Author Response

Responses to Comments

Response to Reviewer 1

General comment. This is an excellent work. This report will be important for clinicians.

Response. We appreciate the reviewer's words of encouragement. We are submitting a revised manuscript that addresses the concerns raised.

Comment 1. I have only one question.

Do the authors have any data about the differences of duration of COVID-19 illness between patients with and without BE?

Response 1. Thank you for your comment. Unfortunately, data about the duration of COVID19 illness are not provided by the Korean Health Insurance Service (NHIS) database. Thus, we cannot provide the exact duration of COVID-19 illness in each group. We acknowledged the limitation in the revised manuscript (pages 5–6, lines 117–119).

"First, since the NHIS database for COVID-19 did not provide data on smoking history, pulmonary function tests, laboratory findings, medications, and the duration of hospital stay, we could not include this information in our study results."

Response to Reviewer 2

Comment 1. This study mainly represents an interrogation of a database of people diagnosed with bronchiectasis. There are no clinical datails about the patients other than their comorbidities. We don't know if they had severe bronchiectasis before they contracted COVID. This would be based on their exacerbation frequency, FEV1, HRCT thorax and P aeruginosa in their sputum. Also bronchiectasis aetilogy is the end result of a number of different processes- 40% idiopathic, post-infectious, immunodeficiency, reflux, dysphagia, congenital causes and chronic airway diseases. Which of these would be most vulnerable to COVID? A major limitation of this study is that 57% have COPD and this makes it more a COPD study. We already know that these patients get more severe COVID. 50% of COPD patients attending hospital clinics have secondary bronchiectasis. Also 62.1% of patents have asthma - this is considerably higher than any previous aetiological /co-morbidity study of bronchiectasis before. Also the prevalence of asthma is not higher in COVID-19 patients. In fact asthmatics may be protected from COVID -19 (Curr Opin Pulm Med 2021 Jan;27(1):45- 53.) Also linear regression analysis would have to be done on this population to make certain is not the co-morbidities that is causing the increased prevalence and severity of COVID. Final point -how can patients need more oxygen, ECMO, have a higher mortality but not need an elevated ICU admission rate. Was there an age cut-off for COVID-19 patients to ICU?

Response. We appreciate the reviewer's helpful comments that have substantially improved the quality of our manuscript. We agree that our study was limited by the lack of detailed clinical information. Although our data is imperfect, we believe that this real-world data will provide clinicians—specifically pulmonologists managing patients with bronchiectasis—with useful clinical information amid COVID-19 pandemic. We are submitting a revised manuscript that addresses the concerns raised. A detailed, point-by-point response to these concerns is attached.

Response 1-1. Lack of clinical details

Thank you for your comment. Since the national insurance claims data were used, this study could not provide information about bronchiectasis in detail: aetiology of bronchiectasis, exacerbation history, and Pseudomonas colonisation in sputum. Accordingly, reports from international bronchiectasis registries are warranted shortly; we hope our research will be helpful to clinicians in the meantime. We have revised manuscript as follows (page 6, lines 119–123):

"Second, for the same reason above-mentioned, this study could not provide information about bronchiectasis in detail: aetiology of bronchiectasis, exacerbation history, and Pseudomonas colonisation in sputum. Accordingly, reports from international bronchiectasis registries are warranted shortly."

Response 1-2. Comorbid airway diseases: COPD and asthma

Thank you for pointing this out, as it was not fully acknowledged in our original manuscript. Although asthmatics were suggested to be protected from COVID-19,1 this study showed significantly higher asthma rate in COVID-19 patients with bronchiectasis than those without bronchiectasis. Bronchiectasis may serve as a leverage to more severe COVID-19 in asthmatics; however, future research is necessary to clarify the mechanistic link. Additionally, the important point you pointed out is the severity of COVID-19 patients with bronchiectasis plus airway disease: COPD and asthma. Previous research revealed patients with COPD or asthma showed more severe clinical course and worse outcome if they have comorbid bronchiectasis.2 In line with the study, comorbid airway disease may play a major role in poorer clinical outcomes in bronchiectasis patients with COVID-19. We clarified this issue in the revised manuscript (page 5, lines 104–112).

"Although asthmatics were suggested to be protected from COVID-19,1 this study showed significantly higher asthma rate in COVID-19 patients with bronchiectasis than those without bronchiectasis. Bronchiectasis may serve as a leverage to more severe COVID-19 in asthmatics; however, future research is necessary to clarify the mechanistic link. Previous research revealed that patients with COPD or asthma showed more severe clinical course and worse outcome if they have comorbid bronchiectasis.2 In line with the study, comorbid airway disease may play a major role in poorer clinical outcomes in bronchiectasis patients with COVID-19."

References

1. Assaf SM, Tarasevych SP, Diamant Z, et al. Asthma and severe acute respiratory syndrome coronavirus 2019: current evidence and knowledge gaps. Curr Opin Pulm Med 2021; 27: 45-53. 2020/10/17. DOI: 10.1097/MCP.0000000000000744.
2. 2. Choi H, Lee H, Ryu J, et al. Bronchiectasis and increased mortality in patients with corticosteroid-dependent severe asthma: a nationwide population study. Ther Adv Respir Dis 2020; 14: 1753466620963030. 2020/10/17. DOI: 10.1177/1753466620963030.

Response 1-3. Linear regression analysis

We appreciate your valuable comment. We agree with the reviewer that regression analysis considering comorbidities would provide more accurate results. Although we tried to perform a

regression analysis adjusting for comorbidities, we could not establish a well-fit regression analysis model accounting whether increased prevalence and more severe clinical course of COVID-19 did not result from comorbidities in bronchiectasis patients. After an in-depth discussion with statistical specialists about this issue, we have concluded that this was caused by the very low rate of COVID-19 patients with bronchiectasis; the proportion of bronchiectasis patients with COVID-19 was only 1.34% of all study population, and the ratio of bronchiectasis with severe COVID-19 was 0.50% of all COVID-19 patients. We added this information as a limitation of our study in the revised manuscript (page 6, lines 123–126).

"Third, as the number of COVID-19 patients with bronchiectasis was small (1.3% of all study population), we could not establish a well-fit regression analysis model accounting whether increased prevalence and more severe clinical course of COVID-19 did not result from comorbidities in bronchiectasis patients."

Response 1-4. ICU admission rate

Thank you for your comment. The ICU admission rate was 3.04% in COVID-19 patients with bronchiectasis and 3.00% in those without bronchiectasis (p = 0.983). However, the rates of supplemental oxygen, mechanical ventilator treatment, ECMO were higher in COVID-19 patients with bronchiectasis than those without bronchiectasis. We interpreted the result as COVID-19 patients with bronchiectasis revealed worse clinical course finally than those without bronchiectasis although both groups revealed similar severity when admitted to ICU initially. Plus, there was no age cut-off for COVID-19 patients to ICU. We add this point to the revised manuscript (page 5, lines 96–99).

"Considering similar ICU admission rates, COVID-19 patients with bronchiectasis revealed worse clinical course finally than those without bronchiectasis although both groups had similar severity when admitted to ICU initially."