

Investigation of Levels of Periostin, HIF-1 α and Phospholipase A2 in COVID19 Patients

COVID-19 Hastalarında Periostin, HIF-1 α ve Fosfolipaz A2 Düzeylerinin Araştırılması

Merve Zeytinli Akşit¹  Yasemin Delen Akçay²  Çiğdem Gözde Aslan³ 
Yusuf Ali Altuncı⁴  Murat Ersel⁴  Alper Bozdoğan⁴ 

- 1 Bakırçay Üniversitesi, Çiğli Eğitim ve Araştırma Hastanesi, Tıbbi Biyokimya, İzmir, Türkiye
- 2 Ege Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya, İzmir, Türkiye
- 3 Biruni Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya, İstanbul, Türkiye
- 4 Ege Üniversitesi, Tıp Fakültesi, Acil Tıp, İzmir, Türkiye

Received / Başvuru Tarihi: 06.08.2025

Accepted / Kabul Tarihi: 06.10.2025

ABSTRACT

Aim: We aimed to reveal the potential roles of periostin, hypoxia-inducible factor-1 α (HIF-1 α), and phospholipase A2 (PLA2) in inflammation, hypoxia, and tissue damage in patients with coronavirus disease 2019 (COVID-19) and to investigate whether they are useful potential markers in the follow-up and evaluation of disease severity.

Materials and Methods: Serum levels of periostin, HIF-1 α , and PLA2 were measured in 32 patients with COVID-19 on days 1, 3, and 7 of hospitalisation. Additionally, samples from 30 healthy individuals were analysed for comparison.

Results: When biomarker levels of the patient and control groups were compared, a statistically significant difference was observed only in periostin levels ($p = 0.023$). Periostin levels were statistically significantly higher on days 3 and 7 compared with the first day of hospitalisation in patients with COVID-19 ($p = 0.018$ and $p = 0.021$, respectively).

Yazışma adresi: Yasemin Delen Akçay

Ege Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya, İzmir, Türkiye

e-posta: yasemindakcay@gmail.com

Etik onay: Ege Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya, Etik Kurulu 23.09.2021 tarihli ve 21-9.1T/20 sayılı kurul kararı

Conclusion: Our study showed that periostin protein is an important biomarker in COVID-19. To the best of our knowledge, our study is one of the first to include the simultaneous analysis of periostin, HIF-1 α , and PLA2 in patients with COVID-19. We believe that our study, which provides comprehensive data, is important for the evaluation of the course and severity of COVID-19 infection.

Keywords: Coronavirus disease, Periostin, Hypoxia-inducible factor-1 alpha, Phospholipase A2

ÖZET

Amaç: Bu çalışmada, 2019 Koronavirüs Hastalığı (COVID-19) olan hastalarda periostin, hipoksiyle indüklenen faktör-1 alfa (HIF-1 α) ve fosfolipaz A2 (PLA2)'nin inflamasyon, hipoksi ve doku hasarındaki potansiyel rollerini ortaya koymayı ve bu parametrelerin hastalık şiddetinin takibi ve değerlendirilmesinde yararlı ve potansiyel belirteçler olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntem: Otuz iki COVID-19 hastasında, hastaneye yatışın 1., 3. ve 7. günlerinde serum periostin, HIF-1 α ve PLA2 düzeyleri ölçüldü. Ayrıca, karşılaştırma amacıyla 30 sağlıklı bireyden alınan örnekler analiz edildi.

Bulgular: Hasta ve kontrol gruplarının biyobelirteç düzeyleri karşılaştırıldığında, yalnızca periostin düzeylerinde istatistiksel olarak anlamlı bir fark gözlemlendi ($p = 0,023$). Periostin düzeyleri, COVID-19 hastalarında ilk hastaneye yatış gününe kıyasla 3. ve 7. günlerde istatistiksel olarak anlamlı derecede daha yüksekti (sırasıyla $p = 0,018$ ve $p = 0,021$).

Sonuç: Çalışmamız, periostin proteininin COVID-19 hastalığında önemli bir biyobelirteç olduğunu göstermiştir. Bildiğimiz kadarıyla bu çalışma, COVID-19 hastalarında periostin, HIF-1 α ve PLA2'nin eş zamanlı analizini içeren ilk çalışmalardan biridir. Kapsamlı veriler sunan çalışmamızın, COVID-19 enfeksiyonunun seyri ve şiddetinin değerlendirilmesine katkı sağlayacağını düşünüyoruz.

Anahtar Sözcükler: Koronavirüs hastalığı, Periostin, Hipoksiyle indüklenen faktör-1 alfa, Fosfolipaz A2

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a pandemic-causing infection caused by the SARS-CoV-2 virus. COVID-19 has a broad clinical spectrum, ranging from asymptomatic infection to severe acute respiratory distress syndrome (ARDS) and multiple organ failure. The immune system, hypoxia and inflammation play a role in the pathophysiology of the disease (1).

Tissue damage caused by the excessive inflammatory response that occurs in COVID-19 is an important determinant of disease severity and mortality (2). Therefore, better elucidation of inflammatory processes and hypoxia mechanisms is crucial in understanding the pathophysiology of the disease and developing treatment strategies.

Periostin is a matrix glycoprotein released in response to cellular stress and inflammation and has been suggested to play an important role in inflammatory diseases and fibrotic processes (3). Considering the intensity of

inflammatory processes in COVID-19 patients, it has been suggested that periostin levels may be associated with disease severity (4). In respiratory diseases, periostin stands out as a biomarker that generally reflects inflammation and tissue remodelling processes (5). Considering that COVID-19 may lead to similar inflammatory and fibrotic processes in lung tissue, the potential role of periostin in disease severity is worth investigating.

Hypoxia Inducible Factor-1 alpha (HIF-1 α) is an oxygen-sensitive transcription factor that is induced under hypoxic conditions (6,7). Angiotensin converting enzyme 2 (ACE2) expression, which facilitates the entry of SARS-CoV-2 into cells, is reported to be regulated by HIF-1 α . Pulmonary damage and hypoxia processes associated with COVID-19 are associated with overexpression of HIF-1 α (7).

Phospholipase A2 (PLA2) initiates the production of proinflammatory eicosanoids by catalysing the release of arachidonic acid

from membrane phospholipids and plays a role in various inflammatory diseases (8). It has been reported that PLA2 may affect lung function indirectly by producing lipid mediators or directly by changing the lipid composition of cell membranes or pulmonary surfactant. Increased PLA2 expression has been observed in bronchoalveolar lavage fluid and plasma of ARDS patients, and it has been suggested that PLA2 plays a role as a potential biomarker of ARDS (9). In addition, PLA2 level was found to be significantly higher in the plasma of COVID-19 patients and correlated with the severity of the disease (8,10).

Our study aimed to investigate whether serum levels of periostin, HIF-1 α and PLA2 parameters in COVID-19 patients are useful and potential markers in the follow-up and evaluation of the severity of COVID-19 disease.

MATERIALS AND METHODS

Our study was conducted between 20.11.2021 and 20.09.2022 at the Departments of Emergency Medicine, Intensive Care Unit and Medical Biochemistry, Research Laboratory. Our study was supported by Ege University Scientific Research Projects Coordinatorship with the budget transferred to the project code TGA-2021-23420. Approval for the study was obtained from Ege University Medical Research Ethics Committee dated 23.09.2021 and decision number 21-9.1T/20.

Identification of patients to be included in the study

Thirty-two patients over the age of 18 who presented to the emergency department and were hospitalised with a diagnosis of COVID-19 and who approved the Informed Consent Form were included in the study. Patients who refused treatment, had additional foci of infection, malignancy and acquired or congenital immunodeficiency were excluded. Thirty healthy volunteers were compatible with the average age of the patient group,

and who approved the Informed Consent Form were included in the control group.

Collection of Samples

Blood samples of patients diagnosed with COVID-19 and hospitalised were taken by the emergency department and hospitalisation unit nurses on the first day of diagnosis and on the 3rd and 7th days of follow-up and transferred to the Department of Medical Biochemistry. In total, blood samples were taken from 32 patients on the first day of diagnosis, 17 patients on the 3rd day of hospitalisation and 9 patients on the 7th day of hospitalisation. Blood samples were centrifuged at 4000 rpm and +4 $^{\circ}$ C and serum samples were stored at -80 $^{\circ}$ C until analysis. The same procedures were performed for healthy control samples.

Biochemical Analysis

Periostin, HIF-1 α and PLA2 biomarker levels in serum samples were analysed spectrophotometrically by sandwich enzyme-linked immunosorbent assay (ELISA) method using FineTest brand ELISA kit (catalogue numbers: EH0255, EH0551, EH3302; Fine Biological Technology Co. Ltd, Wuhan, Hubei, China).

The percentage coefficients of variation (%CV) for the intra-assay variability of the periostin ELISA kit were 4.93, 5.22, and 4.89 for low, medium, and high concentrations, respectively. The inter-assay %CV values were 4.82, 4.68, and 5.12, respectively. For the HIF-1 α ELISA kit, the intra-assay %CV values were 5.91, 5.26, and 4.68, while the inter-assay %CV values were 5.22, 5.36, and 4.83 for low, medium, and high concentrations, respectively. For the PLA2 ELISA kit, the intra-assay %CV values were 4.68, 5.22, and 5.36, and the inter-assay %CV values were 4.83, 5.02, and 5.08 for low, medium, and high concentrations, respectively.

In addition, White Blood Cell (WBC), C-Reactive Protein (CRP), D-Dimer, ferritin and procalcitonin values, which are routinely

checked in COVID-19 patients, were obtained from the laboratory information management system. In our laboratory, the WBC test is performed on Sysmex XN3100 (Sysmex Corporation, Kobe, Japan), D-Dimer and fibrinogen on Sysmex CN6000 (Sysmex Corporation, Kobe, Japan), CRP on Roche cobas 702 (Roche Diagnostics GmbH, Mannheim, Germany), ferritin and procalcitonin tests on Roche cobas e801 (Roche Diagnostics GmbH, Mannheim, Germany).

Statistical Analysis

Statistical Package of Social Science (SPSS) Version 20.0 (SPSS, Inc., Chicago, IL, USA) was used to analyse the data. The conformity of the data to the normal distribution was analysed by the Shapiro-Wilk test. Data were expressed as mean \pm standard deviation or median (25th-75th percentile). Mann-Whitney U test and Independent samples T test were used to compare the biomarkers of the control-patient group and discharged-died patients. The Friedman test was used to compare biomarkers on the day of diagnosis, days 3 and 7. Paired samples T test and Wilcoxon signed-rank test were used for pairwise comparisons. The relationship between disease severity and biomarkers was analysed by the Spearman correlation test. Statistical significance level was accepted as $p < 0.05$.

RESULTS

The mean age of the patients was 70 ± 15 (min 36-max 102) years. Among the 32 COVID-19 patients, 19 were male and 13 were female. During the follow-up, 16 patients were discharged, while 16 patients died. The patient group had WBC levels of $10.51 \pm 6.28 \times 10^3/\mu\text{L}$, CRP levels of 139 ± 110 mg/L, D-Dimer 4360 ± 7129 $\mu\text{g/L}$, ferritin 878 ± 1312 ng/mL, fibrinogen 472 ± 157 mg/dL, and procalcitonin levels of 3.05 ± 6.64 ng/mL. When the biomarker levels of

the patient and control groups were compared, a statistically significant difference was observed only in periostin levels ($p=0.023$) (Table 1).

Periostin levels were statistically significantly higher on days 3 and 7 compared to the first hospitalisation day of COVID-19 patients ($p=0.018$, $p=0.021$, respectively). Although mean HIF-1 α and PLA2 levels tended to increase on day 7 compared to day 1, these changes were not statistically significant, and no significant differences were observed between patients and controls for either parameter (Table 2).

With increasing inflammation, a twofold increase in mean periostin levels was observed on day 3 and an approximately fourfold increase on day 7 compared with the first day of hospitalisation. A slight increase in HIF-1 α was noted on day 3 compared with day 1 ($p = 0.044$), and on day 7, a twofold and 1.5-fold increase in HIF-1 α and PLA2 levels, respectively, was observed compared with day 1. However, no consistent statistically significant differences were found among the follow-up days (Figure 1).

No statistically significant correlation was found between periostin, HIF-1 α and PLA2 biomarkers and the number of hospitalisations, mechanical ventilation and intensive care unit days. There was a weak correlation between the number of days of mechanical ventilation and WBC and ferritin levels ($r=0.357$, $p=0.045$; $r=0.417$, $p=0.034$, respectively) and a moderate correlation between procalcitonin ($r=0.562$, $p=0.008$). A weak correlation was observed between the number of intensive care unit days and procalcitonin levels ($r=0.456$, $p=0.038$) (Table 3).

When biomarker levels were compared according to prognosis, a statistically significant difference was observed only in ferritin levels between the died and discharged patients ($p=0.037$) (Table 4).

Table 1. Comparison of periostin, HIF-1 α and PLA2 biomarkers between groups

Tablo 1. Gruplar arası periostin, HIF-1 α ve PLA2 biyobelirteçlerinin karşılaştırılması

Parameter	Control group N= 30	Patient group N= 32	p value
Periostin (pg/mL)	12.01 (8.18-15.65)	8.95 (1.28-13.20)	0.023^a
HIF-1 α (pg/mL)	1.15 \pm 0.77	1.31 \pm 0.76	0.408 ^b
PLA2 (pg/mL)	11.90 \pm 9.33	16.81 \pm 17.76	0.183 ^b

^a: Mann Whitney U test, ^b: Independent samples T test

Table 2. Changes in periostin, HIF-1 α and PLA2 biomarkers over time in patient group

Tablo 2. Hasta grubunda periostin, HIF-1 α ve PLA2 biyobelirteçlerinin zaman içindeki değişimi

Parameter	Patient group						
	First day N= 32	3rd day N= 17	7th day N= 9	Friedman test p value	First- 3rd day p value	First- 7th day p value	3rd-7th day p value
Periostin (pg/mL)	10.46 \pm 12.12	23.59 \pm 22.55	15.74 (12.19-57.51)	0.032	0.018^a	0.021^b	0.110 ^b
HIF-1 α (pg/mL)	1.31 \pm 0.76	1.29 (1.04-2.68)	1.42 (1.02-4.08)	0.459	0.044^b	0.515 ^b	0.108 ^b
PLA2 (pg/mL)	16.81 \pm 17.76	3.96 (1.42-21.41)	24.93 \pm 36.56	0.169	0.831 ^b	0.392 ^a	0.139 ^b

^a: Paired samples T test, ^b: Wilcoxon signed ranks test

Table 3. Relationship between biomarkers and number of hospitalisations, mechanical ventilation and intensive care days in patient group

Tablo 3. Hasta grubunda biyobelirteçler ile hastaneye yatış sayısı, mekanik ventilasyon ve yoğun bakım günü sayısı arasındaki ilişki

Parameter	Number of hospitalisation days		Number of mechanical ventilation days		Number of intensive care days	
	r	p	r	p	r	p
Periostin (First day)	-0.177	0.333	-0.283	0.117	-0.333	0.062
HIF-1 α (First day)	0.063	0.733	-0.062	0.735	0.064	0.728
PLA2 (First day)	-0.295	0.101	-0.244	0.178	-0.264	0.144
Periostin (3rd day)	-0.262	0.311	0.005	0.984	0.130	0.619
HIF-1 α (3rd day)	-0.424	0.090	0.063	0.809	-0.006	0.981
PLA2 (3rd day)	-0.203	0.434	0.143	0.584	0.043	0.870
Periostin (7th day)	-0.450	0.224	-0.252	0.512	-0.267	0.488
HIF-1 α (7th day)	-0.467	0.205	-0.383	0.309	-0.333	0.381
PLA2 (7th day)	-0.433	0.244	0.157	0.687	-0.217	0.576
WBC (First day)	0.041	0.822	0.357*	0.045	0.231	0.204
CRP (First day)	0.155	0.396	0.322	0.072	0.090	0.625
D-Dimer (First day)	0.052	0.780	0.157	0.399	0.085	0.650
Ferritin (First day)	0.000	1.000	0.417*	0.034	0.355	0.075
Fibrinogen (First day)	0.358	0.073	0.065	0.753	0.207	0.309
Procalcitonin (First day)	0.097	0.675	0.562**	0.008	0.456*	0.038

Table 4. Comparison of biomarker levels according to prognosis**Tablo 4.** Prognozaya göre biyobelirteç düzeylerinin karşılaştırılması

Parameter	Discharged patients N= 16	Died patients N= 16	p value
Periostin (First day)	13.54 ± 15.28	7.38 ± 7.08	0.154 ^a
HIF-1α (First day)	1.40 ± 1.02	1.21 ± 0.37	0.476 ^a
PLA2 (First day)	22.36 ± 23.03	11.25 ± 7.44	0.083 ^a
Periostin (3rd day)	22.70 ± 28.32	24.21 ± 19.18	0.897 ^a
HIF-1α (3rd day)	1.21 (0.92-1.32)	1.76 (1.05-3.54)	0.329 ^b
PLA2 (3rd day)	1.76 (1.44-6.64)	5.48 (1.40-27.44)	0.525 ^a
Periostin (7th day)	18.71 (14.73-75.43)	14.93 (8.06-78.54)	0.462 ^b
HIF-1α (7th day)	1.48 (1.25-5.35)	1.17 (0.73-5.22)	0.327 ^b
PLA2 (7th day)	23.99 ± 35.74	25.68 ± 41.39	0.950 ^a
WBC (First day)	8.36 ± 4.37	12.66 ± 7.25	0.051 ^a
CRP (First day)	121.59 ± 122.97	156.40 ± 96.13	0.380 ^a
D-Dimer (First day)	2757 ± 2891	6069 ± 9689	0.221 ^a
Ferritin (First day)	317 ± 254	1289 ± 1613	0.037^a
Fibrinogen (First day)	492 ± 163	458 ± 157	0.591 ^a
Procalcitonin (First day)	0.19 ± 0.10	4.48 ± 7.81	0.061 ^a

^a: Independent samples T test, ^b: Mann Whitney U test

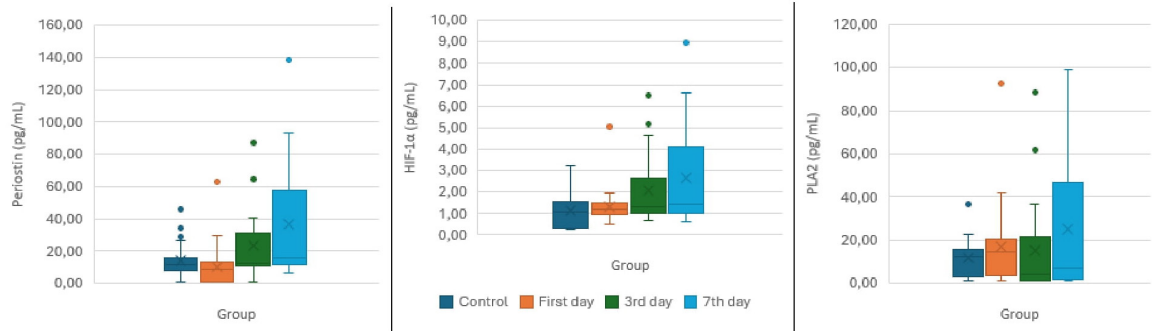


Figure 1. Comparison of periostin, HIF-1α and PLA2 levels
Şekil 1. Periostin, HIF-1α ve PLA2 düzeylerinin karşılaştırılması

DISCUSSION

In our study, periostin, HIF-1α and PLA2 serum levels were evaluated in COVID-19 patients, and a significant difference was observed only in periostin levels between the patient and control groups, and a significant increase was found on days 3 and 7 compared to the first hospitalisation day. A slight increase in HIF-1α was noted on day 3 compared to day 1, and on day 7, a 2- and 1.5-fold increase in HIF-1α and PLA2 parameters, respectively, was observed

compared to day 1. However, no consistent statistically significant difference was found between follow-up days.

Periostin is a protein that plays a role in inflammation, fibrosis and tissue repair. It is a part of the extracellular matrix and is reported to be observed at high levels in tissues undergoing fibrotic changes (3). In our study, a statistically significant increase in periostin levels of COVID-19 patients was observed 2-fold on day 3 and approximately 4-fold on day 7 compared to the first

hospitalisation day. The increase in periostin levels in COVID-19 patients supports the role of this parameter in the inflammation process. Cabalak et al. reported that periostin levels were significantly higher in both mild/moderate and severe COVID-19 patients compared to the control group and could be used as a biomarker (4). In the study by Ali et al. investigating the relationship between disease severity and periostin levels in COVID patients, it was found that high serum periostin levels were associated with disease severity and post-COVID lung complications (11). In the study by Tuna et al., periostin levels were found to be significantly higher in COVID-19 patients compared to the control group, and it was suggested that elevated periostin levels observed in the early period may be useful in predicting the development of macrophage activation syndrome (12). In addition to COVID-19, periostin has been shown to play important roles in various non-neoplastic diseases. Yang et al. reviewed the multiple roles of periostin in conditions such as brain injury, allergic diseases, dental diseases, cardiovascular diseases, lung diseases, liver diseases, chronic kidney diseases, inflammatory bowel disease, and osteoarthritis (13). These findings suggest that periostin levels may be influenced by comorbidities, and therefore, caution should be exercised when interpreting its potential role as a biomarker in COVID-19 patients.

It has been reported that HIF-1 α and transcriptionally regulated genes are expressed in the lung cells of COVID-19 patients and may be an important marker of COVID-19-related hypoxia and lung injury (7). In COVID-19 with hypoxia and HIF-1 activity, it has been suggested that suppression of HIF-1 transcription or inhibition of its activity may be effective in reducing inflammation caused by viral infection (6). In a study conducted by Devenci et al., serum HIF-1 α levels were found to be higher in the COVID-19 patient group compared to the healthy control group, and levels on the day of hospitalization were

higher than those after hospitalization. It has been suggested that low HIF-1 α levels in COVID-19 patients, especially in the first week of illness, may contribute to increased clinical severity (14). HIF-1 α upregulation observed in a study investigating HIF-1 α expression in COVID patients suggests that HIF-1 α can be used as a target in molecular therapy as a potential marker for COVID-19 severity (7).

In the study by Kuypers et al., it was suggested that PLA2 level was associated with COVID-19 severity in children and played a role in disease pathogenesis. It has been reported that PLA2 may be a useful biomarker to classify risk and guide patient management in children with acute COVID-19 (15). In the study by Snider et al., it was reported that PLA2 levels were significantly higher in the plasma of COVID-19 patients and correlated with the severity of the disease (10). In Urazov et al.'s study, PLA2 levels increased statistically significantly in patients who died and were transferred to the intensive care unit (as the severity of COVID-19 infection increased), and it was suggested that PLA2 could be considered as an early marker of worsening of COVID-19 infection (9). The results from these studies support the possible benefit of PLA2 inhibitors in the treatment of COVID-19.

An important negative finding of our study is that no statistically significant differences were observed in HIF-1 α and PLA2 levels, either between COVID-19 patients and healthy controls or across the follow-up days. Although a trend toward increased values was noted on day 7, these changes did not reach statistical significance. Reporting such negative results is scientifically valuable, as it indicates that, within the limitations of our cohort, HIF-1 α and PLA2 may not serve as reliable biomarkers for monitoring disease severity.

In addition, we observed a moderate correlation between procalcitonin levels and the number of mechanical ventilation days. This finding suggests that elevated

procalcitonin may reflect the severity of systemic inflammation and the presence of bacterial co-infections, which could contribute to prolonged respiratory support needs in COVID-19 patients. Previous studies have similarly reported that higher procalcitonin levels are associated with worse outcomes. For example, Lippi and Plebani showed that elevated procalcitonin is linked to increased risk of severe disease in COVID-19 patients (16). Hu et al. demonstrated that procalcitonin was an independent predictor of disease severity and prognosis of COVID-19 (17). Likewise, elevated procalcitonin levels have been reported to be associated with higher mortality in hospitalized COVID-19 patients (18). Our results are consistent with these findings and highlight the potential of procalcitonin as a prognostic biomarker, not only for identifying severe disease but also for predicting the duration of mechanical ventilation in critically ill patients.

To our knowledge, our study is one of the first to include the simultaneous analysis of periostin, HIF-1 α , and PLA2 in COVID-19 patients, providing preliminary data on their potential roles. We think that our study, which provides comprehensive data by measuring these parameters together in COVID-19 patients, is important in terms of public health and public interest in the follow-up and evaluation of the severity of COVID-19 infection.

Limitations of our study include the relatively small number of patients and the further reduction in sample size at day 3 and day 7 follow-up due to discharge or death. This significantly reduces the statistical power of the analysis and may have caused the observed differences in HIF-1 α and PLA2 levels to be statistically insignificant. Furthermore, the short follow-up period limits the generalizability of our findings. Therefore, our results should be interpreted

with caution and validated in larger, prospective studies with longer follow-up periods. Another limitation is that routine laboratory tests, including WBC, CRP, D-dimer, fibrinogen, ferritin, and procalcitonin, were systematically requested from all patients only on admission (the first day). Because these tests were performed selectively on days 3 and 7, depending on the patient's clinical condition and treatment needs, statistical comparisons could not be made due to missing data. Another limitation of our study is the relatively high mean age of the patient population (70 ± 15 years). Therefore, the generalizability of our findings to younger COVID-19 patients is limited, and further studies involving broader age groups are warranted.

In conclusion, periostin levels were significantly increased in COVID-19 patients, suggesting that periostin may play a role in the inflammatory response associated with the disease. No significant changes were observed in HIF-1 α and PLA2 levels, which may be related to the limited sample size and clinical heterogeneity of the study population. These findings provide preliminary insight into the potential involvement of periostin in COVID-19 pathophysiology.

Conflicts of interest: The author declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Research funding: Our study was supported by Ege University Scientific Research Projects Coordinatorship with the budget transferred to the project code TGA-2021-23420.

Acknowledgements: We would like to thank Ege University Scientific Research Unit for providing budget support for our study.

REFERENCES

1. Pinney SP, Giustino G, Halperin JL, Mechanick JI, Neibart E, Olin JW, et al. Coronavirus historical perspective, disease mechanisms, and clinical outcomes: JACC focus seminar. *J Am Coll Cardiol*. 2020;76(17):1999-2010. doi:10.1016/j.jacc.2020.08.058.
2. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0.
3. Stanković S, Mitić B, Jovanović A, Stoiljković V, Stefanović N, Nikolić VN. Evaluation of serum periostin and PIIINP as biomarkers of renal fibrosis and function decline in renal transplant patients. *FU Med Biol*. 2024. doi:10.22190/FUMB240710006S.
4. Cabalak M, Doğan S, Bal T, Dikmen N. Serum periostin levels in COVID-19: Is it useful as a new biomarker? *Int J Clin Pract*. 2021;75(11):e14728. doi:10.1111/ijcp.14728.
5. Izuhara K, Conway SJ, Moore BB, Matsumoto H, Holweg CT, Matthews JG, et al. Roles of periostin in respiratory disorders. *Am J Respir Crit Care Med*. 2016;193(9):949-956. doi:10.1164/rccm.201510-2032PP.
6. Jahani M, Dokaneheifard S, Mansouri K. Hypoxia: a key feature of COVID-19 launching activation of HIF-1 and cytokine storm. *J Inflamm (Lond)*. 2020;17:33. doi:10.1186/s12950-020-00263-3.
7. Taniguchi-Ponciano K, Vadillo E, Mayani H, Gonzalez-Bonilla CR, Torres J, Majluf A, et al. Increased expression of hypoxia-inducible factor 1 α mRNA and its related genes in myeloid blood cells from critically ill COVID-19 patients. *Ann Med*. 2021;53(1):197-207. doi:10.1080/07853890.2020.1858234.
8. Letsiou E, Htwe YM, Dudek SM. Secretory phospholipase A2 enzymes in acute lung injury. *Cell Biochem Biophys*. 2021;79(3):609-617. doi:10.1007/s12013-021-01003-x.
9. Urazov S, Chemov A, Popov O, Klenkova N, Sushentseva N, Polkovnikova I, et al. Secretory phospholipase A2 and interleukin-6 levels as predictive markers of the severity and outcome of patients with COVID-19 infections. *Int J Mol Sci*. 2023;24(6):5540. doi:10.3390/ijms24065540.
10. Snider JM, You JK, Wang X, Snider AJ, Hallmark B, Seeds MC, et al. Group IIA secreted phospholipase A2 plays a central role in the pathobiology of COVID-19. *J Clin Invest*. 2021;131(19):e149236. doi:10.1172/JCI149236.
11. Ali MH, Abdullah SF. The correlation of serum periostin level with disease severity in patients with COVID-19. *KCMJ*. 2024;20(2):101-105. doi:10.47723/pvshyd77.
12. Tuna ME, Kerget B, Aksakal A, Eğılmez E, Araz Ö, Uçar EY, et al. Investigation on the relationship between serum periostin, MMP-7, TGF- β , and IL-18 levels and the clinical course and prognosis of COVID-19. *Eur Rev Med Pharmacol Sci*. 2024;28(7):2960-2968. doi:10.26355/eurrev_202404_35927.
13. Yang L, Guo T, Chen Y, Bian K. The multiple roles of periostin in non-neoplastic disease. *Cells*. 2022;12(1):50. doi:10.3390/cells12010050.
14. Deveci K, Özmen ZC, Şay Coşkun U, Çam S. Can hypoxia-inducible factor 1 α be used as a biomarker to evaluate disease severity and prognosis in COVID-19 patients? *J Contemp Med*. 2021;11(4):462-468. doi:10.16899/jcm.857806.
15. Kuypers FA, Rostad CA, Anderson EJ, Chahroudi A, Jaggi P, Wrammert J, et al. Secretory phospholipase A2 in SARS-CoV-2 infection and multisystem inflammatory syndrome in children (MIS-C). *Exp Biol Med (Maywood)*. 2021;246(23):2543-2552. doi:10.1177/15353702211028560.
16. Lippi G, Plebani M. Procalcitonin in patients with severe coronavirus disease 2019 (COVID-19): a meta-analysis. *Clin Chim Acta*. 2020;505:190-191. doi:10.1016/j.cca.2020.03.004.
17. Hu R, Han C, Pei S, Yin M, Chen X. Procalcitonin levels in COVID-19 patients. *Int J Antimicrob Agents*. 2020;56(2):106051. doi:10.1016/j.ijantimicag.2020.106051.
18. Liu ZM, Li JP, Wang SP, Chen DY, Zeng W, Chen SC, et al. Association of procalcitonin levels with the progression and prognosis of hospitalized patients with COVID-19. *Int J Med Sci*. 2020;17(16):2468-2476.