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LETTER TO THE EDITOR

Pleural Fluid and Tuberculosis: Are All Interferon Gamma Release Assays Equal?

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We have read the recently published review of Aggarwal and colleagues (1) with great interest. The use of interferon gamma release assays (IGRA) in extrasanguineous body fluids as potential diagnostic tests for active tuberculosis (TB) does have our special attention. We would like to address two important methodological decisions made in this review with considerable consequences for the results.

First, in the sensitivity analysis, the authors decided to categorize indeterminate results in tuberculous pleural effusion (TPE) patients as false negative, with the argument that this reflects the real-life clinical decision-making scenario, where any "nonpositive" report is indicative of the absence of disease. We do not recognize this argument in clinical practice of indeterminate IGRA results in the assessment of active TB, and moreover, this is not demonstrated in the review by Aggarwal et al., as 83% (50/60) of patients with indeterminate QuantiFERON results in pleural fluid and 52% (28/54) of patients with indeterminate T-SPOT.TB results in pleural fluid have pleural tuberculosis (1). According to the assay manufacturer's instructions, an indeterminate IGRA result should not have clinical consequences in the workup for a patient with active TB and therefore should be excluded from the calculation of diagnostic accuracy.

Second, the authors decided to combine QuantiFERON and T-SPOT.TB results in pleural fluid to calculate pooled sensitivity and specificity. Since the value of IGRA in extrasanguineous body fluids is still under discussion, considering that the two tests are based on different laboratory techniques with different diagnostic accuracies reported in literature thus far (2), ánd because of the heterogeneity of the included studies, we suppose that it would be better to distinguish the accuracy of the two "pleural fluid" tests.

In order to better comprehend the consequences for the results of the study by Aggarwal et al., we composed a new table (Table 1) based on the data presented in Table 1 of the recent review (1). In our table, we used the total of the true-positive, false-negative, and indeterminate test results of the QuantiFERON and T-SPOT.TB assays separately for the group of patients with TPE. For the non-TPE patients, we used the total of true-negative, false-positive, and indeterminate test results. Results of the IGRA in blood were excluded because we specifically aimed to address the accuracy of IGRA in pleural fluid.

We observed that in Table 1 of the recent review (1) (according to the results of Zhang et al. [3]), the shown sum of true-negative ($n = 42$), false-positive ($n = 75$), and indeterminate ($n = 47$) T-SPOT.TB results exceeds the total number of non-TPE patients ($n = 49$). We tried to retrieve the correct numbers from the original article, which are, if we are correct, the following: true negative, 42; false positive, 7; and indeterminate, 0 (3). We cannot determine which numbers were used in the sensitivity and specificity analyses of Aggarwal and colleagues (1).

TABLE 1 Sensitivity and specificity for QuantiFERON and T-SPOT.TB results in pleural fluid

Assay	Result	No. of patients with:		Sensitivity (%)	Specificity (%)
		Pleural TB	No pleural TB		
QuantiFERON in pleural fluid	Positive	126	32	73.3	80.8
	Negative	46	135		
	Indeterminate	50	10		
T-SPOT.TB in pleural fluid	Positive	244	54	91.7	78.3
	Negative	22	195		
	Indeterminate	28	26		

After exclusion of the indeterminate results, we calculated the sensitivity and specificity for the QuantiFERON and T-SPOT.TB assays in pleural fluid (Table 1). Although we did not correct for the heterogeneity of the studies so far, the comparison of our results with those of the review by Aggarwal et al. gives insight into the consequences of including indeterminate results as false negatives in accuracy analysis. Importantly, the difference in sensitivity between the QuantiFERON and T-SPOT.TB assays underlines that the two tests should not be combined in one analysis.

According to these results, we invite the authors to further discuss the clinical value of IGRA (especially the T-SPOT.TB assay) in pleural fluid. In this discussion, we would like to emphasize two additional items. We point the authors to another important study regarding this topic, which, as far as we know, was not included in their review (4). In addition, Aggarwal et al. (1) appropriately describe that false positives may have compromised the specificity due to latent TB in non-TPE patients. To overcome this probable confounder, evaluating the local immune response with respect to the systemic response is considered to improve the specificity of IGRA in extrasanguineous body fluids because of the homing and concentration of *Mycobacterium tuberculosis*-specific lymphocytes at the site of infection (5). This perspective is not addressed in the review by Aggarwal et al.

We are looking forward to the authors' reply.

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