Inflammatory bowel disease and risk of mortality in COPD

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ABSTRACT Patients with chronic obstructive pulmonary disease (COPD) have higher incidence and prevalence of other chronic inflammatory diseases, including inflammatory bowel disease (IBD). We assessed whether IBD onset increases mortality risk in patients with COPD or asthma-associated COPD.

Two population-based cohorts of COPD and asthma-COPD subjects were identified using the administrative health databases in Québec, Canada, 1990–2007. Death records were retrieved from the death certificate registry. Cox proportional hazards models were used to assess the impact of newly developed IBD on mortality risk.

The COPD and asthma-COPD cohorts included 273 208 and 26 575 patients, respectively, of which 697 and 119 developed IBD. IBD increased the risk of all-cause mortality in both COPD (hazard ratio 1.23, 95% CI 1.09–1.4) and asthma-COPD (hazard ratio 1.65, 95% CI 1.23–2.22). In asthma-COPD patients, IBD increased the risk of mortality from respiratory conditions (hazard ratio 2.18, 95% CI 1.31–3.64); in COPD patients, IBD increased the risk of death from digestive conditions (hazard ratio 4.45, 95% CI 2.39–8.30).

IBD is a risk factor for mortality in patients with pre-existing COPD or asthma-COPD. IBD increased mortality by respiratory and digestive conditions in patients with asthma-COPD and COPD, respectively.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory condition with a major public health impact, affecting about 210 million people worldwide [1] and ranked in the top five of the most frequent cause of death [1, 2]. COPD is the major contributor to increases in deaths observed in high-income countries [1, 3]. Only a third of all deaths in COPD patients are estimated to result from progressive respiratory failure [4]; therefore, other factors likely play an important part.

Approximately 20% of COPD patients present with a mix of asthma and COPD features [5–7], and there is evidence supporting an increased risk of morbidity, and possibly of comorbidity and mortality in such patients compared with those with COPD alone [5, 7].

The association with comorbid conditions may also impact COPD mortality [8]. While the association with neoplasms and cardiovascular diseases has been extensively explored, along with the role of cigarette smoke and systemic inflammation in the pathogenesis of these conditions, other comorbid conditions have received far less attention. COPD has been shown to be associated with other chronic inflammatory diseases, such as inflammatory bowel disease (IBD) [9, 10]. Epidemiological studies have shown significant increases in incidence [11] and prevalence [12, 13] of IBD in patients with airway diseases. Furthermore, among IBD patients, mortality due to respiratory conditions in general [14] and COPD in particular [15] was found to be increased. To date, it is not known whether IBD may, in turn, impact COPD mortality. Therefore, we sought to assess whether new-onset IBD may constitute a risk factor for mortality among patients with COPD or asthma associated COPD.

Methods

Data source

The study was conducted using the healthcare administrative databases of the Régie de l'Assurance Maladie du Québec (RAMQ) and linked records from the death certificates registry provided by the Institut de la Statistique du Québec (Canada). The healthcare databases consist of routinely collected data regarding hospitalisations, procedures, outpatient physician visits, prescription claims filed under the provincial public drug plan as well as patient demographics. The public drug plan covers over 40% of the Québec population, including all residents aged 65 years and older, residents receiving social assistance and their dependents, and all residents without a private drug plan. The accuracy and comprehensiveness of the prescription claims data were evaluated, and the RAMQ prescriptions database was found to be one of the most accurate means to assess drugs dispensed to individuals in Québec [16].

Study design and population

In this population-based retrospective cohort study the source population consisted of all Québec residents who received one or more prescriptions for a specific respiratory medication from 1990 to 2007. The respiratory medications included: any form of β-agonist, theophylline, ipratropium bromide, tiotropium, sodium cromoglycate, nedocromil, ketotifen, leukotriene antagonists (montelukast and zafirlukast) and inhaled corticosteroids. A base population of airway disease subjects was identified as all individuals with three or more prescriptions for a respiratory medication in any 1-year period and on at least two different dates. The cohort entry was considered the date of the third prescription for a respiratory medication. These criteria were successfully employed for identification of subjects with airway diseases in several RAMQ database studies addressing IBD incidence, risk of fractures, cataracts, glaucoma, tuberculosis or pneumonia [11, 17–22].

Due to the differences in disease characteristics described in patients with associated asthma features [5–7], two mutually exclusive cohorts of subjects with COPD and asthma-COPD were subsequently selected from the base population of individuals with airway diseases. The COPD cohort included all individuals aged 41 years or older at cohort entry for whom no record of asthma as principal diagnosis on a hospital discharge was identified in the database and no prescription was ever dispensed for any of the following medications: leukotriene antagonists (montelukast and zafirlukast), sodium cromoglycate, nedocromil or ketotifen. The selection criteria for the COPD cohort were consistent with our previous work addressing the incidence of IBD in COPD patients [11]. The asthma-COPD cohort included the individuals in the base population aged 41 years or older at cohort entry who did not satisfy the inclusion criteria for the COPD cohort.

IBD patient identification

We identified all subjects with new-onset IBD (either Crohn's disease or ulcerative colitis) occurring after entry in the COPD and asthma-COPD cohorts using an algorithm developed and validated in Alberta, Canada [23]. IBD patients were defined as the subjects with at least four physician billings in a 2-year interval or one hospital discharge with a principal diagnosis of Crohn's disease or ulcerative colitis.

A 2-year IBD-free period prior to the Crohn's disease or ulcerative colitis patient-defining period was also applied as an additional condition to ensure incident IBD patients were captured. The identified subjects were considered as IBD patients at the time they fulfilled the algorithm criteria, whether that occurred at the time of the hospitalisation or at the fourth physician billing. The methodological approach is consistent with our previous work [11, 24].

Assessment of mortality

The death registry database contains the diagnostic code listed as the initial cause of death on the death certificates and up to 25 diagnostic codes for secondary causes of death. For the assessment of cause-specific mortality, the death counts were computed using the diagnostic code listed as the initial cause of death. Depending on the date of death, the diagnostic codes were classified according to International Classification of Diseases (ICD) revision 9 (prior to April 1, 2006) or 10 (April 2006 to December 2007). The following ICD codes were used in the analyses: J00–J99 (ICD-10) and 460–519 (ICD-9) for respiratory conditions; K00–K93 (ICD-10) and 520–579 (ICD-9) for digestive conditions; C00–D48 (ICD-10) and 140–239 (ICD-9) for neoplasms; I00–I99 (ICD-10) and 390–459 (ICD-9) for circulatory conditions.

Statistical analysis

Descriptive statistics were used to characterise the subjects making up the COPD and asthma-COPD cohorts. The impact of newly developed IBD on mortality was assessed using Cox proportional hazards models. The exposure, the presence of IBD, was modelled as a time-dependent variable. All the covariates used for model adjustment were assessed at cohort entry (baseline). These covariates included age at cohort entry, and use of antibiotics, anticoagulants, antihypertensives, antidiabetic and antirheumatic drugs, β-agonists, bronchodilators, cardiotropes, oral and inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, nervous system-specific drugs, and vasodilators in the year prior to cohort entry. The number of hospitalisations in the year prior to cohort entry was also included as a covariate in the adjusted models as a marker of severity of comorbidities. Data analysis was performed using SAS/STAT® software (version 9.3, SAS for Windows; SAS Institute, Cary, NC, USA). Ethical approval for this study was granted by the Research Ethics Committee of the Sir Mortimer B. Davis Jewish General Hospital (Montreal, Québec, Canada).

Results

A total of 273 208 subjects fulfilled the selection criteria for the COPD cohort and 26 575 for the asthma-COPD cohort, providing 1 753 986 and 219 409 person-years of follow-up. There were 697 subjects who developed IBD after a mean±SD follow-up of 4.63±4.31 years in the COPD cohort; 119 subjects developed IBD after a mean±SD follow-up of 5.40±4.03 years in the asthma-COPD cohort. Table 1 presents the characteristics at cohort entry for the subjects with COPD or asthma-COPD stratified by the presence or absence of IBD during the follow-up. In the COPD cohort, subjects with IBD were less likely to have more than three hospitalisations and to have used anticoagulants, bronchodilators and cardiotropes in the year prior to cohort entry compared with subjects who never developed IBD; also, they were more likely to have used antirheumatics and nonsteroidal anti-inflammatory drugs. In the asthma-COPD cohort, subjects with IBD were less likely to have used anticoagulants, bronchodilators and inhaled corticosteroids in the year prior to cohort entry compared with those without IBD. Asthma-COPD subjects with IBD were more likely to have been hospitalised more than three times in the year prior to cohort entry than those who did not develop IBD.

The results for the association between IBD and all-cause mortality are presented in table 2. There were a total of 123 125 deaths in the COPD cohort, of which 243 occurred in the subjects who developed IBD. In the asthma-COPD cohort there were 8231 deaths, of which 45 were in subjects with IBD. There was an increased risk of mortality associated with developing IBD in both COPD (hazard ratio 1.23, 95% CI 1.09–1.4) and asthma-COPD cohorts (hazard ratio 1.65, 95% CI 1.23–2.22). The analysis stratified by type of IBD (table 3) revealed that Crohn's disease was associated with an increased risk of mortality among asthma-COPD patients (hazard ratio 1.78, 95% CI 1.15–2.74); ulcerative colitis significantly increased the risk of mortality in both COPD (hazard ratio 1.27, 95% CI 1.07–1.5) and asthma-COPD patients (hazard ratio 1.55, 95% CI 1.03–2.32).

The most common causes of death in both COPD and asthma-COPD cohorts were, in order of frequency, circulatory conditions, neoplasms, respiratory and digestive conditions. There was an increased risk of mortality due to digestive conditions in the COPD subjects with IBD (hazard ratio 4.45, 95% CI 2.39–8.3) (table 4). No increase in mortality risk for neoplasms, respiratory or circulatory conditions was associated with development of IBD in COPD subjects. Among asthma-COPD subjects, the presence of IBD was associated with an increased risk of mortality due to respiratory conditions (hazard ratio 2.18, 95% CI 1.31–3.64) (table 5). As only one death by digestive conditions occurred in asthma-COPD subjects with

TABLE 1 Characteristics of chronic obstructive pulmonary disease (COPD) and asthma-COPD patients at cohort entry

	COPD		Asthma-COPD	
	IBD[#]	No IBD	IBD[#]	No IBD
Subjects n	697	272511	119	26456
Age years	65.5±11.3	68.7±11.8	63.5±10.9	65.7±12
Male	38.7	45.1	30.3	32.9
Medication dispensed in the year prior to cohort entry				
Circulatory				
Anticoagulants	4.2	8.6	1.7	5.4
Antihypertensives	53.1	58.8	52.9	52.7
Cardiotropes	3.2	8.4	5.9	5.1
Vasodilators	17.5	20.7	18.5	15.4
Respiratory				
β-agonists	73.6	76	74	70.3
Bronchodilators	14.8	21.3	9.2	12.8
Inhaled corticosteroids	46.3	45.2	38.7	49.1
Oral corticosteroids	11.3	13.8	16.8	20.5
Other				
Antibiotics	75.5	68.4	68.1	71.1
Antidiabetics	8.6	12.5	8.4	10
Antirheumatics	2.9	1.1	1.7	1.1
Nervous system drugs	70.7	67.7	65.6	65.6
NSAIDs	41.6	34.5	36.1	37.8
Hospitalisations in the year prior to cohort entry				
0	68.7	66.1	68.1	69.6
1	19.8	20.8	21	20.6
2	7.6	7.9	4.2	6.2
⩾3	3.9	5.3	6.7	3.6

Data are presented as mean±SD or %, unless otherwise stated. IBD: inflammatory bowel disease; NSAID: nonsteroidal anti-inflammatory drug. [#]: subjects IBD-free at cohort entry who develop IBD during the course of follow-up.

IBD, the risk of digestive conditions mortality was not assessed. The hazard ratios for the association between IBD and mortality due to neoplasms and circulatory conditions did not show any increase in risk of mortality in the asthma-COPD cohort. Also, we found no increase in risk of mortality from lung cancer or digestive cancers in either COPD or asthma-COPD subjects with IBD (data not shown). A stratification of cause-specific analyses by type of IBD was not performed due to the small number of deaths.

Discussion

In this large population-based study we found that new-onset IBD is a risk factor for all-cause mortality in patients with COPD or asthma-associated COPD. Both Crohn's disease and ulcerative colitis were associated with an increased mortality risk among asthma-COPD patients, while ulcerative colitis also impacted mortality among COPD patients. The risk of mortality due to respiratory conditions among

TABLE 2 Crude and adjusted hazard ratios for the association between inflammatory bowel disease (IBD) and all-cause mortality in patients with chronic obstructive pulmonary disease (COPD) and asthma-COPD

	Patients	Deaths	Total follow-up (person-years)	Mortality (deaths per 100 person-years)	Crude hazard ratio	Adjusted hazard ratio (95% CI)
COPD						
No IBD	272511	122882	1751058	7.02	1.00	1.00 (Reference)
IBD	697	243	2928	8.30	1.14	1.23 (1.09–1.4)
Asthma-COPD						
No IBD	26456	8186	218827	3.74	1.00	1.00 (Reference)
IBD	119	45	582	7.74	1.53	1.65 (1.23–2.22)

Data are presented as n, unless otherwise stated.

TABLE 3 Crude and adjusted hazard ratios for the association between Crohn's disease and ulcerative colitis and all-cause mortality in patients with chronic obstructive pulmonary disease (COPD) and asthma-COPD

	Patients	Deaths	Total follow-up (person-years)	Mortality (deaths per 100 person-years)	Crude hazard ratio	Adjusted hazard ratio (95% CI)
COPD						
Crohn's disease						
No	272511	122882	1749618.9	7.02	1.00	1.00 (Reference)
Yes	372	105	1477.6	7.11	0.97	1.19 (0.98–1.44)
Ulcerative colitis						
No	272511	122882	1749268.5	7.02	1.00	1.00 (Reference)
Yes	325	138	1450.5	9.51	1.3	1.27 (1.07–1.5)
Asthma-COPD						
Crohn's disease						
No	26456	8186	218484.9	3.75	1.00	1.00 (Reference)
Yes	59	21	308.6	6.80	1.39	1.78 (1.15–2.74)
Ulcerative colitis						
No	26456	8186	218525.5	3.75	1.00	1.00 (Reference)
Yes	60	24	273.1	8.79	1.66	1.55 (1.03–2.32)

Data are presented as n, unless otherwise stated.

asthma-COPD subjects with new-onset IBD was double that observed in subjects without IBD. COPD subjects who developed IBD had a four-fold increase in risk of mortality due to digestive diseases compared with COPD subjects without IBD. These are novel findings that underscore the importance of IBD assessment in patients with COPD who present with digestive symptoms indicative of IBD, such as diarrhoea (even low grade), changes in bowel function, rectal bleeding, abdominal pain, unexplained weight loss, anal fissures or fistula.

Although IBD was shown to be more prevalent among COPD patients [12, 13], and our previous work indicated that IBD can occur in COPD patients even in older age groups regardless of smoking history [11], the impact of developing IBD on important outcomes, such as mortality, has not been assessed.

The reviews of the underlying mechanisms that can explain the association between the two chronic inflammatory conditions point towards systemic inflammation and immunological dysfunctions [9, 10] triggered by environmental factors that IBD and COPD seem to share, such as smoking [25, 26] or air pollution [27, 28]. Furthermore, pulmonary involvement [29–31] is a common extra-intestinal

TABLE 4 Crude and adjusted hazard ratios for the association between inflammatory bowel disease (IBD) and cause-specific mortality in chronic obstructive pulmonary disease patients

	Patients	Deaths	Total follow-up (person-years)	Mortality (deaths per 100 person-years)	Crude hazard ratio	Adjusted hazard ratio (95% CI)
Deaths due to respiratory conditions						
No IBD	272511	19497	1751058	1.11	1.00	1.00 (Reference)
IBD	697	40	2928	1.37	1.02	1.12 (0.82–1.53)
Deaths due to digestive conditions						
No IBD	272511	1812	1751058	0.1	1.00	1.00 (Reference)
IBD	697	10	2928	0.34	4.02	4.45 (2.39–8.3)
Deaths due to neoplasms						
No IBD	272511	37506	1751058	2.14	1.00	1.00 (Reference)
IBD	697	64	2928	2.19	1.17	1.19 (0.93–1.52)
Deaths due to circulatory conditions						
No IBD	272511	38805	1751058	2.22	1.00	1.00 (Reference)
IBD	697	62	2928	2.12	0.92	1.12 (0.6–2.09)

Data are presented as n, unless otherwise stated.

TABLE 5 Crude and adjusted hazard ratios for the association between inflammatory bowel disease (IBD) and cause-specific mortality in asthma-associated chronic obstructive pulmonary disease patients

	Patients	Deaths	Total follow-up (person-years)	Mortality (deaths per 100 person-years)	Crude hazard ratio	Adjusted hazard ratio (95% CI)
Deaths due to respiratory conditions						
No IBD	26 456	1935	218 827	0.88	1.00	1.00 (Reference)
IBD	119	15	582	2.58	1.95	2.18 (1.31–3.64)
Deaths due to neoplasms						
No IBD	26 456	2007	218 827	0.92	1.00	1.00 (Reference)
IBD	119	8	582	1.38	1.21	1.39 (0.69–2.8)
Deaths due to circulatory conditions						
No IBD	26 456	2414	218 827	1.1	1.00	1.00 (Reference)
IBD	119	10	582	1.72	1.18	1.12 (0.6–2.09)

Data are presented as n, unless otherwise stated.

manifestation of IBD and an increased intestinal permeability, one of the factors that may increase susceptibility to develop IBD, was described in COPD patients [32].

The increase observed in digestive mortality in COPD may be due to the fact that IBD itself is associated with increases in mortality, including mortality by digestive conditions [14, 33–36]. The four-fold increase in digestive mortality may have also driven the observed rise in all-cause mortality in COPD. In patients with asthma-COPD, the presence of IBD was associated with a two-fold increase in mortality due to respiratory conditions. There is yet insufficient evidence as to whether IBD may lead to alterations in pulmonary function [30] that could result in disease exacerbations and an increased number of deaths. However, the literature shows that patients presenting with mixed features of asthma and COPD have a greater impairment in lung function [37], experience more severe and more frequent exacerbations than those with COPD alone [38, 39], and have a higher mortality rate [40]. Further studies are needed to confirm whether the observed increase in risk of mortality may be due to the differences in disease severity between COPD and asthma-COPD patients.

Our study has limitations. One may result from the selection of subjects into the COPD and asthma-COPD cohorts. In the past decade a growing number of studies have addressed the asthma–COPD overlap syndrome (ACOS), a clinical entity grouping patients who present with mixed asthma and COPD features. There is no consensus yet regarding a clear clinical definition for ACOS [41] and no validated algorithm recommended for studies based on administrative claims databases. Our methodological approach to differentiate between COPD subjects and those with a mix of asthma and COPD followed the work of BLANCHETTE et al. [38], who classified as ACOS all subjects with claims for both asthma and COPD. We have extended these criteria to include in the asthma-COPD cohort all subjects for whom prescriptions were dispensed for asthma-specific medications. While it is not possible to ascertain what proportion of the asthma-COPD cohort would fulfil the clinical criteria for ACOS, our approach has increased the likelihood that the COPD cohort was cleared of any subjects that may have had associated asthma.

As for most studies based on administrative data, the lack of information regarding smoking is an important limitation. However, previous studies have shown that the IBD association with COPD extends to ulcerative colitis patients as well [11, 13]. Tobacco smoking plays a protective role in ulcerative colitis [25]; therefore, it is unlikely that confounding by smoking can explain the observed association between IBD and COPD.

In this study we used a population-based cohort design that facilitates the assessment of outcomes of clinical importance, such as mortality, even in rare conditions. The use of a 2-year IBD-free interval prior to the first diagnostic code contributing to the IBD patient definition increased the probability that only incident IBD subjects were included in the analysis. The models were adjusted for the number of hospitalisations and the medication dispensed in the year prior to cohort entry to account for the impact of disease severity and comorbid conditions.

In conclusion, this study further substantiates the previously described association between IBD and COPD, and indicates that IBD could be one of the comorbidities contributing to the already high and increasing COPD mortality. Our findings highlight the importance of awareness of the IBD–COPD association and of IBD assessment in COPD subjects who present with digestive symptoms indicative of

IBD. Failure to perform an IBD assessment in these patients could lead to delays in diagnosis and treatment, and to an increase in number of complications. Patients with associated asthma-COPD features, in particular, should be carefully evaluated, as there is evidence suggesting they are more severely ill and, therefore, more susceptible to the impact of comorbid conditions than patients with COPD alone.

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