An Overview of Asthma Copd Overlapping Syndrome (ACOS)

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Abstract

Asthma-COPD overlap Syndrome (ACOS) is a syndrome in which a patient suffers from both chronic obstructive pulmonary disease (COPD) and asthma. Standard definition and diagnostic criteria of this overlap syndrome is not established yet. It is important to formulate a definition of ACOS for accurate diagnosis and studies. Few biomarkers have been found which can be useful for diagnosis but much research is needed. The prevalence of ACOS depends upon the definition, diagnosis criteria and population analyzed. Different single nucleotide polymorphism (SNPs) has been identified in limited population.

Keywords: Asthma, COPD, ACOS, Overlap, Diagnosis, Biomarker, SNP.

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INTRODUCTION

An overlap syndrome is conditions in which there are signs and symptoms of more than one disease clinically and exists in a single individual that add complexities for diagnosis and treatment of the syndrome due to complex endo phenotypes [1]. Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common respiratory disease having common features such as airflow limitation and inflammation but they have different pathophysiology, etiology, prognosis and treatment outcomes [2]. According to “Dutch hypothesis”, proposed by Orie and coworkers in 1960s, that all types of airway disorders such as asthma, chronic bronchitis, and emphysema should be considered as single entity of “chronic non-specific lung disease” sharing common genetic origins [3]. But an opposition was raised and the “British hypothesis” was proposed that says that COPD and asthma are different disease with different disease mechanisms. This debate remained persistant for over half a century. However, both hypotheses have some merits [4-7]. Previously both COPD and Asthma were considered as separate entity with different clinical features, however, recently overlapping of both diseases has been found and a unique clinical phenotype asthma–COPD overlap syndrome (ACOS) has been reported. ACOS is identified by continuous airway obstruction along with many characteristics of COPD and asthma [2,8,9].

ACOS has been perceived by the Global Initiative for Asthma (GINA) and Global Initiative for Chronic Obstructive Lung Disease (GOLD), and has been incorporated into a few national guidelines of COPD [8-10]. ACOS is considered to grow primarily by two distinctive pathways: firstly, the patient with COPD creates asthma characteristics or asthma-like characters and secondly asthmatic patient keeps on smoking and in the long run creates non-reversible airway obstruction demonstrating COPD [11,12]. Smoking is regarded as an important factor for ACOS diagnosis [11,13].

ACOS prevalence with COPD or asthma patients rely upon the criteria used [12], and is increased by age [14]. Past researches on ACOS have been performed in COPD cohorts, and ACOS patients are accounted to have more recurrent exacerbations and hospitalisations, less physical activity, poor quality of life, and expanded dyspnea and wheezing, when compared to COPD patients alone [14-17].

ACOS vary from asthma most obviously by the higher concentration of serum IL-6 and blood neutrophils and lower concentration of pulmonary diffusing capacity. ACOS patients have larger reversibility of the airways and diminished lung function when contrasted with asthma, in spite of the same medicines used. As compared to asthma patients, ACOS patients have a more prominent number of comorbidities without COPD. Moreover, controlling asthma in ACOS patients is quite worse than with patients of asthma alone [18]. According to Novkovic and coworkers patients with ACOS are found to be younger, low Body Mass Index (BMI), low Forced...
Expiratory Volume (FEV₁) % and low Forced Expiratory Volume/Forced Vital Capacity (FEV₁/FVC) ratio (p=0.001) contrasted to patients with COPD alone. Compared with COPD patients, ACOS patients have distinctively high level of total serum IgE and reversibility [19].

Definition of ACOS

Some research publications have highlighted that ACOS must be considered as a separate disease entity albeit no concurrence on definition has been come to so far [14,20,21]. In 2012, a Spanish accord paper was published in which 11 participating experts in pulmonary medicine settled upon criteria for ACOS and acknowledged it as a one of a kind clinical phenotype [22]. Besides Spanish paper, Finnish COPD guidelines and a research by Kitaguchi and coworkers point to sputum and paraclinical discoveries recommending eosinophil airway inflammation, large levels of peripheral eosinophil counts and high level of exhaled nitric oxide in ACOS or asthma-like COPD patients [8,11,23]. GOLD and GINA have collaborated and managing to form a clinical description of ACOS. The document reports shared characteristics of both COPD and asthma in ACOS along with non-reversible airflow confinement, but in the meantime the document emphasizes that it is just for clinical work and not to be utilized as a definition of ACOS [24]. More research is required for a generally acknowledged definition. However, different definitions have been presented by various researchers. Brzostek and coworkers defined ACOS as blended phenotype having mixed features of COPD and asthma [25]. Chung defined ACOS as FEV₁/FVC ratio of 0.7 along with a record of self-reported wheeze [26], though according to de Marco et al. ACOS is a self-reported diagnosis of both COPD and asthma by physician [14].

Aside from having respiratory symptoms, ACOS patients in the study conducted by Fu et al were required to have expanded airflow variability, characterized as airways hyperresponsiveness or bronchodilator reversibility, and not completely reversible airflow hindrance [27]. In the investigation by Kauppi et al. ACOS is defined as patients having both GINA defined asthma and GOLD defined COPD [28]. The definition recommended by GOLD and GINA is “ACOS is defined by constant airflow limitation with many characteristics usually linked with asthma and COPD. ACOS is therefore identified by the features it shares with both asthma and COPD” [24]. Another definition was proposed by Gibson and Simpson that states ACOS patients have firm airflow hindrance along with bronchial hyperresponsiveness (BHR) or bronchodilator reversibility (BDR) [29]. This definition was based on the results of spirometry. It is simple and broad when compared to GINA and GOLD.

According to a proposition by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), which is supported by the Spanish COPD Guidelines (GesEPOC) and the Spanish Guidelines on the Management of Asthma (GEMA), writers of the two papers have brought together the criteria for the diagnosis of ACOS that states that ACOS patients have 3 elements includes: notable contact, asthma and chronic airflow restriction. Diagnosis criteria are: patient’s age ≥ 35 years, ex-smoker or smoker for 10 years, airflow hindrance (post-bronchodilator FEV₁/FVC < 0.7) that remains consistent after treatment with inhaled corticosteroids (ICS) and bronchodilators and current diagnosis of GEMA’s defined asthma. In some cases asthma is not diagnosed then positive diagnosis is done on the basis of raised blood eosinophil count (≥300 eosinophils/µL) or bronchodilator test (FEV₁ ≥15% and ≥400 ml) [30].

Prevalence

Due to different definitions and no availability of general definition of ACOS, different study designs and population characteristics the prevalence varies a lot even within same population [31-33]. ACOS is a mixed group of disorder in which distinctive subtypes results in different clinical results and is divided into early and late-onset asthma group where higher rate of mortality was seen in late-onset asthma linked ACOS [34]. Depending on the definition, diagnosis criteria and population analyzed the prevalence of ACOS varies widely in different studies such as it is 0.9-11.1% in general population [33] but it is also found in the range of 1.6- 4.5% in COPD patients between 12.1% and 55.2% [11,15,20,35,36]. In a metaanalysis review that included 19 studies, the prevalence of ACOS was 27% with a COPD diagnosis. In different studies, prevalence varies from 11- 25% due to variation in definition [37,38].

According to CHAIN study conducted in Spain in which modified GesEPOC criteria was used the prevalence was found to be 15%. In other studies conducted in Spanish population the prevalence was found to be 15.9% [39] and 12.1%, respectively [38]. It was 13% in COPD Gene study [40] and 18.3% in MAJORICA study (cohort population of Balearic Islands) [41]. According to Kumbhare et al. ACOS prevalence in USA was 3.2% [42]. In short, due to different disease criteria the prevalence lays between 1.6-4.5% in general adult population.

Symptoms

The available studies proposes that patients with ACOS suffers from more wheezing and dyspnea contrasted with patients with just COPD or asthma, and additional studies reports more phlegm and cough. ACOS patients have increasingly associative wheezing, more sputum and cough production and more severe and frequent exacerbations in contrast to COPD and asthma patients alone [14-17,25,43,44]. The studies shows that ACOS patients have higher rate of exacerbation and more symptoms than asthma and
Belgian pulmonologists developed criteria for the diagnosis of ACOS in COPD patients. Major criteria for the diagnosis of ACOS in COPD patients was bronchodilator response ≥12% and >200 mL and inconsistency in airway smooth muscle function whereas anti-IFN-3 and anti-IFN-3 controls appose, cellular differentiation, and tissue architecture. MicroRNA: Some studies have detected miRNA expression in COPD and asthma, however, the role of miRNA-338 and miRNA-195 in the role of airways inflammation and fibrosis in asthma is still unclear. Recent findings by Lacedonia and colleagues evaluated the role of microRNAs in COPD and asthma. They found that miRNA-338 levels were lower in COPD patients compared to healthy controls, while miRNA-195 levels were higher. These findings suggest that miRNAs may play a role in the pathogenesis of ACOS.

**MicroRNA**

- miRNA-338: Lower levels in COPD patients compared to healthy controls.
- miRNA-195: Higher levels in asthma patients.

**Systemic Inflammation**

- IL-6, TNF-α levels are increased in COPD and ACOS.
- CRP levels are elevated in ACOS.

**Biomarkers for ACOS**

- NGAL: A biomarker for airway inflammation in asthma and COPD.
- MMP-9: A biomarker for extracellular matrix remodeling.
- EPOC: A biomarker for emphysema.

**Phenotype of ACOS**

ACOS is a heterogeneous phenotype with poorly characterized clinical features. The diagnosis requires a combination of clinical, functional, and systemic features. The phenotype is characterized by symptoms of both asthma and COPD, such as dyspnea, wheezing, and productive cough. The biomarkers for ACOS include NGAL, MMP-9, and EPOC, which are associated with airway inflammation and emphysema. The phenotype is important for the management of ACOS patients, as it requires a distinct medication approach compared to asthma or COPD alone.

**Sputum Biomarker**

- MPO: Myeloperoxidase, a biomarker for neutrophilic inflammation.
- IL-13: A biomarker for eosinophilic inflammation.

**Classification of ACOS on the basis of disease severity**

ACOS is not a disorder that has been widely studied, and therefore, there is no universally accepted classification system. However, some studies have proposed that ACOS can be divided into four phenotypes based on clinical features, symptoms, and biomarkers. These phenotypes are characterized by different pathophysiologies and require distinct medication approaches. The four phenotypes are as follows:

1. **Type 1 ( asthma with COPD)**: This phenotype is characterized by symptoms of both asthma and COPD, such as dyspnea, wheezing, and productive cough. The biomarkers for Type 1 ACOS include NGAL, MMP-9, and EPOC, which are associated with airway inflammation and emphysema.
2. **Type 2 ( COPD with asthma)**: This phenotype is characterized by symptoms of COPD and asthma, such as dyspnea, wheezing, and productive cough. The biomarkers for Type 2 ACOS include MPO, IL-13, and MMP-9, which are associated with neutrophilic and eosinophilic inflammation.
3. **Type 3 ( asthma with COPD and allergy)**: This phenotype is characterized by symptoms of both asthma and COPD, as well as allergy, such as dyspnea, wheezing, and productive cough. The biomarkers for Type 3 ACOS include NGAL, MMP-9, and EPOC, which are associated with airway inflammation and emphysema.
4. **Type 4 ( COPD with asthma and allergy)**: This phenotype is characterized by symptoms of COPD and asthma, as well as allergy, such as dyspnea, wheezing, and productive cough. The biomarkers for Type 4 ACOS include MPO, IL-13, and MMP-9, which are associated with neutrophilic and eosinophilic inflammation.

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degeneration. Both miRNA expressions were higher in ACOS as compared to control group that indicates these miRNA as potential biomarkers for ACOS. No correlation of these miRNA with age, FEV\textsubscript{1} and sputum cellularity was observed [61].

Mitochondrial DNA
Mitochondrial DNA is susceptible to oxidative stress and can be damaged in terms of quantity. As oxidative stress plays an important role in COPD and asthma pathogenesis and it might have role in ACOS. Carpagnano et al. checked the ratio of MtDNA/nDNA in ACOS patients. Rise in MtDNA/nDNA ratio in ACOS patients concludes that mitochondrial dysfunction is present in this syndrome. MtDNA/nDNA ratio can be a useful marker for ACOS diagnosis but further studies are needed to validate MtDNA/nDNA ratio potential [62].

Single Nucleotide Polymorphism (SNP)
A few numbers of studies have been done to investigate ACOS clinical feature but no study have been carried out on the genetics of this overlap group. Asthma and COPD have identified genetic risk factors and are heritable diseases. Genome-wide association studies (GWAS) and candidate gene studies have found different genetic variants linked to asthma and COPD individually and several of these variants are associated with both diseases [63,64].

Harden and coworkers selected COPD patients who are smoker and ex-smoker African-Americans (AA) and non-Hispanic whites (NHW). GWAS was performed to identify SNPs linked to ACOS on both populations. In NHW, SNPs were identified in CSMD1 gene (chromosome 8, rs11779254) and intronic region of sex-determining region Y-box5 (SOX5) gene (chromosome 12, rs59569785). SNPs in protein coupled receptor 65 (GPR65) gene are most significant. In AA, SNP in PKD1L1 gene (chromosome 7, rs2686829) was the most significant [16]. Recently, a study was carried out to identify SNPs in ACOS patients of Korea using GWAS but no significant SNPs were found [65].

CONCLUSION
In conclusion, the current literature suggests that ACOS patients display more symptoms, comorbidity and exacerbations in contrast to COPD and Asthma patients alone, that indicates a severe outcome. Also a generalized standard definition and diagnostic criteria is much needed for further research and treatment.

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