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Effect of fractional exhaled carbon monoxide on patients with sleep apnea-hypopnea syndrome and its mechanism.

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Keywords: Sleep-disordered breathing; fractional exhaled carbon monoxide; eosinophils; erythrocyte sedimentation rate; C-reactive protein.

Abstract. Sleep-disordered breathing (SDB) is a common sleep disorder associated with chronic airway inflammation and lung function impairment. This article aimed to investigate the fractional exhaled carbon monoxide (FeCO) expression level in obstructive sleep apnea-hypopnea syndrome (OSAHS) and its correlation with disease indicators. Subjects with OSAHS, asthma, chronic obstructive pulmonary disease (COPD), and healthy subjects were selected to collect clinical data. FeCO concentration, eosinophil (Eos), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), FEV_1, and FEV_1/FVC were measured. The Pearson correlation coefficient and receiver operating characteristic (ROC) curve were used for statistical analysis. The FeCO concentration, Eos count, ESR and CRP levels, and lung function in the OSAHS group were higher than the healthy and COPD groups ($p<0.05$) and slightly lower than the asthma group. FeCO was positively correlated with Eos, ESR, and CRP ($p<0.05$), but there was no apparent correlation between FeCO and lung function. FeCO has a high sensitivity and specificity in the diagnosis of OSAHS. There is chronic airway inflammation and systemic inflammation in patients with OSAHS. Lung function impairment in patients with OSAHS is mild, but some limitations remain. FeCO may be an auxiliary diagnostic index particularly valuable in diagnosing OSAHS.

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Efecto de la fracción exhalada de monóxido de carbono en pacientes con síndrome de apnea-hipopnea del sueño y su mecanismo.

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Palabras clave: Respiración alterada durante el sueño; fracción de monóxido de carbono exhalado; eosinófilos; velocidad de sedimentación globular; proteína C-reactiva.

Resumen. Los trastornos respiratorios del sueño (TRS) son un desorden del sueño común asociado con inflamación crónica de las vías respiratorias y deterioro de la función pulmonar. Este artículo tuvo como objetivo investigar el nivel fraccional de exhalación de monóxido de carbono (FeCO) en el síndrome de apnea-hipopnea obstructiva del sueño (SAHOS) y su correlación con los indicadores de la enfermedad. Se seleccionaron sujetos con SAHOS, asma, enfermedad pulmonar obstructiva crónica (EPOC) y sujetos sanos para recopilar datos clínicos. Se midieron la concentración de FeCO, eosinófilos (Eos), velocidad de sedimentación globular (ESR), proteína C reactiva (PCR), FEV1 y FEV1/FVC. Para el análisis estadístico se utilizaron el coeficiente de correlación de Pearson y la curva de características operativas del receptor (ROC). La concentración de FeCO, el recuento de Eos, los niveles de VSG y PCR y la función pulmonar en el grupo de OSAHS fueron claramente más altos que en los grupos sanos y con EPOC ($p<0,05$) y ligeramente más bajos que en el grupo de asma. FeCO se correlacionó positivamente con Eos, ESR y CRP ($p<0,05$), pero no hubo correlación aparente entre FeCO y la función pulmonar. El FeCO mostró una alta sensibilidad y especificidad en el diagnóstico del SAHOS. Existe inflamación crónica de las vías respiratorias e inflamación sistémica en pacientes con SAHOS. El deterioro de la función pulmonar en pacientes con SAHOS es leve, pero persisten algunas limitaciones. El FeCO puede ser un índice diagnóstico auxiliar particularmente valioso en el diagnóstico del SAHOS.

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INTRODUCTION

Sleep-disordered breathing (SDB) is a common sleep disorder. SDB refers to diseases in which the respiratory system is damaged during sleep, resulting in weakened respiratory function and decreased oxygenation [1,2]. Etiologically, SDB can be caused by a variety of reasons. The most common cause of SDB is obstructive sleep apnea-hypopnea syndrome (OSAHS), which is apnea and hypopnea caused by airway obstruction. Other causes may include neuromuscular disorders (such as muscle weakness and spinal cord injury), central hypoventilation syndrome (such as obesity and craniocerebral injury), and the effects of certain medications [3,4]. The clinical symptoms of SDB include nocturnal snoring, frequent sleep disruption, apnea, oxygen desaturation, poor sleep quality, daytime sleepiness, and inattention. Long-term failure to receive adequate treatment may

lead to severe consequences such as cardiovascular disease, metabolic disorders, and cognitive impairment [5].

Researchers are committed to improving the diagnosis and screening methods of SDB, including improving and developing sleep monitoring technology to improve the early identification and intervention of the disease. In addition, the etiology and mechanism of SDB are also being actively explored, including abnormalities in respiratory control centers, changes in neck and upper airway structures [6,7]. These studies contribute to a better understanding of the disease and provide a basis for developing therapeutic methods. Treatment for SDB continues to evolve and includes behavioral and lifestyle changes such as weight loss, improved sleep position, and avoidance of alcohol and sedatives. In addition, surgical intervention may be an option for some specific etiologies, such as obstructive sleep apnea syndrome, due to structural abnormalities of the upper airway. Surgical methods include palatal tonsillectomy, palatal ptosis, and uvula surgery to expand airway access [8,9]. The use of drug therapy in SDB is relatively limited and is usually reserved for specific conditions or in combination with other treatments. Some medications can enhance respiratory function by stimulating respiratory centers or improving muscle tone.

Fractional exhaled carbon monoxide (FeCO) is the carbon monoxide gas discharged from the lungs through the respiratory system. It is a colorless, odorless gas produced during combustion reactions during metabolic processes, especially tobacco combustion [10,11]. Carbon monoxide enters the circulation mainly through gas exchange between the alveoli and capillaries and is then expelled from the lungs by respiration. FeCO measurement can be performed by a carbon monoxide breath test, which measures the concentration of carbon monoxide in the breath and thus assesses the production and metabolism of carbon monoxide in the body. The measurement of FeCO can be used as one of the indicators to evaluate exposure to combustion products or environmental pollutants, as well as to monitor the degree of inflammation and oxidative stress[12-14]. Studies have shown a correlation between SDB and FeCO levels [15]. The lack of oxygenation caused by apnea and hypopnea during sleep in patients with SDB may lead to an increased demand for oxygen, affecting the metabolism and excretion of carbon monoxide. Therefore, FeCO levels may vary in patients with SDB. Some studies have shown that FeCO levels may be valuable in assessing SDB [16-17]. The repeated hypoventilation and hypoxia events during sleep in patients with SDB may lead to oxidative stress and inflammation. Carbon monoxide is a biomarker related to oxidative stress and inflammation. Therefore, some studies have attempted to assess the oxidative stress and inflammation status of SDB patients by measuring FeCO levels [18,19]. In addition, it has been suggested that FeCO levels may be associated with the severity and prognosis of SDB. Higher FeCO levels may be associated with more severe disease and poor prognosis, including an increased risk of cardiovascular complications [20]. Despite some association observations, there is currently insufficient evidence to support using FeCO levels as a diagnostic criterion or an independent diagnostic indicator for SDB. The diagnosis of SDB relies primarily on polysomnography, which assesses respiratory events, oxygenation measures, and other relevant parameters. In conclusion, although there may be a correlation between FeCO and SDB, further studies are needed to clarify its exact value in diagnosing and evaluating SDB.

MATERIALS AND METHODS

Study subjects

Forty-eight patients with OSAHS who were treated in the Respiratory Department of Shanxi Changzhi Second People's Hospital from February 2021 to October 2022 were enrolled in the OSAHS group, 50 patients

with asthma as asthma group, 52 patients with chronic obstructive pulmonary disease (COPD) as COPD group, and 48 healthy people who underwent physical examination in the same period as a healthy group. There were no apparent differences in gender, age, course of disease, and smoking history among the four groups.

Inclusion criteria

OSAHS group: aged between 18 and 65 years old. Patients were diagnosed with moderate or severe OSAHS according to the diagnostic criteria of the American Academy of Sleep Medicine (AASM). The patients had apparent symptoms of sleep apnea, such as frequent snoring, poor sleep quality, and daytime sleepiness.

Asthma group: aged between 18 and 65 years. Asthma was diagnosed according to the Global Initiative for Asthma (GINA) diagnostic criteria. Asthma-related symptoms such as cough, shortness of breath, and dyspnea were present.

COPD group: aged between 40 and 85 years. COPD was diagnosed according to the diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD). Respiratory symptoms included chronic cough, expectoration, and associated lung function impairment.

Healthy group: aged between 18 and 65 years old. No respiratory disease was diagnosed as OSAHS, asthma, or COPD. There were no obvious respiratory or sleep-related symptoms.

Exclusion criteria

Patients with severe heart disease, kidney disease, nervous system disease, or other serious underlying diseases. Patients undergoing respiratory surgery or treatment. Patients with severe cognitive or communication impairments and unable to cooperate with the trial requirements.

Healthy group: Patients with any chronic disease or other serious health problems. History of smoking within 24 hours.

The Medical Ethics Committee of Shanxi Changzhi Second People's Hospital approved the trial, and all patients signed an informed consent.

FeCO concentration detection

We ensured the breath analyzer was in working condition and calibrated the instrument to ensure accurate measurements. The breath analyzer was kept clean and free of dirt or residue. We made the subjects sit or stand, ensuring they were comfortably exhaling. The subjects were instructed to take several deep breaths to verify adequate ventilation of the lungs. We explained the procedure and purpose of the test and informed the subject to keep breathing normally during the test. The test subjects were connected to the breath analyzer (U-breath BA200, Zhejiang E-link care Medical Technology Co., LTD.) using an appropriate-size mask or expiratory tube. The connection site was well-sealed to avoid gas leakage. The subjects could breathe normally and pass the breath into the breath analyzer through the mouth. The breath analyzer measured and recorded the concentration of carbon monoxide in the breath.

Two or three breath measurements were carried out to obtain a stable average. The results of each measurement were recorded, including the time, date, and measurement value. For each subject tested, the average FeCO concentration was calculated.

Detection of other indicators

Eosinophils (Eos): Samples were extracted from the peripheral blood of the tested subjects, venous whole blood samples were collected using an anticoagulant collection vessel, and Eos counts were performed in an automated blood cell analyzer (BC-760 CS, Mindray Medical International Co., LTD.) under laboratory conditions. Samples were placed into the hematology analyzer for analysis according to the instrument's instructions. The hematology analyzer measured the number of Eos in the sample and

generated the results. Average Eos absolute count: 0-0.4×10^9/L for adults.

Erythrocyte sedimentation rate (ESR): samples were extracted from the peripheral blood of the tested subjects, and venous whole blood samples were collected using anticoagulant blood collection vessels. A certain amount of blood samples was taken and placed in the ESR tube of an ESR instrument (BK-ESR40, Shandong Biobasebaby Technology Co., LTD.). The ESR tube was placed vertically in the ESR meter, allowing the blood to drop freely. The ESR tube was placed into the ESR meter for measurement according to the device's specifications and instructions. The erythrocyte sedimentation rate in the ESR tube was recorded, and the normal ESR range was 0-20mm/h for adult females and 0-15mm/h for adult males.

C-reactive protein (CRP): samples were extracted from the peripheral blood of the tested subjects, and venous whole blood samples were collected using anticoagulant blood collection tubes. The blood samples were sent to the laboratory, and the CRP level in the blood was quantitatively measured by the immunofluorescence method. According to the method, sample processing and measurements were performed according to the corresponding operating instructions. The CRP concentration in the blood was recorded or reported based on the measurements. The normal concentration should generally be less than 10mg/L.

Pulmonary function

FEV_1 (the volume of air expelled from the beginning of forced exhalation to the end of one second of exhalation) and FEV_1/FVC (the ratio of forced expiratory volume in one second to forced vital capacity) were measured by adopting a pulmonary function instrument (MSA99, Beijing Maibang Photoelectric Instrument Co., LTD.). First, the pulmonary function meter was in normal working condition, performing the necessary calibration and verification with a respirator mask of the appropriate size. The subjects were placed in a comfortable position. The test procedure and purpose were explained to the subjects, and necessary instructions were provided. A respirator of the appropriate size was adopted to the subjects' mouth according to the requirements of the spirometer, making sure the mask was well sealed to avoid gas leakage. The subjects began to take normal resting breaths as directed by the spirometer. Next, the subjects were asked to take a maximal, hard breath, taking in as much air as possible and then forcing to expel air. Immediately after a hard inhalation, the subjects were asked to perform a hard exhalation, then push the air out of the lungs as hard as possible, ending the exhalation entirely as quickly as possible. The spirometer automatically measured and recorded FEV_1 and FVC. Based on the measured FEV_1 and FVC results, the FEV_1/FVC ratio was calculated.

Statistical analysis

IBM SPSS 20.0® software was adopted for data statistical analysis, analysis of variance was adopted, and the measurement data were expressed as the mean ± standard deviation ($\bar{X}\pm SD$). Count data were expressed as a percentage (%). The χ^2 test and the Pearson correlation analysis were applied. The significance level was $p<0.05$, indicating that the difference was statistically significant.

RESULTS

Comparison of FeCO concentrations, Eos counts, ESR, CRP, FEV_1 and FEV_1/FVC values

The FeCO concentration of the OSAHS group was higher than the healthy and COPD groups ($p<0.05$), but slightly lower than the asthma group. In the OSAHS group had Eos count, ESR level, CRP level, FEV_1 value, and markedly higher FEV_1/FVC value than healthy and COPD groups ($p<0.05$), but a lower EOS count, inferior ESR level, inferior

CRP level, lower FEV_1 value and lower FEV_1/FVC value than the asthma group ($p<0.05$). (Fig. 1).

Correlation analysis between FeCO and each index

Pearson analysis was used to analyze the correlation between FeCO and various indicators. It can be observed that FeCO was positively correlated with Eos, ESR, and CRP ($p<0.05$), and there was no apparent correlation between FeCO and lung function (Table 1).

The diagnostic value of FeCO for OSAHS

The diagnostic value of FeCO for OSAHS was analyzed using the receiver operating characteristic (ROC) curve. The sensitivity (0.857) and specificity (0.835) of FeCO in

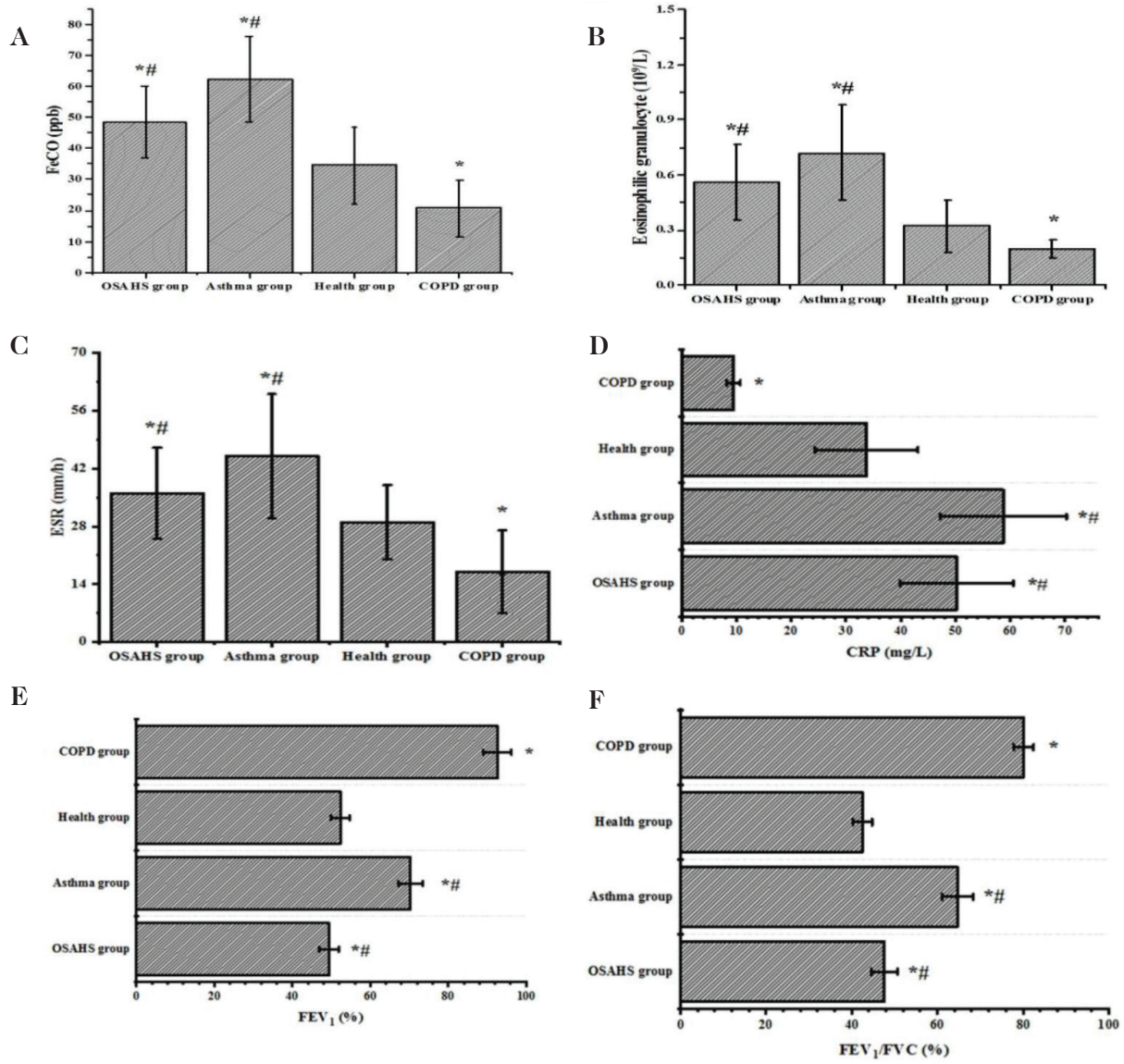

Fig. 1. Contrast of fractional exhaled carbon monoxide (FeCO) concentrations (Fig. 1A), Eosinophil (Eos) comparison (Fig. 1B), Contrast of Erythrocyte sedimentation rate (ESR) levels (Fig. 1C), Contrast of C-reactive protein (CRP) (Fig.1D), Contrast of Forced expiratory volume (FEV1) values (Fig. 1E), Contrast of Forced expiratory volume/forced vital capacity (FEV_1/FVC) values (Fig. 1F). [Note: * relative to healthy group ($p<0.05$), # relative to COPD group ($p<0.05$)].

Table 1
Correlation analysis between fractional exhaled carbon monoxide and each index.

Indicators	OSAHS group (n=48)		Asthma group (n=50)		COPD group (n=52)	
	r	P	r	P	r	P
Eos	0.725	0.015	0.625	0.024	0.719	0.017
ESR	0.562	0.036	0.465	0.044	0.611	0.032
CRP	0.762	0.008	0.633	0.028	0.768	0.014
FEV_1	0.135	0.332	0.089	0.527	0.125	0.343
FEV_1/FVC	0.128	0.346	0.077	0.593	0.059	0.665

OSAHS= obstructive sleep apnea-hypopnea syndrome, COPD= chronic obstructive pulmonary disease, Eos= eosinophil, ESR= erythrocyte sedimentation rate, CRP= C-reactive protein, FEV1= Forced expiratory volume, FVC= forced vital capacity.

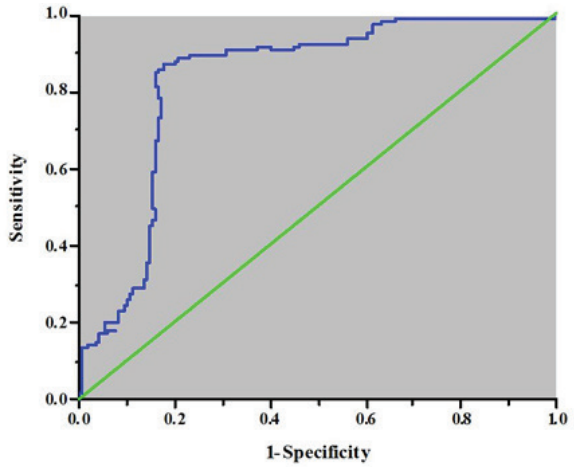

Fig. 2. Receiver Operating Characteristic (ROC) curve of FeCO (fractional exhaled carbon monoxide) in the diagnosis of OSAHS (obstructive sleep apnea-hypopnea syndrome).

diagnosing OSAHA were both high. The area under the ROC curve was 0.824, and the 95% interval was 0.77-0.89 (Fig. 2).

DISCUSSION

This article explored the value of FeCO as a potential biomarker in diagnosing and evaluating OSAHS. FeCO has shown its potential as a rapid and non-invasive detection index in many respiratory diseases. However, studies on its application and relevance in OSAHS are still limited. To further understand the potential role and diagnostic value of FeCO in OSAHS patients, asthma patients, COPD patients, and healthy controls, FeCO concentration was compared, and correlation analysis with other clinical indicators was carried out.

The FeCO concentration in the OSAHS group was still higher than against healthy and COPD groups, which may result from chronic airway inflammation and poor oxygenation due to SDB caused by OSAHS. Eos is a type of white blood cell whose increase is often associated with airway inflammation and allergic reactions. The high Eos count in the OSAHS group may reflect airway inflammation and abnormal gas exchange caused by OSAHS [21]. As against the asthma group, the Eos count of the OSAHS group was lower, which may be due to the different pathological mechanisms of OSAHS and asthma. The high level of ESR in the OSAHS group may be related to the chronic airway inflammation and hypoxia caused by OSAHS. As against the asthma group, the OSAHS group had a lower ESR level, possibly due to the different inflammatory mechanisms and course of disease between OSAHS and asthma [22].

CRP is an acute-phase protein, and its increase is usually associated with inflammatory responses and tissue damage. In the OSAHS group, higher CRP levels may reflect the presence of abnormal gas exchange and

chronic inflammation. In contrast, CRP levels were lower in the OSAHS group than in the asthma group, which may result from differences in inflammatory mechanisms and pathological processes between OSAHS and asthma [23]. FEV_1 is an essential indicator in pulmonary function testing to evaluate expiratory flow rate. The OSAHS group suggested higher FEV_1 values, which may reflect the relatively mild airway stenosis caused by OSAHS. This situation may be because OSAHS is mainly caused by partial upper airway obstruction, unlike asthma and COPD. The FEV_1/FVC ratio was adopted to assess the degree of airway obstruction. The OSAHS group suggested higher FEV_1/FVC values, which may imply that lung function limitation caused by airway stenosis is relatively mild in OSAHS patients. Zhao *et al.* [24] discussed the role of FeCO in the auxiliary diagnosis and evaluation of allergic rhinitis (AR). They selected AR patients for comparison with healthy controls. Symptom scores distinguished the severity of AR disease, and the FeCO tested both groups. The results suggested that the level of FeCO in the AR group was higher than that in healthy people and positively correlated with the severity of AR symptoms. The detection of FeCO can monitor the changes in AR and has high accuracy as an indicator for the auxiliary diagnosis of AR.

The positive correlation between FeCO and Eos, ESR, and CRP ($p<0.05$) indicated that FeCO might be associated with inflammatory processes. These indicators play an essential role in the inflammatory response so that the elevated FeCO may reflect the presence of chronic airway inflammation in OSAHS patients. In terms of lung function, the correlation between FeCO and lung function is not apparent, which may mean that the relationship between FeCO and the degree of lung function impairment in OSAHS is unclear. Using ROC curve analysis, the value of FeCO in diagnosing OSAHS can be evaluated. The high sensitivity, specificity and large area under the ROC curve indicated that FeCO may be adopted as a potential auxiliary diagnostic index for the screening and diagnosis of OSAHS.

The correlation between FeCO and OSAHS suggests that FeCO may serve as a valuable indicator to reflect the presence of chronic airway inflammation and play a role in the diagnosis of OSAHS. It should be noted that as an auxiliary diagnosis method, FeCO still needs to be comprehensively evaluated in combination with other clinical information. The diagnosis of OSAHS is usually based on a comprehensive analysis of medical history, physical examination, sleep monitoring, and pulmonary function testing. As an index, although FeCO has shown a specific diagnostic value in the experimental results, it still needs to be combined with other clinical indicators to make a comprehensive judgment.

In conclusion, FeCO level was increased in OSAHS patients and was associated with chronic airway inflammation, systemic inflammatory response, and mild pulmonary dysfunction. In addition, FeCO has shown potential as an auxiliary diagnostic index and has a particular value in diagnosing OSAHS. However, there are some limitations in this article, such as the limited number of study samples and age and gender differences across groups that may affect the interpretation of the results. Therefore, future studies are needed to further explore the physiological mechanism of FeCO in OSAHS and optimize the diagnostic threshold and its application in clinical practice. The clinical significance of this article is that it provides a new potential indicator for early screening and diagnosis of OSAHS.

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Conflict of competence

The authors declare no conflict of interest.

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Authors' Participation

QJ and LG contributed to the conceptualization of the study, the design of the methodology, the acquisition of data, and the analysis and interpretation of data. XZ contributed to the drafting and revision of the manuscript. GL was actively involved in data collection and played a key role in the statistical analysis. LL contributed to the interpretation of results and critically revised the manuscript. All authors participated in the final approval of the version to be published and agreed to be accountable for the accuracy and integrity of the work.

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