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ORIGINAL ARTICLE
ORİJİNAL ARAŞTIRMA

Mild COVID-19 Does Not Reduce the Risk of Developing Pulmonary Fibrosis: A DKK3 Level-Based Study

Hafif Geçirilen COVID-19 Akciğer Fibrozisi Gelişme Riskini Azaltmaz: DKK3 Düzeyine Bağlı Bir Çalışma

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ABSTRACT

Aim: The medical world has experienced the administration of Coronavirus Disease of 2019 (COVID-19)-induced organ dysfunctions, particularly pulmonary. Dickkopf-related protein 3 (DKK3) is attributed to fibrosis in the human body. Our study aimed to evaluate DKK3 levels during COVID-19 infection and to locate a link between high levels of DKK3 and pulmonary fibrosis (PF).

Material and Method: This prospective case-control study was conducted with COVID-19 patients and an age-gender-matched control group. Both groups were subjected to blood DKK3 measurements using the ELISA technique. Then, the sixth month after recovery, the patient group was reevaluated for pulmonary fibrosis via high-resolution computed tomography.

Results: Totally, 100 patients (mean age: 54.05±9.16) with COVID-19 and 100 controls (mean age: 54.18±9.32) participated. All patients were identified as non-severe (n=61) and severe (n=39). DKK3 levels were significantly higher in the patient group than in the control group (p=0.001). DKK3 levels were higher in the non-severe group. Patients healed with a convalescent plasma (CP) based-treatment produced more DKK3. PF was more frequent in these patients. Involvement of the basal lobe, particularly significant involvement of the right middle lobe, showed a strong association with fibrosis, characterized by elevated levels of DKK3.

Conclusion: DKK3 may be a supportive marker for detecting COVID-19 positivity or COVID-19-induced PF. Comprehension of PF in patients with a CP-based treatment would be more complicated.

Keywords: COVID-19, convalescent plasma, Dickkopf-related protein 3, pulmonary fibrosis

ÖZ

Amaç: Tıp dünyası, özellikle akciğer fonksiyon bozukluklarına yol açan koronavirüs-2019 (COVID-19) hastalığı tarafından tetiklenen organ fonksiyon bozukluklarını deneyimlemiştir. Dickkopf ile ilişkili protein 3 (DKK3), insan vücudunda fibrozis ile ilişkili bir protein olarak bilinmektedir. Çalışmamız, COVID-19 enfeksiyonu sırasında DKK3 seviyelerini değerlendirmeyi ve yüksek DKK3 seviyeleri ile akciğer fibrozu (AF) arasında bir bağlantı bulmayı amaçlamaktadır.

Gereç ve Yöntem: Bu prospektif vaka-kontrol çalışması COVID-19 hastaları ve yaş-cinsiyet uyumlu kontrol grubuyla gerçekleştirildi. Her iki grup da ELISA tekniği kullanılarak kan DKK3 ölçümlerine tabi tutuldu. Hasta grubu nekahattan altı ay sonra yüksek çözünürlüklü bilgisayarlı tomografi ile akciğer fibrozisi açısından yeniden değerlendirildi.

Bulgular: Değerlendirmeye toplamda 100 COVID-19 hastası (54.05±9.16 ortalama yaş) ve 100 kontrol (54.18±9.32 ortalama yaş) alındı. Hastalar, hafif (n=61) ve ağır (n=39) olarak tanımlandı. DKK3 seviyeleri hasta grubunda kontrol grubuna göre önemli ölçüde yüksekti (p=0.001). DKK3 seviyeleri hafif vakalarda daha yüksekti. Konvalesan plazma (KP) temelli tedaviyle iyileşen hastalar daha fazla DKK3 üretti. AF bu hastalarda daha sık görüldü. Basal lobun katılımı, özellikle sağ orta lobun belirgin tutulumu, yüksek DKK3 seviyesi ile birlikte fibroz ile ilişkilendirildi.

Sonuç: DKK3, COVID-19 pozitifliğini veya COVID-19 kaynaklı akciğer fibrozunu tespit etmek için destekleyici bir belirteç olabilir. KP temelli tedavi alan hastalarda AF değerlendirilmesi daha kompleks olabilir.

Anahtar Kelimeler: COVID-19, Dickkopf-ilişkili protein 3, konvalesan plazma, pulmoner fibrozis

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INTRODUCTION

The Coronavirus 2019 (COVID-19) pandemic, the medical world has conducted many trials to predict COVID-19 intricacies using productive data. Similar to the complications of recent adenovirus outbreaks, pulmonary fibrosis was the prominent sequelae of COVID-19 pneumonia (1-3). It was concepted that lung damage due to viral and immune-mediated mechanisms is involved in the pathogenesis of pulmonary fibrosis (4).

Cytokines play an essential role in the immune response against viral infections (5). However, tissue damage may be inevitable if an excessive inflammatory response develops (6). Overall, pulmonary fibrosis primarily emerges as a secondary consequence of remodeling pathology (7). The Wingless and Int-1 (WNT) signaling pathway also contributed to the progression of pulmonary fibrosis (8, 9). Wnt5a levels were indicative of a poor prognosis in patients with COVID-19, whereas Wnt11 levels were identified as a predictor of recovery (10).

A modulator of the WNT/β-catenin pathway, the Dickkopf family (DKK), has been associated with Wnt signal inhibition and organ fibrosis (11). The effects of DKK1 and DKK2 from family members can be clearly expressed; nevertheless, the effect of DKK3 on the Wnt signal is biphasic (11), an inhibition (12) or an augmentation (13, 14).

The effects of DKK3 on pulmonary fibroblasts are not fully known. Therefore, we investigated the relationship between DKK3 levels at hospitalization and the status of pulmonary fibrosis in COVID-19 survivors.

MATERIAL AND METHOD

Study Design

This prospective, case-control study conducted with COVID-19 patients and a healthy control group between 2020 and 2023, after receiving approval from Necmettin Erbakan University Meram Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 04.12.2020, Decision no: 2020/2916). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This work was also partially subsidized by the current university's scientific research project under grant number 211518008. Informed consent was obtained from all patients and control groups prior to the study.

Patients whose COVID-19 positivity was confirmed by a quantative polymerase chain reaction (qPCR) test and recovered in the internal medicine clinics were reevaluated concerning pulmonary fibrosis via high-resolution computed tomography (HRCT) in their sixth months after recovery.

The patient group was split into two groups. Accordingly, those with clinics (headache, cough, fever, sore throat, diarrhea, and anosmia) and minimal irregularities on computed tomography (CT) were accepted as non-severe. Patients with critical clinics (SpO2 ≤ 93%, ≥ 30 breaths/min, PaO2/FiO2 <300 mmHg, pulmonary involvement >50% within 24–48 h) were ranked as severe (15).

Diagnostic admission CTs were evaluated by a radiologist blind to patients' clinic status with the CT severity scoring proposed by Pan et al. (16). Accordingly, 0 points for no involvement; 1 for < 5% involvement; 2 for 5–25% involvement; 3 for 26–50% involvement; 4 for 51–75% involvement; and 5 for >75% involvement were cumulated. In the following sixth month, patients' current HRCTs were assessed based on CT involvement scores regarding pulmonary fibrosis (17).

The control group consisted of individuals without chronic disorders. Laboratory results of the patient group at admission, demographic characteristics of both groups, and DKK3 levels were noted throughout the study.

Patient selection criteria: Patients above 18 years of age with PCR positivity were preferred. Among them, those with comorbidities such as chronic pulmonary, cerebral, renal, cardiac, or rheumatic disease, diabetes mellitus, hypertension, active malignancy, smoking, and alcohol consumption were excluded.

Diagnose Tests

To assess the serum DKK3 level, 5 cc blood samples were obtained from the patient group at admission and during the study period using anticoagulant-free tubes. Similarly, blood samples were collected from the control group during the same study period, following the same procedure. In patients scheduled for a steroid-based treatment, blood sampling was completed prior to steroid administration. The samples were centrifuged at 4000 rpm for 5 min and stored at -800C until the analysis time. DKK3 levels were measured with the 96-test Human DKK-3 Elisa Kit (Catalog number: EH0114, Wuhan Fine Biotech Co., LC. Wuhan-Hubei, China), according to the manufacturer's instructions. The samples were quantified using a quantitative sandwich enzyme immunoassay technique. The formula obtained with the standard curve graph's support was used for the concentrations to calculate all corresponding absorbances in pg/mL.

Statistical Analysis

The study data were analyzed with SPSS version 21. Frequency data were expressed using numbers (n) and percent (%), and numerical data were expressed using mean + standard deviation, median (quartiles). Data distributions were evaluated using Kurtosis and

Skewness values. An independent T-test was used to compare the DKK3 results between the groups. In subgroups, the Mann-Whitney U test was preferred for DKK3 comparison according to disease severity, and the chi-square test was preferred for categorical comparisons. Pearson was used for the correlations of normally distributed data, and Spearman was used for skewed data. The area under the receiver-operating characteristics (ROC) curve (AUC) and 95% confidence intervals (CI) were used to assess the ability of each DKK3 result of the patient and control groups to the COVID-19 distinction. In all evaluations, $p < 0.05$ was considered acceptable to reject the H0 hypothesis.

RESULTS

A hundred patients and 100 controls enrolled in the study. The mean age of the patients and control group was 54.05±9.16, and 54.18±9.32, respectively. The female and male populations were comparable in both groups (25:35). No statistical discrepancy was found between the groups regarding age and gender. The mean hospitalization for all patients was 11 days. Patient characteristics, clinical evaluation findings, and laboratory results according to patient groups are given in Table 1.

In comparing the DKK3 levels between the groups, we detected higher levels of DKK3 in the patient group compared to the control group (p=0.001, η2=0.210) (**Figure 1a**). In addition, the mean DKK3 of the patient group (1671.55±680.87 pg/mL) was more than 50% of the control group (1036.24±551.63 pg/mL). The distinguishability of this difference was moderately significant (p=0.001, AUC=0.746, CI=0.680-0.813) (**Figure 1b**). Accordingly, a cut-off of 1341 pg/mL in the level of DKK3 yielded a sensitivity of 63% and specificity of 65% in detecting COVID-19 positivity.

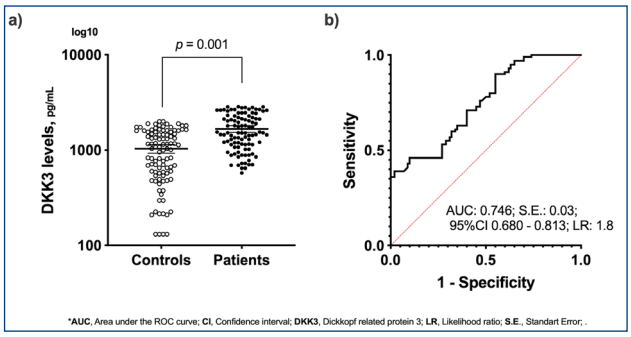

Figure 1. a) DKK3 dispersion in patient and control groups; b) ROC curve analysis for indicative value of DKK3.

Pulmonary fibrosis was frequently located in the patient group in the sixth-month HRCT reports (69%). **Figure 2a** demonstrates the impact of disease severity on pulmonary fibrosis, as indicated by the HRCT reports. Nevertheless, no directly link was observed between DKK3 levels and pulmonary fibrosis scores (p >0.05) (**Figure 2b**). This finding persisted in subgroup evaluations (p > 0.05).

Table 1. Patients' characteristics, pneumonic backgrounds and laboratory results

	All patients	Non-Severe (n=61)	Severe (n=39)	p value
Age, (year)	54.23±9.09	52.91±9.39	56.28±8.29	0.071
Gender, Female/Male	43 / 57	25 /36	18 / 21	0.610
BMI*, (%)	30.2±4.22	30.12±4.39	30.31±4.01	0.834
Vital status				
Pulse, bpm	92.93±12.82	93.95± 12.14	91.33±13.83	0.322
Saturation, (%)	86.38±7.13	88.03±5.06	83.79±8.98	0.010
Need for O2	87 (87)	49 (80.3)	38 (97.4)	0.041
Radiologic outcome				
CT-IS†	15.23±3.13	13.24±1.31	18.33±2.59	0.001
Fibrosis score	1.5 (0-6)	1 (0 - 6)	2 (0 - 6)	0.356
Fibrosis, n (%)	69 (69)	44 (72.1)	25 (64.1)	0.397
Prognostic laboratory results				
WBC‡, x109/L	6.88 (4.95-9.03)	6.15 (4.67-7.99)	8.16 (5.7-10.24)	0.013
ALC§, x109/L	1.1 (0.69-1.55)	1.17 (0.71-1.62)	1.07 (0.59-1.47)	0.626
Hemoglobin, gr/L	13.47±1.86	13.77±1.64	13.01±2.11	0.044
Ferritine, ng/mL	396 (199-826)	379 (152 - 737)	417 (339 - 959)	0.392
Creatinine, mg/dL	0.97 (0.78-1.16)	0.96 (0.78-1.09)	1 (0.75-1.29)	0.026
LDH¶, U/L	347 (301-420)	341 (263 - 382)	417 (324 - 450)	0.001
D-Dimer, ng/mL	273 (204-447)	255 (216- 405)	350 (202- 539)	0.158
Fibrinogen, mg/dL	547 (456 - 657)	524 (442 - 593)	592 (481- 763)	0.006
DKK3*†, pg/mL	1671.55±680.9	1811.37±629.1	1452.84±780.8	0.010

p values are the comparison of non-severe and severe groups, (The independent t-Test, Chi-Squared test or Mann Whitney U test); * Body mass index; † Computed tomography involvement score; ‡ White blood cell; § Absolute lymphocyte count; ¶ Lactate dehydrogenase; *† Dickkopf related protein 3.

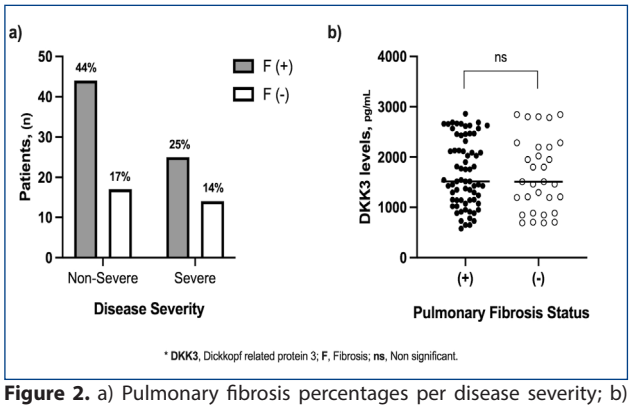

Figure 2. a) Pulmonary fibrosis percentages per disease severity; b) Comparison of DKK3 levels according to pulmonary fibrosis status.

However, in comparing DKK3 levels regarding disease severity, the non-severe group had higher DKK3 levels (p=0.010, 2=0.067) (**Figure 3a**). Similarly, in non-lymphopenic ones, non-severe patients (n=35) had much higher DKK3 levels (p=0.001, η2=0.245) (**Figure 3b**).

Moreover, in patients with a convalescent plasma (CP) based-treatment (n=69), DKK3 levels at admission were higher in patients with pulmonary fibrosis identified in the sixth-month HRCT (p=0.026, η2=0.073) (**Figure 3c**).

The fraction of the pulmonary involvements in thorax CTs at admission are shown in **Figure 4a**. Accordingly, involvement of the right middle lobe and both inferior lobes were prominent in patients with pulmonary fibrosis. In addition, a synchronous increase in DDK3 levels was found in patients with right middle lobe involvement (p=0.009, η2=0.094) (**Figure 4b**). There was no such outcome in other local or extensive lobe involvements (**Figures 4c, 4d, 4e** and **4f**).

Among the logical correlations, DKK3 levels were negatively correlated with absolute lymphocyte count (p=0.024, r=-0.225) and pulmonary involvement (p=0.005, r=-0.279).

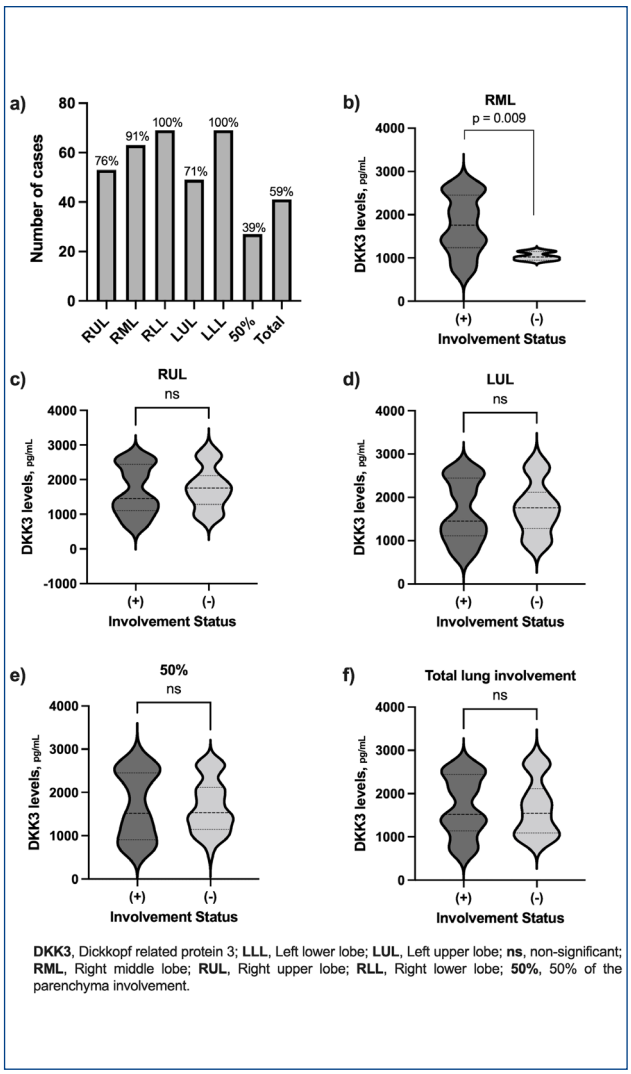

Figure 4. DKK3 levels and the CT scan on the admission of patients diagnosed with pulmonary fibrosis, a) Fraction of lobe involvements; b) DKK3 levels in the right middle lobe involvement status; c) DKK3 levels in the right upper lobe involvement status; d) DKK3 levels in the left upper lobe involvement status; e) DKK3 levels in 50% lung involvement; f) DKK3 levels in total lung involvement.

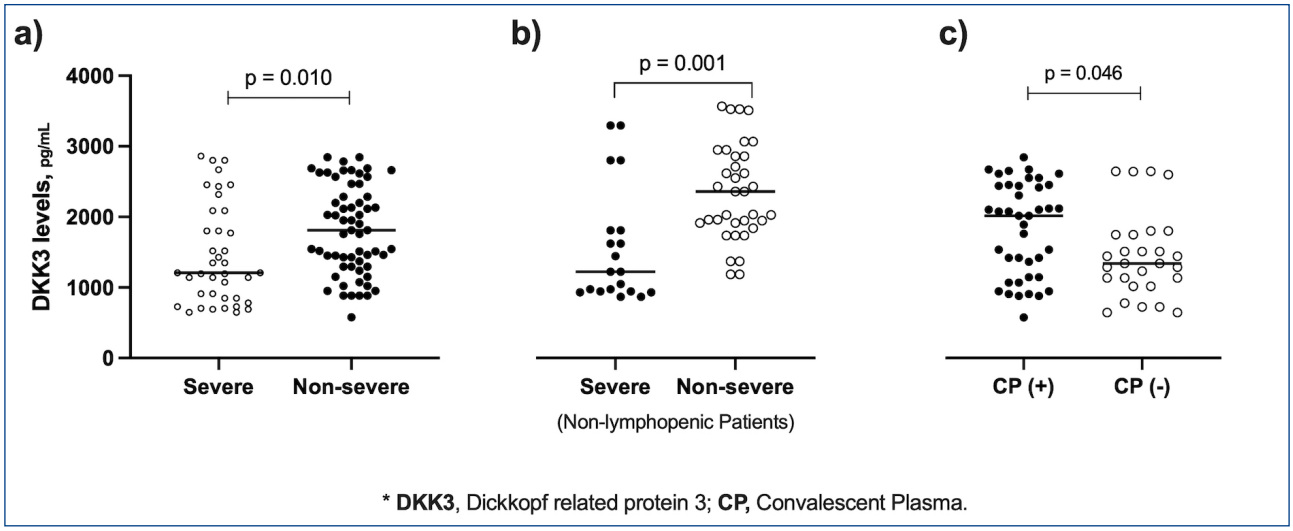

Figure 3. DKK3 level comparisons according to a) Disease severity; b) Convalescent plasma treatment status

DISCUSSION

Our study evaluated DKK3 levels during COVID-19-induced pneumonia and focused on the feasibility of DKK3 in the prediction of pulmonary fibrosis. Among the notable results, DKK3 was high enough to indicate COVID-19 positivity in the patients. Pulmonary fibrosis was observed broadly, even in COVID-19 survivors. In addition, disease severity had a reducing effect on DKK3 levels. Therefore, DKK3 levels found elevated in non-severe patients, linked with more pulmonary fibrosis. Moreover, DKK3 levels and pulmonary fibrosis scores were elevated in patients healed with a CP-based treatment. Finally, basal lobe involvements, but essentially the right middle lobe involvement was more tended to develop fibrosis.

The detection of early fibrosis favors involved organs. In this context, many fibrosis markers linked to fibrosis formation have been researched. Consequently, several studies have identified an increased level of DKK3 associated with organ fibrosis (18-19). In patients with glomerular or tubular disease, an increase in urinary DKK3 levels was reported to be inversely proportional to the glomerular filtration rate (18). Moreover, urinary DKK3 levels were positively correlated with fibrosis in kidney biopsies (14).

In a study with WNT ligands in COVID-19, WNT5a, and WNT11 expressions were analyzed regarding disease progression. WNT5a was linked to a poor prognosis, whereas WNT11 was associated with healing (10). Even though DKK3 levels in our study did not effectively predict pulmonary fibrosis as of January 2023, our study is the first to detect increased DKK3 blood concentrations in COVID-19 patients. Moreover, detecting COVID-19 positivity with roughly 63% specificity and sensitivity above 1341 pg/mL may indicate that DKK3 has a diagnostic significance for COVID-19.

Among the fibrosis detected survivors, those with high DKK3 levels during infection and those who received CP-based treatment had more fibrosis. An enhanced immune response due to the COVID-19 antibodies already existing in CP-based regiment may have induced this.

Function of DKK3 in pulmonary tissue is not known precisely. A study on organ fibrosis determined that WNT/β-catenin signal activation in respiratory cells caused pulmonary fibrosis by transforming perivascular fibroblasts into myofibroblasts (20). It has been revealed that TGF-β causes subsequent fibrosis by stimulating the WNT/β-catenin pathway in COVID-19 cases (21, 22). In this context, the contribution of DKK3 to pulmonary fibrosis in patients with COVID-19 might be more plausible in the form of stimulation of the WNT/β-catenin pathway, not inhibition.

Disease severity frequently worsens the prognosis of many diseases. Here, we found higher levels of DKK3 in non-severe patients compared to severe ones. Intriguingly, pulmonary fibrosis was more common in non-severe patients as well. The fact that such an effective marker in indicating fibrosis is high in a group with a higher prevalence of pulmonary fibrosis indicates that even patients with mild disease may be predisposed to pulmonary fibrosis.

The prevalence of lung involvement is a solemn phase in transforming inflammation into fibrosis. Our study showed that the prevalence of right middle lobe involvement was increased, similar to basal lobe involvement among those with fibrosis. One additional anecdote is that the DDK3 elevation in the right middle lobe involvement markedly differed from the other involvements. In this regard, additional explanations are needed to anatomical determinations.

The primary deficiency of our study was the absence of the second DKK3 sampling to be taken simultaneously with the HRCT. If this had been performed, pulmonary fibrosis detected in HRCTs could have been better firmly proven to be caused by COVID-19. Another limitation was the absence of identification of COVID-19 variants during patient admission. Outcomes containing the variants could have revealed more comprehensive insights into the defects of COVID-19.

CONCLUSION

Overall, this study evaluated DKK3 levels in COVID-19 patients. We found a significant increase in DKK3 levels compared to the control group. These DKK3 elevations were robust enough to determine COVID-19 positivity. In subgroup evaluations, we can say that DKK3 levels were higher in the non-severe group. In addition, high levels of DKK3 detection persisted in patients without lymphopenia. Furthermore, DKK3 levels indicate the long-term effects of COVID-19 inflammation rather than instantaneous severity. We could not detect a logical relationship between DKK3 levels and pulmonary fibrosis. However, among the patients with pulmonary fibrosis, those with higher DKK3 levels had received CP-based treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Necmettin Erbakan University Meram Faculty of Medicine Non-drug and Medical Device Researches Ethics Committee (Date: 04.12.2020, Decision no: 2020/2916).

Informed Consent: All patients signed the free and informed consent form.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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