DETERMINING SERUM ASYMMETRIC DIMETHYLARGININE (ADMA) LEVEL IN COVID-19 PNEUMONIA AND ITS RELATION WITH THROMBOSIS AND MORTALITY ADMA LEVEL IN COVID-19 PNEUMONIA

COVİD-19 PNÖMONİSİNDE SERUM ASİMETRİK DİMETİLARJİNİN (ADMA) DÜZEYİNİN TESPİTİ VE TROMBOZ, MORTALİTE İLE İLİŞKİSİNİN BELİRLENMESİ COVİD-19 PNÖMONİSİNDE ADMA DÜZEYİNİN TESPİTİ

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ABSTRACT

Objective: COVID-19 can cause widespread inflammation in endothelial cells. Asymmetric dimethylarginine (ADMA) is a molecule recognized as an important marker of vascular endothelial dysfunction. The aim of this study was to determine serum ADMA levels during the course of COVID-19 pneumonia and to assess the relationship between serum ADMA levels, susceptibility to thrombosis, and mortality. Another aim of this study was to identify mortality-associated risk factors and evaluate the effectiveness of different sepsis scores, laboratory measurements, and prognostic markers.

Materials and Methods: Data from 60 patients diagnosed with COVID-19 pneumonia were analyzed. Blood samples for ADMA measurement were collected in the morning within the first three days after symptom onset. Additionally, samples were collected from 60 healthy volunteers to serve as a control group.

Results: The mean serum ADMA level in inpatients with COVID-19 pneumonia was 95.35 ± 223.8 ng/mL, while the mean level in the control group was 266.56 ± 606.14 ng/mL. The ADMA level in COVID-19 patients was found to be significantly lower compared to the control group (p = 0.042). The inpatient mortality rate was 21%. Mortality was significantly associated with higher SOFA and qSOFA scores at admission.

Conclusion: Serum ADMA concentrations measured in the early period of hospitalization were found to be significantly lower in patients with COVID-19 pneumonia compared to the control group. It is important to note that patients with a SOFA score ≥ 3, qSOFA score ≥ 1, CRP/Albumin ratio ≥ 30, and Neutrophil/Lymphocyte Ratio ≥ 5 are at high risk of mortality and require early intervention.

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ÖZET

Amaç: Covid-19, endotel hücrelerinde yaygın inflamasyona neden olabilir. Asimetrik dimetilarjinin (ADMA), vasküler endotel disfonksiyonunun önemli belirteçlerinden olarak kabul edilen bir moleküldür. Bu çalışmanın amacı, Covid pnömonisinin seyri sırasında serum ADMA düzeyini saptayıp, serum ADMA düzeyi ile tromboza yatkınlık ve mortalite arasındaki ilişkiyi belirlemektir. Çalışmanın diğer bir amacı da mortaliteyle ilişkili risk faktörlerini belirlemek ve farklı sepsis skorlarının, laboratuvar ölçümlerinin ve prognostik belirteçlerin etkinliğini araştırmaktır.

Gereç ve Yöntemler: Covid-19 pnömonisi tanısı alan 60 hastanın verileri analiz edildi. ADMA için kan örnekleri, pnömonisi olan hastalarda semptom başlangıcından sonraki ilk 3 gün sabah saatlerinde ve 60 sağlıklı gönüllüden alındı.

Bulgular: Hastaneye yatan covid pnömonili hastaların ortalama serum ADMA düzeyi 95,35±223,8 ng/mL idi. Kontrol grubunda ölçülen ortalama serum ADMA düzeyi 266,56±606,14 ng/mL idi. Covid hastalarında ölçülen ADMA değerinin kontrol grubuna göre anlamlı derecede düşük olduğu görüldü. (p 0,042) Yatan hastalardaki ölüm oranı %21 idi. Ölüm oranı, başvuru anında daha yüksek düzeyde saptanan SOFA ve qSOFA düzeyleri ile ilişkiliydi.

Sonuç: Hastaneye yatışın erken döneminde ölçülen serum ADMA konsantrasyonunun Covid-19 pnömonisi olan hastalarda kontrol grubuna göre anlamlı derecede düşük olduğu belirlendi. SOFA skoru≥3, qSOFA skoru≥1, CRP/Albümin oranı≥30 ve Nötrofil/Lenfosit Oranı ≥5 olan vakaların mortalite riskinin yüksek olduğu ve erken müdahale gerektirdiği unutulmamalıdır.

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Introduction

A novel coronavirus causing severe acute respiratory syndrome was identified in 2019 and named COVID-19. The disease, which led to a global pandemic, often progresses with many asymptomatic cases (1). Dyspnea and hypoxemia are indicators of severe disease and typically appear approximately one week after symptom onset (2). Complications in affected patients may include atypical pneumonia, respiratory failure, acute respiratory distress syndrome (ARDS), acute renal failure, venous thromboembolism, pulmonary embolism, disseminated intravascular coagulation (DIC), and death (3).

The upper and lower respiratory tracts are the primary sites of infection in COVID-19 pneumonia. A study by Varga et al. in 2020 provided evidence that COVID-19 can cause widespread inflammation in endothelial cells (4). Exacerbation of endothelial dysfunction may impair organ perfusion and contribute to severe disease progression. In addition to endothelial dysfunction, several other mechanisms—such as disseminated intravascular coagulation syndrome, cytokine storm, antiphospholipid antibody syndrome, macrophage activation syndrome, complement activation, and dysregulation of the renin-angiotensin-aldosterone system—may play a role in the pathogenesis of thrombosis during the course of viral infection.

Asymmetric dimethylarginine (ADMA) is a molecule recognized as an important marker of vascular endothelial dysfunction (5). Nitric oxide (NO), the most important vasodilator produced by the endothelium, plays a key role in maintaining vascular health. ADMA is an endogenous competitive inhibitor of endothelial nitric oxide synthase (eNOS), reducing both the production and bioavailability of NO. A decrease in NO production can contribute to the development and progression of atherosclerosis and thrombosis.

Numerous studies in the literature focus on cytokines, particularly interleukin-6 (IL-6), a key marker of the cytokine storm involved in the pathogenesis of COVID-19 (6). However, the relationship between ADMA—an established marker of endotheliitis—and COVID-19 infection remains unclear.

COVID-19 pneumonia can become life-threatening when complications arise, making it vitally important to identify high-risk patients early and initiate appropriate treatment promptly. Determining which patients require intensive care can be challenging and should be based on individual, patient-centered assessments. However, understanding the key prognostic factors in this clinically complex group can greatly aid in patient management. Therefore, reliable prognostic indicators are essential for identifying severe disease and guiding clinical decisions.

The Quick Sequential Organ Failure Assessment (qSOFA) is a scoring system designed to quickly and easily assess the risk of mortality associated with sepsis, without the need for laboratory tests. It is particularly useful at the time of emergency department presentation (7). In contrast, the Sequential Organ Failure Assessment (SOFA) score is a comprehensive tool developed to predict survival in intensive care patients with severe organ dysfunction or failure. Although it is not intended to diagnose sepsis, it is highly effective in identifying patients at high risk of death (8).

The aim of this study was to determine serum ADMA levels—known to be associated with endothelial dysfunction—during the course of COVID-19 pneumonia, and to assess the relationship between serum ADMA levels,

susceptibility to thrombosis, and mortality. Another objective was to identify mortality-associated risk factors in patients hospitalized with COVID-19 pneumonia and to evaluate the effectiveness of various sepsis scores, laboratory parameters, and prognostic markers in predicting mortality in this clinical population.

Material and Methods

Data from 60 patients admitted to the internal medicine and infectious diseases clinics with a diagnosis of COVID-19 pneumonia were analyzed. Real-time polymerase chain reaction (RT-PCR), the gold standard for diagnosing SARS-CoV-2, was performed on nasal and throat swab samples taken in the emergency department. Regardless of RT-PCR results, patients showing typical signs of COVID-19 pneumonia on thoracic computed tomography (CT) were included in the study.

All patients were isolated and treated according to their individual clinical needs. Depending on disease severity and the presence of respiratory distress, some patients were transferred to the intensive care unit for follow-up. Blood samples for ADMA measurement were collected in the morning within the first three days after symptom onset and stored at –80 °C until analysis. The healthy volunteer group consisted of individuals aged 18–90 years who presented to the internal medicine outpatient clinic, had no history of COVID-19 infection, and no known history of thrombosis. Their blood samples were also collected in the morning.

qSOFA and SOFA scores were calculated for each patient at the time of admission to the clinic, and again upon transfer to the intensive care unit, if applicable. Based on laboratory data obtained at hospital admission, the Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Monocyte/Lymphocyte Ratio (MLR) were also calculated.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as frequencies and percentages (n, %) for categorical variables, and as mean ± standard deviation (SD) or median with interquartile range (IQR) for continuous variables.

When the data of the study were analyzed in terms of normality assumptions, Independent t-test, one of the parametric tests, was applied to determine whether there was a significant difference between Kolmogorov-Smirnov values between ADMA groups. Cox regression model was used for multivariate analysis. Chi Square test was used to compare categorical variables. receiver operating characteristic (ROC) analysis results regarding the prediction of death by ADMA scores are given. Kaplan-Meier method was used to compare survival times between covid-19 pneumonia and control groups. $p<0.05$ was considered statistically significant. We determined the optimum cutoff points for the SOFA, qSOFA, CAR, NLR, PLR, MLR as a predictor for hospital survival based on the ROC curve. Gender, age, SOFA, qSOFA, CAR, NLR, PLR, MLR scores all were tested in the multivariate analysis. $p < 0.05$ was considered statistically significant.

Measurement of ADMA

Serum ADMA levels in both patient and control groups were analyzed using the enzyme-linked immunosorbent assay (ELISA) method on a Biotek semi-automatic ELISA device (Elabscience, 14780 Memorial Drive, Suite 216, Houston, Texas 77079), employing ELISA kits with a coefficient of variation (CV%) of 10%. After serum samples were thawed at room temperature, precipitated protein molecules at

the bottom were resuspended using a vortex mixer to ensure a homogeneous mixture. The analysis was conducted in accordance with the test procedure provided in the ELISA kit. Serum samples were evaluated using the competitive ELISA method, and absorbance values were measured spectrophotometrically at 450 nm. ADMA concentrations were calculated based on the standard absorbance curve generated from the known standards.

Results

Sixty patients diagnosed with COVID-19 pneumonia and admitted to the clinic were included in this study. Among them, 52 patients (87%) had a positive COVID-19 PCR test, and all cases were confirmed by high-resolution thoracic computed tomography (CT). Sixteen patients experienced a deterioration in their general condition and were transferred to the intensive care unit (ICU). Of these ICU patients, 15 developed respiratory failure. Invasive mechanical ventilation was initiated in 6 patients, noninvasive ventilation in 4, and high-flow oxygen therapy via face mask in 6. One patient was transferred to the ICU due to intracranial hemorrhage. All patients who required invasive mechanical ventilation died. Additionally, 3 patients received positive inotropic or vasopressor support upon ICU admission. In total, 13 of the 16 ICU-admitted patients died.

The characteristics of patients diagnosed with COVID-19 pneumonia and those in the control group are summarized in **Table 1**.

Table 1. *Patients characteristics of Covid-19 pneumonia and control group*

	Control group (n:60)	Covid-19 pneumonia (n:60)	*p*-value
Age (years)	62.86±14	62.5±17	0.90[a]
Gender (male/female)	29/31	24/36	0.36[b]
Hemoglobin (mean±SD.g/dL)	13.38±1.6	11.96±2	**0.0001[a]**
Lymphocyte(mean±SD.10^9/L)	2.6±8.6	1.4±1.5	**0.004[a]**
Platelet (mean±SD.10^9/L)	234±81	226±102	0.63[a]
Albumine (mean±SD. g/L)	4.45±0.3	3.35±0.5	**0.0001[a]**
C-reactive protein (mg/L)	5.89±14	98±84	**0.0001[a]**
eGFR (ml/min)	78±21	69±32	0.07[a]
D-dimer (ng/ml)	164±171	877±140	**0.001[a]**
Ferritin (ug/L)	54.8±59	451±494	**0.0001[a]**
ADMA (ng/ml)	266±56	95.35±223	0.042[a]
LDH (U/L)	167±40	316±166	**0.0001[a]**

[a]:independent t test, [b]:Chi Square test. **GFR,** glomerular filtration rate **ADMA**, asymmetric dimethylarginine **LDH**, Lactic dehydrogenase

The mean serum ADMA level in inpatients with COVID-19 pneumonia was 95.35 ± 223.8 ng/mL (range: 12.2–1705), whereas the mean level in the control group was 266 ng/mL. The ADMA level in COVID-19 patients was significantly lower compared to the control group (p = 0.042).

Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cutoff point for serum ADMA levels. The median ADMA level was 40.88 ng/mL. Based on this cutoff, patients were categorized into two groups: a high ADMA group (≥ 40.88 ng/mL) and a low ADMA group (< 40.88 ng/mL), with a sensitivity of 62% and specificity of 38%. A total of 25 patients (41.6%) had low ADMA levels, while 35 patients (58.3%) had high ADMA levels. According to these classifications, there was no statistically significant association between ADMA levels and survival in the intensive care unit (p = 0.55).

Among the 60 patients included in the study, one developed acute ischemic cerebrovascular disease during hospitalization, and another developed lower extremity arterial thrombosis. Additionally, one patient was treated for a left iliac arterial thrombus one month after discharge. Due to the low number of patients with acute thrombotic events, no statistically significant relationship could be established between thrombosis and serum ADMA levels.

Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal cutoff points for the SOFA and qSOFA scores, as well as the NLR, PLR, MLR, and CAR ratios (**Table 2**). Patients with high SOFA scores were found to have significantly longer hospital stays (p = 0.0001).

Table 2. *Roc curve analysis for Covid-19 pneumonia patients.*

	Cut-off	Sensitivity %	Spesificity %	p
SOFA	2,5	62	38	0,0001*
qSOFA	0,5	20	77	0.008*
NLR	5,52	53	45	0,003*
PLR	189,83	46	53	0,34
LMR	0,40	54	40	0,12
CAR	29,36	31	69	0,05*
AST/ALT	1,33	40	54	0,017*

SOFA: Sequential Organ Failure Assessment; qSOFA: quick Sepsis-related Organ Failure Assessment; NRL: Neutrophil-Lymphocyte Ratio; PLR: Platelet-Lymphocyte Ratio; LMR: Lymphocyte-to-Monocyte Ratio; CAR: C-reactive Protein-Albumin Ratio; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; *p<0,05 statistically significant.

A total of 46 patients had a low qSOFA score, and these patients were found to have a significantly shorter duration of hospitalization (p = 0.008).

Patients with a high CRP/Albumin Ratio (CAR) had a mean hospitalization time of 23.8 ± 3.8 days (range: 16.2–31.5), which was significantly longer (p = 0.05). Among the 29 patients with a high Neutrophil/Lymphocyte Ratio (NLR), eight died, and the mean hospitalization time was 23.6 ± 2.9 days (range: 17.8–29.4), also significantly prolonged (p = 0.03). **Table 3** summarizes the patients' mean laboratory findings measured at the time of admission and during hospitalization.

Table 3. Laboratory findings and mean hospital stays of patients with Covid-19 pneumonia patients

Laboratory findings	Number of patients	Mean hospital stay	P value
Lymphocytes,x10^9/ml			0,18
<800	17	21,7±3(15-28,5)	
>800	43	16±2(12-20)	
Platelets,x10^9/ml			0,15
<100.000	13	21±2,7(15-26)	
>100,000	47	17±2(1,9-21)	
CRP,mg/dl			0,001*
<50	21	11±1,3(9-14,4)	
>50	29	22,5±2,7(17-28)	
D-dimer,ng/ml			0,57
≤1000	51	17,9±2(14-22)	
>1000	9	18±2,9(12,4-23,8)	
Ferritin,ml/ng			0,07
<500	44	16,3±2(12-20,4)	
>500	16	23,3±3,5(16-30,2)	

CRP: C-reactive Protein-Albumin Ratio. *p<0,05 statistically significant

Sex, age, platelet count, lymphocyte count, ferritin levels, and D-dimer levels were not found to have a significant impact on mortality or total hospitalization time.

Discussion

This is a prospective study designed to evaluate the efficacy of serum ADMA levels—an indicator of endothelial dysfunction—in predicting length of hospital stay, thrombosis, and mortality in patients hospitalized with COVID-19 pneumonia.

Deaths associated with COVID-19 pneumonia have been reported at varying rates, ranging from 16% to 78% across different studies. A large study involving 20,133 patients reported an in-hospital mortality rate of 26% for those in general wards, with even higher rates among patients treated in intensive care units (ICUs) (9). In our study, the mortality rate was found to be 21%, which is consistent with findings in the existing literature.

ADMA is an endogenous inhibitor of nitric oxide (NO) synthesis. Its accumulation leads to inhibition of NO-mediated vasodilation, resulting in endothelial dysfunction. Elevated ADMA levels have been identified as an independent risk factor for cardiovascular diseases. A comprehensive meta-analysis involving 19,842 patients across 22 studies found a significantly increased risk of coronary artery disease and stroke in individuals with high ADMA levels (10). Additionally, several studies have shown that elevated ADMA levels are associated with increased short- and long-term mortality in critically ill patients (11).

The primary site of infection in COVID-19 pneumonia is the upper and lower respiratory tract. The relationship between respiratory tract diseases and ADMA levels has been explored in

several studies. In 2017, Vögeli et al. investigated the association between ADMA levels and mortality in 268 patients with community-acquired pneumonia (12). They found that ADMA levels were not a strong predictor of 30-day mortality (p = 0.086). However, elevated ADMA levels were associated with long-term mortality over a six-year follow-up, though this correlation was largely attributed to comorbidities and advanced age. Additionally, ADMA, a known nitric oxide synthase (NOS) inhibitor, has been detected in the sputum of patients with chronic obstructive pulmonary disease (COPD), another respiratory tract condition (13).

Only one study in the literature has examined the relationship between ADMA levels, mortality, and organ failure in patients diagnosed with COVID-19 pneumonia. This was a retrospective study involving just 31 patients, and it did not specify whether the patients had pneumonia. Serum ADMA concentrations were measured at admission, and levels were found to be higher in the 9 patients who died compared to those who survived (14). Notably, 16 of the patients in that study were diagnosed with COVID-19 pneumonia at other centers and referred to the study center only after requiring mechanical ventilation. The time interval between COVID-19 diagnosis and the development of respiratory failure was not clearly reported. Furthermore, only 15 patients were included at the time of diagnosis. Despite this, ADMA levels at admission were relatively low. n contrast, our study was a prospective investigation specifically involving patients diagnosed with COVID-19 pneumonia. Serum ADMA concentrations were measured in 60 patients using blood samples collected at the time of hospital admission. In our findings, ADMA levels were significantly lower in patients with COVID-19 pneumonia compared to the control group (p = 0.042). However, no significant relationship was observed between ADMA levels and length of hospital stay.

Low ADMA levels were first reported in 2003 in blood samples of 25 mice with endotoxemia (15). Subsequently, a prospective study involving 17 healthy young volunteers without comorbidities showed a decrease in serum ADMA levels 3.5 hours after injection of *Escherichia coli* (16). In our study, blood samples were collected within hours of diagnosis and stored under appropriate conditions. These findings suggest that ADMA levels in infection-related conditions may vary depending on the stage of the disease, with levels potentially being lower in the early phase.

The pathogenesis of COVID-19 has not yet been fully clarified. In patients admitted to intensive care units (ICUs), the primary cause of death is often related to viral sepsis. Some studies have reported a relationship between the severity of sepsis and plasma ADMA levels, while others have not found significant associations (17). A prospective study conducted in 2012 involving 27 ICU patients with septic shock and 17 with cardiogenic shock found no correlation between in-hospital mortality and ADMA levels measured at ICU admission (18). In contrast, another prospective study involving young ICU patients with sepsis reported lower ADMA levels on the first day of admission compared to healthy volunteers (19). The lack of serious comorbidities in this younger patient group was a notable strength, as it excluded additional risk factors known to elevate ADMA levels—such as kidney failure, atherosclerosis, and liver dysfunction—which are more common in older populations.

In patients with COVID-19 pneumonia, D-dimer, ferritin, C-reactive protein (CRP), and lactate dehydrogenase (LDH) levels measured

at admission were significantly elevated compared to the control group, consistent with findings in the literature (20). Natural killer (NK) cells and cytotoxic T lymphocytes play a critical role in the immune response to viral infections. Recent studies have shown that patients with severe COVID-19 pneumonia often present with lymphopenia, and lymphocyte levels are significantly lower in patients who succumb to the disease compared to survivors (21). In our study, lymphocyte counts were also significantly lower in COVID-19 patients compared to the control group ($p = 0.004$), and patients with lymphopenia had a longer duration of hospitalization.

Another aim of this study was to investigate the relationship between ADMA levels and thrombosis in patients with COVID-19 pneumonia, given that ADMA is a key marker of vascular endothelial dysfunction and is associated with atherosclerosis. Among the 60 patients included in the study, one developed acute ischemic cerebrovascular disease during hospitalization, while another developed lower extremity arterial thrombosis, underwent peripheral angiography, and subsequently received a stent. Both of these patients died during hospitalization. A third patient was treated for a left iliac arterial thrombus one month after discharge. In total, three patients experienced a thrombotic event. Due to the small number of such cases, a meaningful statistical relationship between ADMA levels and thrombosis could not be established.

The SOFA score is commonly used as a prognostic tool to assess organ dysfunction in critically ill patients, including those with chronic liver disease, hematological malignancies, and other severe conditions (22). In the context of COVID-19 pneumonia, several studies have demonstrated the prognostic value of the SOFA score, with a mean score of 2 reported among patients who later died (23, 24). Our study specifically focuses on a subset of COVID-19 patients with pneumonia—a group that holds a distinct clinical profile within the broader COVID-19 population. The mean SOFA score calculated at the time of hospital admission for all patients in our cohort was 2.43 ± 1.5 (range: 0–6), slightly higher than values reported in the literature. This elevated score was expected, given the severity of illness in this pneumonic subgroup. Among patients who later required intensive care, the mean ICU SOFA score was 5.18 ± 3.2 (range: 2–14), supporting findings by Raschke et al. in ICU patients requiring mechanical ventilation (25). These results suggest that initial SOFA scores may be insufficient for long-term prognostic assessment, as the clinical condition and laboratory parameters of patients evolve over time. Serial measurements may provide more meaningful insights into disease progression and outcomes.

In our study, consistent with the findings of Liu et al., patients with a qSOFA score of 1 or higher exhibited increased mortality rates (26). Notably, all patients in our cohort who had a high qSOFA score (≥ 1) at the time of referral to the intensive care unit died ($p = 0.07$). Given that the qSOFA score can be quickly and easily calculated at the bedside without the need for laboratory tests, it should be considered a valuable prognostic tool—especially during the COVID-19 pandemic, which has placed a significant burden on emergency services.

C-reactive protein (CRP), an acute-phase reactant, has been reported to increase in cases of COVID-19 pneumonia and may serve as an early predictor of severe infection—even before radiological findings are evident on CT scans (27). In our study, elevated CRP levels at the time of referral were significantly associated with prolonged hospitalization. Another pa-

rameter that showed a significant association with both hospitalization time and mortality was the CRP/albumin ratio (CAR). This finding is consistent with previous studies in the literature (28). Given that both CRP and albumin can be easily measured in most healthcare settings, these two parameters may serve as practical and accessible tools for predicting disease severity at the time of patient admission.

Recently, the Neutrophil/Lymphocyte Ratio (NLR), Platelet/Lymphocyte Ratio (PLR), and Monocyte/Lymphocyte Ratio (MLR) have been increasingly utilized as prognostic indicators in various inflammatory conditions. These ratios have shown potential as useful parameters in assessing disease progression and prognosis in patients with COVID-19 pneumonia as well.

In a retrospective analysis of clinical data from 443 COVID-19 pneumonia cases, Shang et al. reported that NLR, CRP, and platelet counts could aid in assessing disease severity, with NLR identified as the most reliable marker among them (29). The association between elevated NLR and increased disease severity in COVID-19 pneumonia has also been confirmed by other studies (30). In our study, although patients with low lymphocyte counts had longer hospitalization durations, this difference was not statistically significant. However, patients with higher NLR values exhibited both longer hospitalization times and higher mortality rates ($p = 0.03$). In contrast, PLR and MLR ratios were not effective in predicting prognosis in our patient cohort.

Limitations

The patient group included individuals with comorbidities known to increase plasma ADMA levels. Some studies have reported elevated ADMA levels, particularly in patients with active infections such as chronic obstructive pulmonary disease (COPD) (31). Despite the presence of comorbidities, ADMA levels in our patient group were lower than those in the control group. It is important to note that plasma ADMA levels were measured only once—using blood samples obtained at admission—and were not monitored during the follow-up period. Serial measurements could have provided insight into dynamic changes in ADMA levels over the course of the illness. Additionally, the number of patients who experienced thrombotic events was low, likely due to the limited sample size.

Conclusion

Serum ADMA concentrations measured in the early period of hospitalization were found to be significantly lower in patients with COVID-19 pneumonia compared to the control group. However, no correlation was observed between ADMA levels and length of hospital stay. Given the complex and not yet fully understood pathogenesis of COVID-19, larger prospective studies are needed to further evaluate the role of ADMA as a marker of endothelial dysfunction. COVID-19 pneumonia cases requiring ICU admission continue to have high mortality rates. Therefore, assessing the degree of organ dysfunction is essential when making decisions about hospitalization and ICU referral. It is important to recognize that patients with a SOFA score ≥ 3, qSOFA score ≥ 1, CRP/Albumin ratio ≥ 30, and Neutrophil/Lymphocyte Ratio ≥ 5 are at high risk of mortality and require early and aggressive clinical intervention.

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