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.

case number decreases from 117 to 102, but the sensitivity of Xpert and Xpert Ultra remains similar to that in the previous study (34 of 102 [33.33%] and 66 of 102 [64.71%], respectively; 40 of 117 [34.19%] and 74 of 117 [63.25%], respectively, in our previous study). The 15 Xpert-positive but microbiologic examination-negative cases would then be categorized into the probable pleural TB group; but this change would not affect the total sensitivity and specificity of the study. Therefore, we presume that evaluation of a new TB diagnostic, using the composite reference standard, is valuable and feasible.

Beside the CRS, we further analyzed the sensitivities of the diagnostics among all the patients with any bacterial evidence of TB, including the Xpert Ultra assay itself. We compared the performance of Xpert and Xpert Ultra in parallel to demonstrate the superiority of Xpert Ultra in sensitivity over Xpert. This strategy is often used in studies with very low positive case numbers,[2] or specimens with a very low bacillus-positive rate.[4] This practice requires that the evaluated test have very high specificity, so that we can assume that the positive outcome of the new diagnostic may be trusted. This further analysis could improve the understanding of the new diagnostic, and could be used as a supplemental analysis.

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Zinc and Coronavirus Disease 2019

Causal or Casual Association?

To the Editor:

We read with interest the article by Yao et al[1] this issue of *CHEST* whereby they have studied the effect of zinc supplementation in hospitalized patients of coronavirus disease 2019 (COVID-19) infection.[1] In reference to the patient assessment parameters and results, one very important aspect needs attention. Although the authors have evaluated in detail the baseline clinical and treatment characteristics, they have no data pertaining to serum zinc levels before or after zinc supplementation. We do understand because this was a retrospective analysis with waiver of consent, but one should be cautious about the interpretation of results in this scenario. Before concluding that zinc supplementation did not lead to a statistically significant decrease in mortality or other outcome parameters, we should have data clarifying which patients were zinc deficient and which were not before receiving zinc supplementation. This could have been done by measuring serum zinc levels. It is well mentioned in literature that patients with certain respiratory illnesses, for example, asthma, have decreased serum zinc levels. Ibraheem et al[2] recorded the prevalence of 98.3% for low serum zinc levels in children with acute lower respiratory tract infection than that in control subjects of 64.2%.[2] Rerksuppaphol and Rerksuppaphol[3] have also shown that zinc supplementation reduces the number of hospital days in children with acute lower respiratory tract infection, and their results were substantiated by measuring pre and post supplementation serum zinc levels. Serum zinc level is also the recommended modality to estimate dietary zinc status in individuals.[4] Also, in COVID-19 disease, C-reactive protein has emerged as one of the key inflammatory markers, and serum zinc levels also have been found to be inversely proportional to C-reactive protein levels in some surveys.[4] This further highlights the importance of getting serum zinc levels before making any conclusions about zinc therapy in such patients. The work done by the authors is worth appreciation; however, a prospective cohort study with pre and post zinc supplementation zinc levels would probably yield better or probably different answers.

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Response

To the Editor:

We thank Dr Khurana et al for their thoughtful response to our letter[1] and for pointing out the value of serum zinc levels. Our study assessed the association between zinc supplementation and survival among hospitalized patients with coronavirus disease 2019 (COVID-19), using a causal inference approach to retrospective data. Our institutions do not routinely measure serum zinc levels. Although our study population consisted of patients admitted to a single hospital, our study assessed the effect of zinc in the contexts in which it was routinely used in the inpatient setting at the peak of the COVID-19 pandemic in the United States. Our findings may inform assessment of zinc's utility as it was commonly used in the inpatient setting for COVID-19, awaiting the results of randomized controlled trials.

We appreciate the references provided by Dr Khurana et al that demonstrated an association between lower zinc levels and worse pulmonary outcomes in children.[2,3] We note, however, that neither of these studies was conducted in adults or among patients with COVID-19. Although our study does not definitively rule out the clinical benefit of zinc among hospitalized patients with COVID-19, our research question looks into the routine use of zinc alone or as an adjunct to other candidate therapies in hospitalized patients with COVID-19––a question similar to those of current randomized trials for COVID-19 that involve zinc.[4] The role of zinc among COVID-19 patients with a deficiency of the trace mineral is unknown. Furthermore, the protective role of zinc against severe acute respiratory syndrome coronavirus 2 infection is another question that is left unanswered.[5] Therefore, we agree with Dr Khurana et al that prospective studies among patients with COVID-19 that take into account serum zinc levels before and after supplementation are needed.

Although our findings are based on retrospective data, thoughtful and thorough analyses of such data in light of the urgency of the ongoing pandemic will likely continue to play a valuable role in paving the way forward.[6] We recognize that prospective randomized controlled trials remain the gold standard of clinical studies. However, situations in which randomized trials are too costly, too slow, or not feasible may necessitate taking into consideration causal inference studies such as ours in informing clinical decisions.

We also must stress that, regardless of the methods employed, efforts must be made to broaden generalizability of the findings by incorporating patients from various clinical and sociodemographic backgrounds. Our hope is that future COVID-19 research ensures inclusion of diverse patient populations and clinical contexts to better identify groups that benefit the most from heterogeneous care strategies.

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