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Contents

Weekly Volume 25 Number 42 November 14, 2019

MINIREVIEWS

6289 *Helicobacter pylori* in ancient human remains
Maixner F, Thorell K, Granehäll L, Linz B, Moodley Y, Rattei T, Engstrand L, Zink A

ORIGINAL ARTICLE

Basic Study

6299 Knockdown of lncRNAXLOC_001659 inhibits proliferation and invasion of esophageal squamous cell carcinoma cells
Li FZ, Zang WQ

6311 MicroRNA-30c inhibits pancreatic cancer cell proliferation by targeting twinfilin 1 and indicates a poor prognosis
Sun LL, Cheng M, Xu XD

Case Control Study

6322 MicroRNA signature in patients with hepatocellular carcinoma associated with type 2 diabetes
Elemeery MN, Mohamed MA, Madkour MA, Shamseya MM, Issa NM, Badr AN, Ghareeb DA, Pan CH

Retrospective Study

6342 Changes of gastric ulcer bleeding in the metropolitan area of Japan
Kubosawa Y, Mori H, Kinoshita S, Nakazato Y, Fujimoto A, Kikuchi M, Nishizawa T, Suzuki M, Suzuki H

6354 Risk of inflammatory bowel disease in patients with chronic obstructive pulmonary disease: A nationwide, population-based study
Lee J, Im JP, Han K, Park S, Soh H, Choi K, Kim J, Chun J, Kim JS

Observational Study

6365 Epidemiologic characteristics of *Helicobacter pylori* infection in southeast Hungary
Bálint L, Tiszai A, Kozák G, Dóczi I, Szekeres V, Inczefi O, Ollé G, Helle K, Róka R, Rosztóczy A

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Contents

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ORIGINAL ARTICLE

Retrospective Study

Risk of inflammatory bowel disease in patients with chronic obstructive pulmonary disease: A nationwide, population-based study

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Abstract

BACKGROUND

There is a growing evidence regarding an increased risk of inflammatory bowel disease (IBD) among patients with airway diseases.

AIM

To investigate the influence of chronic obstructive pulmonary disease (COPD) on the risk of IBD.

METHODS

A nationwide, population-based study was conducted using data from the National Health Insurance Service database. A total of 1303021 patients with COPD and 6515105 non-COPD controls were identified. The COPD group was divided into the severe and the mild COPD group according to diagnostic criteria. The risk of IBD in patients with COPD compared to controls was analyzed by Cox proportional hazard regression models. The cumulative

incidences of IBD were compared between the groups.

RESULTS

The COPD group had higher incidences of IBD compared to non-COPD controls (incidence rate, 9.98 *vs* 7.18 per 100000 person-years, $P < 0.001$). The risk of IBD in the COPD group was increased by 1.38 (adjusted hazard ratio (HR); 95%CI: 1.25-1.52). The incidence rate of IBD was higher in the severe COPD group than in the mild COPD group (12.39 *vs* 9.77 per 100000 person-year, $P < 0.001$). The severity of COPD was associated with an increased risk of IBD (adjusted HR 1.70 in severe COPD, 95%CI: 1.27-2.21 and adjusted HR 1.35 in mild COPD, 95%CI: 1.22-1.49)

CONCLUSION

The incidences of IBD were significantly increased in COPD patients in South Korea and the risk of developing IBD also increased as the severity of COPD increased.

Key words: Claim data; Inflammatory bowel disease; Chronic obstructive pulmonary disease; Crohn's disease; Ulcerative colitis

Core tip: In this nationwide population-based study, we showed that the incidence of inflammatory bowel disease (IBD) was higher in chronic obstructive pulmonary disease (COPD) patients compared to age-and sex-matched controls without IBD in South Korea. And the risk of developing IBD also increased as the severity of COPD increased. It is important to be aware of the gastrointestinal symptoms indicative of IBD in COPD patients. Accurate clinical assessment should be done, especially in patients with severe COPD in order to prevent complications and avoid excess medical expenses.

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INTRODUCTION

Inflammatory bowel disease (IBD), which is divided into Crohn's disease (CD) and ulcerative colitis (UC), is a chronic idiopathic disorder causing inflammation of the gastrointestinal tract. However, IBD should be regarded as a systemic disorder not limited to the gastrointestinal tract because extraintestinal manifestations of IBD are frequent and may occur before or after IBD diagnosis[1]. Extraintestinal manifestation frequently affect joints, skin, hepatobiliary tract and eye. Although the lung is less affected than other organ, IBD is known to be associated with a variety of lung disease and airway disease is the most common respiratory manifestation in IBD patients[2-5].

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation, which is caused by chronic airway inflammation and lung parenchymal destruction. It is well-known that not only respiratory symptoms but also extra-pulmonary manifestations such as cardiovascular compromise, dysfunction of skeletal muscles, osteoporosis, and anemia can result in impaired functional capacity and increased mortality in COPD patients. The gastrointestinal manifestations are no exception to this, and a recent report showed that complaints of gastrointestinal symptoms may be higher in patients with COPD than in healthy individuals[6]. Furthermore, the associations of COPD with specific gastrointestinal disease were investigated. And there is a growing evidence regarding an increased risk of IBD incidence among patients with airway diseases including COPD[7-10].

South Korea has a considerably higher prevalence of COPD than other countries, with 15.5/1000 people diagnosed with COPD annually[11,12]. Meanwhile, the incidence of IBD in South Korea has increased approximately 10-fold over the last two decades, which has led to South Korea having one of the highest incidence of IBD among Asian

countries[13-16]. These trends of incidence and prevalence may lead to considerable economic burdens and challenge for the healthcare system. Asian IBD is known to be different from that of the Western countries in s pathophysiology, clinical manifestation and response to treatment[17-19].

Thus, in the present study, we aimed to investigate the association between COPD and IBD represented by CD and UC using the large data in Asia. We also aimed to study the influence of COPD on the risk of IBD according to the severity of COPD. Consideration of this association may maximize the efficacy of prevention and treatment approaches to these chronic disease.

MATERIALS AND METHODS

Data source

This nationwide, population-based study was conducted using data from the National Health Insurance Service (NHIS) database. The South Korean government administers the NHIS as a mandatory health insurance system covering approximately 97% of the South Korean population; the remaining 3% represent the lower income population covered by the Medical Aid program. The NHIS database provides comprehensive information about demographics, medical treatments, procedures, outpatient and inpatient care, and disease diagnoses according to the International Classification of Disease, 10th revision (ICD-10). In addition, in 2007, the NHIS established a registration program for rare intractable disease (RID), which included IBD, to provide enhanced reimbursement for medical costs that were associated with rare diseases (affecting < 20000 people in Korea). To qualify for enrolment in the RID program, patients require a diagnosis from a certified physicians and approval by the NHIS.

Study population and patient identification

We identified COPD patients based on the following diagnostic criterion: Conditions for which an individual should visit the medical facility at least twice per year with both a COPD diagnostic code and a prescription for one or more COPD medications between January 2010 and December 2014. Similar to previous studies[20-22], the detailed diagnostic criteria of COPD are as follows: > 40 years of age; ICD-10 codes for COPD (J43-J44, except J430); and use of more than one drug for COPD such as a long-acting muscarinic antagonist (LAMA), long-acting beta-2 agonist (LABA), inhaled corticosteroid (ICS), ICS plus LABA, short-acting muscarinic antagonist (SAMA), short-acting beta-2 agonist (SABA), SAMA plus SABA, methylxanthines, systemic corticosteroids, and systemic beta agonists. Patients with COPD were divided into the mild COPD group and severe COPD group and severe COPD was defined according to the following severity criteria: (1) Tertiary hospital care patient who met the definition of COPD described above; and (2) Use of triple inhaler therapy at least once per year (ICS+LABA+LAMA). In addition, patients in the COPD group were subsequently 1:5 matched with individuals without COPD (non-COPD controls) for age and sex.

Incident cases of IBD were defined when the patients in the COPD group and non-COPD controls met the case definition for CD or UC during January 2010 and December 2014 and had been free of IBD diagnosis for at least 2 years prior to the beginning of the COPD case-defining period. We identified IBD patients using codes from the ICD-10 and the RID registration system (V code). Cases that involved CD were identified if they had both ICD-10 code K50 and V code V130, while cases that involved UC were identified if they had both ICD-10 code K51 and V code V131. Since IBD-unclassified is not registered in NHIS database and RID system as a definite diagnostic code, it was excluded from the analysis. We defined the time point at which this diagnosis was claimed using ICD-10 code and V code as "time 0" and identified IBD patients.

For inclusion in the present study, patients had to fulfill the diagnostic criteria for IBD, which were based on the clinical features, endoscopic findings, and histologic findings that are required for registration in the RID program. Previous studies have validated the accuracy of the RID database for both UC and CD diagnoses[14,23,24].

Statistical analysis

Statistical analyses were performed with the R program, version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org) and SAS, version 9.2 (SAS Institute Inc., Cary, NC, United States) for Windows. Random selection of age- and sex-matched controls was performed using the SAS algorithm. Data for continuous variables are presented as the mean and standard

deviation[25]. Data for categorical variables are presented as the numbers and percentages. Differences in baseline characteristics and comorbidities between the COPD group and non-COPD controls were analyzed with independent t-tests and χ^2 tests, as appropriate. Incidence rates of IBD were calculated by dividing the number of events by 1000000 person-years of follow-up for each group. Cox proportional hazard regression models considering time-varying covariates were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) for the risk of IBD in patients with COPD compared to controls[26]. The cumulative incidences of IBD were compared between the groups with the Kaplan-Meier method and the log-rank test. A P value < 0.05 was considered statistically significant.

Ethical consideration

All data were obtained without identifiable information, such as the registration number, patient's name, or medical institution. This study's protocol was approved by the institutional review board of Seoul National University Hospital (H-1703-107-840). All data base was encrypted and anonymous; we did not obtain informed consent from the study population.

RESULTS

Baseline characteristics of study population

A total of 1303021 patients with COPD and 6515105 non-COPD controls were included in this study. The mean age of the study population was 57.1 ± 10.7 years and the mean duration of follow-up was 3.9 ± 1.4 years. The number of patients with severe COPD was 111459, representing 8.6% of all COPD patients and 1191562 patients (91.4%) had mild COPD. (Table 1) Compared to non-COPD controls, the COPD group had lower proportions of urban. However, the COPD group had significantly higher proportions of individuals with the lower 20% incomes than non-COPD controls. In the case of comorbidity, the COPD group had a higher prevalence of diabetes mellitus, hypertension, and dyslipidemia.

Development of IBD in patients with chronic obstructive pulmonary disease

Comparison of the incidence rate and risk of IBD between patients with chronic obstructive pulmonary disease and con-COPD controls is presented in Table 2. In the COPD group, 513 patients (0.04%) developed IBD in the follow-up period, whereas 1,846 non-COPD controls (0.03%) developed IBD. The COPD group had higher incidences of total IBD compared to non-COPD controls (Figure 1). The risk of IBD in the COPD group was increased by 1.38 (adjusted HR; 95%CI: 1.25-1.52). Among the 513 patents with IBD in the COPD group, 406 were diagnosed with UC and 107 with CD. The incidence rate of UC was higher in the COPD group than in the non-COPD controls. CD also developed more frequently in the COPD group than in non-COPD controls. There was an increased risk of developing both UC and CD in the COPD group compared to in non-COPD controls.

Incidence rates and relative risks of IBD according to chronic obstructive pulmonary disease severity

Table 3 reports the number of events, calculated incidence rates, and unadjusted and adjusted HRs for IBD in the COPD group according to COPD severity. The incidence rate of overall IBD was higher in the severe COPD group than in the mild COPD group) (Figure 2). Both UC and CD were developed more frequently in the severe COPD group than in the mild COPD group. The severity of COPD was associated with an increased risk of developing IBD. When IBD is classified as UC and CD separately, patients with severe COPD also had increased risk of developing UC and CD compared to not only non-COPD controls but also the mild COPD group. This tendency of increased risk of IBD according to the severity of COPD was more prominent in CD than in UC.

Subgroup analysis according to sex and age

For the subgroup analysis, of the entire study population was dichotomized according to sex and age. The risk of IBD in the COPD group compared to the non-COPD controls was analyzed according to sex and age (Table 4). Male patients with COPD had increased risks of developing CD and UC compared to male patients without COPD. This result was same for female patients with COPD. When the risk of developing IBD was analyzed according to age, the risk of developing IBD in the COPD group was higher than that in the non-COPD controls at all ages. In addition, the risk of IBD increased with the severity of COPD irrespective of sex and age, and

Table 1 Baseline characteristics of study population, *n* (%)

	Non-COPD controls (*n* = 6515105)	COPD group (*n* = 1303021)	*P* value
Sex (Male %)	2867470 (44.0)	573494 (44.0)	1
Age (yr)	57.1 ± 10.72	57.1 ± 10.72	1
40-64	5025580 (77.1)	1005116 (77.1)	
65-	1489525 (22.9)	297905 (22.9)	
COPD severity			
Mild		1191562 (91.4)	
Severe		111459 (8.6)	
Income Low[1]	1597508 (24.5)	357627 (27.5)	< 0.001
Urban residents	2965581 (45.8)	567359 (44.1)	
Comorbidity			
Diabetes mellitus	640544 (9.8)	164860 (12.7)	< 0.001
Hypertension	1703988 (26.2)	418880 (32.2)	< 0.001
Dyslipidemia	1002279 (15.4)	272449 (20.9)	< 0.001
Follow up duration (yr)	3.9 ± 1.4	3.9 ± 1.4	0.8803

[1]Denotes subjects with annual income lower than 20% among total population. COPD: Chronic obstructive pulmonary disease.

this tendency was more prominent in CD than in UC.

DISCUSSION

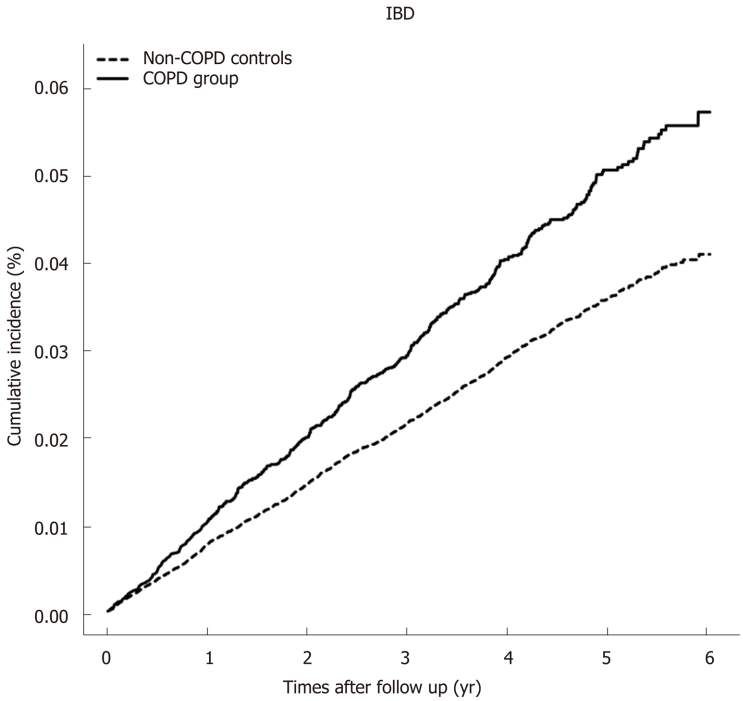
This is a large-scale and nationwide study to assess the risk IBD in COPD patients compared to non-COPD controls. Several studies of regions with high incidence of IBD such as Europe and Canada have reported similar findings[7-9]; however, this is the first study conducted in Asia with a previously low prevalence of IBD. In addition, to our best knowledge, this is the first study that revealed a close association between the severity of COPD and the risk of developing IBD.

We found that the incidence of IBD (UC and CD) in COPD patients was higher compared to that in non-COPD controls. The higher risk of IBD in COPD patients might be explained by the genetics, pathological background, and environmental factors shared by these two disease. There are several reports investigating genes that contribute to the development of both IBD and COPD. NOD2 is a cellular protein that recognizes the bacterial muramyl dipeptide as a major component of the bacterial cell wall. NOD2 mutations were significantly identified in patients with CD, and recent studies have also reported this mutation in COPD patients[27].

The Hedgehog-interacting protein gene that is shown to be a potential susceptibility locus for COPD is also important in the development of the intestinal crypt axis and further studies are required to identify whether this gene contributes to the disease overlap between COPD and IBD[28]. Dysregulation of protease activity also has a role in both COPD and IBD. Increased levels of epithelial and leukocyte matrix metalloproteinases, which have a role in the digestion of key components in mucosal structural integrity have been associated with the pathogenesis of COPD and IBD[29-33].

Development of IBD in patients with COPD can also be explained by the hypothesis that systemic inflammation is caused by overspill of multiple inflammatory mediators including C-reactive protein, IL-6, fibrinogen and activated leucocytes resulting from lung inflammation[34]. Especially, several studies revealed that plasma tumor necrosis factor (TNF-α) and its soluble receptor are increased in patients with COPD than in healthy controls[35-37]. TNF-α is a pivotal cytokine in IBD pathogenesis and IBD can be assumed to be one of the systemic inflammation caused by COPD. However, despite this evidence and hypothesis, treatment with TNF-α inhibitors have not shown significant benefit in patients with COPD[38]. This may suggest that COPD is a highly complex inflammatory disease in which many other cytokines and mediators are involved, and blocking a single cytokine does not necessarily lead to a clinically significant effect[39].

In addition, microbiomes common to the lung and gastrointestinal tract, as well as autoimmune components of both diseases, can support the link between the two diseases. We also demonstrated that the risk of developing UC and CD in COPD patients also increased with the severity of COPD and this tendency was more



	Number at risk of IBD						
Non-COPD controls	6515105	6514603	5657746	4593652	3322617	1720757	6343
COPD group	1191562	1191441	1039289	845868	613548	318883	1176

Figure 1 The cumulative incidence of inflammatory bowel disease in chronic obstructive pulmonary disease group and non-chronic obstructive pulmonary disease controls. IBD: Inflammatory bowel disease; COPD: Chronic obstructive pulmonary disease.

pronounced in CD than in UC. This can be explained by understanding the effect of hypoxia on IBD pathogenesis. The intestinal mucosal barrier is made up of epithelial apical junction complexes, consisting of tight junctions and adherence junctions, which are sensitive to hypoxia. Severe hypoxemia caused by COPD is thought to evoke diminished splanchnic perfusion and result in inadequate oxygen delivery to the intestinal mucosal, causing tissue hypoxia, which is associated with increased enterocyte damage and integrity loss[40,41]. In addition, mucosal barrier loss can be accelerated by inflammatory mediators, which are known to circulate during COPD aggravation as above mentioned[42]. For instance, cytokines can lead to alterations in the structure of tight junctions, thereby resulting in enhanced para-cellular permeability and barrier loss[43]. The effects of hypoxia are expected to be more severe as the severity of COPD increases, and a recent study showed an increased intestinal permeability in patients undergoing acute exacerbations of COPD compared to the same patients in a stable condition of COPD[44].

In this study, the number of IBD patients with UC was higher than those with CD in the COPD group. This can be assumed to be due to the higher incidence of UC in the entire IBD population in Korea compared to that of CD[16]. In addition, it may be because of the nature of the disease that older patients are more likely to be present in the COPD group. Approximately 10%-15% of IBD is diagnosed after the age of 60 and older-onset UC is more common than CD[45-47].

Smoking is the most important risk factor for COPD, also affecting the pathogenesis of IBD, protecting against UC, and promoting the development of CD[48,49]. Nevertheless, our study could not make adjustment for the smoking status due to lack of information, and this is a weakness of this study. However, an analysis of the database including the smoking status of the Korean population from the national health screening program provided by the NHIS revealed that the proportion of ex- and current smokers was significantly higher in the COPD group than in non-COPD controls. (33.3% *vs* 31.1%, $P < 0.001$). And the proportion of IBD patients was also higher in the COPD group than in non-COPD controls (0.04% *vs* 0.03%, $P < 0.001$) (Supplementary material).

Our study could not reflect the actual clinical situation, and this is one of the

Table 2 Incidence rate and risk of inflammatory bowel disease in patients with chronic obstructive pulmonary disease

		Event	DURATION (Person-years)	Incidence rateof IBD	Model 1[1] HR (95%CI)	Model 2[2] HR (95%CI)	*P* value
		IBD					
COPD	No	1846	25697723.08	7.18	1 (Ref.)	1 (Ref.)	< 0.001
	Yes	513	5139283.39	9.98	1.39 (1.26-1.53)	1.379 (1.25-1.52)	
		UC					
COPD	No	1540	25697723.08	5.99	1 (Ref.)	1 (Ref.)	< 0.001
	Yes	406	5139283.39	7.9	1.32 (1.18-1.47)	1.315 (1.18-1.47)	
		CD					
COPD	No	306	25697723.08	1.19	1 (Ref.)	1 (Ref.)	< 0.001
	Yes	107	5139283.39	2.08	1.75 (1.40-2.171)	1.691 (1.35-2.10)	

[1]Model 1: adjustment for age and sex;
[2]Model 2: adjustment for model 1+ place of resident, income, diabetes mellitus, hypertension, dyslipidemia. CD: Crohn's disease; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

weaknesses using administrative data. This limitation is associated with the possibility of overlooking the risk variables that are important for disease development. A well-designed prospective observational cohort study that combine administrative data and actual clinical data including medications and other clinical covariates is needed to reveal more precisely the association between COPD and IBD.

In conclusion, the incidences of both CD and UC were significantly increased in COPD patients in South Korea and the risk of developing IBD also increased as the severity of COPD increased. It is important to be aware of the gastrointestinal symptoms indicative of IBD in COPD patients. Accurate clinical assessment should be done, especially in patients with severe COPD in order to prevent complications and avoid excess medical expenses.

Table 3 Incidence and risk of inflammatory bowel disease in patients with chronic obstructive pulmonary disease according to disease severity

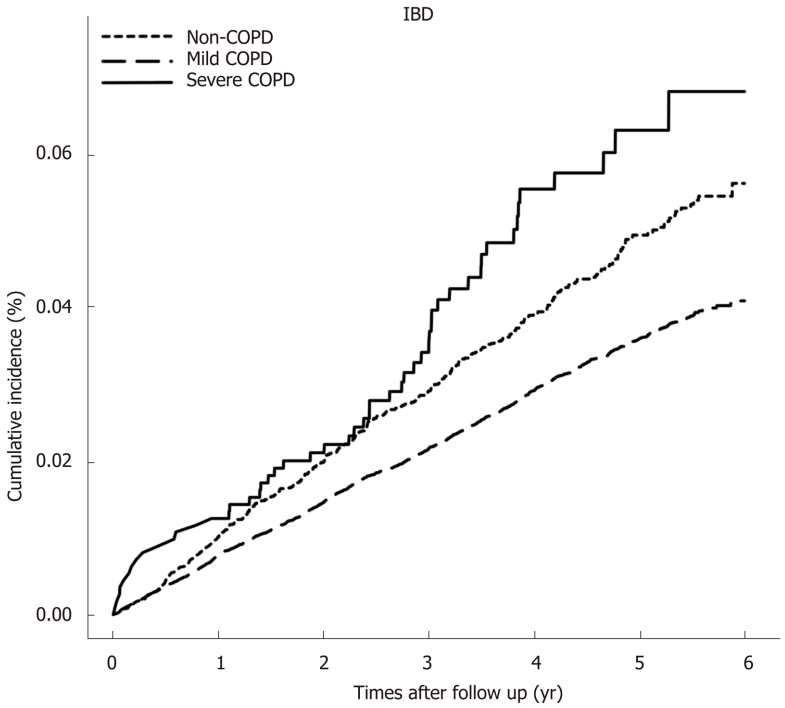
		Event	DURATION (Person-years)	Incidence rateof IBD	Model 1[1] HR (95%CI)	Model 2[2] HR (95%CI)	*P* value
		IBD					
COPD Severity	Non	1846	25697723.08	7.18	1 (Ref.)	1 (Ref.)	< 0.001
	Mild	461	4719752.21	9.77	1.36 (1.23-1.50)	1.35 (1.22-1.49)	
	Sev-ere	52	419531.18	12.39	1.717 (1.29-2.24)	1.70 (1.27-2.21)	
		UC					
COPD Severity	Non	1540	25697723.08	5.99	1 (Ref.)	1 (Ref.)	< 0.001
	Mild	371	4719752.21	7.86	1.31 (1.17-1.47)	1.31 (1.17-1.47)	
	Sev-ere	35	419531.18	8.34	1.39 (0.97-1.91)	1.38 (0.96-1.89)	
		CD					
COPD Severity	Non	306	25697723.08	1.19	1 (Ref.)	1 (Ref.)	< 0.001
	Mild	90	4719752.21	1.91	1.60 (1.26-2.02)	1.548 (1.22-1.95)	
	Sev-ere	17	419531.18	4.05	3.38 (2.00-5.33)	3.29 (1.94-5.20)	

[1]Model 1: adjustment for age and sex;
[2]Model 2: adjustment for model 1+ place of resident, income, diabetes mellitus, hypertension, dyslipidemia. CD: Crohn's disease; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; HR: Hazard ratio; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.

Table 4 Risk of inflammatory bowel disease in patients with chronic obstructive pulmonary disease according to sex and age

	COPD	IBD	UC	CD
Male	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.47 (1.23-1.60)	1.35 (1.16-1.55)	1.75 (1.26-2.39)
Female	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.35 (1.16-1.55)	1.27 (1.07-1.5)	1.64 (1.20-2.21)
Age (40-64)	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.36 (1.21-1.52)	1.31 (1.15-1.48)	1.62 (1.25-2.08)
Age (65-)	No	1 (Ref.)	1 (Ref.)	1 (Ref.)
	Yes	1.46 (1.19-1.79)	1.36 (1.07-1.71)	1.93 (1.23-2.96)

CD: Crohn's disease; COPD: Chronic obstructive pulmonary disease; IBD: Inflammatory bowel disease; UC: Ulcerative colitis.



Number at risk of IBD							
Non-COPD	6515105	6514603	5657746	4593652	3322617	1720757	6343
Severe COPD	111459	111445	92206	72813	50919	25226	93
Mild COPD	1080103	1079996	947083	773055	562629	293657	1083

Figure 2 Comparison of cumulative incidence of inflammatory bowel disease in patients with chronic obstructive pulmonary disease according to the severity of chronic obstructive pulmonary disease. IBD: Inflammatory bowel disease; COPD: Chronic obstructive pulmonary disease.

ARTICLE HIGHLIGHTS

Research background

Inflammatory bowel disease (IBD) is known to be associated with airway disease and there is a growing evidence of increased risk of IBD among patients with chronic obstructive pulmonary disease (COPD).

Research motivation

South Korea has a considerably high prevalence of COPD and is one of the highest incidence of IBD among Asian countries. Previous western studies have reported the risk of IBD in COPD patients, however, no research based on Asian data has been reported.

Research objectives

To estimate the incidence of IBD in patients with COPD compared to non-COPD controls and the risk of IBD development according to COPD severity.

Research methods

From January 2010 and December 2014, patients with COPD were identified using International Classification of Disease, 10th revision (ICD-10 code) and prescription records from the National Health Insurance (NHI) database. The COPD patients were divided into the severe and the mild COPD group. And these patients were subsequently 1:5 matches with individuals without COPD. Newly diagnosed IBD patients with Crohn's disease and ulcerative colitis were identified using ICD-10 code and the rare intractable disease registration program codes from NHI database. The risk of IBD in COPD patients compared to controls was analyzed by Cox proportional hazard regression models. The cumulative incidence of IBD were compared between the groups.

Research results

The COPD group had higher incidences of IBD compared to non-COPD controls and the risk of IBD in the COPD group was increased. The incidence rate of IBD was higher in the severe COPD group than in the mild COPD group.

Research conclusions

The incidences of IBD were significantly increased in COPD patients in South Korea and the risk

of developing IBD also increased as the severity of COPD increased.

Research perspectives

Careful monitoring the gastrointestinal symptoms indicative of IBD in COPD patients is important. Accurate clinical assessment should be done, especially in patients with severe COPD in order to determine the best strategies to prevent complications.

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