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Association of echocardiographic pulmonary hypertension with all-cause mortality in hospitalized AECOPD patients

Zhiqi Zhao [a,b,c,d], Xue He [e], Ruoyan Xiong [a,b,c,d], Yanan Cui [a,f,g,h,i,j], Weiwei Meng [a,b,c,d], Jiankang Wu [a,b,c,d], Jiayu Wang [a,b,c,d], Rui Zhao [a,b,c,d], Huihui Zeng [a,c,d,*], Yan Chen [a,b,c,d,*]

[a] Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[b] Research Unit of Respiratory Disease, Central South University, Changsha, Hunan 410011, China
[c] Clinical Medical Research Center for Pulmonary and Critical Care Medicine in Hunan Province, 410011, China
[d] Diagnosis and Treatment Center of Respiratory Disease, Central South University, Changsha, Hunan 410011, China
[e] Department of Thoracic Surgery, The Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China
[f] Department of Pulmonary and Critical Care Medicine, Center of Respiratory Medicine, China-Japan Friendship Hospital, Beijing, China
[g] National Center for Respiratory Medicine, Beijing, China
[h] National Clinical Research Center for Respiratory Diseases, Beijing, China
[i] Institute of Respiratory Medicine, Chinese Academy of Medical Sciences, Beijing, China
[j] State Key Laboratory of Respiratory Health and Multimorbidity, Beijing, China

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) often coexists with pulmonary hypertension (PH). However, whether pulmonary artery pressure (PAP) or even suspected PH assessed by echocardiography during acute exacerbation stage predicts mortality after discharge is unclear.
Methods: We conducted an retrospective study of hospitalized patients with acute exacerbation of COPD (AECOPD). Peak tricuspid regurgitation velocity (TRV) and additional variables were used to assess PH risk.
Results: Cox regression analysis showed that echocardiographic suspected PH was the independent risk factor for the significantly increased long-term mortality (adjusted HR 1.64; 95% CI 1.06–2.53) after discharge in AECOPD patients. Logistic regression analysis revealed a negative correlation between blood eosinophil (EOS) counts at admission and the prevalence of suspected PH (adjusted OR 0.18; 95% CI 0.04–0.89). Triple therapy (adjusted HR 0.18; 95% CI 0.05–0.61), neither LABA/ICS during stable stage was associated with a significant reduction in long-term mortality in hospitalized AECOPD patients with suspected PH.
Conclusion: Echocardiographic suspected PH was associated with adverse survival in hospitalized AECOPD patients. Low EOS counts at admission emerged as a potential biomarker for elevated estimated systolic PAP. Triple therapy during stable stage was associated with a significant reduction in long-term mortality in AECOPD patients with suspected PH.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a severe worldwide public health problem with an increasing leading cause of morbidity and mortality[1,2]. Acute exacerbation of COPD (AECOPD) is a malignant event during the disease course, which is associated with a negative impact on survival prognosis, especially in patients requiring hospitalization [3].

Abbreviations: COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; AE, acute exacerbation; PH, pulmonary hypertension; PAP, pulmonary artery pressure; EOS, blood eosinophil; LAMA, long-acting muscarinic receptor antagonist; LABA, long-acting beta(2)-agonist; ICS, inhaled corticosteroid; RHC, right heart catheterization; sPAP, systolic pulmonary artery pressure; ESC, European Society of Cardiolog; ERS, European Respiratory Society; GOLD, Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council Dyspnea Scale; CAT, COPD Assessment Test; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

* Corresponding authors at: No.139, Renmin Road Central Changsha, Hunan, China.
E-mail addresses: bonemarrow@csu.edu.cn (H. Zeng), chenyan99727@csu.edu.cn (Y. Chen).

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COPD often coexists with other diseases (comorbidities) [4], during which pulmonary hypertension (PH) is a common finding [5,6]. The mortality significantly increased in COPD patients with concomitant PH [5,7,8]. Meanwhile, ventricular stretch and cardiopulmonary vascular burden increase obviously during acute exacerbation (AE) stage, which leads to worse outcomes for AECOPD patients with concomitant PH [9].

The gold standard for diagnosing and confirming PH is the right heart catheterization (RHC) [10]. Yet it is hard for RHC to be routinely applied for its invasive damage. Echocardiography effectively copies this problem to noninvasively estimate systolic pulmonary artery pressure (sPAP) [11]. Although there is a risk of underestimation or overestimation of sPAP by echocardiography [12], which raises concerns for clinical decision-making, it and/or in combination with other indicators can effectively play a role similar to RHC and accurately predict the survival prognosis of patients to some extent [13,14]. The guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) specify Doppler echocardiography as the primary non-invasive diagnostic instrument for suspected PH in patients [15].

In conclusion, the primary objective of this study was to identify and characterize high-risk PH in AECOPD patients using comprehensive echocardiographic evaluation. Our research aims to (1) assess one-year and long-term prognostic outcomes in this patient population, (2) establish non-invasive predictive indicators for PH risk stratification and mortality prediction in hospitalized AECOPD patients, and (3) integrate laboratory biomarkers with therapeutic interventions and echocardiographic parameters to optimize clinical decision-making and patient management strategies.

2. Methods

This study retrospectively observed a cohort of eligible hospitalized patients with AECOPD from September 2016 to July 2020 in the Department of Pulmonary and Critical Care Medicine, the Second Xiangya Hospital of Central South University. The committee approved the research and all research was performed in accordance with relevant guidelines/regulations. Inclusion criteria included the following: 1) acute exacerbation of COPD diagnosed according to the 2024 GOLD guidelines [16] and 2) signed informed consent. Exclusion criteria included the following: 1) refusal to sign informed consent, 2) with concomitant asthma, 3) with concomitant pulmonary embolism, 4) no echocardiography performed, 5) died during hospitalization and 6) refusal to cooperate with interviews and lost to follow-up (Fig. 1).

2.1. Patients

Echocardiography was performed in all patients. AECOPD with suspected PH was defined by ultrasound experts according to the 2022 ESC/ERS Guidelines [17]. Two experienced ultrasound specialists reviewed the report respectively. Guidelines suggest using peak tricuspid regurgitation velocity (TRV) as a key variable to assess PH risk. A peak TRV $>$ 2.8 m/s may suggest PH [17]. Therefore patients with TRV $>$ 2.8 m/s and abnormal additional variables related to right ventricle (RV) morphology and function (e.g. RV / left ventricle (LV) basal diameter / area ratio $>$ 1.0, pulmonary artery (PA) diameter $>$ 25 mm, right atrium (RA) area (end-systole) $>$ 18 cm^2) were classified into the suspected PH group. Patients with TRV $<$ 2.8 m/s and normal right heart related variables were classified into the Non_PH group. Patients with suspected PH were stratified according to disease severity based on estimated sPAP: severe PH (estimated sPAP $>$ 60 mmHg) and mild-to-moderate PH (estimated sPAP $<=$ 60 mmHg) [18].

2.2. Data collection

The demographic and clinical data of patients including sex, age, body mass index (BMI), smoking status, pharmacological treatment during stable stage and comorbidities were collected, as well as variables during hospitalization such as routine blood examination, blood gas analysis, spirometry, echocardiography, six-minute walking distance (6 WMD) and length of stay (LOS). Dyspnea and respiratory symptoms were evaluated by the modified Medical Research Council (mMRC) Dyspnea Scale and COPD Assessment Test (CAT). The corticosteroid therapy, oxygen therapy and ventilatory support were recorded according to the patient's medical instructions and medical records.

2.3. Follow-up

The enrolled patients were followed up by telephone after discharge. The first-year follow-up information included the frequency of exacerbation and readmission due to AECOPD in the previous year, the time of the first AE after discharge and survival condation. Subsequent annual follow-up only inquired about survival status. We recorded their survival time until death or December 2022 for survival analysis.

2.4. Outcomes

The primary endpoints were the one-year and long-term all-cause

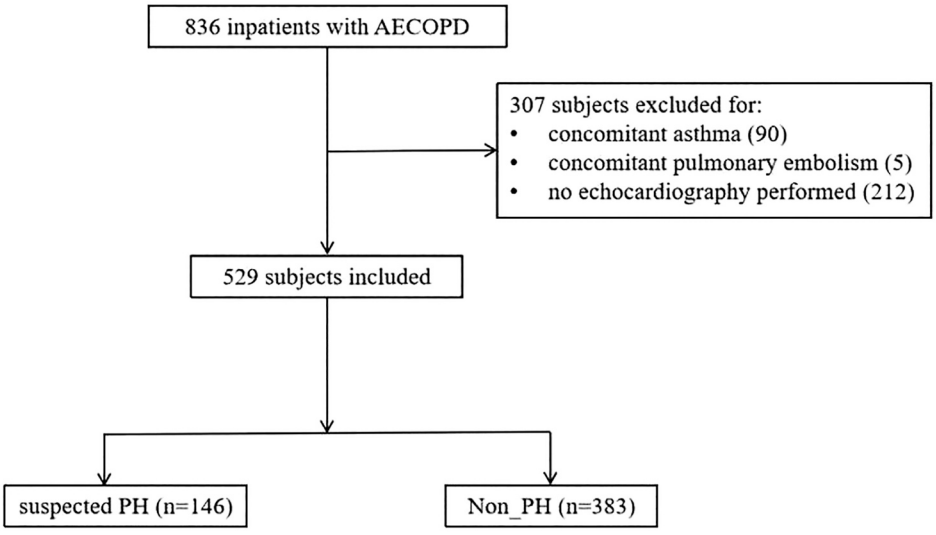

Fig. 1. The flow chart of eligible inpatients with AECOPD. AECOPD: acute exacerbation of chronic obstructive pulmonary disease; PH: pulmonary hypertension.

mortality after discharge. Secondary end points were the improvement during hospitalization and the condition of re-exacerbation during follow-up. Improvement during hospitalization was assessed by comparison of the same variable at admission and at discharge. Changes of symptom assessments and laboratory investigations were analyzed to illustrate the differences in recovery between the Non_PH group and the suspected PH group. The condition of re-exacerbation during one year of follow-up was recorded, including the occurrence of acute exacerbation, the degree and frequency.

2.5. Statistical analysis

SPSS 26.0 (IBM, New York, USA) software was used for all statistical analyses. Nonparametric data are presented as the median and interquartile range (IQR), which were analyzed by the Mann-Whitney test. Categorical variables are presented as numbers and percentages, which were analyzed by the Chi-squared test. Logistic regression analysis was used to analyze the relation between blood eosinophil (EOS) counts at admission and suspected PH. Confounding variables controlled included age, sex, baseline smoking index, BMI and cor pulmonale. Odds ratio (OR) and nominal 95 % confidence interval (CI) are presented. The best cutoff value of estimated sPAP on predicting mortality was calculated according to the Youden index.

Survival was calculated from the date of discharge to death or the last time of follow-up. Kaplan-Meier survival curves were used for univariate survival analysis. Cox proportional hazards regression modeling was used to remove the interference of disturbed factors on multivariate survival analysis. Confounding variables we controlled [19] included age, sex, baseline postbronchodilator forced expiratory volume in 1 s (FEV1) / forced vital capacity (FVC), baseline smoking index, BMI and the frequency of AE during the previous year as well as the use of ICS during stable stage. When analyzing the impact of steroid therapy during stable stage on mortality, adjusting factors included an increase in EOS counts at admission based on the above factors. Hazard ratio (HR) and nominal 95 % CI are presented. $P < 0.05$ was considered significant. Graphs were jointly completed by SPSS 26.0 and GraphPad Prism 9.

3. Results

We conducted a median follow-up of 42.0 months (interquartile range [IQR], 34.5 to 51.5) for the enrolled inpatients with AECOPD. A total of 529 patients were included in this study and participated in the analysis of both one-year and long-term mortality (Fig. 1). Based on the presence or absence of suspected PH, the participants were categorized into two groups: 146 (27.6 %) AECOPD inpatients with suspected PH (suspected PH group) and 383 (72.4 %) AECOPD inpatients without PH (Non_PH group).

3.1. There were more significant cardiac structural remodeling and more severe respiratory symptoms in the suspected PH group

The baseline characteristics of participants are shown in Table 1. Compared to the Non_PH group, the suspected PH group had worse lung function, shorter 6MWD, lower SaO_2 and higher N-Terminal Pro-Brain Natriuretic Peptide (NT-pro BNP). The echocardiographic results showed more significant cardiac structural remodeling and pulmonary arterial dilation accompanied by a significant increase in left atrial diameter at end-systole (LAS), right ventricle diameter (RVD), right atrial diameter at end-systole (RAS) and pulmonary artery (PA) in the suspected PH group compared to the Non_PH group. The estimated sPAP was significantly higher in the suspected PH group compare to the Non_PH group (47 mmHg vs. 28 mmHg, $P < 0.0001$). Additionally, the suspected PH group had a higher prevalence of comorbidities, including arrhythmia (23.3 % vs. 11.2 %, $P < 0.0001$), respiratory failure (57.5 % vs. 35.8 %, $P < 0.0001$), and cor pulmonale (62.3 % vs. 11.2 %, $P < 0.0001$), compared to the Non_PH group. Interestingly, the proportion of

Table 1
Characteristics of AECOPD patients with or without suspected PH at admission.

Variables	Non_PH (n = 383)	suspected PH (n = 146)	P-value
Age, years	68(63,75)	68(62.75,75)	0.956
Male, %	355(92.7)	133(91.1)	0.540
BMI, kg/m2	21.3 (18.83,24.03)	21.1 (19.03,23.92)	0.698
Smoking index, packets/year	40(20,60)	40(20,60)	0.917
Spirometry			
FVC, L	2.18(1.75,2.63)	1.91(1.54,2.38)	<0.0001
FEV1, L	0.76(0.59,1.03)	0.72(0.54,0.95)	0.071
FEV1 % predicted, %	34 (24.47,45.63)	31.32 (23.21,40.28)	0.094
FEV1/FVC, %	37(29.72,47)	38.4 (30.54,46.22)	0.555
FeNO, ppd	26(17,38)	22.5(16,35.75)	0.145
6MWD, m	252(100,370)	197.5 (50,331.25)	0.016
mMRC	3(2,4)	3(2,4)	0.306
CAT	23(18,28)	24(18,29)	0.223
Echocardiography			
LVD, mm	43(40,47)	43(39,47)	0.749
LAS, mm	30(26,32)	31(28,34)	0.007
RVD, mm	28(26,30)	33(29,37)	<0.0001
RAS, mm	28(26,30)	33(30,38)	<0.0001
AO, mm	30(27,32)	30(28,32.5)	0.140
PA, mm	22(20,23)	25(22,28)	<0.0001
EF, %	60(60,63)	60(59,63)	0.553
FS, %	32(30,34)	32(30,33.75)	0.476
Estimated sPAP, mmHg	28(23,30)	47(39,60)	<0.0001
Comorbidities and complications			
Coronary heart disease, %	65(17.0)	30(20.5)	0.338
Hypertension, %	145(37.9)	51(34.9)	0.533
Diabetes, %	46(12.0)	16(11.0)	0.737
Arrhythmia, %	43(11.2)	34(23.3)	<0.0001
Type II respiratory failure, %	119(31.1)	76(52.1)	<0.0001
Prior pulmonary TB, %	133(34.7)	48(32.9)	0.689
Cor pulmonale, %	43(11.2)	91(62.3)	<0.0001
Frequency of AEs in the last 12 months, times	2(1,3)	2(1,3)	0.885
Laboratory investigations on admission			
WBC count, x 109/L	7.08(5.72,9.33)	6.81(5.66,9.17)	0.448
Neutrophil count, x 109/L	5.18(3.95,7.24)	5.23(3.98,6.96)	0.978
Eosinophil count, x 109/L	0.13(0.06,0.23)	0.09(0.04,0.17)	0.001
CRP, mg/l	8.1(3.46,23.15)	9.36 (4.44,33.48)	0.075
PCT, mg/l	0.05(0.05,0.13)	0.05(0.05,0.14)	0.328
NT-pro BNP, pg/ml	100(50,260)	480 (117.5,2725)	<0.0001
PaO_2, mm/Hg	70.35(58,81)	62(46,76.2)	<0.0001
$PaCO_2$, mm/Hg	48(43,58)	52.9 (44.15,73.5)	<0.0001
SaO_2, %	94(90,96)	91.7(81,95)	<0.0001
Inhaler therapy during stable stage			0.019
No inhaler, %	130(33.9)	65(44.5)	
LAMA/LABA + LAMA, %	21(5.5)	14(9.6)	
LABA + ICS, %	82(21.4)	23(15.8)	
Triple therapy, %	150(39.2)	44(30.1)	

Date is presented as median (IQR) or n (%).
PH: pulmonary hypertension; BMI: body mass index; FVC: forced vital capacity; FEV1: forced expiratory volume in 1 s; FeNO: fractional exhaled nitric oxide; 6 MWD:6-minute walking distance; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; LVD: left ventricular diameter; LAS: left atrial diameter at end-systole; RVD: right ventricular diameter; RAS: right atrial diameter at end-systole; AO: aorta; PA: pulmonary artery; EF: ejection fraction; FS: fractional shortening; sPAP: systolic pulmonary artery pressure; TB: tuberculosis; AE: acute exacerbation; COPD: chronic obstructive pulmonary disease; WBC: White Blood Cell; CRP: C-reactive protein; PCT: Procalcitonin; NT-pro BNP: N-Terminal Pro-Brain Natriuretic Peptide; PaO_2: partial pressure of oxygen in artery; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; SaO_2: arterial oxygen saturation; LAMA: long-acting muscarinic receptor antagonist; LABA: long-acting beta(2)-agonist; ICS: inhaled corticosteroid.

patients receiving inhaled corticosteroid (ICS) therapy during the stable stage was significantly lower in the suspected PH group than in the Non_PH group (45.9 % vs. 60.6 %, P = 0.002).

3.2. Lower EOS count was a risk factor for suspected PH and associated with estimated sPAP by echocardiography

Given the EOS was a reliable marker of COPD severity [20], we next analyzed the characteristics of EOS counts between the Non_PH group and the suspected PH group and the relation between EOS counts and estimated sPAP. The results showed that the EOS counts at admission and discharge were both lower in the suspected PH group compared to the Non_PH group (P = 0.001, P = 0.866, respectively) (supplementary Table S1). Additionally, the proportion of patients with EOS counts of < 100 cells/μl at admission was significantly higher in the suspected PH group than that of the Non_PH group (P = 0.003) (supplementary Table S1). Logistic regression analysis revealed a negative correlation between EOS counts at admission and the prevalence of suspected PH (adjusted OR 0.18; 95 % CI 0.04–0.89). Meanwhile, AECOPD patients with lower EOS counts at admission were associated with higher estimated sPAP, the EOS counts at discharge of whom was still lower as expected (supplementary Fig. 1).

3.3. The one-year mortality and long-term mortality after discharge increased significantly in the suspected PH group

Condition changes during hospitalization and follow-up was showed in Table 2. Although the frequency of AEs within one year of follow-up did not differ significantly between the two groups (Table 2), the Chi-squared test revealed that the suspected PH group had significantly higher one-year mortality (17.8 % vs. 9.7 %, P = 0.010) and long-term mortality (53.6 % vs. 32.1 %, P < 0.001) after discharge compared to the Non_PH group (Table 2).

Furthermore, Kaplan-Meier survival analysis was performed to evaluate the survival outcomes of AECOPD patients with or without suspected PH within one year and beyond one year after discharge (Fig. 2). The results (P = 0.001 and P < 0.0001, respectively) were consistent with the findings from the Chi-squared test (Table 2). The median time to death in the suspected PH group was 41.0 months (IQR, 22.2 to 59.8) (Fig. 2). To account for potential confounding factors, Cox proportional hazards regression modeling was employed. The analysis revealed that suspected PH in AECOPD patients was an independent risk factor for both increased one-year mortality (adjusted HR 2.10; 95 % CI 1.04–4.24) and long-term mortality (adjusted HR 1.64; 95 % CI 1.06–2.53) after adjustment.

3.4. Echocardicalgraphy-estimated sPAP ≥ 39.5 mmHg increased significantly the long-term mortality in hospitalized AECOPD patients

Subsequently, we evaluated the association between PH severity and mortality. The analysis revealed that patients with severe PH (estimated sPAP > 60 mmHg) exhibited significantly increased long-term mortality (P = 0.001) compared to those with mild to moderate PH. However, no statistically significant difference was observed in one-year mortality between the groups (P = 0.173) (supplementary Fig. S2). Given that the utilization of estimated sPAP for severity stratification demonstrates limited efficacy in prognostic prediction among hospitalized AECOPD patients we calculated the optimal cutoff value of estimated sPAP on predicting one-year and long-term mortality according to the Youden index. The results suggested the best performance of estimated sPAP of ≥ 34.5 mmHg on predicting one-year mortality and estimated sPAP of ≥ 39.5 mmHg on predicting long-term mortality respectively in AECOPD patients. The results of the Kaplan-Meier survival analysis were consistent with the above results (supplementary Fig. S3). It is worth noting that the long-term mortality after discharge was increased significantly in AECOPD patients with estimated sPAP of ≥ 39.5 mmHg (adjusted HR 2.13; 95 % CI 1.08–4.20) and the median time to death of them was 28.0 months (IQR, 19.1 to 36.9).

Table 2
Condition changes during hospitalization and follow-up between the Non_PH group and the suspected PH group.

Variables	Non_PH (n = 383)	suspected PH (n = 146)	P-value
Changes of symptom assessments and laboratory investigations			
Δ 6MWD, m	59(20,140)	66(20,150)	0.716
Δ mMRC	−1(−1,0)	0(−1,0)	0.236
Δ CAT	−6(−10.75, −2)	−6(−8.25, −2)	0.631
Δ WBC count, x 109/L	−0.8 (−2.66,0.57)	−0.82 (−2.75,0.48)	0.776
Δ Neutrophil count, x 109/L	−0.84 (−2.67,0.51)	−0.95 (−2.72,0.23)	0.633
Δ Eosinophil count, x 109/L	0.02 (−0.02,0.11)	0.08 (−0.01,0.15)	0.004
Δ PaO2, mm/Hg	16(1,24.25)	16.45(2.23,24)	0.785
Δ PaCO2, mm/Hg	−2(−8,2)	−3(−10,4)	0.548
Δ SaO2, %	3(0,7)	5(1,12)	0.072
Oxygen and ventilatory support			
Oxygen, %	286(74.7)	92(63.0)	0.008
NPPV, %	124(32.4)	79(54.1)	<0.0001
IPPV, %	1(0.3)	1(0.7)	1.000
NCS therapy during hospitalization, %	306(79.9)	118(80.8)	0.811
NCS dosage, mg	32.0 (10.0,48.0)	38.0 (15.0,51.0)	0.035
SCS therapy during hospitalization, %	108(28.2)	27(18.5)	0.022
SCS dosage, mg	28.4 ± 69.3	19.7 ± 58.6	0.145
LOS, days, median, IQR	10(8,12)	10(8,13)	0.153
One year of follow-up			
HOT, %	132(34.5)	68(46.6)	0.010
Time of first AE after discharge, months	6(3,8)	4(2,8.25)	0.994
Frequency of AE in the last 12 months, times	0.5(0,2)	0(0,2)	0.789
Incidence of death within one year after discharge, %	37(9.7)	26(17.8)	0.010
Long term of follow-up			
Incidence of death, %	94(32.1)	60(53.6)	<0.0001

Date is presented as median (IQR) or n (%).
Δ Changes of symptom assessments and examinations (Value at discharge – Value at admission).
PH: pulmonary hypertension; 6 MWD:6-minute walking distance; mMRC: modified Medical Research Council; CAT: COPD Assessment Test; WBC: White Blood Cell; PaO_2: partial pressure of oxygen in artery; $PaCO_2$: partial pressure of carbon dioxide in arterial blood; SaO_2: arterial oxygen saturation; NPPV: noninvasive positive pressure ventilation; IPPV: invasive positive pressure ventilation; NCS: nebulized corticosteroid; SCS: systemic corticosteroid; LOS: length of stay; HOT: home oxygen therapy; AE: acute exacerbation.

3.5. Suspected PH significantly increased the one-year and long-term mortality after discharge in certain populations

Subgroup analyses were performed to identify the primary populations impacted by suspected PH. Variables demonstrating significant differences (P < 0.05) in Table 1 were selected for binary subgroup stratification. The analysis revealed that suspected PH emerged as an independent risk factor for elevated one-year mortality across multiple subgroups: patients aged < 65 years (adjusted HR 3.57, 95 % CI 1.07–11.85), those classified as GOLD stage 3 or 4 (adjusted HR 2.25, 95 % CI 1.04–4.87), individuals with < 2 acute exacerbations in the previous year (adjusted HR 4.00, 95 % CI 1.11–14.36), patients presenting with EOS < 300 cells/μl at admission (adjusted HR 2.22, 95 % CI 1.04–4.75), cases with type II respiratory failure (adjusted HR 3.45, 95 % CI 1.09–10.94), subjects without right ventricular hypertrophy (adjusted HR 2.66, 95 % CI 1.19–5.95), and those not receiving ICS

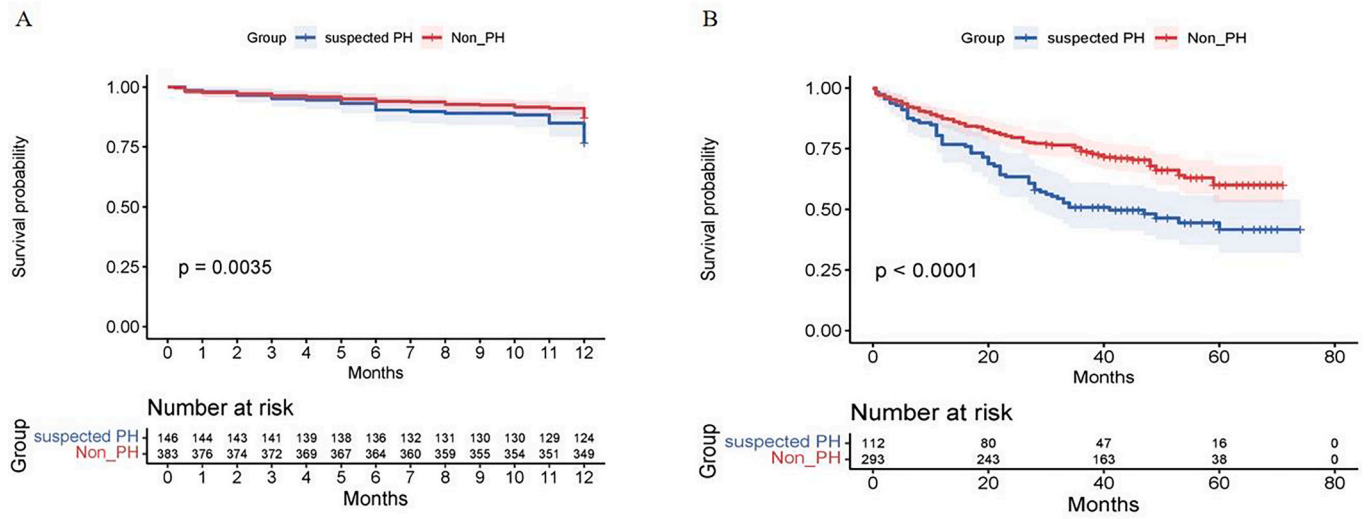

Fig. 2. Kaplan-Meier survival curves for the one-year (A) and long-term (B) mortality after discharge in AECOPD patients with or without suspected PH. PH: pulmonary hypertension.

therapy during stable phases (adjusted HR 4.31, 95 % CI 1.35–13.73) (Fig. 3). Regarding long-term mortality, suspected PH remained an independent risk factor in several patient subgroups: those aged < 65 years (adjusted HR 3.08, 95 % CI 1.38–6.88), patients classified as GOLD stage 3 or 4 (adjusted HR 1.75, 95 % CI 1.09–2.81), individuals presenting with EOS < 300 cells/μl at admission (adjusted HR 1.62, 95 % CI 1.01–2.59), and patients not receiving ICS therapy during stable phases (adjusted HR 2.16, 95 % CI 1.15–4.07) (Supplementary Fig. S4).

3.6. Triple therapy during stable stage reduced long-term mortality after discharge in AECOPD patients with echocardiographic suspected PH

Given the established therapeutic benefits of ICS therapy in COPD management, this study analyzed the impact of ICS therapy during stable stage on long-term mortality after discharge in AECOPD patients (adjusted HR 0.50; 95 % CI 0.32–0.77). Subgroup analysis demonstrated differential effects based on PH status. In the Non_PH cohort, stable-phase ICS therapy did not show significant mortality benefit (adjusted HR 0.76, 95 % CI 0.42–1.34). However, in patients with suspected PH, both Kaplan-Meier survival analysis (P = 0.029, Fig. 4) and Cox regression analysis identified stable-phase ICS therapy as an independent protective factor against long-term mortality (adjusted HR 0.30, 95 % CI 0.13–0.70). We further analyzed and found that triple therapy (adjusted HR 0.19; 95 % CI 0.05–0.67) but not LABA/ICS therapy (adjusted HR 0.36; 95 % CI 0.10–1.27) during stable stage could significantly reduce long-term mortality in AECOPD patients with suspected PH compared to those without inhaler therapy. For the steroid therapy during hospitalization, SCS could significantly reduce the six-month mortality in AECOPD patients with suspected PH (P = 0.009), however, nebulized corticosteroid (NCS) did not play the same positive role (P = 0.127) (supplementary Fig. S5).

4. Discussion

This study revealed significantly elevated one-year and long-term mortality in AECOPD patients with echocardiography-diagnosed suspected PH. Particularly vulnerable subgroups, including patients aged < 65 years, those classified as GOLD grade 3 or 4, individuals presenting with admission EOS < 300 cells/μl, and those not receiving ICS therapy during stable phases, demonstrated substantially increased mortality following echocardiographic detection of suspected PH. Notably, low admission EOS emerged as a potential biomarker for both elevated estimated sPAP and echocardiography-assessed suspected PH. Therapeutic interventions showed differential prognostic impacts: SCS therapy during hospitalization significantly improved six-month survival outcomes in suspected PH patients. Furthermore, stable-phase ICS therapy, particularly triple therapy, was associated with significantly reduced long-term mortality in this patient population.

PH is associated with worse 6MWD, hypoxaemia and airflow limitation [21,22]. COPD patients assessed with suspected PH during AE stage also represented more severe exercise limitations, respiratory symptoms and cardiac structural remodeling. These above conditions will lead to a worse prognosis in AECOPD patients with suspected PH. Additionally, in the subgroup of AECOPD patients with severe airflow restriction or combined with type II respiratory failure, PH is independently associated with poor survival. More attention needs to be paid to such populations.

Severe PH is associated with a substantially increased mortality [23]. Specifically, patients with severe PH demonstrate significantly poorer clinical outcomes and reduced average lifespan compared to those with mild-to-moderate PH [18]. Mostly severe PH may be detected by a severe elevation of PAP in patients with COPD [13]. Our findings not only corroborate this observation but also extend the current understanding by demonstrating that elevated estimated sPAP serves as an independent prognostic factor for survival outcomes in AECOPD patients. Meanwhile, the elevation of estimated sPAP of ≥ 39.5 mmHg indicates the higher risk of death after discharge. These patients with estimated sPAP of ≥ 39.5 mmHg should undergo regular echocardiographic follow-up to evaluate PH progression, promptly monitor clinical symptoms, and initiate appropriate therapeutic interventions when necessary. It is worth noting that estimated sPAP may increase during AE course compared to that during the stable stage, so we consider that echocardiography applied in all AECOPD patients during hospitalization is needful and predicting survival prognosis of patients by echocardiography requires criteria based on the AE course. Previous studies [24,25] and our study found the relation between low EOS counts and the prevalence of PH. Furthermore, EOS counts at admission were negative correlated with estimated sPAP notably. Low EOS counts are associated with less efficacious and increased frequency of AE and mortality in COPD patients [16], as well as estimated sPAP during AE stage, which suggests that more attention needs to be paid to EOS counts at admission in AECOPD patients, especially those with suspected PH.

PH is associated with increases of inflammatory proteins in systemic circulation in COPD patients [26]. Inhaled and oral corticosteroids are effective in reducing serum CRP levels in COPD patients [27]. Meanwhile, SCSs could improve blood gas and reduce sPAP in AECOPD

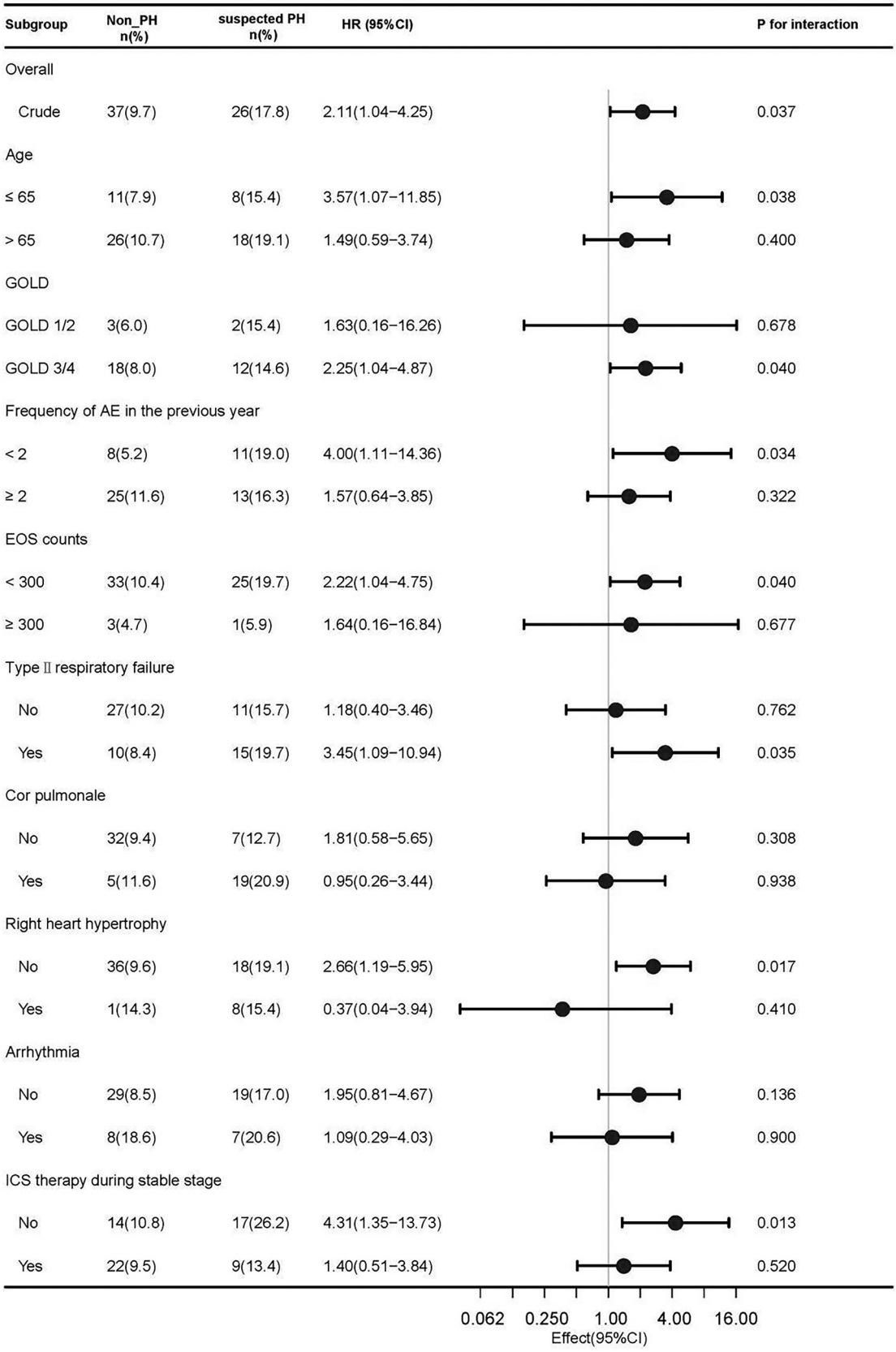

Fig. 3. Forest plot of Subgroup analyses for mortality within one year of follow-up. Hazard ratio (HR) were adjusted for age, sex, baseline post-bronchodilator FEV1/FVC, smoking index, body mass index, the frequency of AEs during the previous year and the use of ICSs during stable stage. PH: pulmonary hypertension; GOLD: Global Initiative for Chronic Obstructive Lung Disease; AE: acute exacerbation; EOS: blood eosinophil; ICS: inhaled corticosteroid.

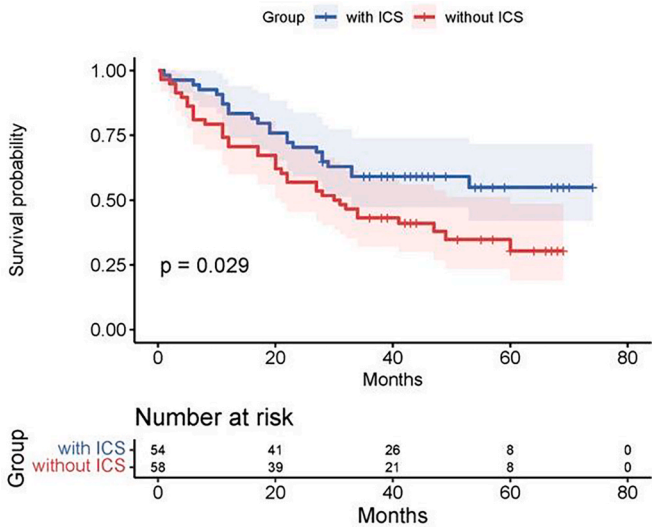

Fig. 4. Kaplan-Meier survival curves for the impact of ICS therapy during stable stage on the long-term mortality after discharge in AECOPD patients with suspected PH. ICS: inhaled corticosteroid.

patients [28]. Therefore, for AECOPD patients at a risk of PH, we suggest administration of steroid for its efficacy of reducing inflammatory level, sPAP and mortality. In EUROSCOP study, fewer cardiovascular (CV) events and CV event-related deaths were observed with ICS-based therapy versus placebo [29]. ETHOS and IMPACT study also have observed major benefit of triple therapy on all-cause mortality and its improvement on cardiovascular outcomes [30,31]. At the same time, pre-treatment with budesonide/glycopyrronium/formoterol fumarate (BGF) triple therapy could prevent PH in addition to ameliorating COPD progression in a mouse model induced by elastase [32]. In our study, we have also observed that ICS-based therapy, especially triple therapy, was an independent protective factor for long-term mortality after discharge in AECOPD patients with suspected PH. Previous study had proven that LAMA therapy was associated with a reduction in the risk of all-cause mortality, CV mortality, and CV events [33], which might be the effect of LAMA on the pathogenesis of suspected PH, given that triple therapy reduces mortality compared to LABA/ICS. Yet this conclusion needs to be further validated in future prospective cohort studies.

This study has several limitations that should be acknowledged. Firstly, the assessment of pH was solely based on echocardiographic evaluation and lacked confirmation through RHC, which remains the gold standard for definitive PH diagnosis. Secondly, a significant limitation of this study is the lack of serial echocardiographic monitoring following patient discharge, which could have offered critical insights into disease progression and long-term outcomes through longitudinal data. Future studies should aim to address this gap by incorporating systematic follow-up protocols to enhance the understanding of post-discharge trajectories. Thirdly, despite efforts to enhance reliability through dual independent readings by experienced echocardiography specialists, inherent variability in echocardiographic measurements remains a constraint. Fourthly, as a retrospective cohort study, potential biases, including selection bias due to the non-randomized design, variability in treatment practices over the extended enrollment period, recall bias during telephone follow-ups, and heterogeneity in follow-up durations, may have influenced the results. Finally, our findings necessitate further validation through large-scale, multicenter, prospective randomized controlled trials to draw more robust and generalizable conclusions.

5. Conclusion

In conclusion, our findings highlight the clinical importance of early identification and risk stratification of pH in hospitalized AECOPD patients through comprehensive echocardiographic evaluation. The study underscores the need for targeted therapeutic strategies in high-risk PH populations, including the implementation of SCS therapy during acute hospitalization and optimization of maintenance therapy with triple therapy during stable phases. These evidence-based interventions may improve post-discharge outcomes and reduce all-cause mortality in this vulnerable patient population.

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Availability of data and materials.

All data supporting the findings of this study are available within the paper and its Supplementary Information.

Declarations.

Ethics approval and consent to participate.

This study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University (No. ChiCTR-POC-17010431). Written informed consent was obtained from all participants.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Zhiqi Zhao: Writing – original draft, Data curation, Conceptualization. **Xue He:** Visualization, Data curation. **Ruoyan Xiong:** Data curation. **Yanan Cui:** Data curation. **Weiwei Meng:** Investigation. **Jiankang Wu:** Investigation. **Jiayu Wang:** Investigation. **Rui Zhao:** Investigation. **Huihui Zeng:** Writing – review & editing, Supervision. **Yan Chen:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2025.101661.

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