Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Spurious undermining of the adjuvant role of vitamin D in COVID-19

Sir,

We read with great interest the systematic review and meta-analysis by Rawat *et al*. The authors did not find any clinical benefit of vitamin D supplementation in COVID-19 [1]. However, the results are in stark contrast to a recently published systematic review and meta-analysis by Pal *et al*. that had included 13 studies and had shown significant benefits of vitamin D supplementation in terms of reduction in mortality and/or intensive care unit (ICU) admission [2].

The systematic review and meta-analysis by Rawat *et al*. had included only 5 studies. As per the exclusion criteria, observational studies were excluded. However, amongst the 5 studies, 2 were quasi-experimental studies. For the purpose of meta-analysis, quasi-experimental studies are often regarded as observational studies [3]. Besides, as per the inclusion criteria, only studies wherein vitamin D had been supplemented prospectively, i.e., after the diagnosis of COVID-19 were meant to be included. However, the study by Annweiler et al. had considered the use of oral cholecalciferol in the week following the suspicion or diagnosis of COVID-19 or during the previous month [4]; hence, the study did not strictly cater to the use of vitamin D prospectively and should not have been included as per the eligibility criteria.

The results of the meta-analysis were largely skewed by the randomized controlled trial (RCT) by Murai *et al*. that found no beneficial effect of vitamin D supplementation on mortality, ICU admission, or requirement of mechanical ventilation [5]. However, the RCT by Murai *et al*. had certain limitations. Of note, the baseline characteristics of the two groups (vitamin D group vs. placebo group) were not matched with the intervention group having a higher prevalence of diabetes, hypertension, and obesity. Besides, there were gender and racial differences between the two groups. Furthermore, adjusted risk estimates were not reported in this RCT [2].

The present meta-analysis by Rawat *et al*. had provided only pooled unadjusted risk estimates, thereby failing to take into account the confounding effect of multiple factors. On the contrary, Pal *et al*. had reported unadjusted as well as adjusted risk estimates, thereby making the results more robust and generalizable.

In short, the results of the systematic review and meta-analysis by Rawat *et al*. should be interpreted with a pinch of salt. Rather, vitamin D supplementation might be associated with improved clinical outcomes, especially when administered after the diagnosis of COVID-19. However, issues regarding the appropriate dose, duration, and mode of administration of vitamin D remain unanswered and need further research [2].

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Declaration of competing interest

None.

Reply to: Spurious Undermining of The Adjuvant Role of Vitamin D In COVID-19.

At the outset of our letter, we must thank Pal & Banerjee [6] for their constructive criticism to our meta-analysis of randomized and quasi-randomized trials [7], that reported no benefit of vitamin D supplementation in SARS- CoV-2 infected patients. Our meta-analysis included 3 RCTs [8–10] and two quasi-experimental studies [11,12] and amongst them one RCT did not report mortality or any other clinical endpoints. We understand limitation of mixing quasi-experimental or observational studies with RCTs for data analysis [13], however, pooled analysis from two RCTs also reported no mortality benefit [RR (95% CI) 0.58 (0.05–7.18), p = 0.67]. In our original analysis, other patients' centric secondary outcomes such as requirement of mechanical ventilation and intensive care unit admission were not reduced with vitamin D supplementation and only RCTs were included in that analysis. Another meta-analysis by Pal et al. [14], referred in this letter, that included 13 RCTs and observational studies, reported benefit of vitamin D, both in adjusted and unadjusted analysis. It's worth mentioning that, adjusted analysis has also it's limitation, as one can only adjust known baseline variables and can't be considered as an alternative to RCT. Observational studies included in the meta-analysis by Pal et al. [14] has some serious limitations, detailed discussion of which is beyond the scope of this letter. It's worth mentioning that majority of the observational studies didn't report baseline disease severity such as PaO_2/FiO_2 ratio or APACHE II score etc., seriously limiting the values of adjusted analysis.

With the limitation of current available evidence, it is prudent to assume both meta-analyses as 'hypothesis generating' and used for estimation of sample sizes for future RCTs.

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