Original Article

Relationship between polycythemia and in-hospital mortality in chronic obstructive pulmonary disease patients with low-risk pulmonary embolism

Lu Guo[1,2], Aamer Rasheed Chughtai[3], Hongli Jiang[4], Lingyun Gao[2], Yan Yang[2], Yang Yang[2], Yuejian Liu[2], Zhenliang Xie[2], Weimin Li[1]

[1]Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu 610041, China; [2]Department of Respiratory Medicine, Sichuan Academy of Medical Science, Sichuan Provincial People's Hospital, University Hospital of Electronic Science & Technology of China, Chengdu 610072, China; [3]Radiology Department, University of Michigan Health System, Ann Arbor, MI 48109, USA; [4]Pneumology Group, Department of Integrated Traditional Chinese and Western Medicine, West China Hospital of Sichuan University, Chengdu 610041, China

Contributions: (I) Conception and design: L Guo, H Jiang, L Gao; (II) Administrative support: Z Xie, W Li; (III) Provision of study materials or patients: L Guo, AR Chughtai, Y Yang, Y Yang, Y Liu; (IV) Collection and assembly of data: L Guo, Y Yang, Y Yang, Y Liu; (V) Data analysis and interpretation: L Guo, AR Chughtai; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Weimin Li, MD. Department of Respiratory Medicine, West China Hospital of Sichuan University, Chengdu 610041, China. Email: weimin003@163.com; Zhenliang Xie, MB. Department of Respiratory Medicine, Sichuan Academy of Medical Science, Sichuan Provincial People's Hospital, University Hospital of Electronic Science & Technology of China, Chengdu 610072, China. Email: 704827217@qq.com.

Backgrounds: Pulmonary embolism (PE) is frequent in subjects with chronic obstructive pulmonary disease (COPD) and associated with high mortality. This multi-center retrospective study was performed to investigate if secondary polycythemia is associated with in-hospital mortality in COPD patients with low-risk PE.

Methods: We identified COPD patients with proven PE between October, 2005 and October, 2015. Patients in risk classes III–V on the basis of the PESI score were excluded. We extracted demographic, clinical and laboratory information at the time of admission from medical records. All subjects were followed until hospital discharge to identify all-cause mortality.

Results: We enrolled 629 consecutive patients with COPD and PE at low risk: 132 of them (21.0%) with and 497 (79.0%) without secondary polycythemia. Compared with those without polycythemia, the polycythemia group had significantly lower forced expiratory volume in one second (FEV_1) level (0.9±0.3 *vs.* 1.4±0.5, P=0.000), lower PaO_2 and SpO_2 as well as higher $PaCO_2$ (P=0.03, P=0.03 and P=0.000, respectively). COPD patients with polycythemia had a higher proportion of arrhythmia in electrocardiogram (ECG) (49.5% *vs.* 35.7%, P=0.02), a longer hospital duration time (15.3±10.1 *vs.* 9.7±9.1, P=0.001), a higher mechanical ventilation rate (noninvasive and invasive, 51.7% *vs.* 30.3%, P=0.04 and 31.0% *vs.* 7.9%, P=0.04, respectively), and a higher in-hospital mortality (12.1% *vs.* 6.6%, P=0.04). Multivariate logistic regression analysis revealed that polycythemia was associated with mortality in COPD patients with low-risk PE (adjusted OR 1.11; 95% CI, 1.04–1.66).

Conclusions: Polycythemia is an independent risk factor for all-cause in-hospital mortality in COPD patients with PE at low risk.

Keywords: Chronic obstructive pulmonary disease (COPD); pulmonary embolism (PE); polycythemia; pulmonary hypertension (PH); mortality

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Introduction

The morbidity and mortality associated with chronic obstructive pulmonary disease (COPD) is rising and is projected to become the third leading worldwide cause of death by 2020 (1,2). COPD is associated with an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE), particularly during exacerbations, and with an increased risk of mortality after PE (3,4). In COPD patients with PE, the 3-month mortality rate is twice compared to the reported 15% to 18% in general population (5); however, risk factors for mortality due to PE in patients with COPD are not well known, even in the COPD patients classified as low risk for PE. Endothelial dysfunction, coexistent pulmonary hypertension (PH), and in general low cardiorespiratory reserve, have been invoked as potential risk factors for mortality (6). Another important physiologic abnormality in COPD is the presence of polycythemia, a potential contributor to the development of PH and pulmonary endothelial dysfunction (7-9). We hypothesize that polycythemia is an independent contributing factor to mortality due to PE in patients with COPD, while controlling for other factors associated with PE related mortality. We tested this hypothesis using clinical data from a multi-center retrospective cohort study in a large population area of Sichuan province in southwestern China.

Methods

Specimens and subject populations

This multicenter, retrospective and administrative data based study was conducted at two largest tertiary university hospitals in Sichuan province serving much of southwest of China: West China Hospital of Sichuan University and Sichuan Provincial People's Hospital with total 7,777 in-patient beds.

Methods

We included all consecutive patients who were admitted in the two hospitals with a diagnosis of PE and COPD during the period of October, 2005 and October, 2015. PE was diagnosed by computerized tomography angiography (CTA). We used clinical and demographic variables to calculate a PESI score for all PE patients. PESI score calculations were performed using the standard PESI definition: low risk (class I and II, PESI score ≤85), moderate to high risk (class III–V, PESI score >85) (10,11). Subjects in risk classes III–V on the basis of the PESI score (>85) were excluded as clinical guidelines do not consider such patients in low risk category. A diagnosis of COPD was based on the Global Strategy for Diagnosis, Management, and Prevention of COPD (GOLD 2011) criteria of a post-bronchodilator forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ≤70% (2). Severity of COPD (COPD stage) was classified according to the Medical Research Council (mMRC) dyspnea score, FEV_1 predicted value ratio (FEV_1 % predicted) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 staging system (2). Patients with incidental findings of PE in CTA examinations (PE was diagnosed by CTA ordered incidentally within 24 hours of hospitalization) were also included.

Pulmonary CTA was performed on a 64-slice multi-detector CT scanner (Definition Flash, 120 kvp, Siemens, Erlangen, Germany) within 24 hours of admission. The diagnosis of PE was made when an intraluminal filling defect surrounded by a rim of intravascular contrast or total occlusion of the pulmonary arterial lumen was detected at any level of the pulmonary arteries (12). The anatomic location of the emboli was noted in the clinical record.

Spirometry was measured within the first 3 days of admission by trained technicians with MS PFT (VIASYS, US) spirometer, and was performed according to standards set by the American Thoracic Society/European Respiratory Society guidelines (13).

Exclusion criteria were patients in risk classes III-V on the basis of the PESI score (>85); primary polycythemia (i.e., polycythemia vera), prior diagnosis of PE already under treatment, known malignancies, paralysis & immobility (bed rest >48 h) (*Figure 1*).

Outcomes

The primary outcome was all-cause in-hospital mortality. To ascertain this, all subjects were followed until discharge and final disposition was confirmed with clinical records. To ascertain this, all subjects were reviewed and data extracted following a standard protocol by four researchers (L Guo, Z Xie, H Jiang and L Gao). Secondary outcomes included length of stay in hospital and frequency of noninvasive and invasive mechanical ventilation during the hospital stay.

Exposure

Polycythemia was defined as a hemoglobin (Hb) level ≥180 g/L

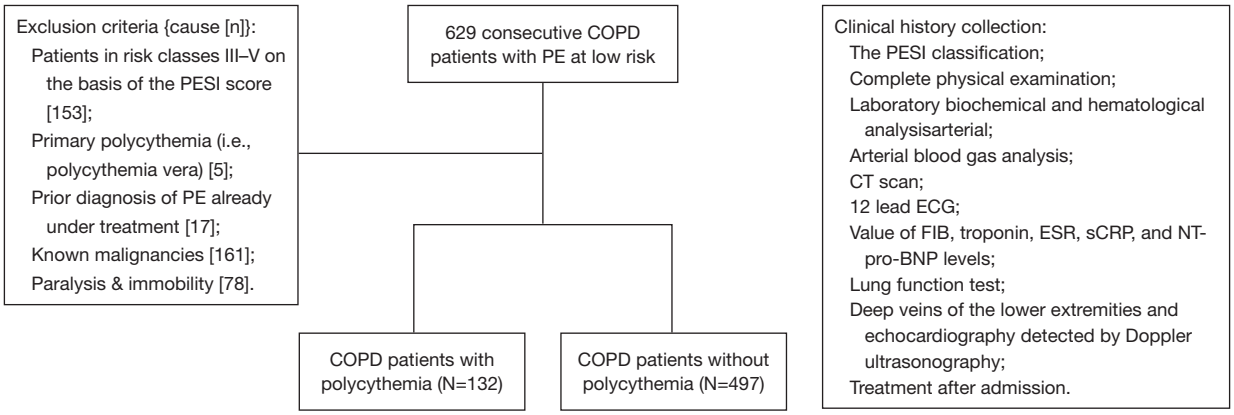

Figure 1 Flow chart of study design. COPD, chronic obstructive pulmonary disease.

in men, and ≥150 g/L in women. All blood analyses were performed in agreement with the "Recommendation on sampling, transport, and storage for the determination of the concentration of ionized calcium in whole blood, plasma, and serum" quality standards (14). Systematically, we recorded the results of blood samples drawn within 24 h of admission in every patient.

Covariates

Baseline characteristics included demographic and clinical data, including smoking history and COPD co-morbidities recorded with international classification of diseases (ICD)-10 codes.

Arterial blood gas (ABG) analysis was performed with a GEM Premier™ 3000 blood gas/electrolyte analyzer (GEM Premier 3000, USA). Laboratory biochemical variables were analyzed by automatic biochemical analyzer according to the same quality standards between the two hospitals (15). All laboratory measures were performed at admission. All electrocardiograms (ECGs) abnormal evidences were tracked for each patient by systematically searching for diagnosis with ICD-10 code and medical records.

Deep veins of the lower extremities and echocardiography detected by Doppler ultrasonography were collected simultaneously for every patient within 5 days of hospitalization by experienced sonographers with Color Doppler Ultrasound (iU22 Ultrasound System; PHILIPS, Netherlands and iE33 xMATRIX Echocardiography System, PHILIPS, Netherland, respectively). All the data and diagnoses were acquired following the standard guideline (16,17).

Estimation of systolic pulmonary arterial pressure (sPAP): the echocardiographic study of a patient with a suspected PH in our study was based on the peak velocity of the tricuspid regurgitation jet (TRV) by continuous-wave (CW) Doppler. We used the simplified Bernoulli equation to assess the TRV [peak pressure; $sPAP = 4 \times (TRV)^2 + RA\ v\text{-}wave \approx 4 \times (TRV)^2 + mean\ RAP$, where RA is right atrium and RAP is right atrial pressure] describes the relationship of TR and RVSP as a surrogate of sPAP in the absence of RV outflow tract (RVOT) obstruction, pulmonary valve stenosis, or PA stenosis (16). PH was diagnosed by echocardiography examination (TRV >2.8 m/s and sPAP >36 mmHg) (18). According to international standards of PH classification, patients were divided into three groups: normal group (sPAP <36 mmHg) the mild to moderate group (36≤ sPAP <70 mmHg) and the severe group (sPAP ≥70 mmHg) (19).

The patient was considered obese if the body mass index (BMI) was ≥30 kg/m² (20). Diagnosis of hypertension, diabetes mellitus, coronary artery disease, known heart failure or known cerebral infarction was based on medical records with compatible ICD-10 codes (21-25). Smoking history in the study included current or former smoking, and pack-years smoked.

Ethical considerations

All procedures were approved by the Research and Ethics Committee of Medicine in both hospitals (number/ID of the approval: 2009-42).

Statistical analyses

Baseline characteristics are reported as the mean and standard deviation for continuous variables and as

percentages for categorical variables. Differences in baseline characteristics between the two groups, based on the presence of polycythemia, of COPD patients were determined using the student "*t*-test" for continuous variable and the chi-square test for categorical variables. A P value <0.05 in 2-tailed tests was considered statistical significant. We analyzed the impact of polycythemia in mortality using multivariate models additionally adjusted for other variables known to influence COPD outcomes (gender, age, hospitalization/year, sPAP and co-morbidities) and secondary polycythemia (FEV_1, pO_2), based on their bivariate association with mortality. All the data was analyzed using the Statistical Package for the Social Sciences 16.0 packet program (SPSS Inc., Chicago, IL, USA).

Results

Demographics, clinical characteristics of the study population

We retrospectively enrolled a total of 1,043 consecutive patients with COPD and PE who were admitted to hospital during the study period. Among them, 414 met the exclusion criteria [cause (number)]: patients in risk classes III–V on the basis of the PESI score [161]; primary polycythemia [5]; prior diagnosis of PE already under treatment [17]; known malignancies [153]; paralysis & immobilized more than 48 hrs [78]. Thus, 629 patients with COPD and low-risk PE fulfilled the inclusion criteria and were finally included [60.5% males; age, 69.6±10.1 years (mean ± SD); FEV_1 % predicted, 57.9%±19.0% (mean ± SD)], in whom there were 132 with COPD and secondary polycythemia (21.0%) and 497 with COPD but no secondary polycythemia (79.0%) (*Figure 1*). Medical records showed 4 patients (3.0%) in polycythemia group and 24 (4.8%) patients in the group without polycythemia were sent to hospital with an initial diagnosis of acute exacerbation of COPD and were diagnosed incidentally of PE with the same complaints during their extended stay in hospital. There were no significant differences in age, gender and BMI (P=0.05, P=0.26 and P=0.09, respectively) as well as smoking pack-year (P=0.28) and history of COPD (P=0.77). A history of annual COPD-related hospitalizations was more frequent (2.4±1.0 *vs.* 1.3±0.8, P=0.000) among COPD with polycythemia. Patients with COPD were less likely to have symptomatic PE. However, COPD patients with polycythemia were more likely to report dyspnea compared to those without polycythemia. A lower FEV_1 level (0.93±0.3 *vs.* 1.4±0.5, P=0.000) and higher mMRC dyspnea scores (3.2±0.7 *vs.* 2.4±1.1, P=0.047) were observed in COPD cohort with polycythemia. Accordingly, more patients with polycythemia belonged to 2011 GOLD COPD stages C and D (more symptoms and high risks) (71.2% *vs.* 58.1%, P=0.01). Our results indicated a higher proportion of COPD patients with polycythemia led high-altitude living than those without polycythemia (25.8% *vs.* 17.3%, P=0.03). Patients with COPD were less likely to have symptomatic PE. However, COPD patients with polycythemia were more likely to report dyspnea compared with those without polycythemia. There were no difference in the frequency of COPD co-morbidities (including hypertension, diabetes mellitus, known heart failure, known cerebral infarction and DVT) observed between the groups with or without polycythemia (all P>0.05).

There was no difference in the initiation of anticoagulant therapy in both groups (1.6±2.2 and 1.8±2.1, respectively). The anticoagulant therapy wasn't initiated immediately at admission in cases with the high risk of bleeding with renal or liver dysfunction (53 patients), uncontrolled hypertension (44 patients), incidental findings of PE (28 patients) or failure to obtain consent from the patient or designated relative with power of attorney (31 patients). Anticoagulant therapy was initiated when their situation permitted.

The laboratory results demonstrated a higher proportion of arrhythmia on ECG (49.2% *vs.* 35.8%, P=0.04) and a higher level of troponin (1.6±4.0 *vs.* 0.5±1.3, P=0.01) among the COPD patients with polycythemia compared to the comparison cohort. The electrocardiographic abnormalities investigated were: (I) sinus tachycardia (>100 beats/min); (II) atrial arrhythmia; (III) ventricular arrhythmia; (IV) bundle branch block (complete or incomplete); and (V) atrioventricular block (multiple ECG abnormalities in some patients). ECG data showed that atrial arrhythmia was significantly more frequent in polycythemia group. The other laboratory findings, as levels of N-terminal pro-brain natriuretic peptide (BNP), fibrinogen, creatinine (Cr), total cholesterol (TC), total triglyceride (TG), low density lipoprotein (LDL) and C-reactive protein (sCRP) were similar in both groups (all P>0.05). Significantly lower levels of PaO_2 (9.0±2.3 *vs.* 12.0±7.4, P=0.03) and blood O_2 saturation (SpO_2) (88.1±5.9 *vs.* 93.4±7.2, P=0.03) as well as higher level of $PaCO_2$ (6.8±2.8 *vs.* 5.5±1.4, P=0.000) on ABG analyses were observed in polycythemia cohort than those in the other group (*Table 1*).

Table 1 Basic characteristics of the study population

Variable	Polycythemia	Without polycythemia	P value
Demographic and general clinical characteristics			
Numbers of patients (n, %)	132 (21.0)	497 (79.0)	
Age (ys, mean ± SD)	67.3±9.7	69.8±10.1	0.05
Male (n, %)	69 (52.3)	287 (57.7)	0.26
BMI (n, mean ± SD)	20.2±3.2	21.9±3.8	0.09
Smoking pack-year (n, mean ± SD)	57.9±77.3	58.2±54.1	0.28
Hospitalization rate/year (n, mean ± SD)	2.4±1.0	1.3±0.8	0.000#
History of COPD (yr, mean ± SD)	13.5±8.6	14.0±10.7	0.77
Initial clinical presentation (n, %)			
Cough, n (%)	101 (76.5)	385 (77.5)	0.82
Extremity swelling, n (%)	64 (48.5)	208 (41.2)	0.17
Dyspnea, n (%)	41 (31.1)	112 (22.5)	0.04#
Chest pain, n (%)	16 (12.1)	47 (9.5)	0.37
Fever, n (%)	8 (6.1)	43 (8.7)	0.33
Hemoptysis, n (%)	4 (3.0)	23 (4.6)	0.42
Fatigue, n (%)	7 (5.3)	15 (3.0)	0.32
Proportion of incidental PE, n (%)	4 (3.0)	24 (4.8)	0.37
High-altitude living, n (%)	34 (25.8)	86 (17.3)	0.03#
Lung function			
FEV_1 (L, mean ± SD)	0.9±0.3	1.4±0.5	0.000#
2011 GOLD COPD stage			
C + D, n (%)	94 (71.2)	289 (58.1)	0.01#
mMRC dyspnea score (N, mean ± SD)	3.2±0.7	2.4±1.1	0.047#
Comorbidities			
Hypertension, n (%)	34 (25.8)	159 (32.0)	0.17
Diabetes mellitus, n (%)	42 (31.8)	129 (26.0)	0.18
Coronary artery disease, n (%)	29 (22.0)	85 (17.1)	0.20
Known heart failure, n (%)	40 (30.3)	184 (37.0)	0.15
Known cerebral infarction, n (%)	29 (22.0)	95 (19.1)	0.47
Present DVT, n (%)	85 (64.6)	318 (64.0)	0.93
Laboratory findings	132	497	
Arrhythmia in ECG, n (%)	65 (49.2)	178 (35.8)	0.04#
Sinus tachycardia	28 (21.2)	82 (16.5)	0.21
Atrial arrhythmia	25 (18.9)	61 (12.3)	0.048#
Ventricular arrhythmia	9 (6.8)	18 (3.6)	0.11
Bundle branch block	6 (4.5)	23 (4.6)	0.97
Atrioventricular block	2 (1.5)	5 (1.0)	0.62

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Polycythemia	Without polycythemia	P value
Troponin (ng/mL, mean ± SD)	1.6±4.0	0.5±1.3	0.01#
BNP (ng/mL, mean ± SD)	460.8±777.4	430.4±756.7	0.74
Fibriogen (g/L, mean ± SD)	3.5±1.4	3.8±1.6	0.21
Cr (μmol/L, mean ± SD)	71.7±25.8	85.0±87.6	0.15
TC (mmol/L, mean ± SD)	4.2±1.2	3.8±1.1	0.68
TG (mmol/L, mean ± SD)	1.2±0.7	1.1±0.5	0.47
LDL (mmol/L, mean ± SD)	2.5±0.9	2.3±0.8	0.07
sCRP (mm/L, mean ± SD)	43.8±50.6	35.7±42.0	0.27
Arterial blood gas analysis			
pH (N, mean ± SD)	7.4±0.1	7.4±0.1	0.62
PO_2 (kPa, mean ± SD)	9.0±2.3	12.0±7.4	0.03#
pCO_2 (kPa, mean ± SD)	6.8±2.8	5.5±1.4	0.000#

#, significance at P<0.05. BMI, body mass index; COPD, chronic obstructive pulmonary disease; PE, pulmonary embolism; DVT, deep venous thrombosis; ECG, electrocardiogram; BNP, brain natriuretic peptide; Cr, creatinine; TC, total cholesterol; TG, total triglyceride; LDL, low density lipoprotein; sCRP, C-reactive protein.

Table 2 Imaging findings

Patients variable	Polycythemia	Without polycythemia	P value
Localization of pulmonary thrombi			
Central, n (%)	105 (79.5)	336 (67.6)	0.01#
Bilateral, n (%)	105 (79.5)	341 (68.6)	0.01#
Doppler ultrasonography			
RV (mm, mean ± SD)	24.1±4.8	23.0±4.7	0.10
LV (mm, mean ± SD)	45.2±8.0	44.0±6.5	0.25
TR (mm, mean ± SD)	3.3±0.6	3.0±0.5	0.000#
sPAP (mmHg, mean ± SD)	48.7±16.1	39.3±3.0	0.000#
Normal group, n (%)	16 (12.1)	56 (11.3)	0.78
Mild to moderate group, n (%)	95 (72.0)	397 (80.0)	0.05
Severe group, n (%)	21 (15.9)	44 (8.9)	0.02#

#, significance at P<0.05. RV, right ventricular; LV, left ventricular; sPAP, systolic pulmonary arterial pressure.

Imaging findings

Central PE (i.e., main and segmental pulmonary arteries) on pulmonary CTA was more common (79.5% *vs.* 67.6%, P=0.01) while bilateral PE were more prevalent (79.5% *vs.* 68.6%, P=0.01) among those with polycythemia. In addition, higher velocity of TR (3.3±0.6 *vs.* 3.0±0.5, P=0.000) and higher level of sPAP (48.7±16.1 *vs.* 39.3±3.0, P=0.000) were also observed via Doppler ultrasonography in the same population. Non-significant differences of the diameters of right ventricular (RV) and left ventricular (LV) were found between groups (P>0.05).

There were 16 (12.1%), 95 (72.0%) and 21 (15.9%) patients classified in the normal, mild to moderate and severe group of PH respectively among patients with polycythemia. Correspondingly, there were 56 (11.3%), 397 (80.0%) and 44 (8.9%) patients classified in the normal, mild to moderate and severe group of PH respectively among patients without polycythemia. More patients with severe PH were in the polycythemia group (P=0.02) (*Table 2*).

Hospital treatment and outcomes by polycythemia group

There was no significant difference in initiation of anticoagulant therapy after admission between groups (1.6±2.2 *vs.* 1.8±2.1, P=0.42). COPD patients with polycythemia had a longer hospital stay (15.3±10.1 *vs.* 9.7±9.1, P=0.001), a higher mechanical ventilation rate (noninvasive and invasive, 53.8% *vs.* 43.9%, P=0.04 and 33.3% *vs.* 22.9%, P=0.01, respectively), and a higher in-hospital mortality (12.1% *vs.* 6.6%, P=0.04) (*Table 3*).

Table 3 Hospital treatment and outcomes by polycythemia group

Patients variable	Polycythemia	Without polycythemia	P value
Starting anticoagulant therapy after admission (d, mean ± SD)	1.6±2.2	1.8±2.1	0.42
Duration of hospitalization (d, mean ± SD)	15.3±10.1	9.7±9.1	0.001#
Noninvasive ventilation rate, n (%)	71 (53.8)	218 (43.9)	0.04#
Intubation rate, n (%)	44 (33.3)	114 (22.9)	0.01#
Mortality rate, n (%)	16 (12.1)	33 (6.6)	0.04#

#, significance at P<0.05.

Table 4 Sensitivity, specificity, PPV, and NPV for mortality in male patients

Male	Death (n)	Survival (n)	Total (n)
Polycythemia (n)	28	41	69
Without polycythemia (n)	4	283	287
Total (n)	32	324	356

PPV, positive predictive value; NPV, negative predictive value.

Table 5 Sensitivity, specificity, PPV, and NPV for mortality in female patients

Female	Death (n)	Survival (n)	Total (n)
Polycythemia (n)	14	49	63
Without polycythemia (n)	3	207	210
Total (n)	17	256	273

PPV, positive predictive value; NPV, negative predictive value.

The receiver-operating characteristic (ROC) curve to evaluate Hb level for mortality

We performed the ROC curve to evaluate Hb level for mortality (male: AUC 0.70, 95 % CI, 0.62–0.79; female: AUC 0.74, 95% CI, 0.68–0.79). The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for mortality were 87.5% (28/32), 87.3% (283/324), 40.6% (28/69), 98.6% (283/287) in male and 82.4% (14/17), 80.9% (207/256), 22.2% (14/63), 98.6% (207/210) in female respectively (*Tables 4*,*5*).

Associations between polycythemia and mortality

Polycythemia was associated with mortality as determined on bivariate analysis (OR 1.05, 95% CI, 1.02–1.17). This association was maintained in models additionally adjusted for demographics (age, gender and hospitalization/year) and co-morbidities (diabetes mellitus and coronary artery disease) (OR 1.05, 95% CI, 1.01–1.13), descriptors of lung function and ABG (FEV_1, PaO_2) (OR 1.06, 95% CI, 1.01–1.12), and markers of RV strain (RV, sPAP) (OR 1.11, 95% CI, 1.04–1.66) (*Tables 6*,*7*).

Discussion

A recent large meta-analysis confirmed the role of the PESI score of I–II in the identification of PE patients at a low risk of mortality (26). However, some of those patients with COPD may still have an elevated risk of clinical deterioration and in-hospital death. Thus, a careful stratification of patients with acute PE seems to be particularly important for clinicians to guide the initial management and to protect patients against the hazard to be treated with an unacceptable level of risk, or to undergo unnecessary and potentially dangerous treatment.

Although data to support a key role for secondary polycythemia with increased the risk of PE is scant, we observed that PE with polycythemia was associated with increased all-cause in-hospital mortality rate in this multicenter, retrospective cohort study. Our results are similar with Weber *et al.* who observed increased mortality due to the presence of polycythemia in 1913 (27).

Medical records showed 4 patients (3.0%) in polycythemia group and 24 (4.8%) patients in the other group were sent to hospital with an initial diagnosis of acute exacerbation of COPD and an incidental diagnosis of PE and with identical complaints during their extended stay in hospital. It was remarkable to observe that no-specific symptoms of PE were described in most of the cases, thus

Table 6 Bivariate analysis associated with mortality

Patients variable	OR	95% CI	P value
Demographic and general clinical characteristics			
Age	1.36	1.07–2.16	0.03#
Male gender	1.11	1.18–4.12	0.02#
BMI	0.59	0.40–2.58	0.09
Smoking pack-year	1.08	0.07–1.53	0.07
Hospitalization rate/year	1.13	1.06–2.49	0.02#
History of COPD	1.02	0.36–1.02	0.33
High-altitude living	2.04	0.71–2.86	0.64
Lung function			
FEV_1 (L, mean ± SD)	0.02	0.03–0.14	0.000#
mMRC dyspnea score (N, mean ± SD)	0.53	0.23–1.24	0.14
Laboratory findings			
Troponin	1.92	0.52–1.66	0.58
BNP	1.03	0.03–1.16	0.40
Fibrinogen	1.15	0.71–1.86	0.57
TG	1.21	0.05–1.23	0.55
LDL	1.01	0.02–1.37	0.62
sCRP	3.15	0.71–4.82	0.51
Arterial blood gas analysis			
pH	0.81	0.19–1.50	0.06
PO_2	0.40	0.24–0.67	0.000#
pCO_2	1.29	1.18–6.06	0.008#
Doppler ultrasonography			
RV	1.38	1.06–2.02	0.04#
LV	1.14	0.81–1.25	0.24
PASP	1.08	1.01–1.48	0.03#
Co-morbidities			
Hypertension	1.08	0.08–1.17	0.28
Diabetes mellitus	1.13	1.08–2.10	0.04#
Coronary artery disease	1.69	1.02–2.06	0.03#
Known heart failure	1.12	0.76–1.27	0.63
Known cerebral infarction	1.01	0.84–1.98	0.06

#, significance at P<0.1. BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; mMRC, the Medical Research Council; BNP, brain natriuretic peptide; TG, total triglyceride; LDL, low density lipoprotein; sCRP, C-reactive protein; RV, right ventricular; LV, left ventricular.

supporting the concept that clinical suspicion of PE in acute exacerbation of COPD is particularly difficult, for clinical symptoms of COPD may mimic PE symptoms. Most of patients with PE were hospitalized for an episode of exacerbation of COPD and it always took 2 or 3 days to make a definite diagnosis of PE.

In this study, we also observed that polycythemia in COPD patients was associated with more frequent re-hospitalization per year, more frequent rate of arrhythmia, a longer hospital stay and increased rate of mechanical ventilation (including noninvasive), compared with COPD patients without polycythemia. Overall, polycythemia could be an indicator of worse outcome in COPD patients with PE which warrants lower threshold for the clinical suspicion of PE in this group.

Lippmann and Fein (28) suggested that the diagnosis of PE in patients with COPD should be suspected in patients with precipitous worsening of their dyspnea that is unresponsive to bronchodilator therapy. The diagnosis is supported by a reduction in the $PaCO_2$ in a previously hypercapnic patient (28). In our retrospective study, it was uncertain that patients were previously hyoxemia and hypercapnic or not. However, we found significantly lower PaO_2 levels as well as a higher $PaCO_2$ levels on ABG analyses in COPD patients with polycythemia. There is good evidence to suggest that hypoxemia has a strong association with advanced COPD. Furthermore, it now seems clear that tissue hypoxia is a key player in many of the maladaptive processes and extra-pulmonary co-morbidities that characterize COPD (29,30). On the other hand, COPD has long been recognized as an important cause of secondary polycythemia due to hypoxemia. Several studies postulate hypercapnia as an independent predictor for survival and in-hospital deaths in the COPD patients (31-33). The finding of an elevation in the $PaCO_2$ in the presence of PE has been reported (34). It may reflect an inability to further increase minute ventilation in the face of a sudden increase in dead space ventilation imposed by the embolus (35). The finding of an elevation in the $PaCO_2$ in the presence of PE has been reported (34). It may reflect an inability to further increase minute ventilation in the face of a sudden increase in dead space ventilation imposed by the embolus (35). Polycythemia, which increases blood viscosity, may increase hypoxemia and hypercapnic risks in COPD patients. Depending on the PaO_2 and $PaCO_2$ levels at admission, these physiological differences may affect survival in the COPD patient group being treated with mechanical ventilation due to respiratory failure, indicating that polycythemia can attenuate lung

Table 7 Associations between polycythemia and mortality[#]

Variable	Model 1		Model 2		Model 3		Model 4	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Polycythemia	1.05	1.02–1.17	1.05	1.01–1.13	1.06	1.01–1.12	1.11	1.04–1.66
Demographic and co-morbidities								
Age			1.13	0.05–2.24	1.12	0.05–2.37	1.10	0.97–1.09
Male			1.62	0.73–2.63	1.54	0.63–2.07	1.22	0.28–2.21
Hospitalization rate/year			1.18	0.67–2.01	1.19	0.70–2.10	1.14	0.91–2.66
Diabetes mellitus			1.28	0.53–2.06	1.05	0.41–1.79	1.22	0.82–1.67
Coronary artery disease			1.66	1.32–2.62	1.72	0.99–2.95	1.45	0.79–1.74
Lung function								
FEV_1 (per 1 L increment)					0.82	0.03–1.54	0.74	0.04–1.86
Arterial blood gas analysis								
PaO_2 (per 1 kPa increment)					0.81	0.59–0.98	0.69	0.31–1.14
$PaCO_2$ (per 1 kPa increment)					1.2	0.82–1.67	1.2	0.79–1.74
Echocardiography								
RV (per 1 mm increment)							1.03	0.04–1.32
PASP (per 1 mmHg increment)							1.11	0.05–1.40

[#], all entries represent odds ratios (ORs) and its 95% CI. Model 1, bivariate; model 2, model 1 additionally adjusted for demographics and co-morbidities; model 3, model 2 additionally adjusted for descriptors of lung function and arterial blood gas; model 4, model 3 additionally adjusted for markers of right ventricular strain. FEV_1, forced expiratory volume in one second; RV, right ventricular.

function via various mechanisms causing worse prognosis.

The most striking difference in our study was that higher proportion of patients with polycythemia were in advanced COPD stage (2011 GOLD COPD stages C and D) with more severe symptomatic dyspnea, higher mMRC dyspnea score) and lower FEV_1 level, which suggests that patients with specific high Hb response to hypoxia and deteriorated lung function may be associated with increased mortality and poor quality of life compared with the general COPD population (36,37). This individualized response to infection or another exacerbation triggers may identify patients more likely to have a pro-inflammatory response to subsequent exacerbations and explain the observed increase in in-hospital mortality, which is significant than previously recognized.

Our data demonstrated centrally and bilaterally located emboli were more common (79.8% and 81.8%, respectively) in COPD patients with polycythemia in our study, which explains the poor outcomes, as the mortality rate remains high in patients with centrally located PE (38).

Although mild to moderate level of PH is a common consequence of COPD, especially in the COPD patients with PE (39,40), we observed more severe PH in the population with polycythemia. Our data supports previous studies which showed the contribution of polycythemia to PH (41,42). One possibility is that the severity of pulmonary vascular remodeling may increase the effect of Hb, thereby worsening PH when pulmonary vascular compliance is decreased by vascular remodeling (41,42). Moreover, a previous study demonstrated that repetitive hemodilution in patients with COPD can improve PH by reducing blood viscosity (43). Increased viscosity is therefore another contributing factor in secondary PH in COPD patients (43). Since PH has an independent prognostic impact on survival (44), the prognosis is poorer in the COPD patients with polycythemia. However, we didn't following up these patients, so the sPAP in our study could probably reflected the situation at acute period.

ECG features showed sinus tachycardia is the most common ECG abnormality in both groups. Moreover, arrhythmia especially atrial arrhythmia was significantly frequent in polycythemia group. It has previously been observed in previous studies that atrial arrhythmia could be an independent predictor of increased mortality in patients with PE (45). On the other hand, COPD is independently associated with an increased burden of cardiovascular disease, and specific ECG abnormalities and cardiac arrhythmias seem to have a significant effect on cardiovascular prognosis of COPD patients (46). Screening for arrhythmia may still be of importance due to its clinical impact on a poor prognosis in this population.

In this study, we demonstrated that COPD patients living in high-altitude area tend to contribute to the development of secondary polycythemia. Red blood cell counts and Hb concentrations increase to maintain oxygen transport in the hypobaric environment at high altitudes which are regarded risk factors for thrombosis as well (47). Early detection and treatment of PE in this population should help decrease the morbidity and mortality significantly.

Co-morbid factors associated with PE in the study including age, gender, obesity, smoking, hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, known heart failure, known cerebral infarction, and DVT were recorded at the baseline as potential confounding factors (48-51). However, our study did not reveal significant relationship between these confounders with in-hospital mortality.

It must be emphasized that multivariate logistic regression analysis in our study showed that polycythemia is an independent risk factor related to mortality in COPD patients with PE. It is also suggested that decreasing PaO_2 and FEV_1 as well as increasing $PaCO_2$, RV and PH may have a significant effect on the poor outcome. There is a trend towards earlier detection and initiating earlier therapeutic interventions in COPD patients to prevent the development of polycythemia. It is also important to note the importance of monitoring lung function in the management of this cohort. Therefore, we aimed to provide an opportunity to identify high risk patients with poor prognosis in COPD population.

Our study had following limitations. This was a retrospective and administrative data based study, therefore, selection bias could be present. The COPD patients with PE were hospitalized and were mostly in critical condition and could not tolerate right heart catheterization. As pulmonary hyperinflation is frequently seen in COPD patients, the likelihood of estimating PASP would be lower in patients with marked pulmonary hyperinflation via echocardiography. In addition, the prevalence and the characteristics of COPD patients with polycythemia have significant geographical diversity. A study with a larger cohort from geographical areas of different altitudes should be undertaken in the future.

In conclusion, polycythemia is an independent risk factor for all-cause in-hospital mortality in COPD patients with PE at low risk and may require a lower threshold for evaluating these patients for PE as they present with severe hypoxia, higher PH, worse pulmonary functions and higher frequency of centrally located PE.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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