Predictive performance of interferon-γ release assays and tuberculin skin test: a study in chance, bias, confounding

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Zhou et al,[1] compared the predictive performance for incident tuberculosis (TB) between interferon-γ release assays (IGRA) and the tuberculin skin test (TST) and concluded better performance of IGRA over TST. We would like to express our concerns about the approaches in design, analysis and interpretation which may explain why their conclusions differ from previous work.[2,3]

First, predictive performance is best compared by estimating the relative risk of incident TB among people with positive tests, compared to negative in head-to-head studies and should account for person-time at risk. This is essential to avoid biases due to systematic differences between study settings, participants and follow-up intervals. The primary analysis performed by Zhou et al. included

all studies without restricting to head-to-head comparisons, claiming statistically significant differences in predictive ability. However, their own head-to-head analyses reported in the study appendix showed no significant difference,[1] suggesting the findings in their primary analysis may have been exaggerated. Moreover, it is unclear how the 12 studies were selected for the head-to-head analysis, given the exclusion of the largest head-to-head prospective study[4] which showed similar predictive performance between TST and IGRA.

Second, only eight studies reported blind assessment of outcomes, and less than 50% of cases were bacteriologically confirmed in 16 studies. This increases the risk of incorporation bias or differential work-up bias of positive tests, and overestimates predictive performance; this should be acknowledged. The risk of incorporation bias is especially high in single test studies where tests were in routine use. This may have further biased their primary analysis.

Third, the findings in this study are not generalizable to most high TB burden countries. The authors did not include five head-to-head studies from countries with TB incidence rate $\geq 100/100000$ population that featured in a similar systematic review which was done for the World Health Organization guidance on TB preventive treatment (Figure).[5] Moreover, the current review included seven studies from countries defined by the authors as high TB burden settings, including six from Taiwan or China, with TB incidence rate far below most high TB burden countries in Africa and Asia. Thus, without good evidence, TST should remain an option.

Aggregate data meta-analyses of diagnostic and prognostic tests are challenging when faced with heterogeneous test cut-offs, outcome definitions and follow-up durations. We need a high-quality individual participant data meta-analysis to provide more robust, head-to-head estimates of predictive ability, allowing adjustment and exploration of heterogeneity.

References

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Figure legend.

Figure. Forest plot of the incident rate ratio for TB in untreated individuals who were positive versus negative by tests for TB infection in head-to-head studies in countries with TB incidence rate ≥ 100/100,000 population

IGRA: interferon-γ release assays; TST: tuberculin skin test; PY: person-year; IRR: incident rate ratio. Note: The figure was reproduced from a systematic review of predictive value of TST and IGRA for incident TB in high-burden countries conducted for "Latent TB Infection : Updated and consolidated guidelines for programmatic management" issued by the World Health Organization in 2018. The meta-analysis was conducted using mixed-effects Poisson regression model, applying continuity correction only to calculate individual study results.