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Asthma and COPD Overlap Syndrome (ACOS): Risk Factors and Contributing Factors

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Abstract

Background: The exact description of asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS) is uncertain. This study aims to determine the frequency and symptoms of ACOS and to verify certain risk factors associated with ACOS.

Methods: Severe asthmatic patients with and without ACOS above 40 years old participated in this cross-sectional study. The receiver operating curve analysis (ROC) was used to assess the best cutoff values of age, body mass index (BMI), and spirometric data to distinguish asthma patients with overlap syndrome from asthma patients without overlap syndrome. Univariable and multivariable binary logistic regression was used to determine demographic and clinical factors that were associated with ACOS and asthma.

Results: Of the 88 patients, 46 (52.2%) had ACOS and 42 (47.7%) had just severe asthma. The mean age of ACOS patients (Sd) was 54.91(12.57) years and in asthma-only patients was 48.69 (13.51). The ROC analysis for age and BMI showed that age $\geqslant$ 49 years and BMI $\geqslant$ 27 kg/m^2 were the best predictors of ACOS in this study. Spirometry data showed that the forced vital capacity (FVC) (lit) > 2.16, forced expiratory volume in the first second (FEV1) > 69, FEV1 / FVC > 96.5, and FVC (%) > 63 cut points could be used to determine the diagnostic criteria between ACOS and asthma only, respectively. Multivariate modeling showed that among the demographic and clinical variables, only age over 49 years (odds ratio [OR], 3.53 [95% CI, 1.07-11.63] p = 0.025) and living in a big city (OR, 7.42 [95% CI, 1.75-31.49] p = 0.007) were significant.

Conclusion: Age over 49 and BMI above 27 have a significant association with ACOS. Also, living in a big city is considered to be another risk factor for ACOS compared with asthma. Spirometry can help distinguish ACOS from severe asthma in this study.

Keywords: Asthma, Pulmonary Disease, Chronic Obstructive, Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome

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Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are 2 of the most common obstructive lung diseases, in which an obstruction in the airways disturbs their normal function. These diseases are accounted for numerous mortalities and morbidities worldwide. Asthma and chronic obstructive pulmonary disease overlap syndrome (ACOS) is a condition in which patients develop symptoms of both asthma and COPD; therefore, they cannot be classified as isolated asthma or COPD case (1).

Persistent airflow restriction with many traits associated

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↑What is "already known" in this topic:
Asthma and COPD are the 2 most common respiratory illnesses. ACOS is another disease that contains the characteristics of both diseases. Some risk factors have been defined in asthma and COPD alone. Few studies explained the spectrum of ACOS and its diagnosis and management.

→What this article adds:
This study provides a complete explanation of risk factors and their association with this disease and it can be used in clinical settings for management and diagnosis.

with asthma and other aspects associated with COPD characterizes asthma-COPD overlap. As a result, Asthma-COPD overlap is diagnosed in the clinic by the characteristics that both asthma and COPD have in common. Asthma-COPD overlap encompasses multiple distinct clinical presentations, and there are likely to be several different underlying processes. This is a description rather than a definition for clinical use (2). COPD is common among adults usually after the age of 40, in whom differentiating asthma from chronic airflow limitation by COPD is often challenging. This issue is especially prominent among smokers (2-4).

A precise definition for this category of obstructive pulmonary disease has not been established to date, and the exact description of ACOS is still uncertain. However, there is a consensus over the fact that patients with certain symptoms, who cannot be classified as isolated asthma or COPD case, usually happen to have a lower quality of life and much more comorbidities than those who have asthma or COPD alone.

ACOS should be defined according to the following characteristics according to the guidelines: Major—(1) continuous airflow limitation in adults 40 years or older, which may include forced expiratory volume in the first second (FEV1)/forced vital capacity(FVC) 0.70 or below the normal limit after bronchodilator; (2) At least 10 packs of cigarettes per year or exposure to air pollution indoor or outdoor; (3) a proven history of asthma before the age of 40 or a Broncodilator response (BDR) of more than 400 mL in FEV1. Minor: (1) Proven history of atopic or allergic rhinitis; (2) BDR FEV1 200 mL and 12% of baseline values at 2 or more hits; (3) Eosinophil count in the blood more than 300 microliters of cells. All of the major criteria and at least one of the minor criteria for the ACOS is recommended for the definition (5, 6).

Studies suggest that the mortality rate is also higher among ACOS patients than among asthma or COPD patients (2-4). Patients with ACOS usually demonstrate a certain clinical feature, including respiratory symptoms such as exertional dyspnea, persistent partially reversible airflow obstruction, and aged 40 years or above, together with a history of allergies and/or atopy validate the asthmatic properties of ACOS. However, lack of atopy in an adult patient does not exclude asthma since nonallergic reasons usually cause adult-onset asthma. Exposure to noxious materials and smoking are often present in patients' history; however, they are not necessary for diagnosing ACOS (3, 4). Evaluation of ACOS patients includes careful history taking (ie, smoking, work exposures, quality and onset of symptoms, etc), laboratory studies, pulmonary function tests, and imaging (4).

This study aims to determine the frequency and symptoms of ACOS among patients with obstructive pulmonary disease and to verify certain risk factors associated with ACOS. Risk factors such as age, gender, smoking history (either passive or active), and the onset of the disease are evaluated. Moreover, such comorbidities as heart disease, gastroesophageal reflux, past or current history of eczema or allergic rhinitis, and the presence of malignancy are also surveyed.

Methods

This cross-sectional study was performed from 2019 to 2021. Severe asthmatic patients with and without overlap syndrome above 40 years referred to a tertiary referral clinic in Shiraz (Iran) participated in this study. All patients were older than 40 years and had severe asthma diagnosed based on the Global Initiative for Asthma (GINA) guideline (1), and ACOS diagnosis was based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline (6).

Data on these patients were gathered, including demographic information such as age, gender, and body mass index (BMI). Information such as living area, age at onset of disease, duration of disease, history of medication use, presence of comorbidities such as gastroesophageal reflux, smoking, heart disease, rheumatologic disease, and atopy were extracted. Current information of patients, *a* complete history, and physical examination were taken, and the criteria were fulfilled. An Asthma, allergy, and clinical immunology fellow filled out a data sheet specifically designed to collect the aforementioned data in order to obtain all of the data. All of the patients had informed consent and the ethics committee of Shiraz University of Medical Sciences approved this study (IR.SUMS.MED.REC.1401.085). The sampling method was census sampling. The sample size was measured by G-power application (ACOS group = 46 and asthma only group = 42).

Spirometry was used to evaluate the pulmonary functions and was used in 2 phases and with bronchodilator challenge. Spirometry data included FVC (Litre and % predicted), FEV1(% predicted), FEV1/FVC (%) before and after using bronchodilator.

Variables of this study include demographic data such as age (years), BMI (Kg/m^2), gender (male or female), marital status (single, married), address (living in a small city and a big city), and active and/or passive cigarette smoking history. Other variables related to the underlying condition of the patients included the history of heart diseases (history of ischemic heart disease, valvular heart disease, hypertension, and heart failure), eczema, allergic rhinitis, gastroesophageal reflux disease, rheumatic disease (history of rheumatoid arthritis, systemic lupus erythematous, osteoarthritis, scleroderma, Sjogren disease), and psychiatric problems (history of major depressive disorder, anxiety, posttraumatic stress disorder). Spirometry variables are FVC (Litre and % predicted), FEV1(% predicted), and FEV1/FVC (%) before and after using bronchodilator. All of the patients were enrolled in the study for 1 year in Shiraz, Iran.

The exclusion criteria in this study were age younger than 40 years, death, leaving the study, mild or moderate asthma, or COPD. Confounding diseases such as heart failure, gastrointestinal esophageal disease, tuberculosis, or other lung infection disease and lung cancer or mass.

Statistical Analysis

The regression coefficients' standard error, level of significance, and 95% confidence interval were calculated. The Kolmogorov–Smirnov test and graphical plots were

used to determine the distribution of the variables. Unless otherwise specified, results are presented as mean and standard deviation. Those with overlap syndrome and patients with asthma alone were compared using chi-squared statistics to determine whether there were any significant differences in general characteristics. The optimal cutoff values for age, BMI, FVC, FEV1, and FEV1/FVC to discriminate between asthma patients with and without overlap syndrome were determined using the receiver operating curve analysis (ROC). When deciding on the optimal cutoff values, sensitivity and specificity were also considered. Furthermore, both positive and negative predictive values were determined. The MedCalc 20.013 statistical programme was used to analyse this section. Personal, demographic, and clinical characteristics linked to ACOS and asthma were studied using univariable and multivariable binary logistic regression. The components that were significant at $p = 0.20$ were included in a multivariable binary logistic regression, and the variables that were significant at $p = 0.05$ were maintained in the final model. Other statistical analyses were performed using STATA's analytical methodologies (StataCorp. 2016. Stata statistical software: Release 14.).

Results

A total of 88 patients were enlisted and participated in the study. Their mean age in patients with overlap syndrome was 54.91(SD, 12.57) years and in the patients with asthma only was 48.69 (SD, 13.51), the BMI in patients with overlap syndrome was 25.42 (SD, 6.01) kg/m^2 and in patients with asthma only was 27.89 (SD, 5.36) kg/m^2. Nineteen (42.2%) of the patients with overlap syndrome were smokers and 28 (60.9%) were women (Table 1). Table 1 shows a comparison of patients with ACOS and patients with asthma. Patients with ACOS were older and smoked more than those who just had asthma, but the differences were not statistically significant. Those with overlap syndrome had a close to significantly lower BMI

Table 1. Characteristics of 88 asthmatics with and without ACOS

Variable		Asthmatic Patients with ACOS (N=46)	Patients with asthma only (N=42)	*P* value
Age (years)		54.91±12.57	48.69±13.51	0.028*
BMI (kg/m2)		25.42±6.01	27.89±5.36	0.054*
Gender	Male	18(39.1)	10(23.8)	0.123†
	Female	28(60.9)	32(76.2)	
Marital status	Single	6(13.3)	9(21.4)	0.318†
	Married	39(86.7)	33(78.6)	
Address	small City	34(75.6)	9(21.4)	≤0.001†
	Big City	11(24.4)	33(78.6)	
Smoking	Yes	19(42.2)	10(23.8)	0.069†
	NO	26(57.8)	32(76.2)	
Heart disease	Yes	10(22.2)	6(14.3)	0.340†
	NO	35(77.8)	36(85.7)	
Eczema	Yes	7(15.6)	8(19.0)	0.667†
	NO	38(84.4)	34(81.0)	
Allergic rhinitis	Yes	17(37.8)	15(35.7)	0.842†
	NO	28(62.2)	27(64.3)	
Gastroesophageal Reflux disease	Yes	18(40.0)	25(59.5)	0.069†
	NO	27(60.0)	17(40.5)	
Rheumatic disease	Yes	5(11.1)	4(9.5)	0.808†
	NO	40(88.9)	38(90.5)	
Psychiatric problems	Yes	7(15.6)	12(29.3)	0.126†
	NO	38(84.4)	29(70.7)	
FVC pre BD (Liter)		1.64(0.65)	2.21(0.75)	≤0.001*
FVC post BD (Liter)		1.72(0.62)	2.75(0.82)	≤0.001*
FEV1 pre BD (%pred.)		49.50(14.37)	70.17(19.10)	≤0.001*
FEV1 post BD (%pred.)		54.66(14.19)	78.44(14.72)	≤0.001*
(%) FEV1/FVC per BD		80.06(15.52)	87.87(12.08)	0.011*
(%) FEV1/FVC post BD		83.02(14.85)	85.90(10.32)	0.408*
FVC pre BD (%pred.)		51.11(13.29)	82.07(14.81)	0.033*
FVC post BD (%pred.)		54.37(12.14)	74.69(15.89)	≤0.001*

Abbreviation: ACOS: Asthma COPD overlap syndrome. BMI, body mass index.
BD: bronchodilator, FEV1: Forced expiratory volume, FVC: Forced vital capacity
* Independent Samples t Test
†Chi-Square Tests

Table 2. The best cut-off values of age, BMI, FVC, FEV1 and FEV1/FVC to detect asthma–COPD overlap syndrome among 88 asthmatics

Variable	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Age ⩾49 years	68.42	73.91	52.0	85.0
BMI ⩾27	68.75	63.64	40.7	84.8
FVC(lit) >2.16	86.96	82.22	71.4	92.5
FEV1 >69	69.57	88.89	76.2	85.1
FEV1/FVC>96.5	4.35	73.33	7.7	60.0
FVC (%)>63	82.61	86.05	76.0	90.2

Abbreviations: COPD, chronic obstructive pulmonary disease; NPV, negative predictive value; PPV, positive predictive value.

than patients with asthma.

In the study population, the ROC analysis for age and BMI found that age 49 years and BMI 27 kg/m^2 were the best predictors of ACOS (Table 2 and Fig. 1). For age and BMI, the area under the ROC curve was 0.724 and 0.626, respectively. To diagnose overlap syndrome, the cutoff point of 49 years old had a sensitivity and specificity of 68.42% and 73.91, respectively, while the cutoff point of 27 BMI had a sensitivity and specificity of 68.75% and 63.64%, respectively (Table 2). FVC (lit) >2.16, FEV1 >69, FEV1/FVC>96.5, and FVC (percent)>63 were the greatest predictors of ACOS in the study population, according to the ROC analysis for FVC, FEV1, and FEV1/FVC to identify ACOS among 88 asthmatics (Table 2 and Fig. 1). For FVC (lit), FEV1, FEV1/FVC, and FVC (%), the area under the ROC curve was 0.861, 0.891, 0.533, and 0.878, respectively (Fig. 1).

Multivariate modeling showed that among the demographic and clinical variables, holding all other predictor variables constant, the odds of asthma–COPD overlap syndrome occurring increased by 3.53 times (95% CI, 1.07-11.63; p = 0.025) for patients who aged ≥49 compared with those aged <49; and holding all other predictor variables constant, the odds of occurring asthma–COPD

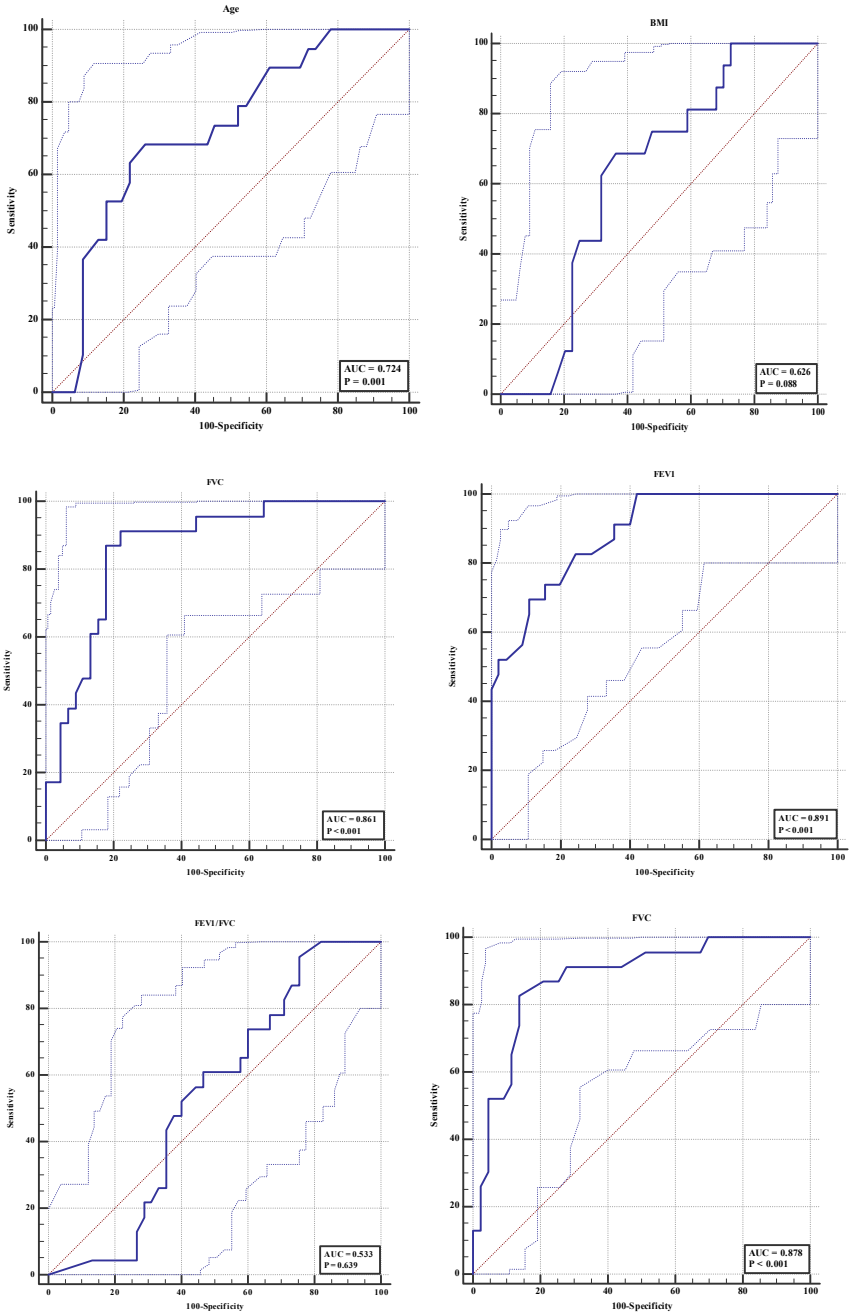

Fig. 1. Receiver operating curve (ROC) analysis of age, BMI, FVC, FEV1 and FEV1/FVC in 88 asthmatics with and without overlap syndrome. The cut-off points of 49 years of age and the cut-off point of 27 BMI to detect overlap syndrome. The cut-off points of FVC (Lit), FVC (%), FEV1, and FEV1/FVC were>2.16, >63, >69, and >96.5 respectively.

Table 3. Asthma–COPD overlap syndrome in association to demographic characteristics in 88 asthmatics with and without overlap syndrome. Results are given by univariable and multivariable binary logistic regression analyses

Variable		Unadjusted		P value	adjusted		*p* value
		OR	95% CI		OR	95% CI	
Age	<49	-	-	0.004	-	-	0.025
	≥49	3.77	1.53-9.27		3.53	1.07-11.63	
BMI	<27	-	-	0.039	-	-	0.092
	≥27	2.54	1.04-6.16		3.45	0.81-14.65	
Gender	Male	-	-	0.126	-	-	-
	Female	2.05	0.81-5.18		-	-	
Marital status	Single	-	-	0.322	-	-	-
	Married	1.77	0.57-5.50		-	-	
Address	small City	-	-	≤0.001	-	-	0.007
	Big City	11.33	4.15-30.89		7.42	1.75-31.49	
Smoking	No	-	-	0.072	-	-	-
	Yes	2.33	0.92-5.89		-	-	
Heart disease	No	-	-	0.343	-	-	-
	Yes	1.71	0.56-5.22		-	-	
Eczema	No	-	-	0.667	-	-	-
	Yes	1.27	0.41-3.89		-	-	
Allergic rhinitis	No	-	-	0.842	-	-	-
	Yes	1.09	0.45-2.61		-	-	
Gastroesophageal Reflux disease	No	-	-	0.042	-	-	-
	Yes	3.25	1.04-10.12		-	-	
Rheumatic disease	No	-	-	0.808	-	-	-
	Yes	1.18	0.29-4.75		-	-	
	Yes	5.12	0.57-45.82		-	-	
Psychiatric problems	No	-	-	0.131	-	-	
	Yes	2.24	0.78-6.41		-	-	

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

overlap syndrome increased by 7.42 times (95% CI, 1.75-31.49; P = 0.007) for patients who were living in a big city compared with those living in a small city (Table 3).

Discussion

The definition of ACOS and its phenotype is not definitive and there is still controversy about its risk factors. Therefore, we designed this study to distinguish ACOS from severe asthma and determine what risk factors are involved.

The most significant risk factor for COPD is smoking (5). As a result, it is not unexpected that ACOS patients smoked more than asthmatic patients in our research. More smoking was also linked to permanent airway blockage in asthma patients in a study by Lee et al (6).

In the present study, individuals with ACOS were shown to be older than patients with asthma alone. Additionally, it has been demonstrated that the risk of developing ACOS increases by 3.53 times for people over the age of 49 compared to those under that age. Those with ACOS were also older than patients with asthma alone in a study by Menezes et al (7). Both that study and the COPD Gene study's individuals with COPD were older than those with overlap (8). In certain cases, these results may imply permanent airway blockage due to overlap. Also, there is evidence that irreversible airway blockage may appear in some patients with asthma during appropriate follow-up (9), and that persistent asthma is linked to irreversible airway obstruction (6).

In the present study, another risk factor that was shown to have an association with ACOS is a BMI above 27. According to earlier research, individuals with ACOS who had a higher BMI had more severe respiratory symptoms than patients with asthma or COPD alone (10, 11). Obesity has been proven in previous research (12) to have a negative impact on individuals with respiratory illness and should be assessed independently. In addition, treating this concomitant condition may assist people with ACOS improve their lung function.

In addition, ACOS has a higher rate in large cities in our study and it is shown that the rate of ACOS in a large city is 7.42 times more than living in a small city. This could be due to environmental pollution in large cities. Previous studies (13) have confirmed this, stating that people who are exposed to higher levels of air pollution are almost 3 times more likely to develop ACOS. As a result, reducing your exposure to high levels of air pollution may lower your chance of developing ACOS. Asthma, COPD, chronic bronchitis, and emphysema are all separate types of airway illness, according to past research. It has been shown that host and environmental variables, such as air pollution exposure, may alter certain diseases or their manifestations. Only a few epidemiological studies have been able to pinpoint the risk of ACOS. Our findings add to the growing body of data that persistent air pollution may cause serious consequences and play a role in the development of COPD in those who already have asthma. A deeper understanding of environmental exposure risk and ACOS may benefit in understanding and creating preventive ways to address the gradual deterioration of lung function that leads to COPD (13, 14).

Also, the present study shows that the variables FVC, FEV1, and FEV1/FVC can have a role in diagnosing ACOS; these variables can be defined as FVC (lit) > 2.16, FEV1 > 69, FEV1/FVC > 96.5 and FVC (%) >63, respectively. This cut point could provide a new definition of

ACOS. Given that there are no distinct biomarkers that distinguish ACOS from asthma or COPD, diagnosis may be challenging (15). Due to the inability of a single component, such as a respiratory sign or spirometric parameter, to discriminate between asthma, COPD, and ACOS (16), major and minor criteria for diagnosing ACOS have been proposed, particularly in the elderly (17) and current or past smokers (18). These diagnostic criteria, however, are not conclusive, and clinicians often revise their diagnoses during follow-up. In addition, identifying ACOS in 2 clinical groups— patients with asthma who have permanent airflow restrictions and patients with COPD who have a history of asthma—may be difficult (19). However, the criteria developed as a result of our research may be used to distinguish between these 2 diseases.

The greatest associated risk factors of ACOS in this study are age older than 49 years and a BMI ≥27. This would mean in real life that not just recognized asthma but also COPD and ACOS should be examined in the case of an older asthmatic with a high BMI whose asthma is difficult to control.

The present study has limitations. First, the study's sample size was insufficient to determine the differences between patients with ACOS and patients with asthma alone. However, the present study showed that being older and residing in a major city both predict ACOS. Second, because we did not examine successive patients, there may be a bias in selection. On the other hand, because patients with COPD are well known and even those who do not use the medications commonly prescribed for COPD, it can be assumed that the outcome may be biased in another way. Aging, on the other hand, produces changes in lung elastic regression and pulmonary mechanics, resulting in a reduction in FEV1/FVC. As a result, regardless of how long they have had asthma, older persons are more likely to match the ACOS diagnostic criteria (20, 21).

This study has some advantages as well. First, we are certain that all of the patients polled had asthma based on the criteria utilized. Second, we tried to improve the ACOS definition by including age and BMI. However, we recommend that other researchers do a study with a larger sample size in the presence of a third group of COPD patients to obtain better findings.

Conclusion

The prevalence of ACOS is higher among patients with age-related asthma and BMI; however, there is no prior diagnosis of COPD. Spirometry can be useful in distinguishing ACOS and asthma in this study. Living in a big city, age over 49, and BMI above 27 were the risk factors of ACOS in this study.

Abbreviations

ACOS: Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome

COPD: Chronic Obstructive Pulmonary Disease

PFT: Pulmonary Function Tests

FEV1: Forced expiratory volume in the first second

FVC: Forced vital capacity

BMI: Body mass index

ROC: receiver operating curve analysis

Ethical Approval

This study was approved by the ethics committee of Shiraz University of Medical Sciences in accordance with declaration of Helsinki. Informed consent was obtained from all participants in this study.

Availability of Data

The datasets generated and/or analysed during the present study are not publicly available due to the role of the ethics committee of Shiraz University of Medical Sciences; however, data are available from the corresponding author upon reasonable request.

Code Avaiability

Data were analyzed with STATA statistical software: Release 14 and MedCalc 20.013 statistical programme.

Acknowledgment

N/A.

Conflict of Interests

The authors declare that they have no competing interests.

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