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Genel Yoğun Bakım Ünitesinde Yatan COVID 19 Hastalarında Mortaliteyi Öngörmede İnflamasyon İndekslerinin Prediktif Değerleri

Predictive Values of Inflammation Indexes in Predicting Mortality in Patients with COVID 19 Hospitalized in General Intensive Care Unit

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ÖZ

Amaç: Küresel bir pandemiye neden olan koronavirüs hastalığı 2019 (COVID-19), milyonlarca insanın enfekte olmasına ve birçok insanın ölmesine neden oldu. Bu çalışmada rutin olarak değerlendirilen klinik ve laboratuvar değerlerinin COVID-19 hastalığı olan hastaların mortalitesini tahmin edip edemeyeceğini araştırmayı amaçladık.

Materyal ve Metot: Çalışmamızda COVID 19 tanısı ile genel yoğun bakım ünitesinde yatırılan 89 hastanın rutin laboratuvar parametreleri retrospektif olarak incelendi. Sistemik inflamasyonun agregat indeksi (AISI) ve diğer infalamatuar değerler COVID-19 polimeraz zincir reaksiyonu testi pozitif olan ve akciğer tomografisinde buzlu cam opasitesi olan hastalarda yapılan kan testlerinden hesaplandı. Hastalar yoğun bakım takiplerinde ölenler (sağ kalamayanlar) ve taburcu olanlar (sağ kalanlar) olarak iki gruba ayrıldı.

Bulgular: Çalışmamızda takipte ölen 48 hastada AISI, diğer inflamatuar parametreler, ferritin, troponin I, d-dimer ve prokalsitonin gibi biyokimyasal paramtereler taburcu edilen hastalardan anlamlı derecede yüksekti. Hipertansiyon ve daha yüksek AISI ve ferritin seviyeleri, Cox regresyon analizinde azalmış sağkalım ile istatistiksel olarak ilişkiliydi (Sırasıyla: Risk oranı (RO)=3,176;%95 Güven aralığı (GA), 1,122-8,991,P=0,03, RO=1,114; %95 GA, 1,060-1,348, P=0,042 ve RO=1,072;95% GA,1,014-1,242, P=0,011).

Sonuç: Kan testlerinden elde edilen inflamasyon indeksleri ile ferritin gibi akut faz reaktanları, yoğun bakım takiplerinde COVID-19'lu hastalarda tedavi stratejisini ve risk sınıflandırmasını planlamada bize yol gösterebilir.

Anahtar Kelimeler: İnflamasyon, kan parametreleri, koronavirüs 2019 hastalığı, pandemi

ABSTRACT

Objective: Causing a global pandemic, the coronavirus disease 2019 (COVID-19) has caused millions of people to become infected and many more to die. In this study we aimed to investigate whether routinely evaluated clinical and laboratory values can predict the mortality of patients with COVID-19 disease.

Materials and Methods: In our study, routine laboratory parameters of 89 patients hospitalized in the general intensive care unit with the diagnosis of COVID 19 were retrospectively analyzed. The aggregate index of systemic inflammation (AISI) and other inflamatuar values were calculated from blood tests in patients with positive COVID-19 polymerase chain reaction test and with ground-glass opacity on lung tomography. Patients were divided into two groups as those who died (non-survivors) and those who were discharged (survivors) during the intensive care follow-ups.

Results: In our study, in 48 patients who died during follow-up, the indexes of AISI, other inflamatuar paramaters and the biochemical parameters such as troponin I, d-dimer, ferritin and procalcitonin were significantly higher than in discharged patients. Hypertension and higher AISI and ferritin levels were statistically associated with reduced survival in Cox regression analysis (Hazard ration (HR): 3.176; 95% Confident interval (CI): 1.122-8.991, p=0.03, HR: 1.114; 95% CI: 1.060-1.348, p=0.042, HR=1.072;95% CI: 1.014-1.242, p=0.011, respectively.

Conclusion: Inflammation indexes derived from blood tests and acute phase reactants such as ferritin can guide us in planning the treatment strategy and risk stratification in patients with COVID-19 in intensive care follow-ups.

Keywords: Blood parameters, coronavirus 2019 disease, inflammation, pandemic

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INTRODUCTION

The Coronavirus disease 2019 (COVID-19) outbreak, which caused the death of 2.2 million patients by infecting 100 million people worldwide, was first identified as pneumonia of unknown origin in Wuhan, China. [1] In June 2020, the outbreak reported in Japan then spread to Europe and America. The disease has been declared as a global pandemic by the world health organization(WHO). Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), the pathogen of coronavirus disease 2019 (COVID-19), severe acute respiratory syndrome-CoV (SARS-CoV), and Middle East Respiratory Syndrome-CoV (MERS-CoV), are viruses, that belong to the β genus CoV family.[2] Although most people have mild symptoms, it can cause acute respiratory distress syndrome (ARDS) in some patients.[3]

COVID-19 can cause cytokine storms, multi-organ failure, sepsis, and thrombosis. Long-term damage has been observed in organs, especially the lungs and heart. Despite having gone through the acute phase of the disease, many patients continue to experience various effects for months.[4] The severity of the disease in patients with COVID-19 is evaluated as mild, moderate, and severe according to the laboratory tests, clinical symptoms, and the level of involvement in the lung tomography. While the majority of patients (average 81%) have mild or moderate symptoms, such as subfebrile fever and cough, twenty percent of them have to be followed up in the intensive care unit.[3] The mortality rate of intensive care units is around 61.5%.[5] There is a need for inexpensive, useful biomarkers that can determine the severity of the disease in early diagnosis and help early aggressive treatment. Routine blood analysis, which is easily studied in all kinds of hospital conditions, can guide us in the diagnosis and treatment of the inflammatory process.[6]

Complete blood analysis can easily give us information about the number and structure of defense cells such as lymphocytes, neutrophils, and monocytes. Furthermore, combined ratios of these parameters can be useful for diagnosis, treatment, and risk stratification. In several studies.[7] It has been determined that the neutrophil to lymphocyte ratio (NLR), derived NLR (dNLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), and systemic inflammation response index (SIRI) were useful for the diagnosis and severity assessment of COVID-19.[8-9]

In our study, we examined the value of parameters such as ferritin, procalcitonin, and troponin I in predicting prognosis in intensive care patients, in addition to these indexes.

MATERIALS AND METHODS

Patients hospitalized in Faculty of Medicine, Tekirdag Namık Kemal University anesthesia intensive care unit (ICU) with the diagnosis of covid 19 between 1 November 2020 and 30 January 2021 were included in our study retrospectively. The study was carried out under the Helsinki declaration and was approved by Tekirdag Namık Kemal University hospital ethics committee (Date: 27/04/2021, decision no: 2021.107.04.02). In all patients, the diagnosis of COVID-19 disease was made by evaluating reverse transcription-polymerase chain reaction test (PCR) and lung tomographies. Intubated patients admitted to the ICU and patients with critical disease, malignancy, known systemic inflammatory disease, and serum creatinine values above 2 mg/dL were excluded from the study. For all our patients hospitalized in the intensive care unit with the diagnosis of COVID-19; ceftriaxone 1x2 grams intravenous, clarithromycin 2x500 milligrams intravenous, enoxaparin 2x0.6 cc subcutaneous, 3x300 milligrams intravenous acetylcysteine, 1x 500 mg ascorbic acid intravenously were given.

Then, a 2x600 mg oral loading dose of favipiravir, 2x1600 mg oral continued. 6 milligrams of dexamethasone intravenously was added to the treatment of patients with severe respiratory distress. Tocilizumab 400 milligrams intravenously was given to 3 patients in the non-survivor group, and immune plasma was given to one patient in the survivor group and two patients in the non-survivor group.

The demographic clinical characteristics and laboratory results of the patients were obtained from the electronic database of our hospital. Systemic inflammation indexes, respectively; NLR (neutrophil/ lymphocyte ratio), dNLR (neutrophils/(white blood cells -neutrophils)), PLR (platelet/lymphocyte ratio), MLR (monocyte/lymphocyte ratio), SIRI ((neutrophils ×monocytes)/lymphocytes), systemic immune inflammation index(SII) ((neutrophils ×platelets)/lymphocytes) and aggregate index of systemic inflammation (AISI) ((neutrophils× monocytes×platelets)/lymphocytes), LCR ((lymphocyte/C reactive protein (CRP) ratio)) were calculated from whole blood assays. The patients were divided into two groups as those who died(non -survivors) and those who were discharged (survivors) during the intensive care follow-ups.

Discharge criteria for patients were: (i) absence of fever for at least 3 days; (ii) signs of improvement on chest computed tomography scan or X-ray; (iii) the presence of two consecutive negative PCR tests performed at least 24 hours apart.

Blood parameters of the patients were measured from blood samples obtained from antecubital veins during ICU hospitalization. Whole blood counts

were performed with an automated whole blood analyzer, and biochemical values were measured with an automatic device. Systemic inflammation indexes were calculated.

Statistical Analysis: SPSS for WYndows VersYon 22.0 (SPSS Inc., IL, USA) was used for all statistical analysis. Continuous variables with normal distrubution were expressed as mean±standard deviation (SD) and categorical variables were expressed as a percentage. Non-normally distributed data were expressed as median and IQR (interquartile range). Descriptive analysis was performed for categorical data. Independent samples T-test was performed for data conforming to a normal distribution, and Mann-Whitney U test was used for data not compatible with a normal distribution. Whether the parameters conformed to the normal distribution was evaluated with the Kolmogorov Smirnov test. Differences between categorical variables were appropriately evaluated by the Fisher test or chi-square test. Receiver operating characteristics (ROC) curve analysis was performed to estimate optimal cut-off values of inflammation indexes. Cox regression analysis was used for hazard ratios of the indexes and other parameters. P <0.05 was considered statistically significant.

RESULTS

A total of 89 (54 men and 35 women) patients who were hospitalized in the ICU and diagnosed with COVID-19 by PCR test and lung tomography were included in the study (Table 1). The median age was 68 (IQR:28-93) years. Forty-one (46%) patients were discharged alive. The remaining 48 (53.9%) patients died during the intensive care follow-up. Most of the patients hospitalized in the intensive care unit had an accompanying chronic disease. Sixty (67.4%) of the patients had a history of hypertension. 37 (41.5%)of the patients were diabetic. Of the 89 patients, 22 (24.7%) had coronary artery disease, 9 (10.1%) had cerebrovascular disease, 17 (19.1%) had heart failure, and 15 (16.8%) had respiratory disease, respectively. The median hospitalization duration was 4 (1-26) days. The non-survivor group was older, although there was no statistically significant difference in age. (70 years, IQR: 41-93 years vs 66 years, IQR: 28-88 years p=0.052).When we look at the demographic characteristics of the patients, there was no difference between the two groups in terms of heart failure, diabetes, coronary artery disease, cerebrovascular disease, age, and gender distribution (Table 1).

Table 1. Demographic, clinical, and hematological features of COVID-19 survivors and non-survivors.

Variables	All Patients (n=89)	Survivors (n=41)	Non- Survivors (n=48)	P-value
Age(Years)	68 (28-93)	66 (28-88)	70 (41-93)	0.052
Gender(F/M)	35/54	20/21	15/33	0.09
Hospital stay(days)	4(1-26)	4(1-19)	4(1-26)	0.87
Respiratory Disease (No/Yes)	74/15	34/7	40/8	0.95
Diabetes(No/Yes)	52/37	25/16	27/21	0.65
Cerebrovascular disease (No/Yes)	80/9	36/5	44/4	0.54
Cardiovascular disease(No/Yes)	67/22	31/10	36/12	0.94
Heart Failure	72/17	32/9	40/8	0.52
Hypertension(No/Yes)	29/60	13/28	16/32	0.87
Wbc($x10^9$)	12.9(0.79-36.7)	12(1-24)	14.67(4-37)	<0.001
Monocytes($x10^9$)	0.781(0.12-23)	0.56(0.1-1)	0.82(0.12-23)	<0.001
Neutrophils($x10^9$)	10.5(0.32-32.5)	8.8(0.32-20)	12.39(4-33)	<0.001
Platelets($x10^9$)	200(16-776)	173(100-334)	225.5(16-776)	0.029
Lymphocytes($x10^9$)	0.8(0.15-6.53)	0.9(0.2-2.2)	0.63(0,15-6,5)	0.051
CRP (mg/L)	120(1.97-476)	82.04(2-338)	150.5(4-476)	0.004
D-dimer(mg/L)	2.17(0.19-35.2)	1.78(0.19-35)	2.37(0.19-35)	0.043
Fibrinogen(mg/dl)	407(56.1-935)	397.3(150-935)	421(56-900)	0.62
Ferritin(ng/ml)	730(25.3-72852)	361.7(25-6260)	1906(74-72852)	<0.001
Procalcitonin(ng/ml)	0.44(0.02-10.95)	0.18(0.02-5)	0.71(0.18-11)	<0.001
Troponin I(ng/l)	25(3-1100)	17(3-1100)	32.5(5-437)	0.007
AST (IU/L)	39(8-1459)	23(8-106)	78.5(24-1459)	<0.001
ALT (IU/L)	34(6-869)	23(9-128)	43(6-869)	0.003
INR	1.23(0.87-10,9)	1.13(1-10.9)	1.3(1-3)	<0.001

F;Female, M;Male, Wbc: White blood cell, CRP: C reactive protein, AST: Aspartate aminotransferase ALT: Alanine aminotransferase, INR: International normalized ratio. All continuous variables are reported as medians and interquartile ranges.

When we look at the cell rates in complete blood count, in the non survivor group, white blood cells (WBC,) monocytes, neutrophils, platelets were higher, WBC WBC (median 12×10^9 L, IQR: (1-24) vs 14.67×10^9 L, IQR: (4-37) $p < 0.001$), monocytes (median 0.82×10^9 L, IQR: (0.12-23) vs 0.56×10^9 L, IQR: (0.1- 1) $p < 0.001$), neutrophils median 12.39×10^9 L, IQR: (4-33) vs 8.8×10^9 L, IQR: (0.32-20) $p < 0.001$), platelets (median 173×10^9 L IQR: (100-334) vs 225.5×10^9 L, IQR: (16-776) $p = 0.029$) respectively (Table 1).

Although lymphocyte counts were low in the non survivor group, it was not statistically significant (median 0.63×10^9 L, IQR: (0.15-6.5) vs $0,9\times10^9$ L (0.2-2.2), IQR: (0.2-2.2) p=0.051). The ratios of acute phase reactants such as CRP, ferritin were significantly higher in the non survivor group. CRP (median 150.5 mg/L, IQR: (4-476) vs 82.04 mg/L, IQR: (2-338), p=0.004), ferritin (median 1906 ng/ml IQR: (74-72852) vs 361.7 ng/ml, IQR:(25-6260), p<0.001). Likewise, procalcitonin levels, an inflammation marker, were higher in the non-survivor group (median 0,71(ng/ml) IQR: (0.18-11) vs 0.18 (ng/ml) (0.02-5) ,p=0.000). D dimer levels were statistically higher in non-survivor group (median 2.37(mg/L) IQR:(0.19-35) vs 1.78(mg/L) IQR: (0.19 -35) p=0.043) (Table 1).

When we look at the inflammation indexes derived from complete blood tests, it was found to be significantly higher in the non-survivor group (SII, AISI, MLR, NLR, PLR, SIRI, LCR, dNLR) p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p<0.001, p=0.004, p<0.001, respectively) (Table 2).

The roc analyzes cut–off values for survival for each inflammatory index were as follows; AISI, 1318.12; dNLR, 6.03; MLR, 0.76; NLR, 16.82; PLR, 250.4; SII, 2189.55; SIRI, 7,43. ROC curve analysis cut–off values for troponin I and ferritin parameters related to survival were; 24.5 and 707.8 respectively (Table 3).The values of area under the curve (AUC) were 0.922 (0.859-0.984) for AISI, 0.737(0.635-0.839) for dNLR, 0.903(0.838-0.967) for MLR, 0.93 (0.877-0.984) for NLR, 0.757 (0.655-0.860) for PLR, 0.922 (0.859-0.984) for SII, 0.946 (0.902-0.990) for SIRI (Table 3).

Table 2. Inflamation indexes of COVID-19 patients.

Indexes	Survivors	Non- Survivors	P value
SII	1472.5(126-2811)	3963(296-24413)	<0.001
AISI	831.08(15.13-1590)	3235(1167-20261)	<0.001
MLR	0.5(0.15-1.15)	1.16(0.32-18.42)	<0.001
NLR	8.48(0.97-19.2)	16.8(9-56.9)	<0.001
PLR	164.2(71.43-609.52)	360.17(10.46-1616)	<0.001
SIRI	4.1(0.12-12.06)	14.5(3.47-426.3)	<0.001
LCR	0.017(0.01-048)	0.0047(0.0007-0.25)	0.004
dNLR	4.5(0.68-11.14)	7(1.63-26.91)	<0.001

AISI: Aggregate index of systemic inflammation, COVID-19: Coronavirus disease 2019; dNLR: derived neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index, LCR: lymphocyte to C-reactive protein ratio. All variables are reported

Table 3. ROC curves and prognostic accuracy of inflammation indexes and biochemical parameters.

	AUC	95% CI	P Value	Cut off	Sensitivity(%)	Specificity(%)
SII	0.922	(0.859-0.984)	<0.001	2189.55	85.4	85.4
SIRI	0.946	(0.902-0.990)	<0.001	7.43	87.5	87.8
NLR	0.93	(0.877-0.984)	<0.001	16.82	50	50
dNLR	0.737	(0.635-0.839)	<0.001	6.03	62.5	63.4
MLR	0.903	(0.838-0.967)	<0.001	0.76	83.3	82.9
PLR	0.757	(0.655-0.860)	<0.001	250.4	72.9	73.2
AISI	0.992	(0.981-1.000)	<0.001	1318.12	93.8	92.7
Troponin I	0.667	(0.550-0.784)	0.007	24.5	60.4	61
Ferritin	0.841	(0.757-0.926)	<0.001	707.8	75	75.6

AISI: Aggregate index of systemic inflammation, dNLR: derived neutrophil to lymphocyte ratio, MLR: monocyte to lymphocyte ratio; NLR: neutrophil to lymphocyte ratio, PLR: platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index

Hypertension and higher AISI and ferritin levels were statistically associated with reduced survival in Cox regression analysis (Hazard ration (HR)=3.176; 95% Confident interval (CI), 1.122-8.991, p=0.03, HR=1.114; 95% CI, 1.060-1.348, P=0,042, HR=1.072; 95% CI,1.014-1.242, p=0.011, respectively) (Table 4).

DISCUSSION AND CONCLUSION

The COVID-19 pandemic, which affects all humanity, has caused many problems in the fields of economy, social and health in the world, and the spread of the new mutant form seen in England, America, and South Africa while vaccination studies continue, worries all humanity. Furthermore, many questions about whether we will be able to keep ahead of future variants of COVID-19, which will certainly arise.[8] Vaccination, early diagnosis, and treatment are important to cope with this urgent problem. COVID-19 (RNA virus,) and its mutants can mutate faster than DNA viruses. Such new mutations could make them more deadly, more transmissible, or both.[9] It makes it difficult to immunize people against the new mutant virus with the vaccine. We planned our study for predicting mortality and directing treatment. Our study adds new ones to the inflammation markers in COVID-19.

In studies performed, a decrease in peripheral T cell subsets is frequently observed in patients with severe acute respiratory syndrome(SARS). In healed patients, peripheral T Cell subsets were found to normalize rapidly; this can be used as a diagnostic tool for SARS.[10] SARS-CoV-2 disrupts the immune system, causing an uncontrollable immune response in the body. Lymphopenia, lymphocyte activation and dysfunction, granulocyte and monocyte abnormalities are seen in these patients. There are high cytokine levels and an increase in immunoglobulin. Patients with severe COVID-19 are more likely to show lymphopenia on admission, indicating an important predictor for severe patients.[11,12] Although there was a significant decrease in the number of CD4 + T, CD8 + T, NK, and B cells, there was a greater decrease in the number of CD8 + T cells in severe cases than in mild ones.[13-16]

Therefore, these data show that lymphopenia, or inflammatory markers to be derived, can be used as an indicator of disease severity and prognosis in patients with COVID-19. An extreme increase in inflammatory cytokines is seen in severe cases. In this cytokine storm, there is an increase in cytokines such as IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-inducible protein-10 (IP10), monocyte chemotactic protein 1 (MCP1), macrophage inflammation protein-1α, IFN-γ, and TNF-α. In particular, IL-1β, IL-6, and IL-10 are the three most

Table 4. Hazard ratios of the indexes and other parameters obtained by Cox regression analysis.

	HR	95% CI	P value
Diabetes Mellitus	0.750	0.293-1.918	0.548
Cerebrovascular disease	0.657	0.138-3.123	0.597
Cardiovascular disease	1.897	0.685-5.257	0.218
Heart Failure	0.363	0.112-1.178	0.092
Hypertension	3.176	1.122-8.991	0.030
Respiratory Disease	1.455	0.531-3.987	0.465
Gender (Male)	0.866	0.371-2.019	0.739
Age	1.029	0.999-1.061	0.059
CRP (mg/L)	1.002	0.997-1.006	0.438
D-dimer(mg/L)	1.012	0.973-1.053	0.545
Ferritin(ng/ml)	1.072	1.014-1.242	0.011
Procalcitonin(ng/ml)	1.099	0.943-1.279	0.226
Troponin I(ng/l)	1.002	0.998-1.005	0.330
SII	1.000	0.999-1.000	0.249
AISI	1.114	1.060-1.348	0.042
MLR	0.679	0.314-1.468	0.326
NLR	1.046	0.997-1.098	0.069
PLR	1.003	0.999-1.006	0.172
SIRI	1.014	0.988-1.041	0.299
dNLR	0.965	0.874-1.065	0.476

AISI: Aggregate index of systemic inflammation, CI: confidence interval, COVID-19: coronavirus disease 2019, CRP: C-reactive protein, dNLR: derived neutrophil to lymphocyte ratio, HR: hazard ratio, MLR: monocyte to lymphocyte ratio, NLR: neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, SII: systemic immune-inflammation index, SIRI: systemic inflammation response index.

elevated cytokines in severe cases.[17,18] CD4 + T cells infected with covid 19 transforms into pathogenic T helper (Th) 1 cell and secrete GM-CSF, IL-6. This situation stimulates CD14 + CD16 + monocytes and promotes inflammation.[19]

Lymphopenia caused by COVID-19 can cause new infections caused by microbes. New bacterial infections trigger neutrophil supplementation and an increase in neutrophil counts in tissues. The COVID-19 virus binds with S proteins (Spike glycoprotein) to angiotensin-converting enzyme 2 receptors (ACE2) on human respiratory epithelial cells and T cells. COVID-19 can directly infect T cells and macrophages and reduce their numbers. High levels of TNFα, IL-6, and IL-10 have also been shown to reduce the number of T cells.[20] Therefore, targeting the IL-6 / IL-6 receptor (IL-6R) signaling pathway is a promising strategy for alleviating inflammation symptoms. Tocilizumab, an anti-IL-6 receptor antibody, and Sarilumab, a monoclonal antibody, are used in severe cases to stop cytokine storm. Lymphopenia, high cytokine levels, and neutrophil levels appear to be parameters that can help us in the progression of the disease. In our study, as in other studies, we found that leukocytosis, lymphopenia, and increased neutrophil count are associated with disease severity in terms of hematological parameters.

NLR values were reported to be a more sensitive biomarker of inflammation than the individual levels of neutrophils and lymphocytes.[21] We found higher NLR and dNLR values in patients with severe COVID-19 disease, consistent with previous studies.[22, 23] In a recent study by Sayar et al., the relationship between inflammatory parameters and COVID-19 disease was investigated. In this study, a significant relationship was found between high d-dimer and ferritin levels and the need for intensive care. In addition, a significant relationship was found between NLR and leukocyte elevation and lung involvement rates.[24] In our study, we found that inflammatory indexes (SIRI, AISI, MLR, NLR, PLR, SIRI, LCR, dNLR) that can be easily calculated and used in the follow-up of patients with COVID-19 are related to the severity of the disease. In the Kaplan-Meier survival curves, which were obtained from the cut-off values of the inflammatory indexes in the roc curve analysis, survival was found to be associated with inflammatory indexes. High ferritin and troponin levels were also found to be associated with mortality.

However, these significant inflammatory indexes can be detected high in septic shock, rheumatological diseases, and some types of cancer. For instance, the SII has also been shown to be associated with poorer survival in small cell lung cancer, hepatocellular carcinoma, colorectal cancer, and stomach cancer.[25,26] In a study conducted by Aksu et al., the relationship between inflammatory parameters and the need for invasive intervention in patients with non-ST myocardial infarction during the COVID-19 pandemic period was investigated. At the end of the study, the authors found high SII values to be significantly higher in patients who needed invasive intervention.[27] In another study, a significant relationship was found between high CRP and in-hospital mortality in COVID-19 patients with coronary artery disease.[28] In our study, CRP and SII values were significantly higher in patients with mortality.

The limitations of our study are the retrospective nature of our study, including a small patient group, and the change in the blood picture during the hospitalization of the patients.

In our study, it was found that especially being hypertensive, having high AISI and ferritin levels were associated with mortality. In the first publications made in patients who died due to COVID-19, diabetes and hypertension rank first among additional diseases. However, in recent studies, it has been accepted that this condition is not only associated with the course of the disease and the risk of death but increases the risk due to accompanying cardiovascular and kidney diseases. Unlike other indexes, the AISI index is an inclusive index derived from platelet, lymphocyte, neutrophil, and monocyte levels. As a result, these indexes, which can be easily calculated, may be useful for patient follow-up. However, more new multi-center, prospective studies with large numbers of patients are needed.

Ethics Committee Approval: The study was approved by the Ethics Committee of the Medical Faculty of Namık Kemal University (Date: 27/04/2021, decision no: 2021.107.04.02).The study was carried out in accordance with international declaration, guideline, etc.

Conflict of Interest: No conflict of interest was declared by the authors.

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