Evaluation of fractional exhaled nitric oxide in interstitial lung disease

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Abstract

Background

No established biomarkers are available to guide the treatment of chronic interstitial lung diseases (ILDs). Nitric oxide reflects the inflammation in the airway, and fractional exhaled nitric oxide (FeNO) is a non-invasive and reproducible biomarker in lung-disease diagnosis and treatment. Whether FeNO can help manage ILDs remains uncertain. This study aimed to determine the role of FeNO in ILDs and the association between FeNO and ILD subtype.

Methods

53 patients with ILDs were retrospectively recruited. Patient characteristics, FeNO values, blood tests for inflammatory markers, and pulmonary function test data were obtained.

Results

This group of patients with ILDs had decreased vital capacity(VC)and total lung capacity(TLC) of 71.75 ± 17.58% and 75.27 ± 14.07%, respectively. The diffusion capacity of the lung for carbon monoxide(DLCO) also declined, with an average level of 38.15 ± 11.10%. The average FeNO value was 20.34 ± 9.97 ppb. According to the characteristics of chest computed tomography, patients were divided into usual interstitial pneumonia (UIP)-ILD (n = 24) and non-UIP-ILD (n = 29). The FeNO value in the UIP-ILD group was 12.58 ± 3.63 ppb. This value was significantly lower than that of the non-UIP-ILD group (26.62 ± 8.61 ppb, P<0.0001).According to the etiology, all patients with ILDs were divided into connective tissue diseases associated with interstitial lung disease (CTD-ILD) (n = 30) and non-CTD-ILD (n = 23). There were more female patients in CTD-ILD group compared to non-CTD ILD group and patients in CTD-ILD group were younger. With regard to the FeNO, PFT values, and systemic inflammatory markers, no significant differences were observed between groups. In the overall ILD population, FeNO level correlated with blood eosinophil (r = 0.3066, P=0.0333), but no statistical significant correlations were observed between the FeNO and blood eosinophil percentage, IgE or systemic inflammatory markers. The FeNO cut-off value of 18.5 ppb showed a sensibility of 83.3% and a specificity of 95.8% in discriminating non-UIP-ILDs from UIP ILDs.

Conclusions

Our study suggested the importance of FeNO test in patients with ILDs. High FeNO levels may indicate the need of systemic treatment, and FeNO can be a helpful biomarker for ILD management.

Background

Chronic interstitial lung diseases (ILD) are diseases involving the lung parenchymal tissue leading to chronic inflammation and fibrosis and finally result in respiratory failure [1]. ILDs are a great challenge for clinicians because they have several issues with regard to the diagnosis, treatment, and prognosis [1].

The etiologies of ILDs can be classified as known and unknown forms. Hundreds of diseases causing ILDs now exist, and the classification is constantly updating in recent years [3]. However, only several drugs, such corticosteroid, immunosuppressive drugs like CTX, MMF, and CsA, and new coming drugs like nintedanib and pirfenidone, are available for ILDs [3–5]. Immunosuppressive drugs can help restrict the progression of several ILDs, such as connective tissue diseases associated with interstitial lung disease (CTD-ILD) in non-idiopathic interstitial lung disease and nonspecific interstitial pneumonitis (NSIP) in idiopathic interstitial lung disease [6–8]. However, these drugs exhibit multiple side effects. Finding good markers to predict the response of immunosuppressive drugs, which may help clinicians decide the right treatment, would be helpful.

Nitric oxide (NO) is produced by airway epithelial cells in the airway and is involved in lung inflammation, nitrosative-oxidative stress, and vasodilation [9]. Fractional exhaled nitric oxide (FENO) is a non-invasive and reproducible biomarker in the diagnostic algorithm of lung diseases. The asthma guideline has suggested FENO as a marker of airway inflammation to determine the optimal dosage of inhaled corticosteroid [10–11]. Only several studies of FENO in ILDs are available. In addition, these works suggested FeNO as a potential severity biomarker in patients with ILDs, but most of the studies focus on systemic sclerosis, and the results were conflicting [12–14]. To the best of our knowledge, no study focusing on FENO as a marker of ILD treatment is available.

Our study aimed to determine whether differences exist in the FENO level between different subtypes of ILD. We carried out a retrospective study of FENO data of patients with ILDs. Patients were divided into two groups, namely, UIP pattern and non-UIP pattern, based on the lung computed tomography (CT) pattern. FENO values were compared between groups, and inflammatory markers were analyzed to investigate the relationship between FENO and disease activity.

Methods

Study population and study design

From December 2017 to December 2019, 53 patients with ILDs were retrospectively recruited at the First Affiliated Hospital of Sun Yat-sen University. Diagnosis was made according to the international guidelines [15–16]. Medical history was reviewed to investigate the inflammatory markers. All patients could perform pulmonary function tests (PFT), including single-breath diffusion capacity of the lung for carbon monoxide (DLCO). All patients received high-resolution computed tomography of the chest for diagnostic purposes to evaluate the specific radiological patterns. All included patients were clinically stable and free of acute respiratory infections and/or acute exacerbations of ILDs for at least 8 weeks. Patients with atopy, asthma, cancer or in current therapy with biological agents were excluded in all cases.

The study was reviewed by the Institutional Research Ethics Committee of our hospital. The requirement for approval and the informed consent form were exempt because this study was not an intervening trial and was retrospective in nature.

Collection procedure and data analysis

Medical history, patient characteristics and data (FeNO values, blood tests, and PFT data) were obtained from the patients' medical charts.

Measurement Of FeNO

FeNO value was determined according to the recommendations of the American Thoracic Society (ATS) by using a conventional chemoluminescence analyser (NIOX MINO; Aerocrine AB, Sweden) [17]. The participants were instructed to use the online standardized single breath technique: inhale air without NO to total lung capacity (TLC) and complete the exhalation immediately into the device at a constant flow rate of 50 mL/s for 10 seconds. Values more than 50 ppb are considered high probability for eosinophilic inflammation. Values less than 25 ppb indicate a low probability, and values between 25 and 50 ppb signify intermediary probability.

Pulmonary Function Test

Participants underwent PFT after the measurement of FeNO .PFT was performed using body plethysmography following the 2014 recommendations of the Chinese National Guidelines of Pulmonary Function Test [18]. All participants performed PFT in a reproducible way and the best values of each subject were selected.

Bronchial Hyper-responsiveness Test (BHR)

After baseline evaluation, patients with forced expiratory volume in 1 s (FEV1) percentage predicted more than 70% should take BHR to rule out bronchial hyper-responsiveness. Airway hyperresponsiveness is expressed as the provocative concentration of histamine when FEV1 decreased by 20% from baseline (PC20). In our study, the positive response was defined as PC20 ≤ 8 mg/ml.

Statistical analysis

All data analyses were performed using SPSS software (version 18.0) (SPSS Inc., Chicago, IL, USA). The results are shown as mean ± standard deviation or number (%) of patients, or median (interquartile range) for quantitative variables or for non-normal variables when appropriate. Comparison of differences between groups were conducted by the Student's t-test for those that were normally distributed or the Mann–Whitney U test for those that were not. Categorical variables were compared using the chi-squared test. The relationship between the FeNO levels and IgE, blood eosinophil counts, blood eosinophil percent, and inflammatory marker level was assessed by determining the Spearman's rank correlation coefficients. ROC curves were used to determine the cut-off value of FeNO in ILD evaluation. $P < 0.05$ was defined as statistically significant. Statistical analyses and figures were performed using GraphPad Prism5.

Results

Characteristics of study subjects

A total of 53 patients in stable phrase of ILDs were enrolled in this study. The majority of the patients were males (62.26%), with the average age of 58.64 ± 13.94 years old, mean %FEV1 of 75.94 ± 18.31%, and mean %FEV1/FVC of 83.04 ± 8.55%. This condition demonstrates a restrictive functional impairment. This group of patients with ILDs had a decreased vital capacity(VC)and TLC of 71.75 ± 17.58% and 75.27 ± 14.07%, respectively. DLCO also declined, with an average level of 38.15 ± 11.10%. The average FeNO value was 20.34 ± 9.97 ppb. The clinical features and PFT data of the study population are shown in Table 1.

Table 1

Clinical features and PFT data of patients with ILD

Parameter	ILD (N = 53)
Mean age, years	58.64 ± 13.94
Sex (M:F),n	33:20
Height (cm)	161.51 ± 7.24
Weight (kg)	61.40 ± 10.78
Body surface area(m^2)	1.64 ± 0.16
BMI in kg/m^2	23.49 ± 3.67 (range = 14.27–32.05)
FVC (% predicted)	74.08 ± 18.14
FEV1 (% predicted)	75.94 ± 18.31
FEV1/FVC	83.04 ± 8.55
PEF (% predicted)	69.57 ± 20.34
MEF (% predicted)	79.09 ± 34.34
MEF25 (% predicted)	56.83 ± 32.48
MEF50 (% predicted)	77.06 ± 34.12
MEF75 (% predicted)	63.13 ± 23.00
MVV (% predicted)	87.23 ± 25.96
VC (% predicted)	71.75 ± 17.58
TLC (% predicted)	75.27 ± 14.07
RV(% predicted)	88.80 ± 19.28
RV/TLC(% predicted)	44.73 ± 7.20
DLCO (% predicted)	38.15 ± 11.10
FeNO(ppb)	20.34 ± 9.97

Notes: Measured pulmonary function values are presented as a predictive percentage. Data are shown as mean ± standard deviation unless indicated otherwise. Abbreviations: M, male; F, female; BMI, body mass index; $FEV1^1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow after 25% of the FVC; MEF50, forced expiratory flow after 50% of the FVC; MEF75, forced expiratory flow after 75% of the FVC; MVV, maximal voluntary ventilation; VC, vital capacity; RV, residual volume, TLC, total lung capacity, DLCO, diffusion capacity of the lung for carbon monoxide; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; ILD, interstitial lung diseases; PFT, pulmonary function test.

FeNO And Clinical-radiological Features

According to the characteristics of chest CT, patients were divided into UIP-ILD (n = 24) (with UIP features and predominant fibrosis) and non-UIP-ILD (n = 29). No significant differences were observed with regard to age, gender, height, weight, and body mass index between these two groups. The FeNO value in the UIP-ILD group was 12.58 ± 3.63 ppb. This value was significantly lower than that of the non-UIP-ILD group (26.62 ± 8.61 ppb, $P < 0.0001$) (Fig. 1). However, no significant differences were observed in the PFT values between these two groups (Table 2). The blood eosinophils and the IgE levels were lower in the UIP-ILD group than those of the non-UIP-ILD group. However, the differences did not reach statistical significance. Concerning the systemic inflammatory markers, such as ESR and CRP, no significant differences were reported between these two groups (Table 2).

Table 2

Clinical features in patients with ILDs with UIP pattern and non-UIP pattern

Parameter	UIP pattern (N = 24)	Non-UIP pattern (N = 29)	P value
Mean age, years	57.54 ±15.45	59.55 ± 12.77	0.606
Sex (M:F),n	13:11	20:9	
Height (cm)	160.83 ± 8.16	162.07 ± 6.47	0.542
Weight (kg)	60.58 ± 11.80	62.07 ± 10.02	0.622
Body surface area (m^2)	1.63 ± 0.18	1.65 ± 0.14	0.528
BMI in kg/m^2	23.35 ±4.02	23.62 ± 3.42	0.794
FVC (% predicted)	75.96 ± 17.13	72.52 ± 19.09	0.497
FEV1 (% predicted)	77.75 ± 19.92	74.45 ± 17.07	0.519
FEV1/FVC	82.79 ±10.72	83.24 ± 6.42	0.851
PEF (% predicted)	67.83 ± 17.94	71.00 ± 22.34	0.578
MEF (% predicted)	82.96 ±43.37	75.90± 24.94	0.462
MEF25 (% predicted)	63.88 ± 41.17	51.00 ± 22.11	0.153
MEF50 (% predicted)	78.42 ± 40.29	75.93 ± 28.73	0.795
MEF75 (% predicted)	61.88 ± 20.76	64.17 ± 25.02	0.721
MVV (% predicted)	86.04 ±28.48	88.21 ± 24.14	0.766
VC (% predicted)	74.08 ± 16.76	69.83 ± 18.29	0.385
TLC (% predicted)	76.14 ± 11.76	74.62 ± 15.77	0.707
RV(% predicted)	90.50 ±19.16	87.52 ± 19.60	0.589
RV/TLC(% predicted)	44.86 ± 7.03	44.62 ± 7.44	0.906
DLCO (% predicted)	45.38 ±17.25	50.00 ± 18.27	0.450
Total serum IgE (IU/ml)	140.04 ± 139.16	202.36 ± 177.83	0.290

Notes: Measured pulmonary function values are presented as a predictive percentage. Data are shown as mean ± standard deviation unless indicated otherwise. Abbreviations: M, male; F, female; BMI, body mass index; $FEV1^1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow after 25% of the FVC; MEF50, forced expiratory flow after 50% of the FVC; MEF75, forced expiratory flow after 75% of the FVC; MVV, maximal voluntary ventilation; VC, vital capacity; RV, residual volume, TLC, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; UIP, usual interstitial pneumonia; PFT, pulmonary function test.

Parameter	UIP pattern (N = 24)	Non-UIP pattern (N = 29)	P value
Blood eosinophils absolute (cells/μl)	164.57 ± 159.88	240.74 ± 198.09	0.126
Blood eosinophil percentage	2.05 ± 2.04	3.07 ± 2.08	0.083
CRP (mg/L)	20.60 ± 15.53	18.47 ± 17.34	0.873
ESR (mm/h)	48.56 ± 36.23	39.92 ± 28.37	0.386
FeNO (ppb)	12.58 ± 3.63	26.62 ± 8.61	< 0.0001

Notes: Measured pulmonary function values are presented as a predictive percentage. Data are shown as mean ± standard deviation unless indicated otherwise. Abbreviations: M, male; F, female; BMI, body mass index; $FEV1^1$, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow after 25% of the FVC; MEF50, forced expiratory flow after 50% of the FVC; MEF75, forced expiratory flow after 75% of the FVC; MVV, maximal voluntary ventilation; VC, vital capacity; RV, residual volume, TLC, total lung capacity; DLCO, diffusion capacity of the lung for carbon monoxide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; UIP, usual interstitial pneumonia; PFT, pulmonary function test.

FeNO And CTD-ILD

According to the etiology, all patients with ILDs were divided into CTD-ILD (n = 30) and non-CTD-ILD (n = 23). There were more female patients in CTD-ILD group compared to non-CTD ILD group (50.00% vs 21.74%). Patients in CTD-ILD group were younger than non-CTD ILD group (P = 0.022). No significant differences were observed with regard to height, weight, and body mass index between these two groups. Regarding the FeNO value and PFT values, no significant differences were observed between groups. No significant differences were reported in systemic inflammatory markers, such as ESR and CRP, between groups (Table 3).

Table 3
Clinical characteristics in CTD-ILD and non-CTD patients with ILD

Parameter	CTD-ILD (N = 30)	non-CTD-ILD (N = 23)	P value
Mean age, years	54.83 ± 14.17	63.61 ± 12.22	0.022
Sex (M/F), n	15:15	18:5	
Height (cm)	161.87 ± 7.09	161.04 ± 7.56	0.686
Weight (kg)	58.80 ± 11.85	64.78 ± 10.27	0.054
Body surface area (m^2)	1.62 ± 0.18	1.68 ± 0.12	0.142
BMI in kg/m^2	23.30 ± 3.56	24.06 ± 3.25	0.235
FVC (% predicted)	75.40 ± 18.80	72.35 ± 17.50	0.549
FEV1 (% predicted)	77.10 ± 20.08	74.43 ±16.02	0.604
FEV1/FVC	83.67± 9.17	82.22 ± 7.79	0.546
PEF (% predicted)	69.03 ± 22.84	70.26 ± 17.00	0.830
MEF (% predicted)	82.43 ± 35.42	74.74 ± 33.15	0.424
MEF25 (% predicted)	63.20 ± 35.48	48.52 ± 26.58	0.103
MEF50 (% predicted)	79.17 ± 35.47	74.30 ± 32.85	0.612
MEF75 (% predicted)	65.77 ± 24.65	59.70 ± 20.67	0.346
MVV (% predicted)	82.33 ± 23.49	93.61 ± 28.11	0.118
VC (% predicted)	72.27 ± 18.06	71.09 ± 17.30	0.811
TLC (% predicted)	76.43 ± 14.74	73.87 ±13.39	0.523
RV (% predicted)	91.54 ± 21.26	85.48 ± 16.39	0.268
RV/TLC (% predicted)	43.61 ± 7.43	46.09 ± 6.81	0.224
DLCO (% predicted)	48.05± 18.34	47.64 ± 17.37	0.948
Total serum IgE (IU/ml)	213.80 ± 184.28	131.23 ± 126.00	0.155
Blood eosinophils absolute (cells/μl)	168.29 ± 164.82	253.18 ± 199.20	0.094
Blood eosinophil percentage	2.04 ± 1.85	3.07 ± 2.24	0.073
CRP (mg/L)	20.33 ± 18.70	17.42 ± 15.25	0.737
ESR (mm/h)	47.34 ± 36.19	38.20 ± 23.86	0.374
FeNO (ppb)	18.33 ± 8.35	22.78 ± 11.05	0.101

Notes: Measured pulmonary function values are presented as a percentage of predictive. Data are shown as mean ± standard deviation unless indicated otherwise. Abbreviations: M, male; F, female; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; MEF, maximal midexpiratory flow; MEF25, forced expiratory flow after 25% of the FVC; MEF50, forced expiratory flow after 50% of the FVC; MEF75, forced expiratory flow after 75% of the FVC; MVV, maximal voluntary ventilation; VC, vital capacity; RV, residual volume, TLC, total lung capacity, DLCO, diffusion capacity of the lung for carbon monoxide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FeNO, fractional exhaled nitric oxide; ppb, parts per billion; CTD-ILD, connective tissue diseases associated with interstitial lung disease.

Correlation of FeNO and blood eosinophil, IgE, and systemic inflammatory markers

In the overall ILD population, the FeNO level correlated with blood eosinophil ($r = 0.3066$, $P = 0.0333$). No statistically significant correlations were observed between the FeNO and blood eosinophil percentage, IgE or systemic inflammatory markers. (Fig. 2).

Notes The correlations between FeNO values and blood eosinophil, IgE or systemic inflammatory markers were determined by calculating Spearman's rank correlation coefficients. Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FeNO, fractional exhaled nitric oxide.

Discriminating UIP-ILDs and UIP-ILDs

Receiver operating characteristic (ROC) curve was performed to find the optimal cut-off value of FeNO to identify non-UIP-ILDs. The area under the ROC curve was 0.933 with a cut-off value of 18.5 ppb, showing a sensibility of 83.3% and a specificity of 95.8% in discriminating non-UIP-ILDs from UIP ILDs (Fig. 3). Table 4 shows the sensitivity and specificity values for different criteria tested.

Table 4
Sensitivity and specificity of different cut-points used to identify non-UIP-ILDs

Parameter	Threshold	Sensitivity (%)	Specificity (%)
FeNO level	> 12.5 ppb	93.1	50.0
FeNO level	> 13.5 ppb	93.1	58.3
FeNO level	> 14.5 ppb	93.1	66.7
FeNO level	> 15.5 ppb	93.1	75.0
FeNO level	> 16.5 ppb	83.3	83.3
FeNO level	> 17.5 ppb	83.3	91.7
FeNO level	> 18.5 ppb	83.3	95.8
FeNO level	> 20.0 ppb	66.7	100
Abbreviations: FeNO, fractional exhaled nitric oxide; ppb, part per billion.			

Discussion

We analyzed the clinical characteristics, including PFT and FeNO level of interstitial lung diseases. In particular, we aim to evaluate the potential utility of FeNO as a potential marker of treatment in ILDs. Our study suggested the FeNO importance in patients with ILDs because ILDs with non-UIP pattern had higher level of FeNO than the UIP pattern. FeNO could be a marker to predict treatment response to systemic corticosteroid or other immunosuppressive drugs in ILDs.

FeNO is a well-known biomarker in lung disease and reflects the inflammatory disorders of the lung [19] To date, limited literature is available on the FeNO level in ILDs. Most of these studies have focused on IPF and CTD-ILD, such as SSS and sarcoidosis. However, the results were controversial.

With regard to the changes of FeNO in IPF, Saleh et al [20], showed that FeNO may be elevated in patients with IPF. Notably, the FeNO increase was related to early to intermediate stage of the disease, suggestive of a protective role of FeNO on lung architecture and pulmonary homeostasis. Further study showed strong expression of nitrotyrosine and NOS in alveolar epithelium in the early to intermediate stage of IPF. This finding suggests the role of FeNO as a marker of early stage in ILDs. The active stage of IPF or other ILDs was associated with increased inflammatory and thus required highly intensive observation and treatment.

The FeNO level of patients with ILDs in our study was 20.34 ± 9.97 ppb, with 12.58 ± 3.63 ppb in the UIP-ILD group. This result was comparable with those reported by Paredi et al [21], but relatively lower than previously reported. In one study, Cameli et al. measured FeNO values in patients with idiopathic

interstitial pneumonitis and healthy controls at different flow rates. Patients with IPF showed average FeNO levels of 22.3 ± 8.4 ppb [22]. Another study reported by Guilleminault revealed similar results. The median level of FeNO was 19 ppb in IPF and 25 ppb in CTD-ILD [23]. However, Schildge investigated patients with ILDs including IPF, CTD-ILD, and sarcoidosis and found average level of 27.6 ± 16.3 ppb; this value was higher than the other two studies [24]. Several reasons may elucidate for the differences in FeNO values. One of the main reasons is the patients' characteristics. FeNO is associated with inflammatory disorders of the lung. However, in patients with neutrophil predominant airway diseases, such as cystic fibrosis [25, 26], FeNO is decreased. The underlying mechanism is reduced expression of NO synthase isoenzyme, lack of NOS substrates, and increased decomposition of NO by neutrophilic myeloperoxidase [27–29] Decreased NO can lead to increased airway narrowing and impaired ciliary function, causing further impairment to the lung [30] Therefore, this phenomenon becomes a vicious cycle. In our study, the patients in the UIP-ILD group are characterized with predominant fibrosis of the lung, indicating low active inflammatory level with predominant neutrophil. Low FeNO level is consistent with the patients' features. Another reason for the differences in FeNO levels is the devices used in the studies. Reportedly, the absolute FeNO values are related to the underlying way of NO measurement of the FeNO device. Low FeNO levels have been observed when using the chemiluminescence method (NIOXMino, Aerocrine), which was implied in the Cameli and the Guilleminault studies and in our study. On the contrary, high FeNO levels were noted when the electrochemical method (Hypair FeNO, Medisoft) was used similar to that in Schildge study.

In our study, low FeNO level was correlated with UIP-ILD (predominant fibrosis of the lung). However, no significant differences were observed in CTD-ILD and non-CTD-ILD. Lung involvement is an unfavorable prognosis factor in CTD [31]. Although systemic treatment is always needed in CTD, predicting the response to treatment in CTD-ILD, especially the lung lesions, is difficult. Our study showed no significant differences with regard to the FeNO value, PFT values, and systemic inflammatory markers between patients with CTD-ILD and non-CTD-ILD. This result implies that PFT and systemic inflammatory markers are not good enough to identify the specific group of patients that may benefit from systemic therapy. Given that low FeNO level was associated with predominant fibrosis of the lung, FeNO can be a helpful biomarker predicting the systemic treatment response of ILD, regardless of the presence of CTD or not.

Different FeNO levels in ILDs could suggest different treatment options. As revealed by the ROC curve of FeNO to identify non-UIP-ILDs, a cut-off value of 18.5 ppb shows a sensibility of 83.3% and a specificity of 95.8% in discriminating non-UIP-ILDs from UIP ILDs. Patients with ILDs with high level of FeNO may need urgent systemic treatment like corticosteroid. Among the 29 patients with non-UIP-ILDs in our study, 12 received systemic treatment like corticosteroid and they all responded well. By contrast, low FeNO level may suggest the adverse effect of systemic treatment over benefit. In addition, other treatments, such as lung transplant [32], should be considered because lung fibrosis is severe and irreversible.

This study has several limitations. First, this work is a retrospective study with relatively small number of patients enrolled. Second, the study focused on the baseline features of patients with ILDs. Moreover, the statistical analysis of prognosis and FeNO changes after treatment will be reported in the following

research. Third, some patients were under treatment with bronchodilator therapy or corticosteroids because of their symptoms when admitted. Lastly, although the patients discontinued their treatments within 72 h prior to blood test, PFT, and FeNO test, the results may have still been affected.

Conclusion

Predicting the response to treatment in ILDs is important but difficult. Our study suggested the importance of FeNO test in patients with ILD. High level of FeNO may indicate the need of systemic treatment, and FeNO could be a helpful biomarker in ILD management. Further study is necessary to establish the exact role of FeNO in ILD.

Abbreviations

ILD: interstitial lung diseases; FeNO: fractional exhaled nitric oxide; VC: vital capacity; TLC: total lung capacity ; DLCO: diffusion capacity of the lung for carbon monoxide; PFT: pulmonary function test; $FEV1^1$: forced expiratory volume in 1 s; FVC: forced vital capacity; PEF: peak expiratory flow; MEF: maximal midexpiratory flow; MEF25: forced expiratory flow after 25% of the FVC; MEF50: forced expiratory flow after 50% of the FVC; MEF75: forced expiratory flow after 75% of the FVC; MVV: maximal voluntary ventilation; RV: residual volume; ppb: parts per billion; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; UIP : usual interstitial pneumonia; CTD-ILD: connective tissue diseases associated with interstitial lung disease; ROC, receiver operating characteristic.

Declarations

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Authors' contributions

Conception and design: Feng-jia Chen, Yi-feng Luo; Acquisition the materials and data: Geng-peng Lin, Yu-biao Guo; Analysis and interpretation of data: Jia Shi , Yi-Hui , Yang-li Liu, Can-mao Xie; Drafted the manuscript: Feng-jia Chen ,Yi-feng Luo, Geng-peng Lin and Yu-biao Guo. All authors have read and approved the manuscript.

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Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was reviewed by the Institutional Research Ethics Committee of our hospital. The requirement for approval and the informed consent form were exempt because this study was not an intervening trial and was retrospective in nature.

Consent per publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Raghu G, Brown KK. Interstitial lung disease: clinical evaluation and keys to an accurate diagnosis. CLIN CHEST MED 2004, 25(3):409-419.
2. Cottin V, Hirani NA, Hotchkin DL, Nambiar AM, Ogura T, Otaola M, Skowasch D, Park JS, Poonyagariyagorn HK, Wuyts W, Wells AU. Presentation, diagnosis and clinical course of the spectrum of progressive-fibrosing interstitial lung diseases. Eur Respir Rev 2018, 27(150).
3. Antoniou KM, Margaritopoulos GA, Tomassetti S, Bonella F, Costabel U, Poletti V. Interstitial lung disease. Eur Respir Rev 2014, 23(131):40-54.
4. Wollin L, Distler J, Redente EF, Riches D, Stowasser S, Schlenker-Herceg R, Maher TM, Kolb M. Potential of Nintedanib in Treatment of Progressive Fibrosing Interstitial Lung Diseases. EUR RESPIR J 2019.
5. Somogyi V, Chaudhuri N, Torrisi SE, Kahn N, Muller V, Kreuter M. The therapy of idiopathic pulmonary fibrosis: what is next? Eur Respir Rev 2019, 28(153).
6. Jee AS, Corte TJ. Current and Emerging Drug Therapies for Connective Tissue Disease-Interstitial Lung Disease (CTD-ILD). DRUGS 2019, 79(14):1511-1528.
7. Belloli EA, Beckford R, Hadley R, Flaherty KR. Idiopathic non-specific interstitial pneumonia. RESPIROLOGY 2016, 21(2):259-268.

8. Tomassetti S, Ryu JH, Piciucchi S, Chilosi M, Poletti V. Nonspecific Interstitial Pneumonia: What Is the Optimal Approach to Management? Semin Respir Crit Care Med 2016, 37(3):378-394.
9. Antosova M, Mokra D, Pepucha L, Plevkova J, Buday T, Sterusky M, Bencova A. Physiology of nitric oxide in the respiratory system. PHYSIOL RES 2017, 66(Supplementum 2):S159-S172.
10. Smith AD, Cowan JO, Brassett KP, Herbison GP, Taylor DR. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. N Engl J Med 2005, 352(21):2163-2173.
11. Hoyte F, Gross LM, Katial RK. Exhaled Nitric Oxide: An Update. Immunol Allergy Clin North Am 2018, 38(4):573-585.
12. Tiev KP, Cabane J, Aubourg F, Kettaneh A, Ziani M, Mouthon L, Duong-Quy S, Fajac I, Guillevin L, Dinh-Xuan AT. Severity of scleroderma lung disease is related to alveolar concentration of nitric oxide. EUR RESPIR J 2007, 30(1):26-30.
13. Malerba M, Radaeli A, Ragnoli B, Airo' P, Corradi M, Ponticiello A, Zambruni A, Grassi V. Exhaled nitric oxide levels in systemic sclerosis with and without pulmonary involvement. CHEST 2007, 132(2):575-580.
14. Cameli P, Bargagli E, Refini RM, Pieroni MG, Bennett D, Rottoli P. Exhaled nitric oxide in interstitial lung diseases. Respir Physiol Neurobiol 2014, 197:46-52.
15. Raghu G, Remy-Jardin M, Myers JL, Richeldi L, Ryerson CJ, Lederer DJ, Behr J, Cottin V, Danoff SK, Morell F et al. Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med 2018, 198(5):e44-e68.
16. Hodnett PA, Naidich DP. Fibrosing interstitial lung disease. A practical high-resolution computed tomography-based approach to diagnosis and management and a review of the literature. Am J Respir Crit Care Med 2013, 188(2):141-149.
17. Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. Am J Respir Crit Care Med 2011, 184(5):602-615.
18. The Chinese national guidelines of pulmonary function test (2014). Chin J Tuberc Respir Dis. 2014;37:566–571. Available from: http://zhjhhhxzz.yiigle.com/CN112147201408/860037.htm. Accessed November 11, 2019.
19. Barnes PJ, Dweik RA, Gelb AF, Gibson PG, George SC, Grasemann H, Pavord ID, Ratjen F, Silkoff PE, Taylor DR, Zamel N. Exhaled nitric oxide in pulmonary diseases: a comprehensive review. CHEST 2010, 138(3):682-692.
20. Saleh D, Barnes PJ, Giaid A. Increased production of the potent oxidant peroxynitrite in the lungs of patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1997, 155(5):1763-1769.
21. Paredi P, Kharitonov SA, Loukides S, Pantelidis P, du Bois RM, Barnes PJ. Exhaled nitric oxide is increased in active fibrosing alveolitis. CHEST 1999, 115(5):1352-1356.
22. Cameli P, Bargagli E, Bergantini L, Refini RM, Pieroni M, Sestini P, Rottoli P. Evaluation of multiple-flows exhaled nitric oxide in idiopathic and non-idiopathic interstitial lung disease. J BREATH RES 2019, 13(2):26008.

23. Guilleminault L, Saint-Hilaire A, Favelle O, Caille A, Boissinot E, Henriet AC, Diot P, Marchand-Adam S. Can exhaled nitric oxide differentiate causes of pulmonary fibrosis? Respir Med 2013, 107(11):1789-1796.
24. Schildge J. Nitric oxide in exhaled breath of patients with interstitial lung diseases. Pneumologie 2011, 65(3):143-148.
25. Korten I, Liechti M, Singer F, Hafen G, Rochat I, Anagnostopoulou P, Muller-Suter D, Usemann J, Moeller A, Frey U, Latzin P, Casaulta C, SCILD and BILD study group. Lower exhaled nitric oxide in infants with Cystic Fibrosis compared to healthy controls. J CYST FIBROS 2018, 17(1):105-108.
26. de Winter-de GK, van der Ent CK. Nitric oxide in cystic fibrosis. J CYST FIBROS 2005, 4 Suppl 2:25-29.
27. Grasemann H, Schwiertz R, Grasemann C, Vester U, Racke K, Ratjen F. Decreased systemic bioavailability of L-arginine in patients with cystic fibrosis. Respir Res 2006, 7:87.
28. Chapman AL, Morrissey BM, Vasu VT, Juarez MM, Houghton JS, Li CS, Cross CE, Eiserich JP. Myeloperoxidase-dependent oxidative metabolism of nitric oxide in the cystic fibrosis airway. J CYST FIBROS 2010, 9(2):84-92.
29. Grasemann H, Shehnaz D, Enomoto M, Leadley M, Belik J, Ratjen F. L-ornithine derived polyamines in cystic fibrosis airways. PLOS ONE 2012, 7(10):e46618.
30. Jiao J, Wang H, Lou W, Jin S, Fan E, Li Y, Han D, Zhang L. Regulation of ciliary beat frequency by the nitric oxide signaling pathway in mouse nasal and tracheal epithelial cells. EXP CELL RES 2011, 317(17):2548-2553.
31. Kusmirek JE, Kanne JP. Thoracic Manifestations of Connective Tissue Diseases. Semin Ultrasound CT MR 2019, 40(3):239-254.
32. Brown AW, Kaya H, Nathan SD. Lung transplantation in IIP: A review. RESPIROLOGY 2016, 21(7):1173-1184.

Figures

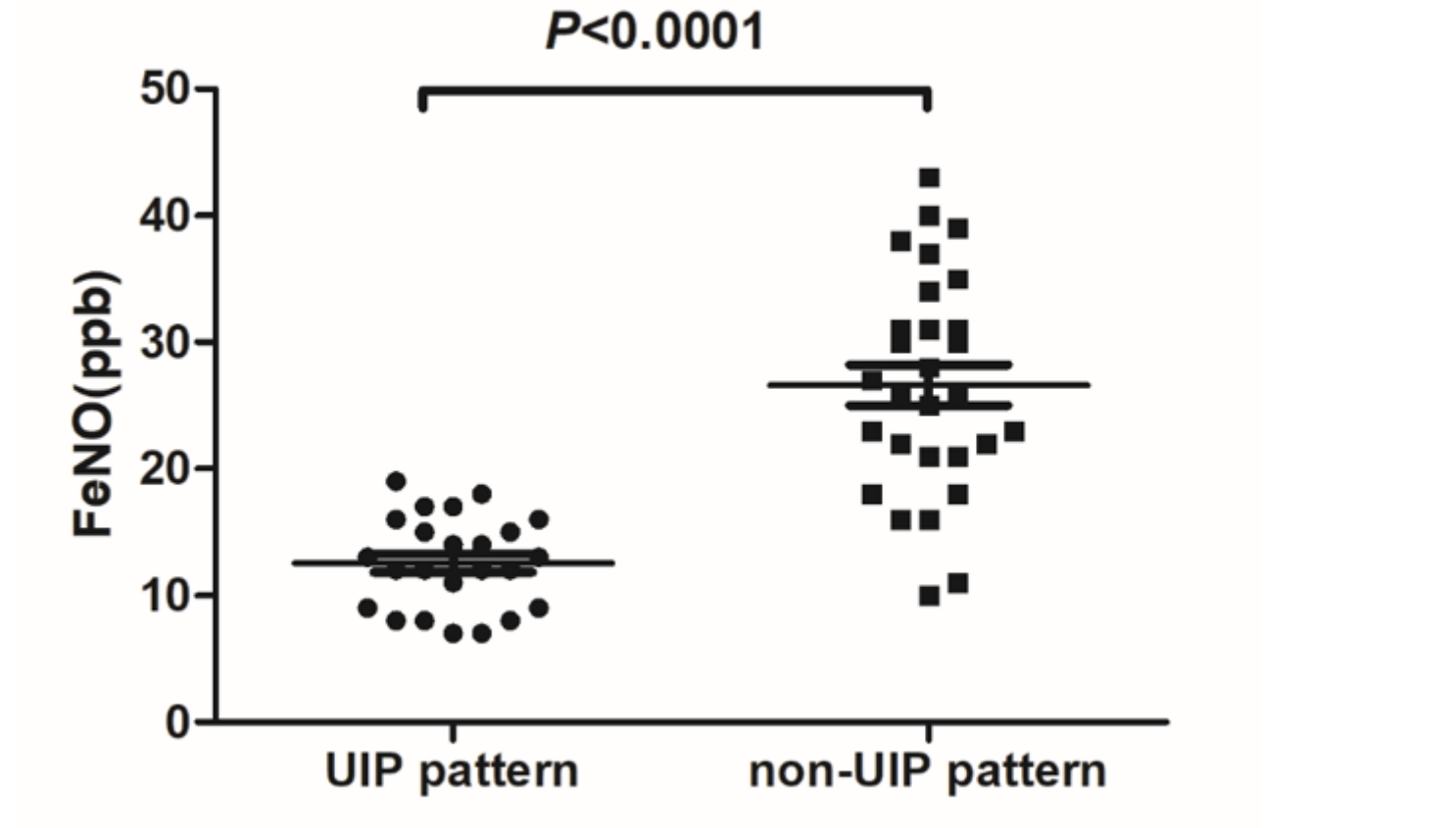

Figure 1

FeNO value between the UIP-ILD and non-UIP-ILD groups.Notes: Given is the median with interquartile range. Abbreviations: FeNO, fractional exhaled nitric oxide; UIP, usual interstitial pneumonia.

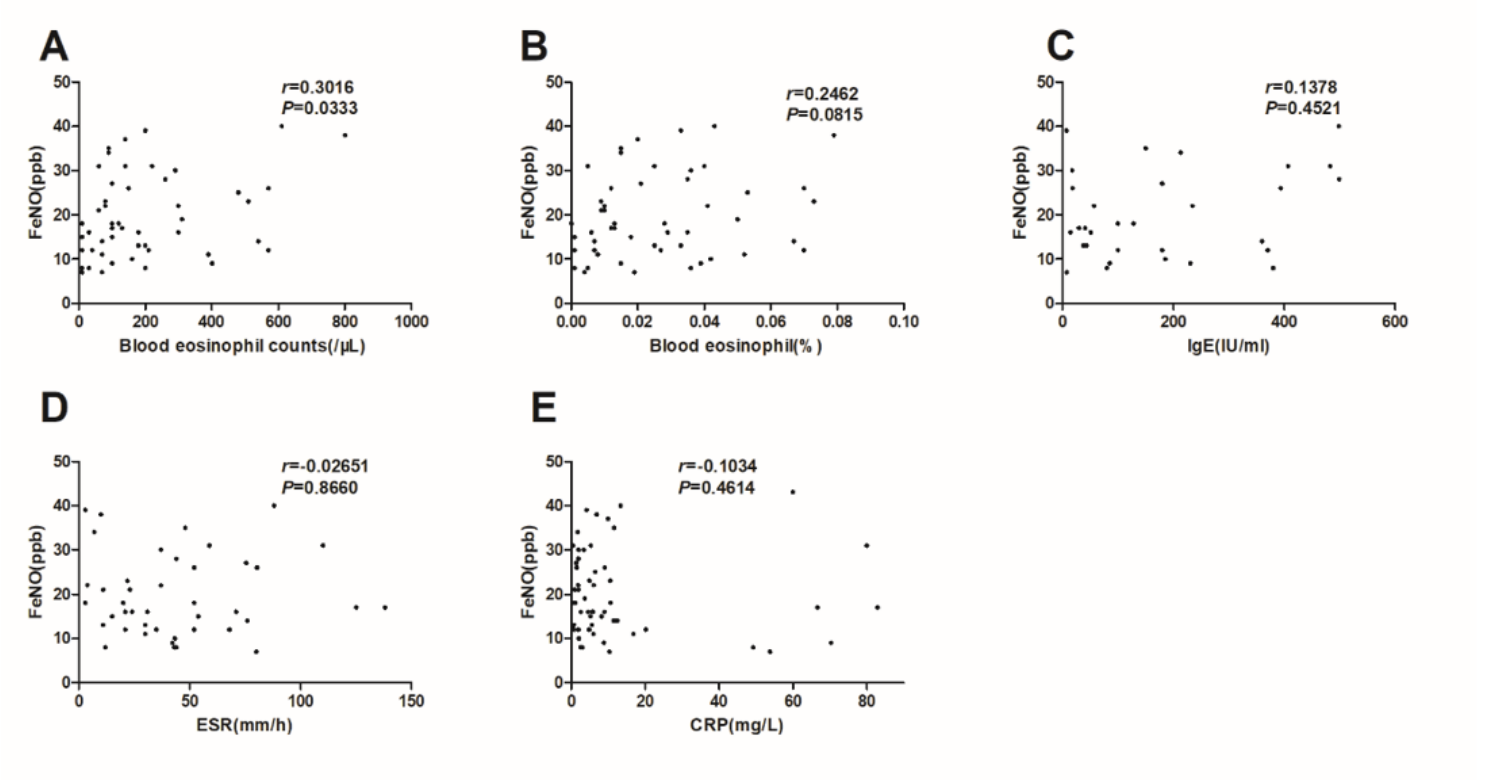

Figure 2

Correlation between FeNO and blood eosinophil, IgE or systemic inflammatory markers. Notes The correlations between FeNO values and blood eosinophil, IgE or systemic inflammatory markers were determined by calculating Spearman's rank correlation coefficients. Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FeNO, fractional exhaled nitric oxide.

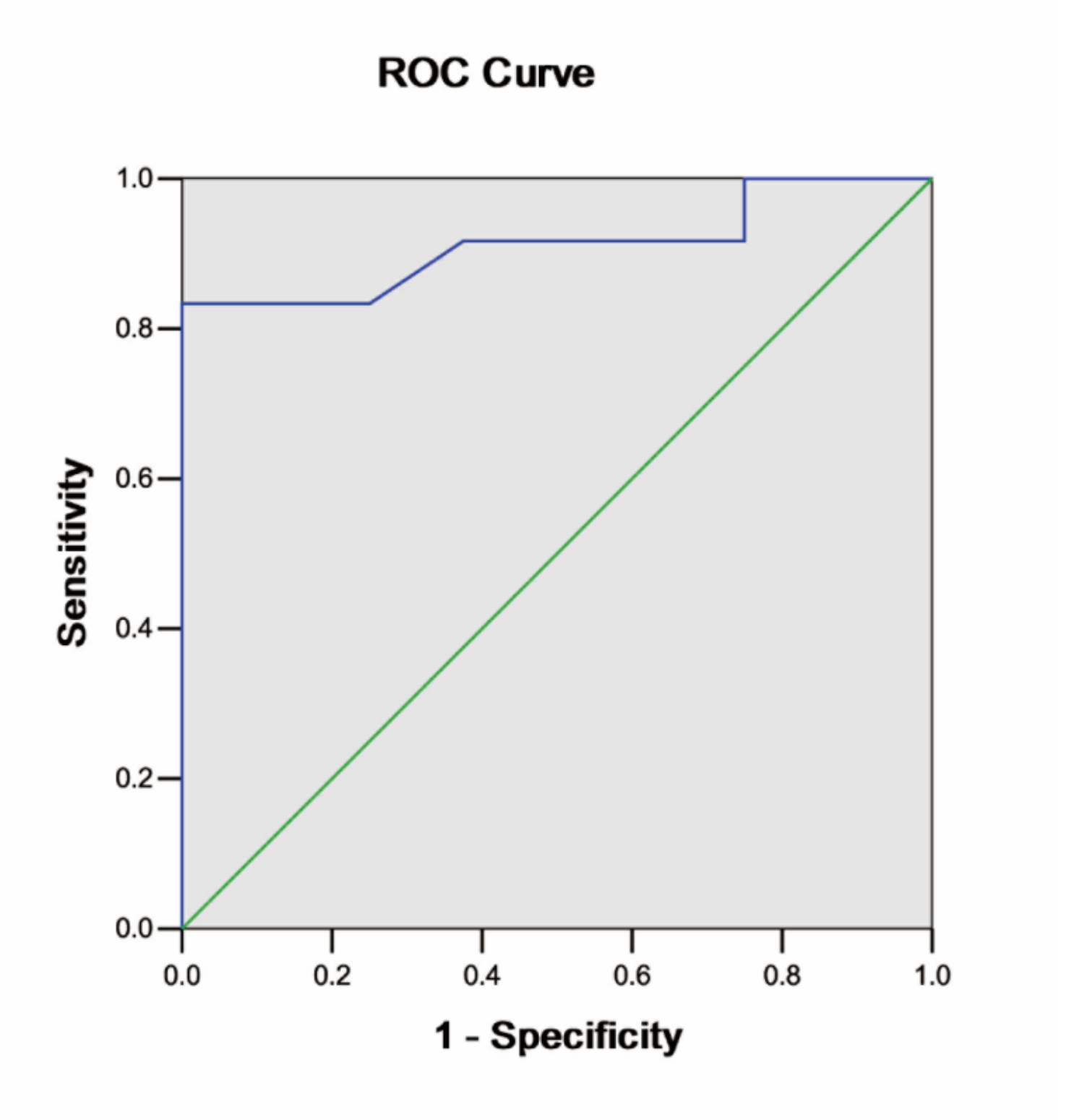

Figure 3

ROC curve analysis of the sensitivity and specificity of FeNO to identify non-UIP-ILDs. Abbreviations: ROC, receiver operating characteristic; FeNO, fractional exhaled nitric oxide.