



The impact of dexamethasone versus methylprednisolone upon neutrophil/lymphocyte ratio in COVID-19 patients admitted to ICU and its implication upon mortality

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ABSTRACT

Background: Up till now, there has been no definite treatment for severe acute respiratory syndrome coronavirus-2 (SARS-COV-2). Some studies have shown favorable effects of corticosteroids on COVID-19. This study aimed to compare the effect of dexamethasone versus methylprednisolone in COVID-19 patients, and their effects upon the neutrophil/lymphocyte ratio (NLR) in correlation to mortality.

Methods: A randomized double-blind clinical trial of 60 patients was divided into two equal groups. Group D, was delivered intravenous dexamethasone 8 mg/day for 7 days. Group M, was delivered intravenous methylprednisolone 1 mg/kg/day in 2 divided doses per day for 7 days. Inflammatory response monitoring by NLR and other markers was compared between the two groups.

Results: The NLR was significantly lower in the methylprednisolone group than the dexamethasone group on the 5th and 7th days (*p*-values of 0.014 and 0.019 respectively). The IL-6 was also significantly lower in the M than the D group on the 7th day (16.70 ± 5.5 versus 39.61 ± 8.19 with *p*-value 0.024). The mortality rate was significantly lower in the methylprednisolone group than dexamethasone group as well (5 versus 13 patients respectively with *p*-value = 0.024). The ROC curve for the NLR and its correlation to the mortality rate showed a higher area under the ROC curve in group M than in group D (0.968 versus 0.81 respectively). The optimal cut-off points were 13.25 in group D versus 10.65 in group M.

Conclusions: Methylprednisolone can reduce inflammatory response and mortality as reflected upon NLR and IL-6 than dexamethasone in COVID-19 patients admitted to ICU.

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1. Introduction

In December 2019, the first case of Coronavirus Illness 19 (COVID-19), a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was reported in Wuhan, China [1]. The infection then spread like a pandemic, affecting 50,446,517 people worldwide and killing 1,256,869 people as of November 9th, 2020 [2]. SARS-CoV-2 is a single-stranded RNA virus categorized as a beta coronavirus with a single stranded RNA genome. The spike's subunit S1 is responsible for virus binding to host cell receptors such as the angiotensin-converting enzyme2 receptor, while the subunit S2 contributes to virus membrane fusion with the cell membrane [3]. The virus's entry into lung epithelial cells will release danger-associated molecular patterns, which will activate local macrophages and dendritic cells, causing the inflammasomes to be released [4].

The condition is characterized by mild to severe lung inflammation as long as the virus's direct and indirect cytotoxicity stays in the epithelium. When endothelial cells are directly infected by a virus or the inflammasome, the endothelium is destroyed [5], then systemic hyperinflammation and multi-organ dysfunction become the hallmark of COVID-19 [6]. As a result, in the fight against COVID-19, modifying the immunological host response to SARS-CoV-2 has quickly become a key priority for the international research agenda. Corticosteroids are the most often utilized immune system-targeting medications in the treatment of a wide range of acute and chronic inflammatory illnesses and autoimmune diseases [7].

So, we designed a study to observe the efficacy and safety of dexamethasone versus methylprednisolone in covid-19 diseased patients upon monitoring the inflammatory response regarding Neutrophil/Lymphocyte ratio as a well-evidenced reflector of outcome in critically ill patients.

2. Patients and methods

This randomized double-blind clinical trial was initially approved by the University's Institutional Review Board (IRB17300610 on 26 May 2021), and a written informed consent was taken from the patients or their relatives. The trial was registered before patient enrollment at the Clinical Trials.gov (NCT04909918), Principal Investigator: Omar Soliman, Date of Registration: 28 May 2021).

2.1. Participants

The study involved adults (age ≥ 18 years) who were diagnosed with covid-19 with destructive inflammatory immune response needing ICU admission (any cases with respiratory rate (RR) > 30 breaths /min, partial pressure of oxygen in arterial blood/ fraction of inspired oxygen (P/F) ratio < 300 or $> 50\%$ infiltrates as in CT chest) to be run on steroid therapy. Patients were excluded for severe immunosuppression like HIV (Human immunodeficiency Virus) or long-term use of immunosuppressants for any other chronic illness, pregnant or lactating females and patients who were on acute or chronic use of corticosteroids like asthma, rheumatoid arthritis.

2.2. Randomization procedure

A random number sequence was created through an internet website (<http://www.random.org/>) and used for patients' allocation. The random number sequence was retained in closed opaque envelopes released on the day of the ICU admission by an independent physician not involved in the study. Patients were assigned randomly to two groups (30 subjects for each group). The study drug was delivered in (**Group D**) by intravenous dexamethasone 8 mg/day given for 7 days, and in (**Group M**) by intravenous methylprednisolone 1 mg/kg/day in 2 divided doses per day given for 7 days. The data collecting physicians and patients were blinded to group assignment throughout.

2.3. Inflammatory response assessment

The first 60 patients admitted to the covid-19 ICU in our university hospital were included, who fulfilled the inclusion criteria and signed informed consent. Baseline oxygen partial pressure mm Hg/ inspired O₂ fraction ratio; PaO₂/ FiO₂ (P/F) ratio, and clinical findings were noted. Baseline labs were sent for complete blood count (CBC) for neutrophil/lymphocyte ratio (NLR), initial level of C-reactive protein (CRP), D-dimer, serum ferritin and lactate levels; then, NLR, CRP, lactate, D-dimer, serum ferritin level were recorded on 2nd, 5th and 7th days. While IL-6 level was analyzed and recorded on admission and on the 7th day. Recordings

were also established regarding the need for further oxygen therapy or ventilatory handling, ICU stay, multi-organ affection and short-term mortality (7 days). Patients were given tocilizumab as and when indicated. In this way, we compared the difference in outcomes in patients receiving methylprednisolone or dexamethasone. Adverse events were treated and recorded, such as hyperglycemia (with therapeutic intervention with insulin therapy at a value greater than 180 mg/dl) [8], or superimposed bacterial infections.

2.4. Outcomes

The primary outcome was monitoring of systemic inflammation by follow up of NLR ratio at days 0, 2, 5, 7 between the two study drugs. Secondary outcomes were P/F ratio, CRP, IL-6 level, lactate level, serum ferritin, need for upgrading oxygenation and or ventilation, ICU stay, multi-organ failure and short-term mortality (7 days) and any recorded complications.

2.5. Statistical analysis

Using G*Power 3 software with an error probability of 0.05 and 80% power on a one-tailed test, we obtained a sample size of 52 patients. To overcome dropouts, 30 patients were needed in each group. Data was analyzed using IBM, SPSS (Statistical Package for Social Sciences), Version 22, 2015. The data distribution was tested for normality by the Shapiro-Wilk test. Means \pm standard deviations or standard errors were computed for quantitative variables, whereas numbers and percentages were calculated for categorical variables. Groups' categorical data were compared through the Chi-square test. Continuous parametric data was compared by unpaired t-test, whereas nonparametric data by Mann Whitney U test (between groups). Nonparametric data comparison within the same group was achieved by the Wilcoxon rank-sum test. The cutoff point of NLR in its correlation to mortality was calculated in each group using the receiver operating characteristic (ROC) curve. A P-value < 0.05 was accepted as statistically significant.

3. Results

Among the 67 patients admitted to the covid-19 ICU who were screened for eligibility, 7 patients were excluded (4 did not sign for consent and 3 were chronic steroid users). 60 patients were finally recruited and equally distributed between the two study groups, as shown in the flow diagram of the studied groups (Figure 1). The demographic data of the enrolled patients (including age, gender, weight, height, body mass index (BMI) and the clinical data (smoking, ICU stay, received Tocilizumab, vasopressors needed, hyperglycemia ≥ 180 mg/dl, multi-organ affection and co-existing diseases) showed no significant differences

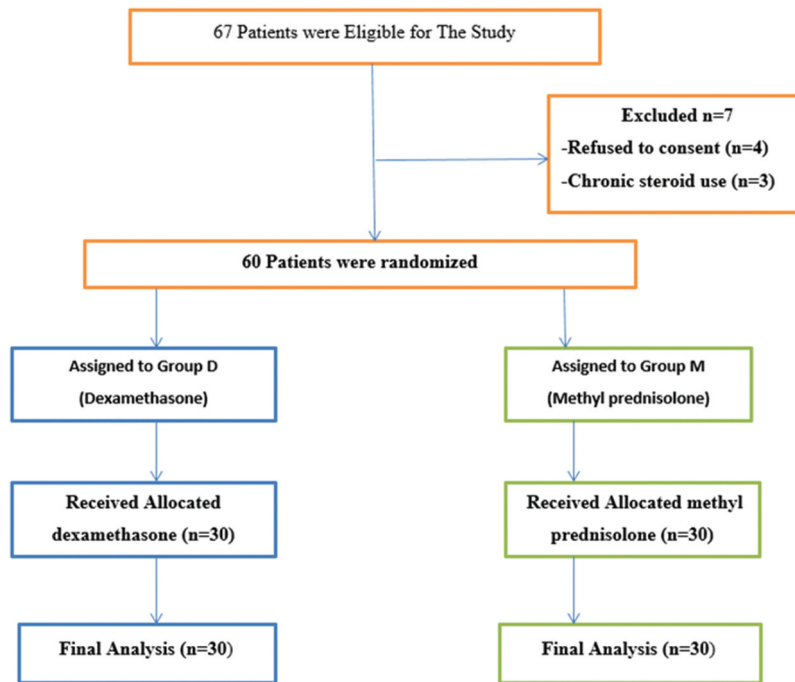


Figure 1. Flow diagram of participants in the two study groups.

between the two study groups. However, the superimposed bacterial infection was of significantly higher incidence in group D versus group M (Table 1).

Regarding the NLR, it was significantly lower in group M in comparison to group D on the 5th and 7th days post-admission. Its values also significantly decreased only in the M group during the whole follow up period (Table 2).

Table 1. Demographic and clinical data in the two study groups.

Variables	Group D n = 30	Group M n = 30	P-value
Age (years)	58.13 ± 7.6	60.60 ± 6.6	0.19
Gender (m/f)	14/16	17/13	0.60
Weight (cm)	91.17 ± 9.5	93.37 ± 7.8	0.33
Height (kg)	167.7 ± 3.65	168 ± 3.8	0.75
Body mass index (kg/m ²)	32.43 ± 3.4	33.09 ± 2.69	0.4
Smoking	20 (66.7%)	22 (73.3%)	0.78
ICU stay (day)	12.67 ± 2.9	13.37 ± 2.7	0.34
Received Tocilizumab	10(33%)	8(26.7%)	0.78
Vasopressors needed	5 (16.7%)	6 (20%)	1
Superimposed bacterial infection	12(40%)	3 (10%)	0.01
Coexisting diseases			
Chronic obstructive lung disease	2 (6.6%)	1(3.3%)	0.5
Obstructive sleep apnea syndrome	5 (16.6%)	6 (20%)	0.5
Hypertensive	17 (56.6%)	17 (56.6%)	1
Ischemic heart disease	4 (13.3%)	5 (16.6%)	0.5
Hepatic impairment	1(3.3%)	2 (6.6%)	0.50
Chronic kidney disease	1(3.3%)	1(3.3%)	1
Diabetes	16 (53.3%)	14 (46.6%)	0.398
Previous cerebrovascular accident (CVA)	1(3.3%)	1(3.3%)	1
Oncology	2 (6.6%)	0 (0%)	0.24

Data are presented as mean ± standard deviation, ratio, number (percentage). $P < 0.05$ is considered statistically significant. Group D (Dexamethasone) and Group M (Methylprednisolone).

The 7th day IL-6 value in group M was significantly lower in comparison to its corresponding value in group D and to the baseline value within the same group as well. On the other hand, CRP data was significantly lower in group M than in group D on the 2nd, 5th, and 7th days. There was a significant decrease in the CRP during the whole follow-up in comparison to the baseline value in group M only (Table 2).

The mortality rate was significantly higher in group D (13 patients died) versus in group M (5 patients died) as shown in supplementary figure 1. The ROC curves for the NLR and its correlation to the mortality rate showed a higher area under the ROC curve in group

Table 2. Inflammatory markers in the two study groups.

Variables	Group D n = 30	Group M n = 30	P-value
Neutrophil/lymphocyte ratio (NLR)			
Admission	12 ± 0.87	10.7 ± 0.49	0.63
2nd day	12.79 ± 1.11	9.80 ± 0.50*	0.09
5th day	13.76 ± 1.39	9.43 ± 0.78*	0.014
7th day	13.12 ± 1.36	8.74 ± 0.90*	0.019
Interleukin-6 (IL-6) pg/ml			
Admission	20.75 ± 3.3	20.12 ± 2.44	0.55
7th day	39.61 ± 8.19*	16.70 ± 5.5	0.024
C-reactive proteins (CRP) mg/dl			
Admission	153.73 ± 18.15	139.27 ± 0.16.67	0.75
2nd day	155.43 ± 14.60	119.33 ± 16.22*	0.039
5th day	157.47 ± 15.40	112.23 ± 16.33*	0.026
7th day	155.33 ± 16.20	105.37 ± 15.80*	0.012

Data are presented as mean ± standard error. (*) significant change from the baseline value in the same group. $P < 0.05$ is considered statistically significant. Group D (Dexamethasone) and Group M (Methylprednisolone).

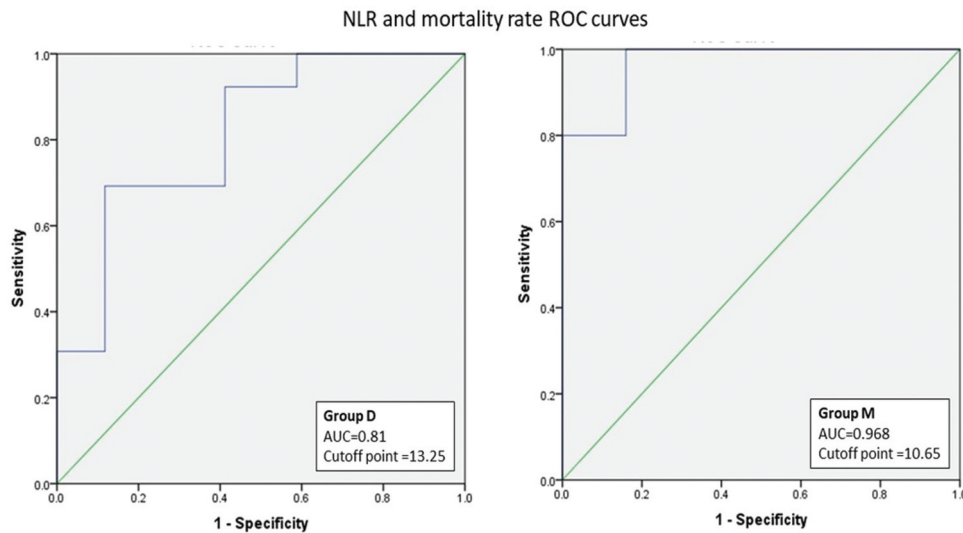


Figure 2. NLR and mortality rate ROC curves in the two study groups.

M than in group D (0.968 versus 0.81). The optimal cut-off points were 13.25 in group D versus 10.65 in group M, as shown in [Figure 2](#).

The number of patients who were in need of further oxygenation &/or ventilation showed an insignificant difference between the two groups. However, the P/F ratio was significantly higher in group M than group D on the 5th and 7th days. The P/F ratio showed a significant increase during the whole follow-up period when compared to its corresponding baseline value in the same group in group M only ([Table 3](#)).

In regards to the D-dimer and serum ferritin levels, there were insignificant differences between the two groups throughout all days of ICU admission. The follow-up value was significantly lower than the baseline value on the 5th day regarding the D-dimer and on the 7th day for both ([Table 4](#)).

There were no significant differences regarding hemodynamics and temperature data as well as the number of affected systems during the follow-up period between the two groups.

Table 3. Oxygenation and Ventilation variables in the two study groups.

Variables	Group D n = 30	Group M n = 30	P-value
Need for ventilation	4 (13%)	10 (33.3%)	0.06
Need for ventilation and/or oxygenation	26 (86.6%)	20 (66.6%)	0.06
P/F ratio			
Admission	61.23 ± 11.2	56.00 ± 8.8	0.05
2nd day	61.03 ± 8.9	61.23 ± 9*	0.93
5th day	58.30 ± 9.8	66.60 ± 11.2*	0.003
7th day	59.50 ± 14.5	70.23 ± 13.3*	0.004

P/F is oxygen partial pressure mm Hg/ inspired O₂ fraction ratio. Data are presented as number (percentage) and mean ± standard deviation. (*) significant change from the baseline value in the same group. $P < 0.05$ is considered statistically significant. Group D (Dexamethasone) and Group M (Methylprednisolone).

4. Discussion

To present, the only medications that have shown a statistically meaningful reduction in fatalities among COVID-19 patients are corticosteroids [9]. Corticosteroids are prescribed for COVID-19 patients who are experiencing acute respiratory failure (ARF) [10]. In our investigation, we found that the methylprednisolone group had a lower inflammatory response and mortality rate than the dexamethasone group in very ill COVID-19 patients admitted to the ICU. In addition, the number of patients with superimposed bacterial infection was lower in the methylprednisolone group than in the dexamethasone group.

A prominent cause of acute respiratory distress syndrome (ARDS) in COVID-19 patients is the excessive and uncontrolled synthesis of soluble inflammatory markers known as cytokine storm [11,12]. The leading cause of death in COVID-19 is ARDS, which is defined

Table 4. Serum ferritin, D-dimer, and lactate levels in the two study groups.

Variables	Group D n = 30	Group M n = 30	P-value
Serum ferritin ng/ml			
Admission	655.60 ± 61.2	784.63 ± 76.9	0.20
2nd day	788.50 ± 74.3*	832.63 ± 73.4*	0.80
5th day	804.03 ± 78.5*	889.60 ± 74.6*	0.31
7th day	840.03 ± 96.2	783.73 ± 74.9	0.06
D-dimer mcg/ml			
Admission	4.690 ± 0.58	4.423 ± 0.67	0.47
2nd day	4.177 ± 0.53	3.960 ± 0.55	0.62
5th day	4.013 ± 0.47	3.547 ± 0.50*	0.34
7th day	3.897 ± 0.51	2.797 ± 0.49*	0.06
Serum lactate mmol/L			
Admission	2.603 ± 0.24	2.467 ± 0.23	0.71
2nd day	2.600 ± 0.23	2.233 ± 0.16	0.22
5th day	2.62 ± 0.25	2.14 ± 0.15	0.18
7th day	2.457 ± 0.23	1.873 ± 0.16*	0.10

Data are presented as mean ± standard error. (*) significant change from the baseline value in the same group. $P < 0.05$ is considered statistically significant. Group D (Dexamethasone) and Group M (Methylprednisolone).

by immune cell infiltration in both the lungs and hypoxemia. In ARDS, inflammation damages alveolar-capillary membranes, resulting in increased lung permeability and the exudation of high protein edematous fluid into air sacs [13].

Pro-inflammatory cytokines (IL-6, IL-12, and Interferon Gamma) and chemokines (CXCL10, CCL2) have been implicated in the pulmonary inflammation associated with ARDS, according to previous research on SARS and the Middle East Respiratory Syndrome-related coronavirus (MERS) [14]. Huang et al. found that pro-inflammatory cytokines and chemokines are higher in SARS-CoV-2 infected individuals in a recent study [15]. T-helper-1 (Th1) immune cells are activated by a storm of pro-inflammatory cytokines and chemokines. The recruitment of IL-4 and IL-10, which have the primary function of reducing inflammation, is triggered by Th1 cell activation. Because of the risk of secondary infections, adverse effects, and other complications associated with corticosteroid use, the potential function of corticosteroids in inhibiting the inflammatory pathway in critical conditions must be carefully examined [16]. COVID-19 is caused by the production of pro-inflammatory cytokines by macrophages in the alveoli of the lungs [17]. Corticosteroids are used to reduce the host's inflammatory response in the lungs, which can contribute to ARDS and severe lung damage [18]. Critical COVID-19 is a life-threatening multi-organ failure syndrome generated by the host's reaction to SARS-CoV-2. It is characterized by refractory hypoxemia caused by ARDS.

One of the anti-inflammatory drugs utilized in critical patients was glucocorticoid [19]. Dexamethasone (a cortisol derivative) is a well-known life-saving medicine that is often used to treat inflammatory and autoimmune diseases. Rheumatoid arthritis, skin illnesses, asthma, numerous types of allergies, chronic obstructive pulmonary disease, brain edema, eye pain from eye surgery, and bronchospasm are all treated with it [20]. Methylprednisolone (Depo-Medrol, Medrol, Solu-Medrol) is a synthetic glucocorticoid used to treat inflammation and suppress the immune system. It's either administered in modest doses for chronic conditions or in large doses concurrently during acute flares. Methylprednisolone and its derivatives can be taken orally or injected intravenously [21].

In accordance with our results; Stern et al. performed a Cochrane search that comprised randomized controlled trials (RCT) comparing systemic corticosteroid therapy, provided as an adjuvant to antibiotic treatment, to placebo or no corticosteroids for adults and children with pneumonia. Corticosteroids significantly reduced mortality in adults with severe pneumonia (RR 0.58, 95% CI 0.40–0.84), according to 17 RCT (n = 2264) [22]. Early (beginning 7 days after admission), low-dose (no more than 80 mg/day), and short-term (no more than 7 days) methylprednisolone

therapy significantly reduced 60-day fatality, according to Yang Z et al [15]. Supporting the findings of the Ji J et al [23]. multicenter retrospective cohort study, methylprednisolone therapy reduced the 60-fatality rate for COVID-19 patients diagnosed as critical, that is, those who developed respiratory failure and required mechanical ventilation, shock, or multiple organ failure requiring ICU monitoring. Furthermore, one prospective trial found that methylprednisolone given within the second week of the onset of symptoms improved the outcome of COVID-19 patients [24]. As a result, methylprednisolone may be beneficial for patients with COVID-19 in the late stage. Edalatifard M. et al. published a controlled clinical trial [9] in which 68 patients were randomized to either standard care with methylprednisolone pulse (intravenous injection, 250 mg/day for 3 days) or standard care alone. They found that the methylprednisolone group had better outcomes (reduced time to discharge and lower mortality rate) than the standard care group.

The Oxford RECOVERY Trial also randomized the use of low-dose dexamethasone, lopinavir-ritonavir, hydroxychloroquine, and azithromycin. Only dexamethasone was successful in lowering the COVID-19-related death rate. The usage of dexamethasone at a dose of 6 mg per day for 10 days was used to examine the clinical effectiveness of dexamethasone versus standard treatment alone in those patients [9]. Dexamethasone lowered the death rate in ventilator-dependent patients by one-third and in oxygen-dependent patients by one-fifth [25]. Dexamethasone reduced mortality risk from 40% to 28% in ventilated patients and from 25% to 20% in patients on oxygen therapy over the course of 28 days, according to preliminary findings. In mild situations, dexamethasone had no major adverse effects and was ineffective [26].

On the other hand, Yang and colleagues, found that patients who received glucocorticoid had a greater mortality rate [15], implying that glucocorticoid treatment may not be beneficial for all patients. When steroids are used to treat viral lung infections, some studies have revealed negative results. Observational studies show that when steroids are administered to treat influenza-induced acute lung damage, there is a greater mortality rate. The use of steroids was linked to increased mortality and length of ICU stay in patients with influenza pneumonia, according to a recent meta-analysis of 10 studies with a total of 6548 patients. These effects could be due to steroids' immunosuppressive effects, which lead to prolonged viremia and an increased risk of bacterial super infection. Furthermore, steroids may raise the risk of various systemic problems, such as autoimmune and cardiovascular events, as well as enhance resistance to neuromuscular blocking drugs, which are commonly used during mechanical breathing in SARS patients [27].

There was also a higher incidence of psychosis associated with high dosages of corticosteroids, as well as hyperglycemia, delayed virus clearance, and avascular necrosis [28]. As a result, these patients must be monitored for the long-term effects of the high-dose glucocorticoid medication they are receiving, and necessary efforts must be made to ensure that they have a higher quality of life.

5. Strengths and limitations

The study's strengths were that we employed low doses of steroids to avoid side effects in our immune-compromised individuals. Furthermore, both groups were randomly assigned, and virtually all of the patients in both groups had co-existing disorders. Limitations; first and foremost, our study lacked a control group; nonetheless, this is unethical because we cannot prohibit these crucial medications in the absence of a definitive COVID-19 treatment. Second, when they were discharged from the ICU, our patients were not followed up on (clinical, laboratory, and CT chest). Our findings cannot be applied to all COVID-19 patients at all stages and degrees.

6. Implications

In severe cases of COVID-19 patients admitted to the ICU, our findings suggest utilizing low doses of steroids, particularly methylprednisolone, to combat the inflammatory response and prevent excessive dosages of these medicines and their associated negative effects. Future researchers should collaborate with other COVID-19 centers and conduct studies with early steroid administration in patients with increased co-morbidities. Finally, further information about corticosteroid dose and timing is required.

7. In conclusion

Methylprednisolone is more efficacious than dexamethasone in lowering the inflammatory response and mortality in patients with severe COVID-19 respiratory failure. Although the use of systemic corticosteroids is controversial due to the delayed onset of injury or virus shedding, they can be administered safely if the right instances, dosing, and timing are chosen.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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