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ORIGINAL RESEARCH

The Main Pulmonary Artery to the Ascending Aorta Diameter Ratio (PA/A) as a Predictor of Worse Outcomes in Hospitalized Patients with AECOPD

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Purpose: The main pulmonary artery (PA) to ascending aorta diameter ratio (PA/A) greater than one is a promising indicator of pulmonary hypertension (PH) in acute exacerbation (AE) of chronic obstructive pulmonary disease (COPD) (AECOPD). This study aims to disclose the associations between the PA/A ratio and clinical outcomes in hospitalized patients with AECOPD.

Patients and Methods: Consecutive AECOPD patients admitted to the Department of Respiratory Medicine from September 2017 to July 2021 were reviewed. The treatment success of AECOPD patients was defined as improvement in the clinical condition when discharged from the hospital. Conversely, treatment failure was considered to be an event of in-hospital death or deterioration of the clinical condition prior to discharge.

Results: A total of 118 individuals were ultimately reviewed in this study: 74 individuals with a PA/A ratio <1 and 44 individuals with a PA/A ratio ≥1. The outcomes of 21 patients were treatment failure, and 97 patients were considered successes. Patients with a PA/A ratio ≥1 had significantly higher PaCO2, red cell distribution width, brain natriuretic peptide, PA diameters, RICU admission rates, and proportions of treatment failure than patients with PA/A ratios <1 ($P < 0.05$). The PA diameter and PA/A ratio were significantly increased in the treatment failure group compared with the success group ($P < 0.05$). A survival analysis indicated that patients with a PA/A ratio ≥1 had worse outcomes than patients with a PA/A ratio <1 during hospitalization ($P < 0.05$). A multivariate analysis showed that a PA/A ratio ≥1 was an independent risk factor for treatment failure in patients with AECOPD.

Conclusions: AECOPD patients with a PA/A ratio ≥1 may have worse outcomes during hospitalization. A PA/A ratio ≥1 may be a promising predictor of treatment failure in patients with AECOPD.

Keywords: pulmonary hypertension, chronic obstructive pulmonary disease, PA/A ratio

Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical syndrome that features chronic respiratory symptoms and structural pulmonary abnormalities leading to lung function impairment with persistent airflow limitation.[1] A recent study indicated that the overall prevalence of spirometry defined for COPD was 8.6% of adults in China, including 11.9% of men aged 40 years or older. The acute exacerbation of COPD (AECOPD) is a key factor that affects the disease prognosis and leads to hospitalization. Thus, AECOPD-related morbidity and mortality should be given more attention.[2,3] Pulmonary hypertension (PH) is a common and severe comorbidity of COPD that results in an increased risk of hospitalization, reduced exercise capacity, and shorter survival. Right-heart catheterization (RHC) is the "gold standard" for the diagnosis of PH. However, RHC related significant risks and its difficulty of placement limits this procedure in

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patients with PH. Echocardiography is a noninvasive method that is widely used to assess PH in patients with AECOPD.[4] A tricuspid regurgitant jet ≥3 m/s tested by echocardiography is diagnosed as PH, which may lead to underdetermined diagnoses of PH.[5] Moreover, pulmonary artery systolic pressure detected by echocardiography is poorly correlated with the mean pulmonary artery pressure (mPAP) in severe COPD. A main pulmonary artery to ascending aorta diameter ratio (PA/A) of greater than one has been reported to be a promising indicator for revealing PH.[6,7] Furthermore, an increased ratio of PA/A was closely associated with the poor survival of patients with COPD, particularly in individuals with moderate-to-severe cases.[8] Nevertheless, the impact of the PA/A ratio in AECOPD remains to be elucidated. In this present study, we aim to disclose the associations between the PA/A ratio and clinical outcomes in hospitalized patients with AECOPD.

Patients and Methods

Study Population

This retrospective observational study was conducted at the Yijishan Hospital affiliated with the Wannan Medical College and was approved by the Research Ethics Committee of Yijishan Hospital. The clinical data of patients was maintained with confidentiality and in compliance with the Declaration of Helsinki. Written informed consent from patients was waived due to the retrospective nature of this study. Consecutive AECOPD patients admitted to the Department of Respiratory Medicine and Respiratory Intensive Care Units (RICU) were reviewed from September 2017 to July 2021. Patients with advanced lung cancer, pneumothorax, stroke, pneumonia, diffuse interstitial lung disease, hemodialysis, or left-heart failure, as well as those who only accepted palliative therapy, or had a lack of chest computed tomography (CT) images, were excluded from the final analysis.

AECOPD is defined as COPD with an acute worsening of respiratory symptoms (typically cough, dyspnea, increased sputum volume, and/or sputum purulence) requiring additional treatments.[9] Indications for RICU admission were made according to the expert consensus released in 2014 on AECOPD in China.[10] In brief, these consisted of a significant increase in symptom intensity (severe dyspnea, changes in mental status, moderate or severe hypoxemia with or without hypercapnia), failure of an exacerbation to respond to initial medical management, hemodynamic instability, and a patient requiring mechanical ventilation (MV). The treatment success of AECOPD patients was defined as improvement in the clinical condition when discharged from the hospital. Conversely, treatment failure was thought to occur as an event of in-hospital death or deterioration of the clinical condition prior to discharge.

Demographic characteristics, including gender, age, the age-adjusted Charlson Comorbidity Index (aCCI), length of stay, body mass index (BMI) and in-hospital death, were collected. Laboratory tests, including an arterial blood gas analysis (pH value, oxygenation index, the ratio of arterial partial pressure of oxygen to the fraction of inspired oxygen), PaCO2, and the blood lactate level), hemoglobin, blood red cell distribution width (RDW), D-dimer, brain natriuretic peptide (BNP), fibrinogen (Fib), and blood platelet (PLT), were initially recorded after admission. The percentage of ICU admissions requiring invasive MV (IMV) was also calculated. A chest CT was performed when the patient was admitted to the hospital. The procedure for measuring the pulmonary artery (PA) diameter and PA/A ratio determined by the chest CT conformed to a previous study.[6] Briefly, the PA diameter and ascending aorta diameter were averaged from two perpendicular measurements at the PA bifurcation level collected from the same chest CT images, as shown in Figure 1.

Statistical Analysis

Continuous data were analyzed using a normal distribution test prior to further analysis. Continuous data are indicated as the mean (standard deviation [SD]) or median (inter-quartile range [25,75]). Categorical variables are presented as the number (n) or percentage. Continuous variables were analyzed using the independent *t*-test or the Mann-Whitney *U*-test, and categorical variables were analyzed using a Chi-square test. The logistic regression model was used as a multivariate analysis to reveal the independent risk factors of in-hospital worst outcomes in patients with AECOPD. The Kaplan–Meier survival method was used to analyze the effect of the PA/A ratio on outcomes of AECOPD patients. A Log rank test was applied to appraise the statistical differences between the two survival curves. A receiver operating characteristic (ROC) curve analysis was conducted to evaluate factors predicting an in-hospital worst outcome. A P value less than

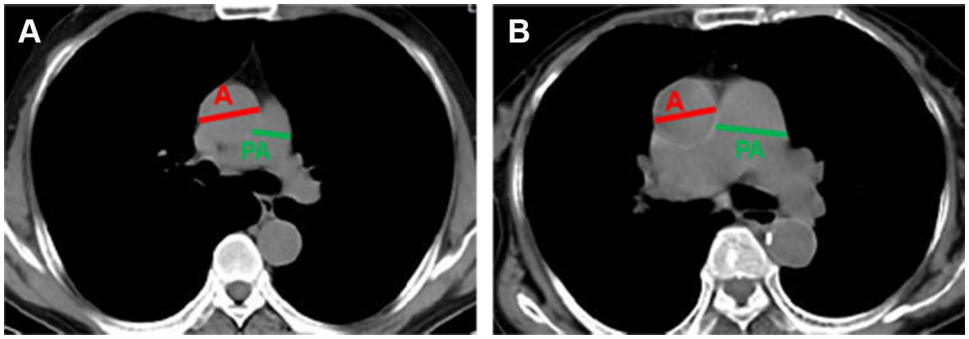

Figure 1 Diameters of the PA and A were determined by CT scan at the PA bifurcation. (**A**) PA/A ratio < 1; (**B**) PA/A ratio > 1.
Abbreviations: A, aorta; PA, pulmonary artery.

0.05 was considered statistically significant. The statistical analyses were performed using SPSS for Windows (release 22.0, IBM Corporation, USA).

Results

As indicated in Figure 2, a total of 229 patients with AECOPD were reviewed. According to the inclusion criteria and exclusion criteria, 111 patients were excluded due to the condition being combined with advanced lung cancer (n = 10), pneumothorax (n = 4) stroke (n = 5), pneumonia (n = 29), diffuse interstitial lung disease (n = 7), hemodialysis (n = 6), left-heart failure (n = 19), palliative therapy (n = 23), and a lack of CT images (n = 10). Ultimately, 118 eligible individuals were reviewed in this study: 74 individuals with a PA/A ratio <1 and 44 individuals with PA/A ratio ≥1. The outcomes of 21 patients were treatment failures, and 97 patients were treatment successes when discharged from the hospital.

Characteristics of the AECOPD Patients with a PA/A Ratio <1 or a PA/A Ratio ≥1

The pH value in the PA/A ratio ≥1 group was significantly lower than that in the PA/A ratio <1 group (p = 0.026). Remarkably, the PA/A ratio ≥1 group had a significantly higher value of PaCO2, RDW, BNP, PA diameter, and RICU

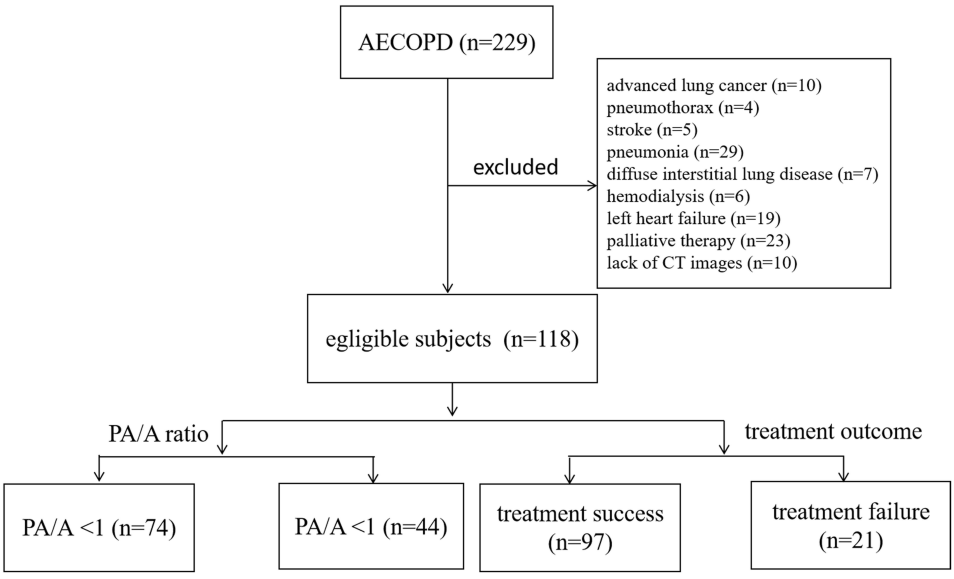

Figure 2 A flowchart of this study.

admissions, as well as worse outcomes than the PA/A ratio <1 group (P < 0.05). However, there were no significant statistical differences for the other indicators between the two groups (Table 1).

Clinical Features of the AECOPD Patients with Treatment Failure

As indicated in Table 2, compared to the treatment success group, the treatment failure group had a much lower pH value (7.34 ± 0.11 vs 7.28 ± 0.13, respectively, p = 0.040) and less count of PLT (median 167 × 10^9/L vs 130 × 10^9/L, respectively, p = 0.018). The treatment failure group had higher levels of D-dimer and BNP compared with the improved group (P < 0.05). In addition, the percentage of RDW, rate of RICU admissions, and the proportion of IMV in the treatment failure group were significantly higher than that in the improved group (P < 0.05). Notably, the PA diameter and PA/A ratio were significantly increased in the treatment failure group than in the improved group (mean PA diameter: 3.71 vs 3.22, p = 0.001; mean PA/A ratio: 1.09 vs 0.89, p < 0.001).

A PA/A Ratio ≥1 Was an Independent Risk Factor for Treatment Failure in AECOPD

The multivariate analysis indicated that the PA/A ratio ≥1 (OR value = 6.129, 95% CI: 1.665–22.565, p = 0.006) and IMV (OR value = 10.798, 95% CI: 2.072–56.261, p = 0.005) were two independent risk factors for treatment failure in patients with AECOPD. Although the RDW, D-dimer, PLT, and RICU admissions had observed significant differences between the two groups according to the univariate analysis, they did not reach significant statistical differences according to the multivariate analysis (Table 3). Additionally, the Kaplan–Meier survival analysis indicated that patients with a PA/A ratio ≥1 had worse outcomes than patients with a PA/A ratio <1 during hospitalization (HR = 5.277, 95% CI: 2.178–12.78, p < 0.001) (Figure 3).

Table 1 Characteristics of AECOPD Patients with Different PA/A Ratio

Characteristics	PA/A <1	PA/A ≥1	*P* value
Total (n)	74	44	
Male (n)	60	32	0.359
Age (y)	73.07 (8.66)	69.93 (8.06)	0.054
BMI (kg/m^2)	21.22 (3.31)	20.86 (3.92)	0.708
aCCI index	3 (3–4)	4 (3–5)	0.065
pH value	7.38 (7.27–7.42)	7.30 (7.22–7.38)	**0.026**
Oxygenation index	222.43 (62.66)	213.73 (58.24)	0.522
PaCO2 (mmHg)	50.60 (40.30–76.45)	67.00 (54.75–91.15)	**0.004**
Lactate (mmol/L)	1.25 (0.80–2.60)	1.10 (0.75–1.55)	0.145
Hemoglobin (g/L)	127.76 (18.53)	131.68 (27.36)	0.402
RDW (%)	13.30 (12.90–14.13)	13.80 (13.03–16.23)	**0.01**
D- dimer, μg/mL	0.84 (0.39–1.50)	0.93 (0.53–1.97)	0.20
BNP (pg/mL)	112.17 (42.84–359.51)	454.50 (142.34–789.5)	**<0.001**
Fib (μg/mL)	3.82 (2.83–5.15)	3.49 (2.80–4.17)	0.178
PLT (×10^9/L)	169.5 (131.25–211.00)	152.00 (120.00–184.75)	0.064
PA diameter (cm)	3.00 (0.47)	3.81 (0.52)	**<0.001**
RICU admission (%)	32.40	61.40	**0.004**
IMV (%)	9.50	15.9	0.379
Length of stay (day)	7.00 (5.00–11.25)	7.00 (5.25–11.00)	0.927
Treatment failure rate (%)	6.80	36.40	**<0.001**

Note: Bold represents statistically significant.

Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; PA/A, main pulmonary artery to ascending aorta diameter ratio; BMI, body mass index; aCCI, age-adjusted Charlson Comorbidity Index; RDW, blood red cell distribution width; BNP, brain natriuretic peptide; Fib, fibrinogen; PLT, blood platelet; PA, main pulmonary artery; RICU, respiratory intensive care units; MV, mechanical ventilation.

Table 2 Characteristics of Treatment Success Group and Treatment Failure Group in Severe AECOPD

Characteristics	Treatment Success Group	Treatment Failure Group	*P* value
Total (n)	97	21	
Male (n)	75	17	1.000
Age (y)	71.73 (8.50)	72.67 (8.95)	0.652
BMI (kg/m^2)	21.40 (3.32)	18.76 (4.05)	0.057
aCCI index	4 (3–5)	4 (3–5.5)	0.371
pH value	7.34 (0.11)	7.28 (0.13)	**0.040**
Oxygenation index	221.55 (58.53)	208.35 (67.07)	0.409
PaCO2 (mmHg)	63.49 (23.78)	78.31 (43.22)	0.058
Lactate (mmol/L)	1.25 (0.70–2.05)	1.10 (0.80–1.60)	0.991
Hemoglobin (g/L)	129.80 (21.90)	126.52 (23.92)	0.542
RDW (%)	13.40 (12.90–14.30)	15.00 (13.25–16.65)	**0.006**
D- dimer, μg/mL	0.77 (0.39–1.47)	1.40 (0.88–2.28)	**0.02**
BNP (pg/mL)	140.70 (55.79–437.49)	457.00 (167.53–1382.06)	**0.002**
Fib (μg/mL)	3.75 (2.85–4.96)	3.24 (2.19–4.33)	0.119
PLT (×10^9/L)	167.00 (128.00–204.50)	130.00 (112.50–175.50)	**0.018**
PA diameter (cm)	3.22 (0.60)	3.71 (0.62)	**0.001**
PA/A ratio	0.89 (0.17)	1.09 (0.20)	**<0.001**
RICU admission (%)	36.10	76.20	**0.001**
IMV (%)	6.20	38.10	**<0.001**
Length of stay (day)	7.00 (5.50–11.00)	7.00 (3.50–11.00)	0.275

Note: Bold represents statistically significant.
Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; PA/A, main pulmonary artery to ascending aorta diameter ratio; BMI, body mass index; aCCI, age-adjusted Charlson Comorbidity Index; RDW, blood red cell distribution width; BNP, brain natriuretic peptide; Fib, fibrinogen; PLT, blood platelet; PA, main pulmonary artery; RICU, respiratory intensive care units; MV, mechanical ventilation.

Predictors of Treatment Failure in Hospitalized Patients with AECOPD

Figure 4 displays the diverse ROC curve of the PA/A ratio, the PA value, the BNP, and the RDW for predicting treatment failure in hospitalized patients with AECOPD. Even though there were no significant statistical differences observed, the area under the curve (AUC) value of the PA/A ratio was numerically larger than that of the other indicators. The best cut-off value of the PA/A ratio for predicting treatment failure was 0.925. The sensitivity was 81.82%, and the specificity was 66.67% (Table 4).

Discussion

The strengths of this study were its primary findings. First, patients with a PA/A ratio ≥1 had significantly higher PaCO2, RDW, BNP, PA diameters, RICU admission rates, and proportions of treatment failure. Second, the PA diameter and PA/A

Table 3 Multivariate Analysis for Risk Factors of Treatment Failure in AECOPD

Factors	OR Value	95% CI	*P* value
RDW	1.219	0.905–1.642	0.192
D- dimer	1.161	0.968–1.391	0.108
PLT	0.993	0.983–1.004	0.214
PA/A ratio ≥ 1	6.129	1.665–22.565	**0.006**
RICU admission	0.858	0.212–3.477	0.830
IMV	10.798	2.072–56.261	**0.005**

Note: Bold represents statistically significant.
Abbreviations: AECOPD, acute exacerbations of chronic obstructive pulmonary disease; RDW, blood red cell distribution width; PLT, blood platelet; PA/A, main pulmonary artery to ascending aorta diameter ratio; RICU, respiratory intensive care units; MV, mechanical ventilation.

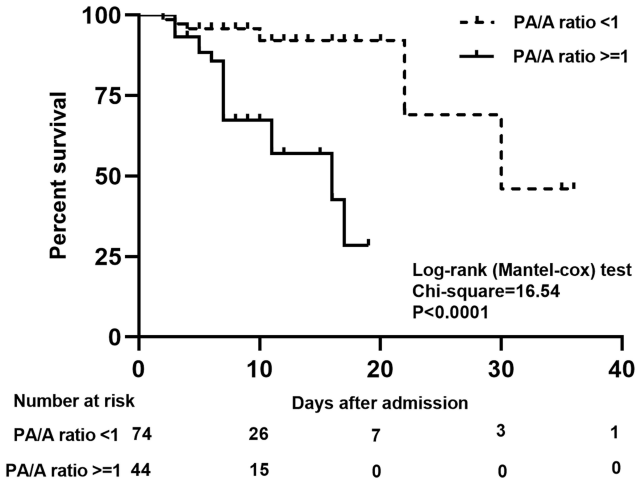

Figure 3 Effect of the PA/A ratio on the outcomes of AECOPD patients.
Note: A Kaplan–Meier survival curve analysis was performed, and a Log rank test was used, and a P < 0.05 was considered statistically significant.
Abbreviation: PA/A ratio: main pulmonary artery to ascending aorta diameter ratio.

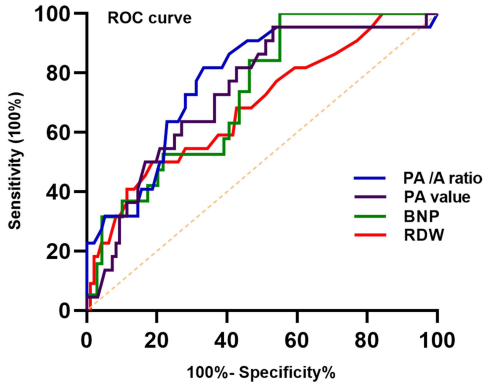

Figure 4 PA/A ratio, PA value, BNP, and RDW for predicting treatment failure in hospitalized patients with AECOPD.
Note: The receiver operating characteristic (ROC) curve analysis was conducted to evaluate factors predicting in-hospital worst outcomes.
Abbreviations: PA/A ratio, main pulmonary artery to ascending aorta diameter ratio; PA, main pulmonary artery; RDW, blood red cell distribution width; BNP, brain natriuretic peptide.

ratio were significantly increased in the treatment failure group compared with the treatment success group. Third, a PA/A ratio ≥1 was an independent risk factor for treatment failure in patients with AECOPD. The Kaplan–Meier survival analysis indicated that patients with a PA/A ratio ≥1 had worse outcomes than patients with a PA/A ratio <1 during hospitalization. Finally, the PA/A ratio may be a promising factor for predicting treatment failure in hospitalized AECOPD patients.

A previous study indicated that the relative pulmonary arterial enlargement (PA/A ratio >1 on CT scanning) predicted hospitalization for AECOPD, and a PA/A ratio >1 with increased blood troponin levels shared close associations with

Table 4 ROC Curve Analysis for Factors Predicting Treatment Failure

Factors	AUC Value	Cut-off Value	Sensitivity (%)	Specificity (%)
PA/A	0.744 (0.668–0.881)	0.925	81.82 (61.48–92.69)	66.67 (56.76–75.29)
PA	0.740 (0.628–0.847)	3.005	94.45 (78.20–99.77)	46.88 (37.21–56.78)
BNP	0.730 (0.615–0.845)	119.4	100.00 (83.18–100.00)	44.93 (33.77–56.62)
RDW	0.688 (0.562–0.813)	14.95	50.00 (30.72–69.28)	81.25 (72.30–87.80)

Abbreviations: PA/A, main pulmonary artery to ascending aorta diameter ratio; BNP, brain natriuretic peptide; RDW, blood red cell distribution width.

increased respiratory failure, ICU admission, and in-hospital mortality.[11] Iliaz et al reported that the PA/A ratio was related to the frequency of hospitalizations and exacerbations due to COPD in one year after hospital discharge.[12] However, the relationships between a PA/A ratio >1 alone and ICU admission or in-hospital mortality are still unclear. In the present study, we found that AECOPD patients with a PA/A ratio ≥1 had a decreased pH value and increased PaCO2 compared with patients with a PA/A ratio <1, implicating increased type II respiratory failure in patients with a PA/A ratio ≥1. A decreased pH value and increased PaCO2 may contribute directly to pulmonary vasoconstriction leading to a rise in pulmonary vascular resistance and pulmonary arterial pressure.[13] In addition, we also disclosed a higher percentage of RICU admissions and a markedly increased rate of treatment failure in hospitalized AECOPD patients with a PA/A ratio ≥1. Thus, an increased PA/A ratio was associated with severity and worse outcomes in inpatients with AECOPD. Many studies have revealed that the RDW is a valuable biomarker for predicting pulmonary hypertension and its associated prognosis.[14–16] In a previous study performed by our group, we indicated that the RDW shared positive relationships with the PA/A ratio in patients with pH secondary to COPD.[17] Similar to previous studies, we found an increase in the RDW in AECOPD patients with a PA/A ratio ≥1. Likewise, the serum level of BNP was drastically elevated. BNP is an important indicator for identifying risk categories in PH. Increased BNP is related to a worse outcome of PH.[18]

In this study, we demonstrated that there was a decreased pH value, lower number of PLTs, and increases in the RDW, D-dimer, BNP, PA diameter, and PA/A ratio in AECOPD patients with treatment failure compared with the improved group. Patients with treatment failure also required more IMV supports and intensive care. It was reported that lower pH values were associated with short or long mortality in hospitalized AECOPD patients.[19,20] RDW is an indicator that reflects the heterogeneity of red blood cell volume. Recently, RDW was found to be an independent negative prognostic factor closely associated with adverse outcomes in hospitalized AECOPD patients.[21,22] Dysregulation of erythrocyte homeostasis and metabolic imbalance may account for significant changes in the RDW in AECOPD patients. However, the underlying pathophysiological mechanisms remain unknown.[23] A hypercoagulable state is a feature of hospitalized AECOPD patients. An increased D-dimer level is not only an important independent risk factor for pulmonary embolism in inpatients with AECOPD but also a predictor of higher mortality in stable COPD patients.[24,25] Cardiac failure is a frequent complication of AECOPD, deeply affecting exercise tolerance and life span in patients with COPD. BNP is widely used to evaluate heart function. BNP can be used to risk-stratify, and an elevated BNP is associated with a higher MV use and worse outcomes in AECOPD patients.[26] An increased PA/A ratio is positively correlated with COPD severity. Previous studies have reported that pulmonary artery enlargement detected by CT is a risk predictor for a severe exacerbation of COPD.[27,28] Intriguingly, the PA/A ratio is an important determinant of mortality in moderate-to-severe COPD.[8] In our present study, we found that a PA/A ratio ≥1 was a strong independent risk-factor of in-hospital treatment failure in patients with AECOPD. In addition, the PA/A ratio might be a better predictor of in-hospital treatment failure compared with other indicators including the PA value, BNP, and RDW. Taken together, the results of the present study provide additional evidence for a close association between the PA/A ratio and the outcome of AECOPD.

In this study, AECOPD patients with a PA/A ratio ≥1 had markedly higher values of PaCO2, RDW, BNP, the PA diameter, ICU admission rates, and proportions of treatment failure and had worse outcomes during hospitalization. A PA/A ratio ≥1 was an independent risk factor for treatment failure in patients with AECOPD. The PA/A ratio may be a promising predictor for treatment failure. It is worth noting that there are several limitations in this study. First, the sample size was small, and this might lead to an interpretation bias in the final analysis. Further work is required to validate the initial conclusion for a larger sample size. Second, the PA/A ratio partially reflects a change in the pulmonary artery pressure. However, the association between the PA/A ratio and the pulmonary artery pressure was not assessed in this study. Finally, to reduce the chance of radioactive exposure, a dynamic change in the PA/A ratio during hospitalization was unclear.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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