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ORIGINAL RESEARCH

TFR1 as a Biomarker of Pulmonary Fibrosis Development in COPD Patients

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Background: Ferroptosis is involved in chronic lung injury, including COPD and pulmonary fibrosis. In this study, we investigated the role of transferrin protein 1 (TFR1), as a ferroptosis marker, in the development of COPD-associated pulmonary fibrosis.

Methods: The expression of TFR1 was elevated in 97 patients with COPD. The correlation analysis of the clinical characteristic was performed including the frequency of acute exacerbation, the fibrosis score, etc. and the expression of TFR1. Animal experiments were carried out to verify TFR1 expression in a rat COPD model.

Results: The results showed that the expression of TFR1 was related to DLCO%, 6 MWT, GOLD grade, frequency of acute exacerbation and fibrosis score. Together, in the rat COPD model, higher TFR1 was related to a higher lung injury score and a higher lung fibrosis score.

Conclusion: In summary, these results indicated that serum TFR1 levels related to the severity of pulmonary fibrosis in clinical practice and may provide a potential target for the treatment of pulmonary fibrosis development from patients with COPD in the future.

Keywords: TFR1, COPD, pulmonary fibrosis, biomarker, ferroptosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic lung disease, including emphysema, chronic bronchitis, and others. Currently, the causes of COPD are not yet clear and may be related to external environmental factors, including smoking, second-hand smoke inhalation, polluting dust, harmful chemical gases, air pollution, and other factors.[1] There are also personal factors, such as genetics, diseases, etc.[2] COPD is more common in people over 40 years of age, possibly due to the decline in physical function and immunity of middle-aged and elderly patients.[3] The pathological and physiological characteristics of COPD are persistent airflow limitation, completely irreversible, and persistent malignant development.[4] Clinical manifestations include dry vomiting, coughing, and sputum production, which worsen with increasing physical activity and seriously affect the patient's quality of life.[5] Treatment for COPD is based on improving lung function, alleviating clinical symptoms, and improving quality of life. Common treatment methods include rehabilitation therapy, medication therapy, and home oxygen therapy.[6] As the disease progresses, some patients may also have pulmonary fibrosis and, if left untreated, there is a risk of developing into pulmonary failure.[7] Therefore, early identification and diagnosis of such patients and timely treatment of medications are of great significance to improve the patient's prognosis.

In recent years, ferroptosis, as a new type of programmed cell death, has gradually attracted widespread attention due to its dependence on intracellular Fe^{2+}accumulation and lipid peroxidation.[8,9] Numerous studies have shown that ferroptosis plays a crucial role in the onset and progression of lung diseases.[10] Ferroptosis not only differs morphologically from other forms of cell death, but also exhibits unique mechanisms at the biochemical level. In particular, oxidative stress caused by iron overload and disorders of lipid metabolism is considered an important factor in the induction of ferroptosis.[11,12] These findings provide

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new opportunities for the treatment of lung diseases by regulating iron metabolism and lipid peroxidation processes, which may effectively promote or prevent ferroptosis, thus improving the therapeutic effect of these diseases.

Transferrin protein 1 (TFR1), also known as CD71 or TFRC, is a type II transmembrane glycoprotein composed of 760 amino acids, exist in the form of a dimer, connected by disulfide bonds on the cell surface. The TFR1 monomer consists of an extracellular C-terminal domain, a transmembrane region, and an intracellular N-terminal domain, where the C-terminal region contains the transferrin (TF) binding site. Each TFR1 monomer can bind 1 molecule of TF and 2 Fe3+ ions, so 1 molecule of TFR1 can bind up to 2 molecule of TF and 4 Fe3+ ions, ultimately delivering iron into the cell in the form of an iron-TF-TFR1 complex.[13,14] Human TFR1 is widely expressed in different tissues and organs. Under physiological conditions, cellular iron absorption is primarily controlled by the plasma membrane protein TFR1, which transports transferrin bound iron into cells through receptor-mediated endocytosis.[15] Therefore, TFR1 is considered a marker protein for ferroptosis. Blocking this process by eliminating TFR1 can prevent ferroptosis.[16] Previous studies have confirmed that high expression of TFR1 in bronchoalveolar lavage fluid (BALF) in asthma patients is associated with impaired lung function, and it is believed that high expression of TFR1 in the sputum is related to the severity of asthma.[17] Down-regulation of TFR1 partially blocked the high secretion of MUC5AC, goblet cell proliferation, and the release of inflammatory factors in COPD model rats, indicating that TFR1 is involved in promoting airway inflammation and airway mucus cell proliferation in COPD.[18] However, TFR1 expression in patients with COPD has not yet been reported.

In the aforementioned study, we have identified ferroptosis involvement in the pathological process of progression of COPD to pulmonary fibrosis in animal models and we found that ferroptosis-related indicators, including GSH and MDA, are correlated with the degree of pulmonary fibrosis. Based on this, this study aims to detect the expression level of TFR1 in COPD patients and analyze its relationship with the severity of COPD and pulmonary fibrosis and to verify the relationship between the expression level of TFR1 and lung injury and pulmonary fibrosis in animal models. The purpose of this study is to provide a reliable biomarker and a potential therapeutic target for patients with COPD progression to pulmonary fibrosis.

Materials and Methods

COPD Patients

97 patients with COPD were included in this study. COPD was diagnosed by pulmonary function test according to the standards of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[19] Inclusion criteria: (1) FEV1/FVC<0.7 after bronchodilators, and excludes other diseases that may cause limitation of airflow (such as asthma and bronchiectasis). (2) Age over 40 years old, COPD duration ≥ 1 year. Exclusion criteria: (1) Other diseases that cause pulmonary fibrosis: connective tissue diseases (such as rheumatoid arthritis, scleroderma), occupational lung diseases (pneumoconiosis, asbestosis), drug-induced pulmonary fibrosis, or idiopathic pulmonary fibrosis. (2) Combined with asthma, bronchiectasis, active pulmonary tuberculosis, and pulmonary embolism. (3) Serious complications, such as active lung cancer, severe heart failure (NYHA III–IV grade), end-stage renal disease, liver failure, etc. (4) Usage of anti-fibrotic drugs (such as pirfenidone, nintedanib) or immunosuppressants (such as cyclophosphamide, rituximab) within 6 months.

Data including sex, age, smoking index, BMI, CRP, IL-6, ESR, LDH, routine blood examination, lung function, 6 MWT, CAT score, grade mMRC, grade GOLD, frequency of acute exacerbation, and fibrosis score based on HRCT examination were collected from hospital electronic records between January 1, 2022 and December 31, 2024. At the same time, peripheral blood samples were collected from all patients for the detection of serum levels of TFR1 and COL3 using the ELISA assay. This study was approved by the Medical Ethics Committee of the Hunan Provincial People's Hospital (2024–260).

Mice COPD Model

4-week-old C57BL.6 J mice (18–20g) were purchased from Hunan Slake Jingda Experimental Animal Co., Ltd. (Changsha, China). All animals were fed in the SPF animal facility with a normal day and night cycle. They also had

free access to a common diet and water. Mice were randomly divided into 3 groups: control group (n=5), model 1 group (COPD / CSE) (n = 5), and model 2 group (COPD-PF / CSE + LPS) (n = 5 as Supplementary Figure 1. The mice COPD model was constructed as in our previous study.[20] All animal experiments were conducted according to the ARRIVE guidelines. The animal study protocol was approved by the Animal Care and Use Committee (ACUC) of Hunan Provincial People's Hospital, protocol number [2024–260]. The study adhered to the guidelines set by the committee.

ELISA Assay

Human sTfR1 (Soluble Transferrin Receptor1) ELISA kit (EH0386), Mouse TFR (Transferrin Receptor) ELISA kit (EM1400) and Human COL3 (Collagen Type III) ELISA kit (EH2866) were purchased from Fine Test Biotechnology (Wuhan, Hubei, China). COL3 was a biomarker of fibrosis. The levels of TFR1 and COL3 in the serum of COPD patients were measured using an ELISA assay according to the manufacturer's instructions. The OD450 was measured by Microplate reader. Each sample was calculated on the basis of a standard curve.

Hematoxylin & Eosin Staining

The lung tissue of the mice was fixed in 4% paraformaldehyde for at least 24 hours, followed by gradient dehydration and paraffin embedding. After embedding in paraffin, tissues were cut into sections with a thickness of 4 (m for H&E staining). After dewaxing, staining with hematoxylin and eosin, dehydration, permeabilization, and sealing, observation, and image collection were performed under an inverted microscope (Olympus, Tokyo, Japan). The lung injury score was referred to the previous study, mainly including pulmonary congestion, hemorrhage, neutrophil filtration and aggregation, and alveolar wall thickness and transparent membrane formation.[21]

Masson Trichrome Staining

Paraffin sections were deparaffinized and sequentially stained with Regaud's hematoxylin staining solution, Masson's acid eosin solution, and aniline blue. After staining, dehydration, permeabilization, and sealing, observation and image collection were performed under an inverted microscope (Olympus, Tokyo, Japan). The lung injury score was evaluated on the basis of Ashcroft score criteria.[22]

IHC Staining

Sections with a thickness of 4 (m obtained from paraffin-embedded lung tissues were deparaffinized, antigen retrieval, blocked, and incubated with primary antibodies against TFR1 (Cat No. 65236-1-Ig, Proteintech, Wuhan, China) with a dilution of 1:200 and (-SMA (Cat No. 14395-1-AP, Proteintech, Wuhan, China) with a dilution of 1:1000. The sections were then incubated with a secondary antibody kit, and observation was performed with a laser scanning microscope (Olympus, Tokyo, Japan).

Statistical Analysis

Parametric data were presented as mean ± standard deviation or mean (range). Nonparametric data were presented as median (interquartile range, IQR). Spearman bivariate correlation analysis was performed between TFR1 and basic demographic information, systemic inflammatory level, and pulmonary function in patients with COPD. The chi-square test was applied to analyze differences in clinical characteristics between the higher TFR1 group and the lower TFR1 group in patients with COPD. Student's *t* test was applied to analyze differences between two groups, while variance (ANOVA) was applied to analyze differences between the three groups. Statistical significance was established at $P<0.05$. SPSS software (version 20.0; SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. GraphPad Prism 8 (GraphPad, San Diego, CA) was used to generate the images.

Results

Characteristics of the COPD Patient

In this study there were 97 patients with COPD. The results of the spearman bivariate correlation analysis between TFR1 and basic demographic information, systemic inflammatory level, lung function in patients with COPD showed that TFR1 levels did not show correlation with gender, age, smoking index, BMI, CRP, IL-6, LDH, WBC, neutrophil count, Hb, EOS%, RV/TLC%, FEV1%pred, mMRC grade. However, TFR1 levels exhibited a positive correlation with FEV1/FVC%, MMEF%, CAT score, GOLD grade, frequency of acute exacerbation and fibrosis score and a negative correlation with lymphocyte count, NLR, DLCO%, DLCO/VA%, 6MWT (see Table 1 for details).

The Frequency of Acute Exacerbation and the Fibrosis Score Differ in COPD Patients with Higher and Lower Levels of TFR1

The TFR1 level of 97 patients was 5.44 ± 0.56 ng/mL. According to the average TFR1 value, they were divided into a low TFR1 group (serum TFR <5.44 ng/mL) and a high TFR1 group (serum TFR1 ≥ 5.44 ng/mL). There were differences in DLCO%, 6 MWT, GOLD grade, frequency of acute exacerbation, and fibrosis score between the two groups (see Table 2 for details). A higher level of TFR1 was associated with a lower percentage of DLCO, a shorter distance of 6 MWT, a higher grade of GOLD, a higher frequency of acute exacerbation and a higher fibrosis score. All of

Table 1 Spearman Bivariate Correlations Analysis Between TFR1 and Basic Demographic Information, Systemic Inflammatory Level, Pulmonary Function in COPD Patients

Correlation	TFR1		
	R	P Value	Cases (N)
Gender	−0.130	0.411	97
Age	0.259	0.095	97
Smoking index	0.051	0.976	97
BMI	−0.224	0.150	97
CRP	0.017	0.973	96
IL-6	0.123	0.432	94
ESR	0.315	0.040*	93
LDH	0.134	0.391	95
WBC	−0.0402	0.798	97
Neutrophil count	0.0226	0.885	97
Lymphocyte count	−0.333	0.029*	97
NLR	−0.360	0.018*	97
Hb	−0.101	0.552	97
EOS%	0.102	0.514	97
RV/TLC%	−0.156	0.245	87
FEV1%pred	0.297	0.064	87
FEV1/FVC%	0.354	0.017*	87
MMEF%	0.304	0.034*	90
DLCO%	−0.369	0.012*	91
DLCO/VA%	−0.274	0.043*	91
6 MWT	−0.314	0.040*	90
CAT score	0.349	0.022*	89
mMRC grade	0.201	0.195	90
GOLD grade	0.651	<0.001*	87
Frequency of acute exacerbation	0.365	0.016*	97
Fibrosis score	0.434	0.004*	85

Note: *Indicate P<0.05.

Table 2 Differences of Clinical Characteristics Between Higher TFR1 Group and Lower TFR1 Group in COPD Patients

Clinical Characteristics	Lower TFR1 <5.44 ng/mL	Higher TFR1 ≥5.44 ng/mL	P Value
Male/Female	36/10	38/3	0.075
Age, years	75(40–92)	76(59–96)	0.999
Smoking index	400(0–2700)	600(0–4000)	0.365
BMI, kg/m^2	22.1(17.67–28.34)	20.1(14.36–25.68)	0.547
CRP, mg/L	40.25(0.08–177.82)	57.22(0.5–243)	0.225
IL-6, pg/mL	23.27(13.30–56.87)	73.82(21.17–65.45)	0.118
ESR, mm/h	32.48(7–65)	44.1(2–102)	0.365
LDH, U/L	197.74(146.8–325)	219.26(155.2–373.1)	0.999
WBC, $\times10^9$/L	8.88(4.16–26.43)	8.63(3.32–18.7)	0.361
Neu, $\times10^9$/L	6.87(2.51–22.83)	7.12(1.8–17.45)	0.346
Lym, $\times10^9$/L	1.15(0.16–2.33)	0.83(0.24–1.82)	0.099
NLR	1.73(0.49–5.35)	1.10(0.29–2.88)	0.326
Hb, g/L	124(68–156)	123.95(82–153)	0.999
EOS%	2.81(0–8.15)	1.66(0–14.07)	0.0536
RV/TLC%	132.15(117.24–155.38)	134.79(116.88–155.79)	0.994
FEV1%pred	44.51(36.87–63.79)	49.80(35.54–64.38)	0.673
FEV1/FVC%	53.38(44.64–62.57)	58.76(48.64–65.96)	0.533
MMEF%	15.7(11.04–24.05)	17.45(12.37–25.84)	0.684
DLCO%	61.92(44.78–73.61)	48.79(32.45–66.78)	0.001*
DLCO/VA%	70.42(56.34–90.75)	64.28(41.75–94.67)	0.065
6 MWT, m	255(20–500)	149(20–500)	0.0148*
CAT score	13(2–20)	17.1(6–28)	0.544
mMRC grade	2.35(1–4)	2.8(1–4)	0.999
GOLD grade	2.3(1–4)	3.5(1–4)	0.0004*
Frequency of acute exacerbation	1.22(0–4)	2.15(0–5)	0.0245*
Fibrosis score	5.2(0–11)	8.65(3–15)	0.0058*

Note: *Indicate P<0.05.

these results suggested that TFR1 was a biomarker positively correlated with the severity of COPD, with higher levels of TFR indicating more severe COPD.

The TFR1 Level Was Associated with the Frequency of Acute Exacerbation in COPD Patients

The gradual progression of COPD to pulmonary fibrosis is a slow process closely related to repeated acute exacerbation of inflammatory damage. The frequency of acute exacerbation was recorded in one year and all patients were divided into two groups according to the frequency of acute exacerbation, with a frequency of less than or equal to 2 per year recorded as the low-frequency group and more than 2 recorded as the high-frequency group. Representative CT images of patients in the low-frequency and high-frequency groups of acute exacerbation were show in Figure 1A. Then we analyzed the plasma levels of TFR1 and COL3 of the patients in the low-frequency and high-frequency groups and found that the levels of TFR1 and COL3 were significantly lower in the low-frequency group and significantly higher in the high-frequency group (Figure 1B and C). The levels of TFR1 were positively correlated with COL3 (Figure 1D). To predict the frequency of acute exacerbation in COPD, the area under the TFR1 curve was 0.9534 (95% CI:0.9167–0.9901), P<0.0001, the area under the COL3 curve was 0.7289 (95% CI:0.6243–0.8334), P=0.0006, and the area under the fibrosis score curve is 0.7969 (95% CI:0.6851–0.9087), P<0.0001 (Figure 1E).

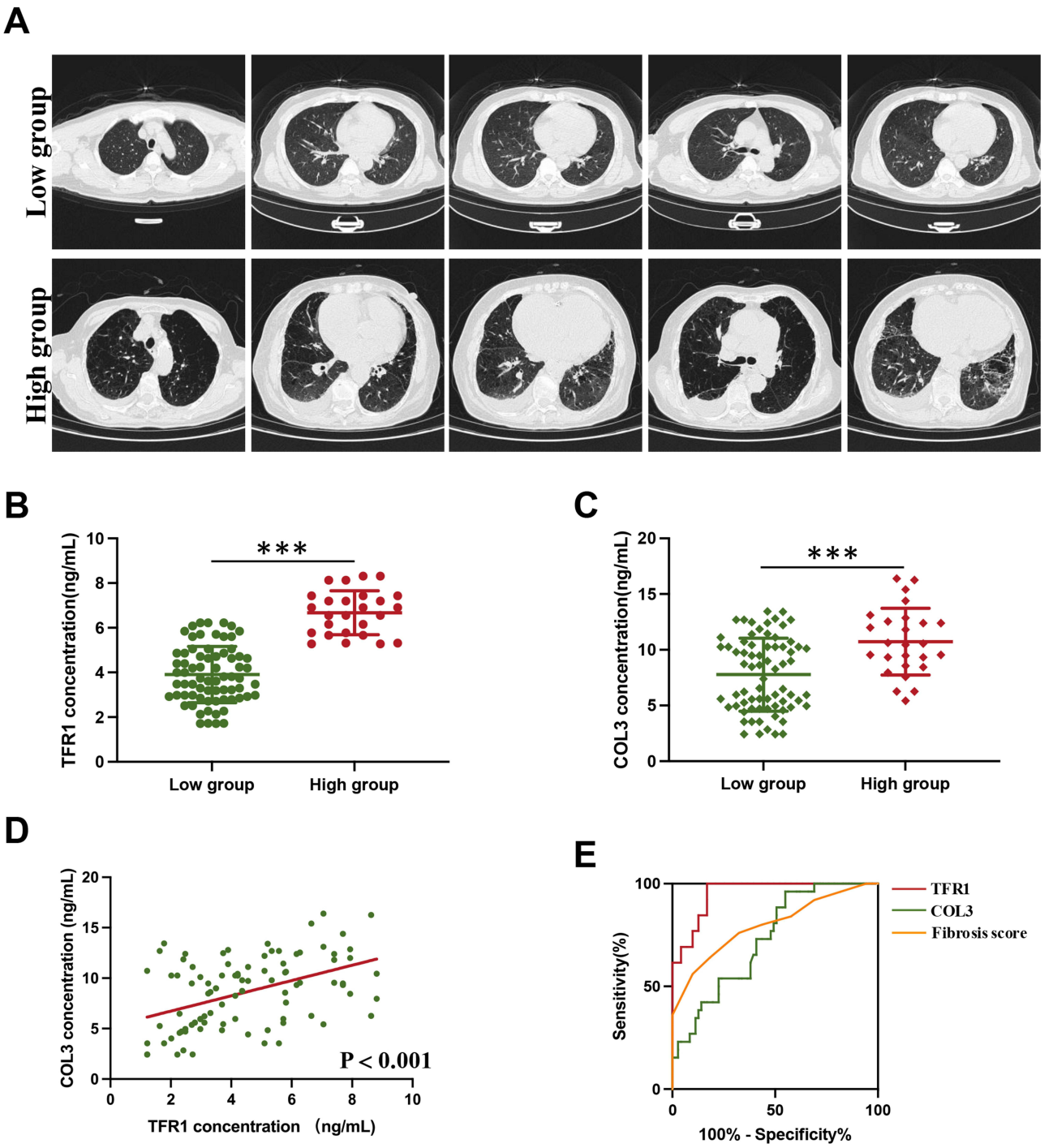

Figure 1 The TFR1 level was associated with the frequency of acute exacerbation in patients with COPD. (**A**) Representative CT images of patients in the low-frequency and high-frequency groups of acute exacerbation. (**B**) Serum TFR1 concentration in the low-frequency and high-frequency groups. (**C**) Serum COL3 concentration in the low-frequency and high-frequency groups. (**D**) The spearman analyzes the serum TFR1 concentration and the serum COL3 concentration. (**E**) ROC cure for TFR1, COL3, and fibrosis scores to predict the frequency of acute exacerbation in COPD.

Notes: the low group stands for the low frequency group with a frequency of acute exacerbation less than 2. The high group represents the high-frequency group with an acute exacerbation frequency greater than 2. ***means P < 0.001.

The TFR1 Level Was Correlated with Lung Injury in COPD Mice

To verify the relationship between TFR1 and lung injury, we constructed lung injury models with different degrees of injury. Model 1 was mainly exposed to cigarettes to simulate stable COPD lung injury. Model 2 added an intraperitoneal

injection of a combination of LPS exposure to cigarettes to simulate the impact of infection after COPD lung injury, that is, AECOPD. As expected, the Model 1 group showed significant lung injury, while the Model 2 group had more significant lung injury and significant interstitial thickening (Figure 2A and B). And the levels of TFR1 were detected in BALF and plasma. Compared to the control group, TFR1 in both model 1 and model 2 groups increased significantly, and the TFR1 level in model 2 group was higher than in the TFR1 group, indicating that the TFR1 level was related to the degree of lung injury (Figure 2C and D).

TFR1 Level Correlated with Lung Fibrosis in COPD Mice

There was a positive correlation between TFR1 levels and COL3 pulmonary fibrosis index, as well as CT pulmonary fibrosis score in patients with COPD. Furthermore, the relationship between TFR1 levels and pulmonary fibrosis was also analyzed in COPD mouse models. Through Masson's trichrome staining, the results showed that varying degrees of pulmonary fibrosis injury were observed in the Model 1 and Model 2 groups, with the Model 2 group showing more significance (Figure 3A and B). Furthermore, TFR1 and a-SMA expression in each group were evaluated by immunohistochemical staining and the results showed that TFR1 was significantly up-regulated in the model groups, with higher

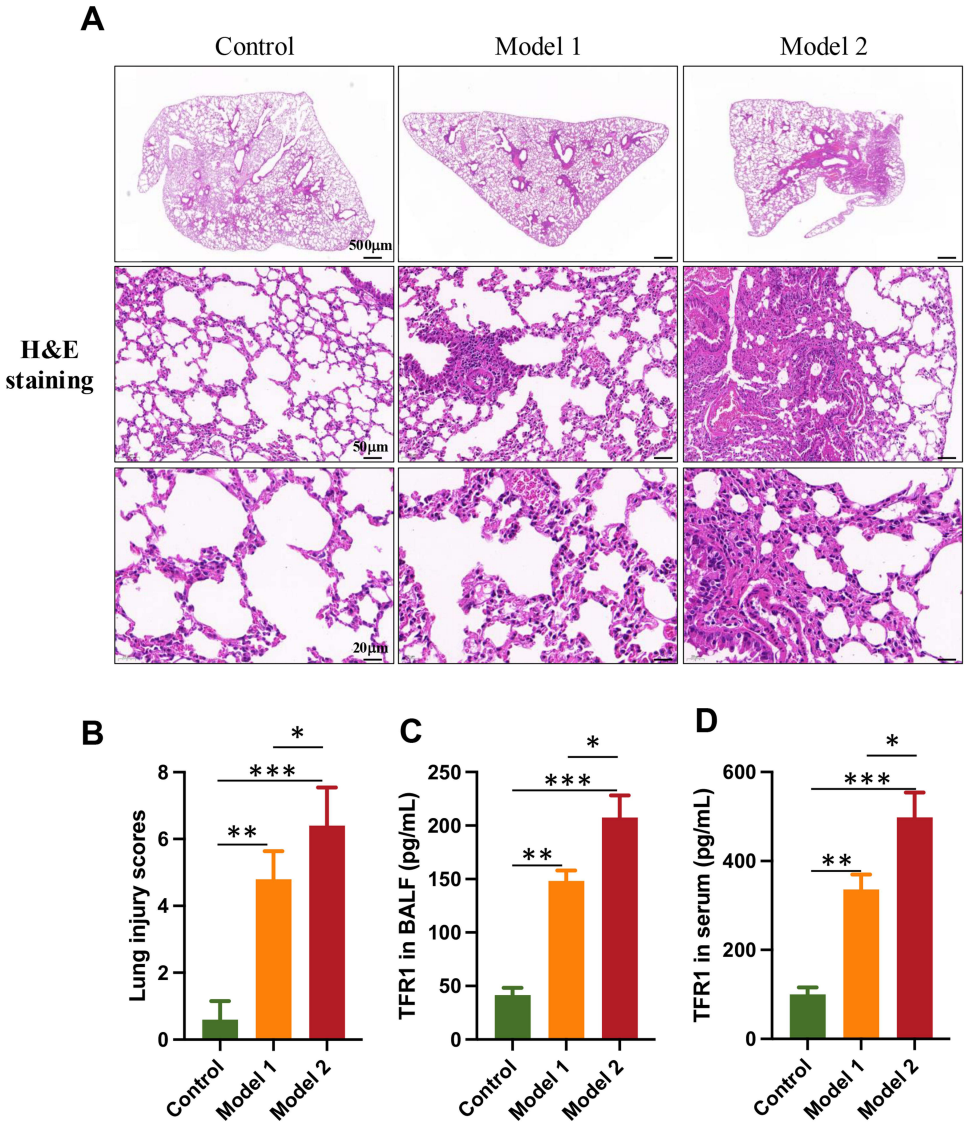

Figure 2 The TFR1 level was correlated with lung injury in COPD mice. (**A**) HE staining of lung tissue. (**B**) Lung injury scores for the three groups. (**C**) The content of TFR1 in the BALF. (**D**) The contents of TFR1 in serum. *means $P < 0.05$. **means $P < 0.01$. ***means $P < 0.001$.

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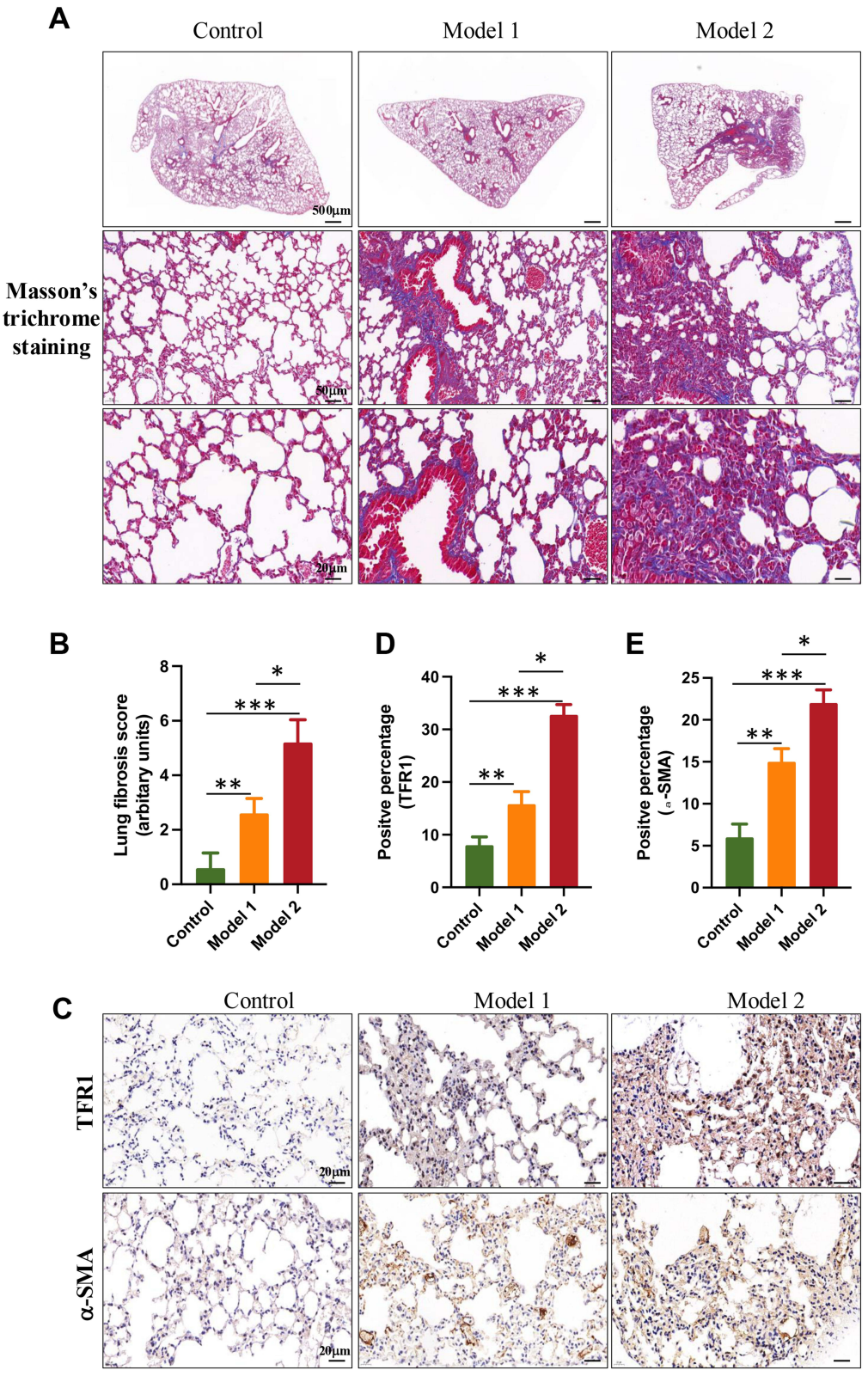

Figure 3 The TFR1 level was correlated with lung fibrosis in COPD mice. (**A**) Masson trichrome staining of lung tissues. (**B**) Lung fibrosis scores for the three groups. (**C** and **A**) IHC staining of TFR1 and α-SMA in lung tissues. (**D** and **E**) the positive percentage of TFR1 and α-SMA based on IHC staining. *means $P < 0.05$. **means $P < 0.01$. ***means $P < 0.001$.

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positivity in the Model 2 group, consistent with the expression of a-SMA (Figure 3C–E). These results indicated that the level of TFR1 was also closely related to pulmonary fibrosis injury.

Discussion

This study is the first to demonstrate that COPD patients with increased serum TFR1 in COPD patients were related to recurrent acute exacerbations and develop pulmonary fibrosis. TFR1, as a marker for ferroptosis, might serve as a potential indicator for the evaluation of the severity of pulmonary fibrosis in clinical practice in the future.

The objective of the evaluation of COPD is to clarify the severity of the disease, its impact on the patient's health status, and the risk of certain events (acute exacerbation, hospitalization, and death), while guiding treatment.[23,24] The comprehensive evaluation included symptoms of the disease, the degree of airflow limitation (lung function test), the risk of acute exacerbation, and comorbidities. MMRC is positively correlated with the severity of airflow limitation and lung function impairment, with mMRC greater than 2 serving as the boundary between "mild respiratory distress" and "severe respiratory distress". A CAT score <10 indicates the need for medical intervention.[25,26] Due to the fact that all of the patients we collected were in the hospital, the mean mMRC values for both the low TFR1 group and the high TFR1 group were greater than 2. The mean values of the CAT score of the patients in both the low TFR1 group and the high TFR1 group were greater than 10. However, it can be seen that the mMRC and CAT scores of the TFR1 high group are higher, which also indicates that the level of the TFR1 group is related to the severity of the disease, although there is no statistical difference. Lung function is another important diagnostic and reference basis for evaluating the condition of COPD. This study examined indicators of lung function such as RV/TLC%, FEV1% pred, FEV1/FVC%, MMEF%, DLCO%, DLCO / VA% and GOLD grade. It also indicated that the levels of TFR1 were related to the lung function. The acute exacerbation of COPD patients is mainly related to infection, and among the infection-related indicators, we observed that TFR1 was only related to the rate of erythrocyte sedimentation and had no relationship with levels of IL-6, C-reactive protein, and LDH. Furthermore, by comparing the differences in inflammatory indicators between high and low levels of TFR1, it was found that there was no significant difference in TFR1 levels and inflammatory indicators. This indicated that the level of TFR1 was associated with lung but not with inflammatory factors.

As COPD progresses and acute exacerbations recur, it can cause airway remodeling and changes in lung interstitial, which eventually develop into pulmonary interstitial fibrosis.[27,28] As a more serious complication in the course of COPD, pulmonary interstitial fibrosis can further aggravate lung function damage as the severity of fibrosis increases.[29,30] Failure to provide timely treatment and control of the disease can lead to respiratory failure or death in patients.[31] Our results indicated that the level of TFR1 is positively correlated with the frequency of acute exacerbations and the score of lung fibrosis in one year. And it was found that by grouping with increased frequency to observe TFR1 levels and indicators related to fibrosis, patients with more frequent acute exacerbation (more than 2 times per year) had higher levels of TFR1 and COL3. The results of predicting the frequency of acute exacerbations based on the level of TFR1, the level of COL3, and the fibrosis score indicated that TFR1 had greater sensitivity and specificity compared to the level of COL3 and the fibrosis score. Taking into account the difficulty of obtaining lung biopsy tissue from COPD patients, we also observed the association between TFR1 levels and lung injury in a mouse COPD model. As expected, we observed a more intuitive correlation between TFR1 levels and lung injury and fibrosis scores in a mouse COPD model. This result supported the use of TFR1 as a biomarker to predict the degree of lung injury and evaluate pulmonary fibrosis.

With the deepening and enrichment of the research on TFR1, it is now clear that TFR1 is closely related to various tumors and some brain diseases, including Parkinson's, stroke, and acute brain injury.[32,33] And based on these studies, a series of drugs targeting TFR1 have also been developed for clinical diseases, which currently in the clinical trial stage.[13,34] We can see the broad applications prospects of drugs targeting TFR1 inhibition. However, currently there is very little research on the relationship between TFR1 and COPD. A study found that TTR1+macrophages are involved in the process of pulmonary fibrosis injury, and DFO treatment can work by reducing ferroptosis.[35]

Conclusion

This study provides some evidence that TFR1 is involved in COPD lung injury, indicating that TFR1 is related to the acute exacerbations of COPD and COPD-associated pulmonary fibrosis, and also provides new evidence for targeted

inhibition of TFR1 therapy for COPD. However, only 97 patients were included in the study, and more patients are needed to clarify the specific levels of TFR1 and the cutoff values for grouping. Patients who have not developed pulmonary fibrosis should be set as controls to clarify the level of TFR1 in pulmonary fibrosis. In summary, the prevention and treatment of COPD are crucial and TFR1 is a highly promising therapeutic target. We hope that our research can help improve and improve the prognosis of patients with COPD.

Data Sharing Statement

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study contained COPD patients was approved by the Ethics Committee of Hunan Provincial Hospital, Hunan Normal University (2024-260) and was carried out according to the Declaration of Helsinki guidelines. All patients signed informed consent. The animal study was approved by the Ethics Committee of Hunan Provincial Hospital, Hunan Normal University (2024-107). All methods were performed in accordance with the relevant guidelines and regulations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of interest.

References

1. Sin DD, Doiron D, Agusti A, et al. Air pollution and COPD: GOLD 2023 committee report. *Eur Respir J*. 2023;61(5):2202469. doi:10.1183/13993003.02469-2022
2. Yang IA, Jenkins CR, Salvi SS. Chronic obstructive pulmonary disease in never-smokers: risk factors, pathogenesis, and implications for prevention and treatment. *Lancet Respir Med*. 2022;10(5):497–511. doi:10.1016/S2213-2600(21)00506-3
3. Fang L, Gao P, Bao H, et al. Chronic obstructive pulmonary disease in China: a nationwide prevalence study. *Lancet Respir Med*. 2018;6(6):421–430. doi:10.1016/S2213-2600(18)30103-6
4. Yong J, Shu H, Zhang X, et al. Natural products-based inhaled formulations for treating pulmonary diseases. *Int J Nanomed*. 2024;19:1723–1748. doi:10.2147/IJN.S451206
5. Agarwala P, Salzman SH. Six-minute walk test: clinical role, technique, coding, and reimbursement. *Chest*. 2020;157(3):603–611. doi:10.1016/j.chest.2019.10.014
6. Vogelmeier CF, Román-Rodríguez M, Singh D, Han MK, Rodríguez-Roisin R, Ferguson GT. Goals of COPD treatment: focus on symptoms and exacerbations. *Respir Med*. 2020;166:105938. doi:10.1016/j.rmed.2020.105938
7. Stolz D, Mkorombindo T, Schumann DM, et al. Towards the elimination of chronic obstructive pulmonary disease: a lancet commission. *Lancet*. 2022;400(10356):921–972. doi:10.1016/S0140-6736(22)01273-9
8. Fan P, Zhang Y, Ding S, Du Z, Zhou C, Du X. Integrating RNA-seq and scRNA-seq to explore the mechanism of macrophage ferroptosis associated with COPD. *Front Pharmacol*. 2023;14:1139137. doi:10.3389/fphar.2023.1139137
9. Yoshida M, Minagawa S, Araya J, et al. Involvement of cigarette smoke-induced epithelial cell ferroptosis in COPD pathogenesis. *Nat Commun*. 2019;10(1):3145. doi:10.1038/s41467-019-10991-7
10. Xu W, Deng H, Hu S, et al. Role of ferroptosis in lung diseases. *J Inflamm Res*. 2021;14:2079–2090. doi:10.2147/JIR.S307081
11. Li C, Chen F, Lin L, Li J, Zheng Y, Chen Q. CSE triggers ferroptosis via SIRT4-mediated GNPAT deacetylation in the pathogenesis of COPD. *Respir Res*. 2023;24(1):301. doi:10.1186/s12931-023-02613-0
12. Liu J, Zhang Z, Yang Y, Di T, Wu Y, Bian T. NCOA4-mediated ferroptosis in bronchial epithelial cells promotes macrophage M2 polarization in COPD emphysema. *Int J Chron Obstruct Pulmon Dis*. 2022;17:667–681. doi:10.2147/COPD.S354896

13. Candelaria PV, Leoh LS, Penichet ML, Daniels-Wells TR. Antibodies targeting the transferrin receptor 1 (TfR1) as direct anti-cancer agents. *Front Immunol*. 2021;12:607692. doi:10.3389/fimmu.2021.607692
14. Wang D, Liang W, Huo D, et al. SPY1 inhibits neuronal ferroptosis in amyotrophic lateral sclerosis by reducing lipid peroxidation through regulation of GCH1 and TFR1. *Cell Death Differ*. 2023;30(2):369–382. doi:10.1038/s41418-022-01089-7
15. Senyilmaz D, Virtue S, Xu X, et al. Regulation of mitochondrial morphology and function by stearoylation of TFR1. *Nature*. 2015;525 (7567):124–128. doi:10.1038/nature14601
16. Chen L, Ma Y, Ma X, et al. TFEB regulates cellular labile iron and prevents ferroptosis in a TfR1-dependent manner. *Free Radic Biol Med*. 2023;208:445–457. doi:10.1016/j.freeradbiomed.2023.09.004
17. Wang Y, Gu LF, Zhao X, Hu C, Chen Q. TFR1 expression in induced sputum is associated with asthma severity. *PeerJ*. 2022;10:e13474. doi:10.7717/peerj.13474
18. Zhou J, Du JY, Xu R, Wu XJ, Zhang GY. Reduced miR-513a-5p expression in COPD may regulate airway mucous cell hyperplasia through TFR1-dependent signaling. *Kaohsiung J Med Sci*. 2024;40(2):139–149. doi:10.1002/kjm2.12777
19. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532–555. doi:10.1164/rccm.200703-456SO
20. Wu Y, Li B, Xuan Y, et al. Fluorofenidone alleviates cigarette smoke exposure-induced chronic lung injury by targeting ferroptosis. *Sci Rep*. 2024;14(1):32149. doi:10.1038/s41598-024-83998-w
21. Schingnitz U, Hartmann K, Macmanus CF, et al. Signaling through the A2B adenosine receptor dampens endotoxin-induced acute lung injury. *J Immunol*. 2010;184(9):5271–5279. doi:10.4049/jimmunol.0903035
22. Ashcroft T, Simpson JM, Timbrell V. Simple method of estimating severity of pulmonary fibrosis on a numerical scale. *J Clin Pathol*. 1988;41 (4):467–470. doi:10.1136/jcp.41.4.467
23. Jones PW, Harding G, Berry P, Wiklund I, Chen WH, Kline Leidy N. Development and first validation of the COPD assessment test. *Eur Respir J*. 2009;34(3):648–654. doi:10.1183/09031936.00102509
24. Ko FW, Chan KP, Hui DS, et al. Acute exacerbation of COPD. *Respirology*. 2016;21(7):1152–1165. doi:10.1111/resp.12780
25. Chuatrakoon B, Uthaikhup S, Ngai SP, Liwsrisakun C, Pothirat C, Sungkarat S. The effectiveness of home-based balance and pulmonary rehabilitation program in individuals with chronic obstructive pulmonary disease: a randomized controlled trial. *Eur J Phys Rehabil Med*. 2022;58(3):478–486. doi:10.23736/S1973-9087.22.07383-X
26. Wang J, Chen X, He S, et al. COPD assessment test and risk of readmission in patients with bronchiectasis: a prospective cohort study. *ERJ Open Res*. 2024;10(2):00867–2023. doi:10.1183/23120541.00867-2023
27. Hage R, Gautschi F, Steinack C, Schuurmans MM. Combined pulmonary fibrosis and emphysema (CPFE) clinical features and management. *Int J Chron Obstruct Pulmon Dis*. 2021;16:167–177. doi:10.2147/COPD.S286360
28. De Rose V, Molloy K, Gohy S, Pilette C, Greene CM. Airway epithelium dysfunction in cystic fibrosis and COPD. *Mediators Inflamm*. 2018;2018:1309746. doi:10.1155/2018/1309746
29. Radicioni G, Ceppe A, Ford AA, et al. Airway mucin MUC5AC and MUC5B concentrations and the initiation and progression of chronic obstructive pulmonary disease: an analysis of the SPIROMICS cohort. *Lancet Respir Med*. 2021;9(11):1241–1254. doi:10.1016/S2213-2600(21)00079-5
30. Beghé B, Cerri S, Fabbri LM, Marchioni A. COPD, pulmonary fibrosis and ILAs in aging smokers: the paradox of striking different responses to the major risk factors. *Int J Mol Sci*. 2021;22(17):9292. doi:10.3390/ijms22179292
31. Haworth CS, Shteinberg M, Winthrop K, et al. Inhaled colistimethate sodium in patients with bronchiectasis and Pseudomonas aeruginosa infection: results of PROMIS-I and PROMIS-II, two randomised, double-blind, placebo-controlled Phase 3 trials assessing safety and efficacy over 12 months. *Lancet Respir Med*. 2024;12(10):787–798. doi:10.1016/S2213-2600(24)00225-X
32. Cai S, Ding Z, Liu X, Zeng J. Trabectedin induces ferroptosis via regulation of HIF-1α/IRP1/TFR1 and Keap1/Nrf2/GPX4 axis in non-small cell lung cancer cells. *Chem Biol Interact*. 2023;369:110262. doi:10.1016/j.cbi.2022.110262
33. Youssef MAM, Mohamed TM, Bakry AA, El-Keiy MM. Synergistic effect of spermidine and ciprofloxacin against Alzheimer's disease in male rat via ferroptosis modulation. *Int J Biol Macromol*. 2024;263(Pt 2):130387. doi:10.1016/j.ijbiomac.2024.130387
34. Ding H, Chen S, Pan X, et al. Ablation of the transferrin receptor 1 ablation in satellite cells impedes skeletal muscle regeneration through activation of ferroptosis. *J Cachexia Sarcopenia Muscle*. 2021;12(3):746–768. doi:10.1002/jcsm.12700
35. Ali MK, Kim RY, Brown AC, et al. Critical role for iron accumulation in the pathogenesis of fibrotic lung disease. *J Pathol*. 2020;251(1):49–62. doi:10.1002/path.5401