

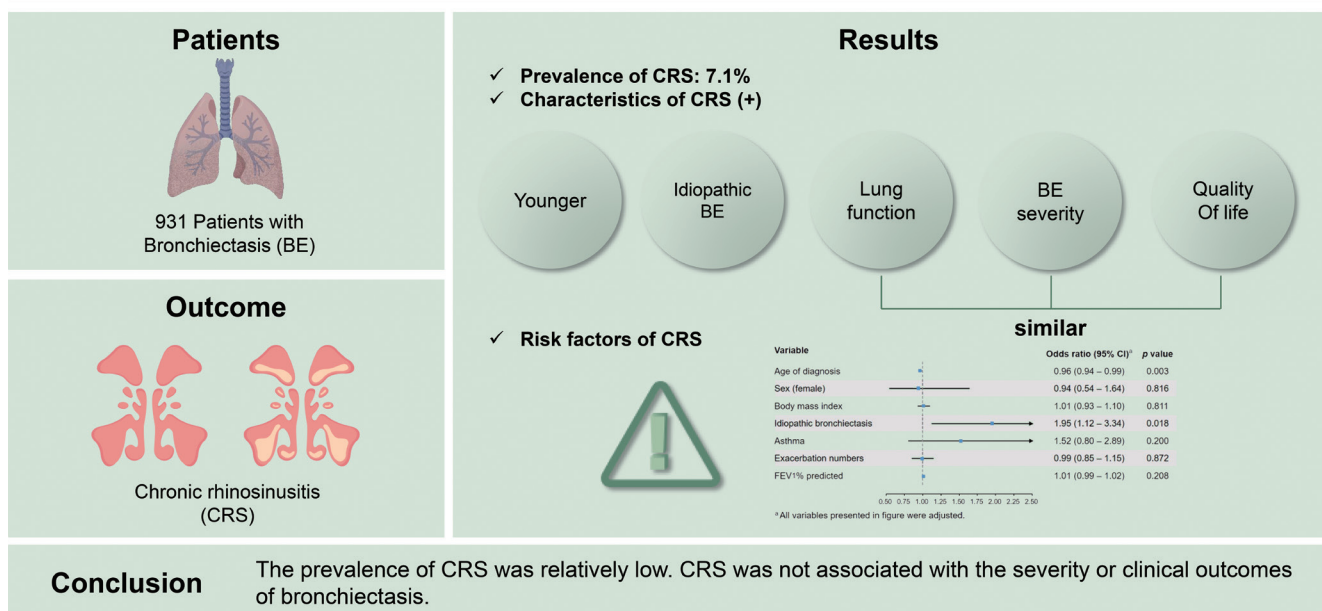


Prevalence of chronic rhinosinusitis and its relating factors in patients with bronchiectasis: findings from KMBARC registry

Iseul Yu¹, Suk Joong Yong¹, Won-Yeon Lee¹, Sang-Ha Kim¹, Hyun Lee², Ju Ock Na³, Deog Kyeom Kim⁴, Yeon-Mok Oh⁵, Ji-Ho Lee¹, and on behalf of the KMBARC

¹Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju; ²Division of Pulmonary Medicine and Allergy, Department of Internal Medicine, Hanyang University Hospital, Seoul; ³Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan; ⁴Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Seoul National University College of Medicine, Seoul; ⁵Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

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Correspondence to Ji-Ho Lee, M.D.

Department of Internal Medicine, Yonsei University Wonju College of Medicine, 20 Ilsan-ro, Wonju 26426, Korea

Tel: +82-33-741-0926, Fax: +82-33-741-0928, E-mail: airwayleejh@yonsei.ac.kr

https://orcid.org/0000-0001-8744-156X

Background/Aims: Patients with bronchiectasis often present with respiratory symptoms caused by chronic rhinosinusitis (CRS). However, studies on the prevalence of CRS and its relationship with bronchiectasis are limited.

Methods: The baseline characteristics of patients with bronchiectasis recruited from the Korean Multicenter Bronchiectasis Audit and Research Collaboration were analyzed. CRS diagnosis was determined by a physician, on the basis of medical records, upper airway symptoms, and/or radiologic abnormalities. Questionnaires for quality of life, fatigue, and depression were administered when patients were stable for a minimum of 4 weeks after the bronchiectasis exacerbation.

Results: The prevalence of CRS was 7.1% (66/931). Patients with CRS were significantly younger than those without CRS (60.5 ± 10.7 years vs. 64.6 ± 9.3 years, $p = 0.001$). Idiopathic bronchiectasis was more common in patients with CRS compared to those without CRS (53.0% vs. 36.0%, $p = 0.006$). Lung function, inflammatory markers, exacerbations, bronchiectasis severity, and scores for quality of life, fatigue, and depression did not differ between the two groups. In a logistic regression analysis, CRS was associated with age of bronchiectasis diagnosis (odds ratio [OR], 0.96; 95% confidence interval [CI], 0.94 to 0.99; $p = 0.003$) and idiopathic bronchiectasis (OR, 1.95; 95% CI, 1.12 to 3.34; $p = 0.018$).

Conclusions: The prevalence of CRS was relatively low. CRS was not associated with the severity or clinical outcomes of bronchiectasis. Early diagnosis and idiopathic etiology were associated with CRS. Our findings reflect the low recognition of CRS in the clinical practice of bronchiectasis and highlight the need for awareness of CRS by adopting objective diagnostic criteria.

Keywords: Sinusitis; Bronchiectasis; Etiology; Idiopathic

INTRODUCTION

Bronchiectasis is defined as an irreversible dilation of the airway that results in impaired mucociliary clearance and accumulation of mucus or bacteria [1]. Thus, patients with bronchiectasis often present with excessive sputum production and recurrent bacterial infections. Although bronchiectasis is quite common, its prevalence and impact have been studied for the past two decades [2]. It is often difficult to determine etiology of bronchiectasis or contributing factors in more than 50% of patients, which is considered idiopathic. Upper airway disease has not been regarded as an etiology of bronchiectasis.

United airway disease is the concept that upper and lower airways are not dissociated, but forms a single organ [3]. Thus, any disease process that affects the upper airway is likely to affect the lower airway and *vice versa*. The archetype is the allergic rhinitis (AR) in asthma [4]. Approximately 80% of patients with asthma have AR. AR was associated with increased risk of the development of asthma and severity of AR was positively correlated with severity of asthma. Chronic rhinosinusitis (CRS) is defined as sinonasal inflammation that persists for ≥ 12 weeks [5]. Respiratory symptoms owing to CRS and abnormalities in sinus radiographs or computed tomography (CT) are commonly observed in

patients with bronchiectasis. A recent meta-analysis reported that the prevalence of CRS was 62% in bronchiectasis [6]. Additionally, CRS was associated with higher bronchiectasis severity, poor quality of life, and frequent exacerbations [6]. However, the study population was small, and the majority of studies were conducted in a few countries.

Considering the insufficient evidence on the relationship between CRS and bronchiectasis, additional studies on the prevalence of CRS and its relationship with bronchiectasis are warranted. This study aimed to determine the prevalence of CRS and related factors in a large cohort of patients with bronchiectasis.

METHODS

Study population

The data source for this study was the Korean Multicenter Bronchiectasis Audit and Research Collaboration (KM-BARC). The KM-BARC was organized to examine the clinical characteristics and phenotypes of patients with bronchiectasis, promote clinical studies, and improve treatment and instructions for the diagnosis and management of bronchiectasis. The KM-BARC protocol primarily followed the European Multicenter Bronchiectasis Audit and Research

Collaboration (EMBARC). The inclusion criteria were adult patients aged ≥ 18 years and those with bronchiectasis affecting one or more lobes demonstrated on chest CT, irrespective of the presence of respiratory symptoms. The exclusion criteria were cystic fibrosis, traction bronchiectasis due to interstitial lung disease, and treatment for pneumonia, pulmonary tuberculosis, or non-tuberculous mycobacterial infection. Baseline data were collected at study enrollment, and follow-up data were scheduled to be obtained annually for a minimum of 5 years. This study was conducted using baseline data. The study protocol and baseline characteristics of KMBARC compared with those of other international cohorts have been described in more detail in recent publications [7,8].

The Institutional Review Board of Wonju Severance Christian Hospital (CR318139) and of all participating institutions approved the study and adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before enrollment in the study.

Data collection

The patients were enrolled by a pulmonologist from 50 hospitals between August 2018 and April 2021. According to the definition of bronchiectasis exacerbation for clinical research, which was suggested by international consensus, bronchiectasis exacerbation was defined when patients with bronchiectasis had deteriorating symptoms in three or more of the six following conditions for a minimum of 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, and hemoptysis, and a change in treatment for the control of respiratory symptoms was required [9]. The number of exacerbations and hospitalizations was restricted to previous 1 year before study enrollment.

The etiology of bronchiectasis was determined at the physician's discretion. The radiological severity of bronchiectasis was evaluated using the modified Reiff score, which assesses the characteristics of bronchial dilatation and number of involved lobes [10]. The clinical severity of bronchiectasis was measured using the following two scoring systems: bronchiectasis severity index (BSI) and FACED [11,12].

The Bronchiectasis Health Questionnaire (BHQ) was developed and validated to measure disease-specific health status in patients with bronchiectasis [13,14]. The BHQ has 10 items answered on a seven points scale (1 to 7 points). The total summation of the BHQ was transformed to a range

of 0 to 100 points, with higher scores indicating a better quality of life. The Fatigue Severity Score (FSS) was used to measure fatigue symptoms. FSS has nine items answered on a seven points scale (1 to 7 points). FSS is the summation of each variable, ranging from 9 to 63 points, with higher scores representing more severe fatigue [15,16]. The Patient Health Questionnaire 9 (PHQ-9) was used to assess depressive symptoms [17]. PHQ-9 has nine items that are answered on a four points scale (0 to 3 points). PHQ-9 ranges from 0 to 27 points, with higher scores indicating more severe depression. These three questionnaires were administered when patients were stable for a minimum of 4 weeks apart from the exacerbation of bronchiectasis.

Outcome variables

The diagnosis of CRS or nasal polyps was determined by patients' response to written questionnaires. No predefined diagnostic criteria were used for the evaluation of CRS in our cohort. The presence of either CRS or nasal polyps was considered as CRS. CRS prevalence was defined as the ratio of patients with CRS among the study population. Bronchiectasis duration was defined as the interval between the first date of bronchiectasis diagnosis and the date of study enrollment. The age at bronchiectasis diagnosis was determined by the first date of bronchiectasis diagnosis, which was based on medical records or patient interviews.

Statistical analysis

Descriptive statistics are presented as mean values with standard deviations for continuous variables and numbers of patients with percentages for categorical variables. An independent *t* test was applied for continuous variables, and the chi-square test was applied for categorical variables to compare baseline characteristics between patients with and without CRS. The factors associated with CRS were examined using binary logistic regression analysis and presented as odds ratios (ORs) with 95% confidence intervals (CIs). The multivariable analysis included factors associated with CRS in previous studies and variables significantly different between patients with and without CRS in univariable analyses. Statistical analyses were conducted using the SPSS statistical software version 25.0 (IBM Co., Armonk, NY, USA) and R software version 4.0.3 (R Development Core Team, Vienna, Austria). Statistical significance was set at $p < 0.05$.

RESULTS

Baseline characteristics

In total, 931 patients with bronchiectasis were enrolled in this study. Among them, 66 were identified as having CRS. Therefore, the prevalence of CRS was 7.1%. The baseline characteristics were compared between patients with and without CRS (Table 1). Patients with CRS were significantly younger than those without CRS (60.5 ± 10.7 years vs. 64.6 ± 9.3 years, $p = 0.001$). The proportion of female was 54.5% and 56.3% for patients with and without CRS, respectively ($p = 0.788$). Duration of bronchiectasis was 2.9 ± 1.6 and 3.3 ± 1.6 years for patients with and without CRS, respectively ($p = 0.136$). Proportion of patients with asthma was 22.7% and 20.0% for patients with and without CRS, respectively ($p = 0.283$). The etiology of bronchiectasis was also compared between the two groups. Post-infectious bronchiectasis was more common in patients without CRS than in those with CRS (20.0% vs. 7.6%, $p = 0.013$).

However, idiopathic bronchiectasis was more common in patients with CRS compared to those without CRS (53.0% vs. 36.0%, $p = 0.006$). Tuberculosis origin was 13.6% in patients with CRS and 20.6% in those without CRS ($p = 0.175$). Colonization of *Pseudomonas aeruginosa* and sputum volume were comparable between the two groups.

Comparison of clinical index and laboratory results

Clinical indices and laboratory test results were analyzed (Table 2). Number of exacerbations for previous 1 year was 1.0 ± 1.3 and 0.9 ± 1.7 for patients with and without CRS, respectively ($p = 0.801$). Hospitalization rate was 10.6% and 17.5% in patients with and without CRS, respectively ($p = 0.153$). Patients with respiratory failure and treated with long term oxygen therapy or noninvasive ventilation were significantly higher in patients with CRS compared to those without CRS (6.1% vs. 2.0%, $p = 0.031$). The modified Reiff score was 11.4 ± 4.4 and 12.1 ± 4.1 for patients

Table 1. Baseline characteristics of study subjects and comparison between patients with and without chronic rhinosinusitis

Variable	CRS (-) (n = 865)	CRS (+) (n = 66)	p value
Age, yr	64.6 ± 9.3	60.5 ± 10.7	0.001
Female sex	486 (56.3)	36 (54.5)	0.788
Duration, yr	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
NTM	39 (4.5)	4 (6.1)	0.563
Asthma or COPD	57 (6.6)	3 (4.5)	0.514
RA	17 (2.0)	0	0.250
Others ^a	19 (2.2)	7 (10.6)	< 0.001
PA colonization	59 (6.8)	7 (10.6)	0.248
Sputum volume, cc/day	26.2 ± 44.1	48.2 ± 113.3	0.130
Sputum volume, ≥ 30 cc/day	215 (25.5)	19 (30.2)	0.416

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

CRS, chronic rhinosinusitis; COPD, chronic obstructive pulmonary disease; NTM, nontuberculosis mycobacterium; RA, rheumatoid arthritis; PA, *Pseudomonas aeruginosa*.

^aInflammatory bowel disease, primary ciliary dyskinesia, antibody deficiency, diffuse panbronchiolitis, gastroesophageal reflux disease, and allergic bronchopulmonary aspergillosis.

Table 2. Comparison of clinical index and laboratory test results between patients with and without chronic rhinosinusitis

Variable	CRS (-) (n = 865)	CRS (+) (n = 66)	p value
Number of exacerbations	0.9 ± 1.7	1.0 ± 1.3	0.801
Hospitalization	151 (17.5)	7 (10.6)	0.153
LTOT or NIV	17 (2.0)	4 (6.1)	0.031
Forced vital capacity, L	2.6 ± 0.8	2.7 ± 0.8	0.469
Forced vital capacity, %	73.7 ± 15.7	75.7 ± 17.3	0.403
Radiologic extent (lobe)	3.4 ± 1.7	3.4 ± 1.6	0.418
Modified Reiff score	12.1 ± 4.1	11.4 ± 4.4	0.212
C-reactive protein, mg/dL	1.5 ± 2.9	1.1 ± 1.6	0.324
White blood cells, × 10 ⁹ /L	7.26 ± 2.59	7.14 ± 2.32	0.779

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

CRS, chronic rhinosinusitis; LTOT, long term oxygen therapy; NIV, noninvasive ventilation.

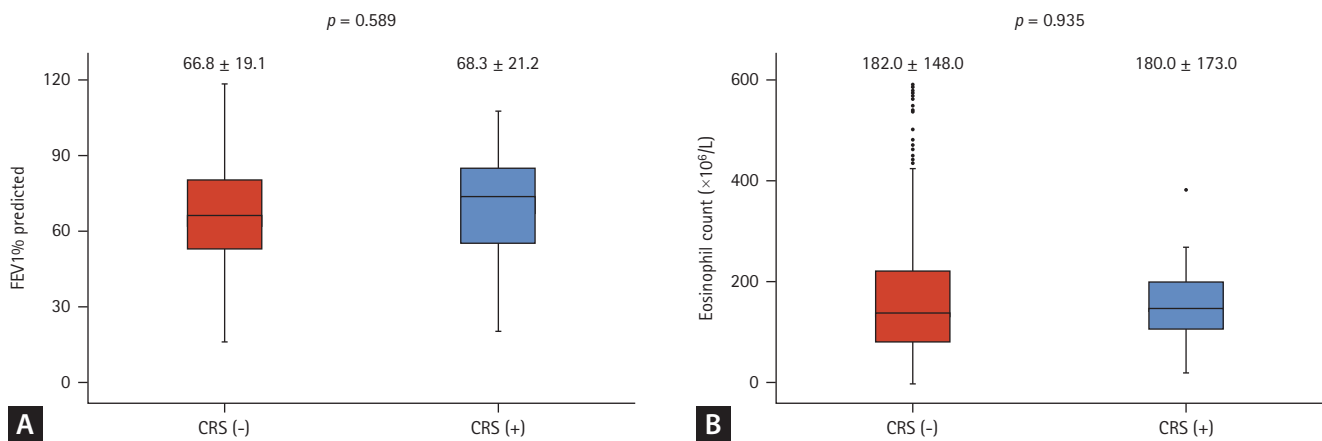


Figure 1. Comparison of forced expiratory volume in 1 second % (FEV1%) predicted (A) and blood eosinophil count (B) according to the presence of chronic rhinosinusitis (CRS).

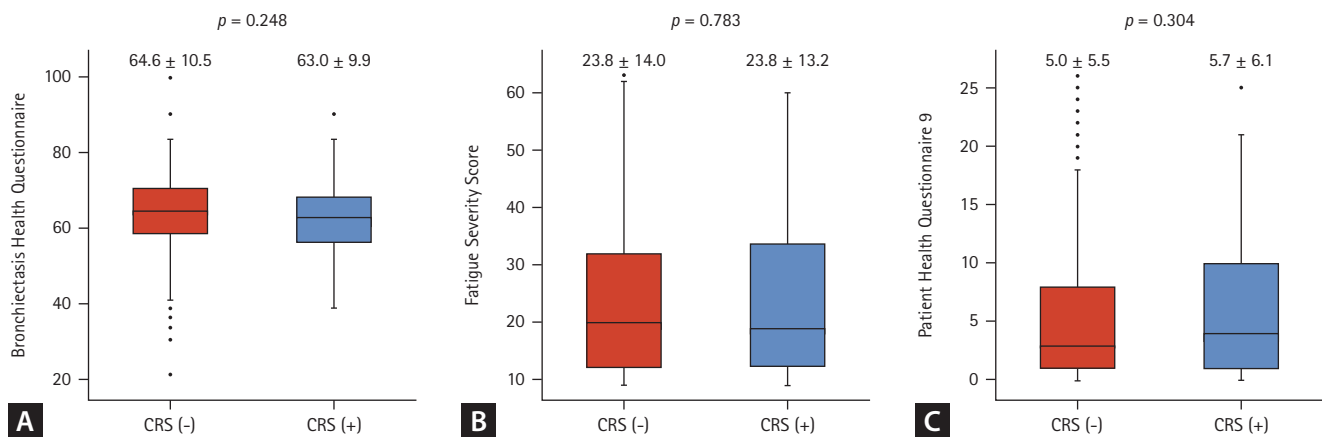


Figure 2. Results of three patient-reported outcomes. (A) Bronchiectasis Health Questionnaire, (B) Fatigue Severity Score, and (C) Patient Health Questionnaire 9 are compared between patients with and without chronic rhinosinusitis (CRS).

with and without CRS, respectively ($p = 0.212$). Forced expiratory volume in 1 second % (FEV1%) predicted (Fig. 1A) and blood eosinophil count (Fig. 1B) was not different in patients with CRS compared to those without CRS.

The BHQ (Fig. 2A), FSS (Fig. 2B), and PHQ-9 depressive symptom score (Fig. 2C) did not differ for patients with CRS and for those without CRS. The severity of bronchiectasis assessed using BSI (Fig. 3A) and FACED (Fig. 3B) was classified into mild, moderate, and severe. No difference was found in the severity classification between the two groups (BSI, $p = 0.169$; FACED, $p = 0.142$).

Relevant factors underlying CRS in bronchiectasis

Univariable and multivariable analyses were conducted to identify the CRS-related factors (Supplementary Table 1). In a multivariable analysis, young age at bronchiectasis diagnosis was identified as a factor associated with CRS (OR, 0.96; 95% CI, 0.94 to 0.99; $p = 0.003$) (Fig. 4). Idiopathic

bronchiectasis was also associated with CRS (OR, 1.95; 95% CI, 1.12 to 3.34; $p = 0.018$).

DISCUSSION

This study presents that the prevalence of CRS in the Korean bronchiectasis cohort was 7.1%. The severity and clinical outcomes of bronchiectasis were comparable between the patients with and without CRS. Early diagnosis and idiopathic etiology of bronchiectasis were significant factors associated with CRS.

The prevalence of CRS in patients with bronchiectasis was examined in a recent systematic review [6]. The mean prevalence of CRS was 62% (range, 32% to 80%) [18-25]. CRS was defined as two or more of the following upper respiratory symptoms: nasal obstruction, congestion, facial pain/pressure, reduction or loss of smell for 12 weeks, and/or

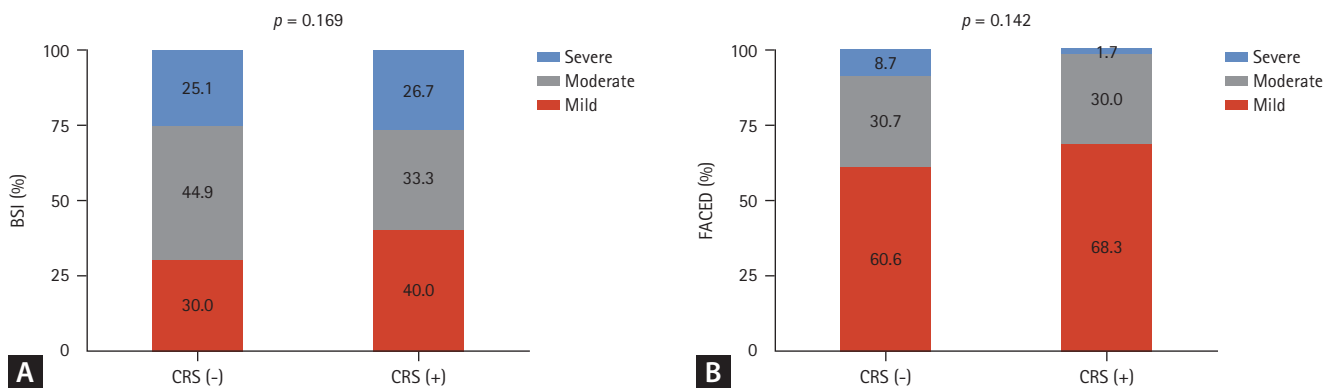


Figure 3. Severity of bronchiectasis classified by (A) bronchiectasis severity index (BSI) and (B) FACED are compared between patients with and without chronic rhinosinusitis (CRS).

Variable	Odds ratio (95% CI) ^a	<i>p</i> 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

Figure 4. Odds ratios predictive of chronic rhinosinusitis in a multivariable analysis. FEV1%, forced expiratory volume in 1 second %; CI, confidence interval. ^aAll variables presented in figure were adjusted.

paranasal sinus inflammation demonstrated by endoscopy or CT according to the European Position Paper on Rhinosinusitis and Nasal Polyp (EPOS) criteria [26]. However, all included studies were conducted with a small number of study participants (range, 60 to 161). Other international and nationwide cohorts of bronchiectasis have rarely reported the prevalence of CRS [27]. A recent Korean population-based study did not address CRS as bronchiectasis-related comorbidity [28]. A study of the baseline characteristics of EM-BARC did not describe CRS in comorbidities [29]. Additionally, studies on the characteristics of KMBARC compared to those of India and Australia registries did not report the prevalence of CRS [8,30,31]. Therefore, an exact comparison of the prevalence of CRS with that of other cohorts is not feasible. Large nationwide cohorts lacking the prevalence of CRS as compared to that in small cohorts reporting a high prevalence of CRS did not employ predefined criteria for CRS, such as EPOS, as with KMBARC. Therefore, the absence of diagnostic criteria may have affected the low prevalence of CRS in our study. Moreover, the prevalence of CRS in general population has been variable, ranging from 1.0% to 12.1% worldwide [32]. The prevalence of CRS based on symptoms and sinus radiology was 3.0% to 6.4% in Netherlands [33]. The prevalence of CRS was 3.86% in the fifth Korea National Health and Examination Survey [34]. Accordingly, the prevalence of CRS in our study was similar or slightly higher than in the general population. Our study results might reflect an underestimation of CRS, and active screening of CRS is necessary in the clinical practice of bronchiectasis.

Previous studies have reported the influence of CRS on clinical outcomes of bronchiectasis. A single study reported significant lower FEV1% for those with CRS compared to those without CRS among patients with bronchiectasis (75.8% \pm 3.0% vs. 90.0% \pm 4.0%, $p < 0.05$) [25]. However, no difference in lung function was noted in other studies [22,24]. Bronchiectasis severity assessed using the CT was significantly higher in patients with CRS than in those without CRS [19,24,25], whereas clinical severity assessed using BSI did not differ [22]. A study reported a greater risk of bronchiectasis exacerbation in patients with CRS than in those without CRS ($p = 0.02$) [22]. On the contrary, FEV1%, severity of bronchiectasis using CT and clinical index, and exacerbation risk was not different between patients with and without CRS in our study. These negative study results might be attributed to the different study populations and protocols used. Meanwhile, considering the small number

of study participants in most previous studies, the results are difficult to generalize. Therefore, further studies of the clinical implications of CRS in bronchiectasis are warranted.

Few studies have compared the clinical manifestations according to the etiology of bronchiectasis. Almost patients with idiopathic bronchiectasis had CRS compared to those with post-infective bronchiectasis (84% vs. 50%, $p < 0.01$) [35]. The age at bronchiectasis diagnosis was lower in patients with CRS (38 \pm 2.5 years) compared to those without CRS (47 \pm 4 years), although statistical significance was not found [24]. Our study results are consistent with previous studies, reporting that early age at bronchiectasis diagnosis and idiopathic bronchiectasis were identified as factors associated with the presence of CRS. When etiology of bronchiectasis is investigated, upper airway disease including CRS is not considered as a cause of bronchiectasis. However, recent observational study reported the temporal relationship between CRS and bronchiectasis [36]. Bronchiectasis was diagnosed after 6 years of precedent CRS. CRS without nasal polyps was strongly associated with bronchiectasis compared to CRS with nasal polyps (OR, 4.46 vs. 2.21). CRS without nasal polyps was more prevalent in young adulthood, whereas CRS with nasal polyps had a significantly older age distribution [37]. These findings are consistent with united airway hypothesis. Potential mechanisms of this hypothesis are drainage of the upper inflammatory mediators into lower airway through aspiration, dissemination of the upper airway inflammation via bloodstream, and neural modulation proven in nasal provocation with allergen [38]. Accordingly, age distribution of CRS phenotype and temporal relationship with bronchiectasis might contribute to the early diagnosis of bronchiectasis in patients with CRS. CRS might be considered as a potential cause of bronchiectasis, particularly before classifying it into idiopathic bronchiectasis.

This study has several limitations. First, this study lacked predefined diagnostic criteria for CRS. We did not collect detailed information on CRS based only on symptoms or accompanying objective tests such as paranasal CT or endoscopy. Diagnosis of CRS was based on merely patients' response to written questionnaires. Meticulous investigation through electronic chart review and history taking for CRS might not be conducted. Therefore, it is presumed that a lack of diagnostic criteria affects low prevalence and overall study outcomes of CRS. However, to the best of our knowledge, this is the first study to report the prevalence of CRS in a large nationwide cohort. Second, apart from the rela-

tively lower prevalence of CRS, the imbalanced sample size between patients with and without CRS might have affected the comparative analysis of clinical outcomes. Third, the etiology of bronchiectasis was determined at the physician's discretion. Idiopathic bronchiectasis is generally diagnosed if its specific causes are unknown. Therefore, it is prone to recall bias because it depends on the patients' memory.

In this study, the prevalence of CRS in bronchiectasis was comparatively low. CRS was not associated with the severity or clinical outcomes of bronchiectasis. Early diagnosis and idiopathic etiology were associated with CRS. Our findings reflect the low recognition of CRS in the clinical practice of bronchiectasis and highlight the need for awareness of CRS by adopting objective diagnostic criteria. The further assessment of the prevalence and implications of CRS may help comprehend the role of CRS and optimize the treatment of bronchiectasis.

KEY MESSAGE

1. The prevalence of chronic rhinosinusitis (CRS) was 7.1% in the Korean bronchiectasis cohort.
2. Early age at bronchiectasis diagnosis and idiopathic bronchiectasis were associated with the presence of CRS.
3. Our findings reflect low recognition of CRS in the clinical practice of bronchiectasis and highlight the need for awareness of CRS by adopting objective diagnostic criteria.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Table 1. Factors associated with chronic rhinosinusitis in logistic regression analysis

Factors	Univariable analysis		Multivariable analysis	
	OR (95% CI)	<i>p</i> value	OR (95% CI) ^b	<i>p</i> value
Age of bronchiectasis diagnosis	0.96 (0.94–0.99)	0.002	0.96 (0.94–0.99)	0.003
Female sex	0.93 (0.57–1.54)	0.788	0.94 (0.54–1.64)	0.816
Body mass index	1.02 (0.95–1.10)	0.636	1.01 (0.93–1.10)	0.811
Idiopathic bronchiectasis ^a	2.01 (1.22–3.33)	0.006	1.95 (1.12–3.34)	0.018
Asthma	1.18 (0.65–1.18)	0.595	1.52 (0.80–2.89)	0.200
Exacerbation numbers	0.98 (0.86–1.13)	0.807	0.99 (0.85–1.15)	0.872
FEV1% predicted	1.01 (0.99–1.02)	0.286	1.01 (0.99–1.02)	0.208

OR, odds ratio; CI, confidence interval; FEV1%, forced expiratory volume in 1 second %.

^aReference was non-idiopathic bronchiectasis.

^bAll variables listed in table were adjusted.