ORIGINAL RESEARCH

Correlation Between HIF1-A Expression and Airway Remodeling in COPD

Lingfang Tan[1], Xuefeng Yang[2], Jianxin Zhang[3], Kebing Zhou[1,2]

[1]The Nanhua Affiliated Hospital, Department of Respiratory Physicians, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China; [2]The Nanhua Affiliated Hospital, Department of General Medicine, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China; [3]The Nanhua Affiliated Hospital, Department of Cardiothoracic Surgeon, Hengyang Medical School, University of South China, Hengyang, Hunan, 421001, People's Republic of China

Correspondence: Kebing Zhou, Tel +86-17397392536, Email zhoukebing9999@163.com

Background: Airway remodeling is a significant pathological characteristic of chronic obstructive pulmonary disease (COPD). In recent years, hypoxia-inducible factor 1-α (HIF-1α), a member of the hypoxia-inducible factor protein family, has gained attention. However, the potential correlation between HIF-1α and COPD airway remodeling remains unclear.

Objective: This study explored the expression patterns of HIF-1α in patients with COPD and its association with airway remodelling. This investigation aims to furnish novel insights for the clinical identification of prospective therapeutic targets for ameliorating COPD-related airway remodelling.

Patients and Methods: A total of 88 subjects were included, consisting of 28 controls and 60 COPD patients. Various staining methods were employed to observe the pathological changes in airway tissues. Immunohistochemistry was utilized to detect the expression of HIF-1α and MMP9 (matrix metalloproteinase 9) in airway tissues. Enzyme-linked immunosorbent assay (ELISA) was used to measure the concentration in serum of HIF-1α and MMP9. Computed tomography (CT) airway parameters were measured in all participants to assess airway remodeling. The relationship between serum HIF-1α and MMP9 concentrations and airway parameters was analyzed.

Results: Staining of airway structures in COPD patients revealed significant pathological changes associated with airway remodelling, including mixed cilia and subepithelial fibrosis. The expression of HIF-1α and MMP9 was significantly higher in both human airway tissue and serum compared to controls. Chest CT scans exhibited typical imaging features of airway remodeling and increased airway parameters.

Conclusion: The findings suggest a correlation between increased HIF-1α expression and COPD airway remodelling. This study provides novel evidence that HIF-1α may be a potential biomarker for airway remodelling in COPD patients.

Keywords: hypoxia-inducible factor 1-α, chronic obstructive pulmonary disease, matrix metalloproteinase 9, airway remodelling

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major global health issue, ranking among the top three causes of death worldwide. Its high morbidity, significant harm, and low awareness have led to severe social and economic burdens. Extensive research is needed to understand COPD's pathogenesis, prevention, and therapeutic targets to reduce the burden of respiratory diseases.[1,2] COPD is a progressive disease characterized by chronic inflammation and airway remodeling, resulting in irreversible lung function damage. Studies have indicated that airway remodeling may occur independently and in parallel with airway inflammation.[3,4]

However, there is currently a lack of effective therapeutic interventions to prevent or reverse airway remodelling in COPD patients. Therefore, it is crucial to investigate the biomarkers and molecular mechanisms associated with airway remodelling in COPD patients. Oxygen homeostasis is critical in maintaining typical lung structure and function.[5] HIF-1α, a critical transcriptional regulator involved in cellular responses to hypoxia, oxidants, and inflammation, is over-expressed in the lungs of COPD patients.[6,7] However, the relationship between HIF-1α and airway remodelling remains

unclear. This study collected human airway tissue and serum samples and employed quantitative airway CT assessment parameters to investigate the correlation between HIF-1α expression and airway remodelling in COPD patients.

Our evaluation of airway remodelling consisted of three main methods: histology, biomarkers, and imaging techniques. The main pathological features of COPD airway remodeling include epithelial-mesenchymal transition (EMT), increased collagen deposition, extracellular matrix degradation and repair, ciliary dysfunction, and inflammatory infiltration.[8] It has been well documented that matrix metalloproteases (MMPs), a family of zinc-dependent protein hydrolases, play a role in respiratory remodelling, particularly MMP9.[9,10] MMP9 is associated with lung function and indicators of small airway disease in COPD patients.[11] With the rapid development of imaging technology, CT has become a valuable tool for assessing airway dimensions and studying airway diseases.[12] Previous studies have indicated that quantitative airway CT assessment parameters correlate with pathological changes in airway remodelling.[13,14] However, limited studies currently investigate the relationship between HIF-1α and airway remodeling. Therefore, this study aimed to investigate the expression characteristics of HIF-1α in COPD patients and analyze its correlation with airway remodelling.

Materials and Methods
Study Design
This clinical case-control study involved 88 participants, including 28 healthy controls and 60 COPD patients. We used various staining methods to observe pathological changes in airway tissues and employed immunohistochemistry to detect HIF-1α and MMP9 expression in these tissues. HIF-1α and MMP9 concentrations in serum were measured using ELISA and airway remodelling in all participants were assessed by measuring CT airway parameters. Our analysis focused on the relationship between serum concentrations of HIF-1α and MMP9 and airway parameters.

Subject
Airway tissues were obtained from lobectomies or segmental resections in three patients with pulmonary macroglossia and three patients with pulmonary macroglossia combined with COPD at Nanhua Hospital, Nanhua University. Serum samples were collected from 88 participants (60 COPD patients and 28 controls) between January 2023 and July 2023. All COPD patients included in the study conformed to the diagnostic criteria outlined in the 2023 GOLD guidelines, were in a stable phase without any acute exacerbations of COPD within the previous two months, and were above 18 years of age. The control group was recruited from our hospital's health check-up center during the same period, comprising healthy adults over the age of 18 with no history of respiratory diseases, including but not limited to chronic obstructive pulmonary disease, asthma, and pulmonary tuberculosis, and no episodes of acute illness or history of long-term medication use in the past six months. Exclusion criteria for participants included severe cardiovascular, hepatic, and renal impairments, hematological disorders, diabetes, malignancy, psychiatric diseases, other pulmonary conditions (such as asthma, acute exacerbation of the chronic obstructive pulmonary disease, pneumonia, cystic fibrosis, active tuberculosis, and interstitial lung disease), and a history of regular use of corticosteroids or immunosuppressive agents. Our study was approved by the Ethics Committee of the Nanhua Affiliated Hospital (2023-KY-196) and complied with the Declaration of Helsinki. Informed consent was obtained from all subjects.

Pulmonary Function Tests
Each subject inhaled 400 μg of salbutamol (Ventolin, GlaxoSmithKline, London, UK) for 15 minutes. Lung function testing was conducted by professional technicians in the Pulmonary Function Room of the hospital, and the results were analyzed and reported by experienced doctors from the Department of Respiratory and Critical Care Medicine. The following parameters were recorded: forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1 as a percentage of predicted value (FEV1%pred), and the FEV1/FVC ratio. According to the GOLD guidelines, a FEV1/FVC ratio of <0.7 is diagnostic for COPD.

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Computed Tomography Scanning and Analysis of the Chest

All scans were performed using a Philips Brilliance 64 (Philips Medical Solutions, Netherlands) and Somatom Definition Flash (Siemens Medical Solutions, Germany). All parameters were obtained through CT plain image reconstruction and reconstructed using a standard algorithm. The lung window (window width 1500 HU, window position −500 HU) and mediastinal window (window width 400 HU, window position 40 HU) were utilized for observation. The scanning parameters were as follows: a tube voltage of 120 kV, a tube current of 150 mA, a layer thickness of 5.0 mm, and a reconstructed layer thickness of 0.625 mm. The quantitative airway measurements of the right upper lobe apical segment (RB1) were performed using the thoracic VCAR software provided by GE. The software automatically measured the square root of the wall area of the 8-mm area within the airway (Ai8), the percentage of bronchial wall area (WA%), and the total airway area (AO).

Determination of HIF1-α and MMP9 Concentrations

Blood samples were collected from all subjects through venipuncture. Serum was obtained by centrifugation at 2000 r/min for 10 minutes and stored at −80°C. HIF1-α and MMP9 concentrations were measured using human enzyme-linked immunosorbent assay (ELISA) kits, following the manufacturer's instructions. The ELISA kits for HIF1-α and MMP9 were supplied by ELK Biotechnology (Wuhan, China).

Histological Staining of Airway Tissues

Human lung tissue was fixed in 4% neutral formalin and embedded in paraffin. Sections of 3–5 μm were prepared for staining purposes. Hematoxylin-eosin (HE) and a Masson staining kit (Servicebio, Wuhan, China) were employed to assess structural changes in the human airways. The experimental procedures were conducted under the manufacturer's instructions. Immunohistochemical staining was conducted to examine the expression of HIF1-α and MMP9 in each section. Antigens were extracted as per the primary antibody protocol. To block endogenous peroxidase activity, a peroxidase blocker was added and incubated for 30 minutes at 37°C. Subsequently, the slides were incubated overnight at 4°C with mouse anti-HIF1-α antibody (Reed Bio# RA10339, Wuhan, China; diluted 1:300) and rabbit anti-MMP9 antibody (Abcam#ab52496, Cambridge, UK; diluted 1:50). After rinsing with PBS, the slides were incubated with biotinylated goat anti-rabbit IgG, followed by streptavidin-peroxidase incubation. Staining was performed using a DAB solution (ZSGB Bio, Beijing, China) and restained with hematoxylin. An optical microscope (OLYMPUS, CX21) was used for visualization. MMP9 and sestrin2 protein expression were semi-quantitatively assessed using Image-ProPlus 6.0 (Media Cybernetics, Inc., USA). The mean integral optical density of protein staining was calculated by dividing the integral optical density of protein-staining-positive epithelium by the corresponding bronchial epithelium area.

Statistical Analysis

Data was analyzed using GraphPad Prism 8.0.2 (San Diego, California, USA) and SPSS 26.0 (IBM, Armonk, NY, USA) software. Categorical variables were presented as counts (%). The chi-square test was utilized to compare differences in sex ratio and smoking status. For normally distributed data, unpaired t-tests were conducted, and mean values (± standard deviation) were reported. Non-normally distributed data were compared using the Mann–Whitney U-test, and the median of the interquartile range was reported. Correlations between serum protein concentrations and other measures in the COPD group were examined through Pearson or Spearman rank correlation analysis. A p-value of less than 0.05 was considered statistically significant.

Results

Demographic Characteristics of All Subjects

All participants enrolled in this study were categorized into the COPD group (n=60) and the control group (n=28). The two groups had no significant differences regarding age, gender, BMI, and smoking index. However, other lung function indices, including FEV1% and FEV1/FVC, were significantly lower in the COPD group (P < 0.001). The demographic characteristics of all participants are summarized in Table 1.

Table 1 Demographic Characteristics of the Control Group and COPD Group

Variables	Control Group (n=28)	COPD Group (n=60)	P value
Age, year	63.14 (8.40)	63.46 (12.55)	0.902[a]
Mal sex, n (%)	23 (82.01%)	48 (80.00%)	0.655[c]
BMI, Kg/m^2	22.99 (2.41)	22.55 (3.09)	0.511[b]
Smoking status			
Never smoked, n (%)	19 (67.86%)	38 (63.33%)	
Current smoker, n (%)	5 (17.86%)	7 (11.67%)	
Ex-smoker, n (%)	4 (14.28%)	15 (25.00%)	
Smoking, pack-years*	27.55 (10.48)	29.75 (11.58)	0.627[a]
Pulmonary function			
FEV1/FVC, %	86.90 (8.76)	52.48 (12.80)	<0.001[b]
FEV1, % of predicted	97.41 (20.67)	61.16 (24.88)	<0.001[b]

Notes: Data are presented as number (%) or means (standard deviation) or median (interquartile range). * (Number of cigarettes per day × number of years of smoking)/20. [a]t-test; [b]mann–Whitney U-test; [c]χ^2 test. **Abbreviations**: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Histological Staining of Airway Tissues

We isolated airway tissue and employed various staining methods to characterize airway remodelling at a pathological level. The HE staining revealed the control group's integral airway epithelial structures and ciliated cells. In contrast, the COPD group displayed various degrees of ciliated cell detachment and retention (Figure 1A). Masson staining exhibited a substantial increase in collagen deposition in the bronchioles' epithelial area within the COPD group compared to the control group (Figure 1B).

Expression of HIF-1α and MMP9 in Airway Tissues

In the DAB immunohistochemical analysis, brown staining indicated positive protein expression. The expression of HIF-1α predominantly localized in the cytoplasm of bronchial epithelial cells and exhibited a significant increase in the COPD group (Figure 2A). Similarly, MMP9 expression was considerably enhanced in the cytoplasm of the COPD group as
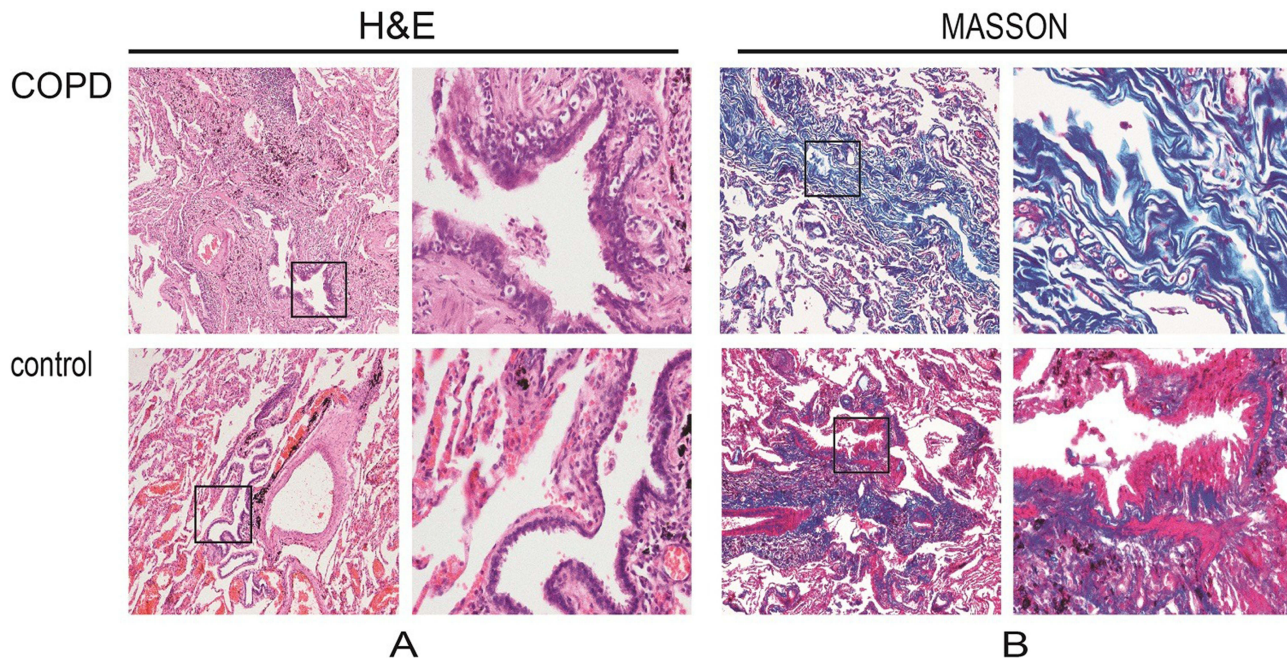
Figure 1 Staining of airway tissues in control and COPD group.
Notes: (**A**) H&E stains in control and COPD group; (**B**) Subepithelial fibrosis by Masson staining in control and COPD group; Magnification, × 400.
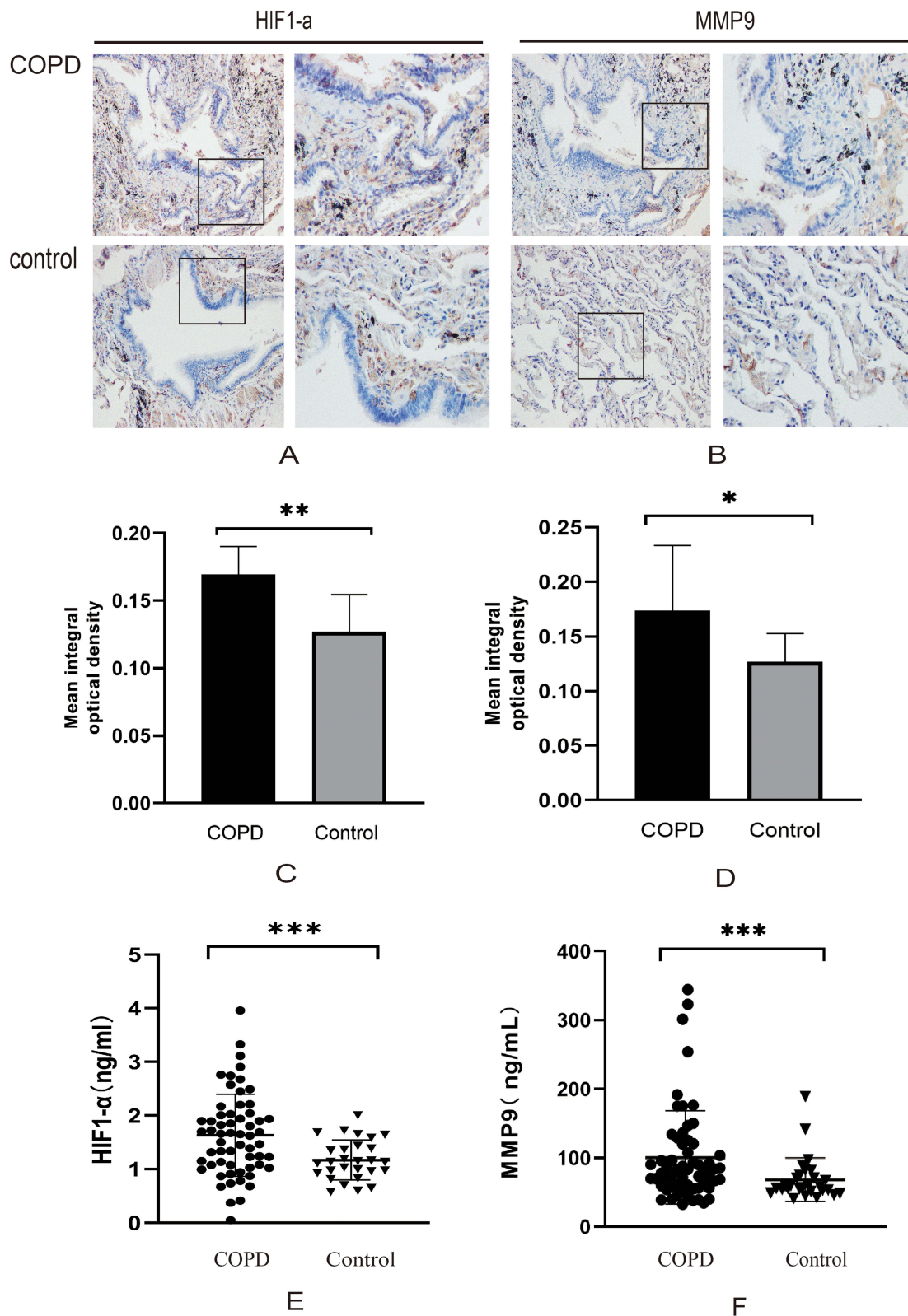
Figure 2 HIF1-α and MMP9 expression in airway tissue and serum in control and COPD group.

Notes: (**A**) Expression of HIF1-α by IHC in control and patients with COPD. (**B**) Expression of MMP9 by IHC in control and patients with COPD. (c) Semiquantitative assessment of HIF1-α expression using Image-Pro Plus. (**D**) Semiquantitative assessment of MMP9 expression using Image-Pro Plus. (**E**) Serum HIF1-A concentrations in control and COPD groups. (**F**) Serum MMP9 concentrations in control and COPD groups. Positive protein staining appears brown and nuclear staining appears blue. Magnification, × 400. *P < 0.05, **P < 0.05, ***P < 0.001 versus control group.

compared to the control group (Figure 2B). The mean integrated optical density of HIF-1α and MMP9 in the COPD group was significantly higher than that in the control group (P < 0.001; Figure 2C–D).

Serum HIF1-α and MMP9 Concentrations

Serum HIF1-α concentrations were significantly higher in COPD patients compared to controls (P < 0.001) (Table 2, Figure 2E). Likewise, the serum expression of MMP9 was substantially elevated in COPD patients compared to controls (P < 0.001) (Table 2, Figure 2F).

Airway Parameters in Chest CT Scans of Subjects

Chest CT scans of COPD patients exhibited thickened bronchial walls and curved bronchial lumens as compared to controls (Figure 3). We observed significantly higher values of airway parameters in chest CT (Ai8, AO, WA%) in COPD patients (p < 0.001) (Table 2, Figure 4).

Relationship Between HIF1-α and MMP9, CT Parameters, and Pulmonary Function in Patients with COPD

To elucidate the relationship between HIF1-α and airway remodeling in COPD patients, we analyzed the serum HIF1-α concentration in correlation with MMP9 and chest CT airway parameters. Results indicated a positive correlation between serum HIF1-α concentration and serum MMP9 concentration (r = 0.286, P = 0.027) (Figure 5A), AO (r = 0.395, P = 0.008) (Figure 5B), Ai8 (r = 0.361, P = 0.017) (Figure 5C), and WA% (r = 0.361, P = 0.016) (Figure 5D). However, there were no significant associations between HIF-α concentration and lung function parameters (Table 3).

Discussion

This study investigated the potential relationship between HIF1-α and airway remodeling in COPD. At the histological level, this was demonstrated by immunohistochemical staining of HIF1-α and MMP9 expression in human airway tissue, revealing significantly higher levels in COPD patients than controls. At the biomarker level, serum concentrations of HIF1-α and MMP9 were also elevated in COPD patients. In addition, the airway structure of COPD patients showed apparent imaging features of airway remodelling and significantly elevated quantitative airway parameters, as revealed by chest CT scans. Further analysis showed that serum levels of HIF1-α were associated with serum MMP9 levels and quantitative airway parameters detected by chest CT scans. Therefore, this study suggests that HIF1-α may play a role in airway remodeling in COPD.

Airway remodelling is characterized by tissue, cellular, and molecular component alterations leading to pathological changes in the epithelium, airway smooth muscle, vasculature, and extracellular matrix.[15] This is a well-recognized phenomenon in COPD, and in our study, we confirmed the presence of typical pathological features of airway

Table 2 HIF1-A and MMP9 Concentrations and Quantitative CT Measurements in the Total Subjects

Test index	Control Group (n=28)	COPD Group (n=60)	P value
Serum assay			
HIF1-A	1.1699 (0.3719)	1.629 (0.763)	0.003[b]
MMP9	68.18 (31.49)	100.52 (67.62)	0.018[a]
Airway parameters on chest CT			
Ai8 (mm)	4.10 (0.72)	5.09 (0.78)	<0.001[a]
WA percent (%)	62.87 (10.97)	76.35 (5.63)	<0.001[a]
Ao (mm2)	14.88 (5.08)	25.00 (8.02)	<0.001[a]

Notes: Data are presented as means (standard deviation) or median (interquartile range). P-values were calculated by statistical analysis of the variable. [a]t-test; [b]Mann–Whitney U-test.
Abbreviations: CT, computed tomography; HIF-1α, hypoxia-inducible factor 1-α; MMP9, matrix metalloproteinases 9; Ai8, Square root of the wall area at an internal airway area of 8 mm2; AO, total airway area; WA%, wall area percentage.
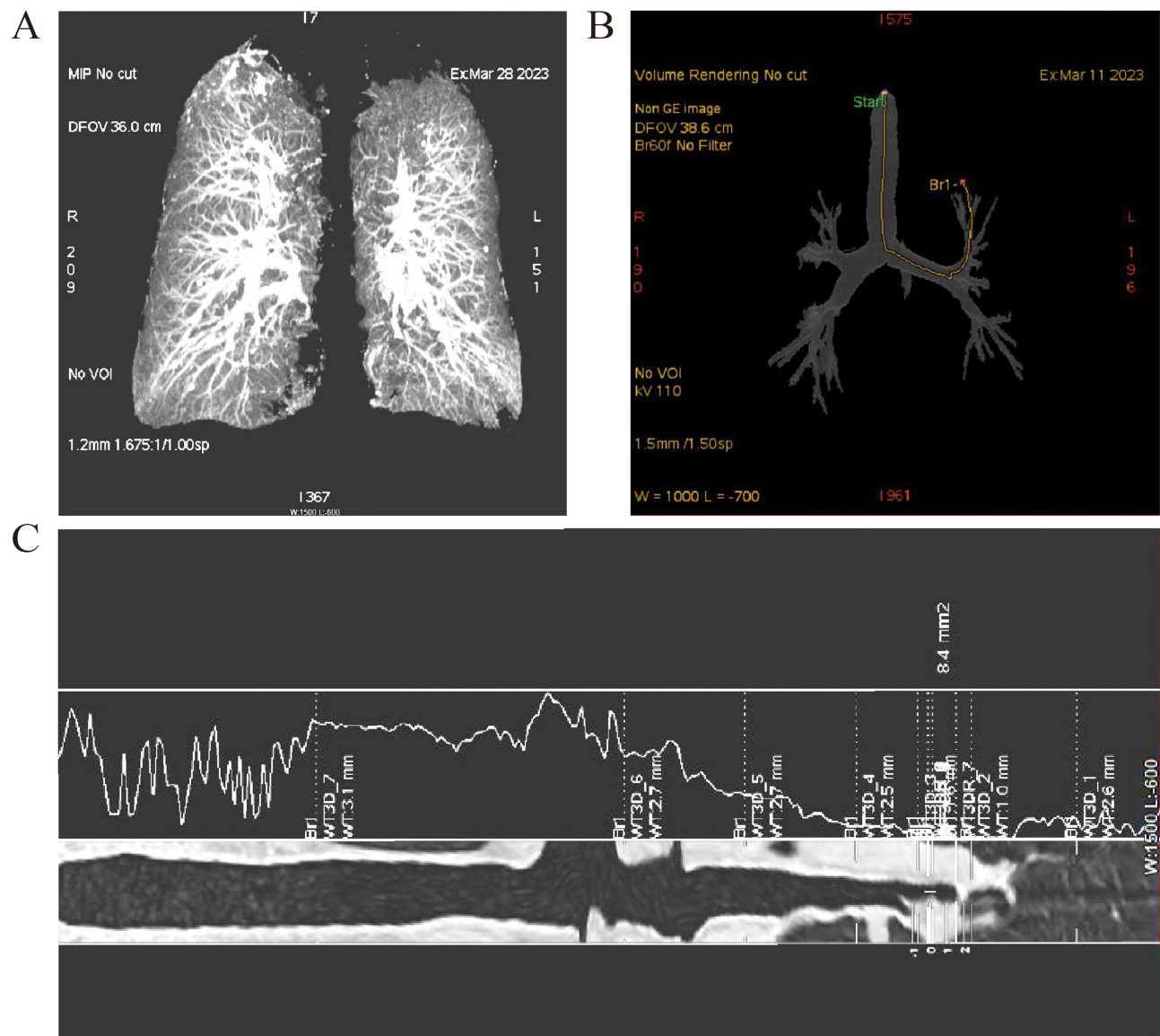
Figure 3 Chest CT image in control and COPD group.
Notes: (**A**) Lung tissue extracted automatically by Thoracic VCAR software; (**B**) Airway tree extracted automatically by software by Thoracic VCAR software; (**C**) Curved planar reformation of the bronchial pathway in COPD group.

remodelling in COPD airway tissues, including airway subepithelial fibrosis and decreased ciliated cells, as observed in histopathological sections of human lungs. Among the various inflammatory pathways and mediators implicated in the development of COPD, matrix metalloproteinases (MMPs) are involved in airway remodelling through direct and indirect mechanisms.[16–18] Consistent with previous studies, it was found that MMP9 expression was significantly elevated in airway tissues and serum of COPD patients, suggesting airway remodelling in these patients.

Considering that oxidative stress plays a crucial role in airway remodeling and that HIF-1α is a key regulator of oxygen homeostasis during hypoxic conditions, recent evidence suggests a correlation between serum levels of HIF-1α and the severity of FEV1/FVC grading in patients with COPD.[19] Furthermore, increased expression of HIF-1α upregulates the platelet-activating factor receptor (PAFR) on the surface of airway epithelial cells, with a higher upregulation observed in smokers, particularly those with COPD.[20] Our present study aligns with previous research, as we observed significantly higher levels of HIF-1α in both human serum and tissues from COPD patients compared to the control group; this suggests that HIF-1α may play an essential role in the development of COPD.
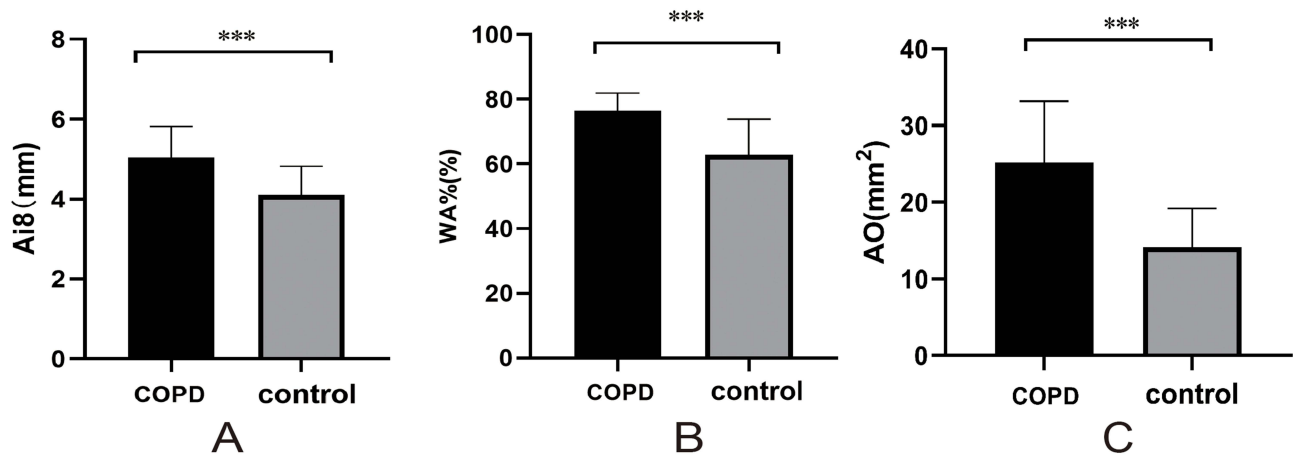
Figure 4 Airway parameters on chest CT in control and COPD group.
Notes: (**A**) Comparison of Ai8 in control and COPD group; (**B**) Comparison of WA% in control and COPD group; (**C**) Comparison of AO in control and COPD group; ***P < 0.001.
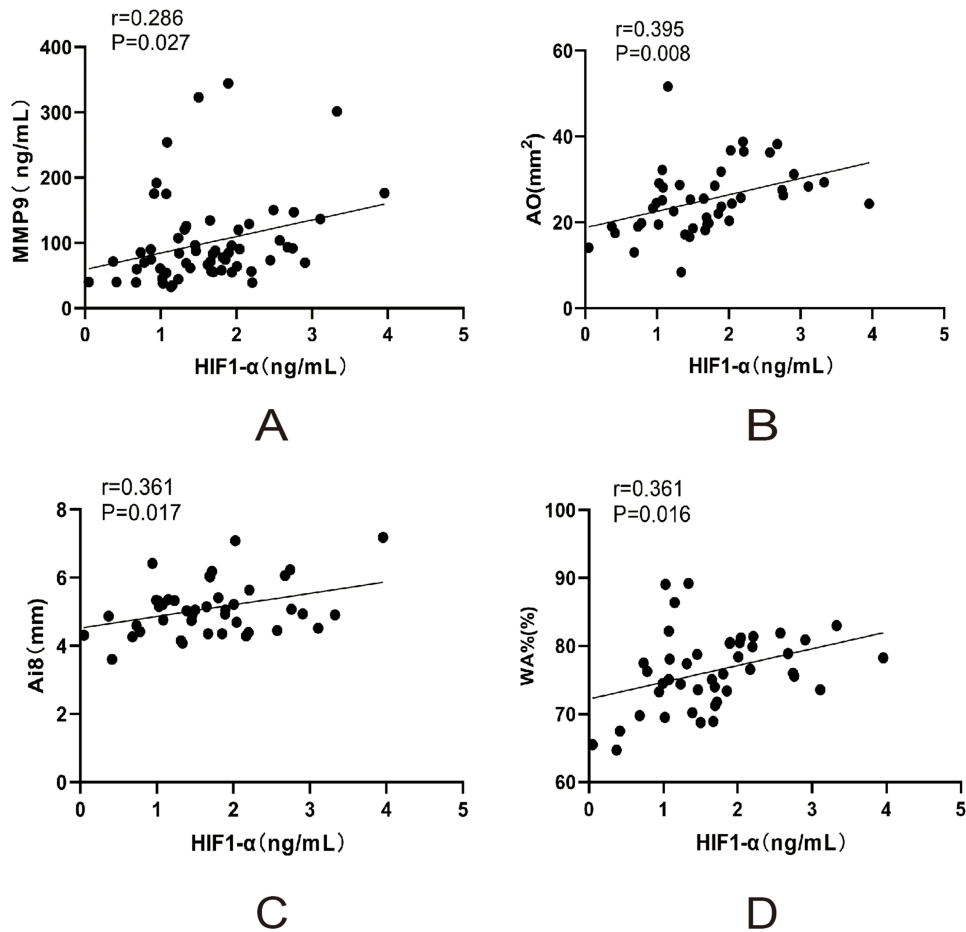

Figure 5 Correlation between serum HIF1-α concentrations and airway parameters on chest CT.
Notes: Correlations between serum HIF1-α concentrations and MMP9 (**A**) AO (**B**) Ai8 (**C**) and WA% (**D**) Correlations were determined by Pearson rank correlation analysis.

Table 3 Association Between Serum HIF1-α Concentrations and Other Measurement Indices in COPD Group

Test Index	r	P-value
Serum assay		
MMP9 (ng/mL)	0.286	0.027[a]
Airway parameters on chest CT		
Ai8 (mm)	0.361	0.017[a]
WA percent (%)	0.361	0.016[a]
Ao (mm2)	0.395	0.008[a]
Pulmonary function		
FEV1/FVC, %	0.0495	0.707[b]
FEV1, % of predicted	0.1468	0.263[b]

Notes: Correlations were determined by Pearson and Spearman rank correlation analysis. [a]Pearson rank correlation analysis; [b]Spearman rank correlation analysis; r, Pearson rank correlation coefficient.
Abbreviations: CT, computed tomography, MMP9, matrix metallo-proteinases 9, Ai8, Square root of the wall area at an internal airway area of 8 mm2, AO, total airway area, WA%, wall area percentage; FEV1, forced expiratory volume in 1s; FVC, forced vital capacity.

To delve further into the relevance of HIF-1α to COPD airway remodeling, we conducted immunohistochemical staining of relevant genes in human lung tissues. We found that the expression of HIF-1α in the airways of the COPD group was significantly higher than that of the control group. Notably, the bronchial epithelial cells displayed a notable increase in MMP9 staining. Additionally, our study revealed a positive correlation between serum HIF-1α concentration and serum MMP9 concentration. Recent research indicates that the upregulation of HIF-1α expression may trigger a cascade of downstream effects, including an increase in MMP9 expression.[21,22] This enzyme directly participates in the structural remodeling of airways and lung tissue. Our discussion of the results further supports this notion through the positive correlation between HIF-1α and MMP9 concentrations, suggesting a potential interactive role between these molecules in the pathological process of COPD, thereby facilitating disease progression. These findings suggest that HIF-1α could be a blood biomarker for evaluating airway remodelling in COPD. Moreover, by understanding the role of HIF-1α in COPD, it may be helpful to develop therapeutic strategies targeting these molecules to slow down the progression of the disease or improve the symptoms of patients.

Considering that chest CT airway parameters have been recognized as radiological biomarkers of COPD and correlate with airflow obstruction in all GOLD phases,[23,24] this study aimed to assess airway remodelling by examining chest CT airway structure and parameters. The findings showed significant alterations in airway structure in the COPD group, characterized by thickening of the bronchial wall and rough curvature of the bronchial lumen. Moreover, all three quantitative airway parameters (Ai8, AO, and WA%) measured on chest CT were statistically elevated, indicating the occurrence of airway remodelling at the imaging level in the COPD group. Additionally, this study substantiates the positive correlation between HIF-1α levels and quantitative airway measurements in chest CT imaging, revealing no significant association between HIF-1α concentrations and pulmonary function metrics. Our observations corroborate that the positive relationship between HIF-1α and CT-derived parameters offers a potential radiographic biomarker for evaluating the extent of airway remodelling and disease severity in patients with COPD. This correlation implies that utilizing imaging modalities to monitor the expression of these molecular markers may facilitate earlier detection of COPD progression and enable the formulation of more targeted therapeutic interventions for affected individuals.

However, it is essential to acknowledge the limitations of this study. Firstly, although three methods were employed to evaluate airway remodelling, more detailed information regarding the correlation between HIF1-α expression levels, serum biomarkers, and airway remodelling during different stages of COPD progression was not provided. Secondly, based on the results of this study, it is proposed to further investigate the expression of HIF1-α using an animal model of COPD for subsequent molecular experiments such as immunohistochemistry and Western blotting.

Conclusion

The study elucidates significant upregulation of HIF-1α alongside a positive correlation with MMP9 concentrations and quantitative CT parameters in patients with COPD. These results underscore the pivotal role of airway remodelling in the pathology of COPD and highlight the prospective utility of HIF-1α as a clinical biomarker for assessing airway remodelling. By providing deeper insights into the mechanisms underlying airway remodelling in COPD, this research suggests novel diagnostic and therapeutic avenues. It significantly advances our understanding of COPD pathophysiology and lays the groundwork for innovative approaches in management.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Christenson SA, Smith BM, Bafadhel M, Putcha N. Chronic obstructive pulmonary disease. *Lancet*. 2022;399(10342):2227–2242. doi:10.1016/S0140-6736(22)00470-6
2. Labaki WW, Rosenberg SR. Chronic Obstructive Pulmonary Disease. *Ann Internal Med*. 2020;173(3):ITC17–ITC32. doi:10.7326/AITC202008040
3. Rahman I. Oxidative stress in pathogenesis of chronic obstructive pulmonary disease: cellular and molecular mechanisms. *CBB*. 2005;43(1):167–188. doi:10.1385/CBB:43:1:
4. Wang Y, Xu J, Meng Y, Adcock IM, Yao X. Role of inflammatory cells in airway remodeling in COPD. *COPD*. 2018;13:3341–3348. doi:10.2147/COPD.S176122
5. Elberson VD, Nielsen LC, Wang H, Kumar HSV. Effects of intermittent hypoxia and hyperoxia on angiogenesis and lung development in newborn mice. *NPM*. 2016;8(4):313–322. doi:10.3233/NPM-15814134
6. Tao HC, Luo W, Pei H, et al. Expression and significance of HIF-1α in patients with chronic obstructive pulmonary disease (COPD) and smokers with normal lung function. *J Cell Mol Immunol*. 2014;30(8):852–855. doi:10.13423/j.cnki.cjcmi.006982
7. Shukla SD, Walters EH, Simpson JL, et al. Hypoxia-inducible factor and bacterial infections in chronic obstructive pulmonary disease. *Respirology*. 2020;25(1):53–63. doi:10.1111/resp.13722
8. Jones RL, Noble PB, Elliot JG, James AL. Airway remodelling in COPD: it's not asthma! *Respirology*. 2016;21(8):1347–1356. doi:10.1111/resp.12841
9. Brajer B, Batura-Gabryel H, Nowicka A, Kuznar-Kaminska B, Szczepanik A. Concentration of matrix metalloproteinase-9 in serum of patients with chronic obstructive pulmonary disease and a degree of airway obstruction and disease progression. *J Physiol Pharmacol*. 2008;59(Suppl 6):145–152.
10. Grzela K, Litwiniuk M, Zagorska W, Grzela T. Airway remodeling in chronic obstructive pulmonary disease and asthma: the role of matrix metalloproteinase-9. *Arch Immunol Ther Exp*. 2016;64(1):47–55. doi:10.1007/s00005-015-0345-y
11. Wells JM, Parker MM, Oster RA, et al. Elevated circulating MMP-9 is linked to increased COPD exacerbation risk in SPIROMICS and COPD gene. *JCI Insight*. 2018;3(22):e123614. doi:10.1172/jci.insight.123614
12. Seagrave J. Introduction to remodeling and repair in respiratory diseases. *Chest*. 2002;122(6):271S. doi:10.1016/S0012-3692(15)32961-5
13. Kurashima K, Hoshi T, Takayanagi N, et al. Airway dimensions and pulmonary function in chronic obstructive pulmonary disease and bronchial asthma. *Respirology*. 2012;17(1):79–86. doi:10.1111/j.1440-1843.2011.02052.x
14. Shimizu K, Hasegawa M, Makita H, Nasuhara Y, Konno S, Nishimura M. Comparison of airway remodelling assessed by computed tomography in asthma and COPD. *Respir Med*. 2011;105(9):1275–1283. doi:10.1016/j.rmed.2011.04.007
15. Jeffery PK. Remodeling in asthma and chronic obstructive lung disease. *Am J Respir Crit Care Med*. 2001;164(supplement_2):S28–S38. doi:10.1164/ajrccm.164.supplement_2.2106061
16. Zhang DW, Wei YY, Ji S, Fei GH. Correlation between sestrin2 expression and airway remodeling in COPD. *BMC Pulm Med*. 2020;20(1):297. doi:10.1186/s12890-020-01329-x
17. Churg A, Zhou S, Wright JL. Matrix metalloproteinases in COPD. *Eur Respir J*. 2012;39(1):197–209. doi:10.1183/09031936.00121611
18. Wells JM, Gaggar A, Blalock JE. MMP generated matrikines. *Matrix Biol*. 2015;44–46:122–129. doi:10.1016/j.matbio.2015.01.016
19. Rong B, Liu Y, Li M, Fu T, Gao W, Liu H. Correlation of serum levels of HIF-1α and IL-19 with the disease progression of COPD: a retrospective study. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3791–3803. doi:10.2147/COPD.S177034
20. Grigg J, Miyashita L, Suri R, Ahmad S. Pneumococcal infection of respiratory cells exposed to welding fumes; Role of oxidative stress and HIF-1 alpha. *PLoS One*. 2017;12(3):e0173569. doi:10.1371/journal.pone.0173569
21. Guan R, Wang J, Li Z, et al. Sodium tanshinone IIA sulfonate decreases cigarette smoke- induced inflammation and oxidative stress via blocking the activation of MAPK/HIF-1α signaling pathway. *Front Pharmacol*. 2018;9:263. doi:10.3389/fphar.2018.00263
22. Chang YC, Chan YC, Chang WM, et al. Feedback regulation of ALDOA activates the HIF-1α/MMP9 axis to promote lung cancer progression. *Cancer Lett*. 2017;403:28–36. doi:10.1016/j.canlet.2017.06.001
23. Nambu A, Zach J, Schroeder J, et al. Quantitative computed tomography measurements to evaluate airway disease in chronic obstructive pulmonary disease: relationship to physiological measurements, clinical index and visual assessment of airway disease. *Eur J Radiol*. 2016;85(11):2144–2151. doi:10.1016/j.ejrad.2016.09.010
24. Han MK, Tayob N, Murray S, et al. Association between emphysema and chronic obstructive pulmonary disease outcomes in the COPDGene and SPIROMICS cohorts: a post hoc analysis of two clinical trials. *Am J Respir Crit Care Med*. 2018;198(2):265–267. doi:10.1164/rccm.201801-0051LE