Reply to “Pleural Fluid and Tuberculosis: Are All Interferon Gamma Release Assays Equal?”

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We thank Dr. Hofland and colleagues for their insightful comments (1) on our meta-analysis (2). They question our strategy of categorizing indeterminate interferon gamma release assay (IGRA) results in patients with tuberculosis as false negatives. We wish to reiterate our stand that a positive IGRA result might support a diagnosis of tuberculosis in real-life clinical decision-making, but anything else (including indeterminate results) does not. It is true that the manufacturers do not recommend using an indeterminate IGRA result in further clinical decision-making, but the studies included in our review did not incorporate any additional protocol for handling indeterminate data. The approach we followed is not something novel and has already been used in previous studies and meta-analysis, as we point out in our review (3, 4). We feel that precious information is lost by excluding indeterminate results from analysis to generate a pure black-and-white data set, when in reality the routine clinical scenario always has shades of gray. As Hofland et al. themselves point out, several patients with indeterminate IGRA results had a “final” diagnosis of pleural tuberculosis, but when IGRA was used as a diagnostic test, the assay failed to reflect this positive result in these patients. While we agree that an indeterminate result alone should not be used as a diagnostic marker and that the diagnosis of pleural tuberculosis would generally require a battery of investigations, this was not the scope of our review, which focused only on the diagnostic performance of IGRA.

We combined results from studies using QuantiFERON or T-SPOT.TB assays for computing pooled estimates. This was done to maintain our focus on commercially available IGRA(s) rather than any particular laboratory technique. This has remained the preferred methodology of most previous systematic reviews and meta-analyses looking at the diagnostic performance of IGRA in extrapulmonary tuberculosis. For this reason, we also excluded studies relying on in-house IGRA protocols, and hence the important study by Liao and coworkers was not part of our data synthesis (5). The question whether one of these two commercial tests is clearly better than the other remains debatable, and we attempted to briefly address this issue through subgroup analysis, both graphically (Forest plots in Fig. 1 in our article [2]) and numerically (Table 2 in our article [2]). As reported in our review, the T-SPOT.TB assay had a substantially higher pooled sensitivity in pleural fluid assays, although differences between QuantiFERON and T-SPOT.TB assay sensitivities were not formally statistically tested. An informal recalculation by Hofland et al. shows slightly higher pooled sensitivity estimates for both the QuantiFERON and T-SPOT.TB assays in pleural fluid, which is expected, as they excluded indeterminate results from their calculations. Although the concept of pooling raw data as such from several studies, without accounting for heterogeneity, may not be a statistically valid process, it does provide some insight into the relative performances of the two assays. However, it is not correct to assume that these differences become apparent only when the indeterminate results are excluded from analysis. If these raw data from 16 evaluations of pleural fluid IGRA are similarly pooled after considering indeterminate results as false negatives, sensitivity estimates for the QuantiFERON and T-SPOT.TB assays are slightly lower, at 0.568 and 0.830, respectively, and the T-SPOT.TB assay continues to show a statistically superior sensitivity (P < 0.0001, using the chi-square test on two proportions). We also feel that pleural fluid IGRA may therefore be theoretically a better option than blood IGRA due to the presence of a local immune response to mycobacteria in patients with tuberculous pleural effusion, even though this issue was not addressed in detail in our review due to constraints on manuscript length.

We apologize for the inadvertent typographical error in Table 1 of our review but can confirm that diagnostic accuracy calculations related to the study by Zhang and coworkers were based on the correct values (40 true positives, 5 false negatives, 42 true negatives, 7 false positives) rather than those provided in this table (6). A formal correction of this error appears in this issue of the Journal of Clinical Microbiology.

REFERENCES


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