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COPD

High Serum Fractalkine/CX3CL1 in Patients with Chronic Obstructive Pulmonary Disease: Relationship with Emphysema Severity and Frequent Exacerbation

Wendong Hao[1,2] · Manxiang Li[1] · Cailian Zhang[2] · Yunqing Zhang[2] · Yani Xue[2]

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Abstract

Objective The purpose of this study was to investigate the relationship between serum fractalkine (CX3CL1/FKN) level and the multi-slice spiral computed tomography (MSCT) emphysema index in Chinese patients with chronic obstructive pulmonary disease (COPD).

Methods We detected chemokine CX3CL1 in serum from 95 Chinese patients with COPD by using an enzyme-linked immunosorbent assay. According to the MSCT emphysema index, the selected cases were divided into an emphysema-dominant group ($n=25$) and a non-emphysema-dominant group ($n=70$).

Results There were significant differences in body mass index and lung function between the two groups. The serum level of CX3CL1 in the emphysema-dominant group was significantly higher than that in the non-emphysema-dominant group. Through multivariate logistic regression analysis, it was found that high serum CX3CL1 levels were independently associated with emphysema, with a relative risk of 2.617 (95% CI 1.018–6.121; $P=0.029$). The percentage of frequent acute exacerbations during the first year of follow-up was significantly higher in the high-level serum CX3CL1 group ($P=0.039$). After 3 years of follow-up, there was no significant difference in the CT emphysema index between the high and low serum CX3CL1 groups ($P=0.503$).

Conclusion Our results suggest that the serum level of CX3CL1 is related to the MSCT emphysema index. Chemokine CX3CL1 might be a useful predictor for identifying frequent exacerbation and emphysema severity in patients with COPD.

Keywords CX3CL1 · Emphysema · Frequent exacerbation · CT emphysema index · Chronic obstructive pulmonary disease

Introduction

Chronic obstructive pulmonary disease (COPD) is a disease with high morbidity and mortality worldwide, which results in substantial economic burdens to society and families [1]. Accordingly, there are increasing numbers of studies on the effectiveness and reliability of potential COPD biomarkers [2–4]. Nevertheless, there is currently no universal biomarker used to assess the development and progression of COPD, mainly due to a combination of factors that lead to this disease. Currently, the pathogenesis of COPD includes oxidative stress, protease-antiprotease imbalance, and chronic inflammation. Mutations in autonomic dysfunction, nutrition, and temperature may also be involved in the occurrence and development of COPD. Chronic inflammation is considered one of the most important pathogenic factors for COPD [5].

In humans, fractalkine (CX3CL1/FKN) is a unique chemokine that is the only representative class of CX3C. It exists in both membrane-bound and soluble forms and has dual roles of adhesion and chemotaxis. After binding to its receptor (CX3CR1), CX3CL1 can participate in a variety of physiological and pathological processes of inflammatory diseases, such as primary Sjögren syndrome, atherosclerosis and cardiovascular diseases, cerebral infarction, ischemia/reperfusion injury, dermatological diseases, and lung cancer [6–10]. Several animal experiments have shown

✉ Wendong Hao
hwdokgood@hotmail.com

[1] Department of Respiratory Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an 710061, Shaanxi, People's Republic of China

[2] Department of Respiratory Medicine, The Affiliated Hospital of Yan'an University, Yan'an 716099, Shaanxi, People's Republic of China

that the expression of CX3CL1 increases in smoke-exposed mice or rat pulmonary arteries and lungs, suggesting that upregulation of CX3CL1 plays an important role in the pathogenesis of animal models of smoke-induced emphysema [11, 12]. Another study observed that the expression of CX3CL1 in the lung tissue of smokers with COPD was significantly increased compared with non-smokers with COPD, and CX3CL1 was the only chemokine that was found to be upregulated [13]. However, the aforementioned animal experiments and clinical studies were unable to distinguish whether CX3CL1 is different in the stable phase and acute exacerbation phase of COPD.

In the diagnosis of human lung disease, the lung is a relatively difficult organ to take a tissue sample from, and commonly used techniques such as bronchoscopy, bronchoalveolar lavage fluid, and percutaneous lung puncture are relatively invasive [14]. The collection of peripheral venous blood samples is the most common, simplest, and quickest method used in clinical practice. Thus, we chose this method for our research.

Quantitative computed tomography (CT) is more objective in measuring emphysema than other techniques. Previous studies showed that there is a strong correlation between quantitative chest CT emphysema and the histopathology of emphysema [15]. In large clinical studies, such as ECLIPSE, the "emphysema index" is the most commonly used indicator for diagnosis of emphysema [16]. However, after consulting a substantial amount of medical literature, no report on the relationship between CX3CL1 and the CT emphysema index was found. Therefore, the aim of this paper was to investigate the relationship between serum CX3CL1 and the CT emphysema index in Chinese patients with COPD.

Methods

Study Participants

This study was approved by the Medical Ethical Committee of the Affiliated Hospital of Yan'an University (Yan'an, Shaanxi Province, P.R. China), and informed consent was provided by the patients. All patients were diagnosed with COPD and admitted to the Department of Respiratory Medicine, Affiliated Hospital of Yan'an University, from January 2011 to December 2014.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 revised diagnostic criteria, the diagnostic inclusion criteria for this study were defined as patients with a ratio of forced expiratory volume in 1 s to forced vital capacity of less than 70% after inhalation of bronchodilators. Exclusion criteria were as follows: (1) lung cancer patients, (2) a history of chest surgery, (3) thoracic congenital malformations due to tuberculosis caused by thoracic deformity, (4) a large amount of pleural effusion, large area of lung consolidation, pleural thickening, bronchial asthma, pneumothorax, active tuberculosis, or pulmonary interstitial fibrosis, and (5) severe heart, liver, or renal insufficiency. A total of 95 patients were recruited in this study.

According to the GOLD criteria, the exacerbation of COPD is an acute onset process characterized by the worsening of respiratory symptoms in patients, such as dyspnea, pustules, and coughing, beyond daily variability and resulting in the need for changes in drug therapy. During the worsening period of COPD, patients need to be hospitalized and require treatment with antibiotics and/or glucocorticoids. Furthermore, patients who experienced two or more exacerbations during the first year of follow-up were classified as frequent exacerbators.

Measurement of CX3CL1

A total of 5 ml of peripheral blood was drawn from all subjects. The serum was centrifuged, and the supernatant was stored in a refrigerator at − 80° C for later use. The level of CX3CL1 was detected by an enzyme-linked immunosorbent assay (ELISA) purchased from Beijing Zhongxi Yuanda Science and Technology Co., Ltd. (Model SS228BEPIII. CX3CL1 Kit: Elabscience Biotechnology Co., Ltd., spec 96T, lot number: E-EL-H0044c). The serum concentration of CX3CL1 was measured using an enzyme-linked immunosorbent assay according to the human CX3CL1 kit instructions.

CT Measurements

The scanning equipment used was a Siemens 64-slice spiral CT scanner (Siemens SOMATOM Sensation 64). The scanning conditions were as follows: a tube voltage of 120 kV, a tube current of 120 mA, a detection collimator of 64 mm × 0.6 mm, a gantry rotation time of 0.5 s/r, and a pitch of 1.0. The thickness of the reconstruction layer was 1 mm; the interval between layers were 1 mm; the matrix was 512 × 512, and the CT reconstruction convolution value was B3if. Before each scan, patients were carefully trained to ensure that deep breath could be achieved during the scan. The patient was placed in a supine position, with both hands on the head, no contrast agent, and a full lung scan from the tip of the lung to the bottom of the lung at the end of a deep breath.

The CT (Siemens SOMATOM Sensation 64) scan images were processed with Pulmo software. A window position of − 600 HU and a window width of 1200 HU were examined. The software automatically sketched an outline of the lungs and manually removed the air tubes and blood vessels. A density lower than − 910 HU was defined as

the area of reduced lung density [17], and the emphysema index was calculated, that is, the percentage of low attenuation area (LAA% lung = low attenuation area/whole lung volume × 100%).

COPD Assessment Test

The COPD Assessment Test (CAT) contained a total of 8 questions [18], the core of which were 6 subjective indicators of cough, sputum, chest tightness, sleep, energy, and emotion. The 2 indicators for endurance evaluation were exercise endurance and daily exercise effects. According to their own circumstances, patients chose a corresponding score for each item (0–5), and the total CAT score range was 0–40. Patients with a score of 0–10 were rated as "slightly affected" by COPD, those with a score of 11–20 as "moderately affected," those with a score of 21–30 as "seriously affected," and those with a score of 31–40 as "very severely affected," A change of ≥ 2 points in the patient's CAT assessment test score may indicate clinically significant differences or changes.

Statistical Analysis

All data were processed using the SPSS 18.0 statistical software package (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA). The measured data were presented as the mean ± SD (median), and Student's *t* test and the Mann–Whitney *U* test (Wilcoxon rank-sum test) were used for continuous variables. Categorical variables were analyzed using Pearson Chi-square test or Fisher's exact test. Logistic regression analysis was used to examine whether independent factors, such as gender, age, BMI, pulmonary function, CX3CL1, and CT emphysema index, were related to the severity of emphysema. According to the degree of airway airflow limitation, the included cases were divided into the GOLD1–GOLD2 group, GOLD3 group, and GOLD4 group. One-way analysis of variance was used to compare the serum CX3CL1 concentrations of the three groups. Changes in the CT emphysema index over time were observed by repeated measures one-way analysis of variance. Establishment of statistical significance was based on a P value < 0.05.

Results

Clinical Characteristics

We used a CT emphysema index of 15% as the cut-off value and divided the subjects into an emphysema-dominant group (≥ 15%) and a non-emphysema-dominant group (< 15%). Surprisingly, we found that the arbitrarily determined critical value of the emphysema index was similar to the median value (16.2%).

There were significant differences in the BMI, CAT scores, pulmonary function, and CT emphysema index between the two groups. The serum CX3CL1 concentration was significantly elevated in the emphysema-dominant group. Nevertheless, there was no difference in the concentration of CX3CL1 in serum between ex-smokers and current smokers (569.2 ± 79.9 pg/ml vs 583.7 ± 86.4 pg/ml). In addition, after statistical analysis, it was found that there were also no significant differences in gender, inhaled ICS, LABA, and LAMA between the two groups (Table 1).

Risk Factors Associated with Severity of Emphysema

Multiple regression analysis showed that serum CX3CL1 concentrations ($\beta = 0.19$, $P = 0.045$) and BMI ($\beta = -1.26$, $P = 0.005$) were both significantly associated with the emphysema index. The higher the serum concentration of CX3CL1 was, the higher the CT emphysema index was ($r = 0.29$, $P < 0.001$). Through multivariate logistic regression analysis, it was found that high serum CX3CL1 levels were independently associated with emphysema, with a relative risk of 2.617 (95% CI 1.018–6.121; $P = 0.029$). Furthermore, serum CX3CL1 and BMI were also found to be independently associated with the emphysema-dominant group (Table 2).

Changes in the Emphysema Index within 3 years of Follow-up

The emphysema index of participants with high serum CX3CL1 concentrations increased slightly at a rate of approximately 0.67% per year over 3 years. Nevertheless, based on repeated measures analysis of variance (excluding 1 drop-out and 3 deaths), there were no significant differences in the changes in the emphysema index between the participants with a high serum CX3CL1 and those with a low serum CX3CL1 ($P = 0.503$) (Table 3).

Acute Exacerbations During the First Year of Follow-up

The average number of acute exacerbations was not significantly different between the high serum CX3CL1 group and the low serum CX3CL1 group ($P = 0.078$). The exacerbation rates of high- and low-level serum CX3CL1 groups also were not significantly different ($P = 0.235$). However, the percentage of frequent acute exacerbations during the first year of follow-up was significantly higher in the high-level serum CX3CL1 group ($P = 0.039$) (Table 4).

Table 1 Clinical characteristics and demographics of the study participants

Parameters	Emphysema index ≥ 15% ($n=49$)	Emphysema index < 15% ($n=46$)	*P* value
Age (years)	68.3 ± 8.7	66.5 ± 6.9	0.201
Sex (M:F)	46/3	44/2	0.989
BMI (kg/m^2)	21.8 ± 3.0	25.1 ± 2.8	< 0.001
Non-, ex-, and current smoker	3/15/31	1/17/28	0.925
Number inhaled ICS/LABA/LAMA	46/43/39	42/44/33	0.782
COPD assessment test[a]	23 ± 5	15 ± 6	0.003
Pulmonary function			
FEV$_1$ (% predicted)	42.5 ± 13.4	48.1 ± 11.8	0.004
FEV$_1$/FVC ratio (% predicted)	49.3 ± 12.5	55.8 ± 14.2	0.029
DLco (% predicted)	58.9 ± 21.1	86.5.9 ± 19.9	< 0.001
Serum CX3CL1 (pg/ml)	584.7 ± 84.3	325 ± 59.7	< 0.001
High serum CX3CL1 (*n*, %)	18 (36.7)	6 (13.0)	0.001
CT emphysema index (%)	32.5 ± 9.8	8.9 ± 4.6	< 0.001

CT computed tomography, *HU* Hounsfield units; the percentage of low attenuation area (LAA% lung = low attenuation area/whole lung volume × 100%), *FEV$_1$* forced expiratory volume in 1 s; high serum CX3CL1 was defined as ≥ 570 pg/ml, *DL$_{CO}$* carbon monoxide diffusion capacity, *ICS* inhaled corticosteroids, *LABA* long-acting β-adrenoceptor agonists, *LAMA* long-acting muscarinic antagonists

[a]The COPD assessment test (CAT) contained a total of 8 questions, the core of which were 6 subjective indicators of cough, sputum, chest tightness, sleep, energy, and emotion. The 2 indicators for endurance evaluation were exercise endurance and daily exercise effects. According to their own circumstances, patients chose a corresponding score for each item (0–5), and the total CAT score range was 0–40

Table 2 Emphysema severity-related risk factors

Parameters	Relative risk	95% CI	*P* value
Serum CX3CL1 (pg/ml)	1.048	1.005–1.104	0.027
High serum CX3CL1[a]	2.617	1.018–6.121	0.029
Ex- and current smoker	0.834	0.358–1.929	0.673
FEV$_1$/FVC ratio (% predicted)	0.996	0.934–1017	0.108
BMI (kg/m^2)	0.879	0.753–0.982	0.039

CX3CL1 is a unique chemokine that is the only representative class of CX3C. It exists in both membrane-bound and soluble forms and has the dual roles of adhesion and chemotaxis. Body mass index (BMI) = weight (kg)/height (m^2)

[a]High serum CX3CL1 was defined as ≥ 570 pg/ml, which was close to the mean serum CX3CL1 concentration in patients with severe COPD

Serum CX3CL1 Levels Associated with Airflow Limitation

The mean concentration of serum CX3CL1 was positively correlated with the severity of airflow obstruction, with more severe airflow restriction being associated with higher concentrations of serum CX3CL1 ($P < 0.001$). High serum CX3CL1 was defined as ≥ 570 pg/ml, which was very close to the mean serum CX3CL1 concentration in patients with severe COPD (Fig. 1).

Discussion

The chronic inflammation of COPD is a complex process involving many cytokines, inflammatory mediators, and immune cells such as macrophages, CD8T lymphocytes, interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α). Macrophages play an important role in the process of

Table 3 Changes in the CT emphysema index over 3 years of follow-up

	No. of patients	High CX3CL1 group	No. of patients	Low CX3CL1 group
CT emphysema index (1 year)	22	31.2 ± 8.6	69	9.1 ± 5.2
CT emphysema index (2 years)	20	32.9 ± 7.9	55	8.8 ± 4.9
CT emphysema index (3 years)	21	33.7 ± 10.2	49	7.9 ± 6.1

Changes in the emphysema index over 3 years of follow-up (excluding 1 drop-out and 3 deaths)

Table 4 Comparison of high and low levels of serum CX3CL1 in acute exacerbations of COPD patients

Parameters	Low serum CX3CL1 ($n=70$)	High serum CX3CL1 ($n=25$)	P value
Average number of acute exacerbations	0.57 ± 0.79	0.89 ± 1.01	0.078
Patients with acute exacerbations, n (%)	31 (48.6)	14 (56.0)	0.235
Frequent exacerbators[a] (≥ two/per year), n (%)	11 (15.7)	8 (32.0)	0.039

High-level CX3CL1, a level of serum CX3CL1 ≥ 570 pg/ml

[a]Frequent exacerbators, COPD patients who experienced two or more acute exacerbations per year

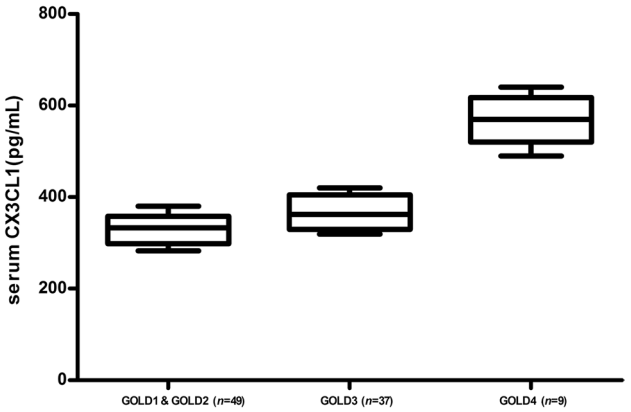

Fig. 1 Severity of airflow limitation. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades of lung function are as follows: mild (GOLD-1), moderate (GOLD-2), severe (GOLD-3), and very severe (GOLD-4)

COPD emphysema protein breakdown by releasing neutrophil elastase and matrix metalloproteinases and ultimately lead to the destruction of lung parenchyma and formation of emphysema [19]. IL-8 selectively adsorbs neutrophils, and there is a high concentration of IL-8 in the induced sputum of patients with COPD. IL-8 serum levels correlate with the number of neutrophils and match the degree of airflow limitation [20]. High levels of TNF-α are present in sputum, serum, and bronchoalveolar lavage fluid in patients with COPD, which can initiate transcription of NF-κB and subsequently switch to IL-8 gene transcription [21]. Nevertheless, there is currently no universal biomarker used to assess the development and progression of COPD. Consequently, the aim of this paper was to explore the relationship between serum chemokine CX3CL1 and the CT emphysema index in Chinese patients with COPD.

CX3CL1 is a kind of small-molecule cytokine with the dual functions of adhesion and chemotaxis that is activated by pro-inflammatory cytokines and is produced by various cells. This cytokine participates in pathophysiological processes such as inflammatory reaction, immune regulation and immunopathological response [22]. The present study showed that patients with COPD who had high levels of CX3CL1 serum concentrations more frequently showed signs of degeneration than those with low CX3CL1 serum concentrations. This study also showed that CX3CL1 serum concentrations were independently associated with the severity of emphysema. Previous animal research demonstrated that the number of T lymphocytes and macrophages expressing CX3CR1 receptors in peripheral airways and lungs of mice induced by cigarettes was significantly increased [11, 12]. A recent clinical study suggested that CX3CL1 levels in plasma and lung tissue are increased in COPD patients during acute exacerbation [23]. However, the relationship between underlying CX3CL1 and acute exacerbations of COPD has not been further explored. Our findings show for the first time that the baseline CX3CL1 level is associated with frequent exacerbations in Chinese patients with COPD.

BMI is an important indicator reflecting the nutritional status of the human body. The current study found that malnutrition affects quality of life for patients with COPD, may induce or aggravate respiratory failure and is an independent risk factor for emphysema severity in patients with COPD. This finding is consistent with those of previous studies on the relationship between BMI and the CT emphysema index in patients with COPD [24, 25].

MSCT has the characteristics of being non-invasive and reproducible, and it has been widely used in clinical practice since it is especially sensitive for the diagnosis of emphysema. Our findings suggested that the level of serum CX3CL1 increased as airflow limitation became more severe. In addition, this study found that the emphysema index was positively correlated with DLCO, indicating that the heavier the degree of emphysema is, the greater the destruction of lung structures is, which is consistent with the study of Wei et al. [26]. Previous studies have shown an increased expression of CX3CL1 in serum, macrophages, T lymphocytes, and lung tissues in animal models of emphysema and COPD patients. However, there is currently no consensus on defining the high level of CX3CL1 in COPD patients. In this study, we determined a high-level cut-off value of CX3CL1, which was very close to the average level exhibited by patients with severe COPD.

Furthermore, in this study, we tried to assess whether the CT emphysema index differed between high- and low-CX3CL1 groups. After 3 years of observation, there was no significant difference between the two groups. A cohort study of male smokers showed that patients with emphysema

progressed slowly, at less than 1% per year [27]. We believe that 3 years may be insufficient to distinguish between the two groups' changes in terms of the CT emphysema severity index. Accordingly, a longer period of follow-up is needed to assess changes in the emphysema severity index in patients with COPD.

Additionally, we divided the subjects into two groups: an emphysema-dominant group and a non-emphysema-dominant group according to a cut-off value of the CT emphysema index of > 15% (not 20%). This is inconsistent with the > 20% cut-off value of the CT emphysema index reported by Kim et al. [25]. The reason may be that the study of Kim was performed at the end of deep inspiration for CT scans, and − 950 Hounsfield units (HU) was used as the cut-off value for distinguishing between normal lung density and low-attenuation areas. However, our study used − 910 Hounsfield units (HU) as a cut-off value to discriminate between normal lung density and low-attenuation areas, and CT scanning was performed at the end of deep exhalation. A previous study found that when comparing the areas occupied by different pixel ranges with gross pathological specimens, the correlation between − 910 HU in the expiratory phase and pathological specimens was the best and superior to the inhalation phase value of − 950 HU [17].

There were some limitations in this study. First, this research was a single-center study, and the sample size of the subgroups was relatively small. Second, relatively few research indicators were included. The differences in expression of chemokine CX3CL1 in sputum, bronchoalveolar lavage fluid, serum, airway epithelial cells, and lung tissue have not been studied in depth. Our future work will explore in which specimen the expression of chemokine CX3CL1 is higher and correlates well with emphysema severity and frequent exacerbation. Third, the subjects included in this study were mostly male. Accordingly, the results should not be generalized to females with chronic obstructive pulmonary disease.

In summary, our results indicate that the serum level of CX3CR1 is related to the CT emphysema index. Chemokine CX3CL1 might be a useful predictor for identifying frequent exacerbation and emphysema severity in patients with COPD.

Compliance with Ethical Standards

Conflict of interest All authors declare no conflicts of interest.

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