Increased bronchiectasis risk and related risk factors in inflammatory bowel disease: a 10-year Korean national cohort study

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Shareable abstract (@ERSpublications)
This nationwide longitudinal cohort study demonstrated that the risk of developing bronchiectasis was higher in individuals with IBD than in those without IBD and showed an increased disease burden in patients with IBD and bronchiectasis. https://bit.ly/3TyXUsM

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Abstract

Background The association between inflammatory bowel disease (IBD) and an increased risk of bronchiectasis, as well as contributing factors, remains unclear. Additionally, whether bronchiectasis increases disease burden in IBD remains unknown. Therefore, this study aimed to: 1) assess whether IBD increases the risk of incident bronchiectasis; 2) compare the risk of bronchiectasis between individuals with Crohn's disease (CD) and those with ulcerative colitis (UC); 3) identify risk factors for bronchiectasis in individuals with IBD; and 4) examine the disease burden in individuals with IBD and bronchiectasis *versus* those without.

Methods We conducted a population-based matched cohort study involving adults aged ⩾20 years with IBD, using data acquired from the Korean National Health Insurance Service-National Sample Cohort database between 2002 and 2012.

Results During the mean follow-up of 9.6 years, the incidence rate of bronchiectasis was 419.63 out of 100 000 person-years (PY) and 309.65 out of 100 000 PY in the IBD and matched cohorts (adjusted hazard ratio (aHR) 1.21, 95% CI 1.05–1.39), respectively. UC was associated with increased bronchiectasis risk (aHR 1.42, 95% CI 1.19–1.69), but CD was not. Multivariate Cox regression analyses showed that age, male sex, medical aid, underweight status, COPD and diabetes mellitus were associated with an increased risk of bronchiectasis in the IBD cohort ($p<0.05$). The mortality, emergency department visit and hospitalisation rates were significantly higher for individuals with IBD and bronchiectasis compared with those without bronchiectasis ($p<0.05$).

Conclusion IBD is associated with increased risk of bronchiectasis, which results in a greater disease burden in individuals with IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic idiopathic inflammatory disease which affects the gastrointestinal tract and comprises two major types: Crohn's disease (CD) and ulcerative colitis (UC) [1].

As a systemic disease, IBD can manifest in extraintestinal organs such as the skin, eyes, liver, lungs and pancreas [2]. Although pulmonary involvement is rare in individuals with IBD, its co-occurrence with gastrointestinal symptoms can pose significant challenges [3, 4]. Additionally, accompanying pulmonary diseases are significant contributors to the mortality of individuals with IBD, suggesting the importance of effective management of pulmonary diseases in this population [5, 6].

Bronchiectasis is the most prevalent airway disease in individuals with IBD, and up to two-thirds of individuals with IBD experiencing airway disease have bronchiectasis [4, 7–10]. Despite the relatively well-recognised coexistence of these two diseases, whether IBD is a risk factor for bronchiectasis remains unknown. Although some previous studies have suggested an association between bronchiectasis and IBD [7, 11–13], most studies utilised cross-sectional designs [11–14] and did not consider potential confounders (such as body mass index (BMI), smoking status and alcohol consumption) that might affect the association between IBD and bronchiectasis [7, 11, 12, 14], resulting in limitations in demonstrating causal inference between the two conditions. Moreover, since bronchiectasis in individuals with CD has been less well described compared to bronchiectasis in individuals with UC [10, 14, 15], whether the risk of developing bronchiectasis is similar between individuals with CD and those with UC is unclear.

Comorbid bronchiectasis is believed to exacerbate the disease burden in individuals with IBD. The information on this issue is limited, with only one study indicating that the pneumonia-related mortality rate is higher in individuals with IBD and bronchiectasis than in those without bronchiectasis [16]. Consequently, whether bronchiectasis results in worse treatment outcomes in individuals with IBD remains unknown.

This study, using a representative nationwide database, aimed to evaluate: 1) whether IBD is a risk factor for incident bronchiectasis, even after considering various confounders; 2) if the risk of bronchiectasis differs between individuals with CD and those with UC; 3) the factors associated with an increased risk of bronchiectasis in individuals with IBD; and 4) whether the disease burden is higher in individuals with IBD and bronchiectasis than in those without bronchiectasis.

Material and methods

Study population

We used data taken from the Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC), a representative population-based retrospective cohort in Korea. The NHIS-NSC database encompasses health data on: 1) major and minor diagnoses using the tenth revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes; 2) drug prescriptions; and 3) health screening examination findings [17].

Between 1 January 2002 and 31 December 2012, the database recorded data for 706 971 adults ⩾20 years of age. After excluding 4164 subjects diagnosed with IBD between 1 January 2002 and 31December 2003, and excluding 1797 individuals diagnosed with bronchiectasis before enrolment and 1738 individuals diagnosed with bronchiectasis within the wash-out period (1 year after IBD diagnosis), a total of 699 272 subjects were included in our analysis. Of these, 6513 individuals were identified as having IBD (the IBD cohort), while 692 759 individuals were not. To establish a matched cohort, we performed a 1:4 matching based on age, sex and type of insurance for each individual with IBD and the controls without IBD. The IBD (n=6513) and matched (n=26 052) cohorts were followed up until death, bronchiectasis diagnosis or 31 December 2012, whichever occurred first (figure 1).

Exposures

IBD was defined as the presence of a major or minor diagnostic code associated with ICD-10 code K50 for CD or ICD-10 code K51 for UC, with special V codes (V130 for CD and V131 for UC) provided by the Rare Intractable Diseases (RID) programme, which is part of the NHIS [18]. In Korea, the RID programme provides a copayment reduction of approximately 10% for various rare and intractable diseases including IBD. To register for this programme, physicians submit diagnostic certification and the certification undergoes thorough review by the NHIS.

Outcomes

The primary outcomes of this study were the incidence and risk of bronchiectasis in the IBD cohort compared with the matched cohort. Bronchiectasis was defined as the presence of at least one claim recorded under the ICD-10 code J47 [19–22]. The secondary outcomes of this study were as follows: 1) comparison of the risk of bronchiectasis according to IBD subtype; 2) identification of risk factors for

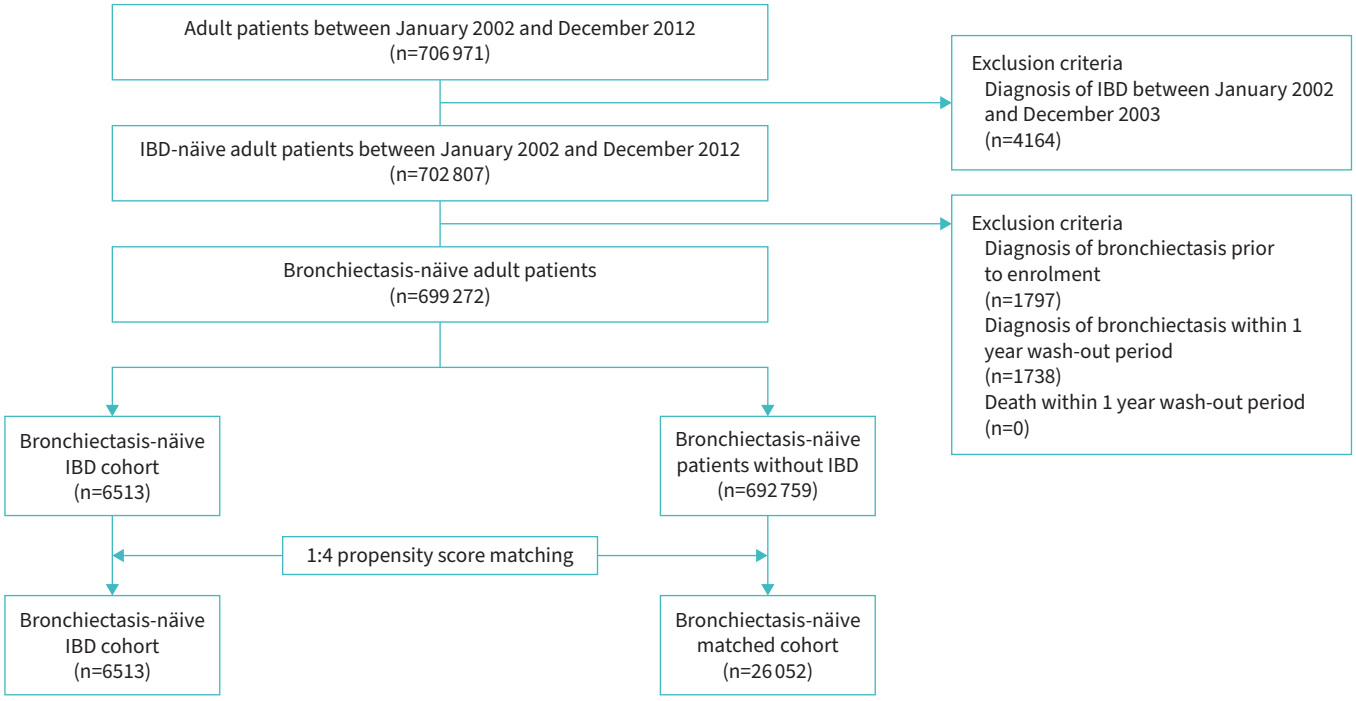

FIGURE 1 Flow chart showing the identification of the study cohorts. IBD: inflammatory bowel disease.

bronchiectasis in individuals with IBD; and 3) comparison of the disease burden, including healthcare utilisation and mortality, according to the presence or absence of bronchiectasis in individuals with IBD.

Covariables

BMI was calculated as the weight of individuals (in kg) divided by the square of their height (in m), and individuals were classified into underweight (<18.5 $kg \cdot m^{-2}$), normal (18.5–22.9 $kg \cdot m^{-2}$), overweight (23.0–24.9 $kg \cdot m^{-2}$) and obese (⩾25.0 $kg \cdot m^{-2}$) groups according to the recommended classification for Asians [23]. Smoking status was classified as never, former or current. Alcohol consumption and physical activity were classified using the number of days per week alcohol was consumed or physical activity was engaged in. The Charlson Comorbidity Index (CCI) was calculated by observing comorbidities over the past year [24]. We collected data on IBD medications, including corticosteroids, immunomodulators (5-aminosalicylic acid, azathioprine, mercaptopurine, cyclosporine, tacrolimus and methotrexate) and biologics (infliximab, adalimumab, golimumab and vedolizumab) [25].

Baseline comorbidities were determined by identifying conditions with at least one claim under specific ICD-10 codes, where these codes were categorised as primary diagnoses during the baseline period, as follows: asthma (J45–J46), COPD (J42–J44, except J43.0 (unilateral emphysema)), cerebrovascular disease (G45–G46, I60–I69), cardiovascular disease including hypertension (I10–I15), angina or myocardial infarction (I20, I21–I22 and I252) and heart failure (I43, I50, I09.9, I11.0, I25.5, I13.0, I13.2, I42.0, I42.5–I42.9 and P29.0), diabetes mellitus (E10–E14), rheumatoid arthritis (M05–M06, M32-34, M315, M351, M353 and M360) and malignancy (C00–C97) [26–31].

Mortality was determined using data obtained from Statistics Korea, an initiative of the Ministry of Strategy and Finance of South Korea. Respiratory disease-related mortality was defined as death in which the primary diagnosis was coded under ICD-10 codes for any respiratory system disease (J00–J99). Respiratory disease-related events (emergency department (ED) visits and hospitalisations) were defined as cases associated with any respiratory system disease classified under ICD-10 codes J00–J99, irrespective of whether they were designated as major or minor diagnoses.

Statistical analysis

Categorical data were presented as numbers (percentages), and continuous data were presented as means (standard deviation) or medians (interquartile range), as appropriate. Categorical data were compared using

the chi-squared test, and continuous data were compared using the t-test or the Mann–Whitney U-test, as appropriate.

The incidence rate (per 100 000 person-years (PY)) of bronchiectasis was compared between the IBD and matched cohorts using the normal approximation test for binominals. The cumulative incidence of bronchiectasis was compared between the IBD and matched cohorts by using a cumulative incidence curve and Gray's test. We used a Cox proportional hazards regression model with adjustments for insurance type, BMI, smoking status, alcohol consumption, physical activity, CCI and medication to determine the hazard ratio (HR) for incident bronchiectasis in the IBD cohort relative to the matched cohort.

The incidence of ED visits or hospitalisations was calculated by dividing the number of ED visits or hospitalisations by the sum of the follow-up durations and presented as the rate per 100 000 PY. All tests were two-sided, and statistical significance was set at p-values <0.05. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board of the Chungbuk National University Hospital (application no. 2021-01-028). The requirement for informed consent was waived because the NHIS database was constructed after anonymisation.

Results

Baseline characteristics

The baseline characteristics of the individuals, including age, sex and type of insurance, exhibited a well-balanced distribution between the two cohorts (table 1). The IBD cohort had a lower rate of individuals with normal weight (59.1% *versus* 64.0%, p<0.01) but a higher rate of ex-smokers (6.2% *versus* 4.7%, p<0.01) and individuals with a CCI ⩾2 (13.0% *versus* 9.0%, p<0.01) than the matched cohort.

Risk of incident bronchiectasis

During a mean follow-up duration of 9.6 years, the incidence rate of bronchiectasis was higher in the IBD cohort than in the matched cohort (419.63/100 000 PY *versus* 309.65/100 000 PY, p<0.01). The IBD cohort had a 1.21-fold (95% CI 1.05–1.39) increased risk of developing bronchiectasis compared with the matched cohort (table 2). Similarly, the cumulative incidence plot showed a significantly higher incidence of bronchiectasis in the IBD cohort than in the matched cohort (Gray's test, p<0.01) (figure 2). Subgroup analyses revealed that age, sex, type of insurance, BMI, smoking status, alcohol consumption and physical activity did not significantly affect the relationship between IBD and the risk of bronchiectasis (p-value for interaction >0.05 for all in Model 2).

IBD subtypes and risk of incident bronchiectasis

The risk of incident bronchiectasis was significantly higher in the UC cohort than in the matched cohort (adjusted HR 1.42, 95% CI 1.19–1.69). Conversely, it was not significantly increased in the CD cohort compared with the matched cohort (adjusted HR 1.24, 95% CI 0.97–1.57) (Supplementary Table 1).

Risk factors for incident bronchiectasis in individuals with IBD

Table 3 summarises the risk factors of incident bronchiectasis in the IBD cohort. In the multivariable analyses, age (the highest adjusted HR in those aged 60–69 years was 11.52, 95% CI 4.95–26.81), male sex (adjusted HR 1.35, 95% CI 1.03–1.77), poor income level (adjusted HR 2.17, 95% CI 1.27–3.72), underweight status (adjusted HR 2.49, 95% CI 1.42–4.37), COPD (adjusted HR 1.64, 95% CI 1.06–2.54) and diabetes mellitus (adjusted HR 1.55, 95% CI 1.07–2.23) were significant factors associated with an elevated risk of incident bronchiectasis.

Mortality and healthcare utilisation

All-cause mortality and healthcare utilisation (ED visits and hospitalisations), and respiratory disease-related mortality and healthcare utilisation, were significantly higher in individuals with IBD and incident bronchiectasis than in those without incident bronchiectasis (p<0.05) (figure 3).

Discussion

This is the largest comprehensive study to evaluate the incidence of bronchiectasis in individuals with IBD compared with that in those without IBD using data from a nationwide longitudinal cohort. The incidence rate of bronchiectasis in individuals with IBD was 419.63 out of 100 000 PY, which was 1.21-fold higher than that in individuals without IBD. Furthermore, additional subgroup analysis according to IBD subtype

TABLE 1 Baseline characteristics of the study individuals

Variable	Total (N=32 565)	IBD cohort (n=6513)	Matched cohort (n=26 052)	p-value
Age (years)				0.99
20–29	4890 (15.0)	978 (15.0)	3912 (15.0)	
30–39	6235 (19.2)	1247 (19.2)	4988 (19.2)	
40–49	7680 (23.6)	1536 (23.6)	6144 (23.6)	
50–59	5750 (17.7)	1150 (17.7)	4600 (17.7)	
60–69	5355 (16.4)	1071 (16.4)	4284 (16.4)	
⩾70	2655 (8.2)	531 (8.2)	2124 (8.2)	
Sex				0.99
Male	16 175 (49.7)	3235 (49.7)	12 940 (49.7)	
Female	16 390 (50.3)	3278 (50.3)	13 112 (50.3)	
Type of insurance				0.99
Self-employed health insurance	14 900 (45.8)	2980 (45.8)	11 920 (45.8)	
Employee health insurance	16 540 (50.8)	3308 (50.8)	13 232 (50.8)	
Medical aid	1125 (3.5)	225 (3.5)	900 (3.5)	
Body mass index				<0.01
Underweight	712 (2.2)	173 (2.7)	539 (2.1)	
Normal	20 525 (63.0)	3846 (59.1)	16 679 (64.0)	
Overweight	4886 (15.0)	1098 (16.9)	3788 (14.5)	
Obese	6442 (19.8)	1396 (21.4)	5046 (19.4)	
Smoking status				<0.01
Never smoker	26 335 (80.9)	5207 (80.0)	21 128 (81.1)	
Ex-smoker	1632 (5.0)	406 (6.2)	1226 (4.7)	
Current smoker	4598 (14.1)	900 (13.8)	3698 (14.2)	
Alcohol consumption (days·week^{-1})				0.01
None	27 310 (83.9)	5403 (83.0)	21 907 (84.1)	
1–4	4536 (13.9)	939 (14.4)	3597 (13.8)	
⩾5	719 (2.2)	171 (2.6)	548 (2.1)	
Physical activity (days·week^{-1})				
None	28 971 (89.0)	5700 (87.5)	23 271 (89.3)	<0.01
1–4	2413 (7.4)	553 (8.5)	1860 (7.1)	
⩾5	1181 (3.6)	260 (4.0)	921 (3.5)	
CCI				<0.01
0–1	29 371 (90.2)	5668 (87.0)	23 703 (91.0)	
⩾2	3194 (9.8)	845 (13.0)	2349 (9.0)	
Medication				
Systemic corticosteroid use	8566 (26.3)	2086 (32.0)	6480 (24.9)	<0.01
Immunomodulator	67 (0.2)	29 (0.5)	38 (0.2)	<0.01

Data are presented as mean±standard deviation or number (%).IBD: inflammatory bowel disease; CCI: Charlson Comorbidity Index.

demonstrated that the risk of bronchiectasis was significantly increased in individuals with UC rather than those with CD. This study also revealed that the risk factors for bronchiectasis in individuals with IBD were age, male sex, poor income, underweight status, COPD and diabetes mellitus. Moreover, regarding the disease burden associated with bronchiectasis, the mortality rate and healthcare utilisation were substantially higher in individuals with IBD and bronchiectasis than in those without bronchiectasis.

To the best of our knowledge, this is the first longitudinal cohort study to reveal that the incidence of bronchiectasis in individuals with IBD was higher than that in those without IBD. Although the coexistence of IBD and bronchiectasis has been relatively well-recognised in several studies [7, 11–13], this relationship has not been clarified by longitudinal cohort studies that comprehensively consider potential confounders, resulting in a paucity of information on causal inferences regarding IBD and bronchiectasis. Accordingly, the major benefit of our study is the adoption of a longitudinal design, which is advantageous over cross-sectional studies or case series regarding causality. Furthermore, our study design has the additional advantage of comprehensively considering many confounders.

The mechanisms underlying the elevated risk of developing bronchiectasis in individuals with IBD remain unclear. Nevertheless, one hypothesis suggests a potential association with enhanced neutrophil-mediated

TABLE 2 Incidence rates and hazard ratios for bronchiectasis in inflammatory bowel disease (IBD) and matched cohorts according to sociodemographic and lifestyle risk factors

Variable	Number of individuals	Cases	Incidence rate (per 100 000 PY)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Overall					
Matched cohort	26 052	776	309.65	1 (Reference)	1 (Reference)
IBD cohort	6513	262	419.63	1.36 (1.18, 1.56)	1.21 (1.05, 1.39)
Age (years)					
20–40					
Matched cohort	8900	65	74.07	1 (Reference)	1 (Reference)
IBD cohort	2225	26	118.73	1.60 (1.02, 2.53)	1.48 (0.94, 2.34)
40–60					
Matched cohort	10 744	314	300.87	1 (Reference)	1 (Reference)
IBD cohort	2686	109	419.53	1.40 (1.12, 1.74)	1.29 (1.04, 1.61)
⩾60					
Matched cohort	6408	397	678.85	1 (Reference)	1 (Reference)
IBD cohort	1602	127	872.49	1.29 (1.05, 1.57)	1.16 (0.95, 1.42)
p-value for interaction				0.65	0.49
Sex					
Male					
Matched cohort	12 940	364	292.66	1 (Reference)	1 (Reference)
IBD cohort	3235	137	443.26	1.52 (1.25, 1.85)	1.32 (1.08, 1.61)
Female					
Matched cohort	13 112	412	326.39	1 (Reference)	1 (Reference)
IBD cohort	3278	125	396.46	1.22 (0.99, 1.48)	1.10 (0.90, 1.34)
p-value for interaction				0.12	0.12
Type of insurance					
Self-employed health insurance					
Matched cohort	11 920	342	297.66	1 (Reference)	1 (Reference)
IBD cohort	2980	107	373.16	1.25 (1.01, 1.56)	1.10 (0.88, 1.37)
Employee health insurance					
Matched cohort	13 232	386	302.82	1 (Reference)	1 (Reference)
IBD cohort	3308	137	432.33	1.43 (1.18, 1.74)	1.27 (1.04, 1.54)
Medical aid					
Matched cohort	900	48	582.57	1 (Reference)	1 (Reference)
IBD cohort	225	18	868.34	1.49 (0.87, 2.57)	1.46 (0.84, 2.52)
p-value for interaction				0.64	0.49
Body mass index					
Underweight					
Matched cohort	539	30	589.21	1 (Reference)	1 (Reference)
IBD cohort	173	14	853.17	1.45 (0.77, 2.73)	1.30 (0.68, 2.50)
Normal					
Matched cohort	16 679	474	296.48	1 (Reference)	1 (Reference)
IBD cohort	3846	138	374.90	1.27 (1.05, 1.53)	1.12 (0.93, 1.36)
Overweight					
Matched cohort	3788	121	329.77	1 (Reference)	1 (Reference)
IBD cohort	1098	45	426.03	1.29 (0.92, 1.82)	1.23 (0.87, 1.74)
Obese					
Matched cohort	5046	151	308.52	1 (Reference)	1 (Reference)
IBD cohort	1396	65	484.25	1.57 (1.18, 2.10)	1.42 (1.06, 1.90)
p-value for interaction				0.02	0.70
Smoking status					
Never smoker					
Matched cohort	21 128	630	310.50	1 (Reference)	1 (Reference)
IBD cohort	5207	212	424.74	1.37 (1.17, 1.60)	1.23 (1.05, 1.44)
Ex-smoker					
Matched cohort	1226	38	320.16	1 (Reference)	1 (Reference)
IBD cohort	406	20	514.77	1.61 (0.94, 2.77)	1.35 (0.78, 2.34)
Current smoker					
Matched cohort	3698	108	301.38	1 (Reference)	1 (Reference)
IBD cohort	900	30	347.28	1.16 (0.77, 1.73)	0.99 (0.66, 1.49)
p-value for interaction				0.38	0.64

Continued

TABLE 2 Continued

Variable	Number of individuals	Cases	Incidence rate (per 100 000 PY)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Alcohol consumption (days·week^{-1})					
None					
Matched cohort	21 907	670	318.52	1 (Reference)	1 (Reference)
IBD cohort	5403	220	425.32	1.34 (1.15, 1.56)	1.20 (1.03, 1.39)
1–4					
Matched cohort	3597	75	213.91	1 (Reference)	1 (Reference)
IBD cohort	939	35	385.55	1.80 (1.21, 2.69)	1.59 (1.06, 2.38)
⩾5					
Matched cohort	548	31	596.85	1 (Reference)	1 (Reference)
IBD cohort	171	7	428.81	0.72 (0.32, 1.63)	0.57 (0.25, 1.33)
p-value for interaction				0.86	0.08
Physical activity (days·week^{-1})					
None					
Matched cohort	23 271	686	306.69	1 (Reference)	1 (Reference)
IBD cohort	5700	217	396.87	1.29 (1.11, 1.51)	1.16 (1.00, 1.35)
1–4					
Matched cohort	1860	53	292.80	1 (Reference)	1 (Reference)
IBD cohort	553	30	566.18	1.94 (1.24, 3.04)	1.74 (1.11, 2.73)
⩾5					
Matched cohort	921	37	419.12	1 (Reference)	1 (Reference)
IBD cohort	260	15	609.79	1.46 (0.80, 2.66)	1.28 (0.70, 2.36)
p-value for interaction				0.07	0.28

Model 1 is the crude model. Model 2 was adjusted for insurance type, body mass index, smoking status, alcohol consumption, physical activity, CCI and medications. PY: person-years; HR: hazard ratio; IBD: inflammatory bowel disease; CCI: Charlson Comorbidity Index.

inflammation in individuals with IBD. Neutrophils are regarded as initial responders in inflammation in the gut mucosal inflammatory milieu in IBD [32, 33]. Moreover, neutrophil-mediated inflammatory processes, known as neutrophil extracellular traps (NET), which are extracellular webs composed of chromatin, microbicidal proteins and oxidative enzymes released by neutrophils, are found in the inflamed gut mucosa, stool or blood of individuals with IBD [34–36]. Additionally, NETs are known to be involved in causing a major tissue damage process in individuals with bronchiectasis, a well-recognised neutrophil-dominant airway disease [37, 38]. This common mechanism of neutrophil-related immune responses may contribute to bronchiectasis development in individuals with IBD. Another potential mechanism is an increased risk of recurrent respiratory infections due to immunosuppressant use. Respiratory tract infections play a pivotal role in the pathophysiology of bronchiectasis through both direct structural damage and their contribution to the chronic inflammatory cycle [39, 40]. As our study was not

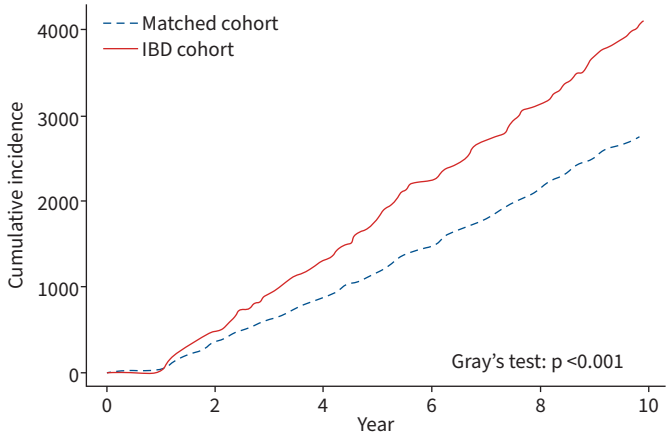

FIGURE 2 Cumulative incidence for bronchiectasis (per 100 000 person-years (PY)) in the inflammatory bowel disease (IBD) and matched cohorts.

TABLE 3 Risk factors for bronchiectasis in individuals with inflammatory bowel disease (IBD)

Variable	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Age (years)		
20–29	1 (Reference)	1 (Reference)
30–39	2.64 (1.06, 6.56)	2.65 (1.06, 6.62)
40–49	5.41 (2.32, 12.62)	5.27 (2.25, 12.38)
50–59	8.62 (3.72, 19.96)	7.76 (3.32, 18.17)
60–69	14.28 (6.25, 32.66)	11.52 (4.95, 26.81)
⩾70	14.20 (6.02, 33.49)	11.50 (4.79, 27.63)
Sex		
Male	1.12 (0.88, 1.43)	1.35 (1.03, 1.77)
Female	1 (Reference)	1 (Reference)
Type of insurance		
Self-employed health insurance	1 (Reference)	1 (Reference)
Employee health insurance	1.16 (0.90, 1.49)	1.14 (0.88, 1.47)
Medical aid	2.35 (1.43, 3.87)	2.17 (1.27, 3.72)
Body mass index		
Underweight	2.28 (1.32, 3.95)	2.49 (1.42, 4.37)
Normal	1 (Reference)	1 (Reference)
Overweight	1.14 (0.81, 1.59)	0.97 (0.69, 1.38)
Obese	1.29 (0.96, 1.73)	1.02 (0.75, 1.40)
Smoking status		
Never smoker	1 (Reference)	1 (Reference)
Ex-smoker	1.21 (0.77, 1.92)	0.99 (0.60, 1.62)
Current smoker	0.82 (0.56, 1.20)	0.82 (0.53, 1.25)
Alcohol consumption (days·week^{-1})		
None	1 (Reference)	1 (Reference)
1–4	0.91 (0.63, 1.29)	1.02 (0.68, 1.52)
⩾5	1.01 (0.48, 2.14)	0.69 (0.31, 1.50)
Physical activity (days·week^{-1})		
None	1 (Reference)	1 (Reference)
1–4	1.43 (0.97, 2.09)	1.34 (0.90, 1.99)
⩾5	1.54 (0.91, 2.60)	1.05 (0.62, 1.79)
Comorbidities		
Pulmonary comorbidities		
Asthma	2.26 (1.58, 3.24)	1.49 (0.99, 2.23)
COPD	2.80 (1.86, 4.19)	1.64 (1.06, 2.54)
Cerebrovascular disease	2.07 (1.57, 2.72)	1.04 (0.76, 1.42)
Cardiovascular disease		
Hypertension	1.98 (1.48, 2.64)	0.70 (0.35, 1.40)
Angina or myocardial infarction	1.82 (1.04, 3.17)	0.89 (0.47, 1.70)
Congestive heart failure	2.20 (1.09, 4.45)	1.01 (0.47, 2.17)
Diabetes mellitus	2.60 (1.87, 3.60)	1.55 (1.07, 2.23)
Rheumatoid arthritis	1.82 (1.10, 3.01)	1.09 (0.60, 1.97)
Malignancy	1.42 (0.81, 2.48)	1.02 (0.57, 1.81)
CCI		
0–1	1 (Reference)	1 (Reference)
⩾2	2.18 (1.64, 2.90)	1.01 (0.70, 1.46)
Medication		
Systemic corticosteroid use	1.41 (1.10, 1.80)	1.19 (0.91, 1.55)
Immunomodulator	3.90 (1.45, 10.46)	2.70 (0.89, 8.25)

Model 1 is the crude model. Model 2 was adjusted for insurance type, body mass index, smoking status, alcohol consumption, physical activity, CCI and medications. HR: hazard ratio; CCI: Charlson Comorbidity Index.

designed to investigate the underlying mechanism, future studies are required to elucidate the underlying mechanism of bronchiectasis in individuals with IBD.

In this study, although the risk of bronchiectasis substantially increased in individuals with UC, CD was not associated with an increased risk of bronchiectasis. This finding has important clinical relevance because limited information is available regarding the risk of bronchiectasis in individuals with CD. The

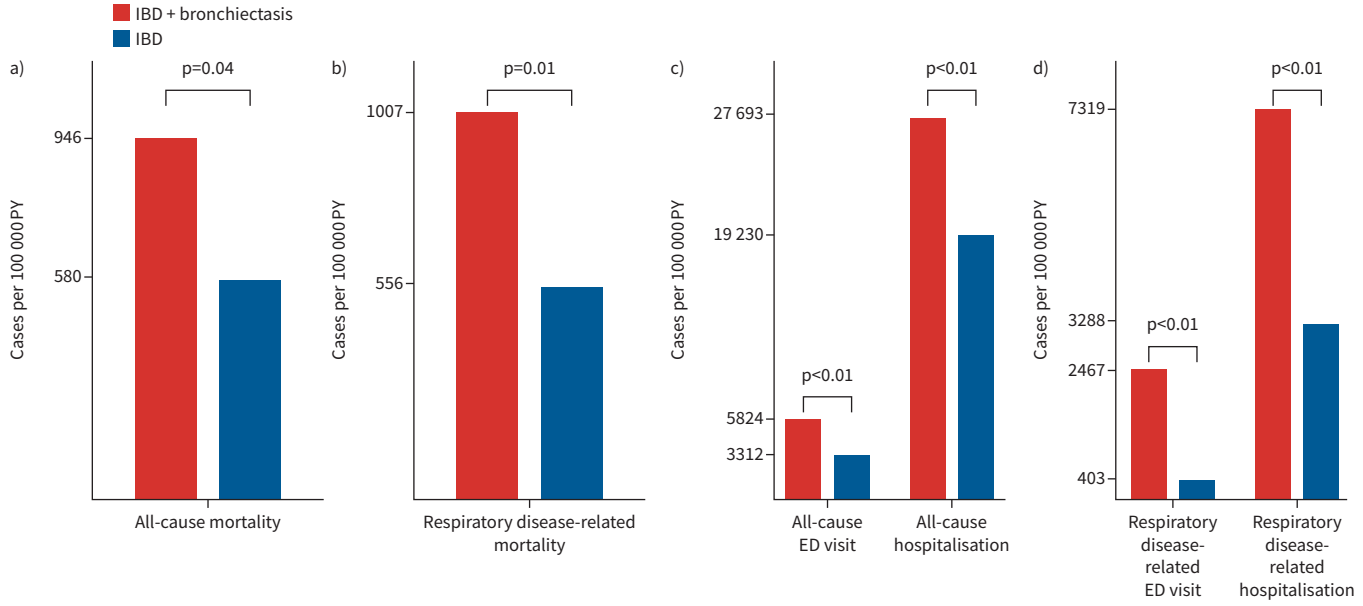

FIGURE 3 Comparison of all-cause mortality, emergency department (ED) visits and hospitalisations during follow-up between individuals with inflammatory bowel disease (IBD) and bronchiectasis *versus* individuals with IBD without bronchiectasis. a) All-cause mortality; b) respiratory disease-related mortality; c) all-cause ED visits and hospitalisations; d) respiratory disease-related ED visits and hospitalisations. PY: person-years.

reasons for this phenomenon remain unclear; however, the difference in neutrophilic inflammation between UC and CD could potentially be a contributing factor. For instance, studies have shown that increased NET formation is consistently observed in UC, while there is controversy regarding the role of NETs in CD [33, 41–44]. Considering that NETs are involved in the pathogenesis of bronchiectasis [37, 38], the heightened association of NETs with UC compared to CD might be related to this phenomenon. As our study is the first to evaluate this issue, future studies are required to provide robust evidence regarding the risk of bronchiectasis in CD.

Extraintestinal manifestations are recognised to be a major cause of morbidity and mortality in individuals with IBD [4, 5, 45]. Therefore, the disease burden of IBD may increase in the presence of bronchiectasis. Supporting this notion, a recent study showed that the presence of bronchiectasis is associated with an increased risk of mortality in individuals with IBD who developed pneumonia [16]. We have provided further robust evidence that bronchiectasis is associated with poor treatment outcomes regarding mortality and healthcare use. These findings highlight the importance of the early detection and appropriate management of this comorbidity. Therefore, the assessment of clinical risk factors for bronchiectasis in individuals with IBD has important clinical implications. Our study revealed that factors, including age, male sex, underweight status, poor income, COPD and diabetes mellitus, were significantly associated with bronchiectasis in individuals with IBD. Although the optimal screening strategies for the early detection of bronchiectasis in IBD remain unknown, an attempt to perform computed tomography of the chest would be helpful when respiratory symptoms develop or worsen, or when recurrent respiratory infections develop in individuals with IBD, especially when these risk factors are present.

This study had some limitations. First, our use of individuals who participated in health screening examinations may introduce selection bias, as healthy people are more likely to participate in health screening examinations. Second, we used the ICD-10 codes to define diseases, including IBD (exposure), bronchiectasis (outcome) and comorbidities (covariates). Although we used special V codes for IBD, which clinicians and NHIS very carefully review, and we used the bronchiectasis definition that has been very widely used in many epidemiologic studies to enhance accuracy [19–22], the use of ICD-10 codes can lead to over- or under-estimation. Finally, as this study was conducted in a Korean population, further studies are needed to generalise the results to other countries.

In conclusion, this nationwide longitudinal cohort study demonstrated that the risk of developing bronchiectasis was higher in individuals with IBD than in those without IBD, which was significant only for individuals with UC and not for individuals with CD. Age, male sex, underweight status, poor income,

COPD and diabetes mellitus are risk factors for bronchiectasis in individuals with IBD. The presence of bronchiectasis in individuals with IBD is associated with an increased mortality rate and healthcare use.

Provenance: Submitted article, peer reviewed.

Data transparency statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethics statement: The study protocol was approved by the Institutional Review Board of the Chungbuk National University Hospital (application number 2021-01-028) but the requirement for informed consent was waived because the NHIS database was constructed after anonymisation.

Conflict of interest: J.S. Lee, B. Yang, H.S. Shin, H. Lee, H.G. Chai, H. Choi, J-H. Han, J.H. Yoon, E-G. Kim and H. Lee have no conflicts of interest to declare.

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