

Peer Review File

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Reviewer A

I have reviewed this interesting study about paradoxical bronchodilator response. The authors analyze the Korean KOCOSS cohort and find a 2.9% of patients with this paradoxical response and it was independently associated with worse dyspnea and poor quality of life and higher CRP levels, but not with exacerbations. I have the following comments:

INTRODUCTION

Comment 1: J Thorac Dis is a specialized journal of respiratory diseases; therefore, I find unnecessary to define what COPD is and how it is diagnosed at the beginning of the introduction. I would refocus the introduction by starting to say that the role of BDR in COPD is undefined.

Reply 1: Thank you for your comment. We modified the INTRODUCTION part as “Post-bronchodilator spirometry is required for the diagnosis of COPD, but the role of bronchodilator response (BDR) is unclear in COPD. Positive bronchodilator reversibility is no longer recommended as a treatment option for COPD, and there is no standard definition yet. In addition, positive bronchodilator reversibility does not predict the clinical outcomes of long-term use of bronchodilators and inhaled corticosteroid (ICS).” (See page 5, line 66-70)

Comment 2: The authors speak about paradoxical bronchoconstriction in the introduction and they speak about paradoxical bronchodilator response in the abstract ... please unify the terms. Is this a paradoxical bronchodilation or bronchoconstriction?

Reply 2: Thank you for your correct comment. We modified paradoxical bronchoconstriction to paradoxical bronchodilator response (BDR) at the abstract. (See page 3, line 36-37)

Comment 3: The majority of the references in the introduction regarding this paradoxical response are referred to asthmatic patients. Therefore, I think the introduction should be completely re-written giving it a more pathophysiological view rather than focus it in COPD from the beginning.

Reply 3: Thank you for your comment. We re-wrote the entire contexts in the introduction part as your recommendation. (See page 5-6, line 66-86)

METHODS.

Comment 4: The methodology is a summary of the KOCOSS cohort. The interesting aspect here is how they manage their data. I find surprising that the authors build lineal regression models instead of logistic regression models and would be more intuitive.

Reply 4: Thank you for your comment. We used a lineal regression model to find out the associations between paradoxical BDR and continuous variables which are represented as clinical symptoms (6MWD, SGRQ-C, mMRC, and CAT). We also used a logistic regression model to reveal the predicted factors associated with paradoxical BDR.

Comment 5: Then they study lung function prediction of exacerbations only in the paradoxical group, which I think it has no sense. The correct approach, I believe, is to do a bivariate analysis to see which variables are different for paradoxical response patients, and a multivariate logistic regression with the paradoxical response as the dependent variables, to see which of those are kept in the model.

Reply 5: Thank you for your valuable comment. We consulted a statistician at our hospital to solve this problem. As you commented, we had confusing information in the aim of this study. This study was aimed to evaluate the effect of paradoxical BDR on clinical outcomes (respiratory symptoms, quality of life, and severe 1-year acute exacerbation) in COPD patients. So we have changed the Background part of abstraction (See page 3, line 36-43) and aim part of the INTRODUCTION to clarify the aim of this study (See page 6, line 83-86). We used a lineal regression model to find out the associations between paradoxical BDR and continuous variables which are represented as clinical symptoms (6MWD, SGRQ-C, mMRC, and CAT). We also used a logistic regression model to reveal the predicted factors associated with paradoxical BDR.

RESULTS.

Comment 6: The authors exclude 288 cases for not being COPD, which does not say much about the quality of the data of this KOCOSS database. Table 1 should reflect the missing information in each variable. This would give an idea of the quality of the data.

Reply 6: Thank for your comment. Actually missing data means that lack of FEV1 or FVC at the time of enrollment. Therefore, we excluded those patients because it was not clear whether those patients had COPD. We change the RESULT part to clarify the meaning as “Two hundred and eighty-eight patients were excluded; 82 patients recorded FEV1/FVC of > 0.7 and 206 patients had missing FEV1 or FVC data at the time of enrollment.” (See page 10, line148-150)

We also added missing data information in the foot note of Table 1 (See page 23-24, line 345-349).

Comment 7: The authors do not give the value on the magnitude of the paradoxical response. They must add another row in table 1 showing the mean (standard deviation) of the result of the broncho-reversibility test in both groups. I would like to know if the authors excluded those cases with a negative response but did not reach their pre-specified limits for a paradoxical response.

Reply 7: Thank you for your comment. We added the bronchodilator response including paradoxical and no-paradoxical BDR as your recommendation in Table 1 (See page 22). In fact, 369 patients had negative response of FEV1 to the short-acting bronchodilator, 38 of them had paradoxical BDR (decreases in >200mL and 12% of FEV1). Of 603 patients who showed negative response of FVC to the bronchodilator, 23 had paradoxical BDR (decreased in >200mL and 12% of FVC). Four patients showed paradoxical response both in FEV1 and FVC.

Comment 8: In table 1, the find that pre-bronco FEV1 in liters is different, but it is no as %. This is interesting, because BMI is not different. They could probably add height and weight to try to find an explanation of this unexpected finding.

Reply 8: Thank you for your comment. We added the height and weight to the table 1 as your recommendation (See page 22). However, there were no difference in body weight and

height between the two groups. Because the reference value for FEV1 depends on age, height, gender and race, this unexpected finding is considered to have been observed.

Comment 9: IMPORTANT: The authors do probably an incorrect statistical approach. They play and mix two different approaches: linear and logistic approaches with different dependent variables. In table 1 they use the dependent variable as dichotomous, however in table 2 they seem to do a linear regression. This is very confusing and probable incorrect. In table 1 only lung function parameters are associated with the paradoxical response, whereas in table 2 there are clinical variables associated with different clinical parameters. In table 1 paradoxical response is the dependent variable, and in table 2 paradoxical response is an independent variable. This is not correct. The paradoxical response must always be the dependent variable as in table 3. Otherwise the authors are giving confusing information.

Reply 9: Thank you for your valuable comment. We consulted a statistician at our hospital to solve this problem. As you commented, we had confusing information in the aim of this study. This study was aimed to evaluate the impact on clinical outcomes (respiratory symptoms, quality of life, and severe 1-year acute exacerbation) in COPD patients. Table 1 showed the comparison of basal characteristics between paradoxical BDR and no-paradoxical BDR groups. We demonstrated whether paradoxical BDR was associated with respiratory symptoms and quality of life using a linear regression model in Table 2. We also described whether paradoxical BDR was a risk factor for severe 1-year acute exacerbation. Therefore, we have changed the Background part of abstraction (See page 3, line 36-43) and aim part of the INTRODUCTION to clarify the aim of this study (See page 6, line 83-86).

Comment 10: In table 3 they should provide the statistical reasons to include these variables in the multivariate analysis and provide the r^2 .

Reply 10: Thank you for your comment. We added the reasons to include those variables in the Method part (See page 8, line 128-132) and Result part (See page 10-11, line 161-169)

Comment 11: Figure 2 has no meaning in this study and should be eliminated

Reply 11: Thank you for your comment. We agreed your comments. We decided removal of Figure 2 as your recommendation (See page 29).

Comment 12: Figure 1 has typos.

Reply 12: Thank your comment. We corrected the typos in table 1 (See page 22-23).

Reviewer B

Comment 1: In previous study, salbutamol has the potential to enhance Goblet cell hyperplasia and airway hyperresponsiveness to methacholine in atopic asthma of animal, when systemically and continuously administered using an osmotic pump. We conclude that the beta agonist enhances Goblet cell hyperplasia induced by the immune response and that this can be completely abolished by simultaneous treatment with glucocorticoids. Although it may be premature to suppose that this phenomenon is applicable to humans, one should keep in mind the possibility that regular use of beta 2 agonists may exacerbate Goblet cell hyperplasia and the resulting mucus hypersecretion in patients with bronchial asthma.

Reply 1: Thank you for your comment.

Comment 2: In this study, the author found that the paradoxical bronchoconstriction after short-acting β 2-agonists in patients with COPD with 12% and 200-mL reduction in FEV1 or FVC after bronchodilator administration. This study is in line with the previous study.

Reply 2: Thank you for your comment.

Comment 3: The asthma with COPD including the $\geq 12\%$ and 200-mL increased in FEV1 or FVC after bronchodilator administration. We my list this groups patients in this study as the "COPD without asthma components"? limitation: the underuse the ICSs in the misclassification of COPD

Reply 3: Thank you for your valuable comment. Although patients with asthma were

excluded, some of them may have been included among patients with positive bronchodilator reversibility. It is also possible that these patients underused ICS. We added this points to the limitation of this study (See page 14, line 244-246)