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The Role of Inflammatory Markers in Predicting Mortality in Critical COVID-19 Patients: A Single-Center, Retrospective, Observational Study

Kritik COVID-19 Hastalarında Mortaliteyi Tahmin Etmede İnflamatuvar Belirteçlerin Rolü: Tek Merkezli, Geriye Dönük, Gözlemsel Bir Çalışma

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ABSTRACT

Introduction: *This study aims to assess the association of inflammatory markers with the clinical progression of patients diagnosed with COVID-19.*

Materials and Methods: *Critically ill patients with COVID-19 were included. Prealbumin, lactate dehydrogenase (LDH), transferrin, procalcitonin, ferritin, D-dimer, troponin T and C-reactive protein (CRP) were monitored. A comparison was performed between patients regarding their need for mechanical ventilation, duration of hospital and intensive care unit stay, discharge, mortality, complications, and response to treatment in order to reveal potential correlations.*

Results: *A total of 107 patients were enrolled in the study. D-dimer levels on the 3rd and 6th days were significantly higher in the exitus group. Prealbumin and transferrin levels measured at baseline and on days three and six were significantly lower in the exitus group compared to the surviving group ($p< 0.05$). In the exitus group, the procalcitonin, CRP, LDH, troponin T, and ferritin levels were significantly higher on days zero, three, and six as compared to the surviving group ($p< 0.05$).*

Conclusion: *Our results suggest that inflammatory markers may be useful as early indicators of mortality in COVID-19 patients.*

Key Words: *COVID-19; Inflammatory; Markers; Mortality*

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ÖZ

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Giriş: *COVID-19 tanısı alan hastaların klinik progresyonu ile inflamatuvar belirteçlerin ilişkisini değerlendirmeyi amaçladık.*

Materyal ve Metod: *COVID-19'lu kritik hastalığı olan hastalar dahil edildi. Prealbümin, laktat dehidrojenaz (LDH), transferrin, prokalsitonin, ferritin, D-dimer, troponin T ve C-reaktif protein (CRP) izlendi. Potansiyel korelasyonları ortaya çıkarmak için mekanik ventilasyon ihtiyacı, hastanede ve yoğun bakımda kalış süresi, taburculuk, mortalite, komplikasyonlar ve tedaviye yanıt açısından hastalar arasında karşılaştırma yapıldı.*

Bulgular: *Çalışmaya toplam 107 hasta alındı. Exitus grubunda üçüncü ve altıncı günlerde D-dimer seviyeleri anlamlı olarak yüksekti. Başlangıçta ve üçüncü ve altıncı günlerde ölçülen prealbümin ve transferrin seviyeleri, canlı gruba kıyasla eksitus grubunda anlamlı derecede düşüktü (p< 0.05). Exitus grubunda prokalsitonin, CRP, LDH, troponin T ve ferritin seviyeleri sıfır, üç ve altıncı günlerde canlı gruba göre anlamlı derecede yüksekti (p< 0.05).*

Sonuç: *Sonuçlarımız, inflamatuvar belirteçlerin COVID-19 hastalarında mortalitenin erken göstergeleri olarak yararlı olabileceğini düşündürmektedir.*

Anahtar Kelimeler: *COVID-19; İnflamatuvar; Belirteçler; Mortalite*

INTRODUCTION

COVID-19, which caused a global pandemic, can be restricted to the symptoms of a simple flu infection, but it can be severe enough to cause death in certain individuals with severe pneumonia and multi-organ failure.

One of the body's defense mechanisms, acute phase reactants (APR), can be used to predict the diagnosis, course, and prognosis of pneumonia. Acute phase reactans are markers that change to abnormal values with an increase or decrease in serum during acute tissue injury, inflammation, or infection. Changes in the concentration of these serum proteins accompany inflammation and tissue damage. In addition to C-reactive protein (CRP), which is the prototype of acute phase reactants, many positive and negative APRs are used as guides in the follow-up and treatment of inflammation in the body[1,2].

D-dimer, which is one of the laboratory markers that best demonstrates coagulation activity today, is a parameter whose level increases in every case of fibrin formation. The use of D-dimer level as a prognostic marker is also becoming widespread in the acute attack of chronic obstructive pulmonary disease or severe community-acquired pneumonia[3,4].

Acute phase reactants have been used to predict outcomes in epidemics at an early stage. Zimmermann et al.[5] demonstrated that CRP serum levels are an independent prognostic factor for mechanical ventilation in pandemic H1N1 influenza A infection. It has been found useful in determining the course of the disease and has been reported to help treatment. Chen et al.[6] found that the level of plasma CRP was positively correlated to the severity of COVID-19 pneumonia.

However, studies on the determinant role of both acute phase reactants and D-dimer, as well as cardiac troponin levels in the intensive care course and treatment stages of COVID-19 disease are limited.

In this retrospective, observational single-center study, we looked for associations between mortality, patient characteristics, comorbidities, and laboratory abnormalities. We aimed to determine the association between various positive

and negative acute phase reactants and D-dimer and the clinical processes of COVID-19 patients in our hospital's intensive care unit. We hypothesized that the course of inflammatory markers in critical COVID-19 patients can be used as a predictor of the prognosis.

MATERIALS and METHODS

Approval was obtained from the Health Sciences University Hamidiye Scientific Research Ethics Committee (Protocol no: 20/159, Date: 05/05/2020). Patients with a definitive diagnosis of COVID-19 who were followed up on in our intensive care unit (ICU) were included in the retrospective observational study.

Demographic characteristics and comorbidities of these patients as well as prealbumin, lactate dehydrogenase (LDH), transferrin, procalcitonin, ferritin, CRP, and D-dimer and troponin T values, which are closely monitored by acute phase reactants, were recorded. The course of acute phase reactant levels of the patients was compared in terms of correlation with the need for and duration of mechanical ventilation, length of hospital stay, length of stay in the intensive care unit, extubation, discharge rates, mortality, complications, and response to treatment parameters.

Inclusion Criteria for the Study

Patients who were followed up in the intensive care unit with a definitive diagnosis of COVID-19, and whose COVID-19 PCR test (+), D-dimer, and all acute phase reactants were recorded, were included in the study.

Exclusion Criteria from the Study

Patients with a positive COVID-19 PCR test who were followed in the emergency department or wards other than the intensive care unit were excluded from the study. Patients with missing data were excluded from the study.

In accordance with the guidelines for the provision of intensive care services, which were published on June 27, 2019, prompt ICU admission was defined as one within four hours following ward or emergency department assessment[7]. Watchful waiting admission included the remaining patients.

Statistical Analysis

Mean, standard deviation, median lowest, highest, frequency, and ratio values were used in the descriptive statistics of the data. The distribution of variables was measured with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used in the analysis of quantitative independent data. The Chi-square test was used in the analysis of qualitative independent data, and the Fisher test was used when the Chi-square test conditions were not met. The analysis was performed using the SPSS 26.0 software.

RESULTS

Between March 22 and June 1, 2020, at the beginning of the pandemic, 151 patients were admitted to the ICU allocated for COVID-19 patients. Of these, the first 107 patients with positive COVID-19 PCR tests were included in the study (Figure 1). No patients were excluded from the study.

The mean age of the patients was 66.6 ± 13.7 years. Of 107 patients, 59.8% were 65 years or older, 69.2% were male and 30.8% were obese. The mean length of stay was 7.13 ± 4.29 days. Eighty-one patients died (75.7%). Septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), acute cardiac event, acute kidney and liver injuries, and lymphopenia were the systemic complications during the treatment of COVID-19 patients (Table 1).

The patients were divided into two groups: exitus and surviving. Age distribution was similar between the two groups (p> 0.05). The ratio of male patients in the exitus group was significantly higher than in the surviving group (75.3% vs 50.0% respectively, p= 0.015). The proportion of patients with a BMI value over 25 in the exitus group was significantly higher than the surviving group (p= 0.021). The comorbidity rate and ICU length of stay did not differ significantly between the exitus group and the surviving group (p> 0.05), the length of hospital stay was shorter in the exitus group than in the surviving group [8.31 ± 5.19 vs. 15.58 ± 4.73 (p= 0.000)], (Table 2).

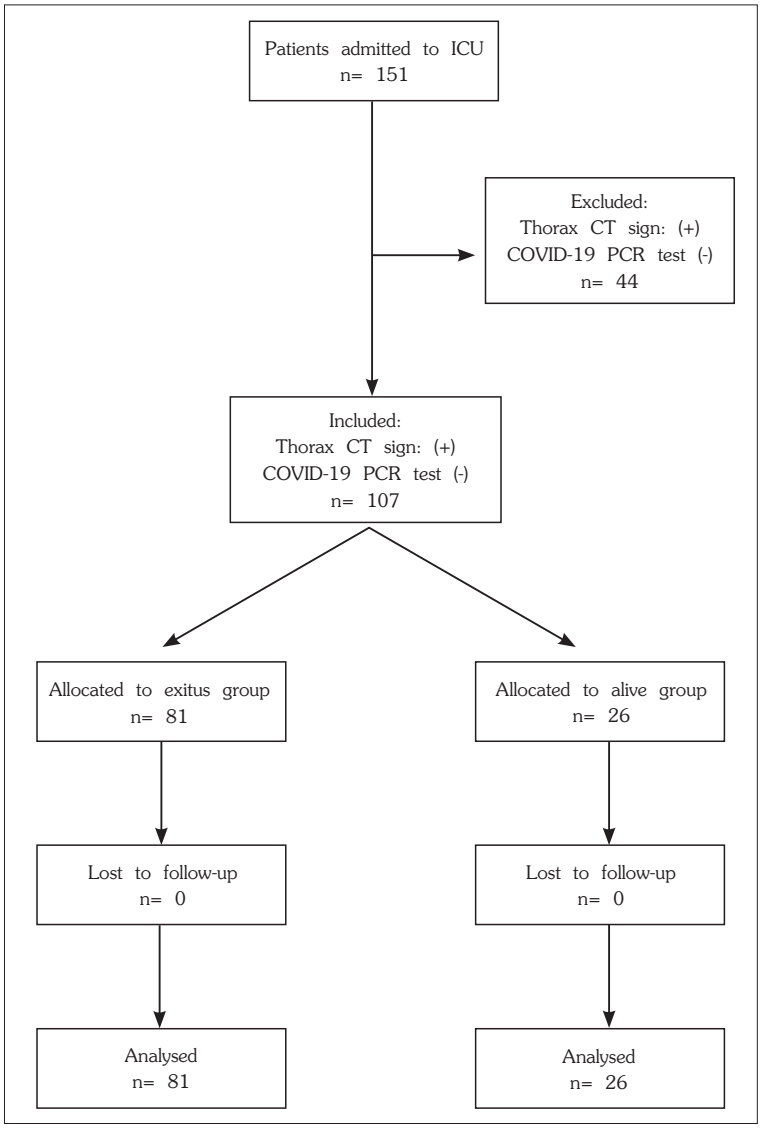

Figure 1. Flow diagram of patients screened.

The rate of patients admitted to the ICU within the first four hours of admission to the hospital was significantly higher in the exitus group than in the surviving group (58.0% vs 19.2%, respectively). Those who were admitted to the ICU within the first three days while being treated in the pandemic wards and those who were admitted within 4-7 days were significantly higher in the exitus group than in the surviving group (61.5% vs 24.75 and 19.2, 5 vs 11.1%, respectively). Five of the patients in the exitus group needed intensive care after being treated in the pandemic ward for more than seven days. On the other hand, there were no patients admitted after seven days in the surviving group (6.2% vs 0.0%). The D-dimer level was not significantly different in both groups at the first hospitalization. However, it was found to be significantly higher in patients who died on the 3rd and 6th days (Table 3). Positive and negative acute phase reactants and troponin T values at baseline (day of hospitalization), day three, and day six were significantly higher in the exitus group than in the surviving group ($p< 0.05$). The rates of septic shock, ARDS, acute cardiac event, acute kidney and liver inju-

Table 1. Distribution of systemic complications during COVID-19 treatment

	Yes	No
Systemic complications	**n (%)**	**n (%)**
Hemodiafiltration	95 (88.8)	12 (11.2)
Septic shock	70 (65.4)	37 (34.6)
ARDS	65 (60.7)	42 (39.3)
Acute cardiac event	18 (16.8)	89 (83.2)
AKI	39 (36.4)	68 (63.6)
Acute liver injury	30 (28.8)	77 (72.0)
MODS	33 (30.2)	74 (69.2)
Lymphopenia	73 (68.2)	34 (31.8)
Tracheal intubation	66 (61.7)	41 (38.3)

ARDS: Acute respiratory distress syndrome, AKI: Acute kidney injury, MODS: Multiple organ dysfunction syndrome.

Table 2. Comparison of demographic characteristics, length of stay, presence of comorbidity, and time to intensive care unit admission of exitus and surviving group

		Exitus group		Surviving group		
		(Mean ± SD)	**n (%)**	**(Mean ± SD)**	**n (%)**	**p**
Age (year)		68.2 ± 11.0		61.5 ± 19.2		0.187^{m}
Age (year)	<65		30 (37.0)		13 (50.0)	0.241$^{X^2}$
	>65		51 (63.0)		13 (50.0)	
BMI (kg/m^2)		29.3 ± 3.8		27.7 ± 4.1		**0.049**^{m}
BMI (kg/m^2)	<19		1 (1.2)		0 (0.0)	**0.021**$^{X^2}$
	19-24.9		5 (6.2)		7 (26.9)	
	25-29.9		48 (59.3)		13 (50.0)	
	>30		27 (33.3)		6 (23.1)	
Duration of ICU stay (day)		6.99 ± 4.18		7.58 ± 4.67		0.718^{m}
Duration of hospital stay (day)		8.31 ± 5.19		15.58 ± 4.73		**0.000**^{m}
Gender	Male		61(75.3)		13 (50.0)	**0.015** ^{X_2}
	Female		20 (24.7)		13 (50.0)	
Comorbidity	(+)		17 (21.0)		5 (19.2)	0.847$^{X^2}$
	(-)		64 (79.0)		21 (80.8)	
Prompt ICU admission	No		47 (58.0)		5 (19.2)	**0.001**$^{X^2}$
	1-3 days		20 (24.7)		16 (61.5)	
	4-7 days		9 (11.1)		5 (19.2)	
	>7 days		5 (6.2)		0 (0.0)	

SD: Standard deviation, ^{m}: Mann-Whitney U test, X²:Chi-square test, BMI: Body mass index, ICU: Intensive care unit.

ry, and MODS were found to be significantly higher in patients in the exitus group compared to the surviving group (p< 0.05), (Figure 2).

Hemodiafiltration was required in 70 patients (86.4%) in the exitus group and 25 patients (96.2%) in the surviving group, and the difference was not significant (p= 0.171). The incidence of septic shock in the exitus group was significantly higher than in the surviving group (76.5% vs 36.8%, p< 0.0001). While the incidence of ARDS was 74.1% in the exitus group, it was 19.2% in the surviving group (p< 0.0001). While acute cardiac events did not occur at all in the surviving group, they were reported in 22.2% of those who died (p= 0.008).

Table 3. Comparison of baseline, 3rd, and 6th-day inflammatory marker values of exitus and surviving groups

	Exitus Group		Surviving Group		
	Median	Min-Max	Median	Min-Max	p
D-dimer (ug/L)					
Day 0	2530	21.32-30000	1920	210-17670	0.410[m]
Day 3	3450	13.30-30000	1920	730-10670	**0.016**[m]
Day 6	3625	1180-30000	2130	136-30000	**0.046**[m]
Prealbumin (mg/dL)					
Day 0	0.05	0-0.32	0.11	0.03-0.16	**0.000**[m]
Day 3	0.05	0.01-2	0.07	0.01-0.28	**0.029**[m]
Day 6	0.05	0.01-0.51	0.10	0.05-0.40	**0.003**[m]
Procalcitonin (ng/L)					
Day 0	0.90	0.05-43.40	0.21	0.07-6.80	**0.009**[m]
Day 3	1.33	0.08-1500	0.17	0.04-2.80	**0.000**[m]
Day 6	1.50	0.10-1500	0.10	0.06-0.32	**0.000**[m]
CRP (mg/L)					
Day 0	154.0	10-498	80.6	3.11-226	**0.018**[m]
Day 3	172.0	21.80-531	104.5	17.70-188	**0.001**[m]
Day 6	192.0	10.8-488	53.6	6.9-175	**0.000**[m]
LDH (U/L)					
Day 0	449.0	191-909	348.0	208-747	**0.008**[m]
Day 3	541.0	224-1150	346.0	204-743	**0.043**[m]
Day 6	511.5	187-9640	321.0	195-505	**0.001**[m]
Troponin T (ug/L)					
Day 0	0.03	0.01-0.56	0.02	0.01-0.21	**0.015**[m]
Day 3	0.04	0-0.60	0.01	0-0.04	**0.000**[m]
Day 6	0.05	0.01-1	0.01	0-0.07	**0.000**[m]
Ferritin (ug/L)					
Day 0	660.0	20.5-3306	171.5	4.8-1500	**0.030**[m]
Day 3	1500.0	153-1500	445.0	54-1265	**0.006**[m]
Day 6	1215.0	169-1500	262.5	55-970	**0.000**[m]
Transferrin (mg/dL)					
Day 0	1.18	0.76-2.75	1.54	1.08-1.96	**0.007**[m]
Day 3	1.09	0.01-2.89	1.54	0.92-2.22	**0.002**[m]
Day 6	1.06	0.01-1.82	1.46	1.17-2.40	**0.000**[m]

[m]: Mann-Whitney U test.

While the incidence of acute liver injury was 33.3% in the patients who died, this rate was 11.5% in the surviving patients (p= 0.031). Thirty-three of the patients died due to MODS (40.7%).

Endotracheal intubation was required in 63 patients (77.8%) in the exitus group. In contrast, only three patients required endotracheal intubation in the surviving group (p< 0.0001). There was no significant difference in baseline,

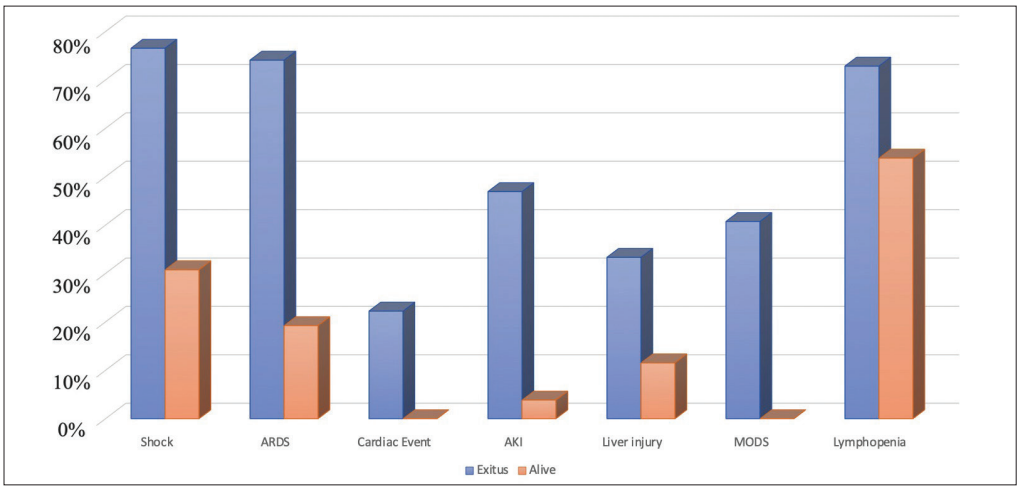

Figure 2. Comparison of patients who survived and died in terms of systemic complications.

3rd day, and 6th day in terms of D-dimer values between the patients who were intubated and non-intubated (p> 0.05, Table 4). PCT, CRP, and LDH values also did not differ significantly in the early period between the intubated and non-intubated patients (p> 0.05). On the other hand, baseline, 3rd and 6th-day prealbumin and transferrin values were significantly lower and, troponin T and ferritin values were significantly higher in the intubated patients compared to the non-intubated patients (p< 0.05).

There was no significant difference between prompt ICU admission and watchful waiting ICU admission patients in terms of D-dimer, CRP, LDH, ferritin, and troponin T levels (p> 0.05, Table 5). In the watchful waiting ICU admission group, the initial, 3rd and 6th-day procalcitonin values were found to be significantly higher when compared with the prompt ICU admission patients. Transferrin values were significantly lower in all measurements in the watchful waiting group.

DISCUSSION

The data of the first 107 patients admitted to the intensive care unit with the diagnosis of COVID-19 were evaluated in this study. Prealbumin and transferrin values, which are negative acute phase reactants, were found to be significantly associated with mortality. Furthermore, PCT, CRP, LDH, and ferritin values, which are positive acute phase reactants, as well as troponin T and D-dimer elevation were found to be significantly associated with mortality.

Existing evidence already clearly indicate that elderly patients with several chronic diseases have poor outcome[8]. In our study, the mean age was 66.6 ± 13.7 years, and the rate of patients over the age of 65 was 59.8%. The mean age of the patients in the exitus group was found to be 68.2 ± 11 years, which was higher than the overall mean age. Causes of mortality included septic shock, ARDS, acute cardiac event, acute kidney and liver injury, and MODS.

Elevated D-dimer levels are also common in COVID-19 patients. Due to extreme inflammation and hypoxia, some COVID-19 patients exhibit abnormalities of coagulation and fibrinolysis with increased thrombotic complications such as pulmonary thromboembolism (PTE) and disseminated intravascular coagulation (DIC). Given that the majority of COVID-19 patients are elderly, sedentary, and have increased blood viscosity due to fever, sweating, and other factors, a high D-dimer level indicates a significant risk of venous pulmonary thromboembolism. However, the same predisposing factors will increase the bleeding tendency of these patients. For these reasons, it may be more accurate to monitor D-dimer levels to check if they are compatible with other inflammatory indicators before misinterpreting high D-dimer levels as PTE. If the

Table 4. Comparison of baseline, 3rd, and 6th-day inflammatory marker values of intubated and non-intubated patients

	Exitus Group		Surviving Group		
	Median	Min-Max	Median	Min-Max	p
D-dimer (ug/L)					
Day 0	2530	29.7-30000	1920	21.32-30000	0.376[m]
Day 3	3290	13.30-30000	2245	16.24-30000	0.170[m]
Day 6	3700	1290-30000	2560	136-30000	0.222[m]
Prealbumin (mg/dL)					
Day 0	0.05	0.01-0.32	0.10	0-0.16	**0.006**[m]
Day 3	0.04	0.01-2	0.06	0.01-0.28	**0.047**[m]
Day 6	0.06	0.01-0.30	0.09	0.03-0.51	**0.009**[m]
Procalcitonin (ng/L)					
Day 0	0.98	0.05-43.40	0.45	0.07-6.80	0.166[m]
Day 3	1.42	0.08-100	0.42	0.04-1500	**0.008**[m]
Day 6	1.28	0.10-27.10	0.22	0.06-1500	**0.013**[m]
CRP (mg/L)					
Day 0	143.0	10-498	148.5	3.11-252	0.226[m]
Day 3	160.0	21.8-514	130.0	17.7-531	**0.046**[m]
Day 6	190.0	10.8-488	98.7	6.9-270	**0.000**[m]
LDH (U/L)					
Day 0	440.0	191-760	368.0	208-909	0.081[m]
Day 3	429.0	224-1150	398.0	204-1006	0.777[m]
Day 6	500.5	187-9640	433.0	195-1270	**0.035**[m]
Troponin T (ug/L)					
Day 0	0.03	0.01-0.56	0.02	0.01-0.21	**0.025**[m]
Day 3	0.04	0.01-0.60	0.02	0-0.15	**0.001**[m]
Day 6	0.04	0.01-1	0.02	0-0.23	**0.015**[m]
Ferritin (ug/L)					
Day 0	764.0	20.5-3306	220.5	4.8-1500	**0.028**[m]
Day 3	1500.0	373-1500	559.0	54-1500	**0.005**[m]
Day 6	1232.0	88-1500	397.0	55-1500	**0.006**[m]
Transferrin (mg/dL)					
Day 0	1.18	0.76-2.75	1.39	0.86-2.37	**0.007**[m]
Day 3	1.00	0.01-2.89	1.38	0.87-2.22	**0.003**[m]
Day 6	1.11	0.01-1.9	1.33	0.86-2.40	**0.013**[m]

[m]: Mann-Whitney U test.

D-dimer level does not decrease in response to anti-inflammatory medication along with other APR, it may indeed be attributable to PTE. This interpretation is supported by similar D-dimer levels in intubated and non-intubated patients, as well as patients with and without mechanical ventilation in the present study.

In the present study, we found a relationship between patient profile, need for mechanical ventilation, length of stay, and mortality with acute

Table 5. Comparison of baseline, 3rd and 6th-day inflammatory marker values according to ICU admission time

	Watchful Waiting ICU Admission (Mean ± SD)		Prompt ICU Admission (Mean ± SD)		
	Median	Min-Max	Median	Min-Max	p
Day 0	2870	21.32-30000	2180	270-17670	0.404[m]
Day 3	3500	16.24-30000	2710	13.30-30000	0.444[m]
Day 6	3665	1290-30000	3245	136-30000	0.361[m]
Prealbumin (mg/dL)					
Day 0		0-0.14	0.07	0.02-0.32	**0.023**[m]
Day 3		0.01-2	0.06	0.01-0.30	0.456[m]
Day 6		0.02-0.30	0.08	0.01-0.51	0.251[m]
Procalcitonin (ng/L)					
Day 0	1.98	0.09-43.40	0.35	0.05-13.20	**0.001**[m]
Day 3	1.10	0.11-1500	0.56	0.04-53.9	**0.034**[m]
Day 6	1.26	0.10-1500	0.45	0.06-22	**0.038**[m]
CRP (mg/L)					
Day 0	154.0	13-498	142.5	3.11-349	0.261[m]
Day 3	165.5	21.8-531	141.0	17.70-514	0.179[m]
Day 6	154.0	10.8-488	158.0	6.90-473	0.409[m]
LDH (U/L)					
Day 0	387.0	191-760	394.0	208-909	0.516[m]
Day 3	385.5	234-1150	464.0	204-1006	0.662[m]
Day 6	448.0	187-9640	465.5	195-3316	0.489[m]
Troponin T (ug/L)					
Day 0	0.03	0.01-0.56	0.02	0.01-0.42	0.225[m]
Day 3	0.03	0.01-0.60	0.02	0-0.54	0.107[m]
Day 6	0.05	0.01-1	0.03	0-0.61	0.183[m]
Ferritin (ug/L)					
Day 0	600.0	20.5-3306	553.0	4.8-1500	0.224[m]
Day 3	730.0	153-1500	1092.0	54-1500	0.833[m]
Day 6	1144.0	88-1500	587.0	55-1500	0.106[m]
Transferrin (mg/dL)					
Day 0	1.11	0.76-2.75	1.36	0.80-2.37	**0.012**[m]
Day 3	1.05	0.66-2.17	1.30	0.01-2.89	**0.050**[m]
Day 6	1.07	0.50-1.90	1.20	0.01-2.4	0.394[m]

[m]: Mann-Whitney U test.

phase reactants, troponin T and D-dimer values in severe COVID-19 patients requiring intensive care. In a meta-analysis of fourteen studies with 4659 COVID-19 patients, it was reported that in patients who died, compared to those who survived, cardiac troponin, CRP, and D-dimer levels were higher at the time of admission. However, a decrease in prealbumin level was noted[9]. In our study, it was revealed that transferrin along with prealbumin decreased in patients who died

due to COVID-19. Therefore, these two negative acute phase reactants seem to have prognostic value in the follow-up of COVID-19 patients. In our study, it was observed that procalcitonin, LDH, and ferritin values increased along with the positive acute phase reactants. In addition, in the present study, these acute phase reactants were found to be a good indicator for mortality, not only at admission but also on the 3rd and 6th day follow-ups. For this reason, we believe that it would be useful to monitor these parameters intermittently in the ICU.

There had been a significant increase in cardiac troponin levels, which is one of the inflammatory biomarkers, in COVID-19 patients. When the details were examined, it was observed that the values measured on the first day in the patients who died, were significantly higher than those who survived, reaching seven times and higher values on the third day and 7.5 times on the 6th day. Increased troponin levels are thought to be associated with fatal outcomes. Possible causes of this include viral myocarditis, microangiopathy, and cytokine-driven myocardial damage[10]. Direct dissemination of the virus into the bloodstream from the lungs, interferon-mediated immune response, type 1 and 2 helper T cells' cytokine response, myocardial interstitial fibrosis, and systemic inflammation are other associated factors[11,12]. The results of our study reveal that more aggressive treatment strategies are needed to reduce mortality in the presence of underlying cardiovascular diseases. Prealbumin and transferrin levels were found to be significantly lower, and ferritin and troponin levels were higher in patients who were given invasive mechanical ventilatory (IMV) support compared to the other group, starting from the first hospitalization measurements. These values can also be a guide in predicting IMV requirement.

In a meta-analysis including 20 retrospective studies and 3.428 patients with confirmed COVID-19, it was revealed that acute liver injury is associated with mortality[13]. The findings of our study support these findings. In addition, it is clear that complications such as AKI, ARDS, septic shock, and MODS, which occur during intensive care, are also indicators of mortality.

Prompt ICU admission is defined as admitting a patient to the intensive care unit within the first four hours of assessment. Prompt admissions were compared to a watchful waiting cohort in a prospective cohort study of 12.380 patients from 48 hospitals[14]. It has been demonstrated that 90-day mortality is lower in prompt admission patients. Lange et al.[15]. suggested that more research should be done on ICU triage. To our knowledge, our study is the first to compare these two values in COVID-19 patients. 48.6% of the patients were admitted to the ICU in the first hours of their arrival to the emergency unit or follow-up in the COVID-19 ward. The rest was admitted to the ICU because of worsening in the following days of ward follow-up and treatment. We found that the survival rates of the patients who were taken to the ICU within the first three days of staying in the ward were significantly higher. Our results revealed that when the symptoms of COVID-19 patients start to deteriorate, it is important to continue their treatment under intensive care conditions without waiting any longer to decrease the mortality rate. Patients who were admitted to the ICU from the watchful waiting group had significantly lower levels of prealbumin and transferrin. A significant increase in procalcitonin levels, on the other hand, may indicate that their condition could be worsened as a result of secondary infections that occurred during treatment in the ward.

Limitation

Our study was a retrospective study with data collection. Therefore, the data analysis was based on the information available in the patients' records.

CONCLUSION

For the first time, serum values of eight different inflammatory markers were analyzed as mortality markers in COVID-19 patients. Our findings suggest that negative and positive acute phase reactants, troponin T and D-dimer, may be useful as early indicators of mortality in COVID-19 disease. Prealbumin, transferrin, and procalcitonin levels have been shown to change rapidly in the early period, particularly in patients who require mechanical ventilation and have a fatal course; however, D-dimer levels change

significantly slower. It has been concluded that evaluating inflammatory markers sooner will be beneficial in making an earlier judgment on the admission of COVID-19 patients to the intensive care unit and, as a result, will reduce the mortality rate.

ETHICS COMMITTEE APPROVAL

The study protocol was accepted by the Health Sciences University Hamidiye Scientific Research Ethics Committee (Protocol no: 20/159, Date: 05/05/2020).

CONFLICT of INTEREST

None of the authors had conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept and Design: EB, KTS

Analysis/Interpretation: AS

Data Collection or Processing: EB, FÇ

Writing: EB, KTS

Review and Correction: EB, AS, KTS, FÇ

Final Approval: RD

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