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Evaluation of the relationship between laboratory parameters and pulmonary function tests in COVID-19 patients

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Abstract

Objective: The novel coronavirus SARS-CoV-2 (COVID-19) rapidly escalated from its origin in an animal market in Wuhan, China in December 2019 to a global pandemic, and the lungs are the most frequently affected organ. The aim of this study was to investigate the relationship between pulmonary function test parameters and laboratory parameters in COVID-19.

Method: A total of 60 patients who were admitted to the chest diseases department and intensive care unit of our hospital and were diagnosed with COVID-19 by real-time PCR analysis of nasopharyngeal swabs were evaluated. Pulmonary function tests and laboratory parameters at admission and on day 7 of treatment were analysed.

Results: On day 7 of treatment, white blood cell count, CRP, and fibrinogen level were significantly lower than at admission ($P = .002$, 0.001, and 0.001, respectively), while forced expiratory volume in the first second (FEV_1) and forced vital capacity (FVC) values were significantly higher compared with admitting values ($P = .001$ for both). Correlation analysis showed that the decrease in CRP from admission to day 7 of treatment correlated with the increase in FEV_1 ($r = 0.616$, $P = .01$) and FVC ($r = 0.51$, $P = .01$) during the same period. A decrease in the fibrinogen level was also correlated with an increase in FEV_1 ($r = 0.345$, $P = .01$) and FVC ($r = 0.357$, $P = .01$).

Conclusion: Fibrinogen and CRP levels are easily accessible parameters that may help identify improvement or deterioration in pulmonary function in COVID-19 patients during follow-up and discharge while reducing the risk of transmission.

What is already known about this topic?

It was also reported that pulmonary function tests performed at discharge revealed no significant difference in forced expiratory volume in the first second (FEV1) or forced vital capacity (FVC) values between COVID-19 patients with mild, moderate, and severe pneumonia, whereas diffusion capacity decreased in correlation with disease severity. Pulmonary function testing is often not recommended for patients with active COVID-19 infection in order to prevent excessive transmission. However, despite clinical improvement in this patient group, ongoing hypoxia and persistent radiological findings cause considerable difficulty in predicting the extent of improvement in pulmonary function.

What does this article add?

While evaluating the laboratory parameters and radiological findings in patients with COVID-19 has become an easily accessible method, the inability to evaluate the pulmonary function

capacities of patients in order to prevent contamination has become the most important problem in follow-up and discharge. Therefore, in our study in which easily accessible parameters were evaluated for guidance, we think that the combined decrease in CRP and fibrinogen levels may be related to increased pulmonary functional capacity.

1 | INTRODUCTION

COVID-19 has infected over 70 million people since it appeared just over a year ago in December 2019, and this number continues to grow daily. The clinical course ranges from asymptomatic or mild (loss of smell and taste, anorexia, muscle and joint pain, fatigue) to severe, particularly in older patients, patients with comorbidities such as hypertension, diabetes mellitus, or chronic kidney disease, pregnant women, and immunocompromised patients.[1]

Acute respiratory failure and macrophage activation syndrome are the most common severe clinical manifestations of COVID-19. Both are characterised by the overproduction of proinflammatory cytokines which can lead to endothelial dysfunction in several vital organs, especially the lungs. Recent studies have shown that COVID-19 causes extensive alveolar epithelial destruction, capillary damage/bleeding, hyaline membrane formation, alveolar septal fibrous proliferation, and pulmonary consolidation. Pulmonary function tests have been the most concrete indicator of this lung damage.[2,3]

Studies involving 2-year follow-up of pulmonary function values in patients with severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) demonstrated that the main pathology was reduced diffusion capacity (15.5-43.6%), followed by decreased total lung capacity (5.2%-10.9%).[4,5] It was also reported that pulmonary function tests performed at discharge revealed no significant difference in forced expiratory volume in the first second (FEV_1) or forced vital capacity (FVC) values between COVID-19 patients with mild, moderate, and severe pneumonia, whereas diffusion capacity decreased in correlation with disease severity. Pulmonary function testing is often not recommended for patients with active COVID-19 infection in order to prevent excessive transmission.[6] However, despite clinical improvement in this patient group, ongoing hypoxia and persistent radiological findings cause considerable difficulty in predicting the extent of improvement in pulmonary function.

The aim of this study was to determine the relationship between pulmonary function tests and laboratory parameters for the demonstration of pulmonary dysfunction, which is an important problem for COVID-19 patients.

2 | MATERIALS AND METHODS

2.1 | Study design

The study included patients who presented to the emergency department of Erzurum Regional Training and Research Hospital with complaints such as recent onset fever, cough, dyspnea, malaise, and sudden loss of taste and smell, and history of international travel or contact with a suspected COVID-19 patient in the last 14 days. Patients (or their relatives) were informed in detail about the aim of the study and all participants provided informed consent forms before being included. Approval was obtained from the local ethics committee prior to study initiation.

2.2 | Study population

All patients assessed as high risk for COVID-19 underwent high-resolution computed tomography (HRCT) examination. Patients with bilateral, predominantly peripheral ground-glass opacities, subsegmental consolidation or linear opacities, cobblestone pattern, and reversed halo sign were evaluated as having typical radiological findings. Patients who had atypical radiological findings but clinical signs consistent with COVID-19 were also admitted. Diagnosis of COVID-19 was based on real-time polymerase chain reaction (PCR) testing of nasopharyngeal swab samples. The study included 60 patients admitted to the Erzurum Regional Training and Research Hospital because of COVID-19 during December 2020 who did not develop acute respiratory distress and macrophage activation syndrome and had a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PO_2/FiO_2) above 200 at admission and on day 7 of treatment.

Starting at admission to the ward, the patients' hematological parameters, biochemical parameters including liver and kidney function tests, coagulation parameters, ferritin, D-dimer, troponin-I, and C-reactive protein (CRP) levels were evaluated daily.

2.3 | Exclusion criteria

Patients with any potential contraindications to pulmonary function testing (recent myocardial infarction, pulmonary embolism, cerebral aneurysm, active hemoptysis, pneumothorax, nausea/vomiting, recent thoracic, abdominal, or ocular surgery) were excluded before conducting the tests. In addition, patients who developed acute respiratory distress or macrophage activation syndrome associated with secondary bacterial infections during the 7-day follow-up were also excluded.

2.4 | Pulmonary function testing

Pulmonary function tests were performed in a negative-pressure room by a technician wearing protective equipment to prevent

transmission. The patients' age, height, and weight were measured and recorded. Before testing, patients were instructed to abstain from smoking (24 hours), alcohol (4 hours), strenuous exercise (30 minutes), and heavy meals (2 hours). Tests were performed with the patients lightly dressed. BTPS correction was performed according to room air and barometric pressure. The technician explained the desired manoeuvers to the patients and they performed three acceptable spirograms. Manoeuvers that met the ATS/ERS 2019 repeatability and acceptability criteria for pulmonary function tests were included. Expected values for the healthy population were also calculated on the spirometer in accordance with the criteria in this report.[7] All spirometry was performed by the same technician using a Plusmed MIR Spirolab III device.

2.5 | Definitions and diagnosis

Fever was defined as an axillary temperature of 37.3°C or above. Secondary bacterial infection was diagnosed based on signs and symptoms of bacteremia or pneumonia with identification of a new bacterial pathogen in endotracheal aspirate or lower respiratory tract sputum culture. For patients diagnosed as having ventilator-associated or hospital-acquired pneumonia, treatment was planned according to available guidelines. Acute respiratory distress was diagnosed and graded according to the Berlin 2015 diagnostic criteria. Patients with daily cardiac-specific troponin levels above the normal range underwent echocardiographic evaluation for emerging cardiac pathologies. Coagulopathy was defined as prothrombin time 3 seconds longer than normal and activated partial thromboplastin time 5 seconds longer than normal. Treatment strategy was determined based on disease severity in accordance with the COVID-19 adult diagnosis and treatment guidelines issued by the Turkish Ministry of Health. Macrophage activation syndrome was presumed in patients who despite treatment exhibited findings such as refractory fever, persistently high or increasing CRP and ferritin levels, elevated D-dimer level, lymphopenia or thrombocytopenia, abnormal liver function indicators, hypofibrinogenemia, or elevated triglyceride levels. If daily follow-up of these parameters showed continued deterioration that could not be explained by secondary bacterial infection, 400 mg tocilizumab for macrophage activation syndrome was administered if not contraindicated. Another dose of 400 mg tocilizumab was administered if no significant improvement in laboratory parameters and vital signs was observed after 24 hours.

2.6 | Biochemical markers

Venous blood samples were obtained from all patients from an antecubital vein after at least 15 minutes of semisupine rest. Blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent coagulation. Troponin-I levels were measured by chemiluminescent immunoassay using an Immulite 2500 device (Siemens Medical Solutions, Erlangen, Germany).

2.7 | Statistical analysis

Data were analysed using IBM SPSS Statistics version 24.0 software (IBM Corp., Armonk, IL). Categorical variables were expressed as number and percentage; numerical variables were expressed as mean and standard deviation. Kolmogorov-Smirnov test was used to test whether the data were normally distributed. Repeated measures were compared using Friedman test and Wilcoxon test with Bonferroni correction for non-normally distributed numerical data. Chi-square analysis was used to compare the percentages of patients whose FEV_1 and FVC values were lower than the expected value. Pearson correlation analysis was used to assess the relationship between changes in laboratory parameters and changes in pulmonary function tests. Results with P value <0.05 were considered statistically significant.

3 | RESULTS

The mean age of the patients was 51.4 ± 18.2 years. Forty-two (70%) of the patients were men and 18 (30%) were women. The mean ages of the male and female patients were 55.1 ± 12.5 years and 50.1 ± 10.4 years, respectively ($P = .04$). The mean height and weight of the patients were 168.8 ± 9.1 cm and 82.3 ± 11.4 kg, respectively. Three of the patients had previously known coronary artery disease, five had diabetes mellitus, and one had asthma.

The patients' laboratory values and pulmonary function test results at admission and on day 7 of treatment are shown in Table 1. White blood cell count, CRP, and fibrinogen values on day 7 of treatment were significantly lower compared with admitting values ($P = .002, 0.001, 0.001$, respectively). FEV_1 and FVC values on day 7 were significantly higher than those at admission ($P = .001$ for both) (Figure 1). FEV_1 and FVC values were lower than expected in 76.3% and 75.3% of the patients at admission, while these rates fell to 43.4% and 38.1% on day 7 of treatment, respectively. Chi-square analysis of these values indicated that the difference was statistically significant ($P = .001$).

Correlation analysis showed that the patients' change in CRP level from day 1 to day 7 (Δ_{1-7}) was correlated with the changes in FEV_1 and FVC from day 7 to day 1 (Δ_{7-1}) ($r = 0.616, P = .01; r = 0.510, P = .01$, respectively) (Figure 2). Similarly, Δ_{1-7} fibrinogen was correlated with Δ_{7-1} FEV_1 and FCV ($r = 0.345, P = .01; r = 0.357, P = .01$, respectively) (Figure 3).

Amongst the laboratory parameters, CRP was found to be correlated with fibrinogen ($r = 0.609, P P = .01$) and ferritin ($r = 0.308, P = .017$).

4 | DISCUSSION

Our study showed that COVID-19 patients' CRP, ferritin, and fibrinogen levels decreased with treatment, consistent with previous studies, while FEV_1 and FVC values increased. The symptoms

	Admission (n = 60)	Day 7 of treatment (n = 60)	P
WBC (/µl)	15 640 ± 44 081.4	9652.1 ± 6065.3	**.002**
Lymphocytes (/µl)	1256.3 ± 786.1	1252 ± 579.7	.982
AST (U/L)	32.9 ± 20.5	31.9 ± 34.1	.189
ALT (U/L)	30.6 ± 25.2	31.3 ± 23.4	.225
LDH (U/L)	311.7 ± 159.1	305.1 ± 199.9	.275
GGT (U/L)	39.9 ± 34.2	40.6 ± 35.7	.317
ALP (U/L)	65.1 ± 31.2	69.2 ± 27.5	.12
CRP (mg/dl)	56.8 ± 45.6	22.1 ± 38.7	**.001**
Fibrinogen (mg/dl)	510.3 ± 168.1	381.9 ± 136.8	**.001**
Ferritin (ng/ml)	521.5 ± 520.5	513.8 ± 469.2	.76
D-dimer (ng/ml)	348.5 ± 557.4	238.7 ± 681.5	.09
Prothrombin time (s)	13.9 ± 3.8	12.6 ± 3.1	.3
Troponin-I (ng/dl)	27.1 ± 17.8	23.7 ± 12.6	.21
FEV_1 (lt)	2.47 ± 0.96	2.73 ± 0.98	**.001**
FVC (lt)	2.82 ± 1.13	3.17 ± 1.13	**.001**

Abbreviations: ALP, Alkaline phosphatase; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; FEV_1, Forced expiratory volume in the first second; FVC, Forced vital capacity; GGT, Gamma-glutamyl transferase; WBC, White blood cells.Bold value indicates statistically significant results.
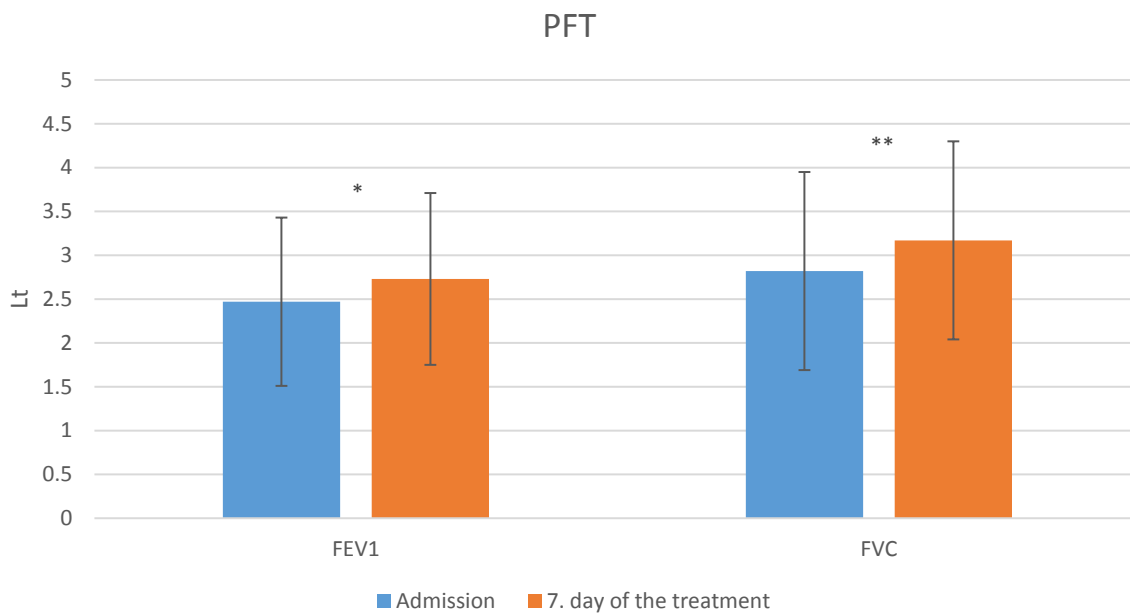

FIGURE 1 Comparison of pulmonary function test (PFT) parameters of COVID-19 patients between admission and day 7 of treatment. FEV_1: Forced expiratory volume in 1 second, FVC: Forced vital capacity, P^*: Comparison of FEV_1 value at admission and day 7 (0.001), P^{**}: Comparison of FVC value at admission and day 7 (0.001)

of restrictive lung disease observed at the start of treatment were improved on day 7 of treatment. Correlation analysis between the 7-day changes in laboratory parameters and pulmonary function tests showed that FEV_1 and FVC values increased in correlation with the change in CRP and fibrinogen levels.

On March 11, 2020, the World Health Organization (WHO) declared COVID-19 a pandemic and as of December 15, 2020, more than 72 million cases had been confirmed worldwide [1]. Large-scale

studies on COVID-19 have documented extensive lung damage both during and after the disease. In a recent report, it was determined that COVID-19 pneumonia patients still showed abnormalities in lung CT scans after discharge, with ground-glass opacities being the most common pulmonary sequelae.[8] Survivors of other coronavirus pneumonias (SARS and MERS) are known to have pulmonary function and exercise capacity impairments persisting for months or even years.[5,9-11] To date, however, there have been few studies
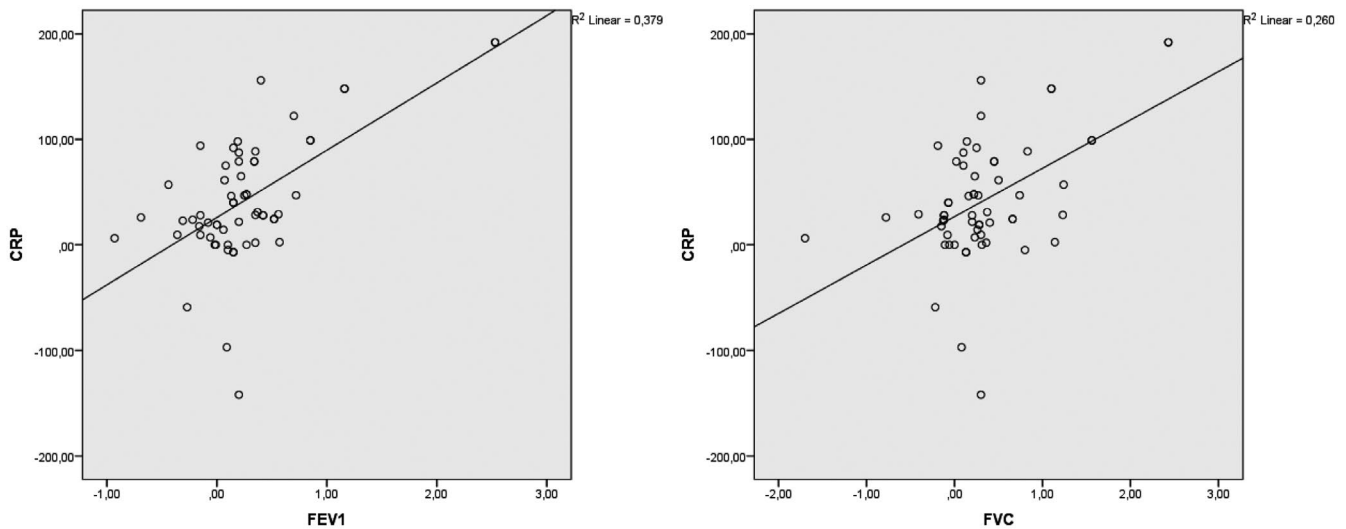
FIGURE 2 Correlation analysis between change in CRP level from day 1 to day 7 (Δ_{1-7}) and changes in FEV_1 and FVC from day 7 to day 1 (Δ_{7-1})
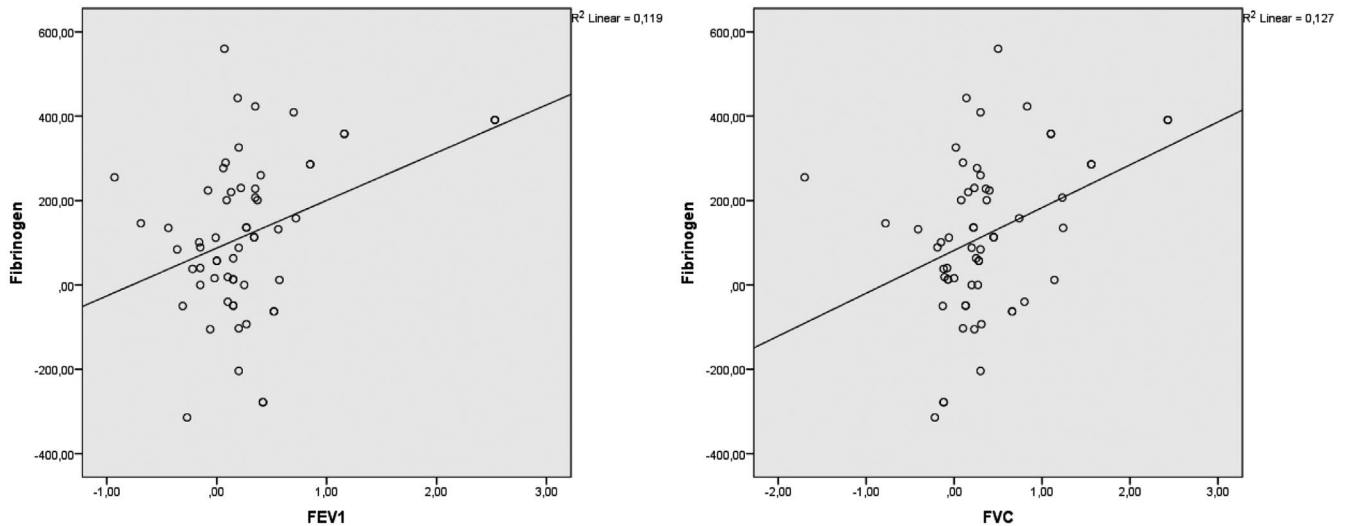

FIGURE 3 Correlation analysis between change in fibrinogen level from day 1 to day 7 (Δ_{1-7}) and changes in FEV_1 and FVC from day 7 to day 1 (Δ_{7-1})

examining the loss of pulmonary function in discharged COVID-19 patients.

SARS-CoV-2 infects the human airway and the vascular and immune cells, potentially leading to severe damage to the respiratory tract, especially within the lungs. Disease severity depends on the effectiveness of the immune system. Current evidence suggests that in some cases, viral infection can cause an exaggerated immune reaction in the host that is severe enough to be classified as the hyperinflammatory condition referred to as macrophage activation syndrome.[12]

Numerous proinflammatory cytokines are released in COVID-19 patients, primarily tumour necrosis factor-alpha, interleukins 1, 2, 6 and 18, and nitric oxide. These cytokines can increase vascular permeability, resulting in impaired tissue perfusion, endothelial damage, and microthrombus formation. Increased

vascular permeability causes fluid accumulation in the lung tissue and interstitial spaces, which manifests clinically with acute respiratory failure.[2,3] Suppression of these proinflammatory cytokines has proven to be therapeutically beneficial in many inflammatory conditions, including viral infections. Increased cytokine levels in the lung cause alveolar epithelial damage, alveolar septal fibrous proliferation, hyaline membrane formation, and the development of pulmonary consolidation.[13] This is the main cause of the restrictive pathology and reduced diffusion capacity seen in the lungs of COVID-19 patients. Studies have shown that this process continues in association with regression even after discharge.[14] In a study including 110 COVID-19 patients, evaluation of pulmonary function tests at discharge showed a reduction in diffusion capacity that was correlated with disease severity. However, a striking aspect of the study was that the diffusing capacity of the lung

for carbon monoxide (DLCO) decreased more than the diffusing capacity divided by alveolar volume (DLCO/VA), suggesting that the impairment of the diffusion membrane was a more important issue than low lung volume.[6]

It was also observed that levels of D-dimer and acute phase reactants such as CRP, ferritin, and fibrinogen were elevated in COVID-19 patients after intense inflammatory cytokine discharge and that these parameters may be associated with morbidity and mortality.[15] Amongst these parameters, levels of CRP, fibrinogen, and ferritin levels were found to be high and inversely correlated with FEV$_1$ and FVC levels.[16-18] These acute phase reactants are elevated in most inflammatory diseases, and studies evaluating the relationship with parenchymal fibrosis in interstitial lung diseases have demonstrated increases in correlation with the extent of parenchymal fibrosis, highlighting their potential usefulness in follow-up.[19,20]

In the present study, we observed that the restrictive pattern initially presented by COVID-19 patients because of parenchymal infiltration in the lungs resolved during follow-up with regression of the lung consolidation. Pulmonary function values increased with the decline in CRP and fibrinogen levels, suggesting that the improvement was secondary to reduced inflammation. However, consistent with our experience with COVID-19, fibrosis may be permanent and patients may show a restrictive pattern with reduced diffusion in long-term follow-up. Plasma fibrinogen level has been associated with increased parenchymal fibrosis in previous studies. Therefore, the decline in plasma fibrinogen levels during follow-up in COVID-19 suggests that this parameter may be useful in evaluating progression to parenchymal fibrosis in this disease, which is characterised by pathologies also observed in interstitial lung diseases, such as hyaline membrane formation and alveolar septal fibrous proliferation.

The most important limitation of our study was the inability to evaluate diffusion capacities and total lung capacities when evaluating the aetiology of the restrictive pathology observed in pulmonary function tests. However, this was a result of the fact that only portable pulmonary function testing equipment could be placed in the negative pressure room established to minimise the chance of transmission.

In conclusion, although the assessment of laboratory parameters and radiological findings has become a convenient method for evaluating COVID-19 patients, the inability to evaluate patients' pulmonary function because of risk prevention measures has become the biggest problem in follow-up and discharge. In this study examined the guiding potential of some of these easily obtained parameters, we observed that decline in both CRP and fibrinogen levels may be associated with improved pulmonary functional capacity.

CONFLICT OF INTEREST

All authors disclosure no Conflict of Interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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