Acta Med. Okayama, 2017
Vol. 71, No. 1, pp. 11–17
Copyright© 2017 by Okayama University Medical School.

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Original Article

Frequency of Exacerbations and Hospitalizations in COPD Patients Who Continue to Smoke

Serap Argun Baris[a]*, Tugba Onyilmaz[b], Ilknur Basyigit[a], Hasim Boyaci[a], and Fusun Yildiz[a]

[a]*Department of Pulmonary Diseases, Kocaeli University School of Medicine, Kocaeli 41380, Turkey,*
[b]*Department of Pulmonary Diseases, Private Konak Hospital, Kocaeli 41100, Turkey*

We evaluated the frequency of exacerbations and hospitalizations in chronic obstructive pulmonary disease (COPD) patients who continue to smoke.: We retrospectively analyzed the medical records of the COPD patients treated in Chest Diseases Clinic of Kocaeli University School of Medicine in 2007-2013. Their demographic characteristics, smoking status (non-smoker, current smoker, ex-smoker), Charlson Comorbidity Index (CCI), and history of COPD exacerbation and hospitalizations were evaluated. The cases of 120 patients (11 females, 9.2%; 109 males, 90.8%) were analyzed. Sixteen (13.3%) of the patients were current smokers, and 104 patients were ex-smokers (n = 99) or non-smokers (n = 5). The mean age was 69.7 ± 7.9 years in the ex-smokers and 62.94 ± 6.8 years in the current smokers. There were no significant differences between the current and ex-smokers regarding smoking history, FEV_1 value, frequencies of exacerbations and hospitalization per year, or duration of follow-up. The initial stage of the COPD and the frequency of exacerbations were significantly correlated ($p = 0.003$). The CCI values were significantly higher in the ex-smokers compared to current smokers ($p = 0.02$). A correlation analysis of age, hospitalization and CCI revealed that age was significantly correlated with the hospitalization rate ($p = 0.02$). Older age and the presence of comorbidities in ex-smokers might explain the similar rates of exacerbation and hospitalization between these current and ex-smokers.

Key words: COPD, exacerbation, hospitalization, smoking, age

Chronic obstructive pulmonary disease (COPD) is treatable and preventable chronic disease characterized by persistent airflow limitation that is usually progressive and associated with an increased inflammatory response to noxious particles and gases [1]. An interaction between genetic susceptibility and environmental exposure has a role in the development of COPD [2]. Cigarette smoking is the most important etiologic factor. It is reported that nearly 50% of smokers will develop COPD [3]. The reduction and elimination of exposure to risk factors have great importance for the prevention of COPD progression.

The exacerbation of COPD is defined as an acute event characterized by a worsening of respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication [1]. Exacerbations are an important cause of mortality and morbidity in COPD patients [4-6]. The frequency of exacerbations varies from patient to patient, and frequent exacerbations have a negative impact on an individual's quality of life [7]. The main determinants of frequent exacerbations (*i.e.*, ≥ 2 per year) are prior treated exacerbations and an increase in airflow limitation.

Clinical failure after the treatment of a COPD exacerbation is common. Impaired lung function, dyspnea

Received March 9, 2016; accepted July 27, 2016.
*Corresponding author. Phone : +90-262-3037211; Fax : +90-262-3037003
E-mail : serapargun2002@yahoo.com (Baris SA)

Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

and active smoking have been associated with clinical failure [6]. However, Yip *et al.* reported that the active smoking rate of COPD patients was similar among patients with a single hospital admission *versus* those with multiple hospital admissions [8], and Alcazar *et al.* indicated that they found no significant difference in the active smoking rate based on previous hospitalizations [9].

Smoking is known as risk factor for the development of COPD, and in recent guidelines smoking cessation is emphasized as a key intervention for all COPD patients who continue to smoke [1]. However, the similarities and differences in the clinical presentation of COPD patients according to their smoking status have not been fully described [10]. The complete elucidation of a risk factor is the first step in the management and early prevention strategies in COPD patients, as this may reduce the frequency of exacerbations and hospitalizations. We conducted the present study to evaluate the role of active smoking in the frequency of exacerbations and hospitalizations among patients with COPD.

Patients and Methods

We retrospectively analyzed the medical records of the consecutive COPD patients who were treated in Chest Diseases Clinic of Kocaeli University School of Medicine in Turkey in the years 2007-2013. We determined each patient's demographic characteristics, smoking history, Charlson Comorbidity Index (CCI) score, initial forced expiratory volume in 1 sec (FEV_1) value, stage of COPD, duration of follow-up, and history of exacerbations and hospitalizations. Generally, hospitalization due to respiratory symptoms of COPD is regarded as a severe exacerbation. We therefore included the number of hospitalizations in the exacerbation number. The presence of a post-bronchodilator FEV_1/forced vital capacity (FVC) value < 0.70 confirmed the presence of airflow limitation according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline [1].

Smoking history. We defined smoking history of the patients according to consumption of cigarette per day and number of year by self-reports of patients on a questionnaire [Pack years = (Number of cigarettes per day/20) × Number of years]. The consumption of other tobacco products were not considered.

Non-smoker: A patient who had never smoked on a regular basis.

Ex-smoker: A regular smoker who had a smoking history at least 10 pack years and who had stopped smoking > 6 months before admission.

Current smoker: A patient with a smoking history of at least 10 pack years and who had smoked regularly within 6 months.

Severity of COPD. We classified the severity of the patients' COPD according to their post-bronchodilator FEV_1 values, as follows:

GOLD 1: Mild FEV_1, ≥ 80% of the predicted value
GOLD 2: Moderate, 50% ≤ FEV1 < 80% predicted
GOLD 3: Severe, 30% ≤ FEV1 < 50% predicted
GOLD 4: Very severe, FEV1 < 30% predicted

Exacerbation. We defined 'exacerbation of COPD' as an acute event characterized by a worsening of the patient's respiratory symptoms that was beyond normal day-to-day variations and led to a change in medication [1]. The number of exacerbations within the prior 12 months for each COPD patient was determined.

The Charlson Comorbidity Index (CCI). We evaluated the patients' comorbidities by using the predefined list of medical conditions that is used to calculate the CCI (both unadjusted and age-adjusted) [11]. The CCI encompasses 19 medical conditions weighted 1-6, with total scores ranging from 0 to 37. From the weighted conditions, a sum score can be tallied to yield the total comorbidity score. The CCI can be further adapted to account for increasing age. In the validation phase of the CCI in the present study, age was found to be an independent risk factor for death from a comorbid condition. To account for the effects of increasing age, one point can be added to the CCI score for each decade of life over the age of 50 [12].

A CCI score of 1 indicates the absence of comorbidities other than COPD. Patients with a CCI score of 2 were classified as having low comorbidity, and those with scores ≥ 3 were classified as having high comorbidity.

Exclusion criteria. Patients with other lung diseases such as tuberculosis, bronchiectasis and interstitial lung disease were excluded from the present analyses, as were patients who had an airflow limitation due to abnormalities in the large airways.

Statistical analysis. We used the Statistical Package for Social Sciences (SPSS 16.0) program for the

statistical analyses of the data. Categorical variables were recorded as percentages, and numeric variables were recorded as mean and standard deviation (SD). Compliance with the normal distribution of data was evaluated by Shapiro-Wilk test. The chi-square test was used for comparing non-parametric variables. A p-value < 0.05 was considered significant.

Results

The cases of a total of 120 patients (11 females, 9.2%; 109 males, 90.8%) were analyzed. The mean duration of follow-up was 3.2 ± 1.7 years. Sixteen (13.3%) of the patients were current smokers; 5 (4.2%) were non-smokers, and 99 (82.5%) were ex-smokers. The percentages of these three categories are illustrated in Fig. 1.

The patients' characteristics and frequency of exacerbations and hospitalizations according to the patients' smoking status are summarized in Table 1. The mean age of the ex-smokers was 69.7 ± 7.9 years; that of the current smokers was 62.94 ± 6.8 years, and that of the non-smokers was 66.2 ± 6.8 years. The mean ages of current and ex-smokers were significantly different (p = 0.005). There were no significant differences between the current and ex-smokers in smoking pack-years, FEV_1 values, frequency of exacerbations, frequency of hospitalizations in the prior 12 months, or the duration of follow-up. Stage 4 COPD was noted in 7 (7.1%) of the ex-smokers but in none of the current smokers.

Significant correlations were revealed between the initial stage of COPD and the frequency of the exacerbations (p = 0.003, initial stage of COPD and the frequency of exacerbations peryear (p = 0.001), and initial stage of COPD and the frequency of hospitalizations per year, −(p = 0.000)) (Fig. 2).

The CCI scores and age-adjusted CCI scores were significantly higher in the ex-smokers compared to the current smokers (p = 0.02 and p = 0.002, respectively; Table 1, Fig. 3A, B).

In a correlation analysis of the factors of age, hospi-

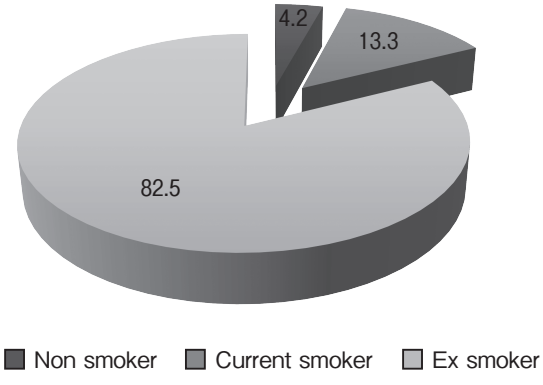

Fig. 1 The 120 COPD patients' smoking status.

Table 1 The characteristics of the 120 COPD patients according to smoking status

	Non-smokers (n = 5)	Current Smokers (n = 16)	Ex-smokers (n = 99)	p
Age (yrs)	66.2 ± 6.8	62.94 ± 6.8[a]	69.7 ± 7.9[a]	0.005
Male/female (n, %)	3 (60%)/2 (40%)	14 (87.5%)/2 (12.5%)	92 (92.9%)/7 (7.1%)	
Smoking package of years				
Pack years = (Number of cigarettes per day/20) X Number of years	0	43.4 ± 25.7	47.2 ± 27.7	0.6
No. of exacerbations	1.8 ± 1.5	1.5 ± 2.1	1.8 ± 2.2	0.6
Duration of follow-up (months; mean)	3.2 ± 1.1	2.9 ± 1.7	3.2 ± 1.7	0.6
No. of hospitalizations	0.2 ± 0.4	0.69 ± 1.4	0.79 ± 1.8	0.8
No. of hospitalizations during the prior 12 months	0.1 ± 0.2	0.23 ± 0.5	0.21 ± 0.4	0.9
CCI	1.4 ± 0.5	1.25 ± 0.4[b]	1.7 ± 0.8[b]	0.02
CCI (age-adjusted)	4.4 ± 1.1	4.0 ± 0.96[c]	4.96 ± 1.2[c]	0.002
FEV_1 initial (l)	1.73 ± 0.5	1.71 ± 0.4	1.68 ± 0.7	0.8
FEV_1 initial %	68.6 ± 16.6	56.8 ± 12.2	57.39 ± 19.4	0.9

CCI, Charlson Comorbidity Index; FEV_1, forced expiratory volume in 1 sec.
Comparison of groups: Statistically significant differences (p < 0.05) were summarized.
Age, [a]Current smokers and ex-smokers, p = 0.005; CCI, [b]Current smokers and ex-smokers, p = 0.02; CCI age adjusted, [c]Current smokers and ex-smokers, p = 0.002.

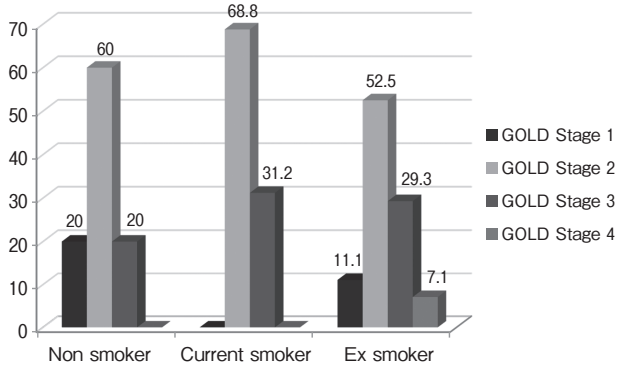

Fig. 2 The distribution of disease severity according to smoking status (%). See the Patients and Methods section for the explanation of GOLD stages.

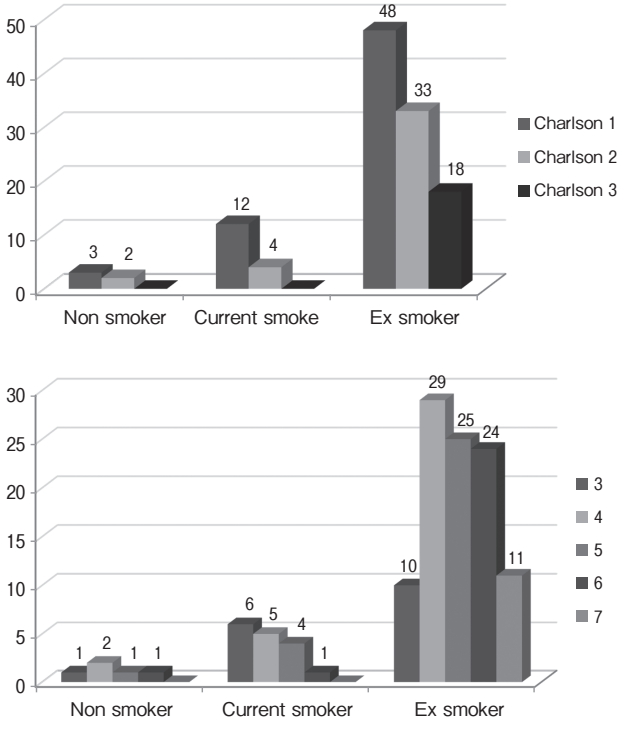

Fig. 3 A: The distribution of CCI scores according to smoking status (n). CCI score of 1 = absence of comorbidity other than COPD. CCI score of 2 = low comorbidity (COPD + 1 comorbidity). CCI score of 3 = high comorbidity (COPD + ≥2 comorbidities). B: Age-adjusted CCI scores according to smoking habits (n).

talization rate and CCI scores, we found that age was significantly correlated with the hospitalization rate ($p = 0.02$). There were 90 hospitalizations among the total patient series during the study period, and 80% of these episodes occurred in patients > 65 years old. No correlation was found between CCI scores and the hospitalization rate, but there were 63 patients (52.5%) who had no comorbid condition other than COPD. We also noted that there were 50 hospitalizations in the remaining 57 patients who had higher CCI scores.

Discussion

Our retrospective analysis of 120 patients with COPD revealed that the rate of active smoking was low in this patient series, and it was lower than those of previous studies as summarized below. We found no significant difference in the numbers of exacerbation episodes or hospitalizations between the current smokers and ex-smokers.

COPD is one of the most important causes of mortality and morbidity throughout the world. In older individuals in the United States, it is among the 10 most important diseases causing hospitalizations and death, with a prevalence that is increasing day by day [13]. COPD is more common in men than women due to males' higher rates of smoking and occupational exposure. However, the increase in cigarette smoking among women and their increasing presence in dangerous work environments have led to an increase in the prevalence of COPD in women [14]. There was also a male dominance in our study; only 11% of the patients were female.

Some of the risk factors of COPD are well known:- smoking, occupational exposure, air pollution, airway hyper-responsiveness, and genetic variations [15]. The assessment of risk factors is important in the management of COPD patients, and smoking is the most important etiologic factor. However, the exposure to passive smoking and biomass fuel used for heating are discriminative for women among non-smoker COPD patients [16]. In our study, 4.2% of the patients were non-smokers whereas 95.8% of the patients had a smoking history (13.3% of the patients were current smokers, plus 82.5% of the patients were ex-smokers). Forty percent of the non-smoker patients were female and they had biomass exposure. Although smoking cessation is the first step in the management of COPD, active smoking rates are still high in COPD patients. In a previous study, many patients continued to smoke after the diagnosis of COPD (16.8%) or lung cancer (15.1%) [16]. The active smoking prevalence varies in

different working groups. In the ESFERA study of COPD patients conducted in Spain, the active smoking rate was 19.3% [6]. An evaluation of the hospitalizations due to COPD exacerbation revealed active smoking in 33% of the patients [16]. The active smoking rate in the present study (13.3%) is relatively low. In our department, we have a separate outpatient smoking cessation clinic and an outpatient COPD clinic designed to treat these two groups of individuals separately. The major goals of our COPD management policy are the education of the patients about both COPD and smoking cessation. This may explain the lower rate of current smokers in our study population.

It has been reported that respiratory symptoms, the annual decrease of FEV_1 values and mortality rates are higher in smokers than nonsmokers [1]. The most effective strategy to prevent declining lung function among COPD patients is smoking cessation [17]. Smoking cessation should be considered for all COPD patients regardless of the level of disease severity [1].

Exacerbations of COPD are the most frequent cause of morbidity, hospital admissions and mortality in COPD patients [17]. The early detection and effective treatment of exacerbations are key factors that may reduce the likelihood of hospital admissions and prevent re-admissions [18]. However, clinical failure after the treatment of COPD is common, and active smoking, impaired lung function, and severe dyspnea are associated with clinical failure [6]. Re-admissions are associated with the degree of lung function impairment (as shown by GOLD grades), lower FEV_1 and the frequency of previous exacerbations [19-21]. As in prior studies, our present analysis showed that the initial stage of the disease (according to GOLD stage) and the frequency of exacerbations are correlated ($p = 0.003$). However, there were no significant differences in FEV_1 values, the frequency of exacerbations or the number of hospitalizations in the prior 12 months between the current smokers and ex-smokers in our series. We suspect that the older age and presence of comorbidities in the ex-smoker group and the absence of stage 4 disease in the current smoker group might explain the similar rates of exacerbation and hospitalization between the current and ex-smokers.

COPD is a chronic, systemic disease with comorbidities that affect respiratory symptoms, worsen the prognosis, and increase the exacerbation frequency and mortality [22, 23]. There is a causal relationship between COPD and comorbidities that influences the clinical course of the disease [24]. The severity and prognosis of exacerbation is best predicted by the presence or absence of significant comorbid conditions [17]. Several reports suggest that cardiovascular disease is associated with the exacerbation of COPD [25, 26].

The CCI, which is a predefined list of medical conditions used to calculate a comorbidity score, has good reliability and an excellent correlation with mortality, and it is easily modified, particularly to account for the effect of age. The CCI is preferred for its ease of use, short rating time, extractability from other indices, and widespread use [10]. The CCI scores of the present study's ex-smokers were significantly higher compared to those of the current smokers. We speculate that the higher comorbidity scores in the ex-smokers compared to the current smokers could be explained by the need to quit smoking based on the fear of a decreased quality of life related to intense comorbidities.

Our correlation analysis regarding patient age, hospitalization and CCI revealed that age is correlated with the rate of hospitalizations, which is not unexpected since 80% of the hospitalizations occurred in patients >65 years old. However, there was no correlation between CCI scores and hospitalization. Nearly half of the study group (47.5%) had at least one comorbid condition other than COPD, and patients with high CCI scores accounted for 55.6% of the hospitalizations. These findings suggest that the CCI is an important factor for hospitalization in COPD patients. We suspect that the limited number of patients with multiple comorbid conditions in this study might be responsible for the nonsignificant relationship between CCI scores and hospitalization.

Limitations of the study. There are several limitations to our study that should be considered. First, it was a retrospective investigation, and the data collection was based on medical records. Second, the number of current smokers was low compared to that of ex-smokers. Third, there was no current smoker in the stage 1 or stage 4 COPD groups. It is possible that stage 4 COPD patients are unable to smoke because of their disease severity, and we suspect that these patients 'stop smoking' simply because they cannot smoke. This may explain why there was no current smoker in the stage 4 COPD group. Since there were no current smokers in the stage 1 or 4 COPD groups, our assessment regarding smoking history concerned mostly stage 2 and 3

patients. This nonhomogeneous distribution of smokers among the patient groups may have affected our results concerning the relationship between current smoking and the exacerbation and hospitalization rates of COPD patients. Future studies are needed to determine whether our results are also applicable for all stages of COPD patients.

Fourth, the goals of COPD assessment are to determine the severity of the disease, its impact on a patient's health status and the risk of future events such as exacerbation, hospitalization and death. However, due to the retrospective nature of this study, we could not determine the patients' health status by using, for example, the modified Medical Research Council (mMRC) Questionnaire or the COPD assessment test (CAT), and we could not evaluate the new classification of COPD. The severity of the patients' COPD was thus classified by using only post-bronchodilator FEV_1 values. Lastly, the gender distribution among our patient groups was not homogenous since smoking was more prevalent in male than females in our country.

It is accepted that assessments of COPD require a combination of parameters including pulmonary functions, exacerbation history, severity of symptoms and comorbid conditions. Our findings suggest that the implementation of a questionnaire inquiring about comorbidities (such as the CCI) in a patient's follow-up might be helpful to predict the hospitalization and exacerbation risks in COPD patients, since the presence of comorbid conditions was shown to be a more important factor in exacerbations than current smoking.

In conclusion, the current smoking rate in our present series of 120 COPD patients was lower than those of previous studies. We observed no significant difference in the numbers of exacerbations or hospitalizations between the current smokers and ex-smokers. The older age and the presence of comorbidities in the ex-smokers group might explain the similar rates of exacerbations and hospitalizations between the current and former smokers. Further prospective trials including more patients both in ex-smoker and current smoker arms are needed to clarify the relationships among exacerbation, smoking status and comorbidities in COPD patients.

References

1. Sen E, Guclu SZ, Kibar I, Ocal U, Yilmaz V, Celik O, Cimen F, Topcu F, Orhun M, Tereci H, Konya A, Ar I and Saryal S: Adherence to GOLD guideline treatment recommendations among pulmonologists in Turkey. Int J Chron Obstruct Pulmon Dis (2015) 10: 2657–2663.
2. Hooper R, Burney P, Vollmer WM, McBurnie MA, Gislason T, Tan WC, Jithoo A, Kocabas A, Welte T and Buist AS: Risk factors for COPD spirometrically defined from the lower limit of normal in the BOLD Project. Eur Respir J (2012) 39: 1343–1353.
3. Lundback B, Lindberg A, Lindström M, Rönmark E, Jonsson AC, Jönsson E, Larsson LG, Andersson S, Sandström T and Larsson K; Obstructive Lung Disease in Northern Sweden Studies: Obstructive Lung Disease in Northern Sweden S: Not 15 but 50% of smokers develop COPD?–Report from the Obstructive Lung Disease in Northern Sweden Studies. Respir Med (2003) 97: 115–122.
4. Celli BR and Mac Nee W: ATS/ERS Task Force. Standards for the diagnosis and care of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J (2004) 23: 932–946.
5. Vestbo J, Hurd SS, Agustí AG, Jones PW, Vogelmeier C, Anzueto A, Barnes PJ, Fabbri LM, Martinez FJ, Nishimura M, Stockley RA, Sin DD and Rodriguez-Roisin R: Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med (2013) 187: 347–365.
6. Miravitlles M, Izquierdo I, Herrejón A, Torres JV, Baró E and Borja J; ESFERA investigators: COPD severity score as a predictor of failure in exacerbations of COPD. The ESFERA study. Respir Med (2011) 105: 740–747.
7. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ and Wedzicha J: Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med (1998) 157: 1418–1422.
8. Yip NH, Yuen G, Lazar EJ, Regan BK, Brinson MD, Taylor B, George L, Karbowitz SR, Stumacher R, Schluger NW and Thomashow BM: Analysis of hospitalizations for COPD exacerbation: opportunities for improving care. COPD (2010) 7: 85–92.
9. Alcázar B, García-Polo C, Herrejón A, Ruiz LA, de Miguel J, Ros JA, García-Sidro P, Conde GT, López-Campos JL, Martínez C, Costán J, Bonnin M, Mayoralas S and Miravitlles M: Factors Associated With Hospital Admission for Exacerbation of Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (2012) 48: 70–76. doi:10.1016/j.arbres.2011.10.009. Epub 2011 Dec 21.
10. Zhang J, Lin XF and Bai CX: Comparison of clinical features between non-smokers with COPD and smokers with COPD: a retrospective observational study. Int J Chron Obstruct Pulmon Dis (2014) 9: 57–63.
11. Charlson M, Szatrowski TP, Peterson J and Gold J: Validation of combined comorbidity index. J Clin Epidemiol (1994) 47: 1245–1251.
12. Hall WH, Ramachandran R, Narayan S, Jani AB and Vijayakumar S: An electronic application for rapidly calculating Charlson comorbidity score. BMC Cancer (2004) 20: 4: 94.
13. Mannino DM: COPD. Epidemiology, prevalence, morbidity and mortality, and disease heterogenity. Chest (2002) 121: 121S–126S.
14. Caracta CF: Gender differences in pulmonary disease. Mt Sinai J Med (2003) 70: 215–224.
15. Bourbeau J, Tan WC, Benedetti A, Aaron SD, Chapman KR, Coxson HO, Cowie R, Fitzgerald M, Goldstein R, Hernandez P, Leipsic J, Maltais F, Marciniuk D, O'Donnell D, Sin DD and Cancold Study Group: Fulfilling the need for longitudinal observational studies in COPD. COPD (2014) 11: 125–132.
16. Vaidya V, Hufstader-Gabriel M, Gangan N, Shah S and Bechtol R: Utilization of smoking-cessation pharmacotherapy among chronic

obstructive pulmonary disease (COPD) and lung cancer patients. Curr Med Res & Opin (2014) 30: 1043–1050.
17. Miravitlles M, Guerrero T, Mayordomo C, Sánchez-Agudo L, Nicolau F and Segú JL: Factors Associated with Increased Risk of Exacerbation and Hospital Admission in a Cohort of Ambulatory COPD Patients: A Multiple Logistic Regression Analysis. Respiration (2000) 67: 495–501.
18. Suh ES, Mandal S and Hart N: Admission prevention in COPD: non-pharmacological management. BMC Medicine (2013) 11: 247.
19. Gudmundsson G, Gislason T, Janson C, Lindberg E, Hallin R, Ulrik CS, Brøndum E, Nieminen MM, Aine T and Bakke P: Risk factors for rehospitalisation in COPD: role of health status, anxiety and depression. Eur Respir J (2005) 26: 414–419.
20. Liu D, Peng SH, Zhang J, Bai SH, Liu HX and Qu JM: Prediction of short term re-exacerbation in patients with acute exacerbation of chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis (2015) 10: 1265–1273.
21. Ozyilmaz E, Kokturk N, Teksut G and Tatlicioglu T: Unsuspected risk factors of frequent exacerbations requiring hospital admission in chronic obstructive pulmonary disease. Int J Clin Pract (2013) 67: 691–697.
22. Warwick E, Scourfield A and Quint J: Systemic manifestations of chronic obstructive pulmonary disease. Br J Hosp Med (Lond) (2015) 76 (Suppl): 324–329.
23. Barnes PJ and Celli BR: Systemic manifestations and comorbidities of COPD. Eur Respir J (2009) 33: 1165–1185.
24. Decramer M, Rennard S, Troosters T, Mapel DW, Giardino N, Mannino D, Wouters E, Sethi S and Cooper CB: COPD as a Lung Disease with Systemic Consequences-Clinical Impact, Mechanisms, and Potential for Early Intervention. COPD (2008) 5: 235–256.
25. Pavasini R, d'Ascenzo F, Campo G, Biscaglia S, Ferri A, Contoli M, Papi A, Ceconi C and Ferrari R: Cardiac troponin elevation predicts all-cause mortality in patients with acute exacerbation of chronic obstructive pulmonary disease: Systematic review and meta-analysis. Int J Cardiol (2015) 191: 187–193.
26 Ko FW, Chan KP, Hui DS, Goddard JR, Shaw JG, Reid DW and Yang IA: Acute exacerbation of COPD. Respirology (2016) 21: 1152–1165.