

Clinical significance of changes in serum inflammatory factors in patients with chronic obstructive pulmonary disease and pulmonary infection

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is often accompanied by pulmonary infection, inflammatory responses, decreased immunity, and decreased lung function. The relationships among the pulmonary inflammation index (PII), lung function, and immunity in COPD patients with pulmonary infection remain unclear.

Methods: This retrospective observational study enrolled 234 participants (patients with COPD and pulmonary infection, patients with COPD without pulmonary infection, and healthy individuals) from January 2017 to December 2019.

Results: Levels of interleukin (IL)-6 were lower and levels of IL-8 were higher in patients with COPD and pulmonary infection. Levels of white blood cells (WBCs), C-reactive protein (CRP), IL-6, IL-8, tumor necrosis factor (TNF)- α and CD8⁺ cells were higher, while levels of CD3⁺ and CD4⁺ cells, the CD4⁺/CD8⁺ ratio, forced expiratory volume in 1 s (FEV1), FEV1 % predicted (FEV1%pred), and FEV1/forced vital capacity (FVC) (FEV1%FVC) were lower in patients with COPD and pulmonary infection. Levels of WBCs, CRP, IL-6, IL-8, and TNF- α were negatively associated with FEV1, FEV1%pred and FEV1%FVC.

Conclusions: Patients with COPD and pulmonary infection have high PIIs, decreased immunity, and poor lung function. PII is closely related to lung function and may represent a useful biomarker for the assessment of patients with COPD and pulmonary infection.

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Keywords

Pulmonary infection, chronic obstructive pulmonary disease, inflammatory index, immune function, lung function, biomarker

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Background

Chronic obstructive pulmonary disease (COPD) is a heterogeneous chronic inflammatory disease characterized by persistent airflow limitations that are progressively aggravated.¹ COPD imposes a large economic burden as well as high mortality and morbidity.^{2,3} COPD was the sixth most common cause of death globally in 1990 and was predicted to become the third most common by 2020.^{4,5} Decreased immune function in patients with COPD can lead to bacterial infections. Therefore, many patients with COPD develop pulmonary infections that are associated with significant inflammatory responses and hypoxia. Pulmonary infections in patients with COPD make treatment challenging and also severely impair lung function. High expression levels of inflammatory factors and diminished immune function in patients with COPD are associated with poor prognosis.^{6,7} However, there have been few reports on the relationships between inflammatory indices, lung function, and immune function in these patients. Changes in inflammatory factors in patients with COPD and pulmonary infection play an essential role in diagnosis, treatment, and prognosis determination. Analysis of correlations between inflammatory factor levels, lung function, and inflammatory indices may help in evaluating treatment of patients. In this study, we investigated levels of white blood cells (WBCs), C-reactive protein (CRP), interleukin (IL)-6, tumor necrosis factor (TNF)- α , CD3+

cells, CD4+ cells, and CD8+ cells, as well as the CD4+/CD8+ ratio, as biomarkers for diagnosis, treatment, and prognosis determination of patients with COPD and pulmonary infection. These data may provide a reference for clinicians to assess the treatment and prognosis of patients with COPD and lung infection during the early stages of disease.

Methods

Study participants

This was a single-center retrospective observational study conducted at a tertiary hospital between January 2017 and December 2019. All participants were enrolled at the Affiliated Hospital of Yangzhou University. Patients with COPD and pulmonary infection were enrolled if imaging results showed obvious pneumonia lesions. Patients with COPD but without obvious pneumonia lesions were enrolled for comparison. In addition, healthy individuals undergoing routine physical examination in our hospital were enrolled as controls. The absence of pre-existing medical conditions in healthy individuals was confirmed by taking their history. According to Anthonisen's criteria, all COPD patients were of type one and had increased difficulty breathing, increased sputum production, and purulent sputum.

Inclusion criteria were as follows: (1) diagnosis of COPD according to the diagnostic criteria for COPD in the 2017 Global

Initiative for Chronic Obstructive Lung Disease guidelines; (2) COPD consistent with lung function test results and imaging findings of pulmonary emphysema; (3) for patients with COPD and pulmonary infection, imaging results showing obvious pneumonia lesions; and (4) patient and/or family member signature of informed consent.

Exclusion criteria were as follows: (1) other pulmonary diseases (e.g., pulmonary embolism, bronchiectasis, pulmonary interstitial disease, tuberculosis, or lung neoplasm); (2) other systemic severe disease (e.g., heart failure, liver disease, or kidney disease); (3) other primary infectious or immune diseases; (4) cardiovascular and cerebrovascular diseases; (5) malignant tumors; (6) mental illness; or (7) incomplete clinical data.

This study was conducted according to the guidelines laid out in the Declaration of Helsinki. The study was approved by the Ethics Committee of the Medical Research, The Affiliated Hospital of Yangzhou University (Yangzhou, Jiangsu, China; approval number: 2017YKL-03; approval date: 1 January 2017). Written informed consent was obtained from each participant or their family before enrollment in the study and for publication of this manuscript.

Assessment of immune indices and lung function

Fasting venous blood (2 mL) was collected for detection of inflammatory factors such as WBCs, CRP, IL-6, and IL-8 the morning after admission. Levels of immune factors were quantitated by enzyme-linked immunosorbent assay (ELISA) using kits from BD Biosciences (San Jose, CA, USA) according to the manufacturer's instructions. WBC counts and CRP levels were assessed using a BC-5390 hematology analyzer (Mindray, Shenzhen, China). Levels of IL-6, IL-8 and TNF- α were quantitated using ELISA. Expression of cell surface markers was assessed by flow cytometry.

Lung function was measured using a CHESTAC-8900 pulmonary function instrument (CHEST M.I., Inc., Tokyo, Japan). Contradictions for pulmonary function examination included active hemoptysis, active pulmonary tuberculosis, pneumothorax without thoracic drainage, myocardial infarction, pulmonary embolism, hemangioma of the chest, upper abdomen, or skull, and recent eye surgery.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (IBM Corp., Armonk, NY, USA). G*Power 3.1⁸ was used to calculate the minimum sample size required for the study. Assuming a significance level for two-sided tests of $\alpha=0.05$ and a confidence interval of 95%, the minimum number of cases required was 111 when the odds ratio was 1.5. Count data were expressed as counts and percentages; differences between groups were assessed using the chi-square test. Continuous data were expressed as mean \pm standard deviation. One way analysis of variance (ANOVA) was used for comparison among three independent, normally distributed and homogeneous variables. Pearson's method was used to evaluate correlations between variables. A two-sided value of $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

A total of 234 individuals were enrolled at the Affiliated Hospital of Yangzhou University: 78 patients with COPD and pulmonary infection, 78 patients with COPD but without obvious pneumonia lesions, and 78 healthy individuals undergoing routine physical examination. No significant differences in sex, age, or smoking status

Table 1. Comparison of baseline data between the three groups.

	Patients with COPD and pulmonary infection	Patients with COPD without pulmonary infection	Healthy controls	χ^2	P
Sex					
Male	40	43	47	0.328	>0.05
Female	38	35	31		
Age (years) ^a	67.33 ± 6.11	67.74 ± 6.16	66.69 ± 6.60	0.552	0.577
Smoking					
Yes	46	43	35	2.538	>0.05
No	32	35	39		

^aMean ± standard deviation.

COPD, chronic obstructive pulmonary disease.

Table 2. Comparison of plasma inflammatory indices in the three groups.

	Patients with COPD and pulmonary infection	Patients with COPD without pulmonary infection	Healthy controls	F	P
WBC (10 ⁹ /L)	17.34 ± 4.79	13.9 ± 4.21	6.41 ± 1.73	166.87	<0.001
CRP (mg/L)	50.43 ± 11.10	40.68 ± 10.78	14.28 ± 10.12	239.32	<0.001
IL-6 (pg/mL)	17.65 ± 3.09	13.90 ± 4.21	5.76 ± 1.51	483.57	<0.001
IL-8 (pg/mL)	72.23 ± 3.74	61.52 ± 3.59	52.01 ± 3.66	593.53	<0.001
TNF- α (pg/mL)	65.22 ± 7.88	54.89 ± 673	37.71 ± 6.80	296.80	<0.001

COPD, chronic obstructive pulmonary disease; WBC, white blood cell; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.

were observed among the three groups (Table 1).

Comparison of plasma inflammatory indices

Levels of WBCs, CRP, IL-6, IL-8, and TNF- α were highest among patients with COPD and pulmonary infections (Table 2). Levels of inflammatory indexes level differed significantly among the three groups of patients as shown by Student's t-tests and chi-square tests ($P < 0.001$).

Comparison of immune indices

As shown in Table 3, levels of immune indices were significantly different among the

three groups ($P < 0.001$). Levels of CD3+ cells, levels of CD4+ cells, and the CD4+/CD8+ ratio gradually increased in the three groups. CD8+ cell levels gradually decreased in the three groups. Levels of immune indices differed significantly among the three groups according to the Student's t-test ($P < 0.001$).

Comparison of pulmonary function indicators

Table 4 shows the results of one-way ANOVA comparing lung function in the three groups. Lung function indices [forced expiratory volume in 1 s (FEV1), FEV1 % predicted (FEV1%pred) and

Table 3. Comparison of immune indices in the three groups.

	Patients with COPD and pulmonary infection	Patients with COPD without pulmonary infection	Healthy controls	F	P
CD3+ cells (%)	55.03 ± 7.06	65.5 ± 7.21	70.7 ± 7.03	99.38	<0.001
CD4+ cells (%)	23.79 ± 3.10	30.70 ± 3.30	32.61 ± 3.18	164.96	<0.001
CD8+ cells (%)	31.81 ± 4.08	29.33 ± 4.06	22.62 ± 4.36	101.25	<0.001
CD4+/CD8+ cell ratio	1.15 ± 0.43	1.46 ± 0.30	1.84 ± 0.38	65.28	<0.001

Data are shown as mean ± standard deviation.
COPD, chronic obstructive pulmonary disease.

Table 4. Comparison of pulmonary function in the three groups.

	Patients with COPD and pulmonary infection	Patients with COPD without pulmonary infection	Healthy controls	F	P
FEV1 (L)	1.22 ± 0.41	1.77 ± 0.42	3.04 ± 0.51	338.56	<0.001
FEV1%pred (%)	49.98 ± 13.41	57.68 ± 10.27	85.50 ± 10.05	215.59	<0.001
FEV1%FVC (%)	48.54 ± 14.01	57.68 ± 10.27	85.50 ± 10.05	215.19	<0.001

Data are shown as mean ± standard deviation.
FEV1, forced expiratory volume in 1 s; FEV1%pred, FEV1 % predicted; FEV1%FVC, FEV1/forced vital capacity.

FEV1/forced vital capacity (FVC) (FEV1% FVC)] were much lower in patients with COPD and pulmonary infection than in patients with COPD without pulmonary infection. Lung function indices were much lower in patients with COPD without pulmonary infection than in healthy individuals.

Correlation between inflammatory indices and lung function indicators

WBC counts were negatively correlated with FEV1 ($r = -0.792$), FEV1%pred ($r = -0.701$), and FEV1%FVC ($r = -0.732$) (all $P < 0.001$, Table 5 and Figure 1). CRP levels were negatively correlated with FEV1 ($r = -0.873$), FEV1%pred ($r = -0.705$), and FEV1/FVC ($r = -0.766$) (all $P < 0.001$, Figure 2). IL-6 levels were negatively correlated with FEV1 ($r = -0.902$), FEV1%pred ($r = -0.753$), and FEV1%FVC ($r = -0.821$)

(all $P < 0.001$, Figure 3). IL-8 levels were negatively correlated with FEV1 ($r = -0.807$), FEV1%pred ($r = -0.701$), and FEV1% FVC ($r = -0.747$) (all $P < 0.001$, Figure 4). TNF- α levels were negatively correlated with FEV1 ($r = -0.871$), FEV1%pred ($r = -0.717$), and FEV1%FVC ($r = -0.762$) (all $P < 0.001$, Figure 5).

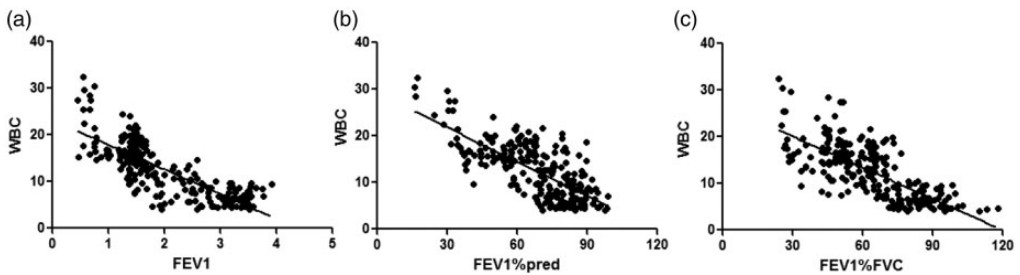
Discussion

COPD is a common chronic lung disease. COPD has a high incidence rate and mortality, seriously affects the lives and health of patients, and imposes a heavy economic burden. Smoking and inhaling harmful particles are risk factors for COPD.⁹ The pathological features of COPD include chronic inflammation of the airway, lung parenchyma, and pulmonary vessels. Inflammatory cells involved in COPD include macrophages, T lymphocytes, and neutrophils.

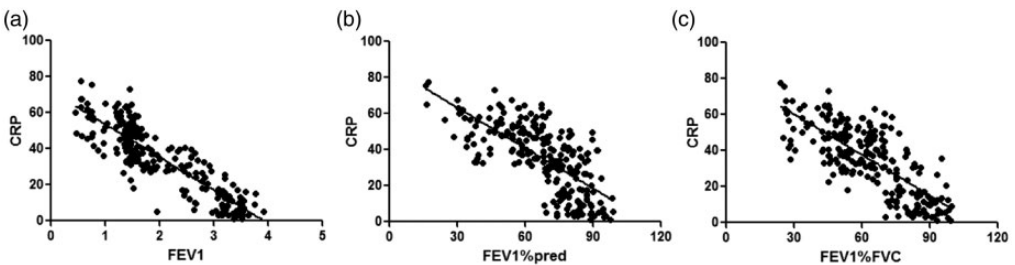
Table 5. Correlation between inflammatory cytokine levels and pulmonary function indicators.

	FEV1		FEV1%pred		FEV1%FVC	
	r	P	r	P	r	P
WBC	-0.792	<0.001	-0.701	<0.001	-0.732	<0.001
CRP	-0.873	<0.001	-0.705	<0.001	-0.766	<0.001
IL-6	-0.902	<0.001	-0.753	<0.001	-0.821	<0.001
IL-8	-0.807	<0.001	-0.701	<0.001	-0.747	<0.001
TNF- α	-0.871	<0.001	-0.717	<0.001	-0.762	<0.001

FEV1, forced expiratory volume in l s; FEV1%pred, FEV1 % predicted; FEV1%FVC, FEV1/forced vital capacity; WBC, white blood cell; CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor.

**Figure 1.** WBC counts were negatively correlated with (a) FEV1 ($r = -0.792$) (b) FEV1%pred ($r = -0.701$), and (c) FEV1%FVC ($r = -0.732$).

WBC, white blood cell; FEV1, forced expiratory volume in l s; FEV1%pred: FEV1 % predicted; FEV1%FVC: FEV1/forced vital capacity.

**Figure 2.** CRP level was negatively correlated with (a) FEV1 ($r = -0.873$) (b) FEV1%pred ($r = -0.705$), and (c) FEV1%FVC ($r = -0.766$).

CRP, C-reactive protein; FEV1, forced expiratory volume in l s; FEV1%pred: FEV1 % predicted; FEV1%FVC: FEV1/forced vital capacity.

Activated inflammatory cells release various inflammatory mediators including leukotriene B4, IL-6, IL-8, and TNF- α . Because of the long course of COPD, patients' resistance to infection can

decrease. Sputum secretion in the airways of COPD patients is increased, and sputum is difficult to discharge because of airway stenosis. Together, these factors promote pulmonary infection.

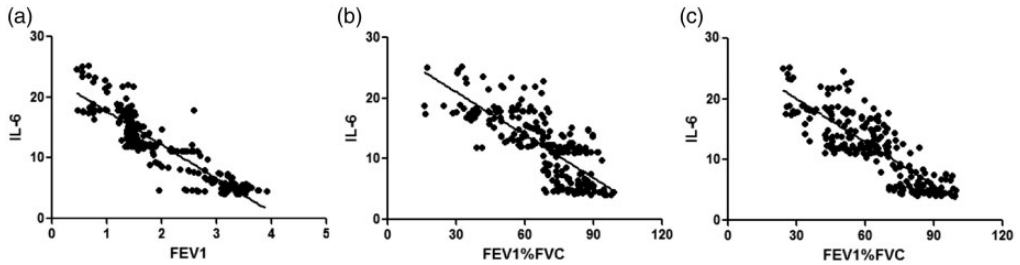


Figure 3. IL-6 level was negatively correlated with (a) FEV1 ($r = -0.902$) (b) FEV1%pred ($r = -0.753$), and (c) FEV1%FVC ($r = -0.821$).

IL, interleukin; FEV1, forced expiratory volume in 1 s; FEV1%pred: FEV1 % predicted; FEV1%FVC: FEV1/forced vital capacity.

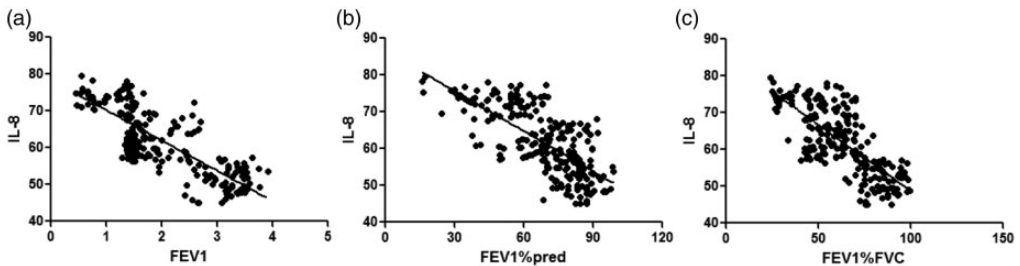


Figure 4. IL-8 level was negatively correlated with (a) FEV1 ($r = -0.807$) (b) FEV1%pred ($r = -0.701$), and (c) FEV1%FVC ($r = -0.747$).

IL, interleukin; FEV1, forced expiratory volume in 1 s; FEV1%pred: FEV1 % predicted; FEV1%FVC: FEV1/forced vital capacity.

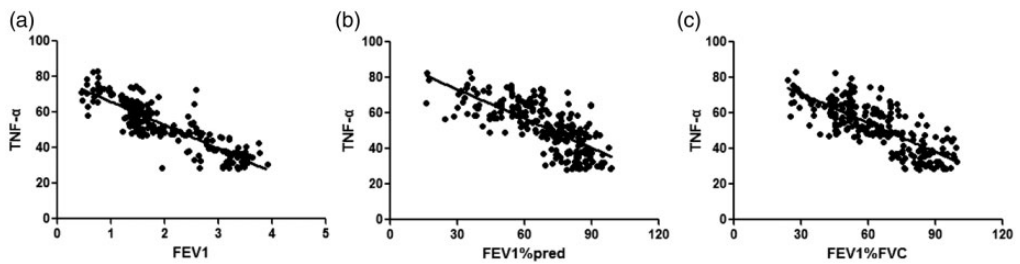


Figure 5. TNF- α level was negatively correlated with (a) FEV1 ($r = -0.871$) (b) FEV1%pred ($r = -0.717$), and (c) FEV1%FVC ($r = -0.762$).

TNF, tumor necrosis factor; FEV1, forced expiratory volume in 1 s; FEV1%pred: FEV1 % predicted; FEV1%FVC: FEV1/forced vital capacity.

Complication of COPD by pulmonary infection can further damage lung function and seriously affect prognosis.¹⁰

Levels of WBCs, CRP, IL-6, IL-8, and TNF- α levels were the highest in patients

with COPD and pulmonary infection among the three groups. These results suggested that levels of inflammatory factors in patients with COPD and pulmonary infection were higher than in the other two

groups, reflecting the severity of COPD. Pulmonary infection may directly affect lung function and the prognosis of patients with COPD. WBCs,¹¹ CRP,²¹ IL-6,¹³ IL-8¹⁴ and TNF- α ¹⁵ are associated with inflammatory cells and the alveolar epithelium in patients with COPD; these factors are closely related to the level of infection, lung function, and severity of illness. Higher levels of inflammatory indicators in the blood are associated with more severe infection and more serious lung damage.

Multiple studies have shown that lymphocyte subsets are closely related to pulmonary infection.^{16,17} Recently Su et al.¹⁸ found that lymphocyte subsets (CD4+ T cells and CD8+ T cells) in patients with coronavirus disease 2019 (COVID-19) differed significantly between mild and severe cases; the frequencies of these cells were closely related to the severity of COVID-19 pneumonia. Our results showed that CD3+ cell levels, CD4+ cell levels, and the CD4+/CD8+ ratio gradually increased in all three groups. By contrast, CD8+ cell levels progressively decreased in all three groups. These results showed that immune function in patients with COPD was significantly reduced, especially in patients with pulmonary infection. It has been reported that T lymphocyte abnormalities play a vital role in the pathogenesis of pulmonary infection.¹⁹ CD3+ cells represent all T cells, and can document total levels of cellular immunity in patients.²⁰ CD4+ cells, also known as T-helper cells, can secrete lymphokines to enhance the immune response and induce relevant immune cells to produce synergistic anti-infective effects.²¹ CD8+ cells are cytotoxic T cells and play a negative role in the immune response. These cells can inhibit the functions of CD4+ cells and B cells as well as production of antibody.^{22,23}

FEV1, FEV1%pred, and FEV1%FVC in patients with COPD and pulmonary infection were much lower than in patients

with COPD without infection. Similarly, these parameters were lower in patients with COPD compared with healthy individuals. The lung tissues of patients with COPD and pulmonary infection promote the proliferation and metaplasia of bronchial mucosa,²⁴ resulting in increased mucus secretion and sputum volume. The inflammatory reaction produces different degrees of stenosis of the bronchial lumen,²⁵ eventually leading to incomplete bronchial blockage affecting ventilation function. Repeated infection of the respiratory tract can easily damage the alveolar interstitium, making the bronchial and surrounding lung parenchyma lose supporting attachment and weakening respiratory function. Acute exacerbation and repeated pulmonary infection lead to progressive decrease of lung function in patients with COPD.²⁶ Thus, pulmonary infection can seriously reduce lung function in patients with COPD and increase the inflammatory index.

Correlation studies showed that inflammatory indices (WBCs, CRP, IL-6, IL-8, and TNF- α) were negatively correlated with FEV1, FEV1%pred, and FEV1%FVC. These results showed that PII might be associated with lung function in the three groups studied here. However, the specific mechanisms underlying the association between PII and pulmonary function need further study.

Several previous studies reported that levels of the inflammatory cytokine IL-6 increased along with increasing severity of COPD, and were correlated with decreasing quality of life and severity of hypoxia.²⁷ Huang et al. found that plasma inflammatory cytokine levels were related to the severity of airway diseases and could be potential markers for evaluation of asthma, COPD, and asthma-COPD overlap syndrome.¹⁰ Our study had the additional benefit of examining healthy persons as a control group and monitoring more diverse

inflammatory markers. These indicators are common and routinely examined in hospitals. Thus, our results have clinical significance and can help guide investigations of patients with COPD.

There were two major limitations of our study. First, it was a single-center study, and the sample size was small. Second, additional variables may be needed to better understand the role of inflammatory indices in patients with COPD and pulmonary infection.

Conclusions

The inflammatory response of patients with COPD and pulmonary infection is severe, and lung function and clinical prognosis are worse in these patients. Therefore, timely prevention and intervention strategies should be applied for patients with COPD to avoid pulmonary infection.

Authors' contributions

JZ and FW, study design and made the decision to submit the article for publication; JZ and FJ, collection, analysis, and interpretation of data; JZ and FJ, conduct of experiments; JZ, FJ and YW, writing of the paper. All authors read and approved the manuscript.

Availability of data and materials

All the data supporting the study findings is contained within the manuscript.

Declaration of conflicting interest


The authors declare that there is no conflict of interest.

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funding bodies had no role in the design of the study, the collection, analysis, and interpretation of data, or in writing the manuscript.

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