ORIGINAL RESEARCH

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Tips for 6 Months After COVID-19 Pneumonia: Acute Inflammatory Parameters

COVID-19 Pnömonisinden 6 Ay Sonrası için İpuçları: Akut Dönem Enflamatuvar Parametreleri

Engin Aynacı[1], Gökhan Karakurt[2]

[1]Beykent University Faculty of Medicine, Department of Chest Diseases, İstanbul, Turkey
[2]Kırklareli Training and Research Hospital, Clinic of Chest Diseases, Kırklareli, Turkey

Abstract

Objective: In our study, we aimed to investigate the long-term effects of the acute phase parameters of C-reactive protein, procalcitonin, D-dimer, lymphocyte, thrombocyte and ferritin on the respiratory function parameters in patients hospitalized due to Coronavirus disease-2019 (COVID-19) pneumonia.

Method: The present study was carried out with the retrospective evaluation of patients with COVID-19 pneumonia, who were hospitalized in Medipol University Hospital between March 2020 and June 2021, and who were 6 months to 1 year after discharge. The relationship between pulmonary function test results and acute period laboratory findings of 52 patients who applied for control purposes 6 months after discharge was examined.

Results: Diffusing capacity for carbon monoxide (DLCO) (pred) value in 26 patients (50%), total lung capacity (TLC) value in 9 patients (17.3%), and residual volume (RV) (pred) value in 10 patients (19.2%) were below 80%. As a result of multiple linear regression analysis in our study, the maximum D-dimer level and maximum procalcitonin level were determined by DLCO (% pred) (adjusted R^2 =0.645; p<0.001), TLC (% pred) (adjusted R^2 =0.582; p=0.003) and RV (% pred) (adjusted R^2 =0.560; p=0.001) values and were independent determinants in predicting these values.

Conclusion: High D-dimer and procalcitonin levels in the acute period in patients with COVID-19 pneumonia may predict losses in respiratory function parameters such as DLCO, TLC, RV in the longer term than 6 months. Long-term follow-up of these patients is important in terms of respiratory function.

Keywords: COVID-19, D-dimer, DLCO

Öz

Amaç: Çalışmamızda Koronavirüs hastalığı-2019 (COVID-19) nedeniyle hastaneye yatırılan hastalarda akut faz parametrelerinden C-reaktif protein, prokalsitonin, D-dimer, lenfosit, trombosit ve ferritinin solunum fonksiyon parametreleri üzerine uzun dönem etkilerini araştırmayı amaçladık.

Yöntem: Çalışmamız Medipol Üniversite Hastanesi'nde Mart 2020-Haziran 2021 tarihleri arasında servise yatırılan ve taburculuk sonrası 6 ay ila 1 yıl zaman geçmiş olan COVID-19 pnömonisi hastalarının geriye dönük olarak değerlendirmesi ile gerçekleştirildi. Taburculuktan 6 ay sonrasında kontrol amaçlı başvurmuş olan 52 hastanın solunum fonksiyon test sonuçları ile akut dönem laboratuvar bulguları arasındaki ilişki incelendi.

Bulgular: Hastaların 26'sında (%50) karbon monoksit difüzyon kapasitesi (DLCO) (% pred), 9'unda (%17,3) total akciğer kapasitesi (TLC) (% pred) ve 10'unda (%19,2) rezidüel hacim (RV) (% pred) %80'in altındaydı. Çalışmamızda çoklu doğrusal regresyon analizi sonucunda maksimum D-dimer düzeyi ve maksimum prokalsitonin düzeyinin DLCO (% pred) (düzeltilmiş R^2 =0,645; p<0,001), TLC (% pred) (düzeltilmiş R^2 =0,582; p=0,003) ve RV (%pred) (düzeltilmiş R^2 =0,560; p=0,001) değerleri ile anlamlı bir ilişkiye sahip olduğu ve bu değerleri öngörmede bağımsız birer belirleyici olduğu saptandı.

Sonuç: COVID-19 pnömonisi hastalarında akut dönemde yüksek seyreden D-dimer ve prokalsitonin seviyeleri 6 aydan uzun dönemde DLCO, TLC, RV gibi solunum fonksiyon parametrelerindeki kayıpları öngörebilir. Bu hastaların solunum fonksiyonu açısından uzun dönem takibi önemlidir.

Anahtar kelimeler: COVID-19, D-dimer, DLCO

Address for Correspondence: Gökhan Karakurt, Kırklareli Training and Research Hospital, Clinic of Chest Diseases, Kırklareli, Turkey
E-mail: gokhankarakurt16@gmail.com **ORCID:** orcid.org/0000-0001-5327-4687 **Received:** 03.01.2023 **Accepted:** 08.06.2023

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Introduction

A coronavirus known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is the cause of Coronavirus disease-2019 (COVID-19). COVID-19 due to SARS-CoV-2 affects multiple organs and has serious effects on lung function (1). Pathophysiological changes such as capillary damage, hyaline membrane formation, alveolar epithelial damage, alveolar septal fibroplasia occurs (2). With these changes, 5-10% of COVID-19 patients develop crucial illnesses, including acute respiratory distress syndrome (ARDS). ARDS causes pulmonary dysfunction with residual volume loss (2,3). Also, these pathological changes in the lungs are associated with impaired diffusion capacity. Correspondingly, a high prevalence of impaired diffusing capacity for carbon monoxide (DLCO) has been found in patients who are more likely to develop pulmonary fibrosis (4). Parameters reflecting inflammation such as C-reactive protein (CRP), D-dimer, lymphocyte, and ferritin in the acute phase of COVID-19 pneumonia have been found to be related in literature in terms of prognostic prediction (5-7). In the review of Ponti et al. (8), low lymphocyte count, increase in inflammatory parameters such as CRP and D-dimer were found to be associated with severe prognosis in the acute phase in COVID-19 patients. In a recent meta-analysis; lymphopenia, thrombocytopenia and increases in inflammatory parameters such as CRP, procalcitonin, D-dimer, ferritin count in the acute period were associated with mortality (9). Inflammatory parameters showing the severity of the disease can give an idea about the long-term effects of the disease. However, as far as we know, a limited number of studies in the literature investigate the relationship between acute phase laboratory findings and long-term respiratory function in COVID-19 pneumonia. The aim of our study was to investigate the relationship of acute phase parameters CRP, procalcitonin, D-dimer, lymphocyte, platelet and ferritin with respiratory function parameters longer than 6 months after discharge in patients with COVID-19 pneumonia.

Materials and Methods

This single-center, retrospective cohort study; was carried out with the retrospective evaluation of COVID-19 pneumonia patients hospitalized in Medipol University Hospital between March 2020 and June 2021. The sample of our study consisted of COVID-19 pneumonia patients aged 18-65 years, who were followed up in the service, with SARS-CoV-2 polymerase chain reaction positivity in the nasopharyngeal swab and who had viral infection related findings in thorax computed tomography. In order to exclude physiological changes in respiratory function that may occur with aging, patients aged 65 and over were excluded (10).

Inclusion criteria were being between the ages of 18-65, being hospitalized with COVID-19 pneumonia, having spent at least 6 months and maximum 1 year after discharge, and having completed pulmonary function tests at the control visit. Exclusion criteria were to have any other chronic lung disease and/or heart failure, to have a history of hospitalization after discharge, to have an active infection at the time of control visit and to be pregnant.

Seven hundred and ten inpatients in the ward were screened and the data of 110 patients who met the inclusion and exclusion criteria were evaluated through the hospital registry system. The data of 52 patients, 24 females and 28 males, who had all their data accessible and who completed the pulmonary function tests at the control visit, were included in the study. Demographic and clinical information, laboratory findings and pulmonary function test results were recorded.

All tests were performed by the same investigator and a pulmonologist was the observer. Spirometric measurements, diffusion capacities and plethysmography measurements were made on the Vyntus body device. For spirometry, flow-volume curves were obtained through and the greatest volume of the three manoeuvres was expressed as the percentage of predicted normal and used for analysis. Plethysmography was performed with the panting maneuver method in a closed cabin.

All pulmonary function test measurements were expressed as percentages of predicted normal values. Spirometry and body plethysmography tests were performed in accordance with the European Respiratory Society (ERS) and American Thoracic Society (ATS) guidelines (11). DLCO was evaluated with a single breath technique in accordance with the ATS/ERS guidelines (12). The percentage of predicted values in spirometry, DLCO, and were calculated according to the Global Lung Function Initiative reference values (13). Written and verbal consent was obtained from all patients before the test.

Statistical Analysis

Statistical analyzes of all data were performed with SPSS Statistics Version 26 (IBM Statistical Package for the Social Science, New York, USA) program. Descriptive data were

given as mean ± standard deviation or percent (%). Normal distribution was evaluated with the Shapiro-Wilk test. One-Way Spearman correlation analysis was performed to determine the relationship between respiratory parameters and laboratory test parameters, and the Spearman correlation coefficient (r) value is given in the results section. Laboratory test parameters that were found to be significantly associated with respiratory parameters according to One-Way Spearman correlation analysis were evaluated with multiple linear regression analysis. As a result of the regression analysis, the regression coefficient was given with the standardized β coefficient value. The significance level was taken as $p<0.05$ for all statistical analyses.

Results

Seven hundred and ten patients were screened for compliance with the inclusion criteria. Fifty-two patients who met the inclusion criteria were included in the study. Demographic and clinical characteristics of the patients, respiratory parameters and laboratory test parameters are given in Table 1.

DLCO (pred) was below 80% in 26 (50%) patients, TLC in 9 (17.3%) patients (pred), and RV (pred) in 10 (19.2%) patients. The results of the One-Way correlation analysis of respiratory parameters and laboratory test parameters of the patients are given in Table 2.

There was no correlation between maximum CRP level, minimum lymphocyte level and minimum platelet level with any respiratory parameter ($p>0.05$). Maximum D-dimer level with DLCO (% pred) ($r=-0.305$, $p<0.001$), TLC (% pred) ($r=-0.270$, $p=0.002$) and RV (% pred) ($r=-0.299$, $p=0.004$), there was a significant negative correlation.

There was no relationship between the maximum D-dimer level and other respiratory parameters ($p>0.05$). There was a significant positive correlation between maximum ferritin level and PEF (% pred) ($r=0.324$, $p=0.019$) and FEF75 (% pred) ($r=0.316$, $p=0.023$). There was no correlation between the maximum ferritin level and other respiratory parameters ($p>0.05$). There was a negative and significant relationship between maximum procalcitonin level with DLCO (% pred) ($r=-0.368$, $p<0.001$), TLC (% pred) ($r=-0.289$, $p=0.010$) and RV (% pred) ($r=-0.269$, $p=0.021$).

The results of multiple linear regression analysis of respiratory parameters and laboratory test parameters of the patients are given in Table 3. When the independent

Table 1. Demographic/clinical/laboratory parameters of the patients

	Mean ± standard deviation (n=52)	Min-max
Age (years)	49.13±9.04	32-65
Gender		
Woman (n)	24 (46.2%)	
Male (n)	28 (53.8%)	
BMI (kg/m²)	30.79±4.81	22-42
Smoking		
Never (n)	39 (75%)	
Ex smoker (n)	11 (21.2%)	
Active smoker (n)	2 (3.8%)	
Comorbidities		
Hypertension (n)	11 (21.2%)	
Diabetes (n)	11 (21.2%)	
Other systemic diseases (n)	10 (19.2%)	
Respiratory parameters		
FEV_1 (% pred)	99.73±17.50	60-154
FVC (% pred)	99.83±16.74	51-149
FEV_1/FVC (%)	82.66±5.05	72-99
PEF (% pred)	90.35±25.02	36-155
FEF_{25} (% pred)	80.73±32.30	32-174
FEF_{50} (% pred)	97.85±29.28	49-176
FEF_{75} (% pred)	95.85±26.04	38-158
DLCO (% pred)	79.65±21.34	55-119
DLCO/VA (% pred)	93.92±24.12	64-130
TLC (% pred)	84.50±20.17	53-112
RV (% pred)	87.71±25.66	46-125
RV/TLC (% pred)	97.35±28.63	54-148
FRC (% pred)	88.86±31.66	53-143
Laboratory test parameters		
Max CRP level (mg/dL)	93.38±70.33	10-295
Max D-dimer level (ng/mL)	1520.38±4051.20	241-29846
Min lymphocyte level (10^3/µL)	889.61±385.40	270-1890
Min platelet level (10^3/µL)	184.28±66.78	85-406
Max ferritin level (mg/L)	1057.69±1179.80	49-5081
Max procalcitonin level (ng/mL)	0.53±2.63	0.02-19.14
Length of stay in hospital (days)	7.88±8.12	2-61
Time after discharge (months)	9±1.81	6-12

BMI: Body mass index, FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak flow rate, FEF_{25}: 25% of forced expiratory flow, FEF_{50}: 50% of forced expiratory flow, FEF_{75}: Forced expiratory flow 75% of current, DLCO: Carbon monoxide diffusion capacity, DLCO/VA: Carbon monoxide diffusion coefficient of alveolar volume, TLC: Total lung capacity, RV: Residual volume, FRC: Functional residual capacity, CRP: C-reactive protein

variables (maximum ferritin level and maximum procalcitonin level) that were significantly associated with the FEF75 (% pred) value were included in the multiple linear regression analysis model, it was seen that a model consisting of these variables was not a significant determinant (Adjusted R^2=0.021, p>0.05). Independent variables (maximum D-dimer level and maximum procalcitonin level) that were significantly associated with the DLCO (% pred) value were evaluated by including them in the multiple linear regression analysis model.

As a result of multiple linear regression analysis, it was determined that both maximum D-dimer level (β=-0.611) and maximum procalcitonin level (β=-0.701) were independent predictors of DLCO (% pred) value and were significant in predicting DLCO (% pred) value. (Adjusted R^2=0.645, p<0.001). Independent variables (maximum D-dimer level and maximum procalcitonin level) significantly associated with TLC (% pred) value were evaluated by multiple linear regression analysis. It was determined that both maximum D-dimer level (β=-0.347) and maximum procalcitonin level (β=-0.380) were

Table 2. Results of One-Way correlation analysis of respiratory parameters and laboratory test parameters

	Maximum CRP level		Maximum D-dimer		Minimum lymphocyte		Minimum platelet		Maksimum ferritin		Maximum procalsitonin	
	r	p	r	p	r	p	r	p	r	p	r	p
FEV_1 (% pred)	-0.103	0.469	0.098	0.490	-0.122	0.388	0.035	0.804	0.071	0.616	0.067	0.638
FVC (% pred)	-0.115	0.415	0.099	0.485	-0.167	0.237	-0.036	0.798	-0.056	0.693	0.069	0.629
FEV_1/FVC (%)	-0.082	0.561	-0.098	0.492	0.058	0.685	0.141	0.318	0.001	0.996	-0.030	0.832
PEF (% pred)	0.076	0.593	0.103	0.469	0.009	0.949	0.152	0.281	0.324	0.019	0.109	0.444
FEF_{25} (% pred)	-0.129	0.361	-0.006	0.964	-0.007	0.960	0.085	0.549	0.146	0.302	0.069	0.628
FEF_{50} (% pred)	0.082	0.561	0.062	0.663	-0.087	0.539	0.059	0.675	0.264	0.058	0.170	0.228
FEF_{75} (% pred)	0.103	0.468	0.203	0.148	-0.024	0.868	0.154	0.277	0.316	0.023	0.353	0.002
DLCO (% pred)	-0.005	0.969	-0.305	<0.001	-0.232	0.098	0.090	0.524	0.204	0.147	-0.368	<0.001
DLCO/VA (% pred)	0.031	0.826	0.050	0.727	-0.143	0.311	0.193	0.169	0.236	0.092	-0.079	0.577
TLC (% pred)	-0.092	0.517	-0.270	0.002	-0.137	0.334	-0.074	0.604	0.027	0.852	-0.289	0.010
RV (% pred)	0.029	0.836	-0.299	0.004	-0.116	0.411	-0.235	0.094	0.085	0.550	-0.269	0.021
RV/TLC (% pred)	0.028	0.845	-0.057	0.687	-0.066	0.643	-0.118	0.406	0.026	0.853	-0.088	0.534
FRC (% pred)	0.048	0.736	0.052	0.712	-0.138	0.330	0.024	0.864	0.013	0.926	-0.006	0.966

FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, PEF: Peak flow rate, FEF_{25}: 25% of forced expiratory flow, FEF_{50}: 50% of forced expiratory flow, FEF_{75}: Forced expiratory flow 75% of current, DLCO: Carbon monoxide diffusion capacity, DLCO/VA: Carbon monoxide diffusion coefficient of alveolar volume, TLC: Total lung capacity, RV: Residual volume, FRC: Functional residual capacity, CRP: C-reactive protein

Table 3. Results of multiple linear regression analysis of respiratory and laboratory parameters

Dependent variable	Independent variable	β	R^2	Adjusted R^2	p
FEF_{75} (% pred)					
	Maximum ferritin level	-0.091	0.028	0.021	0.103
	Maximum procalcitonin level	-0.074			0.084
DLCO (% pred)					
	Maximum D-dimer level	-0.611	0.711	0.645	**<0.001**
	Maximum procalcitonin level	-0.701			**<0.001**
TLC (% pred)					
	Maximum D-dimer level	-0.347	0.695	0.582	**0.003**
	Maximum procalcitonin level	-0.380			**0.002**
RV (% pred)					
	Maximum D-dimer level	-0.420	0.607	0.560	**0.001**
	Maximum procalcitonin level	-0.311			**0.002**

PEF: Peak flow rate, FEF_{75}: 75% of forced expiratory flow, DLCO: Diffusion capacity of carbon monoxide, TLC: Total lung capacity, RV: Residual volume

independent predictors of TLC (% pred) value and were significant in predicting TLC (% pred) value (Adjusted R^2=0.582, p=0.003, p=0.002).

Independent variables (maximum D-dimer level and maximum procalcitonin level) significantly associated with RV (% pred) value were evaluated by multiple linear regression analysis. It was determined that both maximum D-dimer level (β=-0.420) and maximum procalcitonin level (β=-0.311) were independent predictors of RV (% pred) value and were significant in predicting RV (% pred) value (Adjusted R^2=0.560, p=0.001, p=0.002).

Discussion

In our study, we determined that maximum D-dimer level and maximum procalcitonin level were independent predictors of long-term DLCO (% pred), TLC (% pred), RV (% pred) values and were significant in predicting these values. In COVID-19 pneumonia, the lungs are the most affected organ due to alveolar epithelial destruction, capillary damage/bleeding, hyaline membrane formation, alveolar septal fibrous proliferation (14).

These effects are mostly determined as decrease in diffusion capacity (DLCO) and loss of total capacity (TLC) (14). Depending on the severity of the disease, changes occur in inflammatory parameters such as fibrinogen degradation products, lymphocyte, D-dimer, thrombocyte, CRP, procalcitonin, and ferritin (15-17).

In COVID-19 pneumonia, respiratory function losses, which progress with loss of diffusion (DLCO), can be detected even 6 months after discharge from the service (18,19). Despite these understandings of the long-term effects of COVID-19 on lung function, there is a lack of analysis of risk factors for long-term effects. Risk factors for long-term losses in respiratory function parameters, especially DLCO, have been investigated in a limited number of studies in hospitalized patients due to COVID-19 pneumonia. In their study, Zhao et al. (1) found that high D-dimer levels predicted DLCO loss in long-term follow-up. Santus et al. (20) found that D-dimer was the most important parameter predicting impaired DLCO during the service period and 6-week follow-up. A similar result was also found in a meta-analysis evaluating long-term DLCO loss (3).

In our study, we found that D-dimer elevation reflects the decrease in DLCO, consistent with the literature. Moreover, it reflected not only DLCO but also RV and TLC reductions. High D-dimer and procalcitonin values in COVID-19 pneumonia maintain their importance in this respect in long-term follow-up as well as in the acute period in patient follow-up in the service.

Bursac et al. (21) found a significant relationship between the initial CRP elevation and the decrease in DLCO in long-term follow-up. His extensive research with emphasis on other laboratory parameters is limited. In a study conducted with 60 patients 3-6 months after discharge, it was found that high CRP, high D-dimer, and low lymphocyte values in the acute period predict impaired DLCO (22).

Although our study was different from this study, the maximum CRP, minimum lymphocyte, platelet and ferritin values in the acute period did not reflect the long-term effects of pulmonary function, generally consistent with the literature. However, we also found that the maximum procalcitonin level was also significant in predicting DLCO, TLC and RV losses in long-term follow-up. Regarding other respiratory functions, laboratory findings do not reflect long-term pulmonary functional involvement, again in line with the literature. However, as it was emphasized at the beginning of the article, our results are remarkable since DLCO is the most important parameter with the highest loss. More studies are needed to be presented for discussion regarding these parameters.

Study Limitations

Our study has some limitations. First of all, the low number of patients evaluated is among these limitations. However, the exclusion of chronic lung diseases and other comorbid conditions in which respiratory functions are affected and the inclusion of patients with all available data are strengths in terms of both the long-term effects of the disease and its evaluation with laboratory findings. As far as we know, there is no research on risk factors for the pulmonary effects of the disease longer than 6 months in our country. Our research can shed light on long-term follow-up strategies with laboratory findings and different parameters.

Conclusion

It may be important to follow-up patients with high D-dimer and procalcitonin levels in COVID-19 pneumonia, not only in the acute period but also in the long-term, especially in terms of respiratory functions. In patients with COVID-19 pneumonia, the elevation of these parameters during the acute infection period may predict the decrease in DLCO (% pred), TLC (% pred), and RV (% pred) parameters after 6-12 months later. While respiratory function loss is observed even in cases

evaluated for up to 1 year, longer follow-up is required, especially in patients with COVID-pneumonia who are hospitalized and followed up.

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Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki, with the approval of İstanbul Medipol University Non-Interventional Clinical Research Ethics Committee, dated 25.05.2022 and numbered E-10840098-772.02-3116.

Informed Consent: Written and verbal consent was obtained from all patients before the test.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Concept: E.A., Design: E.A., Data Collection or Processing: G.K., Analysis or Interpretation: E.A., G.K., Drafting Manuscript: E.A., G.K., Critical Revision of Manuscript: E.A., G.K., Final Approval and Accountability: E.A., G.K., Writing: E.A., G.K.

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