Answers to reviewer's comments

Dear reviewer

Thank you for opportunity to revise our manuscript, "Risk of Inflammatory Bowel Disease in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide, population-based study". We really appreciate the careful review and constructive suggestion.

Following this letter are the reviewer comments with our response in italics, including how and where the text was modified. Changes made in the manuscript are marked using blue color. The revision had been developed in consultation with all coauthors, and each author has given approval the final form of this revision.

Sincerely,

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Comments by Reviewer 02454185

1. In the introduction section, it is necessary to highlight why the current work is mandatory and how this can add to the existing literature. Based on current description, it seems the study is not novel because there has already been many such studies.

Answer) Thank you very much for your constructive suggestion.

As mentioned in the manuscript, several studies have reported an increased risk of developing inflammatory bowel disease (IBD) in patients with airway disease including chronic obstructive pulmonary disease (COPD). These studies have been conducted in Europe and Canada, where these countries are traditionally known to have a high prevalence of IBD. Asia, including South Korea, is in a relatively low prevalence of IBD and several studies have reported that Asian IBD may differ from Western IBD in its pathophysiology and clinical manifestation.

South Korea has a considerably higher prevalence of COPD than other countries, with 15.5/1000 people diagnosed with COPD annually. At the same time, South Korea has become one of the highest incidences of IBD among Asian countries. This is the first study conducted to address the association between COPD and IBD in Asia. Although similar results were obtained with Western studies, we determined that it is meaningful to examine the relationship between these two diseases with chronic and complex pathophysiology using Asian large sample size.

As you suggest, we will highlight this in the introduction section.

2. Is the database also record time-to-event data? For example, when a patient was diagnosed as having IBD? How did you extract data on the time of IBD diagnosis? This information is necessary for survival analysis.

Answer) Thank you for detailed question.

When diagnosed with Crohn's disease and ulcerative colitis according to the

diagnostic criteria based on clinical manifestations, endoscopic findings, and histologic findings, the patients were registered directly in the National Health Insurance Service (NHIS) database and rare intractable disease (RID) program. The time 0 point of IBD diagnosis was defined as the point of time when the disease code IBD was imposed and we extracted data using this code system. We add these details to the second paragraph of "Study population and patient identification" in material and method section to clarify this data extraction method.

3. Are there any skewed data in the study? If so, I suggest to use median and IQR for these skewed data. Especially in the method section, we need to describe how skewed data were expressed before we see the data. I also suggest to cite a reference for the description (Ann Transl Med. 2016 Mar;4(5):91. doi: 10.21037/atm.2016.02.11.).

Answer) Thank you for detailed comment.

The continuous variables used in our study were age and follow-up duration, but neither was skewed data. Therefore, the skewed data did not need to be considered separately and we use student's t-test for analysis of continuous variables.

As you have recommended, we have read the literature titled "Univariate description and bivariate statistical inference: the first step delving into data" and cited this as a reference.

4. In the survival analysis, it is unclear whether COPD was used as baseline characteristics. Actually it is difficult to define the time 0 point from which the follow up begins. Furthermore, the COPD severity can alternate between severe and mild, contributing to a time-varying covariate. Specify how you handle this problem. I suggest to add reference (Ann Transl Med. 2018 Apr; 6(7):121. doi: 10.21037/atm.2018.02.12.) for the description and discussion if you want to include it as a limitation if further analysis cannot be done.

Answer) We really appreciate to your important comments.

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. The time 0 point of COPD was defined as the point of time when the disease code COPD was imposed and the first prescription for COPD was claimed. "Severe COPD" was defined as a case where a patient has been simultaneously claimed LABA, LAMA and ICS for one year after the COPD claim.

And when we analysed the data, we used the Cox regression hazard model adjusting time-varying covariates that can be obtained from NHIS database. As you recommended, we cited the literature titled "Time-varying covariates and coefficients in Cox regression models" as a reference.

5. For selecting the control group, the authors used sex matched cohort, why not including more potential confounders and use propensity score matching since there is large sample size. PSA was a powerful tool for causal inference.

Answer) Thank you for your constructive suggestion.

As you mentioned, propensity score matching is a very powerful analysis tool, so we wanted to use propensity score matching when analyzing our data. However, because the NHIS database provides data by matching only age and sex, we could not have access to data that would otherwise be more potential confounders. In order to compensate for this limitation, other accessible confounders were adjusted using the Cox proportional hazard regression models. We are planning a prospective observational cohort study that combines administrative data with actual clinical data. As you suggested, we would like to use PSA matching in our further research.

Comments by Reviewer 03479673

Dear Authors, Congratulations for conducting such a good caliber study which left no room for improvement. I would just like to know if you are planning to combine it with prospective data collection and providing more robust level of evidence in future for association between the two diseases?

Answer) Thank you for comments and constructive suggestion.

We are planning a prospective observational cohort study that combines administrative data with actual clinical data to provide more solid evidence for the association between COPD and IBD.

Comments by Reviewer 03474080

I read the manuscript titled "Risk of Inflammatory Bowel Disease in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide, population-based study". Overall it is a globally good presented study with an interesting topic. Abstract was well described and clear. The study is well designed and conducted. Methods are well described and clear. Conclusions are justifiable and prudent enough. I have no additional recommendation.

Answer) Thank you very much. We really appreciate to your favorable comments.

Comments by Reviewer 02926997

This cross sectional study evaluated the risk IBD in patients with COPD compared to controls in a cohort of Korean population. The method of writing and the analysis method is very well.

1. I recommend the respect authors to avoid duplication the data of tables and figures in the text (result section).

Answer) Thank you for detailed recommendation.

We removed all duplicates from the manuscript for the data mentioned in the table and/or figure, except for the numbers that we consider important.

2. There might to be association between the medications used for treatment of both conditions. Please mention this possibility as the future direction of upcoming researches. I want to emphasis that the association of anti TNF medications and COPD is a matter of debate.

Answer) Thank you very much for your important comments.

As you pointed out, medications can be an important risk factor for causing any disease, so we have considered the possibility that drugs used to treat COPD can cause IBD, and have reviewed a lot of literature. However, no studies with robust level of evidence were reported on the association of COPD medication and IBD. In this regards, as you mentioned, further research is needed.

Several studies revealed that plasma tumor necrosis factor (TNF-α) and its soluble receptor are increased in patients with COPD than in healthy controls. It has been hypothesized that inflammation in the lung results in overspill into the circulation causing systemic inflammation by diverse inflammatory mediator. 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 anti TNF-α agents have not shown significant benefit in patients with COPD, although etanercept may reduce hospital admissions. 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.

We have mentioned this further in the discussion part. However, since the present study is about the increased risk of developing IBD in patients with COPD, the impact of anti TNF- α, the major treatment of IBD, on COPD may not be addressed in this study.

Comments by Reviewer 03580207

The incidence rate of complications from lung injuries are rather high in UC patients. Some drugs for inflammatory bowel disease can also cause lung damage. How does the author think about this problem?

Answer) Thank you for your important question.

Pulmonary involvement is a relatively rare extraintestinal manifestation of IBD. The most common pulmonary manifestation of IBD is drug-induced lung disease, frequently attributed to 5-ASA or methotrexate. 5-ASA agents are the mainstay of treatment for mild-to-moderate UC and these agents are effective in inducing remission and also in maintaining remission for patients with mild and some with moderate disease. However, the effect of the 5-ASA preparation is negligible in Crohn's disease. Therefore, lung injury is relatively common in UC, where 5-ASA is the mainstay of treatment.

Comments by Reviewer 03017551

Firstly - very large groups, both the patients with COPD and the control group (non-COPD). Secondly - an interesting conclusion. Thirdly - interesting results of statistical analysis.

Answer) Thank you very much. We really appreciate to your favorable comments.

Comments by Reviewer 03478404

1. Obviously, the merit of this research is to be a population-based one, including millions of people. However, data from results were detected after just simple statistical analysis. The aim of the study was "to investigate the influence of chronic obstructive pulmonary disease (COPD) on the risk of IBD". Well, this aspect was not

clearly addressed. In what way COPD increased the risk of IBD? There was a discussion about hypoxia. However, nothing is mentioned about medication. What about other covariates? They are of paramount importance. Other than gender and age, none was included. The main weakness of this study is not taking into consideration other covariates. Authors just studied simple association. Which is not right.

Answer) We really appreciate to your detailed and constructive comments.

We determined that the higher risk of IBD in COPD patients might be explained by the genetics, pathological background, and environmental factors shared by these two disease. And the effects of hypoxia in COPD on IBD pathogenesis were reported in many studies as we mentioned in our manuscript.

As you pointed out, since medication can be an important covariate, we have reviewed and studied a lot of literature about this. However, we have not been able to find robust level of evidence to support this. Based on our findings of the present study, we are planning a prospective observational cohort study that combine administrative data and actual clinical data including medications. We hope that further study will reveal more precisely the association between COPD and IBD.

2. a. Introduction: 1) IBD is not divided into CD and UC. Actually, IBD-unclassified is included too. Authors did not mention anything about IBD-U. 2) Authors wrote "Thus, in the present study, we aimed to investigate the association between two diseases" – please mention what two diseases, more precisely.

Answer) Thank you for your detailed comments.

1) *We used ICD-10 code and V code to extract data from patients who were diagnosed IBD more clearly. IBD-unclassified is not registered in our NHIS database and RID system. Therefore, we had to extract and analyze only the data of patients who were imposed diagnostic codes for CD and UC according to the diagnostic criteria.*

2) *We aimed to investigate the association between COPD and IBD represented by CD and UC. We clarified this in the last paragraph of introduction section.*

3. b. Materials and Methods 1) What were the criteria for diagnosing UC and CD? References 19 and 20 used as criteria do not refer to them. 2) Why was IBD-U not included?

Answer) We really appreciate to your important point.

1) *Patients are diagnosed with UC if they have (1) clinical manifestations: diarrhea and blood and/or mucus in the stool for at least 4 weeks, tenesmus (2) endoscopic findings: loss of vascularity, friability, or granularity in the colorectal mucosa, and continuous, circumferentially arranged ulceration in the rectum, and (3) pathologic findings: chronic inflammation or distortion of the crypt architecture, inflammation of the crypts, crypt abscess, increased chronic inflammatory cells in the lamina propria, erosions and/or ulcer.*

   Patients are diagnosed with CD if they have (1) clinical manifestations: abdominal pain, malaise, weight loss, diarrhea, and/or rectal bleeding for at least 6 weeks, (2) endoscopic or radiologic findings: linear ulcers, cobblestone-like mucosal appearance, aphthous ulcers, stricture, fistula, skip lesions, and/or perianal disease, and (3) pathologic findings: transmural inflammation, chronic inflammation, which consists of increased lamina propria plasma cells and lymphocytes combined with chronic architectural distortion, neutrophilic inflammation and cryptitis, crypt abscesses, erosions or ulcers.

   Since the references were incorrectly entered, this was corrected. Thank you again for point this out.

2) *For reasons mentioned in the answers to the above question, IBD-U was not included in the analysis.*

4. c. Results 1. Baseline characteristics of study population: 91.5 + 8.6 = >100. Please correct!

Answer) Thank you for the opportunity to make up for the mistake. We corrected the data in the result section 91.5 → 91.4%

Dear Editor-in-Chief, Dr. Andrzej S Tarnawski

We really appreciate to your comments for our manuscript, "Risk of Inflammatory Bowel Disease in Patients with Chronic Obstructive Pulmonary Disease: A Nationwide, population-based study".

Following this letter are the reviewer comments with our response in italics, including how and where the text was modified. Changes made in the manuscript are marked using red colors. The revision had been developed in consultation with all coauthors, and each author has given approval the final form of this revision.

Sincerely,

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Answers to Journal Editor-in-Chief's comments

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JOURNAL EDITOR-IN-CHIEF (ASSOCIATE EDITOR) COMMENTS

While several previous studies reported an increased risk of developing inflammatory bowel disease (IBD) in patients with COPD, these studies were conducted in Europe and Canada known to have a high prevalence of IBD. Therefore, it is not certain whether these studies would apply to entirely different populations in Asian countries. The authors made a compelling argument and pointed out that South Korea has a higher prevalence of COPD (15.5/1000 people diagnosed annually and that the incidence of IBD in South Korea has increased approximately 10-fold over the last two decades. The strengths of this paper are: a large study population, clinical importance, well-conducted, comprehensive discussion, and spelled out study limitations.

1. The previous study on this topic, published in the WJG should be cited - Vutcovici M, Brassard P, Bitton A. Inflammatory bowel disease, and airway diseases. World J Gastroenterol. 2016 Sep 14;22(34):7735-41. doi: 10.3748/wjg.v22.i34.7735.

Answer) Thank you for recommending a great paper.

We read the article you mentioned carefully and studied it. We cited this study in the second paragraph of the "Introduction" part.

2. The paper should be carefully check-spelled, e.g., "Previous wester studies" "n" is missing, and uniformly use either English or US-English spelling.

Answer) Thank you very much for your comment. We rechecked and corrected the spelling mistake. We have ensured that US-English has been consistently used throughout the manuscript.