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Comparison of Clinical Characteristics and Short-Term Prognoses Within Hospitalized Chronic Obstructive Pulmonary Disease Patients Comorbid With Asthma, Bronchiectasis, and Their Overlaps: Findings From the ACURE Registry

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Introduction: Real-world evidence and comparison among commonly seen chronic obstructive pulmonary disease (COPD) phenotypes, i.e., asthma–COPD overlap (ACO), bronchiectasis–COPD overlap (BCO), and their coexistence (ABCO) have not been fully depicted, especially in Chinese patients.

Methods: Data were retrieved from an ongoing nationwide registry in hospitalized patients due to acute exacerbation of COPD in China (ACURE).

Results: Of the eligible 4,813 patients with COPD, 338 (7.02%), 492 (10.22%), and 63 (1.31%) were identified as ACO, BCO, and ABCO phenotypes, respectively. Relatively, the ABCO phenotype had a younger age with a median of 62.99 years [interquartile range (IQR): 55.93–69.48] and the COPD phenotype had an older age with a median of 70.15 years (IQR: 64.37–76.82). The BCO and COPD phenotypes were similar in body mass index with a median of 21.79 kg/m^2 (IQR: 19.47–23.97) and 21.79 kg/m^2 (IQR: 19.49–24.22), respectively. The COPD phenotype had more male gender (79.90%) and smokers (71.12%) with a longer history of smoking (median: 32.45 years, IQR: 0.00–43.91). The ACO and ABCO phenotypes suffered more prior allergic episodes with a proportion of 18.05 and 19.05%, respectively. The ACO phenotype exhibited a higher level of eosinophil and better lung reversibility. Moreover, the four phenotypes showed no significant difference neither in all-cause mortality, intensive care unit admission, length of hospital stay, and COPD Assessment Test score change during the index hospitalization,

and nor in the day 30 outcomes, i.e., all-cause mortality, recurrence of exacerbation, all-cause, and exacerbation-related readmission.

Conclusions: The ACO, BCO, ABCO, and COPD phenotypes exhibited distinct clinical features but had no varied short-term prognoses. Further validation in a larger sample is warranted.

Keywords: chronic obstructive pulmonary disease, exacerbation, asthma, bronchiectasis, phenotype, heterogeneity, prognosis

INTRODUCTION

Patients with chronic obstructive pulmonary disease (COPD), comorbid with asthma (asthma–COPD overlap, ACO) or bronchiectasis (bronchiectasis–COPD overlap, BCO) as well as their coexistence (ABCO), are commonly seen phenotypes, which have been broadly discussed whether they were distinct disease entities, but there is no concluded consensus yet (1). The concept of "ACO" or "asthma + COPD" appeals as a great interest to investigators (2–11), and similar discussion applies to the research of bronchiectasis and COPD overlap (12–16). Few data was reported on the ABCO phenotype.

The prevalence of the above-mentioned phenotypes of COPD varied across studies. Alshabanat A et al. reported a pooled prevalence of ACO phenotype among patients with COPD was 27% and 28% in population- and hospital-based studies, respectively. Hosseini et al. (17) found that a pooled prevalence of ACO phenotype was 29.6% in patients with COPD. Zhou et al. (18) stated an ACO prevalence of 11.51% in Chinese patients with COPD. Ding et al. (19) reported an ACO prevalence of 18.6% in urban Chinese patients with COPD. Uchida et al. (20) summarized the prevalence of ACO phenotype that varied from 0.9 to 11.1% in the general population, from 11.1 to 61.0% in patients with asthma, and from 4.2 to 66.0% in patients with COPD (21). For the BCO phenotype, Ni et al. (22) reported a pooled prevalence of 54.3% (ranging from 25.6 to 69%) in patients with COPD.

Both asthma and bronchiectasis could incur an exacerbation of the chronic pulmonary disease (AECOPD). The ACO and BCO phenotypes present common and distinct clinical characteristics and prognoses. In general, the ACO phenotype exhibits a higher eosinophil level and better bronchodilator reversibility, and the BCO phenotype presents more neutrophil and nonreversible characteristics (23, 24). Additionally, compared with patients with COPD only, the ACO phenotype was characterized with higher probability of exacerbation (5), frequent outpatient and emergency department visits (25, 26), but lower rate of hospital readmission (27) and mortality (28, 29). The BCO phenotype was associated with increased risk of exacerbation, severe airway obstruction, and higher mortality (30).

Although numerous studies have been conducted, findings were still controversial (1). The notable variation may be due to different study designs, sample sizes, and definitions of diseases used. In addition, most previous data were based on stable stage of COPD, and facts on exacerbation of the disease need to be delineated. In the current manuscript, to address these unanswered questions, we utilized data from an acute exacerbation of COPD inpatient registry (ACURE) to investigate the differences in clinical features and short-term prognosis profiles among Chinese hospitalized patients with AECOPD who were comorbid with asthma and/or bronchiectasis, and those patients without the two comorbidities. We anticipated that our findings could help improve clinical management of the disease in clinical practice.

METHODS

Study Design and Settings

Data was retrieved from an acute exacerbation of COPD inpatient registry (ACURE), which was initiated in China to investigate the demographic characteristics, clinical features, diagnoses and treatments, and prognoses among hospitalized patients with COPD who were suffering an acute exacerbation episode (ClinicalTrials.gov registry number: NCT02657525). The ACURE study was started on September 1, 2017 and planned to recruit 7,600 hospitalized patients with AECOPD who were admitted to 161 participating medical centers across China with a maximum of 3-year follow-up. The protocol of the ACURE registry and baseline characteristics of the study population have been published (31, 32).

The study protocol, informed consent, and case report form have been approved by the institutional review board at the China–Japan Friendship Hospital (approval number: 2015-88) and other local participating centers. All the participating patients have provided written informed consent.

Study Population

The ACURE participants underwent screenings at index hospital admission to confirm their eligibilities for enrollments. Subjects would be enrolled if they fulfilled the following eligibility criteria:

Abbreviations: ABCO, chronic obstructive pulmonary disease patients comorbid with asthma and bronchiectasis; ACO, asthma-chronic obstructive pulmonary disease overlap; ACURE, the acute exacerbation of chronic obstructive pulmonary disease inpatient registry; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BCO, bronchiectasis- chronic obstructive pulmonary disease overlap; BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DVT, deep venous thrombosis; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, the Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; ICU, intensive care unit; IQR, interquartile range; PE, pulmonary embolism; RICU, respiratory intensive care unit; SD, standard deviation; VTE, venous thromboembolism.

1) aged 18 years or older; 2) confirmed or suspected to be hospitalized due to AECOPD; 3) not participating in other clinical trial or intervention studies; and 4) agreeing to sign the informed consent. As of February 25, 2020, 4,813 eligible patients met the inclusion and exclusion criteria.

Procedures and Measurements

Data Collection

In the ACURE registry, patient management was at the discretion of clinical physicians. Well-designed and sophisticated questionnaires were administrated to enrolled participants at baseline, i.e., during the index hospitalization, and at planned follow-up visits, i.e., at day 30 (±2 days), month 6 (±12 days), month 12 (±12 days), month 24 (±12 days), and month 36 (±12 days), respectively after the index hospital discharge by trained investigators. The questionnaires consisted of contents on basic and demographic information, inclusion and exclusion criteria, current diagnoses (including symptoms and signs), objective examinations [e.g., routine venous blood, lung function, computed tomography (CT), arterial blood gas, electrocardiograph, cardiac color ultrasound, pulmonary ventilation/perfusion image, lower extremity venous ultrasound, and etiological examinations where necessary], history and management of the disease (especially while in the stable condition), predisposing factors and prevention of the exacerbation, pharmacological and nonpharmacological (e.g., respiratory support) treatments in the hospital, cost, outcomes at hospital discharge, and management and outcomes during the follow-ups. Data of any exacerbations that did not occur in the scheduled visits were also collected.

All data were uploaded to an online electronic data capture system. Data quality was regularly monitored by a concerted project and data management team. For instance, missing values, outliers, and illogical information will be sent to the local participating centers for timely amendment.

Diagnoses of Diseases

In current analyses, spirometric COPD was diagnosed as the presence of a post-bronchodilator forced expiratory volume in 1 s (FEV1) divided by the forced vital capacity (FVC) with a value of less than 0.70, which indicated a persistent airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2021 report (10). Asthma was diagnosed by the presence of both variable expiratory airflow limitation and a characteristic pattern of respiratory symptoms for instance wheezing, shortness of breath (dyspnea), chest tightness, and/or cough in adults according to the Global Initiative for Asthma (GINA) 2021 report (9). Bronchiectasis was diagnosed by the presence of both bronchial dilation on CT and clinical symptoms, such as cough, sputum production, and/or recurrent respiratory infection in adults according to the European Respiratory Society (33) and British Thoracic Society guidelines (34). The ACO phenotype was defined as spirometry-diagnosed COPD and asthma. The BCO phenotype was confirmed by spirometric COPD and CT-based bronchiectasis. Patients with COPD both comorbid with asthma and bronchiectasis were termed ABCO phenotype. Information on disease diagnoses were obtained from patients' medical records during their index hospitalization and critically reviewed by local and central principal investigators/pulmonary physicians. More details on diagnoses of diseases are provided in the **Supplementary Material S1**.

Variables

Data on demographic and clinical characteristics, laboratory, lung function, and image (e.g., CT) tests, short- and long-term prognoses were comprehensively collected. Lung function test was performed when the situation of the patient was relatively stable after admission. If multiple lung function tests were conducted, the latest result was chosen before discharge. Bronchiectasis was diagnosed once any of the CT scan result was confirmed during hospitalization. Classification of the severity of airflow limitation was categorized into four grades based on the 2021 GOLD report: GOLD 1 (mild, FEV1 $\geq$ 80% predicted), GOLD 2 (moderate, 50% $\leq$ FEV1 $<$ 80% predicted), GOLD 3 (severe, 30% $\leq$ FEV1 $<$ 50% predicted), and GOLD 4 (very severe, FEV1 $<$ 30% predicted) (10).

In this manuscript, short-term clinical outcomes referred to the length of index hospital stay, recurrence of exacerbation, and exacerbation-related hospital readmission within 30 days after the index hospital discharge. Definitions of clinical outcomes are explicated in the **Supplementary Material S1**.

Statistical Analyses

Mean and standard deviation (SD) were calculated for normally distributed continuous variables, otherwise median and interquartile range (IQR) were presented for abnormally distributed ones. Frequencies and percentages were calculated for categorical variables. Characteristics of patients within phenotypes were compared with the utilization of Student's *t*-test (normal distributed data, two-group comparison) or Wilcoxon rank-sum test (abnormal distributed data, two-group comparison) or Kruskal–Wallis test (abnormal distributed data, three or above group comparison) as appropriate for continuous variables, and using Pearson's Chi-square test or Fisher's exact test as appropriate for categorical ones.

A multivariable linear regression model was used to assess the associations of predictors with a continuous outcome (i.e., length of hospital stay). Multivariable Cox proportional hazards regression model was adapted to investigate the associations with day 30 outcomes (i.e., recurrence of exacerbation and exacerbation-related hospital readmission). Variables that showed significant associations in univariable analyses ($p <$ 0.10), and factors (e.g., age, gender, BMI, smoking status, and FEV1) that previously had been reported to be associated with prognoses of COPD were further adjusted in the multivariable statistical models (35). A stepwise selection scheme with an entry level of 0.10 and a stay level of 0.05 was applied. Multicollinearity diagnosis was performed before conducting the multivariable analyses. Details on multivariable models employed for stepwise selection of independent predictors are given in the **Supplementary Material S2**. Kaplan–Meier curve and log-rank test were utilized to determine the differences in day 30 outcomes between phenotypes.

Statistical significance was defined as achieving a two-sided *P* value of less than 0.05. Statistical analyses were performed using Statistical Analysis System (version 9.4) and R Project (version 4.0.5).

RESULTS

Of the overall 4,813 eligible patients with AECOPD, 63 (1.31%) patients were comorbid both with asthma and bronchiectasis (ABCO), 338 (7.02%) and 492 (10.22%) patients were identified as ACO and BCO phenotypes, respectively, and 3,920 (81.45%) patients did not coexist with asthma or bronchiectasis (**Figure 1**).

Demographic and clinical characteristics among the ACO, BCO, and ABCO phenotypes as well as those patients without asthma or bronchiectasis are shown in **Table 1**. Relatively, the ABCO phenotype patients had a younger age with a median of 62.99 years (IQR: 55.93–69.48), and the patients without asthma or bronchiectasis had an older age with a median of 70.15 years (IQR: 64.37–76.82). The BCO phenotype patients and patients without asthma or bronchiectasis were similar in BMI with a median of 21.79 kg/m^2 (IQR: 19.47–23.97) and 21.79 kg/m^2 (IQR: 19.49–24.22), respectively. In addition, patients without asthma or bronchiectasis were more of the male gender (79.90%) and smokers (71.12%) with a longer history of smoking (median: 32.45 years, IQR: 0.00–43.91). The ACO and ABCO phenotype patients suffered more prior allergic episodes with a proportion of 18.05 and 19.05%, respectively. The ACO phenotype patients exhibited higher level of eosinophil and better lung reversibility. The four phenotype patients showed no significant difference in all-cause mortality, intensive care unit (ICU)/respiratory intensive care unit (RICU) admission, length of stay, and COPD assessment test (CAT) score change in the index hospitalization, and neither in the day 30 outcomes, i.e., all-cause mortality, recurrence of exacerbation, and all-cause and exacerbation-related hospital readmission (**Table 1**).

Independent predictors associated with hospitalized and day-30 outcomes across the four phenotypes are shown in **Figure 2**. Varied factors were found in predicting the length of hospital stay among different phenotypes. For example, cancer was solely the strong predictor within the ABCO phenotype patients. Peptic ulcer, venous thromboembolism (VTE), and $PaCO_2$ were the independent influencing factors in the BCO phenotype patients. More predicting factors such as age, education level, vaccination within the past 5 years, hospitalization due to AECOPD in the prior year, level of white blood cell, VTE, pulmonary interstitial fibrosis, failure of respiration, etc. were included in the profiles in the patients without asthma or bronchiectasis (**Figure 2**).

The predicting profiles of day 30 outcomes also exhibited distinct features. Community-acquired pneumonia, cancer, and the level of eosinophils were independent predictors of exacerbation recurrence in ACO phenotype patients. In BCO

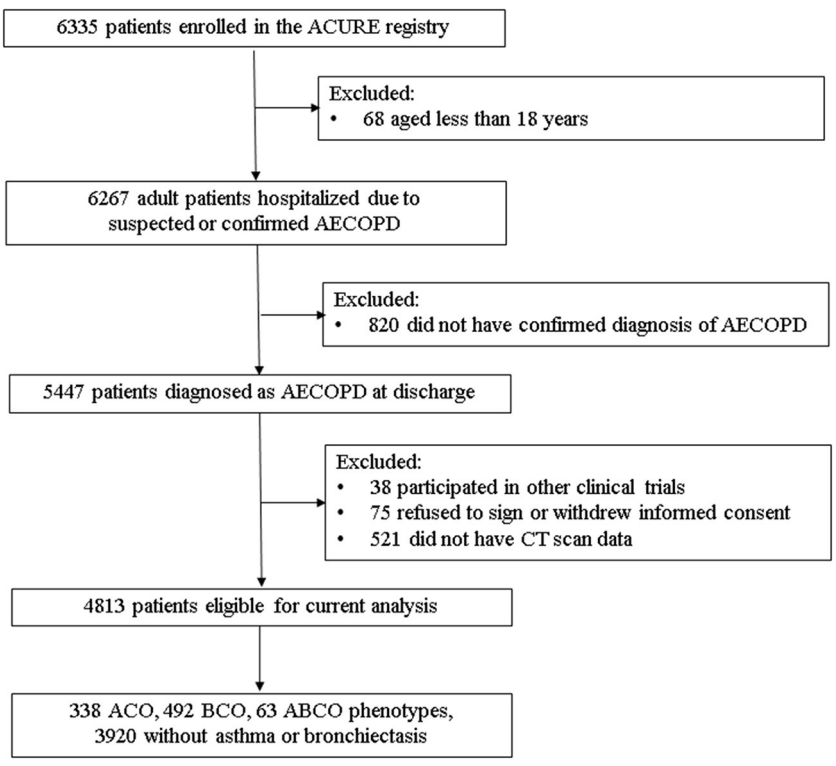


FIGURE 1 | Flowchart of diagram in current analyses. ABCO, chronic obstructive pulmonary disease patients comorbid with asthma and bronchiectasis; ACO, asthma-chronic obstructive pulmonary disease overlap; ACURE, the acute exacerbation of chronic obstructive pulmonary disease inpatient registry; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BCO, bronchiectasis- chronic obstructive pulmonary disease overlap; CT, computed tomography.

TABLE 1 | Main characteristics and comparisons among ACO, BCO, ABCO phenotypes, and those without asthma or bronchiectasis in hospitalized AECOPD patients.

Main variables	All patients (*N* = 4,813)	ACO phenotype (*N* = 338)	BCO phenotype (*N* = 492)	ABCO phenotype (*N* = 63)	Patients without asthma or bronchiectasis (*N* = 3,920)	*P* value for ACO vs. BCO	*P* value among four phenotypes
Demographics							
Age (years), median (IQR)	69.70 (63.72, 76.46)	66.19 (59.63, 73.53)	69.14 (63.16, 75.44)	62.99 (55.93, 69.48)	70.15 (64.37, 76.82)	<0.0001	<0.0001
Gender, n (%)							
Male	3,751 (77.93)	232 (68.64)	342 (69.51)	45 (71.43)	3,132 (79.90)	0.7890	<0.0001
Female	1,062 (22.07)	106 (31.36)	150 (30.49)	18 (28.57)	788 (20.10)		
BMI (kg/m^2), median (IQR)	21.97 (19.53, 24.24)	23.41 (20.57, 25.71)	21.79 (19.47, 23.97)	23.18 (20.20, 26.04)	21.79 (19.49, 24.22)	<0.0001	<0.0001
Education level, n (%)							
Primary school or below	2,372 (49.28)	155 (45.86)	238 (48.37)	23 (36.51)	1,956 (49.90)	0.0457	0.0766
Junior high school	1,570 (32.62)	107 (31.66)	177 (35.98)	23 (36.51)	1,263 (32.22)		
Senior high school	676 (14.05)	57 (16.86)	64 (13.01)	14 (22.22)	541 (13.80)		
Undergraduate or above	195 (4.05)	19 (5.62)	13 (2.64)	3 (4.76)	160 (4.08)		
Smoking status, n (%)							
Former	2,117 (43.99)	114 (33.73)	181 (36.79)	25 (39.68)	1,797 (45.84)	0.0124	<0.0001
Current	1,165 (24.21)	83 (24.56)	80 (16.26)	11 (17.46)	991 (25.28)		
Never	1,531 (31.81)	141 (41.72)	231 (46.95)	27 (42.86)	1,132 (28.88)		
Smoking years (years), median (IQR)	30.71 (0.00, 42.48)	22.50 (0.00, 40.00)	10.00 (0.00, 40.00)	20.00 (0.00, 33.00)	32.45 (0.00, 43.91)	0.2317	<0.0001
Medical history							
Previous allergic episode, n (%)	555 (11.53)	61 (18.05)	55 (11.18)	12 (19.05)	427 (10.89)	0.0050	0.0003
Vaccination within past 5 years, n (%)	137 (2.85)	11 (3.25)	10 (2.03)	2 (3.17)	114 (2.91)	0.2707	0.6914
Emergency visit due to AECOPD in prior year (times), median (IQR)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.00 (0.00, 2.00)	0.00 (0.00, 1.00)	0.00 (0.00, 1.00)	0.4031	0.4868
Hospitalization due to AECOPD in prior year (times), median (IQR)	1.00 (0.00, 2.00)	0.00 (0.00, 1.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.0062	0.0279
Other comorbidities, n (%)							
Respiratory disease							
Community-acquired pneumonia	1,483 (30.81)	103 (30.47)	152 (30.89)	19 (30.16)	1,209 (30.84)	0.8972	0.9984
VTE (including PE and DVT)	43 (0.89)	5 (1.48)	2 (0.41)	0 (0.00)	36 (0.92)	0.1277	0.4201
Pulmonary interstitial fibrosis	121 (2.51)	10 (2.96)	11 (2.24)	2 (3.17)	98 (2.50)	0.5147	0.9093
Pulmonary heart disease	1,015 (21.09)	52 (15.38)	102 (20.73)	14 (22.22)	847 (21.61)	0.0515	0.0621
Failure of respiration	1,209 (25.12)	73 (21.60)	131 (26.63)	24 (38.10)	981 (25.03)	0.0983	0.0371
Cardiovascular disease							
Coronary heart disease	861 (17.89)	59 (17.46)	91 (18.50)	6 (9.52)	705 (17.98)	0.7020	0.3629
Acute heart failure	21 (0.44)	0 (0.00)	5 (1.02)	0 (0.00)	16 (0.41)	0.0836	0.1674
Chronic heart failure	277 (5.76)	22 (6.51)	25 (5.08)	3 (4.76)	227 (5.79)	0.3820	0.8279
Digestive disease							
Gastroesophageal reflux disease	91 (1.89)	12 (3.55)	12 (2.44)	3 (4.76)	64 (1.63)	0.3479	0.0184

(Continued)

TABLE 1 | Continued

Main variables	All patients (*N* = 4,813)	ACO phenotype (*N* = 338)	BCO phenotype (*N* = 492)	ABCO phenotype (*N* = 63)	Patients without asthma or bronchiectasis (*N* = 3,920)	*P* value for ACO vs. BCO	*P* value among four phenotypes
Peptic ulcer	69 (1.43)	3 (0.89)	6 (1.22)	2 (3.17)	58 (1.48)	0.7450	0.4442
Other condition							
Cancer	55 (1.14)	4 (1.18)	5 (1.02)	1 (1.59)	45 (1.15)	1.0000	0.8488
Cerebrovascular disease	230 (4.78)	22 (6.51)	22 (4.47)	2 (3.17)	184 (4.69)	0.1981	0.4328
Peripheral biomarkers, median (IQR)							
White blood cell (*10^9/L)	7.18 (5.57, 9.40)	7.42 (5.70, 9.38)	7.48 (5.76, 10.10)	7.71 (6.13, 10.27)	7.11 (5.51, 9.30)	0.3642	0.0123
Platelet (*10^9/L)	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.02 (0.02, 0.03)	0.02 (0.02, 0.02)	0.02 (0.02, 0.03)	0.6041	<0.0001
Neutrophil (%)	67.90 (55.50, 77.60)	64.10 (53.30, 73.70)	70.00 (58.45, 79.10)	67.10 (57.30, 77.50)	67.90 (55.45, 77.67)	<0.0001	0.0006
Neutrophil (*10^9/L)	5.02 (3.54, 7.20)	4.73 (3.30, 6.93)	5.34 (3.77, 7.86)	5.72 (4.60, 7.22)	4.97 (3.50, 7.19)	0.0027	0.0040
Lymphocyte (%)	16.22 (7.90, 24.40)	18.40 (7.80, 26.60)	15.10 (8.40, 23.20)	16.70 (7.20, 24.20)	16.21 (7.80, 24.30)	0.0124	0.0903
Lymphocyte (*10^9/L)	1.27 (0.86, 1.75)	1.40 (0.94, 1.94)	1.23 (0.87, 1.70)	1.54 (1.10, 2.19)	1.26 (0.85, 1.73)	0.0097	0.0031
Eosinophil (%)	1.10 (0.10, 2.70)	1.40 (0.10, 4.10)	0.90 (0.10, 2.60)	0.90 (0.02, 2.30)	1.10 (0.10, 2.70)	0.0204	0.0407
Eosinophil (*10^9/L)	0.10 (0.02, 0.21)	0.12 (0.03, 0.33)	0.09 (0.02, 0.20)	0.11 (0.04, 0.27)	0.10 (0.02, 0.21)	0.0266	0.1148
Direct bilirubin (umol/L)	3.20 (1.90, 4.70)	3.10 (1.90, 4.40)	3.10 (1.87, 4.60)	3.20 (2.20, 4.10)	3.20 (1.90, 4.70)	0.6448	0.6359
Alkaline phosphatase (U/L)	0.01 (0.01, 0.01)	0.01 (0.01, 0.02)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.01 (0.01, 0.01)	0.1520	0.2242
Gamma glutathione transpeptidase (U/L)	0.00 (0.00, 8.80)	0.00 (0.00, 14.66)	0.00 (0.00, 0.02)	0.00 (0.00, 15.30)	0.00 (0.00, 7.80)	0.0644	0.1028
Arterial blood gas, median (IQR)							
$PaCO_2$ (mmHg)	34.30 (0.00, 43.40)	33.10 (0.00, 41.20)	32.60 (0.00, 43.60)	0.00 (0.00, 40.90)	34.70 (0.00, 43.50)	0.0190	0.0038
PaO_2 (mmHg)	0.00 (0.00, 68.90)	0.00 (0.00, 64.40)	0.00 (0.00, 65.25)	0.00 (0.00, 0.00)	0.00 (0.00, 69.90)	0.5230	0.0004
SaO_2 (%)	0.00 (0.00, 94.80)	0.00 (0.00, 94.80)	0.00 (0.00, 93.80)	0.00 (0.00, 84.40)	68.30 (0.00, 94.90)	0.1940	0.0004
Lung function test							
Post-bronchodilator lung function, median (IQR)							
FEV1 (L)	0.93 (0.65, 1.32)	1.20 (0.87, 1.57)	0.87 (0.62, 1.17)	1.00 (0.74, 1.32)	0.91 (0.64, 1.31)	<0.0001	<0.0001
FVC (L)	1.97 (1.45, 2.54)	2.35 (1.77, 2.94)	1.79 (1.33, 2.27)	2.21 (1.73, 2.81)	1.95 (1.43, 2.53)	<0.0001	<0.0001
FEV1/FVC (%)	0.50 (0.42, 0.59)	0.54 (0.44, 0.61)	0.51 (0.43, 0.58)	0.44 (0.40, 0.52)	0.50 (0.42, 0.59)	0.0383	0.0003
FEV1 % predicted value (%)	0.40 (0.28, 0.56)	0.50 (0.36, 0.64)	0.38 (0.28, 0.51)	0.39 (0.33, 0.51)	0.39 (0.27, 0.56)	<0.0001	<0.0001
FVC % predicted value (%)	0.65 (0.50, 0.82)	0.77 (0.61, 0.90)	0.62 (0.48, 0.76)	0.67 (0.59, 0.79)	0.65 (0.49, 0.82)	<0.0001	<0.0001
GOLD categories, n (%)							
GOLD 1	246 (5.11)	23 (6.80)	22 (4.47)	1 (1.59)	200 (5.10)	<0.0001	<0.0001
GOLD 2	1,102 (22.90)	121 (35.80)	90 (18.29)	12 (19.05)	879 (22.42)		
GOLD 3	1,490 (30.96)	102 (30.18)	178 (36.18)	26 (41.27)	1,184 (30.20)		
GOLD 4	1,185 (24.62)	44 (13.02)	121 (24.59)	12 (19.05)	1,008 (25.71)		
Short-term clinical outcomes							
Within the index hospitalization							

(Continued)

TABLE 1 | Continued

Main variables	All patients (*N* = 4,813)	ACO phenotype (*N* = 338)	BCO phenotype (*N* = 492)	ABCO phenotype (*N* = 63)	Patients without asthma or bronchiectasis (*N* = 3,920)	*P* value for ACO vs. BCO	*P* value among four phenotypes
All-cause mortality, n (%)	3 (0.06)	0 (0.00)	1 (0.20)	0 (0.00)	2 (0.05)	1.0000	0.4598
ICU/RICU admission, n (%)	70 (1.45)	6 (1.78)	4 (0.81)	0 (0.00)	60 (1.53)	0.3315	0.5494
Length of hospital stay (days), median (IQR)	10.00 (8.00, 13.00)	10.00 (8.00, 13.00)	10.00 (8.00, 13.00)	10.00 (8.00, 12.00)	10.00 (8.00, 13.00)	0.7748	0.8653
CAT score change between 4 weeks prior admission and discharge, median (IQR)	−7 (−12, −3)	−7 (−12, −3)	−7 (−12, −3)	−8 (−13, −3)	−7 (−12, −3)	0.8580	0.8526
During 30 days after the index hospital discharge							
All-cause mortality, n (%)	9 (0.19)	0 (0.00)	2 (0.41)	1 (1.59)	6 (0.15)	0.5166	0.0670
Recurrence of AECOPD, n (%)	205 (4.26)	11 (3.25)	25 (5.08)	4 (6.35)	165 (4.21)	0.2043	0.5028
All-cause readmission, n (%)	129 (2.68)	7 (2.07)	15 (3.05)	2 (3.17)	105 (2.68)	0.3889	0.8504
AECOPD-related readmission, n (%)	99 (2.06)	5 (1.48)	13 (2.64)	1 (1.59)	80 (2.04)	0.2584	0.6891

ABCO, chronic obstructive pulmonary disease patients comorbid with asthma and bronchiectasis; ACO, asthma-chronic obstructive pulmonary disease overlap; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BCO, bronchiectasis- chronic obstructive pulmonary disease overlap; BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test; COPD, chronic obstructive pulmonary disease; DVT, deep venous thrombosis; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; GOLD, the Global Initiative for Chronic Obstructive Lung Disease; ICU, intensive care unit; IQR, interquartile range; PE, pulmonary embolism; RICU, respiratory intensive care unit; SD, standard deviation.

phenotype patients, BMI, gastroesophageal reflux disease, and level of alkaline phosphatase were associated with increased probabilities of exacerbation recurrence. Previous allergic episode, pulmonary heart disease, levels of white blood cells, and gamma glutathione transpeptidase were independent predictors in the patients without asthma or bronchiectasis. With respect to the exacerbation-related readmission, acute heart failure was the single strong predictor in the BCO phenotype patients. Times of hospitalization and emergency visit due to exacerbation in the prior year, levels of white blood cells and platelets, and percentage of neutrophils were positively associated with elevated exacerbation-related readmission rate in patients without asthma or bronchiectasis (**Figure 2**).

Kaplan–Meier curves and log-rank tests for recurrence of exacerbation and exacerbation-related readmission within 30 days after the index hospital discharge between ACO and BCO phenotype patients, between ACO or BCO phenotype patients and patients without asthma or bronchiectasis, and among the four phenotype patients are shown in **Figure 3**, respectively. Significant differences were not seen among these phenotypes.

DISCUSSION

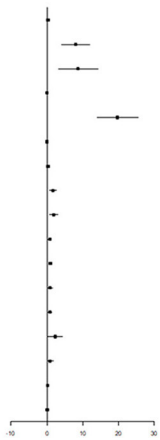
In current manuscript, clinical characteristics and short-term prognosis profiles of hospitalized patients with COPD due to exacerbation comorbid with asthma and/or bronchiectasis, as well as those patients without the two comorbidities were fully analyzed. The prevalence of ACO, BCO, and ABCO phenotypes were 7.02, 10.22, and 1.31%, respectively.

Major findings of our analyses confirmed that patients with COPD comorbid with asthma and/or bronchiectasis or without showed distinct clinical features, particularly in age, gender, BMI, smoking status, prior allergic and COPD history, hospitalization due to exacerbation in the past year, comorbidities (e.g., pulmonary artery hypertension, lung cancer, failure of respiration, diabetes, gastroesophageal reflux disease, and anxiety or depression), levels of peripheral biomarkers (e.g., neutrophil, lymphocyte, eosinophil, creatinine, high-sensitivity C-reactive protein, fibrinogen, and N-terminal probrain natriuretic peptide), and lung function. Differences between ACO and BCO phenotypes were similar to previous research (16, 24, 27), but characteristics of ABCO phenotype were seldom described (23, 24). In our data, compared with ACO and BCO phenotype patients, the ABCO phenotype patients had significantly younger age, experienced more prior allergic episodes, and COPD diagnoses, but had a shorter COPD history, comorbid with more failure of respiration and anxiety or depression. Although demographic and clinical characteristics varied between the four phenotypes of patients, no statistical differences were observed with the short-term outcomes. The findings need to be validated using a larger and an independent sample as well as with longer follow-up information.

The prevalences of ACO and BCO phenotypes in our study were lower than previous reports (17–22, 36), maybe due to varied study populations, actual lower prevalence, different diagnosis criteria used, and underestimation of the diseases.

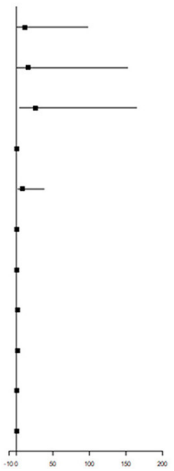
A

Phenotypes	Risk factors	β (95% CI)	P value
ACO phenotype	Neutrophil (*109/L)	0.285 (0.062-0.508)	0.0125
BCO phenotype	Peptic ulcer	8.089 (4.193-11.984)	<.0001
	Venous thromboembolism (including PE and DVT)	8.667 (3.161-14.173)	0.0022
	PaCO2 (mmHg)	0.024 (0.004-0.044)	0.0191
ABCO phenotype	Cancer	19.745 (14.110-25.379)	<.0001
Patients without asthma or bronchiectasis	Age (years)	0.023 (0.002-0.043)	0.0321
	Education level	0.276 (0.066-0.486)	0.0099
	Vaccination within past five years	1.634 (0.675-2.592)	0.0008
	Pulmonary interstitial fibrosis	1.909 (0.793-3.025)	0.0008
	Failure of respiration	0.764 (0.342-1.187)	0.0004
	Coronary heart disease	0.918 (0.455-1.381)	0.0001
	Chronic heart failure	0.822 (0.057-1.586)	0.0352
	Pulmonary heart disease	0.810 (0.365-1.255)	0.0004
	Venous thromboembolism (including PE and DVT)	2.311 (0.260-4.363)	0.0273
	Cerebrovascular disease	0.854 (0.036-1.673)	0.0409
	Hospitalization due to AECOPD in prior year (times)	0.241 (0.095-0.388)	0.0013
	White blood cell (*109/L)	0.066 (0.021-0.110)	0.0038



B

Phenotypes	Risk factors	HR (95% CI)	P value
ACO phenotype	Community-acquired pneumonia	12.227 (1.528-97.831)	0.0183
	Cancer	16.120 (1.706-152.346)	0.0153
	Eosinophil (*109/L)	26.187 (4.166-164.586)	0.0005
BCO phenotype	BMI (kg/m2)	1.122 (1.054-1.194)	0.0003
	Gastroesophageal reflux disease	8.359 (1.847-37.827)	0.0058
	Direct bilirubin (umol/L)	0.680 (0.513-0.902)	0.0075
	Alkaline phosphatase (U/L)	1.015 (1.006-1.025)	0.0017
Patients without asthma or bronchiectasis	Previous allergic episode	1.695 (1.032-2.784)	0.0371
	Pulmonary heart disease	1.968 (1.335-2.899)	0.0006
	White blood cell (*109/L)	1.073 (1.031-1.117)	0.0005
	Gamma glutathione transpeptidase (U/L)	1.004 (1.001-1.007)	0.0106



C

Phenotypes	Risk factors	HR (95% CI)	P value
BCO phenotype	Acute heart failure	24.395 (2.988-199.175)	0.0029
Patients without asthma or bronchiectasis	Hospitalization due to AECOPD in prior year (times)	1.229 (1.048-1.440)	0.0110
	Emergency visit due to AECOPD in prior year (times)	1.194 (1.019-1.398)	0.0285
	White blood cell (*109/L)	1.068 (1.007-1.131)	0.0272
	Platelet (*109/L)	1.004 (1.000-1.008)	0.0473
	Neutrophil (%)	1.014 (1.001-1.026)	0.0279

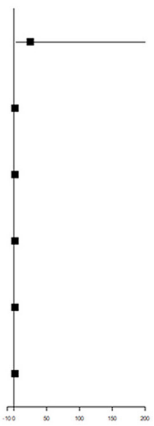


FIGURE 2 | (A) Independent risk factors associated with length of index hospital stay. **(B)** Independent risk factors associated with recurrence of AECOPD within 30 days after the index hospital discharge. **(C)** Independent risk factors associated with exacerbation-related hospital readmission within 30 days after the index hospital discharge. ABCO, chronic obstructive pulmonary disease patients comorbid with asthma and bronchiectasis; ACO, asthma-chronic obstructive pulmonary disease overlap; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BCO, bronchiectasis-chronic obstructive pulmonary disease overlap; BMI, body mass index; CI, confidence interval; DVT, deep venous thrombosis; HR, hazard ratio; ICU, intensive care unit; PE, pulmonary embolism; RICU, respiratory intensive care unit.

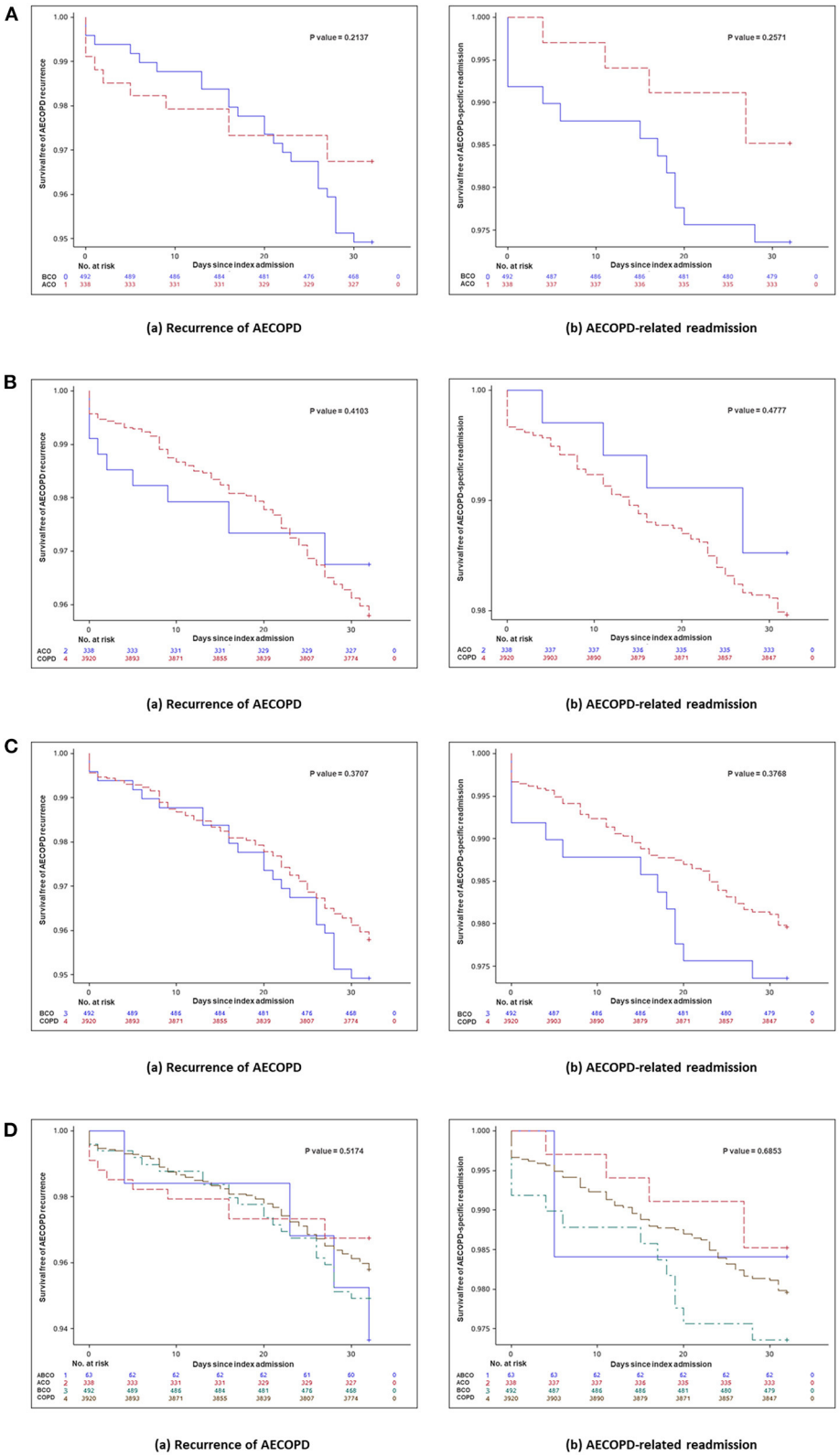


FIGURE 3 | (A) Kaplan–Meier curve and log-rank test for day 30 outcomes between ACO and BCO phenotypes in hospitalized patients with AECOPD. Kaplan–Meier curve and log-rank test for day 30 outcomes (a) recurrent exacerbation ($P = 0.2137$) and (b) exacerbation-related readmission ($p = 0.2571$) between ACO and BCO phenotypes in hospitalized patients with AECOPD. **(B)** Kaplan–Meier curve and log-rank test for day 30 outcomes between ACO phenotype and patients without

(Continued)

FIGURE 3 | asthma or bronchiectasis in hospitalized patients with AECOPD. Kaplan–Meier curve and log-rank test for day 30 outcomes (a) recurrent exacerbation ($p = 0.4103$) and (b) exacerbation-related readmission ($p = 0.4777$) between ACO phenotype and patients without asthma or bronchiectasis in hospitalized patients with AECOPD. **(C)** Kaplan–Meier curve and log-rank test for day 30 outcomes between BCO phenotype and patients without asthma or bronchiectasis in hospitalized patients with AECOPD. Kaplan–Meier curve and log-rank test for day 30 outcomes (a) recurrent exacerbation ($P = 0.3707$) and (b) exacerbation-related readmission ($P = 0.3768$) between BCO phenotype and patients without asthma or bronchiectasis in hospitalized patients with AECOPD. **(D)** Kaplan–Meier curve and log-rank test for day 30 outcomes among four phenotypes in hospitalized patients with AECOPD. Kaplan–Meier curve and log-rank test for day 30 outcomes (a) recurrent exacerbation ($P = 0.5174$) and (b) exacerbation-related readmission ($P = 0.6853$) among four phenotypes in hospitalized patients with AECOPD. ABCO, chronic obstructive pulmonary disease patients comorbid with asthma and bronchiectasis; ACO, asthma-chronic obstructive pulmonary disease overlap; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BCO, bronchiectasis-chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease.

CT scans for bronchiectasis and difficulties with diagnosing asthma clinically could also result in misclassification bias while the phenotypes were categorized. Additionally, differences in genetic backgrounds, allergens, chemical exposures, and dietary dissimilarities from other parts of the world may be alternative explanations, and if demography would play any role among Chinese patients living in other continents needs to be investigated. The latter assumptions should be tested *via* international multicenter collaboration between countries and ethnicities.

Furthermore, the entity of ACO phenotype has been debated for years, and the diagnosis criteria are developing. Cosio BG et al. used a composite criteria to define ACO, which included positive bronchodilator response, medical history of asthma, and higher levels of blood eosinophil and IgE (37). Hansen JE et al. suggested adopting a new bronchodilator response grading strategy based on FEV1 and FVC to identify the distinct ACO phenotype (38) and Fortis et al. (39) found that combined FEV1 and FVC bronchodilator response could be more sensitive to indicate an ACO phenotype, based on the observation that patients with asthma may have a greater bronchodilator response than those with COPD only. However, whether the bronchodilator response has diagnostic value in separating COPD and asthma is doubted (40). Validation studies are needed and consensus has to be achieved.

Current analyses were based on the largest ongoing multicenter registry on hospitalized patients with AECOPD in China. Characteristics and short-term prognoses of common but distinct phenotypes of COPD, i.e., ACO, BCO, ABCO phenotypes and those patients without the two diseases, were fully described. The findings of current analyses could provide the real-world evidence, as well as hints for disease management and further research. Meanwhile, several limitations of current analyses should be stated. First, some estimations of the associations lacked precision, i.e., a broad confidence interval might be due to the limited number of patients or events. Second, some potential impact factors and outcomes were not considered to avoid amplification of multiple testing and the type I error. Third, data on other common phenotypes such as chronic bronchitis and emphysema were not included. Additionally, some factors that would have influences on outcomes of interests were not collected, such as secondhand smoking, biomass fuel exposure, outdoor air pollution, etc, and alternative clinical outcomes including composite ones should be considered. With the ongoing recruitment and follow-up of the ACURE registry, a larger number of patients and long-term prognosis analyses in the future are possible.

CONCLUSIONS

Current findings revealed that ACO, BCO, their overlaps (ABCO), and those patients without the two comorbidities had distinct clinical features, but did not differ in short-term prognoses. Further replication and validation in a larger and independent sample are warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available from the corresponding authors on reasonable request, without undue reservation.

ETHICS STATEMENT

The study involving human participants was reviewed and approved by the Institutional Review Board of the China-Japan Friendship Hospital (approval number: 2015-88). The participants provided their written informed consent to participate in this study.

THE CHINA ACUTE EXACERBATION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE INPATIENT REGISTRY (ACURE) INVESTIGATORS

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AUTHOR CONTRIBUTIONS

JL conceptualized this study, did all statistical analyses, interpreted the data, wrote the first draft, and critically revised the manuscript. CL, KH, and SW took part in manuscript revision, project, and data management. TY and CW supervised the work, had full access to all of the data in the study, and took responsibility for the integrity of the work as a whole, from inception to the published article. All authors have read and approved the final manuscript to be published.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.817048/full#supplementary-material

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