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Relationship between serum Th1/Th2 imbalance and depression in elderly patients with COPD and its clinical implications

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Abstract.
BACKGROUND: Chronic obstructive pulmonary disease (COPD) causes organic damage as well as anxiety, depression, fear, and other psychological disorders, which seriously affect the quality of life and prognosis of patients and cause a huge economic burden to the family and society.
OBJECTIVE: The aim of this study was to investigate the correlation between an imbalance of serum Th1/Th2 indicators and psychiatric depression in elderly patients with COPD and analyze its implications for clinical management.
METHODS: From January 2018 to May 2022, 120 elderly patients with COPD treated at our hospital were categorized into two groups based on the self-rating depression scale (SDS): COPD with depression (SDS score $\geqslant 50$) and COPD alone (SDS score < 50). Blood gas analysis, pulmonary function, and serum Th1/Th2 index were determined. Receiver operating characteristic (ROC) curves were analyzed to explore the diagnostic value of serum Th1/Th2 ratios for COPD complicated by depression.
RESULTS: Compared with the group without depression, the partial pressure of carbon dioxide and COPD assessment test scores were significantly higher, and the oxygenation index, forced expiratory volume in one second (FEV1), and percent predicted FEV1 were significantly lower in the COPD with depression group ($P < 0.05$). Interleukin (IL)-1β, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor-α (TNF-α) were significantly higher in the COPD with depression group than in the group without depression ($P < 0.05$). Logistic regression analysis indicated that the imbalance of serum IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α was a risk factor for mental depression in elderly patients with COPD. When comparing prognostic indices, the interval before the first onset of clinically noticeable deterioration (CID-C) in the COPD with depression group was noticeably shorter than that in the COPD without depression group; the incidence of CID-C within 6 months was noticeably higher in the COPD with depression group than in the group without depression.
CONCLUSION: Elderly patients with COPD and depression had reduced pulmonary function and higher serum Th1/Th2 levels, and an imbalance in serum Th1/Th2 indicators was a potential risk factor for depression. Moreover, elderly patients with COPD and depression were at a higher risk of disease progression and had a worse prognosis. Thus, an imbalance in serum Th1/Th2 indicators is a potential prognostic factor for evaluating depression in patients with COPD.

Keywords: Th1/Th2, imbalance, COPD, depression, prognosis

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1. Introduction

Chronic obstructive pulmonary disease (COPD) affects 8.6% of the Chinese population. The prevalence of COPD is 13.7% in individuals aged $>$ 40 years, affecting nearly 100 million people in China [1]. COPD causes organic damage as well as anxiety, depression, fear, and other psychological disorders, which seriously affect the quality of life and prognosis of patients and cause a huge economic burden to the family and society [2]. COPD diagnosis in China is increasing at an alarming rate, and psychological disorders such as depression or anxiety can complicate this condition [3]. Patients with COPD and depression have reduced treatment compliance, quality of life, and exercise capacity, leading to an elevated risk of acute exacerbation and death [4].

Helper T cells secrete cytokines, where Th1 mediates cellular immunity and Th2 mediates humoral immunity [5,6]. Th1/Th2 is in dynamic balance; pathogen invasion causes a disturbance in the Th1/Th2 ratio, leading to cellular or humoral immunity (Th1/Th2 imbalance) followed by the secretion of inhibitory cytokines [7,8]. The levels of serum Th1/Th2 cytokines (interleukin [IL]-1β, IL-2, IL-6, IL-8, IL-10, and tumor necrosis factor [TNF]-α) have been shown to be noticeably elevated in patients with COPD [9,10]. Additionally, patients with depression display noticeably higher levels of inflammatory cytokines than healthy controls [11]. To survey the effect of serum Th1/Th2 cytokines on pulmonary function and depressive symptoms in patients with COPD, a large-scale prospective cohort study found that inflammatory cytokines may mediate the occurrence of depressive symptoms and the decrease in pulmonary function in patients with COPD, and that depressive complications may affect the quality of life, disease progression, and prognosis of patients with COPD [12–14].

Psychological questionnaires are widely used to evaluate depressive symptoms. However, some respiratory symptoms in elderly patients with COPD often overlap with depressive symptoms on psychological questionnaires. In addition, elderly patients with COPD have varying degrees of hearing and comprehension loss; therefore, completing a psychological questionnaire may be difficult for these patients. Nevertheless, combined with serological indicators for diagnosis, psychological questionnaires are conducive to early diagnosis of COPD complicated by depression and greatly improve clinical efficiency [15].

Systemic inflammation caused by COPD can lead to elevated levels of systemic inflammatory markers, resulting in an imbalance in serum Th1/Th2 indicators [16]. Serum Th1/Th2 indicators are also noticeably elevated in the serum of patients with clinical and subclinical depression [17,18]. The serum Th1/Th2 ratio may be involved in the pathogenesis of depression through elevated cytokine levels, thereby reducing the synthesis of 5-hydroxytryptamine, which is an important mechanism of depression [19]. This pathway produces neurotoxic metabolites that can lead to depression [19]. In addition, inflammatory cytokines persist for a long time, leading to hyperactivity of the hypothalamus-pituitary-adrenal axis and glucocorticoid resistance [20]. The inflammatory cytokines IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α are important in the pathogenesis of depression complicated by COPD. Serum levels of IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α are closely associated with COPD and depression and may have diagnostic value in COPD complicated by depression [21,22]. However, there are few studies on the correlation between serum Th1/Th2 imbalance and depression in elderly patients with COPD, and the relationship between them is not clear. Further research is needed to provide guidance for the prevention and treatment of COPD complicated by depression. Therefore, this study examined the association between an imbalance in serum Th1/Th2 indices and depression in elderly patients with COPD and evaluated its implications for clinical management.

2. Materials and methods

2.1. General information

From January 2018 to May 2022, 120 elderly patients with COPD treated at our hospital were classified into two groups based on the self-rating depression scale (SDS): COPD with depression (SDS $\geqslant$ 50) and COPD without depression (SDS $<$ 50). Patients in the COPD with depression group ($n = 55$) were aged 66–80 years, with a mean age of 74.14 $\pm$ 2.31 years. Among them, 33 were men and 22 were women. Body mass index (BMI) was 20.85–26.39 kg/m^2 (mean = 23.15 $\pm$ 2.12 kg/m^2). The patients' smoking history ranged from 23 to 34 years, with a mean of 27.59 $\pm$ 3.93 years; duration of disease ranged from 2 to 10 years, with a mean of 4.77 $\pm$ 0.86 years; and years of education ranged from 6 to 16 years, with a mean of 8.87 $\pm$ 1.24 years. All patients provided written informed consent before participating in this study. The study was approved by the Medical Ethics Association of our hospital.

The 46 men and 19 women in the COPD without depression group ($n = 65$) were between 64 and 81 years old (mean = 75.63 $\pm$ 2.5 years). BMI ranged from 20.75 to 26.33 kg/m^2 with a mean of 23.81 $\pm$ 2.43 kg/m^2; patients had a smoking history of 22–36 years with a mean of 27.62 $\pm$ 3.12 years. The duration of disease ranged from 1 to 9 years with a mean of 4.72 $\pm$ 0.82 years, and years of education ranged from 6 to 16 years, with a mean of 8.87 $\pm$ 1.24 years. With regards to their general demographic data, the differences between the two groups were not statistically significant ($P > 0.05$).

The inclusion criteria were: (1) a clear diagnosis of COPD that met the diagnostic criteria of the Global COPD Initiative (GOLD) guidelines version 2017 [23]; (2) age $>$ 60 years, with normal cognitive function and absence of communication barriers; and (3) the reimbursement ratio of patients was fixed according to the payment method. The SDS, which contains 20 items, was used to assess depressive symptoms in all patients with COPD [24]. Patients with an SDS score $\geqslant$ 50 were categorized into the COPD with depression group, whereas those with an SDS score $<$ 50 were assigned to the COPD without depression group.

The exclusion criteria were: (1) massive pleural effusion, pneumothorax, and the inability to tolerate a 6 min walking distance or lung function test; (2) mental and psychological disorders such as anxiety and depression diagnosed before the diagnosis of COPD; (3) severe hepatorenal insufficiency, severe cardiovascular disease, neuromuscular disease, cerebral infarction, sequelae of cerebral hemorrhage, or solid or hematological tumors; (4) other chronic respiratory diseases such as active tuberculosis, pulmonary embolism, and chronic thrombotic pulmonary hypertension; and (5) Alzheimer's disease, language communication disorder, and limb movement disorder.

2.2. Observation index

2.2.1. COPD assessment test (CAT) score

The CAT score was used to evaluate the impact of COPD on the patient's health and quality of life and included eight questions [25]. The CAT score ranged from 0–40 points: 0–10 was considered "mildly affected," and 11–20 points and 21–30 points were defined as "very serious impact." The CAT score was calculated on the first day after admission.

2.2.2. Prognostic evaluation index

The prognosis of patients was evaluated using modified clinically noticeable deterioration (CID-

C), specifically by detecting lung function, health status, and early deterioration to evaluate disease deterioration and prognosis [26]. The criteria for CID-C included at least one of the following: (1) after the use of bronchodilators, forced expiratory volume in one second (FEV1) decreased by more than 100 mL compared with baseline; (2) the CAT score was elevated by more than two points compared with baseline; and (3) moderate or severe exacerbations. The patients were followed-up by telephone at 1, 3, and 6 months after discharge, and the interval before the first occurrence of CID-C and the frequency of CID-C occurrence within 6 months was collected.

2.2.3. Serum Th1/Th2 index detection

Within 24 h of admission, 5 mL of venous blood was collected from patients on an empty stomach and centrifuged at 3000 RPM for 10 min. The supernatant was stored in the refrigerator at -80°C. Serum levels of Th1/Th2-related cytokines (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) were measured using an enzyme-linked immunosorbent assay (Jiangsu Kete Biotechnology Co., Ltd.).

2.2.4. Arterial blood gas analysis

For arterial blood analyses, 2 mL of arterial blood was collected immediately on the first day after admission. Arterial blood gas analysis was performed using a blood gas analyzer. The partial pressure of oxygen (PO_2), partial pressure of carbon dioxide (PCO_2), and fractional inspired oxygen (FiO_2) were recorded, and the oxygenation index (OI) was calculated ($OI = PO_2/FiO_2 \times 100\%$) [27].

2.2.5. Pulmonary function test

Pulmonary function tests were performed during the stable phase of COPD (approximately three months). For the test, patients inhaled 400 μg of aerosol salbutamol; fifteen minutes later, pulmonary function tests were performed. FEV1 and percent predicted FEV1 (FEV1%pred) were recorded.

2.3. Statistical analysis

Excel was used for data management, and data were analyzed and processed using SPSS 24.0 statistical software. Data with normal distribution and uniform variance are expressed as mean $\pm$ standard deviation, and independent sample t-tests were used for comparison between groups. Discrete and categorical data are expressed as number and frequency or rate (n [%]), and χ^2 tests were used for analysis. Pearson's correlation was conducted to examine the relationship between serum Th1/Th2 imbalance and depression in elderly patients with COPD. Logistic regression analysis was performed to analyze risk factors for depression, and receiver operating characteristic (ROC) curve analysis was performed to determine risk factors and joint predictors of depression in elderly patients with COPD. Sensitivity and specificity were calculated, and the diagnostic value of each index was evaluated. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Comparison of clinical indices

In terms of clinical indicators, compared with the group without depression, the PCO_2 and CAT scores were significantly higher, and the OI, FEV1, and FEV1%pred were significantly lower, in the COPD with depression group ($P < 0.05$), as shown in Table 1.

Table 1
Comparison of clinical information

Group	N	PCO2 (mmHg)	OI (mmHg)	FEV1 (L)	FEV1%pred (%)	CAT scoring
COPD without depression group	65	45.19 ± 5.92	227.94 ± 22.95	1.22 ± 0.46	61.84 ± 4.91	23.81 ± 2.91
COPD with depression group	55	49.68 ± 3.91	213.69 ± 23.85	1.01 ± 0.11	50.29 ± 5.91	27.49 ± 5.91
t		4.805	3.328	3.304	11.694	4.427
P		< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Table 2
Comparison of serum Th1/Th2 indicators

Group	N	IL-1β	IL-2	IL-6	IL-8	IL-10	TNF-α
COPD without depression group	65	21.58 ± 5.95	22.81 ± 8.29	9.28 ± 2.91	1.49 ± 0.28	98.58 ± 23.84	18.29 ± 4.91
COPD with depression group	55	28.49 ± 8.29	29.48 ± 5.93	12.81 ± 5.95	1.69 ± 0.22	129.49 ± 22.91	21.58 ± 5.81
t		5.299	4.983	4.225	4.292	7.204	3.362
P		< 0.01	< 0.01	< 0.01	< 0.01	< 0.01	< 0.01

Table 3
Logistic regression analysis of risk factors for mental depression in elderly patients with COPD

Group	β	S.E	Chi-square value	P	OR	95% CI for OR
IL-1β	1.484	0.312	22.623	< 0.01	4.411	2.393–8.130
IL-2	1.434	0.358	16.045	< 0.01	4.195	2.080–8.463
IL-6	2.333	1.052	4.918	0.027	10.309	1.311–21.038
IL-8	0.934	0.316	8.736	0.003	2.545	1.370–4.727
IL-10	2.313	0.920	6.321	0.012	10.105	1.665–21.326
TNF-α	0.982	0.224	19.219	< 0.01	2.67	1.721–4.141

3.2. Comparison of serum Th1/Th2 indices

As shown in Table 2, IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α levels were significantly higher in the COPD with depression group than in the COPD without depression group ($P < 0.05$).

3.3. Logistic regression analysis of risk factors for depression in elderly patients with COPD

As shown in Table 3, logistic regression analysis indicated that an imbalance in serum Th1/Th2 indicators (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) was a risk factor for mental depression in elderly patients with COPD ($P < 0.05$).

3.4. The value of serum Th1/Th2 indices in the diagnosis of depression in elderly patients with COPD

Serum Th1/Th2 indices (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) were analyzed using ROC curves; the critical value was determined by the tangent point of the maximum value of the Jordan index, and sensitivity and specificity were calculated. The area under the curve (AUC) for serum IL-1β was 0.791, with a sensitivity of 62.5% and specificity of 82.5%. The AUC for serum IL-2 was 0.827, sensitivity was 81.2%, and specificity was 70.0%. The AUC for serum IL-6 was 0.889, and the sensitivity and specificity were 84.3% and 80.0%, respectively. The AUC for serum IL-8 was 0.789, sensitivity was 62.5%, and specificity was 82.5%. The AUC for serum IL-10 was 0.821, with a sensitivity of 81.2% and a specificity of 67.5%. The AUC for serum TNF-α was 0.895, and the sensitivity and specificity were 93.7% and

Table 4
Diagnosis value of depression in elderly patients with COPD

Variables	Cut-off value	Sensitivity	Specificity	Accuracy rate	Positive predictive value	Negative predictive value	Youden index
IL-1β	1.115	0.625	0.825	0.736	0.740	0.733	0.450
IL-2	1.224	0.812	0.7	0.750	0.684	0.823	0.512
IL-6	1.420	0.843	0.8	0.819	0.771	0.846	0.643
IL-8	1.112	0.625	0.825	0.736	0.740	0.733	0.450
IL-10	1.263	0.812	0.675	0.736	0.666	0.818	0.487
TNF-α	1.728	0.937	0.7	0.805	0.714	0.933	0.637
Union	1.830	0.968	0.750	0.842	0.756	0.967	0.718

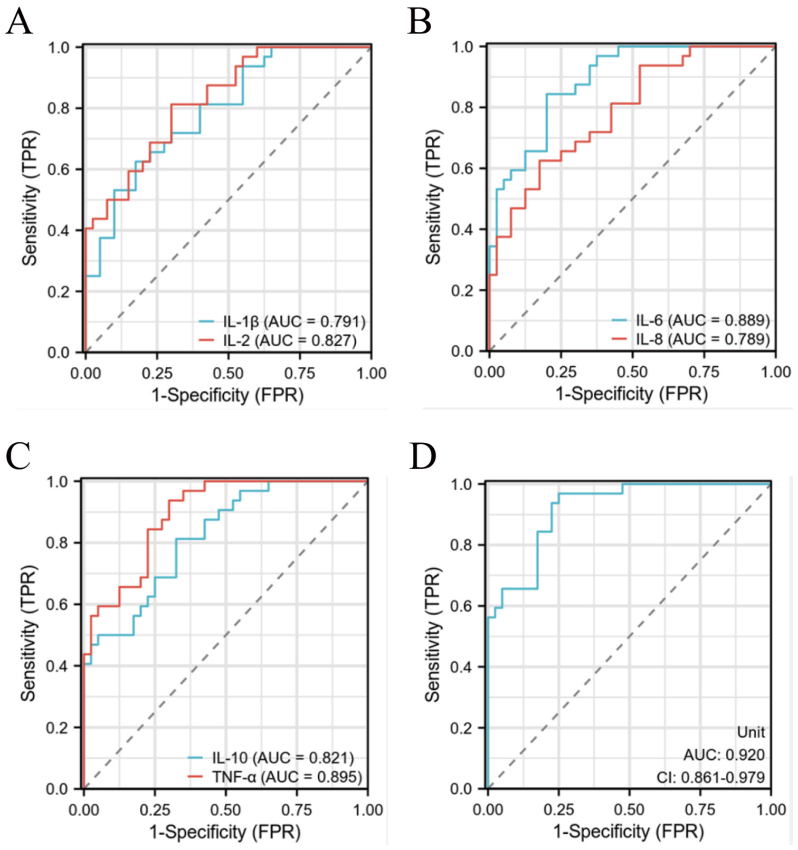

Fig. 1. The ROC curves for the diagnosis of depression in patients with COPD. (A) IL-1β and IL-2. (B) IL-6 and IL-8. (C) IL-10 and TNF- α. (D) Combination.

70.0%, respectively. The combined AUC was 0.920, sensitivity was 96.8%, and specificity was 75.0%. The results of the ROC curve analysis showed that joint diagnosis had the largest AUC and the highest diagnostic value for depression in patients with COPD ($P < 0.05$) (Fig. 1 and Table 4).

3.5. Comparison of prognostic indices

One, three, and six months after discharge, telephone calls were made to follow-up with patients. The interval before the first occurrence of CID-C and the frequency of CID-C within six months after

Table 5
Comparison of prognostic index

Group	N	Number of days between the first occurrence of CID-C (d)	Number of CID-C occurrences in 6 months (times)
COPD without depression group	65	85.59 ± 5.91	2.01 ± 0.11
COPD with depression group	55	63.18 ± 5.91	2.46 ± 0.33
t		20.696	10.342
P		< 0.01	< 0.01

Table 6
Correlation between serum Th1/Th2 and the prognosis of elder COPD with depression

Variables		Number of days between the first occurrence of CID-C	Number of CID-C occurrences in 6 months
IL-1β	r	-0.812	0.648
	P	< 0.01	< 0.01
IL-2	r	-0.744	0.872
	P	< 0.01	< 0.01
IL-6	r	-0.546	0.693
	P	< 0.01	< 0.01
IL-8	r	-0.853	0.722
	P	< 0.01	< 0.01
IL-10	r	-0.789	0.783
	P	< 0.01	< 0.01
TNF-α	r	-0.873	0.692
	P	< 0.01	< 0.01

discharge were recorded, and these prognostic indices were compared between the two groups. The interval before the first onset of CID-C in the COPD with depression group was noticeably shorter than that in the group without depression. The incidence of CID-C within 6 months in the COPD with depression group was noticeably higher than in the group without depression ($P < 0.05$) (Table 5).

3.6. The relationship between serum Th1/Th2 indices and the prognosis of COPD complicated with depression

Pearson correlation analysis indicated that serum Th1/Th2 indicators (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) in patients with COPD and depression was negatively correlated with the interval before the first occurrence of CID-C and positively correlated with the number of CID-C occurrences within 6 months ($P < 0.05$) (Table 6).

4. Discussion

COPD is characterized by chronic inflammation that occurs in the peripheral airways and pulmonary parenchyma. Various cytokines are released during the progression of inflammation, and the concentration of serum inflammatory cytokines, including IL-6, C-reactive protein (CRP), and TNF-α, in patients with COPD is noticeably elevated [28]. These inflammatory cytokines are also elevated in the sera of patients with depression, suggesting that they may be closely associated with depression. A systematic review of longitudinal studies investigated whether an increase in inflammatory cytokines indicated an elevated risk of subsequent depressive symptoms and found that patients with an imbalance of serum Th1/Th2 indicators have a noticeably elevated risk of subsequent depressive symptoms [29]. Systemic inflammation

mediated by these inflammatory cytokines is involved in the pathogenesis of COPD and depression and thus may bring about the close relationship between COPD, depression, and inflammatory cytokines. Cytokines also play an important role in the pathological mechanisms of depression. Cytokine therapy can induce depressive symptoms and increase the incidence of depression [30,31]. When exogenous cytokines such as interferon-α are administered, proinflammatory cytokines are activated, resulting in changes in neurotransmission and endocrine pathways and neurotoxicity [32]. An increasing number of studies have revealed the important role of serum Th1/Th2 imbalance in the pathogenesis of depression. Moreover, serum Th1/Th2 cytokines, such as IL-6, are involved in the pathogenesis of COPD through various signaling pathways, including those involved in chronic airway inflammation and airway remodeling. IL-6 is involved in depression through multiple mechanisms and the pro-inflammatory cytokine IL-6 may induce the activation of indoleamine 2-dioxygenase (IDO) [33]. IDO is a key enzyme in the tryptophan pathway that can reduce tryptophan availability and produce oxygen free radicals and highly potent neurotoxins, leading to changes in the function of the central nervous system. Tryptophan is a precursor of serotonin, a key neurotransmitter mediating depression; systemic inflammation can lead to pathologically low serotonin levels, leading to depression [34]. Moreover, IL-6 and other cytokines stimulate microglia, triggering the release of oxygen free radicals that amplify cytokine production and activate a strong immune response, resulting in neuronal damage and death [35]. Elevated cytokine levels in patients with COPD have been suggested to activate microglia, which can cause intracellular inflammatory signaling. Depression is further exacerbated by the presence of long-term inflammatory factors that overactivate the HPA axis, resulting in glucocorticoid resistance.

In cases of infection or stress, changes in cytokine levels reflect the inflammatory state of the body to a certain extent. During infection, the balance between pro-inflammatory and anti-inflammatory factors is disrupted, alternating between the two, which noticeably affects the development, direction, and outcome of the infection. Helper T lymphocytes secrete various cytokines, assist cytotoxic T cells and B lymphocytes, and play an active role in immune responses [36]. At present, they are mainly divided into four subtypes, Th0, Th1, Th2, and Th3, according to the types of cytokines secreted. Among these, Th1 cells are involved in stimulating the cellular immune response, promoting proinflammatory responses, whereas Th2 cells are involved in mediating the humoral immune response promoting anti-inflammatory responses [37]. The imbalances in Th1/Th2 and the secretion of related cytokines has been shown to lead to immune inflammatory damage [38]. The secretion of Th2 cytokines is noticeably elevated in pulmonary diseases, and the dominant response is Th2, indicating that immune function is suppressed and the ability to eliminate pathogens is decreased. Th1 cells are involved in mediating the cellular immune response by inhibiting, lysing, and destroying killer cells through the secretion of TNF-α, IFN-γ, and IL-2 to promote the clearance of intracellular pathogens, which then further induces a delayed hypersensitivity response [39].

During the inflammatory response, TNF-α is secreted first. It can activate the production of secondary inflammatory mediators like IL-6 and IL-1β under the stimulation of various inflammatory factors, and further promote the transmission of T cell signals to initiate inflammatory responses. Although the release of TNF-α can initiate the inflammatory cascade reaction, its high levels cause an imbalance in the entire inflammatory process, further promoting an imbalance in the inflammatory response, resulting in local and even organ tissue inflammatory damage [40]. High levels of TNF-α can reflect the physiological and pathological state of COPD and help evaluate the condition and severity of COPD at different stages [41].

As an important cell growth factor, IL-2 promotes the activation and proliferation of T cells, promotes the lethality of T cells, and improves immune responses, such as natural killer cell activity and antibody secretion by B cells. Studies have shown that patients with low cellular immune function complicated by COPD can be treated with recombinant IL-2 or genetically cloned IL-2.

Th2 cells participate in the humoral immune response mainly by secreting IL-4, IL-6, IL-10, and other cytokines to produce corresponding antibodies [42,43]. The upregulation of IL-4 expression in patients with pulmonary disease can reflect the extent of the local inflammatory response and the rate of inflammatory development, and thus may be involved in the occurrence and progression of pulmonary diseases. It is possible that IL-6 is produced first upon infection and inflammation, with its levels increasing rapidly in a short period (approximately 1–2 hours). IL-6 can enhance the function of natural killer cell lysis and promote the regulation of inflammatory responses. It is a sensitive index for the early diagnosis of acute infections and is more sensitive than PCT and CRP [44]. Moreover, an increase in IL-6 levels is associated with the severity of infection and can be used to evaluate the severity and prognosis of infection. In addition to its multifunctional negative regulatory role, IL-10 is one of the primary anti-inflammatory factors in the body. It can participate in the biological regulation of immune, inflammatory, tumor, and other cells and block the molecular pathway of Th1/Th2 to produce TNF-α, interferon, and other factors [45]. IL-10 is a potent anti-inflammatory factor that protects the body from tissue damage caused by excessive inflammation. IL-10 plays an important role in many diseases, such as infectious diseases, autoimmune diseases, transplant immunity, COPD, and various tumors [46–48]. Studies have shown that IL-6 and IL-10 levels are closely associated with COPD severity. Therefore, improving the management of patients' inflammatory factor levels will facilitate the diagnosis and treatment of the disease and the assessment of prognosis [49–51].

The comparison of clinical indicators revealed that the PCO_2 and CAT scores of the COPD with depression group were higher, and the OI, FEV1, and FEV1%pred were lower, than those of the group without depression. Compared with the serum Th1/Th2 index, the levels of IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α in patients with COPD and depression were noticeably higher than those in patients with COPD alone. This study found that patients with COPD complicated by depression had more severe symptoms and worse blood gas analysis and pulmonary function indices than patients without depression, suggesting that COPD with depression may have an impact on the treatment, disease activity, progression, and prognosis of patients with COPD. Logistic regression analysis indicated that the imbalance of serum Th1/Th2 indicators (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) was a risk factor for mental depression in elderly patients with COPD. A trained machine-learning model was used by Stokes et al. for pneumonia and bronchitis diagnosis and referral, and they achieved an AUC of 93% [52]. The ROC curve results of our study indicated that the combined diagnosis of serum Th1/Th2 indicators had the highest diagnostic value for COPD complicated with depression. Thus, the serum Th1/Th2 indicators were important in the pathogenesis of COPD complicated by depression. The serum Th1/Th2 index was closely related to COPD and depression and may have potential diagnostic value for COPD complicated by depression. The interval before the first occurrence of CID-C in the COPD with depression group was noticeably shorter than that in the group without depression. Within six months, the incidence of CID-C in the COPD group with depression was higher than that in the group without depression. Pearson correlation analysis indicated that serum Th1/Th2 indicators (IL-1β, IL-2, IL-6, IL-8, IL-10, and TNF-α) in patients with COPD and depression were negatively correlated with the interval before the first occurrence of CID-C and were positively correlated with the number of occurrences of CID-C within 6 months. Thus, serum Th1/Th2 indicators may have prognostic value for patients with COPD and depression.

This study has several limitations. This is a retrospective study, with certain associated risks of bias. The sample size was small and subsequent larger multicenter clinical studies are warranted. Moreover, the clinical follow-up time was short, and long-term clinical follow-ups should be conducted. With the ongoing exploration of the relationship between serum Th1/Th2 imbalance and depression in elderly patients with COPD, a research direction of interest is to develop an artificial intelligence tool to assist in

the diagnosis of depression in elderly patients with COPD. A telemetry system was developed to diagnose asthma and COPD [53], and other studies have investigated the use of various artificial intelligence systems and machine learning models in the diagnosis of various diseases [52,54–58]. We anticipate that an artificial intelligence tool could assist patients with better self-management and enable physicians to rapidly diagnose depression in elderly patients with COPD, monitor patient health status, and potentially provide appropriate professional care or treatment.

5. Conclusion

Elderly patients with COPD and depression had reduced pulmonary function and higher serum Th1/Th2 levels; moreover, serum Th1/Th2 imbalance was a potential risk factor for depression in elderly patients with COPD. Elderly patients with COPD and depression were at a higher risk of disease progression and had a worse prognosis. Thus, an imbalance in serum Th1/Th2 indicators may have prognostic potential for evaluating depression in patients with COPD.

Conflict of interest

None to report.

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