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Authors' reply to the letter: "Evaluation of serum procalcitonin as a diagnostic tool to differentiate bacterial sepsis from rheumatic flare-ups in children with rheumatic disorders"

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Dear Editor,

We are grateful to the reader for their thoughtful engagement with our article[1] and for highlighting both the clinical relevance and broader implications of our findings through the communication.[2] We address the points raised as follows:

Influence of confounders on procalcitonin (PCT) levels (e.g., renal impairment or viral infections):

We agree that certain conditions may affect PCT levels. Renal dysfunction, particularly severe acute kidney injury, has been associated with falsely elevated PCT due to reduced clearance. However, none of the children included in our study had clinical or biochemical evidence of significant renal impairment at admission. Additionally, we excluded children with confirmed viral or non-bacterial infections such as dengue, malaria, or COVID-19, to reduce diagnostic ambiguity. Nevertheless, we acknowledge that in real-world scenarios, mixed infections and underlying renal pathology can confound interpretation, and thus, PCT should be interpreted in conjunction with clinical judgment and other markers.

Sample size and generalizability:

Our prospective study included 73 febrile children with previously diagnosed rheumatic diseases, the majority being cases of juvenile idiopathic arthritis and systemic lupus erythematosus, the most prevalent paediatric rheumatic disorders.[3] While the sample size reflects the constraints of single-centre and pandemic-era data collection, it does provide robust preliminary evidence. We fully agree that multicentre studies with more diverse rheumatological profiles (e.g., vasculitides, mixed connective tissue disease) and larger cohorts are necessary to generalize the findings further. This remains a focus for future research.

Mixed presentations and real-world clinical complexity:

This is a valuable point raised by the reader. While we deliberately excluded cases with overlapping clinical features or diagnostic ambiguity to maintain internal validity, we recognize that real-life scenarios often involve complex, overlapping disease manifestations. Future prospective studies incorporating mixed or evolving presentations — including macrophage activation syndrome and viral co-infections — will better reflect clinical

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practice and test the robustness of PCT-based differentiation in such contexts.

Correlation between PCT and disease activity scores:

Our study did not aim to directly correlate PCT values with Juvenile Arthritis Disease Activity Score (JADAS-27) or Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores in isolation from infection. The major barrier in such analysis is the heterogeneity of the initial disease activity across the study population. The flare-up criteria in both diseases are dependent on the initial severity scores; therefore, a specific value (of JADAS-27 or SLEDAI), taken at a cross-section can neither detect nor exclude the flare-up. The durations of the diseases since onset were not uniform. To date, no relationship between biomarker levels and disease severity scores could be formulated, even with the common inflammatory markers like C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR). Considering these features, we did not intend to establish any correlation between PCT level and the scores. However, we agree that such correlation might offer insight into whether rising PCT levels correlate with flare severity in the absence of infection, if any. Exploring this relationship could potentially refine interpretation thresholds for PCT in the context of disease activity and deserves exploration in follow-up studies.

Cost-effectiveness and feasibility in resource-limited settings:

Cost-effectiveness is a pertinent concern. While PCT testing is costlier and less widely available than CRP or ESR, the potential for timely and accurate differentiation between flare and infection could reduce unnecessary antibiotic use and hospital stays, ultimately offsetting the upfront cost. Moreover, point-of-care PCT testing is becoming increasingly accessible.[4] Nevertheless, cost-benefit studies in resource-constrained settings such as India are warranted before widespread adoption.

We thank the reader once again for raising these important and constructive points. We hope our responses provide clarity and emphasize both the significance of the study and the directions for future research. We remain committed to contributing to the evolving discourse on the use of biomarkers PCT in paediatric rheumatology.

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Conflict of interest

The authors declare that there is no conflict of interest.

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