STUDY REPORT Synopsis

A non-interventional study to investigate the current situation of Asthma-COPD Overlap Syndrome in patients over age 40 with persistent airflow limitation in China

Background/Rationale

Asthma and chronic obstructive pulmonary disease (COPD) are very common chronic airway diseases. A significant proportion of patients with chronic respiratory tract disorder have overlapping features of both asthma and COPD, especially adults over age 40. Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD) added the chapter of asthma-COPD overlap syndrome (ACOS) in 2014 to describe these patients.

Patients with ACOS possibly have a more rapid disease progression, a worse health-related quality of life (HRQoL), more frequent respiratory exacerbations, increased co-morbidities and heavier medical costs than those with asthma or COPD alone.

Although GINA 2014 specifies the definition, features and diagnosis procedures of ACOS, and GINA 2015 and GOLD 2015 also have official descriptions of ACOS, there are still many remaining problems about this disease. Moreover, identifying patients with ACOS, especially from those with COPD alone, is helpful for optimizing treatment strategies in ACOS patients, particularly when considering the early use of inhaled corticosteroids and the avoidance of using long-acting bronchodilators alone, which has significant therapeutic implications for ACOS patients.

The distribution, features, prognosis and clinical practice of ACOS are poorly recognized in China. Further research is needed to improve physicians' understanding of ACOS and to optimize management strategies in China.

Objectives:

Primary objective:

To investigate the distribution of patients with ACOS, asthma and COPD over age 40 with chronic airflow limitation in China.

Secondary objectives:

To know the main characteristics and clinical practice of patients with ACOS, asthma and COPD over age 40 with chronic airflow limitation in China.

To investigate the factors that may influence the exacerbations and severity of ACOS patients over age 40 in China.

Methodology:

Study design: A multi-center, cross-sectional and non-interventional study

Data Source: This study collected data (e.g. medical records, patient or physician-reported data) from 2000 outpatients with persistent airway limitation in around 20 sites in China from quarter (Q) 4, 2015 to Q3, 2016 in a consecutive way.

Study Population: In December 2015, the study started to recruit and screen outpatients who meet all the inclusion criteria and none of the exclusion criteria and with available data from around 20 sites in China successively. As of the end of October 2016, a total of 2016 subjects were recruited from 20 sites and 2003 of them who meet all eligibility criteria were included in the full analysis set (FAS).

Exposure: This study was carried out under routine clinical practice. Drugs were determined by the treating physicians and no investigational drugs were designated to treat ACOS, asthma or COPD. Data about current medications and dosages to treat these diseases and some specific concomitant medications was collected at the visit.

Statistical Analysis: The primary and secondary endpoints were summarized by taking descriptive statistics analysis. For each endpoint, continuous data was summarized by number of patients, mean, standard deviation, median, minimum and maximum. Categorical data was summarized by frequency and percentages. 95% CIs were calculated as appropriate. Summary was provided for ACOS, COPD and asthma separately and overall wherever applicable. In addition, Poisson regression model was used to explore the association between the number of exacerbation episodes and the selected patient characteristics or/and clinical practices. Similar risk analysis was performed on the disease severity among ACOS patients who completed COPD Assessment Test (CAT), Asthma Control Questionnaire-5 (ACQ-5) and Modified British Medical Research Council (mMRC).

Results

Primary objective: The primary objective of this study was to investigate distribution of patients with ACOS, asthma and COPD over age 40 with chronic airflow limitation in China.

The study enrolled 2016 patients in total and 2003 of them who met the inclusion and exclusion criterion were included in the FAS. In FAS, 749 patients were diagnosed with ACOS, accounting for 37.4% (95% CI: 35.3%-39.6%); 971 patients were diagnosed with COPD, accounting for 48.5% (95% CI: 46.3%-50.7%); 283 patients were diagnosed with asthma, accounting for 14.1% (95% CI: 12.6%-15.7%).

Secondary objectives:

1. **To know the main characteristics and clinical practice of patients with ACOS, asthma and COPD over age 40 with chronic airflow limitation in China**

1) Age at initial diagnosis

In this study, mean age at initial diagnosis was 60.27±9.540 years old for ACOS, 61.51±9.837 years old for COPD, and 47.71±16.427 years old for asthma. Mean age at initial diagnosis for ACOS patients was younger than for COPD patients, but older than for asthma patients.

2) Smoking history and biomass fuels exposure history

The proportion of patients with a history of smoking was 81.8% (794/971) among COPD patients which was higher than that in ACOS patients (57.7%, 432/749) and asthma patients (33.9%, 96/283). Among ACOS, COPD and asthma patients with smoking history, mean duration of smoking history was 35.7±12.08 years, 38.5±11.75 years and 30.3±11.94 years respectively; the average consumption amount of cigarrete was 781±541.2 cigarettes/year, 858±576.6 cigarettes/year and 576±473.6 cigarettes/year; proportion of patients with ≥400 cigarettes/year was 77.1%, 81.3% and 57.6% respectively. The proportion of patients with history of severe biomass fuels exposure was 30.9% in those with COPD, higher than 28.0% (210/749) in ACOS patients and 22.3% (63/283) in asthma patients.

3) Family history of asthma and past history of allergy

There were 33.9% (254/749) ACOS patients and 33.2% (94/283) asthma patients had a family history of asthma, and the proportion of asthma family history in both of ACOS and asthma patients were higher than that in COPD patients (20.7%, 201/971). Among ACOS patients, the proportion of patients with a history of drug allergy and with a history of allergic disease were 17.8% (133/749) and 24.4% (183/749) respectively, which were 11.6% (113/971) and 12.0% (117/971) in COPD patients, and 24.4% (69/283) and 43.5% (123/283) in asthma patients respectively. Proportion of ACOS patients with a history of drug allergy and allergic disease was lower than that in asthma patients, but higher than that in COPD patients.

4) Previous diagnosis

Among patients diagnosed with ACOS in this study, 65.3% (489/749) had a previous diagnosis of asthma, and 37.7% (282/749) had a previous diagnosis of COPD; there were 25.4% (190/749), 17.5% (131/749) and 3.6% (27/749) patients with a previous diagnosis of chronic bronchitis, emphysema and chronic bronchitis with emphysema respectively. Among patients diagnosed with COPD in this study, 5.4% (52/971) had a previous diagnosis of asthma; there were 29.8% (289/971), 23.3% (226/971) and 10.2% (99/971) patients with a previous diagnosis of chronic bronchitis, emphysema and chronic bronchitis with emphysema respectively. In ACOS, proportions of patients with a previous diagnosis of chronic bronchitis, emphysema or chronic bronchitis with emphysema were all lower than those in COPD patients.

5) Current respiratory symptoms

Current respiratory symptoms collected in this study mainly included dyspnea, cough, wheeze, expectoration and chest tightness. 40.9% (306/749) ACOS patients had all 5 respiratory symptoms above mentioned concurrently; this proportion in ACOS patients was higher than in COPD patients (36.7%, 356/971) and asthma patients (33.6%, 95/283). The top 3 respiratory symptoms in incidence in ACOS patients were cough (79.4%), expectoration (76.5%) and wheeze (74.6%); which were cough (82.7%), expectoration (81.6%) and dyspnea (69.7%) in COPD patients, and wheeze (76.0%), cough (75.3%) and expectoration (70.0%) in asthma patients, respectively.

6) Lung function test in this study

Current or latest lung function test within 6 months prior to this study visit showed each data of lung function (such as FEV_1%pred, FEV_1/FVC, etc.) in ACOS patients was higher than that in COPD patients and lower than that in asthma patients. The detailed data had been showed as below. Before inhalation of bronchodilator, the mean FEV_1%pred of ACOS, COPD and asthma patients was 47.34±16.531, 45.59±19.571 and 55.41±18.617 respectively; and the mean FEV_1/FVC (%) in the three disease populations was 50.21±10.151, 47.90±11.505 and 55.63±9.816 respectively. After inhalation of bronchodilator, the values of both FEV_1%pred and FEV_1/FVC (%) increased for all three disease populations. the mean FEV_1%pred in the three disease populations was 55.57±17.872, 49.85±20.157 and 65.20±19.243 respectively; and the mean FEV_1/FVC (%) in the three disease populations was 52.60±10.590, 48.97±11.624 and 58.87±9.144 respectively. Compared to pre-bronchodilator, the FEV_1 post-bronchodilator in ACOS, COPD and asthma patients increased by 19.77±15.921%, 11.56±12.063% and

20.11±17.425%, and absolute increase of FEV_1 was 0.22±0.164 L, 0.12±0.115 L and 0.26±0.207 L in the three disease populations respectively. Thus, absolute and percent changes of FEV_1 after inhalation of bronchodilator in ACOS patients were higher than those in COPD patients, but lower than those in asthma patients.

7) Grading of lung function for severity of airflow limitation

In this study, lung function grading in GOLD was used to assess severity of airflow limitation in ACOS, COPD and asthma patients. Overall, most patients had moderate airflow limitation in all three groups, while patients with mild or very severe limitation were relatively few. The distribution of patients with different severity of airflow limitation in those with ACOS was somewhere in between the other two groups. The proportions of patients with mild or moderate airflow limitation in asthma population were 22.3% and 56.9% respectively, higher than those in ACOS (9.4% and 50.9%) and COPD population (8.5% and 36.1%); while the proportions of patients with severe or very severe airflow limitation (17.3% and 3.5%) in asthma patients were lower than those in ACOS (32.6% and 7.1%) and COPD patients (37.9% and 17.4%).

In patients with mild, moderate, severe or very severe airflow limitation (GOLD), proportion of asthma patients was 29.2%, 18.0%, 7.4% and 4.3% respectively. It showed a tendency of gradual decrease with increased severity of airflow limitation. Proportion of COPD patients at each level of airflow limitation (GOLD) was 38.4%, 39.3%, 55.7% and 72.8% respectively. It showed a tendency of gradual increase with increased severity of airflow limitation. Proportion of ACOS patients at each level of airflow limitation (GOLD) was 32.4%, 42.7%, 36.9% and 22.8% respectively, without a obvious tendency of change. Proportion of ACOS in mild to moderate population was 40.6% [(70+381)/(216+893)].

8) Laboratory tests

There were a total of 547 patients who had the data of blood eosinophil count being collected in this study, accounting for 27.3% (547/2003) of the overall population; among them, there were 205 ACOS patients, 261 COPD patients and 81 asthma patients. The mean blood eosinophil count was $(0.27\pm0.275)\times10^9$/L in ACOS patients with collected data of blood eosinophil count, which was lower than that of $(0.31\pm0.324)\times10^9$/L in asthma patients and higher than that of $(0.19\pm0.170)\times10^9$/L in COPD patients. The proportion of patient with value of blood eosinophil count $\geq0.3\times10^9$/L was 34.6% in ACOS patients, 43.2% in asthma patients, and 19.5% in COPD patients; it could be found that proportion of patient with mean value of blood eosinophil count $\geq0.3\times10^9$/L in ACOS was lower than that in asthma and higher than

that in COPD.

There were only 51 patients who had the data of induced sputum cytology available in this study, accounting for 2.5% (51/2003) of the overall population, including 16 ACOS patients, 28 COPD patients and 7 asthma patients. The mean percentage of induced sputum eosinophil was 11.43±14.739% in ACOS patients with collected data of induced sputum cytology, which was lower than that of 13.73±13.179% in asthma patients, and higher than that of 2.97±2.955% in COPD patients; while mean percentage of induced sputum neutrophil was 45.62±29.909% in ACOS patients, lower than 63.81±19.355% in COPD patients and higher than 38.19±14.483% in asthma patients.

9) Acute exacerbation history within 12 months prior to the study visit

Within 12 months prior to the study visit, 42.6% (319/749) of the ACOS patients had acute exacerbation, higher than that of 40.7% in COPD patients and 33.9% in asthma patients; the mean number of acute exacerbation episodes in ACOS patients was 2.2±2.23, while that was 2.0±1.55 in COPD patients and 2.1±1.91 in asthma patients; thus it shown that the proportion of patients with acute exacerbation history and mean number of acute exacerbation in ACOS patients were higher than those in COPD patients and asthma patients., More than half patients underwent one time of episode of acute exacerbation in ACOS, COPD and asthma patients, with similar proportions of 53.9%, 54.4% and 52.1% respectively; proportions of patients with 2 or more episodes of acute exacerbations in the three diseases population were 46.1%, 45.6% and 47.9% respectively; and proportions of patients with 5 or more episodes of acute exacerbations were low in the three diseases population, which were 10.0%, 6.1% and 9.4% respectively.

Forty-four ACOS patients received outpatient systemic hormone therapy due to acute exacerbation within 12 months prior to the visit, with mean duration of treatment of 12.2±11.50 days which was longer than COPD patients (n=44, 10.9±15.11 days) and asthma patients (n=22, 10.1±8.96 days); 125 ACOS patients received outpatient antibiotic treatment due to acute exacerbation within 12 months prior to the visit, with mean duration of treatment of 15.6±18.71 days which was also longer than COPD patients (n=143, 11.5±11.36 days) and asthma patients (n=45, 13.6±15.37 days).

10) Evaluation by GOLD 2015 grouping principles

Using CAT as symptom criteria, evaluation of GOLD 2015 grouping showed: in ACOS

patients, proportions of groups A, B, C and D were 11.7%, 31.0%, 6.9% and 50.3% respectively; in COPD patients, the proportions were 11.2%, 22.2%, 9.7% and 56.8% respectively. Proportion distribution at each group was essentially similar between the two patient populations, with the highest proportion of group D. The proportion of patients with more symptoms (groups B + D) in ACOS was 81.3%, higher than that in COPD patients (79.1%). While the proportion of patients with higher lung function grade and disease risk (groups C + D) in ACOS was 57.2%, lower than that in COPD patients (66.5%).

Using mMRC as symptom criteria, evaluation of GOLD 2015 grouping showed: in ACOS patients, proportions of groups A, B, C and D were 26.7%, 16.0%, 21.6% and 35.6% respectively; in COPD patients, the proportions were 21.1%, 12.4%, 24.1% and 42.4% respectively; which were different from grouping using CAT as criteria, with significantly increased patients in groups A and C, and decreased patients in groups B and D. In ACOS patients, proportions of patients with more disease symptoms (groups B + D, 51.7%) and higher lung function grade and disease risk (groups C + D, 57.2%) were both lower than those in COPD patients (54.8% and 66.5%), which were different from grouping using CAT as criteria.

11) Patient reported outcomes

In this study, mMRC was used to assess severity of dyspnea in ACOS or COPD patients. The mMRC is divided into 5 grades from 0 to 4 grade, higher grades means higher severity of dyspnea. The results showed: in ACOS patients, proportions of patients with mMRC self-assessment of grades 0 to 4 were 17.5%, 30.8%, 31.4%, 16.3% and 4.0% respectively; in COPD patients, the proportions were 14.9%, 30.3%, 32.3%, 18.2% and 4.2% respectively; the trend of patients distribution was similar between the two populations, that the proportions of grades 1 and 2 were relatively higher. In comparison, proportion of mMRC grades 0-1 was higher in ACOS patients than COPD patients. With increased severity of dyspnea (grade 0-4), the proportion of ACOS patients gradually decreased, while COPD gradually increased.

In this study, CAT was used to assess clinical impacts of ACOS and COPD symptoms on patients' daily life and wellbeing with four categories: mild (1-10 points), moderate (11-20 points), severe (21-30 points) and very severe (31-40 points). The results showed: the total mean score of CAT in ACOS patients was 17.0±7.80 points, higher than that of 16.3±7.78 points in COPD patients. In ACOS patients, proportions of patients with CAT grade assessed as mild, moderate, severe or very severe were 22.2%, 42.7%, 30.6% and 4.5% respectively; in COPD patients, the proportions were 24.8%, 45.6%, 25.5% and 4.0% respectively; proportion

distribution was similar in the two populations, with the higher proportion in groups of moderate and severe. The proportion of severe and very severe of CAT grades was higher in ACOS patients than that in COPD patients. With increased severity of clinical impacts, proportion of ACOS patients increased, while proportion of COPD patients decreased.

In this study, ACQ was used to assess asthma control in ACOS and asthma patients and the results fell into three categories: complete control, good control and uncontrolled. The results showed: in ACOS patients, 17.6% patients were under complete control, 18.3% were under good control, while 64.1% patients had uncontrolled asthma; in asthma patients, the proportions were 17.7%, 23.0% and 59.4% respectively; there was a higher proportion of uncontrolled asthma in ACOS patients than in the asthma patients.

12) Therapeutic drug usage

In this study, a total of 1376 patients with ACOS, COPD or asthma were receiving drug treatment, accounting for 68.7% (1376/2003); 31.3% (627/2003) patients weren't receiving any drug treatment. Drugs currently used in more than 10% patients included ICS/LABA combination, Anticholinergics, Xanthines, expectorants, leukotriene receptor antagonists and selective β2 adrenergic receptor agonists. One thousand and eight patients were receiving ICS/LABA combination, accounting for 50.3%, mainly including Fluticasone/Salmeterol, Budesonide/Formoterol, Beclomethasone/Formoterol; 634 patients were receiving Anticholinergics, accounting for 31.7%, mainly including tiotropium bromide, which is a kind of long-acting cholinergic receptor antagonist (LAMA); 315 patients were receiving Xanthines, accounting for 15.7%, mainly including theophylline, aminophylline and doxofylline; 251 patients were receiving expectorants, accounting 12.5%; 248 patients were receiving leukotriene receptor antagonists, accounting for 12.4%, mainly including montelukast; 205 patients were receiving selective β2 adrenergic receptor agonists, accounting for 10.2%, mainly including salbutamol which is a kind of short-acting β2 receptor agonist (SABA).

In ACOS patients, 247 patients were not receiving any drug treatment, accounting for 33.0% (247/749); 502 patients were receiving drug treatment, accounting for 67.0% (502/749); the most commonly used drugs were ICS/LABA combination formulations (51.1%), followed by Anticholinergics (25.1%) and leukotriene receptor antagonists (14.8%). In COPD patients, 315 patients were not receiving any drug treatment, accounting for 32.4% (315/971); 656 patients were receiving drug treatment, accounting for 67.6% (656/971); the most commonly used

drugs were ICS/LABA combination formulations (46.3%), followed by Anticholinergics (43.5%) and Xanthines (18.1%). In asthma patients, 65 patients were not receiving any drug treatment, accounting for 23.0% (65/283); 218 patients were receiving drug treatment, accounting for 77.0% (218/283); the most commonly used drugs were also ICS/LABA combination formulations (61.8%), followed by leukotriene receptor antagonists (27.6%) and selective β2 adrenergic receptor agonists (16.3%).

2. To investigate the factors that may influence the exacerbations and severity of ACOS patients over age 40 in China

In this study, Poisson regression model was used to analyze factors influencing number of acute exacerbation episodes in ACOS patients. Results of univariate analysis showed independent factors influencing number of acute exacerbation in ACOS patients included education level, family income level, state of health insurance, history of allergic disease, history of biofuel exposure, FEV% airflow limitation grade after inhalation of bronchodilator, hyperinflation and other abnormality confirmed by chest X-ray examination, previous diagnosis of emphysema, and disease course. The risk of acute exacerbation increases with the decrease of educational level and family income level. Patients not at their own expense had higher risk of acute exacerbation than those at their own expense. In addition, the factors of history of allergic disease, history of biofuel exposure, FEV% airflow limitation grade after inhalation of bronchodilator, previous diagnosis of emphysema, hyperinflation and other abnormality confirmed by chest X-ray examination, and a disease course of ≥2 years all increase the risk of acute exacerbation. Results of multivariate analysis showed: the factors of family income, smoking history, history of allergic disease, history of biofuel exposure, airflow limitation grade, previous diagnosis of emphysema and disease course all influenced number of acute exacerbation episodes in ACOS patients.

Safety Results:

According to the protocol, this study did not collect safety data actively and only recorded the safety information spontaneously reported by patients. No statistical analysis was performed.

Conclusions:

1. Among 2003 patients over age 40 with persistent airflow limitation included in this study, distribution of ACOS, COPD and asthma showed ACOS accounted for 37.4%, COPD accounted for 48.5% and asthma accounted for 14.1%.

2. Compared with COPD patients and asthma patients, acute exacerbation rate and the average number of acute exacerbation episodes were higher in ACOS patients.
4. ACQ assessment showed that proportion of ACOS patients with uncontrolled asthma was higher than asthma patients.
5. In this study, 31.3% (627/2003) patients were not receiving any drug treatment; while proportion of patients not receiving any drug treatment in ACOS, COPD and asthma patients was 33.0% (247/749), 32.4% (315/971) and 23.0% (65/283) respectively.
6. Results of multivariate analysis showed: factors influencing the number of acute exacerbation episodes of ACOS patients included family income, smoking history, history of allergic disease, history of biofuel exposure, airflow limitation grade, previous diagnosis of emphysema and disease course.