Risk factors of acute cardiovascular events following acute exacerbation period for patients with COPD: a nested case-control study

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Abstract

Background For patients with chronic obstructive pulmonary disease (COPD), the incidence of acute cardiovascular events (CVEs) increases during acute exacerbation (AE) period, causing increased inpatient mortality. Thus, we try to identify risk factors of acute CVEs in patients with AECOPD via a nested case-control study.

Methods A total of 496 cases hospitalized for AECOPD were included into analysis, and followed-up for 6 months after discharge. Acute CVEs in the AE period were defined as the new or worsening acute coronary syndrome (ACS), arrhythmia, left ventricular disfunction (LVD). Risk factors were selected from several variables, including baseline characteristics and treatments in the stable period as well as symptoms, laboratory tests, complications and treatments in the AE period.

Results Thirty cases (6.05%) had acute CVEs, including 2 with ACS, 13 with LVD, 19 with arrhythmia, and 4 deaths, with significantly increased mortality risk (P=0.001, OR=5.81). Moreover, patients who have had CVEs were inclined to have re-exacerbation within 3 months. Multivariate analysis showed that previous LVD history (P=0.004, OR=5.06), 20% increase in heart rate (HR) (P=0.003, OR= 10.19), electrolyte disturbance (P=0.01, OR= 4.24) and diuretics (P=0.002, OR = 6.37) were independent risk factors. In addition, usage of theophylline, fluoroquinolone and inhaled beta agonists in the AE period were not statistically associated with acute CVEs.

Conclusions Our study preliminarily indicated that patients hospitalized for AECOPD with previous LVD history or increased HR need close observation and diuretics should be cautiously used with electrolyte monitoring. These findings needs to be confirmed in a large cohort.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversibly airflow limitation and progressive decline of lung function, ranking third in the death causes worldwide. [1, 2] Among many contributors to mortality in patients with COPD, cardiovascular disease (CVD) was one of the top three leading causes of death, following the respiratory infection and respiratory failure. [3–5] Moreover, prior CVD could additionally increase risks of death in elderly COPD patients with pneumonia. [6]

Patients with COPD tend to have concurrent CVDs with the prevalence of 28–70%, [7] and hyperlipidemia (45%) and hypertension (43%) were most common cardiovascular comorbidities. [8] As for acute cardiovascular events (CVEs), increased risks of acute coronary syndrome (ACS) [9], arrhythmia [7] and sudden cardiac death [10] were also reported for patients with COPD. A large cohort study demonstrated that the prevalence of heart failure among patients with COPD significantly increased, further leading to escalated all-cause mortality. [11] During the acute exacerbation (AE) period, aggravated hypoxia and systemic inflammation are precipitating factors of acute CVEs, especially for high-risk population. [10, 12, 13] Therefore, clinicians should be vigilant for early acute CVEs following AECOPD and identify risk

factors, especially for potentially-inappropriate medication. However, the knowledge of risk factors of CVEs in patients with AECOPD is still incomplete.

Traditional risk factors of CVDs might have warning effects, including previous history, hypertension, diabetes, hyperlipidemia and hyperuricemia. In addition, serious side effects of some drugs are chief culprits of CVEs, such as theophylline [14] and widely-concerned fluoroquinolones [15]. Relationship between inhaled long-acting bronchodilators and CVDs is still highly debated, for their pharmacological mechanisms are contradictory to therapeutics of cardiac remodeling and heart failure. [14] In patients with COPD, new initiation of inhaled bronchodilators was related to short-term elevated severe cardiovascular risk, [16] and adding a second bronchodilators to the previous monotherapy also slightly increased the risk of heart failure in one year. [17] Whereas, dual bronchodilators were proved to improve left ventricular filling by reducing lung hyperinflation. [18]

Hence, we performed a nested case-control study in a prospective COPD cohort in Shanghai, with the aim of screening the predictive factors of acute CVEs following the onset of AECOPD.

Methods

Patient recruitment and data collection

Between January 2015 and July 2017, we recruited patients with AECOPD hospitalized in department of pulmonary medicine of Shanghai Zhongshan Hospital and Shanghai Putuo District People's Hospital into our prospective cohort.

At the timepoint of admission, patients with clearly recorded COPD history were interviewed by two separate pulmonologists, to evaluate whether their deteriorated respiratory symptoms were categorized into AECOPD. Deterioration cases induced by the following coexisted diseases were removed, including asthma, bronchiectasis, congestive heart failure, pulmonary embolism, pleuritis, restrictive lung disease and pneumothorax. Baseline information and conditions in the stable period were asked and recorded at admission, consisting of demographic characteristics, COPD-associated evaluation (risk factors, lung function, assessment scales and previous AE numbers), COPD-associated treatments in stable period (inhaled agents, oral drugs, assistive breathing and vaccination) and comorbidities (common CVDs, other respiratory diseases and other common diseases). As for assessment scales, modified Medical Research Council (mMRC) dyspnea scale [19] and COPD assessment test (CAT) [20] were used to stratify severity of dyspnea and measure COPD's effects on daily life, respectively.

Diagnosis and treatment for each patient in the hospitalization period was carried out according to personal conditions and documents of *Global Strategy for Prevention, Diagnosis and Management of COPD* (GOLD). Detailed examination and therapeutics in the AE period were recorded, including new or worsening manifestations, vital signs at admission, laboratory tests (blood routine examination, blood biochemistry, coagulation tests, arterial blood gas analysis, etc.), sputum culture, computed tomography, assistive breathing and drug usage (antibiotics, inhaled bronchodilators, inhaled or systemic steroids and

others). In addition, we also collected information of precipitating factors and emerging or worsened complications (pneumonia, PE, pneumothorax, acute coronary syndrome [ACS], arrhythmia, left ventricular dysfunction [LVD] and others).

At the timepoint of 1, 3 and 6 month after discharge, patients were followed up either by outpatient department visit or by telephone, to prospectively collect the information of recurrent acute exacerbation (re-AE) and survival.

Electrolyte disturbance was defined when electrolytes (including sodium, potassium, calcium, calcium, phosphorus and magnesium) were not within the normal range at the first examination on admission. Diuretics was composed of the following types: torasemide, spironolactone and furosemide. We also extracted the initiation dates, types and doses of diuretics. Theophylline was composed of the following types: aminophylline, doxophylline and diprophylline.

Outcome

Primary outcome was CVEs in the AE period, which was composed of the emerging or worsening ACS, LVD and arrhythmia. The clinical progress notes of CVE cases, the event time, symptoms and treatments were recorded and carefully reviewed to determine the chronological sequence of diuretics, electrolyte disturbance, and CVEs. Secondary outcomes were defined as length of stay in hospital, mortality in hospital and at 1, 3 and 6 months, and re-AE at 1, 3 and 6 months. Re-AE was defined as the new worsening of respiratory symptoms lasting for over 2 days, which required extra medical intervention. [2]

Statistical analysis

Categorical variables were presented as numbers (%) and compared by Chi-square test or Fisher's exact test for univariate analysis. Continuous variables were described by median (interquartile range [IQR]) and compared by Student's t test or Mann-Whitney U test for univariate analysis. Odds ratio (OR) and corresponding confidence intervals of 95% (95%CI) were used to estimate the association of variables and outcomes. In multivariable analysis, binary logistic regression model with method of Backward LR was used to identify independent predictive factors of acute CVEs in AECOPD patients. Variables with $P < 0.001$ in univariate analysis were included into multivariable analysis.

From the conservative point of view, we managed missing data with the following procedure: firstly, patients with many missing variables were excluded; then, variables with missing number ≥ 5% were removed; thirdly, variables with missing number < 5% were supplemented using negative value. Statistical analysis was performed using IBM SPSS statistics 23 (SPSS Inc, Chicago, IL), and statistical graph was generated with GraphPad Prism 6 (GraphPad Software, CA, USA). The statistical significance level was set as a two-tailed $P < 0.05$.

Result

Baseline characteristics between two groups

Between January, 2015 and July, 2017, we collected 514 AECOPD cases in two hospitals and included 496 cases into analysis after excluding those without the records of acute CVEs in hospitalization. (Fig. 1) A total of 30 cases (6.05%) had concomitant acute CVEs (ACS, n = 2; arrhythmia, n = 19; LVD, n = 13), and 4 cases died in hospital. At the timepoint of 1 month after discharge, 11 patients were lost to follow up.

As the Table 1 showed, acute CVEs group was older than non-CVEs group ($P = 0.027$). Interestingly, senior females were more susceptible to acute CVEs in the AECOPD period ($P = 0.037$, OR = 2.35, 95% CI = 1.03–5.33). As for severity of COPD, two group did not significantly differ in the spirometric grade, symptoms and numbers of previous 1-year AE. Other coexisted respiratory diseases were not associated with acute CVEs. Whereas, prior cardiovascular diseases were strong predictors of acute CVEs in AECOPD, such as coronary heart disease ($P = 0.016$, OR = 2.82, 95% CI = 1.18–6.75) and left heart insufficiency ($P < 0.001$, OR = 6.42, 95% CI = 2.50-16.48). When defined as total cholesterol > 5.2 mmol/l, hyperlipidemia was not associated with increased risk of acute CVEs. Regular usage of inhaled agents in the stable period was a protective factor, especially for the combination of inhaled corticosteroid (ICS) and long-acting beta agonist (LABA) ($P = 0.027$, OR = 0.34, 95% CI = 0.12–0.92).

Table 1
Baseline Characteristics and Cardiovascular Risk Factors of Study Population

Category	Measurements	Acute CVEs group (n = 30)	No CVEs group (n = 466)	*P* value
Basic Information	**Age (year)**	82 (77–84)	78 (68–84)	**0.025**
	Male	21 (70.0%)	394 (84.5%)	**0.037**
	BMI	22.8 (20.0-24.2) (n = 15)	21.7 (20.2–25.4) (n = 314)	NS
	Smoking history (yes or no)	21 (70.0%)	378 (81.1%)	NS
	Smoking history (pack*year)	43.5 (31.8–57.5) (n = 12)	46.0 (34.3–60.0) (n = 192)	NS
COPD severity	FEV_1 (% predicted)	39.7 ± 12.4 (n = 15)	39.0 ± 14.2 (n = 300)	NS
	GOLD grade I	0 (0%)	1 (0.3%)	NS
	GOLD grade II	2 (13.3%)	66 (22.0%)	
	GOLD grade III	6 (40.0%)	144 (48.0%)	
	GOLD grade IV	5 (33.3%)	89 (29.7%)	
	mMRC score	2.65 ± 0.79 (n = 17)	2.57 ± 0.71 (n = 324)	NS
	CAT score	23.5 (12.3–26.8) (n = 16)	22.0 (15.0–28.0) (n = 319)	NS
Cardiovascular risk factors	Hypertension	7/22 (31.8%)	169/380 (44.5%)	NS
	Diabetes	6/22 (27.3%)	50/380 (13.2%)	**0.063**
	Hyperlipemia [a]	0/16 (0%)	14/333 (4.2%)	NS
	Coronary heart disease	10/22 (45.5%)	86/377 (22.8%)	**0.016**
	Cerebrovascular disease	2/21 (9.5%)	18/363 (5.0%)	NS
	Left heart insufficiency	8/22 (36.4%)	31/379 (8.2%)	**< 0.001**
Other respiratory diseases	Asthma	1/22 (4.5%)	3/377 (0.8%)	NS
	Bronchiectasis	5/22 (22.7%)	60/379 (15.8%)	NS
	Interstitial lung changes	2/19 (10.5%)	26/341 (7.6%)	NS
	Lung cancer	0/22 (0%)	8/379 (2.1%)	NS

	Ex-tuberculosis	2/22 (9.1%)	94/379 (24.8%)	NS
COPD-related treatment in stable period	Regular LAMA	6/24 (25.0%)	137/390 (35.1%)	NS
	Regular ICS/LABA	5/24 (20.8%)	170/388 (43.8%)	**0.027**
	Regular ICS/LABA/LAMA	2/24 (8.3%)	94/387 (24.3%)	NS
	Regular theophylline	5/24 (20.8%)	97/384 (25.3%)	NS
	Oxygen therapy	10/24 (41.7%)	167/388 (43.0%)	NS
	Noninvasive mechanical ventilation	3/23 (13.0%)	40/372 (10.8%)	NS
Pre-study exacerbations in 12 months	Total numbers	2.53 ± 2.83 (n = 17)	2.60 ± 2.15 (n = 337)	NS
	Hospitalization numbers	1.53 ± 0.51 (n = 17)	1.27 ± 0.54 (n = 335)	0.062

Acute CVEs were associated with poor outcomes in AECOPD patients

In comparison with non-CVEs group, increased mortality risk in hospital was observed in the acute CVEs group with the constituent ratio of 13.3% versus 2.6%, (P = 0.001, OR = 5.81, 95% CI = 1.75–19.26). (Table 2) Moreover, patients with acute CVEs had longer hospital stay and much more frequent re-exacerbation within 3 months.

Table 2
Clinical Outcomes Between Acute CVEs Group and Normal Group

Outcomes	Acute CVEs group (n = 30)	No CVEs group (n = 466)	*P* value	Odds ratio	95% CI
Hospital mortality	4/30 (13.3%)	12/466 (2.6%)	0.001	5.821	1.75 to 19.30
ICU admission	2/30 (6.7%)	26/466 (5.6%)	NS		
Hospital LOS (d)	14 (12–18)	13 (10–15)	0.022		
Re-AE at 1month	8/26 (30.8%)	64/443 (14.5%)	0.025	2.632	1.10 to 6.31
Accumulative death at 1 month	4/30 (13.3%)	15/455 (3.3%)	0.006	4.513	1.40 to 14.57
Re-AE at 3month	14/26 (53.8%)	138/440 (31.4%)	0.018	2.553	1.15 to 5.67
Accumulative death at 3 month	6/30 (20%)	20/455 (4.4%)	< 0.001	5.438	1.99 to 14.79
Re-AE at 6month	15/24 (62.5%)	195/435 (44.8%)	NS		
Accumulative death at 6 month	6/30 (20%)	25/455 (5.5%)	0.002	4.30	1.61 to 11.47

Risk factors of acute CVEs identified by the univariate analysis

Common respiratory symptoms were not indicators of acute CVEs, such as cough, expectoration, hemoptysis, shortness of breath, chest pain, etc. Fever, chill and cyanosis were also not related to acute CVEs. As Table 3 showed, abnormal escalation of heart rate and new or worsening edema of both lower limbs indicated the subsequent cardiac deterioration.

Table 3
Other Cardiovascular Risk Factors in the Univariate Analysis

Category	Variables	Acute CVEs group (n = 30)	No CVEs group (n = 466)	*P* value	Odd ratio	95% CI
Symptoms and signs	palpitation	2/20 (10.0%)	9/388 (2.3%)	0.039	4.68	0.94 to 23.27
	20% increase in HR	5/20 (25.0%)	11/386 (2.8%)	**< 0.001**	11.36	3.50 to 36.86
	Both lower limb edema	10/20 (50.0%)	70/389 (18.0%)	**< 0.001**	4.56	1.83 to 11.37
	Disturbance of consciousness	4/20 (20.0%)	19/387 (4.9%)	**0.004**	4.84	1.48 to 15.90
Laboratory tests	Neutrophil (%)	80.85 (73.18–86.05)	75.50 (67.55–83.50)	0.035		
	≥ 80	16/30 (53.3%)	165/466 (35.4%)	0.048	2.09	0.99 to 4.38
	CRP (mg/L) (n = 478)	33.4 (12.45–68.55)	19.2 (4.95–61.1)	NS		
	≥ 10	24/29 (82.8%)	280/449 (62.4%)	0.028	2.90	1.09 to 7.74
	Urea nitrogen (mmol/L)	6.80 (4.55–9.88)	5.50 (4.30–7.10)	0.031		
	≥ 7.5	14/30 (46.7%)	102/459 (22.2%)	**0.002**	3.06	1.45 to 6.49
	cTnT (ng/mL) (n = 333)	0.02 (0.01–0.03)	0.01 (0-0.02)	0.054		
	> 0.03	6/28 (21.4%)	39/304 (12.8%)	NS		
	LDH (U/L)	316 (198–404)	208 (181–257)	**0.002**		
	> 245	16/25 (64.0%)	120/413 (29.1%)	**< 0.001**	4.34	1.87 to 10.10

Category	Variables	Acute CVEs group (n = 30)	No CVEs group (n = 466)	*P* value	Odd ratio	95% CI
	NT-proBNP (pg/ml) (n = 218)	993 (268–1875)	296 (139–1070)	0.021		
	≥ 300	13/17 (76.5%)	100/201 (49.8%)	0.043		
	D-dimer (ug/L)	0.77 (0.43–1.21)	0.52 (0.27–1.04)	NS		
	≥ 0.5	16/25 (64.0%)	235/448 (52.5%)	NS		
	FBG (mmol/L)	7.0 (5.6–7.3)	5.5 (4.7–6.8)	0.007		
	≥ 7	9/27 (33.3%)	95/421 (22.6%)	NS		
	Cholesterol (mmol/L)	3.90 (2.92–4.34)	4.19 (3.61–4.98)	0.016		
	LDL (mmol/L)	2.20 (1.58–2.67)	2.62 (2.11–3.11)	0.013		
	PaO2 (mmHg)	80.50 (64.25-108.25)	78.5 (65–100)	NS		
	≤ 60	4/28 (14.3%)	80/422 (19.0%)			
	PaCO2 (mmHg)	51.0 (39.0–66.0)	47 (41–58)	NS		
	≥ 50	15/27 (55.6%)	185/416 (44.5%)			
CT manifestation	**pleural effusion**	9/25 (36.6%)	75/389 (19.3%)	0.046	2.34	1.00 to 5.50
	multiple lobes' lesion	6/23 (26.1%)	94/390 (24.1%)	NS		
Complications	**Pneumothorax**	4/30 (13.3%)	1/466 (0.2%)	**< 0.001**	71.54	7.71 to 663.4
	Pulmonary embolism	2/30 (6.7%)	3/457 (0.6%)	0.03	10.81	1.73 to 67.38
	Electrolyte disturbance	11/30 (36.7%)	53/462 (11.5%)	**< 0.001**	4.47	2.02 to 9.90

Aggravated inflammation, showed by high proportion of elevated neutrophils and C-reactive protein, had a weak association with acute CVEs. Variables of procalcitonin and erythrocyte sedimentation rate were excluded for analysis, because they were not routinely tested for patients with AECOPD. Indices of myocardial damage and heart failure, like lactic dehydrogenase and N-terminal proB-type natriuretic peptide (NT-proBNP), significantly up-regulated in the acute CVEs group. As a promising variable in COPD management, either absolute counts or binary classification (150/μl) of eosinophils had no statistical association with acute CVEs. Patients in the acute CVEs groups had more complications in the AE period, including pneumothorax, pulmonary embolism and electrolyte disturbance. Whereas, pneumonia and respiratory failure were not associated with acute CVEs.

As Fig. 2 showed, usage of inhaled beta receptor agonists and muscarinic agonists in the AE period did not promote the development of acute CVEs but had slightly protective effects. Interestingly, commercial inhaled glucocorticoid was inclined to be beneficial to prevent acute CVEs ($P = 0.066$, OR = 0.49, 95% CI = 0.22–1.02), compared with aerosol inhalation of venous agents ($P = 0.22$). Among 496 cases, 490 cases received antibiotics with nearly 1/5 receiving combined antibiotic therapy. Fluoroquinolone, previously reported with cardiovascular risks of QTc prolongation, [15] were not statistically associated with acute CVEs in our study. In addition, only 3 cases had macrolides and 6 cases had anti-fungal agents, so they were not included into statistical analysis.

Preventive anticoagulation were predictors of acute CVEs, which might be attributed to poor baseline status of patients. (Fig. 2) Nine of 23 patients using digitalis had acute CVEs in the AE period, with 3 treated for LVD and another 6 for controlling ventricular rate.

Increased heart rate, electrolyte disturbance and use of diuretics were independent risk factors

After removing 90 cases with missing data, 406 cases (20 CVEs and 386 non-CVEs) were included into the multivariate analysis. In Table 4, a total of eight variables with $P < 0.001$ in the univariate analysis were included into the binary logistic regression equation. Previous LVD, 20% increase in heart rate (HR), electrolyte disturbance and diuretics use were independent predictors of acute CVEs in the AE period. In our study, approximately 1/3 of the patients receiving diuretics had electrolyte disturbance at admission. In theory, diuretics have causal association with electrolyte disturbances, decreased blood volume and increased HR. The following two typical cases of acute CVEs suggested electrolytes and blood volume should be closely monitored during the AE period, especially in patients receiving diuretics.

Table 4
Predictors of Acute CVEs in a Multivariable Logistic Regression Model

Characteristic	Adjusted OR	95%CI	Adjusted *P*-value
Previous left heart insufficiency	5.06	1.66–15.36	0.004
20% increase in HR	10.19	2.21–46.99	0.003
Both lower limb edema			NS
LDH ≥ 245 U/L			NS
Electrolyte disturbance	4.24	1.40-12.77	0.01
Pneumothorax			NS
Diuretics use	6.37	1.96–20.67	0.002
Digitalis use			NS

Patient A was a typical case with electrolyte disturbance, leading to worsening LVD. Before admission, he had edema of both lower extremities and took oral diuretics on his own. The results of previous echocardiography indicated that he had left ventricular and biatrial enlargement, with the ejection fraction of 31%. On day 1 in hospitalization, he suddenly complained of dyspnea and orthopnea, with HR of 150, temperature of 39 ℃, blood pressure of 140/100 mmHg and oxygen saturation (SpO_2) of 80%. Immediate laboratory tests showed he had hypokalemia (2.6 mmol/L), hypochloridemia (96 mmol/L), slightly increased cardiac troponin I (cTnI, 0.055 ng/ml), and increased BNP (3009 pg/ml). Then, he was given potassium supplementation, digitalis, amrinone, venous and oral diuretics, and noninvasive mechanical ventilation. On day 15, he recovered and was discharged from hospital.

Patient B was a typical case with hypovolemia, leading to atrial fibrillation. He had no edema of both lower extremities before admission, and suddenly presented with left pneumothorax on day 1 in hospitalization. He was prescribed with intravenous diuretics on day 1–4 and converted into oral diuretics on day 5–7. On day 7 of hospitalization, he suddenly presented with a newly onset of atrial fibrillation, with HR of 90, blood pressure of 116/67 mmHg and SpO_2 of 84%. Immediate laboratory tests showed he had hypovolemia (erythrocyte counts = $5.88*10^{12}$ and hemoglobin = 184 g/L), and his electrolytes, cTnT and NT-proBNP were within the normal range. Thus, patient B discontinued diuretics, was given appropriate fluid infusion to expand blood volume, and was required to drink plenty of water. He was also given propafenone for cardioversion and then oral amiodarone for maintenance. On day 9, he restored sinus rhythm and was discharged from hospital on day 12.

Discussion

We demonstrated that the development of acute CVEs during AECOPD period was not only associated with increased hospital mortality but also with increased risks of short-term re-AE after discharge. Moreover, previous LVD, increased HR, electrolyte disturbance and diuretics use were identified as independent risk predictors of CVEs.

Other investigators noted that increased resting HR predicted shortened life expectance and was associated with cardiovascular mortality across all the spirometric grades of COPD, [21] in line with our findings of increased HR and acute CVEs. Our findings of electrolyte disturbance partly validated previous results of poor outcomes of hyperphosphatemia (only for men) [22] and hypocalcemia [23] in AECOPD patients. Whereas, no statistical difference in sodium, potassium and chlorides was observed between acute CVEs and non-CVEs group in our cohort. Another study also reported no correlation between electrolyte imbalance and QTc prolongation in hospitalized patients with COPD. [24]

Cardiovascular risks of diuretics might be associated with electrolyte imbalance, hypovolemia or their originally-targeted heart failure. Two typical cases of acute CVEs in our cohort demonstrated that inappropriate usage of diuretics could result in electrolyte imbalance and hypovolemia, respectively. In addition, a retrospective study reported that prescription of loop diuretics increased risks of AE and death in elderly patients with COPD. [25] Contrarily, thiazide diuretics were recommended as first-line antihypertensive agents for COPD patients, since it did not cause increase in AE. [26] Hence, the use of diuretics should be prudent, and it is necessary to introduce new echocardiographic parameters to assess systemic hypoperfusion in the clinical setting, including tricuspid annular plane systolic excursion (TAPSE) and systolic S' velocity of the tricuspid annulus. [27]

Similar to our results of increased NT-proBNP in acute CVEs group, NT-proBNP [28] were strong indicators of mortality for patients with AECOPD. Likewise, Smith GL et al reported that increased urea nitrogen was associated with cardiovascular mortality in the elderly. [29] Although the above study showed the association of increased creatinine with myocardial infarction (> 88.4 mmol/L) and heart failure (> 97.2 mmol/L),[29] we did not confirm this association in our study. Theophylline, fluoroquinolone and inhaled bronchodilators in AE period, which were previously regarded as cardiovascular risk factors, were not statistically associated with acute CVEs in our cohort.

Since nearly half of AEs are caused by lower respiratory bacterial infection, [30] we try to gain insights from some studies of Community-Acquired Pneumonia (CAP) and cardiac complications. Many observation studies reported about 15–30% of incidence of cardiac complications in hospitalized patients with CAP. [31, 32] Similarly, incident CVEs was a strong negative indicator of 30-day survival. [32, 33] In the comprehensive analysis of these CAP studies (25–40% of subjects with chronic respiratory diseases), several risk factors between acute CVEs group and non-CVEs group were consistent with our research, including age, preexisting coronary heart disease, diabetes, congestive heart failure, pleural effusion, increased pulse, urea nitrogen, and blood glucose. [32–34] Whereas, we did not identify the following different variables in our research: history of stroke, preexisting dyslipidemia, hypertension, prior cardiac arrhythmias (not record), hematocrit < 30% and acute respiratory failure.[32–34] In addition,

pneumonia severity index, a wide-accepted scale for predicting short-term mortality of CAP, was also a good indicator of the occurrence of CVEs. [32, 33]

Some limitations should be noticed for interpreting this study. As a nested case-control study, absolute causal relationship cannot be concluded, and incidence and mortality of acute CVEs in patients with AECOPD cannot be calculated. Second, due to insufficient numbers of acute CVEs and statistical efficacy, some risk factors might be missed. We planned to further validate our results in a large-scale and multicenter cohort with more outcomes of CVEs in future. Third, some baseline information in the stable period was deficient, and usage of cardioprotective medications were not fully recorded, liker anti-platelet agents and statins, which might result in biases. [14, 35] Fourth, baseline comorbidities were reported by patients themselves and not validated by detailed laboratory tests, which might had recall bias. Fifth, we did not take some useful scales of cardiovascular risk assessment into consideration. [36]

Conclusion

Cardiac complications in AE period were significantly associated with poor outcomes in patients with COPD. Patients with 20% increase in HR were susceptible to cardiac complications and needed closely monitoring. Furthermore, diuretics usage in AE period might have underlying cardiovascular risks and should be carefully assessed.

List Of Abbreviations

COPD, chronic obstructive pulmonary disease; CVEs, cardiovascular events; AE, acute exacerbation; ACS, acute coronary syndrome; LVD, left ventricular disfunction; HR, heart rate; CVD, cardiovascular disease; mMRC, modified Medical Research Council; CAT, COPD assessment test; GOLD, Global Strategy for Prevention, Diagnosis and Management of COPD; re-AE, recurrent acute exacerbation; NT-proBNP, N-terminal proB-type natriuretic peptide; SpO2, oxygen saturation; cTnI, cardiac troponin I; RHF, right heart failure; TAPSE, tricuspid annular plane systolic excursion; CAP, community-acquired pneumonia.

Declarations

Ethics approval and consent

The establishment of this prospective COPD cohort was approved by Institutional Ethics Committee of Shanghai Zhongshan Hospital. (No. B2015-119R) All procedures were in line with the ethical standards of the institutional committee and with the 1964 Helsinki Declaration. Informed consent of clinical information collection and follow up was acquired from each patient at admission.

Data sharing statement

Please contact the corresponding author for the analysis dataset.

Conflict of interest statement

None

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Author contributions

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Figures

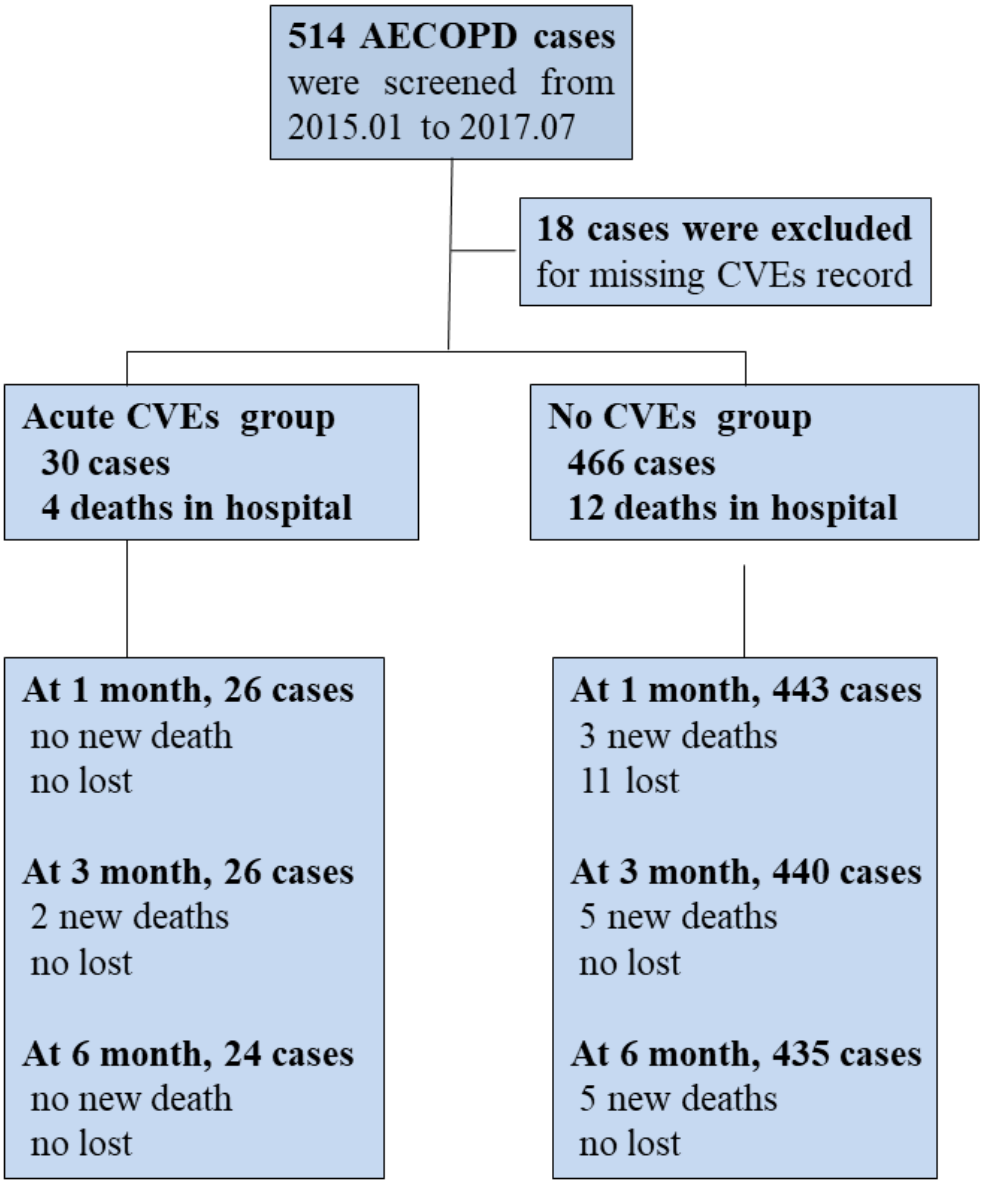

Figure 1

Baseline characteristics between two groups

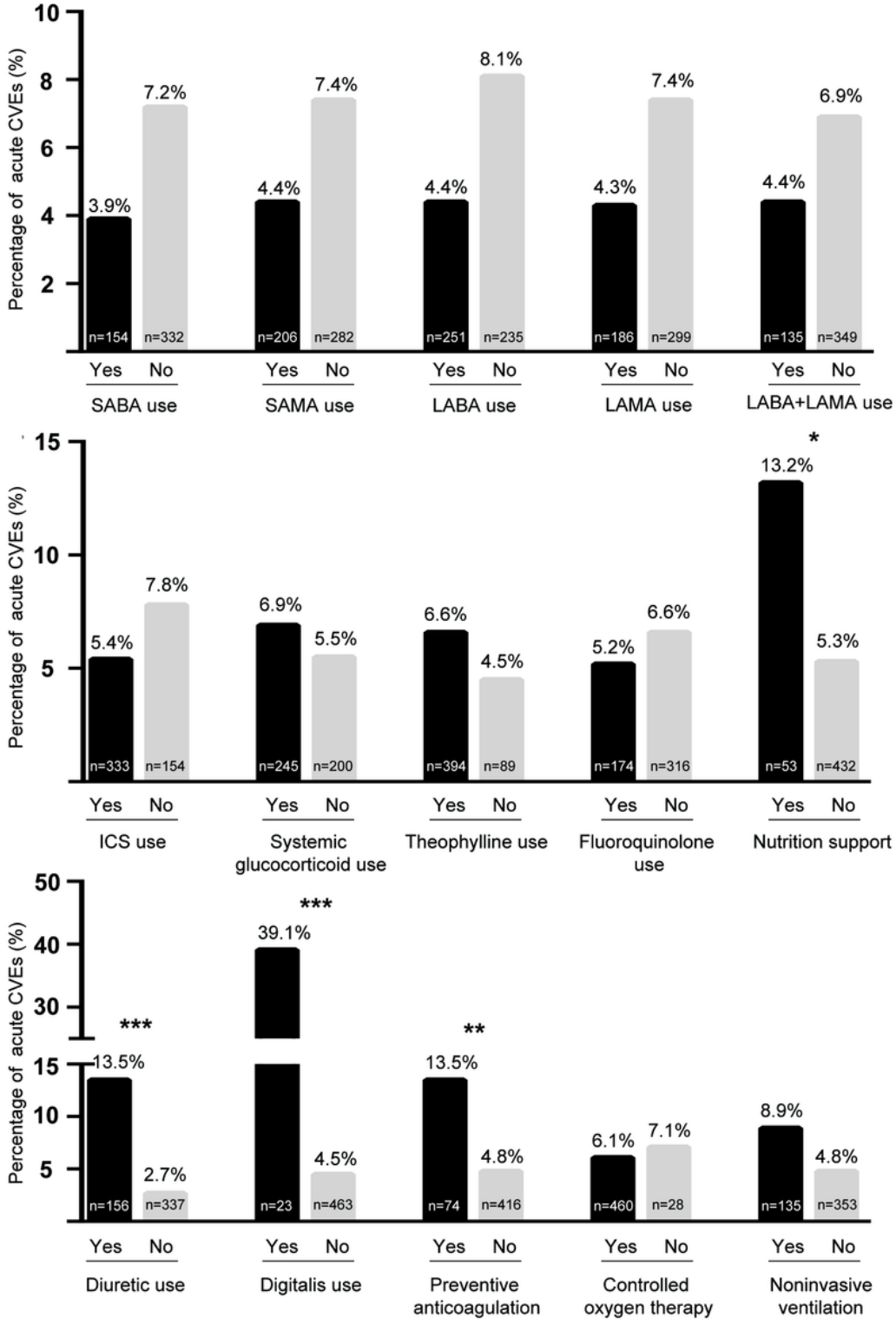

Figure 2

Risk factors of acute CVEs identified by the univariate analysis