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3 **Title: Response to Letter to Editor: Vitamin D supplementation reduces COVID-19**  
4 **severity**  
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## Response to Letter to Editor: Vitamin D supplementation reduces COVID-19 severity

Dear Editor,

We are pleased to respond to the comments received from Dr. Bajpai and wish to thank him for his interest in our study exploring impact of the vitamin D supplementation on COVID-19 severity.<sup>1</sup>

We are herewith responding to the comments in point-by-point manner. The first comment mentioned an issue regarding literature search and the databases used for the review. We acknowledge that from PubMed 34 articles were found. These numbers increased drastically when more comprehensive databases such as google scholar and pre-print platforms were explored. Moreover, as we were not limited to one database (PubMed), other keywords apart from MeSH terms were also included. This has been mentioned in the methodology as the key terms used for review. Additionally, we have explicitly mentioned the literature search and citation review in PRISMA diagram. We agree that Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2009 guideline is used for the review and recently in 2021 a new guideline is published. Though it is an updated guideline, only a familiarity is recommended in the cases where more comprehensive resources such as Cochrane is available.<sup>2,3</sup>

Secondly, A PROSPERO protocol registration was not considered for this review due to variety of reasons 1) It has been previously reported that delays in publishing systematic review registrations in PROSPERO are hindering transparency and may lead to research waste<sup>4</sup> 2) unlike pre-COVID era, systematic reviews registered on COVID in PROSPERO were documented to have poor reporting, mission or confusing information.<sup>5</sup>

We have undertaken extensive work for this review and have considered all the essential methodological aspect. About considering the guideline for conducting overview of reviews, we would like to share recent Cochrane guideline, which clearly recommends inclusion of GRADE assessment.<sup>3</sup> This has been reported by multiple other overview studies also.<sup>6</sup> We emphasize again that for this review, standard guidelines were followed with inclusion of following methodological aspects 1) we have reviewed and summarized published systematic review's findings. It is well established that systematic reviews provide highest quality of evidence from available primary studies 2) PRISMA checklist was followed 3) the review has assessed numerous critical indicators – AMSTAR and GRADE assessment for risk of bias

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3 and quality,  $I^2$  for heterogeneity assessment, publication bias through Begg's and Egger's test,  
4 overlapping matrix presentation and CCA assessment 4) explicit listing of strength and  
5 limitation of all the included systematic reviews 5) clearly mentioning limitation and way  
6 forward recommendations from overall review.  
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11 The parameters pointed out by Dr. Bajpai for assessing certainty of evidence (i.e., degree of  
12 statistical significance, predictive interval, small-study effects, and excess significance bias)  
13 are still under suggestion and currently no formal guideline is available for using this in  
14 overview of reviews.<sup>6</sup> These indicators suggested for credibility assessment are recently  
15 facing a criticism for an arbitrary cut-off and sheer dependance on statistical significance.<sup>7</sup>  
16 Moreover, it's extremely important to decide scope of the review especially during this  
17 pandemic phase where timely delivery of the useful outcome can impart great difference in  
18 management of morbidity and mortality. Mere adherence to unnecessary, time consuming and  
19 non-vital aspects of methodology might delay communication of most important research  
20 findings having potential to improve health outcomes.  
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31 Regarding overlapping of primary study, we had already done an updated meta-analysis  
32 before undertaking this evidence summary. And we are happy to share that the results were  
33 significant and robust. Vitamin D supplementation significantly reduced odds of mortality  
34 (random effect model - OR-0.474, 95% CI-0.265-0.848,  $p=0.012$ ,  $I^2=50\%$ ), ventilation  
35 (random effect model - OR-0.347, 95% CI-0.163-0.738,  $p=0.006$ ,  $I^2=61\%$ ) and ICU (random  
36 effect model - OR-0.291, 95% CI-0.105-0.805,  $p=0.017$ ,  $I^2=67\%$ ) requirements. However,  
37 there were few studies for which primary data was not available, which was provided by the  
38 systematic reviews (the authors of systematic reviews might have contacted the authors of  
39 primary studies for obtaining that data). In that case review of systematic review provided  
40 really good opportunity to synthesize qualitative and quantitative data for an important  
41 problem like this. Moreover, extending to the comment of Dr. Bajpai the same reference from  
42 Cochrane<sup>3</sup> has clearly stated that, if the purpose is to present and describe the current body of  
43 systematic review evidence on a topic (which is essentially the purpose of our study), it may  
44 be appropriate to include the results of all relevant systematic reviews, regardless of topic  
45 overlap. It also states that in case when authors are not able to avoid double-counting outcome  
46 data for methodological or logistical reasons may still opt to include all relevant Cochrane and  
47 non-Cochrane systematic reviews in the Overview and provide a documentation of extent of  
48 the primary study overlapping.  
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5 Apart from the methodological rigor of the review, we have also paid attention to following  
6 details while recommending vitamin D for COVID-19 as an “*Adjunct therapy*” 1) it is already  
7 well established that vitamin D deficiency is widely prevalent across the globe 2) vitamin D  
8 deficiency has been well linked with poorer COVID outcomes 3) vitamin D supplementation  
9 has shown promising outcome in previous respiratory tract diseases 4) it is a safe, widely  
10 available and cost-effective drug 5) last during the time of pandemic other drugs/molecules  
11 having low-moderate efficacy evidences are incorporated in the treatment and management  
12 guidelines. This also applies to vitamin C and zinc supplementation. In comparison to those,  
13 the study provided substantially good evidence for the efficacy of the supplement.  
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22 Thank you for your giving us the opportunity to respond.  
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25 Yours sincerely.  
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