

Study Design and Outcomes of Korean Obstructive Lung Disease (KOLD) Cohort Study

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Background: The Korean Obstructive Lung Disease (KOLD) Cohort Study is a prospective longitudinal study of patients with chronic obstructive pulmonary disease (COPD), asthma, or other unclassified obstructive lung diseases. It was designed to develop new classification models and biomarkers that predict clinically relevant outcomes for patients with obstructive lung diseases.

Methods: Patients over 18 years old who have chronic respiratory symptoms and airflow limitations or bronchial hyper-responsiveness were enrolled at 17 centers in South Korea. After a baseline visit, the subjects were followed up every 3 months for various assessments.

Results: From June 2005 to October 2013, a total of 477 subjects (433 [91%] males; 381 [80%] diagnosed with COPD) were enrolled. Analyses of the KOLD Cohort Study identified distinct phenotypes in patients with COPD, and predictors of therapeutic responses and exacerbations as well as the factors related to pulmonary hypertension in COPD. In addition, several genotypes were associated with radiological phenotypes and therapeutic responses among Korean COPD patients.

Conclusion: The KOLD Cohort Study is one of the leading long-term prospective longitudinal studies investigating heterogeneity of the COPD and is expected to provide new insights for pathogenesis and the long-term progression of COPD.

Keywords: Biological Markers; Pulmonary Disease, Chronic Obstructive; Cohort Studies; Longitudinal Studies; Phenotype

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and is associated with substantial socioeconomic burdens which are increasing continuously in many countries¹. The situation seems particularly serious in Asia because of the high prevalence of tobacco smoking, exposure to outdoor and indoor air pollution related to the burning of wood and other biomass fuels, and exposure to occupational dust². The fourth Korean National Health and Nutrition Examination Survey conducted in Korea revealed that the prevalence of COPD in subjects aged >40 years was 13.4%. However, only a minority of COPD patients still receive physician's diagnosis or treatment not only in its early stages but even when lung function is severely impaired³.

One of the main reasons for under-diagnosis and under-treatment of COPD is that the disease progresses slowly and is heterogeneous. Although chronic airflow limitation is one important characteristic of COPD, the disease shows heterogeneous features in terms of clinical presentation, physiology, imaging, response to therapy, decline in lung function, and survival, even in patients that show a similar degree of airflow limitation⁴. This heterogeneity might arise from differences in environmental factors and/or the patient's genetic background. It follows, therefore, that long-term observational cohort studies should be performed in different countries, or regions in which patients of different genetic backgrounds may have been exposed to different disease etiologies to identify the pathogenesis of COPD heterogeneity.

Asia is a very heterogeneous region containing many countries at various stages of development and of varying socioeconomic status. While several cohort studies of COPD are ongoing in Western countries^{5,6}, a few longitudinal studies are being conducted in Asia⁷. Thus, in terms of ethnic heterogeneity, there is a need to activate longitudinal studies of COPD patients across Asia.

The Korean Obstructive Lung Disease (KOLD) Cohort Study is an ongoing prospective longitudinal study that includes patients with COPD, asthma, or other unclassified obstructive lung disease. The aims of the KOLD Cohort Study were to provide a new disease classification of obstructive lung disease, and to identify interactive prognostic factors for obstructive lung disease. The present article describes the design and interim results of the KOLD Cohort Study.

Materials and Methods

1. Study design

Seventeen centers in South Korea participated in the study. Eleven centers joined in June 2005, and another 6 centers have joined since 2010. Patient screening was based on demo-

graphic data, medical history, physical examination, spirometry and a methacholine bronchial provocation test (if forced expiratory volume in 1 second [FEV₁] >60% predicted). After an initial enrollment visit, initial outcome measurements were taken and the patients were followed up every 3 months. In addition to regular follow-ups, emergency visits were carried out and outcome measurements were taken when patients experienced exacerbations. The present study was approved by the institutional review board of the Asan Medical Center Institutional Review Board (No. 2005-0345) and by the Institutional Review Boards of the other 16 hospitals taking part. Written informed consent was obtained from all patients.

2. Subjects

The inclusion criteria for the KOLD Cohort Study were patients over 18 years-of-age with chronic respiratory symptoms as well as one or both of the criteria, airflow limitation or bronchial hyper-responsiveness. "Chronic" was defined as symptoms lasting for more than 3 months, or repeated symptoms experienced at intervals of more than 3 months. Respiratory symptoms were defined as dyspnea, cough, wheeze, or sputum production. Airflow limitation was defined as a pre-bronchodilator FEV₁ over forced vital capacity (FVC) value of less than 0.7 (FEV₁/FVC<0.7). Bronchial hyper-responsiveness was measured using the methacholine provocation test, and was defined as the provocative concentration that reduces the FEV₁ by 20% below 16 mg/mL (provocative concentration that reduces the FEV₁ by 20% [PC₂₀] \leq 16 mg/mL). Unlike other studies, the KOLD Cohort Study did not use smoking history as an inclusion criterion. In addition, patients with bronchial hyper-responsiveness were included. Furthermore, a pre-bronchodilator FEV₁/FVC<0.7 was used rather than post-bronchodilator FEV₁/FVC<0.7 to allow the inclusion of asthma and other unclassified obstructive lung disease patients in the study.

Exclusion criteria were patients with co-existing illnesses that would interfere with the study results (e.g., malignancy, congestive heart failure, cerebrovascular disorders, chronic renal failure, diabetes with severe complications, and uncontrolled hypertension), and respiratory diseases other than obstructive lung disease (e.g., previous pulmonary resection, tuberculosis-destroyed lung, and bronchiectasis). Patients with a recent (8 weeks before screening) exacerbation or other respiratory illness (such as upper respiratory infection or pneumonia) were also excluded. However, patients who recovered from an exacerbation and had been stable for more than 8 weeks were included in the study.

3. Outcome measurement

The evaluation of the KOLD Cohort Study patients is described in Table 1, along with the measurement intervals. The

Table 1. Evaluations of the Korean Obstructive Lung Disease Cohort Study patients

	Screening	Enrollment	Regular follow up			Emergency
			Every 3 months	Every 1 year	Every 3 years	
Demographic data	●	●	-	●	●	●
Body composition analysis	-	◐	-	◐	◐	-
Medical history	●	●	●	●	●	●
Smoking history	-	●	●	●	●	-
Modified MRC	●	●	●	●	●	●
CAT	-	●	●	●	●	-
AE assessments	●	●	Every month			●
SGRQ	-	●	-	●	●	-
BDI and BAI	-	-	○	●	●	-
IIEF-5*	-	-	○	●	●	-
Comorbidities†	●	-	-	-	-	-
Physical examinations	●	●	●	●	●	●
Spirometry (flow-volume curve)	●	●	●	●	●	●
BDR	-	●	-	●	●	-
Lung volume	-	●	○	●	●	-
Diffusing capacity	-	●	-	●	●	-
MBPT‡	-	◐	-	-	-	-
Airway resistance	-	◐	○	◐	◐	-
Chest PA/lateral	●	●	-	●	●	●
Volumetric CT	-	●	-	◎	●	-
Water's view	-	●	-	-	-	-
Six-minute walk test	-	●	-	●	●	●
CBC, chemistry	-	●	-	●	●	●
Urine analysis	-	●	-	-	-	●
CRP, BNP	-	●	-	-	-	●
Resting oxygen saturation	-	●	-	-	-	●
ECG	●	-	-	-	●	●
Echocardiography	-	●	-	-	●	-
Blood samples for genetic study	-	●	-	●	●	●

●: required; ◐: optional; ○: performed 3 months after enrollment, then again 1 year later; ◎: performed 1 year after enrollment, then again 3 years later.

*Only males. †Charlson's score. ‡Performed if FEV₁>60% predicted.

MRC: UK Medical Research Council; CAT: Chronic Obstructive Pulmonary Disease Assessment Test; AE: acute exacerbation; SGRQ: Saint George's Respiratory Questionnaire; BDI: Beck Depression Inventory; BAI: Beck Anxiety Inventory; IIEF-5: The International Index of Erectile Function Questionnaire; BDR: bronchodilator response; MBPT: methacholine bronchial provocation test; PA: posterior-anterior; CT: computed tomography; CBC: complete blood count; CRP: C-reactive protein; BNP: brain natriuretic peptide; ECG: electrocardiography.

outcome measurements included clinical, pulmonary functional, radiological, genetic outcomes. The clinical outcomes measured were dyspnea (assessed using the modified UK Medical Research Council [MRC] dyspnea scale), exacerbations, patient-reported health outcomes (e.g., Saint George's Respiratory Questionnaire or COPD Assessment Test),

psychological status (depression and anxiety score), sexual function, and comorbidities. Measurements of pulmonary function included spirometry (pre- and post-bronchodilator test), lung volume (body plethysmography) and diffusing capacity for carbon monoxide (single-breath method). Because FEV₁ is the defining characteristic of obstructive lung disease,

all patients performed a spirometry test at follow-up when possible. Upon enrollment, after 1 year, and then at intervals of 3 years, volumetric computed tomography (CT) scans were taken at full inspiration and expiration using 16-multidetector CT scanners produced by three different manufacturers (Somatom Sensation 16; Siemens Medical Systems, Bonn, Germany; GE Lightspeed Ultra; General Electric Healthcare, Milwaukee, WI, USA; and Philips Brilliance 16, Philips Medical Systems, Best, Netherlands). Images of the whole lung were extracted automatically and the attenuation coefficient of each pixel was calculated. Emphysema index (volume fraction of the lung < -950 HU), air trapping index (mean lung density at full expiration over mean lung density at full inspiration), and airway thickening (wall area percentage of two segmental bronchi; RB1 and LB1+2) were used for quantitative assessment using CT. Serum, plasma, DNA and urine samples were collected for biomarker and genetic/proteomic analysis. Other outcome measurements included body composition (measure using whole body impedance), resting oxygen saturation, the 6-minute walk test, airway resistance (measured using impulse oscillometry), and trans-thoracic echocardiography.

Results

From May 2005 to October 2013, a total of 477 subjects were enrolled. All patients were over the age of 40 years (mean age, 66.1±7.9 years). Of these, 433 (91%) were male, 403 (84%) had a smoking history more than 10 pack-years (mean smoking history, 46.3±27.3 pack-years), and 381 (80%) were diagnosed with COPD according to the presence of an airflow limitation that was not fully reversible (post-bronchodilator FEV₁/FVC<0.7) and a smoking history of more than 10 pack-years. To date, 39 (8%) patients have died during follow-up, 110 (23%) ended follow-up in early stages, and 328 (69%) are still being followed-up.

The interim analyses of the KOLD Cohort Study identified various predictors of therapeutic response⁸⁻¹¹. These include clinical, pulmonary functional, radiological or combined factors. Genotypes, such as the *ADRB2* or *CRHR1* gene polymorphisms, were also associated with therapeutic response^{12,13}. The majority of the analyses addressed therapeutic response in lung function to inhaled bronchodilators, either with or without corticosteroids. Combination of clinical and lung function indices was better at predicting acute exacerbations than radiological factors¹⁴. Radiological assessments made using volumetric CT correlated with clinically meaningful outcomes, such as the BODE index and its components¹⁵. Volumetric CT was able to quantitatively assess the regional heterogeneity of emphysema, and showed pulmonary function test values were more influenced by the severity of emphysema in the lower lungs than the severity of emphysema in the upper lungs¹⁶. The *ADRB2* gene polymorphism was

associated with airway wall phenotypes as measured by CT, suggesting that it may be one of the determining factors of the radiological COPD phenotype¹⁷. In addition, cluster analysis identified distinct phenotypes in elderly with obstructive lung disease and factors related to pulmonary hypertension in COPD patients^{18,19}. Furthermore, combining the analysis of KOLD with that of the Cohort for Reality and Evolution of Adult Asthma in Korea (COREA) has identified and characterized an overlap syndrome, which is an intermediate between asthma and COPD in clinical characteristics²⁰.

Discussion

COPD is a heterogeneous disease that may have different etiologies, pathogenesis, and host responses. A particular COPD phenotype may be related to a distinct natural history and respond differently to treatment. Discovering new COPD phenotypes involves identifying patient groups with unique prognostic or therapeutic characteristics. Originally the term “phenotype” referred to the composite of the observable characteristics or traits of an organism. However, a more concise definition of COPD phenotypes is needed to supersede the currently used descriptions, “blue bloater” and “pink puffer.” Recently, a new definition of the COPD phenotype was suggested as follows: a single or combination of disease attributes that describe difference between individuals with COPD that relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)⁴. This definition will help to identify the clinically relevant COPD phenotypes.

The 8-year prospective study conducted by Fletcher et al.²¹ (The Natural History of Chronic Bronchitis and Emphysema, published in 1976) is still the most highly cited summary of COPD natural history. However, it focused primarily on FEV₁ and did not address the natural history of other features of COPD. In addition, the duration of the study was relatively short compared with the natural history of COPD. Because COPD progresses slowly, the heterogeneity of COPD natural history can only be determined by prospective longitudinal studies for longer duration²².

Recent studies suggest that there are racial differences in terms of COPD susceptibility, treatment, and prognosis²³⁻²⁵. Most of these studies looked at the higher susceptibility of African Americans race to tobacco smoke compared with that of Caucasians. This implies that racial differences also exist in Asians. In addition to racial differences in susceptibility to COPD, a growing number of studies have identified COPD risk factors that are not related to smoking. These risk factors include exposure to indoor and outdoor pollutants, workplace exposure to dust and fumes, a history of repeated lower respiratory-tract infections during childhood, a history of pulmonary tuberculosis or, chronic asthma, intrauterine growth retardation, poor nourishment, and poor socioeconomic status²⁶.

These risks are particularly relevant to non-smoking Asian females. However, it is not clear whether COPD phenotype in non-smokers is different from that in smokers. Therefore, ethnic heterogeneity and risk factors for COPD in non-smoker are points that should be assessed in collaborative COPD research projects conducted across various Asian countries.

The KOLD Cohort Study used different inclusion criteria from those used in other longitudinal studies of COPD. First, the KOLD Cohort Study did not use smoking history as an indispensable inclusion criterion. Although most patients enrolled in the KOLD Cohort Study have smoking history more than 10 pack-years, we leave room to take non-smoker COPD patients. Second, a pre-bronchodilator $FEV_1/FVC < 0.7$ was used as an inclusion criterion to include patients with COPD as well as asthma and unclassified obstructive lung disease. Third, the KOLD Cohort Study used bronchial hyper-responsiveness as an inclusion criterion. Bronchial hyper-responsiveness is an important predictor of an accelerated decline in FEV_1 and is thought to be second only to cigarette smoking as a significant risk factor for COPD^{27,28}. This flexibility of inclusion criteria used in the KOLD Cohort Study would facilitate to dissect heterogeneity of obstructive lung disease.

As radiologic characterization of COPD with volumetric CT, the low attenuation area and segmental wall area percentage or thickness are used mostly. These indices are associated with various clinical outcomes of COPD²⁹. In addition, the KOLD Cohort Study used CT air trapping index as small airway obstruction index. This index, as well as the emphysema index and the segmental wall area percentage, was independently correlated with various clinical parameters of COPD^{11,15}.

A better understanding of COPD heterogeneity requires multinational collaborative research. Thus, the Asian Network for Obstructive Lung Disease (ANOLD) has been built as an extension of the KOLD Cohort Study³⁰. In the ANOLD, researchers from 12 regions of Asia have participated and recruited more than 1,000 COPD patients since September 2009. The purpose of the ANOLD is to characterize COPD heterogeneity in Asia by determining the relationship between clinical outcomes and various aspects of the disease. A new insight into the pathogenesis and long-term natural history of COPD could be achieved through collaborative research conducted in various Asian countries. Undertaking longitudinal studies for longer duration in Asian COPD patients would enable to discover distinct COPD phenotypes with new therapeutic and prognostic biomarkers.

In conclusion, the KOLD Cohort Study is one of the leading long-term prospective longitudinal studies investigating the heterogeneity of COPD in Asia. Furthermore, in conjunction with the ANOLD, the KOLD Cohort Study is expected to provide new insights into the pathogenesis and long-term progression of COPD.

Conflicts of Interest

Tai Sun Park, Jae Seung Lee, Yoonki Hong, Jung-Wan Yoo, Byung Ju Kang and Sei Won Lee have no conflicts of interest to disclose. Joon Beom Seo has been an investigator in a government-sponsored study (2006–2008 Korea Science and Engineering Foundation). Yeon-Mok Oh (YMO) has been an investigator in industry-sponsored studies (MSD Korea, AstraZeneca Korea, BoehringerIngelheim Korea, Handok and GlaxoSmithKline) and in university-sponsored studies (Asan Institute for Life Science, University of Ulsan College of Medicine). YMO has participated as a speaker at scientific meetings organized and financed by pharmaceutical companies (Handok, Pfizer Korea, GlaxoSmithKline, AstraZeneca Korea, MSD Korea, and Boehringer Ingelheim Korea) and a magazine company (Korea Doctors' Weekly). YMO developed an educational presentation for a pharmaceutical company (Diachi Sankyo Korea). Sang-Do Lee serves as a consultant to GlaxoSmithKline and Nycomed, and has participated as a speaker at scientific meetings organized and financed by various pharmaceutical companies (GlaxoSmithKline, AstraZeneca Korea, Nycomed and Boehringer Ingelheim).

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