Serum periostin levels in COVID-19: is it useful as a new biomarker?

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Abstract

Objectives: Severe disease characterized by interstitial pneumonia may develop in some cases of coronavirus disease (COVID-19). Periostin has been associated with many respiratory diseases. In this study, we aimed to investigate whether periostin could be a useful new biomarker in the follow-up and severity assessment of the disease in patients with COVID-19 pneumonia. Methods: In the study, 32 patients followed up during May–July 2020 due to COVID-19 and 24 healthy controls were included. The patients were divided into two groups, namely, mild/moderate and severe, according to the severity of the disease. Serum periostin and transforming growth factor beta (TGF-β) levels were tested using an enzyme-linked immunosorbent assay (ELISA) method using commercially available ELISA kits. Results: It was observed that the periostin level was significantly higher in both mild/moderate cases and severe cases compared to the control group at first presentation. However, TGF-β levels at first presentation were similar between the groups. Conclusions: Our study is the first study to investigate periostin levels in patients with COVID-19, and we believe that periostin can be used as a new biomarker. Keywords: COVID-19, Periostin, TGF-β, Pneumonia, New Biomarker Coronaviruses are among the main pathogens that mainly target the human respiratory system. Severe disease characterized by interstitial pneumonia develops in 10-20% of patients. Periostin has recently been shown to be an indicator of disease progression in idiopathic pulmonary fibrosis and asthma. In this study, we aimed to investigate whether periostin could be a useful new biomarker in the follow-up and severity assessment of the disease in patients with COVID-19 pneumonia. This article demonstrated that periostin is a useful new biomarker for disease follow-up and severity in patients with COVID-19 pneumonia. It is also the first study on periostin levels in patients with COVID-19

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Results: It was observed that the periostin level was significantly higher in both mild/moderate cases and severe cases compared to the control group at first presentation. However, TGF-β levels at first presentation were similar between the groups.

Conclusions: Our study is the first study to investigate periostin levels in patients with COVID-19, and we believe that periostin can be used as a new biomarker.

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What is already known about this topic?

Coronaviruses are among the main pathogens that mainly target the human respiratory system. Severe disease characterized by interstitial pneumonia develops in 10-20% of patients. Periostin has recently been shown to be an indicator of disease progression in idiopathic pulmonary fibrosis and asthma. In this study, we aimed to investigate whether periostin could be a useful new biomarker in the follow-up and severity assessment of the disease in patients with COVID-19 pneumonia.

What does this article add?

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Introduction

Coronavirus disease (COVID-19) first emerged in Wuhan, China, in December 2019, and it was found to be caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel coronavirus. Genetic sequencing of the virus has shown that it is a betacoronavirus that is closely linked to the severe acute respiratory syndrome (SARS) virus (1). Coronaviruses are among the main pathogens that primarily target the human respiratory system. SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) causes fatal infections. As a novel betacoronavirus, SARS-CoV-2 is more contagious. Although it has a lower mortality rate than SARS-CoV and MERS-CoV do, the severity of disease is more variable with SARS-CoV-2 (2).

Severe disease characterized by interstitial pneumonia develops in 10%–20% of patients (especially in elderly individuals and those with underlying comorbidities). Particularly, macrophage activation syndrome characterized by hyperferritinemia, hepatic dysfunction, and diffuse intravascular coagulation and rapidly developing acute respiratory distress syndrome (ARDS) characterized by high levels of acute phase reactants or septic shock may occur (3,4).

Periostin has been associated with many respiratory disorders. It has been recently shown to be an indicator of disease progression in idiopathic pulmonary fibrosis (5-7) and asthma (8). It is a matricellular protein. Matricellular proteins are nonstructural, extracellular matrix (ECM) proteins that are highly expressed at sites of injury or inflammation. They interact with other ECM proteins to mediate tissue remodeling, and they bind to growth factors and cytokines to modulate their activities (9). Expression of *POSTN* , the gene encoding human periostin, can be induced by the cytokines transforming growth factor beta (TGF-β), interleukin (IL)-4, and IL-13 (10,11). Periostin interacts with multiple molecules involved in signal cascades to modulate the expression of various genes such as those encoding collagen, chemokines, and TGF-β (12,13).

In this study, we aimed to investigate whether periostin could be a useful new biomarker in the follow-up and severity assessment of the disease in patients with COVID-19 pneumonia. In addition, this is the first study on periostin levels in patients with COVID-19.

MATERIALS AND METHOD

Patients

Our study was conducted in the Infectious Diseases and Chest Diseases Clinic of our hospital between May 2020 and July 2020. For this study, three groups; namely, the mild/moderate COVID-19 group, severe COVID-19 group, and control group, were formed. Patients with symptoms of fever, muscle/joint pain, cough, and sore throat with a respiratory rate of <30/minute and a partial pressure of oxygen (SpO2) level on room air of >90% were regarded as mild/moderate cases (1). In contrast, cases with tachypnea (respiratory rate > 30/min), with an SpO2 level < 90%, with bilateral diffuse pneumonia on chest X-ray

or tomography, or those that developed acute organ dysfunction, ARDS and/or sepsis, and/or septic shock were considered as severe cases. From the 32 patients who were hospitalized with a clinical presentation of COVID-19 and a positive real-time reverse transcription polymerase chain reaction test, a 5-cc sample of blood was collected on their first day of hospitalization and at the first month of their follow-up. The blood samples were centrifuged at 4000 rpm for 10 minutes to obtain the serum and maintained at -80°C until analysis.

Biochemical analysis

Serum levels of creatine kinase (CK) and lactate dehydrogenase (LDH) were measured on Siemens Advia 1800 Chemisty System (Siemens Healthcare Diagnostics, Newark, Germany) while ferritin levels were performed via Siemens Advia Centaur XP Immunassay System (Siemens Healthcare Diagnostics, Newark, Germany). CRP was determined by Siemens Dade Behring BN II System (Siemens Healthcare Diagnostics, Marburg, Germany) via nepholometric method. Leukocyte, neutrophils, lymphocytes, eosinophils, and platelet counts in participating subjects were determined by Mindray BC 6000 Hematology System (MINDRAY Medical International Co., Shenzhen, China). D-dimer levels were studied on VIDAS D-Dimer Exclusion II (BioMerieux, France) while fibrinogen was measured on STA Compact Max (Stago, USA). Procalcitonin was measured by Architecht i2000 SR Immunassay Analyzer (Abbott, USA).

ELISA Measurements

ΤΓΦ-β Μεασυρεμεντ

Serum TGF β1 levels were assayed by ELISA method (Thermo Scientifc Multiskan GO, Finland) using commercially available TGF β1 ELISA Kits (Elabscience catalog no:E-EL-H0110). The assay ranges for the TGF β1 kit were 31.25-2000pg/mL, sensitivity 18.75 pg/mL and the intra- and interassay coefficients of variance (CV%) were 6.7% and 5.1%, respectively.

Periostin Measerement

Serum periostin levels were assayed by ELISA method (Thermo Scientifc Multiskan GO, Finland) using commercially available periostin ELISA Kits (Elabscience catalog no: E-EL-H2452). The assay ranges for the periostin kit were 0.16-10 ng/ml, sensitivity 0.1 ng/mL and the intra- and interassay coefficients of variance (CV%) were 5.8% and 6.1%, respectively

Statistical analysis

All of the statistical analyses were performed using the SPSS software, version 23.0 for Mac (SPSS Inc, Chicago IL, USA). The Shapiro Wilk test was used to evaluate the normality of distribution of continuous variables. Categorical variables were presented as frequencies and percentages and compared with Chi-square test or Fisher's exact test. Normally distributed continuous variables were presented as mean ±standard deviation (SD) and compared by the One-Way ANOVA test between the groups. The paired sample t-test was used for the comparison of normally distributed variables at the different time points in each group. The Spearmen rank-order correlation test was used to determine correlations between different variables. A p value of <0.05 was considered statistically significant.

This single-centered, prospective study was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Prospective Ethics Committee of X X University Faculty of Medicine (reference number: 04.06.2020-65)

RESULTS

The study comprised 56 participants, divided into three groups: mild/moderate (n = 24), severe (n = 8), and control (n = 24). The median age of the participants was 49.75 ± 14.26 years, and 66.1% (n = 37) were males. Table 1 shows the demographic data of the groups.

It was observed that the periostin level was significantly higher in both mild/moderate cases and severe cases compared to the control group at first presentation (p = 0.027 and p = 0.002, respectively) (Figure 1).

However, TGF-β levels at first presentation were similar between the groups (p = 0.302) (Figure 2).

In the severe patient group, a significant increase was observed in serum periostin levels one month from symptom onset compared to the time of symptom onset (p = 0.020). In contrast, although serum periostin level increased slightly in the mild/moderate patient group, this increase was not found to be statistically significant (p = 0,138).

Another result of our study was that there was a weak but significant negative relationship between the basal lymphocyte and periostin levels and a weak, but significant positive relationship between the basal lymphocyte and TGF-β levels (r_s = -0. 410, p = 0.020 and r_s = 0.369, p = 0.038, respectively) (Figure 3).

DISCUSSION

In our study, high periostin levels were detected in both mild/moderate and severe cases after the first month of their follow-up. The periostin level was higher especially in severe cases than in mild cases, and this was statistically significant. We believe that the periostin level can be used in the follow-up of disease severity.

In the case of inflammation and/or stress, the release of cytokines such as IL-4, IL-13, and TGF-β increases from inflammatory cells, and they, in turn, cause the release of periostin from the airway epithelial cells (9-11). In our study, although the periostin level was found to be high, no significant change was found in TGF-β level. This may be because the regulation of periostin is affected not only by the expression of TGF-β but also by IL-4 and IL-13 in patients with COVID-19. We believe that further studies are needed to understand the molecular mechanisms behind the host response. In addition, we believe that the high level of periostin in the first month of the disease despite the clinical improvement may be a guide for complications that may develop in the future, which can be assessed in a longer follow-up period.

In another study, the proinflammatory factor tenascin C and extracellular factor mucin-1 in bronchoalveolar lavage and serum samples were found to be higher in patients with COVID-19 compared to healthy controls. It has been suggested that these molecules can be used as potential biomarker candidates or therapeutic targets (14). Based on the results of our study, we believe that periostin can be used to assess disease severity in patients with COVID-19; however, we recommend conducting further studies with a longer duration and a larger number of cases.

In our study, ferritin level was found to be significantly higher in severe cases. D-dimer, LDH and CRP levels were also found to be higher. In another study, lactate dehydrogenase, ferritin, D-dimer, and IL-6 levels were found to be associated with mortality (15). In yet another study, especially the levels of D-dimer and fibrin degradation products were found to be higher in patients with COVID-19 who died (16). The reason for finding higher levels only for ferritin in our study can be explained by the low number of cases.

In a study analyzing severe cases, lymphopenia was detected in 85% of the cases with COVID-19 pneumonia (4). Older patients with lower lymphocyte and platelet counts were found to have a higher risk of disease and an increased duration of hospital stay (17). A notable result of our study was that there was a weak but significant negative relationship between basal levels of lymphocytes and periostin and a weak, but positive relationship between the basal levels of lymphocytes and TGF-β. In another study, it was shown that lymphopenia in CD8 + T cells was an independent predictor for COVID-19 severity and treatment effectiveness (18). In yet another study, lymphocyte percentage was proposed as a predictive biomarker for disease severity or recovery (19). In the light of these results, lymphopenia associated with COVID-19 has been identified as a key pathological biomarker and a criterion that marks the severity of the disease. Our data also support this finding.

Limitations: The limitations of our study included the small number of cases and short duration of the study. Another limitation was that only TGF-β level was investigated, although the level of periostin is affected by many cytokines.

CONCLUSION

Our study is the first study investigating periostin levels in patients with COVID-19, and it was found to be significantly higher in patients with COVID-19. Periostin can be used as a new biomarker; however, we believe that further studies with larger numbers of cases and longer follow-up periods are needed for its use in the follow-up and severity prediction of the disease.

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Table 1. Baseline characteristics of the patients with and without COVID-19 infection.

	Control group (n=24)	**Mild/moderate group (n=24)**	**Severe group (n=8)**	P **value**
Age, years	44.20 ± 5.23	50.70 ± 16.05	63.50 ± 18.37	**0.022**
Gender, male	13.0 (54.2)	18.0 (75.0)	6.0 (75.0)	0.265
TGF-β, ng/mL	5.40 ± 0.17	5.54 ± 0.75	6.32 ± 1.39	0.302
Periostin, ng/ml	4.00 ± 1.99	5.92 ± 2.59	7.55 ± 2.66	**0.002**
C-reactive protein, mg/L	3.16 ± 0.20	36.04 ± 11.67	48.48 ± 41.77	**0.006**
Procalcitonin, ng/ml	0.08 ± 0.11	0.09 ± 0.17	0.24 ± 0.06	**<0.001**
Fibrinogen, mg/mL	225.66 ± 30.83	433.33 ± 211.35	416.37 ± 164.03	**<0.001**
D-dimer, μg/mL	108.75 ± 17.87	731.20 ± 513.94	1189.25 ± 1385.07	**<0.001**
Ferritin, ng/mL	33.55 ± 22.20	258.91 ± 152.63	557.12 ± 380.14	**<0.001**
Lactate dehydrogenase (LDH), U/L	138.62 ± 19.76	336.00 ± 157.46	325.70 ± 142.25	**<0.001**
Creatine kinase (CK), U/L	70.91 ± 19.63	97.58 ± 84.82	128.25 ± 77.47	0.078
Eosinophil count, x10^3/mm^3	0.22 ± 0.24	0.06 ± 0.08	0.04 ± 0.05	**0.004**
Lymphocyte count, x10^3/mm^3	2.17 ± 0.47	1.66 ± 0.71	0.87 ± 0.46	**<0.001**

TGF- β : transforming growth factor beta. Continuous data were expressed as mean ± standard deviation (SD), while categorical data were expressed as count (percentage).

Figure legends

Figure 1. Comparison of the serum periostin levels in controls and COVID-19 cases at different time points

Figure 2. Comparison of the serum TGF-β levels in controls and COVID-19 cases at different time points.

Figure 3. Correlation coefficients and P values of the Spearman rank correlations between different variables. (A) Periostin and lymphocyte count, (B) TGF-β and lymphocyte count. TGF-β : transforming growth factor-beta

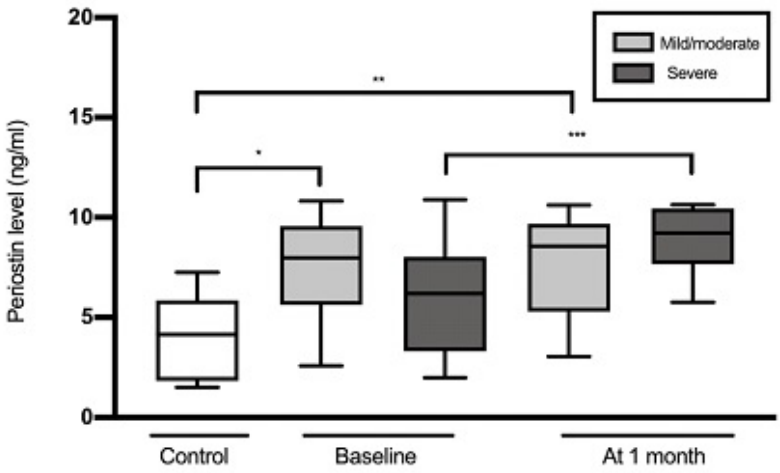


Figure 1. Comparison of the serum periostin levels in controls and COVID-19 cases at different time points. *p=0.027, **p= 0.002,***p=0.020.

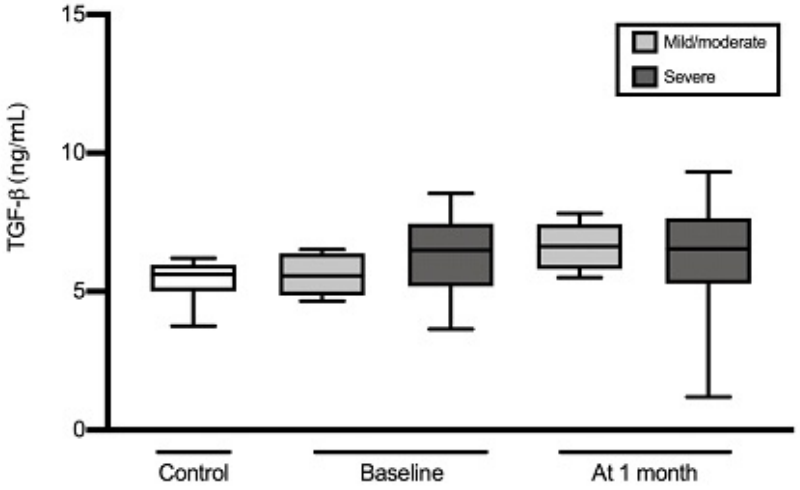
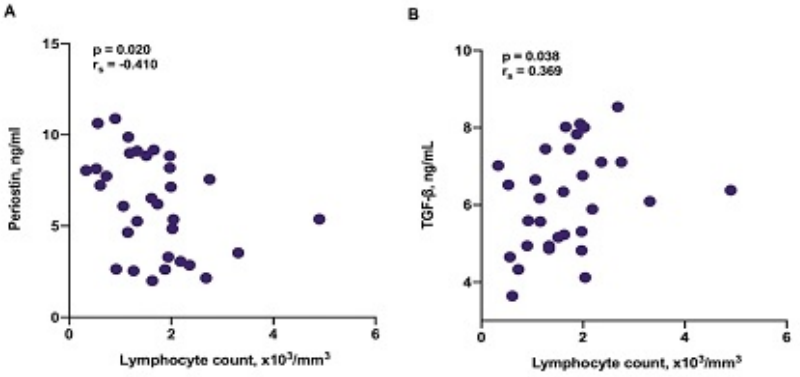


Figure 2. Comparison of the serum TGF-β levels in controls and COVID-19 cases at different time points.



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