From serum clustering to clinical stratification in early rheumatoid arthritis: methodological and translational considerations

Dear Editors,

We read with considerable interest the article by Kidoguchi and colleagues, in which unsupervised hierarchical clustering of baseline serum inflammatory mediator profiles was used to stratify 204 DMARD-naive patients with early rheumatoid arthritis (RA) into two biologically distinct subgroups, identifying an interleukin (IL)-6-driven pathobiological signature in Cluster 1 (1). The study addresses a genuine unmet need in RA precision medicine, and the use of a non-invasive, serum-based stratification approach is a methodologically welcome development. We wish, however, to raise several points regarding the interpretation and translational implications of the findings.

First, the interpretation that clinical improvement in Cluster 1 reflects an IL-6-associated, or potentially IL-6-driven, pathobiological signature may require additional caution because treatment exposure could have influenced mediator dynamics. As shown in Table I, IL-6 receptor inhibitors (IL-6Ri) were used in only a small number of patients overall, but their distribution among biologic/targeted synthetic DMARD-treated patients differed numerically between clusters: 4 of 19 patients in Cluster 1 and 2 of 16 patients in Cluster 2 received IL-6Ri. Although these absolute numbers are small, IL-6 receptor blockade can alter circulating IL-6 concentrations through interference with receptor-mediated clearance and feedback regulation. Therefore, even a limited number of IL-6Ri-treated patients could potentially influence the observed association between ΔIL-6 and ΔCDAI, particularly in subgroup analyses with modest sample sizes. Although the authors incorporated b/tsDMARD use as a time-varying covariate in sensitivity analyses, it remains unclear whether this adjustment materially changed the magnitude or significance of the ΔIL-6 coefficient. A sensitivity analysis excluding IL-6Ri-treated patients, or restricted to patients receiving conventional synthetic DMARDs exclusively, would provide a more rigorous assessment of whether the IL-6 signal reflects an intrinsic disease signature rather than a treatment-related pharmacodynamic effect.

The robustness of the statistical framework also merits comment. The large-scale Spearman correlation analyses – conducted across 13 mediators, multiple clinical parameters, and two clusters – were performed without correction for multiple comparisons, which raises the risk of false-positive findings among the reported associations. In addition, the Elastic Net regression employed the conservative lambda.1se regularisation criterion; the absence of any robustly selected mediator in Cluster 2 may therefore be a method-dependent result rather than a genuine biological characteristic of this subgroup. Reporting results under both lambda.1se and lambda.min specifications, alongside false discovery rate-corrected correlation data, would allow readers to assess more reliably the stability of the proposed signatures (2).

Concerning the proposed clinical application of a low rheumatoid factor (RF) titre as a proxy biomarker for the IL-6-driven subtype (AUC = 0.785), we note that key diagnostic performance metrics (optimal cut-off value, sensitivity, specificity, and positive and negative predictive values) are not provided. Given the substantial overlap in RF seropositivity between clusters (60.7% *vs.* 89.7%, Table I), the misclassification rate at any clinically applicable threshold is likely to be non-trivial. These parameters are indispensable for any meaningful appraisal of whether RF titre could reliably inform therapeutic decision-making in routine practice.

Finally, although CDAI incorporates patient global assessment, the longitudinal evaluation remains largely centred on disease activity indices and radiographic progression. Whether the identified clusters differ in outcomes most consequential to patients, such as physical function, fatigue, morning stiffness, work productivity, and health-related quality of life, remains unknown. This is particularly relevant because the observed 52-week CDAI difference between clusters was small and statistically non-significant. Prospective validation incorporating patient-reported outcomes aligned with the OMERACT core outcome framework would provide a more patient-centred assessment of whether this serum-based stratification approach has practical value beyond biological classification.

We recognise the considerable effort underpinning this work, and we hope these observations will prove useful as the field moves towards more refined stratified approaches in RA management.

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Competing interests: none declared.

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References

1. KIDOGUCHI G, ISHITOKU M, OKA N *et al*.: Patient clustering by serum inflammatory mediators stratifies early disease-modifying antirheumatic drug-naive rheumatoid arthritis and reveals distinct pathobiological signatures: a prospective observational cohort. *Clin Exp Rheumatol* 2026; 44(5): 1004-13. https://doi.org/10.55563/clinexprheumatol/bx6ql2
2. ZOU H, HASTIE T: Regularization and variable selection via the elastic net. *J R Stat Soc Series B Stat Methodol* 2005; 67(2): 301-20. https://doi.org/10.1111/j.1467-9868.2005.00503.x