Comorbidities of bronchiectasis : from mental disorder to upper and lower airway involvement

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Contents

Impact of comorbidities

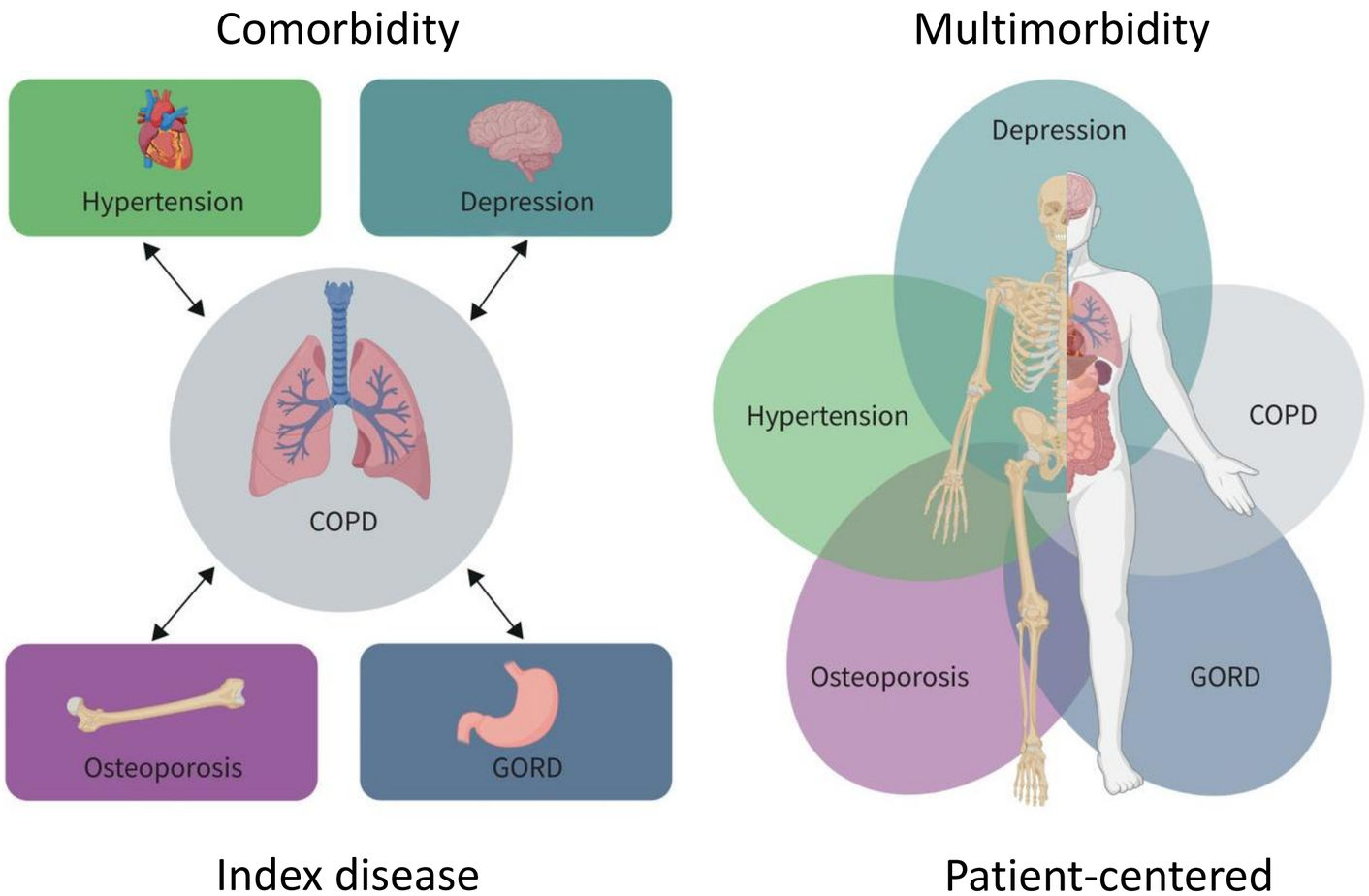
- Bronchiectasis is the third most common chronic airway disease after asthma and COPD.

- Different comorbidities can significantly impact on pulmonary and extrapulmonary manifestations of bronchiectasis, disease severity, prognosis and therapeutic management.

- Despite the high prevalence and relevance of comorbidities in bronchiectasis, their specific impact on clinical outcomes and natural history of the disease is still indeterminate.

- Current guidelines barely include recommendations about their management since the scientific evidence is still scarce.

Definition of comorbidities



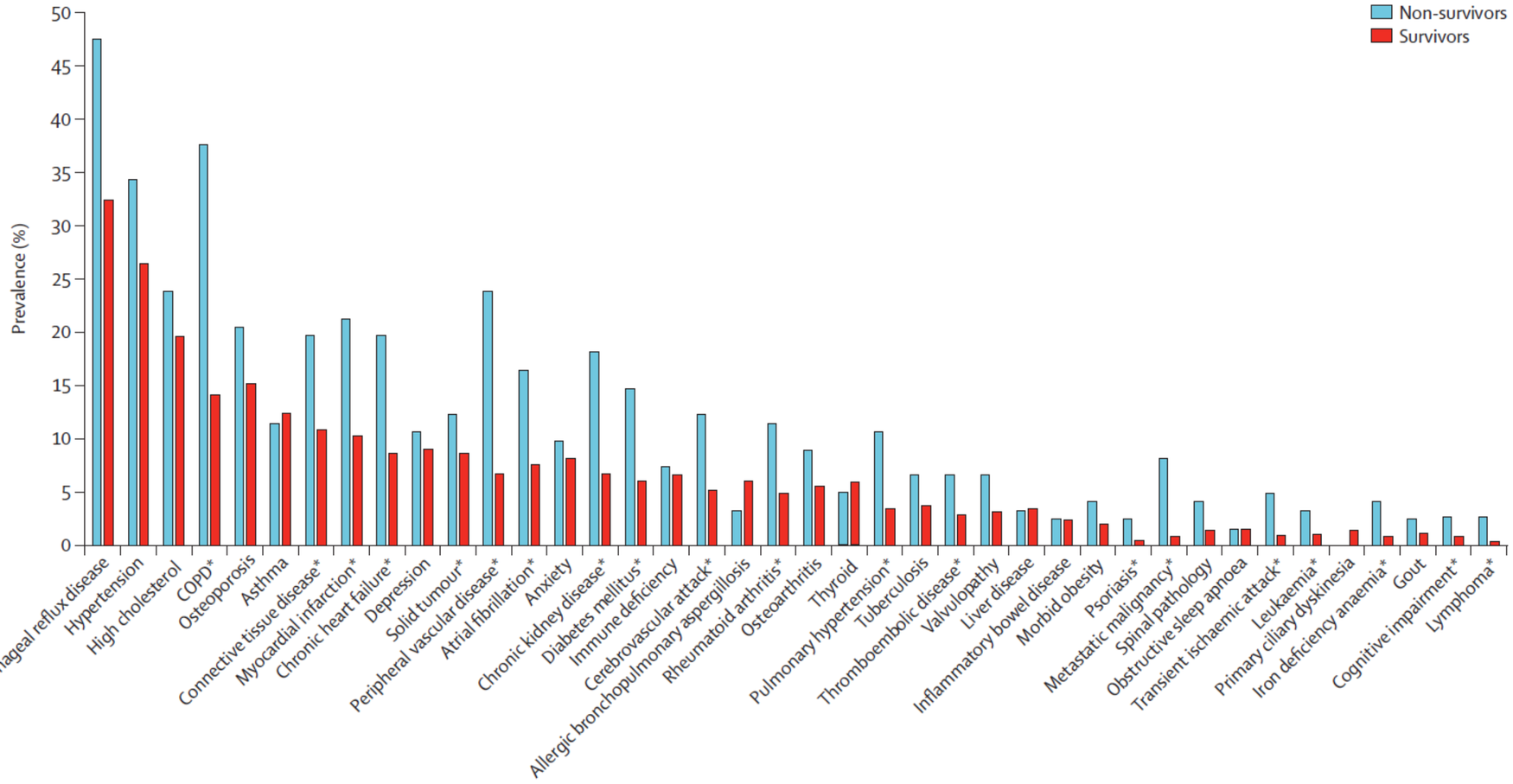
Eur Respir Rev. 2021;30:210041.

Prognostic scores of bronchiectasis

Bronchiectasis Severity Index	FACED	E-FACED
Age	FEV1%	Exacerbation (≥ 2 exacerbation)
BMI	Age	FEV1%
FEV1%	Colonization by pseudomonas	Age
Previous hospital admission	Extension (number of lobes)	Colonization by pseudomonas
Number of exacerbation in previous year	Dyspnea (mMRC)	Extension (number of lobes)
MRC breathlessness score		Dyspnea (mMRC)
Pseudomonas colonization		
Colonization with other oraganisms		
Radiological severity		

Impact of comorbidities

- Bronchiectasis Aetiology Comorbidity Index (**BACI**)
- Dundee (UK), Galway (Ireland), Leuven (Belgium), and Monza (Italy), followed up for 5 years (n = 986)

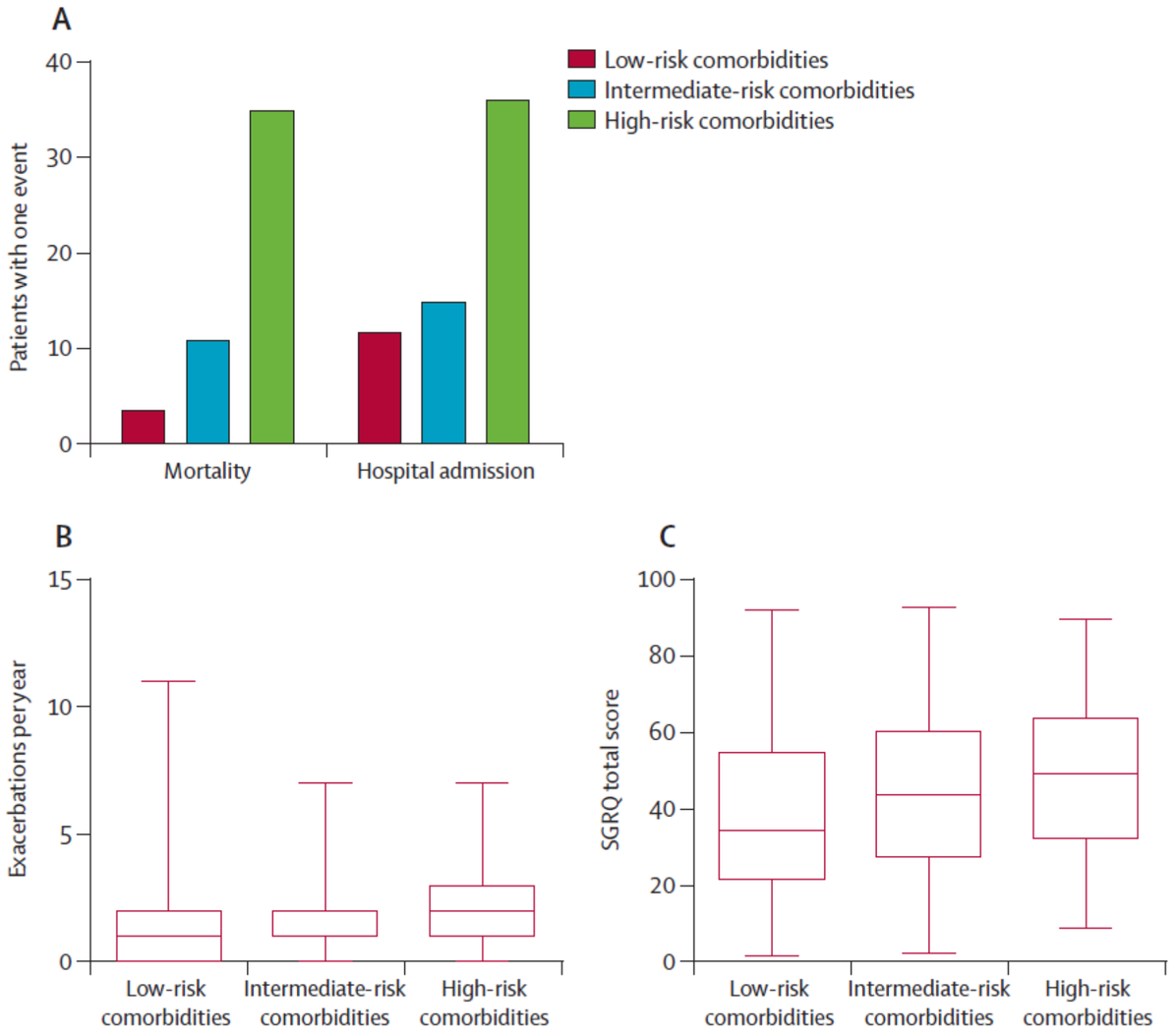


Lancet Respir Med 2016;4:969-979.

Impact of comorbidities

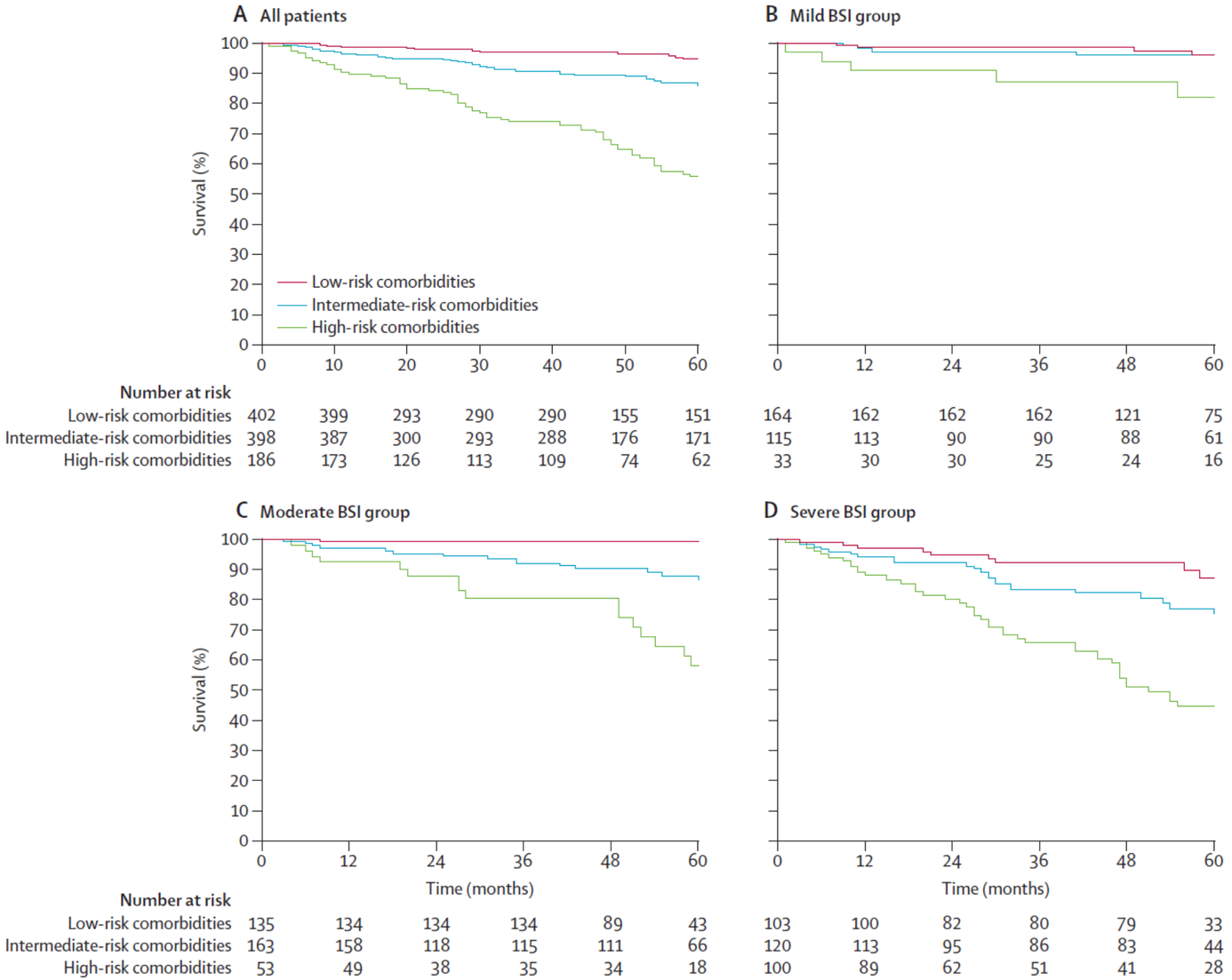
- Bronchiectasis Aetiology Comorbidity Index (**BACI**)

Comorbidity	Points
Metastatic malignancy	12
Hematological malignancy	6
COPD	5
Cognitive impairment	5
Inflammatory bowel disease	4
Liver disease	4
Connective tissue disease	3
Iron deficiency anemia	3
Diabetes	3
Asthma	3
Pulmonary hypertension	3
Peripheral vascular disease	2
Ischemic heart disease	2



Lancet Respir Med 2016;4:969-979.

Impact of comorbidities



- A prediction <u>model incorporating both the BSI and the BACI</u> was superior to either model alone for the prediction of 5 year mortality rate;
  AUC 0.83 (95% CI 0.79–0.87; p=0.01 for combined *vs* BACI, p=0.008 for combined *vs* BSI).

Lancet Respir Med 2016;4:969-979.

Pathogenic mechanism of comorbidities

Systemic inflammation

Rheumatoid arthritis

Inflammatory bowel disease

Immunodeficiencies

Airway inflammation

Asthma/COPD

ABPA

GERD

Shared risk factor

Cardiovascular disease

Osteoporosis

Cancer

Diabetes mellitus

United airway disease

Chronic rhinosinusitis

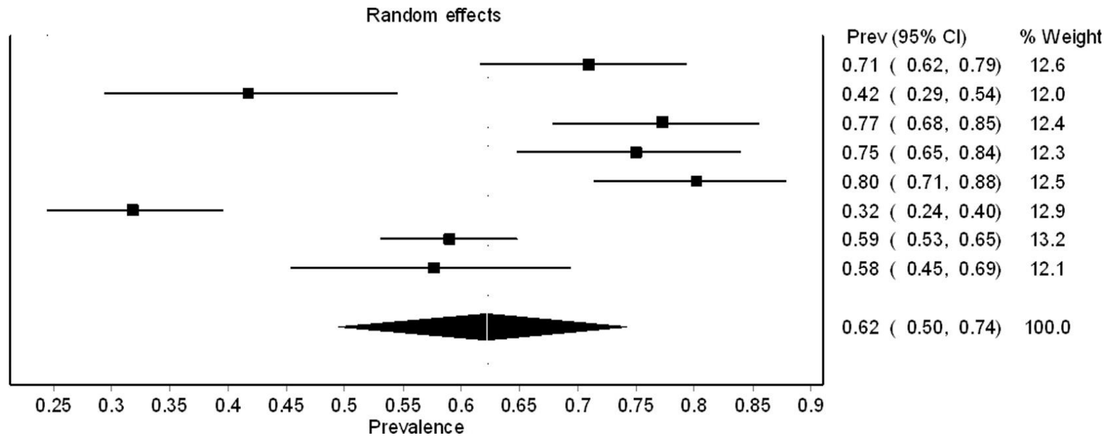
Expert Rev Respir Med 2021;15:623-634.

Chronic rhinosinusitis

- Prevalence of chronic rhinosinusitis (CRS) in bronchiectasis : 62%

TABLE III. Characteristics of included studies

Authors, year	Study design	No. of participants	Age (y), mean ± SD	Sex (% female)	FEV_1 % predicted, mean ± SD	Clinical outcomes
Guilemany et al,[17] 2006	Cohort	60	52 ± 16	65	81.0 ± 3.4	SF-36
King et al,[2] 2006	Cross-sectional	103	56 ± 14	63	76.0 ± 26.0	NR
Guilemany et al,[18] 2009	Cohort	88	55 ± 2	69	83.0 ± 3.0	CRP, lung function (spirometry), bronchiectasis severity (HRCT scoring, 0-3; 0, no involvement; 1, single segment; 2, more than 1 segment; 3, gross cystic bronchiectasis of entire lobe)
Guilemany et al,[19] 2009	Cohort	80	57 ± 2	71	80.8 ± 2.8	Bronchiectasis severity (HRCT scoring, 0-3; 0, no involvement; 1, single segment; 2, more than 1 segment; 3, gross cystic bronchiectasis of entire lobe), SNOT-20, SF-36, SGRQ
Guilemany et al,[20] 2011	Cohort	91	54 ± 3	68	82.5 ± 3	BAST-24 Olfactometry (smell characteristics of detection, identification, and forced choice)
Guan et al,[21] 2015	Cohort	148	CRS group: 44 ± 15 No CRS group: 45 ± 13	63	CRS group: 68.2 ± 24.8 No CRS group: 74.8 ± 21.2	No exacerbations, lung function (spirometry), health care utilization, HRCT scores, HADS, PA colonization, BSI
Wang and Yang,[22] 2016	Cohort	161	Total: NR Rhinosinusitis group: 55 ± 9	50	73.0 (NR)	NR
Yang et al,[23] 2017	Cohort	66*	71 ± 11*	16*	57.0 ± 18.1*	Smith score for extent of bronchiectasis, Bhalla scoring for severity of bronchiectasis, inflammatory markers



J Allergy Clin Immunol Pract 2019;7:2004-2012.

Prevalence and implication of CRS

- High prevalence of CRS: 62%

a. Small sample size (single center cohort)

b. Selection bias

c. Symptom based diagnosis of CRS (over diagnosis)

d. Heterogenous etiology

- Implication of CRS

a. Greater bronchiectasis severity (BSI)

b. Poorer HRQOL (SGRQ)

c. Elevated levels of inflammatory markers (C-reactive protein, peripheral eosinophil count)

d. Reduced time to first exacerbation

e. Airflow obstruction was inconsistent and there was no impact on anxiety or depression.

J Allergy Clin Immunol Pract 2019;7:2004-2012.

Results of KMBARC (1)

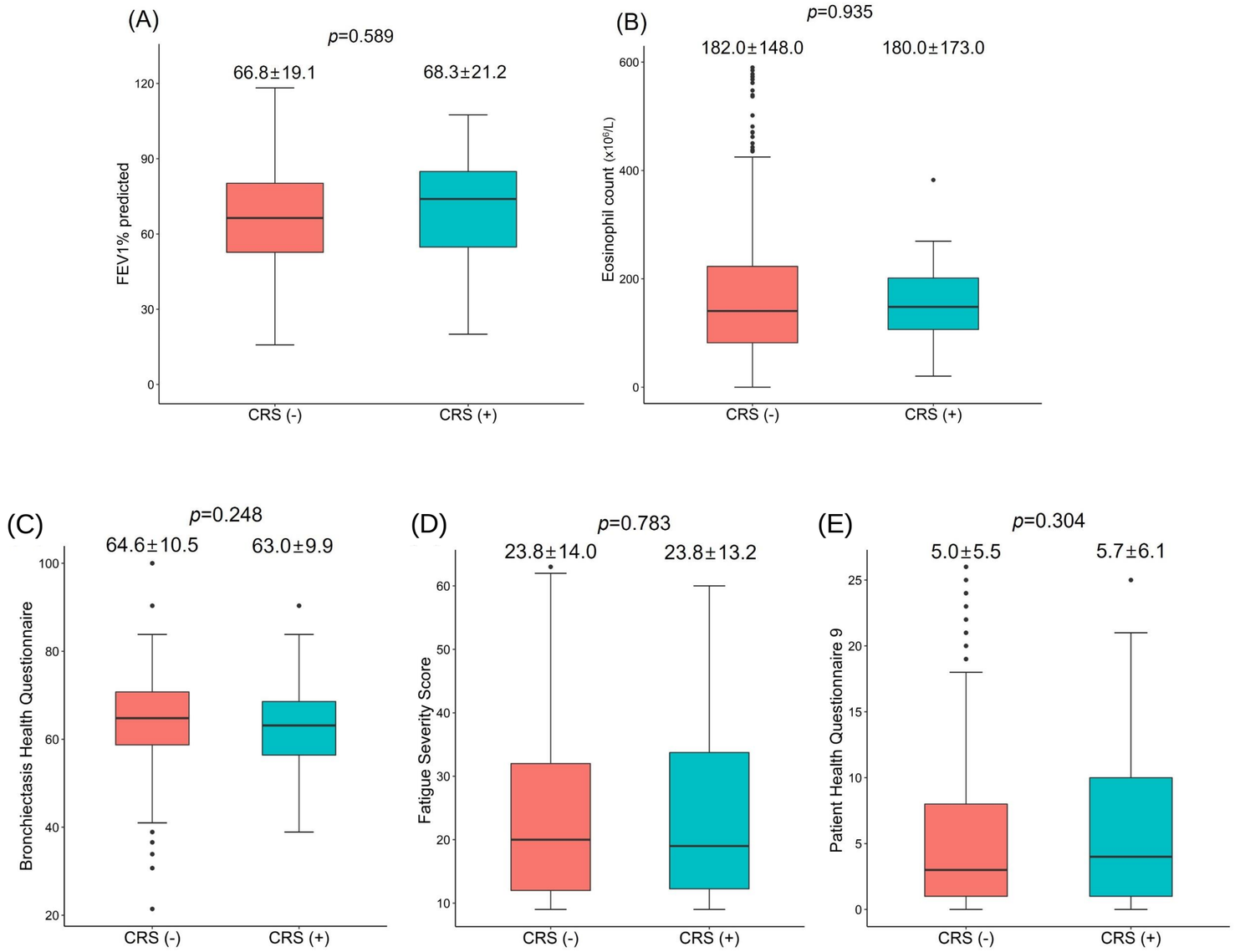
- Prevalence of CRS in KMBARC : 7.1% (66/931)

	CRS (-) (n = 865)	CRS (+) (n = 66)	p value
Age (years)	64.6 ± 9.3	60.5 ± 10.7	**0.001**
Female	486 (56.3)	36 (54.5)	0.788
Duration (years)	3.3 ± 1.6	2.9 ± 1.6	0.136
Ever smoker	295 (34.1)	21 (31.8)	0.701
Body mass index	22.9 ± 3.4	23.1 ± 3.9	0.636
Asthma	173 (20.0)	15 (22.7)	0.283
COPD	295 (34.1)	25 (37.9)	0.387
Etiology			
Post-infectious	173 (20.0)	5 (7.6)	**0.013**
Idiopathic	311 (36.0)	35 (53.0)	**0.006**
Tuberculosis	178 (20.6)	9 (13.6)	0.175
PA colonization	59 (6.8)	7 (10.6)	0.248
Sputum volume (cc/day)	26.2 ± 44.1	48.2 ± 113.3	0.130

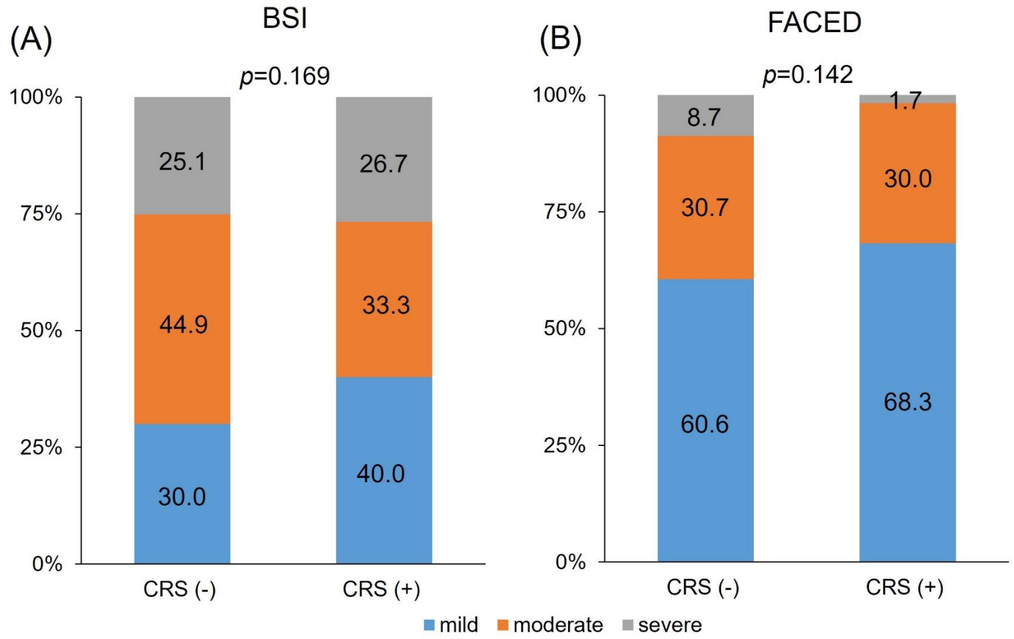
Values are presented as mean ± standard deviation or number (%).

Accepted in Korean J Intern Med.

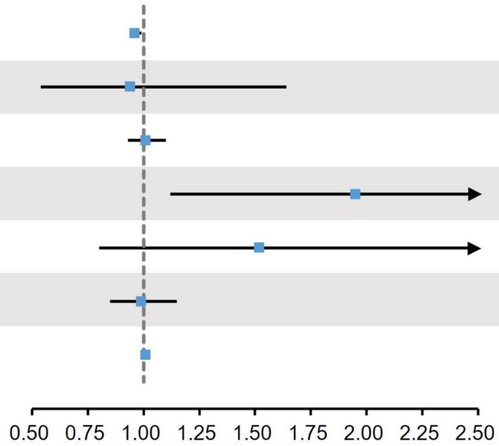
Results of KMBARC (2)



Results of KMBARC (3)



Variable	Odds ratio (95% CI)[a]	*p* value
Age of diagnosis	0.96 (0.94 – 0.99)	0.003
Sex (female)	0.94 (0.54 – 1.64)	0.816
Body mass index	1.01 (0.93 – 1.10)	0.811
Idiopathic bronchiectasis	1.95 (1.12 – 3.34)	0.018
Asthma	1.52 (0.80 – 2.89)	0.200
Exacerbation numbers	0.99 (0.85 – 1.15)	0.872
FEV1% predicted	1.01 (0.99 – 1.02)	0.208



[a] All variables presented in figure were adjusted.

Comparison with other registries

- Other international cohorts of bronchiectasis have rarely reported the prevalence of CRS.

TABLE 1 Patient characteristics

Patients	2596 (100%)
Demographics	
Age years	67 (57–74)
⩾65 years old	1395 (53.7%)
Male	1010 (38.9%)
BMI kg·m^{-2}	24.8 (21.8–28.1)
Smokers and ex-smokers	990 (38.1%)
Comorbidities	
Ischaemic heart disease	453 (17.5%)
Stroke	152 (5.9%)
Diabetes	260 (10.0%)
Liver disease	41 (1.6%)
Chronic renal failure	154 (5.9%)
COPD	431 (16.6%)
Asthma	226 (8.7%)
Connective tissue disease	210 (8.1%)
Neurological disease	68 (2.6%)
Osteoporosis	192 (7.4%)
GORD	394 (15.2%)
Haematological malignancy	33 (1.3%)
Solid tumour	164 (6.3%)
Functional status	
FEV_1 % predicted	73.8 (54.0–92.1)
FEV_1 <50% predicted	502 (19.3%)
Clinical status	
Number of exacerbations in the previous year	2 (0–3)
Three or more exacerbations per year	966 (37.2%)
At least one hospitalisation in the previous year	672 (25.9%)
Disease severity	
BSI score	6 (4–10)
Mild BSI score#	753 (29.0%)
Moderate BSI score¶	927 (35.7%)
Severe BSI score+	916 (35.3%)
Quality of life	
SGRQ§	41.2 (24.5–59.6)

Eur Respir J 2018;51:1701953.

	Korea (n = 598)	Australia (n = 653)	Europe[a] (n = 2596)	India[a] (n = 2195)
Demographics				
Age, years	66 (60–72)	73 (64–79)	67 (57–74)	56 (41–66)
Men	264 (44.1)	195 (29.9)	1010 (38.9)	1249 (56.9)
BMI, kg/m^2	22.9 (20.7–25.4)	25.0 (21.5–29.0)	24.8 (21.8–28.1)	21.5 (18.5–24.5)
Current or former smokers	211 (35.3)	145 (22.2)	990 (38.1)	619 (28.2)
Comorbidities				
Ischaemic heart disease	27 (4.5)	46 (7.0)	453 (17.5)	355 (16.2)
Stroke	11 (1.8)	20 (3.1)	152 (5.9)	9 (0.4)
Diabetes mellitus	73 (12.2)	42 (6.4)	260 (10.0)	315 (14.4)
Liver disease	13 (2.2)	5 (0.8)	41 (1.6)	18 (0.8)
Chronic renal failure	12 (2.0)	12 (1.8)	154 (5.9)	26 (1.2)
COPD	226 (37.8)	95 (14.5)	431 (16.6)	512 (23.3)
Asthma	134 (22.4)	94 (14.4)	226 (8.7)	485 (22.1)
Osteoporosis	70 (11.7)	151 (23.1)	192 (7.4)	130 (5.9)
GORD	89 (14.9)	224 (34.3)	394 (15.2)	346 (15.8)
Solid tumour	50 (8.4)	14 (2.2)	164 (6.3)	17 (0.8)
Disease severity				
BSI score	6 (4–9)	9 (6–12)	6 (4–10)	7 (3–10)
BSI score risk class				
Mild	171 (29.4)	90 (17.9)	753 (29.0)	728 (33.2)
Moderate	257 (44.1)	143 (28.5)	926 (35.7)	674 (30.7)
Severe	154 (26.5)	269 (53.6)	917 (35.3)	793 (36.1)
Radiological status				
Reiff score	5 (3–9)	4 (2–9)	4 (2–6)	6 (3–9)

Respirology 2021;26:619-621.

Comparison with other registries

Rhinosinusitis is associated with increased symptoms and more frequent exacerbations among patients with bronchiectasis- data from the EMBARC registry

Michal Shteinberg, Pieter Goeminne, Michael Loebinger, Charles Haworth, Felix Ringshausen, Katerina Dimakou, Marlene Murris, Montse Vendrell, Rosario Menendez, Robert Wilson, Adam Hill, Antoni Torres, Tobias Welte, Francesco Blasi, Anthony De Soyza, Stuart Elborn, Eva Polverino, James Chalmers, Stefano Aliberti

European Respiratory Journal 2018 52: PA350; **DOI:** 10.1183/13993003.congress-2018.PA350

Introduction: The presence of chronic rhinosinusitis (CRS) is common in bronchiectasis, with a wide range of prevalence. Single center studies suggested that bronchiectasis patients with CRS had more frequent pulmonary exacerbations, but the effects on lung function and bacterial colonization are inconsistent. Our aim was to explore the prevalence of rhinosinusitis and its impact on disease severity in patients with bronchiectasis in EMBARC- a multinational bronchiectasis patient registry.

Methods: Using data on patients with bronchiectasis registered to EMBARC, we classified patients with bronchiectasis as having CRS according to a physician reported diagnosis of 'rhinosinusitis' at baseline. Regression models were used to test the effect of rhinosinusitis on lung function decline, exacerbations and respiratory symptoms during 1 year of follow up.

Results: Out of 10920 patients included, 2265 (**20.7%)** had CRS. At baseline, patients with CRS had better lung function (FEV1= 77% vs. 67%, p<0.0001) than patients without CRS. Patients with CRS had worse respiratory symptom score (-3.03[-1.9-(-4.2)], p<0001) using the QOL-B questionnaire. During 1 year of follow up, people with CRS had more frequent moderate exacerbations (OR 1.2 [1.03-1.39], p=0.01), but less exacerbations that led to hospitalization (OR 0.6 [0.52-0.90] p<0.0001).

Conclusions: CRS is prevalent in bronchiectasis, its frequency may be underestimated in the EMBARC registry. Concomitant CRS is associated with more symptoms and mild- moderate exacerbations despite better lung function and less comorbidities.

CRS in bronchiectasis

- KMBARC CRF

비용종:	☐ Yes	☐ No	부비동염:	☐ Yes	☐ No

- No predefined diagnostic criteria for CRS in KMBARC and other international registries.
- Absence of diagnostic criteria may have affected the low prevalence of CRS in our study

- The prevalence of CRS has been variable in general population, ranging from **1.0% – 12.1%** worldwide.

  The prevalence of CRS based on symptoms and sinus radiology was **3.0% – 6.4%** in Netherlands.

  The prevalence of CRS was **3.86%** in the fifth Korea National Health and Examination Survey.

CRS in bronchiectasis

Table 2 Comparison of characteristics of patients with idiopathic bronchiectasis and patients with bronchiectasis post infection.

	Idiopathic group	Post-infection group	*p*-value
n	43	52	
Gender No. males (%)	15 (35)	17 (33)	ns
Age at onset (SD)	43 (15)	7 (11)	<0.01
Age at referral to Royal Brompton Hospital (SD)	51 (14)	49 (16)	ns
Mean number of lobes involved (SD)	4.1 (1.7)	4.3 (1.7)	ns
Bilateral bronchiectasis (%)	41 (95)	49 (94)	ns
Predominantly lower lobe bronchiectasis (%)	32 (74)	24 (46)	<0.01
Chronic rhinosinusitis (%)	36 (84)	26 (50)	<0.01
Wheezy bronchitis in childhood (%)	11 (26)	11 (21)	ns
P. aeruginosa (%)	14 (33)	17 (33)	ns
Symptoms chronic since onset	36 (84)	25 (48)	<0.01
Smoking history (%)	13 (30)	17 (33)	ns
Lobectomy (%)	1 (2)	5 (10)	ns

Respir Med 2007;101:1163-1170.

Table 1. Epidemiological characteristics of BQ patients included in the study

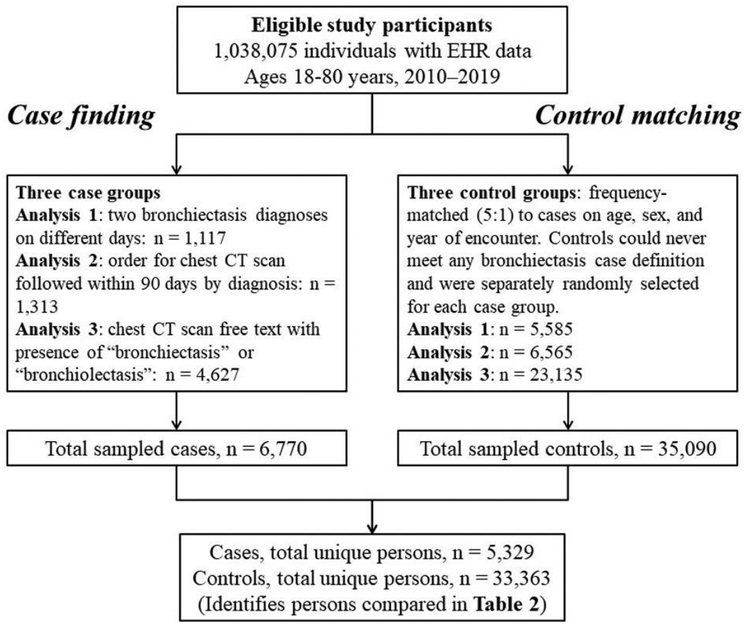
	All BQ patients	No CRS	CRS
Patients, *n* (%)	88	20 (23)	68 (77)
Age (years)†	55 ± 2	59 ± 3	54 ± 2
BQ age diagnosis (years)†	40 ± 2	47 ± 4	38 ± 2.5
Female (%)	69	50	75*
F/M ratio	2.3 : 1	1 : 1	3 : 1
Smoking habit			
Ex-smokers (%)	24	50	16
Smokers (%)	6	0	7
Packs/year†	23 ± 3	25.5 ± 5	22 ± 4
Lung function			
FEV_1 (%)†	83 ± 3	90 ± 4	81 ± 3
FEV_1/FVC (%)†	93 ± 1.5	96 ± 3	92 ± 2

Allergy 2009;64:790-797.

Temporal relationship of CRS with bronchiectasis

Strong and consistent associations of precedent chronic rhinosinusitis with risk of non–cystic fibrosis bronchiectasis

- In a sample representing the general population in in Pennsylvania, electronic health records was examined to identify CRS and bronchiectasis



Variable	Case patients, mean (SD)	Controls, mean (SD)*	*P* value†
Patients (no.)	5,329	33,363	NA
Medical Assistance, percentage of time receiving, no. (%)			
0%	4,570 (85.76)	30,599 (91.72)	<.001
>0%	759 (14.24)	2,764 (8.28)	
Duration of contact before bronchiectasis diagnosis or control selection date (y), no. (%)			
<3	705 (13.23)	5,664 (16.98)	<.001
3 to <10	1,507 (28.28)	9,246 (27.71)	
10 to <15	1,315 (24.68)	7,914 (23.72)	
15-23	1,802 (33.81)	10,539 (31.59)	
Smoking status, no. (%)			
Current	1,121 (21.04)	4,755 (14.25)	<.001
Former	2,702 (50.70)	12,069 (36.17)	
Never	1,391 (26.10)	15,668 (46.96)	
Unknown	115 (2.16)	871 (2.61)	
CRS, diagnoses, no. (%)‡	402 (7.54)	1,302 (3.90)	<.001
CRS, procedures, no. (%)§	332 (6.23)	927 (2.78)	<.001
CRSboth-text: based on sinus CT scan text, no. (%)‖	75 (1.41)	154 (0.46)	<.001
CRSsNP-text: based on sinus CT scan text, no. (%)	34 (0.64)	61 (0.18)	<.001
CRSwNP-text: based on sinus CT scan text, no. (%)	41 (0.77)	93 (0.28)	<.001

- On average, CRS was identified more than **6 years before** bronchiectasis.

J Allergy Clin Immunol. In press.

CRS in bronchiectasis

- United airways hypothesis
  : The upper and lower airways are connected anatomically and share similar pathophysiology.

a. The nose and sinuses are essential for filtration and humidification of inspired air.
   Potentially, inflammation from CRS can lead to mouth breathing.
   Mouth breathing can promote inhalation of microorganisms, pollutants, and allergens into the lower airways.

b. Aspiration of nasal contents from CRS could lead to infectious agents in the lower airways.

c. Nasal allergen provocation leads to airway bronchoconstriction accompanied by a similar type 2 inflammatory response in both the nose and the lungs.

d. Altered airway epithelium with loss of junctional proteins and aberrant epithelial repair to local injury has been demonstrated in CRS and bronchiectasis.

- Further evaluation of the relationship between CRS and idiopathic bronchiectasis is warranted.

Prevalence and implication of depression

Author (year)	Depression	Prevalence	Implication
O'Leary (2002)[1]	HADS ≥ 8	15% (n = 111)	Correlated with breathlessness and exercise performance, fatigue, and SGRQ.
Ryu (2010)[2]	BDI ≥ 16	55% (n = 33)	FEV1% and smoking history were independent risk factors for depression.
Olveira (2013)[3]	HADS ≥ 8	23% (n = 93)	Significantly associated with SGRQ. Not related with FEV1.
Giron (2013)[4]	BDI ≥ 14	34% (n = 70)	Not related with SGRQ.
Ozgun (2016)[5]	HADS ≥ 8	21% (n = 133)	Correlated with hemoptysis and admission to an emergency department within the last year.
Gao (2018)[6]	HADS ≥ 8	30% (n = 163)	Not related to disease severity (BSI and FACED) and FEV1. Sleep disturbance was the sole factor associated with depression. Patients with either depression had more impaired SGRQ than those without.

[1]Respir Med 2002;96:686-92. [2]Korean J Intern Med 2010;25:51-57. [3]Qual Life Res 2013;22:597-605.
[4]Arch Bronconeumol 2013;49:415-420. [5]Neuropsychiatr Dis Treat 2016;12:3005-10. [6]Clin Respir J 2018;12:1485-94.

Screening tool of depression

Table 1. DSM-5 domains that various depression scales measure

	1	2	3	4	5	6	7	8	9	10	11
HDRS	●	●	●	●	●	●	●		●		
MADRS	●	●	●	●	●	●	●	●	●		
BDI-II	●	●	●	●	●	●	●	●	●		
CES-D	●	●	●	●		●	●	●			
PHQ-9	●	●	●	●	●	●	●	●	●	●	
SDS	●	●	●	●	●	●	●	●	●		
HADS	●	●				●	●				
MASQ	●	●			●	●	●	●			
EPDS	●	●		●			●		●		
GDS	●	●			●	●	●	●			
KDS	●				●	●	●	●			
NADS	●	●	●	●	●		●	●	●		

1 : Depressed mood, 2 : Diminished interest or pleasure, 3 : Significant weight loss or gain, 4 : Insomnia or hypersomnia, 5 : Psychomotor agitation or retardation, 6 : Fatigue or loss of energy, 7 : Worthlessness or excessive or guilt, 8 : Diminished ability to think or concentrate, or indecisive, 9 : Recurrent thoughts of death, 10 : Impairment of functioning, 11 : Manic symptoms. HDRS : Hamilton Depression Rating Scale, MADRS : Montgomery-Asberg Depression Rating Scale, BDI-II : Beck Depression Inventory-II, CES-D : Center for Epidemiologic Studies Depression Scale, PHQ-9 : The Nine-Item Patient Health Questionnaire, SDS : Zung Self-Rating Depression Scale, HADS : Hospital Anxiety and Depression Scale, MASQ : Mood and Anxiety Symptom Questionnaire, EPDS : Edinburgh Postnatal Depression Scale, GDS : Geriatric Depression Rating Scale, KDS : Korean Depression Scale, NADS : New Anxiety-Depression Scale

- Diagnostic accuracy of PHQ-9 for depression in meta-analysis

  : Sensitivity of 88%, specificity of 85%, and AUC : 92.2%

Anxiety and mood 2017;53-59.

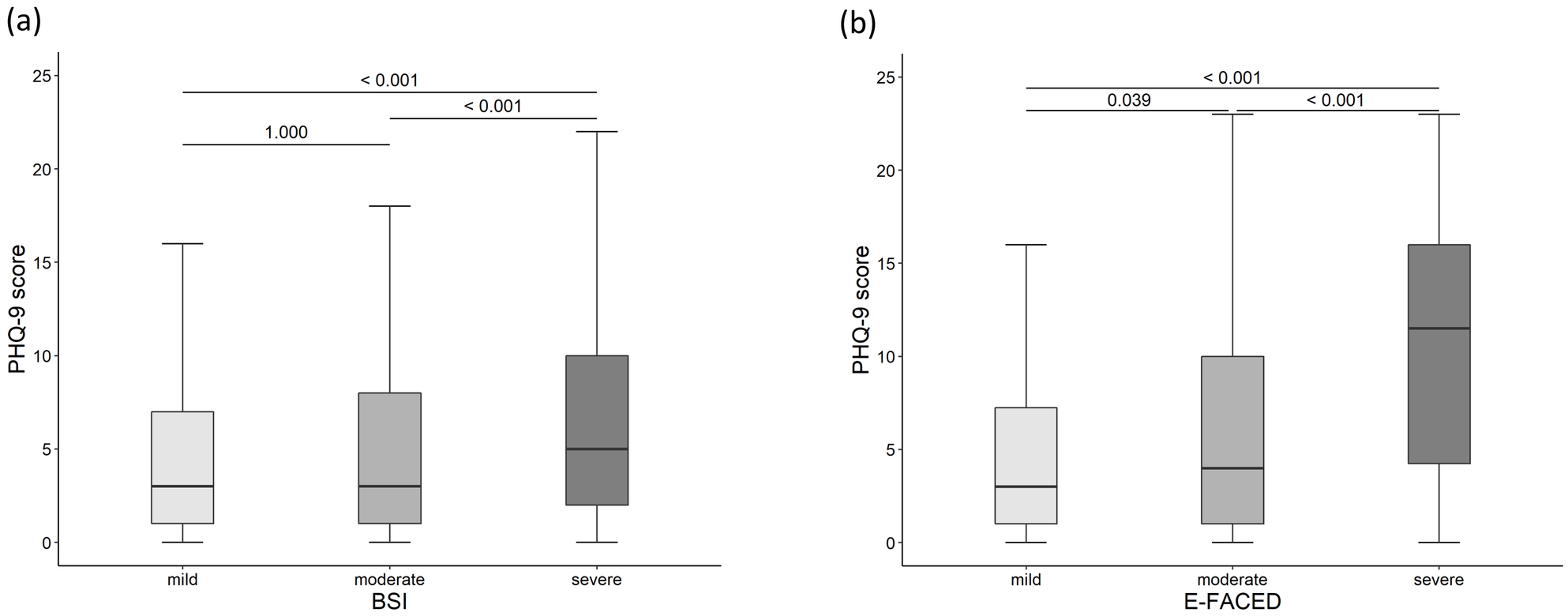
Results of KMBARC (1)

- Prevalence of depression (PHQ-9 ≥ 10): 20.7% (168/810)

	Nondepressed (n = 642)	Depressed (n = 168)	p value
Age (years)	64.6 ± 9.1	63.3 ± 10.2	0.140
Female	355 (55.3)	97 (57.7)	0.631
Duration (years)	3.2 ± 1.6	3.3 ± 1.7	0.432
Ever smoker	216 (33.7)	56 (33.3)	1.000
Body mass index	**23.3 ± 6.9**	**22.5 ± 3.9**	**0.049**
FEV1 (%)	**65.8 ± 20.8**	**60.4 ± 20.8**	**0.005**
FVC (%)	**74.1 ± 17.5**	**68.4 ± 17.1**	**0.001**
Asthma or COPD	294 (45.8)	80 (47.6)	0.737
Number of exacerbation	**1.2 ± 1.9**	**2.0 ± 3.7**	**<0.001**
Hospitalization	**99 (15.4)**	**42 (25.0)**	**0.005**
Etiology			
Post-infectious	249 (43.7)	60 (38.5)	0.281
Idiopathic	229 (40.2)	66 (42.3)	0.698
PA colonization	46 (7.3)	16 (9.6)	0.412
Sputum volume (≥ 30cc/day)	253 (39.4)	64 (38.1)	0.825
Radiological extent (≥ 3 lobes)	342 (53.3)	96 (57.1)	0.418

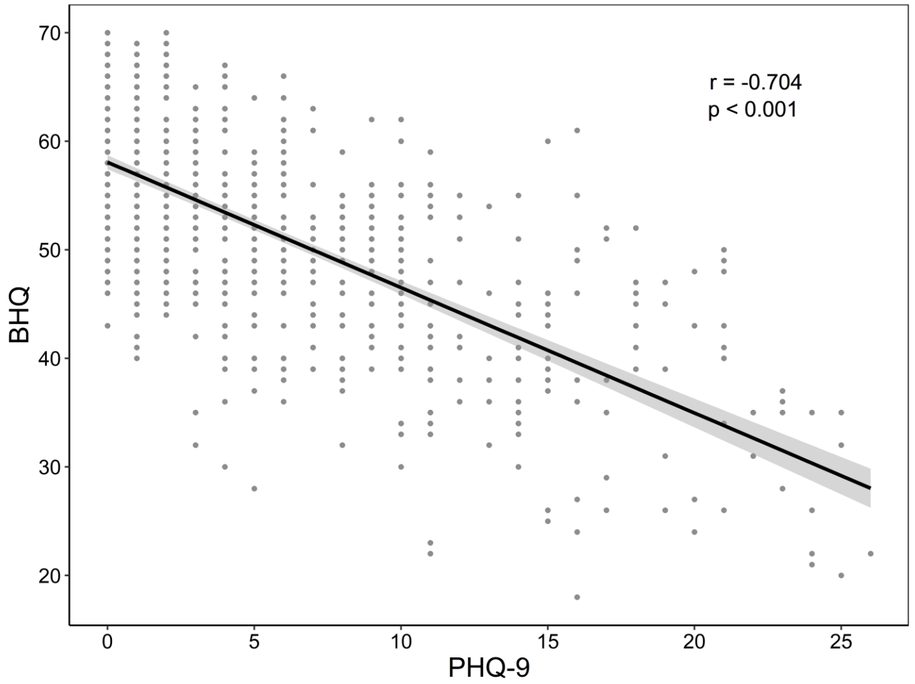
BMC Pulm Med 2021;21:306.

Results of KMBARC (2)

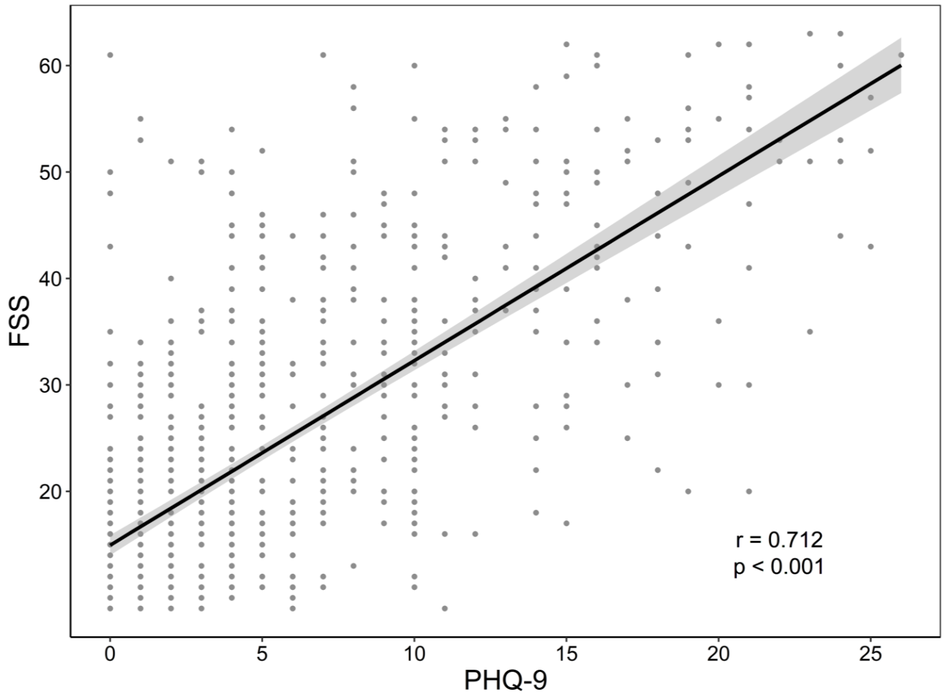


Results of KMBARC (3)

(a)

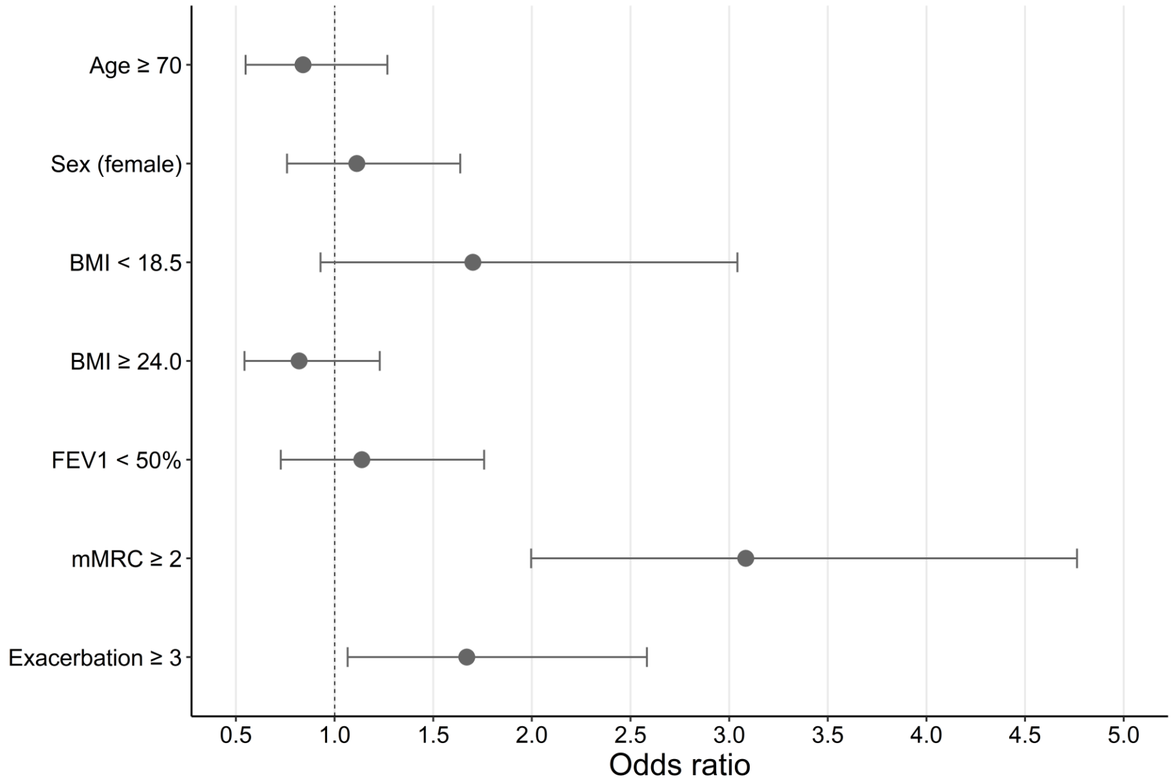


(b)



BHQ, Bronchiectasis Health Questionnaire; FSS, Fatigue Severity Score.

Results of KMBARC (3)



- This multicenter study found a 20.7% prevalence of depression in bronchiectasis.
- The depressive symptoms were aggravated as bronchiectasis worsened (severity) and strongly correlated with quality-of-life and fatigue symptoms.
- Dyspnea and frequent exacerbations were identified as clinical factors associated with depression.

Cognitive impairment in bronchiectasis

- **Wechsler Adult Intelligence Scale**
- Hospital Anxiety and Depression Scale
- Borg scale (dyspnea)

Table 1. Characteristics of the Control Group and Subjects With Bronchiectasis

Characteristic	Bronchiectasis Group ($n = 30$)	Control Group ($n = 25$)	P
Age, mean ± SD y	45.4 ± 14.1	41.4 ± 12.7	.2
Females/males, *n*	18/12	9/16	.07
BMI, mean ± SD kg/m^2	27.4 ± 5.9	27.7 ± 4.1	.8
Education level, mean ± SD	1.9 ± 0.9	2.8 ± 1.2	.002
FEV_1, mean ± SD % predicted	72.7 ± 20.8	100.8 ± 10.9	<.001
FEV_1/FVC, mean ± SD	74.6 ± 11.1	85.6 ± 7.6	<.001
Depression score, mean ± SD	8.6 ± 4.4	6.1 ± 4.0	.03
Anxiety score, mean ± SD	9.7 ± 5.3	6.4 ± 4.5	.01
Borg score after exercise, mean ± SD	5.4 ± 1.8	1.2 ± 1.8	<.001

Table 2. Subtest Scores and Composite Scores of the Control Group and Subjects With Bronchiectasis

Test	Bronchiectasis Group ($n = 30$)	Control Group ($n = 25$)	P
Full-scale IQ	87.5 ± 16.3	106.1 ± 18.8	<.001
Verbal IQ	89.1 ± 18.4	105.3 ± 18.4	.002
Performance IQ	87.1 ± 13.8	105.2 ± 18.0	<.001
Similarities	7.4 ± 2.5	9.6 ± 2.2	.004
Information	6.3 ± 2.6	9.5 ± 1.9	<.001
Digit span	7.3 ± 2.6	9.1 ± 2.9	.03
Arithmetic	6.1 ± 2.4	9.8 ± 2.4	<.001
Digit symbol	6.4 ± 2.3	8.9 ± 2.2	.001
Picture completion	6.6 ± 2.6	9.4 ± 1.9	<.001
Picture arrangement	5.5 ± 2.9	9.6 ± 3.1	<.001
Block design	4.9 ± 2.3	7.3 ± 1.9	.001
Object assembly	8.01 ± 2.2	10.2 ± 1.7	.001
Comprehension	7.2 ± 2.6	9.4 ± 2.1	.002

Respir Care 2015;60:1610-5.

Cognitive impairment in bronchiectasis

Table 4. Simple Correlation Between Cognitive Ability and Study Variables in Subjects With Bronchiectasis

Test	Age		BMI		Depression Score		Anxiety Score		% Predicted FEV_1		S_{aO_2}		P_{aO_2}	
	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Full-scale IQ	−0.41	.002	0.39	.004	−0.50	<.001	−0.47	<.001	0.17	.2	0.53	.003	0.48	.008
Verbal IQ	−0.38	.005	0.29	.03	−0.40	.003	−0.46	<.001	0.05	.7	0.47	.009	0.44	.01
Performance IQ	−0.38	.005	0.29	.03	−0.40	.003	−0.47	<.001	0.05	.7	0.48	.008	0.43	.02

Table 5. Relationship Between Cognitive Ability, Measured by the Wechsler Adult Intelligence Scale-Revised as the Dependent Variable, and Percent-of-Predicted FEV_1 and Resting S_{aO_2} as Independent Variables in Subjects With Bronchiectasis in a Multivariate Model

Variable	Full-Scale IQ Score			
	$r^2 = 0.64$		$r^2 = 0.59$	
	β	*P*	*β*	*P*
Intercept		< .001		< .001
Age	−0.12	.3	0.06	.6
Male	−0.02	.8	−0.10	.4
Education	0.51	.001	0.48	.002
BMI	−0.13	.3	−0.09	.5
Depressive symptoms	−0.38	.009	−0.27	.05
% predicted FEV_1	0.25	.04		
S_{aO_2}			0.27	.03
Smoking	−0.17	.1	−0.11	.3

β is the standardized regression coefficient. Statistical significance of $P < .05$.

a. Negative relationship of age, anxiety, and depression scores
Positive relationship of oxygen saturation and BMI

b. Full-scale IQ scores were negatively associated with depression scores and positively associated with lung function and oxygen saturation.

- Low cognitive ability in subjects with bronchiectasis was associated with reduced lung function, more serious hypoxemia, and greater depressive symptoms.

Respir Care 2015;60:1610-5.

Cognitive function in asthma

Association between cognitive function and asthma in adults

Hyo-In Rhyou, MD; Young-Hee Nam, MD, PhD

Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Republic of Korea

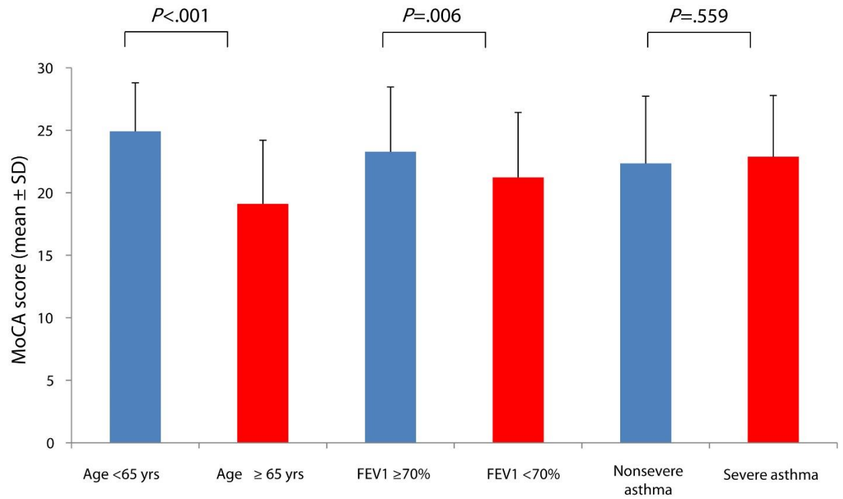


Table 3
Risk factors for Cognitive Impairment by Logistic Regression Analysis

Characteristics	Univariate	*P* value	Multivariate	*P* value
	Odds ratio (95% confidence interval)		Odds ratio (95% confidence interval)	
Age, y	1.112 (1.075-1.15)	<.001	1.07 (1.014-1.13)	.01
BMI, kg/m^2	1.088 (1.004-1.179)	.03	1.065 (0.923-1.227)	.38
Current smoking	0.698 (0.349-1.395)	.30	0.592 (0.187-1.869)	.37
Low income	1.845 (0.823-4.123)	.13	1.471 (0.406-5.324)	.55
Low education	8.986 (4.729-17.072)	<.001	6.068 (2.175-16.927)	.001
Hypertension	4.371 (2.161-8.841)	<.001	3.439 (0.997-11.863)	.05
Upper airway diseases	0.289 (0.152-0.547)	<.001	0.722 (0.233-2.235)	.57
Asthma duration, y	1.005 (1.001-1.009)	.006	1.007 (1.001-1.013)	.02
Prebronchodilator FEV1, %	0.983 (0.969-0.997)	.01	1.0 (1.001-1.013)	.99
ICS treatment	1.097 (0.515-2.327)	.81	0.497 (0.123-2.015)	.32
Severe asthma	0.698 (0.349-1.395)	.30	0.918 (0.277-3.043)	.88

- Montreal Cognitive Assessment (MoCA) was used to screen for cognitive impairments.
- 44.1% (n = 89/202) indicated cognitive impairment.
- Longer asthma duration and lower lung function were more associated with cognitive dysfunction.

Ann Allergy Asthma Immunol 2021;126:69-74.

Cognitive function in asthma and COPD

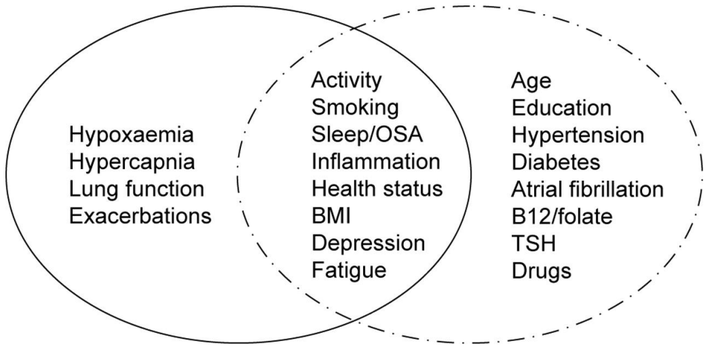
Asthma

- Transient **hypoxia**, high rate of **depression** and **anxiety** disorders, and **corticosteroid** therapy could lead to poor cognition in asthma.
- Cognitive impairment is a predictor of **non-adherence** in patients.
- Adult asthma increases **dementia risk** in a nationwide cohort study (Taiwan)
  : HR of dementia was 1.27 (1.15-1.41)

J Epidemiol Community Health 2015;69:123-128.

COPD

- Rate of neuropsychological deficit rose from 27% in mild hypoxemia to 62% in severe hypoxemia
- Key mechanism for cognitive dysfunction in COPD are **hypoxia** and **inflammation**.



Potential factors thought to effect cognitive function in COPD

Eur Respir J 2010;35:913–922.

MoCA

- Montreal Cognitive Assessment (**MoCA**)

a. Mild Cognitive Impairment (MCI) refers to a transitional state between the cognition of normal aging and mild dementia.
b. MCI is now recognized as a high-risk state of Alzheimer's disease.
c. The Mini-Mental State Examination (MMSE) is most widely used for screening cognitive impairment, including dementia.

- **MoCA** is a neurocognitive test designed to screen for MCI.
  It scores from 0 to 30, where higher scores indicate better cognition and a score below 26 indicates cognitive impairment corresponding to MCI and AD. It can be administered in 10 minutes.
- Korean version of MoCA was used, with a sensitivity of 89% and specificity of 84% for screening MCI, using a cutoff score of 23.

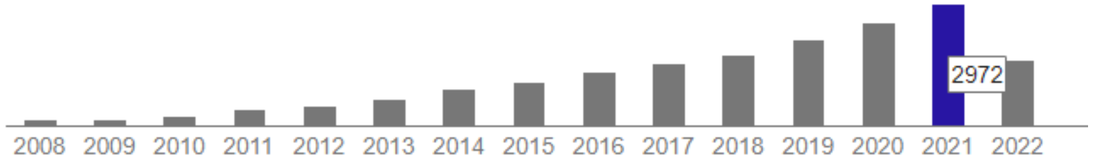
J Geriatr Psychiatry Neurol 2008; 21: 104–10.

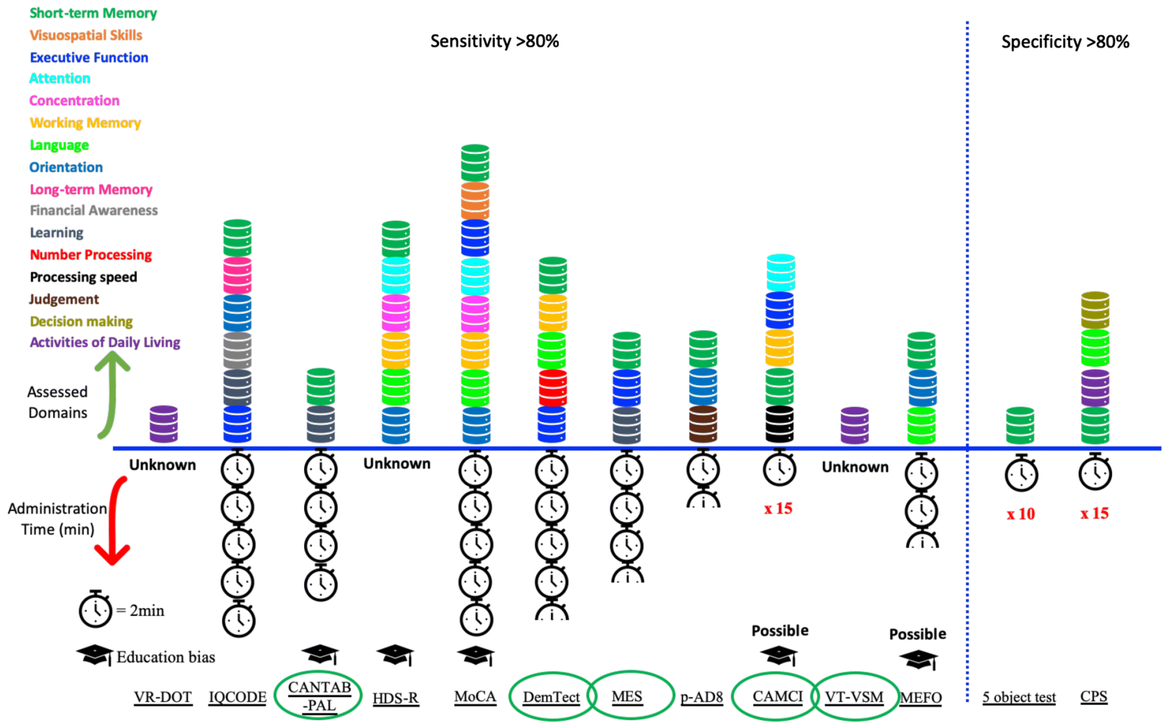
MoCA

The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment

17833회 인용

J Am Geriatr Soc. 2005;53:695-699.





J Neurol 2021;268:1615-1622.

Paper

MoCA Test Full

Korean 7.1

https://www.mocatest.org

MoCA

1. 길만들기

시행 : 검사자는 피검자에게 다음과 같이 지시한다. "숫자에서 글자로 번갈아 가면서 선을 그어 주세요. 여기에서 시작하고 [(1)을 가리킴], (1)에서 (가)로, (가)에서 (2)로, 이와 같이 순서대로 끝[(마)를 가리킴]까지 선을 그어 주세요".

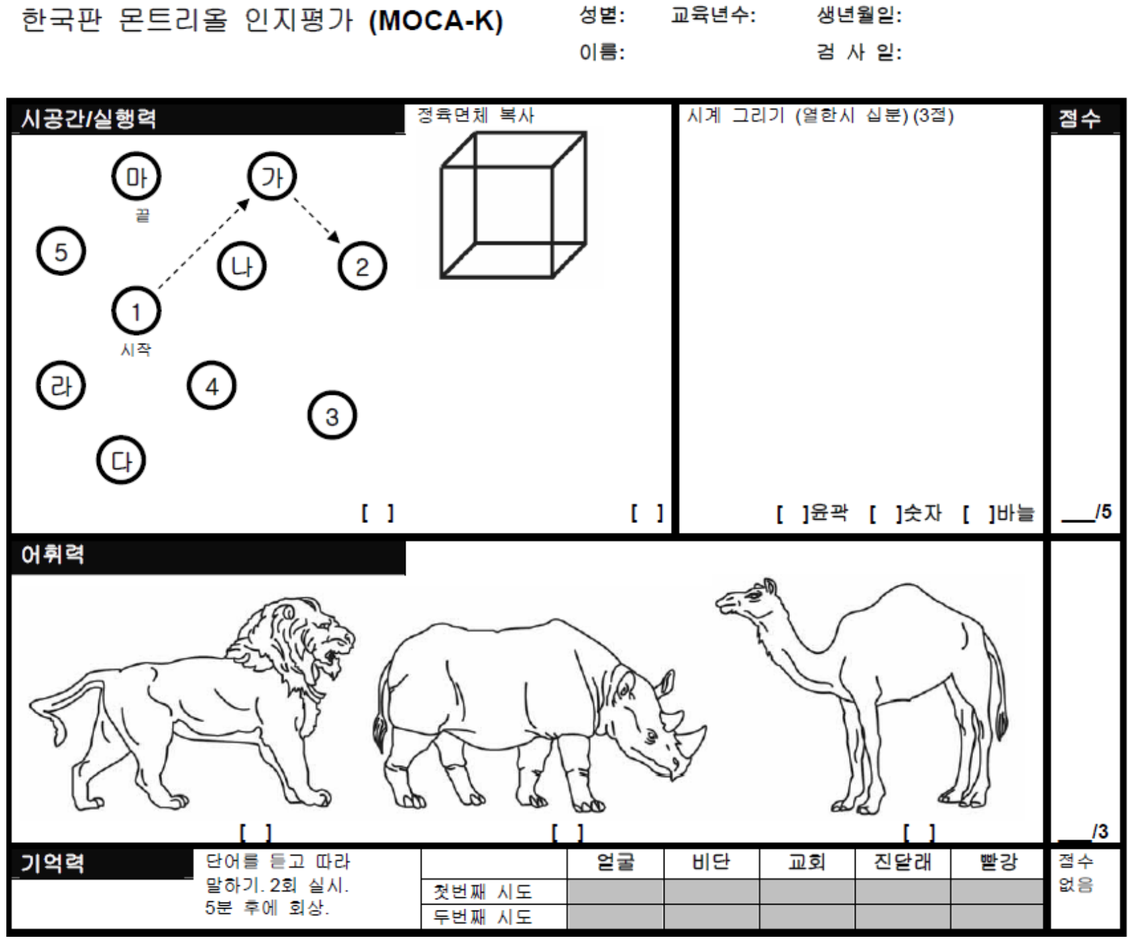
채점 : 피검자가 다음과 같은 순서로 성공했을 경우 1점을 준다 :
1-가-2-나-3-다-4-라-5-마. 피험자의 즉각적인 수정이 이루어진 경우를 제외하고는 점수를 주지 않는다.

2. 시각공간 (정육면체)

시행 : 검사자는 정육면체를 가리키면서 다음과 같이 지시한다. "이 그림과 똑같이 그려주세요".

채점 : 그림이 정확하게 그려졌을 경우 1점을 준다.
- 3차원이어야 한다.
- 모든 선이 그려져야 한다.
- 덧그려진 선이 없어야 한다.
- 대체로 선이 평행해야 하며 길이는 비슷해야 한다.

위에 제시한 기준들이 지켜지지 않았을 경우에는 점수를 주지 않는다.



ABPA

- Prevalence of allergic bronchopulmonary aspergillosis (ABPA)
  : 4% (range 1% – 8%) in patients with bronchiectasis

Table 1
Studies in the last decade describing the prevalence of *Aspergillus* sensitization (AS) and allergic bronchopulmonary aspergillosis (ABPA) in adults with bronchial asthma

Author (year)	Type of Study	Country	Prevalence of AS, n/N	Prevalence of ABPA, n/N (%)
Ma et al,[17] 2011	Prospective	China	11/200 (5.5%)	5/200 (2.5%)
Agin et al,[19] 2012	Prospective	Iran	42/201 (20.9%)	-
Mathur et al,[20] 2016	Prospective	India	27/300 (9%)	8/296 (2.7%)
Kozlova et al,[21] 2017	Prospective	Russia	50/140 (36%)	5/140 (3.6%)
Nath et al,[22] 2017	Prospective	India	135/350 (35.1%)	76/350 (21.7%)
Kalaiyarasan et al,[23] 2018	Prospective	India	13/70 (18.6%)	9/70 (12.9%)
Al-Saleh et al,[24] 2019	Prospective	Bahrain	19/119 (15.9%)	12/119 (10.1%)
Bhankhur et al,[25] 2019	Prospective	India	-	35/50 (70%)
Mahdi et al,[26] 2019	Prospective	Pakistan	77/150 (51.3%)	19/150 (12.6%)
Savio et al,[27] 2019	Prospective	India	122/205 (59.6%)	-
Mortezaee et al,[28] 2020	Prospective	Iran	27/200 (13.5%)	-
Rajagopal et al,[29] 2020	Prospective	India	20/57 (35.1%)	-
Sharma et al,[30] 2020	Prospective	India	30/100 (30%)	5/100 (5%)
Zia-ul-Haq et al,[31] 2020	Prospective	Pakistan	-	20/100 (20%)

Clin Chest Med 2022;43:99-125.

Diagnostic criteria of ABPA

Rosenberg-Patterson criteria (1977)	
Primary	1. Presence of asthma
	2. Transient or fixed radiographic infiltrates
	3. Positive type I skin reaction to *A fumigatus*
	4. Serum total IgE >1000 ng/mL (>417 IU/mL)
	5. Positive *A fumigatus* precipitins
	6. Total eosinophil count >1000 cells/μL
	7. Central bronchiectasis
Secondary	1. Expectoration of mucus plugs
	2. Isolation of *Aspergillus* in the culture of sputum
	3. Positive type III skin reaction to *A fumigatus*
The authors labeled the entity as ABPA-CB (central bronchiectasis) if proximal bronchiectasis was present and ABPA-S (serological), if not. The diagnosis of ABPA is highly probable if the first 6 of the 7 primary criteria are present. The presence of all 7 criteria makes the diagnosis almost certain.	

ISHAM diagnostic criteria for ABPA (2013)	
Predisposing conditions	**Presence of asthma or cystic fibrosis**
Obligatory criteria (both must be present)	1. Positive type I skin reaction to *A fumigatus* or *A fumigatus*−specific IgE >0.35 KUA/L
	2. Serum total IgE levels >1000 IU/mL*
Other criteria (≥2)	1. Positive *A fumigatus* precipitins or *A fumigatus*−specific IgG >27 mgA/L
	2. Chest radiograph favoring ABPA†
	3. Total eosinophil count >500 cells/μL

*IgE level <1000 IU/mL can be accepted if all other conditions are satisfied.

†Transient opacities such as fleeting opacities, tram-track shadows, consolidation, toothpaste shadows, nodules, or finger-in-glove opacities or permanent opacities such as ring shadows, parallel lines, and pleuropulmonary fibrosis.

J Allergy Clin Immunol Pract 2021;9:328-35.

Diagnostic criteria of ABPA

TABLE IV. Performance of different criteria for the diagnosis of ABPA, using LCA

Criteria	Sensitivity	Specificity
Existing criteria		
Patterson criteria*: asthma, chest radiographic infiltrates, type I AST positivity, serum total IgE >417 IU/mL, *A fumigatus*−specific IgG >27 mgA/L, eosinophil count >1000 cells/μL, bronchiectasis, *A fumigatus*−specific IgE >0.35 kUA/L (presence of any 6 of the above)	81.3 (73.3-88.6)	98.2 (96.9-99.6)
ISHAM criteria†: Presence of all of the following: (1) asthma; (2) positive type I skin reaction to *A fumigatus* or *A fumigatus*−specific IgE >0.35 KUA/L; (3) serum total IgE levels >1000 IU/mL; and 2 of the other components: (1) *A fumigatus*−specific IgG >27 mgA/L; (2) chest radiograph favoring ABPA; (3) eosinophil count >500 cells/μL	88.5 (80.2-94.6)	99.1 (98.0-99.8)
Newly evaluated criteria (with certain modifications of the existing ISHAM criteria)		
Criteria 1: Presence of all of the following: (1) asthma; (2) *A fumigatus*−specific IgE >0.35 KUA/L; (3) serum total IgE levels >500 IU/mL; and 2 of the following: (1) *A fumigatus*−specific IgG >27 mgA/L; (2) bronchiectasis on CT chest; (3) eosinophil count >500 cells/μL	100 (96.6-100)	100 (100-100)
Criteria 2: Presence of all of the following: (1) asthma; (2) *A fumigatus*−specific IgE >0.35 KUA/L; (3) serum total IgE levels >1000 IU/mL; and 3 of the following: (1) *A fumigatus*−specific IgG >27mgA/L; (2) bronchiectasis on CT chest; (3) eosinophil count >500 cells/μL; (4) mucus impaction on CT chest	80.2 (71.3-88.1)	100 (100-100)
Criteria 3: Presence of all of the following: (1) asthma; (2) *A fumigatus*−specific IgE >0.35 KUA/L; (3) serum total IgE levels >1000 IU/mL; and 2 of the following: (1) *A fumigatus*−specific IgG >27mgA/L; (2) bronchiectasis on CT chest; (3) eosinophil count >500 cells/μL; (4) mucus impaction on CT chest	100 (100-100)	98.9 (97.8-100)

- Diagnostic performance: Patterson (1977) < ISHAM (2013) < Modified ISHAM (2021)

J Allergy Clin Immunol Pract 2021;9:328-35.

New diagnostic criteria of ABPA

- **Modified ISHAM criteria**

  Presence of all the following:

  1. Asthma.
  2. Aspergillus-specific IgE > 0.35 kUA/L
  3. **Serum total IgE > 500 IU/mL**

  And at least 2 of the following:

  1. A. fumigatus specific IgG > 27 mgA/L
  2. **Bronchiectasis on CT chest**
  3. Peripheral blood eosinophilia > 500 cells/µL.

J Allergy Clin Immunol Pract 2021;9:328-35.

New diagnostic criteria of ABPA

- **Modified criteria proposed by Japan research group**

TABLE I. Clinical diagnostic criteria for ABPM in patients without cystic fibrosis

1. Current or previous history of asthma or asthmatic symptoms
2. Peripheral blood eosinophilia (≥500 cells/mm^3)
3. Elevated total serum IgE levels (≥417 IU/mL)
4. Immediate cutaneous hypersensitivity or specific IgE for filamentous fungi
5. Presence of precipitins or specific IgG for filamentous fungi
6. Filamentous fungal growth in sputum cultures or bronchial lavage fluid
7. Presence of fungal hyphae in bronchial mucus plugs
8. Central bronchiectasis on CT
9. Presence of mucus plugs in central bronchi, based on CT/bronchoscopy or mucus plug expectoration history
10. High attenuation mucus in the bronchi on CT

Filamentous fungi in criteria 4 to 6 should be identical.
Patients that meet 6 or more of these criteria are diagnosed with ABPM.

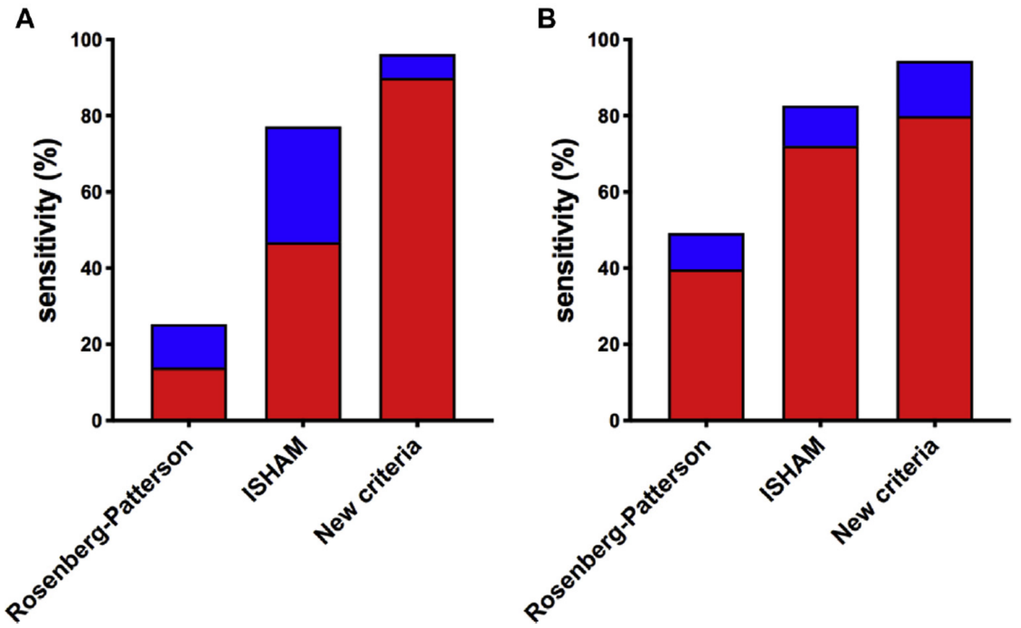


FIG 1. Sensitivity of diagnostic criteria for pathological and physician-diagnosed ABPM. Sensitivity for pathological ABPM (n = 79) **(A)** and physician-diagnosed ABPM (n = 179) **(B)** were compared among the Rosenberg-Patterson criteria, ISHAM criteria, and the new diagnostic criteria. *Red bars* represent definite ABPM. *Blue bars* show probable cases.

J Allergy Clin Immunol 2021;147:1261-68.

Biologic treatment of ABPA

Use of monoclonal antibodies for allergic bronchopulmonary aspergillosis in patients with asthma and cystic fibrosis: literature review

- 32 studies (30 studies with asthma), 161 patients (median age 50.3 years, 1:1 F:M)
- Omalizumab: 17 studies (104 patients), Mepolizumab: 9 studies (32 patients)

  Dupilumab: 2 studies (21 patients), Benralizumab: 2 studies (2 patients)
- ABPA using the diagnostic criteria either by Patterson or the ISHAM.
- All patients had failed to respond adequately to steroids and antifungal therapies.
- Biologics improved the frequency of acute exacerbations, ACT asthma scores, pulmonary function, total IgE, and OCS requirement.
- Evidence comes mainly from case series or case report (no RCT).

Ther Adv Respir Dis 2020;14:1753466620961648.

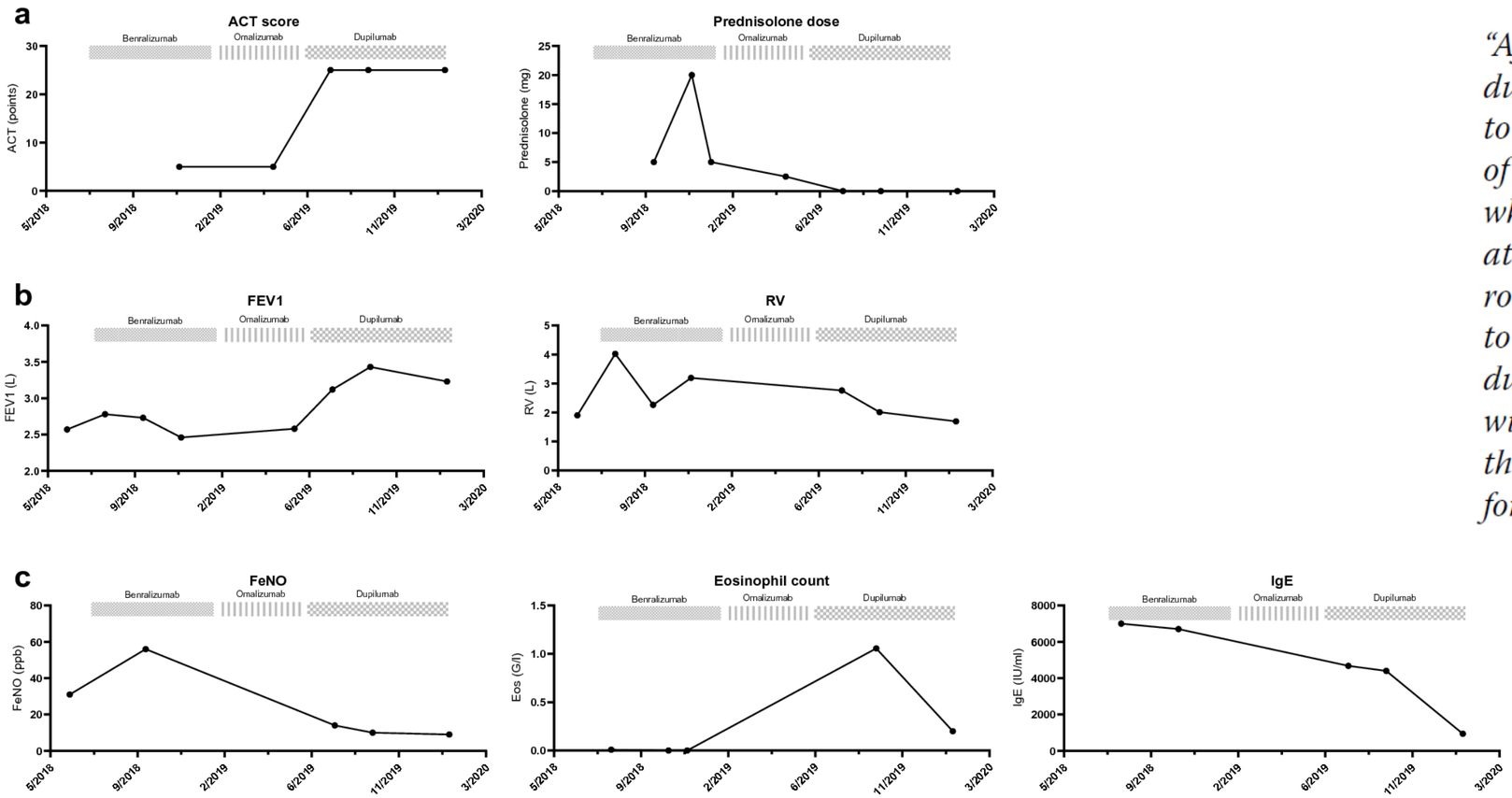
Biologic treatment of ABPA

Table 5. Treatment with dupilumab in patients with ABPA and asthma.

					Pre-treatment clinical variables						Post-treatment clinical variables							
Study ID	**Type of study**	**Sample**	**Gender**	**Age**	**Previous biologic treatment**	**Absolute eosinophil count (cell/μL)**	**Total IgE (IU/mL)**	**FEV1 (% predicted or L)**	**Frequency of acute exacerbations or asthma control test**	**Antifungal treatment**	**Follow-up time**	**Total eosinophil count (cell/μL)**	**Total IgE (IU/mL)**	**FEV1 (%predicted)**	**Frequency of acute exacerbations or asthma control test**	**Systemic steroids**	**Antifungal treatment**	**Adverse effects**
Ramonell *et al.*[30]	Case series	3	F	60	Omalizumab and Mepolizumab	1620	561	1.51 L (58%)	NI	NI	**6 months**	1090 (4 mo)	380 (3 mo)	2.18 L (99%)	Improved	Discontinued	NI	hypereosinophilia
			F	51	Mepolizumab	1040	>2000	2.75 L (95%)	NI	Itraconazole	**3 months**	160	384	2.82 L (97%)	Improved	Discontinued	NI	No
			M	33	No	1750	11.290	1.97 L (37%)	NI	Voriconazole	**3 months**	690	1637	2.33 L (56%)	Asthma exacerbation after onset dupilumab	NI	NI	Hypereosinophilia
Corren *et al.*[31]	Post Hoc analysis of an RCT[f] (35)	18	NI	NI	NI	NI	3383 (1480–5000[b]	2.00 L (68%)[a]	2.28 (1.53)[a,d]	NI	**13 months**	NI	691,5 (323–2617)[b]	24 w 2.26 52 w 2.33[c]	Improved	NI	NI	Injection-site reaction

Ther Adv Respir Dis 2020;14:1753466620961648.

Biologic treatment of ABPA



Patient perspective

"After nearly 50 years of breathlessness, therapy with dupilumab changed my life from one day to the next: to breathe without resistance is really a new quality of life! Perhaps there are two things in my case, which are special to this success. First, I am doing at minimum one hour of sport each day (bicycling, rowing) since 35 years, even when this was hard to practice. And second: I lost, after starting with dupilumab and stopping cortisone, 17 kg of weight within three months with a fasting cure. Altogether, this is giving me a reliable and hopeful perspective for my future."

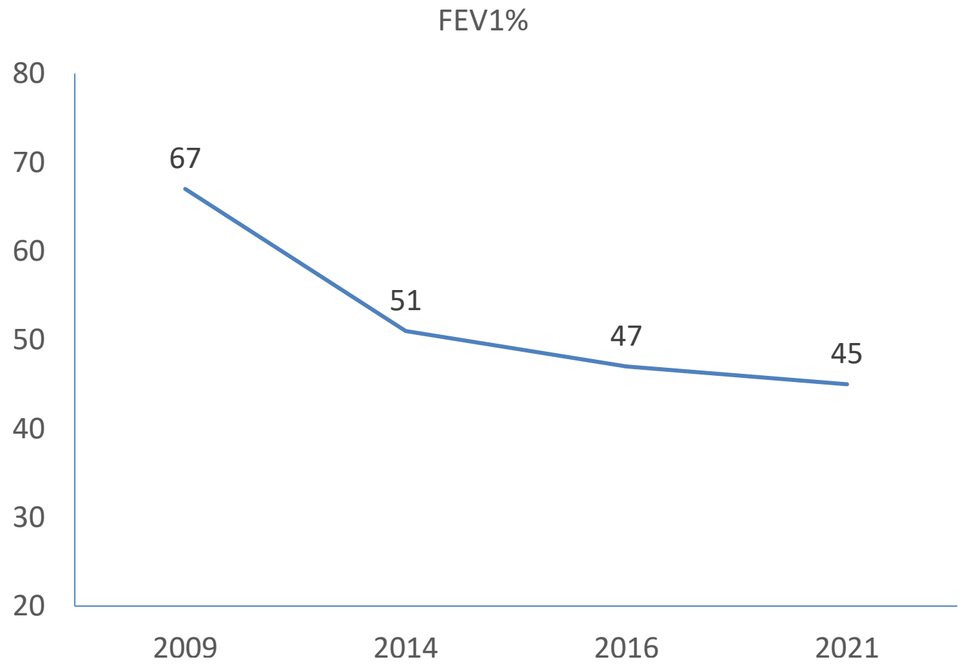
- Switching to dupilumab led to a complete resolution of pulmonary symptoms, exacerbations and complete withdrawal of oral steroids.

Allergy Asthma Clin Immunol 2020;16:55.

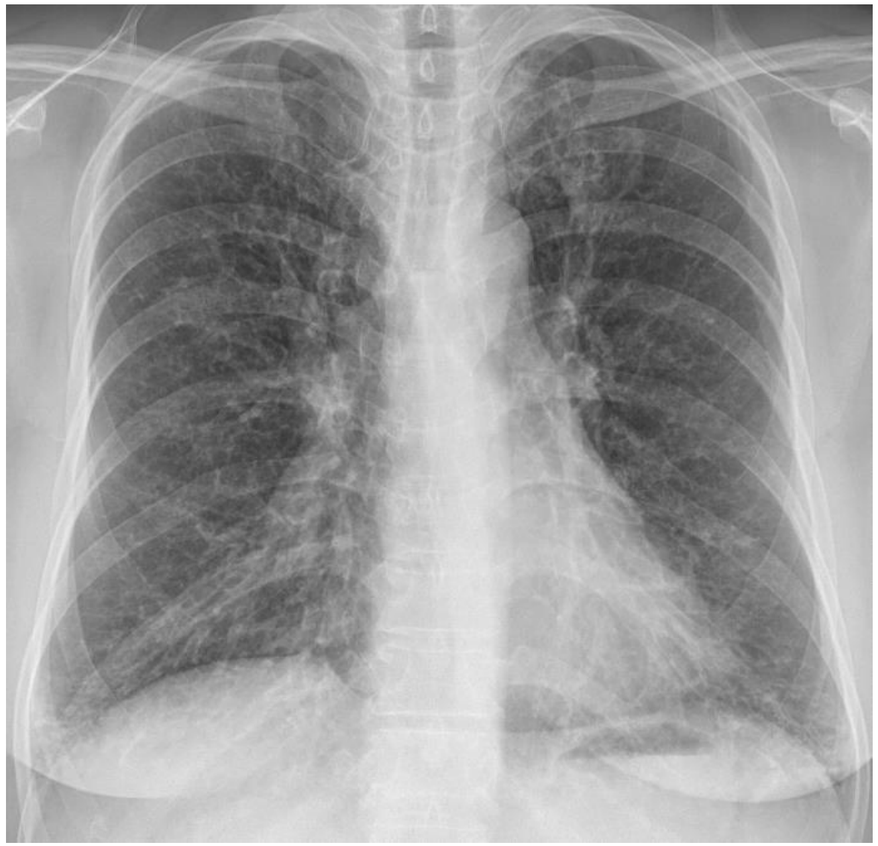
ABPA case

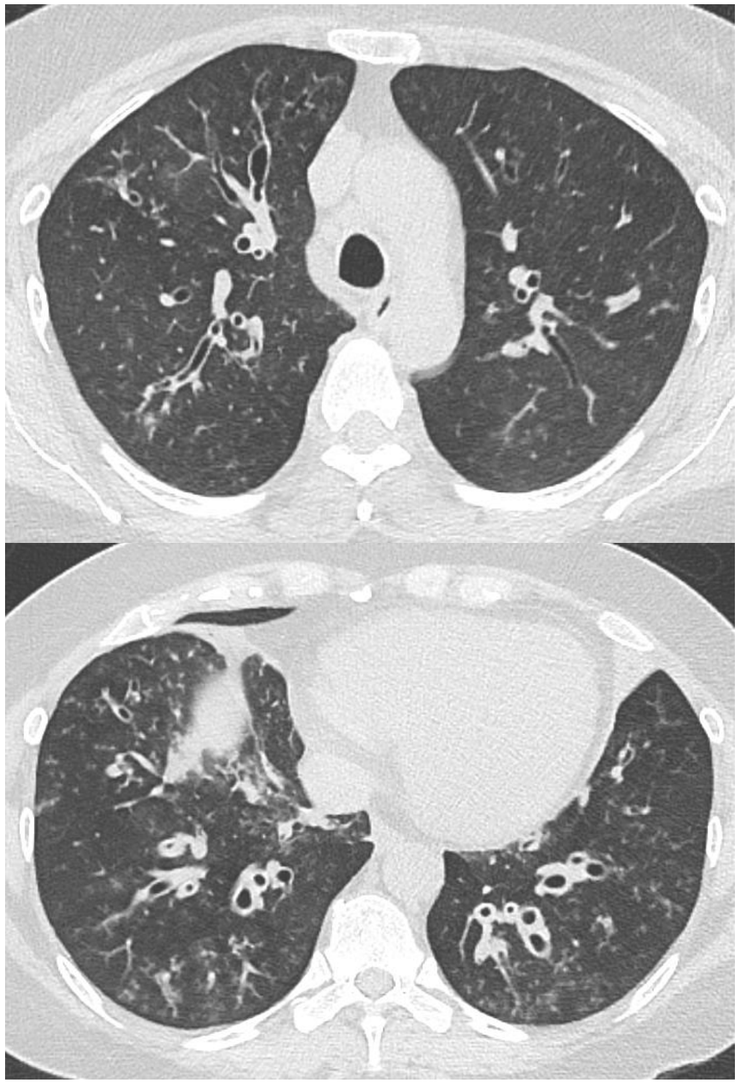
- 50/F
- 천식 (20년), 잦은 악화로 입원 반복함
- Triple therapy 시행 후 악화 없이 유지 중.
- 평지 걸을 때는 문제 없으나, 조금만 뛰거나 경사진 곳 오를 때 숨이 참.

Variable	Result
Blood eosinophil	1,490 (cells/μL)
Total IgE	2,385 (IU/mL)
Aspergillus fumigatus IgE	23.2 (KU/L)
Aspergillus fumigatus IgG	> 200 (U/mL)
Sputum AFB culture	Negative

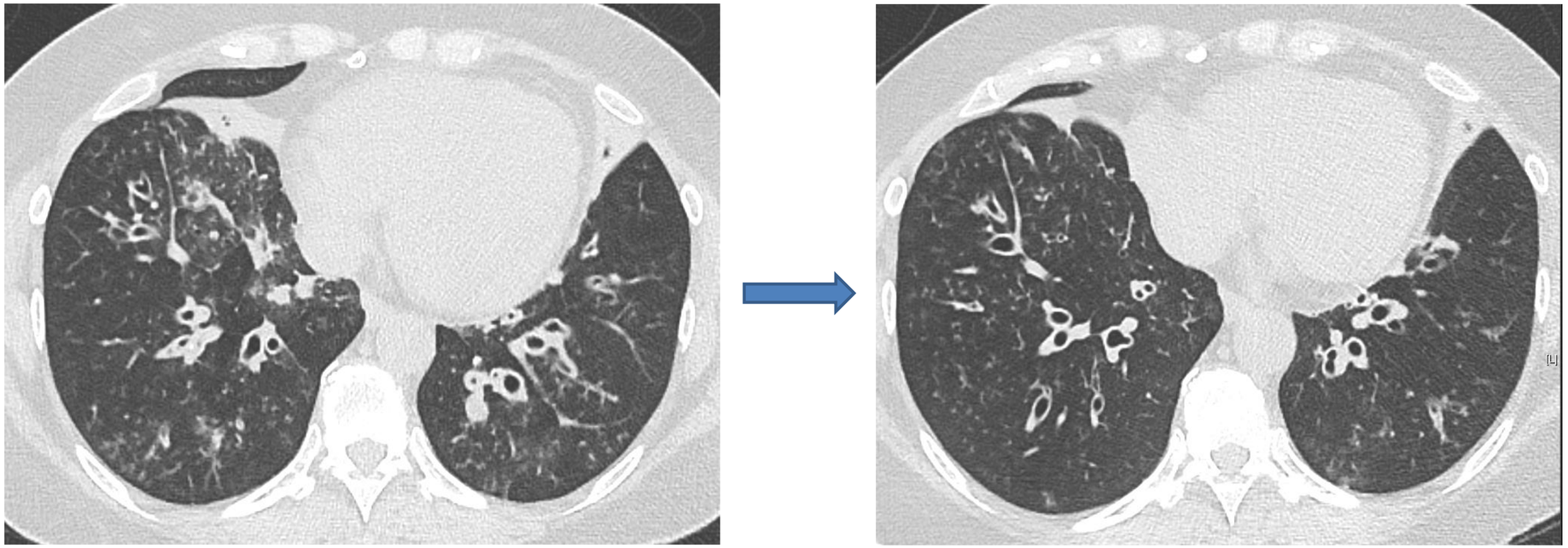


ABPA case



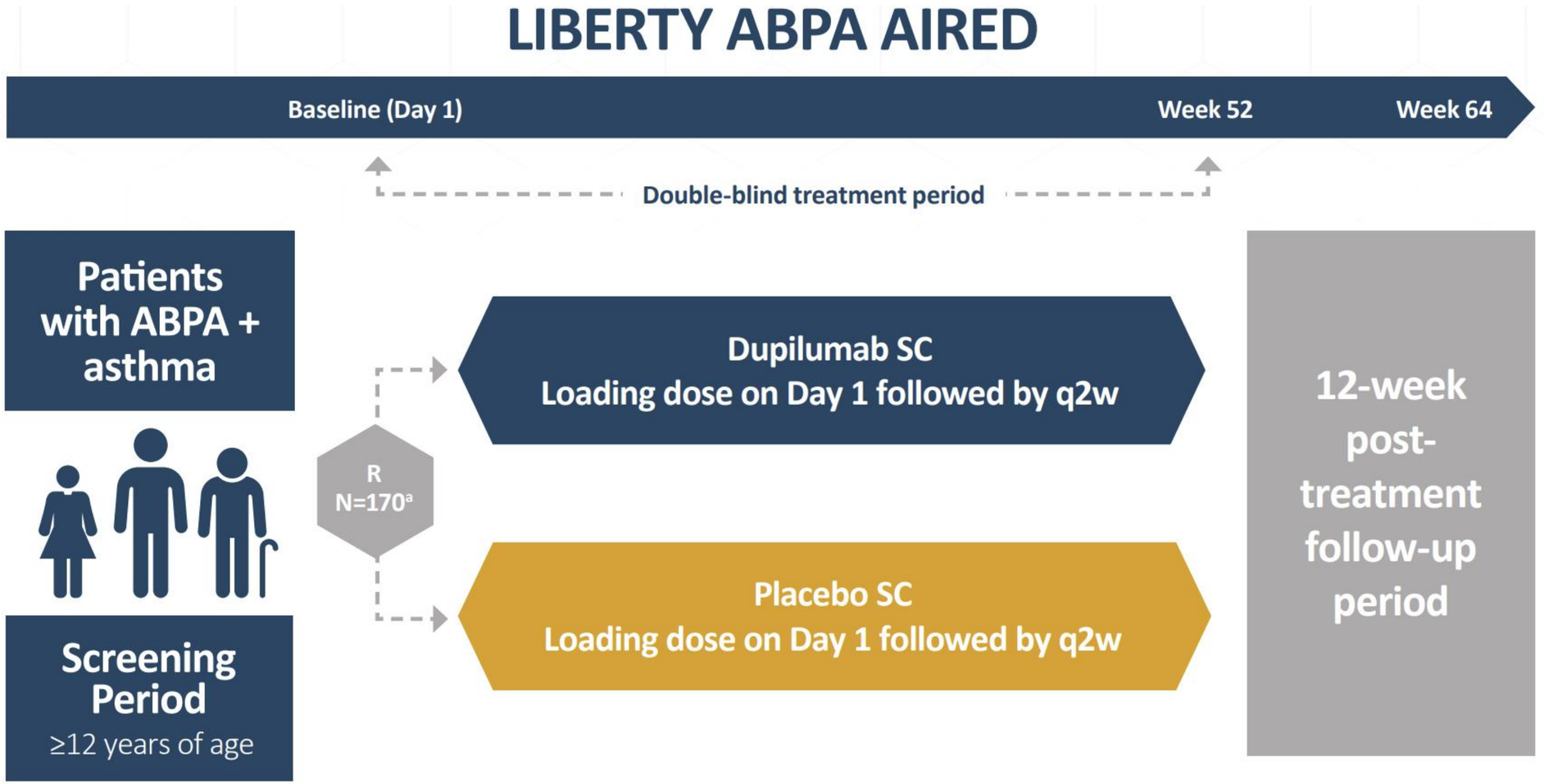


ABPA case



- Omalizumab 300mg for 2month, followed by dupilumab 300mg for 6months (monthly administered)
- FEV1 (%): 45 → 46
- “경사진 곳에 오를 때 더 이상 숨이 차지 않아요“

ABPA clinical trial



https://clinicaltrials.gov/ct2/show/NCT04442269.

Summary

- CRS is closely linked to bronchiectasis, especially with Idiopathic bronchiectasis.
- Depression is common and negative affects bronchiectasis, but undertreated.
- Cognitive impairment is associated with poor outcome of bronchiectasis and depressive symptom.
- New diagnostic criteria of ABPA has been recently proposed.

  However, its diagnostic performance remain undetermined in other population.

  Biologic treatment and switching to other class can help manage ABPA.
- Studies on the prevalence and clinical characteristics of Korean patients with ABPA are urgently needed.