Int J Clin Exp Med 2020;13(11):8250-8258
www.ijcem.com /ISSN:1940-5901/IJCEM0107236

Review Article

miR-126 and miR-21 for prognosis and risk analysis evaluation of patients with asthma

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Received January 1, 2020; Accepted March 18, 2020; Epub November 15, 2020; Published November 30, 2020

Abstract: Objective: To explore the efficacy of using miR-126 and miR-21 levels for determining the prognosis and risk analysis of patients with asthma. Methods: A total of 115 patients diagnosed with asthma in the Department of Respiration of Linyi people's Hospital from May 2015 to May 2018 were enrolled in the study group, and were divided into study group A and study group B in accordance with the severity of the disease. A total of 45 healthy volunteers who underwent physical examination in Linyi people's Hospital during the same period were set as the control group. The expression of miR-126 and miR-21 in three groups of patients were detected. Lung function indices of patients with asthma of different severities were compared and the correlation with the expression of miR-126 and miR-21 were analyzed. The prognosis of patients with asthma of different severities was recorded in follow-up, and ROC curve of prognostic factors, miR-126, miR-21 and the combination for treating asthma patients were studied. Results: miR-126 and miR-21 expression in the study group was notably higher than that in the control group, and miR-126 and miR-21 expression of study group A was notably higher than study group B ($P<0.05$). FEV1/FVC, MMEF and PEF in study group B were higher than those in study group A ($P<0.05$). Pearson correlation analysis revealed that the miR-126 and miR-21 expression level was negatively correlated with the ratio of FEV1/FVC, MMEF and PEF, respectively ($P<0.001$). The number of acute attacks, mean length of hospital stay and mean number of hospital visits in group B were higher than those in group A ($P<0.05$). The results of Logistic regression analysis displayed that the family history of asthma, the increase of miR-126 and miR-21 were independent risk factors for the prognosis of asthma patients ($P<0.05$). ROC curve analysis showed that the area under the curve (AUC) of miR-126 was 0.784 (95% CI: 0.723-0.846), the AUC of miR-21 was 0.853 (95% CI: 0.804-0.902), and the AUC of the two combined was 0.894 (95% CI: 0.853-0.934). Conclusion: The serum levels of miR-126 and miR-21 in patients with asthma are valuable in evaluating lung function and disease diagnosis, and are independent risk factors for prognosis.

Keywords: miR-126, miR-21, asthma, prognosis, risk analysis

Introduction

Bronchial asthma is a type of chronic airway inflammation in which cellular subsets of T lymphocytes, eosinophils and mast cells are involved [1]. It possesses the nature of an allergen disease induced by disorders of the immune system in the body [2]. The incidence of bronchial asthma increases annually, among which the development of severe asthma is a key cause of disability and death from asthma [3]. However, there is no clear standard for the definition of reference for the pathogenesis of severe asthma. High responsiveness of airway inflammation leading to lung function damage is considered as one of the pivotal mechanisms to promote the deterioration of the disease, and many factors such as genetics and environment can have an impact on it, with enhanced mutual effects [4]. However, mycoplasma pneumoniae, as one of the common pathogens of respiratory tract infection, can form a wide variety of diseases inside and outside the lungs at the onset of infection [5]. Currently, there have been great advances in asthma prevention and treatment. In clinical practice, asthma is mainly treated with anti-inflammatory therapy, supplemented by symptomatic treatment for the corresponding clinical symptoms, but no effective radical treatment has been achieved. On the

basis of protecting the normal lung function, it can only control the progress of the disease, and attempts to avoid the occurrence of irreversible airflow obstruction, and improve the quality of life of patients [6, 7]. Although bronchial asthma is often clinically controlled, there are still cases of emergency hospital mortality in severe asthma patients. Hence, early objective and effective indicators with real-time disease state reflection are needed to evaluate the conditions of disease and to guide clinicians to choose treatment methods to improve the prognosis of patients.

miRNA is a highly conserved non-coding single-stranded small RNA with about 22 nucleotides in length. By targeting gene structure and function, the target gene is negatively expressed, and it produces marked effects continuously on physiological and pathological process of the body [8]. Studies have found that multiple miRNAs are often expressed abnormally in the lung tissues of asthmatic patients, which may be associated with the occurrence and development of asthma [9, 10]. miR-21 has been shown to be involved in the control of airway inflammation in asthma through inhibiting the expression of inflammatory factors such as interleukin-12 (IL-12) [11]. miR-126 is located in the epidermal growth factor-like domain gene on chromosome 9, which is involved in the body's inflammatory response and immune response [12, 13]. However, the role of miR-126 and miR-21 in the prognosis of asthma has not been defined. In this study, serum levels of miR-21 and miR-126 and changes in lung function in asthma patients were measured to analyze the correlation of miR-21 and miR-126 with lung function in asthma patients, so as to provide a new theoretical reference target for the treatment of asthma patients.

Data and methods

General data

A total of 115 patients diagnosed with asthma in Department of Respiration of Linyi people's Hospital from May 2015 to May 2018 were enrolled in the study group. They were divided into study group A and study group B in accordance with the severity of the disease. Among them, 59 patients with severe asthma were assigned to study group A, and 56 patients with mild to moderate asthma were assigned to study group B. There were 71 males and 44 females in the study group, aged from 26 to 65 years, with an average age of (43.13±12.63) years. There were 27 patients with smoking history, 7 patients with anaphylactoid purpura history and 9 patients with diabetes history. There were 45 healthy volunteers who underwent physical examination in Linyi People's Hospital during the same period who were enrolled in the control group. Among them, there were 27 males and 18 females, aged from 26 to 65 years, with an average age of (43.63±12.19) years. There were 9 subjects with smoking history, 3 subjects with history of allergies, and 4 subjects with diabetes history. There was no significant difference in basic clinical data between the groups ($P>0.05$), which could be compared equally.

Inclusion and exclusion criteria

Inclusion criteria: Patients whose asthma diagnosis and classification met the diagnostic criteria in the guidelines for the prevention and treatment of bronchial asthma [14]. Exclusion criteria: (1) Patients with severe organ dysfunction such as in the brain, heart, liver and kidney. (2) Patients with other bronchial or chronic obstructive pulmonary disease. (3) Patients with pulmonary tumors. (4) Patients who voluntarily gave up treatment during the study and those with incomplete information. (5) Patients combined with other acute or chronic infectious diseases. Patients or their guardians signed the informed consent after knowing about the procedures and purpose of the experiments in this study, and all experiments were approved by the ethics committee of Linyi People's Hospital.

Experimental instruments and reagents

The plasma centrifuge was purchased from Beijing Haitianyoucheng Technology Co., Ltd., Trizol kit was purchased from Jiangsu MRC Biotechnology Co., Ltd., Art.No. TR118-100. NANODROP 1000 nucleic acid concentration tester was purchased from Shanghai Tripbiotech Co., Ltd., model number: nd1000. miRNA reverse transcription kit was purchased from GeneCopoeia, USA, Art.No. QP013. Sybr@ Premix Ex Taq kit was purchased from Beijing Quanxintuoda Technology Co., Ltd., Art.No. DRR041A. Spirometer was purchased from Nanjing Aobang medical Technology Co., Ltd., model number: HI-801.

Experimental methods

Fresh non coagulated blood was mixed with normal saline at 1:1 ratio and centrifuged at room temperature at 1500×g for 20 min. Then the required monocytes were taken and the total RNA of monocytes was extracted by Trizol. After the purity and concentration of miRNA were determined by NANODROP 1000 nucleic acid concentration analyzer, the miRNA reverse transcription kit was used to perform the reverse transcription steps, and then the miR-126 concentration was determined by SYBR@ Premix Ex Taq kit according to the its instructions. miR-126 concentration was determined through referring to the instructions provided with the kit. The relative expression level of miR-126 were as follows: 2-ΔΔCt=ΔCt average -ΔCt value of each sample. The methods for miR-21 expression detection were the same as above.

Lung function detection methods

Patients were kept still for 0.5 h, and the pulmonary function was continuously measured and recorded by the spirometer, for 3 separate measurments. The detected results included pulmonary indexes of forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), maximum mid-expiratory flow (MMEF), and peak expiratory flow (PEF). The result was rated as qualified when the variation of FVC and FEV1 did not exceed 5%, and the final result was the maximum of the three results.

Outcome measures

(1) The expression differences of miR-126 and miR-21 between asthma patients with different severities and normal healthy people were observed and compared. (2) Lung function of patients with asthma of different severity was compared. (3) Pearson correlation analysis of the association between miR-126 and miR-21 expression and lung function in asthma patients was conducted. (4) According to the prognosis of asthma, the patients were divided into a good prognosis group (the asthma symptoms basically disappeared, and the remission lasted more than 3 months), and a poor prognosis group (asthma-related symptoms were still present in the patients, with insufficient remission duration or recurrence) [15]. The prognosis of patients with asthma of different severities was observed. (5) Multivariate Logistic regression analysis of risk factors affecting the prognosis of asthma patients was performed. (6) ROC curve was applied to evaluate the diagnostic value of serum miR-126 and miR-21 levels in asthma patients.

Statistical methods

SPSS 21.0 was adopted for statistical analysis. Measurement data consistent with a normal distribution and homogeneity test were expressed as mean ± standard deviation. t test was applied to compare serum miR-126 and miR-21 levels and lung function indicators (FEV1/FVC, MMEF and PEF) in patients. Pearson correlation was used to analyze the correlation of miR-126 and miR-21 levels with lung function indicators (FEV1/FVC, MMEF and PEF). The enumeration data were expressed as percentage, and χ^2 test was used for inter-group comparison. Multivariate Logistic regression analysis was applied to detect the prognostic risk factors. The receiver operating characteristic curve (ROC) was drawn to evaluate the value of serum miR-126 and miR-21 levels in the diagnosis of asthma. The inspection level was α=0.05.

Results

Comparison of miR-126 and miR-21 expression between the three groups

The expression of both miR-126 and miR-21 in the study group was significantly higher than those in the control group, and the expression of miR-126 and miR-21 in the study group A was significantly higher than those in the study group B, with statistically significant differences (P<0.05). As shown in **Figure 1**.

Changes of clinical lung function indices of patients with different severities of asthma

FEV1/FVC, MMEF and PEF in study group B were higher than those in study group A (P<0.05), as shown in **Table 1**.

Correlation between miR-126 and miR-21 expression and clinical lung function indices

Pearson correlation analysis showed that the ratio of miR-126 expression to FEV1/FVC, MMEF and PEF were negatively correlated (r=-

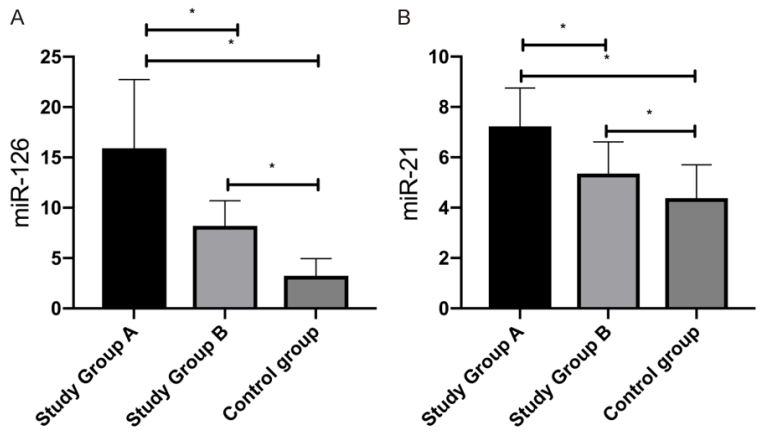

Figure 1. Comparison of miR-126 and miR-21 expression between the three groups. A: miR-126 expression in the study group was notably higher than that in the control group, and miR-126 expression of the study group A was notably higher than study group B. B: miR-21 expression in the study group was notably higher than that in the control group, and miR-21 expression of study group A was notably higher than study group B. Note: * represents comparison between the two groups, P<0.05.

Table 1. Changes of clinical lung function indices of patients with different severities of asthma

Groups	Study group A (n=59)	Study group B (n=56)	T	P
FEV1/FVC (η/%)	66.73±7.26	89.18±3.87	20.530	<0.001
MMEF (L/s)	1.42±0.21	2.61±0.34	22.710	<0.001
PEF (L/s)	4.13±0.46	5.82±0.45	19.900	<0.001

Notes: FEV1/FVC represents the ratio of forced expiratory volume in the first second to pulmonary indexes of forced vital capacity.

0.767, -0.73, -0.869, P<0.001), while the ratio of miR-21 expression to FEV1/FVC, MMEF and PEF were negatively correlated (r=-0.785, -0.63, -0.888, P<0.001). As shown in **Figure 2**.

Comparison of prognosis in patients with different severities of asthma

The number of acute attacks, mean hospital stay duration and mean number of hospital visits in study group B were lower than those in study group A, and the differences were statistically significant (P<0.05). As shown in **Table 2**.

Analysis of prognostic factors in asthmatic patients

Smoking, family history of asthma, personal history of allergy, miR-126 level, miR-21 level and good prognosis of asthma patients were statistically significant (P<0.05). As shown in **Table 3**. Logistic regression analysis was conducted on the influencing factors, and the results revealed that the elevation of family history of asthma, miR-126 and miR-21 were independent risk factors affecting the prognosis of asthma patients (P<0.05), as shown in **Table 4**.

ROC curve analysis of miR-126, miR-21 and combined diagnosis of asthma patients

Based on the expression of miR-126 and miR-21 in asthmatic patients and the combination, a ROC curve was drawn to analyze its diagnostic value for asthma.

The analysis showed that the area under the curve (AUC) of miR-126 was 0.784 (95% CI: 0.723-0.846), the AUC of miR-21 was 0.853 (95% CI: 0.804-0.902), and the AUC of the two combined was 0.894 (95% CI: 0.853-0.934). As shown in **Figure 3**.

Discussion

Bronchial asthma is a chronic airway inflammatory disease that is affected by multiple cellular components and characterized by airflow obstruction or airway hyper responsiveness. Recurrent attacks tend to lead to airway remodeling after aggravation of the disease, and its clinical manifestations often include a series of symptoms such as frequent wheezing, chest distress and shortness of breath, and cough. Due to the similarity of self-neuromodulation, the onset or aggravation of the disease often occurs at night and early morning, but most patient's symptoms can gradually be alleviated after the onset or treatment [16-18]. At present, the occurrence and development of asthma are known to be related to chronic airway inflammation and immune response. Studies have shown that during the onset of asthma, CD4 + T cells can differentiate into Th1 and Th2 cell subpopulations after the body is stimulated by antigens, resulting in a dysfunc-

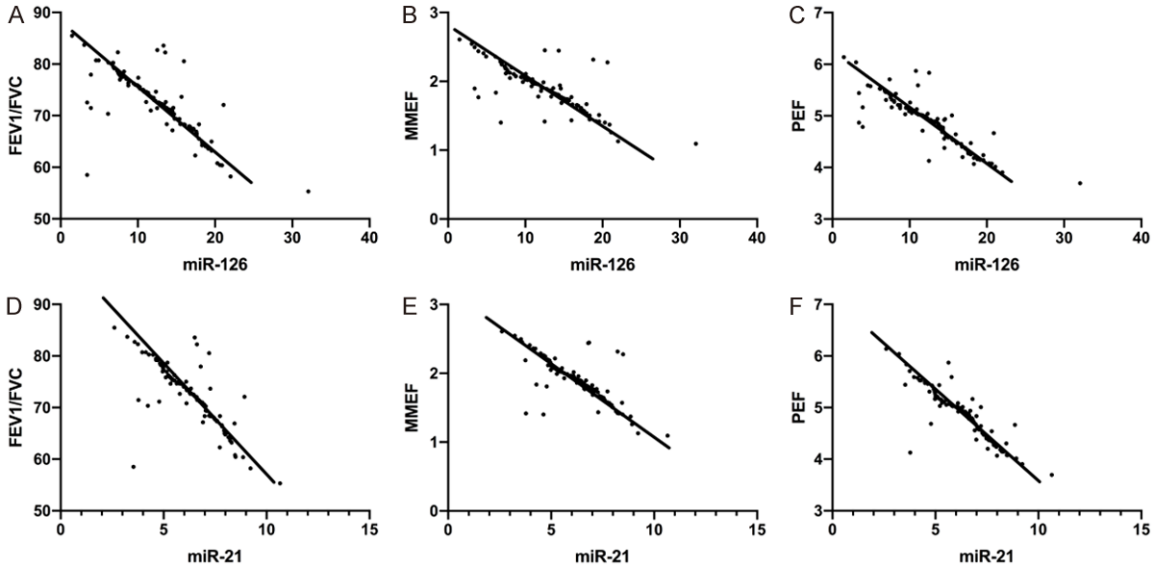

Figure 2. Correlation between miR-126 and miR-21 expression and clinical lung function indices. A: Pearson correlation analysis revealed that miR-126 expression was negatively correlated with the ratio of FEV1/FVC (r=-0.767, P<0.001). B: Pearson correlation analysis revealed that miR-126 expression was negatively correlated with MMEF (r=-0.773, P<0.001). C: Pearson correlation analysis revealed that miR-126 expression was negatively correlated with PEF (r=-0.869, P<0.001). D: Pearson correlation analysis revealed that miR-21 expression was negatively correlated with the ratio of FEV1/FVC (r=-0.785, P<0.001). E: Pearson correlation analysis revealed that miR-21 expression was negatively correlated with MMEF (r=-0.763, P<0.001). F: Pearson correlation analysis revealed that miR-21 expression was negatively correlated with PEF (r=-0.888, P<0.001).

Table 2. Comparison of prognosis in patients with different severities of asthma

Groups	Study group A (n=59)	Study group B (n=56)	T	P
Number of acute attacks (times/year)	3.62±0.72	2.24±0.36	13.100	<0.001
Mean hospital stay (day/year)	7.92±0.99	5.92±0.92	11.230	<0.001
Mean number of hospital stay (times/year)	2.71±0.81	1.29±0.59	10.790	<0.001

tional T lymphatic subpopulation. Due to the abnormal immune response, the Th1/Th2 cytokine ratio becomes unbalanced and decreased [19, 20]. Interferon γ of Th1 cytokines (Interferon γ, IFN-γ) can inhibit IgE-mediated inflammatory responses to prevent chronic airway inflammation. Interleukin-4 (IL-4) in Th2 cytokines can promote the expression of vascular cell adhesion molecules, and then promote the accumulation of eosinophils at the site of inflammation, thereby triggering airway inflammation. Th2 cytokines can be involved in the pathogenesis and development of asthma by activating mast cells and eosinophils [21, 22]. It is known that the abnormal expression of Th1/Th2 cytokines in the pathogenesis of asthma mostly triggers the body's immune response and airway inflammation. miRNAs are also involved in regulating a number of basic biological processes, including cell differentiation, proliferation and apoptosis, as well as participating in Th2-mediated inflammatory responses, whose abnormal regulation may lead to disease occurrence [23]. Therefore, miRNA-126 and miRNA-21 were selected in this experiment to further clarify their role in asthma regulation and prognosis, so as to help the early clinical diagnosis and treatment of asthma patients.

By detecting and comparing the expression of both miRNAs in asthmatic patients with different severity and normal healthy people, it was found that the expression of miR-126 and miR-21 in asthmatic patients was significantly higher than that in the control group. The more severe the asthma condition was, the higher the expression of miR-126 and miR-21 was, suggesting that miR-126 and miR-21 may be involved in regulating changes in lung function

Table 3. Prognostic univariate analysis of asthma patients

Factors	Study group (n=115)	Number of cases with good prognosis	Rate of good prognosis (%)	X^2	P
Gender				0.368	0.544
Male	71	24	33.80		
Female	44	13	29.55		
Age (years)				0.092	0.762
<50	67	22	32.84		
≥50	48	15	31.25		
Smoking history				13.581	<0.001
With	27	4	14.81		
Without	88	33	37.50		
Drinking history				0.827	0.363
With	57	20	35.09		
Without	58	17	29.31		
Family history of asthma				17.531	<0.001
With	45	7	15.56		
Without	70	30	42.86		
Personal history of allergies				6.697	0.010
With	52	12	23.08		
Without	63	25	39.68		
History of diabetes				3.571	0.059
With	9	2	22.22		
Without	104	35	33.65		
miR-126				48.421	<0.001
<12	41	26	63.41		
≥12	74	11	14.86		
miR-21				40.331	<0.001
<6	37	23	62.16		
≥6	78	14	17.95		

Table 4. Results of Logistic nonlinear regression analysis

Variable	β value	SE	Wald	OR value	sig	95% CI
Family history of asthma	1.324	0.373	3.43	3.748	0.035	1.26-8.27
miR-126	1.258	0.282	3.58	3.516	0.021	1.11-7.49
miR-21	1.429	0.396	4.39	4.172	0.032	1.51-10.29

Notes: β value: constant term. SE: standard deviation. Wald: chi-square value. OR value: dominance ratio. sig: *P* value. 95% CI: dominance ratio 95% confidence interval.

to alter the status of asthma patients. In order to confirm the changes in lung function of the study subjects, we observed that FEV1/FVC, MMEF, PEF and other lung functions of the study group B were higher than those of the study group A. Studies support [24, 25] that allergen stimulation releases a variety of active mediators, resulting in increased mucus secretion, contraction of smooth muscle, synthetic infiltration of inflammatory cells, and involvement of bronchus in fibrocyte division in asthma patients, all of which can lead to impaired lung function and aggravated tracheal hyper responsiveness. It was confirmed that the disease worsened and the lung function damage was more serious. Combined with Pearson correlation analysis, the expression of miR-126 and miR-21 was negatively correlated with the detected lung function indices. Previous studies have reported that delayed type hypersen-

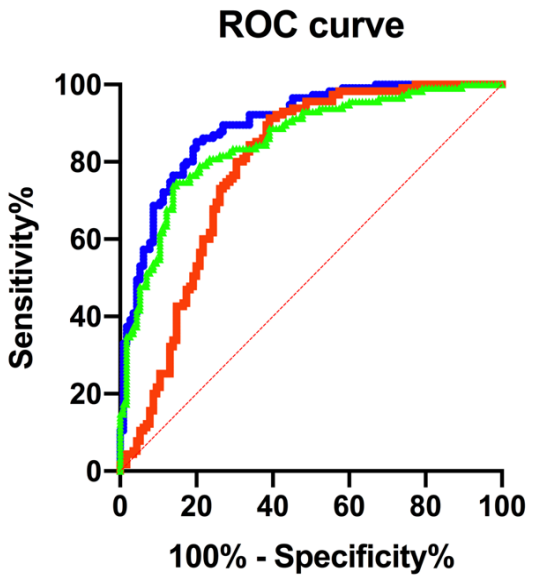

Figure 3. ROC curve analysis of miR-126, miR-21 and combined diagnosis of asthma patients. ROC curve analysis showed that the AUC of miR-126 was 0.784 (95% CI: 0.723-0.846), the AUC of miR-21 was 0.853 (95% CI: 0.804-0.902), and the AUC of the two combined was 0.894 (95% CI: 0.853-0.934).

sitivity is enhanced when miR-21 is lowly-expressed, which can promote the ability of CD 4 + T cells to increase the level of IFN-γ and decrease the level of IL-4. miR-21 is also involved in toll-like receptor signal transduction [26]. Selective blocking of miR-126 expression can inhibit the release of Th2 cytokines and reduce the possibility of airway hyper responsiveness, eosinophil aggregation and airway mucus secretion in asthma [27]. This indicates that the elevated expressions of miR-126 and miR-21 may cause changes in immune metamorphosis and inflammatory response, thereby inhibiting the stable rise of normal indicators of lung function, and hindering the recovery of asthma patients. Logistic regression analysis revealed that the elevation of miR-126 and miR-21 was an independent risk factor for the prognosis of asthma patients, further confirming the diagnostic value of the two for the prognosis of asthma. There have been research reports [28, 29] that miR-21 is affected by the negative regulation of IL-12p35, which regulates the polarization of Th2 cells. miR-126 expression has a tight regulatory effect on the natural and adaptive immune responses of patients with allergic airway inflammation, and it inhibits and regulates the effector function of Th2 cells and the occurrence of eosinophils airway inflammation through antagonism. It was revealed by analysis that miR-126 and miR-21 affected the prognosis of asthma patients by controlling airway inflammatory response. Moreover, the ROC curve was utilized to analyze the value of the two in diagnosing asthma conditions, and it was found that miR-126 and miR-21 also had good predictive value in the diagnosis of asthma patients, and their combined diagnosis performance was better.

In summary, miR-126 and miR-21 mainly regulate the asthma attack by inducing the inflammatory response of the body by affecting the ratio of Th1/Th2 cytokines. As a risk factor for asthma, their expression is bound up with the prognosis of asthma patients. However, there are still some unresolved problems in this experiment. For example, only the lung function indices of the subjects were analyzed and judged, and there are still deficits in the indicators that may cause immune function and inflammatory response. Although the corresponding literature support is provided, it needs to be further summarized by experimental confirmation. These will be the directions of our follow-up experiments with continuous improvement in order to reach a research level of accurate prediction and assessment to help more asthma patients recover.

Disclosure of conflict of interest

None.

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