JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

*Coronavirus Pandemic*

# Corticosteroid effectiveness among hospitalised COVID-19 patients in Malaysia

Najma Kori[1], Farida Islahudin[2], Muhammad Yusuf Zawir Abd Rahim[1], Petrick Periyasamy[1], Noraida Mohamed Shah[2], Ernieda Md Hatah[2], Lau Chee Lan[3]

*[1] Department of Medicine, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*
*[2] Quality Management of Medicines, Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*
*[3] Department of Pharmacy, Hospital Canselor Tuanku Muhriz, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia*

## Abstract

Introduction: Using steroids to manage hospitalised coronavirus disease 2019 (COVID-19) patients caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection has been shown to reduce the need for mechanical ventilation and mortality. To date, low-dose dexamethasone and methylprednisolone corticosteroids have been effective in reducing the infection's progress in hospitalised patients. However, it is unknown if high dosages of corticosteroids can achieve a better clinical outcome. This study aims to compare the clinical outcomes of hospitalised COVID-19 patients who are given a 10-day low-dose corticosteroid treatment (IV 2 mg/kg/day methylprednisolone loading dose (LD) then 0.25 mg/kg four times a day (q.i.d.)) with patients given a 10-day high-dose corticosteroid treatment (IV 20 mg dexamethasone once daily (o.d.) or a 1.5 mg/kg prednisolone tablet o.d.).

Methodology: Retrospective data on hospitalised COVID-19 patients were collected for this study, and the primary outcome measure was the patients' clinical status based on the World Health Organization's (WHO) Ordinal Scale for Clinical Improvement (OSCI) on Day-5 and Day-10 post-steroid.

Results: The results demonstrated that using steroids significantly improved patients' clinical outcomes from a WHO OSCI level of 4 (0.1) on Day-1 to 2.6 (2.5) on Day-5 ($p < 0.001$). There was no significant difference in clinical outcome between low-dose and high-dose corticosteroid treatment on Day-5 ($H = 2.15$; $p = 0.34$) and Day-10 ($H = 1.12$; $p = 0.58$).

Conclusions: This study concludes that using low-dose corticosteroids is recommended for hospitalised COVID-19 patients to ensure clinical outcomes are optimised.

**Key words:** Coronavirus; COVID-19; corticosteroids; outcome.

*J Infect Dev Ctries* 2022; 16(9):1390-1397. doi:10.3855/jidc.16039

(Received 09 November 2021 – Accepted 02 July 2022)



## Introduction

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, was first declared a pandemic by the World Health Organization (WHO) in March 2020 [1]. Since then, the pandemic has threatened millions globally by escalating rapidly around the world [1]. The virus primarily affects the respiratory system, causing symptoms of COVID-19 that are extremely heterogeneous, ranging from moderate symptoms such as fever, aches, sore throat, diarrhea, and the loss of taste or smell, to significant hypoxia and acute respiratory distress syndrome (ARDS) [1,2]. The SARS-CoV-2 virus binds to host cells through the ACE2 receptor that stimulates the host immune system. This leads to the release of cytokines and subsequent inflammation and immune dysfunction through activation or impairment of various immune cells, such as dendritic cells, macrophages, and neutrophils [2,3]. As a result, complications in patients with severe COVID-19 are observed, leading to oxygen saturation that usually falls below 94% with evidence of lung infiltrates, while critically ill patients experience respiratory failure, which can require mechanical ventilation. The results can be septic shock and, in some cases, multiorgan failure [3]. Patients admitted with severe and critical COVID-19 are often prescribed corticosteroids as a treatment modality, due to the overall cytokine dysregulation as the primary pathogenesis of organ dysfunction and disease

progression [4,5]. Given the benefits of the anti-inflammatory corticosteroids, the WHO Guideline Development Group has strongly recommended using systemic corticosteroid therapy for 7 to 10 days in patients with severe and critical COVID-19 [3,6], which has led to its inclusion in local-hospital guidelines [7].

Corticosteroids have been used to treat severe and critical COVID-19 patients due to their immune-suppression effects on other viral infections, such as severe acute respiratory syndrome (SARS) [8]. Corticosteroids inhibit inflammation by binding to intracellular glucocorticoid receptors, inhibiting pro-inflammatory cell proteins via cytoplasmic signaling pathways and mitochondrial translocation through regulation of gene expression, as well as impairment of non-genomic inflammatory cellular activity [9-11]. Although its immune suppressive activity may also worsen the intensity of viral propagation, patients managed with long-term corticosteroids have shown positive outcomes [4-9]. The anti-inflammatory properties of corticosteroids lead to improved hypoxia and minimize the risk of respiratory failure by reducing systemic inflammation and exudative fluid in the lung tissue; these properties can also prevent further alveolar damage [9-10]. Systemic corticosteroids have long been used among critically ill patients with ARDS in view of their role in lowering circulating levels of proinflammatory mediators [8] and reducing mortality in patients [9,10]. The suggested benefit of corticosteroids can lead to their use in severe and critically ill patients in intensive-care units (ICUs) [6,11]. However, the recommended doses of corticosteroids for severe COVID-19 patients to reduce ICU referrals or prevent the use of mechanical ventilation remains unclear.

Low doses of corticosteroids such as dexamethasone and methylprednisolone are often used for severe and critical COVID-19 patients [12]. Among critical patients, low-dose dexamethasone was reported to significantly reduce deaths – by one-third in ventilated patients and one-fifth in other patients receiving only oxygen [10]. However, when comparing the effect of the two corticosteroids in severe COVID-19 cases, it was reported that methylprednisolone demonstrated better results than dexamethasone [12]. Patients who received 2 mg/kg/day methylprednisolone demonstrated a significantly better clinical status based on the 9-point WHO ordinal scale compared to those who received 6 mg/day dexamethasone on Day-5 and Day-10 after admission [12]. The mean length of hospital stay was also significantly shorter in the methylprednisolone group and compared to the dexamethasone group [12]. In contrast, a study among patients with moderate to severe COVID-19 demonstrated no clear difference between 1 mg/kg/day methylprednisolone and 8 mg/day dexamethasone when both were administered for five days [13]. Another common corticosteroid used in viral infections is prednisolone [5], although there is limited information on using low-dose prednisolone in COVID-19 patients. One case study that reported the use of low-dose prednisolone treatment in moderate COVID-19 patients demonstrated that the signs and symptoms of respiratory failure resolved after 72 hours, and none of the patients reported receiving non-invasive or invasive respiratory support [14]. Giving a tapered dose of low-dose prednisolone after using hydrocortisone or methylprednisolone in SARS patients was also observed to be beneficial in a few study populations, as it improved both chest X-rays and oxygenation [15,16]. However, further work is required to determine the effectiveness of prednisolone in reducing the progress of COVID-19 in patients with severe infections, especially when compared with methylprednisolone and dexamethasone treatments [17].

The use of high-dose corticosteroids among COVID-19 patients has also seen conflicting results. Among the hospitalized COVID-19 patients needing oxygen therapy, high-dose dexamethasone (20 mg daily for five days, followed by 10 mg daily for five days) reduced clinical worsening compared to low-dose dexamethasone (6 mg daily for 10 days) [18]. Early administration of higher doses of corticosteroids (methylprednisolone > 1 mg/kg/day or dexamethasone > 0.12 mg/kg/day or prednisone > 0.5 mg/kg/day) has also been associated with better outcomes among moderate or severe COVID-19 pneumonia [19]. However, in a retrospective study comparing high-dose methylprednisolone with low-dose dexamethasone, high-dose methylprednisolone was found to be less effective in preventing ICU admission among non-critical and severe COVID-19 patients [20].

It is still unclear if using corticosteroids to prevent disease progression leads to the need for mechanical ventilation or referral to the ICU among COVID-19 patients. At present, studies that demonstrate the benefits of using low-dose compared to high-dose corticosteroids are limited. Recently, the WHO and local guidelines have recommended using steroids for the first 10 days to prevent disease progression [7]. However, in practice, clinicians are very often left to

decide whether to use low or high doses of corticosteroids to reduce the progression of COVID-19 in severely ill patients. Therefore, identifying the effectiveness of low-dose methylprednisolone or high-dose dexamethasone and prednisolone in clinical improvement, reducing the length of admission, mechanical ventilation, and reducing C-reactive protein (CRP) levels will allow practitioners to streamline their choice of corticosteroids when managing COVID-19 patients. These findings will help clinical practitioners make informed decisions that will allow optimal clinical outcomes and reduce adverse events, complications, and hospital costs. Therefore, this study aims to determine the clinical outcome of 10-day low-dose corticosteroid treatment (IV 2 mg/kg/day methylprednisolone LD then 0.25 mg/kg given q.i.d.) versus 10-day high-dose corticosteroid treatment (IV 20 mg dexamethasone o.d. or a 1.5 mg/kg prednisolone tablet o.d.) in hospitalised patients with severe COVID-19 in a tertiary teaching hospital in Malaysia.

## Methodology

*Study design*

This research was conducted as a retrospective study based on the corticosteroid management of COVID-19 patients in Hospital Canselor Tuanku Muhriz (HCTM), a tertiary teaching hospital in Malaysia (Figure 1). Adult patients admitted to the hospital between July and August 2021, who were diagnosed using a confirmatory test performed with a nasopharyngeal swab using a COVID-19 molecular assay to detect SARS-CoV-2 RNA, were screened. Patients included in the study were those that had been admitted to the ward for at least one day and were at clinical-stage category 4 (severe COVID-19) on nasal-prong oxygen [3]; receiving either a low-dose corticosteroid (IV 2 mg/kg/day methylprednisolone LD then 0.25 mg/kg q.i.d.) or high-dose corticosteroid (IV 20 mg dexamethasone o.d. or a 1.5 mg/kg prednisolone tablet o.d.). Patients excluded from the study were those who were admitted to the ICU from the acute and emergency-care unit, had incomplete medical and medication records had been transferred to another hospital, or had received oxygen via a venturi mask, high-flow mask, or mechanical ventilation on admission.

*Study outcome*

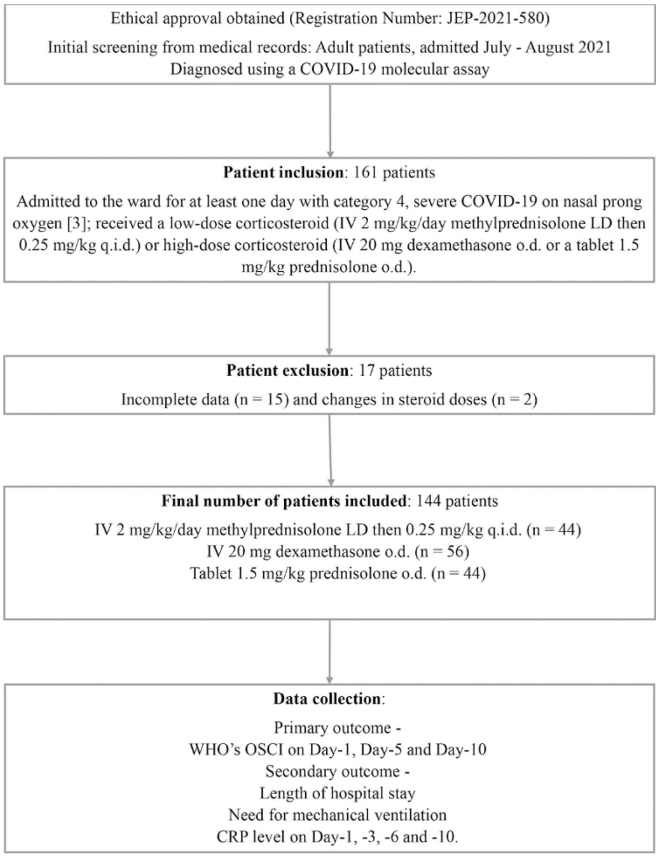
The primary outcome measure was the patient's clinical status on Day-5 and Day-10 post-steroid, which was determined using the WHO Ordinal Scale for Clinical Improvement (OSCI) 9-point scale, ranging from 0 as no clinical or virological evidence of infection to 8, which was assigned as death [21]. A baseline OSCI was also determined for each patient (on Day-1) before steroid treatment. Using the WHO's OSCI enables agreement and consistency in the recording of individual outcomes across studies and trials, facilitating the interpretation of results.

Secondary outcome measures were the length of hospital stay before transfer, referral to the ICU for a high-flow nasal cannula (HFNC) or mechanical ventilation, whether discharged home, the number of patients on mechanical ventilation, and the patient's CRP level on Day-1, -3, -6 and -10.

*Sample size*

Sample size estimation was calculated using ClinCalc.com software. Using values from previous work with an effect size of 0.69 [12], a minimum sample size of 33 patients for each arm was needed with a probability (power) of 0.80. The Type I error probability associated with testing this null hypothesis was 0.05. With an additional 20% dropout rate, the total sample size for each arm was 40 patients.

**Figure 1.** Workflow of the retrospective study.



*Sampling method*

Data were collected retrospectively using the medical records of COVID-19 patients admitted to the hospital from July to August 2021. Patients' data were collected for 10 days or until discharged, for stays of less than 10 days. The date of discharge and number of hospitalised days were also calculated if patients were admitted for longer than 10 days. The reasons for discharge included a referral to the ICU for mechanical ventilation, patient demise, or patient discharged well.

Data were extracted from the patient's medical records using a standardised data collection form that included patients' demographic data, such as age, gender, ethnicity, weight, smoking history and vaccination status. Clinical data included comorbidities, oxygen saturation ($SpO_2$) levels, baseline absolute lymphocyte count (ALC), neutrophil/lymphocyte ratio (NLR), D-dimer, duration to wean off oxygen, duration of symptoms, CRP levels, the WHO's OSCI levels and corticosteroid treatment

**Table 1.** Demographic and clinical characteristics of the study population (N = 144).

| Characteristics | IV methyl-prednisolone 2 mg/kg STAT & 0.25 mg q.i.d. (n = 44) | IV dexamethasone 20 mg STAT & o.d. (n = 56) | Tablet prednisolone 1.5 mg/kg STAT & o.d. (n = 44) | Total (N = 144) | *p* value[c] |
|---|---|---|---|---|---|
| **Age, mean (SD)** | 60.7 (14.6) | 57.3 (17.5) | 52.4(14.5) | 56.8 (15.9) | F (3.05); $p = 0.06$ |
| **Gender, n (%)** | | | | | $\chi^2$ (2.6); $p = 0.27$ |
| Female | 20 (45.5) | 28 (50) | 15 (34.1) | 63 (43.7) | |
| Male | 24 (54.6) | 28 (50) | 29 (65.9) | 81 (56.3) | |
| **Ethnicity, n (%)** | | | | | $\chi^2$ (7.8); $p = 0.25$ |
| Malay | 17 (38.6) | 21 (37.5) | 25 (56.8) | 63 (43.8) | |
| Chinese | 21 (47.7) | 24 (42.9) | 12 (27.3) | 57 (39.6) | |
| Indian | 3 (6.8) | 6 (10.7) | 6 (13.6) | 15 (10.4) | |
| Others[a] | 3 (6.8) | 5 (8.9) | 1 (2.3) | 9 (6.3) | |
| **Weight (kg), mean (SD)** | 68.9 (18.1) | 68.6 (14.5) | 73.2 (14.4) | 70.1 (15.7) | F (1.24); $p = 0.29$ |
| **Smoking history, n (%)** | | | | | $\chi^2$ (8.3); $p = 0.08$ |
| Ex-smoker | 5 (11.4) | 7 (12.5) | 5 (11.4) | 17 (11.8) | |
| Non-smoker | 35 (79.6) | 44 (78.6) | 27 (61.4) | 106 (73.6) | |
| Smoker | 4 (9.1) | 5 (8.9) | 12 (27.3) | 21 (14.6) | |
| **Vaccination status[b], n (%)** | | | | | $\chi^2$ (6.1); $p = 0.19$ |
| Not vaccinated | 13 (29.6) | 12 (21.4) | 16 (36.4) | 92 (63.9) | |
| 1 dose | 4 (9.1) | 2 (3.6) | 5 (11.4) | 41 (28.5) | |
| 2 doses | 27 (61.4) | 42 (75.0) | 23 (52.3) | 11 (7.6) | |
| **Immune modulators, n (%)** | | | | | $\chi^2$ (0.9 ); $p = 0.62$ |
| Tocilizumab | 0 (0) | 0 (0) | 1 (2.3) | 1 (0.7) | |
| Baricitinib | 1 (2.3) | 0 (0) | 1 (2.3) | 2 (1.4) | |
| Comorbidities, mean (SD) | 1.9 (1.2) | 4 (17.2) | 1.6 (1.5) | 2.6 (10.8) | H (1.4): $p = 0.57$ |
| **SpO2, mean (SD)** | | | | | |
| Day 1 | 97.6 (1.4) | 97.3 (1.4) | 97.4 (1.5) | 97.4 (1.43) | H (1.3); $p = 0.53$ |
| Day 3 | 96.4 (2.2) | 96.6 (2.2) | 96.6 (1.6) | 96.5 (2.0) | H (0.2); $p = 0.9$ |
| Day 6 | 95.4 (6.4) | 96.0 (3.4) | 96.3 (1.9) | 95.9 (4.3) | H (0.3); $p = 0.87$ |
| Day 10 | 97.4 (1.6) | 97.1 (1.5) | 96.8 (1.7) | 97.1 (1.6) | H (3.5); $p = 0.18$ |
| Day 1 ALC, mean (SD) | 1.3 (0.6) | 1.2 (0.5) | 1.3 (0.7) | 1.3 (0.6) | H (0.26); $p = 0.88$ |
| Day 1 NLR, mean (SD) | 5.9 (4.7) | 5.9 (4.7) | 4.5 (3.3) | 5.5 (4.4) | H (3.5); $p = 0.18$ |
| Day 1 D-Dimer, mean (SD) | 1.3 (1.7) | 1.0 (0.8) | 1.4 (1.4) | 1.2 (1.3) | H (0.96); $p = 0.61$ |
| Days of illness (from symptoms), mean (SD) | 12.4 (3.1) | 12.8 (3.6) | 11.7 (2.6) | 12.4 (3.2) | H (0.41); $p = 0.82$ |
| Corticosteroids adverse effect, n (%) | 0 (0) | 1 (1.8) | 0 (0) | 1 (0.7) | $\chi^2$ (0.28); $p = 0.87$ |
| Days to wean off oxygenation, mean (SD) | 6.3 (3.5) | 5.1 (3.6) | 5.9 (4.1) | 5.7 (3.8) | H (4.38); $p = 0.11$ |
| **Reason for discharge, n (%)** | | | | | $\chi^2$ (5.2); $p = 0.23$ |
| Discharged well | 32 (72.7) | 44 (78.6) | 33 (75) | 109 (75.7) | |
| Patient demise | 6 (13.6) | 10 (17.9) | 3 (6.8) | 19 (13.2) | |
| Referred to ICU | 6 (13.6) | 2 (3.6) | 8 (18.2) | 16 (11.1) | |

[a] Bangladesh (n = 1); Phillipines (n = 1); Indonesian (n = 4); Myanmar (n = 1); Pakistan (n = 1); Unknown (n = 1); [b] Astra Zeneca (n = 8); Pfizer (n = 4); Sinovac (n = 40); [c] F = ANOVA test; H = Kruskal-wallis; $\chi^2$ = Chi squared test.

**Table 2.** WHO OSCI levels on Day-1, Day-5 and Day-10 of the study population (N = 144).

| WHO OSCI, mean (SD) | Day-1 | Day-5 | Day-10 | *p* value[a] |
|---|---|---|---|---|
| IV methylprednisolone 2 mg/kg STAT then 0.25 mg q.i.d. (n = 44) | 4 (0) | 3.8 (1.6) | 2.9 (2.6) | $\chi^2$ (12.9); < 0.001 |
| IV dexamethasone 20 mg STAT & o.d. (n = 56) | 4 (0) | 3.5 (1.3) | 2.6 (2.6) | $\chi^2$ (61.6); < 0.001 |
| Tablet prednisolone 1.5 mg/kg STAT & o.d. (n = 44) | 4 (0.2) | 3.5 (1.6) | 2.4 (2.3) | $\chi^2$ (19.2); < 0.001 |
| Total (N = 144) | 4 (0.1) | 3.6 (1.5) | 2.6 (2.5) | $\chi^2$ (61.6); < 0.001 |

[a] $\chi^2$ = Friedman chi-squared test, between 3 dependent groups Day-1, Day-5, Day-10.

provided (name of medication, dose and duration of the treatment).

*Ethics approval*

The study was approved by the institutional research ethics committee and was performed following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Ethical approval was obtained from the Medical Research Ethics Committee, University Kebangsaan Malaysia (Registration Number: JEP-2021-580).

*Data analysis*

The obtained data were analysed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, N.Y., USA). Descriptive data were described using frequency and percentage for categorical data; mean and standard deviation (SD) were used for continuous data. The treatment outcomes of patients with corticosteroids were compared using ANOVA and its non-parametric equivalent when data were non-normally distributed or a Chi-squared test for categorical data. The statistical significance was set at $p < 0.05$.

## Results

*Demographic characteristics of the study population*

The study period identified 161 suitable patients. However, 17 patients were excluded due to incomplete data (n = 15) and changes in steroid doses (n = 2). A final total of 144 patients was included in the study: 56 patients were treated with IV 20 mg dexamethasone stat and o.d., and 44 patients were each treated with IV methylprednisolone (2 mg/kg) stat then 0.25 mg q.i.d. or a prednisolone tablet (1.5 mg/kg) stat and o.d. One patient on IV 20 mg dexamethasone stat and o.d. reported an upper gastrointestinal bleed adverse drug reaction. There was no significant difference between the demographic characteristics of patients treated with different steroids (Table 1).

*Clinical outcomes*

The primary outcome of the study was determined by comparing the WHO's OSCI from Day-1 to Day-10 (Table 2). Overall, the use of steroids significantly improved patient clinical status from a WHO OSCI level 4 (0.1) to 2.6 (2.5) ($p < 0.001$). Using IV methylprednisolone, IV dexamethasone and prednisolone tablets was also observed to improve clinical outcomes from Day-1 to Day-10, respectively ($p < 0.001$). There was no significant difference in clinical status between IV methylprednisolone, IV dexamethasone and prednisolone tablets on Day-5 (H = 2.15; $p = 0.34$) and Day-10 (H = 1.12; $p = 0.58$).

The secondary outcomes, which were the length of hospital stay, use of mechanical ventilation, and CRP levels, were then determined. The length of stay excluded patients that were deceased, to ensure data were more accurate [12]. It was found that the average length of stay of the study population was 12.8 (2.9) (range 6–21) days (Table 3). Patients on IV methylprednisolone had an average length of stay of 13 (2.8) (range 6–21) days, while those on IV dexamethasone and prednisolone tablets reported an average of 13.4 (3.2) (range 10–21) and 11.9 (2.3) (range 7–17) days, respectively. There was no

**Table 3.** Length of stay and need for mechanical ventilation of the study population (N = 144).

| Characteristics | IV methyl-prednisolone 2 mg/kg STAT & 0.25 mg q.i.d. (n = 44) | IV dexamethasone 20 mg STAT & o.d. (n = 56) | Tablet prednisolone 1.5 mg/kg STAT & o.d. (n = 44) | Total (N = 144) | *p* value[b] |
|---|---|---|---|---|---|
| Length of hospital stay, mean (SD) | 9.3 (4.8) (4-32) | 8.7 (3.3) (3-18) | 8.6 (3.7) (4-23) | 8.9 (3.9) (6-21) | H (0.16): 0.92 |
| Length of hospital stay, mean (SD) | 13 (2.8) (6-21) | 13.4 (3.2) (10-21) | 11.9 (2.3) (7-17) | 12.8 (2.9) (6-21) | H (4.07): 0.13 |
| Mechanical ventilation [a], n (%) | 5 (11.4) | 4 (7.1) | 5 (11.4) | 14 (9.7) | $\chi^2$ (0.14); 0.93 |

[a] Mechanical ventilation (VM 40% VM 60%, CPAP); [b] H = Kruskal-wallis, $\chi^2$ = Chi squared test.

significant difference in the length of hospital stay between the three corticosteroids ($p = 0.13$).

Fourteen patients required mechanical ventilation during treatment with corticosteroids (Table 3). There was no significant difference in the need for mechanical ventilation between the three corticosteroid groups ($p = 0.93$).

CRP levels were observed to reduce significantly overall from Day-1 at 8.3 (7.0) mg/L to Day-10 at 1.9 (2.3) mg/L ($p < 0.001$) (Table 4). A significant reduction in CRP levels from Day-1 to Day-10 was observed for all three corticosteroid groups ($p < 0.001$). There was no significant difference in CRP levels between the three corticosteroid groups from Day-1 ($H = 0.58$; $p = 0.75$), Day-3 ($H = 1.11$; $p = 0.58$), Day-6 ($H = 2.56$; $p = 0.28$) and Day-10 ($H = 3.46$; $p = 0.18$).

## Discussion

Corticosteroids are frequently given to COVID-19 patients as they provide anti-inflammatory effects by halting cytokine production [22]. Although numerous studies have shown the benefits of giving low-dose corticosteroids to patients on mechanical ventilation or in the ICU [23], i.e., to reduce COVID-19 mortality, very few address the differences between low and high-dose corticosteroids in preventing the infection's progress in severely affected hospitalised patients. Furthermore, using corticosteroids beyond 10 days is only considered in selected severe cases of COVID-19 [24]. With the recommended short-term duration of corticosteroid use, high-dose corticosteroids may be more appealing when trying to reduce disease progression, especially when ICU beds are limited. Therefore, clinicians have been required to make treatment decisions with a lack of substantial evidence.

This study aimed to compare the therapeutic effect of a short-term 10-day low dose of 2 mg/kg methylprednisolone stat then 0.25 mg q.i.d. with a 10-day high dose of 20 mg dexamethasone stat and o.d. or a 1.5 mg/kg prednisolone tablet stat and o.d. to prevent disease progression in hospitalised patients with severe COVID-19. This would allow better clinical judgements to be made when considering using high doses, for example, 20 mg dexamethasone stat and o.d. or a 1.5 mg/kg prednisolone tablet stat and o.d. At present, only category 4 severe patients are hospitalised, while those with less severe symptoms are either monitored at home or in quarantine centres. The patients in this study reported a similar WHO OSCI level of 4 on admission, which eventually improved significantly to an average of WHO OSCI level 2 by Day-10. This clinical improvement aligns with the use of corticosteroids in COVID-19 patients in previous work [12]. However, there were no significant differences in the level of improvements when comparing the use of low-dose methylprednisolone (2 mg/kg) stat then 0.25 mg q.i.d. and high doses of dexamethasone (20 mg) stat and o.d. or prednisolone (1.5 mg/kg) stat and o.d. for 10 days.

The efficacy of low methylprednisolone doses compared to high doses of dexamethasone or prednisolone for 10 days was further supported by similarities in the efficacy of the length of hospitalisation, the need for mechanical ventilation and CRP levels. Studies have shown that 1–2 mg/kg/day methylprednisolone was superior to 6 mg/day dexamethasone in reducing the length of stay and use of mechanical ventilation [12,25]. Furthermore, higher doses of methylprednisolone have been shown to increase mortality exclusively in elderly patients, with recommended doses not exceeding 1–1.5 mg/kg/day for severe COVID-19 patients [26]. This reinforces the rationale of modulating rather than suppressing immune responses in these patients. This work further supports the use of low-dose methylprednisolone, as no significant differences in the length of stay or need for mechanical ventilation were observed when either the low dose of methylprednisolone or the high dose of dexamethasone or prednisolone were used for 10 days. It was noted that the average length of hospitalisation was similar to previous reports of COVID-19 patients, with all corticosteroids reducing the length of hospital stay to approximately 14 days [27]. Similarly, a significant reduction in CRP levels was reported with corticosteroid use [28], as observed in this work.

The main concern with high doses of steroids, despite their short-term use, is the risk of adverse effects, which include bloodstream infections and

**Table 4.** C-reactive proteins (CRP) levels on Day-1, Day-3, Day-6, and Day-10 of the study population (N = 144).

| CRP levels, mg/L, mean (SD) | Day-1 | Day-3 | Day-6 | Day-10 | *p* value[a] |
|---|---|---|---|---|---|
| IV methylprednisolone 2 mg/kg STAT then 0.25 mg q.i.d. (n = 44) | 8.6 (8.8) | 5.8 (4.6) | 2.7 (3.2) | 1.8 (2.8) | $\chi^2$ (26.5): < 0.001 |
| IV dexamethasone 20 mg STAT and o.d. (n = 56) | 8.1 (5.8) | 6.1 (4.5) | 3.8 (5.7) | 1.9 (1.5) | $\chi^2$ (48.8): < 0.001 |
| Tablet prednisolone 1.5 mg/kg STAT and o.d. (n = 44) | 8.4 (6.6) | 7.6 (6.4) | 4.2 (4.7) | 2.2 (2.7) | $\chi^2$ (27.3): < 0.001 |
| Total (N = 144) | 8.3 (7.0) | 6.5 (5.2) | 3.6 (4.8) | 1.9 (2.3) | $\chi^2$ (99.4): < 0.001 |

[a] $\chi^2$ = Friedman chi-squared test, between 3 dependent groups on Day-1, Day-3, Day-6 and Day-10.

hyperglycemia [29,30]. It has also been reported that corticosteroids increase the risk of gastrointestinal bleeding by 40% among hospitalised patients [31]. Stress ulcers occur in response to severe physiological stress in critically ill patients, which may account for this occurrence. This work reported upper gastrointestinal bleeding in one patient who was given a high dose of dexamethasone (20 mg stat and o.d.) and stresses the importance of closely monitoring patients on high-dose corticosteroids.

This study demonstrates that the low doses of methylprednisolone are as effective as high doses of dexamethasone or prednisolone (as previously mentioned), with no reported adverse effects when treating severe COVID-19 patients. This allows clinicians to make informed decisions about using corticosteroids to prevent disease progression in severe COVID-19 patients. Despite this, there were limitations to the study. The retrospective nature of the work could mask other interventions or events that may influence patients' outcomes. The collected data were limited to patients' demographics along with clinical and laboratory measures that were related to clinical outcomes. As such, further multicentered randomised-controlled trials and later follow-ups are required to evaluate the beneficial effects of low and high doses of corticosteroids in patients with severe COVID-19.

## Conclusions

In hospitalised patients with severe COVID-19, using low doses of corticosteroids is recommended and significantly reduces disease progression through clinical improvement, duration of admission, the need for mechanical ventilation and CRP levels. The effectiveness of low doses of corticosteroids enables clinicians to make informed decisions about managing severe COVID-19 patients, allowing for optimal outcomes, fewer complications and reduced healthcare costs.

### Acknowledgements

The authors would like to thank Hospital Canselor Tuanku Muhriz and Universiti Kebangsaan Malaysia for authorising the study.

## References

1. World Health Organisation (2020) Virtual press conference on COVID-19. Available: https://www.who.int/docs/default-source/coronaviruse/transcripts/who-audio-emergencies-coronavirus-press-conference-full-and-final-11mar2020.pdf?sfvrsn=cb432bb3_2. Accessed: 9 September 2021.
2. Centers for Disease Control and Prevention (CDC) (2020) Symptoms of coronavirus. Available: https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed: 9 September 2021.
3. Gandhi RT, Lynch JB, Del Rio C (2020) Mild or moderate Covid-19. N Engl J Med 383: 1757-1766.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395: 497-506.
5. Isidori AM, Arnaldi G, Boscaro M, Falorni A, Giordano C, Giordano R, Pivonello R, Pofi R, Hasenmajer V, Venneri MA, Sbardella E (2020) COVID-19 infection and glucocorticoids: Update from the Italian society of endocrinology expert opinion on steroid replacement in adrenal insufficiency. J Endocrinol Invest 43: 1141-1147.
6. World Health Organisation (2020) Corticosteroids for COVID-19: Living guidance. WHO ref no: WHO/2019-nCoV/Corticosteroids/2020.1. Available: https://www.msic.org.my/download/MSIC_Consensus_Statement_Corticosteroids_for_COVID-19.pdf. Accessed: 2 September 2020.
7. Hospital Canselori Tuanku Muhriz (PPUKM) Guideline (2021) Current consensus #14: COVID-19 treatment and management by infectious disease unit and pharmacy department 19.7.2021.
8. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ (2020) COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 395: 1033-1034.
9. Halpin DMG, Faner R, Sibila O, Badia JR, Agusti A (2020) Do chronic respiratory diseases or their treatment affect the risk of SARS-CoV-2 infection? Lancet Respir Med 8: 436-438.
10. Mahase E (2020) Covid-19: Low dose steroid cuts death in ventilated patients by one third, trial finds. BMJ 369: m2422.
11. Veronese N, Demurtas J, Yang L, Tonelli R, Barbagallo M, Lopalco P, Lagolio E, Celotto S, Pizzol D, Zou L, Tully MA (2020) Use of corticosteroids in coronavirus disease 2019 pneumonia: a systematic review of the literature. Front Med 24: 170.
12. Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, Erfani A, Khodamoradi Z, Saadi MH (2021) Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial. BMC Infect Dis 1: 1-8.
13. Danwang C, Endomba FT, Nkeck JR, Wouna DL, Robert A, Noubiap JJ (2020) A meta-analysis of potential biomarkers associated with severity of coronavirus disease 2019 (COVID-19). Biomark Res 8: 1-3.
14. Ventour D, Sieunarine R, Gopaul C (2022) A short course of prednisolone in patients with moderate Covid 19 respiratory failure-stop the progression a case series. Research Square 23247096221090843.
15. Zheng ZG, Zhong NS (2003) The use of corticosteroid in management of critical SARS. Chin Med J 42: 676-677.

16. Tai DY (2007) Pharmacologic treatment of SARS: current knowledge and recommendations. Ann Acad Med Singap 36: 438.
17. National Institutes of Health (NIH) (2021) COVID-19 treatment guidelines panel. Coronavirus disease 2019 (COVID-19) treatment guidelines. Available: https://www.covid19treatmentguidelines.nih.gov/. Accessed: 6 June 2021.
18. Taboada M, Rodríguez N, Varela PM, Rodríguez MT, Abelleira R, González A, Casal A, Peromingo JA, Lama A, Domínguez MJ, Rábade C (2021) Effect of high versus low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 Pneumonia: an open-label, randomised clinical trial. Eur Respir J 1: 1.
19. Monedero P, Gea A, Castro P, Candela-Toha AM, Hernández-Sanz ML, Arruti E, Villar J, Ferrando C; COVID-19 Spanish ICU Network (2021) Early corticosteroids are associated with lower mortality in critically ill patients with COVID-19: A cohort study. Crit 25: 1-3.
20. Mora-Luján JM, Tuells M, Montero A, Formiga F, Homs NA, Albà-Albalate J, Corbella X, Rubio-Rivas M (2021) High-dose methylprednisolone pulses for 3 days vs. low-dose dexamethasone for 10 days in severe, non-critical COVID-19: A retrospective propensity score matched analysis. J Clin Med 10: 4465.
21. World Health Organization (2020) WHO R&D Blueprint-Novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Available: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis. Accessed: 6 June 2021.
22. Rhen T, Cidlowski JA (2005) Antiinflammatory action of glucocorticoids—new mechanisms for old drugs. N Engl J Med 353: 1711-1723.
23. Cano EJ, Fuentes XF, Campioli CC, O'Horo JC, Saleh OA, Odeyemi Y, Yadav H, Temesgen Z (2020) Impact of corticosteroids in COVID-19 outcomes: systematic review and meta-analysis. Chest 159: 1019-1040.
24. Villar J, Confalonieri M, Pastores SM, Meduri GU (2020) Rationale for prolonged corticosteroid treatment in the acute respiratory distress syndrome caused by coronavirus disease 2019. Crit Care Explor 2: 4.
25. Ko JJ, Wu C, Mehta N, Wald-Dickler N, Yang W, Qiao R (2021) A comparison of methylprednisolone and dexamethasone in intensive care patients with COVID-19. J Intensive Care Med 36: 673-680.
26. Monreal E, de la Maza SS, Natera-Villalba E, Beltrán-Corbellini Á, Rodríguez-Jorge F, Fernández-Velasco JI, Walo-Delgado P, Muriel A, Zamora J, Alonso-Canovas A, Fortún J (2021) High versus standard doses of corticosteroids in severe COVID-19: a retrospective cohort study. Eur J Clin Microbiol Infect Dis 40: 761-769.
27. Spagnuolo V, Guffanti M, Galli L, Poli A, Querini PR, Ripa M, Clementi M, Scarpellini P, Lazzarin A, Tresoldi M, Dagna L (2020) Viral clearance after early corticosteroid treatment in patients with moderate or severe Covid-19. Sci Rep 10: 1-7.
28. Rana MA, Hashmi M, Qayyum A, Pervaiz R, Saleem M, Munir MF, Saif MM (2020) Comparison of efficacy of dexamethasone and methylprednisolone in improving PaO2/FiO2 ratio among COVID-19 patients. Cureus 12: e10918.
29. Giacobbe DR, Battaglini D, Ball L, Brunetti I, Bruzzone B, Codda G, Crea F, De Maria A, Dentone C, Di Biagio A, Icardi G, Magnasco L, Marchese A, Mikulska M, Orsi A, Patroniti N, Robba C, Signori A, Taramasso L, Vena A, Pelosi P, Bassetti M (2020) Bloodstream infections in critically ill patients with COVID-19. Eur J Clin Invest 50: e13319.
30. Zhang Y, Li H, Zhang J, Cao Y, Zhao X, Yu N, Gao Y, Ma J, Zhang H, Zhang J, Guo X, Liu X (2020) The clinical characteristics and outcomes of patients with diabetes and secondary hyperglycaemia with coronavirus disease 2019: a single-centre, retrospective, observational study in Wuhan. Diabetes Obes Metab 22: 1443-1454.
31. Narum S, Westergren T, Klemp M (2014) Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis. BMJ Open 4: e004587.

## Corresponding author

Farida Islahudin, PhD
Associate Professor, Quality Management of Medicines,
Faculty of Pharmacy, Universiti Kebangsaan Malaysia,
50300 Kuala Lumpur, Malaysia
Tel: 603-92897971
Email: faridaislahudin@ukm.edu.my

**Conflict of interests:** No conflict of interests is declared.