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Original Article

The Prevalence of Asthma-COPD Overlap Syndrome in Patients with Obstructive Airway Disease in Kerman, Iran

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ABSTRACT

Background: The coexistence of asthma and chronic obstructive pulmonary disease (COPD) is recognized as asthma–COPD overlap syndrome (ACOS). This study aimed to investigate the prevalence of ACOS and the characteristics of the affected patients in terms of chronic pulmonary airway diseases in the southeastern Iran, Kerman.

Methods: This cross-sectional study was conducted in Kerman province, Iran, from March 2017 to March 2018. 295 patients with a history of chronic pulmonary airway diseases including asthma and COPD were enrolled through convenience sampling. Spirometry was performed and forced expiratory volume (FEV1), forced vital capacity (FVC), and FEV1/FVC were calculated. The physician made the final diagnosis according to GOLD/GINA criteria. Chi-square, Fisher's exact test, t-test, and Mann–Whitney U test were used to compare variables through SPSS version 23.

Results: The ACOS prevalence was 36.9% (95% CI: 31.5- 42.7). Asthma patients were younger than ACOS patients (P = 0.001) and they had higher levels of FEV1 (P = 0.02), FEF (P ≤ 0.001), and FEV1/FVC (P ≤ 0.001) before receiving bronchodilator in comparison to ACOS patients. However, COPD patients were older than the ACOS patients (P ≤ 0.001). The lung function in ACOS patients before and after receiving bronchodilators was higher for FEV1 and FVC in COPD patients.

Conclusion: The prevalence of ACOS was considerable. The present study showed that gender, age, and BMI could be associated with ACOS. The risk factors underlying ACOS and their impact on the patient's life quality and treatment costs can be investigated by future studies.

Keywords: Asthma, COPD, Iran, Asthma-COPD overlap syndrome

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are the major public health problems and the most common chronic airway diseases that contribute to morbidity and mortality worldwide (1, 2). The global prevalence of asthma is 4.3% for physically diagnosed asthma and 4.5% for clinical/treated asthma. Also, wheezing is observed in 8.8% of adults over the age of 21 years among 70 countries (3). This rate is estimated to be 8.9% among Iranian adults (4). In 2015, the mortality of 174 million people affected by COPD and COPD was eight times higher than that of asthma (5). They are considered as different diseases with a unique natural history, pathophysiology, and treatment guidelines (6, 7). Asthma is diagnosed with variable and recurrent respiratory symptoms, reversible obstruction of airflow, and bronchospasm whereas COPD is characterized by persistent airflow limitation that is usually progressive and often irreversible (8, 9).

The coexistence of these two disorders is recognized as asthma–COPD overlap syndrome (ACOS), and refers to the condition in which a person has a persistent airflow limitation with clinical features of both asthma and COPD (9). Several studies have been conducted in different parts of the world to investigate the ACOS prevalence. Moreover, target groups addressed in these studies have been varied with different ACOS prevalence rates(10-15). According to a systematic review, the ACOS prevalence in the general population was 2.0%, while in patients with asthma and COPD, it was 26.5% and 29.6%, respectively (2).

Among demographic and clinical characteristics of patients, age, smoking history, and history of atopy or asthma can play an important role on the prevalence of ACOS (16, 17). In fact, ACOS is more prevalent and is reported in populations over the age of 40 years. Evidence shows that smoking can increase the prevalence of ACOS (16). The study conducted by Sin et al. suggested the major and minor criteria for diagnosis of ACOS (18). Smoking history was a major criterion along with persistent airflow limitation in patients aged 40 years and older with a history of asthma or bronchodilator response (19). Smoking can lead to a major overlap between COPD and asthma. The clinical profile, response to inhaled corticosteroids, and neutrophilic airway inflammation of smoker patients with asthma are similar to those of COPD patients (20).

In addition, ACOS is associated with a high burden of disease. Numerous studies have shown that people with ACOS have more respiratory symptoms, higher mortality rates, poor quality of life, worse health outcomes, higher medication costs, and more comorbidities, and they also experience more respiratory-related hospital visits compared to those with COPD or asthma alone (1, 21-25). According to previous studies, by determining a standard definition concerning the clinical features for ACOS patients, the identification and treatment of these patients will be improved and the problem of physicians in the timely treatment of patients will be reduced (19, 26). Since Kerman province is one of the richest mining and industrial provinces of Iran, occupational hazards account for 3.58% of the causes of pulmonary disease in this province. To the best of our knowledge, no study has been done about ACOS in Iran so far. Therefore, this study aimed to investigate the ACOS prevalence and the characteristics of the affected patients in terms of chronic pulmonary airway diseases in Kerman province, Iran.

Material and Methods

Participants and setting

This cross-sectional study was conducted in the largest province of Iran, Kerman, from March 2017 to March 2018. A total of 275 patients with a history of chronic pulmonary airway diseases including asthma and COPD and with exacerbated respiratory symptoms who referred to the Emergency Ward or were hospitalized in the Pulmonary Ward of Afzalipour Hospital were enrolled through convenience sampling. The inclusion criteria were being at least 18 years old and living in Kerman province with a pulmonary problem. Also, the patients with cardiovascular disease, interstitial lung disease, neuromuscular and skeletal disease, and severe respiratory distress who needed mechanical ventilation were excluded from the study.

Sample size and sampling method

A similar study (27) showed that the ACOS prevalence among patients with asthma and COPD was 30.73% and 18.60%, respectively. The number of patients with COPD who referred to Afzalipour Hospital was greater than that of

asthma patients. Therefore, the sample size for the present study was estimated based on the ACOS prevalence among patients with COPD. Considering the 95% confidence interval (a: 0.05) and error level (d = 0.05), the sample size was approximately calculated as 226.80 persons (Sample size formula). To evaluate the power of the study, 295 patients with asthma and COPD were selected through convenience sampling. In the present study, sampling was restricted to smoking history of patients, and smoker patients with the history of chronic pulmonary airway diseases including asthma and COPD were selected.

Sample size Formula: $n = \frac{1.96^2 * 0.18 * 0.82}{0.05^2} = 226.80 \cong 227$

Data collection

Spirometry with and without bronchodilator (before and after receiving two puffs of inhaler salbutamol) was performed by a trained technician. Spirometry was performed by Spirolab III (MIR Company, Italy) for the patients after being transferred to the Pulmonary Ward. It was done when respiratory distress disappeared and the patient's conditions were stabilized. Spirometry was taken and the patient's chest X-ray was recorded at the same time. Forced expiratory volume (FEV1), forced vital capacity (FVC), FEV1/FVC, and peak expiratory flow (PEF) were calculated. The physician made the final diagnosis according to the spirometry, GOLD-GINA criteria, and chest X-ray. The criteria contain 10 questions, one column for asthma patients and the other one for COPD patients; if the responses in the two columns are equal in number, the patient will be categorized as ACOS, meaning that he/she has symptoms of both COPD and asthma. The GOLD-GINA criteria form was completed while performing spirometry and when the patients were staying in the diagnostic department of pulmonary diseases (28, 29). Finally, the patients were divided into three groups including asthma, COPD, and COPD-asthma overlap syndrome.

Airflow limitation severity

For COPD patients, the airflow limitation severity indexes were post-bronchodilator FEV1/FVC < 0.70% as mild (FEV1 ≥ 80% predicted), moderate (50% ≤ FEV1 < 80% predicted), severe (30% ≤ FEV1 < 50% predicted), and very severe (FEV1 < 30% predicted) (9). For asthmatic patients, the airflow limitation severity indexes were FEV1/FVC < 0.70% as mild (FEV1 > 70% predicted), moderate (FEV1: 60-69% predicted), moderately severe (FEV1: 50-59% predicted), severe (FEV1: 35-49% predicted), and very severe (FEV1 < 35% predicted) (30). For ACOS patients, the airflow limitation severity indexes were FEV1/FVC < 0.70% as mild (FEV1 ≥ 80% predicted), moderate (50% ≤ FEV1 < 80% predicted), severe (30% ≤ FEV1 < 50% predicted), and very severe (FEV1 < 30% predicted) (31). In the present study, in order to match the airflow limitation between the groups, asthmatic patients were categorized into moderate and moderately severe groups.

Ethical considerations

The protocol of this study was reviewed and approved by the Ethics Committee of Kerman University of Medical Sciences (Ethical code: IR.KMU.AC.1395.08). Before the study, a verbal informed consent was obtained from all patients.

Statistical analysis

The data were described using mean ± Standard Deviation (mean ± SD), median (Interquartile Range (IQR)), frequency, and 95% confidence intervals (CI). To compare categorical variables such as gender and body mass index (BMI), the Chi-square and Fisher's exact test were used. The normality of the age of the participants and spirometry indexes were checked by one-sample Kolmogorov–Smirnov test. T-tests and Mann–Whitney U test were used to assess the quantitative variables. A two-sided P < 0.05 was considered significant. The data were described and analyzed by SPSS version 23.

Results

Demographic characteristics of the patients

The mean (SD) age of the patients was 58.02 ± 12.47 years (age range: 18 to 90 years). More than half of the patients were male (n = 175, 59.3%). Based on the BMI classification, overweighing and obesity were frequent among the patients (n = 166, 56.3%). The other patients were normal (n=116, 39.3%) and underweight (n=13, 4.4%). The median (IQR) of pulmonary functions before receiving bronchodilators were

1.29 (1.07 – 1.62), 2.68 (2.00 – 3.22), 51.00 (44.00 – 59.00), and 0.51 (0.43 – 0.60) for FEV1, FVC, FEF, and FEV1/FVC, respectively. These indexes improved after receiving bronchodilators (FEV1: 1.64 (1.34 – 1.96), FVC: 2.78 (2.18 – 3.40), FEF: 61.00 (53.00 – 69.00), and FEV1/FVC: 0.61 (0.53 – 0.69).

The ACOS prevalence

The findings showed that among asthma and COPD patients with the previous diagnosis, 37 patients in asthma group (31.1%, CI 95%: 23, 39.5) and 72 patients in COPD group (40.9%, CI 95%: 33.7, 48.3) were diagnosed as ACOS. Finally, the ACOS prevalence was 36.9% (95%CI: 31.5- 42.7).

Comparison of demographic characteristics and lung function in patients with ACOS versus those with asthma

The findings of the present study revealed that asthma patients were younger (51.37 ± 13.38) than the ACOS patients (57.68 ± 10.37) (P = 0.001). ACOS patients in comparison to asthma patients were more overweight and obese (68.8% versus 53.7%; P = 0.04). The patients with asthma in comparison to those with ACOS had higher levels of FEV1 (1.43 (1.12 – 1.85) vs. 1.28 (1.11 – 1.49); P = 0.02), FEF (62.50 (56.75 – 67.00) vs. 47.00 (42.00 – 52.00); P ≤ 0.001), and FEV1/FVC (0.63 (0.57 – 0.67) vs. 0.47 (0.41 – 0.55); P = 0.001) before receiving bronchodilator. After receiving bronchodilators, these patterns were also repeated for FEF and FEV1/FVC (Table1).

Table 1. Demographic characteristics and lung function of the patients with ACOS versus those with asthma

Variables	Asthma (n=82)	ACOS (n=109)	P-value
Age (Mean ± SD)	51.37 ± 13.38	57.68 ± 10.37	0.001
Gender (%)			
Male	44 (53.7)	55 (50.5)	0.66
Female	38 (46.3)	54 (49.5)	
BMI			
Underweight	6 (7.3)	2 (1.8)	
Normal	32 (39)	32 (29.4)	0.04
Overweight and obese	44 (53.7)	75 (68.8)	
Lung function before bronchodilator, Median (IQR)			
FEV1	1.43 (1.12 – 1.85)	1.28 (1.11 – 1.49)	0.02
FVC	2.27 (1.73 – 3.17)	2.79 (2.16 – 3.29)	0.02
FEF	62.50 (56.75 – 67.00)	47.00 (42.00 – 52.00)	0.0001
FEV1/FVC	0.63 (0.57 – 0.67)	0.47 (0.41 – 0.55)	0.0001
Lung function post bronchodilator, Median (IQR)			
FEV1	1.85 (1.34 – 2.39)	1.68 (1.44 – 1.93)	0.07
FVC	2.66 (1.85 – 3.49)	3.03 (2.43 – 3.45)	0.01
FEF	71.00 (69.00 – 75.00)	57.00 (52.50 – 63.50)	0.0001
FEV1/FVC	0.71 (0.69 – 0.75)	0.57 (0.52 – 0.63)	0.0001

Comparison of demographic characteristics and lung function in patients with ACOS versus those with COPD

The results showed that the COPD patients were older (63.62 ± 11.11 years) than the ACOS patients (57.68 ± 10.37 years) and this age difference was significant (P ≤ 0.001). Almost half of the patients with ACOS were female (n = 54, 49.5%), while the majority of the COPD patients (n = 76, 73.1%) were male (P ≤ 0.001). Overweighting and obesity were more frequent among patients with ACOS (n = 75, 68.8%) compared to those with COPD (n = 47, 45.2%) (P ≤ 0.001). The median of lung functions before receiving bronchodilators was similar for FEV1, FVC, FEF, and FEV1/FVC, between COPD and ACOS patients (Table 2), but after receiving bronchodilator, FEV1 and FVC were higher for patients with ACOS (Table 2).

Table 2. Demographic characteristics and lung function of the patients with ACOS versus those with COPD

Variables	COPD (n = 104)	ACOS (n = 109)	P-value
Age (Mean ± SD)	63.62 ± 11.11	57.68 ± 10.37	0.0001
Gender (%)			
Male	76 (73.1)	55 (50.5)	0.001
Female	28 (26.9)	54 (49.5)	
BMI			
Underweight	5 (4.8)	2 (1.8)	
Normal	52 (50)	32 (29.4)	0.001
Overweight and obese	47 (45.2)	75 (68.8)	
Lung function before bronchodilator, Median (IQR)			
FEV1	1.23 (0.98 – 1.59)	1.28 (1.11 – 1.49)	0.46
FVC	2.71 (1.97 – 3.23)	2.79 (2.16 – 3.29)	0.30
FEF	49.00 (42.00 – 56.00)	47.00 (42.00 – 52.00)	0.26
FEV1/FVC	0.48 (0.42 – 0.56)	0.47 (0.41 – 0.55)	0.51
Lung function post bronchodilator, Median (IQR)			
FEV1	1.39 (1.14 – 1.76)	1.68 (1.44 – 1.93)	0.0001
FVC	2.65 (2.04 – 3.31)	3.03 (2.43 – 3.45)	0.002
FEF	55.50 (48.25 – 62.00)	57.00 (52.50 – 63.50)	0.06
FEV1/FVC	0.55 (0.48 – 0.63)	0.57 (0.52 – 0.63)	0.09

Comparison of symptoms of disease among patients with asthma, COPD, and ACOS according to GOLD/GINA criteria

The findings of the present study showed that the patients with ACOS were significantly different from those with asthma according to the GINA criteria (Table 3). But they were similar to COPD patients in terms of symptoms and airflow limitation. The persistence of symptoms despite treatment (P = 0.21), the record of persistent airflow limitation (P = 0.21), and symptoms slowly worsening over time (P = 0.56) were very similar between the patients with ACOS and those with COPD (Table 4).

Table 3. Comparison of the GINA criteria between asthma and ACOS patients

Criteria	Asthma (n = 82)	ACOS (n = 109)	P-value
Onset age (before 20 years)	36 (43.9)	20 (18.3)	0.001
Variation in symptoms over minutes, hours or days	24 (29.3)	10 (9.2)	0.001
Symptoms getting worse during the night or early morning	68 (82.9)	47 (43.1)	0.001
Symptoms triggered by exercise, emotions including laughter, dust or exposure to allergens	73 (89.0)	67 (61.5)	0.001
Record of variable airflow limitation	69 (84.1)	10 (9.2)	0.001
Normal lung function between symptoms	69 (84.1)	39 (35.8)	0.001
Previous doctor diagnosis of asthma	82 (100)	37 (33.9)	0.001
Family history of asthma or other allergic conditions	47 (57.3)	35 (32.1)	0.001
No worsening of symptoms over time. Symptoms vary either seasonally, or from year to year	29 (35.4)	20 (18.3)	0.008
May improve spontaneously or have an immediate response to BD or to ICS over weeks	77 (93.9)	65 (59.6)	0.001

Table 4. A comparison of the GOLD criteria among the COPD and ACOS patients

Criteria	COPD (n = 104)	ACOS (n = 109)	P-value
Onset age (after 40 years)	100 (96.2)	89 (81.7)	0.001
Persistence of symptoms despite treatment	99 (95.2)	99 (90.8)	0.21
Good or bad days but always daily symptoms and exertional dyspnea	90 (86.5)	62 (56.9)	0.001
Chronic cough and sputum preceded the onset of dyspnea, unrelated to triggers	87 (83.7)	42 (38.5)	0.001
Record of persistent airflow limitation	99 (95.2)	99 (90.8)	0.21
Abnormal lung function between symptoms	89 (85.6)	70 (64.2)	0.001
Previous doctor diagnosis of COPD, chronic bronchitis or emphysema	104 (100)	72 (66.1)	0.001
Heavy exposure to a risk factor: Tobacco smoke, biomass fuels	93 (89.4)	74 (67.9)	0.001
Symptoms slowly worsening over time	88 (84.6)	89 (81.7)	0.56
Rapid-acting bronchodilator treatment provides only limited relief	28 (26.9)	44 (40.4)	0.03

Severity of airflow limitation

The findings showed a significant difference in the severity of airflow limitation among patients with asthma, COPD, and ACOS (P = 0.003). The diagrams show that more than half of the patients with mild airflow limitation were asthmatic patients (n = 15, 62.5%), while more than one-quarter of patients with severe airflow limitation were COPD and ACOS patients (40.9% and 37.9%) (Figure 1).

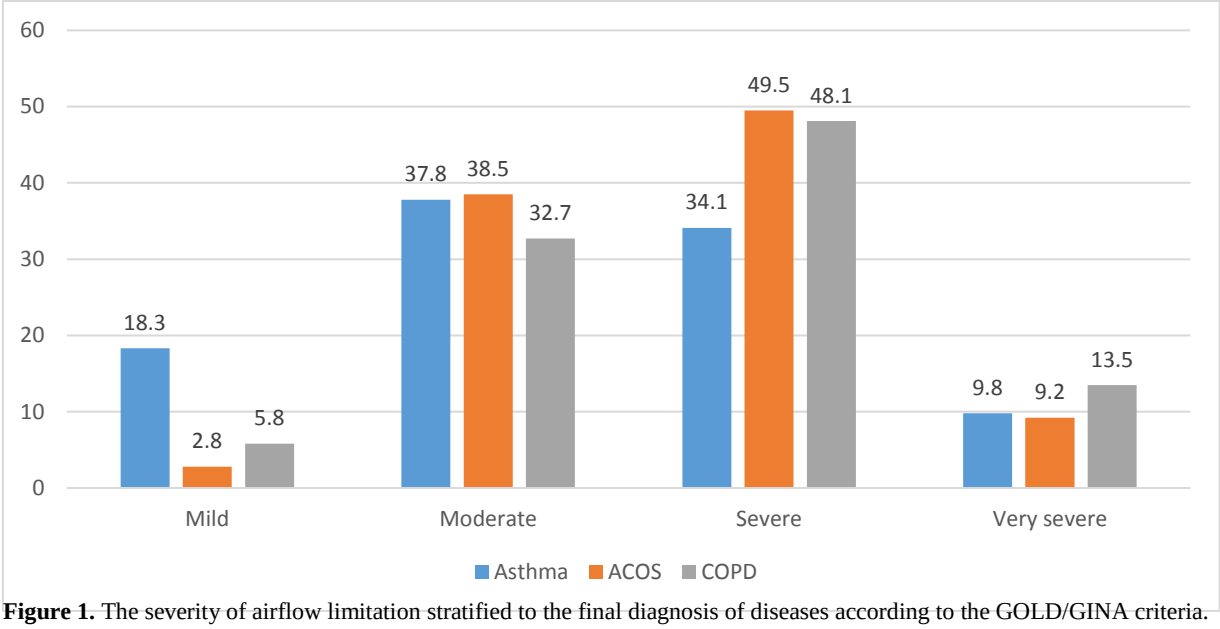

Figure 1. The severity of airflow limitation stratified to the final diagnosis of diseases according to the GOLD/GINA criteria.

Discussion

ACOS is a noticeable issue among patients with chronic airflow obstruction pulmonary diseases such as asthma and COPD. The findings of the present study show that the prevalence of ACOS among patients with previous diagnosis of asthma and COPD was more than one-quarter (36.9%). These results indicate that patients with asthma were younger than ACOS and COPD patients, respectively. Although a significant proportion of ACOS patients were female versus COPD patients, but gender distribution was not statistically different between asthma and ACOS patients. Asthma patients in comparison to ACOS patients had higher spirometry indexes, while these indexes were similar between COPD patients and ACOS patients before receiving bronchodilator. Also, the results show that ACOS patients were more overweight and obese versus COPD and asthma patients.

The results of the present study showed that among asthma and COPD patients with a previous diagnosis, 31.1% and 40.9% were diagnosed with ACOS according to the GINA/GOLD criteria, respectively. A study by Jo et al. (2017) in Korea on 301 patients showed that 46.15% of COPD patients were diagnosed with ACOS according to the GOLD criteria (32). Meanwhile, the study of Ding et al. (2016) in China showed that 18.49% of COPD patients and 30.51% of asthma patients were diagnosed as ACOS patients (27), which is consistent with the findings of this study. In contrast, the results of another study in Denmark showed that the prevalence of ACOS among COPD patients was lower than the findings of the present study (16.4% vs. 41.2%) (33). In addition, the findings of a study in Northern Europe revealed that 13.1% of the patients with asthma were diagnosed as ACOS patients (13). This difference can be owing to some important factors. For instance, the age of patients as well as various diagnosis methods can lead to differences in the prevalence of for ACOS disease.

Age of patients was the other variable which was significantly different between patients. The findings of the present study show that asthma patients in comparison to ACOS patients were younger. However, the results of the studies by Andersén et al. (2013) in Finland and De Verrdier et al. (2015) in Sweden showed that ACOS patients were significantly older than asthma patients (21, 34). The atopic and allergic background as well as the genetic susceptibility are the important risk factors of asthma.

Therefore, one of the reasons for this difference can be related to the incidence of asthma in younger ages (35). COPD occurs in the fifth and sixth decades of life and is due to long standing exposure to hazard environmental factors, for example, tobacco smoking, fossil fuels, occupational injuris (36). The results of this study showed that COPD patients were older than ACOS patients. The results of the studies by Wurst et al. (2016) and Kumbhare et al. (2016) in the USA showed that COPD patients were significantly older than ACOS patients (25, 37). ACOS is an intermediate disease of asthma and COPD, and patients with ACOS have some features of asthma and some symptoms of COPD. As a result, it was stipulated that the age of patients with ACOS is the mean age of the two groups.

Half of the patients with ACOS were female (50%), while the majority of the patients with COPD (72.1%) were male. Moreover, Wurst et al. (2016) and Ding et al. (2016) showed that the number of Chinese female patients in the ACOS group was significantly higher than that of COPD patients (25, 27). In the present study, the overweight and obesity were more frequent among the ACOS patients. Similarly, a study by Kumbhare et al. (2016) in Carolina, the USA, showed that the ACOS patients had a higher BMI (37). In contrast, another study by Ding et al. (2016) in China on 59,935 patients showed that higher BMI was significantly more frequent among COPD patients in comparison to the ACOS and asthma groups (27). Patients with COPD, due to the increasing of TNF-alpha and anorexia, can lose weight over time (38). The findings of the present study show that patients with COPD in comparison to those with asthma and ACOS had lower weight and BMI.

In the present study, the mean of lung function in the ACOS patients before and after receiving bronchodilator was significantly lower for FEV1 and FEV1/FVC in comparison to that in asthma patients. But, the mean of lung function after receiving bronchodilators was significantly higher for FEV1 in the ACOS patients in comparison to COPD patients. A study by Perez de Liano et al showed that the FEV1 for ACOS patients before receiving bronchodilator was similar to that for asthma patients, while this parameter was higher for COPD patients versus ACOS patients(39). Another study revealed that COPD patients had lower FEV1 in comparison to asthma and ACOS patients (40). It is important to notice that COPD is a chronic progressive obstructive airway disease and spirometry indexes decrease over time. In this regard, the pulmonary function of COPD patients was worse than asthma and ACOS patients. In contrast, asthma patients due to responsiveness to inhalation drugs had a better pulmonary function, which is consistent with the results of the present study.

One of the limitations of the present study was the time it needed for patients to reach stable disease conditions to perform spirometry. Another limitation of this study is the patients' education to perform the spirometry. The other limitation is that this study was conducted in one of the provinces of Iran, Kerman, therefore, it is not a multi-center study and conducted on only smoker patients with chronic airflow diseases, which limits the generalizability of the findings of the study.

Conclusion

In the present study, the most common disease was chronic obstructive pulmonary diseases. Meanwhile, a large number of the patients with asthma had mild and moderate airflow obstruction. However, severe airflow obstruction was more frequent among the patients with COPD and ACOS. The present study showed that gender, age, BMI, and spirometry indexes could be associated with asthma-COPD overlap syndrome. The risk factors underlying ACOS and their impact on the patient's quality of life and treatment costs can be explored by future studies.

Conflict of interests

The authors declare that they have no conflict of interests.

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