

Original Research Article

Dexamethasone dose and length of hospital stay among hospitalized COVID-19 patients: a retrospective cross-sectional study in Malaysia

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ABSTRACT

Background: Dexamethasone is a potent corticosteroid that has been widely used as COVID-19 treatment. However, optimal dose of dexamethasone in COVID-19 treatment and how its different doses affect the patient outcomes is uncertain. This retrospective study aimed to evaluate the use of dexamethasone dose and length of hospital stay in COVID-19 patients admitted to two public hospitals in the east coast region of Malaysia between February 2020 and August 2021.

Methods: This study included all hospitalized patients who were receiving dexamethasone during the study period. Dexamethasone doses were categorized into high dose (≥ 15 mg/day), moderate dose (7-14 mg/day) and low dose (≤ 6 mg/day). A multivariable logistic regression was conducted to evaluate the potential risk factors associated with length of hospital stays.

Results: Of 119 patients enrolled, majority (40%) of patients received high dose dexamethasone, followed by 33% received moderate dose and 27% received low dose. Patients who received high doses were associated with extended hospital stays of 4-5 days and more frequently required mechanical ventilation. Multivariable logistic regression showed that elderly (OR=1.03; 95% CI=1.00-1.06, $p=0.001$) and severe stage of COVID-19 (stage 4-stage 5) upon hospital admission (OR=2.79; 95% CI=1.17-6.68, $p=0.021$) increased the risk of prolonged hospital stay.

Conclusions: COVID-19 patients treated with high and moderate doses of dexamethasone were associated with longer hospital stay and required mechanical ventilation compared to those on low doses. Future studies are needed to provide more evidence on benefits of low dexamethasone dose in COVID-19 patients.

Keywords: COVID-19, Dexamethasone, Malaysia, Outcomes

INTRODUCTION

The COVID-19 pandemic has caused significant impact and disruptions to healthcare systems, economies, and daily life globally. It has presented an immense challenge for governments, healthcare professionals, and the public to mitigate its effects and prevent further spread of COVID-19.¹ Researchers and healthcare professionals have repurposed some of the existing available drugs for the treatment of COVID-19. For example, drugs such as

remdesivir, favipiravir, azithromycin that were used to manage respiratory infections like middle east respiratory syndrome (MERS) and influenza were used for the treatment of COVID-19 patients. However, the effectiveness of these drugs in the treatment of COVID-19 is varied, with some being rejected (e.g., hydroxychloroquine and ivermectin) or still under exploratory stages (e.g., ensitrelvir, molnupiravir).²⁻⁴ Basically, repurposing existing available drugs for new indications has been the main approach in dealing with

the pandemic, other than isolation and supportive care as the initial management for COVID-19 patients.⁵

Dexamethasone, a corticosteroid, has been widely used in COVID-19 patients despite being limited studies available on its efficacy in treating COVID-19 patients. Dexamethasone has potent anti-inflammatory properties, which can help prevent hyper inflammation and acute respiratory distress syndrome by reducing inflammation in the respiratory system and expediting patient recovery. According to the National Institutes of Health, dexamethasone is indicated for hospitalized patients with COVID-19 who require supplemental oxygen delivery through a high-flow device or noninvasive ventilation, or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO).⁶ Previous studies have demonstrated the effectiveness of dexamethasone in reducing mortality in patients who required the supplemental oxygen with COVID-19 as well as resulted in shorter length of hospital stay.^{7,8}

In the COVID-19 STEROID 2 trial, dexamethasone was divided into two doses: low dose (6mg once daily for 10 days) and high dose (20 mg once daily for 5 days, followed by 10 mg once daily for an additional 5 days).⁹ The Clinical Practice Guidelines Malaysia for COVID-19 have recommended specific doses of dexamethasone for stage 4 and stage 5 COVID-19 patients. For stage 4a (require nasal prong or face mask oxygen), the dose of intravenous (i.v.) dexamethasone phosphate is 8 mg daily (12 mg if BMI>30) for up to 10 days or until discharge. For both stage 4b (require high flow oxygen mask) and stage 5, the dose of i.v. dexamethasone phosphate is 24 mg daily for 5 days, then reduce to 12 mg daily for 5 days.¹⁰ However, there is limited evidence of the clinical benefits of these recommended doses, and the optimal dose of dexamethasone for severe COVID-19 patients is still uncertain. Despite its widespread use in hospital settings, there is limited evidence on which dexamethasone dose benefits the COVID-19 patients. The current study sought to fill this gap by investigating the dexamethasone in term of dose and its association with the length of hospital stay. This research will provide information to healthcare professionals in making informed decisions in the treatment of COVID-19 patients.

METHODS

Study design

This retrospective cross-sectional study was conducted at two tertiary public hospitals in east coast Malaysia, from February 2020 to August 2021. Data were extracted from medical and prescription database.

Inclusion and exclusion criteria

All COVID-19 patients who received dexamethasone during their hospital stay were included. This study

excluded patients who used systemic dexamethasone for indications other than COVID-19 such as rheumatoid arthritis, asthma, chronic lung disease, invasive fungal infection, active tuberculosis and treatment for asthma in pregnant women.^{9,11} Those who died within 24 hours after admission were excluded because their outcome may not be directly attributed to the dexamethasone administered. Additionally, patients who received dexamethasone doses higher than the recommended dosage (>80 mg/day) were excluded from the study. Such higher doses are typically reserved for patients with immune thrombocytopenia, indicating that these higher doses were not within the scope of the study's focus.¹²

Ethical approval

The study was approved by Medical Research Ethical Committee, Ministry of Health, Malaysia (NMRR-20-1823-56013). The study did not involve direct patient participation, hence written informed consent was not required.

Data source and utilization measures

Patient demographics such as age, gender, medical history, smoking status, presenting symptoms upon hospital admission, comorbidity and case severity upon admission were recorded. Hypertension, diabetes, coronary heart disease, chronic kidney disease, chronic lung disease and hyperlipidemia were among the comorbidities included in this study. The Charlson comorbidity index (CCI) score is a tool used to estimate the likelihood of surviving for 10 years in patients with multiple health conditions. It helps to assess the overall impact of these conditions on a person's health.¹³ Case severity refers to the clinical stages of COVID-19 which categorized into five stages; stage 1: asymptomatic, stage 2: symptomatic with no pneumonia, stage 3: symptomatic and pneumonia without hypoxia, stage 4: symptomatic and pneumonia with hypoxia, require supplemental oxygen, stage 5: critically ill with or without organ failures.¹⁰ This study further categorized stage 1-stage 3 as mild stage, while stage 4-stage 5 as severe stage.^{10,14}

According to COVID-19 clinical practice guidelines, treatment recommendations for patients in stage 4 and stage 5 include i.v. dexamethasone phosphate and initiation of anticoagulant therapy using low molecular weight heparin (LMWH) or unfractionated heparin (UFH). It is also recommended to combine dexamethasone with the antiviral medication i.v. remdesivir. In cases where patients experience increasing oxygen needs and systemic inflammation, a higher dose of i.v. dexamethasone at 24 mg OD along with an immunomodulatory agent, baricitinib or tocilizumab is considered.¹⁰ However, previous hospital practices in Malaysia did not involve combining dexamethasone with either remdesivir, heparin, or baricitinib.¹⁴ Therefore, this study reported concomitant treatment involving other antiviral, anticoagulant and immunomodulatory agents

such as favipiravir, enoxaparin, and tocilizumab in COVID-19 patients receiving dexamethasone.

Utilization measures in the study include dexamethasone dose, requirement of mechanical ventilation and length of hospital stay.

Dexamethasone dose

This study categorized dexamethasone dose into three groups: low dose (≤ 6 mg per day), moderate dose (7 mg per day to 14 mg per day), and high dose (≥ 15 mg per day) based on the previous COVID-19 STEROID 2 trial.⁹ The mean dexamethasone dose per day per patient was calculated as below:

$$\text{Mean dose per day per patient (mg/day)} = \frac{\text{Total dose (mg)}}{\text{Total length of therapy (day)}}$$

Requirement of mechanical ventilation

Dexamethasone is commonly prescribed for conditions involving respiratory distress or inflammation.¹⁰ This study observed the specific type of mechanical ventilation used during the initial treatment of dexamethasone, whether it was non-invasive (deliver respiratory support without direct tracheal intubation) or invasive (using an endotracheal tube or tracheostomy tube). This study recorded whether mechanical ventilation was continued despite receiving low, moderate, or high doses of dexamethasone.

Length of hospital stay

The length of hospital stay was determined by calculating the difference between the initiation date of dexamethasone and the date of discharge from the hospital. Those patients who stayed longer than six days were considered prolonged hospital stay. The cut off for prolonged hospital stay was obtained from 50th percentile of distribution among dexamethasone group in the current study which was 6 days (IQR 4- 10 days).¹⁵

Statistical analysis

Descriptive data was presented in terms of frequency and percentage for discrete variables and mean and standard deviation (SD) for continuous variable. Logistic regression analysis was conducted to examine the risk factors for prolonged hospital stay among patients who had dexamethasone therapy. Careful selection of covariates was crucial in constructing an accurate logistic model.

To ensure the reliability of the analysis, chi-square tests were performed on categorical variables. This step verified that the expected frequency in contingency tables for each covariate was equal to or greater than 5, as

recommended by Josephat and Ame.¹⁶ Categorical variables such as gender, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, coronary heart disease, and disease stage upon hospital admission were included in the regression analysis due to their frequencies being equal to or greater than 5.

For continuous variables, a variance inflation factor (VIF) analysis was carried out to assess multicollinearity as logistic regression is highly sensitive to high correlations among independent variables.¹⁷ Fortunately, no evidence of multicollinearity was observed among the continuous variables, which included age, CCI score, number of COVID-19 symptoms, and mean dexamethasone dose per day. Hence, these variables were considered in the analysis. In the univariable analysis for risk factors of prolonged hospital stay, age and severe stage upon hospital admission were found to be significant. Therefore, these variables were further investigated using multivariable regression to analyze their combined effects on prolonged hospital stay.

Additionally, this study investigated risk factors for mortality among COVID-19 patients who received dexamethasone. This analysis included age, gender, hypertension, diabetes mellitus, hyperlipidemia, chronic kidney disease, coronary heart disease, CCI score, number of COVID-19 symptoms, disease stage upon hospital admission, and high dexamethasone dose/day.

This study considered a p value of ≤ 0.05 as statistically significant. All analyses were conducted using Stata version 15.1 (StataCorp. 2012. Stata Statistical Software: Release 15. College Station, TX: StataCorp LP).

RESULTS

Patient characteristics

A total of 119 COVID-19 patients who were treated with dexamethasone during their hospitalization were included in this study. Mean patients' age was 59 ± 14.5 (mean $\pm$ SD) years old and majority of them were male (55%). Comorbid conditions were present in 69% patients, with the most prevalent comorbidities were hypertension (60%), followed by diabetes (55%), hyperlipidemia (19%) and chronic kidney disease (19%). Majority (73%) of patients were diagnosed with severe (stages 4-5) upon hospital admission and received dexamethasone treatment (Table 1).

Dexamethasone dose, concomitant treatment and mechanical ventilation

The mean dose of dexamethasone for all 119 patients was 11.10 ± 6.85 mg/day. Of these 119, 32 (27%) received low dose (≤ 6 mg/day), 39 (33%) received moderate dose (7-14 mg/day), and 48 (40%) received high dose (≥ 15 mg/day). Most patients were categorized with severe stage (stage 4-5) upon hospital admission and majority of

them were started with high dose (46%, 40/87), followed by moderate dose (33%, 29/87) and low dose (21%, 18/87) of dexamethasone. The mean length of dexamethasone therapy for all included patients was 3.84 ± 2.68 days. The mean length of dexamethasone therapy was longer among high dose group (4.44 ± 3.34 days) compared to moderate (4.15 ± 2.41 days) and low dose group (2.75 ± 1.88 days).

As for concomitant medications, patients were predominately treated with favipiravir (86%), with a slightly higher percentage of patients in the high dose dexamethasone group (92%) receiving it compared to moderate (87%) and low dose groups (75%). Similarly, majority of patients received enoxaparin (73%), with a slightly higher percentage of patients in the high dose dexamethasone group (83%) receiving it. Only a small percentage of patients received tocilizumab (4%), with a slightly higher percentage in the high dose dexamethasone group (8%).

At the start of dexamethasone therapy, 60% of the patients in the study particularly in high dose dexamethasone group (75%) required non-invasive mechanical ventilation for oxygen support. After discontinuing dexamethasone, the majority of patients receiving dexamethasone (52%) continued to require ventilation, with a significant portion of them receiving non-invasive mechanical ventilation (43%) (Table 2).

Dexamethasone dose and length of hospital stay

Patients who received a low dose of the dexamethasone had the shortest mean length of stay (5.75 ± 5.32 days), while those who received a high dose had the longest with an average of 10.94 ± 11.54 days (Table 3). For COVID-19 patients who received dexamethasone during hospitalization, multivariable logistic regression demonstrated that elderly, and severe stage upon hospital admission significantly increased risk for prolonged hospital stay (Table 4).

Table 1: Patient characteristics.

	All patients (n=119)	Low dose (≤ 6 mg/day) (n=32)	Moderate dose (7-14 mg/day) (n=39)	High dose (≥ 15 mg/day) (n=48)
Age, years	59 $\pm$ 14.5	57 $\pm$ 17.7	61 $\pm$ 14.1	59 $\pm$ 12.5
Gender				
Male	65 (55%)	17 (53%)	17 (44%)	31 (65%)
Female	54 (45%)	15 (47%)	22 (56%)	17 (35%)
Smoker	8 (7%)	2 (6%)	2 (5%)	4 (8%)
Comorbidity				
Hypertension	71 (60%)	14 (44%)	26 (67%)	31 (65%)
Diabetes mellitus	65 (55%)	15 (47%)	24 (62%)	26 (54%)
Hyperlipidemia	23 (19%)	1 (3%)	8 (21%)	14 (29%)
Chronic kidney disease	23 (19%)	3 (9%)	11 (28%)	9 (19%)
Coronary heart disease	19 (16%)	3 (9%)	9 (23%)	7 (15%)
Chronic lung disease	2 (1.7%)	1 (3%)	1 (3%)	0 (0%)
Mean CCI score $\pm$ SD	1.45 $\pm$ 1.94	0.90 $\pm$ 1.54	1.8 $\pm$ 1.87	1.47 $\pm$ 2.12
Presented COVID-19 symptoms upon admission				
Dry cough	69 (58%)	14 (44%)	26 (67%)	29 (60%)
Fever	62 (52%)	13 (41%)	24 (62%)	25 (52%)
Runny nose	14 (12%)	4 (3%)	6 (15%)	4 (8%)
Sore throat	7 (6%)	3 (3%)	2 (5%)	2 (4%)
Loss of smell/taste	10 (8%)	2 (2%)	3 (8%)	5 (10%)
Fatigue	42 (35%)	9 (8%)	14 (36%)	19 (40%)
Shortness of breath	34 (29%)	6 (5%)	10 (26%)	18 (38%)
Sputum	25 (21%)	5 (4%)	10 (26%)	10 (21%)
Diarrhea	10 (8%)	2 (6%)	4 (10%)	4 (8%)
Myalgia	6 (5%)	1 (3%)	2 (5%)	3 (6%)
Headache	2 (2%)	0 (0%)	1 (3%)	1 (2%)
Nausea/vomiting	9 (8%)	3 (3%)	5 (4%)	1 (2%)
Chest discomfort	8 (7%)	0 (0%)	5 (4%)	3 (6%)
Loss of appetite	4 (3%)	3 (3%)	0 (0%)	1 (2%)
Mean number of COVID-19 symptoms presented $\pm$ SD	2.53 $\pm$ 1.73	2.13 $\pm$ 1.62	2.84 $\pm$ 1.82	2.60 $\pm$ 1.71
Case severity upon admission				
Mild	32 (27%)	14 (44%)	10 (26%)	8 (17%)
Severe	87 (73%)	18 (56%)	29 (74%)	40 (83%)

Table 2: Concomitant medication, mechanical ventilation and dexamethasone therapy.

	All patients (n=119)	Low dose (≤ 6 mg/day) (n=32)	Moderate dose (7- 14 mg/day) (n=39)	High dose (≥ 15 mg/day) (n=48)
Favipiravir	102 (86%)	24 (75%)	34 (87%)	44 (92%)
Enoxaparin	87 (73%)	18 (56%)	29 (74%)	40 (83%)
Tocilizumab	5 (4%)	-	1 (3%)	4 (8%)
Used of mechanical ventilation				
Patients with non-invasive ventilation when starting dexamethasone	71 (60%)	8 (25%)	28 (72%)	36 (75%)
Patients with invasive ventilation when starting dexamethasone	14 (12%)	2 (6%)	4 (10%)	8 (17%)
Patients still using non-invasive ventilation after discontinuing dexamethasone	51 (43%)	9 (28%)	16 (41%)	26 (54%)
Patients still using invasive ventilation after discontinuing dexamethasone	11 (9%)	2 (32%)	1 (3%)	8 (17%)
Mean length of dexamethasone therapy (days) $\pm$SD	3.84 $\pm$ 2.68	2.75 $\pm$ 1.88	4.15 $\pm$ 2.41	4.44 $\pm$ 3.34

Table 3: Mean length of hospital stay of COVID-19 patients receiving dexamethasone.

Outcome	All patients (n=119)	Low dose (≤ 6 mg/day) (n=32)	Moderate dose (7-14 mg/day) (n=39)	High dose (≥ 15 mg/day) (n=48)
Mean length of hospital stay (days) $\pm$SD	8.10 $\pm$ 8.42	5.75 $\pm$ 5.32	6.54 $\pm$ 3.89	10.94 $\pm$ 11.54

Table 4: Univariable and multivariable logistic regression of dexamethasone use and prolonged hospital stay among COVID-19 patients.

Risk Factors	Crude OR		P value	Adjusted OR		P value
Age, years^{*a}	1.03	1.01-1.06	0.015	1.03	1.00-1.06	0.026
Gender						
Male	1.07	0.52-2.21	0.852	-	-	-
Female	1					
Hypertension						
Yes	1.71	0.82-3.58	0.154	-	-	-
No	1					
Diabetes mellitus						
Yes	1.23	0.59-2.54	0.578	-	-	-
No	1					
Coronary heart disease						
Yes	1.22	0.45-3.29	0.695	-	-	-
No	1					
Chronic kidney disease						
Yes	1.80	0.70-4.64	0.224	-	-	-
No	1					
Hyperlipidemia						
Yes	2.29	0.86-6.05	0.096	-	-	-
No	1					
Charlson comorbidity index^a	1.10	0.89-1.36	0.386	-	-	-
Number of COVID-19 symptoms presented upon admission^a	1.04	0.84-1.28	0.703	-	-	-
Disease stage upon hospital admission						
Severe	2.98	1.28-6.94	0.012	2.79	1.17-6.68	0.021
Mild	1					
Mean dexamethasone dose/day	1.02	0.96-1.08	0.525	-	-	-

*Per 1 unit increase. ^aContinuous variable.

Dexamethasone use and mortality

In this study, 56 (47%) COVID-19 patients who had dexamethasone treatment during hospitalization died with majority of them were among high dose group (58%) (Table 5).

Logistic regression was conducted to explore relationship between the dexamethasone use and mortality and included high dexamethasone dose as one of the parameters in the analysis. Multivariable logistic regression analysis showed that elderly was the risk factor for mortality among COVID-19 patients who received dexamethasone treatment. Also, it was observed that high

dexamethasone dose did not significantly associate with mortality (Table 6).

COVID-19 complications

Acute kidney injury (32%) and acidosis (30%) were among the most common COVID-19 complications observed in this study. Additionally, 25% of the patients developed multiorgan failure, 20% experienced septicemic shock, 13% developed secondary infection and 5% had sepsis during hospitalization. Regarding respiratory complications, 14% of patients experienced acute respiratory distress syndrome (ARDS) and 5% developed respiratory failure (Table 7).

Table 5: Number of deaths among COVID-19 patients receiving dexamethasone therapy.

Outcome	All patients (n=119)	Low dose (≤ 6 mg/day) (n=32)	Moderate dose (7-14 mg/day) (n=39)	High dose (≥ 15 mg/day) (n=48)
Death	56 (47%)	10 (31%)	18 (46%)	28 (58%)

Table 6: Univariable and multivariable logistic regression of dexamethasone use and mortality among COVID-19 patients.

Risk factors	Crude OR		P value	Adjusted OR		P value
Age, years^{*a}	1.04	1.01-1.07	0.006	1.04	1.01-1.08	0.022
Gender						
Male	0.57	0.28-1.19	0.135	-	-	-
Female	1					
Hypertension						
Yes	2.22	1.05-4.72	0.038	0.82	0.28-2.43	0.726
No	1			1		
Diabetes mellitus						
Yes	2.28	1.09-4.80	0.029	1.23	0.40-3.77	0.716
No	1			1		
Coronary heart disease						
Yes	1.01	0.38-2.71	0.976	-	-	-
No	1					
Chronic kidney disease						
Yes	4.14	1.50-11.44	0.006	2.11	0.54-8.18	0.281
No	1			1		
Hyperlipidemia						
Yes	1.04	0.42-2.58	0.935	-	-	-
No	1					
Charlson comorbidity index^a	1.40	1.12-1.75	0.003	1.21	0.87-1.68	0.248
Number of COVID-19 symptoms presented upon admission^a	1.05	0.85-1.29	0.679	-	-	-
Disease stage upon hospital admission						
Severe	3.00	1.25-7.23	0.014	2.46	0.92-6.58	0.072
Mild	1			1		
High dexamethasone dose/day	2.15	1.02-4.53	0.044	2.30	0.99-5.36	0.054

* Per 1 unit increase. ^aContinuous variable.

Table 7: COVID-19 complications.

COVID-19 complications	n (%)
Acute kidney injury	18 (32)
Acidosis	17 (30)
Multiorgan failure	14 (25)
Septicemic shock	11 (20)
Acute respiratory distress syndrome	8 (14)
Secondary infection	7 (13)
Respiratory failure	3 (5)
Sepsis	3 (5)

DISCUSSION

This study investigated dexamethasone dose and its association with the length of hospital stay among COVID-19 patients. It was found that the majority of severe COVID-19 patients who received high dose of dexamethasone (≥ 15 mg/day) stayed in the hospital longer with an additional of 4-5 days compared to patients receiving moderate and low dose.

In the current study, majority of severe COVID-19 patients categorized as stage 4-5 received an average daily dose of dexamethasone dose at 11.10 mg, which aligns with the recommended range of 8-12 mg/day specified in clinical practice guidelines for COVID-19.¹⁰ The compliance to the guideline suggests that healthcare providers took a comprehensive and evidence-based approach to treat severe COVID-19 patients, which is critical for improving patient outcomes. However, this study found that almost 50% of the patients had poor outcome despite receiving recommended dose of dexamethasone. This indicates that further study is needed to identify optimal dose of dexamethasone for COVID-19 patients. Also, it is important to note that the treatment recommendations in the guidelines are subject to change as new evidence emerges, and should be continuously evaluated and updated accordingly.

Concerning length of hospital stay, COVID-19 patients who received dexamethasone in our study was admitted to hospital for approximately 8 days, which was longer duration than those reported in a previous study conducted in Spain that found less than 4 days.¹⁸ The difference in these findings may be due to variation in demographic characteristics of the population and hospital discharge criteria.¹⁹ The genetics, lifestyles, and environmental factors can also vary between different countries which lead to differences in health outcomes and the way individual's response to treatments.²⁰

Although dexamethasone has demonstrated efficacy in improving clinical outcomes in COVID-19 patients, it is also a potent immunosuppressant that can increase the risk of secondary infections and delay recovery in some patients.²¹ The dose dependent adverse effects that could happen with dexamethasone may require detailed benefit-and-risk evaluation. The National Institutes of Health

(2022) preferred to use low dose (6 mg) as maintenance dose for COVID-19 patients.⁶ It has been highlighted that corticosteroids should be used at the lowest dose and in the shortest duration possible to prevent corticosteroid-induced adverse events such as acute psychosis and uncontrolled cytokine storm.²¹

The current study also found that the risk factors for prolonged hospital stay and mortality among patients who received dexamethasone were significantly seen in elderly. In addition, patients diagnosed with severe stages upon hospital admission were at higher risk for prolonged hospital stay. Elderly patients with COVID-19 commonly have weaker immune system and reduced physiological reserves that may impede their body's ability to combat the virus and recover from the disease.^{22,23} Also, elderly patients often have comorbidities or underlying health conditions that can complicate their treatment and necessitate a longer hospital stay. These factors collectively increase the complexity of care required and may result in a longer duration of hospitalization.^{22,23}

For patients with severe stages of COVID-19 disease upon hospital admission, they often required dexamethasone therapy and supplemental oxygen or more intensive respiratory support.¹⁰ These patients have higher risk for COVID-19 complications such as acute respiratory distress syndrome and sepsis.²⁴ Previous study showed that inclusion of dexamethasone into standard care improved patient outcomes, with majority patients remained alive and no longer needing mechanical ventilation.²⁵ This is inconsistent with our study in which about half of the patients were still required mechanical ventilation even after the cessation of dexamethasone therapy, with most of them being supported with non-invasive mechanical ventilation. In addition, it was observed that patients who received high dose continued to require mechanical ventilation. The difference in findings may be influenced by length of dexamethasone therapy, as patients in the previous study were administered dexamethasone for 10 days, which was longer than our study. However, a study conducted in Brazil produced similar results to our study, where the use of high-dose dexamethasone did not lead to an increase in ventilator-free days.¹¹ This finding elucidates why patients in the high-dose group remained in the hospital for a longer duration, as they may require more intensive medical interventions to effectively manage their condition. Regardless, this study found that administering high dexamethasone dose did not associate with mortality among COVID-19 patients.

This study provides important initial insights into the potential impacts of dexamethasone dose on the length of hospital stay. Healthcare providers may use this information to devise safe and effective treatment plans and strategies for COVID-19 patients taking into account the clinical outcomes associated with dexamethasone dosage used.

However, definite conclusion on the benefits or risks of dexamethasone must be carefully interpreted due to inherent limitations of retrospective design and small sample size. Apart from that, the study outcomes were derived from follow-up period during patients' hospital stay, which limited information regarding their long term health outcomes.

CONCLUSION

This study found that patients who received high dose dexamethasone had prolonged hospital stays. Higher risks were seen in elderly patients and those in a severe stage of COVID-19 infection upon hospital admission. Low dose dexamethasone is recommended for COVID-19 patients as it effectively shortens the length of hospital stays. By optimizing the use of dexamethasone, healthcare providers can potentially reduce the length of hospital stay and reduce the burden on healthcare systems. Therefore, further research in this area is crucial for the development of effective treatment strategies for COVID-19 patients. Future studies should include a larger and more diverse sample, and a longer follow-up duration to evaluate the effects of dexamethasone dose and length of therapy on long-term outcomes.

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REFERENCES

1. Organisation for Economic Co-operation and Development. The territorial impact of COVID-19: managing the crisis across levels of government, 2020. Available from: <https://www.oecd.org/coronavirus/policy-responses/the-territorial-impact-of-covid-19-managing-the-crisis-across-levels-of-government-d3e314e1/>. Accessed on 19 March 2023.
2. Venkatasubbaiah M, Reddy PD, Satyanarayana SV. Literature-based review of the drugs used for the treatment of COVID-19. *Curr Med Res Pract*. 2020;10(3):100-9.
3. Mukae H, Yotsuyanagi H, Ohmagari N, Doi Y, Sakaguchi H, Sonoyama T, et al. Efficacy and safety of ensitrelvir in patients with mild-to-moderate coronavirus disease 2019: the phase 2b part of a randomized, placebo-controlled, phase 2/3 study. *Clin Infect Dis*. 2023;76(8):1403-11.
4. Butler CC, Hobbs FR, Gbinigie OA, Rahman NM, Hayward G, Richards DB, et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform-adaptive randomised controlled trial. *Lancet*. 2023;401(10373):281-93.
5. World Health Organization. Clinical Management of COVID-19. 2023. Available from: <https://www.who.int/teams/health-care-readiness/covid-19>. Accessed on 19 March 2023.
6. National Institutes of Health. Corticosteroids. 2022. Available from: <https://www.covid19treatmentguidelines.nih.gov/the-rapies/immunomodulators/corticosteroids/#:~:text=I%20dexamethasone%20is%20not%20available,Pre%20nisone%2040%20mg>. Accessed on 19 March 2023.
7. Recovery Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (Recovery): a randomised, controlled, open-label, platform trial. *Lancet*. 2020;396:1345-52.
8. Dastena ZH, Bahadori A, Dehghani M, Asadi-Samani M, Izadi I, Shahraki HR. Comparison of the effect of intravenous dexamethasone and methylprednisolone on the treatment of hospitalized patients with COVID-19: a randomized clinical trial. *Int J Infect Dis*. 2022;122:659-64.
9. Munch MW, Myatra SN, Vijayaraghavan BKT. Effect of 12mg vs 6mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia: the COVID steroid 2 randomized trial. *J Am Med Assoc*. 2021;326(18):1807-17.
10. Ministry of Health Malaysia. Clinical management of confirmed COVID-19 case in adult and pediatric. 2022. Available from: <https://covid-19.moh.gov.my/garis-panduan/garis-panduan-kkm/ANNEX-2E-CLINICAL-MANAGEMENT-OF-CONFIRMED-COVID-19-31052022.pdf>. Accessed on 17 March 2023.
11. Maskin LP, Olarte GL, Palizas F, Velo AE, Lurbet MF, Bonelli I, et al. High dose dexamethasone treatment for acute respiratory distress syndrome secondary to COVID-19: a structured summary of a study protocol for a randomised controlled trial. *Trials*. 2020;21:1-3..
12. Liu Z, Li X, Fan G, Zhou F, Wang Y, Huang L, et al. Low-to-moderate dose corticosteroids treatment in hospitalized adults with COVID-19. *Clin Microbiol Infect*. 2021;27(1):112-7.
13. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of

- clinimetric properties. *Psychother psychosomat*. 2022;91(1):8-35.
14. Sim BL, Chidambaram SK, Wong XC, Pathmanathan MD, Peariasamy KM, Hor CP, et al. Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: a nationwide observational study. *Lancet Reg Health West Pac*. 2020;4.
 15. Tustumi F. Choosing the most appropriate cut-point for continuous variables. *Rev Col Brasil Cirurg*. 2022;49:e20223346.
 16. Josephat, PK, Ame A. Effect of testing logistic regression assumptions on the improvement of the propensity scores. *Int J Stat Appl*. 2018;8(17):9-17.
 17. Marcoulides KM, Raykov T. Evaluation of variance inflation factors in regression models using latent variable modelling methods. *Educ Psychol Measure*. 2019;79(5):874-82.
 18. Zamarrón E, Carpio C, Villamañán E, Álvarez-Sala R, Borobia AM, Gómez-Carrera L, et al. Impact of systemic corticosteroids on hospital length of stay among patients with COVID-19. *Farm Hosp*. 2023;47(2):55.
 19. Birhanu A, Merga BT, Ayana GM, Alemu A, Negash B, Dessie Y. Factors associated with prolonged length of hospital stay among COVID-19 cases admitted to the largest treatment center in Eastern Ethiopia. *SAGE Open Med*. 2022;10:20503121211070366.
 20. Abdelzaher H, Saleh BM, Ismail HA, Hafiz M, Gabal MA, Mahmoud M, et al. COVID-19 genetic and environmental risk factors: a look at the evidence. *Front Pharmacol*. 2020;11:579415.
 21. Taboada M, Rodríguez N, Varela PM, Rodríguez MT, Abelleira R, González A, et al. 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*. 2022;60(2).
 22. Damayanthi H, Prabani K, Weerasekara I. Factors associated for mortality of older people with COVID-19: a systematic review and meta-analysis. *Gerontol Geriatr Med*. 2021;7:23337214211057392.
 23. Sanyaolu A, Okorie C, Marinkovic A. Comorbidity and its impact on patients with COVID-19. *Springerlink Comprehens Clin Med*. 2020;2:1069-76.
 24. SeyedAlinaghi S, Afsahi AM, MohsseniPour M, Behnezhad F, Salehi MA, Barzegary A, et al. Late complications of COVID-19: a systematic review of current evidence. *Arch Acad Emerg Med*. 2021;9(1).
 25. Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19. *J Am Med Assoc*. 2020;324(13):1-11.

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