# Effect of corticosteroids in patients with COVID-19 early stage pneumonia and risk of disease progression: An uncharted territory

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**SUMMARY**     Corticosteroids are one of the few drugs that have shown a reduction in mortality in coronavirus disease 2019 (COVID-19). In the RECOVERY trial, the use of dexamethasone reduced 28-day mortality compared to standard care in hospitalized patients with suspected or confirmed COVID-19 requiring supplemental oxygen or invasive mechanical ventilation. No benefit in patients not requiring respiratory support at randomization was observed. However, we believe that the use of corticosteroids in patients with COVID-19 pneumonia might not be subject to a decision based solely on oxygen needs. Evidence has shown that 30% of COVID-19 patients in its initial phases will progress to acute respiratory distress syndrome, particularly patients in whom laboratory inflammatory biomarkers associated with COVID-19 disease progression are detected. We postulated that corticosteroids in patients with COVID-19 in its initial phases and risk of progressing to severe disease might lead to a decrease in the development of acute respiratory distress syndrome, and thereby reduce death.

*Keywords*     COVID-19 pneumonia, corticosteroids, adult respiratory distress syndrome, hypoxia, inflammatory biological markers

To the Editor,

Corticosteroids were the first group of drugs that showed clinical benefit in coronavirus disease 2019 (COVID-19) patients. In the RECOVERY Trial, conducted during the first SARS-CoV-2 wave, the use of dexamethasone resulted in lower 28-day mortality in patients hospitalized with COVID-19 who were receiving supplemental oxygen or invasive mechanical ventilation compared to standard care, but not among those receiving no respiratory support at randomization (*1*). This finding was supported by a prospective meta-analysis of seven randomized clinical trials by the WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group, which also confirmed that administration of corticosteroids in critically ill patients with COVID-19 was associated with a lower 28-day all-cause mortality, compared to usual care or placebo (*2*). Although current COVID-19 Treatment Guidelines do not recommend the use of corticosteroids in patients without oxygen needs (*3-5*), the optimal timing for initiating corticosteroids in hospitalized COVID-19 patients remains unclear. Therefore, we read with interest the recent study by Aggarwal *et al.* (*6*) in Drug Discoveries & Therapeutics.

In this study, the authors evaluated retrospectively the role of corticosteroids in preventing hypoxia in symptomatic COVID-19 patients with peripheral capillary oxygen saturation ≥ 94% on room-air. A total of 140 consecutive COVID-19 patients were included. Progression to hypoxia was significantly higher in patients who received corticosteroids before day 7 of symptoms (36.7% *vs*. 14.3%). Kaplan-Meier curves showed that patients with early corticosteroid intake had an increased risk for oxygen requirement at 30 days (HR: 4.38, 95% CI = 1.84-10.4, $p = 0.001$) compared to delayed corticosteroid administration. Findings from this observational study provide real-world evidence demonstrating a significantly increased risk of progression to acute respiratory failure in symptomatic COVID-19 patients who received early treatment with corticosteroids. However, we believe that definitive conclusions regarding the use of corticosteroids in COVID-19 patients without additional oxygen needs should be further discussed.

Even though RECOVERY trial showed that dexamethasone was not effective in reducing mortality

**Table 1. Laboratory biomarkers associated with COVID-19 disease progression** (*8,9*)

| Elevations in | |
| --- | --- |
| D-dimer | > 1,000 ng/mL |
| LDH | > 245 units/L |
| CRP | > 100 mg/L |
| Ferritin | > 500 mcg/L |
| Troponin | > 2 × the upper limit of normal |
| CPK | > 2 × the upper limit of normal |
| Decrease in: | |
| Absolute lymphocyte count | < 800/microL |

*Abbreviations*: CRP, C-reactive protein; LDH, lactate dehydrogenase; CPK, creatine phosphokinase.

in patients with SARS-CoV-2 pneumonia without the need for supplemental oxygen and patients with symptoms for less than 7 days, we postulate that the use of corticosteroids in patients with COVID-19 pneumonia should not be based solely on oxygen needs or time from symptoms onset. Evidence has shown that 30% of COVID-19 patients in its initial phases will progress to severe life-threatening disease, largely due to acute respiratory distress syndrome (ARDS) (*7*). Inflammatory parameters are one of the most significant risk markers to identify patients with a high risk of COVID-19 disease progression and mortality (Table 1). Corticosteroids might have a different effect in patients with COVID-19 in its initial phases depending on the degree of underlying inflammation. Laboratory biomarkers such as C-reactive protein, D-dimer, or lactate dehydrogenase are strictly related to COVID-19 severity and they could be helpful for risk stratification, identifying patients at high-risk of ARDS who might potentially benefit from early treatment with corticosteroids, attenuating the cytokine storm, thereby preventing the progression to ARDS and death (*8,9*). Unfortunately, the RECOVERY trial did not differentiate between patients with elevated inflammatory parameters and without them among patients without oxygen needs. Hence, it is possible that the benefit of glucocorticoids in this subgroup of patients was underestimated. In accordance with this hypothesis, in the previously mentioned study by Aggarwal *et al*. (*6*), the risk of developing hypoxia was higher in patients with a high C-reactive protein (OR: 1.03, 95% CI: 1.02-1.06, $p < 0.001$). However, the analysis might be limited by a small sample size.

Estimating the impact of corticosteroid treatments in COVID-19 patients during its initial phase is challenging. We believe that there is a need for randomized, blinded, placebo-controlled clinical trials for evaluating the impact of corticosteroids in this specific subpopulation of patients with COVID-19 pneumonia.

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