Reviewer's report

Title: Genotype-independent association between profound vitamin D deficiency and delayed sputum smear conversion in pulmonary tuberculosis

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Reviewer: VIDYARANI MOHANKUMAR

Reviewer's report:

1. Major Compulsory Revisions

The work done by Kashaf Junaid et al., adds more impact to the role of vitamin D in tuberculosis and during anti-tuberculous therapy. However, one of the limitations in the present study (which the authors themselves have mentioned in the discussion) is that drug sensitivity was not done for 72% of the isolates. Although the authors claim that sensitivity assay was done for samples which were smear positive for >2 weeks, they could identify only 16 MDR isolates. However, the fully sensitive cases / cases for which sensitivity was not done, have a median TTSC of 15 (7.5-22.5) days which suggests that they could very well include MDR cases. Again, in the hypovitaminosis group (25(OH)D <25nmol/l), the median TTSC is 22.5 (22.5-37.5) days, which also suggests the possibility of MDR cases. Although the results clearly show that TTSC is significantly more in hypovitaminosis D group, the data will be more meaningful if interpreted along with the drug sensitivity results. This is more important because, the authors have found a significant association between isolation of a multidrug-resistant organism on sputum culture with delayed sputum smear conversion.

In an earlier study conducted in Northern India, Rathored et al (Reference 9), had reported that serum 25(OH)D concentrations were significantly lowest in MDR-TB, correlating inversely with time to sputum smear conversion, stating that lower serum 25(OH)D may increase time to MDR-TB sputum smear negativity. Yet another study done in Pakistan by Raheel Iftikhar et al (Reference 23) has shown a significant Vitamin D deficiency in patients with tuberculosis which was more pronounced in MDR-TB patients. Since both these studies claim that a severe vitamin D deficiency is associated with MDR TB, this possibility needs to be verified in the present study. The interpretations in the present study have been made on the assumption that cases with undetermined sensitivity are possibly drug sensitive cases. But, the authors cannot exclude the possibility that a delayed TTSC in the group with undetermined sensitivity could be due to the presence of MDR cases. Without verifying this data, the authors cannot claim an independent association of vitamin D deficiency with delayed sputum smear conversion.

The claim that the authors make in the introduction that ‘studies investigating the potential effect of interactions between vitamin D status and polymorphisms in the vitamin D pathway on response to antituberculous therapy have not
previously been performed' is not completely true since the study by Rathored et al has addressed the same question with a larger number of patients, except that they have studied the polymorphisms only in vitamin D receptor and not the DBP and CYP2R1. This point needs to be clearly mentioned in the introduction and discussion part.

2. Minor essential revisions

A per tables 2,3 and 4, the total number of all three genotypes in any polymorphism does not add up to 260, which means that the results are not available for all participants. The reason for this needs to be mentioned in the text.

3. Discretionary Revisions

a. The authors have shown the number of patients with vitamin D deficiency for each genotype in table2. Additionally, they can also include a graphical representation of actual vitamin D levels between different genotypes, at least for Cyp2R1 polymorphism.

b. The authors can add more experimental details, particularly for allelic discrimination assays, or they can give a reference for the methodology.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests