Corticosteroids were among the first therapies assessed for Covid-19 patients. Low risk of bias trials indicated a benefit in reducing mortality of hospitalized patients treated with dexamethasone compared to placebo.\(^1\)

A systematic review commissioned by the World Health Organization (WHO)\(^2\) included 7 trials (n = 1703) assessing dexamethasone, hydrocortisone, or methylprednisolone for Covid-19 critically ill patients. Although the benefits on mortality reduction were also clear with the combined corticosteroids analysis, the specific drug subgroup analysis was very underpowered for methylprednisolone, as this was restricted to one trial with 47 patients.

Since the publication of these results, corticosteroids were widely adopted as a treatment protocol for Covid-19 patients in several guidelines and recommendations, but clinicians still wonder which corticosteroids are the best choice. Although the robust evidence is based on dexamethasone, there is a hypothesis that methylprednisolone would be a better fit for critically ill patients.

The rationale for preferring methylprednisolone is based on the hypothesis that alternative corticosteroids including prednisone, methylprednisolone, or hydrocortisone may be used if dexamethasone is unavailable (National Institutes of Health (NIH) recommendation rating scheme B - moderate recommendation for the statement III - expert opinion).\(^1\)

This interesting clinical question led to the design and publication of several studies performing a head-to-head comparison of methylprednisolone versus dexamethasone. Although this is a valid research question, there must be caution in interpreting some published research results.

### Caveats

Following the importance of the topic, we read with great interest the recently published research article on BMC Infectious disease “Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial” by Ranjbar et al.\(^4\)
The authors had reported a randomized clinical trial that enrolled 93 patients at Faghihi hospital in Shiraz, Iran, between August 10, 2020, and November 15, 2020. The patients were blindly allocated to receive methylprednisolone or dexamethasone.

As reported in the published manuscript, the clinical trial had been registered in the Iranian Registry of Clinical Trials under the registration number IRCT20200204046369N1. The first version of the protocol was prospectively published on April 08, 2020, and the registry was updated one time on November 20, 2020 (five days after the end of the recruitment period).

After comparing the history versions between the first published registry (April 08, 2020, https://en.irct.ir/trial/46776?revision=128680) and the final registry version (https://en.irct.ir/trial/46776?revision=162028) and the published paper⁴, we have identified that several inconsistencies had not been discussed in the paper published.

The first registry version described the study as “not blinded” and “not randomized.” The target sample size was 48, but no power calculation had been provided. The planned primary outcome had been described as “PAO2/fio2” at five days, and the secondary outcomes were “O2 saturation”, “clinical follow-up including vital signs (temperature, pulse rate, respiratory rate, blood pressure) and laboratory data (CBC and Diff, LFT, BUN, creatinine)” and “Chest CT findings.”

There were several relevant changes in the second registry version in the methodological characteristics and the outcome definition compared to the first registry. The second registry version was following the published paper.⁴ The study was reported as “triple blinded” and “randomized.” The target sample size was increased to 82, and no explanation had been given. The primary outcome was changed to “all-cause mortality in 28 days” and “clinical status at 5 and 10 days after intervention”, and secondary outcomes were changed to “intubation and need for ventilation, and also admission to ICU” and “duration of hospital admission.”

The presented reason for the update of the trial registry provided by the authors was that “corrections were made regarding randomization and the method of conducting the trial.”

We believe that these substantial changes described from the first to the second version of the protocol should be transparent to the scientific community to enable reproducibility. Moreover, all reasons for each decision carried out from the inception to the publication need to be presented and discussed by the study authors, as this is essential to fostering research integrity.⁵

**Author contributions**

All authors participated in the conceptualization of the paper. Pacheco RL, Wiltgen D, Mamede H were responsible for writing. Stein AT was responsible for review and editing. All authors approved the final version.

**Competing interests**

No financial, legal, or political competing interests with third parties (government, commercial, private foundation, etc.) were disclosed for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.).

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