# Original Article

# Prevalence and risk factors of chronic obstructive pulmonary disease in residents from the Dongguan Shilong region of China

Lei Wu<sup>1</sup>, Meihua Chen<sup>1</sup>, Taorong Xu<sup>2</sup>, Yanling Cai<sup>1</sup>

Departments of <sup>1</sup>Respiration Medicine, <sup>2</sup>Nephrology and Gastroenterology, Third People's Hospital of Dongguan, Dongguan 523326, Guangdong, China

Received December 5, 2018; Accepted June 5, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: Objective: The aim of the current study was to investigate prevalence rates and risk factors of chronic obstructive pulmonary disease (COPD) in residents from the Dongguan Shilong region of Guangdong Province, China. Methods: A random sampling of patients aged > 40 years with high-risk COPD from Dongguan Shilong was collected. They underwent pulmonary function testing and completed questionnaire surveys. Prevalence rates of COPD were calculated. Univariate and multivariate factor logistic analyses were carried out, aiming to identify potential risk factors of COPD. Results: The overall prevalence of COPD in Dongguan Shilong was 9.05%. Prevalence rates of the male population were higher than those of the female population. Prevalence of COPD was significantly increased with aging (P<0.05). The severity of COPD was evaluated as grade I-II. Gender, age, education levels, body mass index (BMI), family history of respiratory disease, and smoking indexes (SI) significantly differed between COPD and non-COPD individuals (all P<0.05). Multivariate logistic regression analysis demonstrated BMI, age, gender, and SI to be risk factors for prevalence of COPD (all P<0.05). Conclusion: Prevalence of COPD in Dongguan Shilong is relatively high. High BMI (higher), old age, male gender, and higher SIs are risk factors of incidence of COPD. Therefore, active interventions should be delivered, targeting these risk factors and aiming to reduce prevalence rates of COPD in China.

Keywords: Single factor, chronic obstructive pulmonary disease, smoking index, prevalence

# Introduction

The Global Burden of Disease Study has projected that chronic obstructive pulmonary disease (COPD) was the sixth leading cause of death in 1990 [1]. Based on relevant data, CO-PD-induced mortality rates were ranked fourth, behind cancer, cardiovascular disease, and cerebrovascular disease in 2010 [2, 3]. COPD may become the third leading cause of death, worldwide, by 2020 [4]. Data involving the urban population indicates that respiratory diseases (mostly COPD) account for 13.89% of all deaths and are the fourth leading cause of mortality in China. For residents in rural areas, respiratory diseases account for 22.4% of all mortalities, ranking first among causes of death. In China, approximately one million of patients die from COPD each year [5, 6].

Previous studies [7-9] have shown the pathogenesis and pathophysiologic processes of COPD. Aging populations, environmental pollution, and smoking habits can enhance mortality rates of COPD. Furthermore, studies [10, 11] have demonstrated that COPD is associated with heredity and the environment. In addition, the pathogenesis of COPD is preventable. Therefore, identifying pathogenic characteristics and risk factors for COPD plays a pivotal role in providing guidance for early screening and intervention for high-risk COPD populations, preventing progression of COPD.

In this study, demographic data was collected from December 2011 to December 2012. Prevalence of COPD was investigated in the Dongguan Shilong region of Guangdong Province, China. In addition, distribution patterns of highrisk populations and primary risk factors were identified and statistically analyzed.

## Materials and methods

## Baseline data

Random samples of high-risk COPD patients aged > 40 years from Dongguan Shilong region, Guangdong Province, between December 2011 and December 2012, were collected. Patients that did not undergo pulmonary function testing and those complicated with severe mental illness, cardiovascular diseases, or life-threatening diseases, along with a medical history of major chest surgery within 2 months, were excluded from subsequent analysis. A total of 2,267 questionnaires were distributed. A total of 2,243 valid questionnaires were obtained with an effective response rate of 98.94%. Respondents were aged 41-77 years, with an average age of (55.8±8.6) years.

# Questionnaire surveys

A questionnaire was self-designed by the Third People's Hospital of Dongguan (Title: The prevalence of community high-risk COPD population and its related risk factors), including the following items: (1) Gender, age, education level, occupation, and other demographic characteristics; and (2) Diseases and exposure history, including personal and family histories, smoking history, living habits, economic status, respiratory symptoms, body mass index (BMI), and inducing factors. Enrolled subjects received necessary physical examinations. Questionnaires were surveyed under the guidance of professional training community medical workers. Moreover, investigation standards were uniform, ensuring the reliability and validity of the questionnaire. The entire investigation process was monitored by the same person in charge.

# Lung function testing

A QUARK PFT4 lung function detector (COSM-ED, Rome, Italy) was utilized to test the lung function. It measured lung volume, flow rate, breathing time, and intra-pulmonary pressure. In the process of lung function testing, enrolled subjects were instructed to continue breathing through their mouths when breathing in, ensuring there was no leakage They then breathed out into the instrument as fast as possible. The

following critical indicators were recorded: Forced vital capacity (FVC), percentage of forced vital capacity accounted for the predicted value (FVC%), forced expiratory volume in 1s (FVC1), and ratio of FEV1-to-FVC (FVC1%). All subjects were required to complete two tests. The error range was kept within 5% if possible. The best results were used for statistical analysis.

# Assessment of the COPD high-risk population (12)

Patients were aged > 40 years and met any of the following criteria: (1) Long-term coughing and expectoration that conformed to clinical diagnostic standards of chronic bronchitis; (2) Long-term exposure in a smoking environment or chronic exposure to particles, dust, or harmful gas; and (3) Breathing after exercise or activity was lower than that in the same age group.

# Diagnostic criteria for COPD

Based on COPD Global Prevention and Control Initiative and standards established by the Chinese Respiratory Society [13, 14], diagnostic criteria of COPD were established as follows: 1) 15-30 minutes after pre-treatment with a 200-µg dose of bronchodilator, a FEV1/FVC  $\leq$  0.7 confirmed the presence of airflow limitation that was not fully reversible; 2) Relevant risk factors; and 3) Excluding other systemic diseases.

# Statistical analysis

SPSS 17.0 statistical software was utilized for statistical analysis (SPSS Inc., Chicago, IL, U.S.). Most observation data were counted data. An  $\chi^2$  test or rank-sum test was utilized for single factor analysis (comparisons between groups). Multivariate logistic regression analysis was applied for analysis of these risk factors. Factors with more significant differences were subjected to single factor analysis. Cochran Armitage trend testing was used for certain parameters among subjects of different age. *P*-values less than 0.05 indicate statistical significance.

# Results

# Questionnaire samples

Valid questionnaires were collected from 2,243 subjects. A total of 203 were diagnosed with COPD. The overall incidence rate of COPD in the

Table 1. Distribution of demographic characteristics between COPD and non-COPD subjects

Risk factors		COPD	Non-COPD	X <sup>2</sup>	Р	
NISK Ideleis		No = 203	No = 2040	X	Р	
Age	40~50	26 (12.8%)	855 (41.9%)	154.397	<0.001	
	51~60	36 (17.7%)	624 (30.6%)			
	61~70	80 (39.4%)	307 (15.0%)			
	> 70	61 (30.0%)	254 (12.5%)			
Gender	Male	140 (69.0%)	977 (43.6%)	48.433	<0.001	
	Female	63 (31.0%)	1266 (56.4%)			
SI (per year) <sup>c</sup>	<300	96 (47.3%)	1634 (80.1%)	158.169	<0.001	
	301~600	34 (16.7%)	234 (11.5%)			
	<600	73 (36%)	172 (8.4%)			
Family history of respiratory disease	Yes	171 (84.2%)	978 (47.9%)	97.346	<0.001	
	None	32 (15.8%)	1062 (52.1%)			
Average monthly household income (Yuan)	<1000	73 (36.0%)	824 (40.4%)	3.853	0.146	
	1001~3000	74 (36.5%)	855 (41.9%)			
	> 3000	46 (22.7%)	371 (18.2%)			
Education level	Primary school and below	107 (52.7%)	473 (23.2%)	85.179	<0.001	
	Middle school	52 (25.6%)	959 (47.0%)			
	High school and above	44 (21.7%)	608 (29.8%)			
Dust exposure history	Yes	103 (50.7%)	960 (47.1%)	1.003	0.317	
	None	100 (49.3%)	1080 (52.9%)			
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	<18.5	64 (31.5%)	416 (20.4%)	26.693	<0.001	
	18.6~25	95 (46.8%)	834 (40.9%)			
	> 25	44 (21.7%)	790 (38.7%)			
History of childhood respiratory tract diseases	Yes	90 (44.3%)	1030 (50.5%)	2.798	0.094	
	None	113 (55.7%)	1010 (49.5%)			

 $<sup>^{\</sup>text{e}}\text{The }\chi^{2}\text{ test for categorical variables.} \\ ^{\text{b}}\text{BMI } (\text{kg/m}^{2}), \text{ body mass index. } ^{\text{c}}\text{SI, smoking index. } \\ \text{Bold values are statistically significant.} \\$ 

sampling was 9.05%. The prevalence rate of COPD in the male population was 14.33%, significantly higher than the 4.98% in female counterparts. Most COPD patients were classified as grade I-II COPD. The prevalence rate of COPD significantly increased with aging.

# Single factor analysis

Risk factors that might influence the prevalence and progression of COPD, such as age, gender, and the remaining 10 parameters were included for single factor analysis. Single factor analysis demonstrated that gender, age, education level, BMI, family history of respiration, smoking indexes (SI, an indicator of smoking exposure level by smoking history and daily smoking) significantly differed between COPD and non-COPD individuals (all P<0.05), as illustrated in **Table 1**.

# Multivariate logistic regression analysis

Factors screened by single factor analysis, such as age, gender, and five other factors,

were chosen for subsequent multivariate logistic regression analysis. For the response variable, COPD was defined as 1 and non-COPD as 0. Multivariate logistic regression analysis demonstrated that age, gender, and BMI were positively correlated with prevalence of COPD (all P<0.05; relative risk > 1). In addition, SI was shown to be a vital risk factor. Moreover, BMI had the highest relative risk, up to 1.983 among all risk factors, indicating that BMI was the most critical risk factor for prevalence of COPD. Multivariate logistic regression analyses of alternative factors, such as education levels and family history of respiratory disease, are illustrated in **Table 2**.

# Stratified analysis of different age groups

Based on outcomes of multivariate logistic regression analysis, age and other factors were considered important influencing factors for prevalence of COPD. In contrast, considering subjects aged 40-70 years and the uneven distribution of morbidities, the relationship

Table 2. Results of multivariate logistic regression analysis

Factors	Assignment description		Standard error	Wald chi square	OR (95% CI)	P
Age	40~50				1 (Reference)	
	51~60	0.055	0.046	1.400	1.39 (0.81-2.38)	0.148
	61~70	0.208	0.040	22.060	3.08 (1.90-4.99)	<0.001
	≥70	0.152	0.042	11.654	2.35 (1.43-3.86)	<0.001
Gender	Female				1 (Reference)	
	Male	0.177	0.039	19.788	2.22 (1.56-3.17)	<0.001
BMI (kg/m²) <sup>b</sup>	≤18.5				1 (Reference)	
	18.6~25	0.087	0.042	4.356	1.48 (1.02-2.15)	0.023
	≥25	-0.075	0.044	2.930	0.69 (0.45-1.06)	0.054
SI (per year) <sup>c</sup>	≤300				1 (Reference)	
	301~600	-0.202	0.040	22.701	0.35 (0.23-0.55)	<0.001
	≥600	-0.062	0.041	2.214	0.76 (0.53-1.09)	0.081
Education level	Primary school and below				1 (Reference)	
	Middle School	-0.154	0.041	13.802	0.49 (0.33-0.71)	<0.001
	High school and above	-0.183	0.040	19.407	0.41 (0.28-0.61)	<0.001
Family history of respiratory disease	None				1 (Reference)	
	Yes	-0.053	0.040	1.740	0.80 (0.57-1.12)	0.109

 $<sup>^{\</sup>mathrm{b}}$ BMI (kg/m²), body mass index.  $^{\mathrm{c}}$ SI, smoking index. Bold values are statistically significant.

between prevalence of COPD and different age groups was subsequently subjected to stratified analysis and Cochran Armitage trend testing. The aim was to identify underlying characteristics. As illustrated in Table 3, incidence analysis of COPD was expressed as a function of aging and gender. Results demonstrated that Cochran Armitage  $\chi^2$  testing (P<0.01) was independent of gender, suggesting that prevalence of COPD significantly increased with aging. Trend analysis, with changes in the ages of patients with different severity levels of COPD, is shown in **Table 4**. Cochran Armitage  $\chi^2$  testing (P > 0.05) demonstrated that, with changes in age, the severity of COPD was not significant. All COPD patients were classified as grade I and II. Most were diagnosed with grade I COPD, consistent with the results above.

# Discussion

COPD is a common respiratory disease. Incidence of COPD significantly varies, according to different geographic regions, age groups, study populations, and study methods [15]. Recent studies have been conducted, investigating epidemiological surveys of COPD. Although results are not inconsistent, general trends and epidemiological characteristics are consistent. Data from most nations indicates that prevalence of COPD is less than 6% in the ad-

ult population [16]. In all Latin American cities, prevalence of COPD is appreciably higher in males than in females [17]. In China, a large population-based survey in seven provinces/ cities, including Northern, Eastern, Southern, and Western areas, has demonstrated the overall prevalence of COPD to be 8.2% (12.4% in males and 5.1% in females) in the population aged > 40 years [18]. Prevalence of COPD is significantly higher in smokers and ex-smokers than in non-smokers [19]. In the current study, the overall prevalence rate of COPD was 9.05% in the Dongguan Shilong region of Guangdong Province. Results were slightly higher than 8.2%, which was reported in a large-scale survey in China [18]. Results were significantly higher than the 5.9% reported in an earlier survey in Nanjing municipality, the capital of Jiangsu Province, China [20]. Compared with other studies in similar age groups, prevalence of COPD in the Dongguan Shilong population was slightly lower than that of Japan [10.9%] [19] and Warsaw, Poland [10.7%] [21]. It was significantly lower than Salzburg, Austria [26.1%] [22]. Consequently, these differences might reflect different countries, regions, customs, climate, and environments, as well as different investigation methods. It has been reported [23, 24] that clinical symptoms of COPD are not evident with the inducement of cold, cold air, and smoking. Consequently, asymptomatic CO-

# Prevalence and risk factors of COPD in a general population

Table 3. Comparison of the prevalence of COPD according to gender and age

	Male			Female				Total				
Age group	Sample size	Cases	OR (95% CI)	Р	Sample size	Cases	OR (95% CI)	Р	Sample size	Cases	OR (95% CI)	Р
40-49	334	20 (5.99%)	1		463	6 (1.30%)	1		797	26 (3.26%)	1	
50-59	252	26 (10.32%)	1.72 (0.94-3.16)	0.053	331	10 (3.02%)	2.33 (0.84-6.48)	0.080	583	36 (6.17%)	1.89 (1.13-3.17)	0.010
60-69	256	50 (19.53%)	3.26 (1.89-5.62)	<0.001	331	30 (9.06%)	6.99 (2.88-16.99)	<0.001	587	80 (13.63%)	4.18 (2.65-6.59)	<0.001
> 70	135	44 (32.59%)	5.44 (3.09-9.58)	<0.001	141	17 (12.06%)	9.30 (3.60-24.05)	<0.001	276	61 (22.10%)	7.00 (4.34-11.31)	<0.001
Total	977	140 (14.33%)	2.39 (1.47-3.89)	<0.001	1266	63 (4.98%)	3.84 (1.65-8.93)	<0.001	2243	203 (9.05%)	2.77 (1.83-4.21)	<0.001
Cochran Armitage P	<0.001				<0.001				<0.001			

Bold values are statistically significant.

Table 4. Comparison of the severity of COPD according to age

•	•	_	_		
Age group	Grade I	Grade II	Grade III	Grade IV	Total
40-49	17 (65.4%)	9 (34.6%)	0 (0%)	0 (0%)	26 (100%)
50-59	19 (52.8%)	10 (27.8%)	7 (19.4%)	0 (0%)	36 (100%)
60-69	40 (50.0%)	36 (45.0%)	2 (2.5%)	2 (2.5%)	80 (100%)
> 70	35 (57.4%)	16 (26.2%)	10 (16.4%)	0 (0%)	61 (100%)
Total	111 (54.7%)	71 (35.0%)	19 (9.3%)	2 (1.0%)	203 (100%)
Cochran Armitage P	0.608				

PD patients should be emphasized in differential diagnosis, aiming to eliminate symptom inducement and reduce misdiagnosis and missed diagnosis rates in clinical settings.

Smoking has been recognized as a major risk factor for COPD, worldwide. Moreover, research [25-27] has demonstrated that smoking can increase the prevalence of COPD in clinical practice. It can impair the immune system in a variety of patterns. In the current study, the prevalence rate of COPD was significantly increased when the SI was > 300. Cigarettes contain nicotine, tobacco tar, carbon monoxide, nitrous amines, and other harmful substances. When inhaled, the substances may activate alveolar macrophages, T lymphocytes, and neutrophils, releasing a variety of media. Subsequently, the lung structure is damaged and often exhibits airway inflammatory reactions. In contrast, secretion of airway mucus and airflow obstruction increases have been considered major causes of COPD [28, 29]. A predictive study [30] suggested that patients with persistent smoking enhance mortality rates of COPD in clinical practice. Therefore, quitting smoking plays a significant role in the prevention of progression of COPD and reducing CO-PD-induced mortality rates.

Old age and male gender are predisposing factors for prevalence of COPD. In the present study, occurrence of COPD was positively correlated with the age of COPD patients. Moreover, prevalence rates of COPD in males were significantly higher than those in females from Dongguan Shilong region of Guangdong Province, indicating that prevalence of COPD is considerably elevated while aging, consistent with previous reports [31, 32]. In addition, age and gender are probably associated with persistent inflammation in the lungs, sustained bronchodilation, and continuous reduction of lung volume by the intake of harmful substances through daily smoking. Changes in the

demographic structure of the aging population are major causes of increased prevalence rates of COPD in China.

# Study limitations

There were several limitations to the current study. The sample size of COPD patients was relatively small. The duration of smoking was not included in multi-factor analysis. All information on the questionnaire surveys pertained to diseases. Exposure history was self-reported and subjected to recall bias and misclassification. BMI is an independent influencing factor for incidence of COPD. However, prevalence of COPD in patients with a lower BMI was higher and immune resistance in patients with a low BMI was worse, indicating poor nutritional status. Moreover, COPD also decreases the tolerance of physical exercises and body weight, thereby creating a vicious circle. Family histories were not obtained in this investigation. Education levels presented a significant correlation with COPD, but should be further investigated.

# Conclusion

Smoking significantly increases incidence of COPD when the SI is > 300. Morbidity rates of COPD are positively correlated with the age of COPD patients, especially in elderly males. Moreover, BMI is another independent exposure factor for COPD. It has a positive correlation with prevalence of COPD. Therefore, effective measures and interventions are recommended, targeting these risk factors. The aim should be to prevent and treat COPD in clinical practice.

# Acknowledgements

This study was supported by the Science and Technological Program for Dongguan's Higher Education, Science and Research, and Health Care Institutions (No. 20101051502401).

# Disclosure of conflict of interest

None.

Address correspondence to: Meihua Chen, Departments of Respiration Medicine, Dongguan 523326, Guangdong, China. E-mail: chenmeihua2016@sina.com

#### References

- [1] Murray CJ, Lopez AD. Evidence-based health policy-lessons from the global burden of disease study. Science (New York, NY) 1996; 274: 740-3.
- [2] Organization WH. Package of essential noncommunicable (PEN) disease interventions for primary health care in low-resource settings. 2010.
- [3] Taylor JD. COPD and the response of the lung to tobacco smoke exposure. Pulm Pharmacol Ther 2010; 23: 376-83.
- [4] Mehari A, Gillum RF. Chronic obstructive pulmonary disease in African- and European-American women: morbidity, mortality and healthcare utilization in the USA. Expert Rev Respir Med 2015; 9: 161-70.
- [5] Waatevik M, Skorge TD, Omenaas E, Bakke PS, Gulsvik A, Johannessen A. Increased prevalence of chronic obstructive pulmonary disease in a general population. Respir Med 2013; 107: 1037-45.
- [6] Soriano JB, Ancochea J, Miravitlles M, García-Río F, Duran-Tauleria E, Muñoz L, Jiménez-Ruiz CA, Masa JF, Viejo JL, Villasante C, Fernández-Fau L, Sánchez G, Sobradillo-Peña V. Recent trends in COPD prevalence in Spain: a repeated cross-sectional survey 1997-2007. Eur Respir J 2010; 36: 758-65.
- [7] Hassett DJ, Borchers MT, Panos RJ. Chronic obstructive pulmonary disease (COPD): evaluation from clinical, immunological and bacterial pathogenesis perspectives. J Microbiol. 2014; 52: 211-26.
- [8] van Dijk WD, Heijdra Y, Scheepers PT, Lenders JW, van Weel C, Schermer TR. Interaction in COPD experiment (ICE): a hazardous combination of cigarette smoking and bronchodilation in chronic obstructive pulmonary disease. Med Hypotheses 2010; 74: 277-80.
- [9] Dhariwal J, Tennant RC, Hansell DM, Westwick J, Walker C, Ward SP, Pride N, Barnes PJ, Kon OM, Hansel TT; †Deceased. Smoking cessation in COPD causes a transient improvement in spirometry and decreases micronodules on high-resolution CT imaging. Chest 2014; 145: 1006-1015.
- [10] Zysman M, Patout M, Miravitlles M, van der Molen T, Lokke A, Hausen T, Didier A, Cuvelier A, Roche N. La BPCO et la perception du nou-

- veau document GOLD en Europe. Workshop de la Société de pneumologie de langue française (SPLF). Rev Mal Respir 2014; 31: 499-510.
- [11] Yang L, Lu X, Deng J, Zhou Y, Huang D, Qiu F, Yang X, Yang R, Fang W, Ran P, Zhong N, Zhou Y, Fang S, Lu J. Risk factors shared by COPD and lung cancer and mediation effect of COPD: two center case-control studies. Cancer Causes Control 2015; 26: 11-24.
- [12] Tarleton HP, Ryan-Ibarra S, Induni M. Chronic disease burden among cancer survivors in the California behavioral risk factor surveillance system, 2009-2010. J Cancer Surviv 2014; 8: 448-59.
- [13] Che G, Zhi X. [Status of perioperative airway management in patients with chronic obstructive pulmonary disease and lung cancer]. Zhongguo Fei Ai Za Zhi 2014; 17: 884-8.
- [14] Wang X, Xiao H, Liu L, Li X. Bone metabolism status and associated risk factors in elderly patients with chronic obstructive pulmonary disease (COPD). Cell Biochem Biophys 2014; 70: 129-34.
- [15] Yeh JJ, Wang YC, Sung FC, Chou CY, Kao CH. Nontuberculosis mycobacterium disease is a risk factor for chronic obstructive pulmonary disease: a nationwide cohort study. Lung 2014; 192: 403-11.
- [16] Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. Eur Respir J 2006; 28: 523-32.
- [17] Menezes AM, Victora CG, Perezpadilla R, Team TP. The platino project: methodology of a multi-center prevalence survey of chronic obstructive pulmonary disease in major Latin American cities. BMC Med Res Methodol 2004; 4: 15.
- [18] Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, Chen B, Wang C, Ni D, Zhou Y, Liu S, Wang X, Wang D, Lu J, Zheng J, Ran P. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. Am J Respir Crit Care Med 2007; 176: 753-60.
- [19] Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, Takahashi K, Nishimura K, Ishioka S, Aizawa H, Zaher C. COPD in Japan: the Nippon COPD epidemiology study. Respirology 2004; 9: 458.
- [20] Xu F, Yin X, Zhang M, Shen H, Lu L, Xu Y. Prevalence of physician-diagnosed COPD and its association with smoking among urban and rural residents in regional mainland China. Chest 2005; 128: 2818-23.
- [21] Pływaczewski R, Bednarek M, Jonczak L, Zieliński J. [Prevalence of COPD in Warsaw population]. Pneumonol Alergol Pol 2003; 71: 329-35.

# Prevalence and risk factors of COPD in a general population

- [22] Schirnhofer L, Lamprecht B, Vollmer WM, Allison MJ, Studnicka M, Jensen RL, Buist AS. COPD prevalence in Salzburg, Austria: results from the burden of obstructive lung disease (BOLD) study. Chest 2007; 131: 29.
- [23] Stiell IG, Clement CM, Aaron SD, Rowe BH, Perry JJ, Brison RJ, Calder LA, Lang E, Borgundvaag B, Forster AJ, Wells GA. Clinical characteristics associated with adverse events in patients with exacerbation of chronic obstructive pulmonary disease: a prospective cohort study. CMAJ 2014; 186: E193-204.
- [24] Looker AC. Relationship between femur neck bone mineral density and prevalent chronic obstructive pulmonary disease (COPD) or COPD mortality in older non-Hispanic white adults from NHANES III. Osteoporos Int 2014;25: 1043-52.
- [25] Diaz-Guzman E, Mannino DM. Epidemiology and prevalence of chronic obstructive pulmonary disease. Clin Chest Med 2014; 35: 7-16.
- [26] Salvi S. Tobacco smoking and environmental risk factors for chronic obstructive pulmonary disease. Clin Chest Med 2014; 35: 17-27.
- [27] Guan J, Liu X, Xie J, Xu X, Luo S, Wang R, Xu Y. Surfactant protein a polymorphism is associated with susceptibility to chronic obstructive pulmonary disease (COPD) in Chinese uighur population. J Huazhong Univ Sci Technolog Med Sci 2012; 32: 186-189.

- [28] Zeng G, Sun B, Zhong N. Non-smoking-related chronic obstructive pulmonary disease: a neglected entity? Respirology 2012; 17: 908.
- [29] Qu Y, Yang Y, Ma D, He L, Xiao W. Expression level of histone deacetylase 2 correlates with occurring of chronic obstructive pulmonary diseases. Molecular Biology Reports 2013; 40: 3995-4000.
- [30] Mohammad Y, Shaaban R, Alzahab BA, Khaltaev N, Bousquet J, Dubaybo B. Impact of active and passive smoking as risk factors for asthma and COPD in women presenting to primary care in Syria: first report by the WHO-GARD survey group. Int J Chron Obstruct Pulmon Dis 2013; 8: 473-82.
- [31] Yamane T, Hattori N, Kitahara Y, Haruta Y, Sasaki H, Yokoyama A, Kohno N. Productive cough is an independent risk factor for the development of COPD in former smokers. Respirology 2010; 15: 313-8.
- [32] Graat-Verboom L, Smeenk FW, van den Borne BE, Spruit MA, Jansen FH, van Enschot JW, Wouters EF. Progression of osteoporosis in patients with COPD: a 3-year follow up study. Respir Med 2012; 106: 861-70.