OPEN ACCESS
Haya: The Saudi Journal of Life Sciences
Abbreviated Key Title: Haya Saudi J Life Sci
ISSN 2415-623X (Print) |ISSN 2415-6221 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: http://scholarsmepub.com/haya/

Review Article

An Overview of Asthma Copd Overlapping Syndrome (Acos)

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DOI: 10.36348/SJLS.2019.v04i08.004 | **Received:** 21.09.2019 | **Accepted:** 28.09.2019 | **Published:** 30.09.2019

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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.

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 (FEV_1) % and low Forced Expiratory Volume/Forced Vital Capacity (FEV_1/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 FEV_1/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 ≥ 35years, ex-smoker or smoker for 10 years, airflow hinderance (post-bronchodilator FEV_1/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

COPD patients and higher rate of respiratory-associated morbidity. In accordance with a predetermined number of studies it revealed a higher predominance of comorbidities in ACOS patients in contrasted with the COPD patients alone, particularly to diabetes [43,44]. Majority of the comorbidities noticed among studies were not like asthma comorbidities, they are observed in older patients having arthritis, stroke, and diabetes. Additionally smoking is a co-founder in the link between asthma and commorbidities because of higher number of smokers in ACOS patients as compared to only asthma [37].

Phenotype

Classification of ACOS on the basis of phenotype has not yet been available. Some authors discuss it as a mixed kind of syndrome while some studies have found ACOS phenotype [45-47]. Rhee and coworkers has proposed 4 phenotypes based on smoking history and eosinophilic inflammation. Each of the four phenotypes has distinct pathopysiology and needs distinct medication. These phenotypes were applied by Joo and coauthors in clinical practice to examine the prevalence and to determine different clinical features between the disorders. Smoking history and eosinophilic inflammation was important part in ACOS classification. Phenotype having eosinophil blood count ≥300 and smoking for more than 10 years have severe airways obstruction. Each phenotype represents different features. More research is required on ACOS phenotypes [48].

Diagnosis

Patients suffering with ACOS are generally diagnosed at ≥40years [49], having dyspnoea, wheezing and productive cough that are persistent over time. These symptoms can be reduced by bronchodilators and ICS [50]. ACOS diagnosis is a challenge as there are no precise biomarkers to distinguish it from COPD or asthma [51]. Spirometric tests, lung imaging or sputum cell count are not enough to distinguish COPD, asthma and ACOS particularly in older, smoker and ex-smoker however, some criteria have been proposed for its diagnosis. Likewise, doctors may experience ACOS diagnosis difficulties in asthmatic patients who are suffering from irreversible airflow constraint and COPD patients with asthma history [28,52]. ACOS is linked with low quality of life, high mortality, elevated rate of exacerbation, and a fast decline of lung function [29]. Certain criteria was suggested by GesEPOC: asthma before 40 years, eosinophilia in sputum and bronchodilator test >15% (400ml) and minor criteria was bronchodilator test >12% (200ml), atopy and increased total IgE [53].

According to Cataldo and coworkers, 87 Belgian pulmonologists developed criteria for the diagnosis of ACOS. Major criteria for the diagnosis of ACOS in COPD patients was bronchodilator response ≥12% and >200 mL and inconsistency in airway hinderance over time (FEV_1 ≥400 mL). However, the minor criteria were IgE sensitivity ≥1 airborne allergen and family history of atopy, high body eosinophil levels or elevated (fractional) exhaled nitric oxide, symptoms variability and asthma diagnosis before 40 years. Major criteria for the diagnosis of ACOS in asthmatic patients were consistent airflow hinderance over time (FEV_1/FVC <0.7) and smokers (also ex-smokers) for ≥10 years. However, the minor criteria were age more than 40 years, limited change in airway obstruction, decreased diffusion capacity, absence of response on bronchodilator test and emphysema [54]. Rhinitis is proposed as a clinical marker for the diagnosis of ACOS but clinic trials are needed for confirmation [55].

Biomarkers for ACOS

ACOS is a heterogenic phenotype with poorly characterized clinical features. Due to this reason, there is an urgent requirement to identify biomarkers and specific features of ACOS [56]. Some of the biomarkers are discussed below:

Sputum Biomarker

Gao *et al*. hypothesized that 5 sputum biomarkers causing airway inflammation in asthma and COPD can be used to diagnose ACOS. These biomarkers included myeloperoxidase (MPO), interleukin (IL) 13, IL-6, chitinase-like protein (YKL-40), and neutrophil gelatinase-associated lipocalin (NGAL). The results indicated that these biomarkers manage airway inflammation and have diagnostic values for differentiation of ACOS from COPD and asthma. Only NGAL levels can be used for diagnosis of ACOS to differentiate it from COPD and ACOS [57].

Systemic Inflammation

Systemic inflammation role is defined in COPD but very little information is present about it in ACOS. Many studies identified systemic inflammation in ACOS and similar to COPD [27,52]. The biomarkers of systemic inflammation are tumour necrosis factor-α (TNF α), IL-6, high-sensitivity C-reactive protein (hsCRP), surfactant protein A and receptor of glycation end-products [50]. IL-6 and hsCRP are most studied systemic inflammation biomarker, with increased level of IL-6 in ACOS as compared to asthma and increased level of CRP as compared to COPD [46,58,59]. Huang *et al*. proposed that plasma levels of IL-8, IL-10, IL-4, and TNF-α are linked to severity of airways disorder and are potential biomarker for ACOS [60].

MicroRNA

Some studies have checked microRNA (miRNA) expression in COPD and asthma however in our knowledge no study is conducted on ACOS. Recently, Lacedonia and colleagues evaluated the role of miRNA-338 and miRNA-145 that are involved in airways inflammation. Mi RNA-145 regulates airway smooth muscle function whereas miRNA-338 controls apoptosis, cellular differentiation, and tissue

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_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 PKD1L1gene (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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