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ORIGINAL ARTICLE

Evaluation of the Relationship between CRP/Albumin Ratio and Pulmonary Function Parameters in Patients with Post-Acute COVID-19

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SUMMARY

Background: **Novel coronavirus disease 2019 (COVID-19), which has been a global pandemic for nearly 2 years, presents with highly variable clinical manifestations in both the acute and post-acute periods. This study evaluated the relationship between CRP/albumin ratio and pulmonary function at 12 weeks in patients with post-acute COVID-19.**
Methods: **The study included 157 patients with a previous diagnosis of COVID-19 pneumonia who presented to our outpatient clinic with symptoms of post-acute COVID-19 (12 weeks after first testing positive) between July 2021 and October 2021. Patients who had non-severe pneumonia were included in group 1, severe pneumonia that did not require intensive care in group 2, and severe pneumonia that required intensive care in group 3.**
Results: **At 12 weeks, group 3 had significantly lower percent predicted forced expiratory volume in 1 second (FEV1%), percent predicted forced vital capacity (FVC%), percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO%), and oxygen saturation (SO_2) compared to patients in groups 1 and 2 (p = 0.001, 0.04, 0.001, and 0.001, respectively). CRP/albumin ratio was significantly lower in group 2 compared to groups 1 and 3 (p = 0.001). Correlation analysis independent of age and comorbidity showed that CRP/albumin ratio was negatively correlated with SO_2, FEV1%, FVC%, and DLCO%.**
Conclusions: **CRP and albumin levels have prognostic significance during acute COVID-19 infection. The negative correlation between CRP/albumin ratio and respiratory function observed in our study suggest this parameter may be used in the follow-up of patients presenting at 12 weeks with post-acute COVID-19 symptoms.**
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KEY WORDS

post-acute COVID-19, pulmonary function test, CRP/albumin ratio

INTRODUCTION

Since December 2019, novel coronavirus disease 2019 (COVID-19) has infected nearly 220 million people around the world and caused nearly 5 million deaths. Acute COVID-19 infection may be asymptomatic or present with mild symptoms such as fatigue, muscle and joint pain, decreased appetite, and loss of smell and taste. However, certain individuals develop severe clinical presentations, especially older adults, pregnant

women, immunosuppressed patients, and people with hypertension, diabetes mellitus, or chronic kidney failure [1].

Pulmonary and extrapulmonary symptoms can persist after acute COVID-19 infection, particularly in patients who had severe clinical illness. Post-acute COVID-19 has been defined as the presence of symptoms beyond the first 3 weeks and up to 12 weeks after COVID-19 infection. Symptoms that last longer than 12 weeks have been referred to as chronic COVID-19 [2]. The most common of these were reported to be dyspnea for pulmonary symptoms, and chest pain, myocardial dysfunction, venous thromboembolism, myalgia, weight loss, asthenia, hair loss, diarrhea, anosmia or parosmia, post-traumatic stress, depression, and anxiety among the extrapulmonary symptoms [2]. Pulmonary function tests and laboratory data play an important role in the clinical follow-up of patients with post-acute COVID-19 symptoms. Persistent elevation of established prognostic indicators such as C-reactive protein (CRP), lactose dehydrogenase (LDH), fibrinogen, ferritin, and D-dimer has been observed during follow-up in patients with severe COVID-19. Pulmonary function testing in these patients also revealed limited diffusion capacity [3,4].

An evaluation of the relationship between the ratio of CRP (a positive acute phase reactant) to albumin (a negative acute phase reactant) and disease severity and radiological involvement at time of hospital admission showed that CRP level was positively correlated and albumin was negatively correlated with both disease severity and degree of radiological involvement [5,6].

In the present study, we aimed to compare CRP/albumin ratio and pulmonary function test parameters in patients presenting to our chest diseases outpatient clinic 12 weeks after COVID-19 with various post-acute complaints, especially dyspnea.

MATERIALS AND METHODS

This prospective study was conducted in the post-COVID outpatient clinic in the chest diseases department of Ataturk University Faculty of Medicine Hospital. One hundred fifty-seven patients who had a history of COVID-19 pneumonia and presented to the Post-COVID Outpatient Clinic of Ataturk University Faculty of Medicine Hospital between July and October 2021 were included. The study was approved by the Erzurum Ataturk University Faculty of Medicine Ethics Committee. Before the study, participants were informed about the purpose, methods, and time required for the study. They were informed that their participation was entirely voluntary, the study involved no risk, and they were able to withdraw from the study at any time.

Inclusion criteria

Patients in the study met the following criteria:

1) were diagnosed with COVID-19 by real-time polymerase chain reaction (PCR) test of a nasopharyngeal swab 1 month earlier and had persistent symptoms consistent with post-acute COVID-19,
2) were over 18 years of age,
3) had radiological involvement consistent with COVID-19 pneumonia,
4) did not need intubation or mechanical ventilation, and
5) agreed to attend follow-up visits over a 12-week period specified for the study.

Exclusion criteria

Additional exclusion criteria were:

1) conditions that may be contraindications to pulmonary function testing (recent myocardial embolism, pulmonary embolism, cerebral aneurysm, active hemoptysis, pneumothorax, nausea, vomiting, recent thoracic, abdominal, or ocular surgery),
2) mental retardation or lack of cooperation,
3) any lung pathology previously known or detected during follow-up.

Study groups

The participants were divided into 3 groups based on the severity of acute COVID-19: 59 patients with moderate illness (non-severe pneumonia) were included in group 1; 46 patients who had severe pneumonia but were not treated in the intensive care unit due to respiratory failure or macrophage activation syndrome were included in group 2; and 52 patients who had severe pneumonia and were treated in the intensive care unit due to the development of macrophage activation syndrome or respiratory failure were included in group 3. Severe pneumonia was defined as pneumonia with oxygen saturation (SO_2) $\leq$ 92% and/or respiratory rate $\geq$ 30/min and/or > 50% lung infiltration.

Study procedure

Upon presentation to the post-COVID outpatient clinic, patients were registered and a detailed history was taken, including smoking history and route of disease transmission. Physical examination and symptom inquiry was performed, and common symptoms such as fever, dyspnea, cough, fatigue, loss of taste/smell, arthralgia, myalgia, headache, sore throat, diarrhea, hair loss, and psychiatric disorders were recorded. Complete blood count was requested. Symptom inquiry, routine hemogram and biochemical tests and pulmonary function tests with diffusion capacity were performed at 12 weeks after the first positive COVID-19 test.

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. The participants were instructed to avoid smoking for 24 hours, alcohol for 4 hours, strenuous exercise for 30 minutes, and heavy meals for 2 hours before testing and to wear clothing that did not restrict chest or abdomen move-

Table 1. Comparison of laboratory data at week 12 in patients with post-acute COVID-19.

	Group 1 (n = 59) Mean ± SD	Group 2 (n = 46) Mean ± SD	Group 3 (n = 52) Mean ± SD	p
WBC	7,388.6 ± 2,012.1	8,271.5 ± 2,442.5	10,973.8 ± 3,754.7 [a, b]	0.001
Lymphocytes	2,276.1 ± 653.7	2,576.9 ± 590.6	2,609.1 ± 1,035.3	0.07
Lymphocyte %	32.3 ± 12.2	31.2 ± 8.5	24.4 ± 7.5 [a, b]	0.001
Neutrophils	4,420.9 ± 1,781.9	4,899.7 ± 1,954.9	7,269.5 ± 2,789.2 [a, b]	0.001
Neutrophil %	58.5 ± 9.6	58.7 ± 7.4	60.6 ± 16.7 [a, b]	0.04
Platelets	272,389.8 ± 70,765.5	255,230.7 ± 38,562.6	262,227.3 ± 72,822.1	0.07
MPV	10.1 ± 0.9	9.9 ± 0.6	9.2 ± 0.6 [a, b]	0.001
ALT	31.2 ± 20.9	31.3 ± 15.9	34.1 ± 18.1	0.27
AST	23.8 ± 8.7	21.6 ± 6.4	22.5 ± 7.1	0.38
Albumin	4.2 ± 0.3	4.1 ± 0.5	4.1 ± 0.3	0.11
Fibrinogen	355.8 ± 142.1	318.9 ± 52.9 [a]	360.1 ± 67.7 [b]	0.01
Procalcitonin	0.04 ± 0.03	0.04 ± 0.03	0.03 ± 0.03	0.06
D-dimer	369.1 ± 243.8	328.1 ± 167.1	341.3 ± 180.2	0.33
CRP	7.7 ± 10.6	2.9 ± 1.9[a]	7.4 ± 4.3 [b]	0.001
LDH	221 ± 63.5	215.2 ± 23.2	262.5 ± 53.6 [a, b]	0.003
BUN	13.3 ± 3.9	14.9 ± 4.7	15.9 ± 5.1 [a]	0.02
Ferritin	134.3 ± 154.6	135.3 ± 113.1	303.5 ± 300.4	0.34
Troponin-I	2.2 ± 3.8	2.2 ± 1.2	2.6 ± 2.1	0.44
Pro-BNP	56.2 ± 84.9	50.1 ± 80.2	74.4 ± 57.4 [a, b]	0.001

SD - Standard deviation, WBC - White blood cells, MPV - Mean platelet volume, AST - Aspartate transaminase, ALT - Alanine transaminase, LDH - Lactose dehydrogenase, CRP - C-reactive protein, BUN - Blood urea nitrogen.
Kruskal-Wallis test used for between-group comparisons. p [a] - versus group 1, p [b] - versus group 2.

Table 2. Comparison of pulmonary function parameters, oxygen saturation, heart rate, and CRP/albumin ratio at week 12 in patients with post-acute COVID-19.

	Group 1 (n = 59) Mean ± SD	Group 2 (n = 46) Mean ± SD	Group 3 (n = 52) Mean ± SD	p
FEV1 %	110.8 ± 23.4	111.3 ± 15.4	95.7 ± 21.9 [a, b]	0.001
FVC %	107.4 ± 24.2	104.2 ± 16.7	94.4 ± 20.3 [a, b]	0.04
DLCO %	114.2 ± 26.4	113.2 ± 16.4	103.7 ± 13.2 [a, b]	0.001
FEF25-75 %	81.5 ± 29.1	84.1 ± 31.5	86.3 ± 22.6	0.65
SO_2	94.2 ± 5.5	93.1 ± 1.3	91.2 ± 4.5 [a, b]	0.001
Heart rate	88.1 ± 10.4	90 ± 8.4	104.9 ± 11.6 [a, b]	0.001
CRP/albumin ratio	1.9 ± 2.8	0.63 ± 0.53 [a]	1.6 ± 1.2 [b]	0.001

FVC - Forced vital capacity, FEV1 - forced expiratory volume in 1 second, DLCO/VA - Diffusing capacity divided by the alveolar volume.
Kruskal-Wallis test used for between-group comparisons. p [a] - versus group 1, p [b] - versus group 2.

ments during the test. BTPS correction was performed according to room air and barometric pressure. A technician explained the expected procedure to the participants. Three acceptable spirograms were obtained and those that met the reproducibility and acceptability criteria published by ATS/ERS in 2019 were used for analysis [7]. The lower limits of the normal range determined for the healthy population according to the criteria specified in the same report were also calculated and presented by the spirometry device. All spirometry was

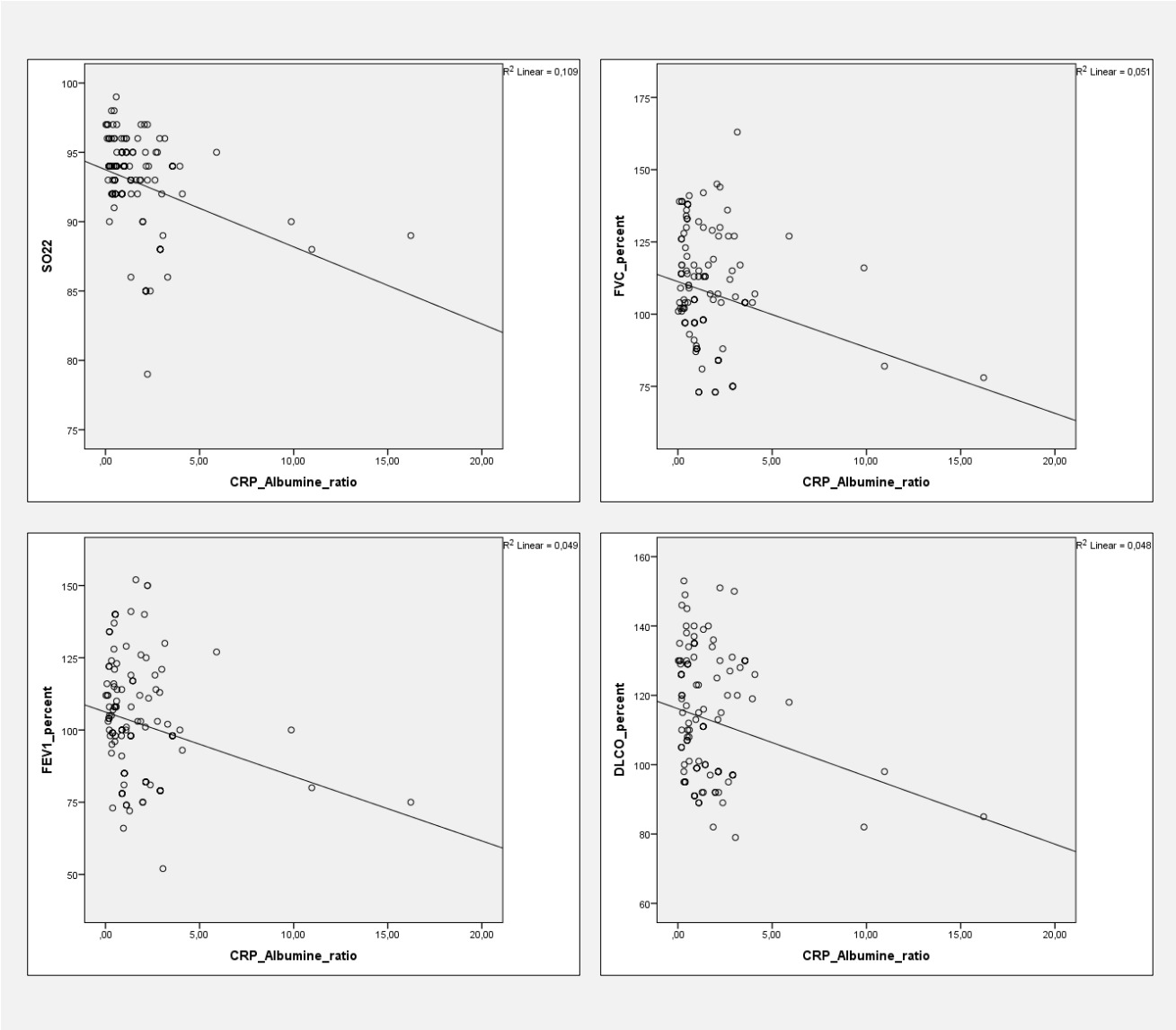

Figure 1. Correlation of CRP/albumin ratio with oxygen saturation and pulmonary function parameters.

performed by the same technician using a Plusmed MIR Spirolab III device.

Medical treatment during follow-up

We noted that among the patients presenting to our outpatient clinic with post-acute COVID-19 symptoms, those in groups 1 and 2 had not been prescribed regular treatment for their symptoms. However, 30 of the 52 patients in group 3 had received long-term oxygen therapy due to hypoxic respiratory failure and a tapering protocol of methylprednisolone that continued from discharge to their presentation to our outpatient clinic. The other patients in group 3 had received methylprednisolone at varying doses and duration that was later discontinued.

Statistical analysis

IBM SPSS version 20.0 software (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA) was used for statistical analyses. Data were presented as mean and standard deviation or number and percentage. Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to evaluate whether continuous variables showed normal distribution. Normally and non-normally distributed continuous variables were compared between multiple independent groups using analysis of variance (ANOVA) and Kruskal-Wallis test, respectively. Tukey's (for homogeneous variances) and Tamhane's T2 (for non-homogeneous variances) post-hoc tests were used after ANOVA. The Kruskal-Wallis one-way ANOVA (k samples) test was performed as a post hoc test after the Kruskal-Wallis test. Relationships between

normally and non-normally distributed quantitative variables were examined using Pearson's and Spearman's correlation analysis. p-value < 0.05 was considered statistically significant.

RESULTS

The participants' mean age was 48 ± 12.4 years overall and 47.3 ± 11.5, 49.3 ± 8.4, and 48.2 ± 10.3 years in groups 1, 2, and 3, respectively (p = 0.41). Men comprised 59.2% of the participants overall and 50.8%, 65.2%, and 86.5% of groups 1, 2, and 3 (p = 0.001).

Sixty-eight (43.3%) of the participants had at least one comorbidity, including hypertension (n = 30), diabetes (n = 15), hypothyroidism (n = 6), coronary artery disease (n = 5), hyperthyroidism (n = 2), and chronic renal failure (n = 1). All of the patients in the study presented with dyspnea on exertion. Other symptoms included chest pain (n = 44), cough (n = 35), hair loss (n = 30), and loss of taste/smell (n = 2).

The laboratory data of post-acute COVID-19 patients at week 12 are shown in Table 1. Patients in group 3 had significantly higher white blood cell (p = 0.001), neutrophil count (p = 0.001) and percentage (p = 0.04), LDH (p = 0.003), and pro-BNP (p = 0.001) levels than patients in groups 1 and 2. Patients in group 2 had significantly lower CRP (p = 0.001) and fibrinogen (p = 0.01) levels when compared with groups 1 and 3. Lymphocyte percentage and mean platelet volume (MPV) were significantly lower in group 3 than in groups 1 and 2 (p = 0.001 for both).

The patients' pulmonary function tests and CRP/albumin ratios are shown in Table 2. Group 3 had significantly lower percent predicted forced expiratory volume in 1 second (FEV1%), percent predicted forced vital capacity (FVC%), percent predicted diffusing capacity of the lungs for carbon monoxide (DLCO%) and SO_2 compared to patients in groups 1 and 2 (p = 0.001, 0.04, 0.001, and 0.001, respectively). CRP/albumin ratio was significantly lower in group 2 compared to groups 1 and 3 (p = 0.001).

The results of correlation analysis between CRP/albumin ratio and pulmonary function test parameters and SO_2 independent of age and comorbidity are shown in Figure 1. CRP/albumin ratio was found to be negatively correlated with SO_2, FEV1%, FVC%, DLCO%.

DISCUSSION

In this study evaluating post-acute COVID-19 patients at 12 weeks, we observed that patients in group 3 had higher LDH, which is known to have prognostic significance, as well as higher white blood cell, neutrophil, and pro-BNP levels than patients in the other groups. CRP and fibrinogen levels were lower in group 2 compared to the other groups. CRP/albumin ratio, which was the focus of our study, was also lower in group 2 than in the other groups. Patients in group 3 had lower pulmonary function parameters at week 12 compared to the other groups. Our evaluation of CRP/albumin ratio in relation to pulmonary function parameters revealed an inverse relationship with FEV1%, FVC%, and DLCO%. In addition, CRP/albumin ratio was also negatively correlated with fingertip saturation in room air. Following COVID-19 patients over the last 2 years in our center has provided much information about the different clinical courses of this complex disease. We have observed that while some patients never develop hypoxemia and respiratory distress, individuals with comorbidities and those who are unvaccinated often exhibit a more severe course [8,9]. In addition, we frequently observed that individuals who do not initially present with respiratory distress can progress to acute respiratory distress and macrophage activation syndrome [10,11]. This provided an opportunity to investigate parameters that could facilitate the early prediction of the clinical course of COVID-19. In studies of individuals infected with dengue virus, initially high CRP levels were found to be associated with severe clinical course [12]. Based on this, studies in COVID-19 patients showed that a high CRP level at presentation was correlated both with clinical disease course and radiological involvement [13]. As CRP level may be affected by age, viral infections, and secondary superinfections, studies have generally been conducted in the acute period and evaluations were made independently of age. Unlike CRP, albumin is a negative acute phase reactant that can decrease physiologically during infection and with age [14]. Evidence suggests that the anti-inflammatory and antioxidant properties of albumin may be protective against cytokine storm and organ failure. In addition, the anticoagulant effect of albumin may reduce platelet activation and clotting tendency associated with oxidative stress [15]. The correlation between low albumin level and poor survival demonstrated in studies of albumin levels in COVID-19 patients may also explain this situation [16]. In our comparison of laboratory parameters at 12 weeks in patients presenting to our outpatient clinic with dyspnea and various other post-acute COVID-19 symptoms, we observed high white blood cell and neutrophil levels in group 3 and attributed this to the significant proportion of patients in this group who continued to use methylprednisolone until they came to our outpatient clinic. Studies of rheumatologic conditions featuring intense cytokine discharge have shown that MPV may decrease secondary to platelet consumption in rheumatoid arthritis and symptomatic systemic lupus erythematosus. Similarly, we observed that MPV was lower in group 3, likely due to the predominance of low-volume platelets in the peripheral circulation as a result of consumption. Furthermore, long-term hypoxia in these patients may have caused an increase in LDH levels as well as elevated pro-BNP levels due to hypoxic pulmonary vasoconstriction. We determined that patients in group 2 had lower CRP and fibrinogen levels at week 12. In accordance with national guidelines, pa-

tients in group 1 received only antiviral therapy. Those in groups 2 and 3 received antiviral therapy starting at hospital admission, as well as anti-inflammatory steroid therapy and antibiotherapy for possible superinfections. The milder disease course in group 2 patients compared to group 3 and the anti-inflammatory treatment they received may have resulted in the lower CRP and fibrinogen levels compared to patients in both group 1 and group 3. Our pulmonary function test results were consistent with other studies that evaluated the pulmonary function parameters of COVID-19 patients in the post-acute period. We observed lower FEV1%, FVC%, and DLCO% in patients with severe clinical course. Low DLCO% level may have caused the low saturation level and an increase in heart rate due to hypoxia. The negative correlation between CRP/albumin ratio and pulmonary function parameters may be related to an increase in CRP levels due to ongoing parenchymal inflammation, especially in group 3 patients.

The most important limitation of our study is that some of the patients in group 3 continued to use long-term methylprednisolone treatment for parenchymal inflammation and deep hypoxia. This may have prevented a sound evaluation of CRP and albumin level in this patient group. However, the effect of methylprednisolone treatment on both parenchymal involvement and related saturation levels in these patients led to their long-term use of this treatment.

In conclusion, although CRP/albumin ratio is affected by many physiological and infective pathologies, when these are ruled out, its inverse correlation with pulmonary function parameters may make it a convenient guiding parameter in settings where pulmonary function testing is not available.

Ethical Approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent:

Informed consent was obtained from all individual participants included in the study.

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Declaration of Interest:

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