To the Editor:

We appreciate the interest of Wang et al in our recently published dataset. We would like to clarify some details pertaining to the points made in their letter. As stated in our published study, Disease Activity Score in 28 joints (DAS28) was not available to collect in this retrospective dataset. The Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) were not available likewise. We were, however, able to evaluate laboratory variables over time (Figure 3 and Supplementary Figure S4) showing red cell distribution width (RDW) increases after starting methotrexate (MTX). This is likely related to the known effect of MTX on red cell homeostasis and RDW (reference 20 and discussed in our published article). Absolute lymphocyte count (ALC) was found to decline after starting MTX, primarily in those with higher ALC at baseline, and ALC was found to increase after starting tumor necrosis factor inhibitor (TNFi) therapy, primarily in those with low ALC.

We agree that RDW and ALC are likely influenced by many variables, including direct effects of therapy as well as inflammatory mediators of disease activity (see Results and Discussion sections of the published manuscript). The reference point of focus in this dataset was before start of MTX, in part to avoid the confounding effect of MTX, and how biomarkers at this typical pretreatment point relate to subsequent 10-year mortality. Although subsequent treatment-related changes and clinical events are an important area of interest and may affect the risk of mortality, they do not affect the data observed at this earlier timepoint and are beyond the scope of the present dataset. Notably, we did adjust for comorbidities and cardiovascular biomarkers known to associate with mortality when calculating the associations of RDW and ALC with mortality. Medication management after start of MTX was focused on a minimum 3-month time window for therapy with or without subsequent addition of TNFi therapy. We agree that on-treatment longitudinal changes in biomarkers are of interest and did investigate change in ALC and RDW after start of MTX and how this related to mortality. As stated in the Results and Discussion sections, among a subset of patients in the present cohort with both pre-MTX and post-MTX (MTX without TNFi therapy) laboratory values present (n=242), we looked at pretreatment values and the change in ALC and RDW. We did not detect an effect from the changes in ALC or RDW on the relation between pretreatment laboratory values and mortality in an adjusted model.

Certainly, as with any observation, reproducibility and mechanistic insight are important follow-up items that are needed. We make no presumption about causation. RDW and ALC may serve as reporters, mediators, or an epiphenomenon of disease activity. As with any observational research effort, the results should be taken as hypothesis generating.

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This study was supported by BX001894 (DDA), IK2CX001471 (CS), CX001791 (DDA). The authors declare no conflicts of interest relevant to this article.

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