Predictors 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 predictors 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). Predictors 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 and 19 with arrhythmia. Four deaths were observed in the CVE group, with significantly increased death risk compared with the non-CVE group (*P*=0.001, OR=5.81). Moreover, patients who have had CVEs were vulnerable 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 predictors. 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 a chronic lung disease and ranks as the third cause of death in the world, with the characteristics of irreversible airflow limitation and progressive decline of lung function. [1, 2] Several cohort studies reported that cardiovascular disease (CVD) was one of the top three leading causes of death in patients with COPD, following the respiratory infection and respiratory failure. [3-5] Moreover, prior CVD could additionally increase risks of death in the elderly COPD patients with pneumonia. [6]

Patients with COPD tend to have concurrent CVDs with the prevalence of 28-70%. [7] Hyperlipidemia (45%) and hypertension (43%) were the most common cardiovascular risk factors. [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 in the 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 the 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 had early warning effects, including previous history, hypertension, diabetes, hyperlipidemia and hyperuricemia. In addition, serious side effects of certain drugs might be chief culprits of some CVE cases. A case-control study reported that theophylline could increase the risks of arrhythmia and acute heart failure by 80%. [14] Moreover, a meta-analysis showed that fluoroquinolones increased the risks of arrhythmia and cardiovascular death by 80% and 71%. [15]. Relationship between inhaled beta-receptor agonists (bronchodilators) and CVDs is still highly debated, for beta-receptor antagonist is well-known therapy of cardiac remodeling and heart failure. [14] In the patients with COPD, new initiation of inhaled bronchodilators was related to short-term elevated risks of severe CVEs, [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 (beta-receptor agonists and muscarinic receptor antagonist) 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

We performed a nested case-control study in a prospective cohort. Between January 2015 and July 2017, we recruited patients hospitalized for AECOPD into our prospective cohort in the Department of Pulmonary Medicine of Shanghai Zhongshan Hospital and Shanghai Putuo District People's Hospital.

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. Exclusion criterion was other respiratory diseases-induced exacerbation, 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). Modified Medical Research Council (mMRC) dyspnea scale [19] and COPD assessment test (CAT) [20] were used to stratify the severity of dyspnea and measure COPD's adverse effects on daily life.

Individualized 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 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 visits 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 notes of CVE cases were recorded and carefully reviewed to determine the chronological sequence of diuretics, electrolyte disturbance, and CVEs. Secondary outcomes were defined as days of stay in hospital, hospitalized death, death within1, 3 and 6 months, and re-AE within1, 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. We analyzed the normality of continuous variables by Shapiro-Wilk normality test, and found that all of these were not normally distributed. Thus, continuous variables were described

by median (interquartile range [IQR]) and compared by 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 the multivariable analysis, binary logistic regression model with method of Backward LR was used to identify the independent predictive factors of acute CVEs in AECOPD patients. Variables with P<0.001 in the univariate analysis were included into the multivariable analysis.

From the conservative point of view, we managed missing data with the following procedure: firstly, patients with many missing variables were excluded; secondly, variables with missing number ≥5% were removed; thirdly, variables with missing number <5% were supplemented with the 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, 514 AECOPD cases were collected in the two hospitals. After excluding those without the records of acute CVEs in hospitalization, we included 496 cases into analysis. (Figure 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, 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, symptom scores 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 >5.2mmol/l, hyperlipidemia was not associated with increased risk of acute CVEs. Regular usage of inhaled agents for treating COPD 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).

Acute CVEs were associated with poor outcomes in AECOPD patients

In comparison with non-CVEs group, increased death 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 of COPD within 3 months.

Risk factors of acute CVEs identified by the univariate analysis

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

Elevated neutrophils and C-reactive protein, suggesting aggravated inflammation, had a weak association with acute CVEs. 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. Additionally, 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 Figure 2 showed, usage of inhaled beta receptor agonists and muscarinic agonists in the AE period did not promote the occurrence of acute CVEs but had slightly protective effects. Interestingly, commercial inhaled glucocorticoid had a tendency of preventing 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, of which nearly 1/5 received combined antibiotic therapy. Although fluoroquinolone was a cardiovascular risk factor of QTc prolongation in the previous study, [15] it was not statistically associated with acute CVEs in our cohort. In addition, only 3 cases had macrolides and 6 cases had anti-fungal agents, so they were not included into statistical analysis.

Preventive anticoagulation and nutrition support were predictors of acute CVEs, which might be attributed to poor baseline status of patients. (Figure 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 addition, approximately 1/3 of the patients receiving diuretics had electrolyte disturbance at admission.

Discussion

We demonstrated that the development of acute CVEs during AECOPD period was not only associated with the increased hospital mortality but also with the 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.

In line with our findings of increased HR and acute CVEs, other investigators noted that the increased resting HR predicted the shortened life expectance and the increased cardiovascular mortality across all the spirometric grades of COPD patients. [21]. However, the relationship between electrolyte disturbance and CVEs is elusive. Our findings partly validated the 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] As for diuretics use, a retrospective study reported that prescription of loop diuretics increased the risks of AE and death in the elderly patients with COPD. [25] In our cohort, we defined the diuretic usage as using loop diuretics and spironolactone, and found that diuretic usage was independently associated with acute CVEs. Contrarily, thiazide diuretics were recommended as the first-line antihypertensive agents for COPD patients, since it did not cause an increase in the numbers of AE. [26] Thus, mild diuretics and low-dosage might be more suitable for patients with AECOPD.

We speculate that cardiovascular risks of diuretics might result from electrolyte imbalance, hypovolemia or pre-existing heart failure. Moreover, increased HR is also one of signs of hypovolemia. Two typical cases of acute CVEs in our cohort demonstrated that inappropriate usage of diuretics could result in electrolyte imbalance or hypovolemia. Patient A was a typical case, whose electrolyte disturbance led to worsening of his previous LVD. Before admission, he had edema of both lower extremities and took oral diuretics on his own. On day 1 in hospitalization, he suddenly complained of dyspnea and orthopnea. Immediate laboratory tests showed he had hypokalemia (2.6 mmol/L), and hypochloridemia (96 mmol/L). 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 another typical example, whose hypovolemia led to the occurrence of arrhythmia. He had no edema of both lower extremities before admission. 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. Immediate laboratory tests showed he had hypovolemia (erythrocyte counts $=5.88*10^{12}$ and hemoglobin =184 g/L). He was given appropriate fluid infusion to expand blood volume, and discontinued diuretics. He was also given propafenone for cardioversion and oral amiodarone for maintenance. On day 9, he restored sinus rhythm and was discharged from hospital on day 12. Thus, the above two cases suggested that electrolytes and blood volume should be closely monitored during the AE period, especially in the patients receiving diuretics. As a golden standard of hemodynamic assessment, right heart catheterization is limitedly applied in patients with AECOPD, for its invasiveness and patient's poor status. Hence, new echocardiographic parameters are recommended 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 death for patients with AECOPD. Likewise, Smith GL reported that increased urea nitrogen was associated with cardiovascular mortality in the elderly. [29] Although Smith GL showed the association of increased creatinine with myocardial infarction (>88.4mmol/L) and heart failure (>97.2mmol/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, [14-16] 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. Similar to our study, two observation studies reported that incident CVEs was a strong negative indicator of 30-day survival of patients with CAP. [31, 32] In the comprehensive analysis of three CAP studies (25-40% of subjects with chronic respiratory diseases), several risk factors of acute CVEs were consistent with our research, including age, preexisting coronary heart disease, diabetes, congestive heart failure, pleural effusion, increased pulse, urea nitrogen, and blood glucose. [31-33]

Some limitations should be noticed for interpreting this study. As a nested case-control study, absolute causal relationship cannot be confirmed, 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 plan to further validate our results in a large-scale and multicenter cohort with more outcomes of CVEs. Third, some baseline information in the stable period was missed, and usage of cardioprotective medications were not fully recorded, liker anti-platelet agents and statins, which might result in biases. [14, 34] 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. [35]

Conclusion

Cardiac complications in AE period were significantly associated with poor outcomes in patients with COPD. Patients with previous history of LVD and 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 electrolyte and blood volume 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.

Consent to publish

Not applicable

Availability of data and materials

Please contact the corresponding author for the analysis dataset.

Competing interests None

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Authors' contributions

Study design: Wei-ping Hu, Tsokyi Lhamo, Shan-qun Li, Jing Zhang; Data Collection: Tsokyi Lhamo, Feng-ying Zhang, Jing-qing Hang, Yi-hui Zuo, Jian-lan Hua; Statistical analysis: Wei-ping Hu, Tsokyi Lhamo; Manuscript writing: Wei-ping Hu, Tsokyi Lhamo; Critical manuscript revision: Wei-ping Hu, Jing Zhang. All authors read and approved the final manuscript.

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Tables

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)	40.2 (29.3-53.7) (n=15)	37.2 (28.4-49.0) (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	3 (2-3) (n=17)	3 (2-3) (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	2/19 (10.5%)	26/341 (7.6%)	NS

	changes			
	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 (1-2.5) (n=17)	2 (1-3) (n=337)	NS
	Hospitalization numbers	2 (1-2) (n=17)	1 (1-2) (n=335)	0.025

Footnote: a, Hyperlipemia was defined as total cholesterol > 5.2mmol/L in the AE period, for lack of lipid profile examination in the stable period.

Data were shown as number (percentage), n/N (percentage) or median (IQR). *P*-values between two group were calculated by Fisher's exact test, Chi-square test, or Mann-Whitney U test.

Abbreviations: CVEs, cardiovascular events; BMI, body mass index; FEV_1, forced expiratory volume in one second; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council; CAT, COPD Assessment test; ICS, inhaled glucocorticoid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

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

Footnote: Data were shown as n/N (percentage) or median (IQR). *P*-values between two group were calculated by Fisher's exact test, Chi-square test, or Mann-Whitney U test.

Abbreviations: CVEs, cardiovascular events; CI, confidence index; ICU, intensive care unit; LOS, length of stay; AE, acute exacerbation.

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
	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

Footnote: Data were shown as n/N (percentage) or median (IQR). *P*-values between two group were calculated by Fisher's exact test, Chi-square test, or Mann-Whitney U test.

Abbreviations: CVEs, cardiovascular events; CI, confidence index; HR, heart rate; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; cTnT, cardiac muscle isoform of troponin T; LDH, lactate

dehydrogenase; NT-pro BNP, N-terminal pro-brain natriuretic peptide; FBG, fasting blood glucose; LDL, low-density liporotein; PaO_2, partial pressure of oxide in artery; $PaCO_2$, partial pressure of carbon dioxide in artery; CT, computed tomography.

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

Abbreviations: CVEs, cardiovascular events; OR, odds ratio; CI, confidence index; HR, heart rate; LDH, lactic dehydrogenase; NS, non-significance.

Figures

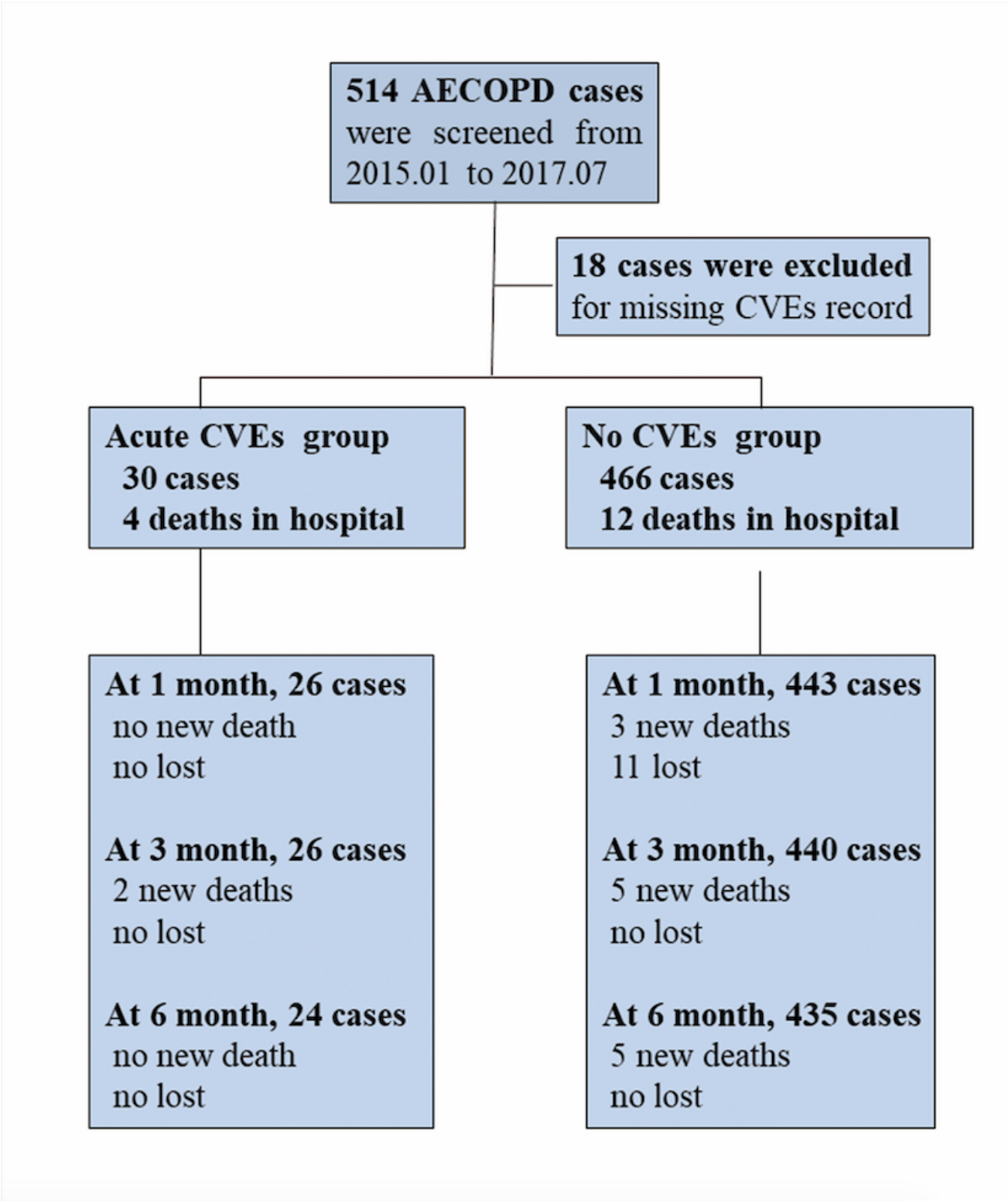

Figure 1

Flow chart of the study Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; CVEs, cardiovascular events.

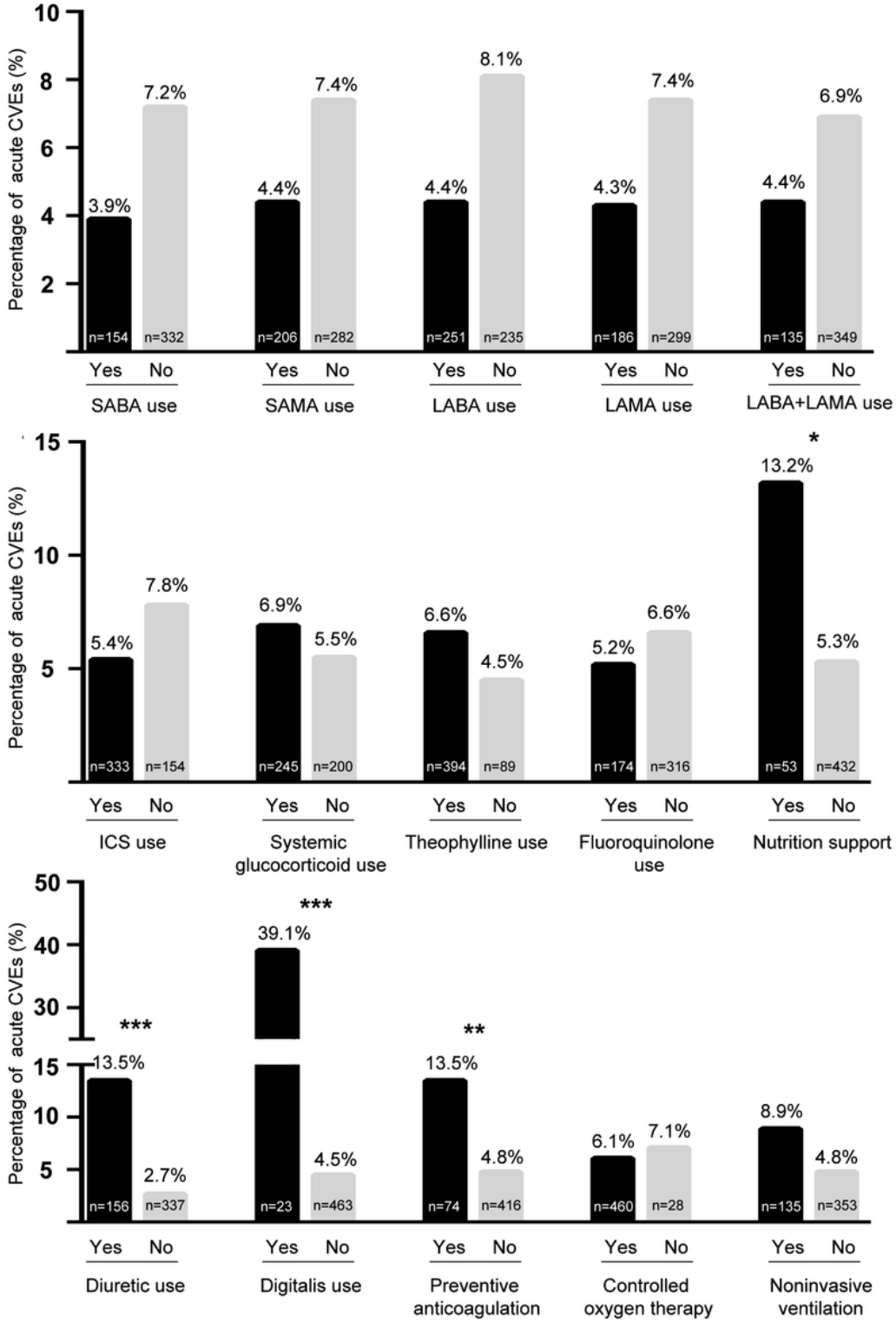

Figure 2

Commonly-used medications and acute CVEs Footnote: Usage of SABA, SAMA, ICS here included either aerosol inhalation or specialized commercial agents. Abbreviation: CVEs, cardiovascular events; SABA, short-acting beta agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled glucocorticoid. *, P <0.05; **, P <0.01; ***, P <0.001