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Clinical significance of serum HMGB1 in COPD and correlation with severity of airflow restriction and immune function

Weiguo Xu[1*], Junhua Wu[1], Yong Feng[2], Jing Zhu[1], Rong Cui[3]

1. Department of Respiratory Medicine, Mianyang Central Hospital, Mianyang 621000, Sichuan Province, China

2. Department of Traditional Chinese Medicine, Mianyang Central Hospital, Mianyang 621000, Sichuan Province, China

3. Department of Ultrasound Medicine, Mianyang Central Hospital, Mianyang 621000, Sichuan Province, China

Abstract

***Background**: To explore the serum HMGB1 levels in patients with smoking-induced chronic obstructive pulmonary disease (COPD) and the correlations with airflow restriction and immune function. **Methods**: A total of 136 COPD patients were divided into mild, moderate and severe + extremely severe groups. Thirty-five healthy subjects were selected as control group. Serum HMGB1 levels were measured by ELISA, and the correlations with pulmonary and immune function indices were analyzed. Receiver operating characteristic (ROC) curve was plotted. **Results**: PaO2, eosinophil count, FEV1/FVC, FEV1% pred, and IgA, IgM, IgG levels of COPD patients were lower than those of control group, and decreased with airflow restriction aggravation. PaCO2, leukocyte count, neutrophil percentage, modified British Medical Research Council (mMRC) scale and COPD Assessment Test (CAT) scores, D-Dimer (D-D), PCT, CRP and HMGB1 levels, myeloid dendritic cell (mDC) and plasmacytoid dendritic cell (pDC) counts, and mDCs/pDCs of COPD patients exceeded those of control group, and increased with airflow restriction aggravation ($P<0.05$). HMGB1 levels of COPD patients were negatively correlated with FEV1/FVC, FEV1% pred, IgA, IgM and IgG levels and positively correlated with mDC count, pDC count and mDCs/pDCs ($P<0.0001$). The area under ROC curve was 0.883, the optimal cutoff value was 3.63 ng/mL, and sensitivity and specificity were 86.7% and 85.9%, respectively. **Conclusions**: Serum HMGB1 level in patients with smoking-induced COPD rises with airflow restriction aggravation and has significant correlations with the decline of pulmonary and immune functions, with high predictive value for COPD. HMGB1 is a potential biomarker for evaluating COPD progression.*

***Keywords**: smoking; chronic obstructive pulmonary disease; airflow restriction; immune function; correlation*

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[*] **Corresponding author**: Weiguo Xu, Department of Respiratory Medicine, Mianyang Central Hospital, Mianyang 621000, Sichuan Province, China. E-mail: xuweiguomch@mail.ru

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterized by persistent respiratory symptoms and airflow restriction, which can be prevented and treated. COPD has been related to the airway and/or alveolar abnormalities caused by the significant exposure of toxic particles or gases (1). According to the World Health Organization, COPD will rank the fifth in the economic burden of diseases and the third leading cause of death in the world by 2021 (2). Acute exacerbation of COPD not only reduces the pulmonary function of patients by 25%, but also significantly accelerates the course of COPD, which ultimately leads to a decrease in patients' quality of life, an increase of hospitalization rate and mortality, and an aggravation of social and economic burdens (3). Smoking is currently recognized as the most important inducement of COPD, which can cause abnormal aggregation of a variety of inflammatory cells in the lungs, and chronic airway inflammation under the influence of proteolytic enzyme-antiproteolytic enzyme system imbalance, oxidative stress and apoptosis mechanisms (4). The high mobility group protein box 1 (HMGB1), which is widely distributed in mammalian nucleus and cytoplasm, can be widely involved in the inflammatory response of the body as an inflammatory cytokine. The latest research found that HMGB1 played an important role in the chronic airway inflammation of COPD (5). At present, there are few reports on the changes of serum HMGB1 levels in patients with smoking-induced COPD. Therefore, this study aims to explore the role and clinical significance of HMGB1 in the pathogenesis of smoking-induced COPD by detecting its serum level in patients with smoking-induced COPD and analyzing its correlation with the severity of airflow restriction and the immune function of the body to provide more reliable and effective means for the monitoring of clinical conditions.

Materials and methods

Baseline clinical data

This study was reviewed and approved by the Medical Ethics Committee of our hospital.

A total of 136 patients with COPD who were treated in our hospital from April 2016 to December 2019 were selected and divided into mild group, moderate group, and severe + extremely severe group according to the severity of airflow restriction. There were 55 cases in the mild group, including 43 males and 12 females, aged between 39 and 74 years old, (56.84 ± 6.23) years old on average; there were 42 cases in the moderate group, including 34 males and 8 females, aged between 40 and 75 years old, (57.14 ± 6.38) years old on average; there were 39 cases in the severe + extremely severe group, including 32 males and 7 females, aged between 39 and 75 years old, (56.79 ± 6.25) years old on average. Meanwhile, 35 healthy subjects were selected as the control group, including 28 males and 7 females, aged between 40 and 74 years old, (57.03 ± 6.41) years old on average. Inclusion criteria: All COPD patients meet the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease revised in 2019 (6); all patients had a history of smoking for more than 10 years; all patients did not receive steroid drugs, inflammatory mediator antagonists, and other cell membrane stabilizers 48 h before admission; the clinical medical records were complete; all of them were informed of this study and signed the consent voluntarily. The severity of airflow restriction was classified according to the FEV1% pred: mild for FEV1% pred ≥ 80%, moderate for 50% ≤FEV1% pred <80 %, severe for 30% ≤FEV1% pred <50%, and extremely severe for FEV1% pred <30% or being accompanied by chronic respiratory failure. Exclusion criteria: Complication with bronchial asthma or dilation, pulmonary tuberculosis, acute pulmonary embolism and other respiratory diseases that affect pulmonary function; complication with

heart, liver, kidney and other serious systemic diseases or malignant tumors; complication with endocrine, autoimmune diseases and systemic infectious diseases that may cause the increase of serum HMGB1; the course of patients in acute exacerbation exceeded one week before admission; patients with a history of trauma and surgery in the past 3 months; patients with mental illness or cognitive impairment who cannot cooperate in examinations.

Recording of basic indices

The patients'gender, age, course of disease, smoking history and smoking amount were recorded. Height and body mass were measured, and body mass index (BMI) was calculated.

Arterial blood gas analysis

The brachial artery blood (2 mL) was taken before oxygen inhalation, and the arterial carbon dioxide pressure ($PaCO_2$) and partial blood oxygen pressure (PaO_2) were detected using an arterial blood gas analyzer.

Detection of blood indices

Fasting venous blood (5 ml) was collected from patients before treatment and the control group in the early morning, and an appropriate amount was taken for routine blood detection. The serum levels of D-Dimer (D-D) (Wuhan Elabscience Biotechnology Co., Ltd., China; catalog No. E-EL-H0864c), C-reactive protein (CRP) (Shanghai Kanglang Biotechnology Co., Ltd., China; catalog No. KLC011.96), procalcitonin (PCT) (Shanghai Tongwei Biotechnology Co., Ltd., China; catalog No. TW14098) and HMGB1 (Wuhan Saipei Biotechnology Co., Ltd., China; catalog No. SP11733) were detected by ELISA kits according to the manufacturers' instructions.

Pulmonary function test

After admission, but prior to treatment, all subjects were tested by the same physician using the same spirometer (QUARK PFT 4 ERGO, Corshema, Italy). The forced expiratory volume in 1 second (FEV1) was recorded and the ratio of FEV1 to forced vital capacity (FEV1/FVC) and percentage of FEV1 to predicted value (FEV1% pred) were calculated.

Questionnaire investigation

Post admission, but prior to treatment , COPD patients completed the modified British Medical Research Council (mMRC) scale and the COPD Assessment Test (CAT). According to the shortness of breath, the physical activity of mMRC can be graded into 0 to 4 levels. Level 4 indicates that the patient has dyspnoea when the activity is minimal. CAT includes six subjective indices (i.e. cough, expectoration, chest distress, sleep, energy and mood) and two tolerance indices (i.e.: exercise endurance and daily exercise impact). Each item has a full score of 5 points, 40 points in total. 0-10 points: mild impact of COPD; 11-20 points: moderate impact; 21-30 points: serious impact; 31-40 points: very serious impact.

Immune function test

Fasting peripheral venous blood (5 mL) was collected from patients before treatment and the control group in the early morning. Immunoglobulin A (IgA), IgM and IgG levels were measured using Cobas c 501 biochemical analyzer (Roche, Switzerland). Flow cytometry and corresponding antibodies were used to detect myeloid dendritic cells (mDCs) and plasmacytoid dendritic cells (pDCs). The ratio of mDCs/pDCs was calculated. In detail, 300 μL of blood was taken from an anticoagulation tube and added into two 12 mm × 75 mm flow cytometry tubes. Then 20 μL of anti-BDCA composite antibody (including the antibodies against specific surface markers BDCA1, BDCA2 and CD14 and CD19 for dendritic cell subsets) was added into the test tube, and 20 μL of composite control an-

tibody (human blood dendritic cell kit purchased from Miltenyi Biotec, Germany) was added into the control tube. Afterwards, 10 μL of dead cell recognition reagent was added and mixed gently. The resulting blood sample was placed on ice and irradiated at 3~5cm away from a 60 W bulb for 10 min. After addition of 4 mL of red blood cell lysis buffer to each tube, the mixture was left still in dark for 10 min and centrifuged at 300 ×g for 5 min). After the supernatant was discarded, the cells were washed with PBS (containing 1% calf serum albumin, 0.1% sodium azide, 2% fetal bovine serum and 1% human serum), adjusted to 1×10^6/mL, fixed, stored in dark at 4°C and tested by Epics Altra flow cytometer (Beckman Coulter, USA) within 24 h. Finally, the data were analyzed by CellQuest software. The anti-BDCA1$^-$PE$^+$ cells were mDCs, and the anti-BDCA2$^-$FITC$^+$ ones were pDCs.

Statistical analysis

All data were statistically analyzed by SPSS 16.0 software. The numerical data were expressed as case (percentage, %) and subjected to the χ^2 test. The normally distributed quantitative data were represented as mean ± standard deviation ($\overline{xx}$ ± S). One-way analysis of variance was used for multigroup comparisons, and the repeated measures analysis of variance was employed for comparisons at different time points. In the case of statistical significance, intergroup comparisons at the same time point were performed by the q test, and intragroup comparisons at different time points were conducted with the paired t test. The quantitative data not conforming to normal distribution were expressed as median (interquartile range) and subjected to the Mann-Whitney U nonparametric test. Pearson's correlation analysis was conducted. The receiver operating characteristics (ROC) curve was plotted to assess the predicted value of serum HMGB1 level for COPD. P<0.05 was considered statistically significant.

Results

Clinical data

There were no statistically significant differences in the sex, age, BMI and course of disease among the subjects in the two groups (P>0.05). The increased years and amount of smoking aggravated the airflow limitation. PaO_2 and eosinophil count in COPD patients were lower than those in control group, and they declined with the aggravation of airflow limitation. However, COPD patients had higher $PaCO_2$, leukocyte count, percentage of neutrophils, mMRC score, CAT score, D-D, PCT, CRP and HMGB1 than control group, which were raised with the exacerbation of airflow limitation, and all the differences of pairwise comparisons between groups were statistically significant (P<0.05) (**Table 1**).

Pulmonary function indices

The pulmonary function indices FEV1/FVC and FEV1% pred were decreased in COPD patients compared with those in the control group, and they were lowered gradually as the degree of airflow limitation was increased, displaying statistically significant differences of pairwise comparisons between groups (P<0.05) (**Table 2**).

Immune function indices

COPD patients exhibited lower levels of IgA, IgM and IgG than the control group, which were decreased along with the exacerbation of airflow limitation. Besides, the levels of mDCs, pDCs and mDCs/pDCs ratio were elevated in COPD patients in comparison with those in the control group, which rose with the increase in the degree of airflow limitation, and there were statistically significant differences of pairwise comparisons between groups (P<0.05) (**Table 3**).

Correlations between serum HMGB1 and pulmonary function indices

The level of serum HMGB1 was significantly negatively correlated with the pulmonary

Table 1. Clinical data

Item	Control group (n=35)	Mild group (n=55)	Moderate group (n=42)	Severe + extremely severe group (n=39)	χ^2/F/Z	P
Sex (male/female, case)	28/7	43/12	34/8	32/7	0.239	0.971
Age (year,`x ± s)	57.03±6.41	56.84±6.23	57.14±6.38	56.79±6.25	0.148	0.860
BMI (kg/m^2,`x ± s)	23.06±3.83	22.16±3.75	21.92±3.73	21.61±3.74	1.125	0.294
Disease course (year,`x ± s)	-	7.39±0.86	7.45±0.91	7.48±0.93	0.473	0.592
Smoking time (year,`x ± s)	-	11.58±1.39	13.87±1.76 [b]	15.29±2.18 [bc]	6.354	0.000
Smoking amount (package year, P25, P75)	-	39(30~50)	51(40~60) [b]	66(50~80) [bc]	5.082	0.000
PaO_2 (mmHg,`x ± s)	86.15±7.29	75.38±6.17 [a]	66.52±5.08 [ab]	54.92±4.76 [abc]	9.576	0.000
$PaCO_2$ (mmHg,`x ± s)	37.42±1.56	46.79±5.85 [a]	55.68±6.47 [ab]	68.75±7.08 [abc]	7.281	0.000
Leukocytes (10^9/L, `x ± s)	6.13±1.07	8.52±1.76 [a]	9.73±2.15 [ab]	10.91±2.84 [abc]	3.118	0.002
Neutrophils (%,`x ± s)	47.28±5.14	58.43±6.02 [a]	69.35±6.86 [ab]	76.52±7.97 [abc]	8.349	0.000
Eosinophils (%,`x ± s)	5.49±0.75	2.36±0.35 [a]	1.27±0.14 [ab]	0.38±0.05 [abc]	24.765	0.000
mMRC score (point, P25, P75)	-	2.0(1.0~2.0)	3.0(2.0~4.0) [b]	4.0(2.0~4.0) [bc]	2.583	0.026
CAT score (point, `x ± s)	-	9.81±1.06	18.73±2.25 [b]	31.67±3.29 [bc]	22.690	0.000
D-D (mg/L,`x ± s)	0.09±0.03	0.42±0.11 [a]	0.91±0.18 [ab]	1.82±0.27 [abc]	17.842	0.000
PCT (μg/L,`x ± s)	0.07±0.02	1.17±0.25 [a]	2.38±0.32 [ab]	3.56±0.41 [abc]	23.926	0.000
CRP (mg/L,`x ± s)	2.15±0.34	18.36±2.07 [a]	29.25±3.18 [ab]	40.69±4.23 [abc]	31.487	0.000
HMGB1 (ng/mL,`x ± s)	1.86±0.42	3.94±1.58 [a]	5.73±2.49 [ab]	8.81±3.15 [abc]	4.593	0.000

Compared with control group, [a]P<0.05; compared with mild group, [b]P<0.05; compared with moderate group, [c]P<0.05.

Table 2. Pulmonary function indices

Item	Control group (n=35)	Mild group (n=55)	Moderate group (n=42)	Severe + extremely severe group (n=39)	F	P
FEV1/FVC (%,`x ± s)	81.06±8.23	64.72±6.51[a]	53.18±5.49 [ab]	41.24±4.05 [abc]	10.264	0.000
FEV1% pred (%,`x ± s)	113.48±12.01	87.14±7.09 [a]	64.37±6.52 [ab]	43.56±4.29 [abc]	15.831	0.000

Compared with control group, [a]P<0.05; compared with mild group, [b]P<0.05; compared with moderate group, [c]P<0.05.

Table 3. Immune function indices

Item	Control group (n=35)	Mild group (n=55)	Moderate group (n=42)	Severe + extremely severe group (n=39)	F	P
IgA (g/L,`x ± s)	3.25±0.51	2.34±0.42 [a]	1.50±0.33 [ab]	0.86±0.27 [abc]	9.651	0.000
IgM (g/L,`x ± s)	2.14±0.43	1.65±0.31 [a]	1.12±0.20 [ab]	0.69±0.13 [abc]	8.347	0.000
IgG (g/L,`x ± s)	14.38±1.62	11.47±1.18 [a]	9.23±0.94 [ab]	7.01±0.65 [abc]	10.276	0.000
mDCs (%,`x ± s)	0.05±0.02	0.12±0.05 [a]	0.36±0.17 [ab]	0.65±0.32 [abc]	6.145	0.000
pDCs (%,`x ± s)	0.02±0.01	0.08±0.03 [a]	0.15±0.06 [ab]	0.27±0.09 [abc]	7.428	0.000
mDCs/pDCs (`x ± s)	2.34±0.21	2.85±0.27 [a]	3.28±0.33 [ab]	3.65±0.38 [abc]	5.689	0.000

Compared with control group, [a]P<0.05; compared with mild group, [b]P<0.05; compared with moderate group, [c]P<0.05.

function indices FEV1/FVC ratio (r=-0.764) and FEV1% pred (r=-0.747) in COPD patients (P<0.0001) (**Figure 1**).

Correlations between serum HMGB1 and immune function indices

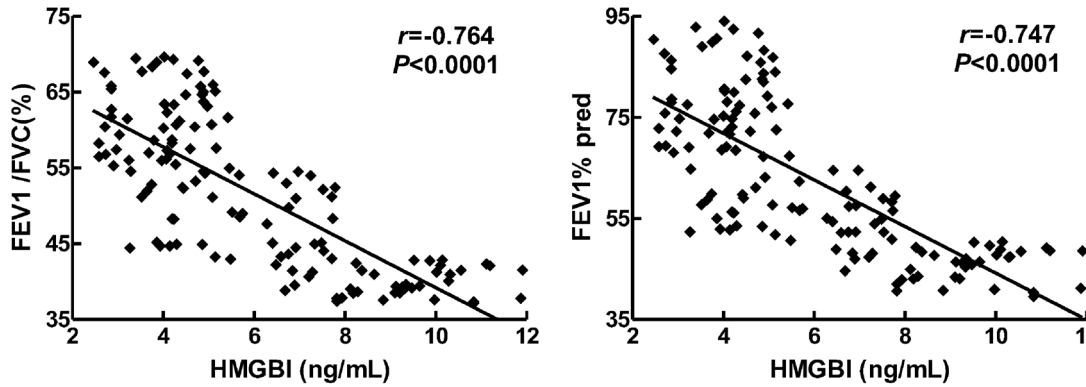
The level of serum HMGB1 had significantly negative correlations with IgA (r=-0.746), IgM (r=-0.731) and IgG (r=-0.761) (P<0.0001). Moreover, the level of serum HMGB1 was significantly positively associated with mDCs (r=0.781), pDCs (r=0.783) and mDCs/pDCs ratio (r=0.782) (P<0.0001) (**Figure 2**).

Predictive value of serum HMGB1 for COPD

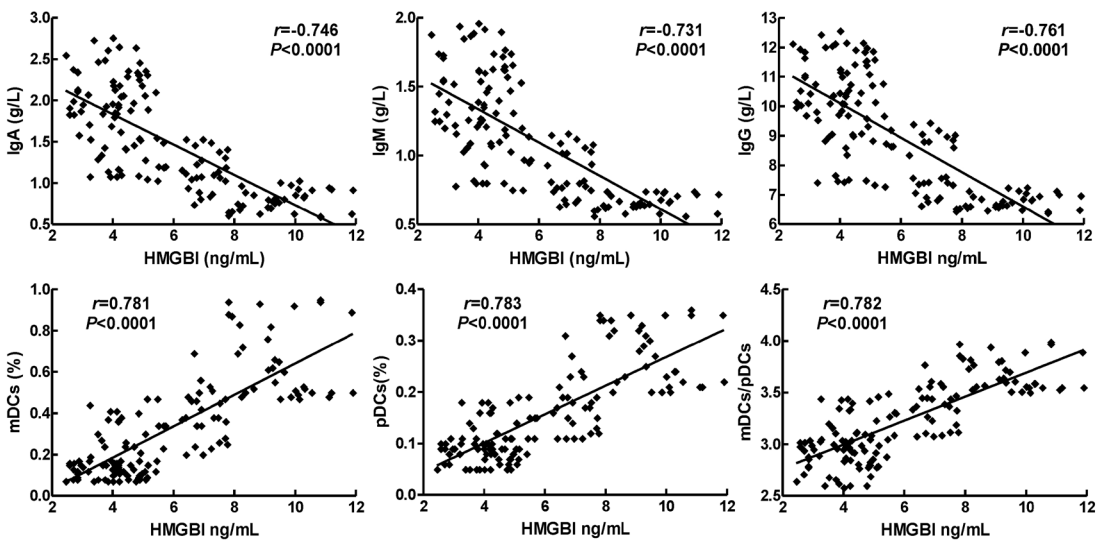
According to the analysis results of ROC curves, the area under the curve was 0.883, the optimal cut-off value was 3.63 ng/mL, the sensitivity was 86.7%, and the specificity was 85.9%, suggesting that the serum HMGB1 level has great predictive value for COPD (**Figure 3**).

Discussion

Poorly reversible and persistent airflow limitation is a prominent feature of COPD. In current clinical practices, the pulmonary function index FEV1%



Fig, 1. Correlations between serum HMGB1 and pulmonary function indices.



Fig, 2. Correlations between serum HMGB1 and immune function indices.

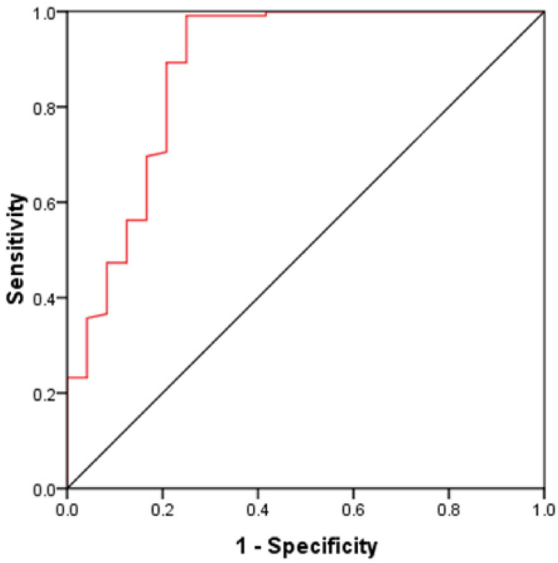


Fig. 3. Predictive value of serum HMGB1 for COPD.

pred is usually applied to judge the severity of airflow limitation, while the FEV1/FVC ratio is adopted to assess the impairment of pulmonary function of COPD patients, both of which can be used to determine the disease condition in patients. A study demonstrated that smoking is the most important risk factor for COPD, 10-15% of smokers will suffer from COPD, and at least 95% of COPD patients are smokers (7). Nie found that smoking index (amount of smoking × years of smoking) was remarkably negatively related to the pulmonary function index FEV1 (8). The above reports support the findings of this study, that is, the increased years and amount of smoking aggravated the airflow limitation. PaO_2, $PaCO_2$, leukocyte count, percentage of neutrophils, percentage of eosinophils, mMRC score, CAT score and D-D can reflect the condition of COPD in patients, and the results of the present study are consistent with numerous early literature reports (9).

The pathogeny and pathogenesis of COPD, a chronic respiratory disease with high morbidity and fatality rates and a long course, have not been completely clarified yet, but it is believed that the most crucial pathogenesis is the airway inflammation affecting the pulmonary parenchyma and even the systemic inflammatory response (10). Both PCT and CRP are commonly used inflammatory biomarkers, whose elevated levels indicate relatively serious bacterial infection or inflammatory response. According to early literature, the higher the levels of serum PCT and CRP are, the more severe the airflow limitation in COPD patients will be, suggesting that PCT and CRP can objectively reflect the pulmonary function and disease severity of patients (11). As a vital inflammatory factor in the late stage, HMGB1 is a kind of nuclear protein widely distributed in eukaryotic cells, which has fairly abundant acidic and basic amino acids in spite of a low relative molecular weight, and it is named for its high mobility in polyacrylamide gel electrophoresis. In recent years, HMGB1 has been discovered to be a type of cytokine that prominently facilitates inflammation. It activates human endothelial cells and up-regulates the expression of its adhesion molecules by activating the inflammatory cells to induce the release of massive inflammatory factors such as tumor necrosis factor-α, interleukin-1 and interleukin-8, thereby amplifying and aggravating inflammatory responses and triggering tissue injury. Meanwhile, the inflammatory factors can in turn stimulate the chemotaxis and aggregation of inflammatory cells, thus sustaining the inflammatory responses in tissues and aggravating the disease. In addition, the inflammatory factors can induce mononuclear macrophages and other immune cells to release HMGB1. Therefore, HMGB1 and multiple inflammatory factors are mutually interacted and promoted. HMGB1 is highly expressed in pulmonary inflammations such as hypersensitivity pneumonitis, acute lung injury and pulmonary fibrosis (12). HMGB1 level is raised obviously in the alveolar lavage fluid of the COPD patient (13). An experimental study on rats revealed that the expression level

of HMGB1 is also elevated distinctly in the bronchial epithelial cells of COPD rats (14). Consistent with the aforementioned reports, it was further indicated in this study that the level of serum HMGB1 had a notably negative correlation with the degree of airflow limitation in COPD patients, implying that HMGB1 is expected to be an important objective indicator for evaluating the pulmonary function and disease condition of patients.

Large quantities of studies have demonstrated that COPD patients have exacerbated disease due to recurrent infections directly because their immune function is decreased. The infiltration degree of $CD4^+$, $CD8^+$ and other T lymphocytes that participate in cellular immune responses are closely associated with the severity of COPD. As an essential link of T lymphocyte differentiation and activation, the migration and aggregation of dendritic cells (DCs) play pivotal roles in the immune responses in COPD patients (15). DCs can be classified as mDCs mainly involved in specific immune responses and pDCs primarily implicated in innate immune responses according to the differences in origin, phenotype and secreted cytokines, and the mDCs/pDCs balance is conducive to inducing the effective immune responses in the body and maintaining homeostasis. Jiang YQ et al reported that the percentages of mDCs and pDCs and the mDCs/pDCs ratio in the peripheral blood of COPD patients were increased markedly in the acute exacerbation period, and they rose continuously with the aggravation of the disease (16). pDC are an important source of type-I interferon and TNF-α during the viral infection. In relation to SARS-CoV-2 infection, in severe COVID-19 cases, the virus was reported to exert negative effects on DCs by decreasing viability and functions of DCs, especially of pDC and reduced type I and III IFNs response in infected cells, leading to improper activation of the immune response (17).

Igs are crucial players in the occurrence and development of COPD (18). It has been confirmed that the levels of such Igs as IgA, IgM and IgG are prominently lower in the stable phase and acute exacerbation period of COPD compared with those in healthy people (19). The findings of the present study were in line with the above literature reports, and it was illustrated at the same time that the level of serum HMGB1 was significantly negatively correlated with IgA, IgM and IgG, but remarkably positively related to mDCs and pDCs and mDCs/pDCs ratio in COPD patients. It was speculated that the low immune function of COPD patients may interact with and mutually affect the pro-inflammatory cytokines-induced inflammatory responses and other pathophysiological mechanisms, thus amplifying the airway, pulmonary parenchyma and even systemic inflammatory response, increasing the degree of airflow limitation and promoting the progression of COPD. Furthermore, the analysis results of ROC curves demonstrated that the serum HMGB1 level has great predictive value for COPD, and the area under the curve, optimal cut-off value, sensitivity and specificity were 0.883, 3.63 ng/mL, 86.7% and 85.9%, respectively.

In conclusion, HMGB1 level is increased in the serum of COPD patients and it rises gradually along with the aggravation of airflow limitation, which is prominently associated with the decline in pulmonary function and immune function. Therefore, HMGB1 has fairly high predictive value for COPD and is expected to become a potential biomarker for assessing COPD.

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Authors' contribution

Weiguo Xu designed this study and prepared this manuscript; Junhua Wu, Yong Feng, Jing Zhu and Rong Cui collected and analyzed clinical

data. All authors have approved the submission and publication of this manuscript.

Conflict of interest

The authors declare no conflict of interest.

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