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Evaluation of factors affecting treatment and mortality in patients over 65 years of age and without chronic disease, followed in the Intensive Care Unit due to COVID-19

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Abstract. – OBJECTIVE: In this study, demographic, clinical, and laboratory data of patients aged 65 and over who are followed on mechanical ventilators due to COVID-19 in intensive care clinics will be useful in terms of strategies to be developed in the fight against COVID-19 and other infectious agents.

PATIENTS AND METHODS: Our study included 299 patients aged 65 years and older, who were not chronically ill, and who were followed up on mechanical ventilators due to COVID-19 in intensive care clinics in the period between 2020 and 2022. Our study was designed as a retrospective cross-sectional study. The demographic characteristics of the patients included in the study, their complaints during hospitalization, the time between the beginning of the complaint and the admission to the hospital, the vital signs at the time of admission to the hospital, the lung computed tomography findings during hospitalization, and the treatments given were examined.

RESULTS: 55.9% of all patients were males, and the mean age was 75.45±7.47 years. While there was no significant difference in terms of mean age between the groups of patients with/without a higher risk of mortality, there was a significant difference in gender (p=0.025). There was a statistically significant difference between the COVID-19 intensive care (p=0.001) and renal failure (p=0.014) and mortality groups. The mean nutric score, Procalcitonin (PCT), Lactate Dehydrogenase (LDH), Blood Urea Nitrogen (BUN), Phosphorus, and lactate values, which are important parameters, were statistically higher in the group with a higher risk of mortality (p<0.001). In addition, there was a statistically significant difference in terms of sepsis, neuromuscular blocker (Nmb), vasopressor, and intubation between the groups of patients with/without a higher risk of mortality (p<0.001). In the group with high mortality, 34.2% (n=55) had plasmapheresis treatment, and 14.2% had hemodiafiltration treatment (p<0.001). According to the results of the multivariate logistic regression model in determining the factors associated with a higher risk of mortality, those who were males (p=0.001), those with kidney failure (p<0.001), those with organ failure (p=0.006), increased in alanine aminotransferase (ALT) values (p=0.019), those with sedation (p=0.001) and those with vasopressors (p<0.001) were found to have an increased risk of mortality.

CONCLUSIONS: We think that our study is valuable in terms of determining the most appropriate treatment strategies by following the patients in terms of parameters that are significant in the findings during their follow-up period in the Intensive Care Unit.

Key Words:
Chronic disease, COVID-19, Intensive care unit, Mortality.

Introduction

Shortly after the detection of pneumonia cases of unknown origin in Wuhan, China, in December 2019, the cause was determined to be a new coronavirus, and the World Health Organization (WHO) gave the virus the name "Severe Acute Respiratory Syndrome-Coronavirus-2" (SARS-CoV-2). The disease it caused is known as Corona Virus Disease 2019 (COVID-19). In the literature, it has been reported that during the course of the COVID-19 disease, the need for intensive care hospitalization developed due to mild organ

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failure in 81%, severe course in 14% and severe organ failure in 5%[1]. Respiratory failure due to acute respiratory distress syndrome (ARDS), which usually develops 7-12 days after the onset of disease symptoms, septic shock, multi-organ failure (myocarditis, arrhythmias, cardiogenic shock, coagulation disorders, endocrinopathies, liver and kidney damage, metabolic acidosis, neurological complications, etc.) may occur. In these patients, noninvasive mechanical ventilation, high-flow nasal oxygen therapy, and invasive mechanical ventilation methods are applied. Life support treatments such as vasopressors, inotropes, and dialysis are provided in patients with renal failure, multiorgan failure, and shock[2]. Risk factors such as male gender, obesity, diabetes mellitus, hypertension, advanced age, smoking, immunosuppressive disease, chronic lung disease, and chronic kidney failure cause higher mortality and morbidity in COVID-19 patients[3]. While it varies according to the countries, the overall mortality rate is 5.2%, while this rate varies between 30% and 100% in critically ill patients who need mechanical ventilation[4].

In its current state, the disease progresses more severely and causes death, especially in the elderly and individuals with chronic diseases. First of all, it should be underlined that the disease is not fatal in most of the elderly, but a significant portion of the patients who need intensive care and die are the elderly. Due to the decline in both the immune system and the anatomical and physiological natural defense systems against pathogens with advancing age, infectious diseases are more common in geriatric patients, and these diseases may progress more severely than in young people[5].

Available data6 suggest that a significant proportion of the elderly may have atypical symptoms of COVID-19. It was found that patients who needed intensive care due to COVID-19 were older, and atypical findings for acute lung infection appeared approximately 6.5 days before dyspnea in these patients. The fact that this period is 2.5 days for COVID-19 patients who do not need intensive care and who are younger is quite striking in terms of the importance of atypical presentations in elderly cases[6]. In addition, another important issue to consider is that the side effects and potential drug interactions of the treatments used in the treatment of COVID-19 may adversely affect the course of the infection in geriatric patients, who are very sensitive in this regard. It should be kept in mind that COVID-19 may show atypical presentations in geriatric cases; therefore, the infection may be present in this patient group, even if the classical symptoms of the disease and especially fever, are not present.

It is very important to determine which patients are at risk for Intensive Care Unit (ICU) admission and mortality in COVID-19 infection. Risk factors vary from demographic factors such as age, gender, and ethnicity to nutritional and lifestyle habits, underlying diseases, and genetic factors[7]. Defining demographic, clinical, and laboratory data other than chronic diseases that will show a severe course will be beneficial for the strategies to be developed in the fight against other infectious agents, such as COVID-19, as well as guiding clinicians in identifying patients who will benefit from early treatment.

Patients and Methods

Patients

This study was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the Çukurova University Faculty of Medicine Scientific Ethics Committee. (Ethics Committee date: 7 October 2022, Issue No.: 126). Our study included 299 patients aged 65 years and older, who were not chronically ill and had positive COVID-19 polymerase chain reaction (PCR) and/or rapid antibody test, who were followed up on mechanical ventilators due to COVID-19 in intensive care clinics in the period between 2020-2022. Our study was designed as a retrospective cross-sectional study. Demographic characteristics of the patients included in the study (age, gender, smoking), chronic diseases, complaints during hospitalization, time between the beginning of the complaint and admission to the hospital, vital signs at the time of admission to the hospital, lung computed tomography findings during hospitalization, hemoglobin (g/dL), platelet (10^9/L), alanine aminotransferase (ALT) (U/L), aspartate aminotransferase (AST) (U/L), total bilirubin (mg/dL), direct bilirubin (mg/dL), lactate dehydrohegenase (LDH) (U/L), creatinine kinase (CK) (U/L), blood urea nitrogen (BUN) (mg/dL), creatinine (mg/dL), albumin (mg/ dL), D -dimer (ng/mL), ferritin (ng/mL), troponin (ng/mL), C-reactive protein (CRP) (mg/L), c) (ng/mL), arterial blood gas values (pH), arterial oxygen pressure and carbon dioxide pressure (PaO_2, $PaCO_2$), bicarbonate value (HCO_3) and lactate values, mechanical ventilation, vasopressor use, treatments

given (plasmapheresis, favipiravir, tocilizumab, anakinra, and steroid use) were retrieved from patient files and electronic records were recorded retrospectively. All of the patients consisted of patients followed up from a single center. The patients consisted of patients who needed a ventilator during admission to the Emergency Department or during follow-up in the service. Patients who were not on mechanical ventilators and had chronic disease were excluded from the study. All the patients had COVID-19 PCR positivity, and all patients were given low molecular weight heparin therapy together with steroid therapy. Pulmonary involvement of the patients was confirmed by computerized tomography as well as pa-lung radiography. All laboratory results were evaluated by the same central laboratory.

The inclusion and exclusion criteria for the study are shown in Table I.

Treatments

Steroid

The patients in the study received a 10-day treatment protocol with 500 mg (milligrams) methylprednisolone intravenously for 3 days, followed by 1 mg/kg (milligrams/kilogram) methylprednisolone for 7 days.

Favipiravir

Favipiravir, a selective RNA-dependent RNA polymerase inhibitor, is an antiviral used in the treatment of influenza in some Asian countries. Apart from influenza, it also has an inhibitory effect against many viruses such as arena-, bunya-, flavi- and filoviruses, and hemorrhagic fever viruses such as ebola[8]. Administration dose, day 1: 1,600 mg (8 tablets) in the morning and 1,600 mg (8 tablets) in the evening, twice a day, 2-5. days: 600 mg (3 tablets) in the morning and 600 mg (3 tablets) in the evening were given twice a day. A 5-day treatment period was applied.

Tocilizumab (Remdesivir)

Remdesivir (RDV, GS-5734) is a nucleotide analog broad-spectrum antiviral. It has potent antiviral activity against various RNA viruses [Ebola, Marburg, MERS-CoV, SARS-CoV, respiratory syncytial virus (RSV), Ni-pah virus and Hendra virus]. Its mechanism of action is thought to be the premature termination of viral RNA transcription. RDV shows potent antiviral effects [SARS-CoV (EC_{50}=0.07 μM), MERS-CoV (EC_{50}=0.07 μM) and bat CoV] in human lung epithelial cell culture. Remdesivir also shows superior antiviral efficacy than lopinavir/ritonavir (LPV/r) plus interferon (IFN) beta-1a (LPV/r-IFNb) regimen in the MERS-CoV mouse model[9]. Tocilizumab treatment was used in patients with complications of macrophage activation syndrome (MAS) who did not respond to glucocorticoid treatment or who had rapidly progressive MAS findings. Tocilizumab was administered to the patients at a dose of 8 mg/kg (maximum 800 mg).

Anakinra

Nod-like receptor family pyrin domain-containing 3 (NLRP3) is an inflammasome secreted to protect the body from harmful stimuli, including viruses. NLRP3 activates caspase-1, which is responsible for the abundant release and activation of interleukin (IL)-1β and IL-18. It was previously shown[10] that SARS-CoV induces NLRP3 with the ion channel forming M protein and open reading frame 8b (ORF8b). Anakinra successfully inhibits IL-1 cytokines, with the exception of IL-18. The recommended

Table I. Inclusion and exclusion criteria for the study.

Inclusion criteria	Exclusion criteria
1. Patients aged 65 and over 2. Patients in the intensive care unit 3. Patients on mechanical ventilator 4. Patients without chronic disease 5. Patients with acute renal failure 6. Patients who have received steroid therapy and low molecular weight heparin.	1. Patients under 65 years of age 2. Patients with coronary artery disease and heart failure 3. Those with chronic obstructive pulmonary disease 4. Patients with malignancy 5. Patients with chronic renal failure 6. Patients with chronic liver parenchyma disease 7. Patients not in the intensive care unit 8. Patients not connected to the ventilator were not included in the study. 9. Patients not given steroid therapy or low molecular weight heparin therapy

dose is 1-2 mg/kg/g, the maximum daily dose is 8 mg/kg. The anakinra dose may be increased to 200 mg every 6 hours in some resistant patients. Anakinra treatment was used in patients with MAS complications and who did not respond to glucocorticoid treatment.

Plasmapheresis

It is an extracorporeal supportive treatment that retains the replication components of the virus or the virus itself with modified (lectin-embedded) dialysis filters and delivers uninfected plasma to the patient. A central venous catheter was generally used for plasma exchange therapy. The treatment was administered 5-7 times, every other day, to patients who did not respond to glucocorticoid therapy or whose clinical course progressed rapidly. Plasma was exchanged 1-1.5 times the calculated plasma volume in each application.

Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) package program was used for data analysis in the study. Descriptive data on the sociodemographic information of the participants are given in the form of frequency tables (n and %). Data belonging to continuous variables are given as mean±SD. When the data of the study were analyzed in terms of normality assumptions, Kolmogorov-Smirnov values were determined as $p>0.05$. Independent *t*-test, one of the parametric tests, was used to determine whether there was a significant difference between various sociodemographic, clinical, and biochemical variables and mortality groups. Chi-Square test or Fisher's Exact test was used to compare categorical variables. Finally, the results of Multivariate Logistic Regression on mortality presence of various clinical factors are given. $p<0.05$ was considered statistically significant

Results

The study included a total of 299 patients, 164 with a higher risk of mortality and 135 without mortality. 55.9% of all patients were males, and the mean age was 75.45±7.47 years. While the mean age did not differ significantly between the groups of patients with/without a higher risk of mortality, gender showed a significant difference. A statistically significant difference was found between the COVID-19 intensive care ($p=0.001$), renal failure ($p=0.014$), and mortality groups. Of the patients with a higher risk of mortality, 23.9% (n=39) had COVID-19 intensive care (IC) admission, 76.1% (n=124) had no COVID-19 intensive care admission, 16% (n=26) had kidney failure, 84% (n=137) did not have renal failure (Table II).

When the results of the comparison of biochemical parameters of the patients with a higher risk of mortality are examined, mean nutric score (5.6±1.96 *vs.* 4.18±1.59; $p<0.001$), mean white blood cell (13.18±18.51 *vs.* 9.61±4.82; $p=0.030$), mean procalsitonin (PCT) max (12.28±21.09 *vs.* 1.63±4.1; $p<0.001$), mean active partial thromboplastin time test (APTT) (30.5±13.79 *vs.* 26.6±9.53; $p=0.011$), mean international normalized ratio (INR) (1.38±1.32 *vs.* 1.12±0.24; $p=0.034$), mean hospitalization glucose (194.1±100.42 *vs.* 163.99±84.21; $p=0.005$), mean hospitalization BUN (47.49±28.92 *vs.* 33.4±22.58; $p<0.001$), mean hospitalization AST (209.14±623.06 *vs.*

Table II. Comparison of sociodemographic and clinical findings with mortality.

		Mortality	
Variables	**Yes (n=164)**	**No (n=135)**	***p***
Age, year, Mean±SD	75.34±7.34	75.67±7.66	0.704[a]
COVID-19 intensive care (IC) n (%)			
Yes	39 (23.9)	12 (9.2)	0.001[b]
No	124 (76.1)	119 (90.8)	
Gender, n (%)			
Female	61 (37.4)	68 (50.4)	0.025[b]
Male	102 (62.6)	67 (49.6)	
Comorbidity kidney failure, n (%)			
Yes	26 (16.0)	9 (6.7)	0.014[b]
No	137 (84.0)	125 (93.3)	

[a]=Independent Samples *t*-test, [b]=Chi Square test, [c]=Fisher's Exact test, $p<0.05$ statistically significant.

57.47±108.31; p=0.003), mean hospitalization ALT (115.46±311.65 *vs*. 50.36±108.05; p=0.013), mean lactate dehydrogenase (LDH) (835±1,423.27 *vs*. 403.61±228.77; p<0.001), mean hospitalization sodium (139.22±6.7 *vs*. 137.59±6.4; p=0.034), mean hospitalization magnesium (2.21±0.57 *vs*. 2.03±0.52; p=0.005), mean hospitalization phosphorus (4.11±2.09 *vs*. 3.29±0.97; p<0.001) and mean hospitalization lactate (2.66±2.54 *vs*. 1.75±1.17; p<0.001) values were found to be higher. However, mean PLT (186.95±118.75 *vs*. 235.78±108.35; p<0.001) and mean hospitalization calcium (8.15±0.93 *vs*. 8.48±1.03; p=0.004) values were found to be lower (Table III).

In the group with mortality, mean hospitalization heart rate (91.23±23.51 *vs*. 85.58±17.5; p=0.039), mean FiO_2 (64.58±24.98 *vs*. 43.68±23.63; p<0.001), mean PCO_2 (45.3±14.06 *vs*. 41.41±9.41; p=0.014), mean O_2 (6.81±3.24 *vs*. 4.32±2.31; p<0.001) and mean intensive care unit length of stay (10.01±9.51 *vs*. 6.59±5.18; p<0.001) values were higher. However, mean hospitalization arterial pressure (77.31±15.38 *vs*. 84.13±12.44; p<0.001), mean PH (7.31±0.15 *vs*. 7.39±0.06; p<0.001), and mean HCO_3 (21.61±8.36 *vs*. 24.63±4.7; p=0.001) values were lower. In addition, there was a statistically significant difference in terms of sepsis (p<0.001), vasopressor (p<0.001), and intubation (p<0.001) between the patients with/without a higher risk of mortality. In the patients with a higher risk of mortality, 51.8% (n=85) had sepsis, 63.4% (n=104) had organ failure, 69.6% (n=103) had sedation, 24%, 7 (n=36) had neuromuscular blocker (Nmb), 78.4% (n=127) had vasopressors, 96.9% (n=158) had intubation (Table IV).

When the results of the comparison of the treatments received in the intensive care unit of the mortality groups were examined, there was a statistically significant difference in terms of antibiotic (p<0.001), antifungal (p<0.001), plasmapheresis (p<0.001), hemodiafiltration (p<0.001) treatments between the patients with/without a higher risk of mortality. In the patients with a higher risk of mortality, 95.1% (n=154) had antibiotic

Table III. Comparison of various biochemical parameters with mortality

	Mortality		
Variables	**Yes Mean±SD (n=164)**	**No Mean±SD (n=135)**	***p***
Nutric score	5.6±1.96	4.18±1.59	**<0.001**
Hemoglobin	11.43±2.24	11.64±2.26	0.429
Hematocrit	34.23±6.54	34.77±5.95	0.461
White blood cell	13.18±18.51	9.61±4.82	**0.030**
Lymphocyte	1.88±11.53	0.88±0.72	0.319
Admission D-dimer	7.12±30.17	3.16±5.72	0.134
Hospitalization ferritin	709.32±1,083.63	502.63±628.34	0.053
Admission CRP	130.31±97.25	117.1±102.41	0.255
PCT max	12.28±21.09	1.63±4.1	**<0.001**
APTT	30.5±13.79	26.6±9.53	**0.011**
INR	1.38±1.32	1.12±0.24	**0.034**
Platelets (thousand)	186.95±118.75	235.78±108.35	**<0.001**
Admission Glucose	194.1±100.42	163.99±84.21	**0.005**
Admission BUN	47.49±28.92	33.4±22.58	**<0.001**
Admission Creatinine	1.66±1.31	2.35±14.73	0.546
Admission AST	209.14±623.06	57.47±108.31	**0.003**
Admission ALT	115.46±311.65	50.36±108.05	**0.013**
Admission LDH	835±1,423.27	403.61±228.77	**<0.001**
Admission sodium	139.22±6.7	137.59±6.4	**0.034**
Hospitalization potassium	4.33±0.87	4.19±0.69	0.121
Hospitalization magnesium	2.21±0.57	2.03±0.52	**0.005**
Hospitalization calcium	8.15±0.93	8.48±1.03	**0.004**
Hospitalization Phosphorus	4.11±2.09	3.29±0.97	**<0.001**
Total bilirubin	1.62±3.9	1.17±3.26	0.300
Hospitalization lactate	2.66±2.54	1.75±1.17	**<0.001**
HbA1c	7.69±7.46	7.11±1.83	0.531

CRP: C-reactive protein. PCT: Procalsitonin. APTT: Active partial thromboplastin time test. INR: International Normalized Ratio. BUN: Blood urea nitrogen. AST: Aspartate aminotransferase. ALT: Alanine aminotransferase. LDH: Lactate dehydrohegenase. Independent *t*-test. p<0.05 statistically significant.

Table IV. Comparison of various clinical parameters with mortality groups.

	Mortality		
Variables	**Yes (n=164)**	**No (n=135)**	***p***
Hospitalization-Fever	36.41±0.53	36.4±0.46	0.849[a]
Hospitalization-Pulse	91.23±23.51	85.58±17.5	**0.039**[a]
Hospitalization-mean arterial pressure	77.31±15.38	84.13±12.44	**<0.001**[a]
FiO_2	64.58±24.98	43.68±23.63	**<0.001**[a]
Ph	7.31±0.15	7.39±0.06	**<0.001**[a]
PO_2	69.26±22.19	69.98±17.7	0.787[a]
PCO_2	45.3±14.06	41.41±9.41	**0.014**[a]
SPO_2	70.58±22.69	73.11±22.81	0.359[a]
HCO_3	21.61±8.36	24.63±4.7	**0.001**[a]
Mechanical vent duration	5.24±8.45	3.13±4.72	0.326[a]
Intensive care time	10.01±9.51	6.59±5.18	**<0.001**[a]
Length of stay in hospital	12.82±10.23	14.93±9.25	0.067[a]
Sepsis n (%)			
Yes	85 (51.8)	13 (9.7)	**<0.001**[b]
No	79 (48.2)	121 (90.3)	
Nmb n (%)			
Yes	36 (24.7)	4 (3.3)	**<0.001**[b]
No	110 (75.3)	117 (96.7)	
Vazopressor n (%)			
Yes	127 (78.4)	10 (7.5)	**<0.001**[b]
No	35 (21.6)	123 (92.5)	

[a]=Independent Samples *t*-test. [b]=Chi Square test. [c]=Fisher's Exact test. $p<0.05$ statistically significant.

Table V. Comparison of treatments received in intensive care with mortality.

	Mortality		
Variables	**Yes (n=164)**	**No (n=135)**	***p***
Oseltamivir n (%)			
Yes	1 (0.6)	2 (1.5)	0.589[b]
No	161 (99.4)	130 (98.5)	
Hydroxychloroquine n (%)			
Yes	3 (1.9)	3 (2.3)	
No	159 (98.1)	129 (97.7)	
Favipravir n (%)			
Yes	95 (58.6)	72 (54.5)	0.481[a]
No	67 (41.4)	60 (45.5)	
Anakinra n (%)			
Yes	37 (23.1)	31 (23.8)	0.885[a]
No	123 (76.9)	99 (76.2)	
immune plasma n (%)			
Yes	6 (3.7)	5 (3.8)	1.000[a]
No	155 (96.3)	125 (96.2)	
Plasmapheresis n (%)			
Yes	55 (34.2)	17 (13.1)	**<0.001**[a]
No	106 (65.8)	113 (86.9)	
IVIG n (%)			
Yes	5 (3.1)	4 (3.2)	1.000[a]
No	155 (96.9)	120 (96.8)	
Hemodiafiltration n (%)			
Yes	21 (14.2)	1 (0.8)	**<0.001**[a]
No	127 (85.8)	122 (99.2)	
Remdesivir n (%)			
Yes	160 (99.4)	130 (100.0)	1.000[b]
No	1 (0.6)	0 (0)	

[a]=Chi Square test. [b]=Fisher's Exact test. $p<0.05$ statistically significant.

treatment, 33.8% (n=54) had antifungal treatment, and 34.2% (n=55) had plasmapheresis treatment. It was determined that 14.2% (n=14.2) of patients had hemodiafiltration treatment (Table V).

When the results of the determination of the factors related to mortality were examined as a result of univariate analysis, there was a statistically significant difference between the groups in terms of gender, renal failure, LDH, organ failure, D-dimer, ALT, sepsis, sedation, Nmb, vasopressor, and ferritin values, according to mortality status (p<0.05). These variables, which were found to be significant as a result of univariate analysis, were included in the Multivariate logistic regression model. According to the results of the multivariate logistic regression model, male gender (OR: 5.03 95% CI: 1.90-13.35; p=0.001), kidney failure (OR: 10.67 95% CI: 2.83-40.13; p<0.001), organ failure (OR: 4.50 95% CI: 1.55-13.60; p=0.006), increase in ALT values (OR:1.00 95% CI:0.99-1.01; p=0.019), those with sedation (OR: 7.07, 95% CI: 2.14-22.91; p=0.001) and those with vasopressors (OR: 17.15, 95% CI: 5.48-53.69; p<0.001) were found to increase the risk in terms of the presence of mortality. It was determined that the variables in the model explained 71% of the factors determining mortality (R^2=0.71, -2 loglikelihood=159.61) (Table VI).

Discussion

Poor glycemic control is an independent mortality factor in patients hospitalized in the intensive care unit due to COVID-19 and is considered to be one of the causes that increase mortality in sepsis. All of the patients followed in the intensive care unit were patients with a high glycemic index because they received steroid treatment. In addition, diabetes is a risk factor not only for lung ciliary epithelial dysfunction and increased vascular permeability but also for immune system dysfunction. It is known[11] that poor glycemic control is an independent risk factor for mortality in pneumonia requiring hospitalization. It has been found[12] that poor glycemic control in COVID-19 pneumonia causes an increase in both the development of pneumonia requiring follow-up in the intensive care unit and an increase in mortality. The high glycemic index in our patient cohort is a parameter independent of HgbA1C, which shows the 3-month average glucose level of the patients, and it was confirmed as a result of our statistical analyses. While the high glycemic index was significant in the mortality of the patients, the HgbA1c did not show a significant difference. It reveals the necessity of close follow-up in terms of the high glycemic index that may develop after the steroid treatment starts during the period of follow-up of the patients in the intensive care unit.

The rates of acute renal failure (ARF) due to COVID-19 vary between 7-27%. The severity of ARF and the number of underlying systems affected are important determinants of mortality[13]. Although the causes of ARF due to COVID-19 cannot be fully elucidated, ischemic type tubular lesion activated by the cytopathic effect of the virus entering the kidney cells through ACE2 receptors, high positive end-expiratory pressure (PEEP) pressure used during mechanical ventilation, fluids used in ARDS treatment, fever, nausea-vomiting, diarrhea due to malnutrition in the

Table VI. Multivariate Logistic Regression Results on mortality with various clinical variables.

	Multivariate	
Variables	**OR (95% CI)**	***p***
Gender (ref: Female)	5.03 (1.90-13.35)	**0.001**
Kidney failure (ref: No)	10.67 (2.83-40.13)	**<0.001**
LDH	1.01 (0.99-1.03)	0.226
Organ failure (ref: No)	4.50 (1.55-13.60)	**0.006**
D-dimer	1.06 (0.99-1.12)	0.066
ALT	1.00 (0.99-1.01)	**0.019**
Sepsis (ref: No)	1.32 (0.39-4.74)	0.650
Sedation (ref: No)	7.07 (2.14-22.91)	**0.001**
Nmb (ref: No)	0.58 (0.10-3.20)	0.545
Vazopressor (ref: No)	17.15 (5.48-53.69)	**<0.001**
Ferritin	1.00 (0.99-1.01)	0.955
R^2=0.71. -2 loglikelihood=159.61		

prehospital period of the patients, deterioration of fluid balance, aggressively managed diuresis treatments can be counted[14]. High PEEP pressure may increase renal obstruction and decrease renal perfusion, leading to a decrease in venous return and cardiac output. It is stated[15] that proteinuria, hematuria, serum creatinine, and blood urea nitrogen (BUN) are high in patients hospitalized due to COVID-19, and proteinuria increases even more during the hospital stay. The incidence of in-hospital death is 33.7% in patients with high serum creatinine values at the time of first hospitalization, and 13.2% in patients with normal serum creatinine. It has been emphasized[16] that patients with high serum creatinine require higher ICU and mechanical ventilation. In our study population, it has been shown that the presence of ARF in patients has a significant effect on mortality, in parallel with the literature data. In addition, when the laboratory data of the patients were evaluated, it was observed that the BUN values were high, and it was revealed that hypocalcemia and hyperphosphatemia caused by ARF also had a negative effect on mortality in the patients. However, the reason why creatinine values were not high in our study is thought to be related to the low muscle mass of the patients. During their follow-up in the intensive care unit, patients should be followed closely in terms of renal failure, and it is necessary to closely monitor not only the creatinine value but also the BUN, calcium, and phosphorus values.

In a study conducted by Corwin and Krantz[17] in intensive care units, it was reported that 95% of intensive care patients had lower hemoglobin (Hb) levels than normal on their third day in the ICU[17]. Studies[18] have shown that one-third of the patients received blood transfusions during their stay in the intensive care unit. In sepsis, inflammatory markers such as IL-1, IL-6, tumor necrosis factor (TNF-α), and Interferon-gamma are known to cause anemia by suppressing erythrocyte production through apoptosis of pro-erythrogenic cells. In addition, hepcidin-induced functional iron deficiency due to infection is an important cause of anemia in intensive care patients[19]. Anemia was also observed in our patient cohort and is thought to be due to the inhibitory effect on erythropoiesis via inflammatory markers and cytokines. We think that the risk of anemia increased due to the prolonged length of stay in the intensive care unit, the continuation of suppression of erythrocyte production with the prolongation of blood loss, and the prolongation of the inflammatory process in correlation with the length of stay.

Based on the assumption that not all ICU patients have the same nutritional risk, Heyland et al[20] proposed the Nutrition Risk (Nutric) score for critically ill patients in the intensive care unit. This can be used to identify patients who would benefit from aggressive nutritional support based on their risk of malnutrition. The nutric score is designed on the concept that age, inflammatory state, and patient's nutritional status will influence nutritional deficiencies, immune dysfunction, and clinical outcome. The nutric score includes age, acute physiology, and chronic health assessment (APACHE II), sequential organ failure assessment (SOFA), number of comorbidities, time from hospital to ICU admission, and interleukin-6 data. Patients get 1-3 points for each variable, and the highest score is 10[20]. Zhang et al[21] (2020) found that patients with high nutritional risk at the time of admission to the ICU exhibit higher mortality in the 28 days and are 2 times more likely to die than patients with low nutritional risk. Therefore, they[21] stated that the nutric score might be an appropriate tool in the nutritional risk assessment and prognosis estimation of COVID-19 patients hospitalized in the intensive care unit. In our patient population, it has been shown that the nutric score has a significant effect on mortality, and statistically significant results were obtained. In addition to inadequate nutritional support in intensive care follow-ups, increased inflammatory cytokines are thought to be a factor that increases mortality. In addition, it was observed that the mortality of the patients was improved by the removal of cytokines with plasmapheresis treatment applied to the patients. Therefore, it is thought that mortality can be improved by monitoring the nutric score, and the improvement can be achieved during the time the patients are hospitalized in the intensive care unit.

The percentage of lymphopenia was found to be lower in the group with high mortality in the patients hospitalized in our intensive care unit (percentage of lymphocytes 9% *vs.* 12%), which was not statistically significant (p=0.056). This is thought to be due to the decreased cytokine response with age since our patient cohort is an elderly population over 65 years of age. When the literature data was evaluated, it has been reported that there was a decrease in the number of lymphocytes, mitogen-induced lymphocyte proliferation, IL-2 concentration, polymorphonuclear neutrophils, and monocytes, and NK cells during

aging in immunological terms. The decrease in T-cell proliferation with age also leads to insufficient effective response to antigenic stimuli[24]. Literature data also support our findings.

The probability of developing thrombocytopenia in COVID-19 infection is around 13%[25]. In a meta-analysis[26] of patients with COVID-19 infection, 399 (22.4%) of whom were severe, including nine studies, a decrease in platelet count was observed in severe patients. The platelet count decreased between 27,000-31,000 μL in mild cases and between 29,000-35,000 μL in severe cases. The mechanism of thrombocytopenia is multifactorial. Viral infection and mechanical ventilation cause endothelial damage, and platelet activation is associated with the use of platelets in the formation of thrombosis in the lungs. In addition, decreased secretion of platelets from megakaryocytes in the lung, virus infection of the bone marrow, and intravascular coagulation are also factors that trigger thrombocytopenia. There is a close relationship between low platelet count and mortality.

In COVID-19 infection, patients are predisposed to thrombotic position due to increased inflammation, platelet activation, endothelial dysfunction, and stasis. The most common hemostatic abnormalities observed in the disease are mild thrombocytopenia and increased D-dimer levels[27]. Patients usually have an increase in fibrinogen levels at the time of admission. However, fibrinogen levels should be closely monitored in patients. Fibrinogen levels begin to decrease in patients who develop disseminated intravascular coagulation (DIC). Apart from the fibrinogen level, factor VIII and IX levels may also be found to be high. These features may indicate the tendency of COVID-19 infection to coagulate[28]. Increased D-dimer and the presence of thrombocytopenia are associated with the need for mechanical ventilation, the need for intensive care, and mortality. In clinically severe patients, prothrombin time (PT) and international normalized ratio and thrombin time (TT) are prolonged, while activated partial thromboplastin time (aPTT) tends to shorten29. In a study[30], in which 21 patients died from COVID-19, D-dimer (approximately 3.5 times), fibrin (approximately 1.9 times) degradation products increased, and PT increased 14%. In another study[24], 71% of patients who died due to COVID-19 met the DIC criteria[24] of the International Society for Thrombosis and Hemostasis, while 0.6% of patients who survived met this rate. Antiphospholipid antibody elevation was detected in COVID-19 patients with cerebral, bilateral extremity infarction. The role of this condition in the pathophysiology is unknown. In multicenter studies[6], increased D-dimer levels (≥0.5 mg/L) were found in 46% of patients. The increase in D-dimer level is more prominent, especially in severe cases (59.6% *vs.* 43.2%). In another study[31], D-dimer (2.4 *vs.* 0.5 mg/L) and PT levels (12.2 *vs.* 10.2 sec) were found to be higher in patients who needed intensive care compared to patients who did not need intensive care. Cardiac damage is likely to occur in COVID-19 patients with coagulation disorders. Troponin-T levels tend to be higher in patients with increased PT, aPTT, and D-dimer levels in COVID-19 patients. When 201 patients with COVID-19 pneumonia have prolonged PT levels and increased D-dimer levels (p=0.002), the risk of developing ARDS increases.

COVID-19 patients are at high risk of developing venous thromboembolism (VTE). Immobilization in the disease, dehydration, acute inflammatory state, presence of other cardiovascular risk factors (hypertension, diabetes, obesity) or cardiovascular diseases (coronary artery disease, ischemic stroke history, peripheral artery disease), presence of VTE history, genetic thrombophilia are causes that increase the probability of VTE. In addition, endothelial cell activation/damage via the ACE2 receptor of the virus may contribute to the formation of VTE and may cause endothelial damage in mechanical ventilation, central venous catheterization, and surgical procedures. Inflammatory substances can increase blood viscosity. For all these reasons, pharmacological thrombophylaxis will be beneficial in patients with COVID-19.

In a retrospective cohort study of 2,273 patients with COVID-19 and liver injury, patients were classified as those with mild, moderate, and severe (>5 times upper limit of normal) liver injury, and 45% of patients with COVID-19 had mild and 21% had moderate. However, 6.4% of them had severe liver damage. The resulting liver damage is mostly associated with drugs and inflammation[32].

In a meta-analysis[33] of 3,772 patients obtained from 326 studies examining COVID-19 and liver damage, it was concluded that there was a relationship between liver dysfunction and mortality. It was stated that especially the drugs used and the severity of COVID-19 were effective on liver dysfunction and mortality.

Although there is not much information in the literature about favipravir, it has been stated[34] that all drugs used in the treatment of CO-

VID-19 are potentially hepatotoxic, and it has been emphasized that caution should be exercised in terms of liver damage when using these drugs alone or in combination.

In many studies[35], it has been reported that mortality is high in patients with COVID-19 who need high FiO_2. In our study, mortality was higher in patients with high FiO_2 requirements, but it was observed that PH and PO_2 values were similar in deceased and surviving patients. As expected, thanks to the high FiO_2, the oxygenation of the patients and their acid-base balance were within normal ranges. On the other hand, it was observed that mortality was higher in patients with low bicarbonate levels, as expected, and it was concluded that the current situation is related to the acute kidney failure we mentioned. In our study, the necessity of using noradrenaline was observed in most of the patients, and it was observed that the rates were similar to other studies[16,36].

Although there is no definitive scientific evidence about favipiravir, it was used as an antiviral in a certain group of patients because it was recommended in the COVID-19 diagnosis and treatment guide of the Ministry of Health of the Republic of Turkey. However, when the patients who were given and not given favipravir were compared, it was seen that it did not make a significant contribution to mortality. In clinical studies[37] on favipiravir, it has been shown to be neither effective in terms of mortality nor acceleration of clinical recovery.

In our study, it was observed that there was no significant statistical difference in terms of mortality in patients with and without tocilizumab. Initially, studies[38,39] on this drug indicated that it positively affected both clinical benefit and mortality. However, there are also studies[40,41] concluding that the drug has no clinical benefit and does not affect mortality.

Plasmapheresis is a treatment method that is used in many areas to remove plasma and replace it with normal human plasma. With the membrane filtration technique, large molecules can be removed from the circulation. There are publications[42] showing the benefit of plasmapheresis in MERS and SARS infections.

Since antibodies, lipoproteins, immune complexes, cryoglobulins, myeloma proteins, protein-bound toxins, platelets, and leukocytes can be easily removed from the human body, this method is preferred in cytokine storms. Although there are studies in literature showing that this treatment method reduces mortality in patients with COVID-19, there are many studies[42-44] claiming the opposite. In our study, it was shown that plasmapheresis treatment applied in the cytokine storm has a significant effect on mortality, and we believe that it is effective on mortality because it is preferred in selected patients and in patients with severe cytokine release.

When randomized controlled studies[44] on remdesivir were examined, it was shown that it had no effect on mortality, especially in severe cases, but it was shown that it could prevent the transition to mechanical ventilation in patient groups used in the early period. In our study, it was shown that remdesivir did not have a significant effect on mortality, and we think that these results were achieved because the patients receiving this drug were in advanced stages and were currently on mechanical ventilation.

The present study has some limitations. First, this study is a single-center study. Second, the long-term diagnostic efficacy of these indices is lacking, as all patient data did not include long-term follow-up.

Conclusions

According to the results of our study, the steroid treatment started during the follow-up period of the patients in the intensive care unit, and the high glycemic index that may develop afterward should be closely monitored. During their follow-up in the intensive care unit, patients should be followed closely in terms of renal failure. Not only creatinine values but also BUN, calcium, and phosphorus values should be followed closely. We think that the risk of anemia increases due to the prolonged length of stay in the intensive care unit, the continuation of suppression of erythrocyte production with the prolongation of blood loss, and the prolongation of the inflammatory process in correlation with the length of stay. We think that in addition to inadequate nutritional support in intensive care follow-ups, increased inflammatory cytokines are factors that increase mortality. In addition, it has been observed that the removal of cytokines with plasmapheresis treatment applied to the patients improved the mortality of the patients. However, in our study, it was shown that plasmapheresis treatment applied in case cytokine storm development has a significant effect on mortality, and we believe that it is effective on mortality because it is preferred in selected patients and patients with severe cytokine release. In our study, it was shown that remdesivir did not

have a significant effect on mortality, and we think that these results were achieved because the patients taking this drug were in advanced stages and currently on mechanical ventilators. The results of our study need to be supported by multicenter and larger patient participation.

Conflict of Interest
The Authors declare that they have no conflict of interest.

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None.

Informed Consent
The authors declare that the patients included in the study signed informed consent forms to use their medical information in the studies.

Authors' Contributions
Concept: M.T.I., A.O.Y., E.O., O.O.I.; Design: M.S., D.L.T., F.K., E.B.; Supervision: M.A.U., E.B., F.K.; Funding: M.T.I., A.O.Y., E.O., M.A.U.; Materials: M.S., D.L.T., M.T.I., A.O.Y., E.O.; Data: M.T.I., A.O.Y., F.K., E.B.; Analysis: M.T.I., A.O.Y., M.A.U., E.B., F.K.; Literature search: M.T.I., A.O.Y., F.K., E.B.; Writing: M.T.I., A.O.Y.; Critical revision: M.A.U., E.B., F.K., M.S., D.L.T.

Data Availability
The data used and analyzed during this research are available from the corresponding author upon reasonable request.

Ethics Approval
This study was conducted in accordance with the Principles of the Declaration of Helsinki and was approved by the Çukurova University Faculty of Medicine Scientific Ethics Committee. (Ethics committee date: 7 October 2022, Issue No.: 126).

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