Original Article

Comparison of standard dose with high dose of methylprednisolone in the management of COVID-19 patients admitted in ICU

Abhishek Singhai[1], Parneet Kaur Bhagtana[2], Neeraj Pawar[3], G. Sai Pavan[1]

[1]Department of Medicine, [2]MBBS (Intern), Department of Anaesthesia and Critical Care, [3]Department of Community and Family Medicine, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India

Abstract

Context: The pathological progression in severe Coronavirus Disease 2019 (COVID-19) includes an excessive and unregulated pro-inflammatory cytokine storm. Though the efficacy of corticosteroids like methylprednisolone (MPS) in severe COVID-19 is proven now, its dose and duration are not precise. **Aims:** Our study aimed to compare the effect of a standard dose (SD) of MPS (60–120 mg/day) to a high dose (HD) of MPS (>120 mg/day) on the outcome of hospitalized COVID-19 patients. **Settings and Design:** This study was a cross-sectional study. Patients admitted to AIIMS, Bhopal's intensive care unit (ICU) from July 2020 to March 2021 were enrolled in the study. **Methods and Material:** The patient's medical records were extracted from the medical record section of the hospital. The primary endpoint was the all-cause mortality during the hospital stay. The secondary endpoints were the need for mechanical ventilation, the use of vasopressors, the occurrence of acute kidney injury (AKI), and secondary infections. **Statistical Analysis Used:** Data were entered in the MS Excel spreadsheet and coded appropriately. **Results:** Our data showed that survival, the need for mechanical ventilation, the occurrence of AKI, and secondary bacterial infection are comparable among the two groups with no significant difference. The logistic regression analysis showed that there is a slightly higher risk of death for patients with an acute respiratory distress syndrome (ARDS) receiving HD of corticosteroids compared to SD, though these results were found to be statistically non-significant. **Conclusions:** In hospitalized patients suffering from severe COVID-19 pneumonia, an SD of MPS is as effective as an HD of MPS in terms of reduction in mortality and need for mechanical ventilation.

Keywords: Corticosteroid, COVID-19, methylprednisolone, respiratory failure, sepsis

Introduction

Coronavirus Disease 2019 (COVID-19) is an infection of the respiratory tract identified in Wuhan, China, in December 2019, due to a newly emerging coronavirus. While a majority of the COVID-19 patients experience only moderate or uncomplicated illness, approximately 14% develop a serious disease that necessitates hospitalization and oxygen treatment, and 5% need admission to an intensive care unit (ICU). COVID-19 can cause sepsis, septic shock, acute respiratory distress syndrome (ARDS), multi-organ failure, involving acute kidney damage, and cardiac injury in serious cases. The pathogenic viral response, accompanied by host inflammatory responses with different levels of severity, may occur in the two overlapping phases.[1,2] The pathological progression in severe COVID-19 includes an excessive and unregulated pro-inflammatory cytokine storm leading to immunopathological lung injury, diffuse alveolar damage with the development of ARDS, and death.[3,4]

Address for correspondence: Dr. Parneet Kaur Bhagtana, Intern, Department of Anaesthesia & Critical Care, All India Institute of Medical Sciences, Bhopal, Madhya Pradesh, India.
E-mail: parneet.aiimsb1159@gmail.com

Received: 17-05-2021 **Revised:** 03-07-2021
Accepted: 05-07-2021 **Published:** 29-11-2021

Access this article online

Quick Response Code:

Website: www.jfmpc.com

DOI: 10.4103/jfmpc.jfmpc_908_21

How to cite this article: Singhai A, Bhagtana PK, Pawar N, Pavan GS. Comparison of standard dose with high dose of methylprednisolone in the management of COVID-19 patients admitted in ICU. J Family Med Prim Care 2021;10:4066-71.

Since no antiviral therapy has demonstrated its effectiveness, the current clinical management consists primarily of supportive care, supplemental oxygen, and mechanical ventilatory support. Adjunctive treatment with immunomodulatory agents targeting the inflammatory cytokine storm is being evaluated. As a possible successful therapy for COVID-19, corticosteroids have gained worldwide attention. The majority of the efficacy data on glucocorticoids in these meta-analyses come from a large, randomized open-label trial in the United Kingdom wherein oral or intravenous dexamethasone reduced 28-day mortality among the hospitalized patients compared with usual care alone.[5] However, many ICU physicians feel comfortable with an intermediate-acting corticosteroid, Methylprednisolone (MPS). In a majority of randomized controlled trials, this agent has been the primary corticosteroid used in the ICU management of ARDS. Another reason for wider use of MPS is that MPS achieves higher lung tissue concentration in animal models than dexamethasone, which may be more effective for lung injury.[6] Earlier studies done in Severe acute respiratory syndrome (SARS) patients have also shown the effectiveness of MPS in the treatment.[7,8] Though the efficacy of the corticosteroid (MPS) in severe COVID-19 is proven now, its dose and duration are not precise. Various guidelines recommended 1–2 mg/kg methylprednisolone for 5–7 days; however, a few clinicians found better results with doses as high as 500–750 mg/day for 3 days and then slowly weaning steroids over several days.[9] Thus, based on this information, we conducted a cross-sectional study to compare the effect of a standard dose (SD) of MPS (60–120 mg/day) to a high dose (HD) of MPS (>120 mg/day) on the outcome of hospitalized COVID-19 patients.

Subjects and Methods

Subjects

Patients hospitalized in the ICU of the All India Institute of Medical Sciences (AIIMS) Bhopal with Severe acute respiratory syndrome- Coronavirus-2 (SARS-CoV-2) infection, which was confirmed by real-time polymerase chain reaction (PCR), were evaluated for possible inclusion in our study. The study included hospitalized patients over the age of 18 years who had an oxygen saturation of less than 93% in room air at the time of admission and received injection MPS within 24 h of admission. The patients who died during the first 24 h of admission or required discontinuation of the corticosteroid due to any complication were excluded from the study.

Study design

This study is a cross-sectional study. Patients admitted to AIIMS' ICU, Bhopal, from July 2020 to March 2021, were enrolled in the study. The patients' medical records were extracted from the medical record section of the hospital. The patients fulfilling the inclusion criteria were divided into two groups. In the SD group, patients received 60–120 mg/day MPS for 7–10 days, while in the HD group, patients received 250–500 mg/day MPS for 3 days followed by 60–120 mg/day MPS for next 7 days. We hypothesized, based on the previous research, that the SD of MPS is non-inferior to the HD of MPS in terms of efficacy. The following patient data were retrieved from the medical record: Demographic features, underlying disease, oxygen saturation on admission, PO_2/SPO_2 ratio, type of oxygen supplementation, use of other drugs, need of non-invasive ventilation (NIV), need of invasive ventilation, the occurrence of acute kidney injury (AKI), secondary infections, and final outcome. Ethical clearance was obtained from the Institutional Ethical Committee before the start of the study (IHEC-LOP/2020/IM0281).

Endpoints

The primary endpoint was the all-cause mortality during the hospital stay. The secondary endpoints were a need for NIV, need for invasive ventilation, use of vasopressors, the occurrence of AKI, and secondary infections.

Statistical analysis

Data were entered in the MS Excel spreadsheet and coded appropriately. To express the quantitative data, the mean and standard deviation was used; the qualitative data were expressed as frequency and percentages. The Student's *t*-test and Chi-square test were performed for quantitative and qualitative data, respectively. Logistic regression was applied to study the effect of both dosages on primary and secondary endpoints. All tests were performed at 95% CI with a P value of < 0.05 labeled as statistically significant. Analysis was done using MS Excel 365, epi info V07, and R software V3.

Results

The research involved a total of 280 patients (65 females, 215 males). The mean age of the study participants was 50 ± 13.4 years. It was found that, while chances of survival and occurrence of secondary infection declined with age, the need for ventilators, vasopressor agents, and the occurrence of AKI increased with age [Figures. 1 and 2] [Table 1].

The majority (81.4%) of the participants had one or more comorbid conditions. The most common comorbidities were diabetes mellitus (DM) and systemic hypertension (HTN), which were present in more than half of the enrolled patients. The data for the baseline characteristics (sociodemographic and clinical) were compared in the two study groups (SD vs. HD steroid). It was found that for most of the baseline parameters, the distribution among the two groups, SD and HD, was found to be statistically non-significant with $P > .05$, which led to a better comparison of the groups with respect to the outcome (s) of interest. Since this is a retrospective analysis, certain parameters like oxygen saturation on admission, the severity of ARDS (PaO_2/SPO_2) on admission, were not matched in the two groups with $P < .05$ [Table 1].

Since the research study question is that the SD is not inferior to the HD steroid because of the need for interventions and clinical outcome, the same reflected in Table 2 which shows that the survival, the need for mechanical ventilation, the occurrence of AKI, and secondary bacterial infection is comparable among the two groups with no significant difference ($P > .05$). However, the need for the vasopressor agent was found to be significantly more among the SD steroid group compared to the HD ($P < .05$).

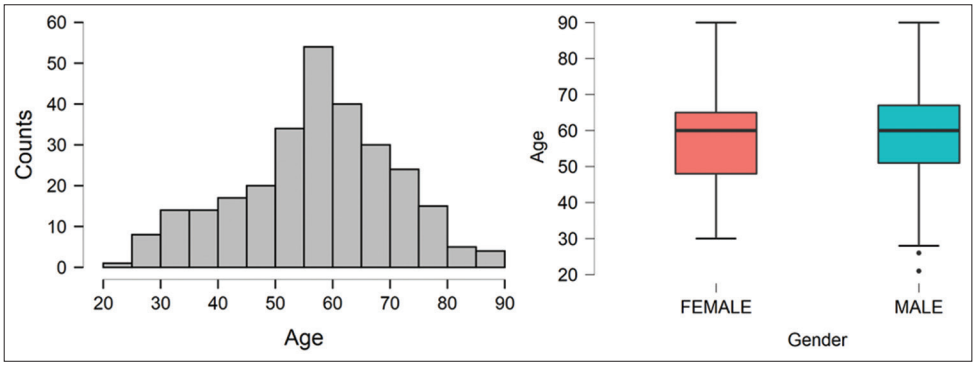

Figure 1: Age and gender-wise distribution of study participants

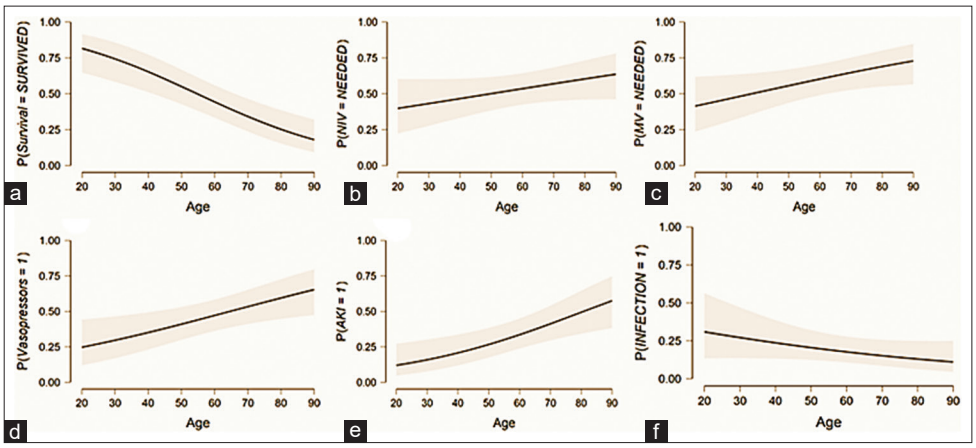

Figure 2: Conditional estimates plots displaying the probability of following dependent variables with respect to age: (a) Survival (b) Need for NIV (c) Need for MV (d) Need for vasopressors (e) Occurance of AKI (f) Occurance of infections

Table 1: Distribution of baseline demographics, clinical parameters among two groups

		Steroid Dose		
	All patients 280; *n* (%)	**Standard dose 77; *n* (%)**	**High dose 203; *n* (%)**	***P***
Age (years)	58±13	59.2±14.2	57.6±13.1	0.36
Gender (female)	65 (23.2)	20 (25.9)	45 (22.1)	0.5
Overall comorbidity (Present)	228 (81.4)	65 (84.4)	163 (80.3)	0.429
DM	149 (53.2)	44 (57.1)	105 (51.7)	0.417
HTN	159 (56.7)	45 (58.4)	114 (56.2)	0.730
CAD	41 (14.6)	09 (11.6)	32 (15.8)	0.389
CKD	16 (5.7)	06 (7.8)	10 (4.9)	0.356
Saturation on admission				
90-92	88 (31.4)	34 (44.2)	54 (26.6)	0.003*
80-89	102 (36.4)	30 (38.9)	72 (35.4)	
70-79	40 (14.3)	07 (9.1)	33 (16.3)	
<70	50 (17.9)	06 (7.8)	44 (21.7)	
PaO_2/SPO_2 (day 1)	137.5±50.3	160.9±49.3	128±47.8	<.001*
Severe ARDS (day 1)	77 (27.5)	08 (10.3)	69 (33.9)	<.001*
Remdesivir use	128 (45.7)	29 (37.6)	99 (48.8)	0.09
Anticoagulant use	272 (97)	75 (97.4)	197 (97)	0.480
Tocilizumab use	16 (5.7)	05 (6.5)	11 (5.4)	0.729

*Significant at $P<.05$. DM, Diabetes mellitus; HTN, Hypertension; CAD, Coronary artery disease; CKD, Chronic kidney disease, PaO_2/FiO_2, PaO_2 (arterial pO_2) from the ABG. FIO_2, the fraction (percent) of inspired oxygen that the patient is receiving expressed as a decimal; ARDS, acute respiratory distress syndrome

When interferential plots were drawn to find out the probability of occurrence of the above-mentioned primary and secondary endpoints for two steroid dose groups, similar trends were observed [Figures. 3].

The logistic regression analysis showed a slightly higher risk of death for patients with an ARDS receiving HD of corticosteroids than SD. However, these results were found to be statistically non-significant (OR 1.077, 95% CI -0.453 to 0.600, $P > 0.05$). Similar results were obtained for need for NIV (OR 1.437, 95% CI -0.167 to 0.892, $P > 0.05$). There was no statistical difference in the need for mechanical ventilation, the occurrence of AKI, and secondary infection between the HD and SD group ($P > 0.05$). Only the need for vasopressor was found to be significantly less (43% less) among the HD group compared to the SD group ($P < 0.05$) [Tables 2 and 3].

Discussion

Corticosteroids can regulate immune-mediated lung injury and decrease the development of respiratory failure and death.

Table 2: Comparison of two groups (high-dose vs. standard dose steroid) with treatment need and clinical outcome

		Survival		Significance
	No. (%)	Died	Survived	
Steroid dose				
SD	77 (100)	42 (54.5)	35 (45.5)	χ^2=0.076, df=1, P=0.078
HD	203 (100)	107 (52.7)	96 (47.3)	
Total	280 (100)	149 (53.2)	131 (46.8)	
Need of NIV				
SD	77 (100)	36 (46.7)	41 (53.3)	χ^2=1.805, df=1, P=0.179
HD	203 (100)	77 (37.9)	126 (62.1)	
Total	280 (100)	113 (40.3)	167 (59.6)	
Need of Invasive Ventilation				
SD	77 (100)	31 (40.2)	46 (59.8)	χ^2=0.964, df=1, P=0.326
HD	203 (100)	95 (46.8)	108 (53.2)	
Total	280 (100)	126 (45)	154 (55)	
Need of Vasopressors				
SD	77 (100)	41 (53.2)	36 (46.8)	χ^2=15.3, df=1, P=0.000*
HD	203 (100)	135 (66.5)	68 (33.5)	
Total	280 (100)	176 (62.8)	104 (37.2)	
Occurrence of AKI				
SD	77 (100)	51 (66.2)	26 (33.8)	χ^2=2.941, df=1, P=0.086
HD	203 (100)	155 (76.4)	48 (23.6)	
Total	280 (100)	206 (73.6)	74 (26.4)	
Occurrence of Secondary Infections				
SD	77 (100)	63 (81.8)	14 (18.2)	χ^2=0.652, df=1, P=0.419
HD	203 (100)	174 (85.7)	29 (14.3)	
Total	280 (100)	237 (84.7)	43 (15.3)	

*Significant at P<.05. HD, High dose steroid; SD, Standard dose steroid; NIV, non-invasive ventilation; AKI, acute kidney injury

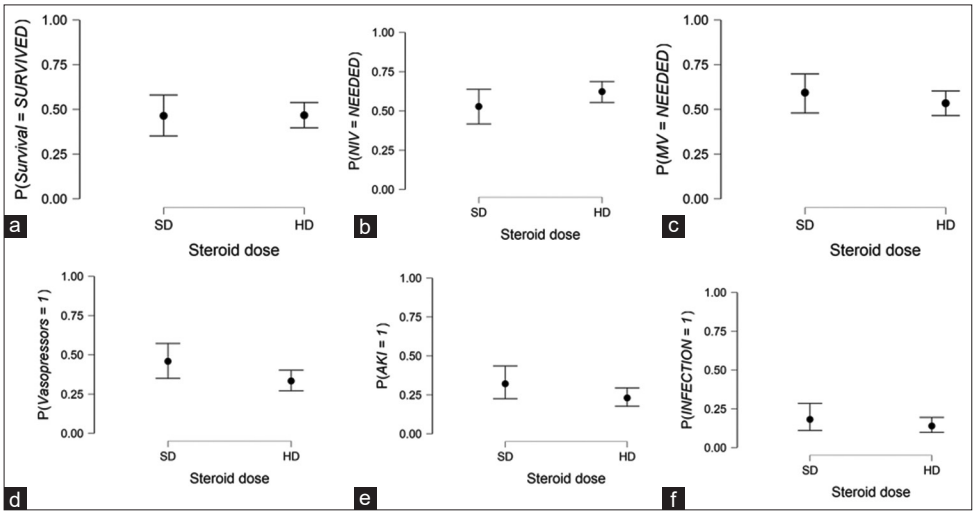

Figure 3: Probability estimate of survival (a), treatment need (b, c, d), and other clinical outcomes (e,f) with respect to steroid dose

Table 3: Primary and secondary outcomes of patients receiving high dose of corticosteroids

Outcomes[a]	Odds Ratio	95% confidence interval		*P*
		Lower bound	Upper bound	
Primary endpoint				
Death	1.077	-0.453	0.600	0.783
Secondary endpoints				
Need for NIV	1.437	-0.167	0.892	0.180
Need for Invasive Ventilation	0.766	-0.799	0.226	0.327
Need for vasopressor	0.574	-1.090	-0.022	0.041*
AKI	0.607	-1.071	0.074	0.088
Secondary infections	0.750	-0.988	0.412	0.420

*Significant at *P*<.05. NIV, non-invasive ventilation; AKI, acute kidney injury. [a]Comparisons are performed with standard dose (SD) of steroids as reference

Various studies have been conducted to study the efficacy of corticosteroids in COVID-19. Corticosteroids of different doses and types were included in numerous ongoing clinical trials. Their safety and efficacy in managing the symptoms of COVID-19, especially in the pneumonia stage, were tested. [10-12] In these trials, approximately 3,880 ARDS patients were recruited with disease stages ranging from moderate to severe respiratory distress, of which MPS was the most commonly used corticosteroids. The dangers of using large doses of corticosteroids to treat COVID-19 pneumonia include secondary infections, long-term complications, and prolonged virus shedding and escalating toward advanced stages.[13] Another study conducted by GC Khilnani and H Vijay[14] registered an increased mortality rate (35.7%) with the HD of corticosteroids. Moreover, excessive levels of glucocorticoids have shown to precipitate heart failure by aggravating fluid retention, triggering risk factors like glucose intolerance, dyslipidemia, and worsening atheromatous vascular disease.[15] Thus, the usage of corticosteroids at mild to moderate stages of COVID-19 is still questionable, with higher mortality rates than the comparator. The aim of our study was to see how different doses of MPS worked as an add-on treatment to the regular COVID-19 treatment protocol in hospitalized COVID-19 patients. Our data showed that survival, need for mechanical ventilation, the occurrence of AKI, and secondary bacterial infection are comparable among the two groups with no significant difference. However, the need for the vasopressor agent was found to be significantly more among the SD steroid group compared to the HD. The logistic regression analysis showed that there is a slightly higher risk of death for patients with an ARDS receiving HD of corticosteroids compared to SD though these results were found to be statistically non-significant. Wang *et al*.[16] conducted a retrospective cohort analysis to assess the treatment of the COVID-19 patients with a low dose of MPS with short-term duration in which it was found that the patients who received 1–2 mg/kg/day MPS for 5–7 days had a shorter hospital course duration and less need for mechanical ventilation. Still, there was no difference in the mortality rate from those who received standard care, which is in line with our results. Ranjbar K, *et al*.[17] also concluded that 2 mg/kg of MPS led to better outcomes in hypoxic hospitalized COVID-19 patients than high doses. Cano *et al*.[18] conducted a meta-analysis of 35 studies and found high heterogeneity in the doses of steroids; in 74.2% of the studies, steroids were given in low doses, in 11.4%, in high or pulse doses, and in 5.6%, a mixed regimen was used. This meta-analysis failed to prove a beneficial effect of one regimen over another. Hamed DM, *et al*.[19] found that the use of SD of MPS for 7 days was associated with significantly lower ICU admission, lower invasive ventilation, and reduced mortality at 45 days. Cheng B, *et al*.[20] also concluded that SD of corticosteroid administration was associated with a 27% risk reduction in mechanical ventilation (hazard ratio [HR]: 0.73 [0.64–0.83]) and a 20% reduction in the mortality of critically ill/severe COVID-19 patients (HR: 0.80 [0.65–0.98]).

Conclusion

In hospitalized patients suffering from severe COVID-19, an SD of MPS is as effective as an HD of MPS in terms of the reduction in mortality and a need for mechanical ventilation. Considering the increased numbers of hospital-acquired infections and mucormycosis cases in COVID-19 patients, we should use the lowest effective dose of corticosteroid in these patients.

Key Messages

During the second wave of COVID-19, considering a large number of patients, many primary care physicians are involved in patient management. The primary care physicians should not use corticosteroids in mild to moderate cases. Even in hospitalized patients suffering from severe COVID-19 pneumonia, an SD of MPS is as effective as an HD of MPS in terms of the reduction in mortality and the need for mechanical ventilation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, *et al*. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The experience of clinical immunologists from China. Clin Immunol 2020;25:108393.
2. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 2020;39:405-7.
3. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, *et al*. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497-506.
4. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420-2.

5. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, *et al*. Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 2021;384:693-704.
6. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, *et al*. Critical illness-related corticosteroid insufficiency (CIRCI): A narrative review from a multispecialty task force of the Society of critical care medicine (SCCM) and the European society of intensive care medicine (ESICM). Intensive Care Med 2017;43:1781-92.
7. Hui DS, Sung JJ. Severe acute respiratory syndrome. Chest 2003;124:12-5.
8. Papamanoli A, Yoo J, Grewal P, Predun W, Hotelling J, Jacob R, *et al*. High-dose methylprednisolone in nonintubated patients with severe COVID-19 pneumonia. Eur J Clin Investig 2021;51:e13458.
9. So C, Ro S, Murakami M, Imai R, Jinta T. High-dose, short-term corticosteroids for ARDS caused by COVID- 19: A case series. Respirol Case Rep 2020;8:e00596.
10. Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, *et al*. COVID-19 management task force. Early short-course corticosteroids in hospitalized patients with COVID-19. Clin Infect Dis 2020;71:2114-20.
11. Alzghari SK, Acuña VS. Supportive treatment with tocilizumab for COVID-19: A systematic review. J Clin Virol 2020;127:104380.
12. Salvi R, Patankar P. Emerging pharmacotherapies for COVID-19. Biomed Pharmacother 2020;128:110267.
13. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, *et al*. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. JAMA 324:1317-29.
14. Khilnani GC, Hadda V. Corticosteroids and ARDS: A review of treatment and prevention evidence. Lung India 2011;28:114-9.
15. El Hadidi S, Rosano G, Tamargo J, Agewall S, Drexel H, Kaski JC, *et al*. Potentially inappropriate Prescriptions in Heart Failure with Reduced Ejection Fraction (PIP-HFrEF). Eur Heart J Cardiovasc Pharmacother 2020;pvaa108. doi: 10.1093/ehjcvp/pvaa108. Online ahead of print.
16. Wang Y, Jiang W, He Q, Wang C, Wang B, Zhou P, *et al*. A retrospective cohort study of methylprednisolone therapy in severe patients with COVID-19 pneumonia. Signal Transduct Target Ther 2020;5:57.
17. Ranjbar K, Moghadami M, Mirahmadizadeh A, Mirahmadizadeh A, Javad Fallahi M, Khaloo V, *et al*. 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 2021;21:337.
18. Cano EJ, Fuentes XF, Campioli CC, O'Horo JC, Abu Saleh O, Odeyemi Y, *et al*. Impact of corticosteroids in coronavirus disease 2019 outcomes. Chest 2021;159:1019.
19. Hamed DM, Belhoul KM, Al Maazmi NA, Ghayoor F, Moin M, Al Suwaidi M, *et al*. Intravenous methylprednisolone with or without tocilizumab in patients with severe COVID-19 pneumonia requiring oxygen support: A prospective comparison. J Infect Public Health 2021;14:985-9.
20. Cheng B, Ma J, Yang Y, Shao T, Zhao B, Zeng L. Systemic corticosteroid administration in Coronavirus disease 2019 outcomes: An umbrella meta-analysis incorporating both mild and pulmonary fibrosis-manifested severe disease. Front Pharmacol 2021;12:670170.