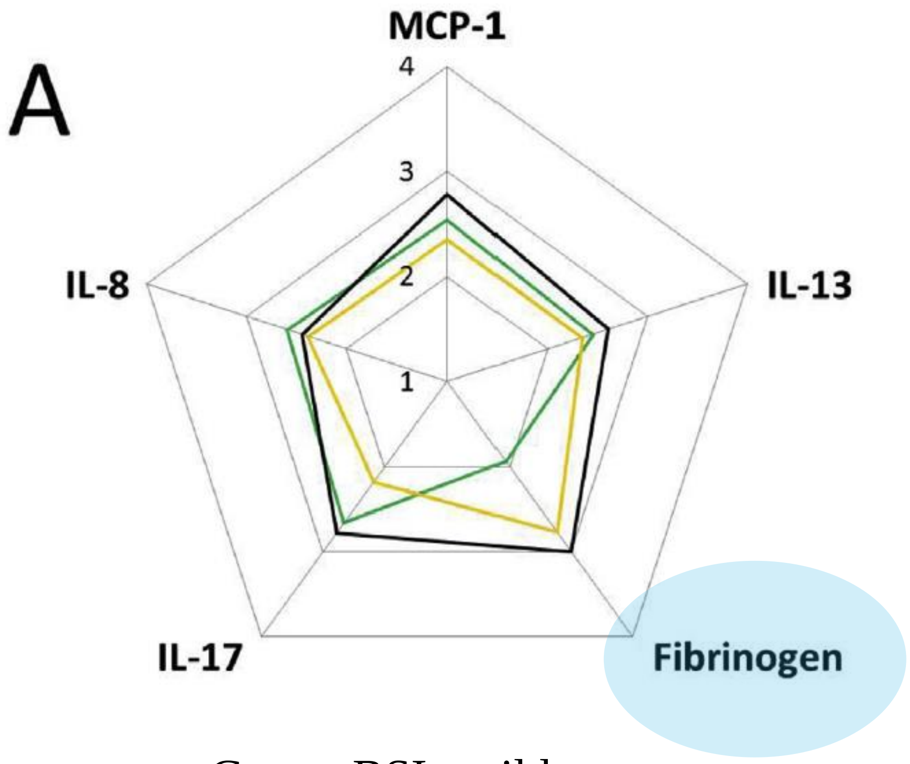
Principle Component Analysis (PCA)

- Great heterogeneity was observed in the analysis of systemic protein markers across the dataset.

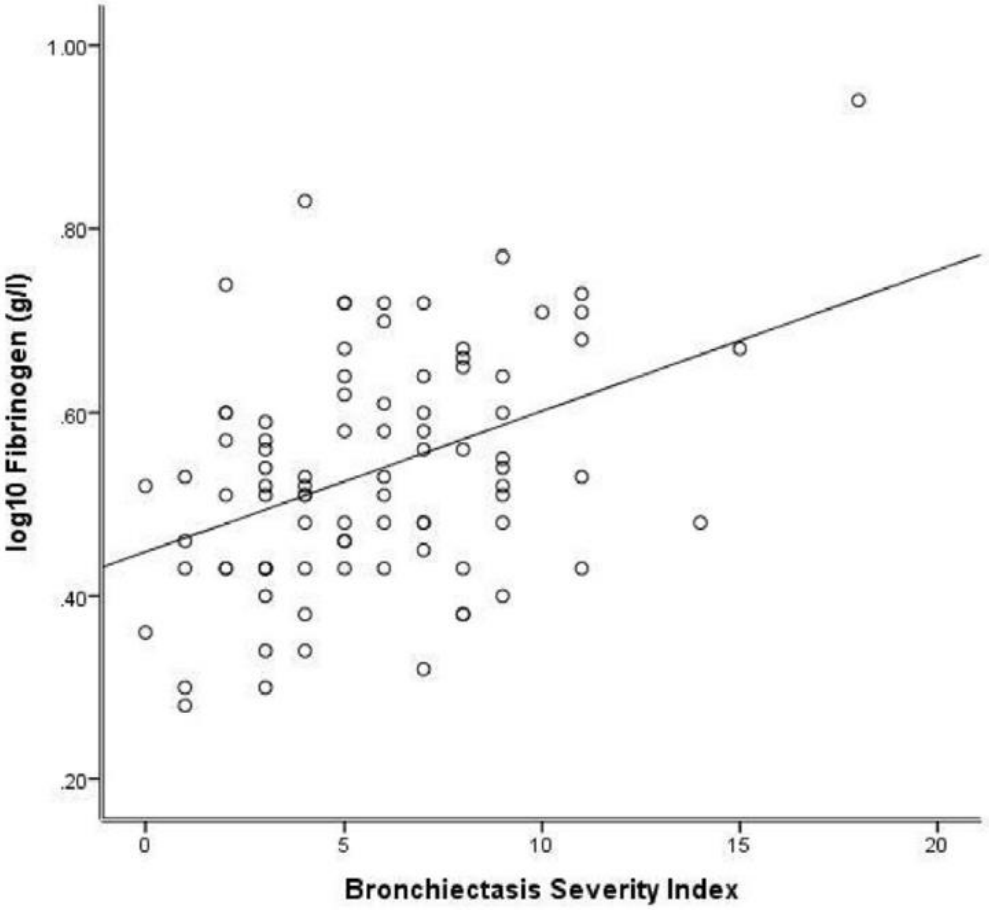
Principal Component analysis of 31 proteins in the blood of 90 patients with bronchiectasis in the derivation cohort identified five components that explained 52% of variance. The number in brackets represents the strength of the association between that marker and the respective principal component.

Component	Nature	Correlates
1	'Mononuclear Chemotaxis'	MCP-1 (0.841); MDC (0.773)
2	'Immune Regulation'	IL-13 (−0.759); IL-12p70 (−0.729)
3	'Acute Phase Response'	Fibrinogen (0.719); CRP (0.711)
4	'Immune Activation'	IL-17 (0.796); IL-12p40 (0.596)
5	'Polymorphonuclear Chemotaxis'	IL-8 (0.638); IL-16 (0.633)

BSI and systemic inflammatory proteins

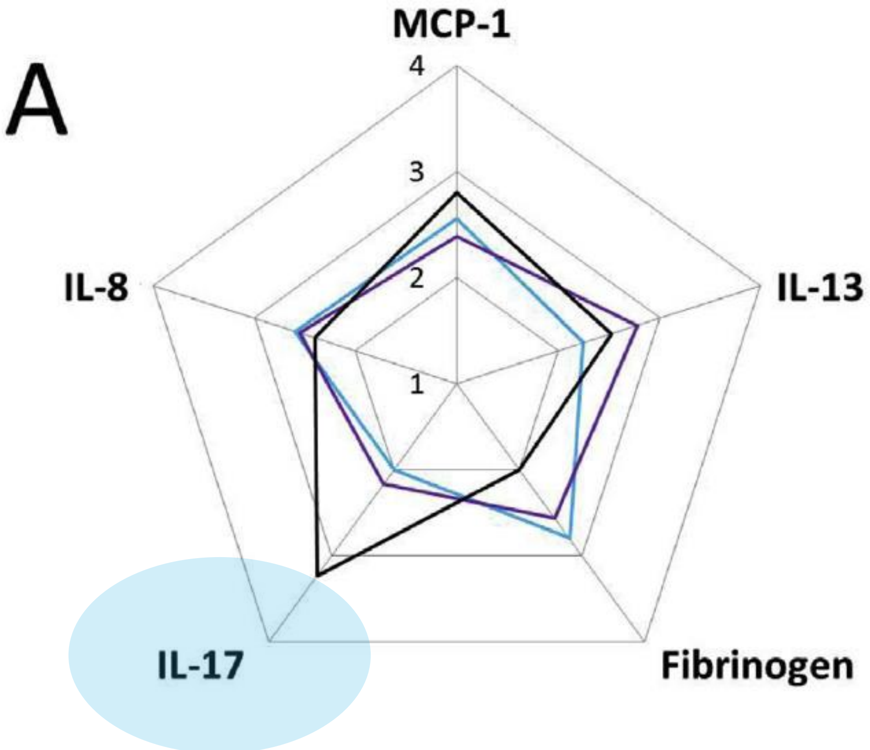


Green: BSI , mild
Yellow: BSI, moderate
Black: BSI, severe



Rho = 0.34, p = 0.001
Rho = 0.36, p < 0.001 in validation cohort

Bronchiectasis etiology and proteins



-Blue :idiopathic patients,
-Purple :post-infectious patients
-Black :patients with primary immunodeficiency

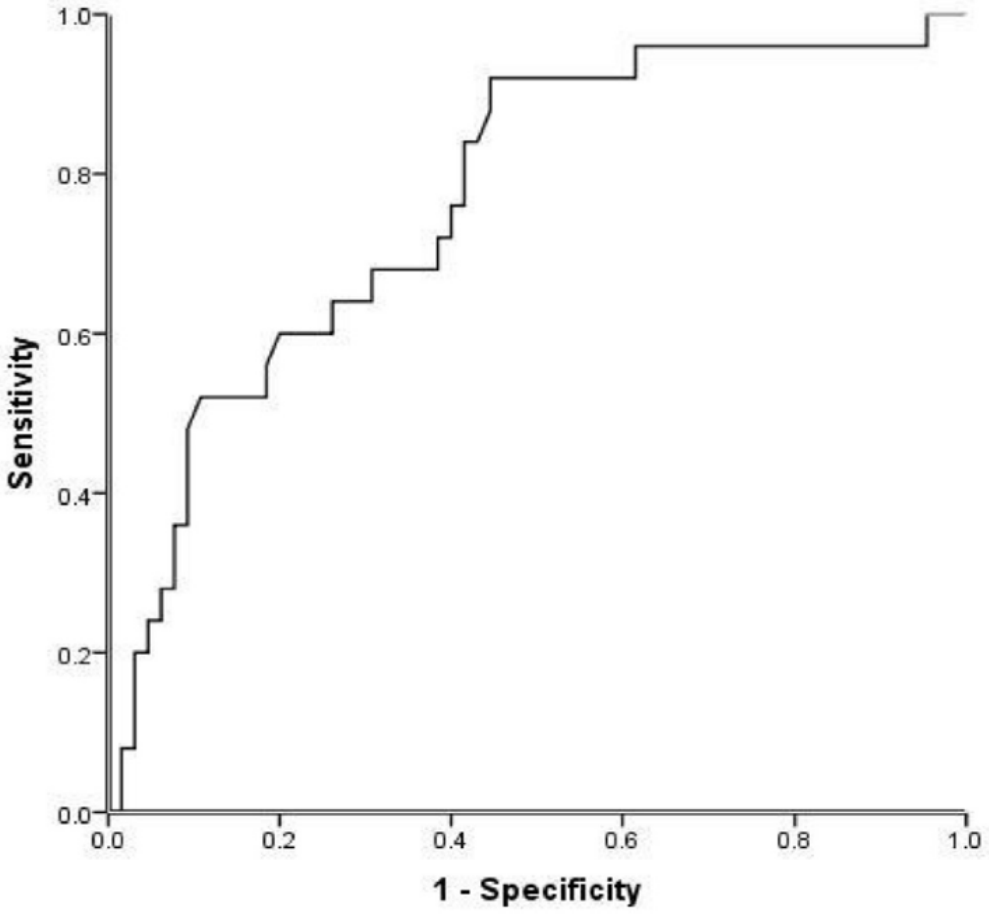


Fig. 4. Receiver Operating Characteristic (ROC) curve for the ability of serum IL-17 concentration to differentiate primary immunodeficiency from other causes of bronchiectasis in the derivation cohort (AUC = 0.769 (95%CI) 0.661-0.877 $p < 0.001$).

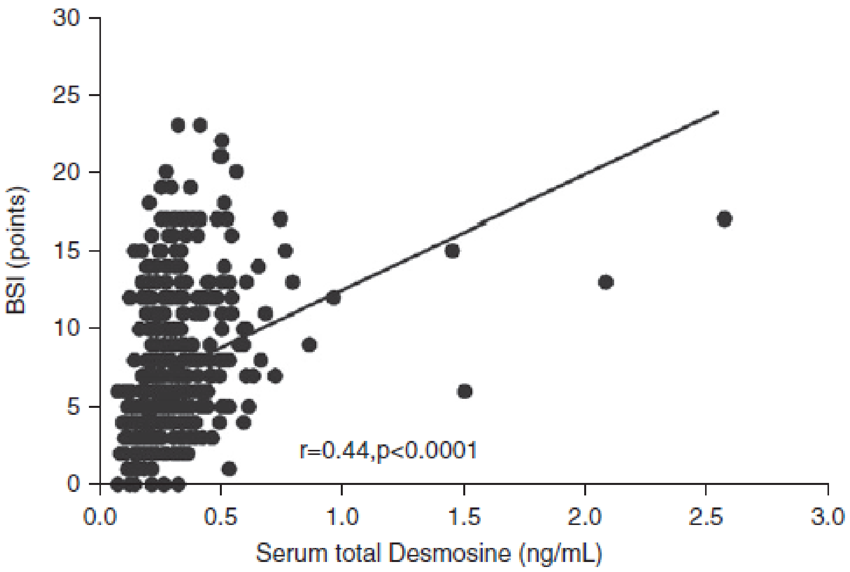
Serum Desmosine is Associated with Long-term All-cause and Cardiovascular Mortality in Bronchiectasis

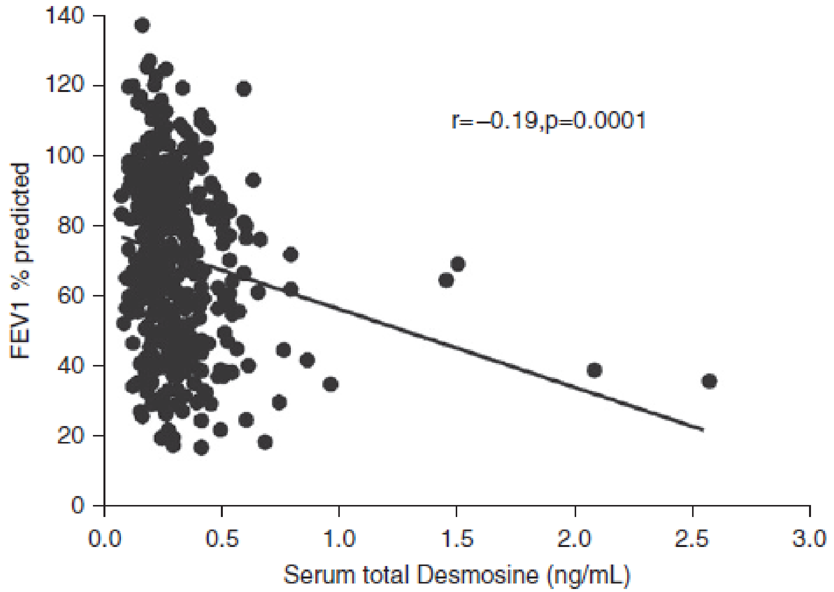
Jeffrey T.-J. Huang, PhD[1], Elena Kuzmanova, PhD[1], Alison J Dicker, PhD[1], Holly R Keir, BSc[1], Simon Finch, MD[1], Stefano Aliberti, MD[2], Thomas C Fardon, MD[1], James D Chalmers, MD, PhD[1]

- **Desmosine** is an amino acid found uniquely in elastin, a protein found in connective tissue such as skin, lungs, and elastic arteries.
- Detection of desmosine in urine, plasma or sputum samples can be a marker for elastin breakdown due to high elastase activity related to certain diseases
- N=433

Neutrophil Elastase Activity Is Associated with Exacerbations and Lung Function Decline in Bronchiectasis

James D. Chalmers[1,2], Kelly L. Moffitt[3], Guillermo Suarez-Cuartin[4], Oriol Sibila[4], Simon Finch[1], Elizabeth Furrie[2], Alison Dicker[1,2], Karolina Wrobel[2], J. Stuart Elborn[5,6], Brian Walker[3], S. Lorraine Martin[3], Sara E. Marshall[2], Jeffrey T.-J. Huang[2*], and Thomas C. Fardon[1*]





- Strong relationship between cDES and severe exacerbations (HR, 6.0; 95% CI, 3.61–10.0; p<0.0001)

AJRCCM 2017; 195 (10): 1384-1393

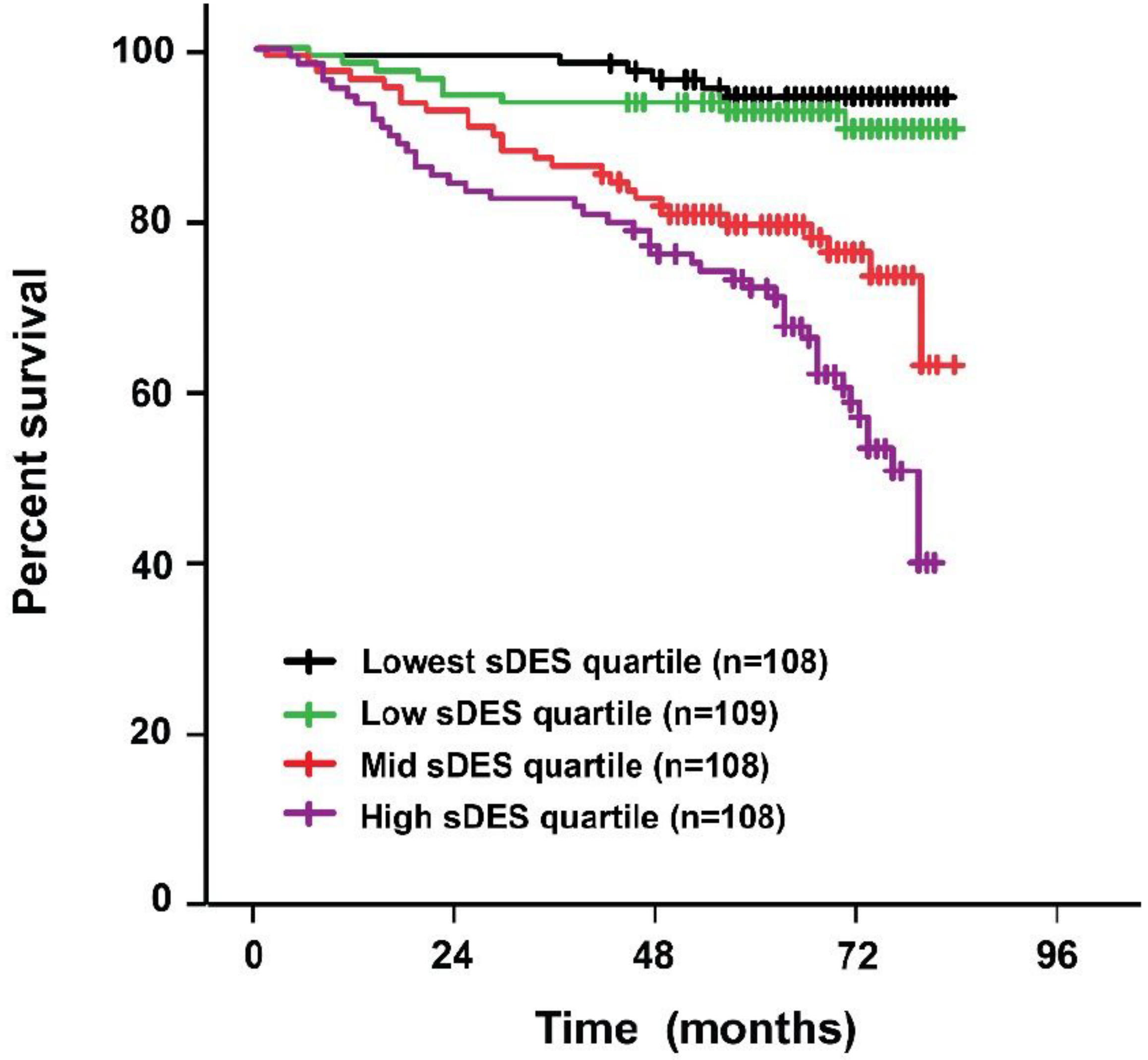


Figure 1. Kaplain-Meier survival curves of the relationship between sDES quartiles and all-cause mortality. Patients were divided into four quantiles based on sDES levels. The sDES cut-offs of the quartiles were 0.21, 0.28 and 0.36ng/ml. The HRs compared to the lowest quartile (reference) were 1.54 (0.55-4.34,p=0.41), 5.07 (2.09-12.3,p<0.0001) and 9.04 (3.86-21.2,p<0.0001) respectively from the low to high quartiles.

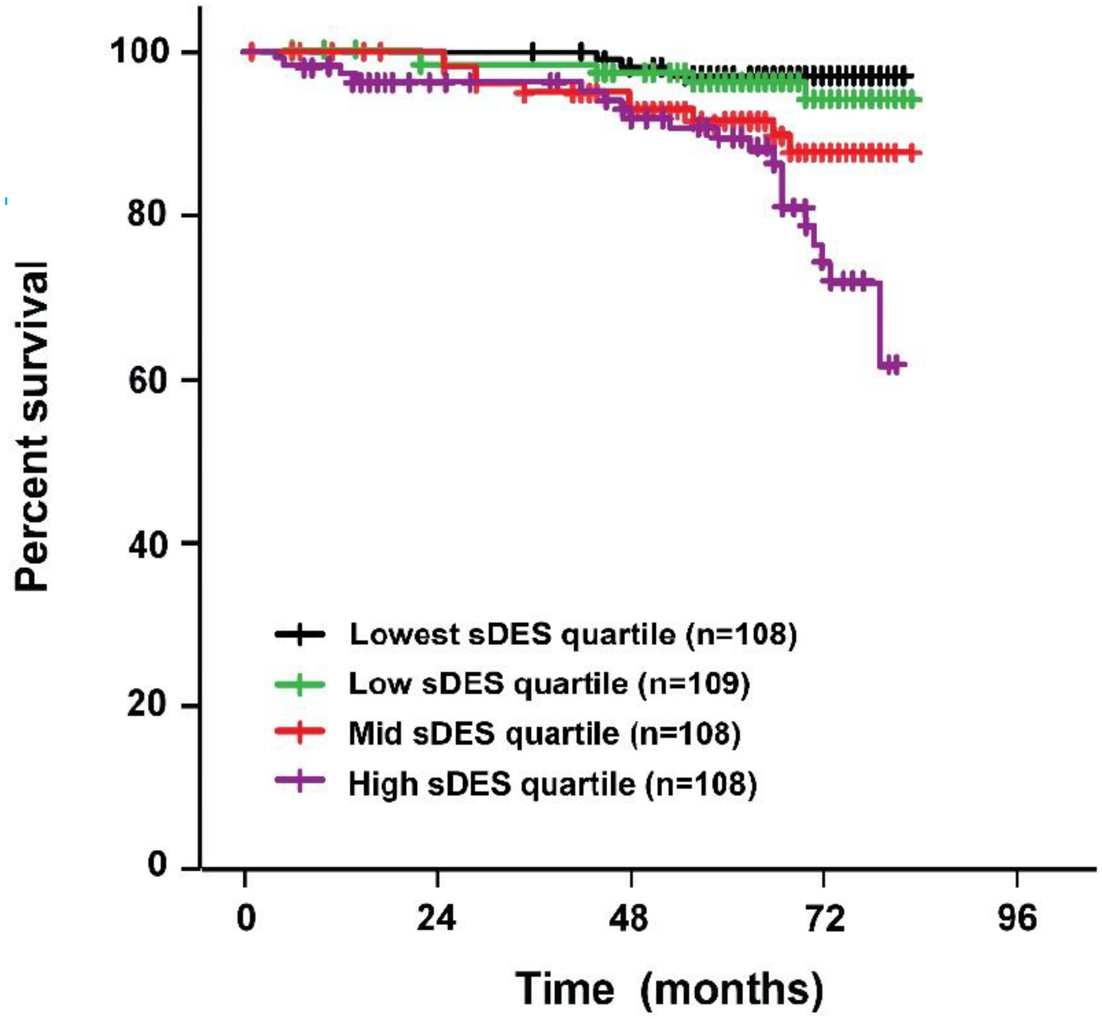


Figure 2. Kaplain-Meier survival curves of the relationship between sDES quartiles and cardiovascular mortality. Patients were divided into four quantiles based on sDES levels. The HRs compared to the lowest quartile (reference) were 1.73 (0.41-7.26,p=0.5), 4.03 (1.11-14.7,p=0.034) and 8.37 (2.50-28.1,p=0.001) for the low to high quartiles respectively.

Results

- sDES levels were associated with increasing all-cause mortality (HR 2.30 per standard deviation (SD) (95% CI 1.85-2.84),p<0.0001, figure 1), a relationship which persisted when adjusted for BSI (HR 1.90 per SD (1.52-2.37),p<0.0001)

- sDES was associated with increased cardiovascular mortality (HR 2.21 per SD (1.60-3.05),p<0.0001, figure 2), a relationship that was still significant after adjustment for BSI (HR 1.97 per SD (1.41-2.74),p<0.0001)

- **The AUC/ROC for sDES to predict mortality was 0.76(0.71-0.82, p<0.0001) which was not significantly different to the BSI (0.73(0.67-0.79), p=0.24)**

January 28, 2021 as 10.1513/AnnalsATS.202002-094OC

Thrombocytosis during Stable State Predicts Mortality in Bronchiectasis

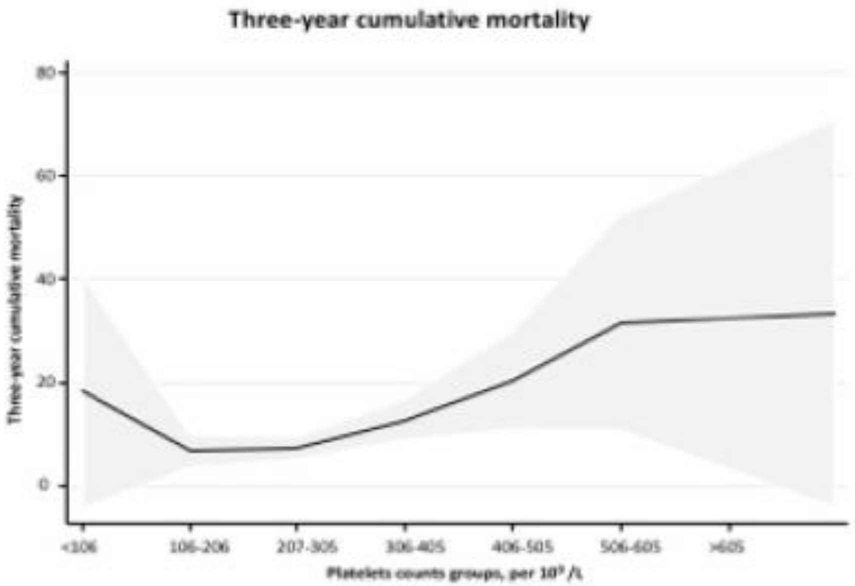
Stefano Aliberti MD[1,2], Giovanni Sotgiu MD, PhD[3], Andrea Gramegna MD[1,2], Melissa J. Amati MD[1,2], Angelo G. Corsico MD[11], Francesco Blasi MD[1,2], James D. Chalmers MD, PhD[12]

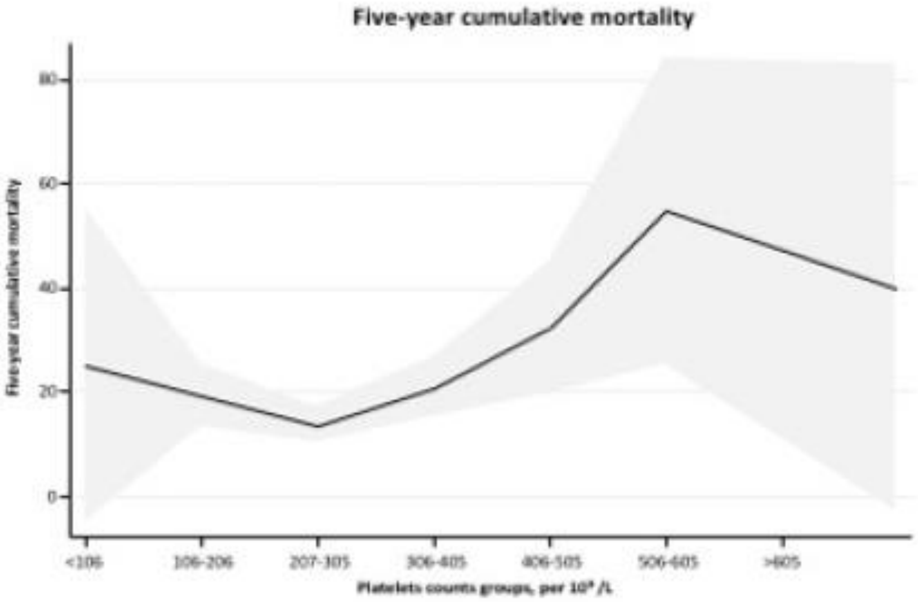
- N=1,771, 10 centers in Europe and Israel
- Platelet count in stable state, prospective EMBARC cohort

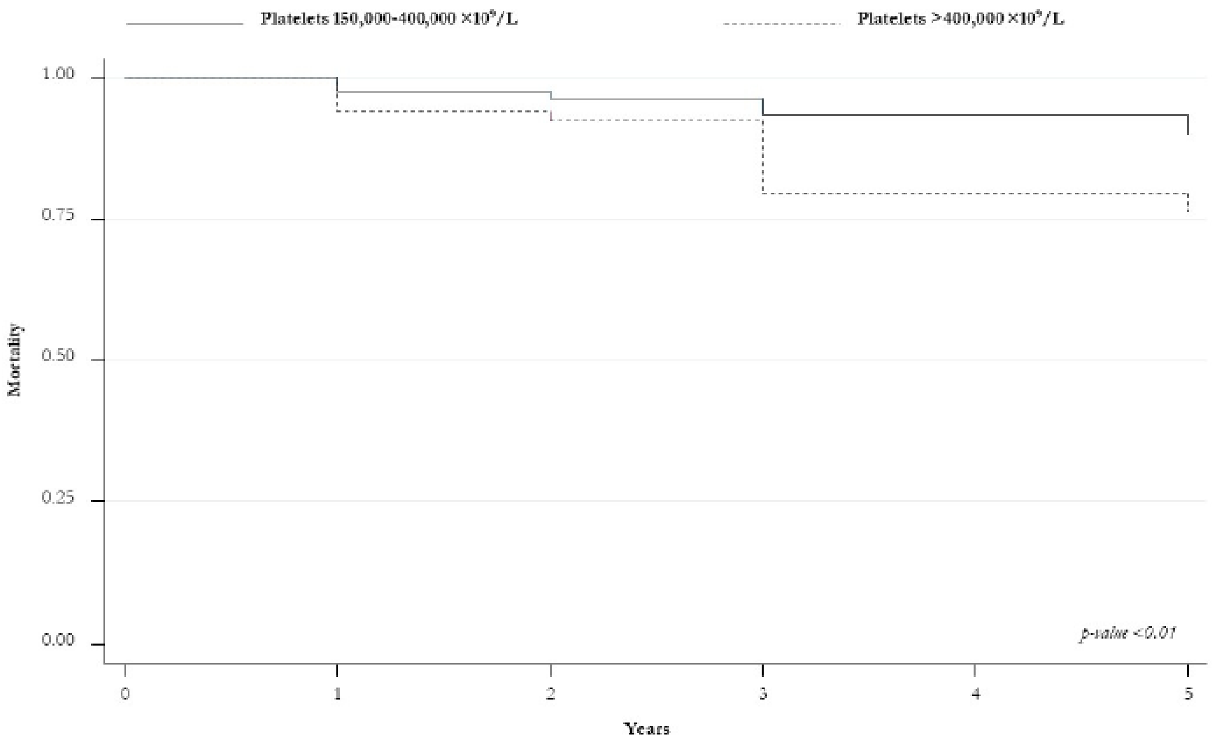
Table 1A. Demographics and comorbidity data of the study population and the three study groups.

Variables		Study population	Thrombocytopenia (<150,000)	Normal platelets (150,000-400,000)	Thrombocytosis (>400,000)
n.		1,771	70	1,565	136
Disease severity					
Median (IQR) BSI score,		7 (4-11)	7 (3-12)	6 (4-10)	9 (5-14)
BSI score Risk Class, n (%)	Mild	504 (28.6)	27 (38.6)	450 (28.9)	27 (20.0)
	Moderate	610 (34.6)	17 (24.3)	554 (35.5)	39 (28.9)
	Severe	651 (36.9)	26 (37.1)	556 (35.6)	69 (51.1)

Median (IQR) follow-up exacerbations	1 (1-2)	1 (1-2)	1 (0-2)	2 (1-3)	0.05	0.01
Follow-up hospitalization, n(%)	307 (20.4)	16 (27.6)	251 (18.9)	40 (33.1)	<0.01	<0.01


Three-year cumulative mortality
Three-year cumulative mortality
80
60
40
20
0
<106
106-206
207-305
306-405
406-505
506-605
>605
Platelets counts groups, per 10⁹ /L


Five-year cumulative mortality
Five-year cumulative mortality
80
60
40
20
0
<106
106-206
207-305
306-405
406-505
506-605
>605
Platelets counts groups, per 10⁹ /L

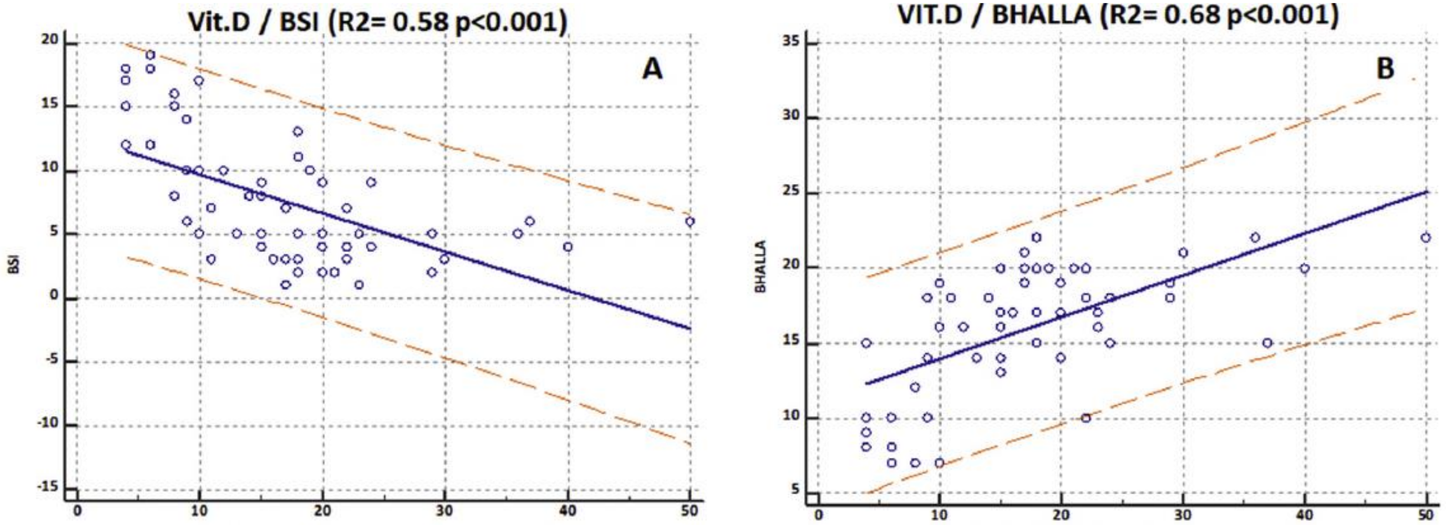

Platelets 150,000-400,000 ×10⁹/L
Platelets >400,000 ×10⁹/L
Mortality
1.00
0.75
0.50
0.25
0.00
0
1
2
3
4
5
Years
p-value <0.01

Contents lists available at ScienceDirect
Respiratory Medicine
journal homepage: www.elsevier.com/locate/rmed

Vitamin D and disease severity in bronchiectasis

S. Ferri[a], C. Crimi[a], E. Heffler[b,c,*], R. Campisi[a], A. Noto[d], N. Crimi[a]

- N=57, University of Catania, Italy
- Retrospective observational study



Differences among groups when divided by Vitamin D levels.

	25-OH-D < 20 ng/ml (n = 37)	25-OH-D ≥ 20 ng/ml (n = 20)	P value
Bhalla, *median (IQR)*	16 (10–19)	19 (17–20)	.018
Exacerbation freq., *median (IQR)*	3 (2–4)	2 (1–3)	.013
BSI, *median (IQR)*	8 (5–13)	4 (3–6)	.001
Age, *mean (95% CI)*	60 (56–65)	60 (55–66)	.97
FEV1, *mean (95% CI)*	0.77 (0.66–0.88)	1.03 (0.91–1.13)	.004

Cureus Open Access Original Article DOI: 10.7759/cureus.9728

Neutrophils to Lymphocyte Ratio as a Biomarker in Bronchiectasis Exacerbation: A Retrospective Study

- N=80, Sismanogleio Hospital in Athens
- Retrospective observational study
- NLR in BE exacerbation

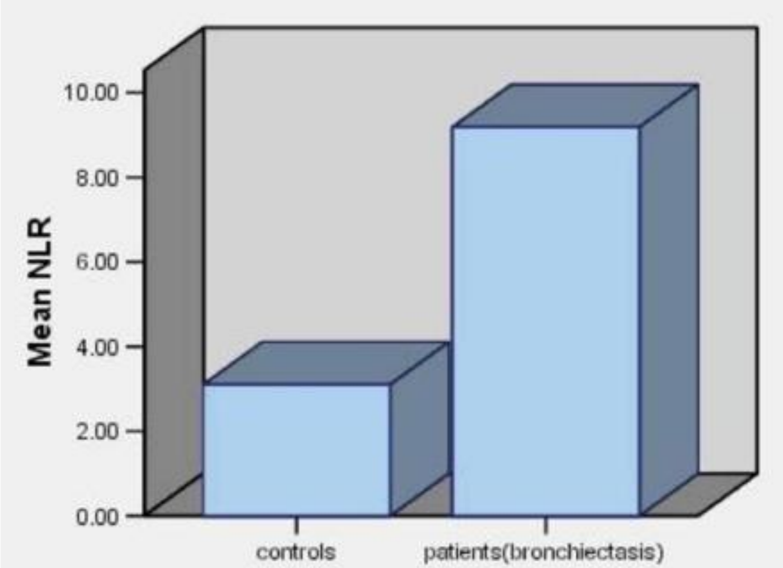


FIGURE 1: Mean NLR values in patients with bronchiectasis exacerbation and healthy controls

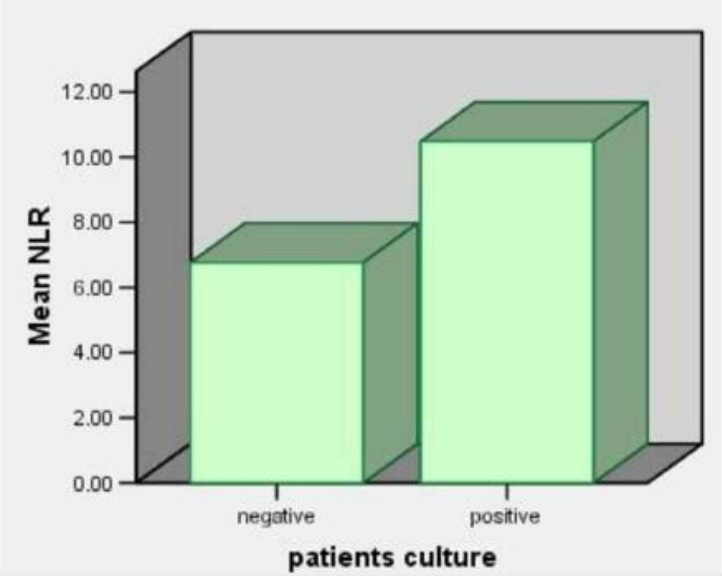


FIGURE 3: Mean NLR values in patients with positive and negative sputum cultures

Serum Albumin and Disease Severity of Non-Cystic Fibrosis Bronchiectasis

Seung Jun Lee MD, Hyo-Jung Kim MD, Ju-Young Kim MD, Sunmi Ju MD, Sujin Lim MD, Jung Wan Yoo MD, Sung-Jin Nam MD, Gi Dong Lee MD, Hyun Seop Cho MD, Rock Bum Kim MD, Yu Ji Cho MD, Yi Yeong Jeong MD, Ho Cheol Kim MD, and Jong Deog Lee MD

- N=107, GSNUH, 2013-2014

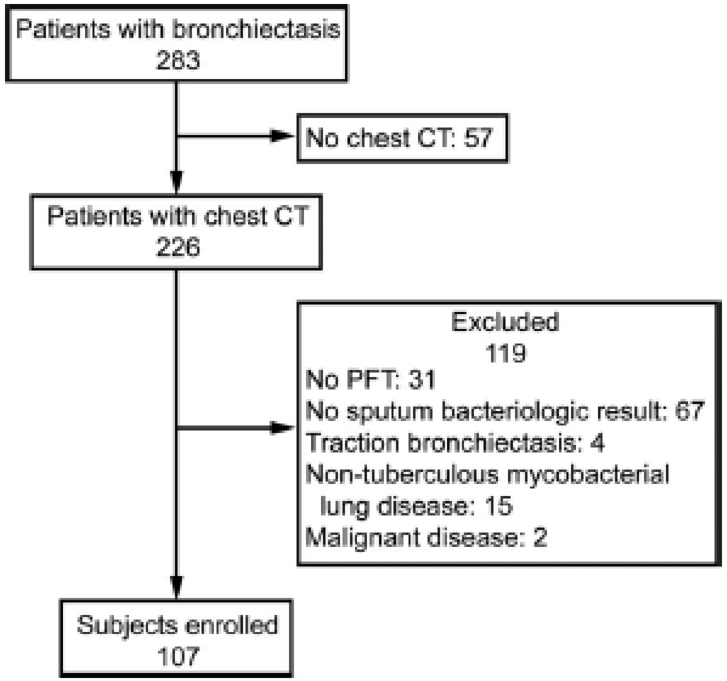


Table 3. Correlation Coefficient for Continuous Variables

Variables	BSI, All Subjects		FACED Score, All Subjects		BSI, Male Subjects		FACED Score, Male Subjects		BSI, Female Subjects		FACED Score, Female Subjects	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
White blood cell	0.06	.55	0.16	.10	0.16	.28	0.13	.37	−0.13	.34	0.16	.23
Neutrophil	0.09	.36	0.10	.32	0.31	.033	0.30	.038	−0.13	.34	−0.10	.46
Lymphocyte	−0.13	.20	−0.14	.15	−0.30	.040	−0.33	.02	0.07	.63	0.08	.57
NLR	0.08	.43	0.12	.22	0.26	.07	0.31	.033	−0.14	.31	−0.09	.51
Platelet	0.19	.053	0.15	.13	0.23	.11	0.22	.13	0.15	.25	0.08	.53
PLR	0.31	.001	0.14	.16	0.38	.007	0.34	.02	0.30	.02	−0.02	.89
Hemoglobin	−0.20	.036	−0.10	.33	−0.29	.046	−0.33	.02	−0.25	.059	−0.06	.66
BUN	−0.09	.36	−0.09	.37	−0.17	.24	−0.24	.10	−0.07	.61	−0.03	.81
Creatinine	−0.12	.22	−0.03	.77	−0.39	.008	−0.37	.009	−0.11	.41	0.02	.90
Uric acid	−0.07	.47	0.04	.71	−0.37	.008	−0.20	.17	0.14	.29	0.14	.29
Total protein	−0.11	.26	−0.10	.33	−0.07	.64	−0.02	.89	−0.18	.18	−0.17	.20
Albumin	−0.49	<.001	−0.37	<.001	−0.64	<.001	−0.57	<.001	−0.29	.03	−0.17	.20
Total bilirubin	−0.31	.001	−0.25	.01	−0.41	.004	−0.39	.006	−0.30	.02	−0.23	.08
C-reactive protein	0.22	.02	0.17	.09	0.23	.12	0.28	.050	0.18	.18	0.04	.80

BSI = bronchiectasis severity index
NLR = neutrophil/lymphocyte ratio
PLR = platelet/lymphocyte ratio
BUN = blood urea nitrogen

Table 4. Multiple Linear Regression Analysis of the Laboratory Variables Associated With the Bronchiectasis Severity Index and FACED Scores

Dependent Variables	Explanatory Variables	β Coefficient	95% CI	*P*
BSI	PLR	0.01	−0.01 to 0.02	.37
	Hemoglobin (g/dL)	0.37	−0.09 to 0.83	.11
	Albumin (g/dL)	−3.78	−5.23 to −2.33	<.001
	Bilirubin (mg/dL)	−3.50	−5.56 to −1.43	.001
	C-reactive protein (mg/L)	0.02	−0.04 to 0.08	.52
FACED score	Albumin (g/dL)	−1.18	−1.72 to −0.65	<.001
	Bilirubin (mg/dL)	−0.84	−1.71 to 0.02	.055

Albumin as a predictor of exacerbation

N=177, GSNUH

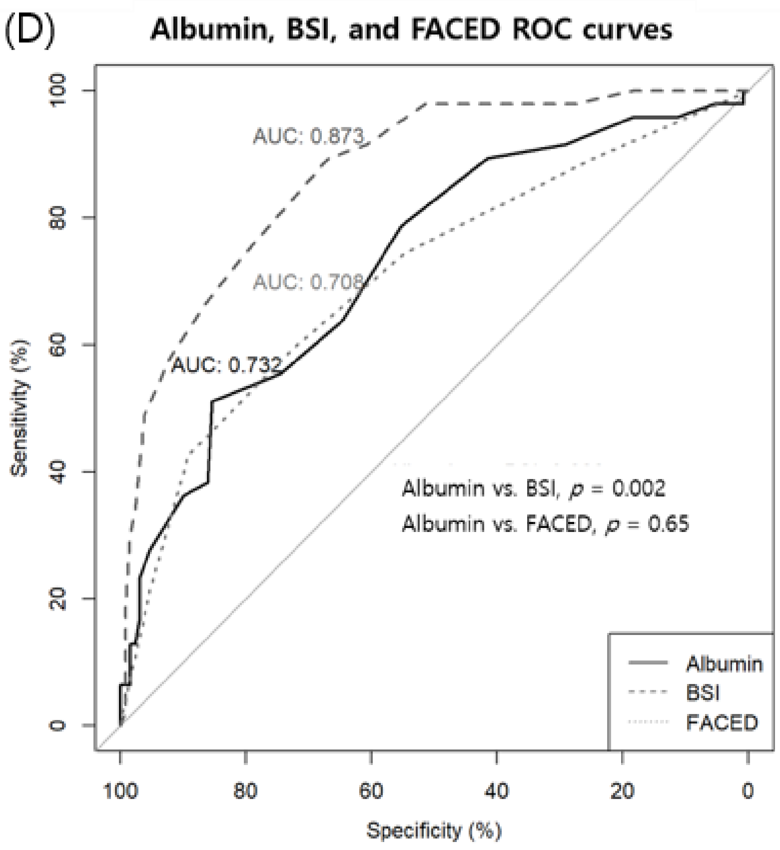


Table 2. Predicting factors for respiratory hospitalization in patients with non-cystic fibrosis bronchiectasis

	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Albumin						
≥ 3.5 g/dL	1			1		
< 3.5 g/dL	9.625	2.891-32.05	<0.001	5.814	1.209-27.955	0.028
C-reactive protein, (mg/L)	1.061	1.026-1.097	<0.001	1.053	1.010-1.099	0.016
Body mass index (kg/m^2)	0.843	0.755-0.941	0.002	0.921	0.802-1.058	0.245
FEV_1 (% predicted)	0.963	0.946-0.980	<0.001	0.992	0.967-1.017	0.522
mMRC dyspnea score	2.549	1.513-4.292	<0.001	2.583	1.208-5.527	0.014
Number of exacerbations in the previous year	2.082	1.392-3.113	<0.001	1.474	0.898-2.420	0.125
Chronic colonization with *Pseudomonas*	5.476	2.563-11.696	<0.001	3.466	1.334-9.006	0.011
Chronic colonization with other organisms	2.941	1.380-6.267	0.005	3.428	1.187-9.896	0.023
Number of affected lobes	1.547	1.210-1.977	0.001	1.247	0.868-1.790	0.232
Cystic bronchiectasis pattern [a]	2.731	1.378-5.413	0.004	1.135	0.433-2.976	0.796

Not published

Prospective biomarker studies, blood

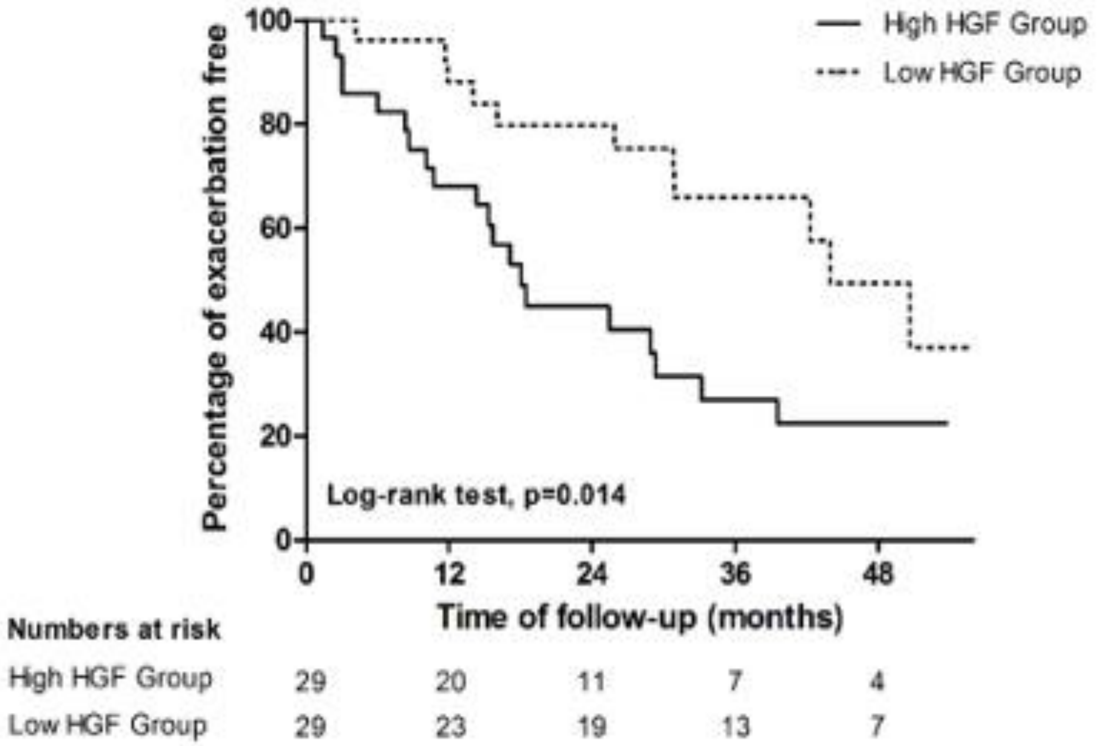
- Constitute prospective bronchiectasis cohort
- Funding source

- Hepatocyte growth factor
- Pentraxin-3
- Osteopontin
- Fibrinogen
- Angiopoietin-2
- Adiponectin
- IL-6
- Lipocalin-2

HGF, disease severity and exacerbation

Table 2. Univariate and Multiple linear regression analysis of laboratory variables associated with BSI and FACED score

		Univariate analysis			Multivariate analysis		
Dependent variables	Explanatory variables	β coefficient	95% CI	p-value	β coefficient	95% CI	p-value
BSI	HGF, ng/ml	5.357	2.370; 8.345	0.001	4.795	0.075; 9.515	0.047
	Pentraxin-3, ng/ml	4.760	1.033; 8.488	0.013	0.227	-5.009; 5.463	0.931
	PLR	0.028	0.002; 0.053	0.033	-0.009	-0.039; 0.021	0.538
	Albumin, g/dL	-3.369	-6.148; -0.589	0.018	-2.745	-5.522; 0.033	0.053
	CRP, mg/L	0.186	0.056; 0.316	0.006	0.111	-0.039; 0.261	0.143
FACED score	HGF, ng/ml	2.400	0.994; 3.806	0.001	1.904	0.315; 3.492	0.020
	NLR	0.548	0.043; 1.052	0.034	0.213	-0.529; 0.956	0.567
	PLR	0.013	0.002; 0.025	0.027	0.002	-0.017; 0.021	0.854
	Uric acid, mg/dL	0.352	0.022; 0.682	0.037	0.321	0.003; 0.640	0.048
	CRP, mg/L	0.068	0.006; 0.130	0.033	0.019	-0.052; 0.090	0.599

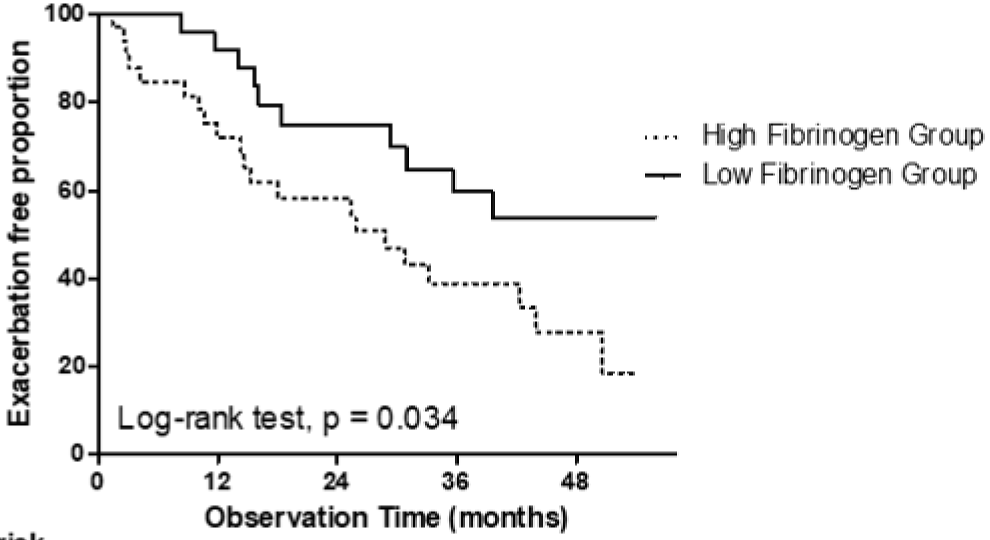


Not published

Fibrinogen, disease severity and exacerbation

Table 2. Univariate and multivariate linear regression analysis of laboratory variables associated with BSI and FACED score

		Univariate analysis			Multivariate analysis		
Dependent variables	Explanatory variables	β coefficient	95% CI	p-value	β coefficient	95% CI	p-value
BSI	Fibrinogen, ug/ml	0.794	0.397; 1.191	< 0.001	0.646	0.244; 1.149	0.002
	Albumin, g/dL	-2.909	-5.537; -0.280	0.031	-1.512	-3.965; 0.940	0.222
	CRP, mg/L	0.189	0.057; 0.321	0.006	0.118	-0.010; 0.246	0.071
FACED score	Fibrinogen, ug/ml	0.404	0.226; 0.583	< 0.001	0.348	0.171; 0.525	< 0.001
	White blood cell, 10^9/L	0.295	0.074; 0.516	0.01	0.261	0.066; 0.456	0.01
	PLR	0.014	0.002; 0.025	0.022	0.003	-0.008; 0.015	0.573
	Uric acid, mg/dL	0.424	0.089; 0.759	0.014	0.230	-0.063; 0.523	0.121
	CRP, mg/L	0.080	0.018; 0.142	0.012	0.026	-0.034; 0.087	0.385



Numbers at risk					
High Group	35	22	16	8	3
Low Group	26	23	15	12	5

Not published

Summary

Biomarkers	Disease severity	Lung function	Exacerbation	Mortality
Neutrophil elastase, sputum	Yes	Yes	Yes	Yes
Cathepsin G, sputum	(Yes)	(Yes)	(Yes)	No
IL-8, sputum	Yes	No	No	No
MMP-9, sputum	Yes	Yes	Yes	No
MMP-8, sputum	Yes	Yes	No	No
Fibrinogen	Yes	No	(Yes)	No
Desmosine	Yes	Yes	Yes	Yes
Platelet	Yes	No	Yes	Yes
Vit D	Yes	No	No	No
NLR	No	No	No	No
Albumin	Yes	Yes	Yes	No
HGF	(Yes)	No	(Yes)	No

Neutrophil elastase, very hopeful

1. Is there a strong biological plausibility in terms of its role in the pathogenesis of disease?
2. Is there a strong, consistent and independent association between the biomarker and chronic obstructive pulmonary disease?
3. Is there a strong, independent association between the biomarker and hard clinical outcomes such as mortality and hospitalization?
4. Is there evidence from randomized controlled trials that the biomarker is modifiable by interventions?
5. Is there evidence from randomized controlled trials that changes in the biomarker status result in changes in an important (and accepted) clinical outcome (e.g. mortality, exacerbation, rate of decline in FEV_1, health status)?

Proc Am Thorac Soc Vol 6. pp 543–545, 2009

감사합니다

GNUH
경상대학교병원
Gyeongsang National University Hospital