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Reply to the letter to the editor: Methodological considerations on the association between eosinophilia and tuberculosis treatment duration

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We read with great interest the letter[1] regarding our recently published article entitled "*The Effect of Eosinophilia on the Duration of Treatment in Patients With New-Case Drug-Sensitive Pulmonary Tuberculosis*."[2] We appreciate the author(s) for their valuable comments, rigorous methodological evaluation, and constructive feedback. Below, we address the specific points raised in their correspondence.

The reader correctly notes that patients with an absolute eosinophil count (AEC) ≥1500 cells/μL were excluded (n=5). Our primary rationale for this strict cutoff was to exclude severe hypereosinophilic syndromes, underlying secondary organ dysfunction, or severe adverse drug reactions (e.g., DRESS syndrome or drug-induced liver injury), which inherently complicate anti-tuberculosis (TB) treatment management and prolong therapy independently of *Mycobacterium tuberculosis* (MTB) clearance. Including these rare, severe systemic cases would have introduced substantial confounding regarding treatment duration. Although we acknowledge that excluding these cases limits generalizability to extreme hypereosinophilic phenotypes, it was necessary to isolate the mild-to-moderate idiopathic/reactive eosinophilic response.

We agree that analyzing AEC as a continuous variable provides valuable insights into potential dose-response dynamics. In our preliminary data exploration, we observed that peak AEC levels within Group 2 varied widely, without a strict linear relationship with treatment shortening once the threshold of ≥500 cells/μL was exceeded. *In vitro* evidence demonstrates that eosinophil products, such as eosinophil peroxidase (EPO), exert direct mycobactericidal activity and induce MTB cell wall damage and lysis.[2] Because national guidelines and clinical practice traditionally mandate

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a standard 6-month core regimen versus extended regimens (>6 months) based on clinical decision-making.[3] Dichotomizing the outcome (≤6 months vs. extended >6 months) therefore aligned directly with real-world clinical endpoints. Nonetheless, we appreciate this suggestion and recommend that future prospective trials incorporate continuous modeling (e.g., restricted cubic splines) to evaluate potential nonlinear dose-response curves.

The author(s) rightly emphasize the critical role of baseline radiological severity (cavitation, bilateral involvement) and microbiological conversion dynamics in determining treatment duration.[4] As explicitly acknowledged in our limitations section, the absence of detailed radiological scoring, such as baseline cavitation, was a limitation of our retrospective database design. In routine practice at our tertiary national reference center, treatment extension beyond 6 months is governed by a holistic assessment, including delayed sputum culture conversion, extensive cavitary lesions, and persistent clinical symptoms. Although we controlled for major clinical comorbidities, such as diabetes mellitus (DM), which strongly predicted prolonged treatment in our cohort (OR: 3.20), residual confounding from unmeasured radiological extent cannot be fully ruled out. Future prospective studies should systematically adjust for cavitary burden and 2-month culture conversion.

Regarding baseline variables, sex was included in both univariate and multivariate logistic regression models and showed no statistically significant association with prolonged treatment duration (p=0.328 and p=0.340, respectively). Although sex was omitted from the main summary table for brevity, the sex distribution (70.2% male in the control group vs. 89.1% in the eosinophilia group, p=0.001) was explicitly detailed in the Results section and controlled for during multivariate adjustment. Furthermore, metabolic and systemic comorbidities such as DM are well recognized to induce chronic subclinical inflammation and impair host immunity, frequently contributing to prolonged TB treatment.[5] This further supports our multivariate approach to controlling for major metabolic confounders.

Our variable selection strategy for the final multivariable model employed a combined approach based on clinical relevance and automated backward stepwise selection. Variables known to influence TB clinical pathways (age, sex, comorbidities including DM and HT, and eosinophilia status) were entered into the model.[4,6] Age was excluded during backward elimination because it showed no univariate trend (p=0.438) and was closely matched across both cohorts (median, 43 vs. 45 years). Diabetes mellitus (OR: 3.20, 95% CI: 1.57–6.52; p=0.001) and the absence of eosinophilia (OR: 2.06, 95% CI: 1.14–3.71; p=0.017) remained robust independent predictors of treatment prolongation in the final parsimonious model.

In summary, we thank the author for highlighting these important methodological points. Although the limitations inherent in the retrospective design necessitate cautious interpretation, our findings provide an intriguing foundation suggesting that mild-to-moderate eosinophilia during drug-sensitive TB therapy may reflect an efficient host immune response rather than merely a drug reaction. We fully support the call for prospective, multicenter studies integrating radiological metrics and detailed cellular immunology to further validate these observations.

Conflicts of Interest
The authors have no conflicts of interest to declare.

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