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ORIGINAL RESEARCH

Long COVID in Elderly COPD Patients: Clinical Features, Pulmonary Function Decline, and Proteomic Insights

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Background: Elderly patients with chronic obstructive pulmonary disease (COPD) face a heightened risk of developing long coronavirus disease (COVID); however the exact clinical characteristics and underlying mechanisms remain unclear.

Methods: We enrolled 85 elderly COPD patients, of whom 43 reported newly onset persistent fatigue (the most dominant complaint of long COVID) within 1 year after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and they were allocated to the Long-COVID group. The remaining 42 patients were assigned to the Control group. Patients completed questionnaires, pulmonary function tests, chest CT, routine laboratory tests, and blood proteomic analysis.

Results: Long-COVID patients had a longer course of COPD (> 5 years, 76.8% vs 52.4%) and duration of SARS-CoV-2 infection (10.0 days vs 7.0 days) (All $P < 0.05$), higher symptom burden, worse pulmonary ventilation function and a more rapid decrease in DL_{CO} (All $P < 0.05$). Proteomic analysis indicated disruptions in inflammation and energy metabolism, potentially underlying long COVID in these patients. The machine learning model identified wheezing, the duration of SARS-CoV-2 infection, EIF2S3 (eukaryotic translation initiation factor 2 subunit gamma), current FEV1/FVC (%), and the course of COPD as key features distinguishing Long-COVID patients, and exhibited excellent performance.

Conclusion: Elderly COPD patients with a longer COPD course and duration of COVID-19 are more prone to develop long COVID, with decreased pulmonary ventilation and diffusion ability. Disordered inflammation regulation and energy metabolism may be the potential mechanisms, highlighting the importance of monitoring inflammation and metabolic dysregulation in elderly COPD patients after recovery from COVID-19.

Keywords: elderly, COPD, long COVID, risk factors, proteomics

Introduction

Coronavirus disease 2019 (COVID-19) has become the greatest public health crisis of the 21st century. It has imposed an unprecedented burden on global health and economy. As of April 20, 2025, more than 777 million individuals were diagnosed with COVID-19, and more than 7.0 million deaths have been reported worldwide according to the World Health Organization (WHO).[1] Increasing studies have reported that COVID-19 survivors might develop sustained postinfection sequelae, which are called long-COVID, also known as post-acute sequelae of COVID-19 (PASC).[2] The

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latest 2024 NASEM (National Academies of Sciences, Engineering, and Medicine) definition of long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems.[3] Fatigue, shortness of breath, and cognitive dysfunction are its most common presentations, and these symptoms usually have an adverse impact on daily functioning.[4,5]

A wide range of comorbidities, including chronic obstructive pulmonary disease (COPD), are related to an elevated risk of long COVID.[6] COPD patients are reportedly more susceptible to SARS-CoV-2 infection and are at increased risk of having more severe clinical outcomes.[7,8] A systematic review and meta-analysis reported that pre-existing COPD was associated with 32% increased odds of long COVID.[9] COPD prevalence tends to increase with age. Elderly COPD patients may be more susceptible to immune dysregulation, given the chronic inflammation and higher levels of senescent cells, which could predispose them to long COVID.[10] Despite the growing body of research on long COVID, its pathophysiology in COPD patients is still not well understood. It remains largely unclear which elderly COPD patients will develop long COVID, as well as the medium- and long-term impacts of SARS-CoV-2 infection on this patient group.

In this study, we recruited a group of elderly COPD patients who were infected with SARS-CoV-2 nearly one year prior, and used fatigue to discriminate COPD patients with long COVID from those without because fatigue is the most common complaint of long COVID.[5,11,12] While COPD patients can report fatigue as a result of impaired pulmonary function, fatigue due to long COVID is typically more severe and persistent, with a notable impact on daily life. Other long COVID symptoms, such as cough and dyspnoea, are also common clinical manifestations of COPD itself and are thus not suitable for discriminating long COVID in COPD patients. The enrolled COPD patients, with or without long COVID, completed questionnaires, physical examinations, and serum proteomics. The primary endpoints of this study encompassed a comprehensive evaluation of clinical characteristic, pulmonary function assessments, and chest CT imaging analyses. Additionally, proteomic analysis served as the secondary outcome measure, providing further insights into the underlying mechanisms.

Methods

Study Design and Participants

Detailed methods are provided in the Supplementary Material. This longitudinal cohort study was conducted between November 2023 and February 2024 at Beijing Hospital in 85 elderly COPD patients, nearly one year after they had been infected with SARS-CoV-2 (Figure 1), ensuring that any observed fatigue and other symptoms were persistent and not related to the acute phase of infection. All inclusion and exclusion criteria are provided in Supplementary Table 1. Forty-three of the enrolled 85 patients reported persistent and remarkable fatigue within 1 year after SARS-CoV-2 infection and were allocated to the Long-COVID group. The remaining 42 patients without fatigue were assigned to the Control group.

The enrolled patients then completed the questionnaire assessment, blood tests, pulmonary function tests (PFTs), and chest CT. Randomly selected 60 patients (30 patients in each group) further performed serum proteomic analysis. The clinical and proteomic data of the 60 patients were used for machine learning model training to identify important features of elderly COPD patients with long COVID (Supplementary Figure 1).

Face–to–face Follow-up at the Hospital

The questionnaires were conducted by well-trained medical staff, collecting baseline demographic information and medical history. Other questionnaires included the mMRC dyspnoea scale,[13] the EuroQol Visual Analogue Scale (EQ-VAS) to assess quality of life,[14,15] the Generalized Anxiety Disorder-7 (GAD-7) to screen for anxiety,[16] the Fatigue Severity Scale (FSS),[17] the Patient Health Questionnaire-9 (PHQ-9) to screen for depression,[18] and the COPD Assessment Test (CAT) to assess the burden of symptoms and their impact on the daily life of COPD patients.[19] Then the patients performed physical examinations, included routine blood tests, PFTs, and chest CT. Blood tests included complete blood count, biochemical, C-reactive protein (CRP), and serum amyloid A (SAA) analyses. PFTs were performed under the supervision of well-trained technicians, and multiple lung function parameters were assessed. These patients had PFTs at Beijing Hospital within two

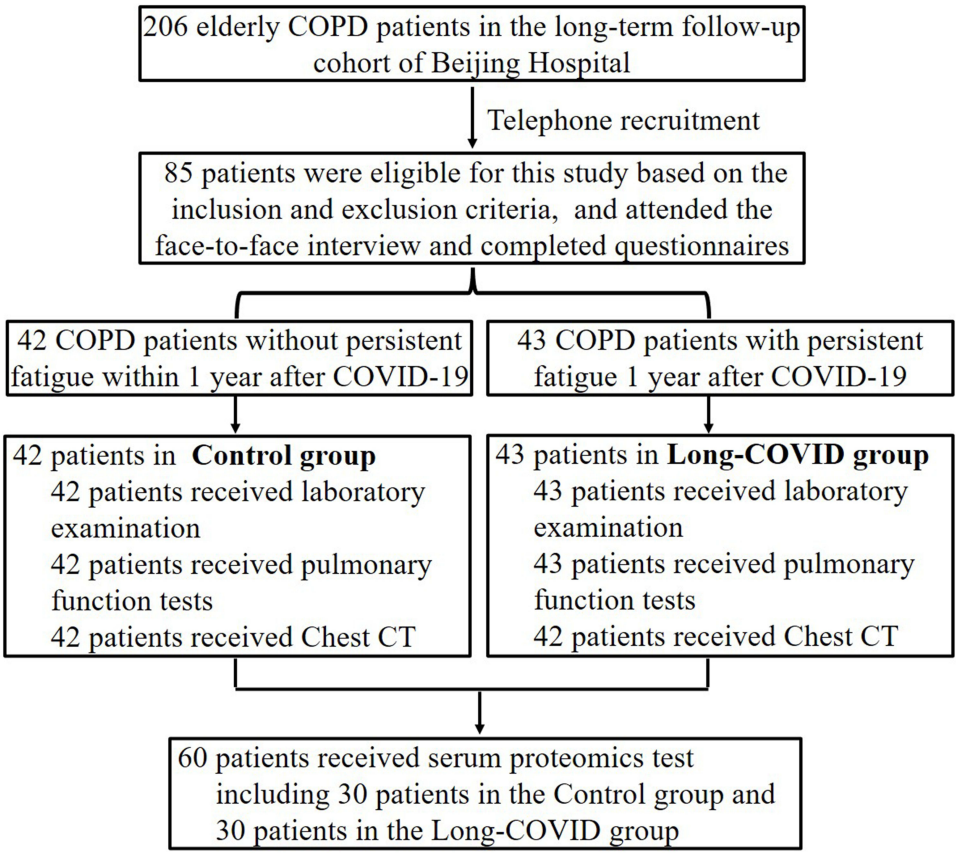

Figure 1 Flow chart of the study.

years before the COVID-19 epidemic, and the corresponding lung function parameters were extracted from electronic medical care data. We calculated the annual variation according to the time interval between the two PFTs. Chest CT was used to evaluate the extent of emphysema, bronchial wall thickening, interstitial changes, and tractive bronchiectasis. Detailed descriptions of chest CT evaluation are provided in the Supplementary Material.

DIA (Data-Independent Acquisition) Proteomic Analysis

The detailed processes of proteomic analysis can be found in the Supplementary Material. Sixty randomly selected serum samples, including 30 samples from the Control group and 30 samples from the Long-COVID group, were processed for DIA proteomic analysis. Proteins with a fold change > 1.2 or < 0.83 and a P value < 0.05 (Student's t test) were identified as differentially expressed proteins (DEPs). Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis, and reactome pathway analysis were used to explore the functions of DEPs.

Machine Learning Model Training

The detailed flow of machine learning model training is provided in Supplementary Figure 1. Briefly, all data underwent initial screening and missing data imputation. Boruta was used to select the important features. Then three machine learning algorithms, including Random Forest, Support Vector Machine (SVM), and Ridge Regression, were used for model training based on the selected important features. Finally, we evaluated the model performance using area under the operating characteristic (ROC) curves (AUC) and analysed the feature importance via SHAP (Shapley Additive exPlanations) values.

Statistical Analysis

Baseline demographic characteristics are presented as medians (IQRs) or means ± SDs for continuous variables and n/N (%) for categorical variables. For continuous variables, *P* values were calculated using Student's *t* test or the Mann–Whitney *U*-test. Categorical variables were compared by Fisher's exact test or Pearson's chi(2) test. A two-sided *P* value less than 0.05 was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 25.0.

Results

Baseline Characteristics of the Participants

A total of 85 patients were ultimately enrolled at the 1-year follow-up visit (Table 1). These COPD patients were all clinically stable. Results of routine blood tests, including indicators of acute inflammation, were comparable between the two groups (Supplementary Table 2). Characteristics such as age, sex, BMI (body mass index), cigarette smoking, and vaccination status were matched. Most included patients were male (88.2%) and had a median age of 71.0 years (IQR 69.0–76.0), with a high smoking rate (78.8%). Sixty-two (72.9%) patients had received one or more doses of SARS-CoV-2 vaccination. Besides, comorbidities were also comparable between the two groups (Table 1). Hypertension (51.8%) and diabetes (23.5%) were the most common comorbidities. More patients in the Long-COVID group used inhaled corticosteroids (ICSs) than patients in the Control group (74.4% vs 61.9%), but the difference was not statistically significant (Table 1). In addition, a greater proportion of patients in the Long-COVID group had COPD for more than 5 years (76.8% vs 52.4%). Lung function was not significantly differ between the two groups before the COVID-19 epidemic according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades (Table 1). The duration of SARS-CoV-2 infection was also longer in the Long-COVID group (10.0 days vs 7.0 days), but the severity of SARS-CoV-2 infection did not differ between the two groups (Table 1).

Clinical Characteristics of Long COVID in Elderly COPD Patients

Within one year following SARS-CoV-2 infection, the Long-COVID group had a higher rate of hospital visits due to COPD exacerbation (11.9% vs 30.2%, $P < 0.05$). A significantly higher proportion of patients in the Long-COVID group experienced exacerbations of chest tightness (16.5% vs 4.7%, $P < 0.01$) and wheezing (32.9% vs 11.8%, $P < 0.001$) compared to those without long-COVID. However, the proportions of patients who experienced cough and sputum production exacerbation were similar between the two groups (Table 2). Significant dyspnoea (mMRC ≥ 2) was observed in 72.1% of patients in the Long-COVID group compared with 26.2% of patients in the Control group (Figure 2a). The CAT questionnaire aims to assess and quantify the symptom burden of COPD patients. In this study, 90.7% of patients in the Long-COVID group had CAT scores > 10, compared with 42.9% in the Control group, indicating a higher symptom burden associated with COPD in the Long-COVID group (Figure 2b).

All enrolled patients completed a series of questionnaires to assess their health-related quality of life (EQ-VAS), anxiety (GAD-7), depression (PHQ-9) (Supplementary Table 3). The EQ-VAS is used to assess the patients' own perceptions of their own overall health. Patients in the Long-COVID group had significantly lower EQ-VAS scores, indicating impaired health-related quality of life after SARS-CoV-2 infection. The GAD-7 score, which is usually used to screen for generalized anxiety disorder (GAD), did not markedly differ between the two groups. More than half of patients in the Long-COVID group experienced various degrees of depression, ranging from mild to moderately severe, as indicated by the PHQ-9 scores. These questionnaires collectively demonstrated that COPD patients with long COVID had lower health-related quality of life and signs of depression.

Pulmonary Function and Chest CT Evaluation

All enrolled COPD patients underwent PFTs to evaluate their current status of lung function (Table 3). As shown in Table 1, the severity of airflow obstruction was not significantly differ between the two groups before SARS-CoV-2 infection. However, multiple pulmonary function parameters were lower in the Long-COVID group than in the Control group one year after SARS-CoV-2 infection, including FEV1% pred (FEV1/estimated value of FEV1), PEF % pred

Table 1 Baseline Characteristics of Recruited Patients

Characteristic	Total N=85	Control N=42	Long-COVID N=43	*P* value
Age, years	71.0 (69.0–76.0)	72.5 (69.0–76.0)	71.0 (69.0–76.0)	0.558
Sex, Male	76/85 (89.4%)	38/42 (90.5%)	38/43 (88.4%)	0.753
BMI, kg/m^2	25.5±0.4	25.7±3.9	25.3±3.9	0.649
Cigarette smoking				0.824
Never smoker	18/85 (21.2%)	10/42 (23.8%)	8/43 (18.6%)	
Current smoker	16/85 (18.8%)	8/42 (19.0%)	8/43 (18.6%)	
Former smoker	51/85 (60.0%)	24/42 (57.2%)	27/43 (62.8%)	
Vaccination				
Unvaccinated	23/85 (27.1%)	11/42 (26.2%)	12/43 (27.9%)	0.350
One dose	2/85 (2.4%)	2/42 (4.8%)	0	
Two or more dose	60/85 (70.5%)	29/42 (69.0%)	31/43 (72.1%)	
ICS	58/85 (68.2%)	26/42 (61.9%)	32/43 (74.4%)	0.215
Comorbidities				
Asthma	7/85 (8.2%)	3/42 (7.1%)	4/43 (9.3%)	1.000
Bronchiectasis	2/85 (2.4%)	0	2/43 (4.7%)	0.494
Pulmonary interstitial fibrosis	5/85 (5.9%)	2/42 (4.8%)	3/43 (7.0%)	1.000
Lung cancer	3/85 (3.5%)	0	3/43 (7.0%)	0.241
Hypertension	44/85 (51.8%)	22/42 (52.4%)	22/43 (51.2%)	1.000
Diabetes	20/85 (23.5%)	11/42 (26.2%)	9/43 (20.9%)	0.568
Chronic cardiac dysfunction	3/85 (3.5%)	1/42 (2.4%)	2/43 (4.7%)	0.571
Chronic kidney disease	6/85 (7.1%)	2/42 (4.8%)	4/43 (9.3%)	0.676
Cerebrovascular diseases	7/85 (8.2%)	2/42 (4.8%)	5/43 (11.6%)	0.433
Course of COPD				0.049
≤ 3 years	12/85 (14.1%)	10/42 (23.8%)	2/43 (4.6%)	
3–5 years	18/85 (21.2%)	10/42 (23.8%)	8/43 (18.6%)	
5–10 years	29/85 (34.1%)	11/42 (26.2%)	18/43 (41.9%)	
> 10 years	26/85 (30.6%)	11/42 (26.2%)	15/43 (34.9%)	
GOLD grades*				0.608
GOLD 1	17/85 (20.0%)	9/42 (21.4%)	8/43 (18.6%)	
GOLD 2	49/85 (57.6%)	26/42 (61.9%)	23/43 (53.5%)	
GOLD 3	15/85 (17.6%)	6/42 (14.3%)	9/43 (20.9%)	
GOLD 4	4/85 (4.7%)	1/42 (2.4%)	3/43 (7.0%)	
Course of SARS-CoV-2 infection, days	7.0 (5.0–15.0)	7.0 (2.3–10.0)	10.0 (7.0–19.3)	0.013
Severity of SARS-CoV-2 infection				
Severe	6/85 (7.1%)	3/42 (7.1%)	3/43 (7.0%)	1.00
Non-severe	79/85 (92.9%)	39/42 (92.9%)	40/43 (93.0%)	

Notes: The date are presented as median (IQR), mean ± SD, or n/N (%). For continuous variables, *P* values were calculated using Student's *t* test or the Mann–Whitney *U*-test. Categorical variables were compared by Fisher's exact test or Pearson's chi(2) test. A two-sided *P* value less than 0.05 was considered statistically significant. *GOLD grades based on post-bronchodilator FEV1 values tested before SARS-CoV-2 infection.

Abbreviations: BMI, body mass index; ICS, inhaled corticosteroid; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

(PEF/estimated value of PEF), MEF75% pred (MEF75/estimated value of MEF75), MEF50% pred (MEF50/estimated value of MEF50), and MVV % pred (MVV/estimated value of MVV) (Table 3).

The DL_{CO} % pred (DL_{CO}/estimated value of DL_{CO}) was slightly lower in the Long-COVID group than that in the Control group, but the difference was not statistically significant (Table 3). According to the calculated annual variation rate, DL_{CO} declined faster annually in the Long-COVID group (−0.14 mmol/min/kPa/year, *P* value < 0.05) (Supplementary Table 4). Thus, SARS-CoV-2 infection may significantly impair pulmonary ventilation function, small airway function, and diffusion ability in the Long-COVID group, which may partially account for the exacerbation in COPD-associated symptoms, such as chest tightness and wheezing.

Table 2 Hospital Visits and Symptom (Cough, Sputum Production, Chest Tightness, and Wheezing) Exacerbation Within One year After SARS-CoV-2 Infection

Characteristic	Control	Long-COVID	*P* value
Hospital visits due to COPD exacerbation	5/42 (11.9%)	13/43 (30.2%)	0.039
Cough exacerbation	7/42 (8.2%)	11/43 (12.9%)	0.315
Sputum production exacerbation	9/42 (10.6%)	8/43 (9.4%)	0.745
Chest tightness exacerbation	4/42 (4.7%)	14/43 (16.5%)	0.009
Wheezing exacerbation	10/42 (11.8%)	28/43 (32.9%)	0.001

Notes: The date are presented as n/N (%). *P* values were calculated using Pearson's chi(2) test. A two-sided *P* value less than 0.05 was considered statistically significant.

Additionally, we assessed the severity of emphysema, bronchial wall thickening, and interstitial changes through chest CT and found no significant differences between the two groups (Supplementary Table 5), indicating that long COVID may not predominantly result in structural abnormalities on lung imaging.

Proteomic Profiling of Serum Revealed Dysregulated Inflammation and Metabolic Processes in the Long-COVID Group

A total of 1868 comparable proteins were identified, and 28 proteins were identified as DEPs, including 23 up-regulated proteins and 5 down-regulated proteins (Supplementary Figure 2a). Several inflammation-related proteins were dysregulated. Suppressor of cytokine signalling 5 (SOCS5), which has been reported to inhibit inflammation in both a COPD mouse model and an influenza mouse model,[20,21] was decreased in the Long-COVID group. High mobility group box 3 (HMGB3) can promote monocyte recruitment and inflammatory responses.[22] Enhanced HMGB3 expression was observed in the Long-COVID group. EIF2S3 encodes the largest subunit of eukaryotic initiation factor 2 (eIF2), which is involved in the early steps of protein synthesis. White blood cells infected with the SARS-CoV-2 beta variant expressed higher levels of EIF2S3 than cells infected with the alpha variant.[23] We observed higher expression of EIF2S3 in the Long-COVID group.

GO enrichment analysis of the up-regulated DEPs revealed several metabolism-related pathways, including the NADH metabolic process, NAD metabolic process, and dicarboxylic acid metabolic process (Supplementary Figure 2b). NAD^+/NADH metabolism participates in regulating multiple pathophysiological processes, such as

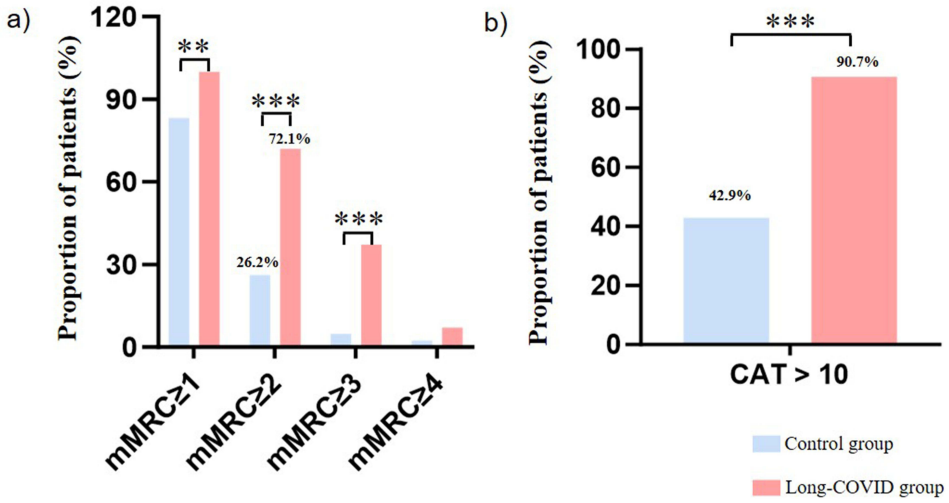

Figure 2 Patients in the Long-COVID group had higher mMRC and CAT scores. (**a**) mMRC scores; (**b**) CAT scores. *P* values were calculated by Fisher's exact test or Pearson's chi (2) test. A two-sided *P* value less than 0.05 was considered statistically significant. **$P < 0.01$; ***$P < 0.001$.
Abbreviations: mMRC, modified Medical Research Council dyspnoea scale; CAT, COPD Assessment Test.

Table 3 Several Pulmonary Function Test Parameters Were Lower in the Long-COVID Group Than in the Control Group at the 1-year Follow-up

	Control	Long-COVID	*P* value
FVC (% of predicted)	89.20 (76.68 to 98.45)	88.20 (69.50 to 96.10)	0.377
FEV1 (% of predicted)	64.85 (54.45 to 78.78)	54.70 (42.20 to 70.20)	0.036
FEV1/FVC (%)	59.49 (51.12 to 66.39)	54.30 (41.21 to 65.68)	0.106
PEF (% of predicted)	78.60 (65.05 to 95.15)	65.80 (48.30 to 87.30)	0.014
PEF improvement rate	4.30 (0.30 to 8.85)	5.90 (−0.30 to 12.10)	0.312
MEF 75 (% of predicted)	35.75 (24.23 to 58.78)	27.20 (12.60 to 48.60)	0.031
MEF 50 (% of predicted)	24.15 (14.48 to 28.90)	17.50 (9.70 to 26.50)	0.037
MEF 25 (% of predicted)	15.75 (12.93 to 23.83)	14.50 (12.45 to 36.46)	0.840
MMEF 75/25 (% of predicted)	20.20 (14.28 to 26.10)	16.40 (10.20 to 22.90)	0.058
MVV (% of predicted)	62.30 (46.80 to 70.50)	50.60 (37.03 to 62.55)	0.009
TLC (% of predicted)	86.35 (76.08 to 91.30)	82.40 (72.30 to 90.40)	0.242
RV (% of predicted)	97.35 (85.73 to 111.50)	96.30 (81.30 to 109.90)	0.450
RV/TLC (%)	49.89 (43.76 to 52.61)	47.67 (43.16 to 54.28)	0.782
DL_{CO} (% of predicted)	72.75 (61.08 to 85.88)	66.70 (52.30 to 85.20)	0.165
DL_{CO}/VA (% of predicted)	87.40 (73.45 to 108.25)	84.80 (63.60 to 107.30)	0.437

Notes: The date are presented as the median (IQR). *P* values were calculated using the Mann-Whitney *U*-test. A two-sided *P* value less than 0.05 was considered statistically significant.

mitochondrial functions, energy metabolism, antiviral defence, and inflammation regulation.[24,25] Elevated levels of dicarboxylic acids may facilitate physical and cognitive fatigue.[26] KEGG enrichment analysis of up-regulated proteins revealed pathways involved in the citrate cycle, ribosome, and coronavirus disease-COVID-19 (Supplementary Figure 2c). In the citrate cycle pathway, isocitrate dehydrogenase (NAD(+)) 3 catalytic subunit alpha (IDH3A) and phosphoenolpyruvate carboxykinase 2, mitochondrial (PCK2) were up-regulated. Ribosomal protein L35 (RPL35), ribosomal protein L31 (RPL31), and ribosomal protein L7a (RPL7A) were enriched in both the ribosome pathway and coronavirus disease-COVID-19 pathway (Supplementary Figure 2c). Additionally, the reactome pathway analysis of the DEPs identified pathways such as disease of glycosylation, viral infection pathways, nervous system development, platelet activation, interferon signalling, and signalling by interleukins (Supplementary Figure 3). Multiple studies have reported associations between these pathways and long COVID.[27–31]

Five Important Features Were Identified Between the Two Groups via Machine Learning Model Training

The clinical and proteomics data of 60 patients were used to train a machine learning model. Five of the 31 filtered features were selected by Boruta for model training, including wheezing, duration of SARS-CoV-2 infection, EIF2S3, current FEV1/FVC (%), and course of COPD. Three machine learning algorithms, Ridge Regression, SVM, and Random Forest, were subsequently used for model training based on the five selected important features (Figure 3a, 3b and 3c). The SVM had the highest AUC of 0.86 (Figure 3b). The feature importance was measured via SHAP values, and the five important features were presented in descending order of their SHAP values (Figure 3d), elucidating the predictions made by the SVM model. The details of the five important features were shown in Supplementary Figure 4, which revealed more severe wheezing, a longer duration of SARS-CoV-2 infection, higher EIF2S3 expression, lower FEV1/FVC (%), and a longer course of COPD in the Long-COVID group. The five identified features were of great significance, and models based on these features had good discriminative performance in differentiating COPD patients with long COVID from those without long COVID.

Discussion

To our knowledge, this is the first study to focus on long COVID only in elderly COPD patients. Briefly, the course of COPD and duration of SARS-CoV-2 infection were significantly longer in the Long-COVID group than in the Control

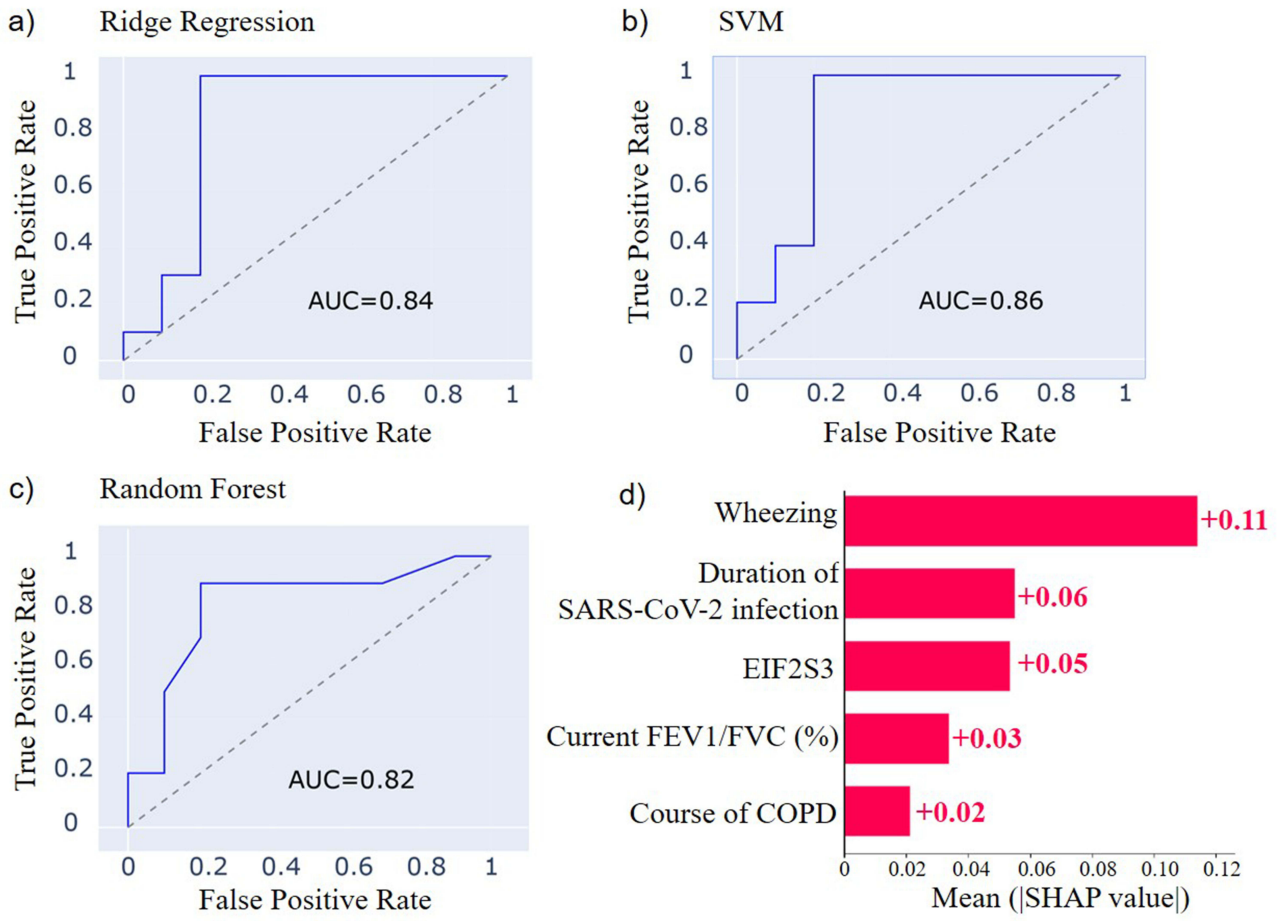

Figure 3 Machine learning analysis of clinical and proteomics data from 60 patients. Model performance evaluation using ROC curves for (**a**) Ridge Regression, (**b**) SVM, and (**c**) Random Forest. (**d**) SHAP feature importance plot showing the five key features identified by the SVM machine learning model.

group. COPD patients with long COVID mainly presented with exacerbations in chest tightness and wheezing, and they were more likely to develop depression, to have a lower quality of life and higher CAT scores. Additionally, pulmonary ventilation function, small airway function, and diffuse ability were worse in the Long-COVID group one year after SARS-CoV-2 infection. Proteomic analysis revealed dysregulated inflammatory responses and metabolic processes, which might be potential mechanisms of long COVID in elderly COPD patients. Machine learning model training identified five important features for differentiating COPD patients with long COVID from those without long COVID, including wheezing, duration of SARS-CoV-2 infection, EIF2S3, current FEV1/FVC (%), and course of COPD.

Previous studies reported the 10 most prevalent symptoms of long COVID: fatigue, dyspnoea, myalgia, cough, headache, joint pain, chest pain, altered smell, diarrhoea, and altered taste in order.[12] In our study, patients in the Long-COVID group more frequently experienced exacerbations of chest tightness and wheezing. The proportions of patients who experienced cough or sputum production exacerbation were similar between the two groups. This suggests that COPD patients with long COVID predominantly exhibit symptoms associated with ventilation deficiency, such as chest tightness and wheezing, rather than airway inflammation symptoms, such as cough or expectoration. In addition, researches reported that long COVID can impair patients' quality of life, and contribute to depression.[5,32,33] Patients with long COVID showed lower EQ-VAS score compared to those without long COVID at 90-day after COVID-19 diagnosis.[32] PHQ-9 testing revealed that approximate 42% of patients who presented to the Post-COVID-19 clinic showed moderate to severe depression.[5] Consistent with these previous findings, our study also observed a significant lower EQ-VAS score (60.0 vs 80.0) and a higher proportion of patients exhibited moderate to severe depression (21.0%

vs 4.8%) in the Long-COVID group. These results indicated the adverse impact of long COVID on elderly COPD patients, exacerbating symptom burden and negatively affecting their quality of life.

SARS-CoV-2 infection can have long-term impacts on the pulmonary function of survivors. A study observed a constant decline in lung function from the 1-year to 2-year follow-up.[34] Approximately 29.4% of COVID-19 survivors showed impaired DL_{CO}, and 4.7% had a decrease in lung volume parameters at 6 months postinfection.[35] In our follow-up study, patients in the two groups had similar lung function before COVID-19. However, after SARS-CoV-2 infection, several parameters of pulmonary function, such as FEV1% pred, PEF % pred, MEF75% pred, MEF50% pred, and MVV % pred, were lower in the Long-COVID group. DL_{CO} declined faster in the Long-COVID group and was slightly lower than that in the Control group one year after SARS-CoV-2 infection. Furthermore, FEV1/FVC (%) was identified as an important feature in the machine learning model, and COPD patients with long COVID had slightly lower FEV1/FVC (%) than the Control group. These results suggest that SARS-CoV-2 infection may accelerate ventilation function, small airway function, and diffuse ability decline in some COPD patients.

The mechanisms of Long COVID remain poorly characterised. Post-acute virus persistence, chronic inflammation, endothelial damage, fibroblast activation, and complement and platelet activation can combine to cause long-term sequelae of COVID-19 in the lungs.[36,37] Multiple mechanisms can lead to post-COVID-19 fatigue, such as chronic inflammation of the brain and neuromuscular junctions, sarcolemma damage and skeletal muscle fiber atrophy.[36] Clearly, chronic inflammation is critical in the pathogenesis of long COVID. Our proteomic analysis revealed several dysregulated inflammation-related proteins, such as SOCS5, HMGB3 and Fc gamma binding protein (FCGBP). Furthermore, SARS-CoV-2 infection can cause mitochondrial dysfunction and metabolic disorders.[38] Impaired oxidative phosphorylation may contribute to post-COVID-19 exercise limitations and fatigue in long COVID.[39] This study also revealed the dysregulation of several metabolic processes, including citrate cycle, and metabolism of NADH, NAD, and dicarboxylic acid. EIF2S3 is an important protein identified by the machine learning model. It encodes the largest subunit of eIF2 and is related to stress responses. EIF2 participates in regulating the integrated stress response activated by various stimuli, such as the ageing process.[36] The elevated EIF2S3 in the Long-COVID group may be a response to the ageing process, which is closely related to long COVID.[40]

In the context of COVID-19 normalization prevention and control, long-term management is crucial, especially for elderly COPD patients. Identifying those at high risk of long COVID is essential for efficient resource allocation. Based on our findings, elderly patients with a longer course of COPD and a longer duration of SARS-CoV-2 infection may be at greater risk of developing long COVID, emphasizing the need of long-term coping strategies. These patients should prioritize COVID-19 vaccination and adhere to COPD standard treatment to avoid acute exacerbation.[41] Early antiviral therapy is also of great significance to them, which is reported to reduce the risk of PASC and PASC-related hospitalizations or deaths.[42] In addition, long-term follow-up, frequent PFTs, and pulmonary rehabilitation, such as endurance, strength, and inspiratory muscle training, can also be beneficial.[43]

Our study has several limitations. First, self-reported data may introduce recall bias, though we minimized this by using multiple well-designed questionnaires. Second, the single-center design and limited sample size may affect generalizability. However, even in non-severe COVID-19 patients and with a relatively small sample size, we still observed remarkable fatigue sequelae in some COPD patients. We obtained rather elaborate data from these enrolled patients, which made our results more convincing. The pathophysiology of long COVID in COPD patients remains inadequately understood, particularly regarding elderly individuals who may have unique responses to the virus and post-infection recovery. Future multi-center studies with larger sample sizes, patients of varying severities, and longer follow-up periods are essential to explore and validate the complex relationship between pre-existed COPD and long COVID development.

Conclusions

This study identified longer COPD course and duration of COVID-19 as key long COVID risk factors in COPD patients, with the Long-COVID group exhibiting worsened respiratory symptoms (chest tightness, wheezing) and lung function. Proteomic profiling revealed inflammatory and metabolic protein dysregulation linked to long COVID progression. Integrated clinical-proteomic machine learning models effectively predicted long COVID risk, supporting early

screening. Further investigation is required to elucidate the precise roles of these proteins and to delve deeper into the mechanisms of long COVID in COPD patients.

Ethical Approval

This study was approved by the Research Ethics Committee of Beijing Hospital (2023BJYYEC-355-02). Prior to participation, written informed consent was obtained from all study participants. All aspects of the study conformed to the principals of the Declaration of Helsinki.

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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 report no conflicts of interest in this work.

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