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Investigation on the relationship between serum periostin, MMP-7, TGF-β, and IL-18 levels and the clinical course and prognosis of COVID-19

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Abstract. – OBJECTIVE: Cytokines are involved in the inflammatory/anti-inflammatory balance and have been shown to play an important role in the course of COVID-19. This study aimed to evaluate the relationship of periostin, transforming growth factor-beta (TGF-β), interleukin-18 (IL-18), and matrix metalloproteinase 7 (MMP-7) levels with clinical course and mortality in patients with early COVID-19 pneumonia.

PATIENTS AND METHODS: A total of 150 hospitalized patients were diagnosed with COVID-19 between June and October 2021, and a control group of 30 healthy individuals were included in our study. The COVID-19 patients were divided into those who developed macrophage activation syndrome (MAS) in Group 1 and those who did not in Group 2. Serum periostin, MMP-7, TGF-β, and IL-18 levels were measured from blood samples obtained at admission using Enzyme-Linked Immunosorbent Assay (ELISA).

RESULTS: Periostin, MMP-7, and IL-18 levels were significantly higher in COVID-19 patients compared to the control group ($p<0.001$ for all). Periostin and MMP-7 levels were also significantly higher in Group 1 than in Group 2 ($p<0.001$ for both). Periostin, MMP-7, IL-18, and TGF-β levels were significantly higher in non-surviving patients compared to survivors ($p=0.04$, $p<0.001$, $p<0.001$, and $p<0.001$, respectively). In the receiver operating characteristic (ROC) curve analysis, MMP-7 was found to have high sensitivity (90%) at a predictive value of 2.66 ng/mL.

CONCLUSIONS: It is still not possible to predict which patients with early COVID-19 pneumonia will go on to develop MAS despite receiving standard treatment. The results of our study suggest that elevation of periostin and MMP-7 levels in the early period may predict the development of macrophage activation syndrome.

Key Words:
COVID-19, Macrophage Activation Syndrome, Periostin, TGF-β, IL-18, MMP-7.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the seventh member of the coronavirus (CoV) family that infects humans. As a novel betacoronavirus, it is in the same CoV subgroup as Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV but is distinct from both viruses[1].

COVID-19 symptoms vary between individuals, ranging from asymptomatic infection to severe respiratory failure[2]. Many patients with severe COVID-19 infection rapidly develop dyspnea and hypoxemia, followed by progressive respiratory failure. Severe COVID-19 patients may exhibit systemic hyperinflammatory features described under the umbrella term macrophage activation syndrome (MAS) or cytokine storm syndrome (CSS), also known as secondary hemophagocytic lymphohistiocytosis (sHLH)[3,4]. Controlling the cytokines that cause CSS in the early period is essential in preventing early mortality and later morbidity as a result of lung sequelae.

Although biomarkers for COVID-19 have been the subject of much research since the start of the pandemic, none of these tests are sensitive or specific to COVID-19[5]. Periostin is a matricellular protein, which is a group of nonstructural extracellular matrix (ECM) components typically expressed at sites of inflammation or injury[6]. Periostin mediates various pathophysiological processes of idiopathic pulmonary fibrosis, including myofibroblast differentiation, collagen-1 production, and fiber cross-linking within the lung matrix[7]. Significant pulmonary responses to lung injury include increased expression and activation of enzymes in the matrix metalloprotein-

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ase (MMP) family[8]. Since SARS-CoV-2 infection triggers a characteristic cytokine storm in which molecules such as MMPs are overexpressed, they are believed to have an important role in the pathogenesis of severe COVID-19 infection sequelae[9]. Transforming growth factor-beta (TGF-β) is a multifunctional cytokine that is a key player in tissue repair after injury[10] and is known to inhibit hyperinflammatory responses by exhibiting profibrinogenic, anti-inflammatory, and immunosuppressive activity during and after both sepsis and COVID-19[11]. Interleukin-18 (IL-18) is produced by macrophages in the very early stages of viral infection and induces the production of IL-6 and interferon-gamma (IFN-γ), which are considered critical for optimal viral host defense[12,13]. A study analyzing the immune responses of a series of 113 patients with moderate and severe COVID-19 showed that the increase in IL-18 level was associated with the severity of COVID-19[14]. The inflammatory/anti-inflammatory balance plays an important role in the clinical course and prognosis of COVID-19. In this study, we aimed to determine the relationship between levels of periostin, MMP-7, TGF-β, and IL-18, which are important factors in this balance, and the early clinical course and prognosis of patients hospitalized for COVID-19.

Patients and Methods

Study Design

This prospective study was conducted with patients who were diagnosed with COVID-19 by real-time polymerase chain reaction (RT-PCR) and were admitted to the COVID-19 isolation wards of Atatürk University Faculty of Medicine Hospital and Erzurum Regional Training and Research Hospital and a control group comprising healthy volunteers. The study was approved by the Erzurum Atatürk University Faculty of Medicine Ethics Committee (meeting number: 10, decision No.: 27, date: 17.12.2020). All participants were informed about the purpose of the study and its procedures, and their written consent was obtained before sampling. Funding for the study was provided by the Atatürk University Scientific Research Projects Commission (project No.: 9704). The study was conducted in accordance with the Declaration of Helsinki. A total of 1,496 patients were hospitalized in the COVID-19 wards of both hospitals between June and October 2021. Serum periostin, MMP-7, TGF-β, and IL-18 levels were analyzed from blood samples collected for routine laboratory tests at the time of admission for inpatient treatment for COVID-19. All patients were followed until discharge or death.

Study Groups

A total of 1,496 patients who met the inclusion criteria during the specified study dates were evaluated according to the exclusion criteria in the wards where they were hospitalized after admission. According to these criteria, 418 patients were excluded from the study. Of the other 1,078 patients admitted for inpatient follow-up, 105 patients developed MAS and were treated accordingly. The remaining 973 patients were discharged after completing inpatient follow-up. Microsoft Excel was used to randomly select 75 of the 105 patients who developed MAS (Group 1) and 75 of the 973 patients without MAS (Group 2), and their serum samples were retrieved for analysis (Figure 1). The healthy volunteers comprising the control group were selected from companions of the patients hospitalized in the chest diseases ward of Atatürk University who were compatible in sex and age with the patient sample (n=30).

Exclusion Criteria

Patients meeting the following criteria were excluded from the study: under 18 years of age; presence of acute respiratory distress syndrome at the time of admission; use of steroid-containing drugs before or during hospitalization; being pregnant or breastfeeding; presence of hematological disease; need for intensive care at admission; history of fibrotic lung disease or past COVID-19 with sequelae changes on chest computed tomography; presence of acute cerebrovascular event and acute coronary syndrome with COVID-19 infection.

Measurement of Serum Periostin, MMP-7, TGF-β, and IL-18 Levels

Commercial enzyme-linked immunosorbent assay (ELISA) kits designed for use with serum, plasma, urine, cell culture supernatant, and tissue homogenate were used to measure serum levels of the markers of interest in this study. The periostin ELISA kit (Human Periostin ELISA kit, Catalog No.: E3226Hu, Bioassay Technology Laboratory, China) has a measurement range of 0.5-150 ng/mL and sensitivity of 0.251 ng/mL. The MMP-7 ELISA kit (Human Matrix metalloproteinase 7 ELISA kit, Catalog No.: E0906Hu,

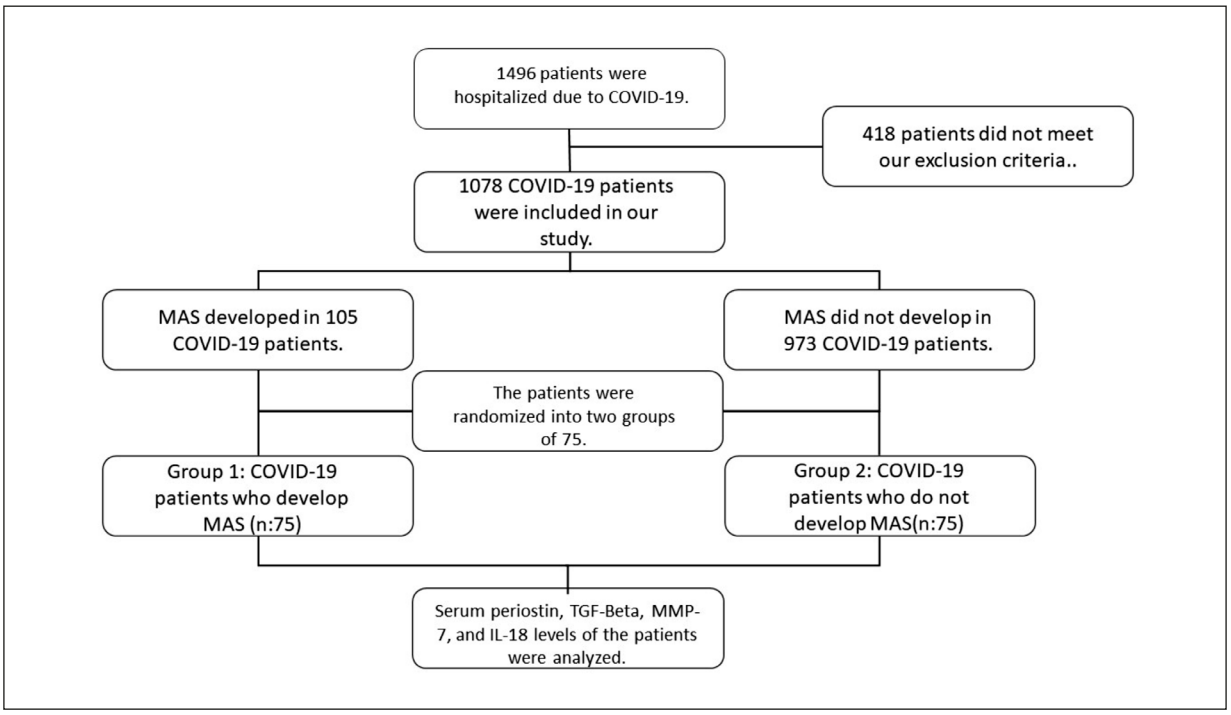

Figure 1. Study flowchart.

Bioassay Technology Laboratory, China) has a measurement range of 0.05-15 ng/mL and sensitivity of 0.026 ng/mL. The TGF-β ELISA kit (Human TGF-β ELISA kit, Catalog No.: E3051Hu, Bioassay Technology Laboratory, China) has a measurement range of 5-2,000 pg/mL and a sensitivity of 2.51 pg/mL. The IL-18 ELISA kit (Human IL-18 ELISA kit, Catalog No.: E0147Hu, Bioassay Technology Laboratory, China) has a measurement range of 0.5-100 ng/L and a sensitivity of 0.2 ng/L. All kits have intra-assay coefficient of variation (CV) values <8% and inter-assay CV values <10%.

Definitions and Treatment

In our study, all decisions regarding admission to COVID-19 isolation wards, treatment administered during hospitalization, and the criteria for MAS were determined according to the COVID-19 Guidelines[15] published and updated as necessary by the Ministry of Health of the Republic of Türkiye. The Anti-cytokine/Anti-inflammatory Therapies and Coagulopathy Management section of the guidelines states that some COVID-19 patients may exhibit MAS-like findings, that these findings may not always be consistent with scoring systems or diagnostic criteria used for MAS/HLH in other diseases, that it is a serious condition that requires close monitoring and early treatment, and it is very difficult to suppress the cytokine storm and prevent endothelial damage if it is not recognized and treatment initiated in a timely manner. Supporting signs of MAS development despite treatment are defined as follows:

- Persistent refractory fever
- Persistent or worsening CRP elevation
- Elevated and increasing ferritin levels (>700 μg/L)
- D-dimer elevation
- Lymphocytopenia, thrombocytopenia, and neutrophilia
- Impaired liver function (abnormal ALT, AST, LDH).

The guidelines also state that unlike in MAS presentations associated with other causes, hypofibrinogenemia may be seen in the late period, and triglyceride elevation and organomegaly may not be detected in COVID-19 patients. Other important points for clinicians are that concomitant secondary infection should be ruled out by negative cultures and normal procalcitonin values and that procalcitonin elevation accompanied by increased ferritin and D-dimer values, especially during sepsis, can be misleading. As specified in the guideline, methylprednisolone treatment was initiated at a dose of 250 mg/day for three

days in patients who met the criteria for MAS. For patients whose proinflammatory cytokine levels were not adequately suppressed and did not show clinical improvement on the third day of treatment, a request for the off-label use of tocilizumab was sent to the Ministry of Health. Patients considered eligible for treatment were given 400 mg/day of tocilizumab. If no response was observed after 24 hours, tocilizumab was increased to the maximum dose of 800 mg.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics for Windows version 24.0 (IBM Corp., Armonk, NY, USA). Pearson's Chi-square test was used to compare normally distributed numerical data between groups, and the Mann-Whitney U test was used to compare nonnormally distributed numerical data. Kruskal-Wallis' analysis was used to compare laboratory parameters among the groups. An independent-sample *t*-test was used for pairwise comparisons of demographic data and laboratory parameters between the groups. Pearson correlation analysis was used to evaluate correlations between laboratory data. Receiver operating characteristic (ROC) curve analysis was used to analyze the sensitivity and specificity of serum periostin, MMP-7, IL-18, and TGF-β levels between patients with and without MAS. $p<0.05$ was accepted as significant in all statistical analyses.

Results

The patients' mean ages were 64.21±16.56 years in Group 1, 66.75±14.83 years in Group 2, and 62.73±7.04 years in the control group, with no significant difference between the groups according to statistical analysis ($p>0.05$). There were 38 men (51%) in Group 1, 39 men (52%) in Group 2, and 16 men (53%) in the control group. The sex distribution did not differ statistically among the groups ($p>0.05$).

The most common comorbidities in both Groups 1 and 2 were hypertension (37% and 40%, respectively), diabetes mellitus (29% and 32%, respectively), and chronic obstructive pulmonary disease (17% and 15%, respectively). There was no statistically significant difference between Groups 1 and 2 in terms of comorbidities ($p>0.05$).

The routine laboratory test results and hospital length of stay of the patients in Groups 1 and 2 during hospitalization are shown in Table I. Compared to Group 2, Group 1 had significantly higher neutrophil count ($p=0.01$), AST ($p<0.001$), ALT ($p<0.001$), LDH ($p=0.001$), ALP ($p=0.02$), GGT ($p=0.001$), troponin-I ($p=0.03$), PCT ($p=0.03$) values, and longer length of hospital stay ($p=0.04$).

The comparison of periostin, MMP-7, IL-18, and TGF-β levels of the groups is shown in Table II. Periostin, MMP-7, and IL-18 levels were sig-

Table I. Comparison of routine laboratory parameters obtained at hospital admission and length of hospital stay in Groups 1 and 2.

	Group 1 (n = 75) mean ± SD	Group 2 (n = 75) mean ± SD	*p*
WBC count (/μL)	11,009.6 ± 5,759.8	8,717.9 ± 4,110.3	0.06
Lymphocyte count (/μL)	876.7 ± 604.9	756.7 ± 604.9	0.2
Neutrophil count (/μL)	9,582.1 ± 5,470	7,533.3 ± 3,931.9	**0.01**
NLR	17.8 ± 18.8	15.8 ± 15.2	0.49
AST (U/L)	36 ± 26.8	22.6 ± 13.6	**< 0.001**
ALT (U/L)	57.4 ± 54.9	32.4 ± 22	**< 0.001**
LDH (U/L)	390 ± 182.5	295.9 ± 134	**0.001**
ALP (U/L)	88.2 ± 47.5	73.6 ± 25.1	**0.02**
GGT (U/L)	102.4 ± 114.4	73.6 ± 56.8	**0.001**
Troponin-I (pg/mL)	185.4 ± 655	9.9 ± 15	**0.03**
D-dimer (ng/mL)	2,756.7 ± 5,614.5	2,160.8 ± 2,614	0.4
Ferritin (ng/mL)	708 ± 561.9	671.9 ± 930.9	0.78
Fibrinogen (mg/dL)	384.8 ± 171.7	432.9 ± 148.3	0.07
CRP (mg/L)	45.7 ± 58.8	44.6 ± 50.5	0.89
PCT (ng/mL)	0.5 ± 1.1	0.2 ± 0.3	**0.03**
Length of hospital stay (days)	28 ± 14.7	20.6 ± 16.1	**0.04**

Values are presented as mean ± standard deviation. WBC: White blood cells; NLR: Neutrophil-to-lymphocyte ratio; AST: Aspartate transaminase; ALT: Alanine transaminase; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; GGT: Gamma-glutamyl transferase; CRP: C-reactive protein PCT: Procalcitonin.

Table II. Levels of periostin, MMP-7, TGF-β, and IL-18 in Groups 1 and 2 and the Control Group.

	Group 1 (n = 75) mean ± SD	Group 2 (n = 75) mean ± SD	Control Group (n = 30) mean ± SD	p
Periostin (ng/mL)	43.9 ± 20[a,b]	37.2 ± 22[b]	27.4 ± 14.1	< 0.001
MMP-7 (ng/mL)	3.7 ± 1.5[a,b]	3 ± 1.7[b]	2.5 ± 1.1	< 0.001
TGF-β (pg/mL)	467.4 ± 293.9	507.8 ± 342.4	376.5 ± 201.8	0.4
IL-18 (ng/L)	15.7 ± 8.7	15.6 ± 10.5	8.2 ± 3.9	< 0.001

p^a: Group 1 *vs*. Group 2; p^b: Group 1 and 2 *vs*. Control Group. Values are presented as mean ± standard deviation. MMP-7: Matrix metalloproteinase-7; TGF-β: Transforming growth factor-beta; IL-18: Interleukin-18.

nificantly higher in COVID-19 patients compared to the control group (p<0.001 for all). In the comparison between COVID-19 patients, periostin and MMP-7 levels were significantly higher in Group 1 compared to Group 2 (p<0.001 for both).

Comparisons of serum periostin, MMP-7, IL-18, and TGF-β levels between surviving and non-surviving patients in Group 1 are shown in Table III. All non-surviving patients in our study were in Group 1. Serum periostin, MMP-7, TGF-β, and IL-18 levels were significantly higher in non-surviving patients (p=0.04, <0.001, <0.001, and <0.001, respectively).

The results of correlation analysis between periostin, MMP-7, IL-18, and TGF-β levels, which were the focus of our study, and routine laboratory parameters of COVID-19 patients in Groups 1 and 2 at hospital admission are shown in Table IV. Periostin, MMP-7, IL-18, and TGF-β levels were positively correlated with one another (p=0.01 for all). CRP levels were also positively correlated with NLR (r=0.311, p=0.01), ferritin (r=0.252, p=0.01), and fibrinogen levels (r=0.659, p=0.01). Lymphocyte level decreased with increasing age (r=-0.221, p=0.01).

In the ROC curve analysis for predicting the development of MAS in COVID-19 patients, MMP-7, periostin, and IL-18 levels could significantly discriminate between Groups 1 and 2 (Figure 2). MMP-7 had an area under the ROC curve of 0.73, and a predictive value of 2.66 ng/mL had 90% sensitivity and 61% specificity. Periostin had an area under the curve of 0.685, and a predictive value of 28.8 ng/mL had 80% sensitivity and 57% specificity. For IL-18, the area under the curve was 0.641, and at a predictive value of 12.4 ng/L its sensitivity and specificity were 58% and 68%, respectively.

Discussion

In our study, it was observed that periostin, MMP-7, and IL-18 levels were higher in the early COVID-19 period compared to the healthy control group. However, only periostin and MMP-7 levels were found to be effective in predicting the development of MAS in early COVID-19 patients. All parameters at the time of diagnosis were higher in non-surviving MAS patients compared to those who survived. When determining the predictive value of the markers in differentiating patients who did and did not develop MAS, we observed that the MMP-7 level showed higher sensitivity and specificity compared to periostin and IL-18.

Table III. Comparison of serum periostin, MMP-7, TGF-β, and IL-18 levels between surviving and non-surviving patients in Group 1.

	Non-surviving Group 1 patients (n = 11) mean ± SD	Surviving Group 1 patients (n = 64) mean ± SD	p
Periostin (ng/mL)	45.1 ± 15.4	39.9 ± 19.6	0.04
MMP-7 (ng/mL)	3.4 ± 1.8	3 ± 1.9	< 0.001
TGF-β (pg/mL)	528.4 ± 200.4	443.4 ± 212.5	< 0.001
IL-18 (ng/L)	19.4 ± 7.2	15.2 ± 8.1	< 0.001

Values are presented as mean ± standard deviation. MMP-7: Matrix metalloproteinase-7; TGF-β: Transforming growth factor-beta; IL-18: Interleukin-18.

Table IV. Correlation analysis of the laboratory parameters of COVID-19 patients in Groups 1 and 2.

		IL-18	MMP-7	Periostin	TGF-β	Lymphocytes	NLR	D-dimer	Ferritin	Fibrinogen	CRP	Age
IL-18	**r**	1										
	p											
MMP-7	**r**	.818**	1									
	p	.000										
Periostin	**r**	.818**	.823**	1								
	p	.000	.000									
TGF-β	**r**	.871**	.799**	.828**	1							
	p	.000	.000	.000								
Lymphocytes	**r**	-.088	-.106	-.084	-.063	1						
	p	.284	.200	.310	.443							
NLR	**r**	.086	.003	.086	-.072	-.529**	1					
	p	.293	.972	.299	.384	.000						
D-dimer	**r**	-.058	-.066	-.005	-.107	-.046	.183*	1				
	p	.478	.425	.949	.195	.577	.025					
Ferritin	**r**	.019	.023	-.002	-.010	-.175*	.369**	.277**	1			
	p	.821	.781	.983	.907	.034	.000	.001				
Fibrinogen	**r**	.075	.010	.001	-.013	-.103	.052	-.159	.159	1		
	p	.359	.904	.994	.872	.210	.524	.051	.054			
CRP	**r**	.128	.087	.086	.030	-.122	.311**	-.046	.252**	.659**	1	
	p	.121	.293	.300	.714	.137	.000	.576	.002	.000		
Age	**r**	-.063	-.043	-.067	-.075	-.221**	.151	-.035	-.081	.054	.163*	1
	p	.400	.570	.371	.321	.007	.065	.674	.332	.512	.046	

*$p<0.05$, **$p<0.01$; IL-18: Interleukin-18; MMP-7: Matrix metalloproteinase-7; TGF-β: Transforming growth factor-beta; NLR: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein.

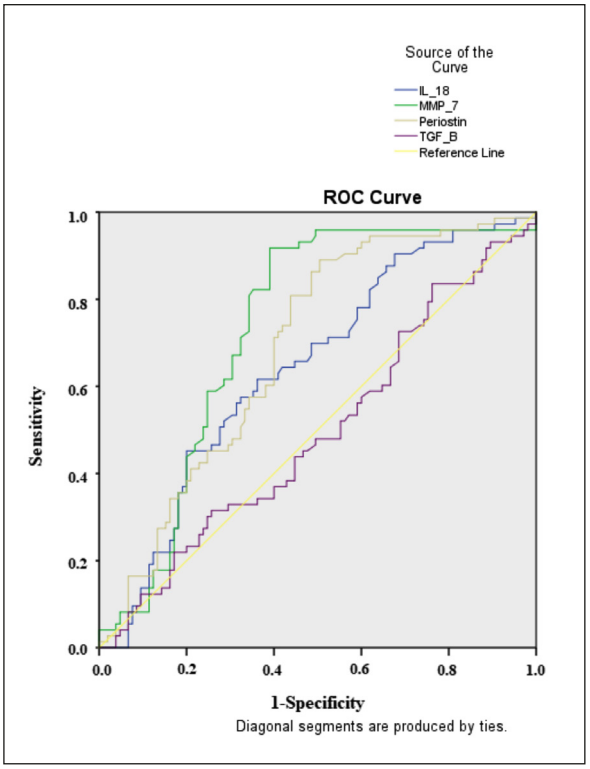

Figure 2. Receiver operating characteristic (ROC) curve analysis of IL-18, TGF-β, MMP-7, and periostin levels between patients with and without macrophage activation syndrome (MAS).

Since December 2019, SARS-CoV-2 infection has been confirmed in more than 650 million people worldwide and has caused more than 6.5 million deaths. In Turkey, it has caused approximately 17 million cases, with more than 100,000 deaths as of December 2022[16]. One of the main challenges in determining initial treatment for COVID-19 patients is the early identification of patients who will develop more severe forms of the disease and need specific interventions or treatments[17]. Numerous studies are being conducted in literature to determine whether the presence of specific biomarkers makes a patient more susceptible to severe infection. The identification of such biomarkers can help predict the expected clinical severity of infection, thereby helping to anticipate the level of medical intervention that will be most beneficial and enabling its early administration[18].

Many cytokines are involved in the regeneration of both the lung parenchyma and ECM at the onset and after COVID-19 infection. Periostin is a matricellular protein. Matricellular proteins are ECM proteins with nonstructural properties that are largely expressed at sites of inflammation or injury[6]. Periostin synthesis can be induced by important cytokines such as IL-4, IL-13, and TGF-β. In a study conducted on COVID-19 patients, it was observed that periostin levels were higher in severe patients compared to the mild/moderate and control groups, while there was no significant difference in TGF-β levels. The increase in periostin levels was attributed to intense inflammation in the parenchyma and ECM in patients with severe disease. TGF-β is thought to reduce excessive immune response and restore or maintain immune homeostasis[19,20]. Other studies compared TGF-β levels in mild, severe, and critical COVID-19 patients with healthy control groups and showed that TGF-β levels increased with disease severity[19,21,22]. IL-18, mostly in combination with IL-12, activates T lymphocytes and natural killer cells to produce IFN-γ and replicate, which is crucial in defending against infections. IL-18 regulates Th1 and Th2 responses, and its increased production may exacerbate the disease because of inflammation[23,24]. Many studies have analyzed IL-18 in infections (especially viral), metabolic and inflammatory diseases (adult-onset Still's disease, systemic juvenile idiopathic arthritis, HLH/MAS), where it is an important factor in host response[25]. MMP-7, another important biomarker in viral infections, is a protease involved in the progressive ECM degradation that occurs after intense lung damage. MMP-7 was shown to be significantly associated with cytokine storm and intense lung involvement in COVID-19 patients, with higher levels observed in patients who require mechanical ventilation[26].

In our study, liver function tests and cardiac biomarkers were higher in patients with severe disease than in patients with mild disease, consistent with previous COVID-19 studies. This is related to the hepatotropic and cardiotropic activity of the viral agent causing COVID-19 infection. Our analysis of the cytokines of interest in this study showed that periostin, MMP-7, and IL-18 levels were higher in COVID-19 patients compared to the control group, and only periostin and MMP-7 levels were higher in severe patients in the initial period. The lack of cytokine discharge in the initial period may have been responsible for the lack of increase in TGF-β, which plays a role in balancing extreme immune responses. Interstitial pneumonia, which presents with ECM involvement in atypical infections such as COVID-19 infection, may have caused an increase in periostin and MMP-7 levels, which

play a role in ECM formation and degradation of over-synthesized ECM at the onset of the disease. The rise in IL-18 level may have occurred to induce an increase in IFN-γ, which plays a role in antiviral activity. Although the number of non-surviving patients was low in our study, we observed that periostin, MMP-7, IL-18, and TGF-β levels were higher in these patients in the early period. This may be related to the intense viral activity in non-surviving patients and the subsequent increase in cytokine levels. In the correlation analysis, we observed no correlation between our cytokines of interest and routine laboratory parameters considered important in the prognosis of COVID-19. This may be due to the fact that in the early period, the hypermetabolic activity evidenced by increasing cytokine levels is not yet reflected in laboratory parameters. It also demonstrates once again the importance of cytokine levels in early prognosis estimation compared to routine laboratory parameters. In the ROC analysis between patients with and without MAS, MMP-7 and periostin levels showed high sensitivity. This may be due to ECM progression (increased periostin) caused by viral infections and the increase in MMP-7 level in an attempt to balance it.

Limitations

A limitation of this study was that samples were obtained at diagnosis, and there were no post-treatment follow-up samples. However, we believe that the revision of treatment based on the patients' clinical condition and the national COVID-19 guidelines may affect their cytokine levels during follow-up. Therefore, we only analyzed serum samples from the time of diagnosis.

Conclusions

In conclusion, early diagnosis and treatment play an important role in bacterial and viral infections that show a progressive course, especially COVID-19. Clinical follow-up of patients has yielded many parameters associated with prognosis in routine practice. The search continues for laboratory parameters that can provide early insight into the patient's risk of disease progression. As observed in our study, MMP-7, periostin, and IL-18 in the early period may be valuable markers for predicting the clinical course and prognosis of atypical pneumonia that manifests with ECM progression, especially COVID-19.

Conflict of Interest

None to declare.

Informed Consent

Patients or their legal representatives provided written and verbal consent to the study.

Ethics Approval

The Institutional Review Board at Erzurum Atatürk University Faculty of Medicine Ethics Committee approved this study (meeting number: 10, decision No.: 27, date: 17.12.2020), which was conducted in compliance with the 2013 version of the Helsinki Declaration.

Authors' Contributions

Buğra Kerget: conceptualization, methodology, data curation, investigation, resources, writing, and original draft preparation. Mehmet Eren Tuna: methodology, data curation, investigation, resources. Esra Eğilmez: data curation, investigation. Alperen Aksakal: data curation, writing, reviewing and editing. Ömer Araz: methodology, data curation. Elif Yılmazel Uçar: investigation, resources. Leyla Sağlam: investigation, resources.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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