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

Mehmet Cabalak[1] | Serdar Doğan[2] | Tayibe Bal[1] | Nursel Dikmen[3]

[1]Department of Infection Disease and Clinical Microbiology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey

[2]Department of Biochemistry, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey

[3]Department of Chest Disease, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey

Correspondence
Çabalak Mehmet, Department of Infection Disease and Clinical Microbiology, Faculty of Medicine, Hatay Mustafa Kemal University, Hatay, Turkey.
Email: mehcab@yahoo.com

Abstract

Objectives: Severe disease characterised 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 to July 2020 because of 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 with the control group at first presentation. However, TGF-β levels at first presentation were similar between the groups.

Conclusions: The current manuscript may be the first one performing periostin ELISA on COVID serum, and we believe that periostin can be used as a new biomarker.

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

Periostin (PN) and TGF-β are paralogs that contain a single emilin and four fasciclin-1 modules and are secreted from cells. PN receives attention because of its up-regulation in cancer and degenerative and allergic diseases. TGF-β is highly enriched in cornea and best known for harbouring mutations in humans associated with corneal dystrophies.[5] Periostin has been associated with many respiratory disorders. It has been recently shown to be an indicator of disease progression in idiopathic pulmonary fibrosis.[6-8] 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 remodelling, and they bind to growth factors and cytokines to modulate their activities.[9] Expression of *POSTN*, the gene encoding human

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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, the current manuscript may be the first one performing periostin ELISA on COVID serum.

What's known

Coronaviruses are among the main pathogens that mainly target the human respiratory system. Severe disease characterised 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. 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's new

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 one performing periostin ELISA on COVID serum in patients with COVID-19.

2 | MATERIALS AND METHOD

2.1 | 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 hospitalised 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 hospitalisation and at the first month of their

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		
				Overall	Control vs mild/moderate	Control vs severe
Age, y	44.20 ± 5.23	50.70 ± 16.05	63.50 ± 18.37	**.022**	.089	**.001**
Gender, male	13.0 (54.2)	18.0 (75.0)	6.0 (75.0)	.265	.131	.050
TGF-β, ng/mL	5.40 ± 0.17	5.54 ± 0.75	6.32 ± 1.39	.302	.139	.588
Periostin, ng/mL	4.00 ± 1.99	5.92 ± 2.59	7.55 ± 2.66	**.002**	**.027**	**.002**
C-reactive protein, mg/L	3.16 ± 0.20	36.04 ± 11.67	48.48 ± 41.77	**.006**	**.007**	**.008**
Procalcitonin, ng/mL	0.08 ± 0.11	0.09 ± 0.17	0.24 ± 0.06	**<.001**	**<.001**	**.004**
Fibrinogen, mg/mL	225.66 ± 30.83	433.33 ± 211.35	416.37 ± 164.03	**<.001**	**<.001**	**.003**
D-dimer, μ g/mL	108.75 ± 17.87	731.20 ± 513.94	1189.25 ± 1385.07	**<.001**	**<.001**	**.001**
Ferritin, ng/mL	33.55 ± 22.20	258.91 ± 152.63	557.12 ± 380.14	**<.001**	**<.001**	**<.001**
Lactate dehydrogenase (LDH), U/L	138.62 ± 19.76	336.00 ± 157.46	325.70 ± 142.25	**<.001**	<.001	<.001
Creatine kinase (CK), U/L	70.91 ± 19.63	97.58 ± 84.82	128.25 ± 77.47	.078	.154	.032
Eosinophil count, $\times 10^3/mm^3$	0.22 ± 0.24	0.06 ± 0.08	0.04 ± 0.05	**.004**	**.003**	**.013**
Lymphocyte count, $\times 10^3/mm^3$	2.17 ± 0.47	1.66 ± 0.71	0.87 ± 0.46	**<.001**	.047	.012

Note: Continuous data were expressed as mean ± standard deviation (SD), while categorical data were expressed as count (percentage). *P* values in bold indicate values that are significant at $P < .05$.

Abbreviation: TGF-β, transforming growth factor beta.

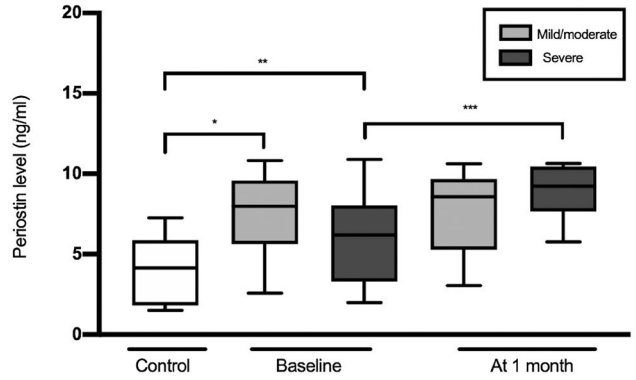

FIGURE 1 Comparison of the serum periostin levels in controls and COVID-19 cases at different time points. A value of $P < .05$ values were considered as significant. *$P = .027$, **$P = .002$, ***$P = .020$)

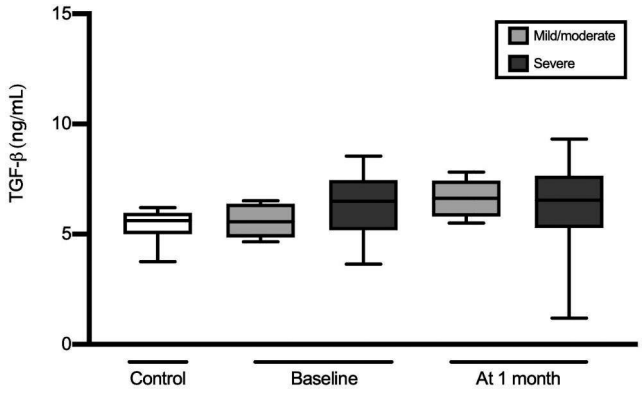

FIGURE 2 Comparison of the serum TGF-β levels in controls and COVID-19 cases at different time points

follow-up. In our study, 24 age- and gender-matched healthy individuals without any acute/choronic infectious, chronic diseases such as coronary heart disease, chronic pulmonary disease, diabetes mellitus, and chronic kidney disease, a rheumatological disease were included as a control group. The blood samples were centrifuged at 1500 ***g*** for 10 min to obtain the serum and maintained at −80°C until analysis.

2.2 | Biochemical analysis

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

2.3 | ELISA measurements

2.3.1 | TGF-β measurement

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

2.3.2 | Periostin measurement

Serum periostin levels were assayed by ELISA method (Thermo Scientific Multiskan GO) using commercially available periostin ELISA Kits (Elabscience catalogue 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.

2.4 | Statistical analysis

All of the statistical analyses were performed using the SPSS software, version 23.0 for Mac (SPSS Inc). 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. Receiver operating characteristic (ROC) curve analyses were performed to assess the diagnostic value of periostin in identifying patients with COVID-19 infection. A $P < .05$ was considered statistically significant.

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

3 | 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 with the control group at first presentation ($P = .027$ and $P = .002$, respectively) (Figure 1). However, TGF-β levels at first presentation were similar between the groups ($P = .302$) (Figure 2).

In the severe patient group, a significant increase was observed in serum periostin levels one month from symptom onset compared with the time of symptom onset ($P = .020$). In contrast, although serum periostin level increased slightly in the mild/moderate patient group, this increase was not found to be statistically significant ($P = .138$).

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 ($r_s = -0.410$, $P = .020$ and $r_s = 0.369$, $P = .038$, respectively) (Figure 3 and Table 2). While there was a weak but significant negative relationship between the basal eosinophil and periostin levels ($r_s = -0.341$, $P = .029$) (Table 2). However, these correlations were not statistically significant when controlled for age ($P = .812$, $P = .470$ and $P = .375$, respectively).

Periostin levels showed a reasonable ability to distinguish COVID 19 patients from controls (AUC: 0.765, 95%CI: 0.638-0.892, $P = .001$). The optimal cut-off value for the periostin to be able to differentiate COVID 19 patients from controls were 7.04 (specificity: 96%, sensitivity: 48%) (Figure 4).

In another result of our study, the amount of eosinophils at the first admission was found to be lower in both the mild/moderate and severe groups compared with the control group.

4 | 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 with 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 analysing 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]

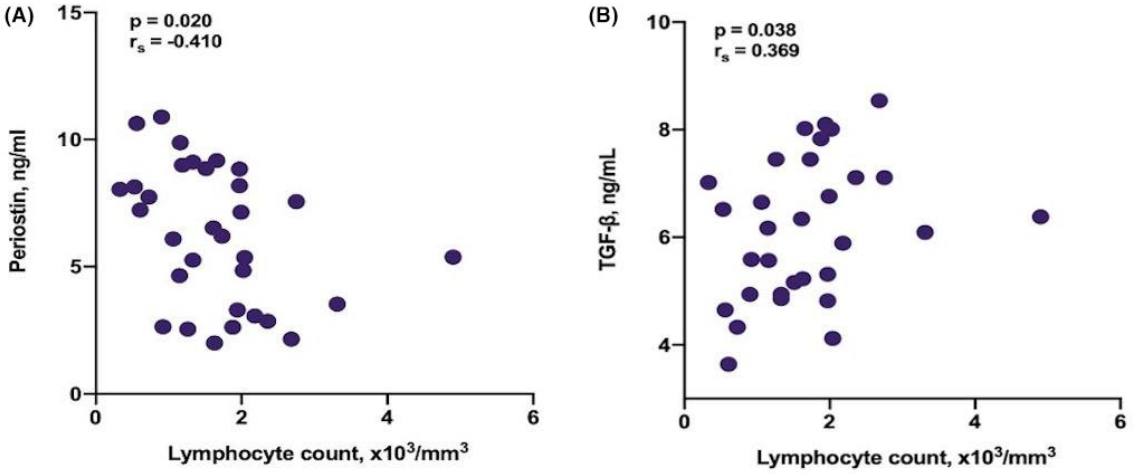

FIGURE 3 Correlation coefficients and *P* values of the Spearman rank correlations between different variables. (A) Periostin and lymphocyte count, (B) TGF-β and lymphocyte count. TGF-β, transforming growth factor-beta

TABLE 2 Correlations of the serum periostin and TGF-β levels with biochemical parameters in patients

Variables	Periostin		TGF-β	
	r_s	*P* value	r_s	*P* value
C-reactive protein, mg/L	0.253	.110	0.033	.809
Procalcitonin, ng/mL	−0.90	.575	−0.131	.341
Fibrinogen, mg/mL	0.087	.589	−0.20	.886
D-dimer, μ g/mL *P* value	0.232	.145	0.012	.930
Ferritin, ng/mL	0.304	.053	0.074	.590
Lactate dehydrogenase (LDH), U/L	0.330	**.035**	0.000	.999
Creatine kinase (CK), U/L	−0.047	.768	−0.134	.330
Eosinophil count, $\times 10^3/mm^3$	−0.341	**.029**	0.050	.719
Lymphocyte count, $\times 10^3/mm^3$	−0.410	**.020**	0.369	**.038**

Note: Statistically significant *P* values less than .05 were indicated as bold.
Abbreviation: TGF-β, transforming growth factor beta.

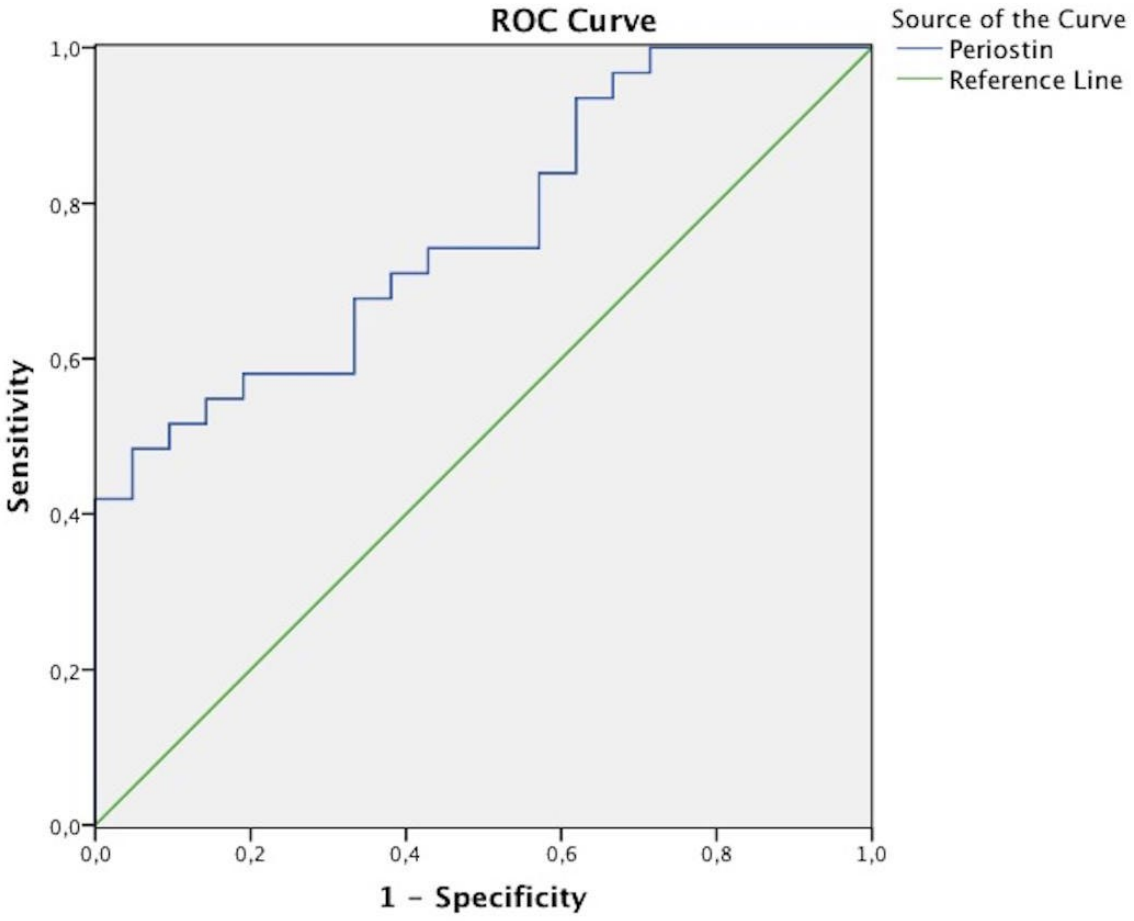

FIGURE 4 ROC curve representing the diagnostic ability of periostin in identifying patients with COVID-19

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.

A detailed investigation of 140 hospitalised patients suggested that eosinopenia with lymphopenia may be both a diagnostic and prognostic indicator for COVID-19.[20] In another study, the combination of eosinopenia with high sensitivity CRP could effectively distinguish patients with suspected COVID-19 from other patients with fever.[21] Eosinopenia indicated poor prognosis also in another study.[22] The amount of eosinophils in our study was found to be lower in both mild/moderate and severe groups compared with the control group. In the light of these studies, it can be thought that eosinopenia can be used both diagnostically and prognostically in patients with COVID-19.

4.1 | 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.

5 | CONCLUSION

Our study is the first one performing periostin ELISA on COVID serum 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.

ORCID

Mehmet Cabalak https://orcid.org/0000-0003-1148-2247
Serdar Doğan https://orcid.org/0000-0001-6854-2197
Tayibe Bal https://orcid.org/0000-0002-5315-122X
Nursel Dikmen https://orcid.org/0000-0002-5923-400X

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