Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial

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Take-Home Message

The study showed that methylprednisolone pulse administration at the beginning of the early pulmonary phase of illness decreased the mortality rate and improved pulmonary involvement, oxygen saturation, and inflammatory markers in COVID-19 patients.
Abstract

Background

There are no determined treatment agents for the severe coronavirus disease 2019 (COVID-19); therefore, it is suggested that methylprednisolone, as an immunosuppressive treatment, can reduce the inflammation of the respiratory system.

Methods

We conducted a single-blind, randomized, controlled, clinical trial involving severe hospitalized patients with confirmed COVID-19 at the early pulmonary phase of the illness in Iran. The patients were randomly allocated in a 1:1 ratio by block randomization method to receive standard care with methylprednisolone pulse (intravenous injection, 250mg/day for 3 days) or standard care alone. The study endpoint was the time of clinical improvement or death, whichever came first. Primary and safety analysis was done in the intention-to-treat (ITT) population.

Results

Sixty-eight eligible patients underwent randomization (34 patients in each group) from April 20, till Jun 20, 2020. In the standard care group, six patients received corticosteroids by the attending physician during treatment and excluded from the ITT population. Patients with clinical improvement were higher in the methylprednisolone group than in the standard care group (94.1% vs 57.1%), and the mortality rate was numerically lower in the methylprednisolone group (5.9% vs 42.9%; P <0.001). We demonstrated that patients in the methylprednisolone intervention group had a significantly increased survival time compared with the patients in the standard care group [Log rank test: P<0.001; Hazard ratio: 0.293; 95% CI: 0.154-0.556]. A total of two patients in each group (5.8% and 7.1% respectively) showed severe adverse events between initiation of treatment and the end of the study.
Conclusions

Our results suggested that methylprednisolone pulse could be an efficient therapeutic agent for hospitalized severe COVID-19 patients at the pulmonary phase.

Trial registration

The study was registered (15 April 2020) in the Iranian Registry of Clinical Trials (IRCT ID: IRCT20200404046947N1).

Keywords

Corticosteroid, COVID-19, Methylprednisolone
1. Introduction

The world is experiencing the pandemic of a novel coronaviruses-induced respiratory illness named coronavirus disease 2019 (COVID-19). The diseases caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) belongs to the positive beta-coronavirus [1]. Beta-coronaviruses are positive-single strand RNA (+ssRNA) viruses which have caused two other severe outbreaks, the middle east, and severe acute respiratory syndrome (MERS, SARS) just over the past decades [2]. COVID-19 has rapidly spread across the world, and the number of infected people is increasing since it was first discovered in China in late 2019. The virus can be transmitted person to person even in 2-14 days asymptomatic incubation period. The illness signs ranged from fever, dry cough, fatigue, myalgia, and mild respiratory tract symptoms to serve manifestations including breath shortness, pneumonia, and acute respiratory distress syndrome (ARDS) dependents on the patient's age, genetics factors, and the function of the immune system [3, 4]. Extra-pulmonary involvements such as hepatic and gastrointestinal are also presented in some patients [5].

Typically, in the early phase of the disease, specific and proper immune system responses eliminate the virus reproduction and prevent disease progression into the hyper-inflammation phase. If the infection is not eliminated by the appropriate and strong immune responses, the disease enters to the severe inflammatory response phase when cytokine storm and elevated inflammatory markers produced by innate immune cells induced pulmonary fibrosis, shortness of breath, reduction in O2 saturation, and systemic injuries resulted in ARDS and patient’s death [6]. Cytokine storm induction by SARS-CoV-2 was confirmed in COVID-19 patients at the intensive care unit (ICU), and elevated plasma levels of inflammatory cytokines have been associated with disease severity and prognosis [7, 8].

ARDS is the main reason for death in COVID-19 patients [8], and there are no efficient specific treatment agents for the disease, therefore, it is suggested that glucocorticoids and
immunosuppressive treatment can reduce the inflammation of respiratory system and prevents cytokine storm and ARDS induction [9]. Methylprednisolone is a glucocorticoid medication used to suppress the autoimmune and inflammatory responses in rheumatic diseases.[10] Previously, methylprednisolone was administrated in SARS and MERS patients, and the results were controversial [11-13], however glucocorticoid administration in COVID-19 patients in the hyper-inflammation stage are likely to have survival benefits due to cytokine storm suppression. Hence in this study, we investigated the methylprednisolone pulse effects as a glucocorticoid therapy on the treatment, clinical symptoms, and laboratory signs of hospitalized severe COVID-19 patients.

2. Patients and methods

2.1. Study design

This study is conducted as a single-blind, two-arm parallel, randomized, controlled trial from April 20, 2020, till Jun 20, 2020. We enrolled 68 subjects from the Imam Khomeini Hospital, Tehran University of Medical Sciences (TUMS), and Khorshid Hospital, Isfahan University of Medical Sciences (IUMS) in this study. The protocol of this study has been written and mediated in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement [14] and the study was registered in the Iranian Registry of Clinical Trials on 15 April 2020 (IRCT ID: IRCT20200404046947N1). Since there are no published clinical trials of the effect of methylprednisolone in patients with COVID-19, the minimum sample size was estimated 60 plus 10% potential missing data based on the effect size of methylprednisolone on pulmonary and lung function diseases [15-17].

This trial was performed based on the Declaration of Helsinki guidelines and was approved by the Ethics Committee of the Tehran University of Medical Science (Approval ID: IR.TUMS.VCR.REC1399.54).
2.2. Patients

The diagnosis of COVID-19 in subjects was performed based on the following criteria: 1. Identification of SARS-CoV-2 via reverse transcription-polymerase chain reaction (RT-PCR) in nasopharyngeal swab or sputum samples and 2. Abnormal computed tomography (CT) scan finding (bilateral, subpleural, peripheral ground-glass opacities) with oxygen saturation <90% at rest. All patients had signed informed consent before enrolled in the study. The early pulmonary phase was defined as the start of the pulmonary involvement including hypoxia (SO2<93%) tachypnea (RR> 18) and little dyspnea and based on CT scan findings.

2.2.1. Inclusion criteria

Patients were included in our trial if they met the following requirements: 1. Aged 18 years or older; 2. Confirmed COVID-19 with blood oxygen saturation <90%, elevated C-reactive protein (CRP >10), and interleukin (IL)-6 (>6) at the early pulmonary phase of disease before connecting to the ventilator and intubation and 3. agreed to give informed consent (Figure 1).

2.2.2. Exclusion criteria

Individuals were excluded from the study if they met the following specifications: 1. Patients were intolerant or allergic to any therapeutic agents used in this research; 2. Pregnant or lactating women; 3. Patients with blood oxygen saturation <75%, positive pro-calcitonin (PCT) and troponin test, Acute Respiratory Distress Syndrome (ARDS), uncontrolled hypertension (HTN), uncontrolled diabetes mellitus (DM), gastrointestinal problems or gastrointestinal bleeding (GIB) history, heart failure (HF), active malignancies and received any immune-suppressor agents.

2.3 Randomization and masking

Once eligibility has been confirmed, (24-48 hours after hospitalization) the patients randomly allocated in control (n=34) and intervention group (n=34), in a 1:1 ratio by block randomization method. Patients allocated to receive methylprednisolone pulse (intravenous
injection, 250mg/day for 3 days), or not receive methylprednisolone or other glucocorticoids. All patients received standard care (Hydroxychloroquine sulfate, Lopinavir, and Naproxen) for COVID-19 according to the protocol for diagnosis and treatment of COVID-19 in Iran [18]. In this study, patients did not know which group of them used medicine. Physicians and clinicians team know about the medicine and intervention groups. Due to the emergency nature of this trial, placebos of methylprednisolone were not prepared.

2.4. Procedures and Outcome

The clinical and demographic characteristics of the study participants were obtained before enrolled in the study. All patients were followed-up from day 0 to day 3, improvement, hospital discharge, or death, and one week after hospital discharge, which was scheduled at three or four consecutive visit points. Clinical signs of the patients including heart rate, body temperature, blood pressure, oxygen saturation (SO2), and, dyspnea, cough, gastrointestinal involvement (GI) symptoms, myalgia, chest pain, and BORG score were assessed before and after treatment (by 3 days of treatment and discharge time). The need on oxygen therapy (nasal cannula, mask oxygen, reserve mask, noninvasive ventilation (NIV), and invasive ventilation) was recorded before and after treatment (by 3 days of treatment and discharge time). CT scan findings were also assessed before and one week after treatment only in patients agreed to give informed consent. Other clinical outcomes including mortality rate, the duration of hospitalization in improved patients, and the time (in days) from the initiation of treatment to death were assessed in each group. Laboratory test results including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), vein blood gas analysis (VBG) including PH, Bicarbonate (HCO3), and partial pressure of carbon dioxide (PCO2), IL-6, Ferritin, Troponin, D-dimer, lactic acid dehydrogenase (LDH), and creatine phosphokinase (CPK) were recorded before and after treatment (by 3 days of treatment and discharge time). Clinical signs of the improved patients, including cough,
GI symptoms, myalgia, chest pain, and BORG score, were assessed one-week after discharge time.

All data were considered during the study and follow-up time and recorded on case report forms (CRFs) and the Excel database. The primary endpoint was the time of clinical improvement and discharge from the hospital or death whichever came first. Hospital discharge was determined according to the patients clinical and laboratory findings. Improvement was defined as BORG score>3, improved dyspnea, stopped fever for 72 hours, SO2> 93%, tolerated oral regimen (PO), normal urinary output and reduced CRP level without any treatment side effects.

2.5. Adverse events

All undesirable effects (adverse events) experienced by patients during the study, whether or not related to methylprednisolone treatment, were defined and recorded.

2.6. Statistical analysis

In this study, all data were presented as the mean ± standard deviation for continuous variables. Categorical variables are presented as N (%). The Kolmogorov–Smirnov normality test was performed on all data. Repeated measures ANOVA was used for comparison of the trends over time between both groups in each studied variable. Moreover, Student's t-test (parametric) or the Mann Whitney test (non-parametric) was used to test for statistical differences (two-tailed) between two independent groups. Also paired t-test (parametric) or the Wilcoxon signed-rank test (non-parametric) was used to test for statistical differences between two-time points in each of intervention groups. Two-sided Chi square/Fisher’s exact tests were used to assess the associations between intervention groups and the categorical variables. Kaplan–Meier survival curve analysis and the log rank test was used to analyze time-to-death between both intervention groups. After analyzing the baseline data, using the intention-to-treat (ITT) test, the multiple imputations were conducted by an expectation–
maximization (EM) algorithm for making an unbiased comparison between intervention groups in handling missing data. The false discovery rate was corrected using the Benjamini-Hochberg correction method for multiple comparisons. All statistical analysis was analyzed using STATA software (Versions 11.2). Statistical significance was considered at p<0.05.

3. Results

3.1. Patients

This study is conducted from April 20, 2020, until Jun 20, 2020. Of the 68 patients who underwent randomization, 34 patients were assigned to receive standard care and methylprednisolone, and 34 patients to standard care alone. In the standard care group, six patients received corticosteroids by the attending physician during treatment and excluded from the intention-to-treat (ITT) analysis. Based on the analysis per protocol, the results for the outcomes does not significantly different from the results of ITT. The randomization, enrollment, and treatment assignment are described in Figure 2. The mean age of patients was 58.5 ± 16.6 years old (23 (37.1%) women and 39 (62.9%) men). 22 patients (35.5%) had respiratory rate (RR)>24 breaths/minute and 13 patients (21.0%) had heart rate (HR)>100 beats/min. Patients coexisting conditions, demographic and clinical characteristics in each group have been shown in Table 1. RR and HR levels were significantly higher in the intervention group. Except for diabetic comorbidity, which was significantly higher in the standard care group, there were no major between-group differences in demographic and clinical characteristics at enrollment. The median interval time between disease symptom onset and hospitalization was 6.8 ± 2.97 days. The average blood oxygen saturation level and BORG score of patients were 82.7% ± 5.3 and 7.4 ± 2.14 respectively at baseline. The majority of patients had 30-50% (24 (38.7%)) and 50-70% (19 (30.6%)) pulmonary involvements respectively and all patients were receiving oxygen support. Table 2 shows patients’ status and pulmonary involvement level at baseline of the patients in each group.
Except for the difference in pulmonary involvement zone, there were no between-group differences in patients’ status and pulmonary involvement at enrollment.

3.2. Primary outcome

Patients assigned to the methylprednisolone group significantly have a reduced time to event (discharge, or death) compared to patients assigned to the standard care group (median, 11.62 ± 4.81 days vs 17.61 ± 9.84 days; P=0.006). Besides, time to improvement time was significantly lower in the methylprednisolone group, (median, 11.84 ± 4.88 days vs 16.44 ± 6.93 days; P=0.003) in comparison to the standard care group and methylprednisolone treatment was related to the shorter time to event in patients (Table 3). The percentage of improved patients was higher in the methylprednisolone group than in the standard care group (32 (94.1%) vs 16 (57.1%); P =0.001) and the mortality rate was significantly lower in the methylprednisolone group (2 (5.9%) vs 12 (42.9%); P <0.001).

Using Kaplan–Meier estimator of time to death (day), we demonstrated that the patients in methylprednisolone intervention group had a significantly increased survival time compared with the patients in standard care intervention [Log rank test: P<0.001; Hazard ratio: 0.293; 95% CI: 0.154-0.556] (Figure 3).

The incidence of death was significantly lower in patients receiving NIV, reserve mask and nasal cannula in the methylprednisolone group (7.7%, 8.3%, and 0% respectively) compared to standard care group (60%, 57.1%, and 22% respectively) (Supplementary Figure 1). The CT scan findings from all of the dead patients in the methylprednisolone group (N=2) and 75% of patients in the standard care group (N=9) showed bilateral GGO at enrollment.

3.3. Secondary outcome

Blood SO2 level and the BORG score of patients was significantly improved after 3 days of treatment and at discharge time in the methylprednisolone group. While blood oxygen saturation level was significantly decreased in the standard care group after 3 days of
treatment and the increase of SO2 at discharge time was not significant in this group. Besides, the BORG score of patients did not change after 3 days of treatment in the standard care group and a significant decrease was only observed at discharge time in this group (Table 4).

Heart rate and temperature of patients were significantly decreased after 3 days of treatment and at discharge time only in the methylprednisolone group. Respiratory rate was also significantly reduced in the methylprednisolone group after treatment, while it is significantly increased in the standard care group after 3 days of treatment. The clinical characteristics of patients including GI Symptom, myalgia, chest pain, and cough were significantly improved in the methylprednisolone group after 3 days of treatment, and at discharge time, however, chest pain, and cough did not change significantly in the standard care group after treatment. Clinical characteristics of patients before and after treatment are shown in Table 4.

6 of 34 patients, by 3 days of treatment, and 26 of 32 patients at discharge time did not need oxygen support in the methylprednisolone group. Whereas, in the standard care group, 2 of 28 patients by 3 days of treatment and 10 of 16 patients at discharge time did not need oxygen support (Table 4). 19 of 34 patients (55.8%) showed an improvement, and 3 of 34 patients (8.8%) showed worsening in the oxygen-support status by 3 days of treatment, in the methylprednisolone group, whereas 6 of 28 patients (21.4%) showed improvement and 14 of 28 patients (50%) showed worsening in the standard care group (Supplementary Figure 1). The patient's regarding their oxygen supports before and after treatment and the status main outcome of each group have been shown in the Supplementary Figure 1.

To assess the percent of pulmonary involvement of patients in the methylprednisolone group, CT scan was performed at discharge time on 11 of 31 discharged patients who agreed to give informed consent. The results showed that in 8 of 11 patients, pulmonary involvements were improved 20-30%, and in 3 of 11 patients, pulmonary involvements were improved 50-60%
after treatment (Supplementary Figure 2). The CT scan findings and improvement in pulmonary involvements after treatment in a patient of methylprednisolone group have been shown in Supplementary Figure 3.

3.4. Laboratory findings

White blood cells (WBCs) count was significantly increased after 3 days of treatment and at discharge time in the methylprednisolone group. While WBC count was not changed in the standard care group by 3 days of treatment and was only significantly increased at discharge time. Hemoglobin and lymphocytes count was significantly decreased in the methylprednisolone group after 3 days of treatment and were restored at discharge time. We did not find a significant change in hemoglobin and lymphocyte count in the standard care group before and after treatment. While the platelet count remains unchanged during treatment in the standard care group, it was significantly increased in the methylprednisolone group after treatment. VBG PH, HCO3, and PCO2 levels remain unchanged until discharge time in patients of the methylprednisolone group. Although, VBG HCO3 and PCO2 levels were increased in patients of standard care group after treatment. The decrease in CRP and IL-6 levels was only shown in the methylprednisolone group after treatment. D-Dimer, Ferritin, LDH, and CPK levels did not show any significant changes before and after treatment in neither group of patients (Table 5).

3.5. Safety and follow up

A total of two patients (5.8%) in the methylprednisolone group and two patients (7.1%) in the standard care group showed severe adverse events between initiation of treatment and the end of the study. There were one infection and one edema adverse event in the methylprednisolone group and two shock adverse events in the standard care group (Supplementary Table 1). All events and deaths during the study were judged by the site investigators to be unrelated to the intervention. In addition, no psychiatric or delirium events
have been detected in patients. Following the use of high dose of corticosteroids, most of the patients required insulin due to their known or hidden diabetes, and the insulin requirement was increased in the intervention group especially in diabetic and overweight patients. However, the insulin requirement level was controlled by physicians and returned to the normal level at discharge time and there were not any adverse events according to uncontrolled diabetes in patients. The BORG score and clinical characteristics of the recovered patients (n=48) were assessed one week after discharge time. The BORG score was significantly diminished one week after discharge time in both groups). None of the patients in the methylprednisolone group has GI symptoms, myalgia, and chest pain after discharge. Two patients in the standard care group still had GI symptoms and myalgia after discharge. 6 of 32 patients (18.8%) in the methylprednisolone and 3 of 16 patients (18.8%) in the standard care group still had cough one week after discharge (Supplementary Table 2).

4. Discussion

The current study is the first randomized controlled trial that has evaluated changes in clinical symptoms and laboratory signs of COVID-19 patients by methylprednisolone therapy and found that methylprednisolone pulse administration at the beginning of the early pulmonary phase of illness decreased remarkably the mortality rate and improved pulmonary involvement, oxygen saturation, and inflammatory markers in COVID-19 patients. Given the increased incidence and mortality of COVID-19 across the world, the helpful and effective treatment for patients in the early pulmonary phase is still of paramount importance. There have been some reports, surrounding beneficial [1] or harmful evidence [2, 3] of corticosteroid therapy during previous SARS and MERS outbreaks, but the reports are not conclusive [4]. However, the clinical evidence for the efficacy of receiving corticosteroid in COVID-19 patients and the time for administration is undetermined.
In the current study, a severely ill population of COVID-19 patients in the early pulmonary phase (not intubated) was enrolled. The mortality rate was observed to be significantly lower among patients treated with methylprednisolone than patients treated with standard care. 94.1% of patients in the methylprednisolone group have been recovered by the median duration of 11.8 days. However, only 57.1% of patients in the standard care group have been recovered by the median duration of 16.4 days. Methylprednisolone treatment was related to the shorter time to event in patients, and survival analysis showed the patients in the methylprednisolone intervention group had a significantly decreased death hazard rate compared with the patients in the standard care intervention.

In the clinical trial by the RECOVERY collaborative group, the effect of dexamethasone on the clinical symptoms of hospitalized COVID-19 patients was studied. A total of 2104 patients have received dexamethasone and 4321 received standard care. Their results showed that the incidence of death was significantly lower in patients receiving oxygen support and invasive mechanical ventilation. In our study, all patients received oxygen support and neither of them received mechanical ventilation, however, in line with the RECOVERY trial, the incidence of death was significantly lower in patients receiving NIV and reserve mask in the methylprednisolone group (7.7% and 8.3% respectively) compared to standard care group (60% and 57.1% respectively). Besides, some observational studies report recent clinical findings on the administration of corticosteroids in the treatment of COVID-19 [5]. Some studies did not find significant benefits of corticosteroid admission and reported that pulmonary involvements caused by the SARS-CoV-2 were not inhibited by corticosteroid treatment[6-8]. However, it was also reported that the administration of corticosteroid for patients with ARDS resulted in reduced risk of death [9]. The observed differences can be due to the difference in the amount and duration of treatment, small sample size, age of patients, and severity of the disease. The clinical and laboratory
characteristics and pulmonary involvements of patients were not fully determined and reported in those observational studies. It seems that the administration time and pulmonary phase of patients are key factors in the corticosteroid treatment efficacy.

In our study, patients in the methylprednisolone group had a faster improvement in SO2 level, BORG score, and dyspnea. Improvement and worsening in oxygen-support status were observed in 55.8% and 8.8% of patients in the methylprednisolone group by day 3 of treatment, respectively. While in the standard care group, only 21.4% of patients showed improvement in oxygen supports, and 50% showed worsening. Our results showed that patients in the methylprednisolone group are less likely to receive invasive ventilation. Only 8.8% of patients in the methylprednisolone group received invasive ventilation, however, in the standard care group, 32.1% of patients received mechanical ventilation after treatment. In line with our results, in a cohort study by Wang et al, it was demonstrated that patients with methylprednisolone treatment had a faster improvement of oxygen saturation, decrease in CRP, and IL_6 level and were less likely to receive invasive ventilation. However, they did not observe significant differences in the mortality rate between groups [10].

entilation in patients. VBG Our results also showed that corticosteroid therapy can improved v analysis showed an increase in HCO3 and PCO2 levels in the standard care group which can indicat e respiratory acidosis and decreased ventilation in patients [11]. While in the methylprednisolone group, VBG markers did not change significantly.

The clinical characteristics of patients, including HR, RR, and temperature were also significantly improved in the methylprednisolone group while they did not change or worsen in the standard care group during treatment. While GI symptoms and myalgia were improved in patients from both groups, chest pain and cough were only significantly improved in methylprednisolone group patients. Intravenous methylprednisolone administration increased blood pressure in patients which is due to hypertensive side effects of glucocorticoids [12].
It is demonstrated that elevated serum level of IL-6 and CRP as an inflammatory marker is associated with the severity of COVID-19 and can be used as a predicted factor to disease risk [13]. Patients included in this trial had an increased CRP and IL-6 serum level at enrollment. A significant decrease in the serum level of these inflammatory markers was shown only in the methylprednisolone group after treatment.

Previous studies reported that corticosteroid administration can increase the risk of post-treatment infection in the viral disease, however, in our study the incidence of nosocomial infections is very low in both methylprednisolone and standard care group. Improved patients were followed up for seven days after treatment, and clinical symptoms remain unchanged. We will continue to follow-up the patients and CT scans, spirometry, and pulse oximetry will perform six weeks after improvement to evaluate their long-term prognosis.

**Conclusion**

In this study, we assessed the intravenous methylprednisolone effect on the treatment of patients with severe COVID-19 patients. Clinical data showed that methylprednisolone administration at the beginning of the early pulmonary phase of illness improved remarkably pulmonary involvement, oxygen saturation, dyspnea, HR, RR, and temperature and inflammatory markers such as CRP and IL-6 serum level in patients, suggesting that methylprednisolone could be an efficient therapeutic agent for hospitalized severe COVID-19 patients at pulmonary phase. Unfortunately, we could not collect viral load data to assess the effects of methylprednisolone on the viral load changes between baseline and discharge time. Nevertheless, there are several limitations in this study, including the possible existed bias, single-blind design of the study, lack of follow-up to identify late adverse events, such as hip osteonecrosis, or tuberculosis re-activation, and limited sample size. Apparently, further studies need to be undertaken.
Ethics approval
This study was performed based on the Declaration of Helsinki guidelines and was approved by the ethics committee at the Tehran University of Medical Sciences (Approval ID: IR.TUMS.VCR.REC1399.54).

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Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Consent to participate
The written informed consent was signed by all patients before enrolling in the study.

Data availability statement
Data are available upon request.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
MED, MS, ZN, SRN, NJ, ME, BR, HK, TG, HE, SRR, SJMS, and NK: Acquisition of clinical data and patient’s diagnosis and treatment, interpretation of data, drafting the article, and final approval of the article.

MMA, and MRS: Acquisition of laboratory data, interpretation of data, drafting the article, and final approval of the article.

MA, AJ, SM, EF, MM and AR: The conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the article.
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## Tables

### Table 1: Demographic and clinical characteristics of the patients at baseline.

| Characteristic | Total (N=62) | Methylprednisolone (N=34) | Standard care (N=28) | P value |
|----------------|-------------|---------------------------|----------------------|---------|
| Age (years)    | 58.5 ± 16.60 | 55.8 ± 16.35              | 61.7 ± 16.62         | 0.193   |
| Male/female, No (%) | 39 (62.9%) / 23 (37.1%) | 24 (70.6%) / 10 (29.4%) | 15 (53.6%) / 13 (46.4%) | 0.205 |
| Diabetes       | 22 (35.5%)  | 8 (23.5%)                 | 14 (50.0%)           | 0.040   |
| Hypothyroidism | 4 (6.5%)    | 4 (11.8%)                 | 0 (0.0%)             | 0.118   |
| Cancer         | 3 (4.8%)    | 1 (2.9%)                  | 2 (7.1%)             | 0.590   |
| Respiratory disorder | 6 (9.7%)  | 3 (8.8%)                  | 3 (10.7%)            | 0.838   |
| Renal disorder | 7 (11.3%)   | 3 (8.8%)                  | 4 (14.3%)            | 0.532   |
| Cardiovascular disorder | 11 (17.7%) | 6 (17.6%)                 | 5 (17.9%)            | 0.966   |
| Hypertension   | 20 (32.3%)  | 10 (29.4%)                | 10 (35.7%)           | 0.666   |
| Coexisting conditions |
| Body temperature, °C | 37.3 ± 0.8 | 37.4 ± 0.94               | 37.2 ± 0.81          | 0.356   |
| Respiratory rate, breaths/min | 22.6 ± 4.64 | 23.7 ± 4.55 | 21.4 ± 4.52 | 0.048 |
| Respiratory rate >24 breaths/min, no (%) | 22 (35.5%) | 16 (47.1%) | 6 (21.4%) | 0.028 |
| Heart Rate, beats/min | 89.7 ± 14.8 | 93.9 ± 13.18 | 84.6 ± 15.26 | 0.010 |
| Heart Rate >100 beats/min, no (%) | 13 (21.0%) | 10 (29.4%) | 3 (10.7%) | 0.062 |
| Systolic blood pressure, mm Hg | 122.6 ± 14.9 | 121.4 ± 15.25 | 124.0 ± 14.65 | 0.563 |
| Diastolic blood pressure, mm Hg<100, no (%) | 0 | 0 | 0 | NA |
| Fever, no (%) | 32 (51.6%) | 17 (50.0%) | 15 (53.6%) | 0.891 |
| Dyspnea, no (%) | 39 (62.9%) | 23 (67.6%) | 16 (57.1%) | 0.310 |
| Gl Symptom, no (%) | 29 (46.8%) | 16 (47.05%) | 13 (46.4%) | 0.961 |
| Myalgia, no (%) | 32 (51.6%) | 17 (50%) | 15 (53.6%) | 0.779 |
| Headache, no (%) | 8 (12.9%) | 3 (8.8%) | 5 (17.9%) | 0.453 |
| Cough, no (%) | 38 (61.3%) | 23 (67.6%) | 15 (53.6%) | 0.498 |
| Weakness, no (%) | 17 (27.4%) | 9 (26.5%) | 8 (28.6%) | 0.921 |
| Lymphocyte count/MCL | 1169.0 ± 597.12 | 1167.7 ± 580.65 | 1170.7 ± 632.4 | 0.866 |
| WBC count (×1000/MCL) | 7.6 ± 3.92 | 7.7 ± 3.34 | 7.4 ± 4.62 | 0.866 |
| WBC count <4 ×1000/MCL, no (%) | 47 (75.8%) | 25 (73.5%) | 22 (78.6%) | 0.811 |
| Platelet count (×1000/MCL) | 219.9 ± 106.86 | 203.8 ± 69.75 | 241 ± 140.4 | 0.158 |
| Platelet count >150×1000/MCL, no (%) | 10 (16.1%) | 6 (17.6%) | 4 (14.3%) | 0.426 |
| Hemoglobin (gm/dl) | 13.7 ± 4.20 | 13 ± 1.67 | 14.7 ± 5.95 | 0.102 |
| PH             | 7.4 ± 0.04  | 7.42 ± 0.05               | 7.39 ± 0.03          | 0.046   |
| HCO3 (meq/L)  | 24.4 ± 5.59 | 25.5 ± 4.70               | 22.9 ± 6.4           | 0.096   |
| Characteristic                      | Total (N=62) | Methylprednisolone (N=34) | Standard care (N=28) | P value |
|-----------------------------------|--------------|---------------------------|---------------------|---------|
| Days from illness onset to hospitalization | 6.8 ± 2.97 | 6.7 ± 2.92 | 6.9 ± 3.09 | 0.814 |
| BORG score                        | 7.4 ± 2.14  | 7.7 ± 1.72 | 7.14 ± 2.58 | 0.182 |
| SO2 percent                       | 82.7% ± 5.3 | 82.0% ± 5.8 | 83.6% ± 4.7 | 0.267 |
| Need on oxygen therapy, no (%)    | 62 (100%)   | 34 (100%)  | 28 (100%)  | 0.460 |
| Nasal Cannula                     | 13 (21.0%)  | 4 (11.8%)  | 9 (32.1%)  | 0.194 |
| Simple Mask                       | 7 (11.3%)   | 5 (14.7%)  | 2 (7.1%)   |       |
| Reserve Mask                      | 18 (29.0%)  | 12 (35.3%) | 6 (21.4%)  |       |
| NIV                               | 23 (37.1%)  | 13 (38.2%) | 10 (35.7%) |       |
| Ground glass opacity, no (%)      | 53 (85.5%)  | 30 (88.2%) | 23 (82.1%) | 0.334 |
| Unilateral                        | 0            | 0           | 0          | NA     |
| Bilateral                         | 53 (100%)   | 30 (100%)  | 23 (100%)  | NA     |
| Consolidation positive, no (%)    | 43 (69.3%)  | 23 (67.6%) | 20 (71.4%) | 0.911 |
| Unilateral                        | 6 (14.0%)   | 3 (13.0%)  | 3 (15.0%)  | 0.977 |
| Bilateral                         | 37 (86.0%)  | 20 (87.0%) | 17 (85.0%) |       |
| Pulmonary involvement percent, no (%) | A (<10%)  | 0            | 0         | 0.050 |
|                                  | B (10-30%)  | 7 (11.3%)   | 1 (2.9%)  | 6 (21.4%) |
|                                  | C (30-50%)  | 24 (38.7%)  | 13 (38.2%)| 11 (39.3%) |
|                                  | D (50-70%)  | 19 (30.6%)  | 11 (32.4%)| 8 (28.6%) |
|                                  | E (>70%)    | 12 (19.4%)  | 9 (26.5%) | 3 (10.7%) |
| Pulmonary involvement zone, no (%) | All        | 28 (44.4%) | 20 (58.8%)| 8 (28.6%) |
|                                  | Upper       | 5 (8.1%)   | 3 (8.8%)  | 2 (7.1%) |
|                                  | Lower       | 23 (37.1%) | 10 (29.4%)| 13 (46.4%)|

GI, Gastrointestinal; °C, Centigrade; min, Minute; WBC, White blood cell; MCL, Microliter; gm/dl, Grams per deciliter; VBG, Venous blood gas; meq/L, Milliequivalent per liter; mm Hg, Millimeter of mercury; CRP, C-reactive protein; mg/L Milligrams per liter; ESR, erythrocyte sedimentation rate; mm/hr, Millimeters per hour; pg/ml, Pictogram per milliliter; ng/ml, Nanogram per milliliter; LDH, Lactic acid dehydrogenase; CPK, Creatine phosphokinase; U/L, Unit per liter; NA, Not available
Table 3. Primary outcomes in methylprednisolone and standard care group.

| Characteristic | Methylprednisolone (N=34) | Standard care (N=28) | P value |
|----------------|---------------------------|----------------------|---------|
| Time to event (discharge or death), day | 11.62 ± 4.81 | 17.61 ± 9.84 | 0.006 |
| Time to improvement, day | 11.84 ± 4.88 | 16.44 ± 6.93 | 0.011 |
| The outcome, no (%) | | | <0.001 |
| Recover | 32 (94.1%) | 16 (57.1%) | |
| Death | 2 (5.9%) | 12 (42.9%) | |

P value in the bold form is statistically significant (P value < 0.05)

Table 4. Clinical characteristics of patients before and after treatment by repeated measures ANOVA.

| Characteristic | Before treatment | After treatment (Day 3) | After treatment (Discharge or death) |
|----------------|-------------------|------------------------|-------------------------------------|
| Methylprednisolone | Standard care | Methylprednisolone | Standard care | Methylprednisolone | Standard care |
| BORG score | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| SO2 percent | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Systolic blood pressure, mm Hg | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Diastolic blood pressure, mm Hg | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Heart rate, beats/ min | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Respiratory rate, breaths/min | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Body temperature °C | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |

P value in the bold form is statistically significant (P value < 0.05)

SO2, Oxygen saturation; mm Hg, Millimeter of mercury; min, Minute; °C, Centigrade; GI, Gastrointestinal; NA, Not available
Table 5. Laboratory findings of patients before and after treatment by repeated measures ANOVA.

| Characteristic       | Before treatment | Standard care | Methylprednisolone | After treatment (Day 3) | After treatment (Discharge or death) |
|----------------------|------------------|---------------|--------------------|-------------------------|--------------------------------------|
|                      |                  |               |                    |                         |                                      |
|                      | Mean  | SD   | Mean  | SD | P value | Mean  | SD   | Mean  | SD | P value | Mean  | SD   | Mean  | SD | P value |
| WBC count (×1000/MCL) | 7.7    | 3.34 | 7.4   | 4.6 | 9.5     | 3.80  | 0.008 | 8.1   | 4.6 | 0.36   | 10.5  | 4.9  | 0.002 | 9.6 | 5.6  | 0.03  |
| Lymphocyte count (MCL) | 1167   | 580 | 1170 | 7   | 632   | 804   | <0.001 | 1212  | 689 | 0.95   | 1085  | 667  | 0.77  | 1315 | 813  | 0.72  |
| Hemoglobin (gm/dl)   | 13     | 1.67 | 14.7  | 5.95 | 2.06   | 15.0  | 0.007 | 7.8   | 0.79 | 0.59   | 12.6  | 1.7   | 10.7  | 1.8 | 0.13  |
| Platelet count (×1000/MCL) | 203.8 | 69.7 | 241  | 140 | 9.5     | 3.80  | 0.008 | 8.1   | 4.6 | 0.36   | 10.5  | 4.9  | 0.002 | 9.6 | 5.6  | 0.03  |
| VBG                  | 7.42   | 0.05 | 7.39  | 0.03 | 7.42   | 0.04 | 0.40  | 7.4   | 0.1 | 0.88   | 7.4   | 0.08 | 0.35  | 7.4 | 0.08 | 0.06  |
| PH                   | 25.5   | 4.70 | 22.9  | 6.4 | 26.4   | 4.64  | 0.73  | 27.4  | 1.64 | 0.011  | 27.4  | 8.9  | 0.48  | 31.3 | 4.4  | 0.001 |
| HCO3 (meq/L)         | 39.7   | 11.10 | 35.4  | 8.14 | 40.9   | 10.7  | 0.85  | 50.8  | 16.2 | 0.017  | 45.4  | 16.4 | 0.39  | NA  | NA  | NA    |
| PCO2 (mmHg)          | 76.3   | 85.2 | 79.3  | 60.9 | 15.9   | 22.9  | <0.001 | 32.5  | 6.5 | 0.160  | 3.93  | 9.1  | 0.001 | NA  | NA  | NA    |
| CRP (mg/L)           | 99.1   | 79.98 | 92.6  | 70.3 | 40.8   | 30.6  | <0.001 | 91.9  | 68.0 | 0.66   | 30.6  | 23.1 | 0.001 | 77  | 83.0 | 0.20  |
| ESR (mm/hr)          | 44.2   | 27.1 | 57.4  | 32.8 | 50.9   | 35.3  | 0.11  | 57.0  | 33.6 | 0.86   | 55.7  | 22.6 | 0.09  | 80  | 25.7 | 0.77  |
| IL-6 (pg/ml)         | 76.3   | 85.2 | 79.3  | 60.9 | 15.9   | 22.9  | <0.001 | 32.5  | 6.5 | 0.160  | 3.93  | 9.1  | 0.001 | NA  | NA  | NA    |
| D-Dimer (ng/mL)      | 2573   | 2668 | 1391 | 491 | 1751   | 2155  | 0.41  | 2131  | 2252 | 0.25   | 1762  | 830  | 0.16  | NA  | NA  | NA    |
| Ferritin (ng/mL)     | 807.9  | 521 | 676.5 | 463 | 766   | 400   | 0.17  | 777   | 467 | 0.62   | 275   | 303  | 0.18  | 476 | 219  | 0.28  |
| LDH (U/L)            | 672.1  | 285.5 | 644.9 | 179.3 | 897   | 558   | 0.74  | 706   | 453 | 0.91   | 633   | 153  | 0.49  | NA  | NA  | NA    |
| CPK (U/L)            | 158.9  | 151.7 | 213.7 | 209 | 249   | 154   | 0.78  | NA    | NA  | NA     | 85    | 203  | 0.81  | NA  | NA  | NA    |

SD, Standard deviation; WBC, White blood cell; MCL, Microliter; gm/dl, Grams per deciliter; VBG, Venous blood gas; meq/L, Milliequivalent per liter; mm Hg, Millimeter of mercury; CRP, C-reactive protein; mg/L, Milligrams per liter; ESR, erythrocyte sedimentation rate; mm/hr, Millimeters per hour; pg/ml, Pictogram per milliliter; ng/ml, Nanogram per milliliter; LDH, Lactic acid dehydrogenase; CPK, Creatine phosphokinase; U/L, Unit per liter; NA, Not available

*P value in the bold form is statistically significant (P value< 0.05)*
**Figure captions**

**Figure 1.** Appropriate time for methylprednisolone administration and inclusion/exclusion criteria of the patients. Patients in the intervention group received methylprednisolone pulse (intravenous injection, 250mg/day for 3 days) at the early pulmonary phase of the disease before connecting to the ventilator and intubation.

**Figure 2.** Randomization, enrollment, and treatment assignment.

**Figure 3.** Kaplan–Meier estimator of survival rate (%) between methylprednisolone and standard care interventions.
Incubation and symptomatic phase

Early pulmonary phase

Late pulmonary phase

Viral stage

Inflammation stage

Time

COVID-19 patients

- With symptoms
  - Hospitalized
  - Not hospitalized
- Without symptoms

Inclusion criteria:
- > 18 years old
- Blood oxygen saturation <90%
- CRP > 10 and IL-6 > 6
- Positive SARS-CoV-2 PCR

Exclusion criteria:
- Positive pro-calcitonin (PCT) and troponin test
- Acute Respiratory Distress Syndrome (ARDS)
- Blood oxygen saturation <75%
- Uncontrolled hypertension (HTN) and Diabetes mellitus (DM)
- Gastrointestinal problems, heart failure (HF), active malignancies

Methylprednisolone pulse administration (250mg/day for 3 days)
Enrollment

Assessed for eligibility (n=151)

Excluded (n=83)
- Not meeting inclusion criteria (n=45)
- Declined to participate (n=22)

Randomized (n=68)

Allocation

Assigned to the methylprednisolone group (n=34)
- Received allocated intervention (n=34)
- Did not receive allocated intervention (give reasons) (n=0)

Assigned to the standard care group (n=34)
- Received allocated intervention (n=34)
- Did not receive allocated intervention (give reasons) (n=0)

Follow-Up

Lost to follow-up (give reasons) (n=0)
Discontinued intervention (give reasons) (n=0)

Lost to follow-up (give reasons) (n=0)
Discontinued intervention (received corticosteroids) (n=6)

Analysis

34 included in analysis

28 included in analysis
Kaplan-Meier curves

P-value < 0.001; HR = 0.293, 95% CI = 0.154-0.556

Survival Rate

Time to Death (Day)

- Intervention = Standard care
- Intervention = Methylprednisolone
### Supplementary Figure 1.
The patient's status regarding their oxygen supports before and after treatment and the main outcome of each group. For each oxygen-support category (invasive ventilation, noninvasive ventilation (NIV), reserve mask, simple mask, and nasal cannula), percentages were calculated with the number of patients at baseline and after 3 days of treatment in both groups. Improvement (green cells), no change (blue), and worsening (orange) in oxygen-support status are shown.

| Number of patients in oxygen support group after 3 days of treatment (%) | Methylprednisolone group | Standard care group |
|---|---|---|
| | NIV (13) | Reserve Mask (12) | Simple Mask (5) | Nasal Cannula (4) | Negative (0) | NIV (10) | Reserve Mask (7) | Simple Mask (2) | Nasal Cannula (9) | Negative (0) |
| Invasive Ventilation | 2 (23.1%) | 0 | 0 | 0 | 0 | 5 (50.0%) | 3 (42.8%) | 0 | 1 (11.1%) | 0 |
| NIV | 1 (23.1%) | 0 | 0 | 0 | 0 | 3 (30.0%) | 1 (14.3%) | 1 | 1 (11.1%) | 0 |
| Reserve Mask | 5 (38.5%) | 5 (41.7%) | 0 | 0 | 0 | 1 (10.0%) | 0 | 0 | 2 (22.2%) | 0 |
| Simple Mask | 1 (7.7%) | 1 (8.3%) | 1 (20.0%) | 0 | 0 | 0 | 0 | 1 (50.0%) | 0 | 0 |
| Nasal Cannula | 2 (15.4%) | 1 (8.3%) | 2 (40.0%) | 2 (50.0%) | 0 | 2 (22.2%) | 0 | 4 (44.4%) | 0 |
| negative | 0 | 1 (8.3%) | 2 (40.0%) | 2 (50.0%) | 0 | 0 | 0 | 1 (11.1%) | 0 |
| Outcome | Discharged | 12 (84.6%) | 11 (91.7%) | 5 (100%) | 4 (100%) | 0 | 4 (40.0%) | 3 (100%) | 2 (77.7%) | 0 |
| Death | 1 (7.7%) | 1 (8.3%) | 0 | 0 | 0 | 6 (60.0%) | 4 (57.1%) | 0 | 2 (22.2%) | 0 |
### Supplementary Figure 2

Number of patients in different pulmonary involvement groups before and after treatment in the methylprednisolone group. For each pulmonary involvement category (A-E), the number of patients at baseline and at discharge time in the methylprednisolone group has been shown. Improvement (green cells), no change (blue), and worsening (orange) in pulmonary involvements status are shown.

| Number of patients in pulmonary involvements group at discharge time | E (>70%) | D (50-70%) | C (30-50%) | B (10-30%) | A (<10%) |
|-------------------------------------------------------------------|----------|------------|------------|------------|----------|
| E (>70%)                                                          | 0        | 0          | 0          | 0          | 0        |
| D (50-70%)                                                        | 0        | 0          | 0          | 0          | 0        |
| C (30-50%)                                                        | 3        | 3          | 0          | 0          | 0        |
| B (10-30%)                                                        | 0        | 0          | 4          | 0          | 0        |
| A (<10%)                                                          | 0        | 0          | 0          | 1          | 0        |
Supplementary Figure 3. Improved pulmonary involvement in a chest computed tomography (CT) of a 55 years old, confirmed COVID-19 patient from methylprednisolone group after 21 days of treatment (at discharge time).
Supplementary Table 1. Summary of adverse events in patients.

| Characteristic                | Methylprednisolone (N=34) | Standard care (N=28) | P value |
|-------------------------------|---------------------------|----------------------|---------|
| Infection, no (%)             | 1 (2.9%)                  | 0                    | 0.548   |
| Edema, no (%)                 | 1 (2.9%)                  | 0                    | 0.548   |
| Shock, no (%)                 | 0                         | 2 (7.1%)             | 0.208   |
| Digestive bleeding, no (%)    | 0                         | 0                    | NA      |
| Others                        | 0                         | 0                    | NA      |

NA: Not applicable
### Supplementary Table 2. Clinical characteristics of the recovered patients one week after discharge (Methylprednisolone n=32, Standard care n=16).

| Characteristic | Before treatment | One week after discharge |
|---------------|-----------------|--------------------------|
|               | Methylprednisolone | Standard care | Methylprednisolone | Standard care | P value | Methylprednisolone | Standard care | P value |
| BORG score    | Mean 7.6, SD 1.7 | Mean 6.43, SD 2.6 | Mean 0.75, SD 0.62 | 0 < 0.001 | Mean 1, SD 0.63 | 0.001 |
| GI Symptom    | no 16, % 50 | no 43.8 | no 0 | 0 < 0.016 | no 1, % 6.3 | 0.50 |
| Myalgia       | Mean 17, SD 53.1 | Mean 7, SD 43.8 | Mean 0, SD 0 | 0.043 | Mean 1, SD 6.3 | 0.50 |
| Chest pain    | Mean 7, SD 22 | Mean 3, SD 18.8 | Mean 0, SD 0 | 0.125 | Mean 0, SD 0 | 0.69 |
| Cough         | Mean 22, SD 68.8 | Mean 9, SD 56.3 | Mean 6, SD 18.8 | 0.250 | Mean 3, SD 18.8 | 0.55 |

*P value in the bold form is statistically significant (P value < 0.05)*

SD, Standard deviation; GI, Gastrointestinal;