flora

RESEARCH ARTICLE/KLİNİK ÇALIŞMA

FLORA 2023;28(1):77-86 • doi: 10.5578/flora.20239907

Could Metrnl be a New Biomarker to Predict the Development of Macrophage Activation Syndrome in COVID-19 Patients?

Metrnl, COVID-19 Hastalarında Makrofaj Aktivasyon Sendromunun Gelişimini Tahmin Etmek için Yeni Bir Biyobelirteç Olabilir mi?

Dursun Erol AFŞİN[1](İD), Esra LALOĞLU[2](İD)

[1] Clinic of Chest Diseases, Erzurum Regional Training and Research Hospital, Erzurum, Türkiye
[2] Department of Biochemistry, Atatürk University Faculty of Medicine, Erzurum, Türkiye

Cite this article as: *Afşin DE, Laloğlu E. Could metrnl be a new biomarker to predict the development of macrophage activation syndrome in COVID-19 patients? FLORA 2023;28(1):77-86.*

ABSTRACT

Introduction: *Failure to maintain the inflammatory and anti-inflammatory balance during COVID-19 treatment may result in a severe clinical course. In our study, we aimed to determine the relationship between the meteorin-like protein (metrnl), which plays a role in the anti-inflammatory balance, and the clinical course.*

Materials and Methods: *Between October 2021 and December 2021, 160 patients who were hospitalized in our hospital and whose delta variant COVID-19 infection was confirmed and 80 healthy controls, were enrolled in the study. Patients were divided into two groups according to the severity degree of COVID-19 (Group 1: Moderate COVID-19, Group 2: Severe COVID-19 MAS).*

Results: *When comparing the metrnl levels of the groups, it was observed that the metrnl level was statistically significantly lower in Group 2 patients ($p< 0.001$). While no statistically significant difference was observed between the healthy control group and Group 1, it was observed that the metrnl level of Group 2 patients was statistically significantly lower than the healthy control group ($p= 0.77$, <0.001 respectively). In the ROC curve analysis of Metrnl level performed in Group 1 and 2 patients, the cut-off value was taken as 17.54 ng/mL, its sensitivity was observed as 80% and the specificity was observed as 60% in predicting the development of severe COVID-19 in patients whose levels were below this value.*

Conclusion: *The low level of metrnl, which is thought to play a key role in anti-inflammatory balance, contributes to the development of macrophage activation syndrome, which leads to the severe clinical course in COVID-19 patients.*

Key Words: *COVID-19; Macrophage activation syndrome; Metrnl*

Received/Geliş Tarihi: 06/10/2022 - Accepted/Kabul Ediliş Tarihi: 20/12/2022

Available Online Date: 03.03.2023

ÖZ

Metrnl, COVID-19 Hastalarında Makrofaj Aktivasyon Sendromunun Gelişimini Tahmin Etmek İçin Yeni Bir Biyobelirteç Olabilir mi?

Dursun Erol AFŞİN[1], Esra LALOĞLU[2]

[1] Erzurum Bölge Eğitim Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, Erzurum, Türkiye
[2] Atatürk Üniversitesi, Biyokimya Anabilim Dalı, Erzurum, Türkiye

Giriş: *COVID-19 seyrinde inflamatuvar ve anti-inflamatuar dengenin sağlanamaması hastalığın ağır klinik seyir göstermesine neden olabilmektedir. Çalışmamızda anti-inflamatuvar dengede rol oynayan meteorin-like protein (metrnl) ve klinik seyir arasındaki ilişkiyi tespit etmeyi amaçladık.*

Materyal ve Metod: *Ekim 2021 ve Aralık 2021 tarihleri arasında hastanemize yatmış olan; gerçek zamanlı PCR yöntemiyle delta varyant COVID-19 tespit edilmiş 160 hasta ve 80 sağlıklı kontrol grubu çalışmaya dahil edildi. Hastalar COVID-19 ağırlık derecesine göre iki gruba ayrıldılar (Grup 1: Moderate (Orta Şiddetli) COVID-19, Grup 2: Severe (Ağır) COVID-19 MAS).*

Bulgular: *Grupların metrnl düzeylerinin karşılaştırılmasında, Grup 2'deki hastaların metrnl düzeyinin istatistiksel olarak anlamlı düzeyde düşük olduğu görüldü (p< 0.001). Sağlıklı kontrol grubu (25.6 ± 5.7 ng/mL) ile Grup 1 arasında istatistiksel olarak anlamlı fark gözlenmezken Grup 2'deki hastaların metrnl düzeyinin sağlıklı kontrol grubuna göre istatistiksel olarak anlamlı düzeyde düşük olduğu gözlendi (sırasıyla p= 0.77, <0.001). Metrnl düzeyinin Grup 1 ve 2'deki hastalarda yapılan ROC curve analizinde eğri altında kalan alan (AUC) 0.754, cut-off değer olarak 17.64 ng/mL alındığında bu değerin altındaki hastalarda ağır COVID-19 gelişme durumunu tahmin etmede duyarlılığı %80, özgüllüğü ise %63 olarak bulundu.*

Sonuç: *Anti-inflamatuvar dengede önemli bir rol oynadığı düşünülen metrnlin COVID-19 hastalarında düşük düzeyde olması, ağır klinik seyirde önemli rol oynayan makrofaj aktivasyon sendromu gelişiminde önemli paya sahiptir. COVID-19 hastalarında başlangıç döneminde tespit edilen düşük metrnl düzeyi, erken anti-inflamatuvar tedavi için yol gösterici olabilir.*

Anahtar Kelimeler: *COVID-19; Makrofaj aktivasyon sendromu; Metrnl*

INTRODUCTION

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) pandemic has been the most serious health issue in the world for more than two years[1]. While the disease presents with a milder clinical course in vaccinated individuals, it manifests with a severe clinical course such as acute respiratory failure syndrome (ARDS) and macrophage activation syndrome (MAS) in unvaccinated individuals[2].

Tumor necrosis factor-alpha (TNF-alpha), interleukins 1, 2, 6, and 18, and nitric oxide (NO), which are synthesized intensively in the body in COVID-19 patients with MAS, are reported to play an important role in the development of this process[3]. The inability to adequately balance the intensely synthesized pro-inflammatory response with anti-inflammatory cytokines has made anti-cytokine therapies and anti-inflammatory therapies important parts of treatment in these patients recently[4]. The most important agent used in anti-inflammatory therapy has been methylprednisolone[5]. High levels of methylprednisolone significantly reduced mortality in COVID-19 patients presenting with MAS. However, high-level steroid treatment in patients with MAS may lead to comorbidities[6,7].

An important newly discovered biomarker synthesized from adipose tissue is metrnl. Metrnl is synthesized in the body from many tissues, especially by white adipose tissue, the digestive system, and the lung[8]. Metrnl synthesized from adipose tissue plays an important role in the regulation of glucose metabolism and M_2 macrophage activation and catecholamine discharge by increasing IL-4 and IL-13 expression over eosinophils. Following M_2 macrophage activation in the lung, anti-inflammatory cytokines, particularly IL-10, TGF-beta CCL18, and CCL22, are synthesized[9]. Increased serum metrnl levels have been demonstrated to have a significant function

in the anti-inflammatory balance in inflammatory diseases and have been considered as an important adipocytokine that may play a role in future treatment modalities[8,10].

Inflammatory and anti-inflammatory balance has an important place in the course and prognosis of COVID-19. We also aimed to compare serum metrnl levels between COVID-19 patients who developed MAS, COVID-19 patients with moderate clinical course, and the healthy control group in our study.

MATERIALS and METHODS

Study Design

We included patients who were admitted to the emergency department of Erzurum Regional Training and Research Hospital with shortness of breath, fever, cough, malaise, and general malaise and were found to be COVID-19 positive in the nasopharyngeal PCR sample and required hospitalization in accordance with the Adult Diagnosis and Treatment Guidelines of the Republic of Türkiye Ministry of Health[11]. A total of 419 patients were followed up in our service between October 2021 and December 2021, and a total of 294 patients were found eligible for the study based on the exclusion criteria stated below. According to the G power analysis performed prior to the design of our study (d= 0.60, p< 0.05), including 80 patients in each group was deemed sufficient. Accordingly, two groups of 80 patients each were randomly selected as indicated in Figure 1. Local ethics committee approval was obtained before starting the study (B.30.2.ATA.0.01.00/406).

Study Population

High-resolution computed tomography (HRCT) was performed in a standardized manner on patients at high risk for COVID-19. Patients with bilateral ground-glass opacity, sub-segmental consolidation or linear opacities, cobblestone appearance, and reverse halo sign, with peripheral localization in the foreground, were considered typical findings, and patients with radiological atypical findings but compatible clinical complaints were hospitalized[12]. The diagnosis of COVID-19 was performed by real-time PCR method by taking nasopharyngeal swabs from the patients. A total of 240 people were included in the study from Erzurum Regional Training and Research Hospital between October 2021 and December 2021, including 160 patients admitted to the intensive care unit and ward due to moderate to severe COVID-19 pneumonia and 80 patients from the healthy control group. The healthy control group in our study was drawn from the volunteer population without active infection who had never been vaccinated before and who presented to our COVID-19 outpatient clinic for the first dose of mRNA or inactivated viral vaccine without COVID-19 PCR positivity.

After hospitalization, biochemical parameters including hematological parameters, liver and kidney function tests, coagulation parameters,

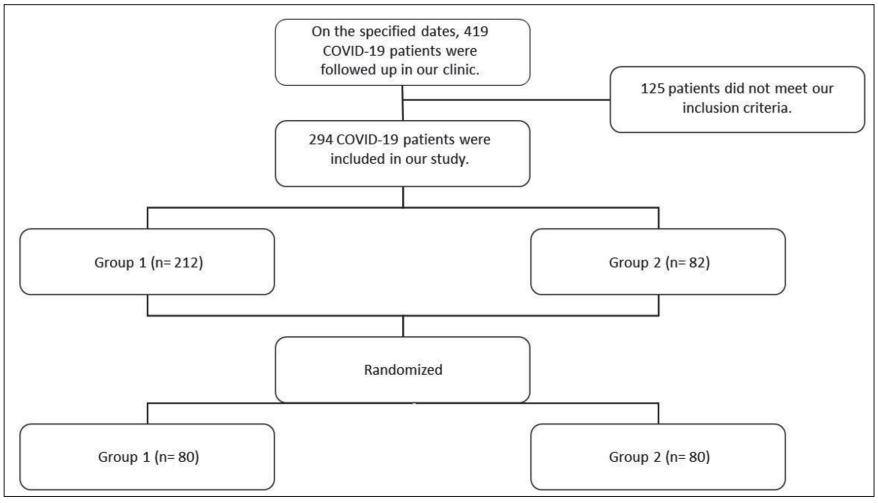


Figure 1. CONSORT diagram.

ferritin, fibrinogen, D-dimer, troponin-I, and CRP levels were obtained daily.

Study Group

The patients included in our study were divided into three groups according to their follow-up status due to COVID-19. Control group: Healthy control group with negative COVID-19 PCR test result (n= 80), Group 1: Moderate illness; patients with clinical signs of pneumonia with no signs of severe pneumonia (Severe pneumonia: Pneumonia meeting any one of the following criteria; respiratory rate ≥30 breaths/min; $SpO_2 \leq 92\%$; patients with a lung infiltration rate of >50%) (n= 80), Group 2: Patients admitted to the hospital with severe pneumonia and monitored in the intensive care unit due to development of macrophage activation syndrome or respiratory failure during their follow-up (n= 80).

Exclusion Criteria

Patients with psoriasis, active inflammatory arthritis, Type 2 diabetes mellitus patients with impaired glucose regulation, patients who were followed for acute coronary syndrome within the last one month or who developed acute coronary syndrome during the COVID-19 period, patients with known obstructive pulmonary disease and patients followed for colitis were not included in our study.

Plasma Metrnl Measurement

Venous blood samples were obtained from all patients from an antecubital vein after at least 15 minutes of semi-supine rest. All blood samples were collected into tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent coagulation. The collected plasma samples were studied using a "Human meteorin-like protein ELISA Kit" (BT LAB, Cat. No. E3941Hu, China) according to the manufacturer's instructions. The detection range of this kit is 0.05-15 ng/mL. The sensitivity of this assay is 0.023 ng/mL. The interassay coefficient of variance and the intraassay coefficient of variance are given as <10% and <8% for meteorin-like protein measurement by the kit manufacturer, respectively. Briefly, each standard (16, 8, 4, 2, 1, and 0.5 ng/mL) and sample were added into appropriate wells pre-coated with a human meteorin-like protein antibody. The meteorin-like protein present in the sample was bound to antibodies coated on the wells. And then biotinylated human meteorin-like protein antibody was added and bound to the meteorin-like protein in the sample. Then streptavidin-HRP was added and bound to the biotinylated meteorin-like protein antibody. After incubation unbound streptavidin-HRP was washed away. A substrate solution was added, and color developed in proportion to the amount of human meteorin-like protein. The reaction was terminated by the addition of an acidic stop solution and absorbance was measured at 450 nm. Meteorin-like protein concentrations were determined by comparing their optical density (OD) with the standard curve. Dynex automated ELISA reading device (Dynex Technologies Headquarters, Chantilly, USA) in our laboratory was used for the evaluation of the meteorin-like protein human ELISA kit.

COVID-19 Nasopharyngeal Swab PCR Test Analysis

Nasopharyngeal swabs of the patients included in our study, which were taken to make a definitive diagnosis of COVID-19, were analyzed on the CFX96 touch real-time PCR detection system Bio-Rad (California, USA) in our hospital. Swab samples were analyzed with the DS Coronex COVID-19 Q PCR test kit (Clydebank, UK).

Definitions and Diagnosis

Fever was defined as an axillary temperature of 37.3°C or higher. In patients with a high fever while under treatment for COVID-19, blood, urine, and sputum cultures were obtained to test for possible bacterial and fungal superinfections, and empiric antibiotherapies were revised according to the culture results. Diagnosis and grading of acute respiratory distress were done using the Berlin 2015 diagnostic criteria[13]. Patients with elevated daily cardiac-specific troponin levels underwent echocardiographic evaluation for nascent cardiac pathologies. Coagulopathy was defined as prothrombin and partial thromboplastin times three times and five times longer than normal, respectively. The treatment strategy for each patient was determined based on their clinical severity and the Turkish Ministry of Health COVID-19 Adult Diagnosis and Treatment

Guidelines[11]. Patients with findings such as refractory fever, persistently high or increasing CRP and ferritin levels, elevated D-dimer level, cytopenia (lymphopenia or thrombocytopenia), abnormal liver function tests, hypofibrinogenemia, or elevated triglyceride levels despite treatment were monitored for MAS[11]. If serial measures demonstrated further deterioration in these parameters that could not be explained by secondary bacterial infection, the patients were treated for MAS with >250 mg/day methylprednisolone if they had no contraindication. The patients were followed up for 72 hours and those who did not show a clinical response were treated with 400 mg of tocilizumab. After 24 hours, patients who still did not exhibit clinical and laboratory response received a second dose of tocilizumab[11].

Statistical Analysis

Analyses were performed using IBM SPSS version 20.0 software (IBM Corp, Armonk, NY). Data were presented as median, minimum, maximum, count, and percentage. In the comparison of continuous variables between more than two independent groups, analysis of variance (ANOVA) was used if normally distributed, and the Kruskal-Wallis test if non-normally distributed. Following the ANOVA, post hoc tests were carried out. Relationships between two quantitative variables were examined using Pearson correlation analysis if normally distributed and Spearman correlation analysis if non-normally distributed. ROC analysis was used to determine whether the continuous variable had a diagnostic value. In addition, the cut-off value was determined using the Youden index. $p< 0.05$ was considered statistically significant.

RESULTS

While the median age of the patients included in our study was 58 (23-80) in Group 1, it was 56 (26-80) in Group 2. The median age of the healthy control group was 56 (49-69). In the statistical analysis performed for the age between the groups, no significant difference was observed (p= 0.33). While 50% of Group 1 patients were male, 76.3% of Group 2 patients were male. A statistically significant difference was observed in the comparison of the groups according to gender (p= 0.03).

While 15 of the patients in Group 1 had hypertension, six had diabetes mellitus and three had coronary artery disease, 20 of the patients in Group 2 had hypertension, 10 had diabetes mellitus and five had coronary artery disease. The patients included in the control group did not have comorbidities.

The comparison of patients' laboratory test results was given in Table 1. Accordingly, NLR, LDH, ferritin, fibrinogen, and CRP levels were statistically significantly higher in Group 2 compared to Group 1 (p= <0.001, <0.001, <0.001, 0.02, <0.001). PaO_2/FiO_2 ratio and lymphocyte levels were statistically significantly lower in Group 2 compared to Group 1 (p= <0.001 for both).

The comparison of metrnl level and length of hospital stay between the groups was shown in Table 2. Accordingly, while no statistically significant difference was observed between Group 1 and the control group, it was observed that Group 2 patients had statistically significantly lower metrnl levels (p= <0.001). In addition, the length of hospital stay was statistically significantly longer in Group 2 compared to Group 1 (p= <0.001).

In the comparison of metrnl levels by gender in COVID-19 patients, the median value was 19.3 (min-max: 5.5-47.6) in male patients and 19.2 (min-max: 3.9-50.9) in female patients. In Group 1, the median value of metrnl was 23.9 (min-max: 5.4-47.6) in males and 21.8 (min-max: 3.9-50.9) in females. In Group 2, it was 17.1 (min-max: 5.3-26.9) in males and 12.7 (min-max: 7.4-26.8) in females. No statistically significant difference was observed in gender and metrnl levels both in the overall population and between groups (p= 0.7, 0.6, 0.6 respectively)

In the regression analysis of laboratory parameters in terms of comorbidities and MAS development by adjusting gender, it was observed that the decrease in lymphocyte and metrnl levels and the increase in ferritin levels were statistically significant (p= 0.004, <0.001, <0.001, respectively) (Table 3).

Table 1. Comparison of age and laboratory parameters of the groups

	Group 1 (n= 80) median (min-max)	Group 2 (n= 80) median (min-max)	p
Age (year)	58 (23-80)	56 (26-80)	0.28
WBC (/µL)	8056 (2010-20110)	13598 (4115-22345)	0.001
Lymphocyte (/µL)	774 (360-3180)	423 (120-1124)	<0.001
Neutrophil (/µL)	6146 (2151-20180)	8154 (2900-16510)	0.05
NLR	7.6 (1.2-41.3)	20.5 (3.9-134.8)	<0.001
AST (U/L)	48.5 (15-245)	46 (24-169)	0.65
ALT(U/L)	55 (12-472)	56 (17-319)	0.69
LDH (U/L)	429.5 (164-750)	701 (373-1425)	<0.001
ALP (U/L)	96 (51-410)	86 (31-221)	0.2
GGT (U/L)	78 (15-191)	39 (16-185)	0.28
Troponin-ı (ng/dL)	12 (0-452)	21 (0.1-155)	0.63
D-Dimer (ng/dL)	874.5 (190-11078)	1500 (289-9812)	0.23
Ferritin (ng/mL)	572.5 (64-1650)	1440 (861-2015)	<0.001
Fibrinogen (ng/mL)	406.5 (165-770)	449 (312-783)	0.02
CRP (mg/L)	44.5 (3-150)	155 (53-317)	<0.001
PaO_2/FiO_2	230 (150-390)	175 (120-213)	<0.001

SD: Standard deviation, WBC: White blood cells, AST: Aspartate transaminase, ALT: Alanine transaminase, GGT: Gamma-glutamyl transferase, LDH: Lactose dehydrogenase, ALP: Alkaline phosphatase, CRP: C-reactive protein.

Table 2. Comparison of metrnl levels and the duration of hospitalization of the groups with the control group and in between themselves

	Group 1 (n= 80) median (min-max)	Group 2 (n= 80) median (min-max)	Control (n= 80) median (min-max)	p
Metrnl (ng/mL)	22.6 (3.9-50.9)	16.9[a] (5.5-26.8)	23.1 (6.1-48.9)	<0.001
Length of stay (day)	6 (4-10)	13[a] (9-20)	-	<0.001

p[a]: Comparison of Group 2 patients with Group 1 and control group.

A correlation analysis of laboratory parameters was shown in Table 4. Accordingly, while the metrnl level was observed to be inversely correlated with ferritin, CRP, and length of hospital stay, it was observed to be positively correlated with PaO_2/FiO_2 ratio (r= -0.32, p= 0.01, r= -0.158, p= 0.01, r= -0.53, p= 0.01, r= 0.227, p= 0.01, respectively).

In line with the regression analysis, the ROC curve analysis of lymphocyte and metrnl levels was shown in Figure 2. Accordingly, when the cut-off value for lymphocyte level was taken as 550/µL, its sensitivity was observed as 88% and its specificity was observed as 63% in predicting MAS development in patients below this value. For the metrnl level, when the cut-off value was taken as 17.54 ng/mL, sensitivity and specificity were observed as 80% and 60%, respectively, in predicting MAS development.

DISCUSSION

In our study, serum metrnl levels were observed to be lower in patients with MAS compared to patients without MAS and the healthy control group. In addition, in the regression analysis performed by adjusting comorbidities and gender together with all laboratory parameters, it was observed that the decrease in metrnl level and lymphocyte level were two important

Table 3. Regression analysis of laboratory parameters between patients with and without MAS

	Unstandardized	Coefficients	Standardized coefficients			95.0% Confidence Interval for B	
Model	B	Std. Error	Beta	t	p	Lower Bound	Upper Bound
(Constant)	0.235	0.140		1.679	0.095	-0.041	0.512
WBC	-3.043E-6	0.000	-0.033	-0.442	0.659	0.000	0.000
Lymphocyte	0.000	0.000	-0.166	-2.890	0.004	0.000	0.000
Neutrophil	5.217E-6	0.000	0.046	0.582	0.561	0.000	0.000
NLR	-0.001	0.001	-0.072	-1.001	0.318	-0.004	0.001
LDH	0.000	0.000	0.145	1.919	0.057	0.000	0.001
D-dimer	-1.850E-5	0.000	-0.078	-1.334	0.184	0.000	0.000
Ferritin	0.001	0.000	0.515	7.375	0.000	0.000	0.001
Fibrinogen	0.000	0.000	-0.081	-1.335	0.184	-0.001	0.000
CRP	0.001	0.000	0.128	1.596	0.112	0.000	0.002
Metrnl	-0.013	0.003	-0.244	-4.844	0.000	-0.018	-0.008

Dependent variable: MAS, adjusted: comorbidity, gender.

parameters in predicting the development of MAS. In addition, a higher correlation was found between the decrease in serum metrnl levels, and the length of hospital stay compared to other parameters.

More than two years of follow-up of COVID-19 has enabled us to gather more information about different clinical courses[14]. While hypoxemia and respiratory stress were not observed in some patients, we observed that individuals with comorbidities and those who were not vaccinated may present with a more severe course. In addition, we have frequently observed that individuals without respiratory distress at the beginning may progress to acute respiratory distress and MAS in a progressive manner[7].

Mononuclear phagocytic cells (about 90% of which are macrophages) are the first barrier to the progression of infection in acute attack. Lung macrophages (LM) are divided into two: M1 and M2[15]. M1 LMs are responsible for high levels of pro-inflammatory cytokine synthesis. They are also called classically activated (pro-inflammatory) macrophages. M2 macrophages are primarily induced by fungi, immunocomplexes, helmites, complement components, apoptotic cells, macrophage colony-stimulating factor, IL-4 and IL-13, and synthesis of anti-inflammatory cytokines, mainly IL-10, TGF-beta CCL18 and CCL22 takes place[16,17].

Metrnl is a newly discovered adipocytokine synthesized from adipose tissue. In addition to adipose tissue, it is intensely synthesized from the skin, oral and pharyngeal mucosa, and M2 macrophages[8,18]. It was observed that the level of macrophages in the bronchoalveolar lavage is increased in the studies performed in acute exacerbation of COPD and related to active smoking. In addition, in the evaluation of the serum metrnl level in patients presenting with COPD acute exacerbation, it was observed that the level was increased in order to maintain the anti-inflammatory balance during the exacerbation and although the serum level decreased after the treatment, it was still higher than the levels in healthy people. This situation was evaluated due to the ongoing inflammation in COPD disease even if the attack resolves[19].

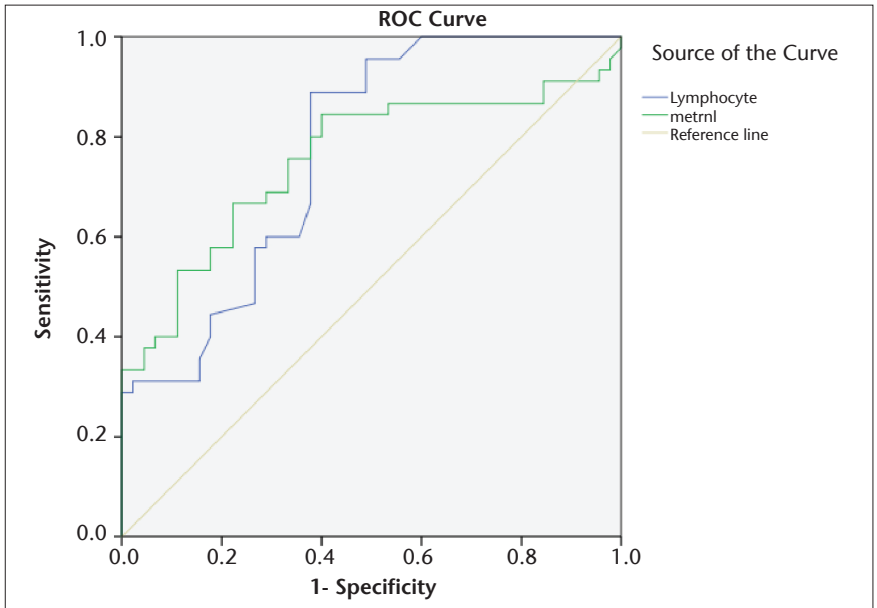
In our study, we observed that NLR, LDH, ferritin, fibrinogen, and CRP levels, which are associated with prognosis in COVID-19 patients, were higher in severe patients. The development of macrophage activation syndrome in the group of patients with severe COVID-19 may have caused this situation to be observed more clearly. When serum metrnl levels were compared,

Table 4. Correlation analysis between laboratory parameters and length of the stay

		NLR	LDH	D-dimer	Ferritin	Fibrinogen	CRP	PaO_2/FiO_2	Metrnl	Length of stay
NLR	R	1	0.440**	-0.100	0.404**	0.009	0.416**	-0.216**	-0.091	-0.309**
	p		0.000	0.184	0.000	0.909	0.000	0.004	0.225	0.000
LDH	R	0.440**	1	0.213**	0.564**	0.244**	0.578**	-0.614**	-0.088	0.417**
	p	0.000		0.004	0.000	0.001	0.000	0.000	0.239	0.000
D-Dimer	R	-0.100	0.213**	1	0.253**	0.250**	0.420**	-0.185*	0.001	0.047
	p	0.184	0.004		0.001	0.001	0.000	0.013	0.991	0.530
Ferritin	R	0.404**	0.564**	0.253**	1	0.405**	0.560**	-0.740**	-0.320**	0.629**
	p	0.000	0.000	0.001		0.000	0.000	0.000	0.000	0.000
Fibrinogen	R	0.009	0.244**	0.250**	0.405**	1	0.546**	-0.330**	-0.084	0.160**
	p	0.909	0.001	0.001	0.000		0.000	0.000	0.263	0.000
CRP	R	0.416**	0.578**	0.420**	0.560**	0.546**	1	-0.490**	-0.158*	0.358**
	p	0.000	0.000	0.000	0.000	0.000		0.000	0.034	0.000
PaO_2/FiO_2	R	-0.216**	-0.614**	-0.185*	-0.740**	-0.330**	-0.490**	1	0.227**	-0.519**
	p	0.004	0.000	0.013	0.000	0.000	0.000		0.002	0.000
Metrnl	R	-0.091	-0.088	0.001	-0.320**	-0.084	-0.158*	0.227**	1	-0.530**
	p	0.225	0.239	0.991	0.000	0.263	0.034	0.002		0.000
Length of stay	R	-0.309**	0.417**	0.047	0.629**	0.160*	0.358**	-0.519**	-0.530**	1
	p	0.000	0.000	0.530	0.000	0.000	0.000	0.000	0.000	

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

no significant difference was found between the healthy group and moderate COVID-19 patients (Group 1), however lower serum metrnl levels were observed in patients with severe COVID-19 who developed MAS. Failure to maintain inflammatory and anti-inflammatory balance in COVID-19 pneumonia is among the most important causes of clinical worsening. The low level of metrnl, which enables macrophages to differentiate into M2 macrophages, which play a role in anti-inflammatory cytokine discharge, may suggest that it may play a role in



				Asymptotic 95% Confidence Interval	
Test Result Variables	**Area**	**Std. Error[a]**	**p**	**Lower Bound**	**Upper Bound**
Lymphocyte (/μL)	0.770	0.035	0.000	0.701	0.838
Metrnl (ng/ml)	0.754	0.037	0.000	0.681	0.828

Figure 2. ROC curve analysis of metml and lymphocyte level in patients with severe and moderate COVID-19.

clinical worsening in patients with MAS. In the regression analysis, a significant correlation was observed between the decrease in lymphocyte and metrnl levels and MAS outflow. This could be because SARS-CoV-2, a lymphotropic virus, causes reduced lymphocyte levels in patients with a severe course, as well as lower metrnl production, which plays a role in anti-inflammatory activity. In addition, inadequate anti-inflammatory balance is the most important cause of morbidity and mortality in COVID-19 patients. The prolongation of hospital stay in correlation with low metrnl levels may also have contributed to this condition.

One of the most important limitations observed in our study was the inability to measure the metrnl levels of the patients before discharge. The fact that metrnl and similar adipokines are frequently affected by drug treatments led to this limitation in our study. Due to the heterogeneous treatment protocol applied according to the clinical course in COVID-19 patients, the metrnl levels were not measured before discharge.

CONCLUSION

In conclusion, corticosteroid therapy is one of the most important criteria in the follow-up and prognosis of the treatment of COVID-19. Even though several antiviral medications were explored, corticosteroid treatment provided better results in terms of survival and clinical course. As a result, as demonstrated in our study, early corticosteroid treatment may be an efficient strategy for shortening the poor clinical course and hospitalization in the population whose metrnl levels are low at the time of diagnosis.

ETHICS COMMITTEE APPROVAL

This study was approved by Atatürk University Faculty of Medicine Clinical Research Ethics Committee (Decision no: B.30.2.ATA.0.01.00/406, Date: 28.04.2022).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: DEA, EL

Analysis/Interpretation: EL

Data Collection or Processing: DEA

Writing: DEA

Review and Correction: EL

Final Approval: EL

REFERENCES

1. *Kerget B, Çelik E, Kerget F, Aksakal A, Uçar EY, Araz Ö, et al. Evaluation of 3-month follow-up of patients with post-acute COVID-19 syndrome. J Med Virol 2022;94:2026-34. https://doi.org/10.1002/jmv.27579*
2. *Köktürk N, Babayiğit C, Kul S, Çetinkaya PD, Naycı SA, Barış SA, et al. The predictors of COVID-19 mortality in a nationwide cohort of Turkish patients. Respir Med 2021;183:106433. https://doi.org/10.1016/j.rmed.2021.106433*
3. *Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. Inflamm Regen 2020;40:1-6. https://doi.org/10.1186/s41232-020-00131-w*
4. *Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: Pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol 2020;39:2085-94. https://doi.org/10.1007/s10067-020-05190-5*
5. *Annane D. Corticosteroids for COVID-19. J Intensive Med 2021;1:14-25. https://doi.org/10.1016/j.jointm.2021.01.002*
6. *Corral-Gudino L, Bahamonde A, Arnaiz-Revillas F, Gómez-Barquero J, Abadía-Otero J, García-Ibarbia C, et al. Methylprednisolone in adults hospitalized with COVID-19 pneumonia. Wien Klin Wochenschr 2021;133:303-11. https://doi.org/10.1007/s00508-020-01805-8*
7. *Chaudhuri D, Sasaki K, Karkar A, Sharif S, Lewis K, Mammen MJ, et al. Corticosteroids in COVID-19 and non-COVID-19 ARDS: A systematic review and meta-analysis. Intensive Care Med 2021;47:521-37. https://doi.org/10.1007/s00134-021-06394-2*
8. *Zheng SI, Li ZY, Song J, Liu JM, Miao CY. Metrnl: A secreted protein with new emerging functions. Acta Pharmacol Sin 2016;37:571-9. https://doi.org/10.1038/aps.2016.9*
9. *Wang K, Li F, Wang C, Deng Y, Cao Z, Cui Y, et al. Serum levels of meteorin-like (metrnl) are increased in patients with newly diagnosed type 2 diabetes mellitus and are associated with insulin resistance. Med Sci Monit 2019;25:2337-43. https://doi.org/10.12659/MSM.915331*
10. *Miao ZW, Hu WJ, Li ZZ, Miao CY. Involvement of the secreted protein metrnl in human diseases. Acta Pharmacol Sin 2020;41:1525-30. https://doi.org/10.1038/s41401-020-00529-9*
11. *T.C. Sağlık Bakanlığı. Available from: https://covid19.saglik.gov.tr/Eklenti/43095/0/covid-19rehberieriskinhastayonetimivetedavi-12042022pdf.pdf (Erişim tarihi: 12.04.2022).*
12. *Akçay MŞ, Özlü T, Yılmaz A. Radiological approaches to COVID-19 pneumonia. Turk J Med Sci 2020;50:604-10. https://doi.org/10.3906/sag-2004-160*
13. *Sjoding MW, Hofer TP, Co I, Courey A, Cooke CR, Iwashyna TJ. Interobserver reliability of the Berlin ARDS definition and strategies to improve the reliability of ARDS diagnosis. Chest 2018;153:361-7. https://doi.org/10.1016/j.chest.2017.11.037*
14. *Brodeur A, Gray D, Islam A, Bhuiyan S. A literature review of the economics of COVID-19. J Econ Surv 2021;35:1007-44. https://doi.org/10.1111/joes.12423*
15. *Yamasaki K, Eeden SFV. Lung macrophage phenotypes and functional responses: Role in the pathogenesis of COPD. Int J of Mol Sci 2018;19:582. https://doi.org/10.3390/ijms19020582*
16. *Kopf M, Schneider C, Nobs SP. The development and function of lung-resident macrophages and dendritic cells. Nat Immunol 2015;16:36-44. https://doi.org/10.1038/ni.3052*
17. *Binger KJ, Gebhardt M, Heinig M, Rintisch C, Schroeder A, Neuhofer W, et al. High salt reduces the activation of IL-4-and IL-13-stimulated macrophages. J Clin Invest 2015;125:4223-38. https://doi.org/10.1172/JCI80919*
18. *Ushach I, Arrevillaga-Boni G, Heller GN, Pone E, Hernandez-Ruiz M, Catalan-Dibene J, et al. Meteorin-like/Meteorin-β is a novel immunoregulatory cytokine associated with inflammation. J Immunol 2018;201:3669-76. https://doi.org/10.4049/jimmunol.1800435*
19. *Kerget B, Afşin DE, Kerget F, Aşkın S, Akgün M. Is metrnl an adipokine involved in the anti-inflammatory response to acute exacerbations of COPD? Lung 2020;198:307-14. https://doi.org/10.1007/s00408-020-00327-4*

Address for Correspondence/Yazışma Adresi

Dr. Dursun Erol AFŞİN

Clinic of Chest Diseases,
Erzurum Regional Training and Research Hospital,
Erzurum-Türkiye

E-posta: d.erol@hotmail.com