Peer Review File
Article information: https://dx.doi.org/10.21037/jtd-24-62

Reviewer A

The study is interesting as the PA/Ao ratio has been identified as one of the best predictors of exacerbation in COPD patients and as it is associated with elevated pulmonary arterial pressures.
Patients were identified by means of a spirometric FEV1/FVC<0.7 and criteria for acute exacerbation, leading to admission to a tertiary and a secondary hospital between 2016 and 2021. Patients were characterized by relatively advanced age, a high proportion of tuberculosis changes, and very small number of pack years. About one out of three patients had an enlarged PA trunk as compared to the aorta. This was associated with female gender, poorer FVC and FEV1 and higher pCO2 levels. It was also associated with a higher need of NIV, however, not with increased mortality or readmission to hospital.
Major:

Comment 1:
It is not clear to me, how many of these patients suffered from COPD.
Reply 1:
Thank you for your comment. The diagnosis of COPD was based on the GOLD guidelines as described in method section. (See page 7, line 54-55)

Comment 2:
The pH in the PA/A ratio <1 group was 7.61. This seams implausible and sheds doubt on all other data.
Reply 2:
As a result of your reasonable suspicions, we have carefully reviewed the study data again. Upon reviewing the data, we discovered that one subject's pH value in the PA/A ratio <1 group was incorrectly recorded as 72.30. It was determined that the subject's actual pH value was 7.23. Consequently, the data for this study have been corrected. Accordingly, the average pH of the PA/A <1 group has been adjusted to 7.39. Table 2 has been modified to reflect these corrections. We would like to thank you again for your accurate comment.
Changes in the text: See page 10, line 114-115 and table 2

Comment 3:
The NIV rate was much higher in the PA/A >1 group, because they had poorer lung function and gas exchange. It would not give sense to go for a CT scan to decide on NIV indication or to predict the NIV risk. The same is true for the indication for oxygen etc.
Reply 3:
Thank you for your comment. I agree with your viewpoint. Obtaining a chest CT to

evaluate the PA/A ratio is not necessary. However, if the PA/A ratio from a chest CT scan of a patient with an acute exacerbation of COPD exceeds 1, it indicates a high risk of type 2 acute respiratory failure, which means that active treatment may be required.

Comment 4:
The really disappointing result is that there were no differences in morbidity and mortality outcomes as well as readmission rates. This may be due to relatively poor power and to the fact that the causes of death were too diverse in this cohort of patients.
Reply 4:
Thank you for your valuable comments. We analyzed the in-hospital and 1-year mortality and readmission rates according to the PA/A ratio from various perspectives but did not find any significant differences. In our study, the mortality rate was lower than in other studies, which may be due to enrolling COPD patients with relatively low severity or excluding severe patients during enrollment. Additionally, our study evaluated the one-year survival rate, and the relatively short follow-up period may have influenced the results. (See page 13-14, line 178-187) It is necessary to conduct a multicenter long-term study to overcome these limitations.

Minor:
Comment 5:
In the Kaplan Meier charts, the number of remaining patients is not given.
Reply 5:
Thank you for your comments. We have modified figures 2 and 3 according to your suggestions.
Changes in the text: See fig 2 and fig 3.

Reviewer B

Comment 1:
The PA/A ratio is considered an independent predictive factor for events such as the incidence of type 2 acute respiratory failure and the need for high-flow nasal cannula, non-invasive ventilation, and tracheal intubation. However, it is unclear what analytical methods led to this conclusion.
Reply 1:
Thank you for your comments. According to Table 2, COPD patients with a PA/A ratio >1 have a greater frequency of type 2 ARF than those with a PA/A ratio <1, based on chi-square analysis. Using logistic regression analysis, we evaluated whether PA/A >1 is an independent risk factor for advanced treatments such as NIV, HFNC, and intubation. We adjusted for the following clinical indicators: age, sex, pack-years, body mass index, hypertension, diabetes, pulmonary tuberculosis, bronchiectasis, ischemic

heart disease, atrial fibrillation, chronic kidney disease, previous cerebrovascular disease, forced vital capacity (% pred), forced expiratory volume in 1 second (% pred), diffusion lung capacity of carbon monoxide, GOLD group, white blood cells, hemoglobin, platelets, blood urea nitrogen, creatinine, and C-reactive protein. Additionally, ventilation-perfusion mismatch, hypoventilation, and ventilation-perfusion mismatch were considered. This method is detailed in the statistical analysis section.

Changes in the text: See page 8-9, line 90-98

Comment 2:

Given that the study is based on the fact that the PA/A ratio reflects pulmonary hypertension, it would be worth investigating whether the need for non-invasive ventilation (NIV) was considered along with minimal necessary oxygen flow, arterial blood gas analysis results, and factors reflecting alveolar hypoventilation and ventilation-perfusion imbalance in lung function tests. If so, what were the results?

Reply 2:

Thank you for your valuable comments. Due to the retrospective nature of the study, it was not possible to identify the minimal oxygen flow required. The results of arterial blood gas analysis performed at hospitalization were used to evaluate alveolar hypoventilation and ventilation-perfusion mismatch. Hypoventilation and ventilation-perfusion mismatch were significantly more common in patients with a PA/A ratio >1 (18.0% vs. 9.6%, P = 0.017). In univariate logistic regression analysis, hypoventilation and ventilation-perfusion mismatch were identified as risk factors for NIV requirement (OR, 4.862; 95% CI, 2.437-9.702; P <0.000). These results have been added to the methods and table 2.

Changes in the text: See page 7, line 69-70, table 2

Comment 3:

If these factors differ from the PA/A ratio and do not remain as predictors of NIV risk, while arterial blood gases and lung function test results reflecting alveolar hypoventilation and ventilation-perfusion imbalance are causes of pulmonary hypertension, then it would be necessary to explain why the PA/A ratio is an independent predictor of the need for NIV, distinct from these factors.

Reply 3:

Thank you for your valuable comments. Univariate logistic regression revealed that PA/A >1, as well as hypoventilation and ventilation-perfusion mismatch (OR, 4.862; 95% CI, 2.437-9.702; P <0.000), were all risk factors for NIV requirement. After adjusting for various clinical indicators, **PA/A ratio >1 (OR, 4.801; 95% CI, 1.977-11.658; P = 0.001) and hypoventilation and ventilation-perfusion mismatch (OR, 2.719; 95% CI, 1.067-6.931; P = 0.036)** remained significant risk factors for NIV requirement. However, the OR for PA/A >1 was greater than for hypoventilation and

ventilation-perfusion mismatch.

Comment 4:
Moreover, if both the factors reflecting alveolar hypoventilation and ventilation-perfusion imbalance in lung function tests and the PA/A ratio are independent predictors of the need for NIV, the more sensitive factor should be emphasized.

Reply 4:
Thank you for your comments. As you suggested, PA/A ratio >1 and hypoventilation and ventilation-perfusion mismatches were analyzed using ROC curves to predict the use of NIV. The AUC values for the two variables were similar (PA/A ratio >1: AUC, 0.632; 95% CI, 0.544-0.720; P = 0.003 vs. hypoventilation and ventilation-perfusion mismatch: AUC, 0.618; 95% CI, 0.526-0.710; P = 0.007). Since hypoventilation and ventilation-perfusion mismatch can increase the PA/A ratio, hypoventilation and ventilation-perfusion mismatches cannot be considered independent factors from the PA/A ratio. **The highlight of this study is that the PA/A ratio is a simple measurement tool, and a PA/A ratio >1 is associated with a high incidence of type 2 respiratory failure. It is also a risk factor for the use of NIV in patients with acute COPD exacerbations.**

Comment 5:
The PA/A ratio >1 suggests pulmonary hypertension, as noted by the authors themselves. Pulmonary hypertension occurring in COPD includes the contraction response of blood vessels to hypoxia caused by the worsening of respiratory status, in addition to the original reduction of the pulmonary vascular bed. The severely impaired respiratory status requiring NIV, i.e., severe hypoxia necessitating NIV, may result in the kind of condition that causes pulmonary hypertension. It can be considered that PA/A ratio >1 is not a predictive factor for respiratory status requiring NIV but rather a consequence of the severely impaired respiratory status requiring NIV. If one were to summarize, it would be necessary to examine the PA/A ratio of patients who experienced acute exacerbation prior to the onset of acute exacerbation.
Reply 5:
Thank you for your comments. Most COPD patients experience chronic pulmonary hypertension rather than acute pulmonary hypertension. This study did not analyze changes in the PA/A ratio before and during acute exacerbations. Therefore, analyzing the PA/A ratio before and after an acute exacerbation of COPD could help determine if the increase in the PA/A ratio is related to the exacerbation. A multicenter prospective study is needed in the future. We have added the limitations you mentioned to the discussion section in response to your comments.
Changes in the text: See page 13, line 174-177

Reviewer C

Comment 1:

Over all good analysis. Exclusion criteria were not overly complicated and made sense. Good for publication very explicit.

Reply 1:

Thank you for your valuable comments.

Reviewer D

The article provides a detailed investigation of the clinical implications of the pulmonary artery-to-aorta (PA/A) ratio in patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (COPD). It offers a comprehensive analysis spanning patient demographics, clinical outcomes, and the impact of PA/A ratio on treatment requirements and mortality rates. Strengths: Extensive Dataset: The study analyzes data from a substantial number of patients over several years, providing a robust dataset for assessing the PA/A ratio's clinical relevance in COPD exacerbations. Significant Findings: It identifies a higher PA/A ratio as an independent predictor for the need for advanced respiratory support, such as high-flow nasal cannula, non-invasive ventilation, and intubation. Detailed Analysis: The multivariate analysis strengthens the credibility of the findings, adjusting for various confounders that could affect the outcomes.

Comment 1:

Weaknesses: Limited Mortality Impact: Despite the detailed analysis, the study finds no significant association between the PA/A ratio and in-hospital or one-year mortality, which may limit the ratio's usefulness as a prognostic tool for these specific outcomes.

Reply 1:

Thank you for your valuable comments. We have added the limitations you mentioned in the limitation section in response to your comments.

Changes in the text: See page 14, line 195-198

Comment 2:

Generalizability Concerns: Conducted in only two hospitals, the findings may not be applicable universally across different settings or populations. Retrospective Nature: The inherent limitations of retrospective studies, including potential biases in data collection and analysis, might affect the results' accuracy.

Reply 2:

Thank you for your valuable comments. We have added the limitations you mentioned in the limitation section in response to your comments.

Changes in the text: See page 14, line 188-190

Comment 3:

Overall, the article provides valuable insights into the PA/A ratio's role in managing acute exacerbations of COPD, suggesting that patients with a higher ratio require more aggressive treatment. However, its impact on mortality remains inconclusive, which warrants further prospective studies to confirm these findings and explore the

mechanisms underlying these associations.

Reply 3:

Thank you for your valuable comments. We have added the limitations you mentioned to the limitations section in response to your comments.

Changes in the text: See page 14, line 195-198