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COMMENTARY

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Elevated MUC1 and MUC5AC mucin protein levels in airway mucus of critical ill COVID-19 patients

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Patients with coronavirus disease 2019 (COVID-19) exhibit a spectrum of respiratory symptoms like cough and dyspnea.[1-3] Airway mucus is an adhesive viscoelastic gel composed mostly of high-molecular-weight mucous glycoproteins and water, which is important in maintaining lung function and health, pathological mucus hypersecretion may cause airway obstruction and lead to respiratory distress. Mucin (MUC) glycoproteins are the major macromolecular components of mucus, which are classified into two major types: the gel-forming secreted MUC5AC and the membrane-tethered MUC1.[4] Here, with an attempt to understand the lung changes, we sought to provide a delineation of the components of airway mucus from patients with COVID-19.

To clean airway obstruction, respiratory tract mucus was aspirated and collected via bronchoscopy from COVID-19 patients with a critical illness, and optical coherence tomography (OCT) was applied via bronchoscopy to obtain cross-sectional images of the bronchiole. For healthy control, sputum was induced by inhaled hypertonic (3%) saline solution delivered with an ultrasonic nebulizer. After collection, sputum was processed as previously described for components analysis.[5] Medical history, and clinical and laboratory data of the participants were extracted from electronic medical records. The study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University (No. 2020-65). The requirement for informed consent was waived because the study was observational and the family members were in quarantine.

MUC5AC (sc-21701; Santa Cruz, Shanghai, China) and MUC1 (sc-6827; Santa Cruz) in airway mucus were measured using enzyme-linked immunosorbent assay, and MUC1-cytoplasmic tail (CT, clone EP1024Y; Abcam, Shanghai) levels were measured by Western blot analysis as described previously.[5] The levels of MUC5AC and MUC1 were normalized to their average signal reading of a healthy control group.

A total of 16 patients with COVID-19 were included in this study, the clinical characteristics of the recruited subjects were shown in Table S1. There was no significant deviation in the distribution of age, or sex between the cohorts of case and control subjects. All the patients with COVID-19 were admitted to the intensive care unit because of low oxygenation index (199 ± 23 mm Hg), and 79% of them received mechanical ventilation. Blood laboratory tests showed elevated inflammatory indexes including leukocyte count, C-reactive protein, and interleukin-6 in most of the patients with COVID-19 (Table S2).

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OCT indicated clear bronchiole in healthy controls (Figure 1A) and mucus retention in the bronchiole of patients with COVID-19 (Figure 1B). A volume of 1-8 mL white to gray sputum with high viscosity (Figure 1C) was aspirated from the respiratory tract of 16 patients with COVID-19. Induced sputum from healthy control was clear and transparent with low viscosity. Compared to healthy control, airway mucus from patients with COVID-19 had a higher level of MUC5AC (Figure 1D), MUC1 (Figure 1E), and MUC1-CT fragment (Figure 1F). However, there were no significant differences in the concentration of total protein, sodium, or chloride in the airway mucus from patients with COVID-19 when compared to healthy control (Table S3).

Although more than half of patients with COVID-19 presented with a dry cough,[6] this study provided direct evidence showing mucus retention in the small airway of patients with COVID-19, and patients were not able to expectorate by themselves and need bronchoscopy aspiration to help them to clean respiratory tract. The sputum from these patients with COVID-19 was viscous, which is not surprising as MUC5AC levels are extremely high, hyperconcentration of this gel-forming MUC dehydrates airway surfaces and causes mucus adhesion, which may contribute to airflow obstruction and respiratory distress. Clearance of airway mucus is an important way to increase oxygen and carbon dioxide exchange, bronchoscopy aspiration of airway mucus was used in all our patients to relieve hypoxia. In our center, all the 16 critical ill COVID-19 patients recovered and were discharged from hospitalization, which may attribute to our aggressive clearance of the respiratory tract. It is of note that bedside bronchoscopy may not be available in some hospitals as the medical resources are limited during the COVID-19 pandemic, carbocisteine has been reported to inhibit airway MUC5AC secretion, which could be used to reduce sputum viscosity and elasticity in patients with COVID-19. In addition, hydration of sputum by aerosolized hypertonic saline solutions or mannitol, and dilation of bronchi via aerosolized salbutamol may facilitate sputum expectoration.

MUC1 is a membrane-tethered MUC expressed on the apical surface of epithelial cells.[7,8] Since MUC1-CT fragment is on the cytoplasmic side of the cells, the elevated sputum CT fragment in patients with COVID-19 could come from detached and disrupted epithelial cells, which is evidenced by the pathological findings of diffuse alveolar damage with fibromyxoid exudates and macrophage infiltration in the lung tissue from patients with COVID-19.[9]

The limitation of this study is that induced sputum was used in the control group to compare airway mucus aspirated via bronchoscopy from patients with COVID-19, because it was very difficult for the patients with COVID-19 to expectorate sputum even with hypertonic saline solution inhalation.

The findings may suggest that increased level of MUCs in the airway mucus may contribute to the high viscosity of airway mucus

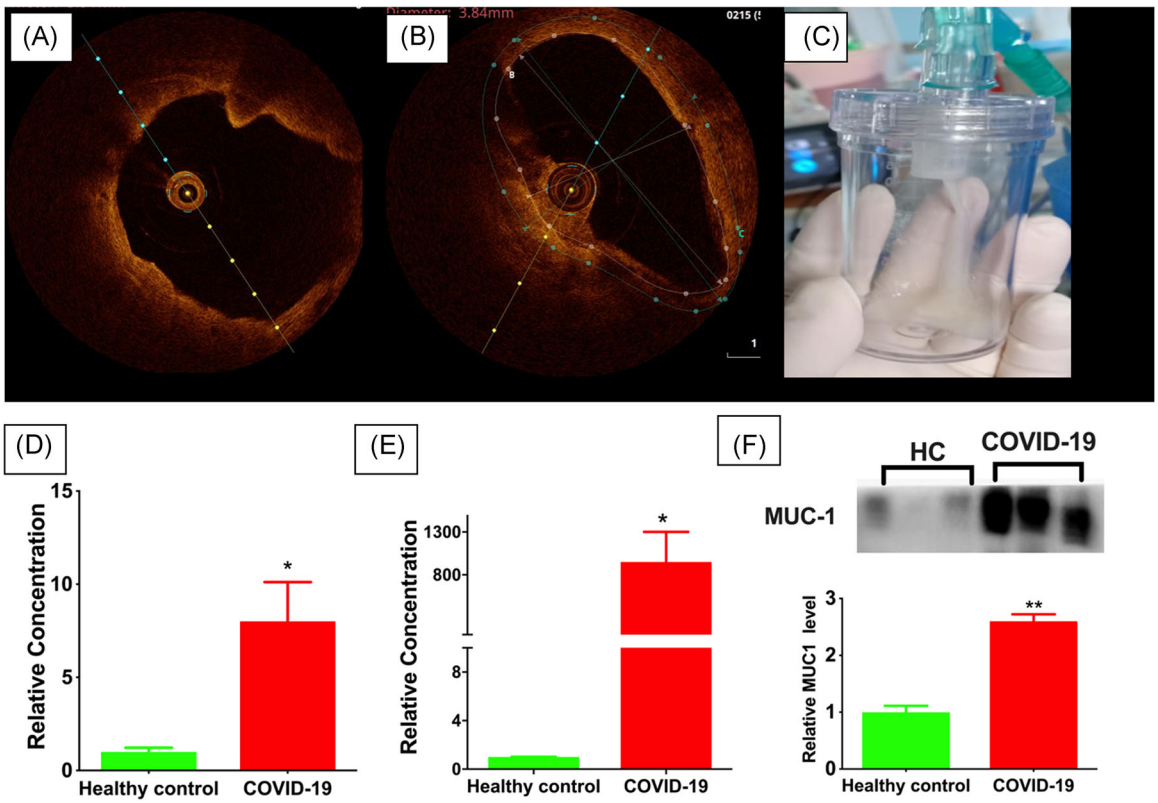

FIGURE 1 Representative cross-sectional images of bronchioles in (A) healthy and (B) critical ill COVID-19 patients were obtained with optical coherence tomography and bronchoscopy. C, Airway mucus aspirated by bronchoscopy. D, MUC1 and (E) MUC5AC protein levels as measured by ELISA, and (F) MUC1-CT level as measured by Western blot analysis in the airway mucus from COVID-19 patients and healthy control (HC). The levels of MUC5AC and MUC1 were normalized to their average signal reading of healthy control group. COVID-19, coronavirus disease 2019; CT, cytoplasmic tail; ELISA, enzyme-linked immunosorbent assay; MUC, mucin

and sputum retention in the small airway of patients with COVID-19, airway mucus clearance may be indicated to relieve respiratory distress, and MUC5AC may serve as a target for mucolytic agents in treating COVID-19. And MUC1-CT may serve as an indicator reflecting the severity of airway and alveolar epithelial cell damage.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

NZ, YL, WL, and JZ conceived and designed the experiments. TW and WL analyzed the data and wrote the manuscript. XL, FY, and JH collected the samples and clinical data. FL, AZ, YL, and JL performed the experiments. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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