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Early View

Correspondence

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Is high-dose glucocorticoid beneficial in COVID-19? Response to Correspondence

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To the editor

In the recent correspondence "Is high-dose glucocorticoid beneficial in COVID-19?" Muthu et al. raised some issues related to our recent clinical trial "Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial" [1]. This provides a welcome opportunity to further explain the outcome of using a high dose of glucocorticoid for the treatment of severe COVID-19 patients.

Muthu and colleagues suggested that our mortality rate was higher than expected based on the RECOVERY trial, however, there are clear differences in the patient populations that make this an inappropriate comparison. The mortality rate of our control group is more than the mortality rate of the RECOVERY trial because all of the patients included in this study were hospitalised in an intensive care unit (ICU) and all of them received oxygen support. However, in the RECOVERY trial 6425 hospitalised COVID-19 patients were included (not mentioned at ICU or

general units) and 24% of them did not receive oxygen support [2]. Besides, the mortality rate of COVID-19 is different among different ethnic groups. In an observational study conducted on 905 COVID-19 patients hospitalised in Imam Khomeini hospital complex in Tehran, Iran, the mortality rate of ICU admitted patients was reported 50% [3]. Muthu et al. also claimed that a higher mortality rate in the control arm may be due to the better supportive care provided to the intervention arm. We believe this is an inappropriate suggestion because, according to the moral and ethical guidelines, equal supportive care was provided for all patients enrolled in this study in both standard care and intervention arms.

Muthu et al. also stated that the justification provided for our sample size is inadequate. To address this point we note that, although the beneficial use of corticosteroid for treatment of COVID-19 patients who are in the pulmonary phase have now been shown in different clinical studies, the use of corticosteroids for the treatment of COVID-19 was doubtable when we conducted this clinical trial (April 20, 2020), and WHO recommended against the routine use of systemic corticosteroids for the treatment of viral pneumonia [4]. Therefore, for using a high dose of methylprednisolone, the minimum sample size was estimated.

Muthu and colleagues expressed that clinical improvement in our study was defined by quick fever subsidence and a sense of well-being in subjective parameters. We postulated that hospital discharge was performed based on the national discharge protocol for COVID-19 at that time in our trial and the clinical improvement was determined based on SO2 more than 93%, BORG score more than 3, stopped fever for 3 days, improved dyspnea, normal urinary output, tolerated oral regimen (PO), and reduced C-reactive protein (CRP) level without any treatment adverse effects. However, we followed up discharged patients in both groups, and the general symptoms, clinical features, and characteristics of the recovered patients were also evaluated one week after discharge time. The data regarding patients' clinical features 7 days after discharge time were presented in Supplementary Table 2 of the article [1].

Muthu et al. also declared that a higher prevalence of diabetes mellitus (DM) in the control group in our study resulted in reduced adverse events in the intervention group. Since the patients in our study were randomly allocated into two groups, we did not match them according to their coexisting conditions. Although the prevalence of DM in the patients of the usual care group was higher, the level of respiratory rate and the level of heart rate were significantly elevated in the methylprednisolone group. Besides, the number of patients who have

pulmonary involvement upper than 70%, and the number of patients who need non-invasive ventilation or reservoir mask before enrollment was higher in the methylprednisolone group. Besides, we did not observe a difference in the level of patients' blood sugar regarding their clinical status. It is worth mentioning that uncontrolled DM is one of our exclusion criteria and COVID-19 patients with uncontrolled DM were excluded from this study [1]. Regarding the use of high doses of glucocorticoid and an increased risk of infectious complications in patients, we emphasised that we did not see any infectious adverse events in the methylprednisolone group including COVID-associated pulmonary aspergillosis and mucormycosis.

To conclude, we appreciate the interest of Muthu and colleagues in our article and appreciate the opportunity to share our experience regarding using glucocorticoids for the treatment of COVID-19 patients. Our data support the beneficial use of a high dose of methylprednisolone for the treatment of severe COVID-19 patients, however, more clinical studies with a higher sample size are needed.

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