

## Peer Review File

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### Reviewer A

#### General comments

This is a retrospective study aimed to assess the admission frequencies for COPD-related exacerbation observed in a single hospital in China during a period of 5 years in COPD patients to identify the characteristics of so called frequent exacerbators and the risk factors for future exacerbations in these subgroups of patients.

The main findings of the study (if I understand the results correctly) are:

The frequent exacerbators as defined for having three or more COPD-related exacerbations within 5-year period as compared with non-frequent exacerbators (less than 3 COPD-related exacerbations within the same period) had not surprisingly heavier smoking history, more severe lung diseases (as inferred by great percentage of patients with long-term oxygen therapy and home non-invasive ventilation) and more comorbidities.

In average only 12% of COPD patients had more than one hospital admission because of COPD-related exacerbation for each calendar year of the study.

COPD patients with 2 and 3 or more annual hospital admissions because of COPD-related exacerbations had 4 and 7 times greater risk of readmission in the next year because of COPD-related exacerbations, respectively, as compared with COPD patients with only one annual hospital admission because of COPD-related exacerbation.

Only about 15% of COPD patients with only one annual hospital admission because of COPD-related exacerbation had future readmissions because of COPD-related exacerbation, suggesting, in contrast with widespread recommendations, that only one COPD-related exacerbation even if hospitalized is not a strong predictor for future COPD-related exacerbations in COPD patients.

#### Major comments

Comment 1: There is no data about lung function to compare between frequent and non-frequent exacerbators.

Reply 1: Yes. This is a retrospective study, and most of the COPD-related acute exacerbators were unable to cooperate with lung function tests.

Comment 2: In this retrospective study the hospital admissions because of COPD-related exacerbation seem to occur in COPD patients also for non-severe exacerbations.

Reply 2: Yes, in our study, only about half the exacerbators with admission were severe AECOPD (graded by blood gas analysis, which do not show in the manuscript). That is very common in China. The evidences has shown in the reference 16 in the manuscript, that was national AECOPD registration study in China, in which the average PaO<sub>2</sub> of 5334 admission patients with AECOPD was 69mmHg, and only 23.3% of them were GOLD stage IV.

Comment 3: Definitions of frequent and nonfrequent exacerbators are confusing throughout the manuscript and the results are difficult to understand.

Reply 3: In fact, there are two definitions or descriptions of "frequent exacerbators" in our paper. Those with three or more admissions in 5 years were defined as frequent exacerbators, and those patients with two or more admissions in 1 year were also considered as frequent exacerbators. The former is described and defined in the Methods part. The latter is from our findings that patients with two or more admissions in 2017 had a similar risk of future exacerbations as patients with three or more admissions in 5 years, both of them were more than 4 times as high as the risk among non-frequent exacerbators. Therefore, such patients are also considered to be "frequent exacerbators". This definition has practical clinical implications and may help clinicians to identify frequent exacerbators within different periods. The existence of two "definitions" in the manuscript may lead to some confusion.

Comment 4: Given the retrospective nature of the study, it is unknown the number of hospital readmissions because of COPD-related exacerbations that occurred in these COPD patients in other hospitals within the five-year period.

Reply 4: Yes, unable to statistics, and we have already made a corresponding explanation on this issue, in the Limitations part of our paper. As a retrospective study, there are some limitations. A small number of exacerbation patients may go to other clinics for treatment after discharge from our hospital, resulting in a small number of exacerbation data missing. But we think the missing data is small, because we did telephone follow-up for part of discharged patients, and about 20% of them went to another clinic after an exacerbation.

#### Minor comments

Comment 5: The Authors recruited 1516 COPD patients with hospital admission because of COPD-related exacerbation over the 5-year study period (1350 with less than 3 and 165 with 3 or more admissions) and analyzed data of 380 COPD patients (one group with frequent hospital admissions n = 156 and another with non-frequent hospital admission n = 224). Where are the other 1136 COPD patients?

Reply 5: Of the enrolled 1516 patients, 39 with missing data more than 25% (see line 123-125) , and 1097 patients hospitalized in 2018-2021 who did not meet our

definition of fewer than three admissions in 5 years, were excluded. These 1136 patients were excluded from the data cluster for analysis of clinical characteristics and risk factors but still were used for the analysis of admission frequency in 5 years. We did not describe it clearly in the article.

Comment 6: The Fig. 4 is difficult to understand and should be better explained.

Reply 6: We have added the description in Figure 4 and try to make it be understood better.

## **Reviewer B**

Comment: Thanks to the authors for this retrospective analysis and conclusions which they have been released. However, I can not agree with their conclusions based on the COPD is heterogeneous and unpredictable disease. And we can not assess the readmission rate just based on time for disease features. It is clear that even one exacerbation in the past year is a risk factor for next exacerbation in the current year. But there is consideration above readmission after exacerbation of COPD and no consideration the place of patient management related to exacerbation (self-managed, moderate related to administration of systemic corticosteroids and antibiotics, and severe exacerbation which required hospital or ICU admission). Previous hospitalization for acute exacerbation of COPD is a strong predictor for future readmission. The European COPD audit involving >400 hospitals reported a 90-day readmission rate of 35.1% and a nationwide study in the US showed that the 30-day readmission rate for COPD patients was 22.6%. Similarly, in the UK approximately a quarter (24%) of patients with COPD exacerbations were readmitted at least once within 30 days of discharge and early administration of pulmonary rehab after discharge significantly reduced the readmission rate in patients and so I think even once hospitalization related to severe exacerbation of COPD is a strong predictor for exacerbation and readmission for COPD in future. And so I can not agree with the authors who concluded an incident of hospitalization once a year is not a good predictor of future readmission. I just advise to authors consider the patient age, BMI, comorbidities, respiratory failure with hypercapnia, the use of LTOT, and use of NIV for hypercapnic failure at home. All of the factors above are associated with an increased risk of readmission after discharge of patients. I would be added some biomarkers which also strongly associated with readmission rate regardless of exacerbation rate last five years: high CRP level, high >2% eosinophil level, the presence of bacterial colonization of the lower airways, and low serum total IgG<7.0g.L level are associated with increased incidence of readmission rate. And there are several predictive models for readmission regardless of previous history for COPD exacerbation (ADO, BODEX, DOSE, LACE, and last one is PEARL) which are demonstrated the several predictive factors together with previous admission per year. And so I think that we have to approach to the readmission with multiple positions but not just based on one exacerbation of year.

Reply: As we all know, the Medicaid Services System in China is different from the

western countries, we have no strict standard for AECOPD admission. Commonly, non-severe exacerbations even mild to moderate AECOPD were admitted to hospitals in China. So, it is not reasonable that an incident of one admission previously is recommended as an index to identify frequent exacerbators in China.

"SPIROMICS cohort" study (Lacet Respir, 2017:5:619) found that, the exacerbation status of most patients with COPD (with a history of exacerbation) varies markedly from year to year. The great majority of patients (91%) was no exacerbation or inconsistent exacerbators during the 3 study years. Only 9% of patients were frequent exacerbators who had an exacerbation each year. So, one admission(especially, no-severe exacerbation) may be an occasional event, which does not mean certainly a high risk of exacerbation in the future.

Also, our study indicated that, in addition to the patient's history of acute exacerbation or admission, many other factors, such as age, complicated heart disease, diabetes, oral corticosteroid use, and blood eosinophilia are associated with the risk of repeated exacerbation too. The risk factors differ in different studies, suggesting that the risk factors are diversified and individualized.

### **Reviewer C**

I think the authors' exploratory study on the frequency of hospitalization and readmission of patients with acute exacerbations of chronic obstructive pulmonary disease is a worthwhile contribution to treatment strategies for patients with acute exacerbations of chronic obstructive pulmonary disease. However, it needs some modifications.

Comment 1: The explanation regarding the sample size is unclear.

Reply 1: We used the two analysis datasets to describe the frequent exacerbators, One to analyze the clinical characteristics of patients in 5 study years (156+224 patients), and the other to study the risk of readmissions in the next 4 years of patients in 2017 (263 patients) grouped by different admission frequency. We have redrawn Fig.1 to describe our datasets and let it be more clear.

Comment 2: In Figure 1, of the 1516 patients, 156 are classified as frequent admissions and 224 as non-frequent admissions; why were the remaining 1136 patients excluded? Are frequent and non-frequent admissions not included in the "263 patients admitted in 2017?"

Reply 2: This question is answered in reply 5 to Reviewer A. We have redrawn the Figure 1.

Comment 3: In any case, please make the change so that the reader can see how patients were selected and excluded when looking at Figure 1 only.

Reply 3: We have modified the Figure 1.

Comment 4: The definition of terms is unclear. All terms in the text should mean the

same thing.

What do the terms "frequent admission" and "non-frequent admission" mean as they appear in the text and in the figures? The authors write "We defined three or more admissions ... (Lines 81 - 83)", but this definition does not seem to make sense for "non-frequent admissions" in Figure 3. Please confirm.

Reply 4: Figure 3a shows that the percentage of patients with frequent exacerbation was only 11.79%, but their admission frequency accounted for 30.61% of the total admission frequency in Figure 3b.

Comment 5: Please specify how "the accumulated readmission rates (Line 135)" was calculated. When revising, please note the difference in meaning between a rate and a percentage.

Reply 5: "The accumulated readmission rates": the number of patients who had readmissions during 2018-2021 / the number of patients who admission in 2017. Rate is the percentage of readmission, as indicated in the Figure 4.

Comment 6: "The incidence of AECOPD-related hospitalization ... (Lines 97 - 98)" does not appear in the results and is confusing. Please use the same terms in the methods and results.

Reply 6: We have already expressed the number of admissions in per person per year, results in the Lines 143-145

Comment 7: Is there a difference in the meaning of the term's "hospitalization" and "admission"? If they mean the same thing, please unify them.

Reply 7: We have already modified them as "admission" uniformly.

Comment 8: The authors report that "The interval time of readmission: During the five years, the intervals of readmission in the frequently and infrequently admitted groups were ... (Lines 120 - 122)", it seems natural that frequently admitted patients would have shorter intervals of readmission than non-frequently admitted patients. If this is not necessary for your discussion, please delete it.

Reply 8: The suggestion is reasonable and constructive. We've deleted it.

Comment 9: I recognize that the purpose of this study is an exploratory study of the clinical characteristics of the patients with frequent AECOPD and the risk factors associated with frequent readmission due to AECOPD. Because this is an exploratory study, I believe that it is difficult to conclude even "the risk of readmission by the history of admission events (Line 142)" and "risk factors associated with frequent hospitalization due to AECOPD (Line 150)".

Reply 9: As a retrospective study, there are some limitations. A small number of exacerbation patients may go to other clinics for treatment after discharge from our hospital, resulting in a small number of exacerbation data missing. But we think the missing data is small, because we did telephone follow-up for part of discharged patients, and about 20% of them went to other clinics after an exacerbation.

Our study showed that only 14.8% of readmission in the patients who had one admission in the previous year. In the ECLIPS study (see ref. 10 of the manuscripts), the rate of acute exacerbations in the following year was 58% among the frequent exacerbators. The rate of exacerbations in the following year among non-frequent exacerbators was 21%. Therefore, in our study patients who had one admission in the previous year would be more likely non-frequent exacerbators. Even if, the loss of a small number of data does not have a major impact on our conclusions.

Comment 10: The confounding factor between hospitalization event history and readmission has not been adjusted for, which may introduce bias into the results of table 2. Based on the results of this study, it is difficult to conclude that hospitalization event history increases the risk of readmission.

Reply 10: Much evidence shows that the history of acute exacerbation is the strongest predictor of readmission and the results were adopted in GOLD guideline. Our study did not adjust for confounding factors because grouping was too complicated and had not enough sample size to adjust for all confounding factors.

Comment 11: In addition, when examining risk factors in multivariate analysis, it is common to select and examine risk factors by referring to the literature and medical observations without looking at the data, and the stepwise method does not produce correct results. Therefore, it seems an overstatement to say that "smoking, comorbidity with diabetes, mechanical ventilation and, infection with pseudomonas aeruginosa were associated with readmission (Lines 205 – 206)".

Reply 11: We select and examine risk factors by referring to the literature and medical observations, such as age, diabetes, corticosteroid use, and blood eosinophilia, etc. in references 19-22, they are also associated with the risk of repeated exacerbation. The risk factor *Pseudomonas aeruginosa* was added by clinical observation, and the high risk of *Pseudomonas aeruginosa* infection in readmitted patients has been rarely reported in the past literature. We identified risk factors by stepwise screening, which is the most common method for screening candidate risk factors.

Comment 12: If this study includes "the risk of readmission by the history of admission events" and "risk factors associated with frequent hospitalization due to AECOPD," I believe that the multivariate analysis needs to be redone with the advice of a statistical expert. Alternatively, I suggest that the content be changed to an exploratory study that examines the characteristics of patients with frequent AECOPD and the factors associated with frequent readmissions due to AECOPD, without conducting a multivariate analysis.

Reply 12: The author Sun Xin is an expert in biostatistics, who participated in the data statistical analysis in this study. The most important part of the study is to explore the influence and the risk of past exacerbation history on future readmission, and the risk factors for readmission is not key contention in our study.

## **Reviewer D**

Comment 1: The article is easy to understand for the most part, except in some places where the language is not clear. Recommend revision for language.

Reply 1: We've modified.

Comment 2: COPD is a common disease with a high burden globally. It continues to be important to assess factors associated with high exacerbation risk. Previous studies have shown that prior exacerbation history is a strong predictor of future exacerbation risk. In that regard, this article does not bring to light a new finding. This paper shows that only one prior hospitalization for AECOPD is not a strong predictor of future admissions for AECOPD and so the authors suggest that it should not be recommended as a predictor for future exacerbations by the GOLD guidelines. However, as the paper only captures hospitalizations to one hospital, we cannot tell if these patients with only one prior hospitalization for AECOPD had any other exacerbations that were managed in the outpatient, as only an ER visit or in the other hospitals. Overall, this paper supports prior data that history of 2 or more prior hospitalizations is a stronger predictor of future hospitalizations for AECOPD than only one prior admission for AECOPD. However, from prior studies like ECLIPSE, we also know that infrequent exacerbators still have a higher risk of exacerbation which may or may not lead to hospitalization compared to those with no exacerbation history. Due to this reason, it is still important to consider history of only one prior AECOPD.

Reply 2: This question is answered in reply 9 to the Reviewer C. Our hospital is a regional general hospital, and the patients with AECOPD mainly come from the nearby the hospital. Therefore, most patients with exacerbation again after discharge would go back to our hospital, and only a minor may go to other clinics.

Comment 3: The authors also found that frequent exacerbators had higher eosinophil counts. This is also in agreement with prior data. Recommend adding a line about this under results.

Reply 3: Blood eosinophil count was not found to be an independent risk factor for readmission in our study.

Comment 4: Also recommend adding to results a line about higher per centage of positive pseudomonas aeruginosa cultures in frequent exacerbators which was a significant finding.

Reply 4: We have modified our text as advised (see line 250-251).