RESEARCH ARTICLE

Pulmonary Circulation · PVRI · WILEY

Pulmonary artery enlargement predicts poor survival in patients with COPD: A meta-analysis

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Funding information
Chongqing municipal health and Health Committee, Grant/Award Number: ZQNYXGDRCGZS2019001

Abstract

No previous meta-analysis has evaluated the relationship between pulmonary artery enlargement (PAE) measured by computed tomography (CT) and prognosis for patients with chronic obstructive pulmonary disease (COPD). Recently, several studies have suggested poor survival and reduced exercise capacity in COPD patients with PAE on CT scan, but there were conflicting results. We aimed to assess the prognostic value of PAE-CT in patients with COPD. Relevant studies were identified by searching major databases. Pooled outcomes were determined to assess the prognostic value of PAE-CT in COPD patients. Eighteen studies including 5694 participants were included. PAE indicated higher mortality in COPD patients (odds ratio [OR] = 3.06; 95% confidence interval [95% CI]: 1.76–5.32; $p < 0.0001$), shorter 6-minute walk distance (mean difference [MD] = −67.53 m; 95% CI: −85.98 to −49.08; $p < 0.00001$), higher pulmonary artery systolic pressure (MD = 15.65 mmHg; 95% CI: 13.20–18.11; $p < 0.00001$), longer length of hospital stay (MD = 2.92 days; 95% CI: 0.71–5.12; $p = 0.009$) and more severe symptom such as dyspnea (COPD Assessment Test MD = 3.14; 95% CI: 2.48–3.81; $p < 0.00001$). We also conducted a subgroup analysis regarding the lung function and blood gas analysis for a stable period and acute exacerbation of COPD patients. In conclusion, PAE is significantly associated with mortality, lower exercise tolerance, and poor quality of life in patients with COPD. PAE may serve as a novel imaging biomarker for risk stratification in patients with COPD in the future.

KEYWORDS
chronic obstructive pulmonary disease, computed tomography, odds ratio, prognosis, pulmonary vascular disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a highly prevalent disease and is the third leading cause of death worldwide in 2019.[1] It is associated with substantial morbidity and mortality and is characterized by progressive, irreversible airflow limitations, resulting in disabling respiratory symptoms and devastating complications.[2] Pulmonary hypertension (PH), a complication in the advanced stages of COPD,

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is an independent risk factor for morbidity and mortality.[3,4] The gold standard for diagnosis of PH is right-sided heart catheterization (RHC), but RHC is not routinely performed in patients with COPD because of its invasive nature and the lack of effective treatments.[5-8] Instead, the most commonly used noninvasive screening for PH is echocardiography by estimating pulmonary artery systolic pressure (PASP). However, this tool is not accurate enough, especially in patients with COPD due to hyperinflation and adipose tissue in the lungs obscuring echocardiographic examination.[9]

The incidence of PH varies in patients with COPD. It is usually associated with a severe degree of airway obstruction and is prevalent in 25%–35% of the severely affected COPD population, but it has also been described as frequent in 5%–7% of patients with only mild to moderate degree.[10] Several small studies have reported that the diameter of the pulmonary artery (PA) and the ratio of the diameter of the PA to the diameter of the ascending aorta (AA; PA:AA ratio) measured by computed tomography (CT) showed a correlation with the mean PA pressure (mPAP).[11,12]

A finding of a PA enlargement (PAE) defined PA diameter >30 mm or PA:AA ratio >1 may indicate a poor clinical outcome.[13,14] Apart from PH, other factors, including peripheral capillary destruction related to emphysema and subsequent centralization of blood flow and hyperinflation, may also contribute to PAE presented on CT scans.[15] Furthermore, PAE may serve as a composite endpoint for various other comorbid conditions seen in COPD, including right heart failure[16] and sleep apnea.[17] These factors are related to poor prognoses in COPD, and CT scans are frequently used to verify these conditions. Thus, several studies have explored the relationship between PAE and the prognosis of COPD patients,[13,14,18-33] but the results are controversial.

The aim of the present systematic review and meta-analysis was to assess the prognostic value of PAE-CT in patients with COPD.

METHODS

Protocol and registration

The present study was registered on the International Prospective Register of Systematic Reviews repository (PROSPERO) (CRD42020203539). The study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[34]

Information sources and search strategy

We searched for relevant studies in PubMed, EMBASE, Cochrane Library, Web of Science, and China National Knowledge Infrastructure up to August 1, 2021. Key search terms included "pulmonary artery enlargement," "pulmonary artery diameter," "pulmonary artery to aorta ratio," "PAE," "chronic obstructive pulmonary disease," "COPD," "acute exacerbation of chronic obstructive pulmonary disease," and "AECOPD". Additionally, we reviewed the reference lists of the selected articles.

Study selection

The search results were gathered in EndNote (version X9.1). After excluding duplicates, two reviewers (H. C. and T. S.) independently screened the remaining studies by scanning the title, abstract, and full text. We included studies (1) in which the participants were diagnosed with COPD or acute exacerbation of (AECOPD); (2) compared the PAE on CT imaging and without PAE on CT imaging; (3) reported outcomes in both PAE group and non-PAE group; and (4) were observational cohort studies. Duplicate studies were removed and the study with the largest sample size from the same institute remained. Any discrepancies were resolved by the involvement of the corresponding author (W. H.).

Data extraction

Two reviewers (L. W. and L. Y.) independently extracted data from the included trials using a predefined form in EXCEL and resolved differences with the corresponding author. The following data were extracted: (1) study-related information (first author, publication year, sample size, and follow-up period); (2) identification or quantification for PAE; and (3) clinical outcomes. The primary outcomes were mortality and 6-minute walk distance (6-MWD). Secondary outcomes included (1) PASP measured by echocardiology, the length of hospital stay, and the dyspnea severity evaluated by the modified British Medical Research Council dyspnea scale (mMRC) and COPD Assessment Test (CAT); (2) the parameter of pulmonary function test and oxygen metabolism, including forced expiratory volume in one second (FEV1) expressed as a normalized percent of the predicted value (FEV1% pred), forced vital capacity (FVC), the ratio of FEV1 and FVC (FEV1/FVC), pH, arterial partial pressure of oxygen (PaO_2), and partial pressure of carbon dioxide ($PaCO_2$).

Risk of bias in individual studies

Two reviewers (C. H. and S. D.) analyzed each trial for risk of bias utilizing the Newcastle-Ottawa Quality Assessment scale.[35] This tool consists of three categories having nine items: selection, comparability and outcomes, rating item as "low," "moderate," or "high risk." Full details of the quality assessment are provided in the Supporting Information: Materials.

Statistical analysis

Statistical analysis was performed using RevMan version 5.4 (The Cochrane Collaboration, 2020). In this meta-analysis, the association between PAE and dichotomous outcomes was estimated for each study by a pooled odds ratio (OR) along with its 95% confidence interval (CI). We computed a 95% CI of mean difference (MD) for the continuous outcomes. A random-effects model (Mantel–Haenszel method) was selected a priori given the heterogeneity in study design across the included studies.[36] Heterogeneity in effect estimates was assessed using the I^2 value, which was independent of the number of studies. Values <25% indicated low heterogeneity, and values >75% indicated severe heterogeneity.[37] If there was considerable bias, we explored the effect of bias by conducting a sensitivity analysis. The sensitivity analysis was performed by excluding low-quality studies or subgroups with different periods of COPD. Publication bias was assessed by funnel plots.[38]

RESULTS

Study selection and study characteristics

Initially, 1250 potential studies were screened based on title and abstract after duplicate studies were removed. In total, 56 studies were reviewed in full text, and 36 studies were excluded because they did not meet the inclusion criteria. Therefore, 18 studies[13,14,18-24] with 5694 participants were included in the analysis (Figure 1). All eligible studies were published between September 31, 2012 and July 1, 2021. The follow-up duration ranged from 0.3 to 83 months (median: 12 months). Among the 18 studies, there were nine studies of stable COPD, and the remaining were AECOPD. These studies covered patients with COPD, from mild to severe. All studies measured the main PA diameter and the greatest diameter of the AA at the same level of PA bifurcation transverse CT images. PAE was defined as PA:AA ratios of more than 1 in 14 studies. Four studies' cut-off values

of ≥30 mm[18,20,26] or >29 mm[24] were applied to distinguish the patients with and without PAE, and the PA:AA ratios were considered an indirect marker. Only one was a multicenter trial[14] that included 3463 participants. Four studies[14,20,24,29] were prospective observational studies, and the rests were retrospective observational studies. The characteristics of included studies are summarized in Table 1.

Risk of bias within studies

In the evaluation of comparability and the outcome bias, four studies reported high risks, which accounted for 22%. The high-risk proportions of the remaining various biases were all less than 20%. The included studies in the present study were of high quality. Details for the risk of bias assessment of individual studies are shown in Supporting Information: Figure S1.

FIGURE 1 Flow diagram of the study selection

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TABLE 1 Characteristics of the included studies

First author (year)	N	Diagnosis	Age (years)[a]	Male (%)	BMI (kg/m²)[a]	Smoking history (pack-year)[a]	FEV1% (pred)[a]	PASP (mmHg)[a]	Study design	Follow-up (months)[a]	Identification or quantification for PAE
Xi et al. (2020)	208	Stable COPD	75.2	63.9	NA	NA	NA	NA	Retrospective observational	NA	Unclear[b]
de-Torres et al. (2018)	188	Stable COPD	65.0	82.0	26.0	51.0	70	NA	Prospective observational	83	PA diameter ≧ 30mm
Dou et al. (2018)	480	Stable COPD	69.5	76.0	23.7	28.2	42	39	Retrospective observational	NA	PA:AA ratio > 1
Oki et al. (2016)	64	Stable COPD	73.0	21.9	21.7	40.0	64	NA	Retrospective observational	NA	PA:AA ratio >1
Wells et al. (2015)	24	Stable COPD	60.0	67.0	29	NA	57	NA	Retrospective observational	NA	PA:AA ratio > 1
Iyer et al. (2014)	60	Stable COPD	55.0	43.0	24.1	48.3	28	39	Retrospective observational	NA	PA:AA ratio > 1
Shin et al. (2014)	65	Stable COPD	59.3	50.7	26.8	NA	NA	NA	Retrospective observational	24	PA:AA ratio > 1
Qiuyun et al. (2013)	151	Stable COPD	65.0	88.7	22.3	33.2	59	NA	Prospective observational	25	PA diameter > 29 mm
Wells et al. (2012)	3464	Stable COPD	63.8	55.7	28.2	53.1	51	NA	Prospective observational	25	PA:AA ratio > 1
Wei et al. (2021)	223	AECOPD	71	54.7	22.4	NA	45	52	Retrospective observational	NA	PA:AA ratio> 1

TABLE 1 (Continued)

First author (year)	N	Diagnosis	Age (years)[a]	Male (%)	BMI (kg/m²)[a]	Smoking history (pack-year)[a]	FEV1% (pred)[a]	PASP (mmHg)[a]	Study design	Follow-up (months)[a]	Identification or quantification for PAE
Zhaoguang et al. (2018)	78	AECOPD	68.5	60.2	NA	NA	53	NA	Retrospective observational	NA	PA diameter > 30 mm
Yun et al. (2018)	115	AECOPD	60.0	56.5	NA	NA	NA	NA	Retrospective observational	NA	PA:AA ratio > 1
Fei et al. (2018)	31	AECOPD	64.9	64.5	NA	NA	NA	NA	Retrospective observational	NA	PA:AA ratio ≧ 1
Run et al. (2017)	90	AECOPD	65.5	68.9	NA	NA	37	46	Prospective observational	12	PA:AA ratio > 1
Wells et al. (2016)	134	AECOPD	65.0	47.0	26.8	52.0	46	NA	Retrospective observational	12	PA:AA ratio > 1
Ortaç Ersoy et al. (2016)	106	AECOPD	71.1	46.0	NA	NA	NA	51	Retrospective observational	0.4	PA:AA ratio > 1
Wei et al. (2015)	118	AECOPD	74.8	51.7	NA	NA	31	60	Retrospective observational	0.3	PA:AA ratio > 1
Ming et al. (2015)	95	AECOPD	71.4	73.0	20.8	NA	NA	NA	Retrospective observational	4	PA:AA ratio > 1

Abbreviations: AA, ascending aorta; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV1% pred, forced expiratory volume in one second expressed as a normalized percent of the predicted value; N, number; NA, not available; PA, pulmonary artery; PAE, pulmonary artery enlargement; PASP, pulmonary artery systolic pressure.

[a]Data are presented as mean.

[b]The authors did not make a detailed definition of PAE.

Mortality and exercise capacity

Mortality was reported in four studies with 444 patients.[20,23,29,31] Compared with the patients without PAE, the PAE group had higher mortality (OR = 3.06; 95% CI: 1.76–5.32; $p < 0.0001$) under the randomized model ($I^2 = 16\%$) (Figure 2a).

The 6-MWD was reported in six studies with 4017 patients.[13,14,20,21,24,29] The 6-MWD was significantly shorter in COPD patients with PAE (MD = −67.53 m; 95% CI: −85.98 to −49.08; $p < 0.00001$) under the randomized model ($I^2 = 55\%$) (Figure 2b).

PAP

The PASP measured by echocardiology was reported in six studies with 887 patients.[13,19,25,29,31,32] The PAE group had higher PASP than the non-PAE group (MD = 15.65 mmHg; 95% CI: 13.20–18.11; $p < 0.00001$) under the randomized model ($I^2 = 0\%$) (Figure 3).

Length of hospital stay

The length of hospital stay was reported in only three studies with 338 patients.[25,28,30] Compared with the patients without PAE, the PAE group had longer hospital stay (MD = 2.92 days; 95% CI: 0.71–5.12 days; $p = 0.009$) under the randomized model. Moderate heterogeneity was observed among these studies, with $I^2 = 72\%$ (Figure 4).

Degree of dyspnea

The mMRC was reported in five studies with 721 patients.[20,21,24,25,33] There was no significant difference between patients with or without PAE regarding the degree of dyspnea (MD = 0.26; 95% CI: −0.29 to 0.81; $p = 0.35$; $I^2 = 93\%$) (Figure 5a). The CAT was reported in five studies with 610 patients.[21,25,27,29,32] Compared with the patients without PAE, the PAE group had worse health status (MD = 3.14; 95% CI: 2.48–3.81; $p < 0.00001$) under the randomized model ($I^2 = 0\%$) (Figure 5b).

Lung function

The FEV1% pred was reported in 12 studies with 5074 patients.[13,14,19-22,24-26,29,30,32] The PAE group had more severe degree of airway obstruction than the non-PAE group (MD = −7.13%; 95% CI: −11.54 to −2.72; $p = 0.002$) under the random model. High heterogeneity was observed among these studies, with $I^2 = 90\%$ (Figure 6a). In the subgroup analysis, no matter whether in a stable period of COPD or exacerbation of COPD, the patients with PAE had lower FEV1% pred ($p = 0.01$, 0.02, respectively).

The FEV1/FVC was reported in 11 studies with 5072 patients.[13,14,18-22,24-26,30] Compared with the patients without PAE, the PAE group had lower FEV1/FVC (MD = −4.09; 95% CI: −7.43 to −0.75; $p = 0.02$) under the random model. High heterogeneity was observed among these studies, with $I^2 = 91\%$ (Figure 6b). However, in subgroup analysis, there was no significant difference between patients with or without PAE in AECOPD ($p = 0.30$).

Blood gas analysis

In addition, the PAE group had lower PaO_2 (MD = −7.93 mmHg; 95% CI: −12.02 to −3.83; $p = 0.0001$; $I^2 = 67\%$; seven studies with 1192 patients; Figure 7b) and higher $PaCO_2$ (MD = 10.47 mmHg; 95% CI: 5.63 to 15.31; $p < 0.0001$; $I^2 = 85\%$; eight studies with 1287 patients; Figure 7c). There was no significant difference in pH between the PAE group and non-PAE group (MD = −0.04; 95% CI: −0.09 to 0.02; $p = 0.16$; $I^2 = 96\%$; six studies with 1086 patients; Figure 7a).

Heterogeneity analysis and publication bias

This analysis showed high heterogeneity in mMRC, FEV1% pred, FEV1/FVC, $PaCO_2$, and pH ($I^2 > 75\%$). For mMRC, in a stable period of COPD, the heterogeneity was at a moderate level with $I^2 = 69\%$. But in the AECOPD subgroup, the value of I^2 was 97%. Through sensitivity analysis, after removing Ming et al.'s study,[33] the heterogeneity of mMRC was reduced to a moderate level, the value of I^2 was decreased from 93% to 55%, and still had no statistical significance (MD = 0.05; $p = 0.74$). For FEV1% pred, in the subgroup analysis, the heterogeneity was at a moderate level with $I^2 = 64\%$ in a stable period of COPD. However, the value of I^2 was 91% in the AECOPD subgroup. After removing Wei et al.'s study[32] with disequilibrium grouping, the value was decreased from 90% to 74%. For FEV1/FVC and $PaCO_2$, in the subgroup analysis, the heterogeneity was high in both the stable and AECOPD subgroups. After removing Xi et al.'s study[18] with an unclear definition of PAE, the heterogeneity of FEV1/FVC was reduced to a low level in the stable period of the COPD subgroup (MD: −2.17;

(a)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Ebru Ortaç Ersoy,2016	20	40	24	66	36.6%	1.75 [0.79, 3.88]
Juan P. de-Torres,2018	12	22	31	166	28.9%	5.23 [2.07, 13.19]
Rong Sun,2017	7	42	3	43	13.7%	2.67 [0.64, 11.10]
Stephanie Shin,2014	11	21	9	44	20.8%	4.28 [1.39, 13.20]
Total (95% CI)		125		319	100.0%	3.06 [1.76, 5.32]
Total events	50		67			

Heterogeneity: Tau² = 0.05; Chi² = 3.56, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 3.98 (P < 0.0001)

(b)

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anand S. Iyer,2014	236	58	22	279	65	38	17.2%	-43.00 [-74.85, -11.15]
J. Michael Wells,2012	300	137	819	367	26	2645	32.3%	-67.00 [-76.43, -57.57]
Juan P. de-Torres,2018	374	129	22	482	103	166	8.3%	-108.00 [-164.14, -51.86]
Qiuyun Xing,2013	425.6	59.5	12	457.9	91.8	139	14.6%	-32.30 [-69.26, 4.66]
Rong Sun,2017	272.4	53.8	45	353.7	68.5	45	21.1%	-81.30 [-106.75, -55.85]
Yutaro Oki,2016	336	162	29	454	85	35	6.5%	-118.00 [-183.34, -52.66]
Total (95% CI)			949			3068	100.0%	-67.53 [-85.98, -49.08]

Heterogeneity: Tau² = 251.23; Chi² = 11.17, df = 5 (P = 0.05); I² = 55%
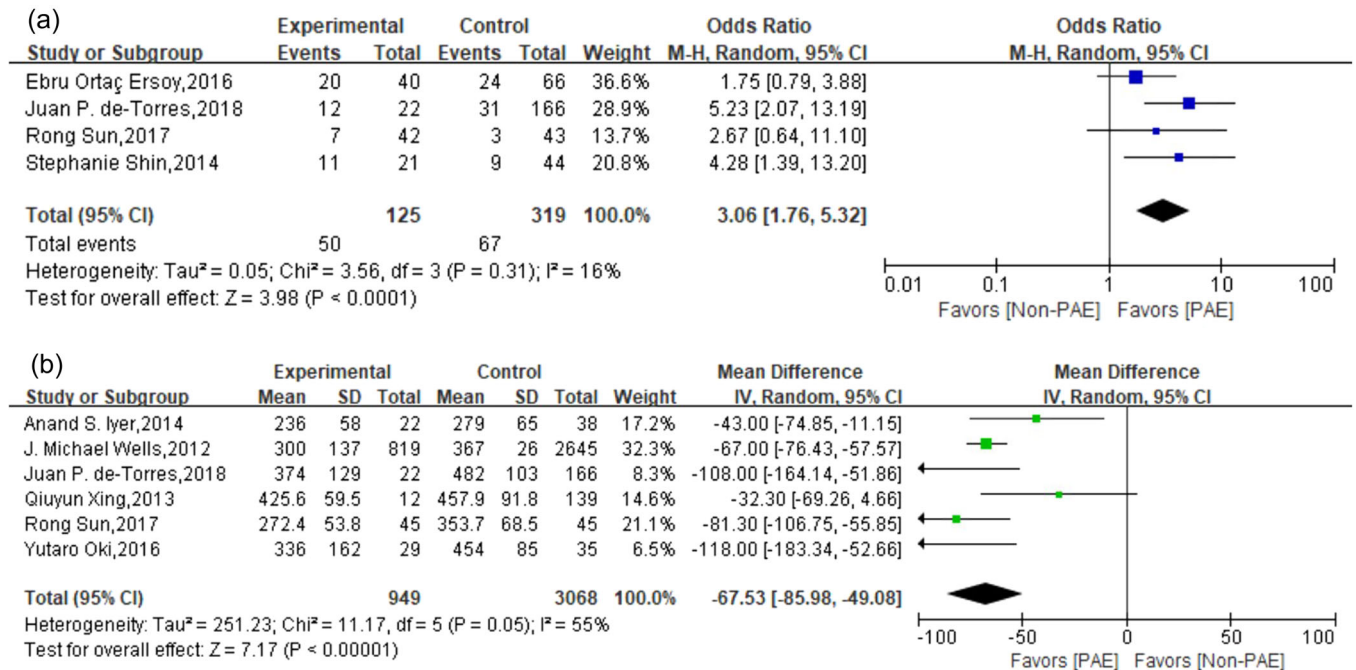Test for overall effect: Z = 7.17 (P < 0.00001)

FIGURE 2 Forest plot demonstrating the pooled odds ratio for mortality and exercise capacity. (a) Forest plot of mortality and (b) Forest plot of the 6-min walk distance. CI, confidence interval; PAE, pulmonary artery enlargement.
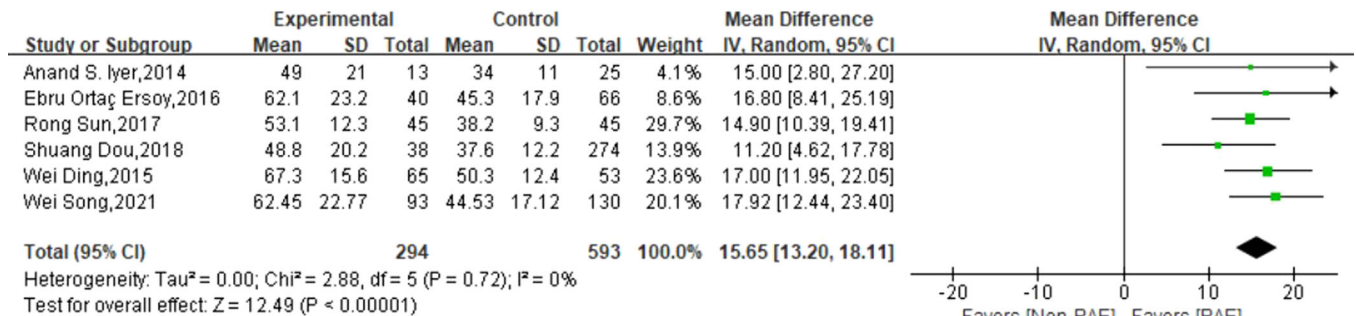
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Anand S. Iyer,2014	49	21	13	34	11	25	4.1%	15.00 [2.80, 27.20]
Ebru Ortaç Ersoy,2016	62.1	23.2	40	45.3	17.9	66	8.6%	16.80 [8.41, 25.19]
Rong Sun,2017	53.1	12.3	45	38.2	9.3	45	29.7%	14.90 [10.39, 19.41]
Shuang Dou,2018	48.8	20.2	38	37.6	12.2	274	13.9%	11.20 [4.62, 17.78]
Wei Ding,2015	67.3	15.6	65	50.3	12.4	53	23.6%	17.00 [11.95, 22.05]
Wei Song,2021	62.45	22.77	93	44.53	17.12	130	20.1%	17.92 [12.44, 23.40]
Total (95% CI)			294			593	100.0%	15.65 [13.20, 18.11]

Heterogeneity: Tau² = 0.00; Chi² = 2.88, df = 5 (P = 0.72); I² = 0%
Test for overall effect: Z = 12.49 (P < 0.00001)

FIGURE 3 Forest plot of pulmonary artery systolic pressure measured by echocardiology. CI, confidence interval; PAE, pulmonary artery enlargement.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fei Yang,2018	15.7	4.2	13	12.9	3.3	18	27.2%	2.80 [0.05, 5.55]
J. Michael Wells,2016	8.6	1.5	57	7	1	77	46.0%	1.60 [1.15, 2.05]
Wei Song,2021	17.95	13.57	93	12.65	2.2	130	26.8%	5.30 [2.52, 8.08]
Total (95% CI)			163			225	100.0%	2.92 [0.71, 5.12]

Heterogeneity: Tau² = 2.70; Chi² = 7.22, df = 2 (P = 0.03); I² = 72%
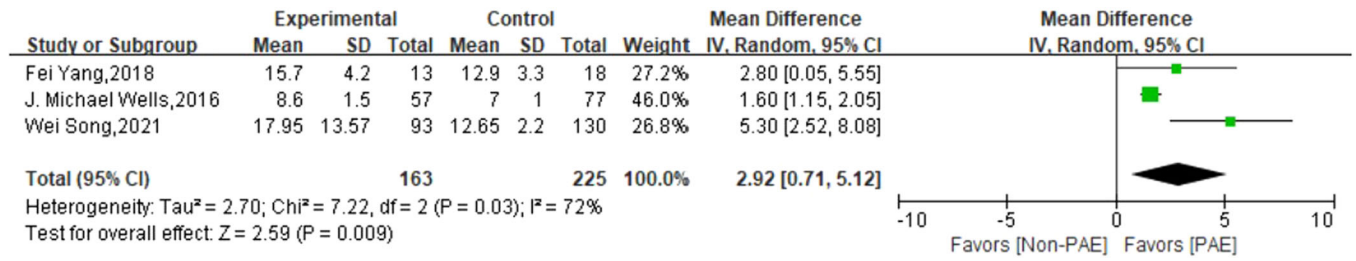Test for overall effect: Z = 2.59 (P = 0.009)

FIGURE 4 Forest plot of the length of hospital stay. CI, confidence interval; PAE, pulmonary artery enlargement.

$p = 0.004$; $I^2 = 15\%$). The heterogeneity of $PaCO_2$ was decreased from 85% to 81% after removing Run et al.'s study,[29] but still at a high level. For pH, the heterogeneity was 99% in the stable period of the COPD subgroup and 64% in the AECOPD subgroup. After removing Dou et al.'s study,[19] the heterogeneity of pH was reduced to a moderate level and still had no statistical significance (MD: −0.01; $p = 0.41$; $I^2 = 52\%$). There was no publication bias assessed by funnel plots (Supporting Information: Figure S2).
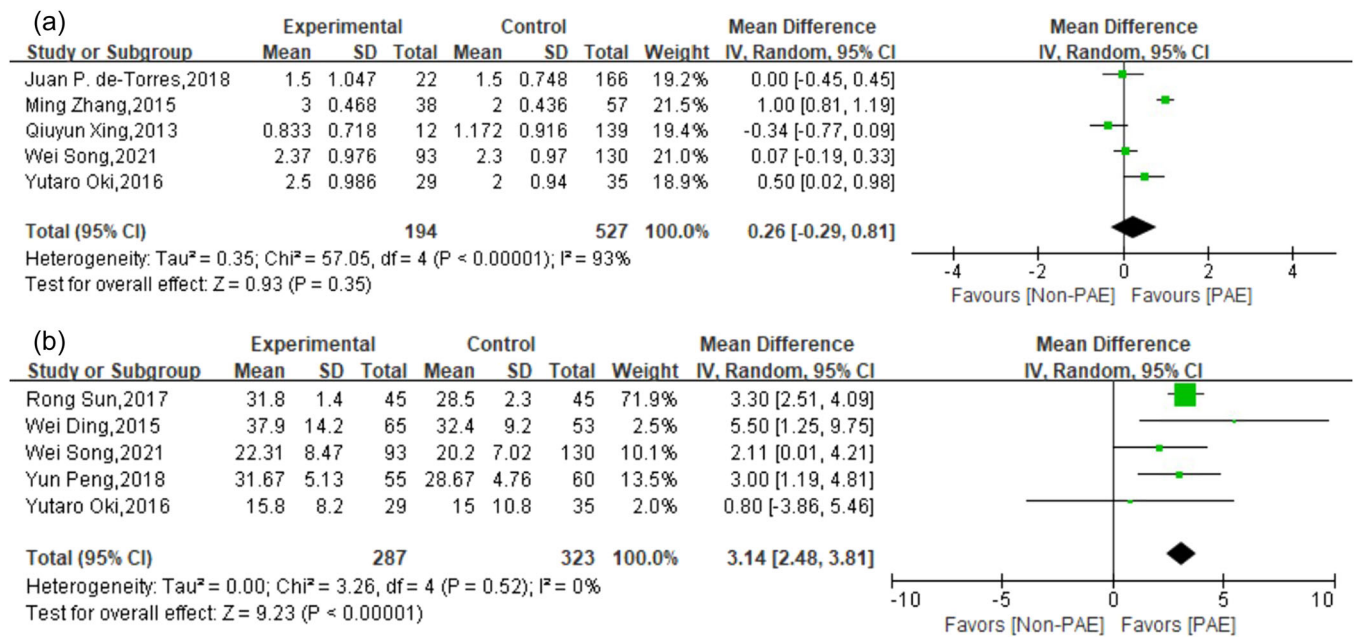
FIGURE 5 Forest plot of the degree of dyspnea. (a) Forest plot of modified British Medical Research Council dyspnea scale. (b) Forest plot of COPD Assessment Test. CI, confidence interval; COPD, chronic obstructive pulmonary disease; PAE, pulmonary artery enlargement.

DISCUSSION

This meta-analysis evaluated the prognostic value of PAE in COPD. Our results demonstrated that the COPD patients with PAE on CT had poor survival, impaired exercise capacity, high PAP, long hospital stay, and severe health status. In regard to the lung function and blood gas analysis, the PAE was correlated with worse airway obstruction and more likely complicated respiratory acidosis in COPD patients. The present study indicated that PAE may be a powerful prognostic marker in COPD patients.

Many previous studies have assessed the relationship between PAE and prognosis for patients with COPD. However, there is no consensus regarding whether PAE predicts poor survival. From the Forest plot, the group of COPD patients with PAE had higher mortality. In this current meta-analysis, Ortaç Ersoy et al.[31] studied 106 critically ill patients with COPD and failed to show any significant association between PAE and mortality. Although the mortality rate of patients with PAE was higher (50%) than that of patients without PAE (36.4%), the difference in mortality did not reach statistical significance ($p = 0.26$). In contrast, de-Torres et al.[20] studied 188 patients with moderate or severe COPD and reported that the presence of PAE was an independent predictor of the composite endpoint of mortality (adjusted hazard ratio [HR] = 2.78; 95% CI: 1.35–5.75; $p = 0.006$). Shin et al.[23] also suggested that PAE was independently associated with increased mortality in

COPD patients (adjusted HR = 5.05; 95% CI: 1.63–15.6). This discrepancy may be due to the patients included in Ortaç Ersoy et al.'s study, who were diagnosed with AECOPD and required intensive care unit (ICU) admission, which was different from other studies. Additionally, the small number of patients included in their analyses may result in low statistical power. Nevertheless, Ortaç Ersoy et al.'s study, although different from other studies in terms of mortality, still suggested that PAE was an important cause of poor clinical outcomes. For example, the PAE group had higher PAP measured by echocardiography than the non-PAE group (62.1 ± 23.2 vs. 45.3 ± 17.9 mmHg; $p = 0.002$).

A multicenter prospective observational trial, which included 3464 participants,[14] not only reported the correlation between PAE and the risk of future acute exacerbation in the COPD Gene longitudinal cohort but also evaluated the OR of the risk of future acute exacerbation from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) trial,[39] which was a validation cohort. In the 1- and 3-year follow-up, both cohorts suggested that the PAE group had a higher risk of acute exacerbation in patients with COPD.

PH is well recognized as being associated with increased mortality in COPD.[40] The marker of PH in the CT scan is the enlargement of the main trunk of the PA, which leads to hilar prominence and a reduction in the diameter of the peripheral PAs (the centralization phenomenon). Therefore, widening of the PA trunk is an
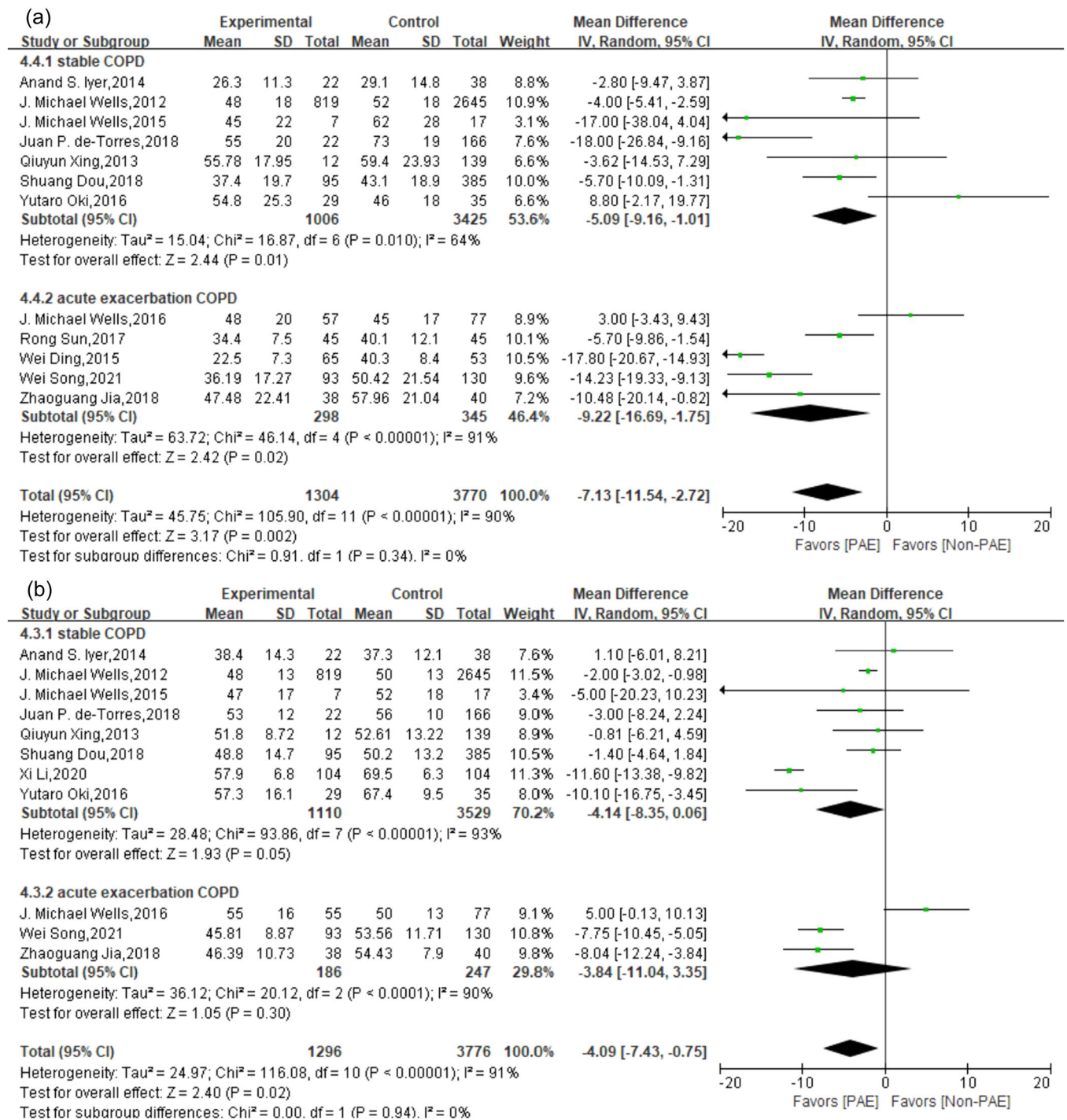
(a)

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.4.1 stable COPD								
Anand S. Iyer,2014	26.3	11.3	22	29.1	14.8	38	8.8%	-2.80 [-9.47, 3.87]
J. Michael Wells,2012	48	18	819	52	18	2645	10.9%	-4.00 [-5.41, -2.59]
J. Michael Wells,2015	45	22	7	62	28	17	3.1%	-17.00 [-38.04, 4.04]
Juan P. de-Torres,2018	55	20	22	73	19	166	7.6%	-18.00 [-26.84, -9.16]
Qiuyun Xing,2013	55.78	17.95	12	59.4	23.93	139	6.6%	-3.62 [-14.53, 7.29]
Shuang Dou,2018	37.4	19.7	95	43.1	18.9	385	10.0%	-5.70 [-10.09, -1.31]
Yutaro Oki,2016	54.8	25.3	29	46	18	35	6.6%	8.80 [-2.17, 19.77]
Subtotal (95% CI)			1006			3425	53.6%	-5.09 [-9.16, -1.01]

Heterogeneity: Tau² = 15.04; Chi² = 16.87, df = 6 (P = 0.010); I² = 64%
Test for overall effect: Z = 2.44 (P = 0.01)

4.4.2 acute exacerbation COPD								
J. Michael Wells,2016	48	20	57	45	17	77	8.9%	3.00 [-3.43, 9.43]
Rong Sun,2017	34.4	7.5	45	40.1	12.1	45	10.1%	-5.70 [-9.86, -1.54]
Wei Ding,2015	22.5	7.3	65	40.3	8.4	53	10.5%	-17.80 [-20.67, -14.93]
Wei Song,2021	36.19	17.27	93	50.42	21.54	130	9.6%	-14.23 [-19.33, -9.13]
Zhaoguang Jia,2018	47.48	22.41	38	57.96	21.04	40	7.2%	-10.48 [-20.14, -0.82]
Subtotal (95% CI)			298			345	46.4%	-9.22 [-16.69, -1.75]

Heterogeneity: Tau² = 63.72; Chi² = 46.14, df = 4 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.42 (P = 0.02)

Total (95% CI)			1304			3770	100.0%	-7.13 [-11.54, -2.72]

Heterogeneity: Tau² = 45.75; Chi² = 105.90, df = 11 (P < 0.00001); I² = 90%
Test for overall effect: Z = 3.17 (P = 0.002)
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² = 0%

Mean Difference IV, Random, 95% CI
-20 -10 0 10 20
Favors [PAE] Favors [Non-PAE]

(b)

Study or Subgroup	Experimental			Control			Weight	Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
4.3.1 stable COPD								
Anand S. Iyer,2014	38.4	14.3	22	37.3	12.1	38	7.6%	1.10 [-6.01, 8.21]
J. Michael Wells,2012	48	13	819	50	13	2645	11.5%	-2.00 [-3.02, -0.98]
J. Michael Wells,2015	47	17	7	52	18	17	3.4%	-5.00 [-20.23, 10.23]
Juan P. de-Torres,2018	53	12	22	56	10	166	9.0%	-3.00 [-8.24, 2.24]
Qiuyun Xing,2013	51.8	8.72	12	52.61	13.22	139	8.9%	-0.81 [-6.21, 4.59]
Shuang Dou,2018	48.8	14.7	95	50.2	13.2	385	10.5%	-1.40 [-4.64, 1.84]
Xi Li,2020	57.9	6.8	104	69.5	6.3	104	11.3%	-11.60 [-13.38, -9.82]
Yutaro Oki,2016	57.3	16.1	29	67.4	9.5	35	8.0%	-10.10 [-16.75, -3.45]
Subtotal (95% CI)			1110			3529	70.2%	-4.14 [-8.35, 0.06]

Heterogeneity: Tau² = 28.48; Chi² = 93.86, df = 7 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.93 (P = 0.05)

4.3.2 acute exacerbation COPD								
J. Michael Wells,2016	55	16	55	50	13	77	9.1%	5.00 [-0.13, 10.13]
Wei Song,2021	45.81	8.87	93	53.56	11.71	130	10.8%	-7.75 [-10.45, -5.05]
Zhaoguang Jia,2018	46.39	10.73	38	54.43	7.9	40	9.8%	-8.04 [-12.24, -3.84]
Subtotal (95% CI)			186			247	29.8%	-3.84 [-11.04, 3.35]

Heterogeneity: Tau² = 36.12; Chi² = 20.12, df = 2 (P < 0.0001); I² = 90%
Test for overall effect: Z = 1.05 (P = 0.30)

Total (95% CI)			1296			3776	100.0%	-4.09 [-7.43, -0.75]

Heterogeneity: Tau² = 24.97; Chi² = 116.08, df = 10 (P < 0.00001); I² = 91%
Test for overall effect: Z = 2.40 (P = 0.02)
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.94), I² = 0%

Mean Difference IV, Random, 95% CI
-20 -10 0 10 20
Favors [PAE] Favors [Non-PAE]

FIGURE 6 Forest plot of the lung function. (a) Forest plot of FEV1% predicted. (b) Forest plot of FEV1/FVC. CI, confidence interval; COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity; FEV1, forced expiratory volume in one second; PAE, pulmonary artery enlargement.

indication of PH in COPD patients.[41] Iyer et al.[13] also indicated that mPAP was independently associated with the presence of PAE (OR = 1.44; 95% CI: 1.02–2.04; $p = 0.04$), and the sensitivity and specificity between PAE and PH were 73% and 84%, respectively. Chronic hypoxemia secondary to hyperinflation and emphysematous destruction of lung tissue causes pathological changes in the pulmonary vasculature, including vessel elongation, vasoconstriction, and loss of vasculatures, resulting in vascular remodeling and endothelial dysfunction,[15,20,42] which may be common features of PAE and PH. Therefore, CT scan-measured relative PAE
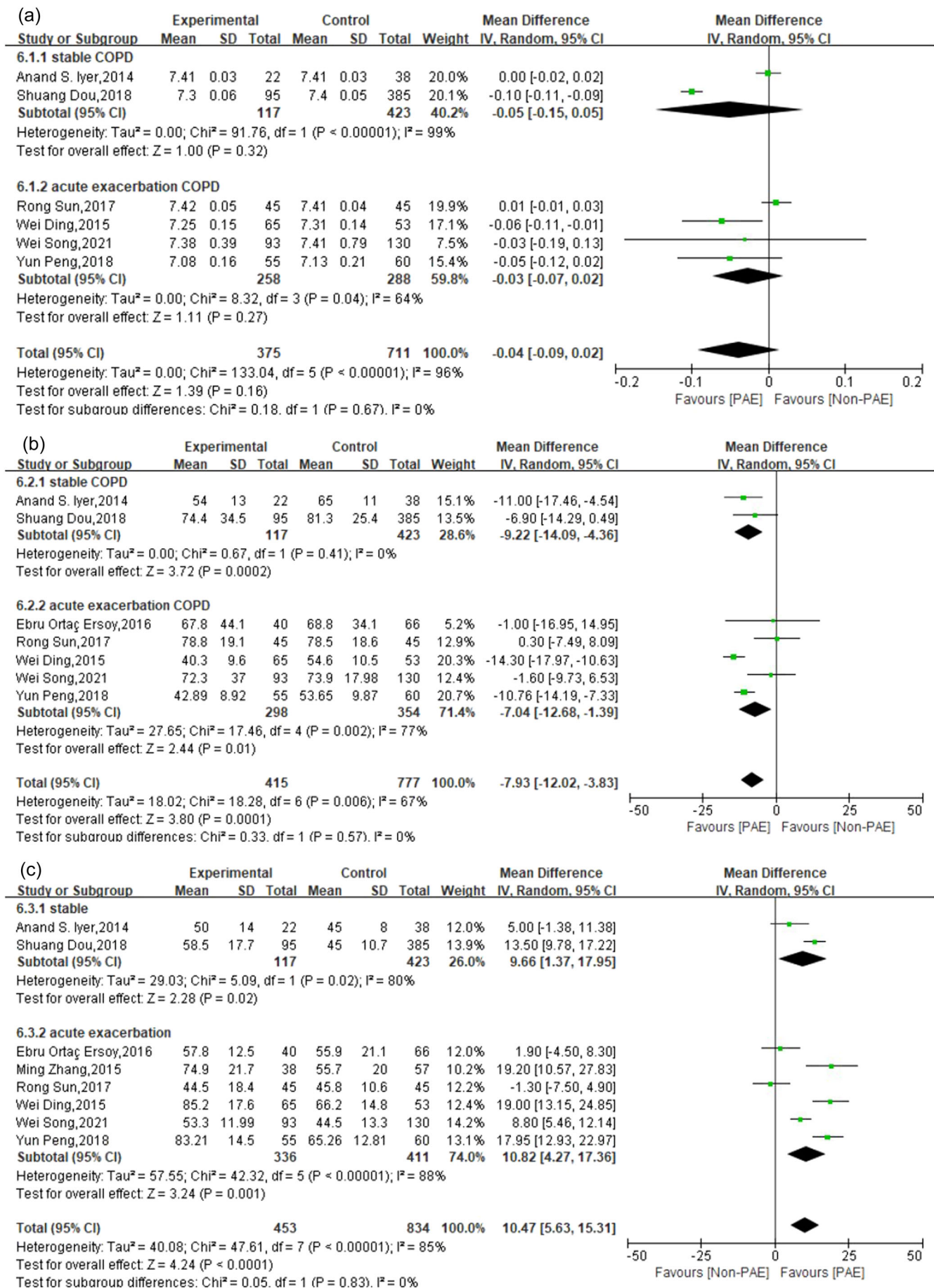
Pulmonary Circulation

FIGURE 7 (See caption on next page)

should be the preferred screening tool for PH in this patient population. Shin et al.[23] said that PH was not associated with mortality in their Cox hazards model. Iyer et al.[13] showed that relative PAE was only partially explained by intrinsic PH itself. Both raise the possibility that other factors may also affect the PA diameter, including obstructive sleep apnea, undiagnosed cardiovascular disease, venous thromboembolism, or a combination of these mechanisms. Therefore, the underlying disease of PAE may potentially have effects on the prognosis.

This meta-analysis underscored the importance of PAE as an index in evaluating patients with COPD. First, these measurements are noninvasive, easily accessible, reproducible, and require minimal training, and relate to mortality in patients with COPD. They are much less problematic for evaluating the central vasculature, including the main PA, the right and left branches, and the AA, by using routine contrasted and noncontrasted CT scans.[43] In addition, although FEV1 was the traditional predictor of prognosis in patients with COPD based on the severity of airflow obstruction, it is exceedingly difficult to measure FEV1 in acute patients because of severe shortness of breath and respiratory failure.[31] Therefore, CT is a valuable and routine tool in the evaluation of both lung disease and intrathoracic vasculature in patients with COPD. Furthermore, de-Torres et al.[20] found that PAE was the most powerful predictor of all-cause mortality along with age in COPD patients and was even stronger than most of the clinical and physiologic prognostic parameters for the disease, including the well-validated multidimensional BODE index (body mass index, obstruction, dyspnea and exercise capacity). The significance of focusing on PAE might lie in the ability to identify patients at high risk of pulmonary vascular disease, exacerbations, or mortality. The PA:AA ratio could be utilized in therapeutic decision-making and risk stratification and screen patients most likely to benefit from the agents that reduce COPD exacerbations and mortality.

Heterogeneity in effect estimates was assessed using the I^2 value, and we thought the values >75% indicated severe heterogeneity. In our meta-analysis, there was significant heterogeneity in mMRC, FEV1% pred, FEV1/FVC, pH, and $PaCO_2$; thus, we performed subgroup and sensitivity analysis. In the subgroup analysis, the heterogeneity of the AECOPD group was high. For some

outcomes, such as mMRC and FEV1% pred, the heterogeneity was reduced after removing the AECOPD subgroup. Three studies[27,28,32] provided PA:AA ratio in both acute exacerbations and stable periods. We found that the PA:AA ratio increased during acute exacerbation of COPD compared with the stable period, and the difference was statistically significant ($p < 0.05$). The heterogeneity may due to decreased ability of pulmonary arterial wall dilatation during the stable period of COPD,[44] but during acute exacerbations, various factors such as hyperventilation, hypoxic pulmonary vasoconstriction, pulmonary edema, increased cardiac output, and inflammation, as well as the pulmonary vascular elasticity were restored.[45,46] Patients with acute exacerbation of COPD are often accompanied by hypercapnia, which increases the concentration of nitric oxide and causes vasodilation, and this pathophysiological change is reversed after recovery.[45] Moreover, previous studies have reported that neutrophils are one of the most important inflammatory cells involved in chronic airway inflammation in COPD, and infiltration of inflammatory cells into the PA adventitia leads to changes in the structure of pulmonary vasculature and enhances during the acute exacerbation.[45,47] Therefore, various pathophysiological mechanisms in AECOPD may lead to transient PA dilation, and thus we removed the AECOPD subgroups.

In the sensitivity analysis, after removing Wei et al.'s study,[32] the heterogeneity of FEV1% pred reduced to the moderate level. Compared with other studies, the study of Wei et al. showed a significant difference in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage between the PAE group and the non-PAE group. Patients in the PAE group were in Stage IV, but patients in the non-PAE group were in Stage III. This unbalanced grouping may result in the discrepancy. For FEV1/FVC, the heterogeneity was high in both the stable and AECOPD subgroups. In the stable COPD study, after removing Xi et al.'s study, the heterogeneity was reduced to a low level. Xi's study did not describe the definition of PAE, such as PA diameter >30 mm or PA:AA ratio >1. Instead, they grouped the COPD patients into PAE and non-PAE based on the radiologists' reports, which may attribute to the heterogeneity. Therefore, in the quality assessment of included studies, this study was a moderate risk because of the vague definition of exposure.

FIGURE 7 Forest plot of the blood gas analysis. (a) Forest plot of pH, (b) Forest plot of PaO_2, and (c) Forest plot of $PaCO_2$. CI, confidence interval; COPD, chronic obstructive pulmonary disease; PAE, pulmonary artery enlargement; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen.

This study is a systematic review and meta-analysis of real-world studies and therefore carries the inherent limitations of observational research. First, there were only four studies reporting mortality, and the meta-regression analysis was limited by the small sample size of included studies, which may influence the reliability of the conclusions. Second, the high prevalence of PAE in patients with COPD in included studies may suggest sampling bias when patients were recruited. Finally, because of the limited sample size of studies, we only conducted a qualitative exploration of PAE. With more clinical studies with a larger sample size, the PA:AA ratio subgroups may be analyzed in the future and even an algorithm to predict the prognosis of COPD patients.

The current meta-analysis showed that the assessment of pulmonary vascular change with PAE-CT is significantly associated with mortality in patients with COPD. In addition to the pulmonary parenchyma, pulmonary vessels should also be considered when evaluating chest CT in patients with COPD. PAE may thus serve as a novel imaging biomarker for risk stratification in patients with COPD. This conclusion needs to be confirmed with prospective, randomized, large sample size and multicenter studies.

AUTHOR CONTRIBUTIONS

Huaqiao Chen conceived the project, conducted this systematic review and statistical analysis, assisted with data analysis, created tables and figures, and wrote and edited the manuscript. Tingting Shu conducted this systematic review, assisted with data analysis, and wrote and edited the manuscript. Lu Wang analyzed the data and wrote and edited the manuscript. Lingzhi Yang conducted the statistical analysis, created the tables and figures, and wrote and edited the manuscript. Changchun Hu and Shanshan Du assisted with data collection and analysis and wrote and edited the manuscript.

ACKNOWLEDGMENTS

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ETHICS STATEMENT

All analyses were based on previously published studies; thus, no ethical approval and patient consent are required.

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Additional supporting information can be found online in the Supporting Information section at the end of this article.