Early Detection and Assessment for COPD

동아의대 호흡기 내과
엄수정

Definition of Early COPD

Definition of Early COPD

1. When is the beginning of the disease?
2. Do we know all the risk factors of the disease?
3. Is only a single natural history of the disease?
4. Can we monitor the natural course of COPD only by Lung function tests?
5. Do we know all the phenotypes or endotypes of this disease?

Respiratory Medicine 140 (2018) 127–131

Am J Respir Crit Care Med. 2018 Jun 15;197(12):1540-1551. doi: 10.1164/rccm.201710-2028PP.

At the Root: Defining and Halting Progression of Early Chronic Obstructive Pulmonary Disease.

Martinez FJ[1,2], Han MK[2], Allinson JP[3], Barr RG[4], Boucher RC[5], Calverley PMA[6], Celli BR[7], Christenson SA[8], Crystal RG[1], Fagerås M[9], Freeman CM[2,10], Groenke L[11], Hoffman EA[12], Kesimer M[5], Kostikas K[13], Paine R 3rd[14,15], Rafii S[1], Rennard SI[11], Segal LN[16], Shaykhiev R[1], Stevenson C[17], Tal-Singer R[18], Vestbo J[19], Woodruff PG[8], Curtis JL[2,10], Wedzicha JA[3].

⊕ Author information

Table 1. Components of Operational Definition for Early Chronic Obstructive Pulmonary Disease

Required	One or More of the Following:
<50 yr of age ≥10 pack-years smoking history	FEV_1/FVC less than lower limit of normal Compatible computed tomography abnormalities (visual emphysema, air trapping, or bronchial thickening graded mild or worse) Evidence of accelerated FEV_1 decline (≥60 ml/yr)

Exclusion criteria include other known chronic lung diseases, including interstitial lung diseases, but not asthma (*see text*).

The Scope of Early COPD

- **"Early disease COPD"**
- **GOLD 0**
  ; Chr Bronchitis and $FEV_1/FVC \geq 0.7$
- **PRISm (preserved ratio impaired spirometry)**
  ; $FEV_1/FVC \geq 0.7$ & $FEV_1 < 80\%$
- **Undiagnosed COPD**
- **Mild to Moderate COPD**

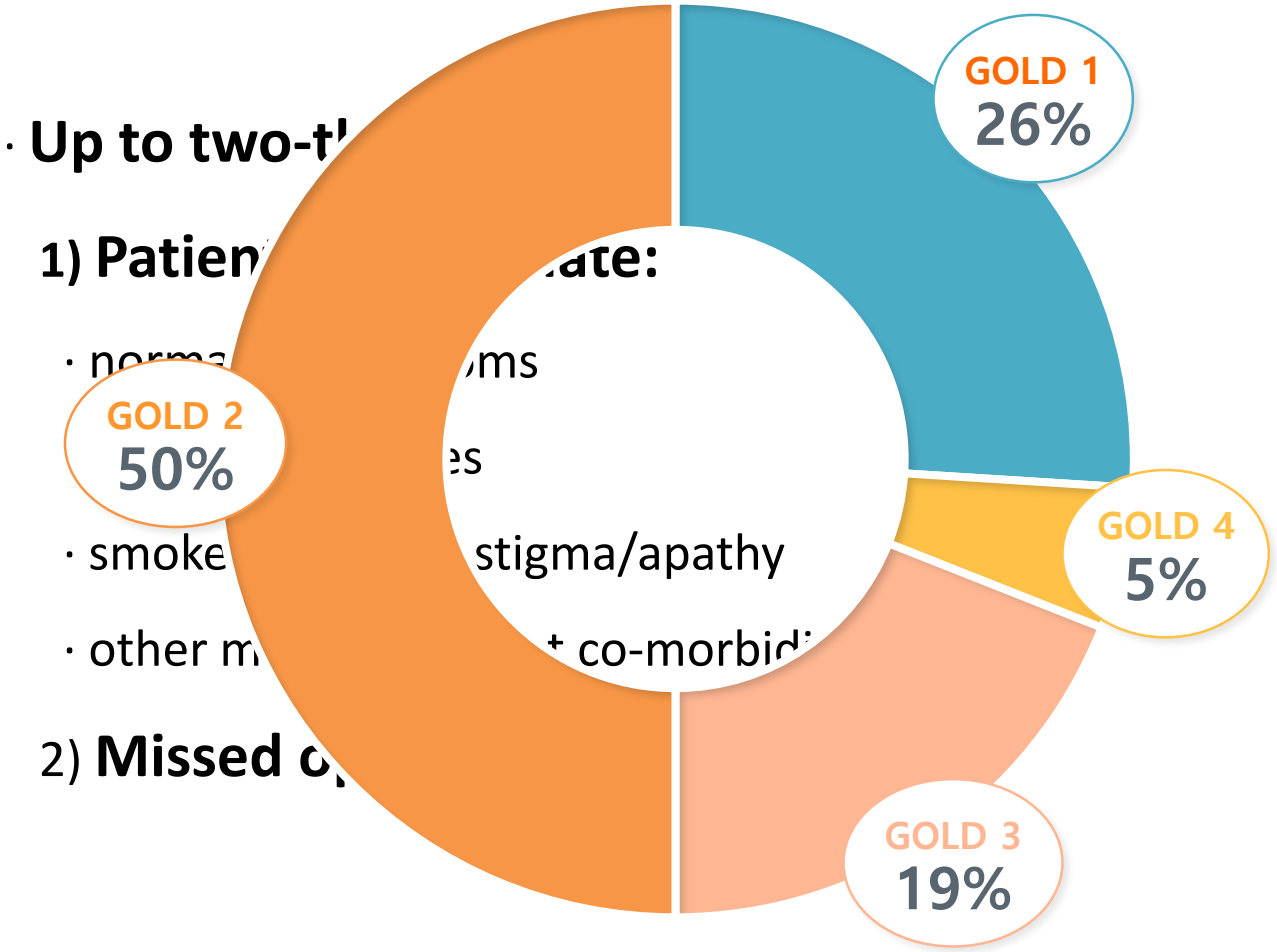
CONTENT

1. Early Detection of Undiagnosed COPD
    1) Undiagnosed COPD
    2) Active case finding
2. Diagnostic methods of early disease
    1) PFT
    2) Chest CT
    3) Blood

CONTENT

1. Early Detection of Undiagnosed COPD
    1) Undiagnosed COPD

Significant under-diagnosis worldwide



· Up to two-t

1) Patien ate:

· norma oms

· smoke es

· other m stigma/apathy

2) Missed o t co-morbid

Mapel DW, et al. Int J Chron Obstruct Pulmon Dis 2011; 6: 573–581

Jones et al, Lancet Respir Med 2014; 2: 267-76

Significant under-diagnosis worldwide

· **Up to two-thirds remain undiagnosed**

1) **Patients present late:**

· normalise symptoms

· self-limit activities

· smokers afraid of stigma/apathy

· other more important co-morbidities

2) **Missed opportunities by GPs**

Jones et al, Lancet Respir Med 2014; 2: 267-76

Opportunities to diagnose chronic obstructive pulmonary disease in routine care in the UK: a retrospective study of a clinical cohort

*Rupert C M Jones, David Price, Dermot Ryan, Erika J Sims, Julie von Ziegenweidt, Laurence Mascarenhas, Anne Burden, David M G Halpin, Robert Winter, Sue Hill, Matt Kearney, Kevin Holton, Anne Moger, Daryl Freeman, Alison Chisholm, Eric D Bateman, on behalf of The Respiratory Effectiveness Group**

- 40세이상 COPD 환자 (Code, COPD 연관 처방이 연간 2회이상)
- 진단 최소 2년전부터 20년전까지의 1차 및 2차 의료기관의 기록 분석
- Missed opportunity for COPD diagnosis

Jones et al, Lancet Respir Med 2014; 2: 267-76

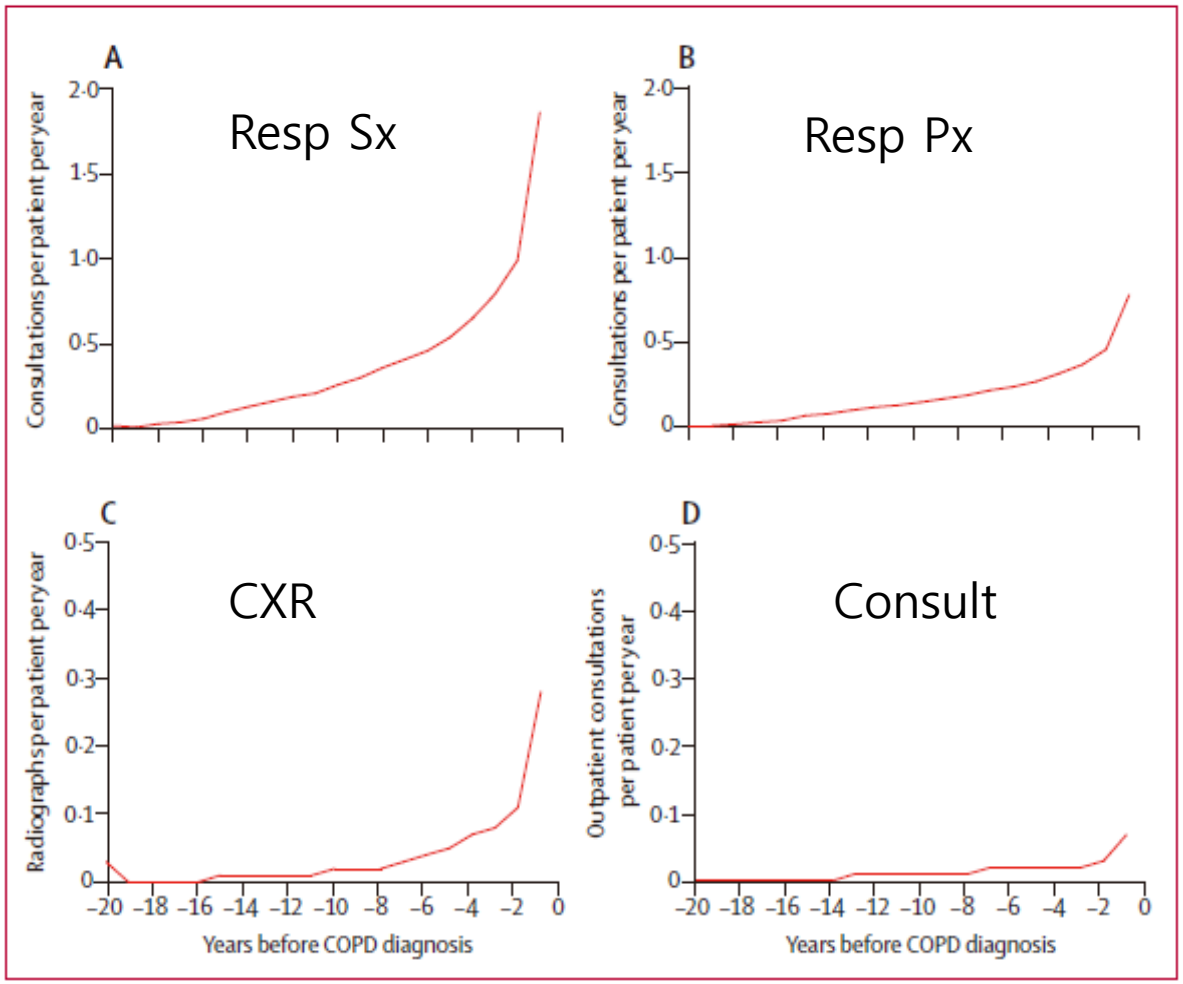


Figure 2: **Mean frequency of missed opportunities to diagnose COPD**
For consultations for lower respiratory symptoms (A), lower respiratory prescribing consultations (B), chest radiography (C), and outpatient consultations (D). Too few data were available to present number of admissions to hospital. COPD=chronic obstructive pulmonary disease.

Missed opportunity for COPD diagnosis

진단 5년전 ; 85%

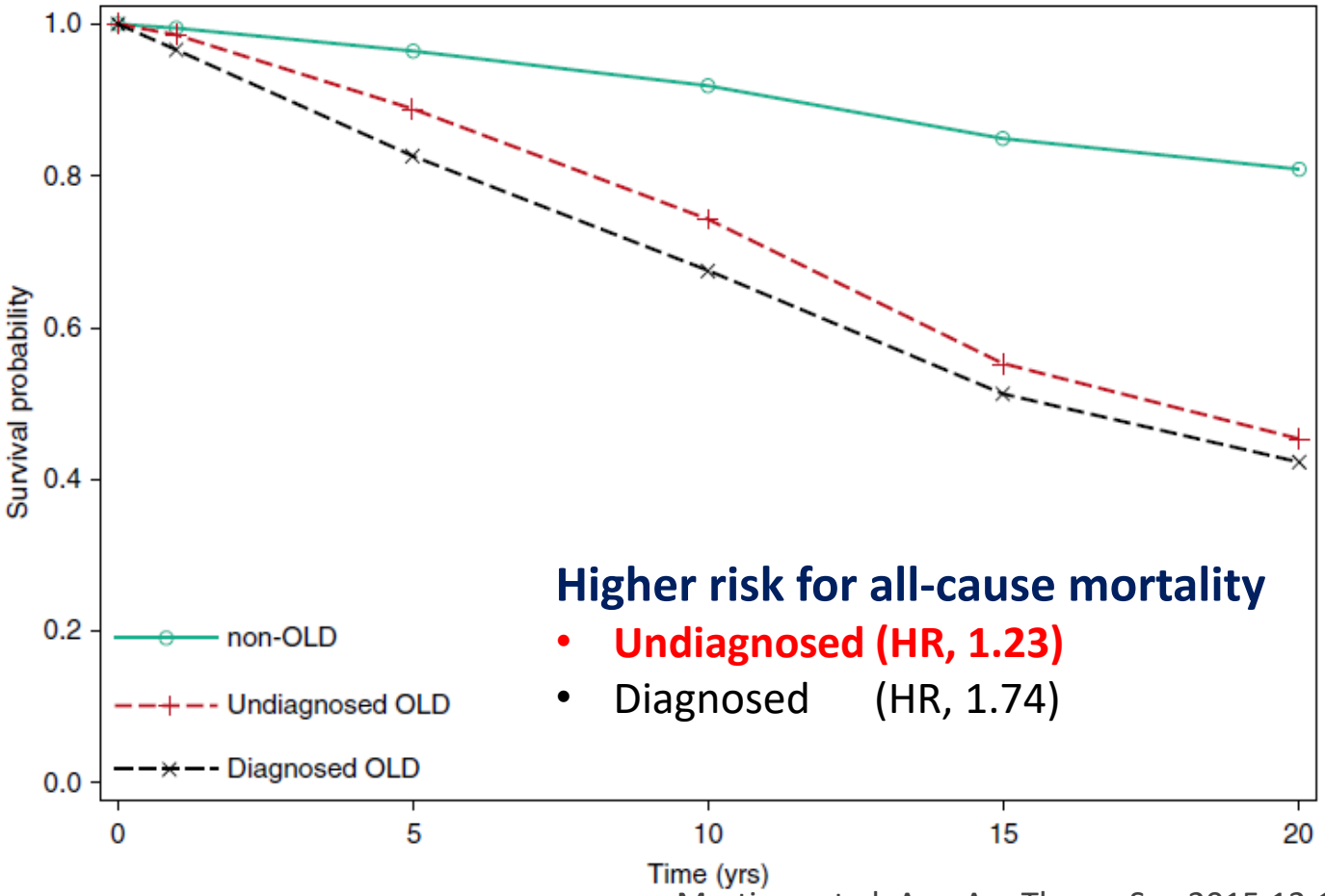
6~10년전 ; 58%

11~15년전 ; 42%

16~20년전 ; 8%

Importance of undiagnosed COPD - Impact on mortality -

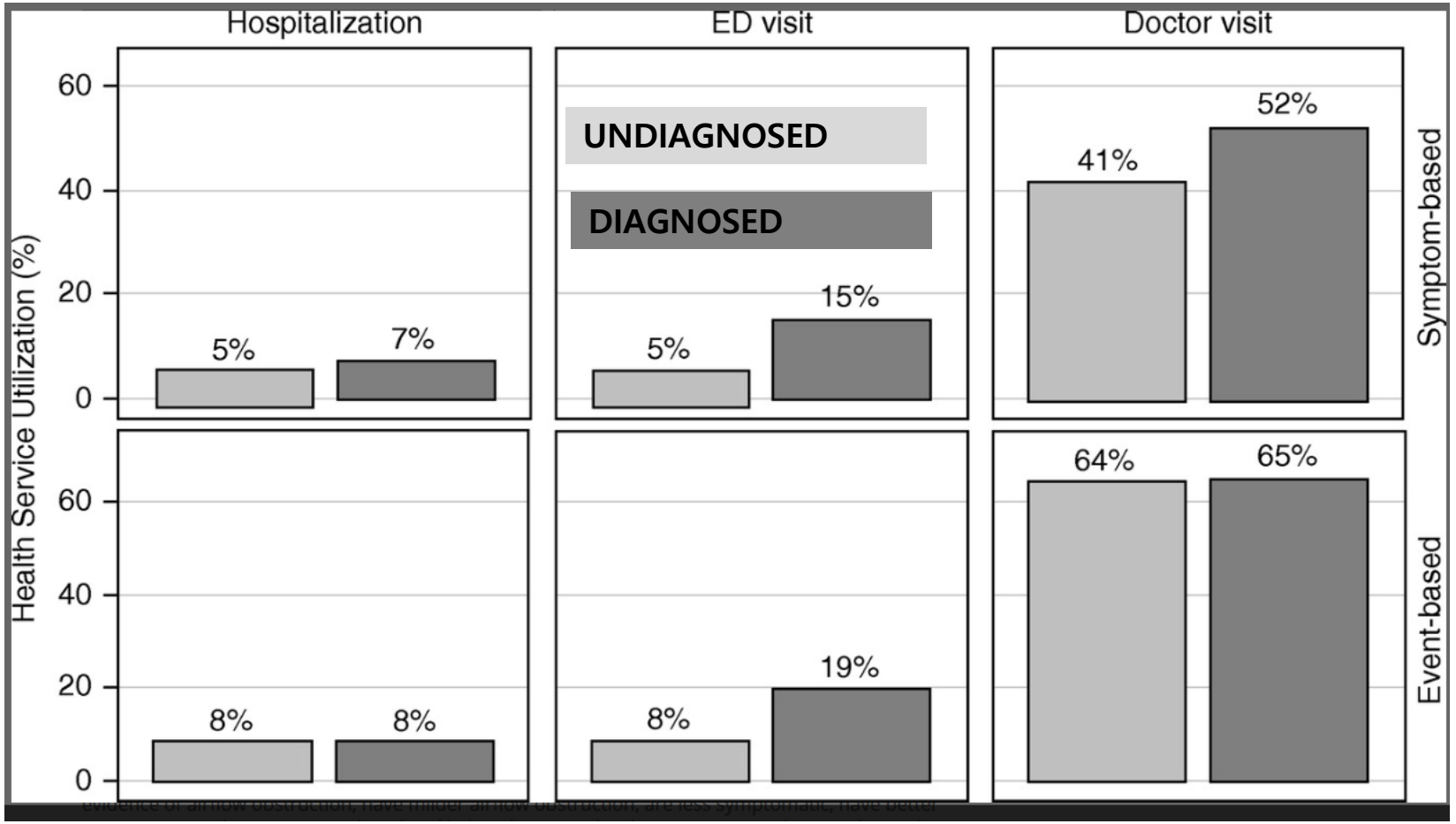
- **NHANES participants long term F/u (median 14.5 yrs)**
- **71.2% of those with obstruction did not have a COPD diagnosis**



Martinez et al. Ann Am Thorac Soc 2015;12:1788–1795.

Burden of Undiagnosed COPD

- **Canada : population based study (CANCOLD)**
- **N=505 COPDs (355 (70%)) undiagnosed**



Labonte et al, AJRCCM 2016

What is the evidence for screening for COPD?

JAMA
The Journal of the American Medical Association

5th April, 2016

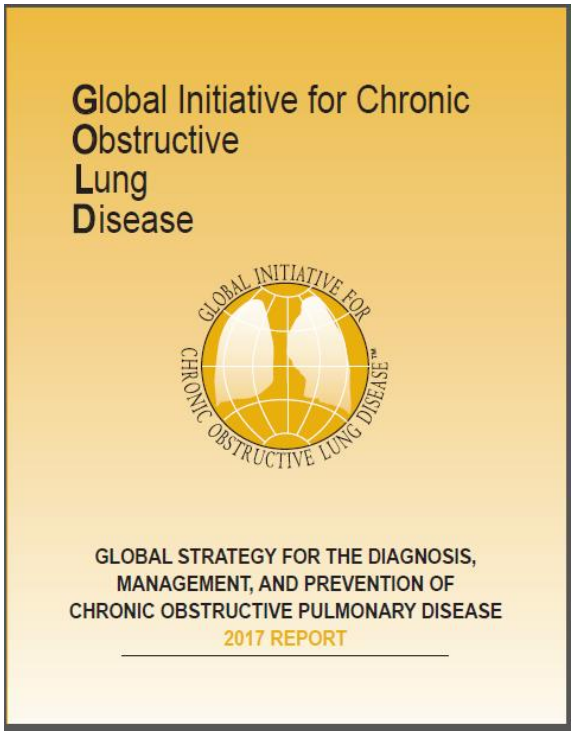
Screening for COPD. Evidence Report and Systematic Review for the US Preventive Services Task Force (USPSTF)

There was no direct evidence available to determine the benefits and harms of screening asymptomatic adults for COPD using questionnaires or office-based spirometry or to determine the benefits of treatment screen-detected populations.

33 studies analyzed

Grade D : Recommends against screening for COPD among asymptomatic adults

(Guirguis-Blake J et al, JAMA 2016;315(13): 1378-1393)



- **Active case finding**

performing spirometry in patients with symptoms and/or risk factors, where the diagnostic yield for COPD is relatively high)
but not routine screening spirometry in asymptomatic individuals without COPD risk factors

SCREENING

- 어떤 질병의 조기단계에서 이를 진단하기 위해 증상이 없는 사람을 대상으로 집단검진으로 행해지는 검사

1) 집단선별검사(mass screening)
; 위험요인(risk factor)을 고려하지 않은 대상집단에 대한 검사

2) 다상선별검사(multiphasic screening)
; 동시에 여러 질환에 대한 검사

3) 표적선별검사(targeted screening)
; 특정위험요인에 노출된 그룹만을 대상으로 하는 검사

4) 환자발견(case finding) 또는 기회검진(opportunistic screening)
; 병원에 내원한 환자를 대상으로 하는 검사

CONTENT

1. Early Detection of Undiagnosed COPD
    1) Undiagnosed COPD
    2) Active case finding

Knowledge and Attitudes of Family Physicians

Table 2 Use of guidelines with respondent characteristics

Type of health professional	Medical doctor n = 178	Nurse practitioner/ Physician's assistant n = 100	Has spirometry in office n = 148	Age <50 n = 149	Age ≥50 n = 130
Uses GOLD or ATS COPD guidelines	56 (31%)	34 (34%)	62 (42%)	47 (32%)	42 (32%)
Uses none or does not know	59 (33%)	40 (40%)	43 (29%)	59 (40%)	42 (45%)

Table 4 Perceived barriers in the diagnosis of COPD

Type of health professional	Lack of specific symptoms	Failure of patients to recognize and report dyspnea	Multiple chronic conditions	Lack of knowledge and training	Lack of access to spirometry	Lack of effective treatment
MD n = 178	35 (20%)	85 (48%)	80 (45%)	39 (22%)	51 (29%)	13 (7%)
NP/Pas n = 100	22 (22%)	50 (50%)	64 (64%)	33 (33%)	21 (21%)	5 (5%)

Abbreviations: MD, medical doctor; NP, nursing practitioner; PA, physician's assistant.

International Journal of COPD 2008:3(2) 311–317

Accuracy of diagnosis of COPD and factors associated with misdiagnosis in primary care setting. E-DIAL (Early DIAgnosis of obstructive lung disease) study group

Stefano Nardini[a,1], Isabella Annesi-Maesano[b,*,1], Marzia Simoni[b], Adriana del Ponte[c], Claudio Maria Sanguinetti[d], Fernando De Benedetto[c]

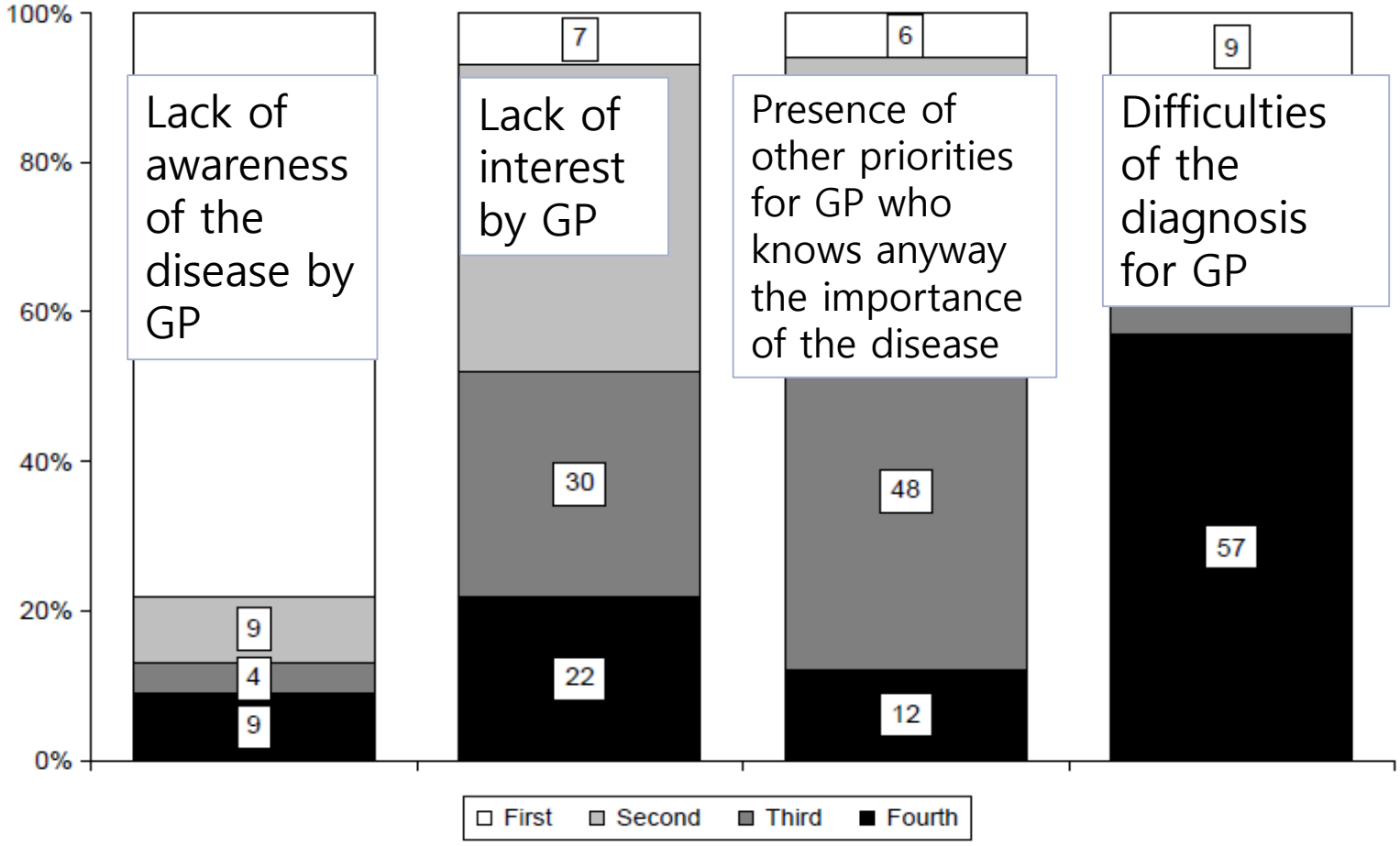
Table 3
Agreement between general practitioners (GP) and pulmonologists (gold standard) as regards the diagnosis of chronic obstructive pulmonary disease (COPD).

Sensitivity, % (95% CI)	40.62 (32.04–49.66)
Specificity, % (95% CI)	86.91 (83.87–89.56)
Positive Likelihood ratio (95% CI)	3.10 (2.31–4.18)
Negative Likelihood ratio (95% CI)	0.68 (0.59–0.79)
Positive predictive value, % (95% CI)	40.94 (32.30–50.02)
Negative predictive value, % (95% CI)	86.76 (83.71–89.42)
Absolute agreement, %	78.46
Kappa (95% CI)	0.28 (0.20–0.35)

95% CI: 95% confidence interval.

Res Med 2018;143:61-66

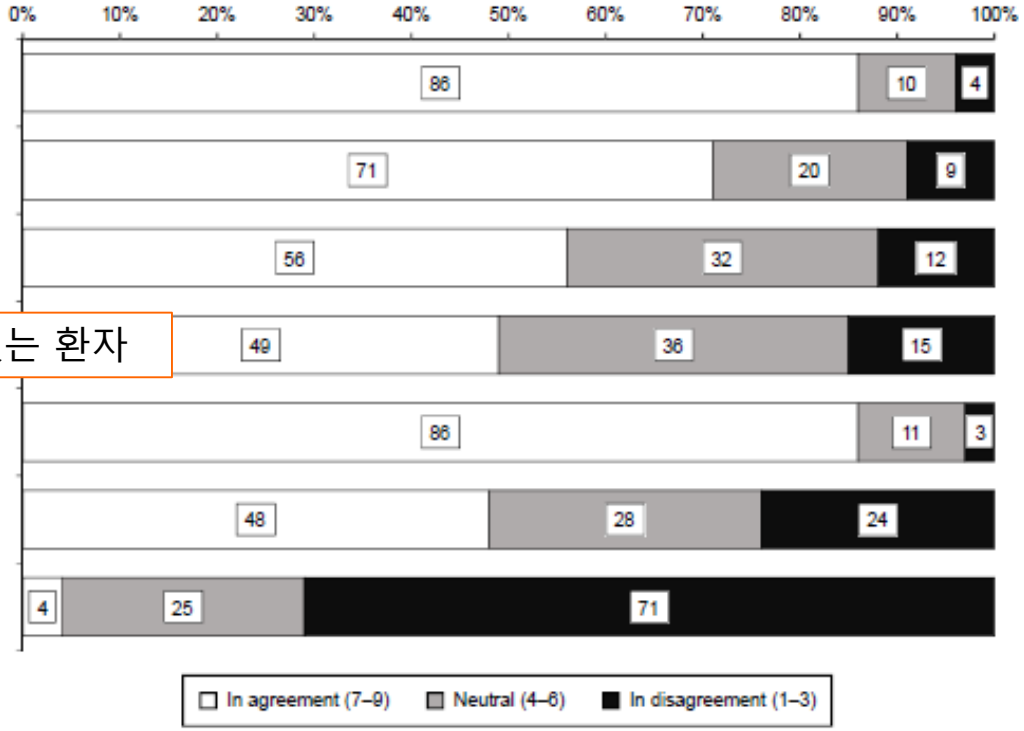
Relevance of Factors Limiting Early diagnosis of COPD



International Journal of COPD 2019:14 353–360

Level of Consensus on the Early Management of COPD (Specialist in Pulmonology)

Items	Median	IQR	IPRAS	Assessment
Early diagnosis of COPD	8	7–9	6.85	Appropriate
도구; 설문조사와 risk card		6–8	6.1	Appropriate
도구; GP database에서 BD 투약한 환자				
도구; GP database에서 steroid 투약한 경험이 있는 환자				
방법GP가 전문가에게 의뢰		7–9	7.6	Appropriate
방법GP가Spirometry 후 선택적 의뢰				Uncertain
방법GP가 진단과 치료	2	1–4	6.85	Inappropriate



International Journal of COPD 2019:14 353–360

【 ORIGINAL ARTICLE 】

Early Detection of Chronic Obstructive Pulmonary Disease in Primary Care

Seiichi Kobayashi, Masakazu Hanagama and Masaru Yanai;
for the Ishinomaki COPD Network (ICON) Investigators

- A prospective multi-center, observational study
- Patients ≥ 40 yo, outpatient care for chronic disease at primary care clinics

COPD-PS and Handiheld spirometry

⇩ Possible COPD

Conventional spirometry

⇩

COPD

Intern Med 56: 3153-3158, 2017

Table 2. Final Diagnosis of Patients with Possible COPD.

Spirometric results and diagnosis	Number (%)
Normal spirometry	
No lung disease	46 (40.9)
Chronic bronchitis without COPD	9 (8.2)
Emphysema without COPD	7 (6.4)
Sarcoidosis	1 (0.9)
Old tuberculosis	1 (0.9)
Obstructive pattern	
COPD	27 (24.5)
No lung disease*	9 (8.2)
Emphysema without COPD	2 (1.8)
Old tuberculosis	1 (0.9)
Chronic bronchitis without COPD	1 (0.9)
Asthma	1 (0.9)
Old pneumonia	1 (0.9)
Bronchiectasis without COPD	1 (0.9)
Restrictive pattern	
Chronic bronchitis without COPD	1 (0.9)
Old tuberculosis	1 (0.9)
Obesity	1 (0.9)

COPD

Data are shown as number (%).

* These patients showed post-bronchodilator $FEV_1/FVC>0.7$ and normal image in chest radiograph.

Open Access Full Text Article

ORIGINAL RESEARCH

Multicenter study of the COPD-6 screening device: feasible for early detection of chronic obstructive pulmonary disease in primary care?

Denmark

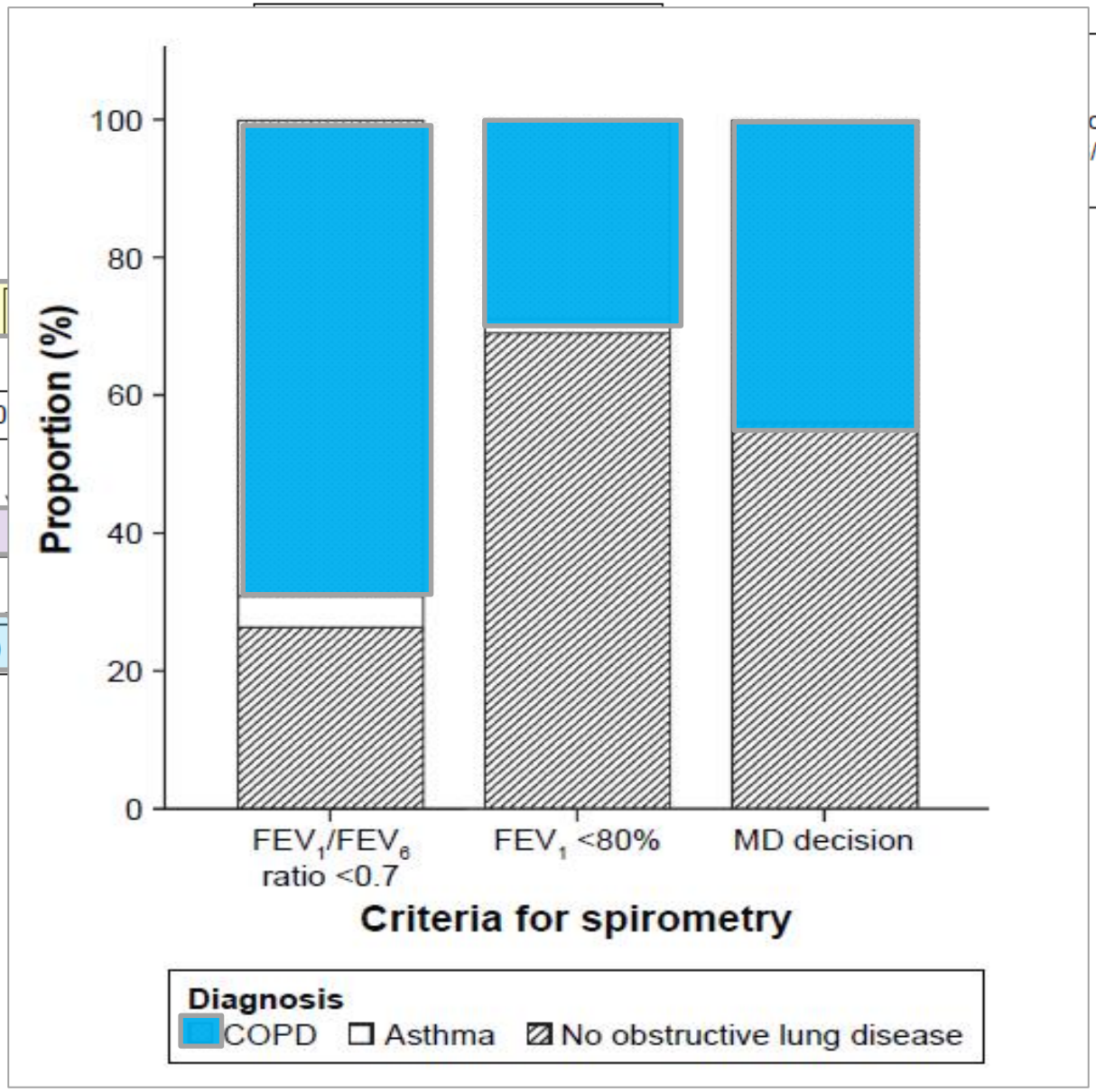
- age ≥35 years,
- smoker/ex-smoker or other risk exposures for COPD
- at least one respiratory symptom
  (dyspnea, cough, wheeze, sputum, or recurrent respiratory tract infections)
- no previous diagnosis of obstructive lung disease or treatment with inhaler medication within the last 12 Mo

International Journal of COPD 2017:12 2323–2331

on 82
/spirometry 34

FEV$_1$ <80

COPD



A New Approach for Identifying Patients with Undiagnosed Chronic Obstructive Pulmonary Disease

Fernando J. Martinez[1], David Mannino[2], Nancy Kline Leidy[3], Karen G. Malley[3], Elizabeth D. Bacci[4], R. Graham Barr[5,6], Russ P. Bowler[7], MeiLan K. Han[8], Julia F. Houfek[9], Barry Make[7], Catherine A. Meldrum[8], Stephen Rennard[10,11], Byron Thomashow[12], John Walsh[13], and Barbara P. Yawn[14]; on behalf of the High-Risk-COPD Screening Study Group*

Please answer each question	No	Yes
1. Have you ever lived or worked in a place with dirty or polluted air, smoke, second-hand smoke, or dust?	☐	☐
2. Does your breathing change with seasons, weather, or air quality?	☐	☐
3. Does your breathing make it difficult to do things such as carry heavy loads, shovel dirt or snow, jog, play tennis, or swim?	☐	☐
4. Compared to others your age, do you tire easily?	☐	☐

	0	1	2 or more
5. In the past 12 months, how many times did you miss work, school, or other activities due to a cold, bronchitis, or pneumonia?	☐	☐	☐

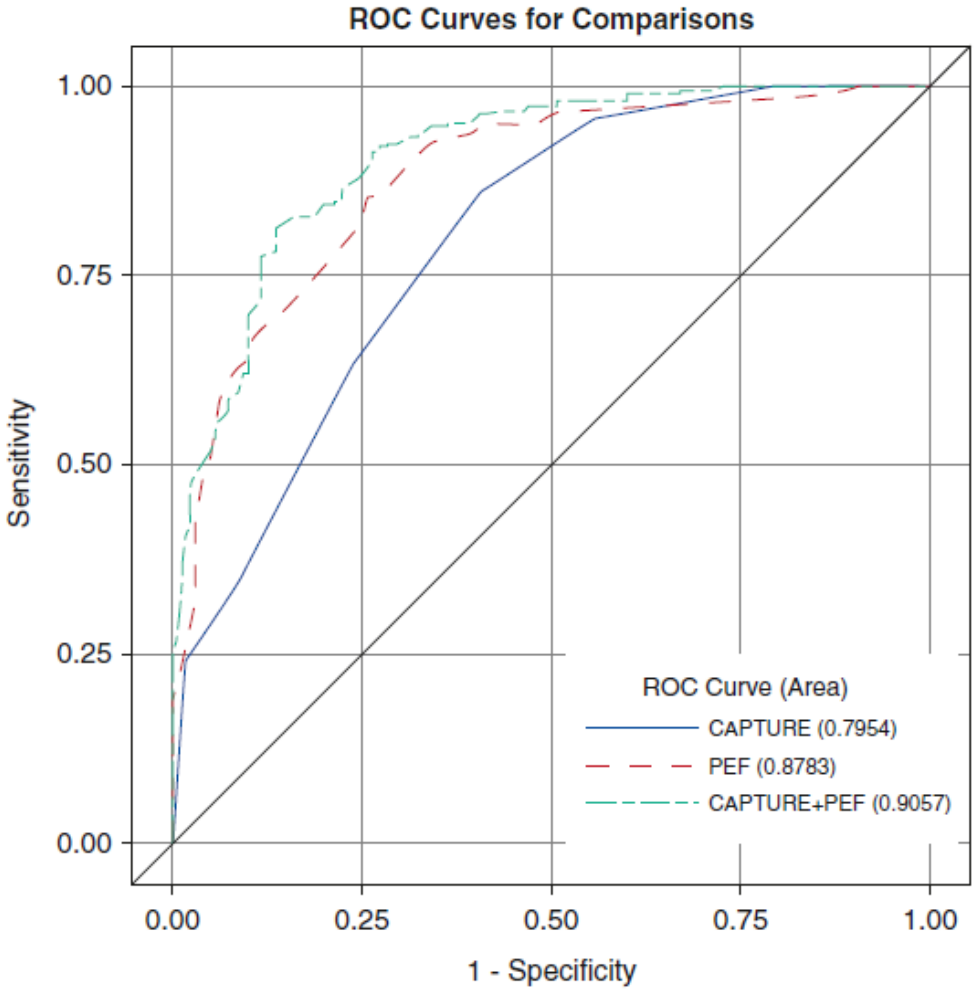
*COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease & Exacerbation Risk

Figure 1. The CAPTURE questionnaire (Chronic Obstructive Pulmonary Disease Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk).

males;350 L/min
females; 250 L/min

Am J Respir Crit Care Med. 2017 Mar 15;195(6):748-756.

COPD Assessment in Primary Care to Identify Undiagnosed Respiratory Disease and Exacerbation Risk.



Case ;
COPD and 1 exacerbation or FEV1≤ 60%

Control;
FEV1 ≥60% and No exacerbation

Am J Respir Crit Care Med. 2017 Mar 15;195(6):748-756.

PLOS | ONE

RESEARCH ARTICLE

Prevalence and Global Initiative for Chronic Obstructive Lung Disease Group Distribution of Chronic Obstructive Pulmonary Disease Detected by Preoperative Pulmonary Function Test

Sun Mi Choi, Jinwoo Lee, Young Sik Park, Chang-Hoon Lee, Sang-Min Lee, Jae-Joon Yim, Young Whan Kim, Sung Koo Han, Chul-Gyu Yoo*

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University

Table 3. Distribution of airflow limitation, level of symptoms, and exacerbation of COPD among COPD patients.

Post-BD FEV_1 (% predicted)	mMRC $\geq$ 2	CAT $\geq$ 10	Experience of exacerbation	Severe exacerbation	Total
$FEV_1 \geq 80$	44 (11.8)	92 (24.7)	7 (1.9)	5 (1.3)	372 (100)
$50 \leq FEV_1 < 80$	29 (33.3)	37 (42.5)	9 (10.3)	2 (2.3)	87 (100)
$30 \leq FEV_1 < 50$	7 (50)	7 (50)	2 (14.3)	2 (14.3)	14 (100)
$FEV_1 < 30$	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Total	80 (16.9)	136 (28.7)	18 (3.8)	9 (1.9)	474 (100)

Data are presented as numbers (%).

Post-BD: postbronchodilator, FEV1: forced expiratory volume in 1 s, mMRC: modified Medical Research Council, CAT: COPD assessment test.

doi:10.1371/journal.pone.0115787.t003

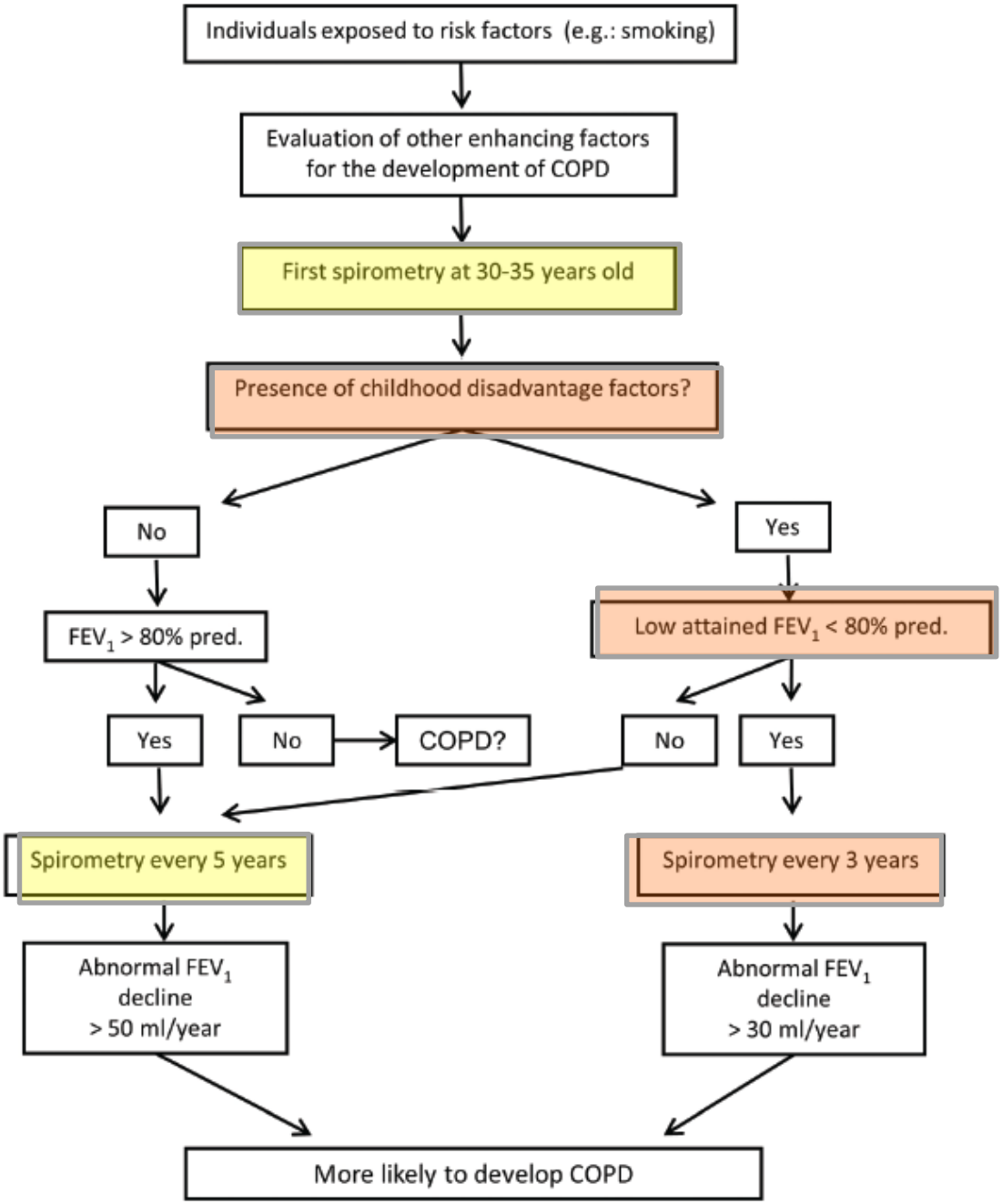
Early imaging biomarkers of lung cancer, COPD and coronary artery disease in the general population: rationale and design of the ImaLife (Imaging in Lifelines) Study

Congying Xia[1] · Mieneke Rook[1,2] · Gert Jan Pelgrim[1] · Grigory Sidorenkov[3] · Hendrik J. Wisselink[1] · Jurjen N. van Bolhuis[4] · Peter M. A. van Ooijen[5] · Jiapan Guo[5] · Matthijs Oudkerk[6,7] · Harry Groen[8] · Maarten van den Berge[8] · Pim van der Harst[9] · Hildebrand Dijkstra[1] · Marleen Vonder[3] · Marjolein A. Heuvelmans[3] · Monique D. Dorrius[1] · Peter Paul De Deyn[10] · Geertruida H. de Bock[3] · Aafje Dotinga[4] · Rozemarijn Vliegenthart[1]

CONTENT

1. Early Detection of Undiagnosed COPD
    1) Undiagnosed COPD
    2) Active case finding
2. Diagnostic methods of early disease
    1) PFT

with risk
ıt of COPD



s (Miami). 2016; 3(3): 653-667

SCIENTIFIC REPORTS

OPEN

New Spirometry Indices for Detecting Mild Airflow Obstruction

Surya P. Bhatt[1,2], Nirav R. Bhakta[3], Carla G. Wilson[4], Christopher B. Cooper[5], Igor Barjaktarevic[5], Sandeep Bodduluri[1,2], Young-il Kim[1,6], Michael Eberlein[7], Prescott G. Woodruff[3], Frank C. Sciurba[8], Peter J. Castaldi[9], MeiLan K. Han[10], Mark T. Dransfield[1,2] & Arie Nakhmani[11]

ved: 28 August 2018
ted: 13 November 2018

COPDGene

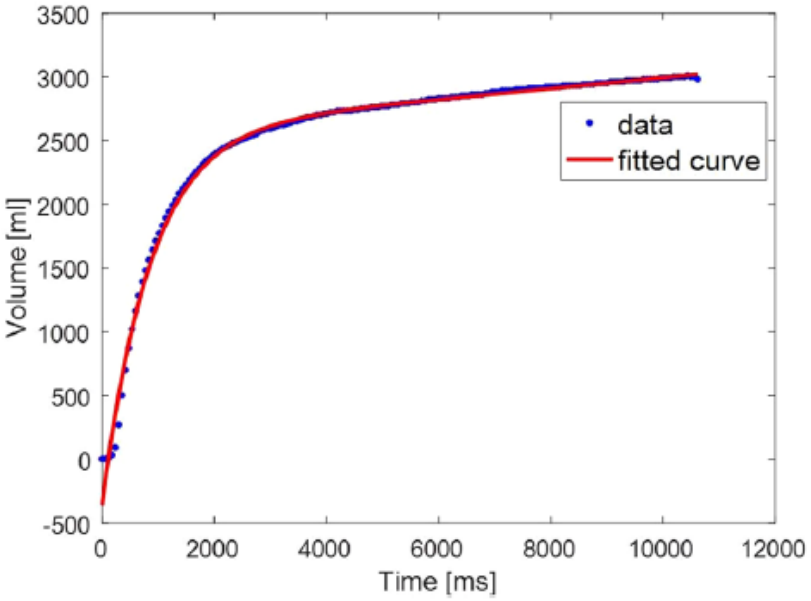


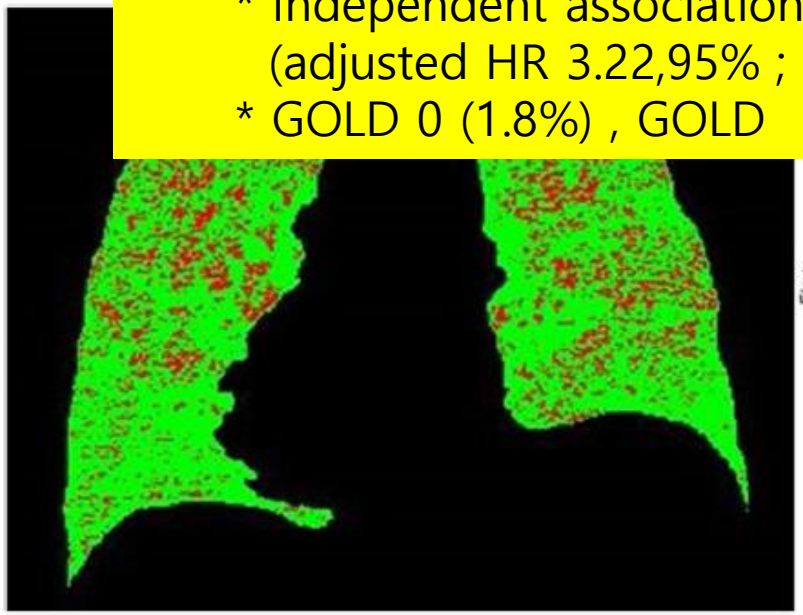
Figure 1. Model fitting of the Volume-time curve.

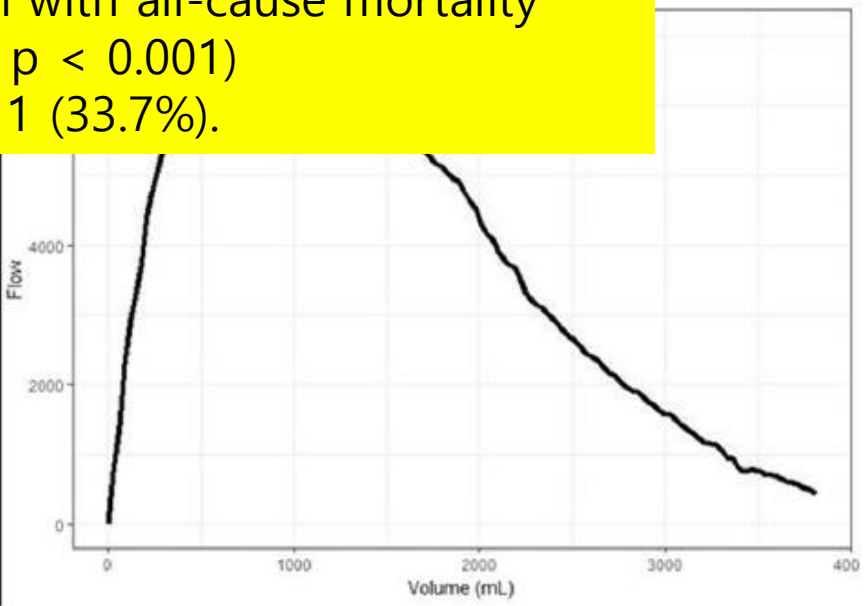
Parameter D ;
Rate of volume increase in V-T curve

Scientific Reports 2018;8:17484

54 yo M
34PY smoking
mMRC 3
SGRQ 48
FEV_1/FVC 0.72, FEV_1 100.1%

- Highest quartile of Parameter D ;
  * Independent association with all-cause mortality (adjusted HR 3.22,95% ; p < 0.001)
  * GOLD 0 (1.8%) , GOLD 1 (33.7%).



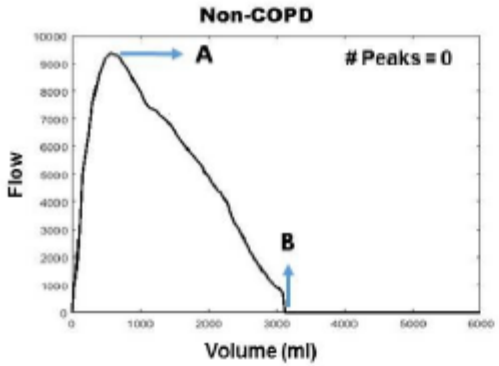


0.5% emphysema & 25% fSAD (red)

Parameter D ;−0.08 (Abnormal)

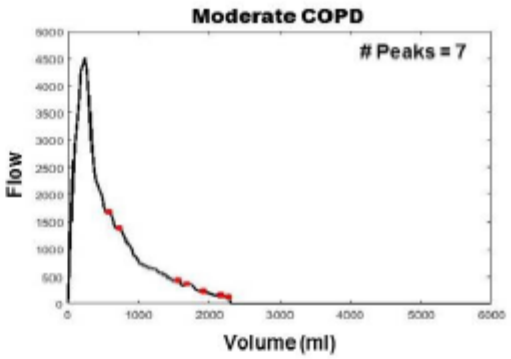
The Peak Index: Spirometry Metric for Airflow Obstruction Severity and Heterogeneity

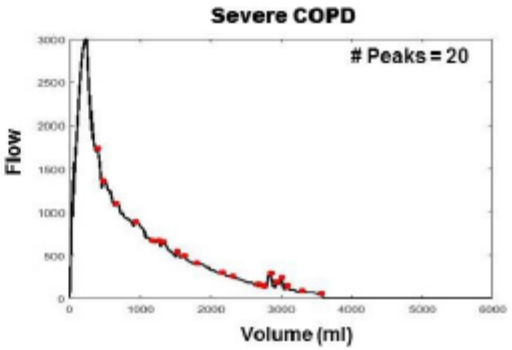
Surya P. Bhatt, M.D.,[1,2*] Sandeep Bodduluri, Ph.D.,[1,2] Vrishank Raghav, Ph.D,[3] Nirav R. Bhakta, M.D.,[4] Carla G. Wilson, M.S.,[5] Young-il Kim, Ph.D.,[1,6] Michael Eberlein, M.D., Ph.D.,[7] Frank C. Sciurba, M.D.,[8] MeiLan K. Han, M.D.,[10] Mark T. Dransfield, M.D.,[1,2] Arie Nakhmani, Ph.D.,[11] for the COPDGene Investigators

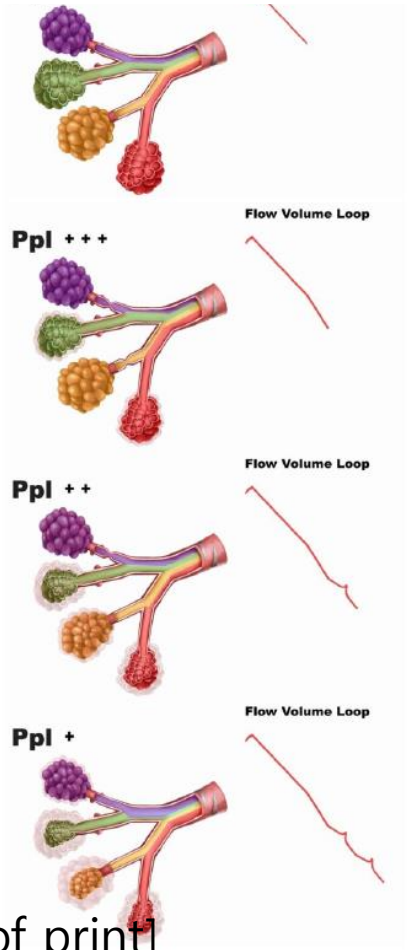


A = Peak Expiratory Volume (PEV)
B = Residual Volume (RV)

$$\text{Peak Index} = \frac{\#\ \text{Peaks}}{\text{B (volume)} - \text{A (volume)}}$$

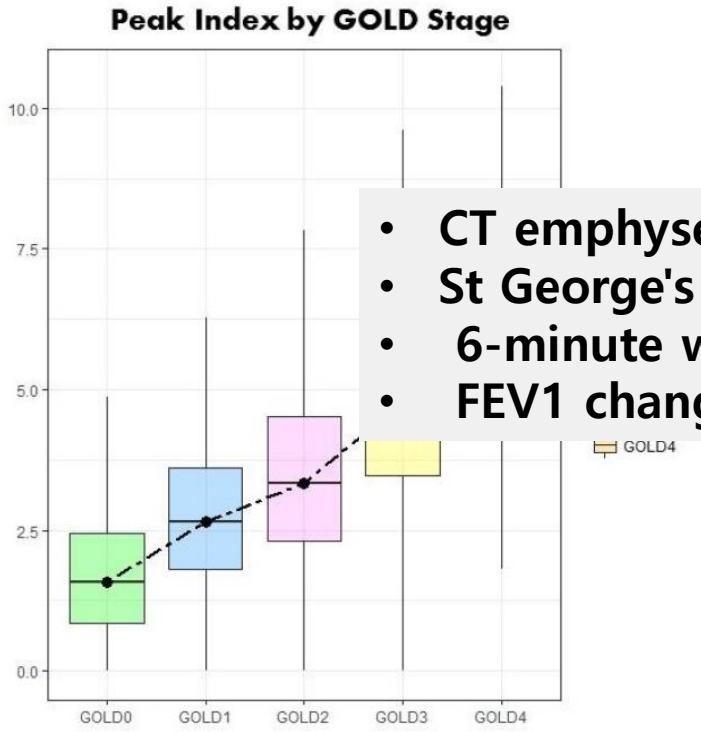


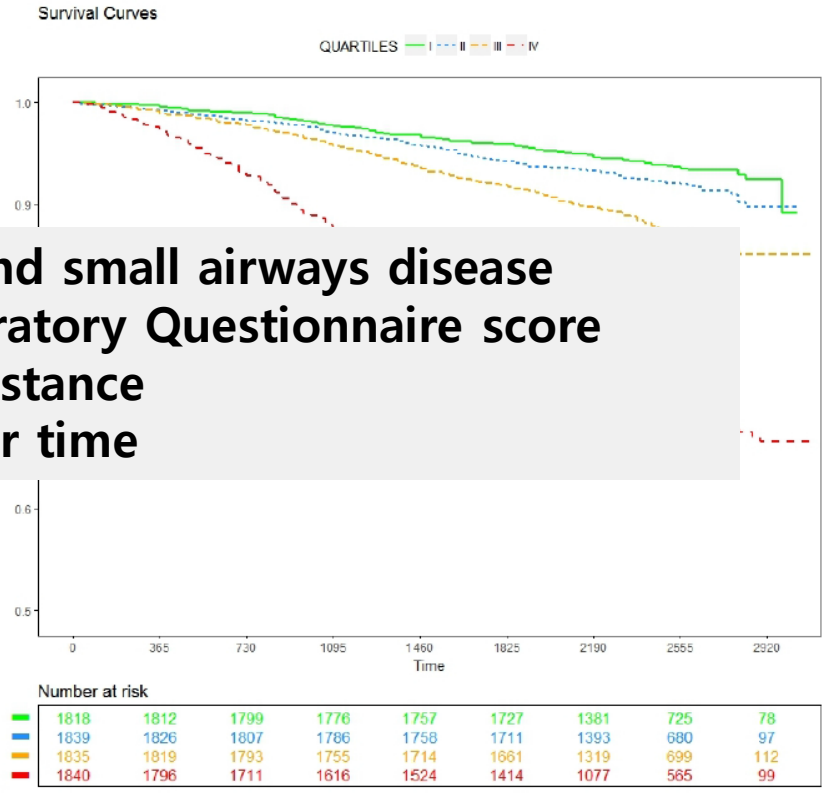




Ann Am Thorac Soc. 2019 [Epub ahead of print]

Peak Index as Diagnostic and Prognostic Measure





- CT emphysema and small airways disease
- St George's Respiratory Questionnaire score
- 6-minute walk distance
- FEV1 change over time

Ann Am Thorac Soc. 2019 [Epub ahead of print]

Risk for COPD with Obstruction of Active Smokers with Normal Spirometry and Reduced Diffusion Capacity

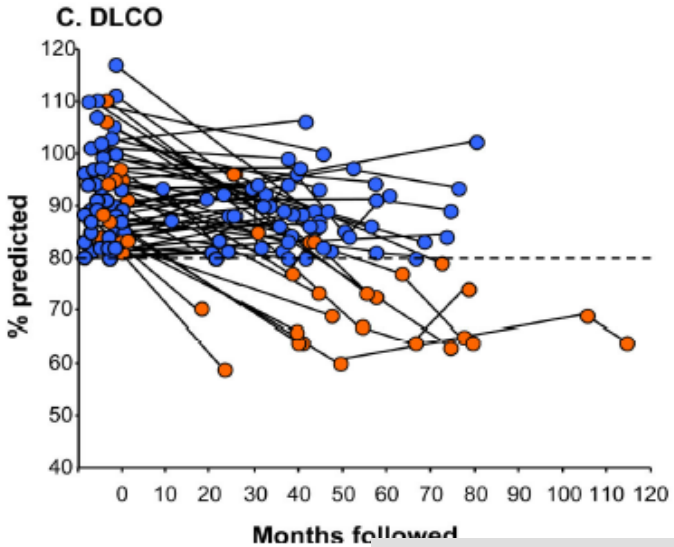
Ben-Gary Harvey[#1,2], **Yael Strulovici-Barel**[#1], **Robert J. Kaner**[1,2], **Abraham Sanders**[2], **Thomas L. Vincent**[1], **Jason G. Mezey**[1,3], and **Ronald G. Crystal**[1,2]

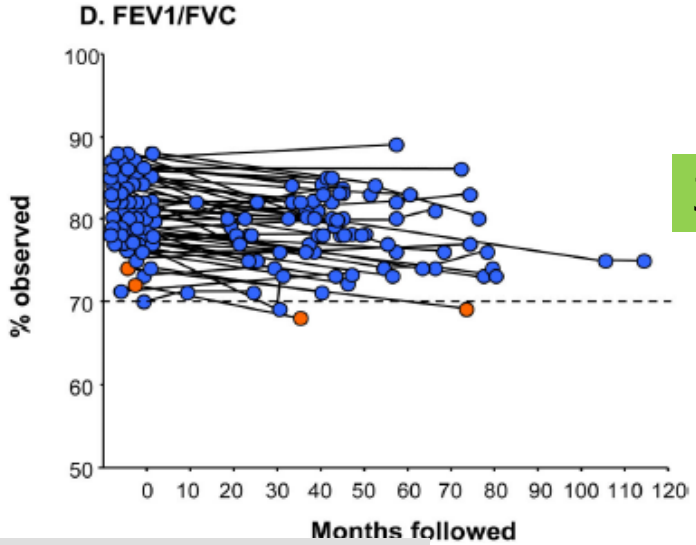
- From a cohort of 1570 smokers in the New York City
- Normal spirometry (normal FEV1, FVC, FEV1/FVC, TLC)
- 25.3% (397); Normal spirometry and Low Dlco
  No difference in Respiratory symptom and emphysema in CT compared to Normal DLco group
- 13 yr F/U

Eur Respir J. 2015 ; 46(6): 1589–1597

Lung Function Overtime

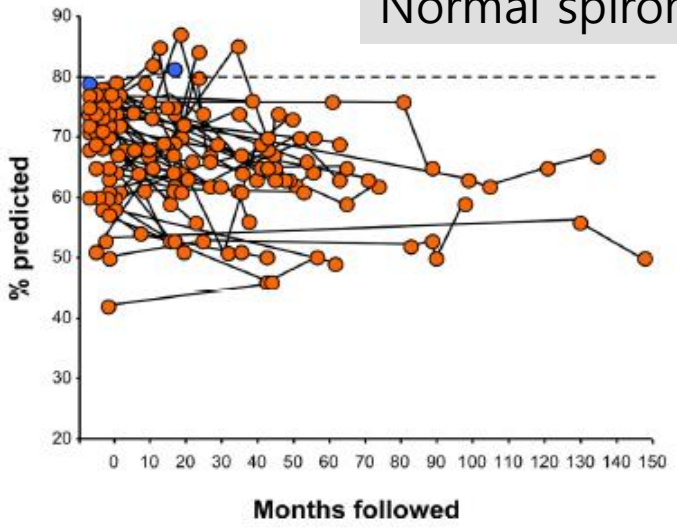
Normal spirometry/Normal DLco

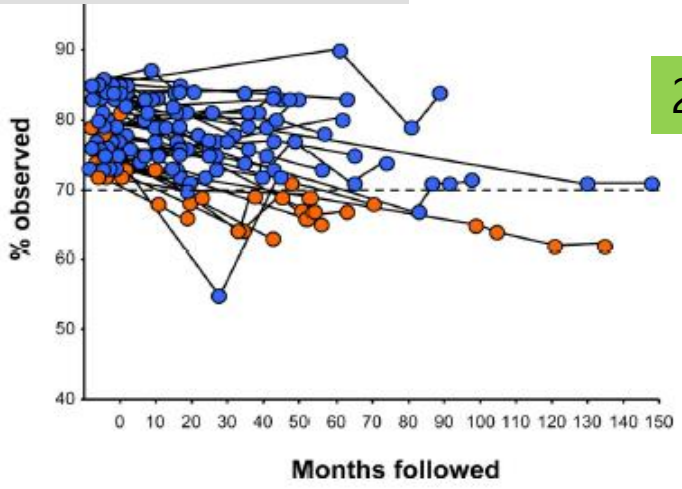




3%

Normal spirometry/Low DLco





22%

Forced Oscillation Technique / Impulse Oscillometry System

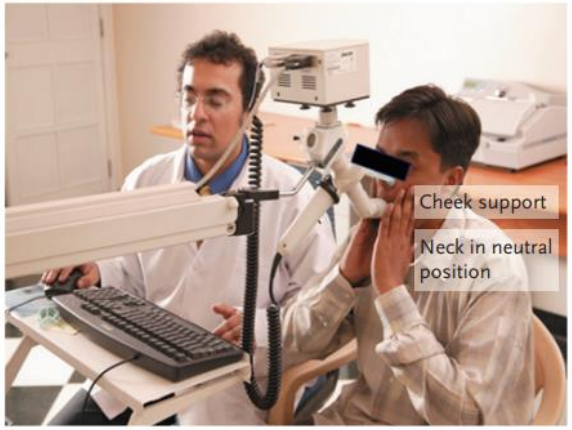


Figure 4
Position of the patient while performing IOS. Note how the cheeks are held firmly.

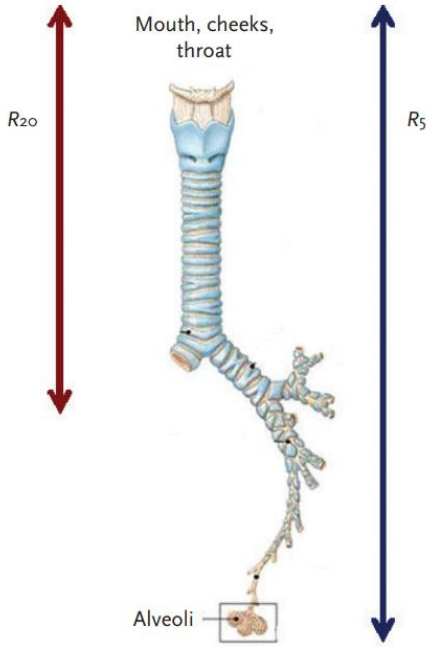
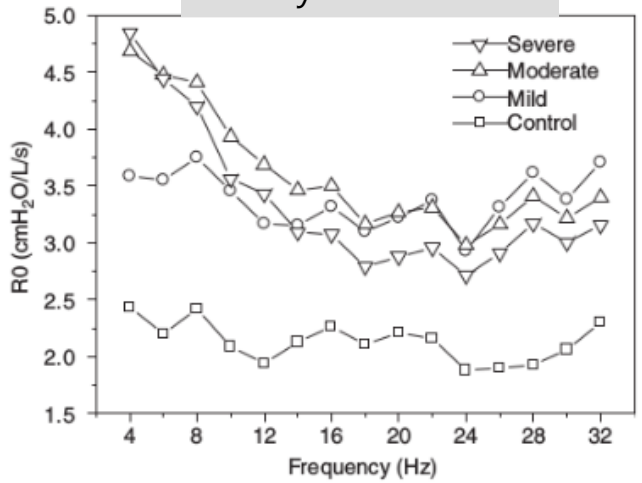
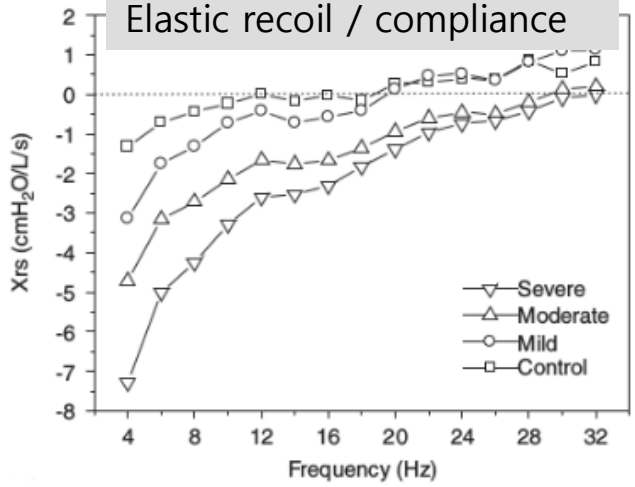


Figure 1
Type of sound waves in FOT and IOS and distances travelled by sound waves of different frequencies.

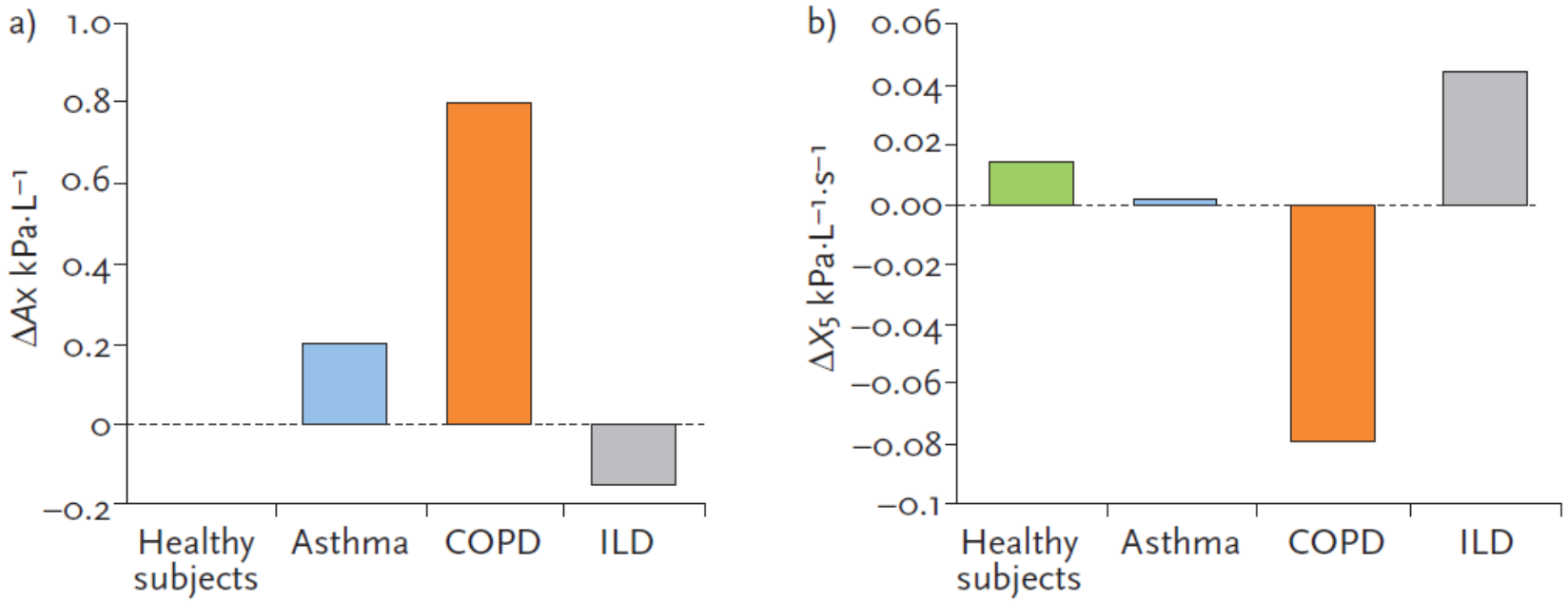
Airway resistance



Elastic recoil / compliance



Forced Oscillation Technique / Impulse Oscillometry System



CONTENT

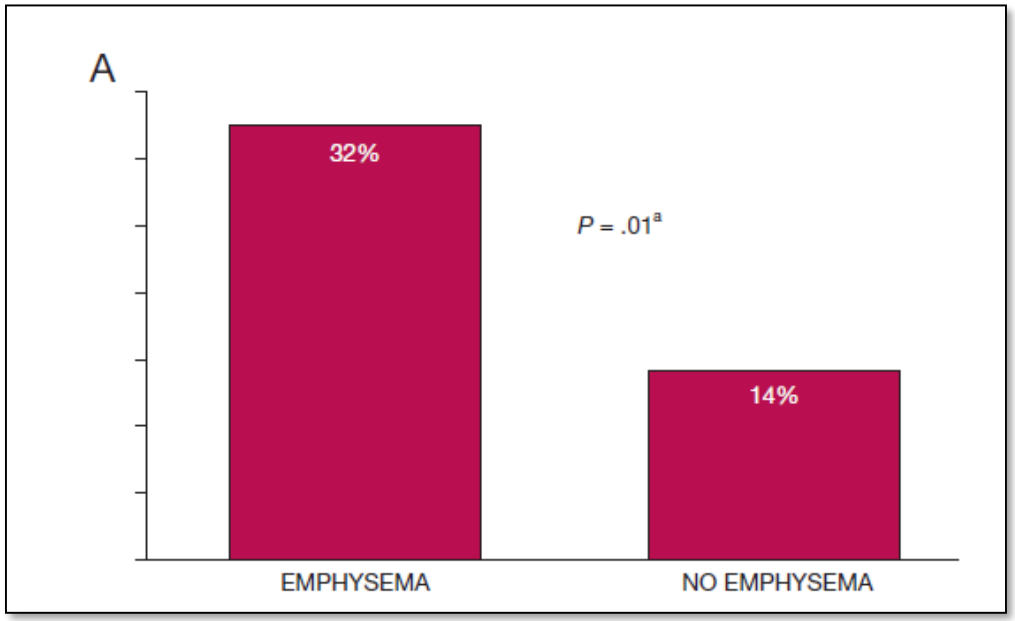
1. Early Detection of Undiagnosed COPD
   1) Undiagnosed COPD
   2) Active case finding
2. Diagnostic methods of early disease
   1) PFT
   2) Chest CT

CHEST

Clinical Features of Smokers With Radiological Emphysema But Without Airway Limitation

Ana B. Alcaide, MD; Pablo Sanchez-Salcedo, MD; Gorka Bastarrika, MD; Arantza Campo, MD; Juan Berto, MD; Maria del Mar Ocon, RN; Alejandro Fernandez-Montero, MD, PhD; Bartolome R. Celli, MD; Javier J. Zulueta, MD; and Juan P. de-Torres, MD

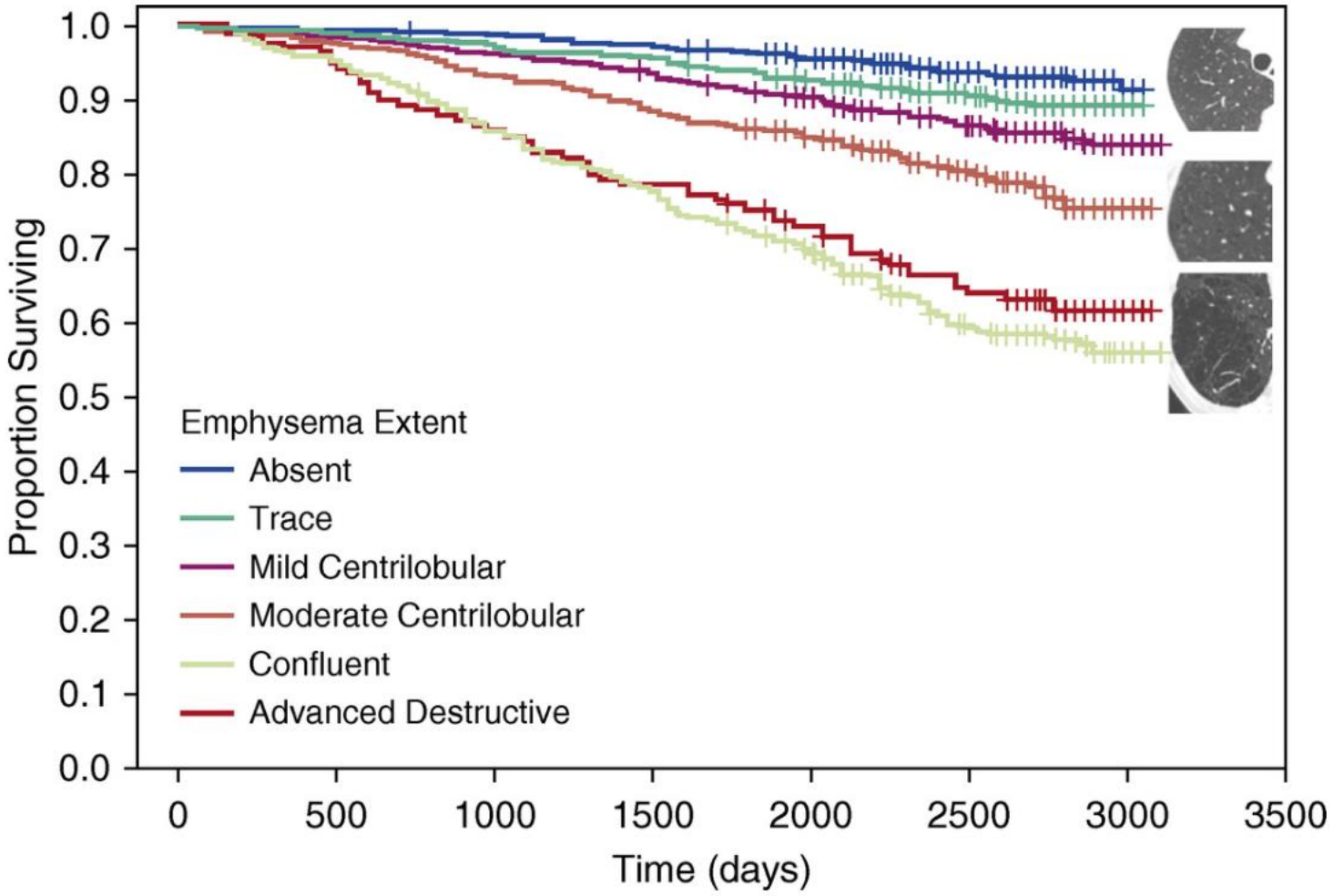
◆ Percentage of patients with CAT scores > 10



- Lower DLCO
- More exacerbations
- Significant drop in SpO2% during the 6MWT

CHEST 2017; 151(2):358-365

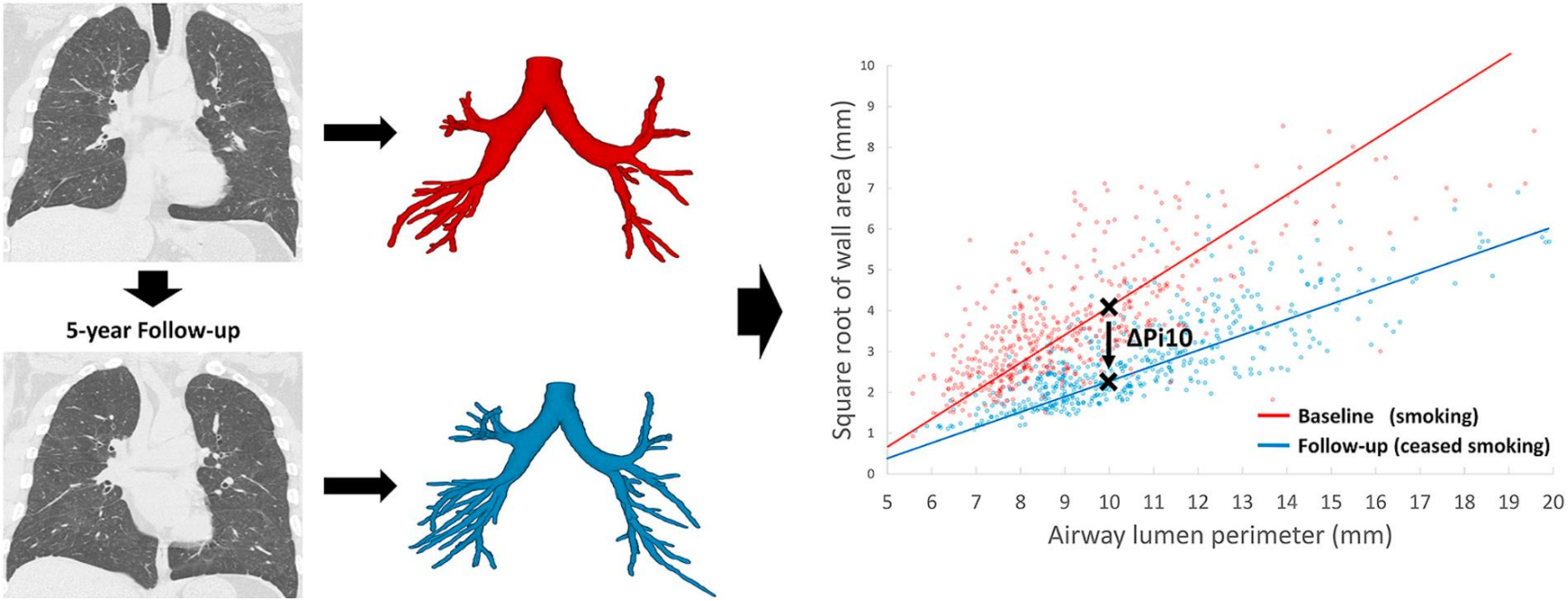
CT-based visual classification of emphysema (COPDGene)



Lynch et al. Radiology 2018;288:859–866

Airway wall thickening on CT: Relation to smoking status and severity of COPD

Jean-Paul Charbonnier[a,b,*], Esther Pompe[c], Camille Moore[d], Stephen Humphries[e], Bram van Ginneken[b], Barry Make[f], Elizabeth Regan[f], James D. Crapo[f], Eva M. van Rikxoort[a,b], David A. Lynch[e], COPDGene investigators

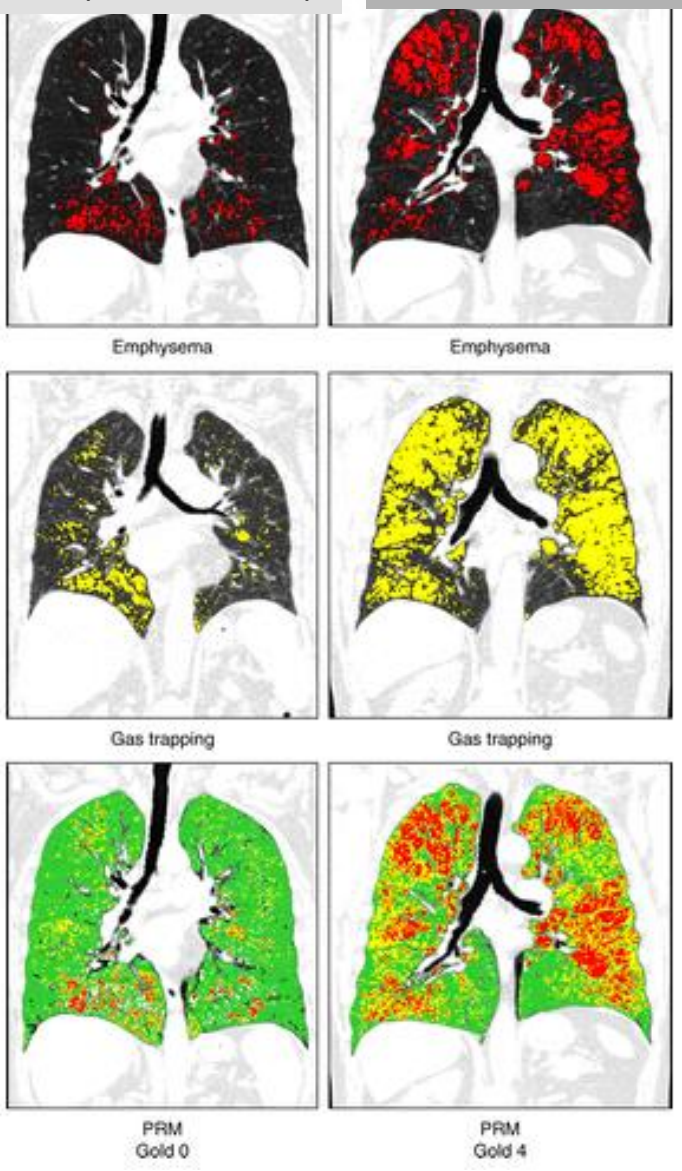


Pi10 ; clinically relevant biomarker of smoking-related airway injury in smokers with and without COPD

Respiratory Medicine 146 (2019) 36–41

Parametric Response Mapping

GOLD 0 (FEV1 100%) – GOLD 4 (FEV1 23%)



Emphysema (Red)
Gas trapping (yellow)
Normal (Green)

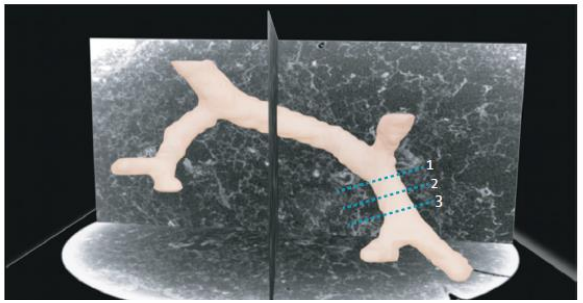
Gold 0에서 이미 Functional small airway dis가 있고 질환이 진행될수록 emphysema portion이 증가

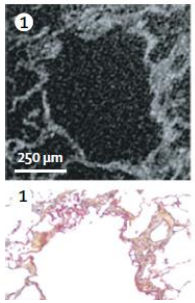
Gold 0 에서 fSAD만이 FEV1 DECLINE과 연관이 있었음

Bhatt SP, et al. Am J Respir Crit Care Med 2016;194:178–184.

Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study

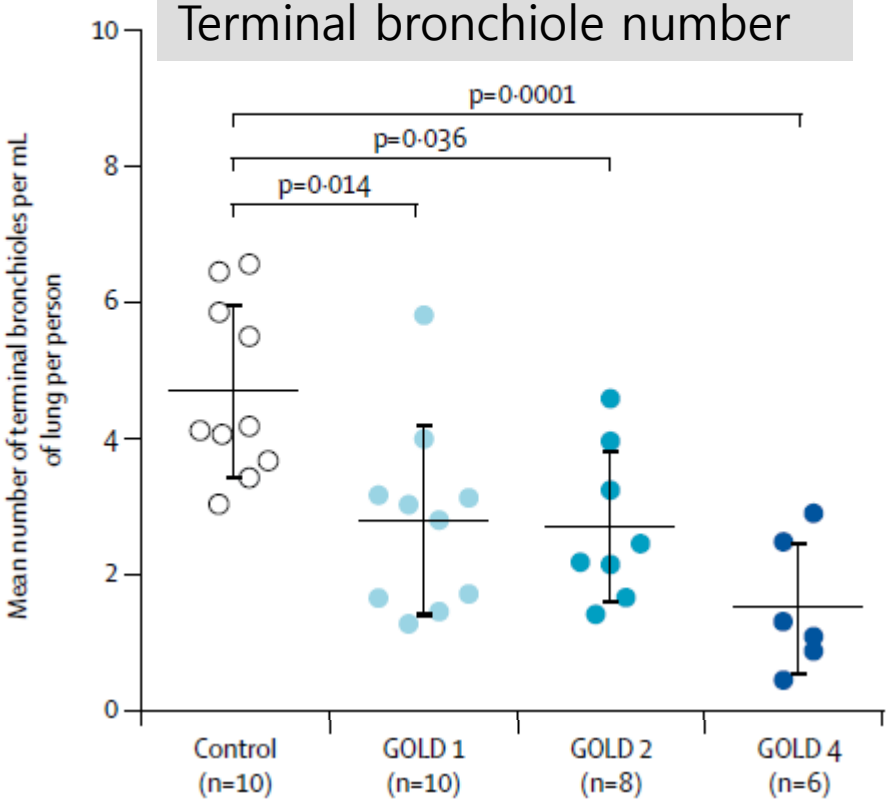
Hyun-Kyoung Koo, Dragoş M Vasilescu*, Steven Booth*, Aileen Hsieh, Orestis L Katsam*
Peter Lackie, Ian Sinclair, Jane A Warner, Joel D Cooper, Harvey O Coxson, Peter D Paré, Jan





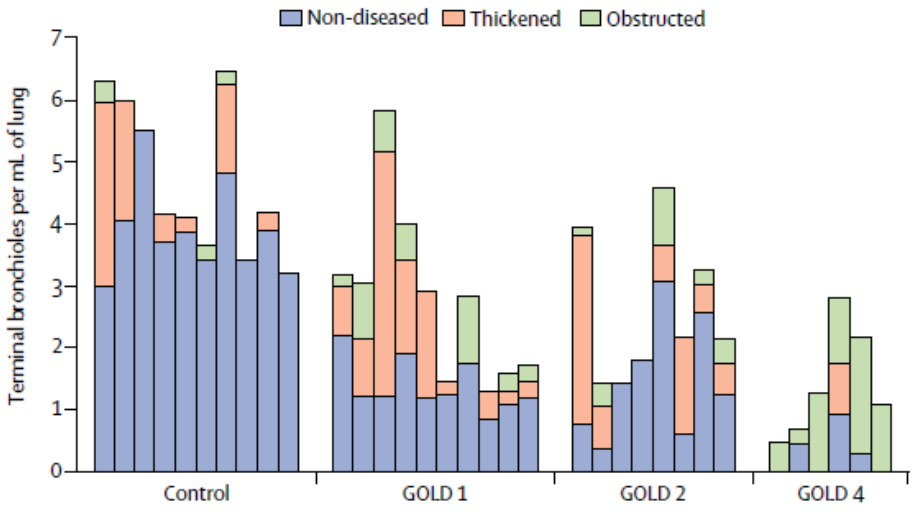
A

Terminal bronchiole number



B

Diseased Bronchiole

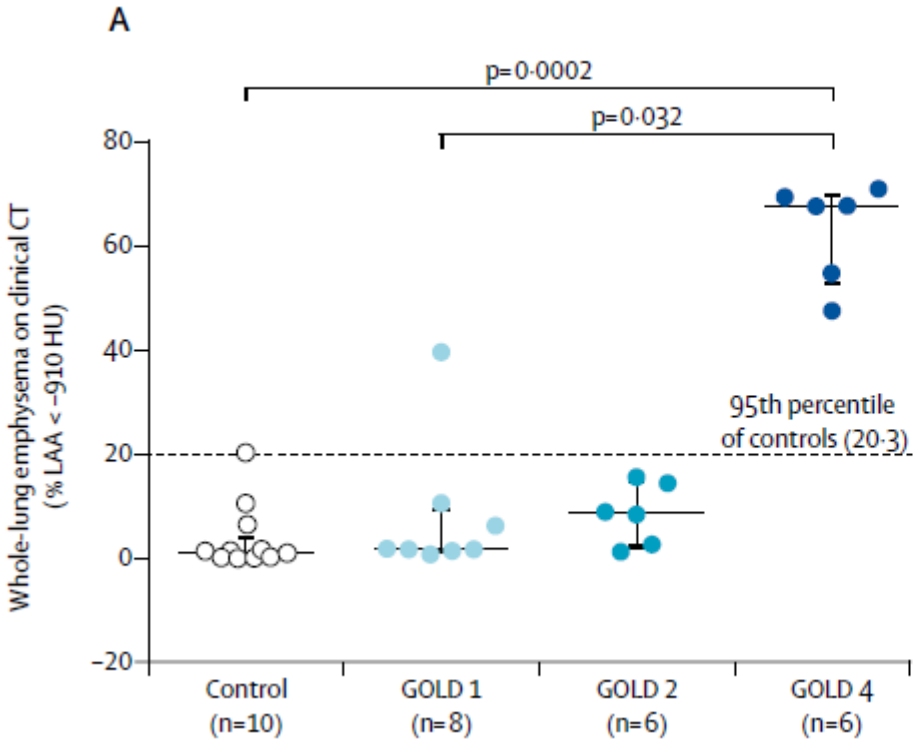


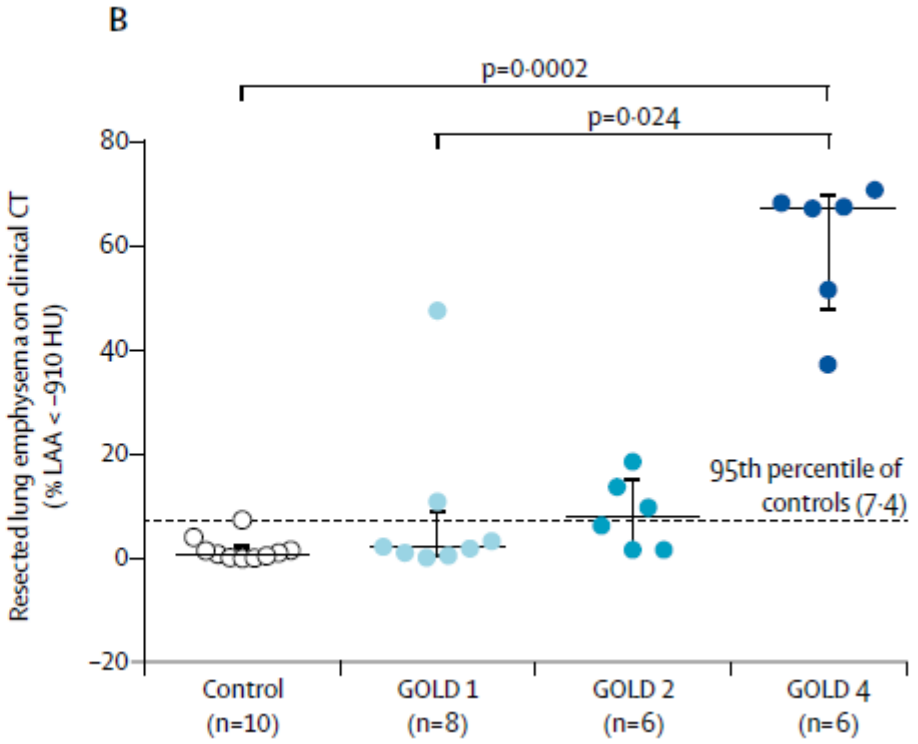
Lancet Respir Med 2018;6: 591–602

Small airways disease in mild and moderate chronic obstructive pulmonary disease: a cross-sectional study

Hyun-Kyoung Koo, Dragoş M Vasilescu*, Steven Booth*, Aileen Hsieh, Orestis L Katsamenis, Nick Fishbane, W Mark Elliott, Miranda Kirby, Peter Lackie, Ian Sinclair, Jane A Warner, Joel D Cooper, Harvey O Coxson, Peter D Paré, James C Hogg, Tillie-Louise Hackett*

Emphysema quantification





Lancet Respir Med 2018;6: 591–602

CONTENT

1. Early Detection of Undiagnosed COPD
    1) Undiagnosed COPD
    2) Active case finding
2. Diagnostic methods of early disease
    1) PFT
    2) Chest CT
    3) Blood

[Original Research]

CHEST

Systemic Markers of Inflammation in Smokers With Symptoms Despite Preserved Spirometry in SPIROMICS

Suresh Garudadri, BS; Prescott G. Woodruff, MD, MPH; MeiLan K. Han, MD; Jeffrey L. Curtis, MD; R. Graham Barr, MD, DrPH; Eugene R. Bleecker, MD; Russell P. Bowler, MD, PhD; Alejandro Comellas, MD; Christopher B. Cooper, MD; Gerard Criner, MD; Mark T. Dransfield, MD; Nadia N. Hansel, MD, MPH; Robert Paine III, MD; Jerry A. Krishnan, MD, PhD; Stephen P. Peters, MD, PhD; Annette T. Hastie, PhD; Fernando J. Martinez, MD; Wanda K. O'Neal, PhD; David J. Couper, PhD; Neil E. Alexis, PhD; and Stephanie A. Christenson, MD

Symptomatic smokers with preserved lung function
= Asthmatic (Type 2 inflammation) ?

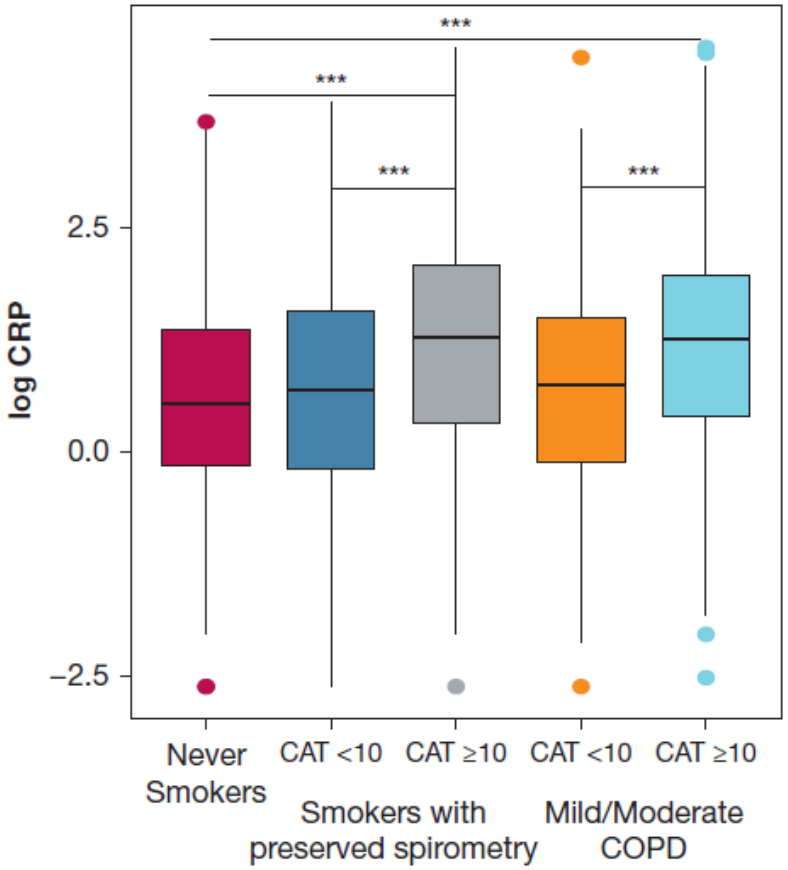
Chest. 2019 Jan 23. [Epub ahead of print]

Inflammatory Marker	
	No.
CRP	429
Fibrinogen	429
sTNFRSF1A	429
sTNFRSF1B	429
Blood neutrophils	815
Sputum neutrophils	375
IgE	799
Blood eosinophils	815
Sputum eosinophils	375

CAT>10, Chronic Bronchitis 와 유의함

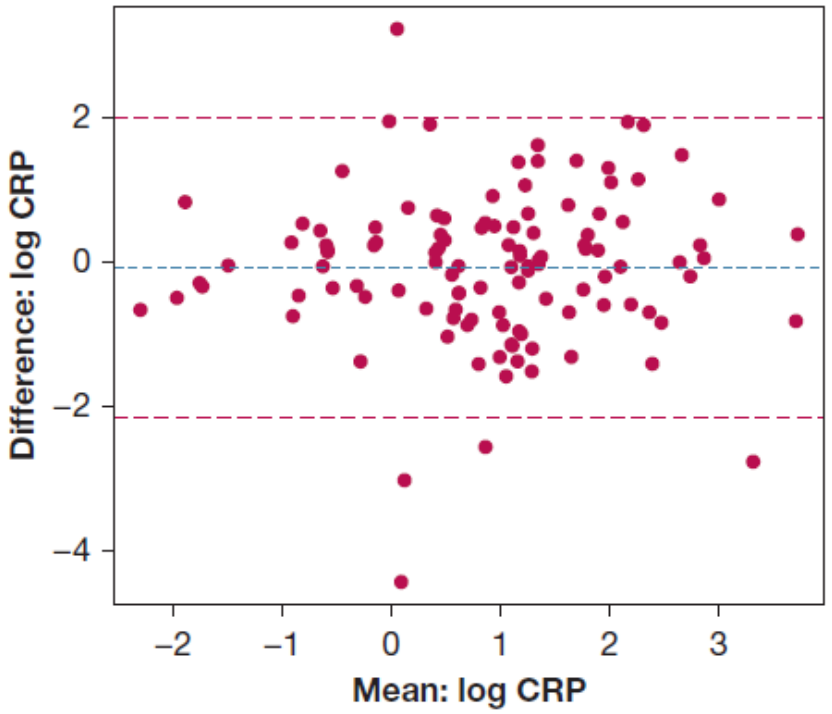
Exacerbation 과 유의함

CRP levels according to patients characteristics



B

Stability of CRP during 1 yr F/U



Summary

1. Early Detection of Undiagnosed COPD
   1) Undiagnosed COPD
      - 진단되지 않은 환자의 Burden
      - screening
   2) Active case finding
      - GP 역할
      - 설문조사 / COPD-6 or PEF /CAPTURE
      - 술전검사, 건강검진, 폐암 검진
2. Diagnostic methods of early disease
   1) PFT
      - Serial check / New spirometric indexs / Forced oscillatory method
   2) Chest CT
      - Emphysema / Fsad, Pi10, PRM
   3) Blood