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Baseline IL-6 is a biomarker for unfavourable tuberculosis treatment outcomes: a multisite discovery and validation study

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Abstract

Background Biomarkers of unfavourable tuberculosis (TB) treatment outcomes are needed to accelerate new drug and regimen development. Whether plasma cytokine levels can predict unfavourable TB treatment outcomes is unclear.

Methods We identified and internally validated the association between 20 *a priori* selected plasma inflammatory markers and unfavourable treatment outcomes of failure, recurrence and all-cause mortality among adults with drug-sensitive pulmonary TB in India. We externally validated these findings in two independent cohorts of predominantly diabetic and HIV co-infected TB patients in India and South Africa, respectively.

Results Pre-treatment interferon-γ, interleukin (IL)-13 and IL-6 were associated with treatment failure in the discovery analysis. Internal validation confirmed higher pre-treatment IL-6 concentrations among failure cases compared with controls. External validation among predominantly diabetic TB patients found an association between pre-treatment IL-6 concentrations and subsequent recurrence and death. Similarly, external validation among predominantly HIV co-infected TB patients found an association between pre-treatment IL-6 concentrations and subsequent treatment failure and death. In a pooled analysis of 363 TB cases from the Indian and South African validation cohorts, high pre-treatment IL-6 concentrations were associated with higher risk of failure (adjusted OR (aOR) 2.16, 95% CI 1.08–4.33; p=0.02), recurrence

(aOR 5.36, 95% CI 2.48–11.57; p<0.001) and death (aOR 4.62, 95% CI 1.95–10.95; p<0.001). Adding baseline IL-6 to a risk prediction model comprised of low body mass index, high smear grade and cavitation improved model performance by 15% (C-statistic 0.66 *versus* 0.76; p=0.02).

Conclusions Pre-treatment IL-6 is a biomarker for unfavourable TB treatment outcomes. Future studies should identify optimal IL-6 concentrations for point-of-care risk prediction.