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CASE REPORT

The Dual Threat Combined Pulmonary Fibrosis and Emphysema (CPFE): Two Cases

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Abstract: Emphysema is common in fibrotic interstitial lung diseases, and its combination with pulmonary fibrosis is known as "Combined Pulmonary Fibrosis and Emphysema (CPFE) syndrome". The diagnosis of CPFE significantly impacts treatment strategies and prognosis. In this article, we report the clinical, imaging, and especially the pathological features of two CPFE patients. **Case 1**: A 51-year-old male patient with a history of smoking. CT scans revealed interstitial lung disease combined with pulmonary bullae. Pathology showed extensive deposition of mononuclear cells in the alveolar spaces, with some cells phagocytosing pigment. Mild fibrous tissue hyperplasia was present in the lung interstitium, along with chronic inflammation and lymphoid nodule formation. The histological findings were consistent with desquamative interstitial pneumonia (DIP), and the clinical, imaging, and pathological correlation confirmed a diagnosis of CPFE. **Case 2**: A 58-year-old male, a driver with a history of dust exposure and smoking, was admitted due to chest tightness and a cough for 2 years. Chest CT revealed interstitial changes, emphysema, and bullae in both lungs. Histopathology showed fibrous widening of alveolar septa, mild chronic inflammation, and dust cell deposition, along with emphysematous changes and bulla formation, consistent with CPFE. The purpose of this report is to increase pathologists' awareness of this complex disease and emphasize the importance of multidisciplinary cooperation in the diagnosis and treatment of CPFE. Furthermore, this article encourages further research into CPFE.

Keywords: CPFE, pulmonary fibrosis, emphysema, pathological diagnosis, multidisciplinary cooperation in diagnosis and treatment

Introduction

As the global population ages, the incidence of pulmonary fibrosis and emphysema has increased annually. The coexistence of these two conditions is termed "Combined Pulmonary Fibrosis and Emphysema (CPFE)". Radiologically, CPFE presents as airspace enlargement combined with fibrosis (AEF), observed in idiopathic pulmonary fibrosis (IPF) with emphysema, smoking-related interstitial fibrosis (SRIF), and fibrosis-related interstitial lung diseases (f-ILD). CPFE's clinical manifestations are complex, often presenting with overlapping features of chronic obstructive pulmonary disease (COPD) and pulmonary fibrosis, including chronic cough, dyspnea, and impaired diffusing capacity (DLCO), sometimes accompanied by pulmonary hypertension or lung cancer. The prognosis is generally poor, emphasizing the importance of early and accurate diagnosis for treatment planning and prognosis evaluation.

This report presents two CPFE cases diagnosed through clinical imaging and pathological analysis to improve awareness among clinicians, radiologists, and pathologists.

Case 1

Clinical Information

A 51-year-old male with a 30-year smoking history (1 pack/day) and a history of photosensitive dermatitis. He was admitted due to "lung interstitial changes found on physical examination for over a year". Chest CT in November 2022

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showed interstitial pneumonia and pulmonary bullae, which were not given significant attention at that time. After six months, he presented with "chest tightness, wheezing, cough, and sputum" following physical activity. Chest CT revealed findings consistent with bilateral interstitial lung disease, including reticular opacities, ground-glass attenuation, and features of chronic inflammation. Emphysematous changes and pulmonary bullae were also noted, along with a small nodule in the right upper lobe. Based on imaging characteristics, the radiologist suggested a pattern most consistent with nonspecific interstitial pneumonia (NSIP). Pulmonary function tests indicated normal ventilation function but moderate impaired diffusing capacity. Anti-neutrophil cytoplasmic antibody (p-ANCA) was positive, while anti-nuclear antibody and myositis antibody profiles were negative, was unlikely immune-related diseases. The patient still experiences chest tightness and wheezing after activity, along with dry mouth, dry eyes, and tooth loss, as well as dental caries. There is no joint redness, swelling, or mobility impairment, and no Raynaud's phenomenon. A follow-up chest CT scan performed on December 29, 2023, demonstrated bilateral interstitial inflammation and a small nodule in the right upper lobe. Bilateral lung transparency was reduced, with diffuse thickening of the interlobular septa observed throughout both lung fields. High-density opacities—manifesting as linear, nodular, ground-glass, and reticular patterns—were predominantly distributed in the peripheral zones of both lungs, with ill-defined margins. In addition, localized honeycombing and traction bronchiectasis were present. A small, calcified nodule was also identified in the right upper lobe (Figure 1).

Pathology

A cryobiopsy was taken from the basal segment of the right lower lobe. Microscopic examination and pathological diagnosis: Five tissue samples were sent for examination, with the largest diameter being 3 mm (1 sample) and 2 mm (4 samples). Lung parenchyma accounted for approximately 90%, respiratory bronchioles for about 10%, and a small amount of pleural tissue. The lung parenchyma was primarily composed of tissue surrounding the respiratory bronchioles, with atrophy of the lung parenchyma (reduced alveolar septa). There was a significant deposition of mononuclear cells in some alveolar spaces, with pigment-phagocytosing histiocytes (consistent with smoker's pigment). Mild fibrous widening of the alveolar septa was noted (like fibrotic nonspecific interstitial pneumonia, NSIP), accompanied by a small number of chronic inflammatory cells (mainly B lymphocytes) and focal lymphoid nodule formation. There was an increase in smooth muscle around the small pulmonary arteries and alveolar ducts near the respiratory bronchioles. A small amount of pleural tissue showed carbon deposition.

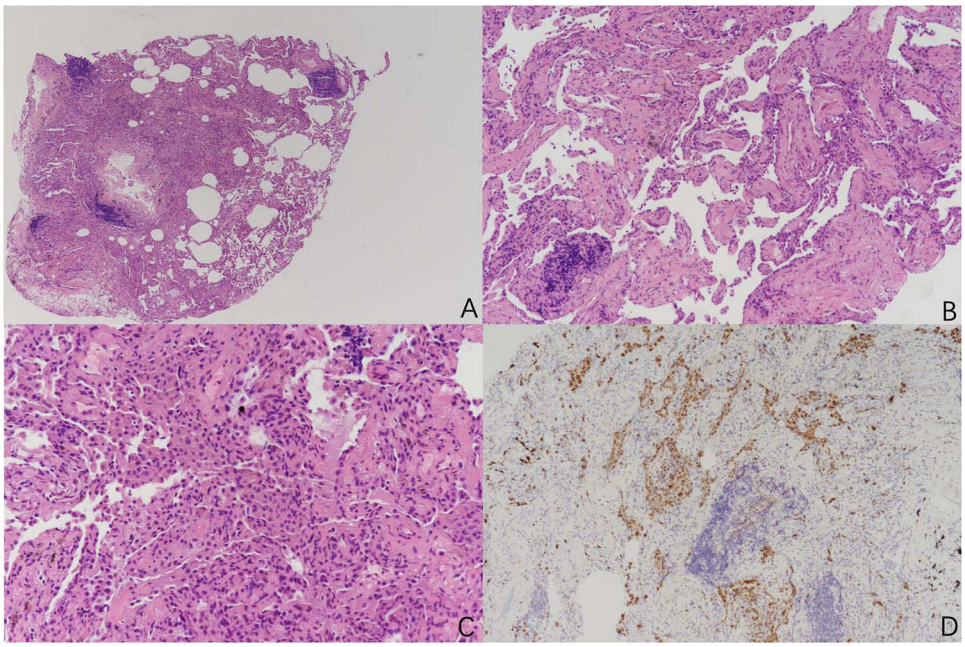

Figure 1 Pathological findings of the cryobiopsy sample from the right lower lobe basal segment in Case 1. (**A**) ×40 magnification, low magnification shows partial lung tissue consolidation and cystic dilation of some areas with scattered inflammatory cell infiltration. (**B**) ×100 magnification, shows diffuse fibrous thickening of the alveolar septa, focal lymphocytic nodular infiltration, and scattered tissue cell deposits within the alveolar lumen. (**C**) ×200 magnification, some areas show a significant amount of mononuclear tissue cell deposits within the alveolar lumen, accompanied by lung parenchymal collapse. (**D**) ×100 magnification, CD68 positive tissue cells observed in the alveolar lumen.

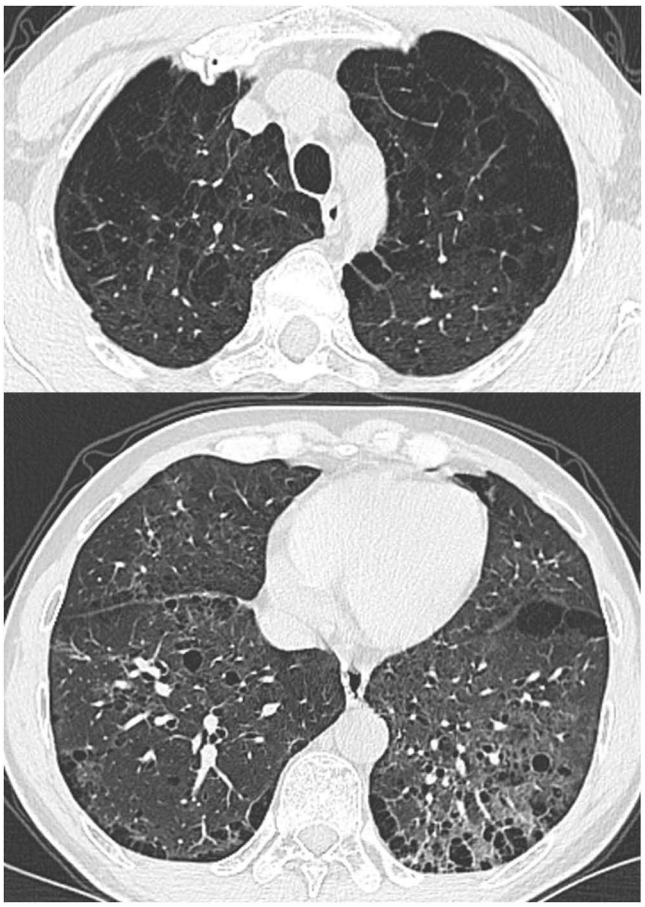

Figure 2 HRCT findings of Case 1 (2023-12-29). Top image: Significant decreased translucency in both upper lungs, showing emphysema changes. Bottom image: Diffuse thickening of the interlobular septa in both lower lungs, with strip-like, nodular, ground-glass, and reticular high-density shadows. Local honeycomb changes and traction bronchiectasis are visible.

Immunohistochemistry

The histiocytes expressed CD163 (++), CD68 (++), and CD31 (+); interstitial immune cells expressed CD3 (+), CD20 (++), CD4 (+), and CD8 (+, scattered); vascular structures expressed CD31 (+) and CD34 (vascular +); epithelial cells expressed CK7 (+). Special stains: Congo Red (-) (Figure 2).

Diagnosis

Histologically consistent with desquamative interstitial pneumonia (DIP), confirmed as CPFE by clinical-radiological-pathological multidisciplinary discussion.

Follow-Up

The patient has quit smoking and initiated systemic steroid therapy at a dose of 15 mg twice daily. After one-month, slight symptomatic improvement was observed, and the steroid dose was tapered to 10 mg twice daily. Despite another month of treatment, symptoms persisted. The regimen was then adjusted to 15 mg once daily for three months, during which inhaled corticosteroids were also introduced. Symptoms remained largely unchanged. Subsequently, the oral steroid dose was reduced to 10 mg daily, which has been maintained. Throughout the treatment course, supportive therapies including oxygen supplementation and gastric protection were provided. At the most recent follow-up, Nintedanib (an anti-fibrotic agent) was added to the regimen. Symptoms have improved mildly but not significantly, with occasional skin rashes.

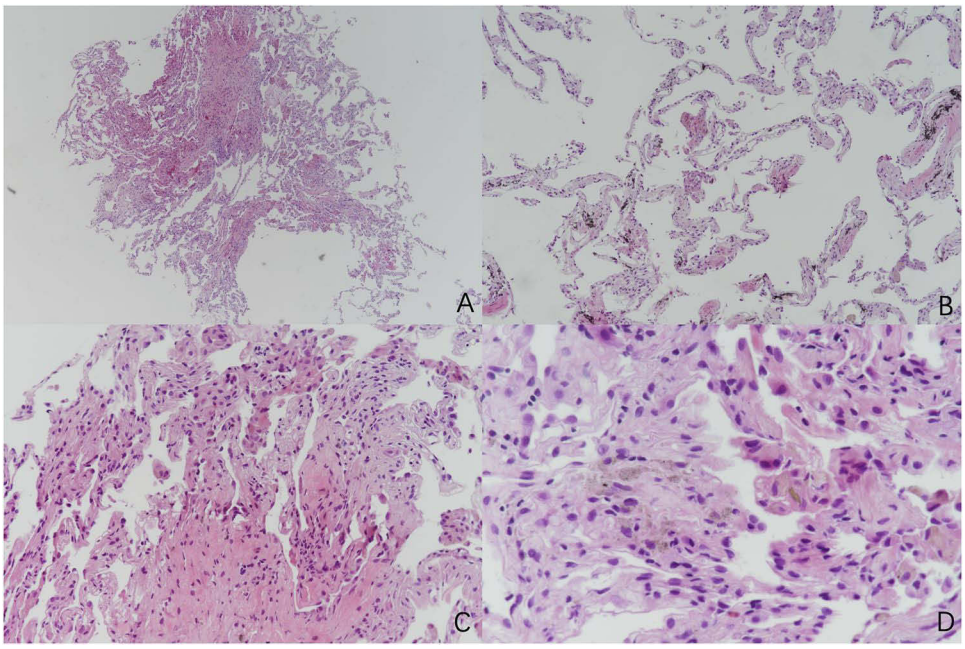

Figure 3 Pathological findings of the cryobiopsy sample from the posterior segment of the right upper lobe in Case 2. (**A**) ×40 magnification, low magnification shows some areas of lung consolidation and cystic dilation. (**B**) ×100 magnification, shows minimal chronic inflammatory cell infiltration in the alveolar septa, mild fibrous thickening, single mononuclear tissue cell deposits in the alveolar lumen, and some alveolar septa floating within the alveolar lumen, which may indicate emphysema changes. (**C**) ×200 magnification, some areas show significant increase in fibrous stroma in the alveolar septa, accompanied by alveolar collapse and single mononuclear tissue cell deposits. (**D**) ×400 magnification, high magnification shows alveolar collapse with increased interstitial fibrous stroma, tissue cell deposits within the alveolar lumen and septa. The tissue cells contain brown-yellow granular particles indicative of dust cells.

Case 2

Clinical Information

A 58-year-old male truck driver with a 40-year smoking history (2 packs/day) and dust exposure. He was admitted due to "chest tightness and worsening cough and sputum over 2 years". In March 2023, chest CT showed subpleural reticulation, multiple honeycombing changes, patchy ground-glass opacities, calcified nodules in the lower lobes, and enlarged mediastinal lymph nodes. The clinical diagnosis was interstitial lung disease with infection, and he was treated with antibiotics and cough suppressants, with symptom improvement. However, in November 2023, due to persistent cough with blood-streaked sputum, repeat CT revealed fibrotic interstitial pneumonia with emphysema and bullae (Figure 3). Pulmonary function tests showed moderate small airway ventilation dysfunction and moderate impairment of diffusing capacity of carbon monoxide. Upon admission, symptomatic supportive treatment including anti-inflammatory, expectorant, and antioxidant therapies was administered, along with a cryobiopsy.

Pathology

Cryobiopsy of the right upper lobe was performed. Two lung tissue samples were sent for examination, with the largest diameters being 3 mm and 4 mm, respectively. The lung parenchyma accounted for approximately 80%, and small airways and blood vessels accounted for about 20%. In some areas, there was fibrous widening of the alveolar septa, with mild chronic inflammatory cell infiltration. In other areas, there were deposits of histiocytes phagocytosing dust particles in the alveolar septa and alveolar spaces. Additionally, some areas exhibited emphysema with bulla formation (Figure 4).

Diagnosis

Histologically consistent with emphysema and fibrosis, confirmed as CPFE by clinical-radiological-pathological discussion.

Follow-Up

The patient has not yet quit smoking, but exposure to dust has decreased. Symptoms have not improved significantly, and the patient still experiences chest tightness, cough, and sputum.

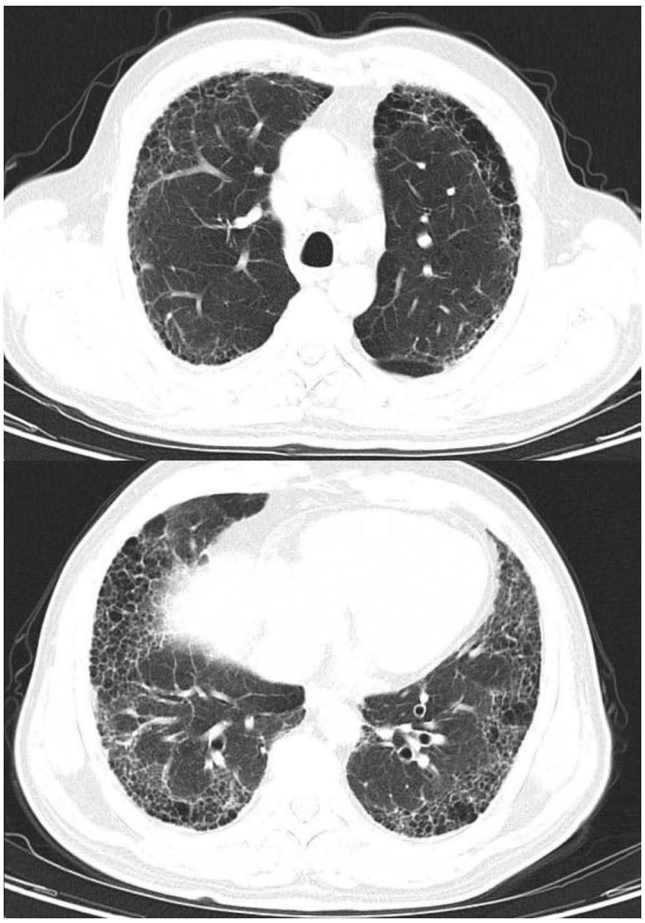

Figure 4 HRCT findings of Case 2 (2023-11-29). Top image: Interstitial changes in both lungs, emphysema, and bullae in both upper lungs with fine reticular shadows. Bottom image: More pronounced reticular shadows and interlobular septal thickening in both lower lungs.

Discussion

The concept of CPFE was first proposed in 1948, and it was later recognized as a clinical syndrome.[1] Patients with CPFE typically have normal or mildly reduced lung volume, but severe diffusion impairment, with histopathology showing emphysema, inflammation, and fibrosis.

The exact reasons for the coexistence of emphysema and pulmonary fibrosis are not yet fully understood.[2] Firstly, both conditions share common risk factors, such as smoking and environmental exposures (eg, asbestos, silica dust, etc) Emphysema primarily affects the airways, while pulmonary fibrosis mainly involves the lung interstitium, causing structural damage and fibrosis.[3] Secondly, chronic inflammatory responses in the lungs serve as a common pathological basis for both conditions. Genetic changes related with telomere dysfunction and alveolar surfactant production also play a significant role in the pathogenesis of CPFE.[4,5] Finally, both emphysema and pulmonary fibrosis are age-related changes. In some animal models, emphysema and pulmonary fibrosis have also been observed to occur simultaneously.[6,7]

The diagnosis of CPFE relies on a comprehensive analysis of the patient's clinical presentation, imaging, and pathology. Clinicians should utilize lung function tests as a cornerstone of assessment. While reduced carbon monoxide diffusing capacity (DLCO) is a notable finding, a critical nuance must be emphasized: the obstructive component caused by emphysema may be offset by the restrictive component induced by fibrosis. This physiological counterbalance can lead to an underestimation of the true severity of lung function impairment, underscoring the need for meticulous interpretation of test results. High-Resolution Computed Tomography (HRCT) is the preferred imaging method, as it can clearly display the coexistence of emphysema and pulmonary fibrosis. However, imaging alone can sometimes make it difficult to distinguish from other pulmonary diseases, and pathology diagnosis provides crucial evidence for confirming the disease.

In pathology diagnosis, emphysema is a necessary condition for diagnosing CPFE. In addition to emphysema, the patient should also exhibit interstitial pneumonia-related features, such as respiratory bronchiolitis-related interstitial lung disease (RB-ILD) and smoking-related interstitial fibrosis (SRIF), and may also have other types of pulmonary fibrosis, especially desquamative interstitial pneumonia (DIP), SRIF, usual interstitial pneumonia (UIP), and pulmonary Langerhans cell histiocytosis (PLCH).

RB-related interstitial pneumonia typically shows macrophage accumulation in the distal bronchioles and surrounding airspaces, with a distribution centered around the lobular core, without associated inflammation or fibrosis. DIP, on the other hand, shows relatively uniform, diffuse pulmonary interstitial inflammation and fibrosis, with the presence of alveolar macrophages that have phagocytized pigments. SRIF typically presents on chest CT as subpleural cystic lesions. Histopathologically, these correspond to thick-walled cysts resulting from distal (paraseptal) emphysema, with the cystic spaces primarily composed of degenerating alveolar epithelial cells. UIP shows honeycomb changes, with fibrosis distributed in a patchy pattern. Normal lung structure collapses, and fibrosis includes fibroblast foci and mild patchy lymphocytic infiltration, in contrast to the uniform, low-cellularity, dense eosinophilic fibrosis in SRIF.

The two most common complications of CPFE are lung cancer and pulmonary hypertension.[8,9] In CPFE, lung cancer tends to occur in areas of dense fibrosis, primarily in the peripheral and lower lobes, supporting the possibility that cancer development is related to fibrotic regions. Additionally, patients with CPFE combined with pulmonary hypertension experience more severe symptoms than those with isolated IPF or COPD. This may be due to the combined effects of emphysema and fibrosis, leading to a reduction in the pulmonary capillary bed and hypoxic vasoconstriction, which in turn increases pulmonary vascular resistance more significantly.

One of our cases presented with intermittent cutaneous eruptions. For over two decades, the patient experienced recurrent rashes on sun-exposed areas during the spring and summer months, with spontaneous improvement in the autumn. This clinical pattern suggests a possible association with seasonal hypersensitivity reactions. The patient's report of symptom relief following corticosteroid therapy further supports a potential underlying allergic or autoimmune component. Nevertheless, whether this phenomenon is mechanistically linked to the pathogenesis of combined pulmonary fibrosis and emphysema (CPFE) remains uncertain and warrants further case accumulation and comprehensive investigation.

The treatment of CPFE needs to be tailored to the individual patient's specific situation,[10] typically including smoking cessation, pulmonary rehabilitation, pharmacotherapy (such as antifibrotic drugs, bronchodilators, corticosteroids, and immunosuppressants), vaccination, oxygen therapy, and, in end-stage cases, lung transplantation.[11] Both IPF and COPD increase the risk of lung cancer compared to the general population, but the risk in CPFE patients may exceed that of patients with isolated emphysema or IPF. Early identification, diagnosis, and timely intervention, combined with regular follow-up monitoring, can help improve patient prognosis.

Conclusion

This case highlights CPFE as a complex pulmonary disorder requiring vigilance from clinicians, radiologists, and pathologists. Clinicians should prioritize lung function tests: reduced CO diffusing capacity (DLCO) is common, but the counterbalance between emphysema-induced obstruction and fibrosis-induced restriction may mask true impairment severity, necessitating careful interpretation. Radiologists identify characteristic imaging (eg, upper-lobe emphysema and subpleural fibrosis on HRCT) for early detection, with pathologists confirming diagnosis via histopathology. Multidisciplinary collaboration—led by clinicians—is critical for accurate diagnosis. Ongoing research into mechanisms and targeted therapies remains essential for improving outcomes.

Ethics Approval and Informed Consent

This report was published with the patients' written informed consents and approval from the Ethics Committee of "Nanjing Drum Tower Hospital, Affiliated Hospital of Medical School, Nanjing University". Written informed consents were obtained from the patients for both participation in this case report and the publication of relevant case details. The patients were informed in writing that all efforts would be made to ensure anonymity and that no identifiable information (such as name, images, or personal details) would be disclosed in the publication. They also acknowledged and understood that the published report may be accessible in public and academic domains.

Consent for Publication

All the authors reviewed and agreed on all versions of the article before submission, agreed to the submission of this article, and agreed to take responsibility and be accountable for the contents of the article.

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 there is no conflict of interest regarding the publication of this paper.

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