# Computed tomography manifestation of acute exacerbation of chronic obstructive pulmonary disease: A pilot study

TING CHENG[1], HUANYING WAN[1], QIJIAN CHENG[1], YI GUO[2], YANRONG QIAN[2], LIANG FAN[2], YUN FENG[2], YANYAN SONG[3], MIN ZHOU[2], QINGYUN LI[2], GUOCHAO SHI[2] and SHAOGUANG HUANG[2]

[1]Department of Respiratory Medicine, Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, Shanghai 201800; [2]Department of Respiratory Medicine, Ruijin Hospital; [3]Department of Biostatistics, Shanghai Jiaotong University School of Medicine, Shanghai 200025, P.R. China

Received September 15, 2014; Accepted August 5, 2015

DOI: 10.3892/etm.2015.2930

**Abstract.** Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is an acute event characterized by the worsening of a patient's respiratory symptoms. To the best of our knowledge, few studies have investigated the computed tomography (CT) manifestation of AECOPD. Thus, the aim of the present study was to examine the CT manifestations during AECOPD. In total, 40 patients with AECOPD admitted to the emergency department were enrolled. CT images obtained at the time of exacerbation and at the 3-month follow-up were paired. Clinical characteristics and routine blood test results were also recorded. Airway dimensions and attenuation per patient were quantified from the 3rd to the 6th generation of four bronchi by Airway Inspector Slicer 2.8. The emphysema extent was also quantified and lung infiltration was detected, classified and measured. The CT images showed an increased wall area percentage (WA%) and increased mean and peak wall attenuation during the AECOPD; however, the extent of emphysema did not change significantly. In total, 60% of AECOPD patients presented with lung infiltration, compared with those at the follow-up CT scanning. The presence and extent of segmental distribution consolidation was correlated with the neutrophil percentage (N%), with a statistically significant difference observed. The total volume of lung parenchymal infiltration was correlated with the white blood cell (WBC) count and N%; however, no significant correlations were detected between the presence or extent of acinar shadow, air space consolidation with lobular distribution, ground-glass attenuation with lobular distribution, thickening of the interlobular septa and signs of infection (including the number of main symptoms, body temperature, WBC count and N%). The WA%, mean wall attenuation and peak wall attenuation increased during AECOPD, but the emphysema extent was unchanged. Lung infiltration existed frequently; however, only consolidation with segmental distribution appeared to be associated with bacterial infection.

*Correspondence to:* Professor Qijian Cheng or Professor Huanying Wan, Department of Respiratory Medicine, Ruijin Hospital North, Shanghai Jiaotong University School of Medicine, 999 Xiwang Road, Jiading, Shanghai 201800, P.R. China
E-mail: chengqijian@aliyun.com
E-mail: hy_wan2013@163.com

*Abbreviations:* AECOPD, acute exacerbation of COPD; Ai, inner lumen area; Ao, outer area of the bronchus; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV1, forced expiratory volume in 1 sec; ILS, interlobular septa; N%, neutrophil percentage; WA%, wall area percentage; WBC, white blood cell; WT, wall thickness

*Key words:* acute exacerbation of chronic obstructive pulmonary disease, chronic obstructive pulmonary disease, emphysema, airways disease, pneumonia, X-ray computed tomography, computer-assisted radiographic image interpretation

## Introduction

Chronic obstructive pulmonary disease (COPD) is a condition characterized by persistent airflow limitation. The disease is usually progressive and is a leading cause of morbidity and mortality worldwide, with a prevalence between 0.5-4% depending on the region and ~2.7 million deaths in 2000 (1,2). Patients with COPD may have recurrent exacerbations that contribute to the overall severity. Acute exacerbation of COPD (AECOPD) is an acute event characterized by a worsening of the respiratory symptoms of a patient (including dyspnea, cough and sputum production) that is beyond normal day-to-day variations and that requires additional therapy. AECOPD is associated with accelerated loss of lung function and poor quality of life (2).

Computed tomography (CT) is frequently performed in AECOPD to screen for pneumonia, lung cancer, pneumothorax and hydrothorax; however, to the best of our knowledge, there are few studies on the CT manifestation of AECOPD. Furthermore, only a limited number of studies have investigated the pathology of COPD exacerbations, since a lung biopsy is considered unnecessary and unfeasible for patients in a poor condition (3,4). The pathology of the lung can be well reflected using CT; therefore, additional studies are required on the CT manifestation of AECOPD.

Several factors can precipitate COPD exacerbations, including infections and air pollution (4). The manifestation of COPD exacerbation can be divided into two parts: The

deterioration of COPD manifestation (including symptoms of dyspnea, cough and sputum), and the manifestation of lung infection (including symptoms of fever and purulent sputum).

Numerous studies have demonstrated that the main pathological changes in COPD include emphysema, airway wall thickening and reduced lumen caliber (4-7). The emphysema extent can be evaluated by the percentage of lung volume occupied by low attenuation areas (LAA%) (8). Airways with an internal diameter <2 mm, which is below the resolution of CT, are the major sites of airway obstruction in COPD; however, their dimensions are reflected by the dimensions of large airways, which are easily measured on CT scans (9). In addition, impaired lung function has been demonstrated to be significantly correlated with emphysema extent (LAA%) and bronchial dimensions (10).

Lung infection can manifest as lung infiltration, which can be evaluated by radiography, although it is more clearly evaluated by CT. Radiographic lung consolidation is common in patients with AECOPD, which affects 36.3% of inpatients in the USA (11). In the present study, three aspects of the CT manifestation of AECOPD were investigated, including the airway dimension, the extent of emphysema and lung infiltration.

## Patients and methods

*Patients*. Patients with a primary diagnosis of AECOPD that were admitted at the emergency department of Ruijin Hospital in Shanghai, China between December 2011 and May 2012 were recruited (Fig. 1). The Ethics Committee of Ruijin Hospital approved the study protocol (approval no. 2009-23), and all participants provided informed consent. The admitting physician diagnosed the patients with AECOPD, based on the patient presenting two of the following three characteristics: Increased dyspnea, increased sputum volume or increased sputum purulence from COPD that were beyond the normal day-to-day variations and required emergency treatment (12). COPD was diagnosed on the basis of a patient's history and spirometry results. A diagnosis of COPD was considered based on the following criteria: i) The patient had a clear medical history of COPD; ii) the patient had history of chronic bronchitis or persistent dyspnea and the lung function test performed in emergency department showed a forced expiratory volume in 1 sec/forced vital capacity (FEV1/FVC) of <70%. If the patients had a history of asthma or wheezing, the bronchodilation test was performed. COPD was considered only if the patient had persistent dyspnea, post-bronchodialation FEV1/FVC of <70% (Fig. 1). Spirometry was performed using a Cosmed® Spirolab-II spirometer (Cosmed Srl, Rome, Italy) and Jaeger® MasterScreen Body/Diff system (CareFusion Corporation, San Diego, CA, USA) in follow-up according to the American Thoracic Society/European Respiratory guidelines (13). Whenever possible, the diagnosis was confirmed by spirometry when the patients were in a stable condition.

The exclusion criteria included the following: A history of other respiratory illnesses, including lung cancer, pneumothorax, hydrothorax, severe bronchiectasis, thorax malformation, destroyed lung; illness (such as hemodynamic instability) too severe to allow a patient to undergo routine examinations; and patients that were admitted at the emergency department for reasons other than COPD exacerbation. Routine history recording, physical examinations and routine blood tests were performed on the patients. The patients were treated in accordance with the guidelines of the Global Initiative for Chronic Obstructive Lung Disease (2).

*CT scan acquisition*. A chest CT scan without contrast media was performed at the first visit and 3 months after the exacerbation. The scanner (Light Speed 16; GE Medical Systems, Milwaukee, WI, USA) and protocol used were according to those reported in a previous study (14). The technical parameters were as follows: Tube voltage, 120 kV; tube current, 220 mA; tube rotation time, 0.8 sec; and 1.25 mm collimation. Images were reconstructed using a standard algorithm: Section thickness, 1.25-mm; interval, 1.25 mm; and matrix, 512 x 512 (14). The patients were placed in a supine position and held their breath during the scan following a deep inspiration.

*CT image analysis*

*Assessment of airway dimension*. The B1 (which is the apical/apical-posterior segmental bronchus of the upper lobe) and B10 (which is the posterior basilar segmental bronchus of the lower lobe) bronchi of both sides of the lung were selected, as well as the longest bronchus visible at the subsegmental and the more distal bifurcations. For each patient, the airway dimension was measured every 2.5 mm or as dense as possible on the four bronchi from the origin of the 3rd generation to the end of the 6th generation. The generation of each site was registered. For all patients, the average airway dimensions of each generation of each bronchus were calculated. The dimensions were calculated on the plane perpendicular to the long axis of the airway using the Airway Inspector module of 3D Slicer, version 2.8 (Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA) (15). The mean inner lumen area (Ai), mean outer area of the bronchus (Ao), wall area percentage [WA%; calculated as follows: WA% = (Ao-Ai)/Ao x 100)], mean outer and inner radii, mean wall thickness (WT), mean wall, mean peak wall and lumen attenuation values were calculated using the full width at half-maximum algorithm (16).

*Assessment of the emphysema severity and lung volume*. The commercial software Myrian, version 1.12 (Intrasense, Montpellier, France) was used to automatically calculate the lung volume and LAA% with the acquiescent threshold of -950 Hounsfield units (HU), in order to represent the severity of emphysema, as performed in a previous study (17).

*Assessment of lung infiltration*. One pulmonologist and one radiologist reviewed the CT images. Final decisions were reached by consensus. The presence of a centrilobular or acinar shadow, air space consolidation with lobular distribution or segmental distribution, ground-glass attenuation with lobular distribution and thickening of the interlobular septa (ILS) were assessed as in a previous study (18). In addition, the extent of each shadow or consolidation was calculated using the 'ABC/2' method, in which A is the greatest diameter on the largest shadow slice, B is the diameter perpendicular to A, and C is the number of axial slices with the shadow multiplied by the slice thickness (19). The most severe type of lung parenchymal

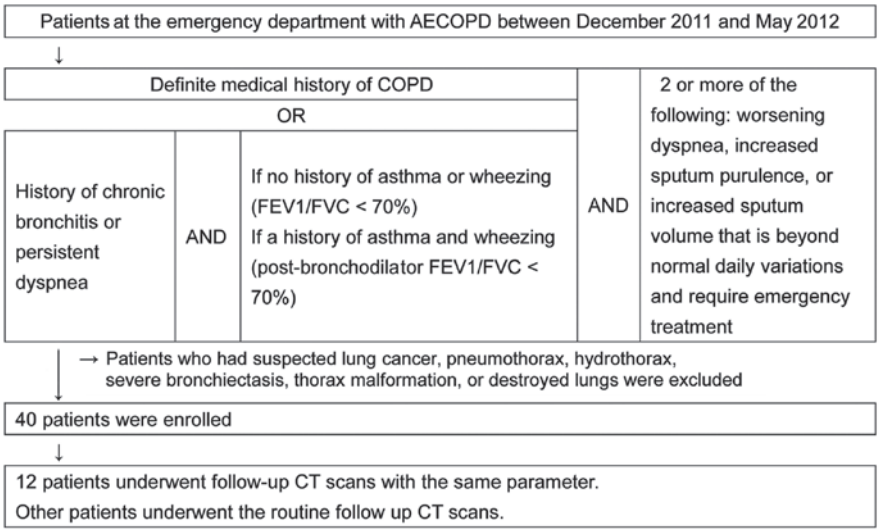


Figure 1. Flow chart of the cohort enrollment and follow up. AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; CT, computed tomography; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity.

infiltration was defined for each patient based on the following order (in increasing severity): Centrilobular/acinar shadow; lobular consolidation; and segmental/lobe consolidation for CT image review. The total consolidation volume was calculated using the formula Σ = the density of infiltration x volume of each type of lung parenchymal infiltration, which included acinar shadow and air space consolidation with lobular or segmental distribution. Furthermore, the density of infiltration was an arbitrary score based on the percentage of volume of focus occupied by a consolidation. It was classified into four grades: 25, 50, 75 and 100%. The assessments were performed with the reviewers blinded to the clinical and laboratory data of the patients.

*Statistical analysis*. The emphysema extent and the airway dimensions between the exacerbation and the stable phase were compared by paired sample Student's *t*-test. Comparisons of the mean airway dimension or attenuation of the four bronchi in each generation between the exacerbation and stable phases were analyzed by random block design two-way analysis of variance. The correlation between them was assessed by Pearson's correlation test, as they had a normal distribution. In addition, the correlation of clinical characteristics with the type or extent of lung infiltration was assessed by Spearman's correlation. The association between ranked data and dichotomic categorical variables was assessed by the Mann-Whitney U-test. The association between dichotomic categorical variables was assessed by $\chi^2$ test (exact method). Statistical analyses were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). P<0.05 was considered to indicate a statistically significant difference.

## Results

*Characteristics of AECOPD patients*. A total of 40 patients with AECOPD that underwent follow-up CTs were included in the present study (Table I). The majority of the patients were male (37/40) and former smokers, with a mean age of 75±11 years. The FEV1/FVC [mean ± standard deviation (SD)] was 50±13% and the predicted FEV1% (mean ± SD) was 42±21%. In total, 12 patients underwent a follow-up CT using the same scan parameters and their data were eligible for the quantitative CT image analysis. No statistically significant differences in characteristics were observed between the patients who underwent CT follow-up with the same or different scan parameters.

*Comparison of the airway dimensions and attenuation between the acute exacerbation and the stable phase*. The absolute values of each airway dimension were calculated separately for the generation and for the bronchus. At exacerbation, the mean values of the WA% in the 3rd, 4th, 5th and 6th generations were significantly negatively correlated with FEV1 ($r$=0.673, P=0.016) and FEV1% predicted ($r$=0.668, P=0.018). The FEV1 was also significantly negatively correlated with the average mean wall attenuation ($r$=0.677, P=0.016) and peak wall attenuation ($r$=0.723, P=0.008). The predicted FEV1% was significantly correlated with the average values of the inner radius ($r$=0.599, P=0.040) and the Ai ($r$=0.594, P=0.042).

The mean wall attenuation increased during exacerbation compared with the stable phase values in the 3rd (-215±91 vs. -283±101 HU, respectively; P<0.001), 4th (-312±115 vs. -382±119 HU, respectively; P=0.001) and 5th (-414±138 vs. -463±139 HU, respectively; P=0.027) generations of bronchi, with statistically significant differences observed. In addition, the peak wall attenuation increased during exacerbation, compared with the stable phase values, in the 3rd (-128±105 vs. -212±111 HU, P<0.001), 4th (-242±130 vs. -330±133 HU, P<0.001) and 5th (-361±156 vs. -429±156 HU, P=0.008) generations of bronchi, with statistically significant differences observed. Furthermore, the lumen attenuation increased during exacerbation, compared with the stable phase values, in the 3rd (-922±114 vs. -961±26 HU, P=0.02), 4th (-891±128 vs. -929±66 HU, P=0.032) and 6th generation

Table I. Characteristics of the patients in the study.

| Patient characteristics | All patients (n=40) | Follow-up CT with the same parameters (n=12) | P-value[a] |
|---|---|---|---|
| Male/total | 37 | 10 | 0.308 |
| Age, years | 75±11 | 74±8 | 0.801 |
| BMI, kg/m$^2$ | 20±3 | 21±3 | 0.474 |
| Smoking status | 35 | 10 | 0.209 |
| Current smoker | 8 | 2 | |
| Ex-smoker | 27 | 8 | 1.000 |
| Packs-year | 33±20 | 32±17 | 0.703 |
| Years since quitting smoking | 14±13 | 11±7 | 0.418 |
| Clinical presentations | | | |
| Increase in cough | 35 | 10 | 0.613 |
| Increase in sputum volume | 34 | 11 | 1.000 |
| Increase in sputum purulence | 20 | 7 | 0.726 |
| Increase in dyspnea | 39 | 11 | 1.000 |
| Fever | 19 | 7 | 0.460 |
| Clinical score | | | |
| CRB-65 score | 1 (1-1) | 1 (1-1) | 0.520 |
| mMRC grade | 3 (2-4) | 4 (2-4) | 0.536 |
| Performance status | 2 (1-3) | 1.5 (1.0-2.75) | 0.342 |
| CAT score | 27±8 | 28±9 | 0.988 |
| Comorbidities | | | |
| Asthma | 3 | 0 | 0.543 |
| Diabetes mellitus | 3 | 0 | 0.545 |
| Hypertension | 15 | 4 | 1.000 |
| Coronary artery disease | 10 | 3 | 1.000 |
| Left-sided heart failure | 3 | 2 | 0.548 |
| Lung function test during exacerbation | | | |
| FEV1, L | 1.08±0.52 | 1.16±0.49 | 0.379 |
| FEV1, % predicted | 42±21 | 48±24 | 0.168 |
| FVC, L | 2.17±0.75 | 2.29±0.72 | 0.337 |
| FEV1/FVC, % | 50±13 | 52±13 | 0.499 |
| Blood test during exacerbation | | | |
| WBC count, x10$^9$/l | 9.1±4.5 | 8.9±5.0 | 0.700 |
| N% | 74±11 | 70±11 | 0.220 |
| Hb, g/l | 136±18 | 135±10 | 0.914 |
| PLT count, x10$^9$/l | 206±65 | 186±91 | 0.337 |
| pH | 7.40±0.03 | 7.42±0.01 | 0.223 |
| $PaO_2$, kPa | 9.02±2.69 | 10.0±0.7 | 0.422 |
| $PaCO_2$, kPa | 5.57±0.95 | 5.55±0.22 | 0.976 |

Data are presented as mean ± standard deviation or mean (interquartile range). [a]P-value in characteristics between the patients who underwent CT follow-ups with the same or different scan parameters. BMI, body mass index; Pack-year, packs smoked per day x years as a smoker; CAT score, chronic obstructive pulmonary disease assessment test; CRB-65 score, confusion, respiratory rate ≥30/min, systolic blood pressure <90 mmHg or diastolic blood pressure ≤60 mmHg and age ≥65 years; CT, computed tomography; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity; Hb, hemoglobin; mMRC, modified Medical Research Council Dyspnea scale; N%, neutrophil percentage; $PaCO_2$, arterial partial pressure of carbon dioxide; $PaO_2$, arterial partial pressure of oxygen; PLT, platelet; WBC, white blood cell.

of bronchi (-863±118 vs. -912±67 HU, P=0.029). The WA% also increased in the 3rd generation of bronchi during an exacerbation compared with the stable phase (82.7±6.1 vs. 79.8±5.6%, respectively; P=0.003), with a statistically significant difference observed. In addition, the WA% in the 4th to 6th generations and wall thickness tended to increase during the exacerbation. The inner radius and Ai tended to decrease during the exacerbation (Fig. 2).

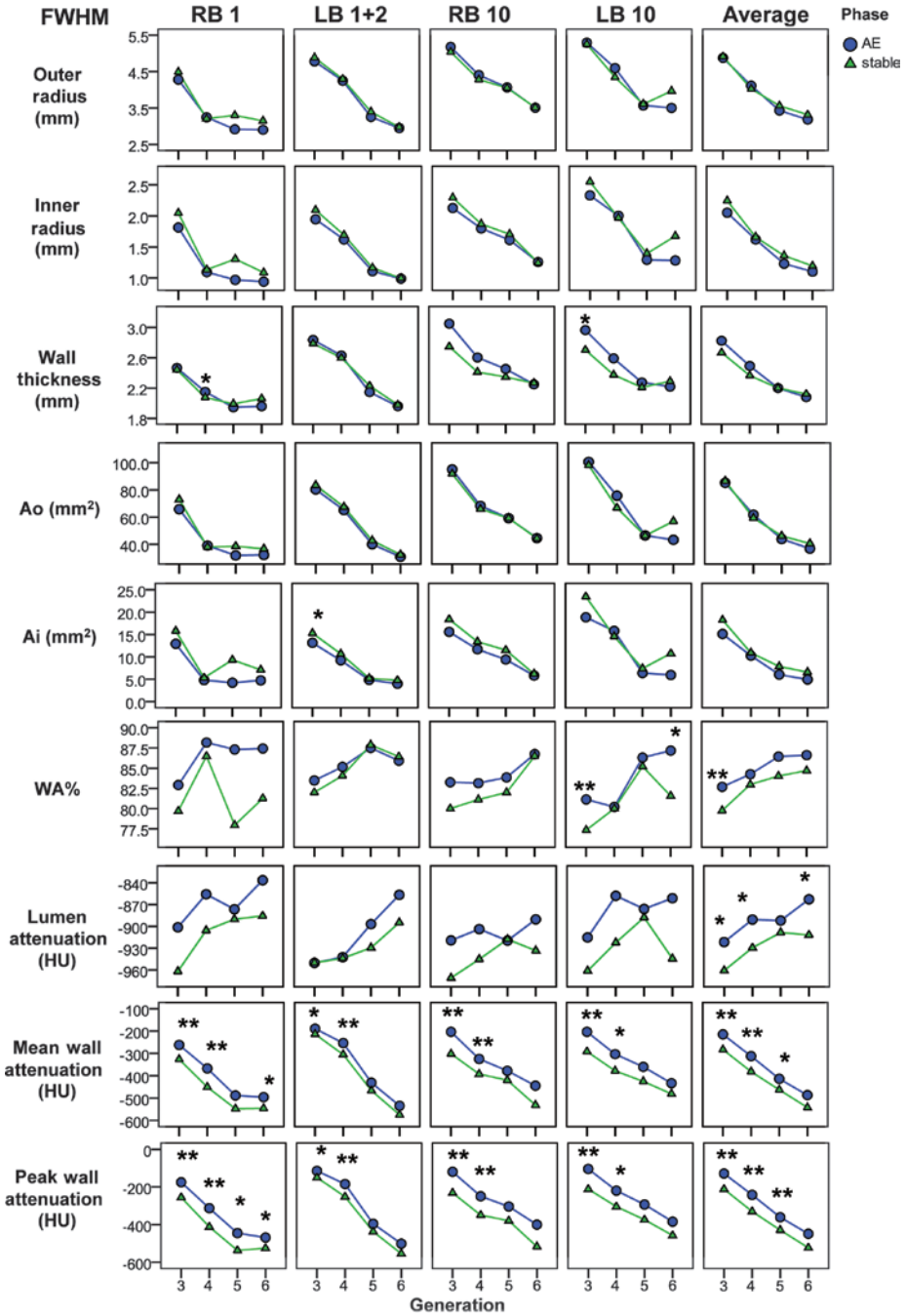


Figure 2. Airway dimensions and attenuation during the AE and stable phases of each generation. *P<0.05 and **P<0.01 compare differences in the AE and stable phases in the airway dimension or attenuation. AE, acute exacerbation; Ai, inner luminal area; Ao, outer area of the bronchus; FWHM, full width at half-maximum; WA%, wall area percentage; HU, Hounsfield units; LB 1+2, posterior apical bronchus of the left upper lobe; LB 10, posterior basal bronchus of the left lower lobe; RB 1, apical bronchus of the right upper lobe; RB 10, posterior basal bronchus of the right lower lobe; average, mean value of the four bronchi.

Table II. Comparison of the lung volume and the LAA% on CT between the AE and the stable phases.

| Parameter | AE | Stable phase | P-value |
|---|---|---|---|
| Lung volume (ml) | 5,482±1,038 | 5,666±985 | 0.237 |
| LAA% | 9.54±6.54 | 9.62±6.68 | 0.910 |

Data are presented as the mean ± standard deviation. CT, computed tomography; AE, acute exacerbation; LAA%, percentage of low-attenuation areas on CT imaging using a threshold of -950 Hounsfield units.

*Comparison of the emphysema extent and lung volume between the exacerbation and stable phases*. The LAA% and lung volume during exacerbation were correlated with LAA% and lung volume during the stable phase (Fig. 3). No statistically significant differences were observed in the LAA% and the lung volume between the CT images obtained during exacerbation and during the stable phase (Table II).

*Assessment of lung infiltration*. Table III shows the incidence of specific CT findings of lung infiltration in the 39 patients with AECOPD (the CT images of one patient could not be acquired from our image archiving system). In total, 24/39 patients

Table III. Overall patterns, range and distribution of lung infiltration on computed tomography (CT) during exacerbation.

| Lung infiltration parameters | Original scan | Follow-up scan |
|---|---|---|
| Overall lung infiltration | 24/39 | 23/39 |
| Pattern | | |
| Acinar shadow | 8/39 | 7/39 |
| Air space consolidation with lobular distribution | 19/39 | 16/39 |
| Consolidation with segmental distribution | 4/39 | 4/39 |
| Ground-glass attenuation with lobular distribution | 6/39 | 3/39 |
| Ground-glass attenuation with thickened interlobular or intralobular septa | 1/39 | 1/39 |
| Thickening of the interlobular septa | 5/39 | 4/39 |
| Range, lobes | | |
| 0 | 15/39 | 16/39 |
| 1 | 6/39 | 8/39 |
| 2 | 10/39 | 9/39 |
| 3 | 4/39 | 2/39 |
| 4 | 3/39 | 3/39 |
| 5 | 1/39 | 1/39 |
| Distribution | | |
| Right upper lobe | 12/39 | 11/39 |
| Right middle lobe | 8/39 | 7/39 |
| Right lower lobe | 15/39 | 12/39 |
| Left upper lobe | 5/39 | 5/39 |
| Left lower lobe | 15/39 | 14/39 |

Table IV. Volume occupied by each type of lung infiltration on the follow-up computed tomography scan.

| | With absorption | | No absorption | |
|---|---|---|---|---|
| Infiltration pattern | N | Volume ($cm^3$) | N | Volume ($cm^3$) |
| Acinar shadow | 7 | 24±39 | 1 | 11 |
| Air space consolidation with lobular distribution | 16 | 23±29 | 3 | 4±3 |
| Consolidation with segmental distribution | 4 | 181±113 | 0 | NA |
| Ground-glass attenuation with lobular distribution | 3 | 12±14 | 3 | 1±1 |
| Ground-glass attenuation with thickened interlobular or intralobular septa | 1 | 143 | 0 | NA |
| Thickening of the interlobular septa | 4 | 4±3 | 1 | 45 |
| Total volume | 22 | 11 (0.5-34) | 6 | 1.3 (0.6-10.3) |

Data for 1 patient are not included, since it was difficult to calculate their infiltration volume. Total volume = Σ (density of infiltration x volume) of each type of lung parenchymal infiltration (including acinar shadow and air space consolidation with lobular or segmental distribution). Data are presented as the mean ± standard deviation or median (interquartile range).

(61.5%) presented lung infiltration to some extent on CT. According the follow-up CT, 23/39 patients with AECOPD (59.0%) presented lung infiltration with absorption, while the lung infiltration was present in only 1 lobe in 8/39 patients (20.5%) and in several lobes in 15/39 patients (38.5%). Furthermore, the left lower lobe (14/39 patients), right lower lobe (12/39 patients) and right upper lobe (11/39 patients) were most frequently involved, whereas the left upper lobe (5/39 patients) was less frequently involved. The 'air space consolidation with lobular distribution' was the most frequent manifestation of lung infiltration (16/39 patients).

No changes were observed in the follow-up CT scans of 3/6 cases with 'ground-glass attenuation with lobular distribution' infiltration, 3/19 cases with 'air space consolidation with

Table V. Association between the existence of lung parenchymal/interstitial infiltration and signs of infection.

| Infiltration pattern | Patients with infiltration | Patients without infiltration | P-value |
|---|---|---|---|
| Acinar shadow | | | |
| Number of main symptoms | 2.5 (2-3) | 2.5 (2-3) | 0.952 |
| Fever (T-37), ˚C | 0.4 (0-0.9) | 0.2 (0-1.4) | 0.851 |
| CRB-65 | NA | 1 (0-1) | NA |
| WBC count | 7.78 (6.68-9.21) | 8.12 (6.05-11.95) | 1 |
| N% | 75.6 (65.5-86.4) | 74.4 (64.8-82.2) | 0.584 |
| Air space consolidation with lobular distribution | | | |
| Number of main symptoms | 3 (2-3) | 2 (2-3) | 0.467 |
| Fever (T-37), ˚C | 0 (0-0.8) | 0.8 (0-1.2) | 0.641 |
| CRB-65 | 1 (1-1) | 1 (0-1) | 0.677 |
| WBC count | 8.35 (6.68-10.5) | 6.74 (6.44-10.1) | 0.776 |
| N% | 74.3 (65.5-86.0) | 74.5 (66.2-81.5) | 0.751 |
| Consolidation with segmental distribution | | | |
| Number of main symptoms | 2.5 (2-3) | 2.5 (2-3) | 0.979 |
| Fever (T-37), ˚C | 1.2 (0-2.5) | 0.2 (0-1.2) | 0.731 |
| CRB-65 | 0.5 (0-1) | 1 (1-1) | 0.476 |
| WBC count | 19.6 (11.79-27.41) | 7.63 (6.16-9.71) | 0.082 |
| N% | 89.1 (87.8-90.4) | 73.2 (63.3-81.5) | 0.012 |
| Ground-glass attenuation with lobular distribution | | | |
| Number of main symptoms | NA | 2 (2-3) | NA |
| Fever (T-37), ˚C | 1.2 (0.6-1.2) | 0 (0-1) | 0.688 |
| CRB-65 | 1 (1-1.5) | 1 (0-1) | 0.219 |
| WBC count | 6.44 (4.745-12.7) | 8.17 (6.57-10.1) | 0.549 |
| N% | 70.3 (66.8-81.65) | 74.5 (66.2-81.6) | 1 |
| Ground-glass attenuation with thickened interlobular or intralobular septa | | | |
| Number of main symptoms | NA | 2.5 (2-3) | NA |
| Fever (T-37), ˚C | NA | 0.2 (0-1.2) | NA |
| CRB-65 | NA | 1 (0.5-1) | NA |
| WBC count | NA | 8.12 (6.3-10.9) | NA |
| N% | NA | 74.4 (64.8-82.2) | NA |
| Thickening of the intralobular septa | | | |
| Number of main symptoms | 3 (2.5-3) | 2 (2-3) | 0.654 |
| Fever (T-37), ˚C | 1.2 (0.6-1.2) | 0 (0-1) | 0.218 |
| CRB-65 | NA | 1 (0-1) | 0.673 |
| WBC count | 7.2 (5.12-13.1) | 8.17 (6.44-10.1) | 0.787 |
| N% | 69.6 (66.4-81.3) | 74.5 (66.2-81.6) | 1 |
| Parenchyma infiltration | | | |
| Number of main symptoms | 3 (2-3) | 2 (2-3) | 0.620 |
| Fever (T-37), ˚C | 0.4 (0-1) | 0 (0-1.2) | 0.812 |
| CRB-65 | 1 (1-1) | 1 (0-1) | 0.571 |
| WBC count | 8.74 (7.20-11.8) | 6.74 (6.05-8.88) | 0.114 |
| N% | 79.6 (69.6-87.8) | 72.2 (64.8-76.2) | 0.285 |
| Interstitial infiltration | | | |
| Number of main symptoms | 3 (2.5-3) | 2 (2-3) | 0.374 |
| Fever (T-37), ˚C | 0.6 (0-1.2) | 0.2 (0-1.25) | 0.508 |
| CRB-65 | 1 (1-1.5) | 1 (0-1) | 0.235 |
| WBC count | 6.82 (4.74-13.1) | 8.26 (6.36-10.9) | 0.450 |
| N% | 70.0 (66.4-81.6) | 75.1 (63.8-82.2) | 0.827 |

Table V. Continued.

| Infiltration pattern | Patients with infiltration | Patients without infiltration | P-value |
|---|---|---|---|
| Overall infiltration | | | |
| Number of main symptoms | 3 (2-3) | 2 (1.5-2) | 0.199 |
| Fever (T-37)˚C | 0.6 (0-1.2) | 0 (0-1.3) | 0.742 |
| CRB-65 | 1 (1-1) | 0.5 (0-1) | 0.243 |
| WBC count | 8.54 (6.30-12.3) | 6.74 (6.12-8.88) | 0.185 |
| N% | 77.0 (66.4-89.1) | 73.4 (63.8-76.2) | 0.280 |

Data are presented as the medium (interquartile range). Associations between the existence of lung infiltration and signs of infection were analyzed by the Mann-Whitney U-test. NA, patients with or without certain manifestation were too few to calculate an interquartile range and thus underwent the Mann-Whitney U test; CRB-65 score, confusion, respiratory rate of ≥30/min, systolic blood pressure of <90 mmHg or diastolic blood pressure of ≤60 mmHg, and age of ≥65 years; N%, neutrophil percentage; T, body temperature; WBC, white blood cell.

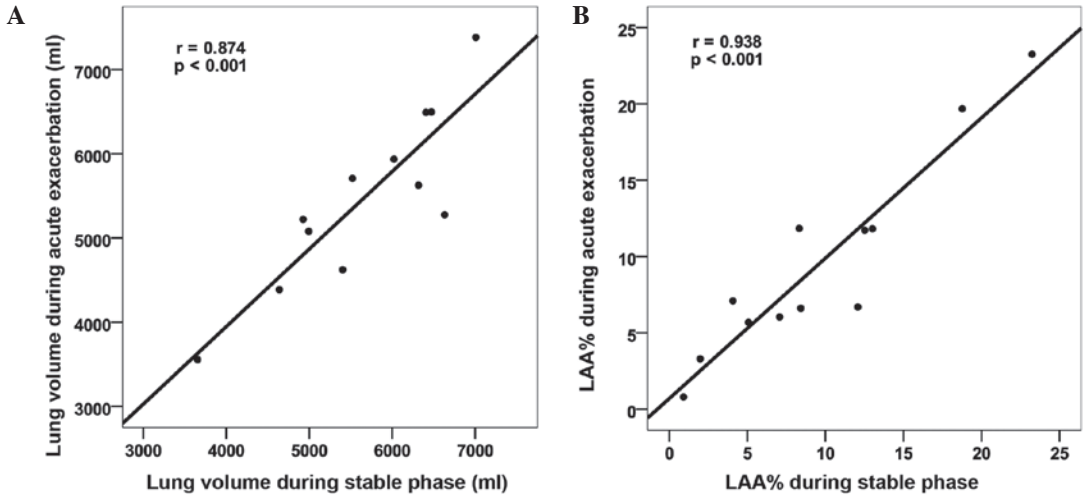


Figure 3. Correlation of the (A) lung volume and (B) LAA% between the exacerbation and stable phases (Pearson's correlation). LAA%, percentage of low-attenuation areas on computed tomography imaging, using a threshold of -950 Hounsfield units.

lobular distribution' infiltration, 1/5 cases with 'thickening of the ILS' infiltration and 1/8 cases with 'acinar shadow' infiltration (Table IV).

Furthermore, no statistically significant differences were observed in the risk of mortality (P=0.211), number of main symptoms of AECOPD, body temperature, CRB-65 score (confusion, respiratory rate of ≥30/min, systolic blood pressure of <90 mmHg or diastolic blood pressure of ≤60 mmHg, and age of ≥65 years), WBC count and neutrophil percentage (N%) between the AECOPD patients with and without lung infiltration. The N% was significantly higher in patients with segmental distribution consolidation compared with patients without segmental distribution consolidation (88.2 vs. 72.4%, respectively; P=0.012; Table V). The number of lobes and the volume occupied by the segmental distribution consolidation were correlated with N%, with statistical significance. In addition, the total volume of lung parenchymal consolidation was correlated with the WBC count and N%. The number of lobes and volume occupied by the ground-glass attenuation with thickened interlobular or ILS were correlated with the highest body temperature. No significant correlations were observed between the extent of acinar shadow, air space consolidation with lobular distribution, ground-glass attenuation with lobular distribution, thickening of the ILS and signs of infection [including the number of main symptoms, body temperature, WBC count, N% and the severity of exacerbation (such as the CRB-65 score); Table VI].

## Discussion

To the best of our knowledge, no previous studies have been conducted on the CT manifestation of AECOPD. Therefore, the present study investigated the CT manifestation during an acute exacerbation in patients with COPD.

The morphology of the airways from the 3rd to the 6th generation was examined and it was demonstrated that WA%, mean wall, peak wall and lumen attenuations were increased during the exacerbation. The increased peak wall attenuation is derived from a true increase in the bronchial wall structure density and a decrease in the contrast reduction caused by an increase in bronchial wall thickness (20). Therefore, the peak wall attenuation can be used to simultaneously assess the overall

Table VI. Correlation between the index of lung parenchymal/interstitial infiltration and signs of infection.

| | Main symptoms | | Body temperature | | CRB-65 | | WBC count | | N% | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic | r | P-value | r | P-value | r | P-value | r | P-value | r | P-value |
| Most severe pattern of lung parenchymal infiltration | 0.114 | 0.503 | 0.048 | 0.789 | 0.029 | 0.884 | 0.281 | 0.096 | 0.276 | 0.103 |
| Number of lobes involved | | | | | | | | | | |
| Acinar shadow | -0.001 | 0.994 | -0.036 | 0.841 | 0.300 | 0.121 | -0.012 | 0.946 | -0.114 | 0.508 |
| Air space consolidation with lobular distribution | 0.128 | 0.452 | -0.030 | 0.865 | 0.130 | 0.509 | 0.145 | 0.400 | 0.130 | 0.448 |
| Consolidation with segmental distribution | -0.010 | 0.951 | 0.073 | 0.683 | -0.195 | 0.319 | 0.298 | 0.078 | 0.408 | 0.013 |
| Ground-glass attenuation with lobular distribution | 0.343 | 0.038 | 0.078 | 0.660 | 0.307 | 0.112 | -0.111 | 0.518 | 0.005 | 0.978 |
| Ground-glass attenuation with thickened interlobular or intralobular septa | 0.068 | 0.688 | 0.382 | 0.026 | 0.060 | 0.761 | 0.220 | 0.198 | 0.268 | 0.113 |
| Thickening of the ILS | 0.091 | 0.591 | 0.231 | 0.188 | 0.108 | 0.583 | -0.053 | 0.758 | -0.005 | 0.978 |
| Total | 0.263 | 0.116 | 0.089 | 0.617 | 0.318 | 0.099 | 0.257 | 0.131 | 0.239 | 0.159 |
| Volume occupied | | | | | | | | | | |
| Acinar shadow | -0.087 | 0.613 | -0.064 | 0.724 | 0.302 | 0.126 | 0.081 | 0.643 | 0.006 | 0.971 |
| Air space consolidation with lobular distribution | 0.107 | 0.529 | -0.124 | 0.484 | 0.150 | 0.446 | 0.137 | 0.426 | 0.142 | 0.409 |
| Consolidation with segmental distribution | 0.000 | 0.996 | 0.083 | 0.642 | -0.205 | 0.295 | 0.305 | 0.071 | 0.406 | 0.014 |
| Ground-glass attenuation with lobular distribution | 0.342 | 0.038 | 0.078 | 0.661 | 0.307 | 0.113 | -0.129 | 0.452 | -0.011 | 0.948 |
| Ground-glass attenuation with thickened interlobular or intralobular septa | 0.057 | 0.738 | 0.386 | 0.024 | 0.060 | 0.761 | 0.220 | 0.198 | 0.268 | 0.113 |
| Thickening of the ILS | 0.099 | 0.558 | 0.248 | 0.158 | 0.108 | 0.584 | -0.042 | 0.808 | 0.008 | 0.965 |
| Total | 0.074 | 0.668 | 0.014 | 0.938 | 0.095 | 0.638 | 0.398 | 0.018 | 0.392 | 0.020 |

CRB-65 score, confusion, respiratory rate of ≥30/min, systolic blood pressure of <90 mmHg or diastolic blood pressure of ≤60 mmHg, and age of ≥65 years; ILS, interlobular septa; N%, neutrophil percentage; WBC, white blood count.

situation of thickness and density. Yamashiro *et al* (16) demonstrated that peak bronchial wall attenuation is significantly correlated with FEV1 in patients with COPD, particularly in the distal airways. In addition, Lederlin *et al* (21) revealed that the mean wall attenuation value, rather than other parameters of airway dimension and emphysema extent, discriminated between smokers with and without COPD, and between smokers without COPD and healthy controls. Furthermore, the mean wall attenuation value was correlated with pulmonary function test (PFT) results, and the correlation coefficients of the mean wall attenuation value with each parameter of PFT were greater compared with those obtained for any other bronchial dimension (21).

In the present study, the mean peak bronchial wall attenuation and mean bronchial wall attenuation were also the most sensitive indices to differentiate between the AE and stable phases.

Hasegawa *et al* (22) demonstrated that the WA% and Ai were significantly correlated with the FEV1% predicted. Han *et al* (14) also revealed that airway wall thickness was correlated with the COPD exacerbation rate, independent of the FEV1. In the present study, the WA% increased significantly, the Ai tended to decrease and the bronchial wall thickness tended to increase during an exacerbation; however, the Ao did not appear to change. Bronchial wall thickening may be caused by inflammatory infiltration in the mucosa and by mucus secretion. The Ai decrease may be caused by the bronchial wall thickening and bronchial spasm. The increase of WA% was a combined effect of bronchial wall thickening and decrease in the Ai.

Emphysema extent is an important index in predicting lung function and survival. In the present study, there was a good correlation and no statistically significant difference in the LAA% between the exacerbation phase and at 3 months after the exacerbation. Previous studies have indicated that, in patients with an exacerbation, the annual change in LAA% remains much smaller compared with the basal LAA% (2.1/36.9%) (23). Therefore, the emphysema extent on CT during exacerbation can also reflect the basal emphysema extent and the irreversible part of airflow limitation of AECOPD to a certain degree.

Although numerous clinical trials regarding AECOPD have excluded patients with pneumonia (24-26), a few patients with AECOPD present lung parenchymal consolidations. The morbidity of lung parenchymal consolidation in AECOPD varied across different studies: It was found to be 12% in a study in Israel (27); 16% in the UK (28); and 36.3% in the USA (11), according to national audit data.

The present study also revealed that 61.5% of patients with AECOPD exhibited lung infiltration on the CT images, which was, at least partly, absorbed at follow-up CT scans. These data were clearly higher compared with those presented in previous studies (27,28). This may be due to the higher sensitivity of CT compared with chest radiography in diagnosing pneumonia, particularly in patients with COPD (29); however, the clinical significance of lung infiltration on a CT image with a negative radiograph image remains unclear (30).

Lieberman *et al* (27) showed that AECOPD patients with pneumonia generally manifest more severe clinical and laboratory parameters, while pneumococcal and viral etiologies are more common, compared with AECOPD patients without pneumonia. Several studies also revealed that mortality is significantly higher in pneumonic exacerbations than in non-pneumonic exacerbations (28,31). The present study, however, showed no significant differences in the risk of mortality, the number of main symptoms of AECOPD, body temperature, CRB-65 score, WBC count and N% between AECOPD patients with and without lung infiltration.

The difference in the clinical significance of lung infiltration between CT imaging and chest radiography may be due to the small lung infiltration foci in CT not having definite clinical significance; these foci are too inconspicuous to be noticed on chest radiographs (29,32). The current results suggested that the gap between AECOPD patients with and without lung infiltration is not large. In addition, there may be a continuous spectrum between pure AECOPD and AECOPD complicated by pneumonia.

The lung infiltration during AECOPD is not necessarily associated with the exacerbation. For instance, in the study by Lieberman *et al* (27), 15% of the chest radiographs of AECOPD inpatients during exacerbation indicated pneumonia, although only 10% of the patients were classified as having pneumonia compared with the follow-up radiograph. In the present study, 24/39 patients (61.5%) with AECOPD were observed to have lung infiltration on CT images during the exacerbation, and 23/39 patients (59.0%) with AECOPD were assessed as having lung infiltration associated with the exacerbation, which were at least partly absorbed. This may be due to the misclassification of fibroproliferative foci and vascular texture as lung infiltration on radiographs. Furthermore, we hypothesize that CT may be more sensitive than chest radiography in detecting the absorption of lung infiltration. Among the different patterns of lung infiltration, the ground-glass attenuation with lobular distribution, air space consolidation with lobular distribution, and small foci may not always be associated with the exacerbation; however, the consolidation with segmental distribution and large foci are more likely to be associated with the exacerbation.

The WBC count and N% indicated bacterial infection. In the present study, the existence and the extent of consolidation with segmental distribution were correlated with the N% value, whereas the existence and the extent of acinar shadow, air space consolidation with lobular distribution, ground-glass attenuation and thickening of the ILS were not correlated. The total volume of lung parenchymal infiltration was also correlated with the WBC count and N%. This finding suggested that consolidation with segmental distribution, rather than other types of lung infiltration, may be associated with bacterial infection. The total volume of lung parenchymal infiltration may be associated with the severity of bacterial infection. This result is consistent with the findings of previous studies, such as Tanaka *et al* (18) which revealed that bacterial pneumonia frequently manifested as air space consolidation with segmental distribution, whereas atypical pneumonia frequently manifested as centrilobular shadow, acinar shadow, air space consolidation with lobular distribution and ground-glass attenuation with lobular distribution.

There are several limitations in the present study. Firstly, the sample size was rather small. In addition, the etiological diagnosis was unavailable for the patients with AECOPD in the emergency department. The etiology of the exacerbation

can only be conjectured from its clinical manifestation, fever and routine blood tests. Furthermore, a biopsy was not applicable for patients with AECOPD, therefore, radiological and pathological correlations could not be shown. Finally, CT images prior to the exacerbation were unavailable.

In conclusion, the present study demonstrated that during AECOPD, the WA%, mean wall and peak wall attenuations increased and the Ai tended to decrease; however, the emphysema extent did not change. Approximately 60% of patients presented lung infiltration on CT images. The consolidation with segmental distribution may be associated with bacterial infection; however, acinar shadow and air space consolidation with lobular distribution may not have an evident clinical significance.

## Acknowledgements

This study was funded by grants from the Chronic Disease Prevention and Treatment Programme of the Shanghai ShenKang Hospital Development Centre, Shanghai, China (no. SHDC12012305) and the 11th National 5-year Development Plan (no. 2008BAI52B00).

## References

1. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, Schmid V and Buist S: Chronic obstructive pulmonary disease: Current burden and future projections. Eur Respir J 27: 397-412, 2006.
2. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011. Available from: http://www.goldcopd.org/ and http://www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf.
3. Hogg JC and Timens W: The pathology of chronic obstructive pulmonary disease. Annu Rev Pathol 4: 435-459, 2009.
4. Szilasi M, Dolinay T, Nemes Z and Strausz J: Pathology of chronic obstructive pulmonary disease. Pathol Oncol Res 12: 52-60, 2006.
5. Hogg JC: Pathophysiology of airflow limitation in chronic obstructive pulmonary disease. Lancet 364: 709-721, 2004.
6. Snider GL: Chronic obstructive pulmonary disease - a continuing challenge. Am Rev Respir Dis 133: 942-944, 1986.
7. Dunnill MS, Massarella GR and Anderson JA: A comparison of the quantitative anatomy of the bronchi in normal subjects, in status asthmaticus, in chronic bronchitis, and in emphysema. Thorax 24: 176-179, 1969.
8. Litmanovich D, Boiselle PM and Bankier AA: CT of pulmonary emphysema - current status, challenges, and future directions. Eur Radiol 19: 537-551, 2009.
9. Nakano Y, Wong JC, de Jong PA, Buzatu L, Nagao T, Coxson HO, Elliott WM, Hogg JC and Paré PD: The prediction of small airway dimensions using computed tomography. Am J Respir Crit Care Med 171: 142-146, 2005.
10. Nakano Y, Muro S, Sakai H, Hirai T, Chin K, Tsukino M, Nishimura K, Itoh H, Paré PD, Hogg JC and Mishima M: Computed tomographic measurements of airway dimensions and emphysema in smokers. Correlation with lung function. Am J Respir Crit Care Med 162: 1102-1108, 2000.
11. Perera PN, Armstrong EP, Sherrill DL and Skrepnek GH: Acute exacerbations of COPD in the United States: Inpatient burden and predictors of costs and mortality. COPD 9: 131-141, 2012.
12. Burge S and Wedzicha JA: COPD exacerbations: Definitions and classifications. Eur Respir J (Suppl) 41: S46-S53, 2003.
13. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P *et al*; ATS/ERS Task Fore: Standardisation of spirometry. Eur Respir J 26: 319-38, 2005.
14. Han MK, Kazerooni EA, Lynch DA, Liu LX, Murray S, Curtis JL, Criner GJ, Kim V, Bowler RP, Hanania NA, *et al*; COPD Gene Investigators: Chronic obstructive pulmonary disease exacerbations in the COPD Gene study: Associated radiologic phenotypes. Radiology 261: 274-282, 2011.
15. Estepar RSJ, Washko GG, Silverman EK, Reilly JJ, Kikinis R, and Westin CF: Airway inspector: An open source application for lung morphometry in First International Workshop on Pulmonary Image Processing. New York City, USA, 293-302, 2008.
16. Yamashiro T, Matsuoka S, Estépar RS, Dransfield MT, Diaz A, Reilly JJ, Patz S, Murayama S, Silverman EK, Hatabu H and Washko GR: Quantitative assessment of bronchial wall attenuation with thin-section CT: An indicator of airflow limitation in chronic obstructive pulmonary disease. AJR Am J Roentgenol 195: 363-369, 2010.
17. Martinez CH, Chen YH, Westgate PM, Liu LX, Murray S, Curtis JL, Make BJ, Kazerooni EA, Lynch DA, Marchetti N, *et al*: COPD Gene Investigators: Relationship between quantitative CT metrics and health status and BODE in chronic obstructive pulmonary disease. Thorax 67: 399-406, 2012.
18. Tanaka N, Matsumoto T, Kuramitsu T, Nakaki H, Ito K, Uchisako H, Miura G, Matsunaga N and Yamakawa K: High resolution CT findings in community-acquired pneumonia. J Comput Assist Tomogr 20: 600-608, 1996.
19. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M and Khoury J: The ABCs of measuring intracerebral hemorrhage volumes. Stroke 27: 1304-1305, 1996.
20. Washko GR, Dransfield MT, Estépar RS, Diaz A, Matsuoka S, Yamashiro T, Hatabu H, Silverman EK, Bailey WC and Reilly JJ: Airway wall attenuation: A biomarker of airway disease in subjects with COPD. J Appl Physiol (1985) 107: 185-191, 2009.
21. Lederlin M, Laurent F, Dromer C, Cochet H, Berger P and Montaudon M: Mean bronchial wall attenuation value in chronic obstructive pulmonary disease: Comparison with standard bronchial parameters and correlation with function. AJR Am J Roentgenol 198: 800-808, 2012.
22. Hasegawa M, Nasuhara Y, Onodera Y, Makita H, Nagai K, Fuke S, Ito Y, Betsuyaku T and Nishimura M: Airflow limitation and airway dimensions in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 173: 1309-1315, 2006.
23. Tanabe N, Muro S, Hirai T, Oguma T, Terada K, Marumo S, Kinose D, Ogawa E, Hoshino Y and Mishima M: Impact of exacerbations on emphysema progression in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 183: 1653-1659, 2011.
24. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA and van den Berg JW: Oral or IV prednisolone in the treatment of COPD exacerbations: A randomized, controlled, double-blind study. Chest 132: 1741-1747, 2007.
25. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, Dickinson G, Brison R, Rowe BH, Dreyer J, *et al*: Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 348: 2618, 2003.
26. Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, Rouleau M, Boukhana M, Martinot JB and Duroux P: Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: A randomized controlled trial. Am J Respir Crit Care Med 165: 698, 2002.
27. Lieberman D, Lieberman D, Gelfer Y, Varshavsky R, Dvoskin B, Leinonen M and Friedman MG: Pneumonic vs nonpneumonic acute exacerbations of COPD. Chest 122: 1264-1270, 2002.
28. Myint PK, Lowe D, Stone RA, Buckingham RJ and Roberts CM: U.K. National COPD Resources and Outcomes Project 2008: Patients with chronic obstructive pulmonary disease exacerbations who present with radiological pneumonia have worse outcome compared to those with non-pneumonic chronic obstructive pulmonary disease exacerbations. Respiration 82: 320-327, 2011.
29. Hayden GE and Wrenn KW: Chest radiograph vs. computed tomography scan in the evaluation for pneumonia. J Emerg Med 36: 266-270, 2009.
30. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS, *et al*; Infectious Diseases Society of America; American Thoracic Society: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 44 (Suppl 2): S27-S72, 2007.
31. Steer J, Norman EM, Afolabi OA, Gibson GJ and Bourke SC: Dyspnoea severity and pneumonia as predictors of in-hospital mortality and early readmission in acute exacerbations of COPD. Thorax 67: 117-121, 2012.
32. Syrjälä H, Broas M, Suramo I, Ojala A and Lähde S: High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 27: 358-363, 1998.