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The Cohort Study for Bronchial Asthma in China

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1. INTRODUCTION

1.1 Background

Bronchial asthma (asthma) is a common chronic airway disease worldwide, affecting 1 – 18% of the global population [1]. According to the global burden of disease (GBD) study in 2015, there are about 358 million asthma patients in the world, and 400,000 people die of asthma every year [2]. According to the Chinese China pulmonary health (CPH) survey, the prevalence of asthma in Chinese people aged 20 and above is 4.2%, and the total number of patients is 45.7 million, of which about 26.2%, or 13.2 million patients, have developed irreversible airflow limitation. The above data show that asthma has become a public health and health care problem that needs to be seriously faced and solved in China.

Asthma is a heterogeneous disease whose etiology, pathogenesis, and response to existing standardized therapies vary from person to person, requiring identification of its phenotype and endotype. The study of the phenotype and endotype of asthma is helpful to the diagnosis, management and individualized treatment of asthma. Therefore, this study intends to establish an asthma cohort study, construct an information network platform system and a biological specimen bank for asthma cohorts, establish clear follow-up standards and norms, observe the outcome of asthma, and explore biomarkers for predicting the outcome of asthma.

1.2 Rationale

Bronchial asthma is a heterogeneous disease, which is caused by the complex and diverse pathogenesis, genetics and molecular mechanisms of asthma. In recent years, in view of the heterogeneity of asthma, the study of its phenotype and endotype has been gradually carried out. In the past, asthma was thought to occur in children or before the age of 18, but epidemiological measurements show that a considerable number of asthma occurs in adults, even after the age of 40 or 60 [3].Moreover, studies have also shown that elderly patients with late-onset asthma are more likely to have severe (or refractory) asthma, that is, the patient's condition is more severe, lung function declines faster, the condition is more difficult to control, and the response to standard anti-asthma therapy (inhaled corticosteroids) is not good [4-6].Similar to COPD patients, some asthma patients have clinical manifestations of progressive decline in lung function, which may be related to the duration of the disease, the type of inflammation and airway remodelling [7]. There are differences in the rate of decline of lung function among asthmatic patients, which may be related to different clinical phenotypes. At present, the study of bronchial asthma phenotype classification is mainly divided into inflammation classification, clinical classification, intrinsic phenotype classification and so on. Although there are many clinical studies on the characteristics of airway inflammation in asthmatic patients, the

results are inconsistent because of the inconsistent inclusion criteria of patients. Some studies have shown that there is no difference in airway inflammation between elderly asthma and young asthma, both of which are Th2 inflammatory reactions, while other studies have shown that compared with young asthma, the level of IgE in elderly asthma is lower and the specificity is not obvious [8,9].

The establishment of standardized longitudinal studies or biological databases of asthma biomarkers is the key to understand asthma phenotype and endotype, disease mechanism and disease progression. Its implementation will help to reveal the new mechanism of asthma and provide theoretical basis for exploring new therapeutic targets.

1.3 Objective

Establish a standardized asthma cohort study, build an information network platform system and biological specimen bank for asthma cohort, establish clear follow-up standards and norms, observe the outcome of asthma and identify biomarkers to predict the outcome of asthma.

2. OBJECTIVES

2.1 Primary Objective & Outcome Measure

Primary Objective	**Outcome Measure**
● To observe the control of asthma and explore the relationship between biomarkers and the pathogenesis and prognosis of asthma.	● Asthma control in patients with asthma at 2 years ● Clinical Features * and Biomarkers * to Identify Phenotypes * ● Use different phenotypic/biomarkers to predict clinical outcomes of asthma * ● Phenotypes and biomarkers of asthma patients to know the clinical outcome from specific treatment regimen

* Clinical characteristics: allergic history, smoking/exposure to passive smoking, occupational exposure, Bio-fuel exposure, respiratory symptoms, pulmonary function measurements, presence of emphysema or chronic bronchitis on CT scan
* Biomarkers: Blood samples are used to detect biomarkers, Such as total IgE test, phadiatop, interleukin (IL) -4, IL-5, IL-6, IL-8, IL-13, IL-33, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), blood eosinophil (EOS) and so on. Sputum

samples are used to detect biomarkers, such as cytokines, chemokines, sputum cell count and classification.
* Phenotypes: allergic asthma, non-allergic asthma, late-onset asthma in adults, asthma with persistent airflow limitation, asthma with obesity, etc.
* Clinical outcomes: asthma control, frequency of asthma exacerbations, change in quality of life, decrease in lung function FEV1, change in 6-minute walk test (6MWT)
* Specific treatment: e.g. ICS + LABA vs SABA. For example, inflammatory cytokines under different treatment regimens were used to predict clinical outcome as assessed by frequency of asthma exacerbations, asthma-related mortality, and all-cause mortality

2.2 Exploratory Objective and Outcome Measure

Exploratory Objective	**Outcome Measure**
● Explore the factors affecting the acute attack of asthma patients ● Explore factors that predict outcomes from specific treatment regimen	● Multivariate analysis of asthma exacerbations (biomarkers, demographics, medication adherence, visit adherence, smoking status, medication level, comorbidities, disease severity, quality of life, etc.) ● Adjustments to treatment regimens and reasons for adjustments: Medication was evaluated at each visit (type/duration/dose/frequency/discontinuation) ● Correlation between biomarkers, disease severity and/or control, and different measures taken when efficacy varies ● Biomarker parameters, lung function, risk factor levels, and changes in these measures were assessed at each visit

3. METHODOLOGY

3.1 Funding

This study was funded by the research ward demonstration construction project "Clinical Research Resource Construction-Bronchial Asthma Cohort".

3.2 Study Design

This was a 2-year, observational, prospective cohort study. An asthma cohort of 400 asthmatic subjects was formed and carefully managed, and their baseline data including pulmonary function, chest CT, 6-minute walk test and blood samples were obtained and followed up for 2 years.

3.3 Study Population

This study will recruit about 400 subjects in Beijing Chao-Yang Hospital, Capital Medical University, who are over 18 years old, meet the 2023 version of GINA asthma diagnostic criteria, can participate in the study according to the protocol, and sign the informed consent before participating in the study.

3.4 Inclusion Criteria

Study subjects were required to meet all of the following criteria:

- Age ≥ 18 years;
- Meet the 2023 edition of GINA asthma diagnostic criteria
- Subjects must sign the informed consent before participating in the study, and be able to participate in the study according to the protocol and follow up for 2 years.

3.5 Exclusion Criteria

Study subjects were required to exclude all of the following criteria:

- Suffering from other massive lung tissue destructive diseases such as severe bronchiectasis and tuberculosis.
- Severe pleural disease and/or sternal and rib lesions
- Serious uncontrolled disease of other system

- Thoracic or abdominal surgery in the past 3 months
- Eye surgery in the past three months.
- Retina detachment
- Myocardial infarction within the last 3 months
- Hospitalized for heart disease within the last 3 months
- Ongoing anti-tuberculosis treatment
- Pregnancy or breast feeding

3.6 Study Plan

	V0	**V1 (6 months ±30 days)**	**V2 (12 months ±30 days)**	**V3 (18 months ± 30 days)**	**V4 (24 months ± 30 days)**
Informed consent	√				
Inclusive/exclusive criteria	√				
Demographics, medical history, etc.	√				
Disease outcomes		√	√	√	√
Physical examination	√		√		√
Spirometry	√		√		√
Lung volume measurement	√		√		√
Pulmonary diffusion function	√		√		√
FENO	√		√		√
Daily Activities/Symptoms	√	√	√	√	√
Chest X-ray			√		√
Chest CT (Inspiratory and expiratory phase)	√		√		√

Questionnaire (ACT/ACQ/AQLQ)	√	√	√	√	√
Assessment of inhalation technology	√	√	√	√	√
Blood RT	√		√		√
Induced sputum	√		√		√
Phadiatop	√		√		√
Total IgE	√		√		√
Blood samples	√		√		√
Sputum specimen	√		√		√
6MWT	√		√		√
Perception of Dyspnea	√		√		√
Anxiety/Depression	√	√	√	√	√

4. VARIABLES AND EPIDEMIOLOGICAL MEASURMENTS

4.1 Exposures

The patient's treatment is at the discretion of his or her physician, and no additional investigational drug is given to the patient. The study will collect information about the patient's current medications for the respiratory disease, as well as some specific combinations of medications.

4.2 Variables

- Demographic information and general information: gender, date of birth, height, weight, living environment, education level, heating and cooking conditions, etc.
- Medical history, family history, history of chest surgery, etc.

- Allergic history
- Smoking history/Passive smoking history
- Occupational exposure
- Bio-fuel exposure
- Current respiratory symptoms: breathlessness, chest tightness, cough, wheezing, expectoration, etc.
- Diagnosis of respiratory diseases and time of diagnosis
- Acute exacerbation
  - × Acute exacerbation history in 12 months before the visit (the number of exacerbations, severity of exacerbation (using systemic hormones / antibiotics / emergency / hospitalization) and days of hospitalization or emergency room visit
  - × Acute exacerbation and treatment information during intervals of visits: the number of exacerbations, severity of exacerbation (using systemic hormones / antibiotics / emergency / hospitalization) and days of hospitalization or emergency room visit
- Comorbidities
  - × Former comorbidities before baseline
  - × New-developed comorbidities during intervals of visits
- Asthma-related mortality and all-cause mortality during intervals of visits
- Treatment
  - × Current used medications prescribed by physicians to treat asthma/ chronic respiratory symptoms (type/duration/dosage/frequency)
  - × Treatment regimen modification and reason for modifications during intervals of visits: medicine (type/duration/dosage/frequency) and non-medicine treatment
- Pulmonary function:
  - × The latest pulmonary function results at stable stage in 12 months before baseline
  - × Spirometry and bronchial dilation test: pre/post/pred - FEV1, pre/post/pred - FVC, post - FEV1/FVC
  - × Lung volume measurement: absolute/pred - IC, absolute/pred - VCmax, absolute/pred - RV, absolute/pred - TLC
  - × Diffusion function: absolute/pred DLCO SB, absolute/pred VA
- Exhaled Nitric Oxide Test
- Chest X-Ray
- HRCT Scan of the Chest: Inspiratory and Expiratory HRCT
- Blood routine, Phadiatop, total IgE test
- Blood samples: used to detect IL-4, IL-5, IL6, IL-8, IL-13, IL-33, TNF-α, CRP, etc. Blood samples were stored in the -80 ℃ refrigerator in the laboratory of Beijing Institute of Respiratory Diseases.

- Sputum specimen: used to detect IL-17, IFN-γ, etc.
- Questionnaire: ACT (Asthma Control Test); ACQ (Asthma Control Questionnaire); AQLQ (Asthma Quality of Life Questionnaire)
- Inhalation technique assessment: Inhalation technique assessment was conducted through the Inhalation Technique Score Sheet.
- Measurement of perception of dyspnea: The patient's perception of dyspnea was measured using a dynamic variable airflow resistance instrument
- Daily activities: Evaluated by questionnaire or step counting
- 6-minute walk test
- Anxiety/Depression: Anxiety and depression were assessed using the Generalized Anxiety Disorder questionnaire (GAD-7) and Patient Health Questionnaire (PHQ-9).

* Patient Reported Outcomes (PRO) measure:

The ACT/ACQ/AQLQ questionnaire will be completed independently by the patient. The researcher will explain the specific content of each item when the patient has questions. The investigator should check the questionnaire to avoid missing answers. The investigator is advised to conduct a clinical evaluation after the questionnaire is completed.

* ACT (Asthma Control Test); ACT is a questionnaire to assess the control level of asthma patients, and the ACT score has a good correlation with the asthma control level of patients assessed by experts. ACT is suitable for primary hospitals lacking pulmonary function equipment. Asthma was well controlled with a score of 20 to 25 and poorly controlled with a score of 16 to 19; A score of 5 to 15, representing poor asthma control.

* ACQ (Asthma Control Questionnaire); is a scoring scale for assessing asthma control, consisting of 5 simple questions to assess the patient's asthma control level in the past week. Each question was scored from 0 to 6 points according to its severity. The average score of five questions was less than 0.75 for well controlled, 0.75 to 1.5 for asthma controlled, and more than 1.5 for asthma uncontrolled.

* AQLQ (Asthma Quality of Life Questionnaire): It is a rating scale for evaluating the quality of life of asthmatic patients, which evaluates the asthma control level of patients in the past 2 weeks. The AQLQ consisted of 32 questions, which were divided into four parts: symptoms (12 questions), activity limitation (11 questions), emotional function (5 questions) and environmental exposure (4 questions). Each question was scored from 1 to 7 points according to its severity, with 1 point indicating complete limitation and 7 points indicating no limitation. The total score is calculated as the average of all questions, and each section is calculated as the average of each section.

5. DATA PROCESSING

Full analysis set (FAS) will be used for all analyses, which includes all enrolled subjects who fulfil the inclusion/exclusion criteria. Missing data will be analyzed as it is, no imputation method will be utilized.

Statistical analysis will be conducted by epidemiology & statistics work group from Chinese Academy of Sciences, using SAS and SUDAAN software.

The analysis method will be primarily descriptive. For continuous variables, summary statistics including n, mean, median, standard deviation, min and max will be presented. For categorical variables, frequency and percentage of subjects at each category level will be presented. The variable with missing values will be analysed as is, that is, no imputation method will be utilized.

The Primary variables includes overall asthma exacerbations, asthma-related mortality, all-cause mortality, and differences in serum inflammatory cytokine expression between young and elderly asthmatics.

Other primary and secondary variables will be described in general and in subgroups: sex, date of birth, height, weight, living environment, education level/years of formal education, medical history, allergy history, smoking history/passive smoking exposure history, occupational exposure, Bio-fuel exposure, current respiratory symptoms, pulmonary function test, HRCT.

Linear or logistic regression and multivariate analysis were used to explore phenotypic/biomarkers (total IgE test, IL-4, IL-5, IL-6, IL-8, IL-13, IL-33, TNF, CRP, EOS, etc.), etiology, pathogenesis, different treatment regimens and clinical outcomes (asthma-related mortality and all-cause mortality within 5 years, frequency of exacerbations, Quality of life, FEV1 decline, and 6-minute walk test).

5.1 Interim analysis

An interim analysis was conducted when 200 asthmatic patients were enrolled. The date of the interim analysis was the day the 200th patient was enrolled.

5.2 Data Management

An electronic data capture (EDC) system will be used in this study, and data will be entered through a password-protected web data platform. The spirometry data in the pulmonary function test will be transmitted to the web data entry platform every day. The quality of pulmonary function test (FEV1, FVC, and diffusion) was rated by the investigator at 48-hour intervals according to an academic grading system (A, B, C, D, or E).

The completeness and accuracy of the questionnaire variables were examined. Before uploading the data, the surveyor should identify the obvious errors and omissions in the questionnaire. Before statistical analysis, check the consistency of the double-entry data, and scan the paper questionnaire and keep it properly.

6. MONITORING OF THE STUDY

During the study, PI will be in charge of the monitoring of the whole procedure. Two working group will be recruited, focusing on data cleaning and data analysis respectively. The leader will report the progress of the study to the PI every week.

7. COLLECTION AND REPORTING OF ADVERSE EVENTS/ADVERSE DRUG REACTIONS

7.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs.

7.2 Definition of Serious Adverse Events (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is life-threatening (life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe)
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality/birth defect

- Is an important medical event that may jeopardise the subject or may require intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether other situations should be considered an SAE.

  Any suspected transmission via a medicinal product of an infectious agent is also considered an SAE and may be subject to expedited reporting requirements in some countries. Any organism, virus or infectious particle (for example Prion Protein Transmitting Transmissible Spongiform Encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent.

7.3 Definition of Adverse Drug Reactions (ADR)

An Adverse Drug Reaction (ADR) is an Adverse Event suspected to be causally related to the medicinal product.

An ADR is a response to a medicinal product which is noxious and unintended. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure.

The term ADR is used to include both serious and non-serious ADRs.

7.4 Reporting of Adverse Events

As this study was a non-intervention study, the drugs used by the subjects were prescribed by the investigators according to clinical practice, and adverse events were not collected actively.

The investigator is responsible for ensuring that all personnel involved in the study are familiar with the contents of this section.

8. STUDY TIMETABLE

The study is expected to commence in the first quarter of 2023 and be completed in the fourth quarter of 2027. The end point of the study is defined as "completing all related analysis of the study".

Study progress	**Estimated time**
Protocol approved	June 2023
First subject in	June 2023
Last subject in	December 2025
Last subject last visit	December 2027

Study progress	Estimated time
Database lock	December 2027
Completion of Final Study Report	December 2028
Final Study Report to Publication	December 2028

9. REFERENCES

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