Author’s response to reviews

Title: Aspergillus fumigatus during COPD exacerbation: A pair-matched retrospective study

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Author’s response to reviews:

Editor

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Re: Manuscript No. PULM-D-17-00280R3

Dear Editor Marta Gritti,

Attached please find our revised manuscript entitled “Aspergillus fumigatus during COPD exacerbation: A pair-matched retrospective study”.


We highly appreciate all the valuable comments from you and the reviewers. Based on the reviewers’ suggestion, we revised our manuscript and in the following pages and have included our point-by-point responses to each of the comments from you and the reviewers.

We hope that the revised manuscript and our accompanying responses will be sufficient to make our manuscript suitable for publication in the BMC Pulmonary Medicine.

Sincerely,

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Responses to Comments:

Reviewer #3

Néstor Soler

Comment 1: The number of valid respiratory samples with positive isolations for Aspergillus is scarce and insufficient to consider an analysis of outcomes.

Response: To date available data about Aspergillus identification in respiratory specimen of COPD patients with acute exacerbation are few, comparing with our study which showed its
novelty. Refer to existing studies, the rate of identification of Aspergillus in lower respiratory tract from COPD patients ranged from 16.6% to 36.7%. The sample size of the group with accurate colonization/identification of Aspergillus in above-mentioned studies was around twenty to fifty. In our study, 504 COPD patients were enrolled and among them about forty patients were with positive identification of Aspergillus, which made our data reasonable. The actual detection rate was 8.33% in our study, which was lower than existing studies, because our study included patients with normal immunity and those with lung function stage of I or II according to GOLD. While published studies mainly focused on the role of Aspergillus in invasive pulmonary aspergillosis, our study aimed to reveal a relative different view of Aspergillus colonization in COPD patients.


Comment 2: The authors assume that a single positive isolation already defines colonization. In many cases, the isolates for Aspergillus and other fungi are transient and have no significance.

Response: Thanks for your suggestion. Up to now, there is no widely accepted definition of Aspergillus colonization. The criteria of Aspergillus colonization approved by European Organization for Research and Treatment of Cancer/National Institute of Allergy and Infectious Diseases Mycosis Study Group (EORTC/MSG) were mainly used in previous studies. This set of criteria seemed more suitable for patients with cancer, hematopoietic stem cell transplantation or other immunocompromised diseases, as it was proposed mainly for invasive pulmonary aspergillosis. In 2007, Bulpa and other researchers concluded diagnostic criteria of Aspergillus colonization specifically for COPD patients, which was applied in several subsequent studies. This set of criteria was used for severe COPD patients with a pulmonary functional level of stage III or IV according to GOLD. But neither of those two criteria required repeated microbiology tests of positive identification for Aspergillus. Until now, we can’t answer the question of
duration of Aspergillus existence in lower respiratory tract. The definition of Aspergillus colonization proposed in our study, referred the Bulpa criteria, had more applicability in immunocompetent COPD patients.

Comment 3: The authors point out the treatment with high doses of inhaled corticosteroids (1000 mcg of beclomethasone or equivalent) as the main risk factor for colonization by Aspergillus. Although in previous studies this possibility has been suggested, there is no evidence to demonstrate this association and the pathogenic mechanism is not clear either. The authors also suggest that the presence of Aspergillus spp. in the lower airway may have an impact on episodes of exacerbation of COPD. This statement cannot be derived from the findings of the study since it would require a significant relationship between the persistent isolation of Aspergillus spp in the stable patient and an increase in the frequency of exacerbations. Only a long-term follow-up study of a cohort with repeated cultures could demonstrate this hypothesis.

Response: Thanks for your suggestion. The Aspergillus colonization and its relationship with ICS treatment was seldom noticed and answered in previous studies. Some studies were proved that ICS treatment could directly enhance Aspergillus growth and depress neutrophil and macrophage function, thus predisposing Aspergillus colonization in patients’ lower respiratory tract. We hope the phenomenon provided in our study could attract some attention and the pathogenic mechanism needs further investigation.

As for the results of this study, we’d like to focus on the clinical manifestation and short-term outcome of COPD patients with and without Aspergillus colonization in lower airway during exacerbation. And a previous prospective study reported that there was no significant change of isolation rate of Aspergillus between exacerbation stage and one-year follow-up (16.6% vs. 14.1%). We totally agree with your opinion, a follow-up study or a cohort study could demonstrate the relationship between the persistent isolation of Aspergillus spp and the frequency of exacerbations in COPD patients.

Comment 4: Although the finding that patients of Apergillus group require more intensive treatment with systemic corticosteroids is attractive, it is not clear that a greater degree of inflammatory response of the airway area during the exacerbation is a consequence of the direct effect of the fungus. In my opinion, the potential colonization by Aspergillus spp may be a mere indicator of the severity of the underlying disease and this condition could demonstrate the longer duration of hospital admission and a longer remission time.

Response: As you suggested, the severity of underlying disease and inflammatory condition could longer the duration of hospital admission and remission time. While in our study, lung function severity, underlying disease and inflammation response (WBC, CRP and relevant assay index) showed no significant difference between Aspergillus colonization group and control group. Only wheezing symptom and sign were prominently different between two groups. Therefore, clinical manifestation and short-term outcome of COPD patients with Aspergillus colonization were different from control group. Thus, we aimed to provide new insight for clinicians when managing patients with fungal colonization and indicate the directions for future comprehensive studies.

Reviewer #4
Saad Nseir

Comment 1: Please give more information on the type of multivariate analysis performed (backward, enter method.)

Response: Thanks for your suggestion. We supplemented relevant information of multivariate analysis in Methods in the revised version. (Line 8-12, Page 9)

Comment 2: Were viruses searched for in lower respiratory tract specimen?
Response: Thanks for your suggestion. Since cultivation and molecular examination of viruses are not routine procedures in lower respiratory tract specimen in our hospital, unfortunately, we didn’t search viruses in this study.

Comment 3: A short discussion on the relationship between Aspergillus isolation and outcome (cause or consequence of more severe illness) would be helpful for readers.

Response: Thanks for your kind suggestion. As for the relationship between Aspergillus isolation and outcome, we considered the following aspects: COPD patients are more susceptible to Aspergillus colonization because of the abnormal structure and impaired ciliary function of airway tract. After the spores of Aspergillus adhere in airway, Aspergillus-related allergic reactions were induced by antigen-triggered mast cell degranulation and release of histamine and inflammatory factors, thus aggravating airway inflammation. Although sensitisation to A. fumigatus has been associated with reduced lung function in COPD, it is unclear whether fungal colonization contributes to lower lung function or is a marker of more severe lung disease and aggressive therapy. In our study, we have been unable to clarify the relationship between Aspergillus isolation and outcome in a cohort of patients with repeated visits, emerging knowledge regarding the clinical significance of Aspergillus in airways of COPD patients and even the response to antifungal therapy remains to be determined and needs to be further explored. (Line 14-18, Page 13; Line 5-9 & 11-13, Page 14)

Comment 4: Table 1: p values for age and gender are missing.

Response: Thanks for your kind suggestion. We added the above-mentioned p values in Table 1.

Comment 5: The type of respiratory specimen (BAL, tracheal aspirate, sputum..) should be provided.
Response: Thanks for your kind suggestion. According to the inclusion criteria in this study, the respiratory specimen included BAL, tracheal aspirate and sputum. But all patients enrolled in this research only delivered sputum sample for microbiological cultivation.

Comment 6: The manuscript is rather well written. However, it could benefit from some English editing.

Response: As your suggestion, we invited a native speaker helping us in language modification to improve its clarity and readability.