

A pilot prospective prevalence study of chronic rhinosinusitis associated with inflammatory bowel disease

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Abstract

Background: Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the gastrointestinal tract. Extra-intestinal manifestations such as pulmonary diseases have been reported. Chronic rhinosinusitis (CRS), an inflammatory condition of the sinonasal mucosa, has been associated with several lung diseases. Given the relationship between lung and intestinal pathologies, and lung and sinus pathologies, we aimed to determine the prevalence of IBD among CRS patients.

Methods: Pilot prevalence study. Ninety-two CRS patients were screened for IBD symptoms from October 2018 to January 2020. Patient-reported disease symptoms and overall quality of life were evaluated using the Sino-Nasal Outcome Test 22 (SNOT-22), Short Inflammatory Bowel Disease Questionnaire (SIBDQ), and EuroQol 5 Dimension 5 Level (EQ-5D-5L) questionnaires. The Modified Lund-Kennedy (MLK) endoscopic and Lund-Mackay (LM) grading systems were used to confirm CRS diagnoses. Individuals who reported subjective symptoms of IBD were referred to a gastroenterologist clinic for further diagnostics.

Results: Twenty of the 92 (20.2%, 95% CI: 12.6%–29.8%) CRS patients reported symptoms of IBD and four individuals (4.26%, 95% CI: 1.17%–10.50%) were subsequently diagnosed with IBD. Compared to patients without IBD symptoms ($n = 72$), those with symptoms ($n = 20$) reported significantly worse SNOT-22 ($P = 0.002$), SIBDQ ($P < 0.05$), and EQ-5D-3L ($P = 0.0063$) scores. However, these patients did not exhibit significantly different MLK ($P = 0.81$) or LM ($P = 0.04$) scores.

Conclusion: The prevalence of IBD may be elevated among individuals with CRS relative to the general Canadian population. This pilot study suggests that CRS with IBD is associated with lower quality of life. Further cross-sectional studies with larger sample sizes are required.

KEYWORDS

chronic rhinosinusitis, microbiome, Modified Lund-Kennedy, quality of life, Sino-Nasal Outcome Test 22 (SNOT-22)

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INTRODUCTION

Inflammatory bowel disease (IBD) is a common chronic disease that affects 0.3% of the North American population.¹ IBD is characterized by chronic inflammation of the gastrointestinal tract and is further categorized into Crohn's disease and ulcerative colitis. Both diseases have unknown etiologies but are thought to involve dysregulation of the immune system in response to environmental stimuli or an imbalance in the microflora in addition to genetic predispositions.¹ Over the past decade, IBD has emerged as a global disease, with the highest prevalence and incidence in Europe and North America.¹ Canada, in particular, has one of the highest reported incidence rates and prevalence of IBD with approximately 0.8% of the population suffering from the disease.¹

Since the 1970s, extra-intestinal manifestations of IBD have been reported to affect nearly half of all IBD patients.^{2,3} Among these extra-intestinal manifestations, pulmonary diseases associated with IBD are becoming increasingly recognized in the literature.^{2,3} Pulmonary manifestations of IBD span over a broad range of pathologies: from airway disease, fistulas, thromboembolic disease, drug-related lung disease, and lung parenchymal disease.^{2,3} Past investigations have explored various theories connecting the two pathologies, such as the consideration of common embryonic origins, common submucosal lymphoid tissue, and the migration of leukocytes and cytokines from the bowel tissue to induce damage in the lung parenchyma.^{2,3} However, the mechanisms causing the pulmonary manifestations from IBD are not well defined.

Chronic rhinosinusitis (CRS) is a heterogeneous group of inflammatory diseases affecting the nasal and sinus mucosa, and may result in a myriad of symptoms causing great discomfort in 5% of Canadians.^{4,5} These symptoms include, but are not limited to, nasal congestion or discharge, facial pain or pressure, and loss of smell. Several lung diseases, such as bronchiectasis, chronic obstructive pulmonary disease (COPD), and asthma, have been shown to be associated with CRS.⁵ In a recent study, Yang et al.⁶ showed an association between CRS and a higher prevalence and severity of bronchiectasis in patients with COPD. Furthermore, Shteinberg et al.⁷ investigated the relationship between allergic features and upper airway involvement among bronchiectasis patients. Their findings suggested some evidence that CRS can predispose patients to the development of bronchiectasis, or that the development of both CRS and bronchiectasis are linked through a common mechanism such as allergy. Although there is an increasing interest in investigating the association between CRS and these pulmonary diseases, the exact mechanisms for their concurrent manifestations remain largely unknown.

Given the potential relationship between lung and sinus pathologies and the relationship between lung and intestinal pathologies, this pilot study aims to explore the relation between the development of chronic sinus pathologies and IBDs. To our knowledge, there have been no prospective prevalence studies of patients with CRS who also have IBD using validated disease-specific questionnaires.

MATERIAL AND METHODS

Ethical considerations

A pilot prevalence study was conducted with approval from the University of British Columbia—Providence Health Care Research Board (H18-02330). All personal information was preserved and no identifying information of participants was used in the data collection or analysis.

Patient population

Patients were included in this prevalence study if they were over the age of 18, diagnosed with CRS according to the Rhinosinusitis Task Force, and were receiving care at St. Paul's Sinus Centre in Vancouver, British Columbia between October 2018 and January 2020.⁸ Patients who were unable to undergo bilateral rigid nasal endoscopy were excluded from the study.

Study procedure

Written informed consent was obtained from each individual who participated in the study. Demographic information including age, gender, smoking history, drinking history, diagnosis, and comorbidities was collected from each participant. Participants were given three surveys to fill out: the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), the Sino-Nasal Outcome Test 22 (SNOT-22), and the EuroQol 5 Dimension 5 Level (EQ-5D-5L). The SIBDQ is a 10-item questionnaire used to assess four domains of health-related quality of life related to the impact of IBD: physical, social, emotional, and systemic.⁹ The SIBDQ is scored on a 7-point Likert scale and ranges from 1 (*severe problem*) to 7 (*no problems at all*).⁹ The SNOT-22 is a validated, 22-item CRS-specific patient-reported quality of life questionnaire that is evaluated using a 0–5 Likert scale.¹⁰ Higher scores on the SNOT-22 questionnaire suggest worse quality of life. Furthermore, the EQ-5D-5L is a descriptive survey used to measure the overall quality of life of the patient.¹¹

Participants underwent a nasal endoscopy from which Modified Lund–Kennedy (MLK) endoscopic scores were collected. Furthermore, computed tomography scans within the last three years were collected from patient charts and the degree of sinus disease was quantified using the Lund–Mackay scoring system.¹²

Following the endoscopic exam, participants were asked four questions predetermined by a senior gastroenterologist to screen for IBD symptoms:

- Have you experienced diarrhea in the last 2 weeks?
- Have you noticed any blood in your stool in the last 2 weeks?
- Have you experienced any abdominal pain in the last 2 weeks?
- Have you experienced any joint pain in the last 2 weeks?

Participants who displayed endoscopic evidence of CRS and answered yes to two of the above questions were then referred to a gastroenterologist clinic for further diagnostics.

Statistical analyses

Continuous explanatory variables following a normal distribution and equal variance as determined by a Shapiro–Wilk test and were described using parametric tests. Nonparametric tests were used otherwise. Categorical explanatory variables were summarized by count. A logistic regression was performed to ascertain the impact of pulmonary disease (asthma, bronchiectasis, mycobacterium avium complex [MAC] lung disease) as an independent predictor of IBD symptoms. Results were considered statistically significant with $P < 0.05$. All statistical analyses were performed using RStudio version 3.4.1 (RStudio).

RESULTS

A total of 92 CRS patients were included in this study. Demographic data are summarized in Table 1.

Prevalence

Twenty of the 92 (21.7%, 95% CI: 13.8%–31.6%) CRS patients reported symptoms of IBD and were referred to a gastroenterologist for further diagnostics. Of these, four individuals (4.35%, 95% CI: 1.20%–10.80%) were subsequently diagnosed with IBD, two individuals (2.17%, 95% CI: 0.26%–7.63%) were suspected of IBD but did not undergo a diagnostic colonoscopy, seven individuals (7.61%, 95% CI: 0.31%–0.15%) were diagnosed with irritable bowel syndrome (IBS), three individuals (3.26%, 95% CI: 0.68%–9.23%) were confirmed to not have IBD, and four individuals (4.35%, 95% CI: 1.20%–10.80%) were lost to follow-up. Regression analysis revealed that there was no significant impact of pulmonary disease on the likelihood of IBD symptoms (binomial logistic regression, $X^2 = 0.235$, $P = 0.633$).

Degree of sinus disease outcome measures

MLK endoscopic scores were compared between CRS patients with ($n = 18$) and without IBD ($n = 71$) symptoms. A Shapiro–Wilk test indicated a significant deviation from normal distribution ($P < 0.05$). The median MLK of CRS patients who reported IBD symptoms (median = 2.0) did not significantly differ from those without symptoms (median = 2.0, $P = 0.58$, Wilcoxon rank sum test with continuity correction, Figure 1A).

TABLE 1 Demographic data

Characteristic	Total	CRS	CRS with IBD symptoms
Participants (n [%])	92 (100)	72 (78.3)	20 (21.7)
Age (mean \pm SD)	56.90 \pm 13.01	58.21 \pm 13.50	52.20 \pm 9.22
Gender (n [%])			
Male	40 (43.5)	35 (48.6)	5 (25.0)
Female	52 (56.5)	37 (51.4)	15 (75.0)
Diagnosis (n [%])			
AFRS	37 (40.2)	32 (44.4)	5 (25.0)
CRS _{WNP}	12 (13.0)	9 (12.5)	3 (15.0)
CRS _{sNP}	43 (46.7)	31 (43.1)	12 (60.0)
History of sinus surgery (n [%])			
No history	10 (10.9)	7 (9.7)	3 (15.0)
One surgery	51 (55.4)	42 (45.7)	9 (45.0)
>One surgery	31 (33.7)	23 (34.7)	8 (40.0)
Smoking history (n [%])			
Nonsmoker	78 (84.8)	61 (84.7)	17 (85.0)
Previous smoker	9 (9.8)	7 (9.7)	2 (10.0)
Current smoker	5 (5.4)	4 (5.6)	1 (5.0)
Drinks per week (n [%])			
Nondrinker	35 (38.0)	27 (37.5)	8 (40.0)
1–2 per week	22 (23.9)	17 (23.6)	5 (25.0)
3–4 per week	8 (8.7)	5 (6.9)	3 (15.0)
>4 per week	27 (29.3)	23 (31.9)	4 (20.0)
Comorbidities (n [%])			
Asthma	25 (27.2)	22 (30.6)	3 (15.0)
MAC lung disease	2 (2.2)	1 (1.4)	1 (5.0)
Bronchiectasis	4 (4.3)	3 (4.2)	1 (5.0)
GERD	4 (4.3)	3 (4.2)	1 (5.0)
Wegener's granulomatosis	2 (2.2)	2 (2.8)	0 (0)

Abbreviations: AFRS, allergic fungal rhinosinusitis; CRS, Chronic rhinosinusitis; CRS_{sNP}, chronic rhinosinusitis without nasal polyps; CRS_{WNP}, chronic rhinosinusitis with nasal polyps; GERD, gastroesophageal reflux disease; IBD, inflammatory bowel disease.

Median total Lund–MacKay were compared between CRS patients with ($n = 17$) and without IBD symptoms ($n = 61$). A Shapiro–Wilk test indicated a significant deviation from normality ($P < 0.05$). CRS patients without IBD symptoms (median = 3.00) reported significantly worse Lund–MacKay scores than CRS patients with IBD symptoms (median = 8.00, $P < 0.05$, Wilcoxon rank sum test with continuity correction, Figure 1B).

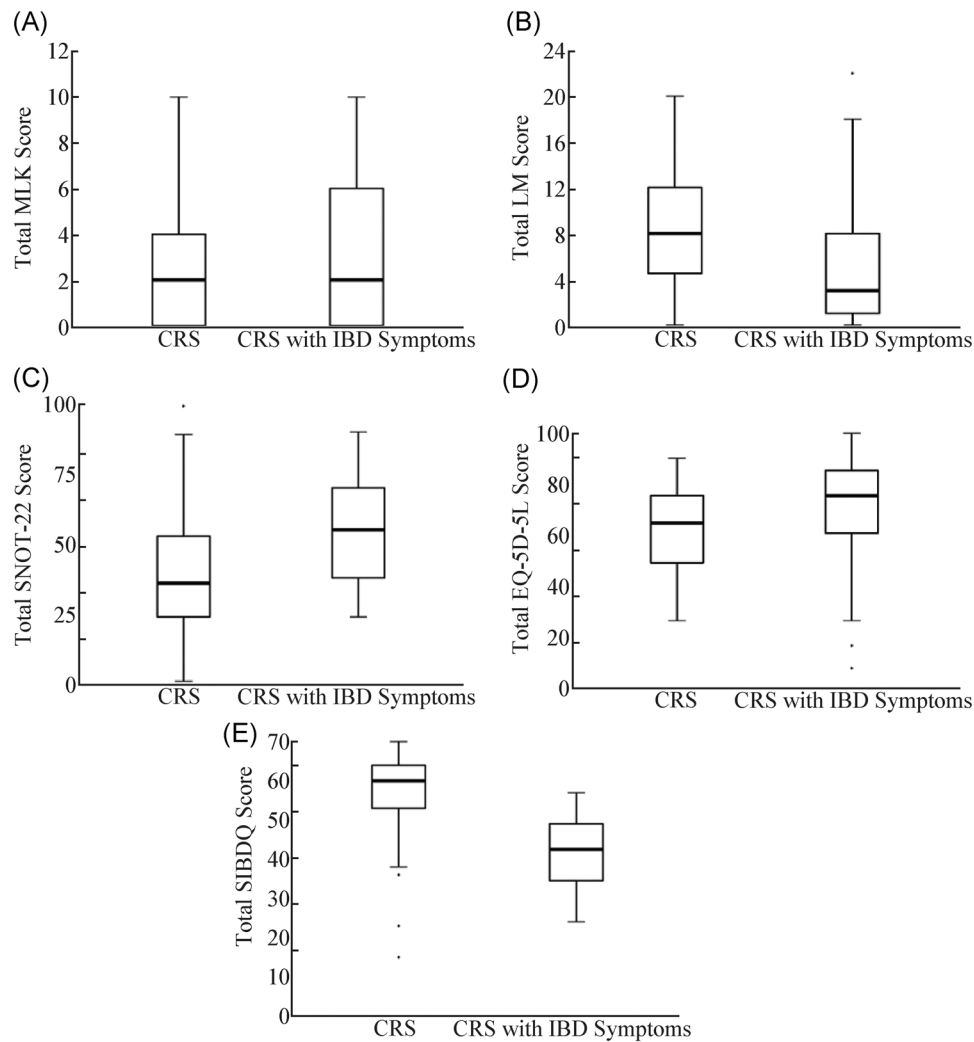


FIGURE 1 Comparisons of scores between chronic rhinosinusitis (CRS) patients without and with inflammatory bowel disease (IBD) symptoms. (A) Comparison of total median Modified Lund–Kennedy (MLK) between CRS patients without ($n = 71$) and with ($n = 18$) IBD symptoms ($P > 0.05$). (B) Comparison of total median Lund–MacKay (LM) between CRS patients without ($n = 61$) and with ($n = 17$) IBD symptoms ($P < 0.05$). (C) Comparison of total mean Sino-Nasal Outcome Test 22 (SNOT-22) between CRS patients without ($n = 72$) and with ($n = 20$) IBD symptoms. (D) Comparison of total median EuroQol 5 Dimension 5 Level (EQ-5D-5L) score between CRS patients without ($n = 69$) and with ($n = 20$) IBD symptoms ($P < 0.05$). (E) Comparison of total median Short Inflammatory Bowel Disease Questionnaire (SIBDQ) score between CRS patients without ($n = 58$) and with ($n = 19$) IBD symptoms ($P < 0.05$). Error bars represent standard deviation

Quality of life outcome measures

Mean total SNOT-22 questionnaire scores were compared between CRS patients with ($n = 20$) and without IBD symptoms ($n = 72$). A Shapiro–Wilk test failed to show a significant departure from normality ($P = 0.19$). A Bartlett test confirmed equal variances ($P = 0.77$). CRS patients who reported IBD symptoms exhibited greater total SNOT-22 scores (mean = 55.84) compared to CRS patients without IBD symptoms (mean = 38.70, $P < 0.05$, two-sample t -test, Figure 1C).

Median total VAS EQ-5D-5L were compared between CRS patients with ($n = 20$) and without IBD symptoms ($n = 69$). A

Shapiro–Wilk test showed a significant deviation from normal distribution ($P > 0.05$). CRS patients with IBD symptoms (median = 75.00) reported significantly worse quality of life than those without symptoms (median = 64.00, $P = 0.02$, Wilcoxon rank sum test with continuity correction, Figure 1D).

Median total SIBDQ were compared between CRS patients with ($n = 19$) and without IBD symptoms ($n = 58$). A Shapiro–Wilk test indicated a significant deviation from normality ($P < 0.05$). CRS patients with IBD symptoms reported significantly worse quality of life (median = 42.50) than CRS patients without IBD symptoms (median = 60.0, $P < 0.05$, Wilcoxon rank sum test with continuity correction, Figure 1E).

DISCUSSION

Given the potential relationship between sinonasal and intestinal pathologies, the primary objective of the study was to determine the prevalence of IBD among a CRS patient population. The prevalence of IBD among this CRS population was found to be 4.35% with an additional 2.17% suspected of also having IBD. As of 2018, the prevalence of IBD in Canada is 0.7% with this rate increasing to 1% by 2030.¹³ Although our sample size was limited, the prevalence of IBD among our CRS population was much greater than the population prevalence suggesting that IBD may disproportionately impact CRS patients and thus, warrants the need for further research.

The association of CRS with comorbidities has previously been examined. Chandra et al.¹⁴ performed a retrospective, cross-sectional study which examined the prevalence of CRS with and without nasal polyps in patients with chronic inflammatory comorbidities including IBDs. It was found that among 2259 individuals with IBD, 3.5% of patients also had CRS. Moreover, a study conducted by Book et al.¹⁵ investigated the association of sinonasal disease with IBD in a retrospective survey analysis of 160 IBD patients. It was found that 23% of IBD patients self-reported a history of CRS diagnosis or symptoms. The prevalence of patients with CRS who also have IBD in our population appears to share similar percentages to previous studies investigating patients with IBD who also have CRS despite the smaller sample size present in this study. While Chandra et al.¹⁴ and Book et al.¹⁵ provide preliminary evidence of the association of CRS in an IBD population, they fail to determine the prevalence of IBD within a CRS population. Thus, this study is the first to prospectively determine the association of IBD within a CRS population.

Additional studies in the literature sought to identify common disease processes within the pathophysiology of asthma, CRS, IBD, and other inflammatory diseases such as atopic dermatitis and eosinophilic esophagitis. A review by Sugita and Kabashima outlines the role of tight junctions within the involved tissues as a possible common trait and point of manifestation for the aforementioned diseases.¹⁶ Furthermore, certain cytokines have been identified as a component of the inflammatory pathway in these diseases, such as IL-32, IL-19, and IL-20.^{17,18} Advances in research investigating specific targets along related inflammatory pathways may lead to further understanding the clinical manifestations and relationships between these various inflammatory disorders.

In addition to prevalence, our study assessed disease-specific and overall quality of life through three questionnaires: the SNOT-22, SIBDQ, and EQ-5D-5L. We found that CRS patients with IBD symptoms exhibited significantly worse quality of life scores on all three measures compared to CRS without IBD symptoms. The results of this study correlate well with previous research evaluating the burden of CRS on health-related quality of life. CRS patients have previously been found to have reduced mood, energy level, and physical and social functioning.⁵ Similarly, IBD is associated with poor sleep quality, anxiety, and depression.^{19,20} Furthermore, the impact of extra-intestinal manifestations associated with IBD on quality of

life further corroborates the results of our study. In a study of 159 adolescent patients with IBD, 9.62% of patients exhibited pulmonary manifestations associated with IBD.²¹ It was found that this sub-group of patients experienced greater frequency of respiratory symptoms such as coughing and wheezing, disturbances to physical activity, and impairment of psychosocial functioning resulting in a reduced quality of life.²¹ Similarly, recent literature has found that pulmonary manifestations associated with CRS such as asthma, COPD, and bronchiectasis result in a significant reduction in quality of life as well as, greater disease burden.^{14,22,23} Thus, given the significant negative impact IBD symptoms have on CRS patient quality of life, future research should focus on clinical management of both diseases.

This study also investigated the impact of CRS associated with IBD on CRS disease severity through endoscopic and computed tomographic analysis. Interestingly, compared to CRS patients with IBD symptoms, CRS patients without symptoms exhibited significantly worse Lund–MacKay scores. As well, there was no statistical difference in MLK scores between both groups. These findings suggest that the comorbidity of IBD with CRS does not impact CRS disease severity; however, the combination of the diseases may impact the quality of life of an individual dramatically. While there is little research specifically investigating the relation between IBD and CRS severity, pulmonary disease has been found to increase CRS disease. A study conducted by Lin et al.²⁴ investigated the impact of asthma on CRS disease severity and found that comorbid asthma was associated with worse Lund–Mackay scores, a greater presence of nasal polyposis as well as, higher prevalence of allergic sensitization. Accordingly, larger cross-sectional studies are required to validate the impact of IBD on CRS disease severity.

Interestingly, 7.61% of our CRS population was diagnosed with IBS, a chronic functional gastrointestinal disorder with unknown etiology.¹⁹ IBD and IBS share many pathological mechanisms and symptoms including increased pro-inflammatory cytokines, auto-immune antibodies, angiogenesis factors, and microbiome dysfunction.²⁵ A previous case-control study of 133 subjects investigated the link between IBS and CRS and found that CRS patients had a significantly increased risk of developing IBS.²⁶ Given this increased risk, further research is required to determine the prevalence of IBS among a CRS population and its potential impact on disease severity.

While this prevalence study is the first to prospectively investigate the prevalence of IBD in a CRS population, few limitations merit discussion. There may be an underrepresentation of the actual number of patients who have both diseases, since six patients who were referred to a gastroenterologist for evaluation of IBD did not undergo all diagnostic measures or were lost to follow-up. Furthermore, 40.2% of the CRS population were diagnosed with allergic fungal rhinosinusitis, an IgE mediated subtype of CRS, which may have influenced the results of this study. As well, the screening questions used were based on the recommendations from a senior

gastroenterologist which may have compromised the detection of IBD in the CRS population.

CONCLUSIONS

The prevalence of IBD may be elevated among individuals with CRS. This pilot study suggests that CRS with IBD is associated with lower quality of life; however, IBD does not seem to increase CRS disease severity. Further cross-sectional studies with larger sample sizes are required.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

ETHICS STATEMENT

The study was approved by the Ethics Committee of the University of British Columbia University (H18-02330). Informed consents were obtained from all subjects before enrolment.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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