Response to peer reviewers

Reviewer (1)

(A) ➔ This is an interesting paper for specific population from Taiwan as other similar papers were already published with different populations around the world. It may help the health system responsible of this population to optimize health care conditions of COPD in general, and those eosinophilic specifically.
Comments: Because the authors would point about the role of PBEC in the COPD exacerbation, they should describe clearly the protocol they used to collect blood, extract eosinophils and count them. This will help evaluating the clinical feasibility of such protocol.

Response: Thanks for the valuable comments. We have revised the method section of the manuscript (Page: 2 Line: 17).

"The protocol of PBEC processing was as follows: (1) The nurses or technicians collected 3 mL of venous blood in a lavender-top tube (ethylenediaminetetraacetic acid); (2) the sample was sent to the automated hematology analyzer Sysmex XN-9000™ (Sysmex Corporation, Kobe, Japan); (3) the complete and differential blood counts were reported within one hour; (4) the PBEC (%) was obtained from the differential count; (5) if the PBEC (%) was larger than 30%, the technicians manually recalculated it."

(B) ➔ In the limitation section, the authors attribute the reduction of the % of blood eosinophils to the use of systemic steroids. How about the patients they enrolled in this study? Do they have the treatment before blood collection or after? If they get the treatment before blood collection, can you collect blood immediately after admission into the hospital, collect the blood then treat the patients?

Response: Thanks for the valuable comments. We have addressed the problem in the method section (Page: 2 line: 14).

"We **excluded** patients with a history of asthma and bronchiectasis, **long-term oral steroid use, and those who received systemic steroids within 48 hours before the**

blood test at the index hospitalization."

Reviewer (2)

(A) ➔ The manuscript describes original findings in a local region. The content should be edited to improve presentation. Introduction and discussion sections are poor. Please present them in a deeper form, including new references about the contemporaneous world-situation, enrichment with data from other studies is desirable.

Response: Thanks for the valuable comments. We have revised the introduction section and discussion section accordingly. The new content is marked by black underlines.

introduction section:

Chronic obstructive pulmonary disease (COPD) is characterized by airway obstruction that is not completely reversible. It has been predicted to be the third most common cause of death in 2020 [1]. COPD exacerbation is associated with significant morbidity and mortality. Systemic steroid therapy is a cornerstone of the treatment of COPD exacerbation, but it can exacerbate hyperglycemia, psychiatric problems, and osteoporosis [2]. Patients with COPD are of old age and have multiple comorbidities; therefore, they are vulnerable to the side effects of systemic steroids. Traditionally, asthma is considered as eosinophilic airway disease, while COPD is considered as neutrophilic airway disease. Bafadhel et al. proposed four models of COPD exacerbation: bacterial (55%), viral (29%), eosinophilic (28%), and pauci-inflammatory [3]. A classification of COPD exacerbation based on the phenotype is required for the development of precision medicine.

Eosinophilia in patients with COPD is a marker of steroid response. The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend using the peripheral blood eosinophil count (PBEC) to guide the choice of inhalational steroids to prevent COPD exacerbation, and the cut-off values are the absolute values of PBEC (100 and 300 cells/μL) [1]. Mepolizumab, an interleukin-5 antibody, showed slight efficacy for reducing the rate of exacerbations in patients

with COPD and eosinophilia [4]. Most studies used 2% of the total white blood cell (WBC) count as the cut-off value to diagnose patients with an eosinophilic or a non-eosinophilic COPD exacerbation. However, only a few studies focused on the impact of PBEC on systemic steroid administration for acute COPD exacerbation. Until recently, two prospective studies showed that PBEC-guided systemic steroid therapy could reduce the steroid exposure and improve the health status of patients but without altering survival [5, 6].

The eosinophilic phenotype accounts for 20% – 40% of COPD exacerbations [7]. PBEC is a well-established predictor of the length of hospital stay, steroid response, prognosis, and readmission rate [7-13]. Nevertheless, some characteristics of patients with eosinophilic COPD exacerbation, such as demographics, comorbidities, lung function, etc., are inconsistent across studies [14]. Studies on the impact of the PBEC were primarily focused on the Caucasian race. Only a few studies investigated eosinophilic COPD exacerbation in the Asian populations, including patients from China and South Korea [13, 15]. The aim of the present study was to elucidate the role of peripheral eosinophilia in hospitalized patients with COPD exacerbation in Taiwan.

discussion section:

Infection status and lung functions:

Our findings supported the results of previous studies on the tendency of non-infectious inflammation in the EOS group (PBEC ≥ 2%). The hemogram and antibiotic administration in our study are consistent with those of a previous Chinese study by Xue et al. [15]. Duman et al. reported that the non-EOS group (PBEC ≤ 2%) had higher NLR and CRP levels in a the Turkish population [9]. Saltürk et al. reported similar results for hemogram and CRP levels in the non-EOS group (PBEC ≤ 2%) in the intensive care unit (ICU) population [16].

Our study revealed that the EOS group (PBEC ≥ 2%) showed higher absolute values of FVC. Similarly, Singh reported that the EOS group (PBEC ≥ 2%) was characterized by higher absolute values of FEV1 and FVC [17]. Kang et al. also observed that the EOS group (PBEC > 2%) had higher absolute values of FEV1 and FVC in the Korean population [13]. The aforementioned findings suggest that patients with eosinophilic COPD exacerbation have better lung function. However, a meta-analysis by Wu et al.

revealed that the percentage of predicted FEV1 value showed no significant difference between the EOS (PBEC > 2%) and non-EOS groups (PBEC ≤ 2%) [14].

Readmission:

In the present study, the EOS group (PBEC ≥ 2%) showed a shorter time to first COPD-related readmission. Previous studies that defined the EOS group by 2% eosinophilia or ≥200 cells/μL in the Caucasian [8, 10] and Asian races [15] showed results similar to those of our study. Couillard et al. stated that the EOS group (PBEC ≥ 200 cells/μL and/ or ≥ 2%) had a higher risk of COPD-related readmissions within 12 months and shorter time to the first COPD-related readmission within 12 months [8]. Bélanger et al. reported that in infrequent exacerbations (defined as the first exacerbation in previous 5 years), the EOS group (PBEC ≥ 200 cells/μL and/or ≥ 2%) had a higher risk of COPD-related readmissions and shorter time to the first COPD-related readmission [10]. In Asian races, Xue et al. revealed that the EOS group (PBEC ≥ 2%) had a higher risk of severe exacerbation [15].

Eosinophilic COPD exacerbation is a well-known risk factor for COPD-related readmissions. The current study demonstrated a significant linear correlation between the percentage of blood eosinophil and the number of readmissions. Although our finding was intuitively reasonable, we believe it is novel in the current literature.

Systemic prednisolone administration:

Among all hospitalized patients with acute COPD exacerbation, the EOS group (PBEC ≥ 2%) required a lower systemic steroid dose compared to the non-EOS group (PBEC < 2%) in the present study, consistent with previous retrospective studies [9, 11]. Serafino-Agrusa et al. showed that a lower dose of daily systemic steroids was administered in the EOS group (≥ 2%) than in the non-EOS group (PBEC<2%) [11]. Duman et al. revealed that a lower proportion of the EOS group (PBEC > 2%) received systemic steroids compared to the non-EOS group (PBEC ≤ 2%) [9].

To the best of our knowledge, only two prospective studies addressed the role of eosinophil on systemic steroids. In a prospective study enrolling outpatients, Bafadhel et al. reported that eosinophil-guided therapy (cut-off value: PBEC = 2%) could decrease the proportion of patients receiving steroids (51% vs. 100%) compared to the standard treatment, and steroid treatment in the non-EOS group is

associated with a poorer health status and higher treatment failure rate (15% vs. 2%) compared to placebo [5]. In a prospective study enrolling inpatients by Sivapalan et al., eosinophil-guided therapy (cut-off value: absolute eosinophil count = 300 cells /μL) reduced the duration of steroid treatment (2 vs. 5 days), but there were no differences in the 30-day treatment failure rate (26% vs 26%) and 30-day survival rate (94% vs 96%) compared to the standard treatment [6].

In real-world practice, physicians in charge adjusted the steroid dose according to the clinical response (i.e., reduced the steroid dose according to the relief of breathlessness). Because eosinophilic COPD exacerbation has a better clinical response to systemic steroids, the EOS group required a lower systemic steroid dose than the non-EOS group in the present study.

Length of hospital stay:

The length of hospital stay was shorter in the EOS group (PBEC ≥ 2%) in our study. Many retrospective studies enrolled patients with different in-hospital treatments, such as antibiotics and steroid use, for acute COPD exacerbation. Their findings related to the length of hospital stay are similar and consistent with those of our study [9, 11, 18]. Duman et al. reported that the EOS group (PBEC > 2%) had a shorter length of stay than the non-EOS group (PBEC ≤ 2%) [9]. In a study by Serafino-Agrusa et al., the EOS group (PBEC ≥ 2%) had a shorter length of stay compared to the non-EOS group (PBEC < 2%) [11]. Bafadhel et al. revealed that the length of stay was shorter in the EOS group (PBEC ≥ 200 cells/μL and/or ≥ 2%) than in the non-EOS group [18].

Furthermore, Xue et al. pointed out that the EOS group (PBEC ≥ 2%) showed a better steroid response after evaluation with the COPD assessment test (CAT) than the non-EOS group (PBEC < 2%) [15]. Shorter lengths of hospital stay and better CAT responses are probably due to the fact that the use of steroids had a rationale only in the EOS group.

Morbidity and mortality:

We found no difference in the discharge outcomes between the EOS (PBEC ≥ 2%) and the non-EOS groups (PBEC < 2%) in this study. Because eosinophilia is a risk factor for COPD-related readmissions, we could reasonably infer that eosinophilic COPD exacerbation has higher risks of mortality and morbidity. However, previous

studies showed better mortality and morbidity in eosinophilic COPD exacerbation [12, 13, 16]. Saltürk et al. stated that the EOS group (PBEC > 2%) had a shorter median length of ICU stay and lower ICU mortality compared to the non-EOS group [16]. Kang et al. showed that the EOS group (PBEC > 2%) had lower rate of ICU admissions and lower mortality rate [13]. Mendy et al. reported that after a median follow-up of 3 years, the non-EOS group (PBEC < 2%) was a predictor of long-term COPD mortality [12].

Patients with long-term oral steroid use imply poor COPD control. In our study, we excluded these patients, and therefore, discharge outcomes may be similar. Additionally, eosinophils play an essential role in innate and adaptive immune response and takes part in the defense against various pathogens, including virus, bacteria, etc. [19]. Eosinopenia is associated with sepsis [20]. Eosinophilic COPD exacerbation had a lower risk of pneumonia [21]. These anti-infectious capacities of eosinophil may lead to better mortality and morbidity.

new references

1. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *American journal of respiratory and critical care medicine* 2011; **184**(6): 662-671 [PMID: 21680942 DOI: 10.1164/rccm.201104-0597OC]

2. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *The New England journal of medicine* 2017; **377**(17): 1613-1629 [PMID: 28893134 DOI: 10.1056/NEJMoa1708208]

3. Wu HX, Zhuo KQ, Cheng DY. Prevalence and Baseline Clinical Characteristics of Eosinophilic Chronic Obstructive Pulmonary Disease: A Meta-Analysis and Systematic Review. *Front Med (Lausanne)* 2019; **6**: 282 [PMID: 31921866 PMCID: PMC6916535 DOI: 10.3389/fmed.2019.00282]

(B) ➔Please add a brief paragraph about possible implications of your conclusions.

Response: Thanks for the valuable comments. We have added a brief paragraph about possible implications in the conclusion section (Page: 8 line: 17).

“We should strengthen the management of comorbidities and optimization of inhaled medications to reduce the high readmission risk in the EOS group. Routine survey of the peripheral blood eosinophil count for acute COPD exacerbation is warranted to reduce the side effects of steroids. With meticulous exclusion of possible infections, we could avoid empirical antibiotic therapy since the EOS group has a non-infectious nature.”

Response to the comments

(1)

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office’s comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 12 words).

Response: Thanks for the valuable comments. We have revised the title accordingly.

New title: “Role of peripheral eosinophilia in acute exacerbation of chronic obstructive pulmonary disease”

(2)

(A) ➔ 1 Scientific quality: I have checked the comments made by the science

editor, and I basically agree with the science editor. The topic of the paper is within the scope of the WJCC. (1) Classification: Two Grade B; (2) Summary of the Peer-Review Report: Reviewer 00546034 summarized that this is an interesting paper for specific population from Taiwan; it may help the health system responsible of this population to optimize health care conditions of COPD in general, and those eosinophilic specifically. Reviewer 02446061 points out that the introduction and discussion sections should be improved. The questions raised by the reviewers should be answered;

Response: Thanks for the valuable comments. We have answered the peer review in the **Response to peer review** section below.

(B) ➔ and (3) Format: There are 3 tables and 3 figures. A total of 19 references are cited, including 7 references published in the last 3 years. There are no self-citations. 2 Language evaluation: I agree with the comments made by the science editor. A language editing certificate issued by Editage was provided. 3 Academic norms and rules: I have checked the documents, including the Conflict-of-Interest Disclosure Form, Copyright License Agreement, Biostatistics Review Certificate, Institutional Review Board Approval, and the Informed Consent Statement, all of which are qualified. No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. Supported by Taipei Tzu Chi Hospital. 5 Issues raised: (1) I found that the title page include the author contributions, abstract, key words, core tip, is missing. Please provide the title page; (2) I found the article highlight section is missing. Please write the “article highlights” section at the end of the main text; (3) I found the PMID and DOI numbers are missing in the reference list. Please provide the PubMed and DOI numbers to the reference list and list all authors of the references. Please revise throughout; (4) I found that the figures can’t be edited. Please provide the original figure documents. All submitted figures, including the text contained within the figures, must be editable. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (5) I found that approved grant application form is not submitted. Please upload the approved grant application form(s) or funding agency copy of any approval

document(s). 6 Recommendation: Conditionally accepted.

Response: Thanks for the valuable comments. We have revised accordingly.

(3)

I have checked the comments written by the science editor. The informed consent of treatment should be provided.

Response: Thanks for the valuable comments. The study design was retrospective. The institutional review board agreed with waiver of informed consent of treatment.

(4)

1 Scientific quality: The manuscript describes a clinical and translational research of role of peripheral eosinophilia in hospitalized patients with acute exacerbation of chronic obstructive pulmonary disease. The topic is within the scope of the WJCC. (1) Classification: 2B. (2) Summary of the peer-review report: This is an interesting paper. The authors should describe clearly the protocol they used to collect blood, extract eosinophils and count them. The article requires enrichement on the introduction (background) and discussion. (3) Format: 3 tables and 3 figures. 19 references were cited, including 7 references published in the last 3 years. No self-citation. 2 Language evaluation: B and A. Language editing certificate was provided by editage. 3 Academic norms and rules: The biostatistics review certificate was provided. The authors signed the conflict-of-interest disclosure form and copyright license agreement. The institutional review board approval form was provided. The written informed consent was waived. No academic misconduct was found in the CrossCheck investigation and the Bing search. 4 Supplementary comments: (1) Unsolicited manuscript. (2) supported by Taipei Tzu Chi Hospital TCRD-TPE-108-RT-4 and TCRD-TPE-108-4. (3) The corresponding author has not published articles in BPG journals. (Xiao-Quan Yu)

Response: Thanks for the valuable comments. We have answered the peer review in the **Response to peer review** section.

(5)

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Response: Thanks for the valuable comments. We have revised the manuscript accordingly.