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CLINICAL PROFILE AND RISK FACTORS OF COPD IN NON - SMOKERS IN A TERTIARY CARE CENTRE

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ABSTRACT

Background:

Tobacco smoking has been recognized as the most important risk factor for chronic obstructive pulmonary disease (COPD) for a long time, but recent studies have shown that non-smokers also contribute to a significant proportion of COPD. The aim of the present study is to explore the different causes of non-smoker COPD patients and to assess their clinical profile.

Methods:

This study was an observational cross‑sectional study conducted in Department of Respiratory Medicine, Rajshree Medical Research Institute Bareilly. A total of 108 COPD patients of either gender with COPD, diagnosed by GOLD guideline were included in the study.

Results:

Out of the 108 cases studied, majority were females constituting 74.1% and mostly 83.3% belonged to rural areas. Most affected age group was 41-50 years (41.7%). The duration of illness was < 5 years among majority 67.6% subjects. History of exposure to ETS was present in all 108 patients, most of the patients i.e. 98.1% gave history of ETS exposure for >3 hours and 62% patients gave history of ETS exposure for > 10 years. Majority of the study population had symptoms of Cough and Sputum (100.0%) followed by Breathlessness (65.7%), Wheezing (21.3%) and swelling of lower limb (17.6%). Biomass fuel use was found among 79.6% subjects.

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Conclusions:
This study revealed that non-smokers contribute a significant proportion of COPD patients. Multiple risk factors other than smoking also play a major role in the development of COPD, particularly exposure to biomass smoke.

INTRODUCTION

Chronic obstructive pulmonary disease is a common, preventable, and curable disease characterized by persistent respiratory symptoms and airflow limitation caused by airway and/or alveolar abnormalities, which are typically caused by significant exposure to noxious particles or gases and influenced by host factors such as abnormal lung development.[1]

Other risk factors, such as indoor air pollution (biomass fuel, wood, and coal), occupational exposure (crop and animal husbandry, dust exposure-coal, gold, iron, and steel formation), chemical exposure, and outdoor air pollution, are emerging as relevant, particularly in developing nations.[2] Biomass exposure is another significant risk factor for COPD.[3]

COPD symptoms include breathlessness, persistent cough, and sputum production. Use of spirometry can confirm the diagnosis of COPD. FEV1/FVC value of <0.7 post bronchodilator demonstrates the existence of airway obstruction and consequently COPD. COPD is a disease that causes low quality of life owing to frequent exacerbations and persistent concomitant illnesses. COPD has become a costly condition to treat. It is difficult to reduce the rising burden of COPD in a resource-poor nation like India.[4,5]

Most COPD cases could be avoided by limiting exposure of predisposing factors such as smoking, indoor and outdoor pollutants. Although therapy may help in delaying the progression of the disease, there is no proven evidence that any drugs can reverse the long-term deterioration of lung function. Smoking cessation, vaccines, pulmonary rehabilitation, inhaled bronchodilators, and corticosteroids are all COPD therapies.[6]

Materials and method

This present cross-sectional study was conducted in the Department of Respiratory Medicine, Rajshree Medical Research Institute, Bareilly, U.P. during the period 2020-2022. Patients fulfilling inclusion and exclusion criteria from 01/02/21 to 31/07/2022 were included in the study.

Inclusion criteria

1. Non-smoker COPD patients fulfilling GOLD criteria

2. Patients with $FEV_1/FVC < 0.7$.

Exclusion criteria

1. Smokers

A detailed history complete physical examination and routine & appropriate investigations were done for all patients. Data was collected by using a proforma meeting the objectives of the study after appropriate consent from the patient. A computerized spirometer was used to perform lung function tests. Three satisfactory efforts of the patient from the test were

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recorded and the best effort among them was considered. Bronchodilation was done using 200 micrograms of inhaled salbutamol using a metered dose inhaler and test was repeated after 15 minutes. The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS version 21.0. The Quantitative (Numerical variables) were present in the form of mean and SD and the Qualitative (Categorical variables) were present in the form of frequency and percentage.

The student t-test was used for comparing the mean values between the 2 groups whereas chi-square test was applied for comparing the frequency. The p-value was considered significant when less than 0.05.

RESULTS

Table 1: Distribution of study population according to gender.

Gender	Frequency	Percent
Male	28	25.9%
Female	80	74.1%

Out of the 108 cases studied, majority were females constituting 74.1% and males constituting 25.9%.

Table 2: Distribution of study population according to place of residence.

Place of residence	Frequency	Percent
Rural	90	83.3%
Urban	18	16.7%

There were 83.3% rural and 16.7% urban subjects.

Table 3: Distribution of study population according to Age groups

Age groups	Frequency	Percent
31-40 years	9	8.3%
41-50 years	45	41.7%
51-60 years	31	28.7%
Above 60 years	23	21.3%

Most affected age group was 41-50 years (41.7%).

Table 4: Distribution of study population according to duration of illness

Duration of illness	Frequency	Percent
< 5 years	73	67.6%
> 5 years	35	32.4%

The duration of illness was < 5 years among 67.6% and > 5years among 32.4% subjects.

5. Environmental tobacco smoke exposure

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Table 5a: Distribution of study population according to hours of exposure/day

ETS (Hours/day)	Frequency	Percent
<3	2	1.9%
>3	106	98.1%
Total	108	100.0%

ETS exposure was >3 hours/day among 98.1% subjects.

Table 5b: Distribution of study population according to Duration of exposure in years

ETS (Years)	Frequency	Percent
< 10 years	41	38.0%
> 10 years	67	62.0%

History of exposure to ETS was present in all 108 patients among these 98.1% gave history of ETS exposure for >3 hours and 62% gave ETS exposure duration for > 10 years.

Table 6a: Distribution of study population according to Biomass fuel use

Biomass fuel use	Frequency	Percent
No	22	20.4%
Yes	86	79.6%

Biomass fuel use was found among 79.6% subjects.

Table 6b: Distribution of study population according to hours of exposure/day

Biomass fuel use duration (h/d)	Frequency	Percent
2-4 hours	15	17.4%
5-6 hours	59	68.6%
> 6 hours	12	14.0%

Biomass fuel use duration (hours /day) was 2-4 hours among 15 (17.4%), 5-6 hours among 59 (68.6%) and > 6 hours among 12 (14.0%) subjects.

Table 6c: Distribution of study population according to years of exposure/day

Fuel use (years)	Frequency	Percent
5-10 years	29	33.7%
11-15 years	6	7.0%
> 15 years	51	59.3%

Fuel use was 5-10 years among 29 (33.7%), 11-15 years among 6 (7.0%) and > 15 years among 51 (59.3%) subjects.

Table 6d: Distribution of study population according to nature of fuel

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Nature of fuel	Frequency	Percent
Firewood	70	81.4%
Firewood + cowdung	16	18.6%

Fuel use was Firewood among 81.4% and Firewood with cowdung among 18.6% subjects. Out of 108 patients,86 patients gave history of biomass fuel usage and exposure. All 22 patients who didnot have biomass fuel exposure were males. Of the 86 patients,17.4% gave history of exposure <6hours/day,68.6% gave history of exposure for 5-6 hours & 14% gave history of exposure >6 hours/day. 33.7% gave duration of exposure for biomass fuel <10 years,7% gave duration of exposure for biomass fuel for 10-15 years and 59.3% gave duration of exposure of biomass fuel >10 years. Increased duration of exposure to biomass fuel was associated with increased risk of COPD.

Nature of fuel

81.4% patients gave history of firewood usage and 16 patients (18.6%) gave history of firewood and cowdung usage.

Table7: Distribution of study population according to occupation

Occupation nature	**Frequency**	**Percent**
Nil	72	66.7%
Dust	26	24.1%
Dust +Husk	2	1.9%
Husk	4	3.7%
Coal dust	1	0.9%
Textile Mill	3	2.8%

Out of study population, 33.3% had occupational exposure.

Table 8: Distribution of study population according to Duration of illness (years)

	Duration of illness (years)				
Type of COPD	Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
I	2.39	0.63	1.708	0.170	N/A
II	4.08	0.95			
III	5.73	0.47			
IV	7.00	0.71			

The mean Duration of illness (years) was compared between type I, II, III and IV COPD using the one-way ANOVA test with post-hoc bonferroni test for inter-group comparisons. The mean Duration of illness (years) increased with severity of COPD.

Table 9: Distribution of study population according to clinical features

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	Frequency	Percent
Cough	108	100.0%
Sputum	108	100.0%
Breathlessness	71	65.7%
Weight loss	12	11.1%
Fatigue	13	12.0%
Cyanosis	0	0.0%
Wheezing	23	21.3%
Swelling of lower limb	19	17.6%
Fever	11	10.2%
Chest pain	1	0.9%

Majority of the study population had symptoms of Cough and Sputum (100.0%) followed by Breathlessness (65.7%), Wheezing (21.3%) and swelling of lower limb (17.6%).

Table 10: Distribution of study population according to clinical examination

	Frequency	Percent
Raised JVP	19	17.6%
Pedal edema	18	16.7%
Increased use of Accessory muscles of respiration	7	6.5%
Barrel chest	46	42.6%
Decreased chest movements	39	36.1%
Rhonchi	69	63.9%
Crepts	43	39.8%

Raised JVP was reported among 17.6%, pedal edema among 16.7%, increased use of accessory muscles of respiration among 6.5%, barrel chest among 42.6%, decreased chest movements among 36.1%, rhonchi among 63.9% and crepts among 39.8

Table 12a: Distribution of study population according to BMI

BMI	Frequency	Percent
< 18	24	22.2%
18-24.9	64	59.3%
25 and above	20	18.5%

BMI was < 18 among 22.2%, 18-24.9 was 59.3% and 25 and above among 18.5% subjects.

Table 16: Distribution of study population according to FEV1/FVC

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FEV1/FVC	Type of COPD	Mean	Std. Deviation	F-value	p-value	Post-hoc comparisons
Pre	I	64.75	3.26	2.607	0.001*	I > II > III > IV
	II	57.92	3.86			
	III	35.45	11.60			
	IV	22.37	6.27			
Post	I	66.16	2.68	0.795	0.001*	I > II > III > IV
	II	59.43	4.21			
	III	37.64	11.08			
	IV	23.67	6.35			

The mean Pre and Post FEV1/FVC was compared between type I, II, III and IV COPD using the one-way ANOVA test with post-hoc bonferroni test for inter-group comparisons. The mean Pre and Post FEV1/FVC was significantly more among type I and II compared to type III which was significantly more than IV COPD.

Table 18: Distribution of study population according to Chest X-ray

Chest X-ray	GOLD Severity			
	I	II	III	IV
Bilateral Hyperinflation	6	22	10	5
	9.0%	88.0%	90.9%	100.0%
Normal	61	3	1	0
	91.0%	12.0%	9.1%	0.0%
	67	25	11	5
	100.0%	100.0%	100.0%	100.0%
χ^2value = 77.932, p-value = 0.001*				

Bilateral Hyperinflation were significantly more among type IV compared to type II and III which was significantly more than I COPD.

DISCUSSION

Non-smoker COPD is a newer subgroup that has received a lot of attention recently.

In the present study,108 cases were selected from medical wards of Rajshree medical research institute, Bareilly, who had post bronchodilator FEV1/FVC <0.7.

The proportion of non-smokers in the total COPD cohort varies widely (9.4-68.6%) among Indian literature.[7] According to Bajpai et al.,[8] the proportion of non-smoker COPD patients in the total COPD patient cohort was 40%. According to Ehrlich et al.[7] non-smokers made up 47.6% of patients with airway obstruction.

Brashier et al.,[9] discovered a similar result, stating that the proportion of COPD patients who never smoked over the age of 45 years in India was 68.6%.

Age

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In our study there was no significant difference in mean age between type I, II, III and IV COPD. The mean age of the study population was 53.09±8.75 with a range of 9-78 years. Pazare and Mehta.[10] found that mean age of the patients was 65.7±7.95.
It was similar to other studies of Bakr RM et al (65.08±5.03) and Zhou et al (65.7±11.3).
Jain and Malik.[11] found that the age of study participants ranged from 18-76 years with mean age of study participants was 58.2 years. Majority of the study participants 42% belonged to the age group of 60-70 years which was followed by 24% study participants in more than 70 years age group which was followed by 20% study participants in the age group of 50-60 years followed by 12% study participants in the age group of 30-50 years and 10% study participants were in age group of 18-30 years of age.

Gender

In our study, there were 25.9% males and 74.1% females. In concordance with our study,Zhou Y et al.[12] found 88.7% females in their study.
Pazare and Mehta.[10] reported that there was male predominance (65% male) in their study
In the studies by Bakr RM et al.,[13] there were 58.3% males, this may be due to different geographic area, genetic and environmental factors.

Severity of COPD

It was found in our research that 62.0% had Gold severity type I, 23.1% had type II, 10.2% had type III and 4.6% had type IV.
According to Bajpai et al.,[8] majority of non-smoker COPD patients (56.94%) were in GOLD grade II followed by 22.92% in GOLD grade III severity.

Symptoms

In our study, majority of the study population had symptoms of Cough and Sputum (100.0%) followed by Breathlessness (65.7%), Wheezing (21.3%) and Swelling of lower limb (17.6%).

Pazare and Mehta.[10] reported that the commonest symptoms were Dyspnoea, Cough and Expectoration.

Jain and Joshi.[11] found that all research participants had symptom of dyspnoea. A total of 92% patients experienced a cough, which was followed by expectoration in 56% of the patients, wheezing in 28% of the patients, fever in 10% of the patients.

Similar findings were found in a research by Gudaguntiet al.[13] that included 200 patients with chronic obstructive pulmonary disease. They discovered that the least severe COPD patients developed fever, for instance, in 22% of the cases. 83% of cases had cough. In 98% cases, breathlessness was found to be the problem.

The primary symptoms of COPD are a persistent cough and sputum brought on by increased mucus production in the major airways.[12] Jing et al.[14] showed that smokers had a greater prevalence of both cough and sputum. Güldavalet al. [15] discovered that while sputum symptoms were more prevalent in smokers, cough symptoms were more prevalent in non-smokers.

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By contrast, Bajpai et al. [8] discovered that while cough symptoms were more prevalent in non-smokers, complaints of shortness of breath and sputum were more prevalent in smokers.

Signs

In our study, Raised JVP was reported among 17.6%, Pedal edema among 16.7%, use of accessory muscles of respiration among 6.5%, Barrel chest among 42.6%, decreased movements of chest among 36.1%, Rhonchi among 63.9%, Crepitations among 39.8% and CVS-PH among 16.7% cases.

Pazare and Mehta.[10] reported that the most common sign on examination was Rhonchi (93.33%) and least common was intercostal chest retractions (4.84%). Hyperinflation was the most common chest x-ray abnormality (61.67%) followed by tubular heart (55%).

Jain and Malik.[11] reported that the most common finding was rhonchi among 96% patients which was followed by hyper resonance among 32% patients followed by obliterated liver dullness, obliterated cardiac dullness and crepitation among 28% patients respectively. 26% patients had loud p2 sound which was followed by reduced chest movements and Reduced Crico-sternal distance among 24% patients respectively. 18% patients had barrel chest which was followed by finding of accessory muscles among 12% patients. Reduced air entry seen in 8% patients and 4% patients had Intercostal chest retractions.

Chest x ray

In our study hyperinflation was found in 38.1% cases while 60.18% cases had normal chest x-ray

Pazare and Mehta.[10] reported that hyperinflation was the most common chest x-ray abnormality (61.67%) followed by tubular heart (55%).

ETS

In current study, ETS (Hours) was <3 among 2 (1.9%) and >3 hours among 106 (98.1%) subjects. ETS (Years) was < 10 years among 41 (38.0%) and > 10 years among 67 (62.0%) subjects.

ETS exposure is known to be a risk factor for COPD.[16] ETS exposure at home and at workplace was present in 100% cases in my study which is comparable to Güldavalet al. [15] study.

Biomass fuel use

In current study, Biomass fuel use was found among 79.6% subjects. Biomass fuel use duration (hours /day) was 2-4 hours among 15 (17.4%), 5-6 hours among 59 (68.6%) and > 6 hours among 12 (14.0%) subjects. Fuel use was 5-10 years among 29 (33.7%), 11-15 years among 6 (7.0%) and > 15 years among 51 (59.3%) subjects.

biomass smoke was most important risk factor (53.98%) for COPD development.

Mahesh et al.[18] discovered that chronic bronchitis was substantially related with a minimal biomass exposure index of sixty. Furthermore, when the mean biomass exposure index rose, so did the severity of COPD.

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BMI

In our study, there was no significant difference in mean BMI between type I, II, III and IV COPD.BMI was < 18 among 22.2%, 18-24.9 was 59.3% and 25 and above among 18.5% subjects.

A gradual decrease of skeletal muscle mass has been linked to COPD, and multiple studies have found that a low BMI is an independent predictor of mortality risk. [19,20] Denguezli et al. [21] stated that non-smokers with low BMIs (20 kg/m2) had an elevated risk of COPD. In addition, the link between BMI changes and the occurrence of GOLD grade I+ COPD was stronger in men than in women in the non-smoking group. The same findings, which indicated higher risks of COPD among non-smokers with a BMI under 20 kg/m2, were published by Lamprecht et al. [22]

Mathew et al. [3] demonstrated that exposure to biomass smoke is the primary cause of COPD in non-smokers. This supports the finding of Salvi et al. [2] that biomass smoke exposure is the main risk factor. A prior study by Hu et al.,[23] found a 2.3-fold increased risk of COPD was linked to exposure to biomass fuel smoke. According to Lopez et al.,[24] 3 billion persons today are exposed to biomass smoke worldwide compared with 1.1 billion smokers, it appears likely that exposure to biomass smoke is the major risk factor for COPD internationally.

Airway parameters

In current study, the mean Pre and Post FVC was significantly more among type I compared to type II and III which was significantly more than IV COPD. The mean Pre and Post FEV 1 was significantly more among type I compared to type II and III which was significantly more than IV COPD. The mean Pre and Post FEV1/FVC was significantly more among type I and II compared to type III which was significantly more than IV COPD. The mean Pre and Post PEFR was significantly more among type I compared to type II and III which was significantly more than IV COPD.

Bajpai et al. [8] found that spirometry parameters between smokers and non-smokers differed significantly in COPD cases. In comparison to smokers, non-smokers had considerably higher mean FEV1 and FVC values. As a result, non-smokers had a considerably higher FEV1/FVC ratio than active smokers (68.8±3.7 vs. 61.8±5.7). Compared to smokers with COPD, non-smokers with COPD had less severe airflow obstruction.

CONCLUSION

In my study maximum patients were females.

Most of the patients were in age group 41-50 years.

Cough and sputum production were most common presenting complains among study population.

Most patients were from rural background.

Most frequent risk factor in current study population with COPD was exposure to biomass fuel and environmental tobacco smoke exposure.

Mean systolic blood pressure and diastolic blood pressure was significantly more among GOLD stage 4 compared to stage 1, 2 and 3.

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Maximum patients had a normal basal metabolic index (BMI).

Based on GOLD criteria maximum patients belong to GOLD stage 1 > GOLD stage 2 > GOLD stage 3 > GOLD stage 4 and the mean Pre and Post FEV1/FVC was significantly more among stage I and II compared to stage III which was significantly more than stage IV COPD, this suggests that disease severity was less among non-smoker COPD patients in my current study.

Bilateral hyperinflation was significantly more among GOLD stage 4 compared to stage 2 and stage 3 which was significantly more than stage 1.

Bibliography

1. GOLD guidelines 2020 updated www.goldcopd.com.
2. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. Lancet. 2009;374:733–43.
3. Mathew N, Xavier Z, Deshmukh AS, Deshmukh H, Jadhav S, Kasat S. The study of aetiology of chronic obstructive pulmonary disease (COPD) in Non-smokers. J Pulmon Respir Med. 2015;5:304.
4. Wig KL, Guleria JS, Bhasin RC, Holmes Jr E, Vasudeva YL, Singh H. Certain clinical and epidemiological patterns of chronic obstructive lung disease as seen in northern India. Indian J Chest Dis. 1964;6:183-94.
5. Jindal SK, Aggarwal AN, Gupta D, Agarwal R, Kumar R, Kaur T, et al. Indian study on epidemiology of asthma, respiratory symptoms and chronic bronchitis in adults (INSEARCH). Int J Tubercul Lung Dis. 2012;16(9):1270-7
6. Dobler CC, Morrow AS, Beuschel B, et al. . "Pharmacologic Therapies in Patients With Exacerbation of Chronic Obstructive Pulmonary Disease: A Systematic Review With Meta-analysis". Annals of Internal Medicine.2020; 172 (6): 413–422
7. Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Predictors of chronic bronchitis in South African adults. Int J Tuberc Lung Dis 2004;8:369‑76.
8. Bajpai J, Kant S, Bajaj DK, Pradhan A, Srivastava K, Pandey AK. Clinical, demographic and radiological profile of smoker COPD versus nonsmoker COPD patients at a tertiary care center in North India. J Family Med Prim Care 2019;8:2364-8.
9. Brashier B, Gangavane S, Valsa S, Gaikwad SN, Ghorpade SV, Mandrekar S, et al. Almost half the patients treated for pulmonary tuberculosis (TB) show evidence of obstructive airways disease (OAD). In: European Respiratory Society Annual Congress, Stockholm, Sweden; 2007 Sep 15‑19. [Abstr. E2585].
10. Amar R, Pazare AR, Mehta PK. Etiology and clinical profile of COPD in non-smoker in urban area. Int J Adv Med 2018;5:1100-4.
11. Jain MK, Joshi N. Assessment of the clinical profile of chronic obstructive pulmonary disease among non-smokers at tertiary care centre. Int J Med Sci Educ. 2020;7(4):23-27.
12. Zhong N, Wang C, Yao W et al. Prevalence of chronic obstructive pulmonary disease in China: A large, population-based survey. Am J Respir Crit Care Med. 2007;176:753-760.

13. Gudagunti AK, Hasabi I, S. A. A study of clinical profile of patients with chronic pulmonary obstructive disease at a tertiary care centre in North Karnataka, India. Int J Adv Med. 2019;6(2):455.
14. Zhang J, Lin XF, Bai CX. Comparison of clinical features between non-smokers withCOPD and smokers with COPD: a retrospective observational study. Int J Chron Obstruct Pulmon Dis. 2014;9:57-63.
15. Güldaval F, Polat G, Doruk S, Karadeniz G, Ayranci A, Türk M, et al. What are the Differences Between Smoker and Non-smoker COPD Cases? Is it a Different Phenotype? Turk Thorac J. 2021;22(4):284-288.
16. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global burden of disease study. Lancet. 1997;349:1498–504.
17. Mahmood T, Singh RK, Kant S, Shukla AD, Chandra A, Srivastava RK. Prevalence and etiological profile of chronic obstructive pulmonary disease in nonsmokers. Lung India. 2017;34(2):122-126. doi: 10.4103/0970-2113.201298. PMID: 28360458; PMCID: PMC5351352.
18. Lopez AD, Mathers CD, Ezatti M, Jamison DT, Murray CJL (2006) Global burden of disease and risk factors. Washington, DC: World Bank.
19. Grydeland TB, Dirksen A, Coxson HO, Pillai SG, Sharma S, Eide GE, et al. Quantitative computed tomography: Emphysema and airway wall thickness by sex, age and smoking. Eur Respir J 2009;34:858‑65.
20. Jindal SK. Chronic obstructive pulmonary disease in non‑smokers‑Is it a different phenotype? Indian J Med Res. 2018;147:3379.
21. Denguezli M, Daldoul H, Harrabi I, Gnatiuc L, Coton S, Burney P, et al. COPD in nonsmokers: Reports from the Tunisian population-based burden of obstructive lung disease study. PLoS One. 2016;11:e0151981.
22. Echave-Sustaeta JM, Comeche Casanova L, Cosio BG, Soler-Cataluña JJ, Garcia-Lujan R, Ribera X. Comorbidity in chronic obstructive pulmonary disease. Related to disease severity? Int J Chron Obstruct Pulmon Dis. 2014;19(9):1307-14.
23. Young RP, Hopkins R, Eaton TE. Forced expiratory volume in one second: not just a lung function test but a marker of premature death from all causes. Eur Respir J. 2007;30:616-22.
24. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers
Am J Respir Crit Care Med. 2007;176:285-90.