Proposed Etiotypes for COPD - Controversial Issues

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- Change in COPD definition – for what?
- Controversial issues
  - COPD-I
  - BE with AO
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- Summary

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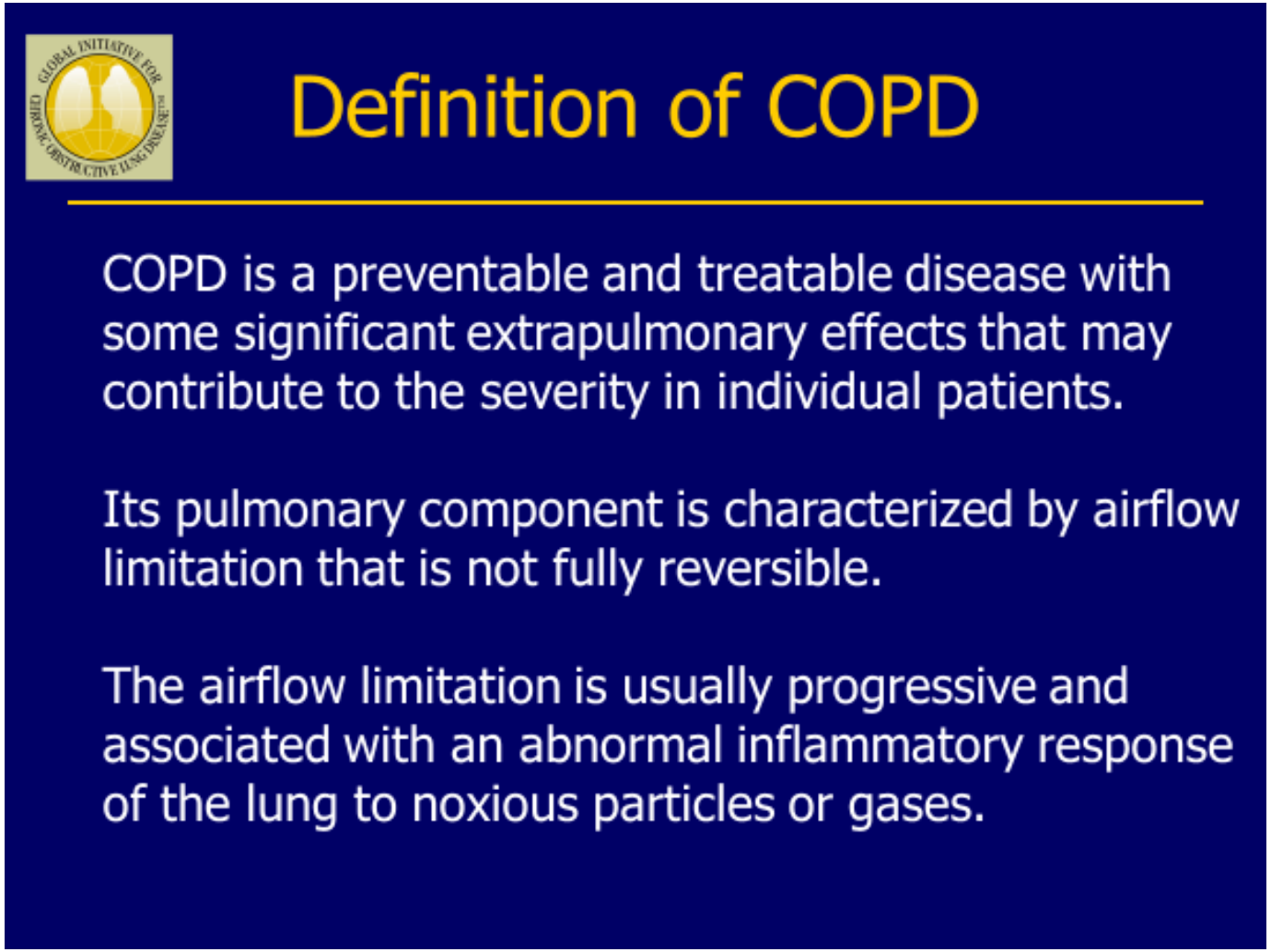
Definition of COPD

- 2007-2010



GOLD 2007

Definition of COPD

- **2011 - 2016**
  - Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by **persistent airflow limitation** that is usually progressive and associated with an enhanced **chronic inflammatory response** in the airways and the lung to **noxious particles or gases**. Exacerbations and comorbidities contribute to the overall severity in individual patients

- **2017 – 2019**
  - Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to **airway and/or alveolar abnormalities** usually caused by significant exposure to **noxious particles or gases**

GOLD Report 2011-2019

Definition of COPD

- 2020-2022
  - COPD is a common, preventable, and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to **noxious particles or gases** and influenced by host factors including **abnormal lung development**. Significant comorbidities may have an impact on morbidity and mortality

- 2023
  - COPD is a **heterogenous lung condition** characterized by chronic respiratory symptoms (dyspnea, cough, sputum production and/or exacerbations) due to abnormalities of the airway (bronchitis, bronchiolitis) and/or alveoli (emphysema) that cause persistent, often progressive, airflow obstruction

GOLD Report 2020-2023

Change in COPD definition

	2011-2016	2017-2019	2020-2022	2023
Symptoms		**Persistent respiratory symptoms**	**Persistent respiratory symptoms**	**Chronic respiratory symptoms** (dyspnea, cough, sputum and/or AE)
Physiology	**Persistent AFL**	**Persistent AFL**	**Persistent AFL**	**Persistent, often progressive, AO**
Pathology in the airway and lung	**Chronic inflammatory response**	**Airway and/or alveolar abnormalities**	**Airway and/or alveolar abnormalities**	**Airway and/or alveoli** (bronchitis, bronchiolitis, emphysema)
Etiology	**noxious particles or gases**	**noxious particles or gases**	**noxious particles or gases**	
			lung development	

Background

The Lancet Commissions

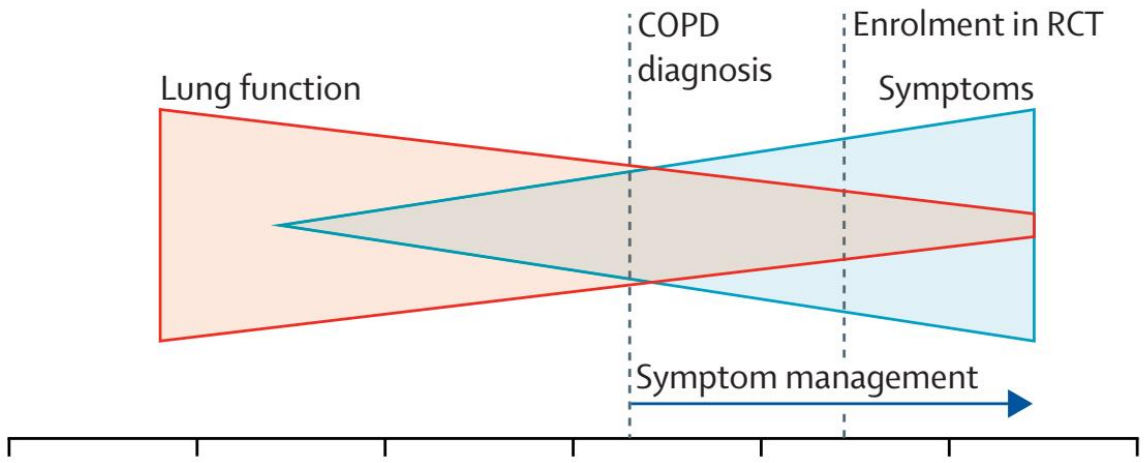
Towards the elimination of chronic obstructive pulmonary disease: a *Lancet* Commission

Daiana Stolz, Takudzwa Mkorombindo, Desiree M Schumann, Alvar Agusti, Samuel Y Ash, Mona Bafadhel, Chunxue Bai, James D Chalmers, Gerard J Criner, Shyamali C Dharmage, Frits M E Franssen, Urs Frey, MeiLan Han, Nadia N Hansel, Nathaniel M Hawkins, Ravi Kalhan, Melanie Konigshoff, Fanny W Ko, Trisha M Parekh, Pippa Powell, Maureen Rutten-van Mölken, Jodie Simpson, Don D Sin, Yuanlin Song, Bela Suki, Thierry Troosters, George R Washko, Tobias Welte, Mark T Dransfield

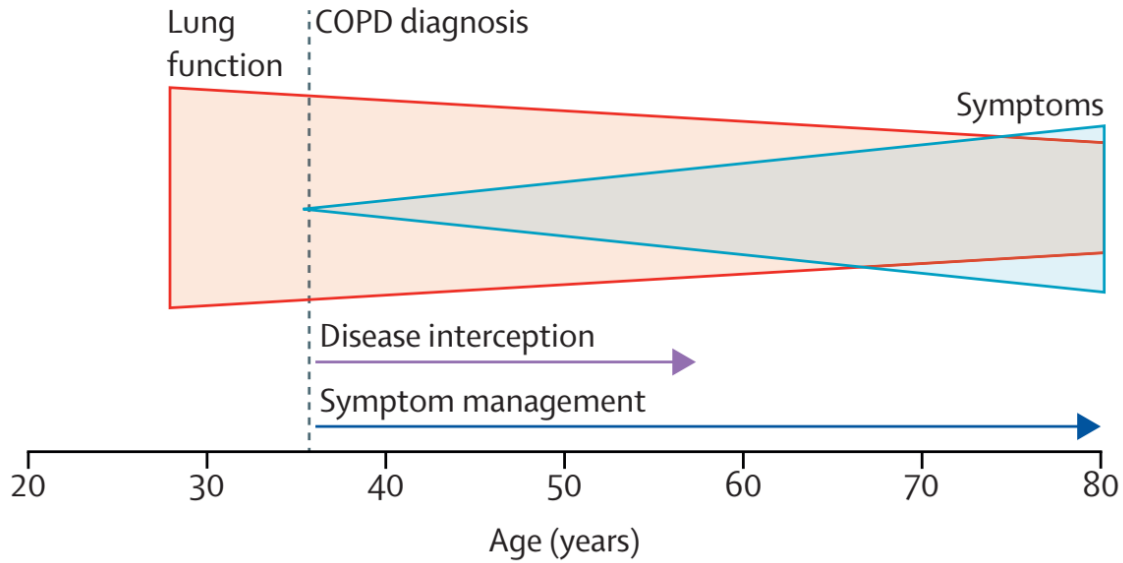
Stolz D et al. Lancet 2022;400:921-72. [PMID: 36075255]

“Early diagnosis” to eliminate COPD

Current



Future



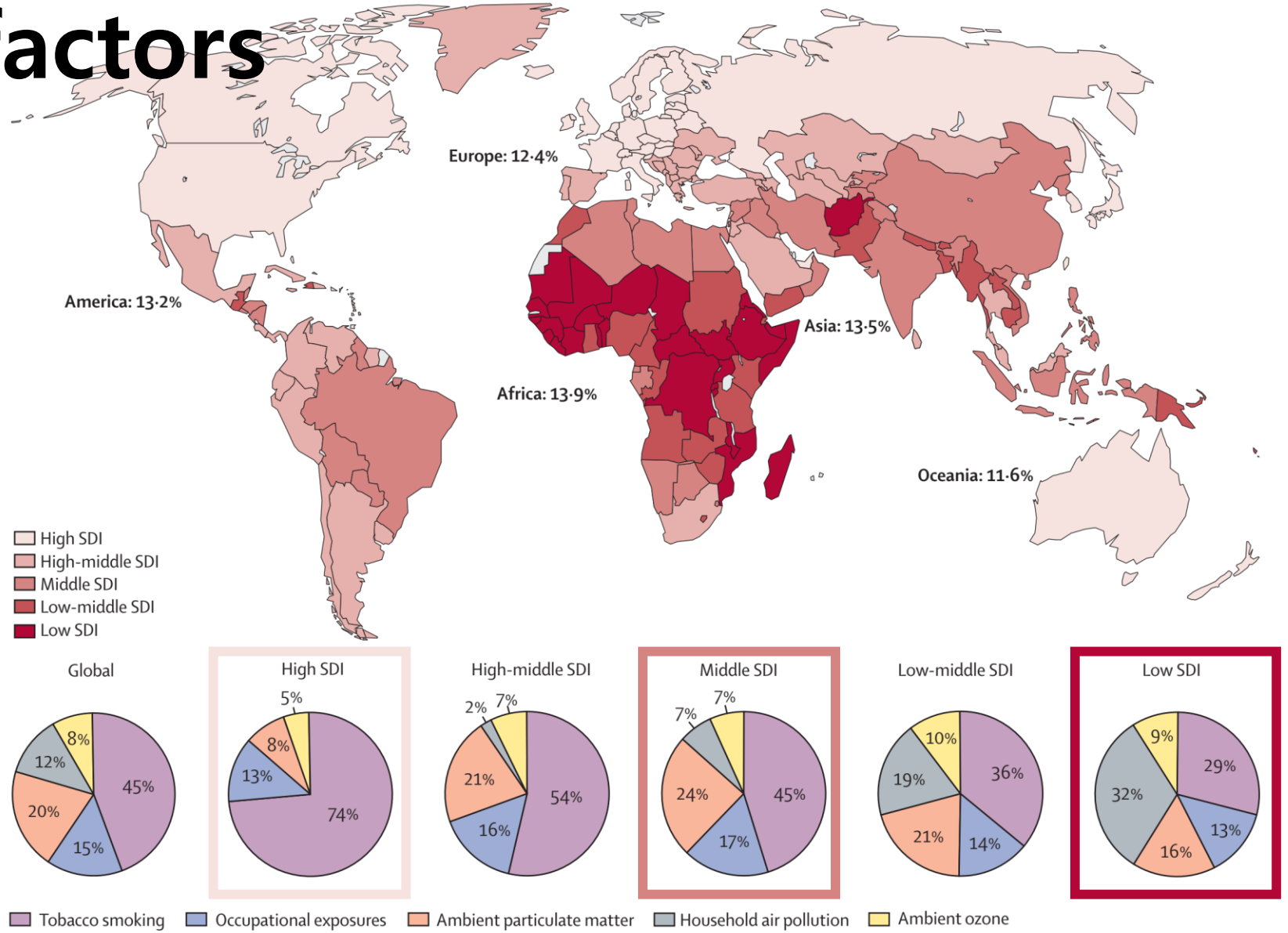
Stolz D et al. Lancet 2022;400:921-72 [PMID 36075255]

Smoking = COPD ?

https://www.patientsengage.com/condition/copd?page=2

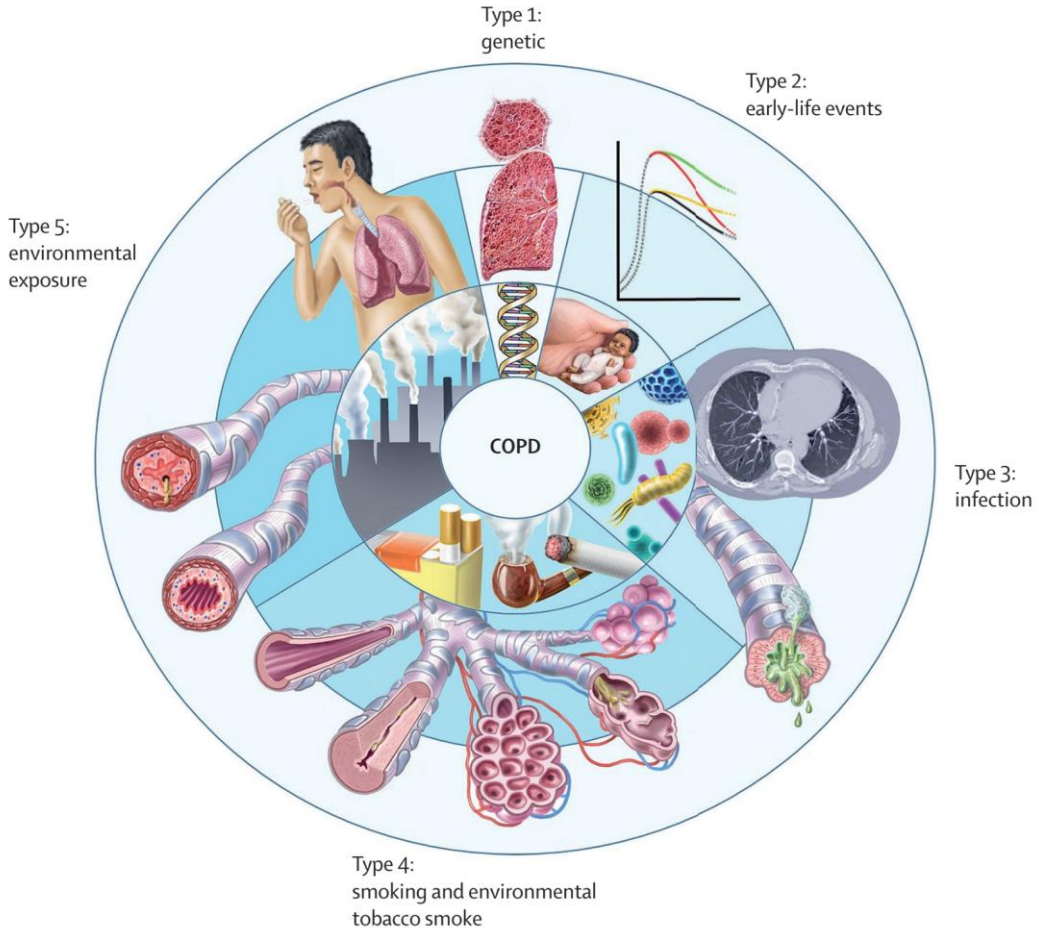
Global risk factors

- High SDI
  - Smoking (75%)
- Low SDI
  - Smoking (30%)



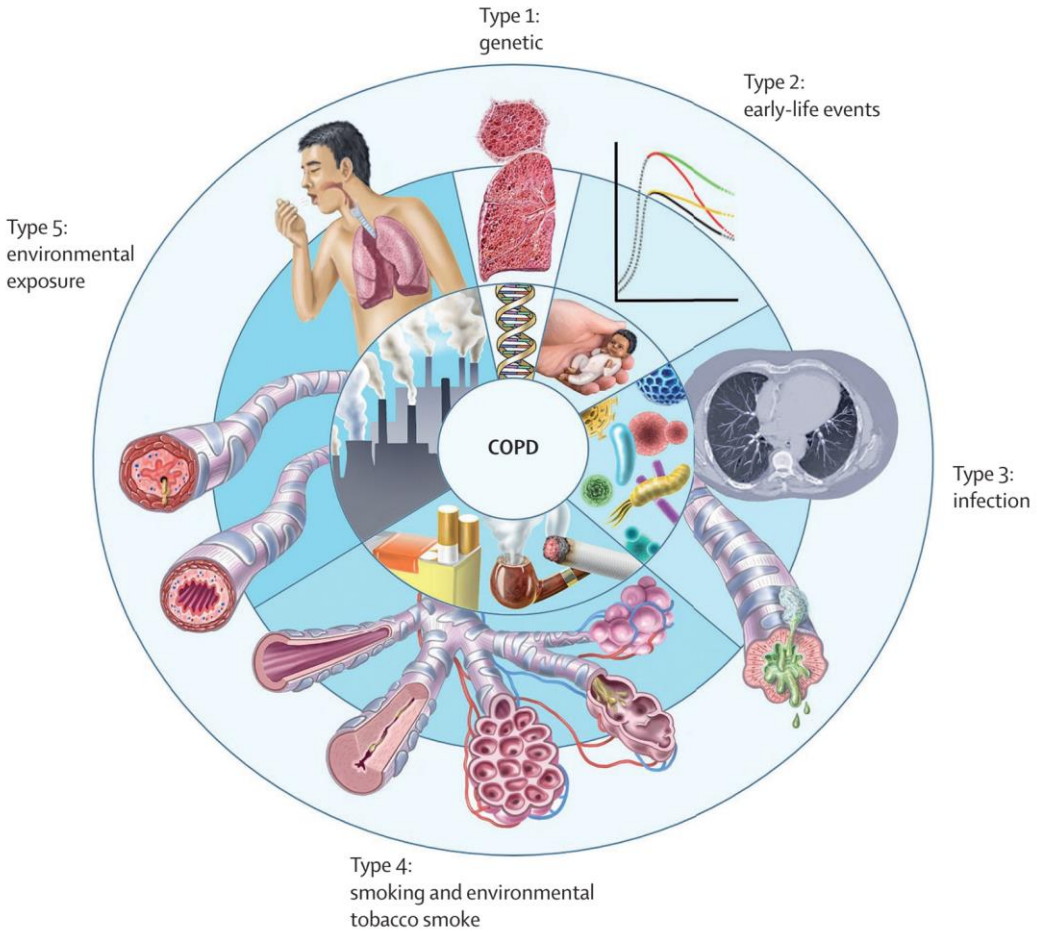
Yang et al., Lancet Respir Med 2022;10:497-511

Better recognition of COPD



https://www.patientsengage.com/condition/copd?page=2

"Eliminate risk factors" to eliminate COPD



***Panel:* Classification of COPD by the *Lancet* Commission on COPD**

Type 1: genetically determined COPD — COPD-G
1.1 α_1 antitrypsin deficiency
1.2 Telomerase reverse transcriptase mutations
1.3 Other genetic variants

Type 2: COPD related to early-life events — COPD-D, COPD-A
2.1 Prematurity (chronic lung disease of prematurity, bronchopulmonary dysplasia)
2.2 Childhood asthma

Type 3: infection-related COPD — COPD-I
3.1 Childhood respiratory infections
3.2 Tuberculosis-associated COPD
3.3 HIV-associated COPD

Type 4: COPD related to smoking or vaping — COPD-C
4.1 Tobacco smoking
4.2 In-utero exposure to tobacco smoke
4.3 Passive smoking (childhood and adult)
4.4 Vaping or e-cigarette smoking
4.5 Cannabis smoking

Type 5: environmental exposure-related COPD — COPD-P
5.1 Exposure to indoor air pollutants
5.2 Outdoor air pollution and smog
5.3 Wildfire smoke
5.4 Occupational exposures (to vapours, gases, dusts, or fumes)

COPD=chronic obstructive pulmonary disease. — COPD-U

Stolz et al. Lancet 2022;400:921-72
Brusselle et al. Lancet 2022;400:869-71

“**Etiotypes**” focus on “**pathogenesis**”

Proposed Taxonomy (Etiotypes) for COPD

Table 1.1

Classification	Description
Genetically determined COPD (COPD-G)	Alpha-1 antitrypsin deficiency (AATD) Other genetic variants with smaller effects acting in combination
COPD due to abnormal lung development (COPD-D)	Early life events, including premature birth and low birthweight, among others
Environmental COPD	
Cigarette smoking COPD (COPD-C)	• Exposure to tobacco smoke, including *in utero* or via passive smoking • Vaping or e-cigarette use • Cannabis
Biomass and pollution exposure COPD (COPD-P)	Exposure to household pollution, ambient air pollution, wildfire smoke, occupational hazards
COPD due to infections (COPD-I)	Childhood infections, tuberculosis-associated COPD, HIV-associated COPD
COPD & asthma (COPD-A)	Particularly childhood asthma
COPD of unknown cause (COPD-U)	

*Adapted from Celli et al. (2022) and Stolz et al. (2022)

For what?

- To broaden the COPD boundary?
- To include all respiratory diseases with AO as COPD?

- **To reveal the heterogeneity of COPD risk factors**
- **To provide tailored strategies to reduce COPD risk factors according to each etiotype.**
- **To eliminate COPD**

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    - BE with AO
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COPD d/t infection (COPD-I)

- COPD-I examples that GOLD specifically described are
  - Childhood infections
  - **Tuberculosis-associated COPD**
  - HIV-associated COPD

INT J TUBERC LUNG DIS 17(1):67–75

http://dx.doi.org/10.5588/ijtld.12.0351

Clinical characteristics of patients with tuberculosis-destroyed lung

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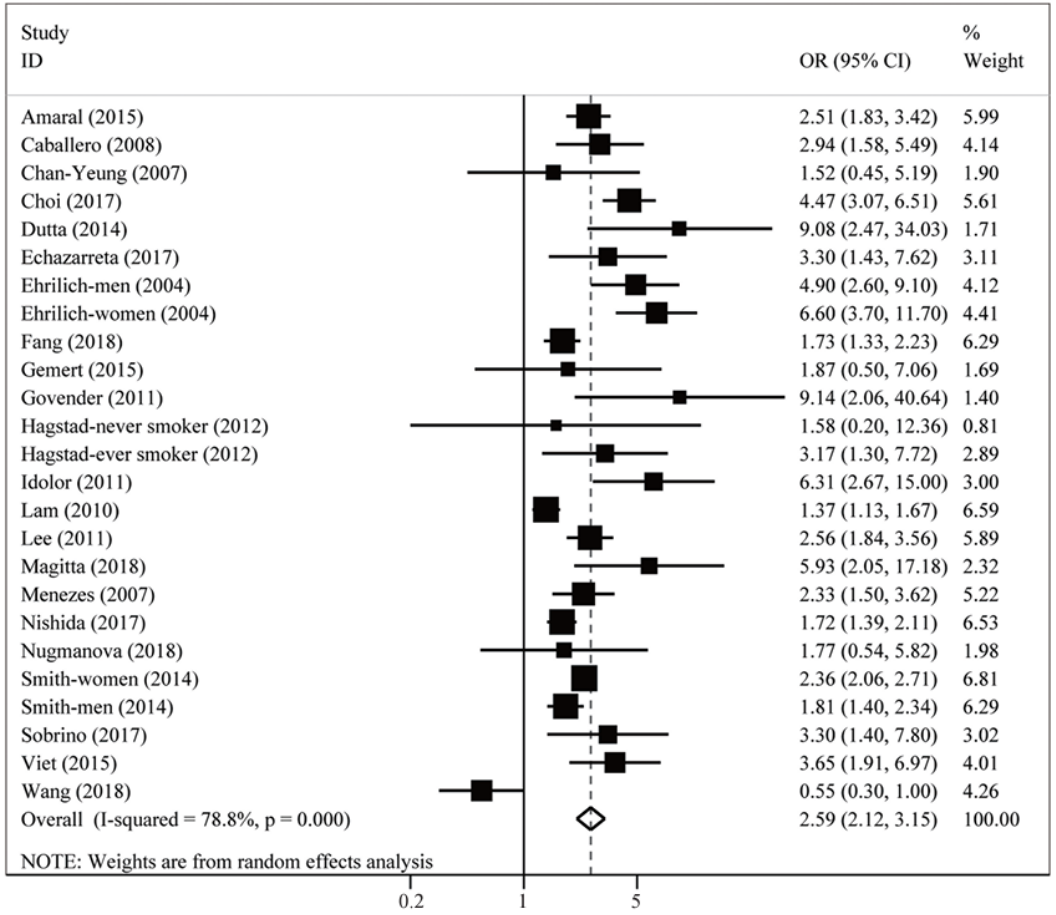
77%

Table 1 Patients' baseline characteristics (n = 595)

Characteristic	Mean ± SE or n (%)
Age, years	65.63 ± 0.47
Male	360 (60.5)
Smoker (n = 559)	
Never	318 (56.9)
Current	49 (8.8)
Former	192 (34.3)
Pack-years (n = 228)	35.68 ± 1.54
Lung involvement	
RUL	426 (71.6)
RML	157 (26.4)
RLL	167 (28.1)
Upper division of LUL	402 (67.6)
Lingula	193 (32.4)
LLL	196 (32.9)
Number of lobes involved	2.59 ± 0.05
Pleural thickening	
No thickening	273 (45.9)
Unilateral thickening	264 (44.4)
Bilateral thickening	58 (9.7)
Bronchiectasis on CT (n = 419)	333 (79.5)
Pulmonary function test	
FVC, l	2.06 ± 0.03
FVC (%)	61.26 ± 0.79
FEV_1, l	1.16 ± 0.02
FEV_1 (%)	49.05 ± 0.84
FEV_1/FVC (%)	58.03 ± 0.70
FEV_1/FVC < 0.7	457 (76.8)
$FEF_{25–75\%}$, l/sec	0.76 ± 0.04
BDR, %	5.70 ± 0.34
Number of exacerbations per year	0.40 ± 0.04
Medication	
LAMA (n = 356)	178 (50.0)
LABA+ICS (n = 349)	157 (45.0)
Methylxanthine (n = 350)	162 (46.3)

SE = standard error; RUL = right upper lobe; RML = right middle lobe; RLL = right lower lobe; LUL = left upper lobe; LLL = left lower lobe; CT = computed tomography; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; $FEF_{25–75\%}$ = forced expiratory flow between 25% and 75%; BDR = bronchodilator response rate; LAMA = long-acting muscarinic antagonist; LABA = long-acting beta-2 agonist; ICS = inhaled corticosteroids.

Tuberculosis and COPD



aOR = 2.59 (95% CI = 2.12–3.15)

Fan et al., *Ann Transl Med*. 2021;9(5):390.

Official Journal of the Asian Pacific Society of Respirology
Respirology

ORIGINAL ARTICLE

History of pulmonary tuberculosis affects the severity and clinical outcomes of COPD

Hye Jung PARK,[1] Min Kwang BYUN,[2] Hyung Jung KIM,[2] Chul Min AHN,[2] Deog Kyeom KIM,[3] Yu Il KIM,[4] Jin Young OH,[5] Hyoung Kyu YOON,[6] Kwang-Ha YOO[7] AND Ki Suck JUNG[8]

Table 3 Symptoms, lung function and exacerbation rate at the first visit for enrolment according to TB history

Characteristics	Prior TB group (n = 468)	Non-TB group (n = 1316)	P-value
Symptoms (missing value = 76)			
CAT score	16.1 ± 7.6	14.8 ± 7.9	0.002
SGRQc total score	36.6 ± 19.5	32.6 ± 18.9	<0.001
SGRQc-symptom	46.5 ± 20.5	42.8 ± 20.9	0.001
SGRQc-activity	49.1 ± 23.2	44.2 ± 23.3	<0.001
SGRQc-impact	26.4 ± 20.3	22.9 ± 19.4	0.001
Lung function (missing value = 71)			
Absolute FVC (L)	3.02 ± 0.85	3.11 ± 0.80	0.060
Predicted FVC (%)	79.3 ± 18.2	82.4 ± 17.4	0.002
Absolute FEV_1 (L)	1.52 ± 0.57	1.65 ± 0.61	<0.001
Predicted FEV_1 (%)	56.4 ± 18.9	61.5 ± 19.0	<0.001
FEV_1/FVC (%)	47.8 ± 12.6	49.9 ± 12.3	0.002
Absolute $FEF_{25–75\%}$ (L/s)	0.58 ± 0.37	0.63 ± 0.42	0.037
Predicted $FEF_{25–75\%}$ (%)	23.0 ± 12.9	25.1 ± 15.0	0.005
Absolute DL_{CO} (mL/mm Hg/min)	13.1 ± 8.6	14.0 ± 6.3	0.039
Predicted DL_{CO} (%)	70.4 ± 22.3	76.5 ± 24.3	<0.001
Absolute DL_{CO}/VA (mL/mm Hg/min/L)	3.1 ± 1.2	3.3 ± 1.9	0.068
Predicted DL_{CO}/VA (%)	81.6 ± 25.3	84.1 ± 25.9	0.125
Exacerbation (/year) (missing value = 163)			
Prevalence of exacerbation	124 (28.8%)	180 (23.5%)	0.031
Prevalence of severe exacerbation	17 (3.9%)	18 (1.5%)	0.002

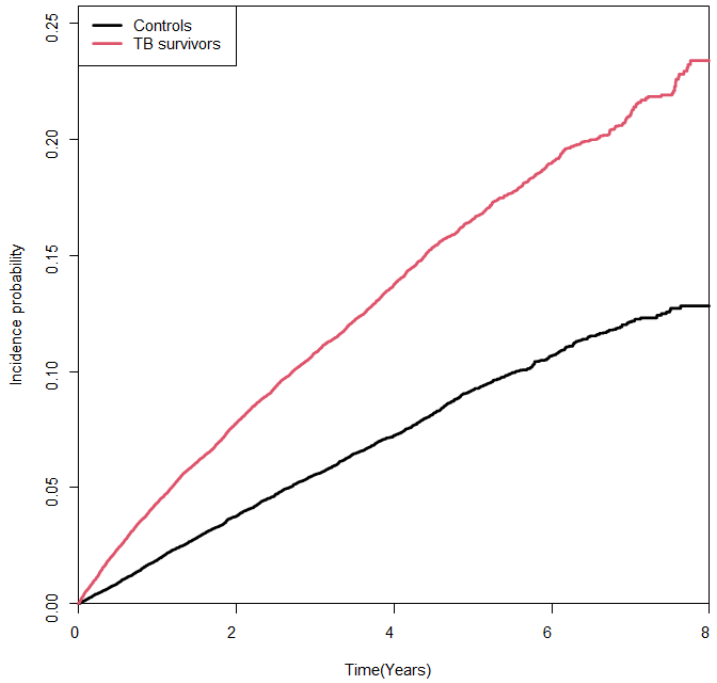
Data are means ± SD or percentages.

CAT, COPD assessment test; DL_{CO}, diffusing capacity of the lung for carbon monoxide; $FEF_{25–75\%}$, forced expiratory flow during the middle half of the FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; SGRQc, St George Respiratory Questionnaire for COPD; TB, pulmonary tuberculosis; VA, alveolar volume.

Burden of TB-related COPD in Korea

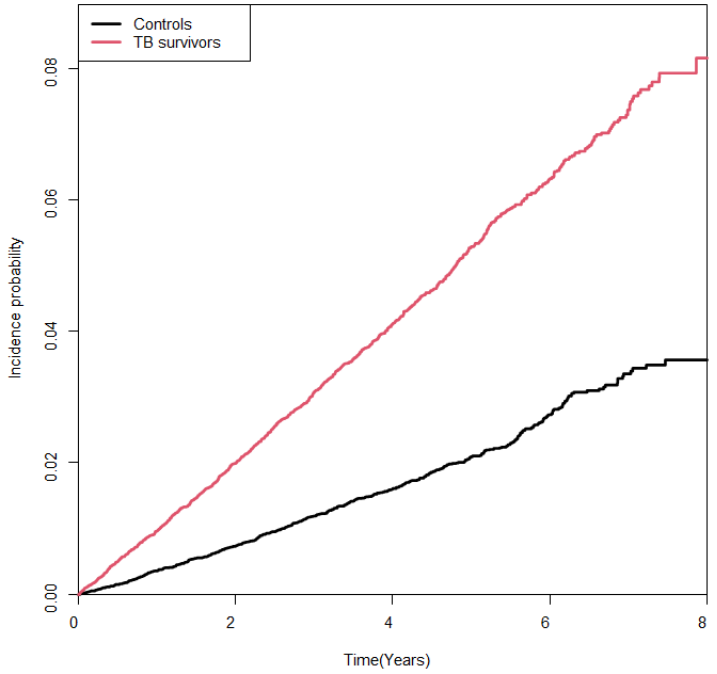
- 2010-2017 NHIS database
  - 31,033 TB survivors
  - 31,033 Age/sex matched controls

Incident COPD



aHR = 1.63 (1.54-1.73)

COPD-related hospitalization



aHR = 1.63 (1.54-1.73)

Unpublished data

Bronchodilators in COPD due to TB

International Journal of COPD

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Open Access Full Text Article

ORIGINAL RESEARCH

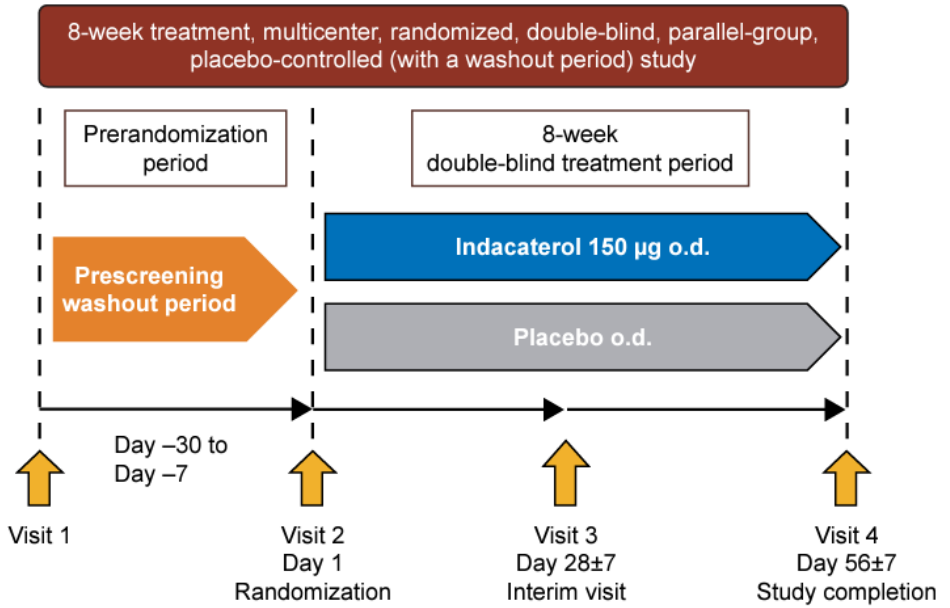
Inhaled indacaterol for the treatment of COPD patients with destroyed lung by tuberculosis and moderate-to-severe airflow limitation: results from the randomized INFINITY study

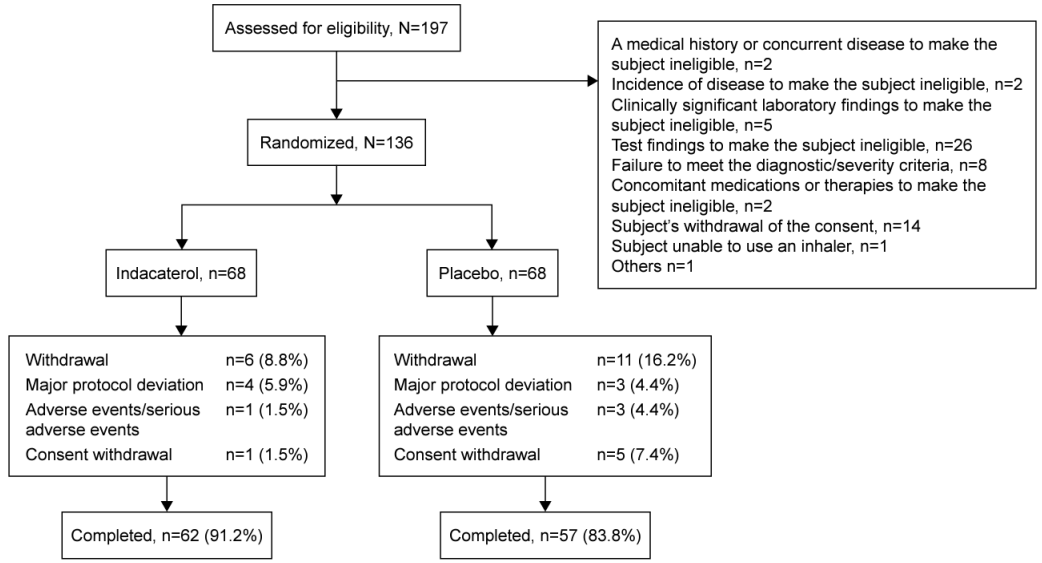
This article was published in the following Dove Press journal:
International Journal of COPD
29 May 2017
Number of times this article has been viewed

Cheong-Ju Kim,[1] Hyoung-Kyu Yoon,[2] Myung-Jae Park,[3] Kwang-Ha Yoo,[4] Ki-Suck Jung,[5] Jeong-Woong Park,[6] Seong Yong Lim,[7] Jae Jeong Shim,[8] Yong Chul Lee,[9] Young-Sam Kim,[10] Yeon-Mok Oh,[11] Song Kim,[12] Chul-Gyu Yoo[13]

Background and objective: Pulmonary tuberculosis (TB) is a risk factor for chronic obstructive pulmonary disease (COPD); however, few clinical studies have investigated treatment effectiveness in COPD patients with destroyed lung by TB. The Indacaterol effectiveness in COPD patients with Tuberculosis history (INFINITY) study assessed the efficacy and safety of once-daily inhaled indacaterol 150 µg for the treatment of Korean COPD patients with destroyed lung by TB and moderate-to-severe airflow limitation.

Methods: This was a multicenter, double-blind, parallel-group study, in which eligible patients





Kim et al., nternational Journal of COPD 2017:12 1589–1596

Bronchodilators in COPD due to TB

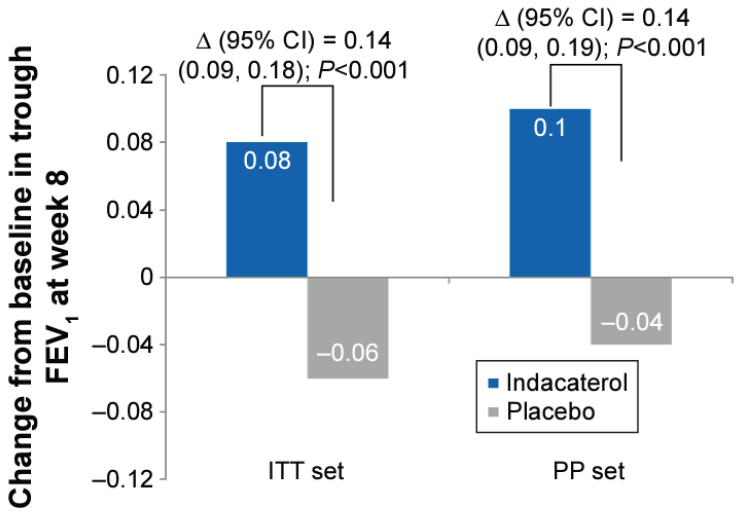


Figure 3 Change from baseline in trough FEV_1 at Week 8 (ITT set and PP set).
Notes: Data are presented as LS means. Δ, Treatment difference LS mean.
Abbreviations: CI, confidence interval; FEV_1, forced expiratory volume in 1 s; ITT, intent-to-treat; LS, least squares; PP, per protocol; SE, standard error.

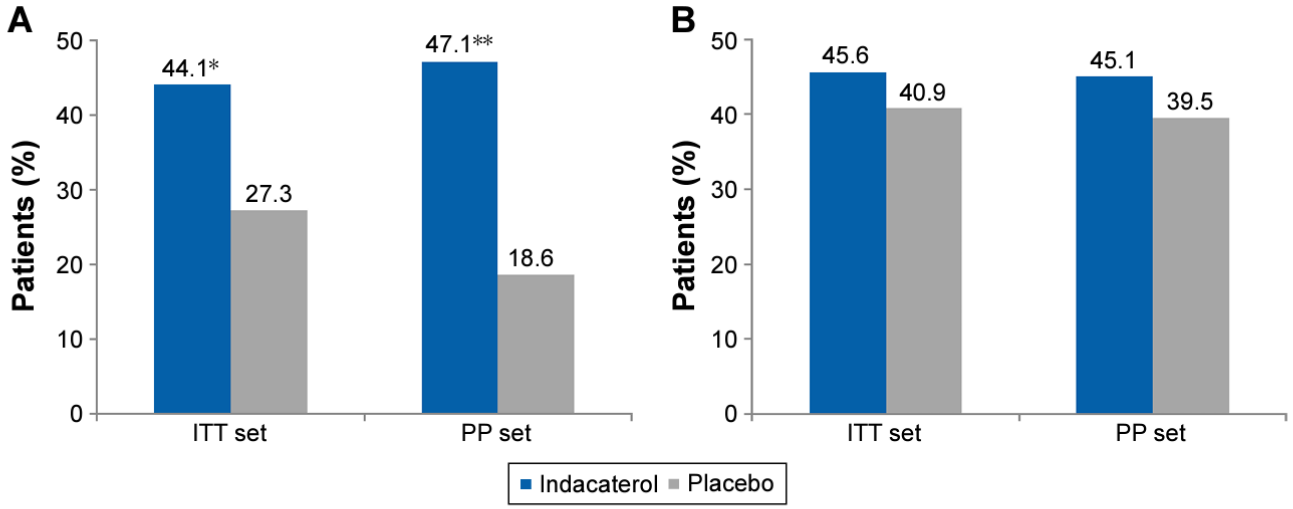


Figure 4 (**A**) Proportion of patients with a clinically important improvement from baseline in TDI total score (≥1 point; ITT and PP population). (**B**) Proportion of patients achieving MCID in St George's Respiratory Questionnaire score.
Notes: Data for TDI total score are least squares means. *$P<0.05$ and **$P<0.01$ versus placebo.
Abbreviations: ITT, intent-to-treat; MCID, minimal clinically important difference; PP, per protocol; TDI, transition dyspnea index.

Kim et al., nternational Journal of COPD 2017:12 1589–1596

Bronchodilators in COPD due to TB

RESEARCH Open Access

Effect of tiotropium inhaler use on mortality in patients with tuberculous destroyed lung: based on linkage between hospital and nationwide health insurance claims data in South Korea

Ho Cheol Kim[1], Tae Hoon Kim[2], Ye-Jee Kim[3], Chin Kook Rhee[4] and Yeon-Mok Oh[1*]

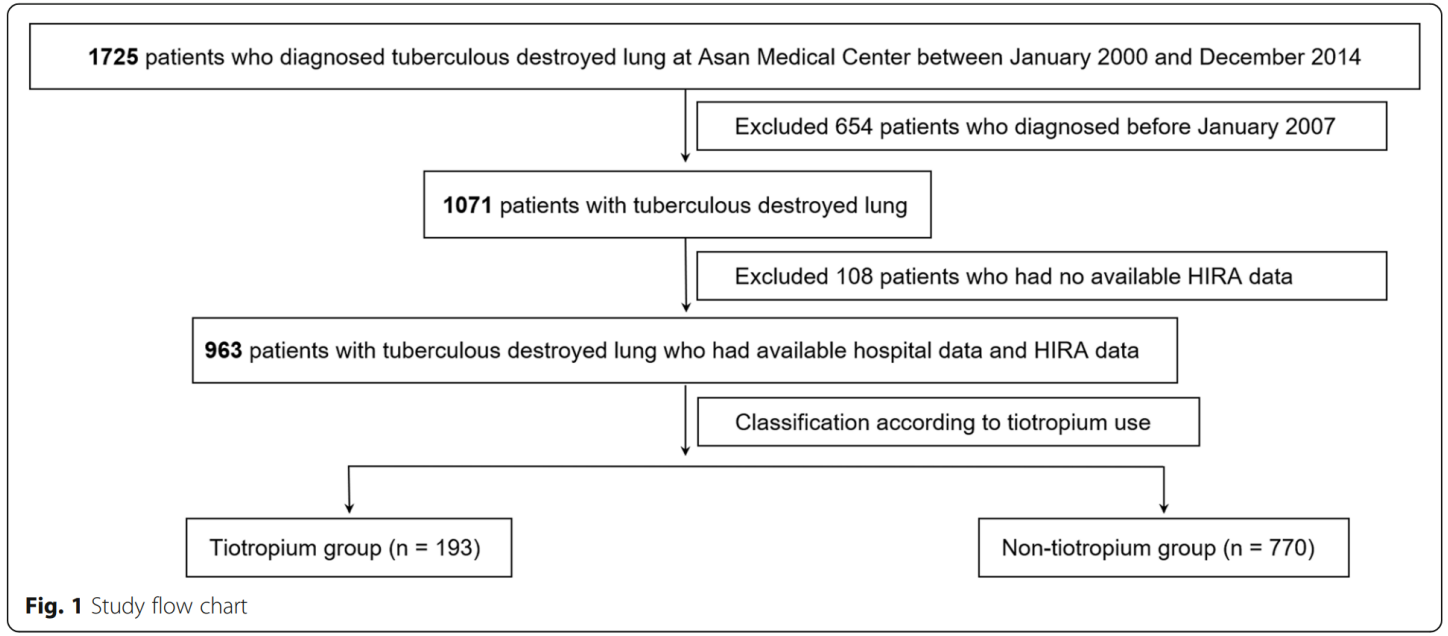
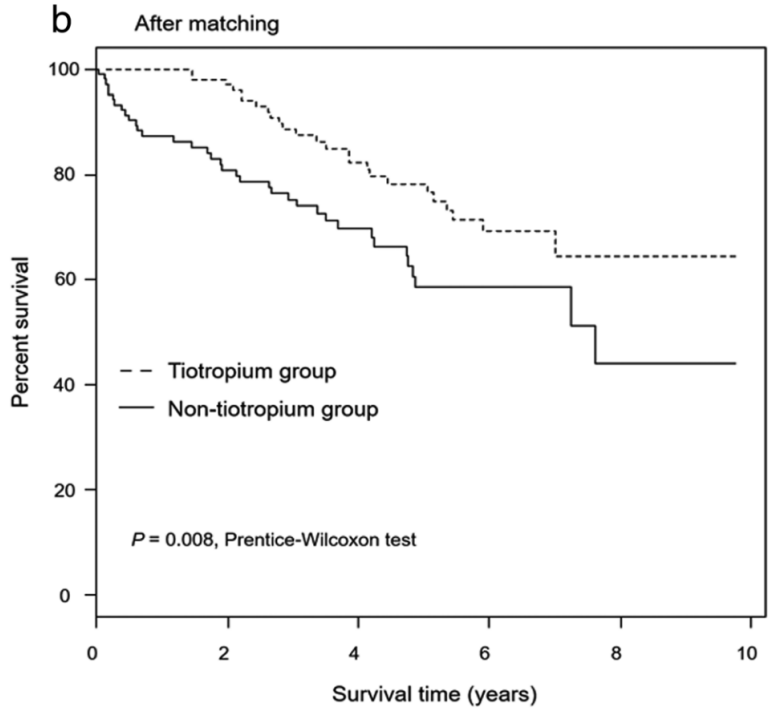
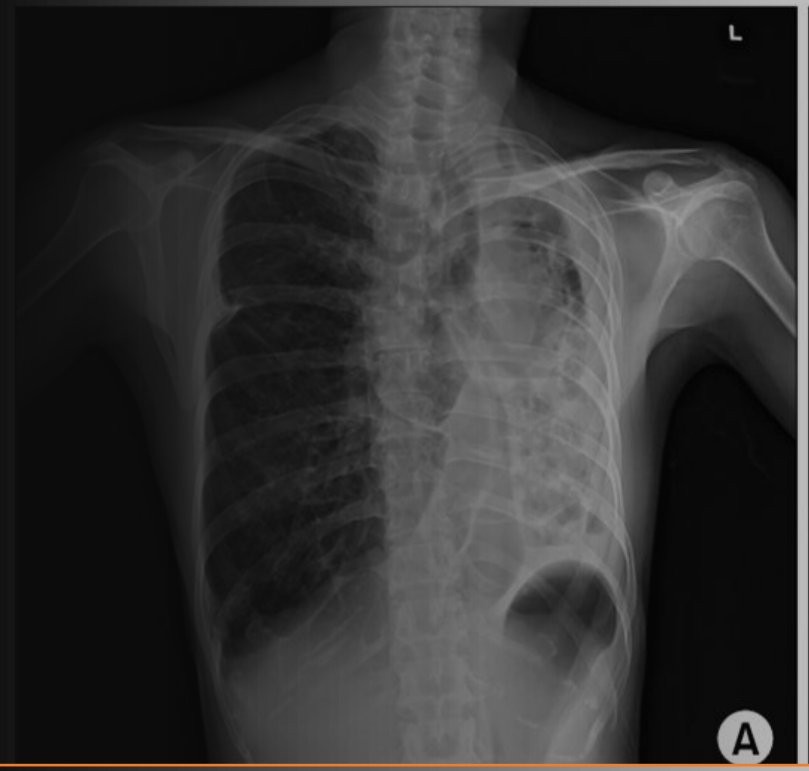


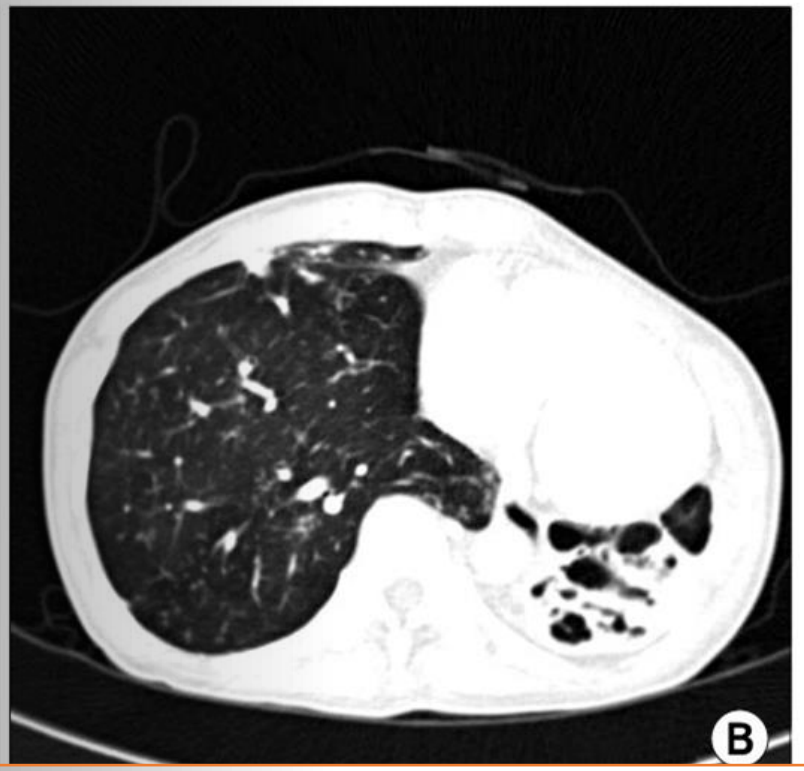
Fig. 1 Study flow chart



HR = 0.528 (0.316-0.880)

Welcome to COPD!



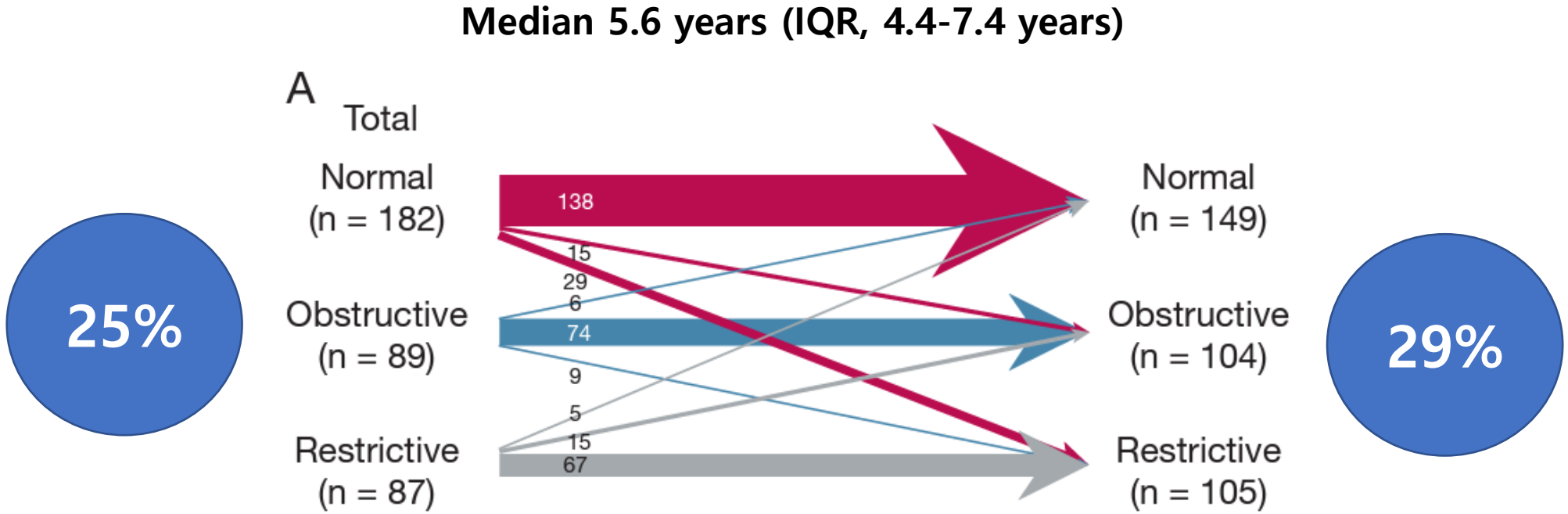


Chae et al., Tuberc Respir Dis 2011;71:202-209

How about chronic pulmonary infections other than TB?

NTM and AO

- NTM-PD

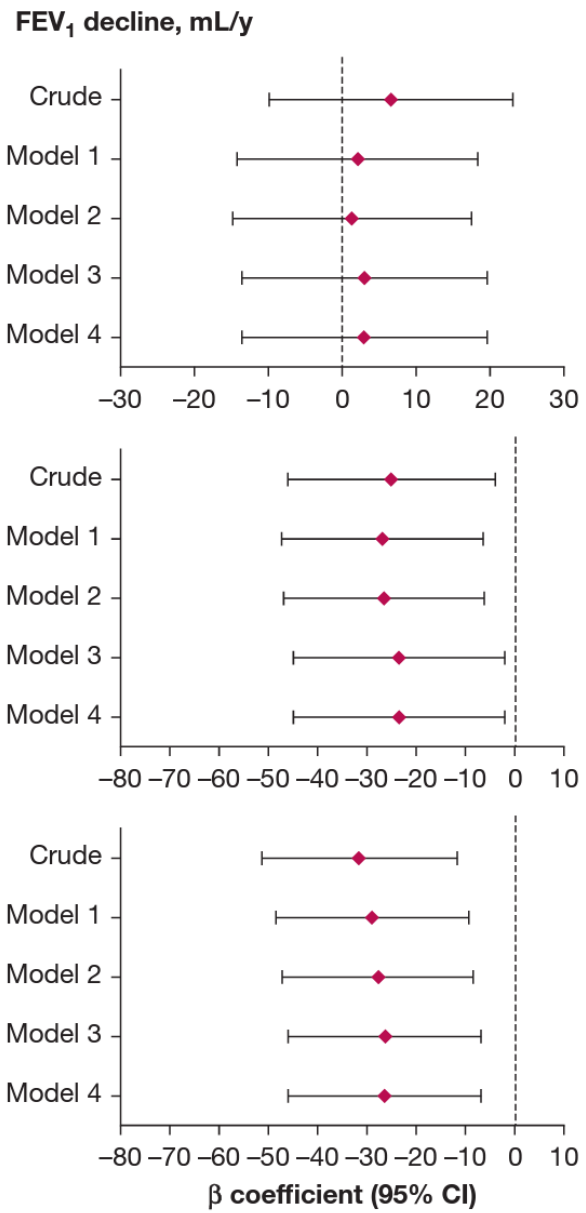


Park & Jeong et al., CHEST 2016;150:1222-1232

Observation vs Treatment success

Observation vs Treatment failure

Treatment success vs Treatment failure



	FEV$_1$ Decline, mL/y		
	β Coefficient	95% CI	*P* Value
Age, y	−0.07	−0.63 to 0.49	.807
Sex (female)	23.11	10.73 to 35.49	< .001
Body mass index, kg/m^2	0.62	−1.80 to 3.03	.616
Smoking status at baseline spirometry procedure			
Never	Reference		.999
Ex-smoker	−0.65	−17.42 to 16.12	.999
Current smoker	4.19	−43.07 to 51.45	
Underlying disease			
Bronchiectasis	−6.40	−25.67 to 12.88	.514
Prior pulmonary tuberculosis	−8.21	−20.44 to 4.02	.188
Malignancy other than lung	−1.03	−20.32 to 18.25	.916
Diabetes mellitus	−12.98	−35.56 to 9.61	.259
Chronic liver disease	−7.99	−32.76 to 16.77	.526
Chronic heart disease	−17.28	−45.78 to 11.23	.234
COPD	23.90	−4.56 to 52.35	.099
Neu			
Causa			
M. a			
M. a			
Othe			
Radiologic type			
Nodular bronchiectatic	Reference		
Fibrocavitary	3.53	−19.64 to 26.70	.999
Nonclassifiable	18.83	−10.18 to 47.84	.290
Presence of cavity on HRCT scan	−4.90	−19.68 to 9.87	.514
Positive smear at diagnosis	−1.52	−13.71 to 10.67	.806
Clinical course of NTM-LD			
Observation	Reference		
Treatment success	6.60	−8.83 to 22.02	.673
Treatment failure	−24.99	−44.64 to −5.34	.009
Baseline spirometry			
FEV$_1$, L	−20.30	−28.88 to −11.72	< .001
FEV$_1$, % predicted	−0.63	−0.97 to −0.30	< .001
FVC, L	−9.37	−16.99 to −1.75	.016
FVC, % predicted	0.00	−0.43 to 0.43	.995
FEV$_1$/FVC	−0.92	−1.40 to −0.44	< .001
Use of bronchodilator during the follow-up period	−7.99	−29.57 to 13.60	.467

Use of bronchodilator during the follow-up period	−7.99	−29.57 to 13.60	.467

Park & Jeong et al., CHEST 2016;150:1222-1232

PLOS ONE

Chronic pulmonary aspergillosis

RESEARCH ARTICLE

Differences in the clinical characteristics of chronic pulmonary aspergillosis according to spirometric impairment

Myoung Kyu Lee[1], Sae Byol Kim[2], Beomsu Shin[3]*

1 Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea,
2 Division of Pulmonology, Department of Internal Medicine, Myongji Hospital, Jecheon, South Korea,
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* bsshin83@gmail.com

Abstract

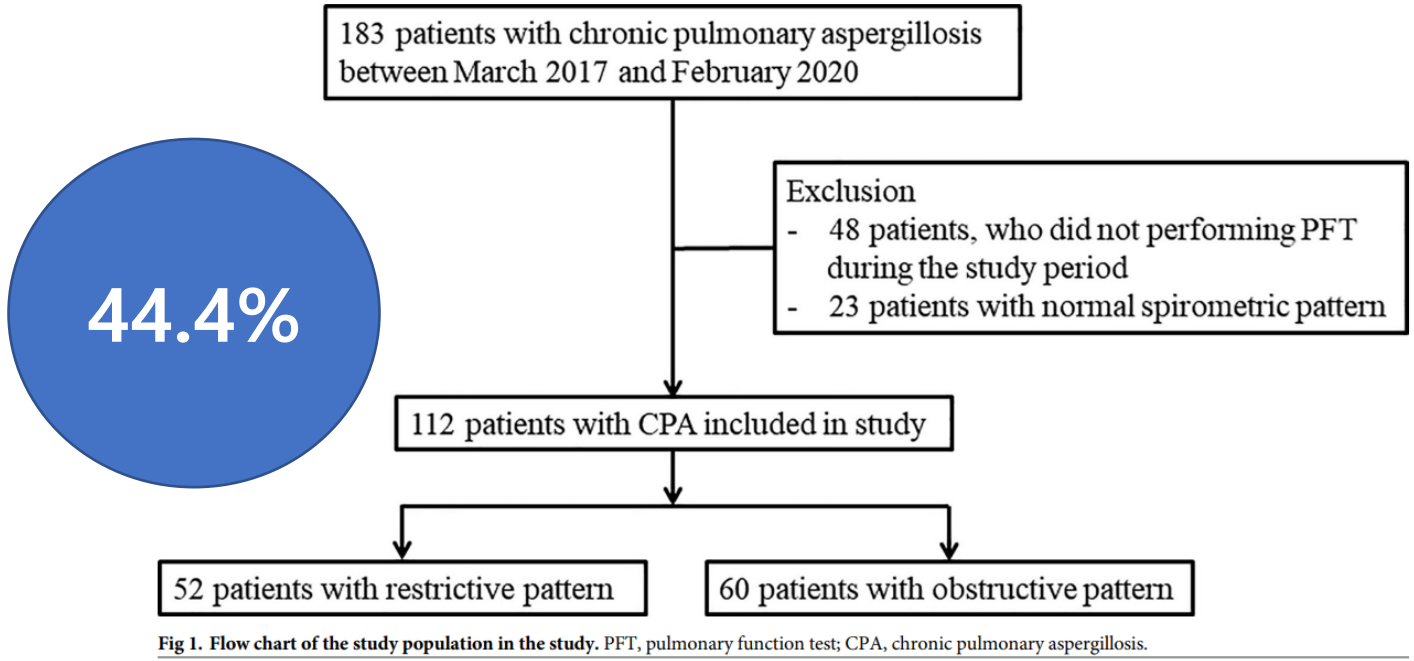

Fig 1. Flow chart of the study population in the study. PFT, pulmonary function test; CPA, chronic pulmonary aspergillosis.

The impact of AO on CPA outcomes

Original Article

Association between airflow limitation and prognosis in patients with chronic pulmonary aspergillosis

Myoung Kyu Lee[1], Sae Byol Kim[1], Ji-Ho Lee[1], Seok Jeong Lee[1], Sang-Ha Kim[1], Won-Yeon Lee[1], Suk Joong Yong[1], Jong-Han Lee[2], Beomsu Shin[1]

[1]Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [2]Department of Laboratory Medicine, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea

Contributions: (I) Conception and design: B Shin, MK Lee, JH Lee; (II) Administrative support: WY Lee; (III) Provision of study materials or patients: B Shin, SJ Yong; (IV) Collection and assembly of data: SB Kim, JH Lee, SJ Lee, SH Kim, WY Lee, SJ Yong; (V) Data analysis and interpretation: B Shin, MK Lee, SB Kim; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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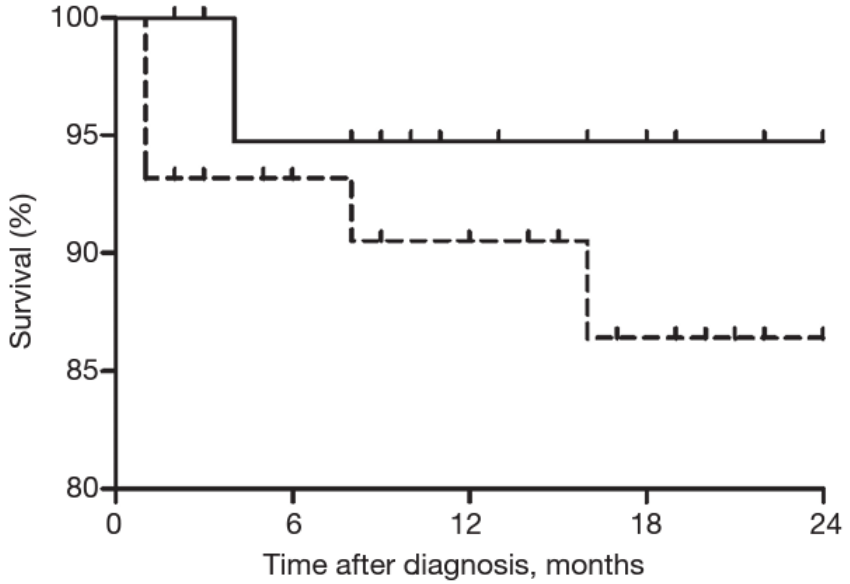
Background: Previous studies have shown that reduced levels of lung function, characterized by forced expiratory volume in 1 second (FEV_1), are associated with higher respiratory events and mortality in general population and some chronic lung diseases. Chronic pulmonary aspergillosis (CPA) is a destructive, fatal lung disease caused by *Aspergillus* infection in non-immunocompromised patients with suboptimal pulmonary function. However, there is limited information on the status and features of CPA according to FEV_1.

Methods: We performed a retrospective observational study to investigate the FEV_1 and airflow limitation in patients with CPA between March 2017 and February 2019 at a tertiary hospital in South Korea.

Results: Of the 144 CPA patients, 104 underwent spirometry, demonstrating median forced vital capacity (FVC) and FEV_1 of 2.35 L (68%) and 1.43 L (62%), respectively. Among them, 56 patients had airflow limitation on PFT, with median FVC, and FEV_1 of 2.47 L (73%) and 1.11 L (47%), respectively. Low body mass index (BMI) (20.1 *vs.* 22.1 kg/m^2; P=0.011), breathlessness (60% *vs.* 20%; P=0.002), and bilateral pulmonary lesions (33.3% *vs.* 4%; P=0.006) were more common in patients with moderate to very severe airflow limitation than in those with normal to mild airflow limitation.



Lee et al., J Thorac Dis 2021;13(2):681-688

Controversy – other infections

- NTM-PD or CPA with AO

- If treatment is not necessary (e.g., observational condition or treatment completion)
  - Can we call them COPD-I?

Contents

- Change in COPD definition – for what?
- **Controversial issues**
  - COPD-I
  - **BE with AO**
  - COPD-P
- Summary

Table 2. Radiologic, pulmonary function, microbiologic, and laboratory test results in patients with bronchiectasis according to their aetiologies.

	Post-TB (*n* = 118)	Post-Infectious (*n* = 117)	Idiopathic (*n* = 244)	Others (*n* = 119)	*p* Value
Radiology					
No c					52
Invo					
RU					01
RM					52
RL					47
LU					01
LU					91
LL					10
Mod					02
Pulmonary function					
FVC, L	2.3 (1.9–3.1)	2.5 (2.0–3.0)	2.5 (2.0–3.0)	2.5 (2.0–3.2)	0.887
FVC, % predicted	70.1 (54.4–84.4)	72.6 (60.5–79.8)	74.4 (64.1–85.6) *	74.7 (63.2–82.9)	0.027
FEV_1, L	1.5 (1.1–1.9)	1.5 (1.1–1.9)	1.7 (1.3–2.1)	1.7 (1.2–2.1)	0.163
FEV_1, % predicted	57.6 (43.0–74.2)	58.7 (46.5–71.3)	65.8 (53.2–81.2) *	64.4 (51.6–77.6)	0.001
FEV_1/FVC ratio	0.6 (0.5–0.7)	0.6 (0.5–0.7)	0.7 (0.6–0.8)	0.7 (0.5–0.7)	0.025
FEV_1/FVC < 0.7	71 (65.7)	71 (68.9)	119 (55.1)	64 (61.0)	0.075

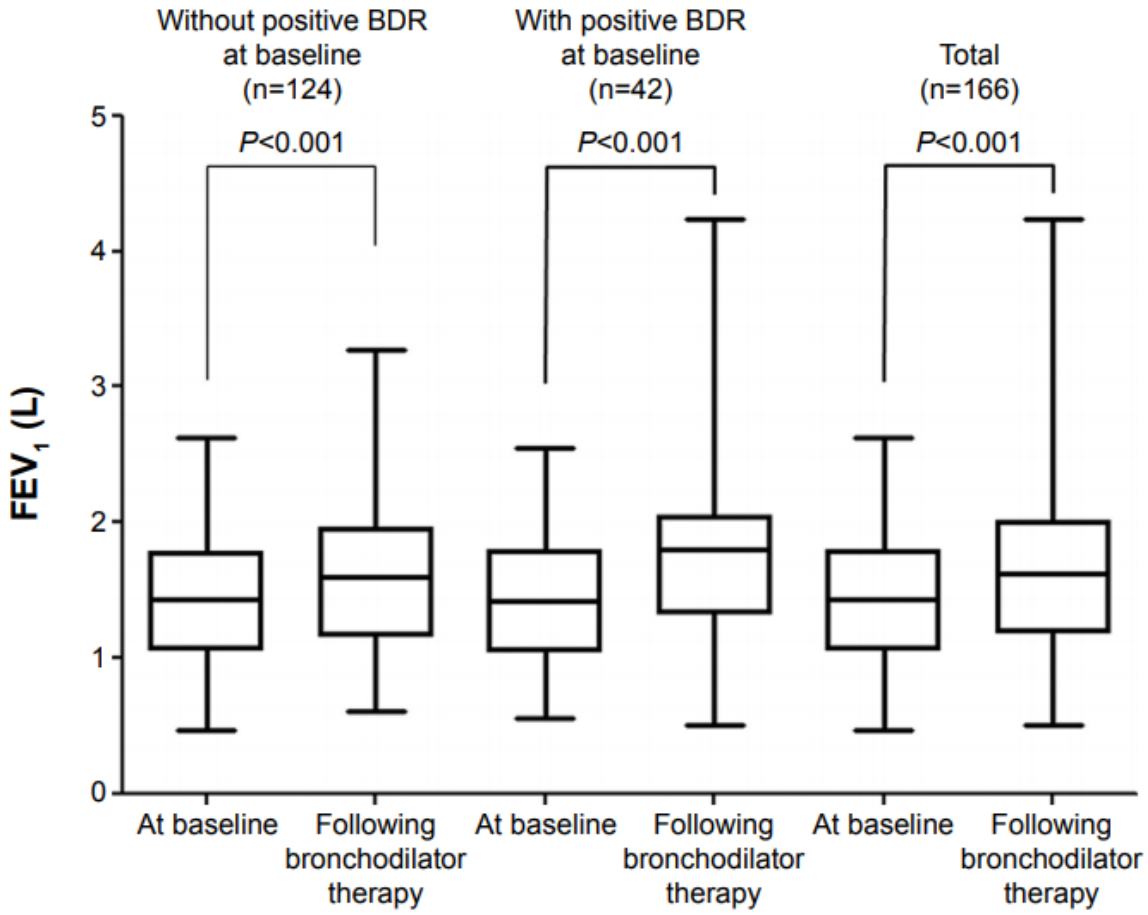
Journal of *Clinical Medicine*

MDPI

Article

Clinical Characteristics of Patients with Post-Tuberculosis Bronchiectasis: Findings from the KMBARC Registry

Bronchodilator effect in BE with AO



Change in FEV_1 130 mL, IQR -10 to 250 mL; P = 0.001

+130 mL

Cheong , International Journal of COPD 2016;11:2757–2764

Tiotropium in BE with AO

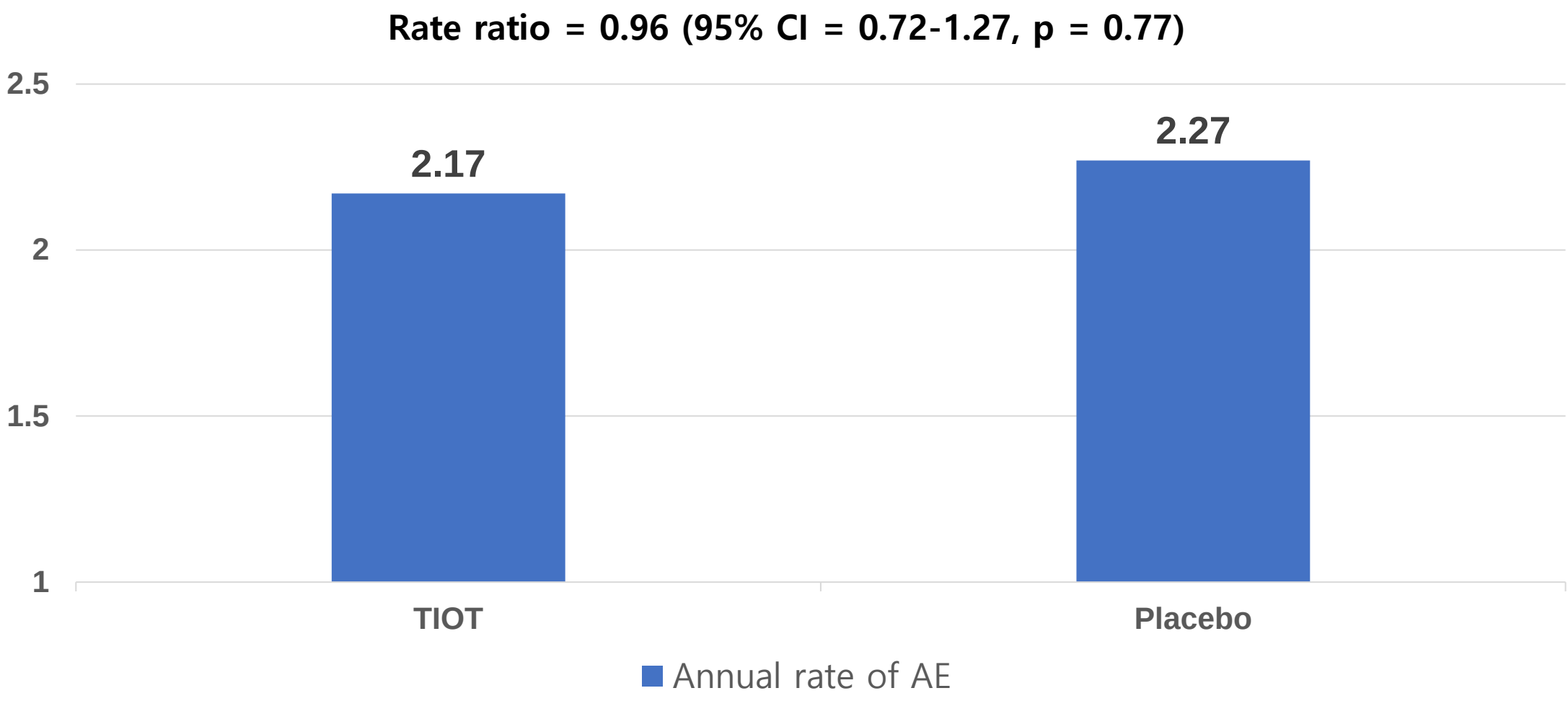
- Inclusion
  - ⩾18 years
  - ⩾ 1 AE requiring antibiotic Tx in the past year
  - BE diagnosis by HRCT
  - Airway obstruction (FEV1/FVC < 0.7) on spirometry

- Exclusion*
  - Cystic fibrosis, primary diagnosis of asthma
  - Smoking Hx > 20 PY
  - Unstable arrhythmia,
  - Narrow-angle glaucoma
  - Symptomatic prostatic hyperplasia
  - Shor- or long-acting anticholinergics and antibiotics within 6 weeks prior to randomization

- Outcomes
  - AE
  - AE days, time to fist AE, 6MWT, SGRQ, LCQ, CAT, Peripheral blood cells, sputum cells

Jayaram L, Eur Respir J. 2022;59(6):2102184.

Primary outcome – Annual rate of AE



Jayaram L, Eur Respir J. 2022;59(6):2102184.

Secondary outcome – lung function

TABLE 2 Lung function at 26 weeks

	Placebo[#]	Tiotropium[#]	Mean difference (95% CI)[¶]	p-value
Absolute (mL)				
Pre-BD FEV_1	1704±528	1778±526	58 (23–92)	0.002
Post-BD FEV_1	1798±555	1871±574	56 (17–92)	0.005
Pre-BD FVC	2880±805	2956±767	78 (25–131)	0.004
Post-BD FVC	2974±827	3011±785	34 (−22–90)	0.24
Percentage predicted (%)				
Pre-BD FEV_1	61.5	64.4	2.67 (1.36–3.98)	0.00006
Post-BD FEV_1	65.0	67.7	2.69 (1.36–4.03)	0.00006
Pre-BD FVC	79.2	81.2	2.09 (0.55–3.64)	0.008
Post-BD FVC	81.3	82.5	1.38 (−0.26–3.01)	0.10

BD: bronchodilator; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity. [#]: absolute values presented as mean±SD; [¶]: adjusted for baseline value at start of period.

Jayaram L, *Eur Respir J*. 2022;59(6):2102184.

Controversy – BE with AO

An etiotype of COPD

- Up to 2/3 of bronchiectasis has persistent AO
- The major etiologies (or comorbidity) of BE include asthma and COPD
- Bronchodilators can be helpful

A different type of disease

- It is a different kind of disease when defining BE as “clinically significant BE”
- The main treatment strategy is different.

Clinically significant BE

Health-care Development

Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations

Stefano Aliberti, Pieter C Goeminne*, Anne E O'Donnell*, Timothy R Aksamit*, Hamdan Al-Jahdali, Alan F Barker, Francesco Blasi, Wim G Boersma, Megan L Crichton, Anthony De Soyza, Katerina E Dimakou, Stuart J Elborn, Charles Feldman, Harm Tiddens, Charles S Haworth, Adam T Hill, Michael R Loebinger, Miguel Angel Martinez-Garcia, Jennifer J Meerburg, Rosario Menendez, Lucy C Morgan, Marlene S Murris, Eva Polverino, Felix C Ringshausen, Michal Shteinberg, Nicola Sverzellati, Gregory Tino, Antoni Torres, Thomas Vandendriessche, Montserrat Vendrell, Tobias Welte, Robert Wilson, Conroy A Wong, James D Chalmers*

Clinically significant BE

- Needs two of the foll owings
  - A cough most days of the week
  - Sputum production m ost of the week
  - A history of AE

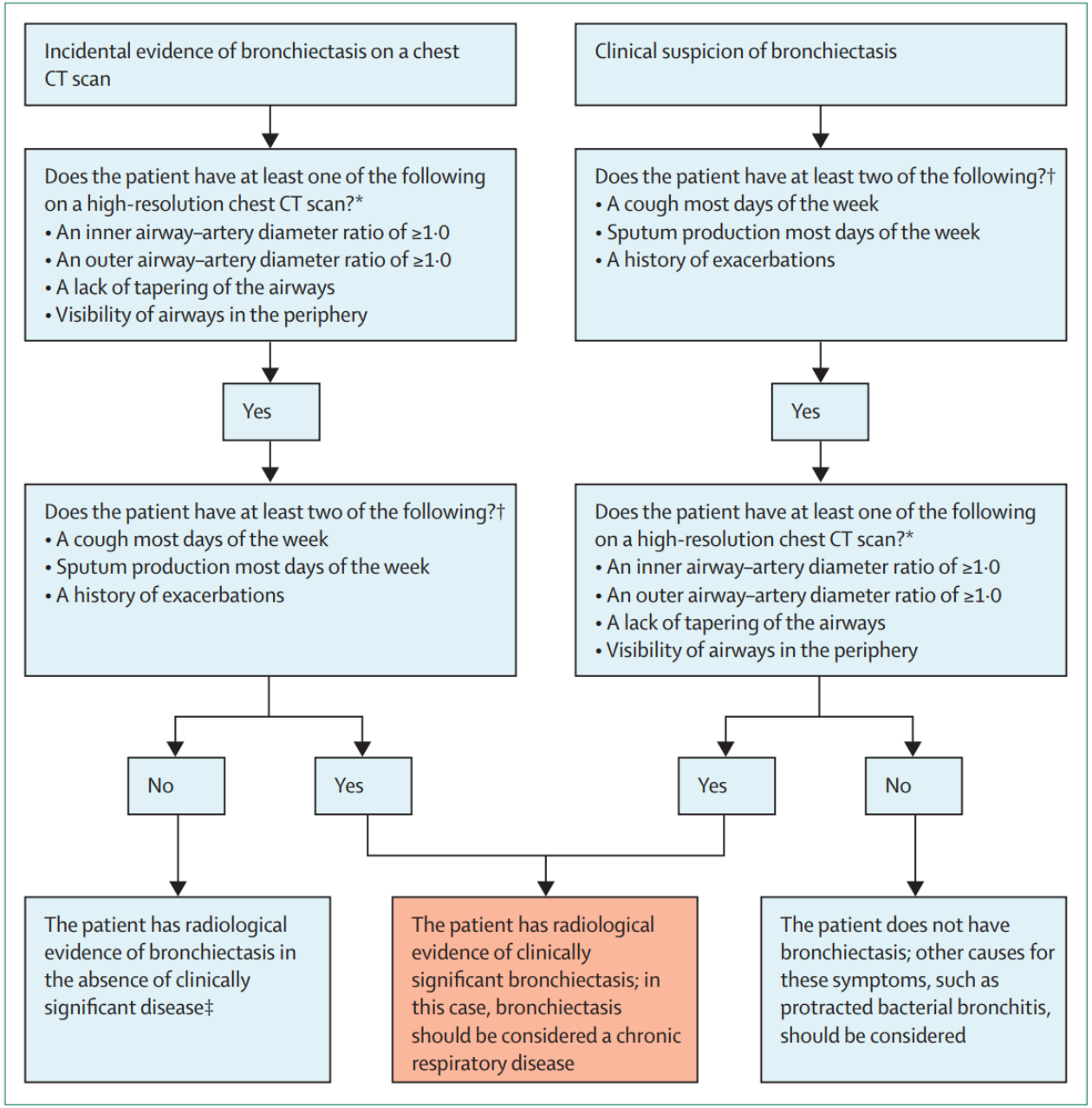


Figure 2: **Flow chart to define clinically significant bronchiectasis**

Aliberti et al., Lancet Respir Med 2022; 10: 298–306

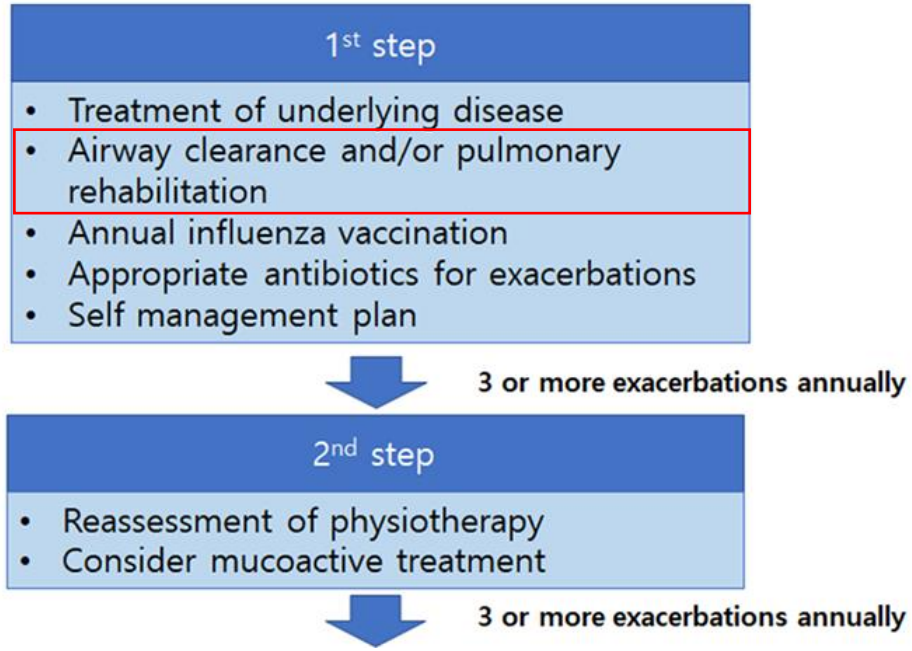
Definition of BCO?

- Future clinical trials, according to the tested intervention and endpoints used, **should exclude individuals with COPD**

- …if the clinical trial investigators wish to include patients with COPD, a subgroup of patients with both diseases could be identified (eg, with COPD defined by a FEV_1/forced vital capacity ratio of < 0.7 and **at least ten packs-years of cigarettes or other substantial smoke exposure**)

Aliberti et al., Lancet Respir Med 2022; 10: 298–306

Stepwise treatment of BE



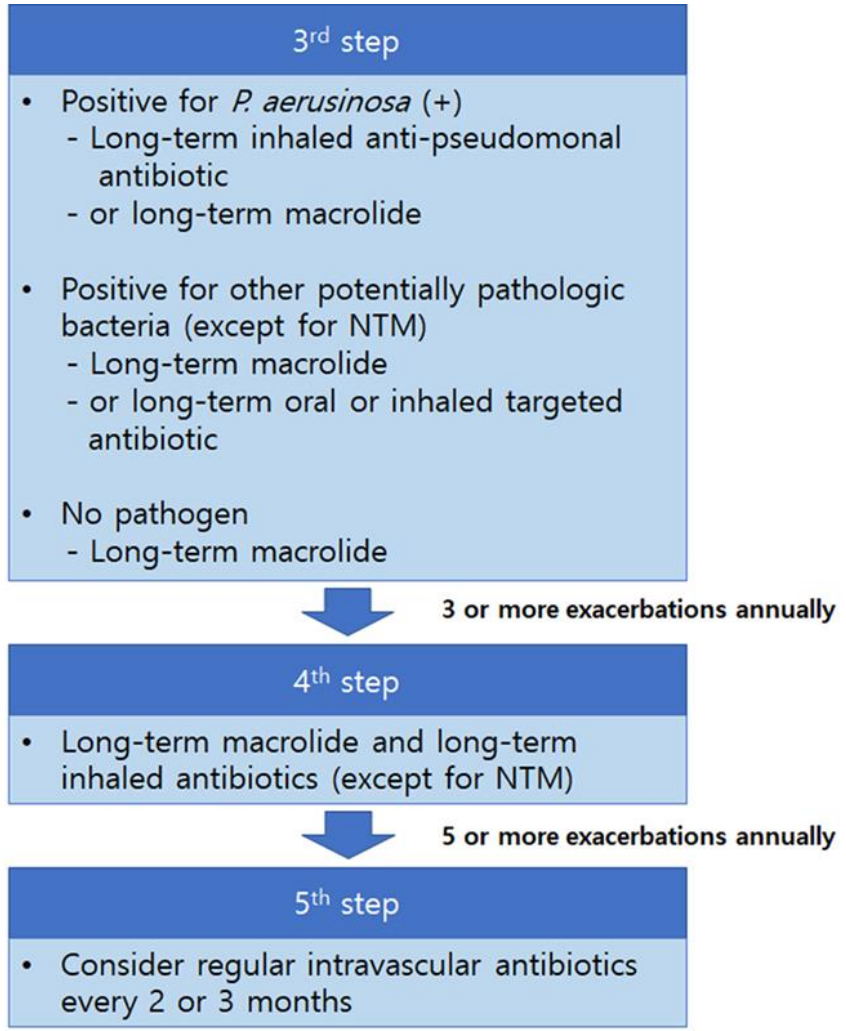


Figure 1. Stepwise management. NTM, non-tuberculosis mycobacteria.

Lee et al., Korean J Med 2020;95:141-1505

2023
Teaching
Slide Set

INITIAL PHARMACOLOGICAL TREATMENT

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**Group C** LAMA	**Group D** LAMA or LAMA + LABA* or ICS + LABA** *Consider if highly symptomatic (e.g. CAT > 20) **Consider if eos ≥ 300
0 or 1 moderate exacerbations (not leading to hospital admission)	**Group A** A Bronchodilator	**Group B** A Long Acting Bronchodilator (LABA or LAMA)
	mMRC 0-1, CAT < 10	mMRC ≥ 2, CAT ≥ 10

FIGURE 4.2

Initial Pharmacological Treatment

Figure 4.2

≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**GROUP E** **LABA + LAMA*** *consider LABA+LAMA+ICS* if blood eos ≥ 300*	
0 or 1 moderate exacerbations (not leading to hospital admission)	**GROUP A** **A bronchodilator**	**GROUP B** **LABA + LAMA***
	mMRC 0-1, CAT < 10	mMRC ≥ 2, CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers

GLOBAL INITIATIVE FOR CHRONIC OBSTRUCTIVE LUNG DISEASE™

Bronchiectasis with AO = COPD-B?

Contents

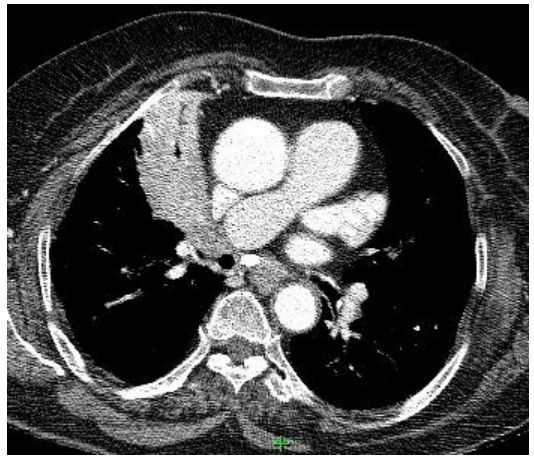
- Change in COPD definition – for what?
- **Controversial issues**
  - COPD-I
  - BE with AO
  - **COPD-P**
- Summary

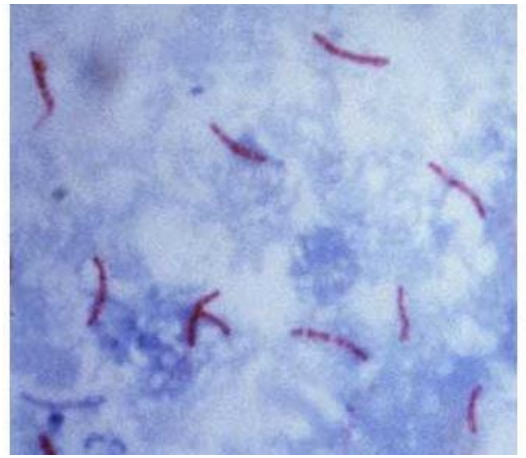
Anthracofibrosis (COPD-P?)

Clinical features of BAF

Older female predominance
No association with **pneumoconiosis or smoking**

Cough and **dyspnea**





Active pulmonary TB > 60%

Chung et al., Chest 1998;113:344-350

Bronchial Stenosis Due to Anthracofibrosis*

Man Pyo Chung, MD; Kyung Soo Lee, MD; Joungho Han, MD; Hojoong Kim, MD, FCCP; Chong H. Rhee, MD, FCCP; Yong Chol Han, MD, FCCP; and O Jung Kwon, MD

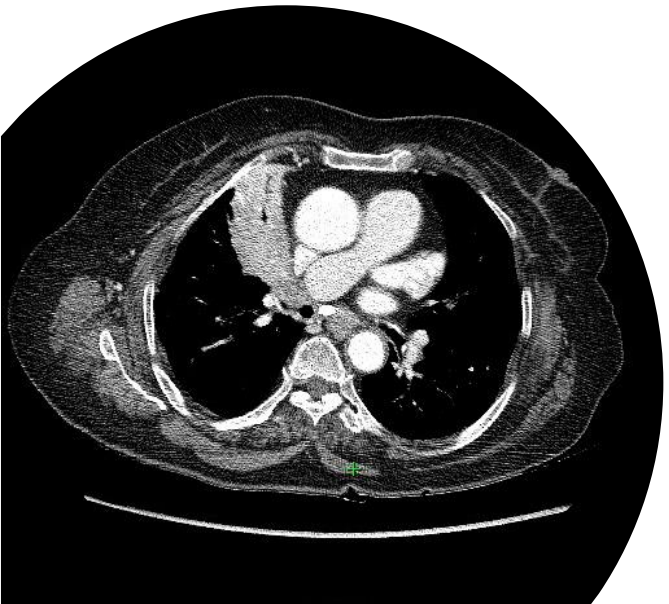
Study objectives: To define the clinical characteristics of the patients showing bronchoscopic findings of bronchial narrowing or obliteration with black pigmentation on overlying mucosa (we named this finding as "anthracofibrosis"), and to determine the association of anthracofibrosis with tuberculosis.

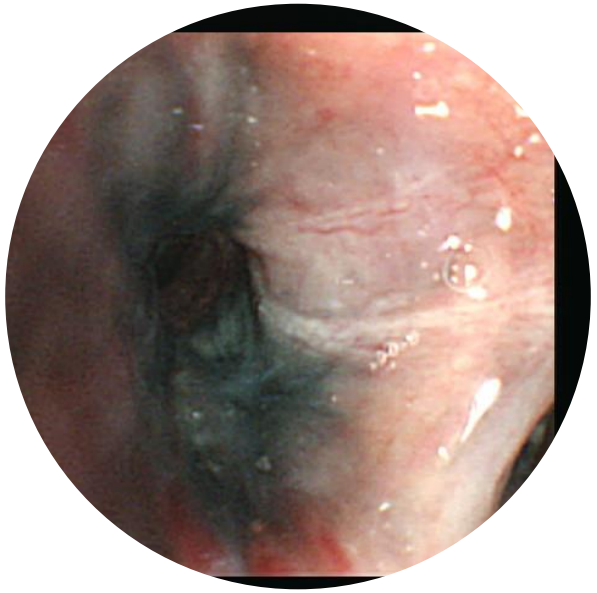
Patients and methods: The subjects of this study consisted of 28 patients; 8 men and 20 women, ranging in age from 42 to 86 years. The distinctive clinical features, natures of bronchoscopic lesions, and radiologic findings were analyzed retrospectively and summarized. Bacteriologic studies and results of pathologic examinations were also assessed.

Results: Chief complaints were cough (20/28) and dyspnea on exertion (17/28). The abnormal bronchoscopic findings were identified most frequently in the right middle lobe bronchus (n=21/28) while more than one part of the bronchial tree was narrowed in 22 patients. Abnormalities of bronchial airways on CT were associated with peribronchial cuffs of soft tissue or surrounding lymph nodes. In 17 patients, active tuberculous infection was confirmed either bacteriologically (n=15) and/or histologically (n=8). Pathologic study of the lesion obtained by bronchoscopic biopsy or thoracotomy showed dense bronchial and/or peribronchial fibrosis with interspersed black pigments.

Conclusions: These findings strongly suggest that bronchial stenosis or obliteration with anthracotic pigmentation in the mucosa was caused by a fibrotic response to active or old tuberculous infection. To prevent the spread of tuberculosis and avoid unnecessary invasive procedures, detailed examinations for the presence of active tuberculosis should be performed in patients with this unique bronchoscopic finding. (CHEST 1998;113:344–50)

anthracofibrosis; bronchial stenosis; bronchoscopy; tuberculosis





Definition of BAF

- Bonchoscopic findings of bronchial narrowing or obliteration with black pigmentation on overlying mucosa

Chung et al., Chest 1998;113:344-350

Clinical characteristics of BAF

	No [03] (N=166) 1998.1-2002.5	Jang [07] (N=54) 2003.1-2006.7	Kim [07] (N=333) 1998.1-2004.12	Park [17] (N=167) 2008.1-2014.3	Yilmazel [14] (N=109) 2002-2012
Age, years	72 (56-91)	75 (50-99)	72 ± 6	77 ± 8	68 ± 10
Female	86%	65%	85%	68%	52%
Never-smoker	78%	80%	78%	89%	-
Rural residency	78%	-		14%	-
Wood smoke exposure	25%	-	100%	-	61% (biomass)
Previous TB	31%	27%	33%	16%	

No et al., 대한내과학회지 2003;6:665-674
Jang et al., Tuberc Respir Dis 2007; 63: 139-144
Kim et al., Respir Med 2009;103:757-765
Park et al., Yonsei Med J 2017;58:355-361
Yilmazel et al., Eurasian J Pulmonol 2014; 16: 17-20

Symptoms

	No [03] (n=166) 1998.1-2002.5	Jang [07] (N=54) 2003.1-2006.7	Kim [07] (N=333) 1998.1-2004.12	Park [17] (n=167) 2008.1-2014.3	Yilmazel [14] (N=109) 2002-2012
Cough	48%	44%	30%	46%	59%
Dyspnea	50%	57%	38%	23%	50%
Sputum	28%	37%	2%	38%	-
Hemoptysis	11%	7%	9%	2%	5%
Fever	11%	11%	6%	4%	-
Wheeze	2%	-	-		
Weight loss	2%	-	-	5%	14%
No symptoms		6%	-	-	-

Jung et al., Tuberc Respir Dis 2005; 59: 368-373; Jang et al., Tuberc Respir Dis 2007; 63: 139-144
Kim et al., Respir Med 2009;103:757-765; Park et al., Yonsei Med J 2017;58:355-361;
Yilmazel et al., Eurasian J Pulmonol 2014; 16: 17-20

Spirometric results

	Obstructive	Restrictive	Normal	Mixed
Jung [05]	50% (56/113)	7% (8/113)	42% (47/113)	2% (2/113)
Jang [07]	62% (13/21)	5% (1/21)	33% (7/21)	
Kim [09]*	24% (79/333)			
Mirsadraee [12]**	95% (38/40)			
Yilmazel [14]	47% (50/109)			

* 35% = mild airflow limitation; 54% = moderate airflow limitation
** Obstructive pattern was defined as $FEV_1/FVC < 75\%$

No et al., 대한내과학회지 2003;6:665-674
Jang et al., Tuberc Respir Dis 2007; 63: 139-144
Kim et al., Respir Med 2009;103:757-765
Park et al., Yonsei Med J 2017;58:355-361
Yilmazel et al., Eurasian J Pulmonol 2014; 16: 17-20

CT findings – Bronchial tree and LN

	No [03] (N=166) 1998.1-2002.5	Jang [07] (N=54) 2003.1-2006.7	Kim [07] (N=333) 1998.1-2004.12	Park [17] (n=167) 2008.1-2014.3
Bronchial tree				
Atelectasis	67%*	75%	61%**	29%
Bronchial narrowing	78%*		63%**	49%
Peribronchial calcification		48%		10%
Lymph node				
LN enlargement	70%	65%	66%	37%
with calcification	45%	53%	45%	37%

*56% had both atelectasis and bronchial narrowing.
**42% had both atelectasis and bronchial narrowing.

No et al., 대한내과학회지 2003;6:665-674
Jang et al., Tuberc Respir Dis 2007; 63: 139-144
Kim et al., Respir Med 2009;103:757-765
Park et al., Yonsei Med J 2017;58:355-361

BAF in patients with COPD AE

	BAF (n=51)	Non-BAF (n=155)	P value
Age, years	**78±7.6**	71±9.8	< 0.001
Female	**61%**	23%	< 0.001
Never-smoker	**52%**	18%	< 0.001
Wood smoke exposure	**59%**	27%	0.001
Symptoms of respiratory infection	73%	90%	0.002
NT-proBNP, pg/mL	425 (133–1,666)	207 (93–755)	0.018
Post-BD FEV1, % pred.	**78±28.3**	59±24.3	< 0.001
PA-to-AA ratio>1	**43%**	11%	< 0.001
RVSP > 40 mmHg	**50%**	18%	0.033

BAF - **Milder airflow limitation**
but, more frequent signs of **pulmonary HTN** in patients with COPD AE

Kim et al., Tuberc Respir Dis 2014;77:124–131

Treatment

- Anti-TB drugs
  - 3 of 5 patients without active TB had improvement after TB treatment
- Steroid
  - 9 of 14 patients who received steroid were improved clinically, and 6 were improved radiologically.
- Bronchodilators
  - 2 cases
    - 1 improvement with bronchodilator and steroid
    - 1 failed
- Intervention

Chung et al., Chest 1998;113:344-350
Jang et al., Tuberc Respir Dis 2007; 63: 139-144
Afridi et al., poster presentation in Chest Annual Meeting 2017
Raouf et al., IJTLD 2013;17:1118–1120

Lung Pathology

SESSION TITLE: Lung Pathology 3

SESSION TYPE: Affiliate Case Report Poster

PRESENTED ON: Tuesday, October 31, 2017 at 01:30 PM - 02:30 PM

A Bronchial Mark: A Case of Bronchial Anthracofibrosis

Faraz Afridi* and Ali Ashraf University of Central Florida College of Medicine, Orlando, FL

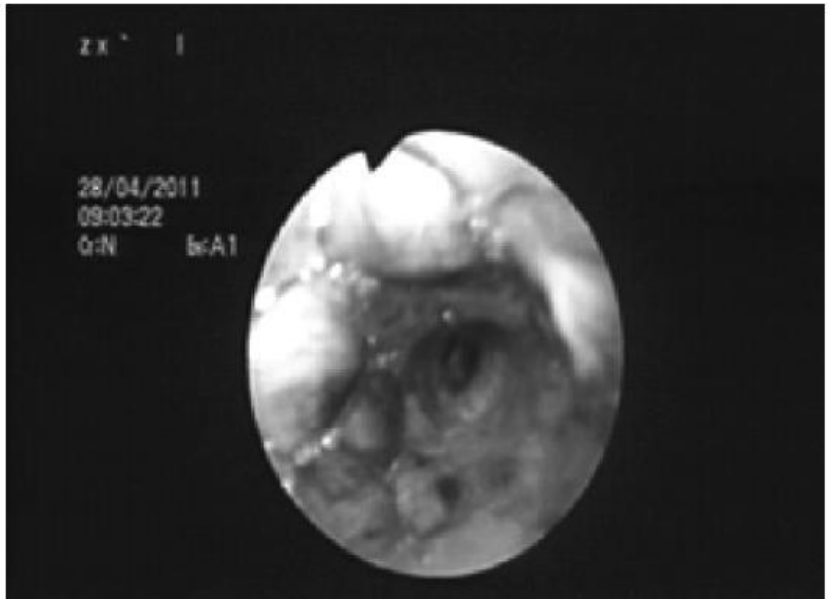
INTRODUCTION: Bronchial anthracofibrosis is characterized by the endobronchial finding of black discoloration on the bronchial mucosa in patients with no pneumoconiosis or a history of smoking. It can lead to bronchial stenosis causing obstructive lung disease and can be associated with *Mycobacterium tuberculosis* (MTB) infection.

CASE PRESENTATION: An 86-year-old male with a medical history of mild intermittent asthma presented with persistent dyspnea. He denied cough, wheezing or fever. He was a lifetime non-smoker with no history of chemical or fume exposure. Vital signs were normal and examination was remarkable for crackles in the left upper lobe. He was initially treated with bronchodilators and a course of oral steroids as an outpatient, but symptoms did not improve. CT chest showed a left upper lobe consolidation with intraluminal narrowing, for which a bronchoscopy evaluation was done. Bronchoscopy showed grayish-black pigmentation with mucosal fragility and edema throughout all segments but sparing the mainstem bronchi bilaterally (Figure 1). The left upper lobe apical segment was found to be extremely narrowed with this hyperpigmentation. A bronchoalveolar lavage was negative for gram stain, bacterial and fungal cultures, acid-fast bacilli (AFB) smear, and cytology for malignancy. No transbronchial or endobronchial biopsies were done secondary to the patient's mucosal fragility and risk of bleeding. The QuantiFERON-TB Gold test and Aspergillus galactomannan antigen test was negative. He was started on long-acting bronchodilators and a tapering course of oral steroids which gradually improved his symptoms.

DISCUSSION: Anthracofibrosis is a condition which involves bronchial stenosis and should be considered in the differential diagnosis in patients with an obstructive lung disease pattern with no history of pneumoconiosis or a history of smoking with bronchoscopy findings of endobronchial hyperpigmentation.[1] In all cases of anthracofibrosis, they should have MTB evaluation as bronchial anthracofibrosis has been associated with MTB in 32.3% of patients according to a recent meta-analysis.[2] There is no established treatment for anthracofibrosis but empirical treatment with bronchodilators, corticosteroids, and antibiotics have been used. However, in those with severe localized bronchial stenosis of the airways, bronchial stents have been used.[1]

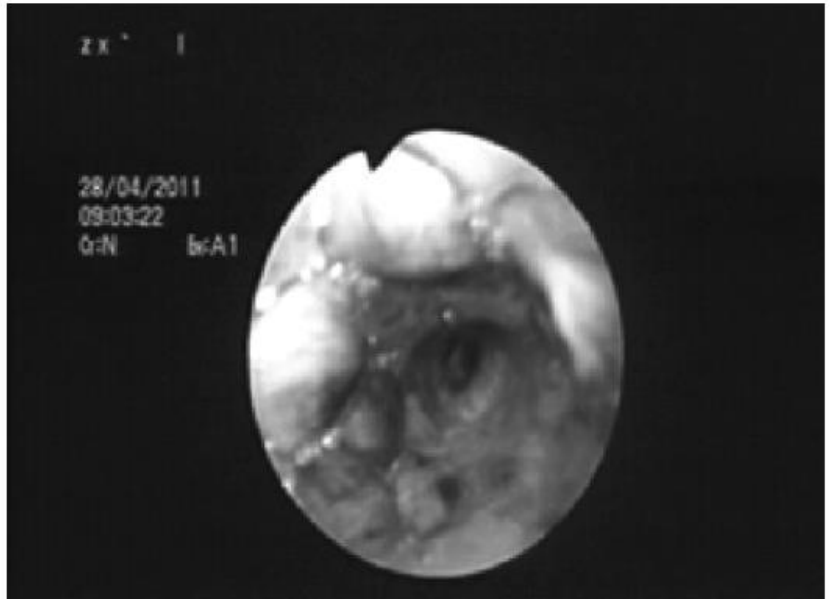
CONCLUSIONS: Bronchial anthracofibrosis is a black discoloration of the bronchial mucosa which can cause stenosis of the bronchial lumen. It is associated with MTB which needs to be evaluated for in all patients. Treatment is similar to that of chronic obstructive pulmonary disease and has a similar chronic course.

that had started 5 years ago. Different bronchodilators failed to relieve her symptoms. Physical examination and pulmonary function tests were normal. Chest X-ray revealed no specific findings, and chest CT showed mild bilateral apical fibrotic changes, but no lymphadenopathy. Pulmonary function tests revealed moderate airway disease (FVC 89%, FEV_1 65.5% of predicted). Fiberoptic bronchoscopy showed severe stenosis of the right upper lobe bronchus, right intermediate bronchus and left lower lobe bronchus, with black discolouration of the mucous membrane. Endobronchial biopsy showed marked anthracotic changes with no evidence of malignancy. Bronchoalveolar culture was negative for TB. Balloon dilation (CRE™; Boston Scientific, Fremont, CA, USA) of the stenosed bronchi was performed. The patient required



Bronchoscopic intervention

- Balloon dilatation + Metal stent
  - A 79-year-old female with severe stenosis in RBI
  - PFT change
    - FEV_1 66%pred → 82%pred
    - FVC 89%pred → 92%pred



Raouf et al., IJTLD 2013;17:1118–1120

Controversy – anthracofibrosis

An etiotype of COPD

- Presence of AO
- Exposure of biomass
- Bronchodilators might be helpful

A different type of disease

- Mechanically obstructive lung disease
- The role of bronchodilator is not well evaluated

Summary

- The purpose of classifying “etiotypes” of COPD
  - To reveal heterogeneity of etiologies and pathogenesis in COPD
  - To provide tailored strategies to reduce COPD risk factors according to each etiotype

- There might be controversy in classifying some diseases as etiotypes of COPD
  - Pulmonary infections other than TB
  - Bronchiectasis
  - Anthracofibrosis, pneumoconiosis