European Review for Medical and Pharmacological Sciences 2022; 26: 4497-4508

Evaluation of personalized methylprednisolone therapy in critically ill COVID-19 patients: an observational comparative study using real-life data

I. DUMAN[1], J.B. CELIK[2], M.S. IYISOY[3], S. DEGIRMENCIOGLU[2], A. KORKMAZ[2], A. DUMAN[2]

[1]Department of Medical Pharmacology, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey
[2]Department of Intensive Care, Selcuk University, Faculty of Medicine, Konya, Turkey
[3]Department of Medical Education and Informatics, Necmettin Erbakan University, Meram Faculty of Medicine, Konya, Turkey

Abstract. – OBJECTIVE: Methylprednisolone is commonly used to attenuate the cytokine storm and prevent mortality in COVID-19 pneumonia. However, the optimal methylprednisolone dose and duration are unclear. Additional data are required on the effectiveness of methylprednisolone in reducing mortality in COVID-19. This real-life retrospective study aimed to analyze the data of a COVID-19 dedicated ICU and compare the mortality rates of standard care, low-dose, and pulse-dose methylprednisolone in patients requiring mechanical ventilatory support.

PATIENTS AND METHODS: Methylprednisolone's indication, dose, and duration were determined according to the severity of COVID-19 pneumonia based on the patient's demographic parameters, comorbidities, laboratory data, radiology, and arterial blood gas analysis results. 867 patients were grouped as: no methylprednisolone (standard care), low-dose (0.5-1 mg/kg/day) methylprednisolone or pulse-dose (250-1,000 mg/day) methylprednisolone.

RESULTS: The overall mortality rate was 63.78%. Adjusting the dose of methylprednisolone according to the severity of the disease resulted in statistically similar mortality rates despite the increase in disease severity. Mortality was 62.71% in standard treatment, 65.76% in low-dose, and 62.10% in pulse-dose methylprednisolone groups ($p = 0.633$). Invasive mechanical ventilation at admission was associated with increased mortality (HR: 1.826 [95% CI: 1.542-2.161]; $p < 0.001$). Hematologic disorders and malignancies, arterial blood pH and HCO_3, neutrophil count, and NLR at admission were also associated with mortality.

CONCLUSIONS: Personalizing the dose and duration of methylprednisolone according to the patient's disease severity assessed with demographic, clinical, and laboratory results may benefit mortality in severe COVID-19 patients receiving ventilatory support in the ICU. Hematologic disorders and malignancies, arterial blood pH and HCO_3, neutrophil count, and NLR at admission were associated with mortality in our patient cohort.

Key Words:
COVID-19, Mechanical ventilation, Methylprednisolone, Mortality, Personalized therapy.

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the cause of the Coronavirus Disease 2019 (COVID-19) pandemic, which has spread globally with extensive morbidity and mortality throughout all populations. COVID-19 is presented with a spectrum of influenza-like symptoms, including fever, headache, cough, and dyspnea. In addition, respiratory symptoms may progress from mild upper respiratory tract disease to pneumonia, Acute Respiratory Distress Syndrome (ARDS), and multiple organ failure[1].

Approximately 31-41% of hospitalized patients develop a "cytokine storm" resulting from excessive cytokine release and are transferred to the Intensive Care Unit (ICU)[2-4]. Although frequencies vary according to series, mortality rates of ICU patients who develop ARDS are more than 50%[2]. In the early era of the pandemic, mainly based on the information from severe acute respiratory syndrome (SARS) coronavirus and the Middle East respiratory syndrome

Corresponding Author: Ipek Duman, MD, Ph.D; e-mail: ipekduman@yahoo.com

(MERS) coronavirus infections, there was hesitation for the use of corticosteroids[5]. Management guidelines for COVID-19 pneumonia have changed rapidly as scientific evidence accumulated on different protocols and drugs[6]. After the RECOVERY trial[7] found dexamethasone to improve mortality outcomes in severe cases of COVID-19 needing ventilatory support, and the METCOVID trial[8] confirmed the beneficial effect of methylprednisolone in elderly patients with severe COVID-19, corticosteroids have been recommended to suppress the virally driven cytokine storm to prevent ARDS and multiple organ failure in the ICU[9,10]. Methylprednisolone is one of the most commonly used corticosteroids for COVID-19 management. However, the optimal methylprednisolone dose, duration, and the benefit/harm relationship are still unclear. In addition, methylprednisolone dosages used in randomized controlled trials (RCTs) are heterogeneous, ranging from 40 mg/day to 1,000 mg / day at varying durations on different severity of COVID-19 pneumonia[8,11-14]. Furthermore, RCTs may not reflect the results of real-life clinical practice in which patients need to be treated on a patient-to-patient basis[15,16]. Therefore, adequate real-life data are needed to provide additional information on the effectiveness and safety of methylprednisolone in severe COVID-19 pneumonia. This study aimed to analyze the data of a COVID-19 dedicated ICU's experience concerning personalized methylprednisolone therapy from the first wave of the pandemic. In addition to comparing the mortality rates of standard care, low-dose, and pulse-dose methylprednisolone, we also examined potential demographic, clinical, and laboratory factors affecting mortality rates in this patient cohort.

Patients and Methods

This single-center retrospective study was conducted in a tertiary University Hospital, COVID-19-dedicated 48-bed ICU. We reviewed the medical records of 936 adult patients (≥ 18 years old) admitted to the COVID-19 ICU between July 1, 2020, and February 28, 2021, with severe pneumonia and ARDS. The study was registered in the Ministry of Health COVID-19 Trials Registry (2021-04-29T18-49-48), and approval was obtained from the Institutional Review Board (334-2021). According to the local Ethical Guidelines, the need for patient consent was waived because this was a retrospective study, and the patients' anonymity was secured. The sample size was not necessary, since we evaluated the total population who met the inclusion criteria. None of the patients was vaccinated against SARS-CoV-2 because the data date was before March 2021, when vaccination started in our country.

Participants

We included all COVID-19 pneumonia and ARDS patients admitted to the ICU with the following criteria: confirmed COVID-19 infection with a positive polymerase chain reaction (PCR) for SARS-CoV-2 and respiratory support with non-invasive ventilation (NIV) *via* High-Flow Nasal Cannula (HFNC) or Continuous Positive Airway Pressure (CPAP), or invasive mechanical ventilation (IMV). Patients who were not on ventilatory support, patients with negative PCR results during their ICU stay, patients already on long-term steroid therapy, patients who stayed in the ICU less than 24 hours, and patients with significant missing data were excluded.

Data Acquisition and Interventions

We extracted the following initial data at admission from the electronic medical records: (1) demographic data, including age, sex, comorbidities; (2) clinical and laboratory data, including forms of ventilatory support, biochemistry, and arterial blood gas analysis; (3) dose and duration of methylprednisolone and concomitant drugs used during ICU stay. Also, patient outcomes were recorded.

According to the Turkey Ministry of Health (TMH) guidelines[17] at the date, all patients with severe COVID-19 pneumonia or ARDS received standard care consisting of supplemental oxygen and respiratory support (invasive ventilation if necessary), a broad-spectrum antibiotic, low molecular weight heparin (unless contraindicated). In addition, antiviral therapy (favipiravir), immune-suppressive medication, convalescent plasma, IL-6 antagonists, and corticosteroids were given at the discretion of the medical team.

A simplified semi-quantitative severity scoring system was used to confirm and score severe pneumonia or ARDS on Chest Computed Tomography (CCT). The scoring system[18] estimates the pulmonary involvement based on the area involved. Each of the 5 lung lobes is visually scored from 0 to 5 as: 0, no involvement; 1, <5%

involvement; 2, 5-25% involvement; 3, 26-49% involvement; 4, 50-75% involvement; 5, >75% involvement. The total CCT score is the sum of the individual lobar scores and ranges from 0 (no involvement) to 25 (maximum involvement). The patients were then classified according to the total score; group 1: mild or no involvement (up to 10 points), group 2: moderate involvement (11 to 15 points), and group 3: severe involvement (>15 points).

There was no standard protocol for methylprednisolone indication or dose for severe COVID-19 pneumonia in the ICU during the study period. Based on our previous experience with viral pneumonia cases and the information concerning corticosteroids during the previous SARS epidemic and community-acquired viral cases of pneumonia, methylprednisolone was added to selected COVID-19 patients' treatment with severe hypoxemia beginning from the early era of the COVID-19 pandemic in 2019[19-21]. The pulse-dose therapy was referenced for its effectiveness in autoimmune vascular respiratory system diseases[22,23]. Our personalized corticosteroid dose approach was developed based on Li et al[24] experience with COPD patients. It was presumed that adjustments in methylprednisolone therapy based on the patient's individual clinical and laboratory data would be essential for optimal therapeutic response.

All patients received standard care according to TMH guidelines. Additionally, the clinical team tailored methylprednisolone's indication, dose, and duration based on the patient's demographic parameters, comorbidities, laboratory data, CCT score, and arterial blood gas analysis results. Typically, hypoxic patients (200 mmHg < $PaO_2/FiO_2 \leq$ 300 mmHg) with a CCT score up to 15 either received no corticosteroids (standard care) or 0.5-1 mg/kg/day of methylprednisolone (low-dose) for 5-10 days. Patients with signs of more severe hypoxia (100 mmHg < $PaO_2/FiO_2 \leq$ 200 mmHg with PEEP $\geq$ 5 cm H_2O) with a CCT score $\geq$ 15 points received 0.5-1 mg/kg/day of methylprednisolone for 5-10 days. Severely hypoxic patients ($PaO_2/FiO_2 \leq$ 100 mmHg with PEEP $\geq$ 8 cm H_2O) with a CCT score $\geq$ 15 received pulse-dose treatment with 250-1,000 mg/day of methylprednisolone for three days followed by 0.5-1 mg/kg/day tapering doses for 5-10 days. i.e., worsening patients with more severe signs of hypoxia and hyper inflammation received higher doses of methylprednisolone.

Statistical Analysis

For analysis, we grouped the patients as no methylprednisolone (standard care), low-dose methylprednisolone, and pulse-dose methylprednisolone. The primary endpoint was death. To assess the association between methylprednisolone therapy and mortality, we performed Cox regression analysis on age, sex, comorbidities, concomitant drugs, the dose of methylprednisolone, initial laboratory data, the form of ventilatory support, and arterial blood gas analysis at admission.

Where appropriate, all variables were described with descriptive statistics like mean, standard deviation, median (Q1-Q3), frequency, and percentage. One-way ANOVA was used when comparing numerical variables among groups. The Chi-Square test was used for categorical variables. Associations with mortality were assessed by using Cox proportional hazards regression. Univariable and multivariable (with Firth's correction) hazard ratios with 95% confidence intervals were presented to evaluate the factors related to mortality. The Log rank test ascertained a comparison of Kaplan Meier survival curves denoting 28-day cumulative survival. All analyses were performed using SAS University Edition 9.4 software (Cary, NC, USA). A p-value of < 0.05 was considered significant.

Results

A total of 867 confirmed severe COVID-19 cases receiving ventilatory support were included in the analysis; 69 patients were excluded, as detailed in Figure 1.

Baseline characteristics of patients on admission, mortality rates, concurrent drugs, and their association with mortality are presented in Table I. The mean age of the study population was 66.38 ± 15.79 years, and 60.44% were men. In the ICU, 413 (47.63%) patients received standard care, 330 (38.06%) received low-dose, and 124 (14.30%) patients received pulse-dose methylprednisolone. The median ICU stay was 6.0 (IQR 3.0-10.0) days, similar in all three treatment groups.

The overall mortality rate was 63.78%. The mortality rate was statistically similar in patients who received standard treatment (62.71%), low-dose (65.76%), and pulse-dose methylprednisolone (62.10%) (p = 0.633). As shown in Figure 2, there was no difference between the Kaplan-Meier survival curves of the treatment groups (p =

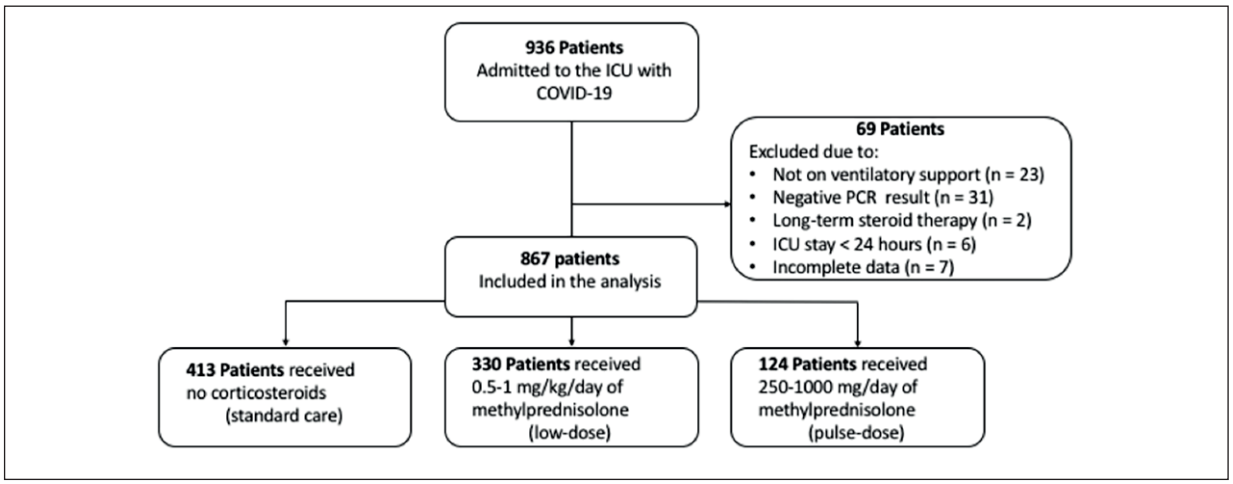

Figure 1. Flowchart of the study population. COVID-19: coronavirus disease 2019, ICU: intensive care unit, PCR: polymerase chain reaction.

0.665). Age was associated with increased mortality according to the Cox regression analysis (HR: 1.012 [95% CI: 1.006-1018]; $p < 0.001$).

A higher rate of antibiotic, convalescent plasma, low molecular weight heparin (LMWH), and IL-6 antagonist use were observed in the methylprednisolone treatment groups compared to standard care. However, according to Cox analysis, none of the concurrent drugs led to significant differences in mortality.

At admission, 591 (68.16%) patients were receiving HFNC or CPAP, while 276 (31.83%) patients were on IMV (Table I). According to Cox regression analysis, we found that IMV at admission was associated with an increased hazard ratio for death (HR: 1.826 [95% CI: 1.542-2.161]; $p < 0.001$). In addition, Log Rank test displayed a significant difference between the survival curves of patients receiving NIV and IMV ($p < 0.0001$) (Figure 3). Concerning laboratory data

Table I. Baseline characteristics of admission, mortality rates, and concurrent drug use of severe COVID-19 patients in the therapy groups and risk factors associated with 28-day mortality identified by the Cox hazards regression model.

Variable	Standard care (n = 413)	Low-dose MP (n = 330)	Pulse-dose MP (n = 124)	Total (n = 867)	*p*-value	Survival analysis		
						HR	95% CI	*p*-value
Male	250/60.53%	201/60.91%	73/58.87%	524/60.44%	0.922	1.024	0.863-1.215	0.785
IMV at admission	132/31.96%	100/30.3%	44/35.48%	276/31.83%	0.571	1.826	1.542-2.161	< 0.001
Age	66.24 ± 15.56	66.95±15.90	65.32 ± 16.31	66.38% ± 15.79	0.61	1.012	1.006-1018	< 0.001
Days in ICU	6.0 (3.0-10.0)	6.0 (3.0-10.0)	5.0 (3.0-10.0)	6.0 (3.0-10.0)	0.948		N/A	
Mortality	259/62.71%	217/65.76%	77/62.10%	553/63.78%	0.633		N/A	
HCQ	81/19.61%	31/9.39%	1/0.81%	113/13.03%	< 0.001	1.166	0.915-1.487	0.215
Antivirals	220/53.27%	204/61.82%	74/59.68%	498/57.44%	0.056	0.924	0.781-1.094	0.359
Antibiotics	357/86.44%	320/96.97%	120/96.77%	797/91.93%	< 0.001	0.873	0.643-1.85	0.383
C. plasma	21/5.08%	71/21.52%	65/52.42%	157/18.11%	< 0.001	0.962	0.769-1.203	0.733
LMWH	319/77.24%	302/91.52%	117/94.35%	738/85.12%	< 0.001	0.966	0.771-1.212	0.767
Antiaggregants	92/22.28%	65/19.70%	28/22.58%	185/21.34%	0.650	0.95	0.769-1.175	0.639
IL-6 antagonists	11/2.66%	31/9.39%	16/12.90%	58/6.69%	< 0.001	1.12	0.791-1.586	0.524

MP: methylprednisolone, IMV: invasive mechanical ventilation, ICU: intensive care unit, HCQ: hydroxychloroquine, C. plasma: convalescent plasma, LMWH: low molecular weight heparin, IL-6: interleukin 6, HR: hazard ratio, CI: confidence interval. Data are presented as the number of patients, median (interquartile ranges), mean ± standard deviation, or percentages. The Cox hazards model was used to calculate the hazard ratio and its 95% confidence interval. A *p*-value of < 0.05 was considered statistically significant. N/A: Not applicable.

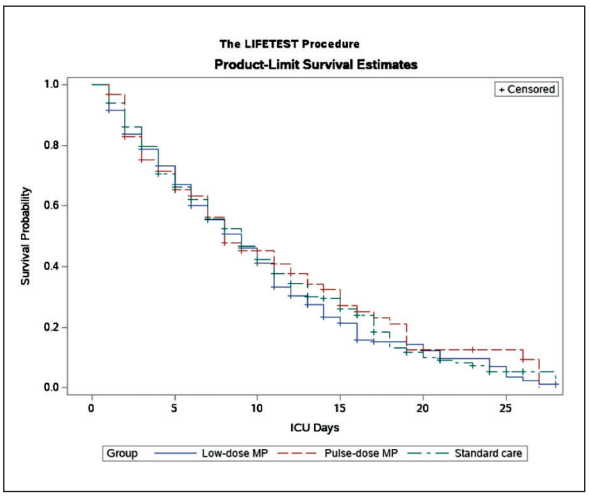

Figure 2. Kaplan-Meier survival curves of methylprednisolone treatment groups. Treatment groups: Standard care: no methylprednisolone (MP), Low-dose MP, and pulse-dose MP, $p = 0.665$.

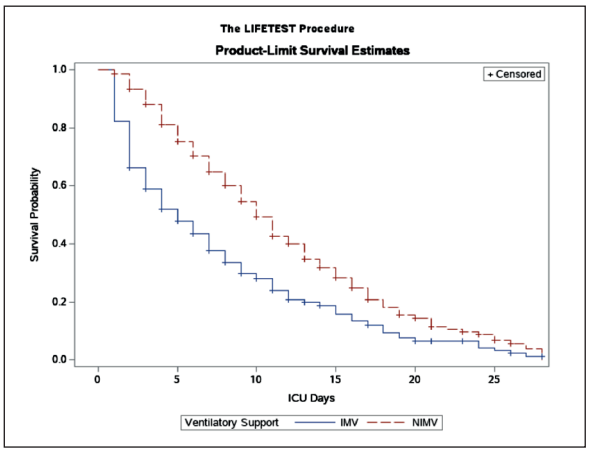

Figure 3. Kaplan-Meier survival curves of invasive mechanical ventilation and non-invasive mechanical ventilation at admission. IMV: invasive mechanical ventilation, NIMV: non-invasive mechanical ventilation, $p < 0.0001$.

at admission, arterial blood pH (HR: 0.794 [95% CI: 0.747-0.843]; $p < 0.001$) and HCO_3 values (HR: 0.956 [95% CI: 0.942-0.971]; $p < 0.001$), neutrophil count (HR: 1.005 [95% CI: 1.000-1.01]; $p = 0.031$), and neutrophil to lymphocyte ratio (NLR) (HR: 1.005 [95% CI: 1.001-1.009]; $p = 0.015$) were associated with increased mortality. D-dimer and CRP levels were significantly different between the groups but not associated with mortality (Table II).

Hypertension (40.6%) followed by diabetes (28.14%), coronary artery disease (19.84%), and chronic pulmonary disease (CPD) (19.15%) were the most common comorbidities which were similar between the treatment groups. The frequency of hyperthyroidism ($p = 0.027$) in the pulse and renal failure ($p = 0.03$) in the low-dose groups was higher than in other treatment groups, although the number of patients with hyperthyroidism was limited to three. Accord-

Table II. Physiological characteristics on the admission of severe COVID-19 patients in the therapy groups and survival analysis associated with 28-day mortality identified by Cox hazards regression model.

Variable	Standard care (n = 413)	Low-dose MP (n = 330)	Pulse-dose MP (n = 124)	Survival analysis		
				HR	95% CI	*p*-value
pH	7.32 ± 0.14	7.33 ± 0.13	7.34 ± 0.12	0.794	0.747-0.843	< 0.001
CO_2 (mmHg)	42.19 ± 15.93	39.74 ± 13.91	40.39 ± 12.67	1.005	0.999-1.01	0.099
SaO_2 (%)	70.22 ± 24.24	73.08 ± 22.89	73.15 ± 21.39	0.998	0.994-1.001	0.186
PaO_2 (mmHg)	60.56 ± 42.63	64.25 ± 44.14	65.27 ± 46.59	1.001	0.999-1.003	0.507
HCO_3 (mmol/L)	21.12 ± 5.91	20.86 ± 6.02	21.35 ± 5.07	0.956	0.942-0.971	< 0.001
Platelet (K/uL)	221.53 ± 120.58	237.69 ± 124.09	242.28 ± 125.54	1.0	0.999-1.00	0.494
Ferritin (ng/mL)	288.80 (88.7-782.65)	348.65 (142.9-852.9)	447.1 (224.95-929.3)	1.0	1.0-1.0	0.871
CRP (mg/L)	76.20 (14.65-150.0)	93.65 (29.93-151.0)	112.0 (50.1-185.0)*	1.0	0.999-1.001	0.567
NLR	10.89 (5.33-21.29)	12.56 (5.8-22.75)	10.89 (5.94-18.98)	1.005	1.001-1.009	0.015
Neutrophil (K/uL)	9.65 (6.1-13.6)	9.0 (5.9-12.6)	8.65 (5.27-12.43)	1.005	1.000-1.01	0.031
Lymphocyte (K/uL)	0.8 (0.4-1.42)	0.7 (0.4-1.2)	0.75 (0.4-1.2)	1.009	0.999-1.02	0.081
D-dimer (ng/mL)	1,955 (966-5,322)	2,020 (992-5,200)	1,322 (756-2,860)**, ***	1.0	1.0-1.0	0.473

MP: methylprednisolone, HR: hazard ratio, CI: confidence interval. Data are presented as median (interquartile ranges) or mean ± standard deviation. The Cox hazards model was used to calculate the hazard ratio and 95% confidence interval. A *p*-value of < 0.05 was considered statistically significant. Unit of change for pH was taken at 0.1. *$p = 0.005$ pulse-dose versus standard care, **$p = 0.01$ pulse-dose versus standard care, ***$p = 0.02$ pulse-dose versus low-dose.

ing to Cox analysis, hematologic disorders (HR: 2.134 [95% CI: 1.275-3.573]; $p = 0.004$) and malignancies (HR: 2.075 [95% CI: 1.706-2.523]; $p < 0.001$) were also associated with increased mortality (Table III).

We conducted a multivariable analysis for 28-day mortality. A multivariable model based on age, pH, HCO_3, IMV, and malignancies and the model's discriminative ability is illustrated in Table IV and Figure 4, respectively.

Discussion

The array of diseases associated with SARS-CoV-2 infection ranges from asymptomatic or mild illness to severe life-threatening disease[25]. ARDS and systemic cytokine storm are the main reasons for death, and there are no proven specific treatment agents for COVID-19[1]. Severe COVID-19 pneumonia patients have elevated interleukin (IL) levels and high acute phase reactants, accompanied by lung injury[4,26]. In addition, cytokines levels are higher in severe COVID-19 patients than in those with mild to moderate disease[8].

Corticosteroids have pleiotropic effects on the human immune system. Glucocorticoids are agonist compounds that act on glucocorticoid receptors (GR) in various cells and receptor proteins and proinflammatory mediators. GRα isoform mediates the anti-inflammatory effects of glucocorticoids[27,28]. Due to the known immunosuppressive, anti-inflammatory, and antifibrotic effects, systemic corticosteroids are used to suppress the respiratory system's systemic inflammatory response and inflammation in COVID-19 patients[4]. However, the anti-inflammatory effectiveness of glucocorticoids in ARDS is affected by the dose, timing, mode of administration of the drug, and duration of use[27,28]. Therefore, glucocorticoid doses need to be adjusted according to the targeted clinical and laboratory improvement and relevant dose-tapering to recover the suppressed hypothalamic-pituitary-adrenal (HPA) axis[27]. Dexamethasone and methylprednisolone are the two most commonly used corticosteroids for COVID-19 management. However, methylprednisolone is five times less potent in its anti-inflammatory potency than dexamethasone, with higher lung penetration[29]. Methylprednisolone is the corticosteroid of choice in pulmonology in treating chronic obstructive pulmonary disease, aspiration pneumonitis, asthma, and fibrotic pulmonary diseases[30]. In a recent meta-analysis[31], methylprednisolone was found to have a better therapeutic effect compared to dexamethasone

Table III. Comorbidities of severe COVID-19 patients in the therapy groups and survival analysis associated with 28-day mortality identified by Cox hazards regression model.

Variable	Standard care (n = 413)	Low-dose MP (n = 330)	Pulse-dose MP (n = 124)	Total (n = 867)	*p*-value	Survival analysis		
						HR	95% CI	*p*-value
Hypertension	167/39.23%	142/43.03%	48/38.71%	352/40.6%	0.518	0.923	0.778-1.095	0.359
CAD	87/21.07%	59/17.88%	26/20.97%	172/19.84%	0.525	0.986	0.800-1.214	0.893
CHF	40/9.69%	27/8.18%	16/12.9%	83/9.57%	0.312	1.259	0.965-1.645	0.090
CPD	81/19.61%	65/19.7%	20/16.13%	166/19.15%	0.653	0.944	0.767-1.163	0.589
CLD	6/1.45%	4/1.21%	2/1.61%	12/1.38%	0.936	1.316	0.624-2.776	0.471
Diabetes	105/25.42%	98/29.7%	41/33.06%	244/28.14%	0.184	0.992	0.824-1.194	0.933
Hyperthyroidism	0/0.0%	1/0.3%	2/1.61%	3/0.35%	0.027	0.381	0.054-2.710	0.335
Hypothyroidism	9/2.18%	9/2.73%	3/2.42%	21/2.42%	0.890	0.717	0.357-1.441	0.350
CRD	24/5.81%	25/7.58%	8/6.45%	57/6.57%	0.627	1.294	0.934-1.794	0.121
RF	12/2.91%	23/6.97%	5/4.03%	40/4.61%	0.03	1.151	0.770-1.721	0.494
Hematologic D.	7/1.69%	7/2.12%	3/2.42%	17/1.96%	0.847	2.134	1.275-3.573	0.004
CVA	76/18.4%	78/23.64%	32/25.81%	186/21.45%	0.100	0.961	0.787-1.173	0.696
IC	9/2.18%	7/2.12%	4/3.23%	20/2.31%	0.761	0.774	0.446-1.342	0.361
Malignancy	79/19.13%	67/20.3%	16/12.9%	162/18.69%	0.187	2.075	1.706-2.523	< 0.001

MP: methylprednisolone, CAD: coronary artery disease, CHF: congestive heart failure, CPD: chronic pulmonary disease, CLD: chronic liver disease, CRD: chronic renal disease, RF: renal failure, Hematologic D.: hematologic disorder, CVA: cerebrovascular accident, IC: Immunocompromised. Data are presented as percentages. HR: hazard ratio, CI: confidence interval. The Cox hazards model was used to calculate the hazard ratio and 95% confidence interval. A p-value of < 0.05 was considered statistically significant.

Table IV. Multivariable analysis for 28-day mortality with Firth's correction.

	HR	95% CI	*p*-value
Age	1.010	1.004-1.017	0.0006
pH	0.886	0.822-0.954	0.0013
HCO_3	0.971	0.955-0.988	0.0009
IMV	1.610	1.339-1.935	< 0.0001
Malignancy	2.114	1.731-2.580	< 0.0001

IMV: invasive mechanical ventilation. Regression analysis includes significant variables related to mortality.

in reducing the mortality of COVID-19 patients. Theoretically, corticosteroids also possess the potential to mitigate pulmonary fibrosis associated with COVID-19 pneumonia[32]. However, they also carry the risk of thrombosis and delayed pathogen clearance from the lungs[12-15].

In our patients cohort, despite the standard ICU care and methylprednisolone, we observed a high mortality rate (63.7%) comparable with Xu et al[25] and Arentz et al[33], who reported 61.5% and 67% mortality rates, respectively, in critically ill patients. There may be several reasons for the relatively high mortality. First, these studies, including ours, comprise data from the early pandemic era when no internationally accepted therapeutic guidelines and effective vaccines were present. Second, the antiviral favipiravir and immunomodulator hydroxychloroquine were used in our patients, which were later proven not to affect mortality[34]. Third, all of our patients were critically ill cases that deteriorated in the ward despite supplemental oxygen and standard care and were put on invasive or non-invasive ventilation before being transferred to our ICU. It should also be noted that the percentage of intubated patients was over 35% at admission.

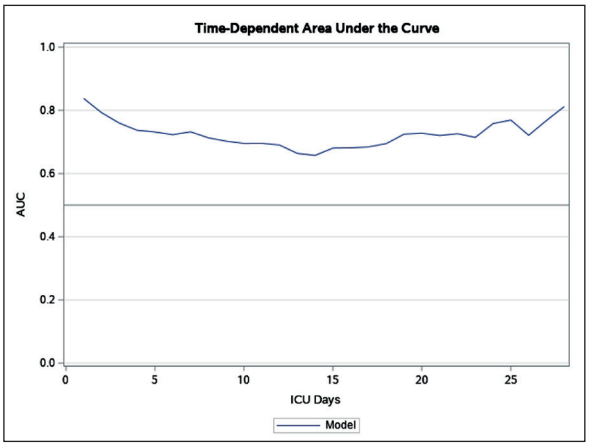

Figure 4. Time-dependent area under the curve for the multivariable model. The discriminative ability of multivariable analysis for 28-day mortality concerning (depending on) age, pH, HCO_3, IMV, and Malignancies. AUC: Area under the curve, ICU: intensive care unit, IMV: invasive mechanical ventilation.

Our primary endpoint: mortality rates were similar in patients who received standard care, low-dose or pulse dose methylprednisolone, in which the doses were adjusted according to the clinical severity of the disease. The absence of an expected additional increase in mortality as the severity of the disease increases can be interpreted as personalizing the methylprednisolone dosing regimen having a beneficial effect on mortality. Our observation supports the recent WHO Rapid Evidence Assessment for COVID-19 Treatments (REACT) Working Group's conclusion that systemic corticosteroid administration compared to standard care or placebo is associated with a low 28-day all-cause mortality[35]. In addition, our results are consistent with recent NIH guidelines, which recommend using dexamethasone or an equivalent dose of methylprednisolone for patients who require mechanical ventilation or extracorporeal membrane oxygenation[36].

Although international recommendations support using corticosteroids in patients who require mechanical ventilation, few prospective trials assess the relationship between dose and efficiency in critically ill patients. In previous randomized controlled trials (RCTs) and observational studies, most patients treated with standard care were compared with patients receiving a defined dose of corticosteroids or two different doses regardless of disease severity. In the comparative observational study by Ruiz-Irastorza et al[37], 242 non-ICU patients received 125-250 mg/day of pulse methylprednisolone therapy for three days. They observed decreased hazard ratio for death compared to the non-pulse therapy group (HR: 0.28 [95% CI: 0.89-0.95]; $p = 0.072$). Their study included all patients treated in the hospital. Edalatifard et al[11] conducted an RCT in a small group of patients with hypoxia and elevated inflamma-

tory markers admitted to the ICU. None of the patients were on mechanical ventilation. Their results showed that patients on pulse-dose of methylprednisolone 250 mg/day for three days given at the early pulmonary phase of disease before connecting to the ventilator resulted in significantly lower mortality than patients receiving standard care ($p < 0.001$). Pinzón et al[12], in their ambispective study of 216 patients with severe COVID-19 pneumonia treated in the ward, pulse-dose methylprednisolone 250-500 mg/day for three days was found to be superior to low-dose dexamethasone 6 mg/day in terms of the recovery time, and the need for ICU. Although they observed benefits from a higher dose of methylprednisolone, the patient groups were similar in disease severity. In another retrospective single-center study, Yaqoob et al[38] compared 184 COVID-19 patients admitted to the ICU. They assessed the results of 0.5 mg/kg/day of methylprednisolone equivalents, 1,000 mg/day of pulse-dose methylprednisolone, and patients who did not receive any corticosteroids. Their results showed that 0.5 mg/kg/day of methylprednisolone but not pulse-dose reduced the odds of mortality compared to no receipt; (adjusted Odds Ratio - aOR: 0.31 [95% CI: 0.12-0.77]; $p = 0.01$). Pulse dose increased the ICU free days but had no impact on mortality.

On the other hand, Liu et al[39] conducted a multicenter retrospective observational study involving 774 patients with ARDS in a similar pandemic period to our study. They concluded that the use of corticosteroids was associated with an increase in 28-day mortality. In addition, a higher dose of corticosteroid and early initiation was found to be associated with higher mortality. However, there are some dissimilarities to our study. Most importantly, although their patients were diagnosed with ARDS, only 10.5% received respiratory support as invasive or non-invasive mechanical ventilation at admission, unlike our patients, whom all received respiratory support. Also, their mortality was 44.3% in the corticosteroid group and 31.0% in the standard care group, considerably lower than our results, indicating that COVID-19 pneumonia was more severe in our patient cohort.

In the present study, unlike RCTs and previous retrospective studies, indications for methylprednisolone, dose, and duration were personalized based on patients' demographic characteristics, clinical and laboratory findings, and the severity of COVID-19 pneumonia. The goal of personalized medicine is to deliver the drug at the right dose for the right disease and at the right time to optimize patient benefit[40]. While individualized drug dose predictions can never be exact, demographic, genetic, and metabolomic factors of the patient and the severity and progression of the disease should be considered for personalized dosage[41]. Corticosteroids have a broad therapeutic range. In an RCT, Li et al[24] compared personalized-dose with fixed-dose prednisolone equivalent in 248 patients with acute exacerbations of COPD. The occurrence of failure of therapy was higher in the fixed-dose group (48.8%) compared with personalized-dose group (27.6%) (HR: 0.40 [95% CI: 0.24-0.68]; $p = 0.001$). The adverse event rate, length of hospital stays, and costs were similar between the two groups. The authors concluded that personalized dosing of steroids reduced the risk of failure.

Despite their efficacy in inflammatory diseases, corticosteroid use is not without adverse effects. Adverse effects depend on prolonged use and dosage and individual patient variability[28]. Besides the long-term adverse effects, equivalent cumulative doses of 1,000 to 2,000 mg of prednisolone were associated with an increased risk of venous thromboembolism[42]. In a retrospective analysis, Yu et al[31] found pulse methylprednisolone therapy for three days followed by dexamethasone for another 3 to 5 days in patients with high COVID-19 scores had a rapid anti-inflammatory effect; however, it also increased the risk for thromboembolism. Therefore, prophylactic LMWH was initiated early in our patients, and none of our patients' treatment was terminated due to side effects.

If the predictors of mortality are identified early at admission, and the patient's treatment is adjusted accordingly, it may provide the possibility to reduce mortality in COVID-19 patients[43]. WHO Scientific Brief[44] calls for "efforts to calculate risk-group-specific estimates of fatality risk to describe better the accurate patterns of fatality occurring in a population". Previously COVID-19-related death was reported to be associated with male gender, greater age, and comorbidities[45]. Also, compared with people of white ethnicity, black and South Asian people were at higher risk of death[46]. Mahendra et al[43] conducted a retrospective study with 560 severe COVID-19 pneumonia patients. They found the following parameters at admission to be independent predictors of mortality: high-flow oxygen or ventilator, age > 50 years, $PaO_2/FiO_2 < 400$mm Hg, comorbidities; diabetes, hypertension and kidney disease, NLR, serum ferritin, random blood sug-

ar, cough, and dyspnea. Likewise, Ruan et al[47], in 150 cases of COVID-19, showed age, underlying diseases, secondary infections, differences in leucocytes, lymphocytes, platelets, albumin, total bilirubin, blood urea nitrogen, creatinine, myoglobin, cardiac troponin, CRP and IL-6 to be predictors of increased mortality. The present study exhibited that besides blood pH, HCO_3, and NLR, invasive mechanical ventilation at admission, increased age, hematologic disorders, and malignancies were associated with increased mortality in our patient population. In a previous study[46], patients with a recent history of hematological malignancy had a $\geq$ 2.5 - fold increased risk. For another form of cancer, increased hazard ratios were smaller and mainly observed with recent cancer diagnoses. There may be heterogeneities concerning mortality risks between and within different population groups, and ethnicity may make a difference[44].

Limitations

This study has several limitations. First, our results are confined to severe cases requiring non-invasive or invasive mechanical ventilatory support; therefore, they cannot be extrapolated to all COVID-19 patients because the study does not include moderate pneumonia cases. Second, our study comprised the pandemic era when no effective vaccines or antivirals were available, limiting our data to non-vaccinated cases. Third, we did not assess adverse effects attributed to steroids. Additionally, there was a considerable number of patients transferred from other hospital wards and ICUs with ongoing treatments, such as antipyretic and vasopressor medications, which may have led to underscoring in risk stratification tools. Therefore, we did not include the admission risk scores in our study design. Co-administration of other immune modulators, convalescent plasma and tocilizumab, and LMWH may have affected our results. Finally, the present study includes patients from a single center, and the data is neither blinded nor prospective. However, despite the limitations mentioned above, our study, which included a large patient cohort, reflects the results of real-life clinical practice.

Conclusions

In conclusion, personalizing the dose and duration of methylprednisolone according to the patient's disease severity assessed with demographic, clinical, and laboratory results may have beneficial effects on mortality in severe COVID-19 patients receiving ventilatory support in the ICU. In addition, hematologic disorders and malignancies, arterial blood pH and HCO_3, neutrophil count, and NLR at admission were associated with mortality in our patients cohort. This study presents real-life data on personalized methylprednisolone dosage in COVID-19 pneumonia patients in the ICU. Personalized dosing of corticosteroids should be considered in future prospective study protocols in severe COVID-19 cases.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors would like to thank the medical teams of the Departments of Infectious diseases, Pulmonology and Radiology for their valuable supports during the COVID-19 pandemic.

Ethical Approval

The study was registered in the Ministry of Health COVID-19 Trials Registry (2021-04-29T18-49-48), and ethical approval was obtained from the Institutional Review Board of Selcuk University Faculty of Medicine (334-2021).

Informed Consent

According to the local Ethical Guidelines, the need for patient consent was waived because this was a retrospective study, and the patients' anonymity was secured.

Funding

This research did not receive any financial support.

Authors' Contribution

Conception and design: I. Duman, J. B. Celik and A. Duman; Acquisition of data: A. Korkmaz and S. Degirmencioglu; Analysis and interpretation of data: A. Duman, A. Korkmaz, M. S. Iyisoy, S. Degirmencioglu and I. Duman; Drafting the article: I. Duman., A. Duman and J. B. Celik; Supervision: I. Duman, M. S. Iyisoy and A. Duman; Validation and final approval: All authors.

Data Availability Statement

Data supporting reported results can be found at https://figshare.com/articles/dataset/Data_of_patients_xls/19625193.

ORCID ID
I. Duman: 0000-0002-0079-6374; J. B. Celik: 0000-0003-2167-9967; S. Iyisoy: 0000-0001-5895-9984; S. Degirmencioglu: 000-0003-4731-6937; A. Korkmaz: 0000-0001-9689-7358; A. Duman: 0000-0003-0394-2485.

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