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Letter to the Editor

## The effect of zinc on the outcome of patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials

Dear Editor

We read with great interest the meta-analysis by Qian et al. that investigated the clinical efficacy and safety in the treatment of patients with COVID-19.[1] Based on the analysis of seven studies, the authors demonstrated that the overall risk of death and hospitalization among COVID-19 patients was significantly lower in the nirmatrelvir plus ritonavir group than control group (odds ratio, 0.22; 95% CI, 0.11–0.45; $I^2$ =93%).[1] In addition to nirmatrelvir plus ritonavir, many studies also evaluated whether other cost-effective agents, such as fluvoxamine,[2,3] famotidine[4] or zinc[5] could be repurposed as potential agents for patients with COVID-19.

Recently, one randomized controlled trial (RCT), which investigated the clinical efficacy of zinc supplement for patients with COVID-19.[6] Ben Abdallash et al. found that compared with placebo, treatment with oral zinc was associated with a lower 30-day mortality, ICU admission rate and shorter duration of symptoms and length of hospital stay.[6] Overall, the findings of this RCT suggest the promising role of zinc in the treatment of patients with COVID-19.[6] However, previous RCT by Thomas et al. reported that zinc could not significantly decrease the duration of symptoms and was early terminated for futility.[7] Similar, the RCT by Abd-Elsalam et al. did not find the additional clinical benefit of zinc supplement.[8] To solve this conflict, we conducted this meta-analysis of RCTs to assess the clinical efficacy of zinc for patients with COVID-19.

We identified RCTs, which investigated the clinical efficacy and safety of zinc in the treatment of patients with COVID-19 from PubMed, Cochrane Library, EMBASE, Clinicaltrial.gov and Google Scholar without language restrictions from inception to December 13, 2022. The search strategy used a combination of controlled vocabulary and free-text words. The outcomes of interest included 28-day mortality rate, hospitalization rate, length of hospital stay, the duration of symptom, symptom recover rate, and the risk of adverse events (AEs). Data were synthesized using the random-effects model. Pooled estimates of the risk difference (RD) and mean difference (MD) with a 95% confidence interval (CI) for dichotomous and continuous data, respectively, were calculated using Review Manager Version 5.4.1.

Four RCTs[6–9] were identified (Table 1). Except one was a single-center phase 2 study,[9] all the other three were multicenter trials.[6–8] In Abd-Elsalam et al's study, the intervention and the comparator was zinc plus hydroxychloroquine (HCQ) and HCQ only, respectively.[8] In other three RCTs, the intervention and the comparator was zinc and placebo or standard of care, respectively.[6,7,9] The treatment duration ranged from 7 days to 15 days.

Overall, the mortality of the study group receiving zinc was 5.5% (22/400), which was numerically lower than that of the control group (7.3% [30/412]). The difference did not reach statistical significance (RD, -0.01; 95% CI, -0.03 to 0.02, $p = 0.55$, Fig. 1) and no heterogeneity was detected ($I^2 = 0\%$, $p = 0.68$). This result remained unchanged using leave-one-out sensitivity test, which assessed the influence of individual studies by performing a series of meta-analyses that leave out one of the studies in the original meta-analysis. Similarly, there were no significant differences between zinc and comparator in terms of hospitalization rate (RD, -0.01; 95% CI, -0.06 to 0.03; $p = 0.55$; $I^2 = 17\%$), length of hospital stay (MD, -2.41 days; 95% CI, -4.99 to 0.70; $p = 0.14$; $I^2 = 90\%$), symptom recovery (RD, 0.01; 95% CI, -0.08 to 0.09; $p = 0.87$; $I^2 = 0\%$), duration of symptom (MD, -1.22 days; 95% CI, -5.23 to 2.80; $p = 0.55$; $I^2 = 89\%$) and risk of AE (RD, 0.07; 95% CI, -0.14–0.29; $p = 0.52$; $I^2 = 93\%$).

Based on our findings, although zinc supplement was safe in the treatment of patients with COVID-19, it did not help improve the clinical outcomes. These findings were supported by the following evidence. There was no significant difference in terms of mortality, the risk of hospitalization, length of study, clinical recovery and the duration of symptoms between the study group receiving zinc supplement and the control group. Therefore, it did not support the routine use of zinc supplement for COVID-19 patients.

However, our findings should be interpreted cautiously due to the following limitations. First, the number of RCTs was limited, and most analyses of outcomes were based on small patient numbers. Second, some findings of the present meta-analyses regarding secondary outcome were associated with high heterogeneity.

In conclusion, zinc supplement did not provide additional benefit for patients with COVID-19. However, further large scale RCT is warranted to clarify the usefulness of zinc for COVID-19.

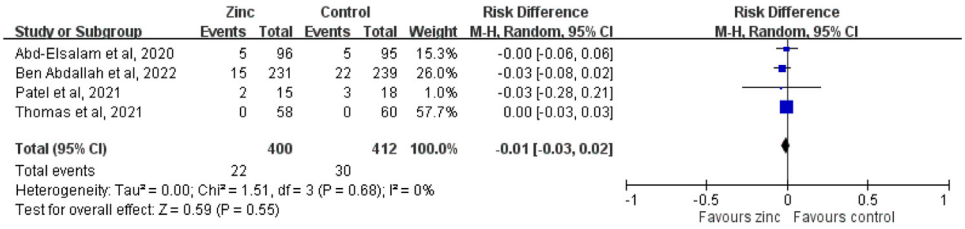


**Fig. 1.** Forest plot of 28-day mortality between zinc and comparator.

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**Table 1**
Characteristics of included studies.

| | Study design | Study site | Study period | Patients | Intervention | Comparator |
|---|---|---|---|---|---|---|
| Abd-Elsalam et al., 2020[8] | Randomized controlled trial | Multicenter in Egypt | From June 23, 2020 to August 23, 2020 | Patient with COVID-19 | 50 mg of elemental zinc twice daily and hydroxychloroquine for 15 days | Hydroxychloroquine |
| Abdallah et al., 2022[6] | randomized, double-blind, placebo-controlled trial | Multicenter in Tunisia | from February 15, 2022 to May 4, 2022 | Adult patients with COVID-19 | 25 mg of elemental zinc twice daily for 15 days | Placebo |
| Patel et al., 2021[9] | Phase 2a double-blind, randomized controlled trial | Single center in Australia | From September 3, 2021 to November 9, 2021 | Hospitalized adults with COVID-19 | 0.24 mg/kg/day of elemental zinc for a maximum of 7 days | Placebo |
| Thomas et al., 2021[7] | randomized clinical open-label trial | Multicenter in US | from April 27, 2020, to October 14, 2020 | Adult patients with COVID-19 | 50 mg of zinc at Bedtime for 10 days | Standard of care |

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