



# Corticosteroids in acute respiratory distress syndrome: outcomes obscured by mortality

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The potential benefit and harm of using corticosteroids to manage acute respiratory distress syndrome (ARDS) have been evaluated since the 1980s [1-8]. However, studies have yielded contradictory results, and clinicians are confused whether corticosteroids are their friend or foe in the management of ARDS.

In an article published in *The Korean Journal of Internal Medicine*, Baek et al. [9] report the results of a propensity-matched cohort study that investigated the effect of corticosteroids administered in the early phase of ARDS. In that study, the use of corticosteroids was not associated with 28 days (odds ratio [OR], 1.031; 95% confidence interval [CI], 0.657 to 1.618;  $p = 0.895$ ) and 90 days (OR, 1.435; 95% CI, 0.877 to 2.348;  $p = 0.151$ ) mortality rates after adjusting propensity scores. However, the corticosteroid-treated group showed a prolonged mechanical ventilation period (12 days in the corticosteroid-treated group vs. 8 days in the control group,  $p < 0.001$ ), which may have contributed to a higher incidence of pneumothorax (10.9% vs. 3.7%,  $p = 0.007$ ) and a longer stay in the intensive care unit (16 days vs. 10 days,  $p < 0.001$ ). Furthermore, bacteremia was significantly more frequent in the corticosteroid-treated group (41.1%

vs. 30.4%,  $p = 0.019$ ), suggesting harmful immunosuppression.

Corticosteroids reduce inflammation and fibrosis, which can be useful in the treatment of ARDS [1-8]. However, corticosteroid therapy has been reported to be ineffective or even harmful in the late phase of the disease [5]. In the Late Steroid Rescue Study (LaSRS), corticosteroids did not benefit the 60 days (29.2% in the corticosteroid-treated group vs. 28.6% in the control group,  $p = 1.0$ ) or 180 days (31.5% in the corticosteroid-treated group vs. 31.9% in the control group,  $p = 1.0$ ) mortality rate. Furthermore, the use of corticosteroids was associated with increased mortality rates (35% vs. 8%,  $p = 0.02$  for 60 days mortality; 44% vs. 12%,  $p = 0.01$  for 180 days mortality) if administered > 14 days after the onset of ARDS.

By contrast, in the early phase of ARDS, particularly before fibrosis develops, the effect of corticosteroids on mortality is contentious [1-3,6-8]. In the randomized controlled trial by Tongyoo et al. [6], administration of corticosteroids was not associated with 28-day mortality (22.5% vs. 27.3%, relative risk, 0.82; 95% CI, 0.50 to 1.34;  $p = 0.51$ ), in line with the findings of Baek et al. [9]. By contrast, a recent randomized controlled trial by Villar et al. [7] showed that treatment with corticosteroids was associated with decreased mortality at

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day 60 (21% vs. 36%; between group difference, -15.3%; 95% CI, -25.9 to -4.9;  $p = 0.0047$ ). The Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial, which included patients with coronavirus disease 2019 (COVID19), also suggested a potential benefit of corticosteroids on 28-day mortality (age-adjusted rate ratio, 0.83; 95% CI, 0.75 to 0.93;  $p < 0.001$ ) [8], indicating that there may be a subgroup that responds to the treatment.

Although mortality is an important endpoint, it is affected by numerous confounders, and thus tends to be poorly replicable in critically ill patients [10-12]. In such cases, secondary outcomes with softer endpoints provide considerable insight for clinicians. Therefore, the increased incidence of pneumothorax and bacteremia in the corticosteroid-treated group reported by Baek et al. [9] is remarkable. Other potential harmful effects of corticosteroids, such as neuromuscular weakness, immunosuppression, superimposed infection, and an increased blood glucose level, have been investigated [13]. The mineralocorticoid effect of steroids is also associated with adverse outcomes in patients with lung injury because it facilitates fluid and sodium retention [14].

Despite several limitations, the present study highlights the potential harm of corticosteroids, which is usually concealed by mortality. On the principle of *primum non nocere* (first, do no harm), there is insufficient evidence to support the routine use of corticosteroids in patients with ARDS. The administration of corticosteroids should be limited to subgroups that may respond to treatment (i.e., patients with COVID19-associated ARDS), and even in such cases clinicians should be aware of the potential harm of the treatment and closely monitor the patient for adverse events.

### Conflict of interest

No potential conflict of interest relevant to this article was reported

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