Turkish Journal of Medical Sciences

Volume 51 | Number 5 Article 3

1-1-2021

# Pulse steroid treatment for hospitalized adults with COVID-19

AYŞE BATIREL

RECEP DEMİRHAN

NURULLAH ESER

EZGİ KÖRLÜ

MEHMET ENGİN TEZCAN

TÜBİTAK

**Turkish Journal of Medical Sciences**
http://journals.tubitak.gov.tr/medical

**Research Article**

Turk J Med Sci
(2021) 45: 2248-2255

doi: 10.3906/sag-2101-243

# Pulse steroid treatment for hospitalized adults with COVID-19

**Ayşe BATIREL[1], Recep DEMİRHAN[2], Nurullah ESER[1], Ezgi KÖRLÜ[1], Mehmet Engin TEZCAN[3,*]**
[1]Department of Infectious Diseases and Clinical Microbiology, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, İstanbul, Turkey
[2]Department of Thoracic Surgery, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, İstanbul, Turkey
[3] Division of Rheumatology, Department of Internal Medicine, University of Health Sciences, Kartal Dr. Lutfi Kırdar City Hospital, İstanbul, Turkey

**Received:** 19.01.2021 **Accepted/Published Online:** 18.04.2021 **Final Version:** 21.10.2021

**Background/aim:** High-dose steroid has been shown to reduce the mortality rate in Corona virus disease 2019 (COVID-19) patients who need oxygen support. Here, we evaluated the effectiveness of pulse-steroid in case of unresponsiveness to treatment with high dose steroid.

**Materials and methods:** The study is a retrospective controlled trial. We divided the patients in 3 groups: standard-care therapy alone, high-dose steroid treatment (6 mg/day dexamethasone equivalent), and pulse-steroid treatment (250 mg/day methyl-prednisolone). One hundred and fifty patients were enrolled in each group. All patients were hospitalized and needed oxygen support. We matched the patients according to disease severity at the onset of hypoxia, weight of co-morbidities, age, and sex. We then compared 3 groups in terms of mortality, length of hospitalization, need for intensive care unit (ICU) admission and mechanical ventilation (MV), length of stay in ICU, and duration of MV.

**Results:** The pulse-steroid group had shorter ICU stay. The median ICU stay was 9.0 (CI 95% 6.0–12.0) days in standard-care group, 8.0 (CI 95% 5.0–13.0) days in high-dose steroid group and 4.5(CI %95 3.0–8.0) days in pulse-steroid group. Moreover, although patients in pulse-steroid group were initially unresponsive to high dose steroid therapy, they achieved similar results compared to the high-dose steroid group in other outcomes except for length of hospital stay.

**Conclusion:** Pulse-steroid treatment would be an option for COVID-19 patients who do not respond to the initial high-dose steroid treatment.

**Key words:** Coronavirus disease 2019, steroid treatment, mortality rate, intensive care unit stay

## 1. Introduction

Coronavirus disease 2019 (COVID-19) is a potentially fatal multisystem disease which is caused by SARS-CoV 2, novel form of Coronavirus [1]. Many organ systems including cardiac [2], nervous [3], renal [4], gastrointestinal [5], and coagulation systems [6] would suffer from the disease. However, respiratory illnesses that require hospitalization and oxygen supplement and in critical cases, requirement of intensive care unit support are the main severe clinical pictures of the disease [7].

The effectiveness of various re-purposed drugs in COVID-19 has been studied in the course of the pandemic [8]. However, there are no proven effective treatment modalities that cure COVID-19 or reduce the mortality rate of the disease so far. Remdesivir, a promising antiviral drug, has recently been shown to shorten the recovery time [9].

Acute pneumonia caused by host immunity, diffuse alveolar damage, and increased tendency to generalized micro-thrombosis are the characteristic pathophysiological features of the disease [10]. Therefore, in special circumstances, well-timed and appropriate doses of antiinflammatory drugs would be a promising treatment option for COVID-19 [11]. Recently, it has been shown that high dose of the key antiinflammatory drugs, corticosteroids, reduce 28-day mortality in the COVID-19 patients who need oxygen supplementation [12]. In addition, several randomized studies have demonstrated the beneficial effect of various doses of corticosteroids on 28-day all-cause mortality from COVID-19 [13]. In these studies, the effect of corticosteroid treatment was compared with standard care only.

In our daily medical practice, we observed that some patients would not respond adequately to the moderate or high dose steroid treatment within the scope of clinical, radiologic and laboratory parameters. In these cases, we speculated that if the high dose steroid treatment fails, add-on very high dosage or pulse steroid treatment would be a treatment option to accompany standard therapy.

In this study, we assessed the effect of add-on 250 mg pulse methyl prednisolone treatment in hypoxic and/or oxygen requiring hospitalized COVID-19 patients despite the failure of high dose steroid treatment. We retrospectively included 3 different COVID-19 cohorts here: patients on standard therapy only, cases on standard therapy plus high dose steroid treatment, and finally the patients that were administered add-on pulse steroid, if high dose steroid treatment fails. We compared these groups for mortality, need for intensive care unit (ICU) admission or frequency of mechanical ventilation (MV), length of hospitalization, and duration of stay in the

* Correspondence: engintez@yahoo.com

ICU, duration of need for MV, and frequency of steroid-related side effects.

## 2. Materials and methods

Four hundred fifty individuals with COVID-19 over the age of 18 were retrospectively enrolled in the study. All patients were hospitalized in a tertiary health-care facility due to COVID-19. Additionally, all study participants had hypoxia and/or needed oxygen support. The COVID-19 patients with any of corticosteroid contraindications, who were transferred to ICU or who needed MV prior to target steroid treatment (in the high steroid dose group before administering any dose of steroid and in the pulse steroid group before starting pulse steroid treatment even if the patient was on high dose of steroid), patients who were pregnant or nursing and had a concomitant bacterial or fungal infection at the time of hypoxia and/or in need for oxygen supplementation and the patients receiving other antiinflammatory treatment such as anticytokine therapies were excluded. In our institute, COVID-19 was diagnosed through two different approaches. First, the individuals with PCR positivity for SARS-CoV-2 were accepted as having microbiologically-documented COVID-19. Moreover, the individuals with a negative PCR test result were diagnosed with COVID-19 if they fulfilled all three clinical criteria: (a) having fever and/or respiratory or other symptoms of COVID-19, (b) having chest imaging findings compatible with COVID-19 [14] and (c) having decreased lymphocyte count while the white blood cell count was normal or decreased. The treatment regimens for COVID-19 were administered based upon the Turkish Health Ministry COVID-19 Guidelines[1]. These guidelines have been regularly revised and updated based upon scientific advances achieved in COVID-19 treatment. Therefore, the patients' treatment modalities may differ according to the currently valid version of the guidelines at the time of the patient's COVID-19 diagnosis. In addition, requirement for ICU or MV was decided by the ICU specialist by referring to the same guidelines.

The aim of the study was to evaluate the efficacy of add-on 250 mg pulse methyl-prednisolone therapy in COVID-19 patients with inadequate response to high dose steroid (6 mg/day dexamethasone equivalent). Here, we compared this treatment with two different treatment approaches. Herein, we compared the efficacy of 250 mg pulse methyl-prednisolone therapy with standard care therapy and high dose steroid treatment (6 mg/day dexamethasone equivalent) plus standard therapy. Briefly, we compared three different patient groups classified according to COVID-19 treatment characteristics during hospitalization.

### 2.1. Treatment features of the study groups

The first group of patients received COVID-19 treatment in the early phase of the pandemic. During this period, the Turkish Health Ministry COVID-19 Guidelines recommended antiviral treatment (both favipravir and hydroxychloroquine), anticoagulation, and oxygen supplement if necessary for COVID-19. In the initial version of the guideline, corticosteroid treatment was not recommended despite hypoxemia unless the patients had another indication for corticosteroids. We categorized the patients on these treatments in the standard care therapy group.

The patients in the second group were diagnosed with COVID-19 after the results of the RECOVERY trial were announced [12]. At this point, the guideline recommendations were revised to allow add- on dexamethasone 6 mg/day or equivalent dose of any steroid drug to the standard care therapy immediately after the development of COVID-19 associated hypoxia and/or the need for oxygen support. Here, the duration of the steroid treatment was recommended as 10 days. Those patients receiving dexamethasone plus standard care therapy were classified as high dose steroid group.

Recently, the Turkish Health Ministry COVID-19 scientific committee recommended pulse steroid treatment under the condition that the patients had inadequate response to high dose steroid therapy. According to the latest guidelines, no clinical, laboratory or radiological improvement or deterioration of these findings after at least three days of high dose steroid treatment may be indicative of need for 250 mg of pulse steroid treatment. The recommended treatment duration for pulse steroid therapy is three days in a row. After pulse steroid treatment, the patients are advised to keep up high dose maintenance steroid treatment for a total of 10 days. Here, the patients who received this therapy were classified as the pulse steroid group. At this stage, all clinical, laboratory or radiological assessments were performed based upon clinical judgment of the physician. In both high dose and pulse steroid treatment groups, the duration of the steroid treatments were decided by the responsible physician according to clinical assessment and laboratory findings. Therefore, the durations of the steroid treatments may vary in accordance with the severity of the patients' clinical condition and physicians' decision.

### 2.2. Patient enrolment methods and study parameters

The patients in all three groups were matched based upon age (age of index case ± SD of pulse steroid group's mean age), sex, national early warning score-2 (NEWS) [15] at the onset of hypoxia or in need of oxygen supplementation and Charlson comorbidity index (CCI) [16]. The primary outcomes of the study were mortality rate, the frequency of MV or ICU requirement, length of hospital stay, length of stay in ICU, and length of MV requirement and side effects related to steroid treatments.

In this study, we have specified the patients in pulse steroid group as the study cluster. First, we identified all consecutive patients that were included in the pulse steroid group in our institute's COVID-19 cohort. Then, we matched those patients with controls from other two groups (standard

[1] Turkish Health Ministry. (2020). Guidance To Covid-19 (SARS Cov2 Infection) [Online]. Website: https://hsgm.saglik.gov.tr/tr/covid-19-ingilizce-dokumanlar.html [accessed 18/05/2020].

care and high dose steroid groups). Here, we identified all potential individuals in both control cohorts that might be eligible to match the individual case in the pulse steroid group based on age, sex, NEWS score at the onset of hypoxia and CCI. Then, we randomly selected one of these patients from the control cohorts respectively. Firstly, we numbered all potential controls for individual case in study group according to appointment date. Then, we selected one of them with using a random-number generator[2]. Finally, we compared the patients in pulse steroid group with both control groups for primary outcome parameters.

We retrospectively collected the patient's data from the hospital's medical database. Here, we have obtained the demographic features of the patients (age, sex), co-morbidities, presenting COVID-19 related symptoms, results of SARS-CoV2 PCR test, treatment history for COVID-19 during hospitalization, requirement of intensive care unit, requirement of mechanical ventilation, duration of hospitalization, length of intensive care unit stay, laboratory values at the onset of hypoxia (blood levels of biochemical parameters including aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, lactate dehydrogenase (LDH), D-dimer, ferritin, C-reactive protein (CRP), and hemograms), length of steroid treatments, steroid related side effects, and outcome of the patients.

The levels of ALT, AST, creatinine, CK, LDH, albumin, and CRP were classified according to the laboratory reference ranges as normal, low, or high. However, ferritin and D-dimer levels were classified based upon their levels related to unfavourable prognosis in COVID-19. These cut-off levels were specified as 300 mg/mL for ferritin and 1000 mg/L for D-dimer [17]. Also, we focused on lymphocyte counts at hemogram. Lymphocytes levels lower than 1 x $10^9$/L were accepted as cut-off value for severe disease. Moreover, NEWS scores were classified as low (0–4), medium (5–6), and high (≥7) [15]. Also, we have defined hypoxia if the oxygen saturation of the patients is 93% or lower in room air[3].

This study was approved by both the Local Research Ethics Committee and the Turkish Health Ministry prior to data collection and carried out in compliance with the Helsinki Declaration.

### 2.3. Statistical analyses

Statistical analyses were carried out using SPSS v: 17.0 (SPSS Inc., Chicago, IL, USA). In order to determine if the data were normally distributed, the Kolmogorov–Smirnov test was performed. None of the parameters distributed normally. Therefore, comparisons of the continuous variables and categorical variables were performed by Kruskal–Wallis and Chi-square test, respectively. Then, we conducted post-hoc analysis with Bonferonni adjusted Mann–Whitney U or chi-square tests if necessary. Kaplan–Meier survival curves were used to show 28-day cumulative survival after the onset of target treatment or hypoxia. Here, we compared the groups for 28-day cumulative survival to standardize the study with similar ones [18]. We used log-rank analysis to compare the curves. We also evaluated the factors related to mortality in pulse steroid group with multivariate analysis. The results were given as inter-quartile range (IQR). A p-value lower than 0.05 was considered as statistically significant.

## 3. Results

### 3.1. Demographic features, baseline laboratory values, and COVID-19 related symptoms

A total of 450 patients, equally distributed among the three treatment groups were included in the study. Age, sex, disease severity, and CCI scores were similar in all three groups. SARS-CoV-2 PCR test positivity was more common in the pulse steroid group compared to patients in the standard care treatment group. Here, at least 4 of the 5 patients had PCR positivity. Cough and shortness of breath was the most common symptoms in all groups. Additionally, the frequency of all evaluated co-morbid diseases was similar between the groups. In the pulse steroid group, the frequency of patients with baseline high transaminases, increased CRP or ferritin levels, and decreased lymphocyte counts was found to be more frequent than the standard care treatment group. In addition, more patients in the high-dose steroid group had increased transaminase levels and lower lymphocyte counts compared to the standard care treatment group. All demographic and laboratory values were similar between the patients in high dose steroid and pulse steroid groups (Table 1).

### 3.2. COVID-19 treatment and outcome parameters

All patients in the study were hospitalized and had hypoxemia or needed oxygen support at the time of enrolment. Pulse steroid treatment was initiated after a median of 4.0 (2.0–6.0) days after the start of need for oxygen support. Therefore, we applied pulse steroid therapy due to unresponsiveness on the fourth day of the high dose steroid treatment. In addition, the duration of any dose previous steroid therapy was longer in the pulse

[2] Research Randomizer (Version 4.0) (2013). Website: http://www.randomizer.org/. [accessed: 22/06/ 2013].
[3] Turkish Health Ministry. (2020). Guidance To Covid-19 (SARS Cov2 Infection) [Online]. Website: https://hsgm.saglik.gov.tr/tr/covid-19-ingilizce-dokumanlar.html [accessed 18/05/2020].

**Table 1.** Demographic and disease-related features of the COVID-19 patients.

| | Standard care treatment n = 150* | High steroid treatment n = 150⁺ | Pulse steroid treatment n =150¶ | Post-hoc analyses | p |
|---|---|---|---|---|---|
| Age (year) | 60.0(48.7–71.0) | 59.5(49.0–71.2) | 59.5(48.0-70.7) | NS | 0.98 |
| Sex (M/F) | 100/50 | 100/50 | 100/50 | NS | N/A |
| Positive PCR test result, n(%) | 122(81.3)* | 133(88.7) | 141(94.0)* | *p < 0.001 | 0.03 |
| Disease severity (NEWS-2 score)* | 6.0(2.0-7.0) | 6.0(4.0-7.0) | 6.0(4.0-7.2) | NS | 0.22 |
| Low | 39 (26.0) | 39 (26.0) | 39 (26.0) | | |
| Moderate | 48(32.0) | 48(32.0) | 48(32.0) | | |
| High | 63(42.0) | 63(42.0) | 63(42.0) | | |
| Presenting symptoms n(%) | | | | | |
| Cough | 93(62.0) | 95(63.3) | 95(63.3) | NS | 0.94 |
| Shortness of breath | 66(44.0)* | 91(60.7) | 113(75.3)* | * p < 0.001 | <0.001 |
| Fever | 75(50.0) | 55(36.7) | 60(40.0) | NS | 0.05 |
| Myalgia | 27(18.0)* | 29(19.3)¶ | 47(31.3)*¶ | *¶p < 0.001 | 0.01 |
| Headache | 11(7.3) | 11(7.3) | 12(8.0) | NS | 0.96 |
| Sore throat | 10(6.7) | 7(4.7) | 7(4.7) | NS | 0.68 |
| Loss of taste or smell | 11(7.3) | 12(8.0) | 11(7.3) | NS | 0.16 |
| Malaise | 47(31.3)* | 56(37.3) | 74(49.3)* | * p = 0.001 | 0.005 |
| Diarrhoea | 7(4.7) | 14(9.3) | 8(5.3) | NS | 0.22 |
| Nausea/vomiting | 13(8.7) | 25(16.7) | 11(7.3) | NS | 0.05 |
| Loss of appetite | 10(6.7) | 16(10.7) | 18(12.0) | NS | 0.25 |
| Charlson comorbidity index score | 3(1–4) | 3(1–4) | 3(1–4) | NS | 0.80 |
| Co-morbidities n(%) | | | | | |
| Diabetes mellitus | 53(35.3) | 46(30.7) | 62(41.3) | NS | 0.15 |
| Hypertension | 66(44.0) | 61(40.7) | 69(46.0) | NS | 0.64 |
| Coronary arterial disease | 34(22.7) | 30(20.0) | 27(18.0) | NS | 0.60 |
| COPD | 8(5.3) | 9(6.0) | 8(5.3) | NS | 0.95 |
| Asthma | 14(9.3) | 12(8.0) | 7(4.7) | NS | 0.25 |
| Malignancy | 6(4.0) | 16(10.7) | 14(9.3) | NS | 0.06 |
| Chronic renal disease | 7(4.7) | 8(5.3) | 10(6.7) | NS | 0.74 |
| Rheumatic diseases | 5(3.3) | 3(2.0) | 4(2.7) | NS | 0.77 |
| Laboratory findings* | | | | | |
| Transaminases (>35 IU/L) | 36(24.0)* | 70(46.7)¶ | 64(42.7)*¶ | *p < 0.001<br>¶p = 0.001 | <0.001 |
| Creatinine (>1.2 mg/dL) | 25(16.7) | 37(24.7) | 33(22.0) | NS | 0.20 |
| LDH ( >240 U/L) | 89(59.3)* | 104(69.3) | 122(81.3)* | *p < 0.001 | 0.01 |
| D-dimer (≥1000 ng/mL) | 53(35.3) | 72(48.0) | 79(52.7) | NS | 0.23 |
| Lymphocyte count ($\leq 1x10^9$/L) | 47(31.3)*¶ | 76(50.7)¶ | 89(59.3)* | *p = 0.001<br>¶p < 0.001 | <0.001 |
| Ferritin ( ≥300 mg/mL) | 36(24.0)* | 94(62.7) | 117(78.0)* | *p < 0.001 | <0.001 |
| CRP (>10 mg/dL) | 123(82.0)* | 138(92.0) | 145(96.7)* | *p < 0.001 | <0.001 |

steroid group (p = 0.01). The antiviral treatment approach was different between standard care therapy group compared to steroid therapy groups related to the currently available versions of our national guidelines. More patients in the standard care treatment group received hydroxychloroquine, antibiotics, and lopinavir-ritonavir than the patients in the other two groups. However, none of the patients in our standard care therapy group received any dose of steroid. Also, favipravir was the most preferred antiviral treatment agent in the steroid therapy groups. There was no difference between the groups according to anticoagulant therapy (Table 2).

Mortality rates were similar in all groups. However, there was a trend for lower mortality rates in both steroid groups. Both ICU or MV requirement rates were lower in the high steroid dose group compared to standard care and pulse steroid therapy groups (p = 0.03 and p = 0.02, respectively). Also, the length of hospitalization was significantly different in all groups. Duration of hospital stay was the shortest in the high dose steroid group [8.0 (5.5–12.2) days]. In addition, the length of stay in ICU was the shortest in the pulse steroid group although the difference was significant only between standard care and pulse steroid groups (p = 0.01) (Table 2). Median duration of ICU stays were 9.0 (CI 95% 6.0–12.0) days in standard care group, 8.0 (CI 95% 5.0–13.0) days in high dose steroid group and finally 4.5 (CI %95 3.0–8.0) days in pulse steroid group.

Steroid- related side effects were more common in the pulse steroid treatment group (p = 0.03). However, less than 5% of the patients had steroid-related side effects in both groups. The most common side effect was increased blood sugar levels. Four patients from pulse steroid group and one patient from high dose steroid group had increased blood sugar levels. Moreover, two patients receiving pulse steroid and one patient from high dose steroid group had dyspeptic complaints. None of the patients had steroid therapy related bacterial or fungal infections. Additionally, none of the patients' steroid treatment was terminated due to any side effect.

In the severe COVID-19 patients (NEWS-2 score >6), both ICU and MV requirements were lower in steroid treatment groups than in standard care group (p = 0.03 and p = 0.008, respectively). Length of hospitalization was also the shortest in high dose steroid treatment group. In addition, the length of stay in ICU was the shortest in the pulse steroid treatment group although the difference was significant only between standard care and pulse steroid treatment groups (p = 0.03) (Table 3).

We performed an analysis of 28-day survival after the initiation of the target therapy or development of hypoxia. There was no difference between the survival curves of the groups (p = 0.36). However, after the fifteenth day, survival curves differentiated between the standard care treatment and steroid treatment groups. At this point, fewer patients died in the steroid groups compared to standard care treatment group (Figure).

**Table 2.** Disease-related features, treatment properties, and outcomes of the COVID-19 patients.

| | Standard care treatment n = 150 | High dose steroid treatment n = 150 | Pulse steroid treatment n = 150 | Post-hoc analyses | p |
|---|---|---|---|---|---|
| Time from onset of symptoms to oxygen supplementation (days) | 4.0 (2.0–7.0)*¶ | 7.0 (3.0–9.5)¶ | 7.0 (4.0–10.0)* | *¶p < 0.001 | <0.001 |
| Time from onset of oxygen supplementation to pulse steroid treatment (days) | N/A | N/A | 4.0 (2.0–6.0) | | N/A |
| Time from onset of oxygen supplementation to ICU requirement (days) | 5.0 (3.0–6.0)* | 4.0 (3.0–7.0)¶ | 2.0 (1.0–3.5)*¶ | *¶p = 0.01 | 0.01 |
| Duration of total steroid treatment (days) | N/A | 6.0 (4.0–9.0) | 7.0 (5.0–9.0) | | 0.01 |
| Duration of pulse steroid dose treatment (days) | N/A | N/A | 3.0 (3.0–3.0) | | N/A |
| Treatment, n(%) | | | | | |
| Hydroxychloroquine | 144(96.0)*¶ | 43(28.7)¶ | 64(42.7)* | *¶p < 0.001 | <0.001 |
| Favipravir | 67(44.7)*¶ | 132(88.0)¶ | 141(94.0)* | *¶p < 0.001 | <0.001 |
| Antibiotics | 127(84.7)*¶ | 51(34.0)¶ | 48(32.0)* | *¶p < 0.001 | <0.001 |
| Remdesivir | 0(0) | 14(9.3) | 7(4.7) | NS | <0.001 |
| Lopinavir–Ritonavir | 12(8.0) | 0(0) | 0(0) | | N/A |
| Anticoagulant treatment | 136(90.6) | 144(96.0) | 146(97.3) | | 0.21 |
| Primary endpoints n(%) | | | | | |
| Deceased | 24(16.0) | 16(10.7) | 14(9.3) | NS | 0.17 |
| Discharged | 126(84.0) | 134(89.3) | 36(90.7) | NS | |
| Requirement of ICU | 32(21.3)* | 17(11.3)* | 20(13.3) | *p = 0.01 | 0.03 |
| Requirement of MV | 28(18.7)* | 13(8.7)* | 16(10.7) | *p = 0.01 | 0.02 |
| Length of hospitalization (days) | 10.0 (6.0–14.0)*+ | 7.0 (5.0–11.0)¶+ | 12.0 (9.0–15.0)*¶ | *¶+p < 0.001 | <0.001 |
| Length of ICU stay (days) | 9.0 (5.7–13.0)* | 8.0 (5.5–12.2) | 4.5 (2.2–8.0)* | *p = 0.01 | 0.03 |
| Length of MV (days) | 7.5 (3.5–11.0) | 6.5 (3.2–8.7) | 3.5 (2.0–7.7) | | 0.13 |
| Steroid side effects | N/A | 2(1.3) | 6(4.0) | | 0.03 |

ICU: intensive care unit; MV: mechanical ventilation. *At the time of the onset of hypoxia
p < 0.05 was shown bold. NS: nonsignificant. p < 0.017 was shown in post-hoc analysis
Comparisons in post-hoc analyses with p value < 0.017 was shown in the table.

**Table 3.** Primary endpoints in patients with severe COVID-19 (NEWS-2 score > 6).

| | Standard care treatment n = 63 | High dose steroid treatment n = 63 | Pulse steroid treatment n = 63 | Post-hoc analyses | P |
|---|---|---|---|---|---|
| Primary endpoints n(%) | | | | | |
| Deceased | 15(23.8) | 11(17.4) | 5(7.9) | NS | 0.06 |
| Requirement of ICU | 21(33.3)*¶ | 12(19.0)¶ | 9(14.3)* | *p = 0.001<br>¶p = 0.01 | 0.03 |
| Requirement of MV | 20(31.7)*¶ | 10(15.8)¶ | 6(9.5)* | *p = 0.001<br>¶p = 0.01 | 0.008 |
| Length of hospitalization (days) | 11.5 (7.0–16.0)* | 7.0 (4.7–12.0)*¶ | 12.0 (8.0–15.0)¶ | *¶p < 0.001 | <0.001 |
| Length of ICU stay (days) | 10.0 (7.0–25.0)* | 7.0 (5.0–13.0) | 3.0 (2.0–7.0)* | *p = 0.01 | 0.03 |
| Length of MV (days) | 8.0 (5.2–15.7) | 7.0 (3.5–9.0) | 4.0 (1.7–8.7) | NS | 0.21 |

ICU: intensive care unit; MV: mechanical ventilation. *At the time of the onset of hypoxia
p < 0.05 was shown bold. NS: nonsignificant p < 0.017 was shown in post-hoc analysis.

Lastly, we conducted multivariate analyses to evaluate the features related to mortality in pulse steroid group. Only creatinine level higher than 1.2 mg/dL was found to be related to mortality in study group (Table 4).

**Table 4.** Multivariate analyses for mortality in pulse steroid group.

| | OR | %95 CI | P |
|---|---|---|---|
| Male sex | 3.11 | 0.70–14.3 | 0.13 |
| Age | 0.94 | 0.89–1.02 | 0.05 |
| Charlson comorbidity index score | 0.96 | 0.70–1.32 | 0.88 |
| NEWS-2 score* | 0.97 | 0.74–1.28 | 0.86 |
| Creatinine (>1.2 mg/dL) | 8.9* | 2.3–34.6* | 0.002* |

NEWS-2: national early warning score-2, *At the time of the onset of hypoxia. Regression analyses include the variables significantly related to mortality in univariate analyses (age, Charlson comorbidity index score, creatinine (>1.2 mg/dL)), NEWS-2 score and sex
*p < 0.05.

## 4. Discussion

In this study, in which we evaluated the effectiveness of add-on 250 mg pulse methyl-prednisolone treatment in addition to high dose steroid treatment (6 mg/day dexamethasone equivalent) in case of unresponsiveness, the pulse steroid group had shorter ICU stay as compared to the other groups. Additionally, patients in the pulse steroid group achieved similar results in other outcome parameters except the total length of hospital stay.

After the RECOVERY trial results were published [12], high dose steroid therapy in an equivalent dose of 6 mg dexamethasone became a treatment option for COVID-19 patients. In the original paper, the therapy had beneficial effect only on the patients who needed oxygen support. As expected, some patients in this study did not respond to high dose steroid therapy. In this case, administration of higher steroid dose would be a treatment option. There are controversial reports about the efficacy of pulse steroid therapy. Some recently published papers have shown the favorable effects of higher steroid doses in COVID-19 patients with pulmonary involvement [19–21]. In these studies, effectiveness of pulse steroid treatment was compared to standard care therapy only without any prior steroid administration. Here, there were significantly better outcome parameters in the results of the pulse steroid groups. In one study, very high dose steroid treatment increased ventilator-free days [21] while in others, this treatment was associated with higher survival rates. In contrary, another study found that pulse steroid therapy was associated with increased mortality compared to standard care therapy, especially in older adults [22]. Our study was unique because we evaluated the effectiveness of pulse steroid treatment on outcome parameters by comparing the two other groups (standard care and high dose steroid groups) for the first time in the literature. In addition, according to our study protocol, we primarily focused on the effects of add-on pulse steroid treatment on COVID-19 patients who did not respond to high dose steroid therapy.

All groups in our study were matched based upon age, sex, disease severity at the onset of hypoxia, and weight of co-morbidities. However, there were some differences between the groups due to the phase of the pandemic in our country when the patients were selected. First of all, the standard care treatment group was included in the first phase of the pandemic. At this phase, these patients did not receive any steroid therapy and antiviral therapy options were different from the subsequent phases of the outbreak. However, since the host immune response is the main pathophysiological mechanisms for the disease [23], these patients did not receive adequate immune modulation therapy. Additionally, the second group of our study was similar to the dexamethasone group of the RECOVERY trial. Finally, pulse steroid group had some important characteristics that influenced the results of the study. Firstly, these patients were nonresponders of high dose steroid treatment group. Although baseline clinical and demographic features of the patients were similar with the other groups, they did not respond to at least 3 days of high dose steroid treatment. Therefore, those patients would have clinically more severe disease. Also, without pulse steroid treatment, they would likely have negative outcomes.

According to our results, patients in the pulse steroid group had similar results to the high-dose steroid group, with shorter ICU stays but longer hospital stays. Since those

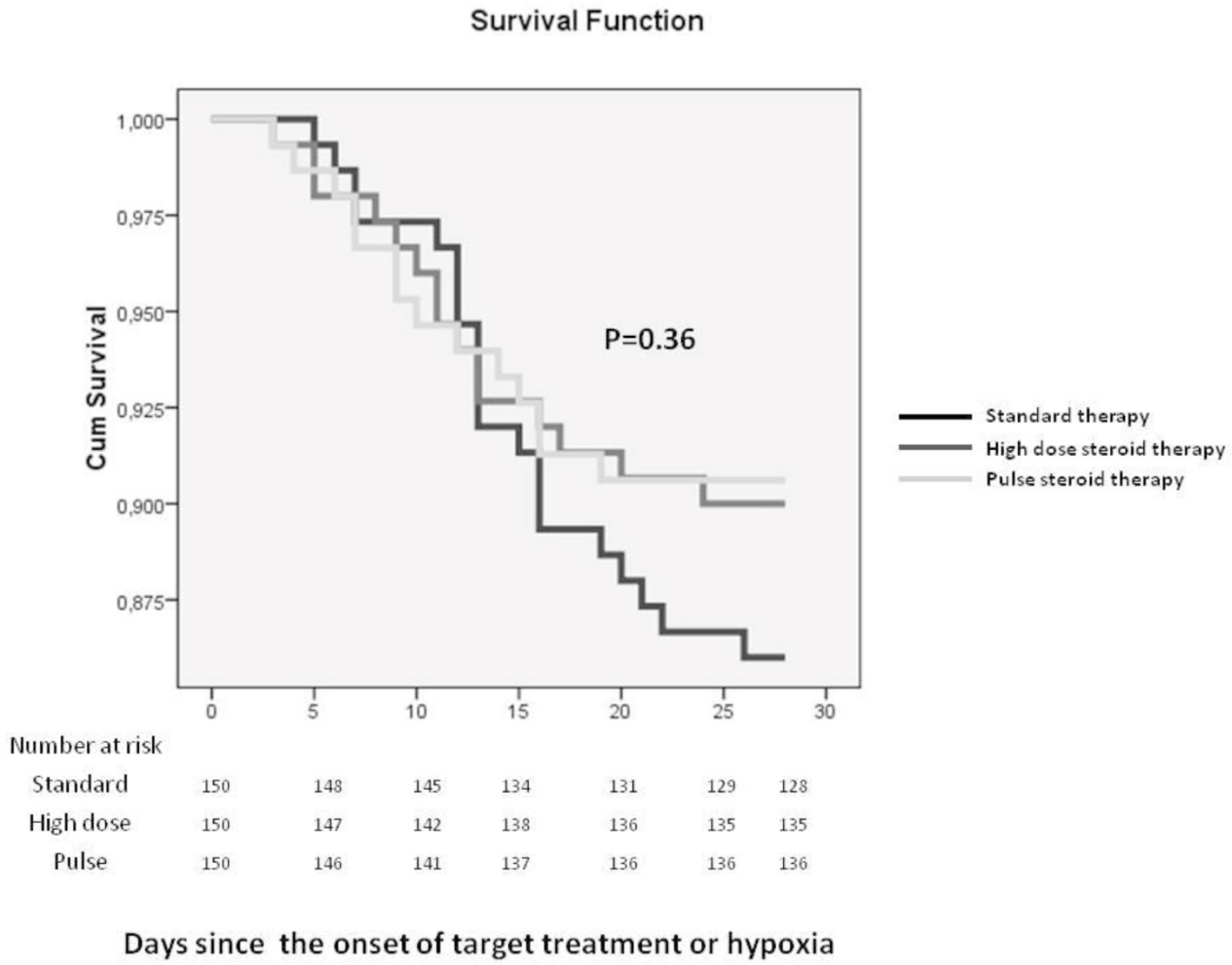


**Figure.** 28-day cumulative survival graphic of the patients in the 3 study groups.

patients had clinically more severe disease, longer treatment duration is expected. However, increasing steroid dose has a beneficial effect with suppressing the host inflammation more efficiently and controlling the severity of the disease with shorter ICU stays. Although not statistically significant, the number of ventilator-free days was also more increased in pulse steroid group than the others. Therefore, we compared high dose steroid group which included both steroid responders and nonresponders, with those who did not respond to this treatment alone. Here, pulse steroid therapy can prevent worse outcomes in these patients.

The mortality rate was similar among the groups. However, standard care treatment group patients had nonsignificantly higher rate of mortality. Furthermore, after the fifteenth day of the treatment or hypoxia, survival curves in both steroid groups flattened compared to standard care group. Also, pulse steroid therapy probably would reduce the mortality rate of the high dose steroid treatment nonresponders.

The high dose steroid treatments have several side effects [24]. In our cohort, less than 5% of the patients in steroid treatment groups had steroid-related side effects. In addition, no patient's steroid treatment was discontinued due to these side effects. Here, the most common side effect was increased blood sugar levels. Furthermore, a study showed that there was no increase in hospital mortality due to any secondary infection in the patients receiving high dose steroid for the treatment of COVID-19 [25]. Therefore, we thought that under these specific conditions, high or very high steroid dose could be tolerated.

Our study has some limitations. First of all, our study is a retrospective controlled study. Although we matched the groups according to several parameters, it is not a randomized controlled study. Additionally, we enrolled the controls from the different stages/phases of the pandemic. Therefore, there were some differences in treatment approaches, especially in the antiviral therapy. Finally, the pulse steroid therapy group would be considered as the more severe form of the higher dose steroid treatment groups, although the groups were also matched in terms of initial disease severity.

In conclusion, pulse steroid treatment would decrease the length of ICU stays and probably may have beneficial effect on outcomes in the nonresponder patients of high dose steroid treatment without significant side effects. Therefore, pulse steroid treatment would be a tolerable treatment

approach for the treatment of the COVID-19 patients who do not respond to the initial high dose steroid treatment.

## Informed consent

None.

## Ethical approval

Kartal Dr. Lutfi Kırdar Şehir Hastanesi Klinik Araştırmalar Etik Kurulu (30.12.2020-514/192/59).

**References**


1. Rothan HA, Byrareddy SN. The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. Journal of Autoimmunity 2020; 109: 102433. doi: 10.1016/j.jaut.2020.102433
2. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nature Reviews: Cardiology 2020; 17: 259-260. doi: 10.1038/s41569-020-0360-5
3. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K et al. Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain, Behavior, and Immunity 2020. doi: 10.1016/j.bbi.2020.03.031
4. Pei G, Zhang Z, Peng J, Liu L, Zhang C et al. Renal involvement and early prognosis in patients with COVID-19 pneumonia. Journal of the American Society of Nephrology 2020. doi: 10.1681/ASN.2020030276
5. Hajifathalian K, Mahadev S, Schwartz RE, Shah S, Sampath K et al. SARS-COV-2 infection (coronavirus disease 2019) for the gastrointestinal consultant. World Journal of Gastroenterology 2020; 26: 1546-1553. doi: 10.3748/wjg.v26.i14.1546
6. Incidence of venous thromboembolism in hospitalized patients with COVID-19. Journal of Thrombosis and Haemostasis 2020. doi: 10.1111/jth.14888
7. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infectious Diseases 2020; 20: 669-677. doi: 10.1016/S1473-3099(20)30243-7
8. Vijayvargiya P, Esquer Garrigos Z, Castillo Almeida NE, Gurram PR, Stevens RW et al. Treatment considerations for COVID-19: a critical review of the evidence (or lack thereof). Mayo Clinic Proceedings 2020; 95: 1454-1466. doi: 10.1016/j.mayocp.2020.04.027
9. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS et al. Remdesivir for the treatment of Covid-19-final report. New England Journal of Medicine 2020; 383: 1813-1826. doi: 10.1056/NEJMoa2007764
10. Carsana L, Sonzogni A, Nasr A, Rossi RS, Pellegrinelli A et al. Pulmonary post-mortem findings in a series of COVID-19 cases from northern Italy: a two-centre descriptive study. Lancet Infectious Diseases 2020; 20: 1135-1140. doi: 10.1016/S1473-3099(20)30434-5
11. Soy M, Keser G, Atagunduz P, Tabak F, Atagunduz I et al. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical Rheumatology 2020; 39: 2085-2094. doi: 10.1007/s10067-020-05190-5
12. Group RC, Horby P, Lim WS, Emberson JR, Mafham M et al. Dexamethasone in hospitalized patients with Covid-19-preliminary report. New England Journal of Medicine 2020. doi: 10.1056/NEJMoa2021436
13. Sterne JAC, Murthy S, Diaz JV, Slutsky AS et al. Association between administration of systemic corticosteroids and mortality among critically ıll patients with COVID-19: a meta-analysis. The Journal of the American Medical Association 2020; 324: 1330-1341. doi: 10.1001/jama.2020.17023
14. Yang Q, Liu Q, Xu H, Lu H, Liu S et al. Imaging of coronavirus disease 2019: a Chinese expert consensus statement. European Journal of Radiology 2020; 127: 109008. doi: 10.1016/j.ejrad.2020.109008
15. Smith GB, Redfern OC, Pimentel MA, Gerry S, Collins GS et al. The National early warning score 2 (NEWS2). Clinical Medicine (London) 2019; 19: 260. doi: 10.7861/clinmedicine.19-3-260
16. D'Hoore W, Sicotte C, Tilquin C. Risk adjustment in outcome assessment: the Charlson comorbidity index. Methods of Information in Medicine 1993; 32: 382-387.
17. Zhou F, Yu T, Du R, Fan G, Liu Y et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020; 395: 1054-1062. doi: 10.1016/S0140-6736(20)30566-3
18. Sterne JAC, Diaz J, Villar J, Murthy S, Slutsky AS et al. Corticosteroid therapy for critically ill patients with COVID-19: a structured summary of a study protocol for a prospective meta-analysis of randomized trials. Trials 2020; 21: 734. doi: 10.1186/s13063-020-04641-3
19. Ruiz-Irastorza G, Pijoan JI, Bereciartua E, Dunder S, Dominguez J et al. Second week methyl-prednisolone pulses improve prognosis in patients with severe coronavirus disease 2019 pneumonia: an observational comparative study using routine care data. PloS One 2020; 15: e0239401. doi: 10.1371/journal.pone.0239401
20. Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. European Respiratory Journal 2020; 56. doi: 10.1183/13993003.02808-2020
21. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. The Journal of the American Medical Association 2020; 324: 1307-1316. doi: 10.1001/jama.2020.17021
22. Monreal E, Sainz de la Maza S, Natera-Villalba E, Beltran-Corbellini A, Rodriguez-Jorge F et al. High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study. European Journal of Clinical Microbiology and Infectious Diseases 2020. doi: 10.1007/s10096-020-04078-1
23. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: a review. Clinical Immunology 2020; 215: 108427. doi: 10.1016/j.clim.2020.108427
24. Noone T. An overview of steroid use and its potential side-effects. Nursing Times 2006; 102: 24-27.
25. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, Sancho-Lopez A, Mills-Sanchez P et al. A retrospective controlled cohort study of the ımpact of glucocorticoid treatment in SARS-CoV-2 infection mortality. Antimicrobial Agents and Chemotherapy 2020; 64. doi: 10.1128/AAC.01168-20