An analysis of the correlations between TNF-α and MCP-1 levels in the induced sputum and serum of patients with stable chronic obstructive pulmonary diseaseand pulmonary function and quality of life

Haiyan Tu[1], Jiawen Yang[2], Zhengxian Chen[3], Jiquan Guo[3], Jing Li[3], Pingping Chen[3]

1 Division of Thoracic Oncology, Cancer Center, Guangdong General Hospital, Guangdong Academy of Medical Sciences , Guangdong Lung Cancer Institute, Guangzhou, Guangdong 510080, China; 2 Critical Care Unit, The Fifth Affiliated Hospital of Sun-yet Sen University, Zhuhai, Guangdong 519000, China; Department of Respiratory Medicine, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong 510080, China

Correspondence: Dr. TU Hai-yan, Division of Thoracic Oncology, Cancer Center, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangdong Lung Cancer Institute, Guangzhou, Guangdong 510080, China (Fax: 86-20-81883300. Email: thy0934789@163.com); Dr. CHEN Zheng-xian, Department of Respiratory Medicine, Guangdong General Hospital ,Guangdong Academy of Medical Sciences , Guangzhou 510080, China (Email: zxchen709@msn.com)

TU Hai-yan and YANG Jia-wen contributed equally to this work.

This study was supported by a grant from Medical Scientific Research Foundation of Guangdong Province, China (No. A2010028)

Abstract: In this study, we investigated the correlations between airway and systemic Tumor Necrosis Factor-alpha (TNF-α) and Monocyte Chemoattractant Protein -1 (MCP-1) levels and pulmonary function and quality of life in patients with stable COPD. A low-risk COPD patient group (32 cases), a high-risk COPD patient group (29 cases) and a healthy control group (30 cases) were included in the study. The TNF-α and MCP-1 levels in the induced sputum and serum of the three groups were compared. The correlation between inflammatory factor levels in the COPD patients and pulmonary function, body-mass index(BMI), airflow obstruction(FEV_1%), dyspnea(MMRC scale), exercise capacity(6WMD), BODE index and SGRQ score was analyzed by a multiple variable linear regression model. The TNF-α and MCP-1 levels in induced sputum and serum of the three groups were all significantly different ($P<0.001$). The MCP-1 level in the induced sputum of the low-risk COPD patient group was negatively correlated with the 6MWD and with the SGRQ symptom score ($P=0.014$). The serum TNF-α level in the high-risk COPD patient group was negatively correlated with the FEV_1/FVC($P=0.001$) and was positively correlated with the SGRQ total score (P=0.005). The serum MCP-1 level in the high-risk COPD patient group was negatively correlated with the FEV_1/FVC and the MMRC dyspnea scale ($P=0.007$).

[Haiyan Tu, Jiawen Yang, Zhengxian Chen, Jiquan Guo, Jing Li, Pingping Chen. **An analysis of the correlations between TNF-α and MCP-1 levels in the induced sputum and serum of patients with stable chronic obstructive pulmonary diseaseand pulmonary function and quality of life.** *Life Sci J* 2013;10(3):956-962] (ISSN: 1097-8135). http://www.lifesciencesite.com. 140

Keywords: chronic obstructive pulmonary disease; tumor necrosis factor-alpha; monocyte chemoattractant protein 1; respiratory function tests; quality of life

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease that is primarily characterised by airflow obstruction resulting from small airway inflammation (chronic bronchitis) and damage to the pulmonary parenchyma (emphysema).[1] Relevant international research has demonstrated that tumour necrosis factor (TNF)-α and monocyte chemoattractant protein-1 (MCP-1) are important inflammatory mediators in COPD inflammation. In particular, TNF-α is involved in the recruitment and migration of inflammatory cells,[2] promotes the secretion of airway mucus, and participates in the remodelling of the organisational structure of the airway tissue,[3-5] whereas MCP-1 has an important role in the recruitment and migration of airway monocytes in the process of airway imflammation.[6-8] However, to date, no research has investigated how the TNF-α and MCP-1 levels in induced sputum and peripheral blood samples from COPD patients are related to these patients' disease severity and quality of life. Therefore, this study examined how TNF-α and MCP-1 levels in induced sputum and serum samples from patients who were in a stable period of COPD were correlated with pulmonary function and quality of life. The study findings are reported below.

Materials and methods

Study subjects

The following three groups were included in the study: a low-risk COPD patient group (30 cases), a high-risk COPD patient group (26 cases), and a

healthy control group (28 cases). All of the subjects signed an informed consent form which ratified by Medical Ethics Committee.The study protocol was adhered to the recommendations for biomedical research involving human subject of the Declaration of Helsinki(1975). The COPD patients were at a stable stage of COPD and treated at Guangdong People's Hospital from January 2010 to June 2011. The subjects in the healthy control group were healthy volunteers recruited during the same period. The diagnosis of stable COPD was based on the 2007 version of the Chronic Obstructive Pulmonary Disease Diagnosis and Treatment Guideline of the Chinese Medical Association.[1] Other respiratory diseases were excluded. The healthy subjects did not have chronic respiratory diseases or a history of infectious disease within the previous eight weeks. Malignancy, severe heart failure, connective tissue disease, metabolic disease, bone and joint diseases, and neuromuscular joint diseases were ruled out in all of the subjects. None of the subjects had experienced myocardial infarction or unstable angina in the month preceding the study; had received surgery in the previous six months; or had received corticosteroids, nutritional support, or lipid-reducing medication within the previous two months. All of the subjects had normal liver and kidney function. All of the COPD patients were classified into low-risk and high-risk groups based on the 2011 COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD).[9] The correlations between the TNF-α and MCP-1 levels in the induced sputum and serum of the patients and pulmonary function and quality of life were investigated.

Methods

The MCP-1 and TNF-α levels in the induced sputum and serum were measured in all of the subjects. Pulmonary function tests and the BODE index [including body-mass index (BMI), the percentage of forced expiratory volume in the first second of expiration over the predicted values (FEV_1%), the British Modified Medical Research Council (MMRC) dyspnea score, and the six-minute walk distance (6MWD)] were completed. The COPD patients were scored according to St. George's respiratory questionnaire (SGRQ).[10]

Measurement of MCP-1 and TNF-α levels in the serum and induced sputum

The subjects fasted for ten hours without inhaling supplemental oxygen, and then 3 ml of venous blood was withdrawn and transferred to a tube. The blood sample was immediately centrifuged (Eppendorf centrifuge 5810R, W/O ROTOR, 230V, Sigma-Aldrich Ltd., United States) at 3000 r/min for 20 minutes to remove the blood cells. The serum was collected, mixed well, and stored at -70℃ for subsequent examinations. Induced sputum was collected according to the revised Pin method.[11] The collected sputum was then processed within two hours. The sputum sample was weighed, and 0.1% dithiothreitol (DTT) was added to the sputum at a sputum weight to 0.1% DTT volume ratio of 1:2. The sample was vortexed (XW-80A, Shanghai Medical Instrument Factory) for 15 minutes and incubated at 37℃ in a water bath for 15 minutes to sufficiently homogenize the sputum. The sample was filtered through a 40-μm mesh screen to remove the mucus. The filtrate was centrifuged (Hettich Universal centrifuge 320R, Hettich Ltd., Germany) at 1500 r/min for ten minutes. The supernatant was collected. The TNF-α and MCP-1 levels in the serum and induced sputum samples were determined with enzyme-linked immunosorbent assays (ELISA) from R&D (SCP00 and STA00C).

Pulmonary function tests

The subjects quietly rested and inhaled 200 μg of the bronchodilator salbutamol. After 10 minutes, the forced vital capacity (FVC), percentage of FVC over the predicted value (FVC%), FEV_1, and FEV_1% were measured with a spirometer (SensorMedics, Vmax 622, Sen Disi Ltd., United States) according to the American Thoracic Society/European Respiratory Society spirometer quality control standards.

SGRQ score

The COPD patients were scored on the SGRQ. The symptom score, activity score, impact score, and total score were calculated using the scoring method provided by the SGRQ.[10]

BODE index measurement

(1) BMI measurement: the subjects' height (H, m) and weight (W, kg) were measured. BMI (kg/m^2) was calculated using the equation $BMI = W/H^2$. (2) FEV_1% measurement: the same method described for the pulmonary function tests was used for the FEV_1% measurement. (3) Dyspnea scale: The dyspnea scale was assessed in the subjects using the MMRC.[12] The following rating scale was used: 0: the subjects only experienced shortness of breath during excessive physical activity; 1: the subjects experienced shortness of breath when walking on level ground or a mild slope; 2: due to shortness of breath, the subjects walked more slowly than their peers or had to stop to catch their breath when walking on level ground; 3: the subjects needed to stop to catch their breath after walking on level ground for a few minutes; and 4: the subjects were unable to leave home due to shortness of breath or experienced shortness of breath when putting on or taking off clothes. (4) 6MWD test: The 6MWD (m) was measured using the guidelines developed by

the American Thoracic Society in 2002.[13] (5) The BODE index was calculated based on the method suggested by Celli et al.[14] The score from each component was calculated first (0: BMI>21kg/m^2, FEV_1%≥65, MMRC dyspnea scale 0-1, 6MWD≥350 m; 1: BMI≤21 kg/m^2, FEV_1%=50-64, MMRC dyspnea scale 2, 6MWD=250-349 m； 2: FEV_1%≥36-49, MMRC dyspnea scale 3, 6MWD≥150-249 m; 3: FEV_1%≤35, MMRC dyspnea scale 4, 6MWD≤149 m). The total score was then calculated as the sum of each component.

Severity assessment in COPD patients

Based on the COPD patients' FEV_1%, MMRC dyspnea scale, and the number of episodes of acute exacerbation in the past one year, the COPD patients were classified into categories A, B, C, and D according to the method described in the 2011 version of GOLD.[9] The patients in categories A and B were assigned to the low-risk group, and the patients in categories C and D were assigned to the high-risk group.

Statistical analysis

The statistical analysis software SPSS13.0 was used. Comparisons among the three groups were analyzed using one-way analysis of variance (ANOVA). If two groups exhibited equal variance, the least significant difference (LSD) test was used to analyze the difference. If two groups exhibited unequal variance, Dunnett's T3 test was applied. A χ^2 test was used to compare ratios. Comparisons of ranked data were analyzed by the Kruskal-Wallis *H* test, which is a completely random sample comparison. The between-group comparisons of measurement data were analyzed based on a one-sided, two-independent-sample *t* test. The multiple-variable linear regression model was analyzed using a stepwise regression method. The individual inflammatory factor levels in the COPD patients were used as dependent variables; the patients' pulmonary function, BODE index, and SGRQ score were used as independent variables. P values＜0.05 were considered statistically significant.

Results

General characteristics of the subjects in the three groups

The low-risk COPD patient group included 28 males and 4 females. The high-risk group included 27 males and 2 females. The healthy control group included 24 males and 6 females. There was no significant difference in the gender distribution of the three groups (χ^2=2.232, *P*=0.328). The average ages of the low-risk, high-risk, and control groups were 70.63±7.78, 69.72±8.62, and 67.47±8.54, respectively. There was no significant difference in age among the groups (*F*=1.176，*P*=0.313).

Comparisons of the inflammatory factor levels, pulmonary function, and BODE index in the subjects

The ANOVA analysis and pairwise comparisons revealed that the TNF-α and MCP-1 levels in the induced sputum and serum and the pulmonary function index were significantly different among subjects of the three groups (Table 1 and Table 2). The inflammatory factor levels increased sequentially from healthy subjects to low-risk COPD patients to high-risk COPD patients; the FEV_1%, FVC%, and FEV_1/FVC decreased sequentially in the same order. Comparisons of the individual components and overall BODE index showed that there was no significant difference in the BMI and 6MWD of the three groups, the MMRC dyspnea scale and BODE index total score increased sequentially in the same order.

General condition of the two COPD patient groups and SGRQ score comparisons

Table 3 illustrates that the duration of COPD in the high-risk patient group was significantly longer than the disease duration in the low-risk patient group; the number of acute attacks in the high-risk patient group was significantly higher than the number of acute attacks in the low-risk patient group. The total SGRQ score, activity score, and impact score in the high-risk patient group were significantly higher than the same parameters in the low-risk patient group, whereas the symptoms score was not significantly different between the two groups.

Multiple-variable linear regression analysis of the inflammatory factor levels, pulmonary function, and quality of life of COPD patients

Table 4 demonstrates that the MCP-1 level in the induced sputum was negatively correlated with the results of the 6MWD and positively correlated with the SGRQ symptoms score in the low-risk COPD patient group. The induced sputum TNF-α level and serum TNF-α and MCP-1 levels were not correlated with pulmonary function and quality of life in the low-risk patient group. In the high-risk patient group, the serum TNF-α level was negatively correlated with the FEV_1/FVC value and positively correlated with total SGRQ score. The serum MCP-1 level was negatively correlated with the FEV_1/FVC value and with MMRC dyspnea scale in the high-risk patient group. The serum levels of the two inflammatory factors were not correlated with pulmonary function and quality of life in the high-risk patient group.

Table 1. Biomarker levels, lung function, BMI, 6MWD, and BODE index for the three groups ($\bar{x} \pm s$)

	Healthy control group (n=30)	Low-risk COPD patient group (n=32)	High-risk COPD patient group (n=29)	*F*	*P*
Inflammatory factor					
Induced sputum TNF-α, pg/ml	5.09±9.50	14.17±10.88*	24.13±20.66*†	12.616	<0.001
Induced sputum MCP-1, pg/ml	102.47±112.34	207.64±180.44*	342.80±275.28*†	10.265	<0.001
Serum TNF-α, pg/ml	0.40±0.99	4.12±5.58*	10.26±10.52*†	15.687	<0.001
Serum MCP-1, pg/ml	92.03±72.92	205.39±205.37*	379.74.53±298.23*†	13.726	<0.001
Pulmonary function					
FEV_1%	106.50±18.42	69.84±18.14*	34.69±6.86*†	156.745	<0.001
FVC%	107.07±20.87	92.19±15.37*	77.76±13.53*†	22.224	<0.001
FEV_1/FVC, %	81.20±4.82	55.03±11.67*	36.41±10.67*†	162.904	<0.001
BODE index					
BMI, kg/m^2	23.21±3.98	22.16±2.76	21.92±3.30	1.246	0.293
FEV_1%	106.50±18.42	69.84±18.14*	77.76±13.53*†	140.488	<0.001
6MWD, m	406.07±112.61	399.47±67.19	371.14±66.43	1.415	0.248
BODE index (Total score)	0.27±0.45	1.09±1.00*	3.97±1.48*†	100.186	<0.001

*$P<0.05$ compared with the healthy control group. †$P<0.05$ compared with the low-risk COPD group.

COPD, chronic obstructive pulmonary disease; TNF-α, Tumor Necrosis Factor-alpha; MCP-1, Monocyte Chemoattractant Protein -1; BODE index, include body-mass index, airflow obstruction, dyspnea, exercise capacity; BMI, body-mass index; FEV_1%, the percentage of forced expiratory volume in the first second of expiration over predicted values; FVC, Forced Vital Capacity; 6MWD, the six-minute walk distance; SGRQ, St. George's respiratory questionnaire.

Table 2. MMRC dyspnea scale in the three groups

Group	MMRC dyspnea scale					Average scale	χ^2	*P*
	0	1	2	3				
Healthy control group (n=30)	30	0	0	0	0	27.00	42.674	<0.001
Mild-moderate COPD patient group (n=30)	18	9	3	1	0	45.05		
Severe-very severe COPD patient group (n=26)	4	15	8	2	0	66.71		

MMRC, modified british medical research council; COPD:chronic obstructive pulmonary diseas

Table 3. Clinical characteristics and SGRQ scores in low-risk COPD patient group and high-risk COPD patient group ($\bar{x} \pm s$)

	Low-risk COPD patient group (n=29)	High-risk COPD patient group (n=28)	*t*	*P*
Duration of the disease, years	7.53±10.47	17.24±15.22	-2.876	0.006
Number of acute attacks, time	0.66±1.12	1.28±1.22	-2.062	0.044
Total SGRQ score	25.82±16.87	39.68±18.77	-3.039	0.004
SGRQ symptoms score	45.41±19.83	54.58±18.19	-1.877	0.066
SGRQ activity score	25.88±22.52	42.75±24.51	-2.531	0.014
SGRQ impact score	18.72±17.02	30.89±20.51	-2.804	0.007

COPD, chronic obstructive pulmonary disease; SGRQ, St. George's respiratory questionnaire

Table 4. Multiple-variable linear regression model for the biomarker levels, lung function, and quality of life of COPD patients

Model parameters				Variable parameters				
	djusted R^2	*F*	*P*	*B*	*SE*	*β*	*t*	*P*
Low-risk COPD group								
Induced sputum MCP-1 model	0.208	5.058	0.013					
6MWD				-0.959	0.431	-0.357	-2.226	0.034
SGRQ symptoms component				-3.562	1.459	0.392	-2.441	0.021
High-risk COPD group								
Serum TNF-α model	0.383	9.675	0.001					
FEV_1/FVC				-0.540	0.146	-0.548	-3.687	0.001
Total SGRQ score				0.201	0.083	0.358	2.411	0.023
Serum MCP-1 model	0.274	6.290	0.006					
FEV_1/FVC				-10.594	4.598	-0.379	-2.304	0.029
MMRC dyspnea scale				191.397	61.532	0.512	3.111	0.004

COPD, chronic obstructive pulmonary disease; MCP-1, Monocyte Chemoattractant Protein -1; 6MWD, the six-minute walk distance; SGRQ, St. George's respiratory questionnaire; TNF-α, Tumor Necrosis Factor-alpha; FEV_1, Forced Expiratory volume in the first second of expiration; FVC, Forced Vital Capacity.

Discussion

Analyses of TNF-α and MCP-1 levels in induced sputum and serum samples from COPD patients

Previous studies have revealed that levels of inflammatory mediators in airways and serum are significantly higher in COPD patients than in healthy individuals.[15-19] To increase the accuracy of assessing the condition of COPD patients and devise improved treatment regimens, the 2011 Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines divide COPD patients into four groups, designated as A, B, C, and D, based on each patient's pulmonary function, level of dyspnoea, and frequency of acute exacerbation of COPD.[9] In this study, to provide a highly comprehensive evaluation of the conditions and prognoses of different patients, COPD patients from groups A and B were regarded as the low-risk group of subjects, and COPD patients from groups C and D were regarded as the high-risk group of subjects. Our results indicated that TNF-α and MCP-1 levels in induced sputum and serum were significantly greater in both the low-risk patient group and the high-risk patient group than in healthy individuals, and this elevation of the TNF-α and MCP-1 levels was more pronounced in patients from the high-risk group than in patients from the low-risk group. These results suggested that even during stable periods of COPD, airway and systemic TNF-α and MCP-1 levels are significantly higher in COPD patients than in healthy individuals of similar age; moreover, the levels of both mediators may tend to increase as the disease progresses. Both inflammatory mediators may participate in the formation and development of COPD-related airway inflammation and affect the progression and prognosis of COPD.

An analysis of the quality of life of COPD patients

The BODE (body mass index (BMI), airflow obstruction, dyspnoea, and exercise capacity) index for COPD is a composite indicator that provides an overall evaluation that encompasses various characteristics of COPD patients, including each patient's nutritional status, airflow limitations, dyspnoea, and exercise capacity; thus, this index comprehensively reflects the disease status of these patients and can be used in combination with the St. George's Respiratory Questionnaire (SGRQ) to indicate the degree of severity of COPD.[14]

In our study, the BODE index was significantly higher for COPD patients than for healthy individuals, indicating that quality of life has been greatly impacted in both the low-risk and the high-risk groups of COPD patients. However, the BMI and six-minute walk distance (6MWD) results for COPD patients did not significantly differ from the corresponding results for healthy individuals. This phenomenon may reflect the relatively small sample size of this study and/or the existence of biases with respect to the subjects who were enrolled in this investigation. The testing locations of this study were in hospitals, and patients considered their general health status prior to reaching a decision regarding participation in the assessments that were conducted during this investigation; thus, weaker patients were frequently unwilling or unable to participate in these assessments. Therefore, the nutritional status and exercise capacity of the enrolled patients may have caused us to overestimate the actual status of the overall population of COPD patients.

The SGRQ index is divided into three domains: symptoms, activity, and impact. An SGRQ score includes not only a total score but also scores for each domain. In this study, SGRQ scores in the symptoms domain were high for both the low-risk and the high-risk groups of patients, whereas SGRQ scores in the impact and activity domains were more elevated from normal levels in high-risk patients than in low-risk patients. Therefore, airway symptoms have already become obvious for patients with relatively mild COPD; as the disease progresses, patients experience gradually declining mobility, leading to additional deterioration of the quality of these patients' everyday lives.

Analyses of how TNF-α and MCP-1 levels in induced sputum and serum are correlated with the pulmonary function and quality of life of COPD patients

Studies by Liu et al.[20] have demonstrated that in COPD patients, serum levels of inflammatory mediators are correlated with smoking indices, forced expiratory volume in one second (FEV_1) percentages, modified Medical Research Council (MMRC) scores, 6MWD levels, BODE index scores, and corticosteroids usage. Agustí et al.[21] conducted a prospective study of a large sample of 1755 COPD patients and demonstrated that the systemic levels of multiple inflammatory mediators were higher than normal in 70% of the examined COPD patients. Moreover, compared with patients with normal systemic levels of inflammatory mediators, these COPD patients demonstrated significantly reduced BMI, lean body mass index, FEV_1, FEV_1%, and 6MWD levels but significantly increased smoking index scores, MMRC scores, SGRQ scores, frequencies of acute exacerbation, hormone usage, and BODE index scores. All-cause mortality rates were significantly greater in patients with continuously elevated levels of systemic inflammation than in patients with normal systemic inflammation levels, suggesting that close correlations exist between systematic inflammation levels and the illness status, quality of life, and prognosis of COPD patients.

Our study investigated both the systemic and airway-specific inflammation levels of COPD patients and analysed how these inflammation levels were related to pulmonary function and quality of life. TNF-α levels in induced sputum were not correlated with pulmonary function and quality of life in either the high-risk or low-risk group of COPD patients. MCP-1 levels in induced sputum were not only negatively correlated with 6MWD levels in the low-risk group of COPD patients but also positively correlated with these patients' SGRQ scores in the symptoms domain. With respect to the serum levels of inflammatory mediators, in the low-risk group of patients, serum TNF-α and MCP-1 levels demonstrated no obvious correlations with either pulmonary function or quality of life. In the high-risk group of patients, serum TNF-α and MCP-1 levels were negatively correlated with FEV_1/forced vital capacity (FVC) ratios, serum TNF-α levels were positively correlated with overall SGRQ scores, and serum MCP-1 levels were positively correlated with MMRC scores. These correlations indicated that the serum levels of these two inflammatory cytokines are elevated in patients with relatively serious disease conditions and obvious reductions in pulmonary function. To a certain extent, this elevation reflects the pathological changes and corresponding aggravating clinical manifestations that occur in bronchial and pulmonary tissues during the course of COPD.

In summary, in the low-risk group of COPD patients, there was an obvious relationship between inflammatory factor levels in induced sputum samples and impaired quality of life. In the high-risk group of COPD patients, the levels of serum inflammatory factors exhibited a correlation with reduced pulmonary function and impaired quality of life. These changes in pulmonary function and quality of life among COPD patients are caused by complicated disease mechanisms that involve a variety of inflammatory mediators. Our findings demonstrated not only that TNF-α and MCP-1 participate in the pathological process of the occurrence and development of COPD but also that changes in TNF-α and MCP-1 levels may be somewhat reflective of changes in a patient's condition and quality of life. Thus, to a certain extent, measurements of the levels of TNF-α and MCP-1 in induced sputum and serum could serve as reference data for monitoring changes in the conditions of COPD patients and evaluating the therapeutic effects of COPD treatments. Examinations of the levels of these inflammatory mediators can also provide inspiration for the study of new targets for drug therapies.

Previous similar studies have typically limited their examinations to serum levels of inflammatory cytokines in COPD patients. However, our study investigated the levels of inflammatory cytokines in both induced sputum and serum samples from patients who were in stable periods of COPD and explored how these levels were related to pulmonary function and quality of life. In the past, the progression of COPD in most patients was thought to be correlated with the severity of airflow limitations; in fact, in prior GOLD guidelines, FEV_1 was used to determine the stage of severity of COPD. However, among COPD patients, only a weak correlation exists between FEV_1 symptoms and the impairment of health-related quality of life. For a COPD patient, FEV_1 is not a reliable indicator of dyspnoea, mobility limitations, and health status. The most recent GOLD guidelines, from 2011, involve assessing disease severity based on a patient's pulmonary function, dyspnoea score, and frequency of acute exacerbation of COPD. This approach provides a more accurate reflection of the complexity of COPD than the prior approach to staging this disease, which involved the unidimensional analysis of airflow limitation.[9] Thus, the current study employed the more advanced COPD classification method, which can provide a more accurate assessment of the disease status and prognosis of COPD, to divide the examined patients into a low-risk group and a high-risk group for analytical purposes. This investigation determined that patients at these two different stages of illness severity demonstrated different characteristics with respect to how the airway and systemic inflammation levels were related to pulmonary function and quality of life.

The limitations of this study include its relatively small sample size, its cross-sectional nature, and its examination of only several selected inflammatory cytokines. The examination of a large sample in a prospective study would allow for further investigation of not only the role of inflammation in the pathogenesis of COPD but also the relationships between inflammation and pulmonary function, quality of life, and prognosis in COPD patients.

References

1. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, Fukuchi Y, Jenkins C, Rodriguez-Roisin R, van Weel C, Zielinski J. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2007; 176(6): 532-5.
2. Spurzem JR, Rennard SI. Pathogenesis of COPD. Semin Respir Crit Care Med 2005; 26(2): 142-53.
3. Salvi SS, Barnes PJ.. Chronic obstructive pulmonary disease in non-smokers. Lancet 2009; 374(9691): 733-43.
4. Khair OA, Devalia JL, Abdelaziz MM, Sapsford RJ,

Tarraf H, Davies RJ. Effect of Haemophilus influenzae endotoxin on the synthesis of IL-6, IL-8, TNF-alpha and expression of ICAM-1 in cultured human bronchial epithelial cells. Eur Respir J. 1994; 7(12):2109-16.

5. Chung KF. Cytokines in chronic obstructive pulmonary disease. Eur Respiratory J . 2001;18: 50s-9s.

6. Premack BA, Schall TJ. Chemokine receptors: gate-ways to inflammation and infection. Nat Med 1996; 2(11): 1174–8.

7. Masubuchi T, Koyama S, Sato E, Takamizawa A, Kubo K, Sekiguchi M, Nagai S, Izumi T. Smoke extract stimulates lung epithelial cells to release neutrophil and monocyte chemotactic activity. Am J Pathol 1998; 153(6): 1903–12.

8. Barnes PJ. Alveolar macrophages in chronic obstructive pulmonary disease (COPD). Cell Mol Biol (Noisy-le-grand). 2004; 50 Online Pub: OL627–OL37.

9. Gold Science Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. updated 2011[S/OL]. (Accessed at *http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=2003.http://ww*w.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf.)

10. Jones PW, Quirk FH, Baveystock CM. The St George's respratory questionnaire. Respir Med, l99l; 85: 25-31.

11. Zeng M, Wu JF, Xie CM, Yan YS, Chen DM, Xuan JM. Safety of sputum induction in subjects with acute exacerbations of chronic obstructive pulmonary disease. Chinese Journal of Tuberculosis and Respiratory Diseases (Chin) 2005; 28(4): 238-41.

12. Mahler D, Wells C. Evaluation of clinical methods for rating dyspnea. Chest 1988; 93(3): 580-6.

13. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002; 166(1): 111-7.

14. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004; 350(10): 1005-12.

15. Traves SL, Culpitt SV, Russell REK, Barnes PJ, Donnelly LE. Increased levels of the chemokines GROα and MCP-1 in sputum samples from patients with COPD. Thorax 2002; 57(7): 590–5.

16. Aldonyte R, Jansson L, Piitulainen E, Janciauskiene S. Circulating monocytes from healthy individuals and COPD patients. Respir Res 2003; 4: 11.

17. Garcia-Rio F, Miravitlles M, Soriano J, Muñoz L, Duran-Tauleria E, Sánchez G, Sobradillo V, Ancochea J, EPI-SCAN Steering Committee. Systemic inflammation in chronic obstructive pulmonary disease: a population-based study. Respir Res. 2010; 11: 63.

18. Dourado VZ, Tanni SE, Vale SA, Faganello MM, Sanchez FF, Godoy I. Systemic manifestations in chronic obstructive pulmonary disease. J Bras Pneumol. 2006; 32:161-71.

19. Eickmeier O, Huebner M, Herrmann E, Zissler U, Rosewich M, Baer PC, Buhl R, Schmitt-Grohé S, Zielen S, Schubert R. Sputum biomarker profiles in cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) and association between pulmonary function. Cytokine. 2010; 50(2): 152-7.

20. Liu SF, Chin CH, Wang CC, Lin MC. Correlation between serum biomarkers and BODE index in patients with stable COPD. Respirology 2009; 14(7): 999-1004.

21. Agustí A, Edwards LD, Rennard SI, MacNee W, Tal-Singer R, Miller BE, Vestbo J, Lomas DA, Calverley PM, Wouters E,Crim C, Yates JC, Silverman EK, Coxson HO, Bakke P, Mayer RJ, Celli B. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. PLoS One 2012; 7(5): e37483.

7/27/2013