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Risk Factors of 90-Day Mortality in Patients with Critical Covid-19 Infection

Ferhan DEMIRER AYDEMIR[1], Necati GOKMEN[2], Vecihe BAYRAK[1], Bilgin COMERT[3], Begum ERGAN[4]

[1]Dokuz Eylül University Faculty of Medicine, Department of Internal Medicine, Division of Intensive Care Medicine, Izmir, Turkey

[2]Dokuz Eylül University Faculty of Medicine, Department of Anesthesiology and Reanimation and Critical Care, Izmir, Turkey

[3]Izmir Medicana International Hospital, Division of Intensive Care Medicine, Department of Internal Medicine, Izmir, Turkey

[4]Dokuz Eylül University Faculty of Medicine, Department of Pulmonary and Critical Care, Izmir, Turkey

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Corresponding Author: Ferhan Demirer Aydemir

E mail: ferhanaydemirer@gmail.com

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ABSTRACT

Aim: Mortality risk factors and effective treatment approaches are still uncertain for the SARS-CoV-2. In this study, we aimed to determine risk factors of 90-day mortality critically ill patients with COVID-19 infection.

Materials and Methods: All patients hospitalized in the intensive care unit of the university hospital with the diagnosis of COVID-19 pneumonia between 15 March and 30 November 2020 were reviewed in this retrospective study. The primary endpoint was 90-day mortality, while the secondary endpoints were in-hospital mortality, therapy responses for tocilizumab and corticosteroid treatments, duration of mechanical ventilation (MV), and length of hospital stay.

Results: A total of 145 patients, 105 (73%) men and 40 (27%) women were included in the study. Median age was 71.0 (58–79.50) years. In-hospital mortality was 62.8%, 28-day mortality was 60%, and 90-day mortality was 66.9% for the whole study population. In-hospital mortality was 58.4% (n=52) and 90-day mortality was 64.0% (n=57) in patients receiving corticosteroid treatment. Both in-hospital and 90-day mortality was found as 60% (n=12) in patients receiving tocilizumab. Age and duration of invasive mechanical ventilation were determined as independent risk factors on logistic regression analysis performed for 90-day mortality (OR 1.060 (1.018–1.103), p=0.005 and OR 1.057 (1.004–1.113, p=0.035), respectively).

Conclusions: Early and late mortality is high in patients with severe COVID 19 infection. Our results showed advanced age and duration of mechanical ventilation are independent risk factors for 90-day mortality. However long-term effect of corticosteroid and tocilizumab treatments on survival could not be demonstrated in this study.

Keywords: Severe Acute Respiratory Syndrome Coronavirus 2, Coronavirus Disease 2019, mortality rate, pulmonary inflammation, critically ill

Introduction

In December 2019, a new coronavirus disease (COVID19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection spread rapidly across continents. Highly increased levels of proinflammatory cytokine concentrations were shown in the first pathology reports of the patients died due to severe infection of SARS-CoV-2 (1). Actually, cytokine storm mediated by the overproduction of proinflammatory cytokines were observed in a large population of critically ill patients infected with COVID-19 (2,3). The patients with cytokine storm progress towards cardiovascular collapse, multiple organ dysfunction, and rapid death. Therefore, early diagnosis, treatment and prevention of cytokine storm are vital for patients. In the treatment management of COVID-19 disease, national treatment guidelines regularly published by the Ministry of Health since the emergence of the first case in Turkey, and these guidelines were updated with the new information obtained about the therapeutical management of the disease and shared with healthcare professionals (4). Initially, empirical antiviral and antibiotic agents can be applied according to symptoms in selected patient groups (4). Besides that, prophylaxis (enoxaparin, heparin, acetylsalicylic acid) for venous thromboembolism can be administered to hospitalized patients, considering information that COVID-19 can cause hypercoagulopathy (5). In the treatment of critically ill patients, dexamethasone and other glucocorticoids, remdesivir, favipiravir, lopinavir/ritonavir, hydroxychloroquine/chloroquine, monoclonal antibodies against IL-6 receptors

(tocilizumab, sarilumab, siltuximab), convalescent plasma and other antibody-based experimental treatments, interferons, IL-1 inhibitors (anakinra) and ivermectin can be used (6). Cytokine storm (CS) is recognized as excessive and uncontrolled release of pro-inflammatory cytokines. Various diseases including infectious diseases, rheumatic diseases and tumor immunotherapy can induce cytokine storm syndrome. It generally manifests itself clinically as systemic inflammation, multiple organ failure, and high inflammatory parameters (7). In infectious diseases, CS usually originates in the focal infected area and spreads throughout the body via circulation. Multiple inflammatory cell infiltration and CS cause acute lung damage, Acute Respiratory Distress Syndrome (ARDS) and death in coronavirus pneumonia, such as Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), accompanied by rapid virus replication (7,8). Systemic corticosteroids due to their anti-inflammatory effects and monoclonal antibodies against IL-6 receptors are frequently used in treatment regimens for COVID-19.

There is limited data on the effect of tocilizumab and steroid therapies on inflammatory activity in COVID-19 patients. Experiences in COVID-19 patients showed that the use of anti-inflammatory treatments might be beneficial (9). In fact, short-term steroid therapy was associated with lower mortality in 201 patients with acute respiratory distress syndrome (ARDS) (10). Additionally, following the data on presence of inflammatory cytokine storm in severe COVID-19, tocilizumab use has been advocated. This monoclonal antibody, which binds to interleukin 6 (IL-6) receptor and blocks the IL-6 mediated inflammatory response, is approved for treatment of rheumatologic disorders and cytokine-release syndrome associated with Chimeric Antigen Receptor T-cell (CAR-T) administration. It was reported to reduce COVID-19-associated inflammation, and was approved in China for this indication (9,10).

In addition, the vast majority of studies are limited with regards to early mortality assessment. Most studies reported 28-day mortality ranging from 28% to 44%. A few European studies have reported 90-day mortality rates. The first one is the French prospective COVID-ICU study that described a cohort of 4244 patients admitted to the intensive care unit with a 90-day mortality rate of 31% (11). Another study is the Dutch retrospective study ProVENT-COVID, which reported 43% mortality at day 90 in a cohort of 533 patients, all undergoing invasive mechanical ventilation (IMV) (12).

There is limited data for ICU outcomes of patients with severe COVID-19 infection. For this purpose, we aimed to investigate short and long term mortality in the first wave of COVID-19 in our center.

Materials and Methods

Study Population

This retrospective cohort study included patients with a diagnosis of severe COVID-19 followed in the tertiary intensive care unit (ICU) of the university hospital. The medical records of all patients admitted to ICU, between 15 March and 30 November 2020 with a definite or probable diagnosis of COVID-19 according to the Ministry of Health COVID-19 guideline definitions, were reviewed using a standard case report form. The study was approved by the local ethics committee of University (approval number: 2021/01–32) and the Ministry of Health of the Republic of Turkey (approval number: 2020-11-14T11_50_24).

Case Definition

Patients who met the definition of diagnostic criteria for confirmed or suspected case of COVID-19 pneumonia were included in the study. Those with a positive PCR test were defined as confirmed cases. According to the guidelines of the Turkish Ministry of Health, the definition of suspected cases included the presence of fever, cough and difficulty in breathing along with radiographic findings consistent with SARS-CoV-2 infection with or without a history of contact with a confirmed case. Patients having signs of persistent fever, increased or persistently increasing C reactive protein (CRP) and ferritin levels, elevated levels of D-dimer, lymphopenia or thrombocytopenia, abnormal liver function tests, hypofibrinogenemia, or high triglyceride levels were considered as macrophage activation syndrome (MAS).

Study population characteristics, disease severity, and evaluation of clinical outcomes

The following parameters were obtained from the medical records: demographic characteristics (age, gender, comorbidities), Charlson Comorbidity Index (CCI), disease severity score [Acute Physiology and Chronic Health Evaluation II (APACHE II), Sequential Organ Failure Assessment (SOFA)], clinical characteristics, (respiratory and other organ failures, non-invasive and invasive ventilation support, duration of mechanical ventilation, vasopressor use and secondary infections), laboratory findings, length of hospital stay, length of ICU stay, mortality. Since the change in laboratory findings within days in patients treated with tocilizumab is considered, the laboratory findings which were white blood cell (WBC), CRP, ferritin, LDH, D-dimer values before tocilizumab administration were chosen as pre-treatment values and changes in values within the ten-day period after tocilizumab administration were taken into account. In-hospital survival of the patients discharged from the ICU was assessed by the hospital death notification system.

COVID-19 Treatment Regimen

Patients were treated with the regimens recommended in the national guidelines on SARS-CoV-2 infection, published by the Ministry of Health of the Republic of Turkey. All patients were evaluated by a multidisciplinary COVID-19 pandemic team (consisting of members from intensive care, chest diseases, infectious diseases, internal medicine, medical microbiology, radiology and cardiology departments) throughout their diagnoses and treatment periods. National guidelines are updated several times based on changing evidence, as SARS-CoV-2 infection is a new disease and a global clinical experience with new data acquired continuously and accumulating rapidly. Tocilizumab and corticosteroids were given to patients with suspected and confirmed SARS-CoV-2 infection according to the benefit/risk ratio at the discretion of the relevant physician, as well as laboratory and clinical findings. Patients with contraindications [pregnancy,

neutropenia (<500/mm^3), active tuberculosis, active hepatitis B or C infections, allergy and hypersensitivity] (4) or did not consent to treatment were administered no medicine. According to the recommendation in the guidelines, corticosteroid therapy was administered as 6 mg/day dexamethasone or 0.5–1 mg/kg prednisolone or equivalent methylprednisolone (up to 10 days). In those patients with increasing oxygen demand or acute phase response within 24 hours despite this treatment, higher doses of glucocorticoids (pulse, ≥250 mg/day methylprednisolone) were used for up to 3 days, considering their risk factors as well.

The patient group of without corticosteroid therapy did not receive steroid treatment because they were hospitalized when steroid treatment was not yet recommended in the national guidelines on SARS-CoV-2 infection published by the Ministry of Health of the Republic of Turkey. Tocilizumab treatment was administered at a dose of 8 mg/kg (max. 800 mg) in patients who had developed MAS symptoms and did not respond to glucocorticoid therapy or displayed rapidly progressing MAS findings. Depending on the severity of the findings in the patient, when the first dose was administered as 400 mg or 800 mg IV, a repeat dose was given as 200–400 mg IV within 24 hours, taking the changes in clinical and laboratory findings into account.

Primary and secondary endpoints

The primary endpoint was 90-day mortality, while the secondary endpoints were in-hospital mortality, therapy responses for tocilizumab and corticosteroid treatments, duration of mechanical ventilation (MV), and length of hospital stay.

Statistical Analysis

All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range values. Categorical variables between groups were compared by using chi-square or Fisher's exact test, and continuous variables were compared by means of Mann-Whitney U-test. The independent risk factors 90-day mortality was assessed by multivariate logistic regression analysis. Both variables found statistically significant between survivors and nonsurvivors and subset of covariates which were considered to be clinically important were selected for the logistic regression model. An adjusted odds ratio (OR) and 95% confidence interval (CI) were reported for each independent factor. Two-tailed p value of 0.05 was considered statistically significant. Statistical analysis was implemented by using the SPSS (Statistical Package for the Social Sciences Version 24; IBM Corporation, Armonk, NY, USA) program.

Results

Patients

A total of 145 patients, 105 (73%) male and 40 (27%) female, having a diagnosis of suspected or confirmed COVID-19 pneumonia were admitted to ICU Median (IQR) age was 71.0 (58.0–79.5) years. Of the patients, 84.8% were COVID-PCR positive and 15.2% were radiologically (confirmed with computerized tomography) –COVID compatible. 74.5% of the patients were admitted to the ICU from the pandemic ward while 25.5% from the emergency service. Forty-eight (33.1%) of the patients were 90-day survivors and 97 (66.9%) were non-survivors. There was a significant difference in age between survivors and non-survivors [58.5 (49.5–70.7) vs. 76.0 (66.0–82.0) years respectively, p<0.001]. No significant difference was found when surviving and non-surviving patients were compared in terms of gender [15 (31.3%) vs. 25 (25.8%), p=0.555], COVID-19 diagnosis [40 (27.5%) vs. 83 (57.2%) COVID-PCR positive, p=0.807] or place of acceptance [10 (20.8%) pandemic service vs. 27 (27.8%) emergency service, p=0.422] respectively (Table 1).

Comorbidities

The most common comorbidities were hypertension in 86 (59.3%) and diabetes mellitus in 57 (39.3%) patients. Median CCI score was 4 (3–5.5) for the whole study group. Survivors and non-survivors groups showed a variation with regard to coronary artery disease [7 (14.6%) vs. 30 (30.9%), p=0.043], dementia [1 (2.1%) vs. 14 (14.4%), p=0.021] and malignancy [1 (2.1%) vs. 15 (15.5%), p=0.021] respectively (Table 1).

Clinical and laboratory findings during admission to the ICU

Glasgow Coma Score (GCS) median (IQR) was 13 (3–15), APACHE II score was 16 (11–22) on ICU admission. Also, 78 (53.8%) were with invasive mechanical ventilation, 67 (46.2%) with noninvasive respiratory support (noninvasive mechanical ventilation or high flow nasal cannula (HFNC) or alternating use of both) when admitted to ICU. GCS [15 (13–15) vs. 3 (3–15), p<0.001], APACHE II score [10.5 (8–14.7) vs. 19 (14–25), p<0.001] and CCI [2 (1–4) vs. 5 (3–6), p<0.001] showed significant differences between the groups that 90 day survivors and nonsurvivors, respectively. When compared in terms of day-zero WBC level [8600 10*3/uL (6675–11750) vs.10600 10*3/uL (7800–14100), p<0.029] and day-zero D-Dimer [0.9 ug/mL (0.5–2.7) vs. 2.0 ug/mL (1.2–7.2), p<0.001], significant difference was found between these groups, respectively.

Median (IQR) duration of invasive mechanical ventilation was 6 (1–13) days, median (IQR) duration of noninvasive respiratory support was 2 (1–5) days, and vasopressor support was median 2 (0–5) days during the ICU follow-up. Invasive mechanical ventilation support on admission [11 (7.5%) vs. 67 (46.2%), p<0.001], invasive mechanical ventilation duration [0 (0–10) vs. 8 (2–15) days, p<0.001] and duration of vasopressor therapy [0 (0–0.7) vs. 3 (1–8) days, p<0.001] showed significant differences between 90 day survivors and nonsurvivors, respectively (Table 1).

COVID-19 specific treatments

There was a total of 89 (61.4%) patients treated with corticosteroids, twenty-one (23.6%) of them had pulse steroid, 20 (13.8%) with tocilizumab, 43 (29.7%) with hydroxychloroquine, 114 (78.6%) with favipravir, and 109 (72.2%) with antibiotics, in accordance with the Ministry of Health's COVID 19 treatment guidelines. When tocilizumab, steroid and pulse steroid treatments were compared, there was no significant difference between 90-day survivors and and non-survivors (Table 1). Of the 20 patients who received tocilizumab, 11 were treated with tocilizumab and corticosteroids, 9 only with tocilizumab, and they displayed

Table 1. Demographic Clinical Characteristics and Disease Severity Status at Admission to Intensive Care Unit of all patients and 90-day survivors and nonsurvivors

		90 day survival		
	Total n=145	**Survivors n=48 (33.1)**	**Nonsurvivors n=97 (66.9)**	**p value******
Age	71.0 (58.0-79.5)	58.5 (49.5-70.7)	76 (66-82)	<0.001
Gender				
Female	40 (27)	15 (31.3)	25 (25.8)	0.555
Male	105 (73)	33 (68.8)	72 (74.2)	
COVID 19 diagnosis				
PCR positive	123 (84.8)	40 (27.5)	83 (57.2)	0.807
CT positive	22 (15.2)	8 (5.5)	14 (9.6)	
Acceptance department				
Emergency	37 (25.5)	10 (20.8)	27 (27.8)	0.422
Pandemic service	108 (74.5)	38 (79.2)	70 (72.2)	
Comorbidities				
Hypertension	86 (59.3)	27 (56.3)	59 (60.8)	0.720
Diabetes mellitus	57 (39.3)	18 (37.5)	39 (40.2)	0.857
Coronary artery disease	37 (25.5)	7 (14.6)	30 (30.9)	0.043
Congestive heart failure	12 (8.3)	2 (4.2)	10 (10.3)	0.338
Chronic obstructive pulmonary disease	10 (6.9)	5 (10.4)	5 (5.2)	0.299
Dementia	15 (10.3)	1 (2.1)	14 (14.4)	0.021
Chronic renal failure	15 (10.3)	3 (6.3)	12 (12.4)	0.386
Malignancy	16 (11)	1 (2.1)	15. (15.5)	0.021
Immunosuppression	7 (4.8)	2 (4.2)	5 (5.2)	1.000
Other comorbidities *	48 (33.1)	10 (20.8)	38 (39.2)	0.038
Charlson Comorbidity Index	4 (3-5.5)	2 (1-4)	5 (3-6)	<0.001
Glasgow Coma Score	13 (3-15)	15 (13-15)	3 (3-15)	<0.001
APACHE II Score **	16 (11-22)	10.5 (8-14.7)	19 (14-25)	<0.001
ABG values				
Ph	7.40 (7.30-7.43)	7.40 (7.36-7.45)	7.40 (7.29-7.40)	0.008
PaO_2 (mmHg)	61 (53-81)	62 (56-81)	60 (51-80)	0.232
$PaCO_2$ (mmHg)	33 (29-42)	33 (30-38)	33 (29-44)	0.630
HCO_3 (mmol/L)	22 (20-25)	24 (21-26)	21 (19-24)	<0.001
Lactate (mmol/L)	1.80 (1.30-2.50)	1.65 (1.10-2.17)	1.90 (1.40-2.70)	0.065
Oxygen Saturation (%)	91 (86-95)	91 (89-95)	90 (83-95)	0.054
WBC D0 (10*3/uL)	9600 (7500-13500)	8600 (6675-11750)	10600 (7800-14100)	0.029
D-dimer D0 (ug/mL)	1.6(0.9-4.2)	0.9 (0.5-2.7)	2.0 (1.2-7.2)	<0.001
CRP D0 (mg/L)	152 (84-230)	132 (75-220)	158 (89-234)	0.106
Ferritin D0 (ng/mL)	636 (355-1125)	559 (323-1108)	671 (372-1144)	0.102
LDH D0 (U/L)	555 (411-692)	499 (398-648)	570 (439-731)	0.320
PaO2/FiO2 ratio	103 (90-136)	104 (93-140)	101 (88-136)	0.244
Respiratory support on admission				
Invasive MV	78 (53.8)	11 (7.5)	67 (46.2)	<0.001
Noninvasive support ***	67 (46.2)	37 (25.5)	30 (20.6)	
Duration of invasive MV (days)	6 (1-13)	0 (0-10)	8 (2-15)	<0.001
Duration of noninvasive support (days)	2 (1-5)	3 (2-6)	2 (0-4)	0.087
Duration of vasopressor therapy (days)	2 (0-5)	0 (0-0.7)	3 (1-8)	<0.001
COVID Therapies				
Tocilizumab	20 (13.7)	8 (16.7)	12 (8.2)	0.609
Steroid	89 (61.3)	32 (66.7)	57 (39.3)	0.372
Pulse steroid	21 (14.4)	7 (4.8)	14 (9.6)	1.000
Lenght of ICU stay (days)	8 (4-16)	7 (5-16)	9 (4-15)	0.717
Lenght of hospital stay (days)	14 (9-22)	16 (12-27)	12 (7-21)	<0.001
In hospital mortality	91 (62.8)	0	91 (62.8)	<0.001

*Other comorbidities: hematological malignancies, connective tissue diseases, benign prostatic hyperplasia, heart valve disorders, heart rhythm disorders, osteoporosis,
COVID 19: Coronavirus diesase 2019, **PCR:** Polymerase chain reaction, **CT:** Computed tomography, **WBC0:** White blood cell on admission, **CRP0:** C-reactive protein on admission, **LDH0:** Lactate dehydrogenase on admission.
****APACHEII:** Acute Physiology and Chronic Health Evaluation II, **ABG:** Arterial Blood Gas, **MV:** Mechanical ventilation, **ICU LOS:** Intensive care unit length of stay
*****noninvasive support includes both noninvasive ventilaiton and high flow nasal oxygen.
******P value is for comparasion between survivors and nonsurvivors for 90 day.
(All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range values.)

Table 2. Demographic Data, Disease Severity Status and Laboratory Data of Severe COVID 19 Patients Receiving and Not Receiving Corticosteroid Therapy

Variable	Receiving corticosteroid therapy	Non receiving corticosteroid therapy	p value
n	89 (61.3)	56 (38.6)	NA
Gender			
Male	71 (79.8)	34 (60.7)	0.021
Mean age	69.0 (56.0-77.0)	74.5 (63.8-86.0)	0.001
Glasgow Coma Score	15 (3-15)	3 (3-15)	<0.001
APACHEII Score	15 (10-23)	16 (13-22)	0.686
Charlson Comorbidity Index	4 (2-5)	5 (3-6)	0.044
Duration of invasive mechanical ventilation (days)	8 (0-14)	5 (2-10.8)	0.663
Noninvasive support (days)	2 (0-5.3)	2 (1-4.5)	0.270
Duration of vasopressor therapy (days)	2 (0-5.5)	1 (0.3-5)	0.280
PaO2/FiO2 ratio	101 (86.5-130)	110 (93-145.3)	0.088
COVID Therapies			
Antibiotics	73 (82)	36 (64.3)	<0.019
Hydroxychloroquine	9 (10.1)	34 (60.7)	<0.001
Favipravir	84 (94.4)	30 (53.6)	<0.001
Plasma	40 (44.9)	12 (21.4)	0.005
Tocilizumab	11 (12.4)	9 (16.1)	0.623
Pulse steroid	21 (23.6)	0	<0.001
Laboratory values			
WBC D0(10*3/uL)	9300 (7550-13550)	9800 (7275-13550)	0.972
WBC D5(10*3/uL)	10800 (8200-14950)	11050 7175-14450)	0.924
Lymphocytes D0	500 (400-800)	800 (600-1200)	0.001
Lymphocytes D5	400 (300-1000)	800 (525-1100)	0.004
D-Dimer D0 (ug/mL)	1.4 (0.8-2.8)	3 (1.03-10.75)	0.011
D-Dimer D5 (ug/mL)	1.8 (1.0-4.4)	3.9 (1.5-6.4)	0.019
CRP D0 (mg/L)	154 (77-229)	148 (94-233)	0.755
CRP D5 (mg/L)	73 (31-124)	196 (94-261)	<0.001
Ferritin D0 (ng/mL)	649 (356-1214)	567 (331-996)	0.374
Ferritin D5(ng/mL)	546 (360-956)	610 (384-916)	0.577
LDH D0(U/L)	573 (412-715)	533 (408-673)	0.381
LDH D5(U/L)	427 (336-632)	436 (321-514)	0.314
In hospital mortality	52 (58.4)	39 (69.6)	0.217
Day 28 mortality	51 (35.1)	36 (24.8)	0.487
Day 90 mortality	57 (39.3)	40 (27.5)	0.372

***APACHEII:** Acute Physiology And Chronic Health Evaluation II, **WBC:** White blood cell count, **CRP:** C-reactive protein, **LDH:** Lactate dehydrogenase, **D0:** First day in the ICU, **D5:** Fifth day in the ICU *(All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range values. Categorical variables between groups were compared by using chi-square or Fisher's exact test, and continuous variables were compared by means of Mann-Whitney U-test.)* (All categorical variables were expressed as numbers and percentages, and continuous variables were expressed as median and interquartile range values.)

no significant difference in terms of mortality (11 (12.4%) vs 9 (26.2%), p=0.623, Table 2). The patient groups with and without corticosteroid treatment displayed a considerable variance in terms of age (69.0 (56.0–77.0) vs. 74.5 (63.8–86.0) years, p=0.001) and the GCS (15 (3–15) vs. 3 (3–15), p<0.001), respectively. Again, these groups, with and without corticosteroid treatment, differed in terms of gender (71 (79.8%) female vs. 34 (60.7%) male, p=0.021) and the CCI (4 (2–5) vs. 5 (3–6), p=0.044), respectively. Day-zero lymphocyte level (500 10*3/uL (400–800) vs.800 10*3/uL (600–1200), p=0.001), day-five lymphocyte level (400 10*3/uL (300–1000) vs.800 10*3/uL (525–1100), p=0.004), day-five CRP level (73 mg/L (31–124) vs. 196 mg/L (94–261), p<0.001), and day-five D-Dimer level (1.8 ug/mL (1.0–4.4) vs. 3.9 ug/mL (1.5–6.4), p=0.019) showed significant differences between the groups that received and did not receive corticosteroid treatment, respectively. There was no difference in terms of in-hospital mortality rates due to all causes between the groups with and without corticosteroids (58.4% vs 69.6%, p=0.217, respectively; Table 2). A decrease was observed on CRP and ferritin levels on the first, fifth and tenth days after tocilizumab treatment (respectively, 165 mg/L (43–419), 12 mg/L (6–101), 6 mg/L (2.1–109.0) and 960 ng/mL (120–4788), 551 ng/mL (90–3333), 360 ng/mL (68–15000)).

Length of ICU and hospital stay, in-hospital and 90-day mortality

Median (IQR) length of ICU stay was 8 (4–16) days and hospital was 14 (9–22) days. In-hospital mortality of the study population was 62.8%, the 28-day mortality was 60%, and the 90-day mortality was 66.9% (Table 1).

In-hospital mortality was 58.4% (n=52) and 90-day mortality was 64.0% (n=57) in patients receiving corticosteroid (Table 2). Patients who received tocilizumab however, in-hospital and 90-day mortality value was 60% (n=12). Length of hospital stay (16 (12–27) vs. 12 (7–21) days, p<0.001) and in hospital mortality (0 vs.

Table 3. Possible independent risk factors associated with 90-day mortality in critically ill adults with COVID-19

	OR (%95 CI)	P Value
Age	1.060 (1.018-1.103)	0.005
Gender	1.370 (0.540-3.474)	0.508
Charlson comorbidity index	1.187 (0.955-1.476)	0.122
PaO2/FiO2 on admission	0.994 (0.988-1.000)	0.064
Tocilizumab treatment	0.834 (0.256-2.716)	0.764
Duration of invasive mechanical ventilation (days)	1.057 (1.004-1.113)	0.035
Pulse steroid treatment	1.327 (±0.400-4.406)	0.644

91 (62.8%), $p<0.001$) showed significant differences between 90 day survivors and nonsurvivors groups, respectively (Table 1). Age and duration of invasive mechanical ventilation were determined as independent risk factors in the logistic regression analysis for 90-day mortality (OR (CI) 1.060 (1.018–1.103), $p=0.005$ and OR (CI) 1.057 (1.004–1.113, $p=0.035$) respectively). No significant relationship was determined between 90-day mortality and gender, PaO_2/FiO_2 (P/F) value on admission, CCI, and tocilizumab and pulse steroid treatments (Table 3).

Discussion

Age and disease severity scores including GCS, APACHE II score and CCI showed significant differences between 90 day survivors and nonsurvivors. Our results are consistent with a study that included 4244 cases (11). According to this study non-survivors were older, and more frequently diabetic or immunocompromised than survivors. At ICU admission, they had a higher renal and hemodynamic SOFA component scores and lower PaO_2/FiO_2 ratio. In our study invasive mechanical ventilation support on admission, invasive mechanical ventilation duration and duration of vasopressor therapy showed significant differences between survivors and nonsurvivors for 90 days. When tocilizumab, steroid and pulse steroid treatments were compared, no significant difference was observed.

Age and length of invasive mechanical ventilation were determined as independent risk factors for 90-day mortality in the regression analysis evaluation of long-term mortality. Our findings were consistent with the study of Grasselli et al. (13) confirming particularly lower rates of survival of critically ill elderly male patients with COVID-19 requiring invasive mechanical ventilation and with pre-existing comorbidities. There is still limited information on basic patient characteristics and risk factors associated with mortality in ICU and in hospital. Age and invasive mechanical ventilation requirement varied widely between different case series, but both were always correlated with high rates of mortality (14–15). Likewise, the patients admitted to the ICU were also older in the study by Wang et al. (16) and they had more comorbidities with respect to those who were not admitted to the ICU (17). This suggests that age and comorbidities may be risk factors for a poor outcome. Frailty is common among patients admitted to ICU, which was correlated with poor outcomes (18). The COVID-19 outbreak affected older patients with comorbidities, increasing their mortality risk (19).

The intubation rate in this study population was 53.8% (n=78). Our results were consistent with the experience in Lombardy, Italy, (13) namely 53.8% of our COVID-19 patients needed invasive mechanical ventilation at ICU admission, which was the main indication for admission to the ICU. However, lower rates (47%) of intubation were reported in ICU patients by Wang et al. in Wuhan, China (16).

Xu et al. found a lower percentage of lymphocytes in 85.0% (n=17/20) of the patients who received tocilizumab, and it returned to normal values within 5 days in 52.6% of the patients (n=10/19), also high CRP values returned to normal (9). A rapid decline in serum CRP levels was the most striking clinical change observed in this study related to tocilizumab, similar to other reports of tocilizumab use in COVID-19 patients (20–23). This is a possible reflection of the immune modulating effect of tocilizumab. In our study, a decrease was observed in CRP and ferritin levels on the fifth and tenth day after tocilizumab treatment for severe COVID-19 in 20 patients (day-five 165, day-ten 12 and day-five 960, day-ten 551, respectively), whereas no significant change was determined in lymphocyte levels. The clinical use of tocilizumab in severe COVID-19 and its effects on mortality are still controversial (20,21,24). We could not demonstrate the effects of tocilizumab treatment on early and late mortality, although laboratory findings revealed a decrease in inflammation after tocilizumab treatment. This may be correlated with the facts that the study group consisted of elderly patients, requiring MV, where the majority suffered very severe COVID-19.

An interesting result of our study was that the groups that received and did not receive corticosteroid treatment displayed considerable differences in terms of age and GCS. Again, these patient groups showed variances with regard to gender and CCI. COVID 19 treatment evolved during the pandemic all over the world. In the light of the new scientific data, the Ministry of Health of the Republic of Turkey revised the national guidelines. National SARS-CoV-2 infection guidelines initially recommended only favipiravir and hydroxychloroquine while the use of corticosteroids in COVID-19 pneumonia was included as of October 23, 2020 (25). For this reason, the patients receiving corticosteroids were those who were hospitalized in the ICU in later stages of the pandemic, hence those who were younger and with higher GCS, which may be interpreted as the milder patients (younger, having less comorbidities, and not requiring intubation) were admitted to the ICU in later periods of pandemic. As for some specific organizational aspects of the intensive care services of the Turkish healthcare system, during this crisis, especially in the first 3 months period, all COVID-19 patients requiring intubation were treated in tertiary intensive care areas, in order to increase our respiratory support capacity and also for the safety of healthcare personnel due to the risk of environmental contamination by aerosol-generating noninvasive mechanical ventilation procedures, and most of the patients who were not intubated were treated in wards. Therefore, the high number of patients requiring invasive mechanical ventilation may explain the variances in GCS.

In-hospital mortality in the whole cohort was 62.8%. It was observed that neither steroid therapy nor tociluzimab therapy had effect on in-hospital mortality in this cohort.

When compared, mortality rate was found to be considerably higher in our study population with respect to the general patient groups. In a study conducted in the United Kingdom, 17% (276/1658) of those who underwent mechanical ventilation were discharged alive, 37% (618/1658) died and 46% (764/1658) remained longer in hospital (26). Our results are in concordance with previously published literature for Turkey. In a multicenter study performed in Turkish ICU's in hospital mortality rate was 53% (27).

28-day mortality is 60% in the present study. This was attributed to >28 days of stay of some patients in ICU. When literature data were evaluated, 28-day mortality was 39% in 257 critically ill COVID-19 patients in New York City, of which 79% (n=203) underwent invasive mechanical ventilation (28), and it was 53.8% (n=394) in 733 Chinese patients admitted to the ICU (29). Again, two case series from the United States reported 50% and 67% mortality rates, respectively (19,30). All-cause in-hospital death rates showed no difference between the groups receiving and not receiving corticosteroids. This was consistent with the study results reported by Zha et al. (31). Furthermore, the RECOVERY study, reporting the most important mortality rate with low-dose dexamethasone, indicated a 35% decrease in mortality among patients with invasive mechanical ventilation and a 20% decrease in patients with non-invasive ventilation (32).

In our study, the 90-day mortality was found as 66.9% (n=97). The 90-day mortality was reported as 31%, in a large prospective case series evaluating 4244 COVID-19 patients requiring ICU care, and even higher among older and obese patients, diabetics, immunocompromised patients, and those with multiple organ dysfunctions at admission to ICU. The 90-day mortality rate was 50% in patients with severe ARDS who underwent mechanical ventilation (invasive or non-invasive) on the first day of the ICU (11). Similarly, 90-day mortality rate in the Gündoğan et al. study was 55.1%. Invasive mechanical ventilation independently associated with 90-day mortality (HR 4.09 [95% CI: [2.20–7.63], P<. 001) (27).

Higher rates of 90-day mortality in patients without corticosteroids was another result of our study, which was not statistically significantly different in comparison to the patients administered with corticosteroids. Li et al. (33) also found no significant difference in terms of 90-day crude mortality between patients treated with and without corticosteroids (97 of 183 patients [53%] and 49 of 111 patients [44%]; p=0.18) (33). Further studies are required to determine whether corticosteroid administration can provide benefits for long-term survival in patients with COVID-19 and ARDS.

No significant difference was found between in-hospital mortality and 90-day mortality when the patients with and without tocilizumab were compared. Of the 20 patients who received tocilizumab, 11 were treated with tocilizumab and corticosteroids, 9 only with tocilizumab, and they displayed no significant difference in terms of mortality. This present study was compatible with the study by Luo et al. (20), suggesting that tocilizumab therapy failed to ameliorate disease activity in critically ill patients even when tocilizumab was used in combination with glucocorticoids. Since the number of patients receiving tocilizumab is very small, it is not possible to comment on its effectiveness. Furthermore, tocilizumab administration time may also be an important issue. In the study of Mikulska et al. (34), the benefit of early tocilizumab and methylprednisolone therapy in 14 and 30-day survival outcomes was noted (92.7% vs. 78.2% and 85.9% vs. 71.9%, respectively). Even though tocilizumab is administered to patients diagnosed with MAS immediately, especially in frail elderly, this may be an indication that disease process is progressing, and may explain the limited response to tocilizumab. Immunosenescence that occurs with advanced age is the other issue to be considered (35). Immunosenescence, especially in elderly patients, may induce the emergence of MAS due to COVID 19. Elaborative further studies on this topic should be performed.

Given the wide range in variation, various factors may play a role in mortality. First of all, centers determined ICU indications according to their own facilities and resources, with a view to be more as effective as possible during the pandemic. For this reason, no matter that the patients were admitted to the ICU, the disease severity of the patients at admission may differ at each center. A study conducted in New York reported the median SOFA score as 11 (8–13) with the recorded lowest median P/F as 129 (80–203) (28). In another study conducted in China, the median SOFA score was found as 4 (1–5), and the APACHE II score as 10 (7–14) (29). Secondly, bed occupancy in ICU may cause late admissions. We observed that the vast majority of our cohort worsened during their stay in the service and later admitted to the ICU accordingly. During this period, we believe bed occupancy related problems caused delays in transferring patients to the ICU. Different characteristics of patients admitted to ICUs and different degrees of work load related stress in health systems may explain these differences (36).

Our study has several limitations. First of all, the study was conducted retrospectively in a single center, so the results cannot be generalized. It was also carried out in the fist wave of pandemics, therefore recommendations for therapy changed very often according to evidence during study period which might influence our results. Second, the study was conducted when the national health system was under extreme pressure with the need for large numbers of ICU beds. Therefore, indications for ICU hospitalization were specific to our center. At the same time, our study has several strengths. First, treatment response to different treatments was evaluated in critical patients, and secondly, 90-day mortality data of critical patients was shared in our study. Long-term survival data are limited in critically ill patients due to COVID-19.

Conclusion

In conclusion, early- and late-term mortality is considerably high in patients with severe COVID 19. Advanced age and length of MV are independent risk factors for long-term survival. Any long-term effect of corticosteroid and tocilizumab treatments on survival could not be determined in this study. Further studies with randomized controlled trials are needed to evaluate the validity of severe COVID 19 treatment recommendations.

AUTHOR CONTRIBUTIONS:

Concept: FDA, BE; **Design:** FDA, BE; **Supervision:** BE; **Resources:** FDA; **Materials:** FDA; **Data Collection and/or Processing:** FDA, VB; **Analysis and/or Interpretation:** FDA, BE; **Literature Search:** FDA; **Writing Manuscript:** FDA, BE; **Critical Review:** NG, BC.

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References

1. Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020;8(4):420-2. [CrossRef]
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020;395(10223):507–13. [CrossRef]
3. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497–506. [CrossRef]
4. The Republic of Türkiye, Ministry of Health, COVID-19 information platform, Adult patient treatment guideline [COVID-19 (SARS-CoV-2 Enfeksiyonu) Erişkin Hasta Tedavisi Bilimsel Danışma Kurulu Çalışması. T.C. Sağlık Bakanlığı. 12 Nisan 2022, Ankara]. https://covid19.saglik.gov.tr/Eklenti/43095/0/covid-19rehberieriskinhastayonetimivetedavi-12042022pdf.pdf
5. Tang N, Bai H, Chen X, et al. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost. 2020;18(5):1094–9. [CrossRef]
6. Phua J, Weng L, Ling L, et al. Intensive care management of coronavirus disease 2019 (COVID-19): challenges and recommendations. Lancet Respir Med. 2020;8(5):506–17. [CrossRef]
7. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–39. [CrossRef]
8. Chousterman BG, Swirski FK, Weber GF. Cytokine storm and sepsis disease pathogenesis. Semin Immunopathol. 2017;39(5):517–28. [CrossRef]
9. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970–5. [CrossRef]
10. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–43. [CrossRef]
11. Schmidt M, Hajage D, Demoule A, et al.; COVID-ICU Group on behalf of the REVA Network and the COVID-ICU Investigators. Clinical characteristics and day-90 outcomes of 4244 critically ill adults with COVID-19: a prospective cohort study. Intensive Care Med. 2021;47(1):60–73. [CrossRef]
12. Schuijt MTU, Schultz MJ, Paulus F, et al. Association of intensity of ventilation with 28-day mortality in COVID-19 patients with acute respiratory failure: insights from the PRoVENT-COVID study. Crit Care. 2021;25(1):283. [CrossRef]
13. Grasselli G, Greco M, Zanella A, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Intern Med. 2020;180(10):1345–55. [CrossRef]
14. Du R-H, Liu L-M, Yin W, et al. Hospitalization and critical care of 109 decedents with COVID-19 pneumonia in Wuhan, China. Ann Am Thorac Soc. 2020;17(7):839–46. [CrossRef]
15. Guan W-j, Ni Z-y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708–20. [CrossRef]
16. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–9. [CrossRef]
17. Muscedere J, Waters B, Varambally A, et al. The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. Intensive Care Med. 2017;43(8):1105–22. [CrossRef]
18. Wang L, He W, Yu X, et al. Coronavirus disease 2019 in elderly patients: Characteristics and prognostic factors based on 4-week follow-up. J Infect. 2020;80(6):639–45. [CrossRef]
19. Arentz M, Yim E, Klaff L, et al. Characteristics and Outcomes of 21 Critically Ill Patients with COVID-19 in Washington State. JAMA. 2020;323(16):1612–4. [CrossRef]
20. Luo P, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020;92(7):814–8. [CrossRef]
21. Ferrey AJ, Choi G, Hanna RM, et al. A case of novel coronavirus disease 19 in a chronic hemodialysis patient presenting with gastroenteritis and developing severe pulmonary disease. Am J Nephrol. 2020;51(5):337–42. [CrossRef]
22. Michot JM, Albiges L, Chaput N, et al. Tocilizumab, an anti-IL-6 receptor antibody, to treat COVID-19-related respiratory failure: a case report. Ann Oncol. 2020;31(7):961–4. [CrossRef]
23. Zhang X, Song K, Tong F, et al. First case of COVID-19 in a patient with multiple myeloma successfully treated with tocilizumab. Blood Adv. 2020;4(7):1307–10. [CrossRef]
24. Fu B, Xu X, Wei H. Why tocilizumab could be an effective treatment for severe COVID-19? J Transl Med. 2020;18(1):164. [CrossRef]
25. T.C. Sağlık Bakanlığı. COVID-19 (SARS-CoV-2 Enfeksiyonu) Ağır pnömoni, ARDS, sepsis ve septik şok yönetimi. Bilimsel Danışma Kurulu Çalışması. 27 Mayıs 2021, Ankara. https://covid19.saglik.gov.tr/Eklenti/40781/0/covid-19rehberiagirpnomoniardssepsisvesep tiksokyontemipdf.pdf
26. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020;369:m1985. [CrossRef]
27. Gündoğan K, Akbudak İH, Hancı P, et al. Clinical Outcomes and Independent Risk Factors for 90-Day Mortality in Critically Ill Patients with Respiratory Failure Infected with SARS-CoV-2: A Multicenter Study in Turkish Intensive Care Units. Balk Med J. 2021;38(5):296–303. [CrossRef]
28. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763–70. [CrossRef]
29. Xie J, Wu W, Li S, et al. Clinical characteristics and outcomes of critically ill patients with novel coronavirus infectious disease

(COVID-19) in China: a retrospective multicenter study. Intensive Care Med. 2020;46(10):1863–72. [CrossRef]

30. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in critically Ill patients in the Seattle region — case series. N Engl J Med. 2020;382(21):2012–22. [CrossRef]
31. Zha L, Li S, Pan L, et al. Corticosteroid treatment of patients with coronavirus disease 2019 (COVID-19). Med J Aust. 2020;212(9):416–20. [CrossRef]
32. Horby P, Lim WS, Emberson J, et al. Effect of dexamethasone in hospitalized patients with COVID-19 – preliminary report. medRxiv. 2020. [Published online June 22, 2020]. [CrossRef]
33. Li Y, Meng Q, Rao X, et al. Corticosteroid therapy in critically ill patients with COVID-19: a multicenter, retrospective study. Crit Care. 2020;24(1):698. [CrossRef]
34. Mikulska M, Nicolini LA, Signori A, et al. Tocilizumab and steroid treatment in patients with COVID-19 pneumonia. PLoS One. 2020;15(8):e0237831. [CrossRef]
35. Cunha LL, Perazzio SF, Azzi J, et al. Remodeling of the immune response with aging: immunosenescence and its potential impact on COVID-19 immune response. Front Immunol. 2020;11:1748. [CrossRef]
36. Millar JE, Busse R, Fraser JF, et al. Apples and oranges: international comparisons of COVID-19 observational studies in ICUs. Lancet Respir Med. 2020;8(10):952–3. [CrossRef]