Title:

Increased erythrocyte mean corpuscular volume by methotrexate predicts clinical response in psoriatic arthritis.

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Key message:

- Elevated MCV at 12-weeks acts as a surrogate biomarker of response to methotrexate in psoriatic arthritis.

Dear Editor,

We previously reported the association between increased erythrocyte mean corpuscular volume (MCV) at 12-weeks from initiation of methotrexate and clinical response at 24-weeks in rheumatoid arthritis (RA) (1). To investigate the generalizability of this finding, we determined whether a rise in MCV by methotrexate is accompanied by a clinical response in psoriatic arthritis (PsA).

This real-world study was performed on adult, treatment-naïve, PsA patients who fulfilled the classification criteria for PsA (CASPAR) criteria (2). Data extraction was performed in June 2020 on two independent cohorts (Cohort 1: University College London Hospital-n=128, Cohort 2: North Middlesex University Hospital-n=42) who were initiated on oral methotrexate from January 2014 to December 2019. Response at 24-weeks was defined as an improvement in at least 2 of the 4 PsA Response Criteria (PsARC)(3), one of which must be related to joint tenderness or swelling, with no worsening in any of the 4 criteria, and no initiation of additional conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or biologics within the 52-weeks of methotrexate initiation. Conventional linear mixed model and logistic regression with a machine learning approach for feature

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selection were adopted (details of the statistical analysis plan are provided in Supplementary Methods) for this analysis. The two cohorts were combined for this analysis.

Overall, 43.5% (74/170) of PsA patients responded to methotrexate according to PsARC criteria. Mean age of onset of PsA was 47 years (SD 15), mean disease duration of 10.5 months (SD 6), and 42% were male (Supplementary Table S1). Median starting dose of methotrexate was 10mg/week (IQR 7.5 to 10), which increased to 15mg/week (IQR 12.5–17.5) at 12-weeks, and to 17.5mg/week (IQR 15–20) at 24-weeks. We noted a significant rise in MCV from 12-weeks onward among responders (Figure 1A), compared to non-responders, with an estimated difference in MCV of 1.66 fL (95%CI 0.42 to 2.89, p=0.009) at 12-weeks.

Area under the Receiver operator characteristic (ROC) curve (AUROC) of monthly MCV change (from baseline) in the first 24-weeks to predict response at 24-weeks is shown in Figure 1B. The earliest time point where the AUROC was >0.70 was at 12-weeks and therefore was selected for the logistic regression model to evaluate MCV as a predictor of response adjusted by other parameters (Supplementary Table S2). Results of univariable logistic regression are shown in Supplementary Table S2.

Change in MCV at 12-weeks was the best performing positive predictor of response at 24-weeks by the sparse partial least squares discriminant analysis (sPLS-DA), followed by PsARC response at 12-weeks and presence of dactylitis (Figure 1C). Nail changes and presence of axial disease were negative predictors. These 5-variables were fitted in a multivariable logistic regression model (Figure 1D). For each 1 fL increase in MCV at 12-weeks from baseline, the odds-ratio (OR) of attaining response by 24-weeks increased by 1.27 (95%CI 1.12 to 1.46, p<0.001). The optimal cut off-point for MCV increment to predict response at 12-weeks was ≥3.9 fL (95%CI 2.6 to 4.2) (AUROC = 0.71). The OR of attaining a favourable response at 24-weeks was 2.97 (95%CI 1.49 to 5.95, p=0.002) if the patients showed a PsARC response at 12-weeks (AUROC = 0.65). A PsARC response at 12-weeks and an increase in MCV≥3.9 at 12-weeks together improved the AUROC to predict response at 24 weeks to 0.80. Indeed, 96% (27 out of 28) of the patients with a raised MCV ≥3.9 and who achieved a 12-week PsARC response, responded at 24 weeks (Figure 1E). By comparison, 70%, 69%, and 56% of patients showed a favourable response at 24 weeks if their MCV ≥3.9 (but no PsARC response at 12-weeks), achieved a PsARC response at 12-weeks (irrespective of their MCV change), or achieved a PsARC response at 12-weeks with concomitant change in MCV<3.9, respectively.

Presence of dactylitis was associated with favourable response to methotrexate with an OR of 3.34 (95%CI 1.34 to 7.17, p=0.010). In contrast, the presence of nail change or axial disease were associated with poorer PsARC response, reducing the chance of response by 50% (95%CI 6% to 76%, p=0.031), and 57% (95%CI 3% to 89%, p=0.041) respectively. Complete case analysis (Supplementary Figure 1) showed similar findings. The overall response rate to methotrexate, and the unfavourable response in the presence of axial disease aligns with previous findings (4-6).

Our results demonstrate that the predictive value of MCV change at 12-weeks with respect to treatment response to methotrexate extends to PsA, in addition to RA (1). Methotrexate is an anti-folate agent that predominantly

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inhibits DNA synthesis through its active metabolite methotrexate-polyglutamate (MTX-PG) (7) leading to an increase in erythrocyte MCV (8). Several studies have examined the association between MTX-PG levels and clinical response in patients with RA (9-11). MTX-PG levels achieve steady state concentrations from 7 weeks after initiation of methotrexate (12), which is consistent with the differences in MCV between responders and non-responders we noted from 3 months after methotrexate treatment. Variability of serum and erythrocyte folate at baseline (13) as well as their changes following initiation of methotrexate (14) could be an important confounder of MCV. Similarly, dosing variability of the co-administered folic acid could affect the MCV and its relationship with clinical response. Nevertheless, these data highlight the potential utility of methotrexate-driven MCV changes at 12-weeks which could complement the contemporaneous clinical disease activity scores in predicting later responses to methotrexate. Prospective studies to assess the utility of early changes in MCV in predicting response to methotrexate are warranted.

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Author Contributions

Designing the study: MRAS, S-AY, MC, MRE. Statistical analysis and interpretation of the data: MRAS. Data collection: LL, BS, MM. Drafting and finalising of the article: MRAS, LL, BS, S-AY, MM, DM, MC, MRE.

Competing Interests statement

The authors have declared no conflicts of interest.

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Patient consent for publication: not required.

Ethical approval: No ethical approval is required for retrospective clinical database analysis as per the National Health Service Research Ethics Committee.

Data availability statement

Patient-related to this paper are subjected to patient confidentiality. Data will be shared upon reasonable request whilst preserving patient anonymity. All codes for data cleaning and analysis with the current submission will be available upon reasonable request to the corresponding author.

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Figure Legend

Figure 1 | Longitudinal change in erythrocyte mean corpuscular volume from baseline to predict response† to methotrexate at 24-weeks in psoriatic arthritis. (A) Longitudinal change in MCV from baseline through to 24-weeks, stratified by their response at 24-weeks. Longitudinal linear mixed-effect model was fitted with random effect of individual patient and fixed effect of response intercepting with observation times between baseline and week 24 and adjusted for screening MCV values, age, gender, concomitant conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), methotrexate dose, and haemoglobin at each time point. Estimated mean with 95% confidence intervals and number of patients at each time points (N) are shown**. (B)** Area under the receiver operator characteristic (ROC) curve (AUROC) of MCV change (from baseline) at each time point to predict response at 24 weeks. **(C)** Sparse Partial least squares discriminant analysis (sPLS-DA) - Factor-loading weights in component 1 are shown for the top 5 ranked parameters that predict methotrexate response. **(D)** Multiple logistic regression with the parameters chosen by sPLS-DA to construct the final model to predict methotrexate response at 24-weeks. **(E)** Number and percentage of the patients who achieved the clinical response by 24-weeks, stratified by increase in MCV ≥3.9 fL from baseline and PsARC response at 12-weeks††. Pairwise comparison was made by Fisher's exact test.

† Response at 24-weeks was defined as an improvement in at least 2 of the 4 Psoriatic arthritis response criteria (PsARC), one of which must be related to joint tenderness or swelling, with no worsening in any of the 4 criteria by 24 weeks and no initiation of additional conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) or biologics within the 52-weeks of methotrexate initiation.

†† Response at 12-weeks was defined as an improvement in at least 2 of the 4 Psoriatic arthritis response criteria (PsARC), one of which must be related to joint tenderness or swelling, with no worsening in any of the 4 criteria by 12 weeks.

**For each 1 fL increase for MCV.*

CI = Confidence interval, OD = Odds ratio, MCV = Mean corpuscular volume.

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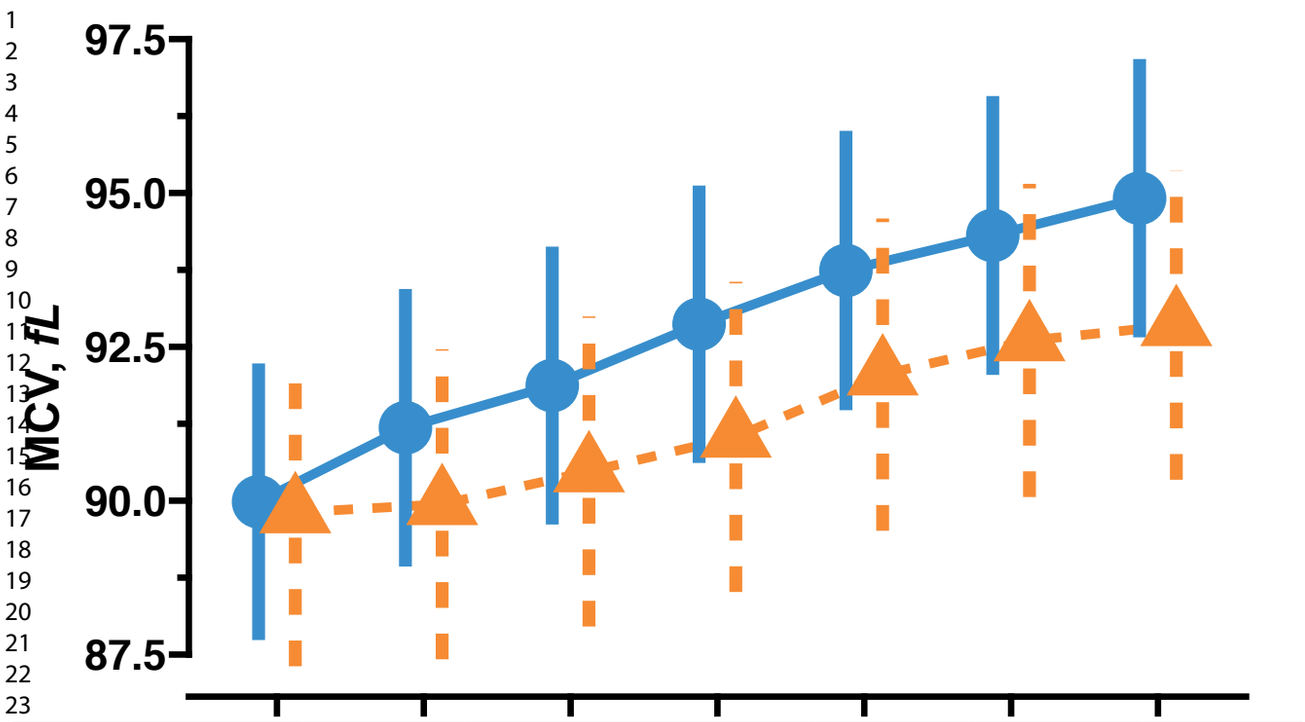
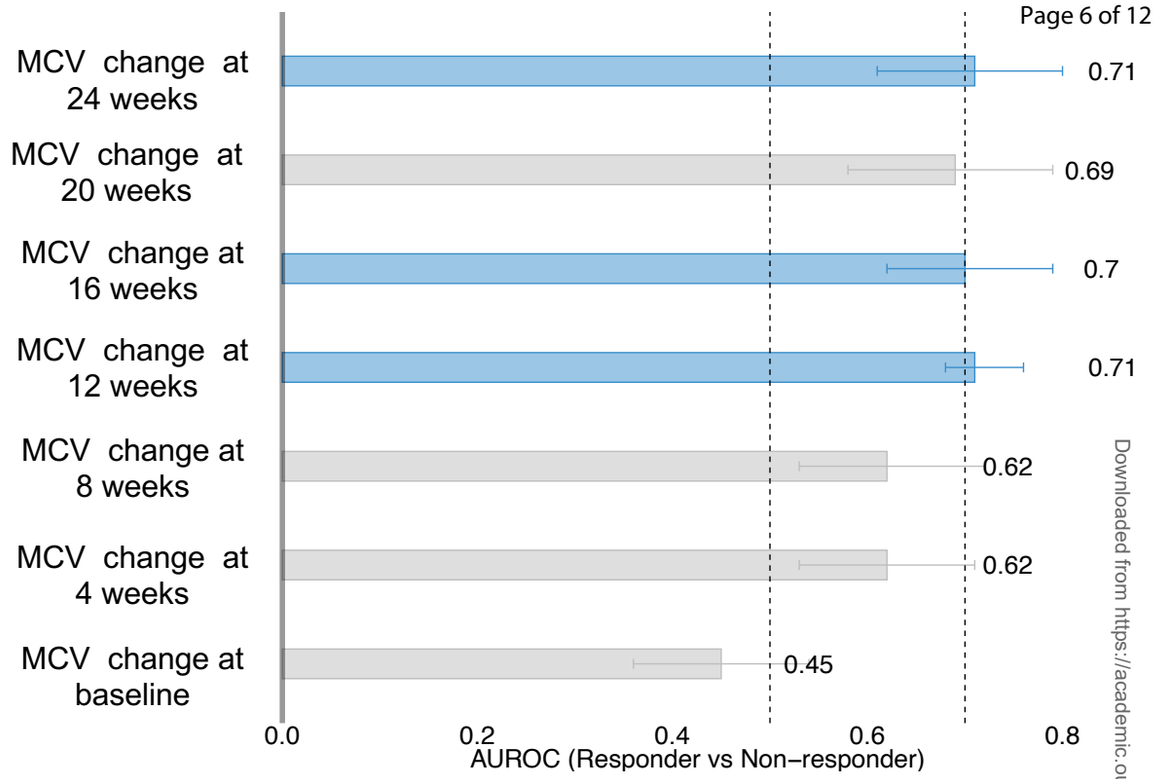
A.



	0 weeks	4 weeks	8 weeks	12 week	16 week	20 week	24 week
Non – responders N. of patients = 74		68	57	53	50	47	59
Responders N. patients = 96		85	83	86	73	66	74
Estimated mean difference (95% CI) **Non-responder** vs **Responder**		-1.07 (-2.30 to 0.17)	-1.22 (-2.46 to 0.02)	-1.66 (-2.89 to -0.42)	-1.52 (-2.81 to -0.22)	-1.53 (-2.85 to -0.21)	-1.89 (-3.12 to -0.66)
p-value		*0.090*	*0.053*	***0.009***	***0.022***	***0.023***	***0.003***

B.



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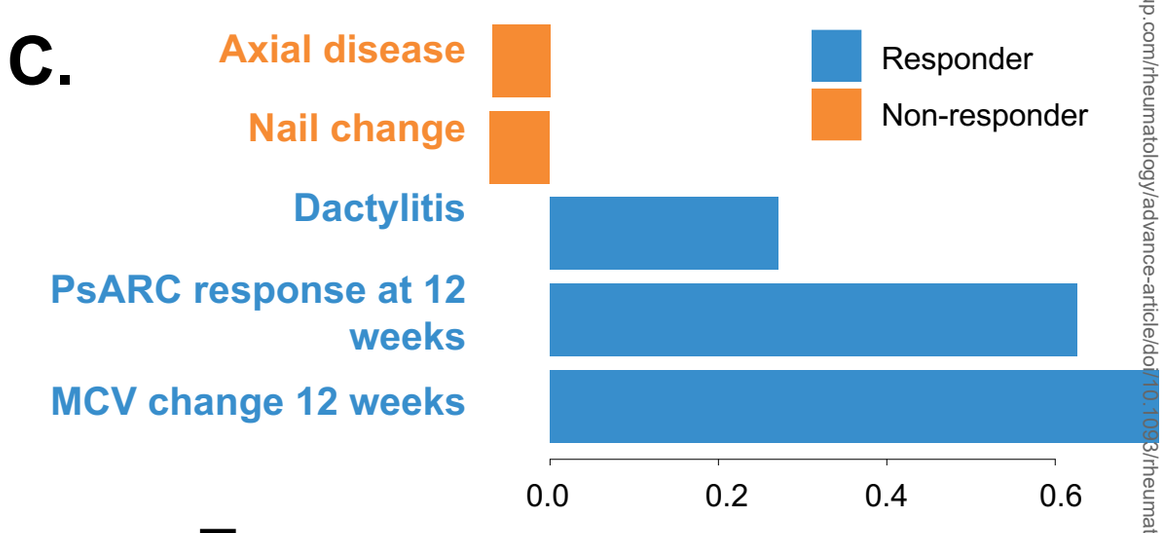
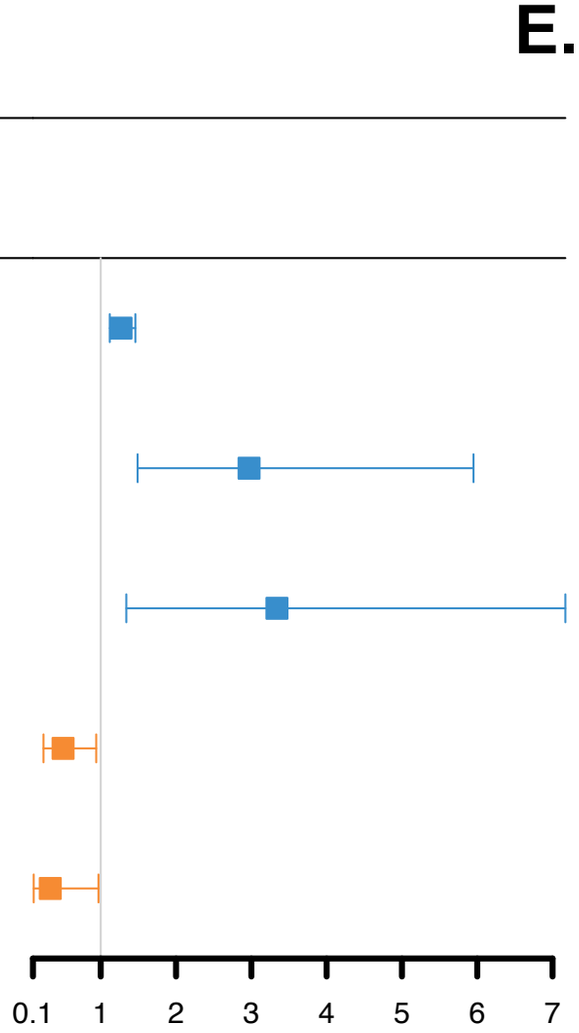


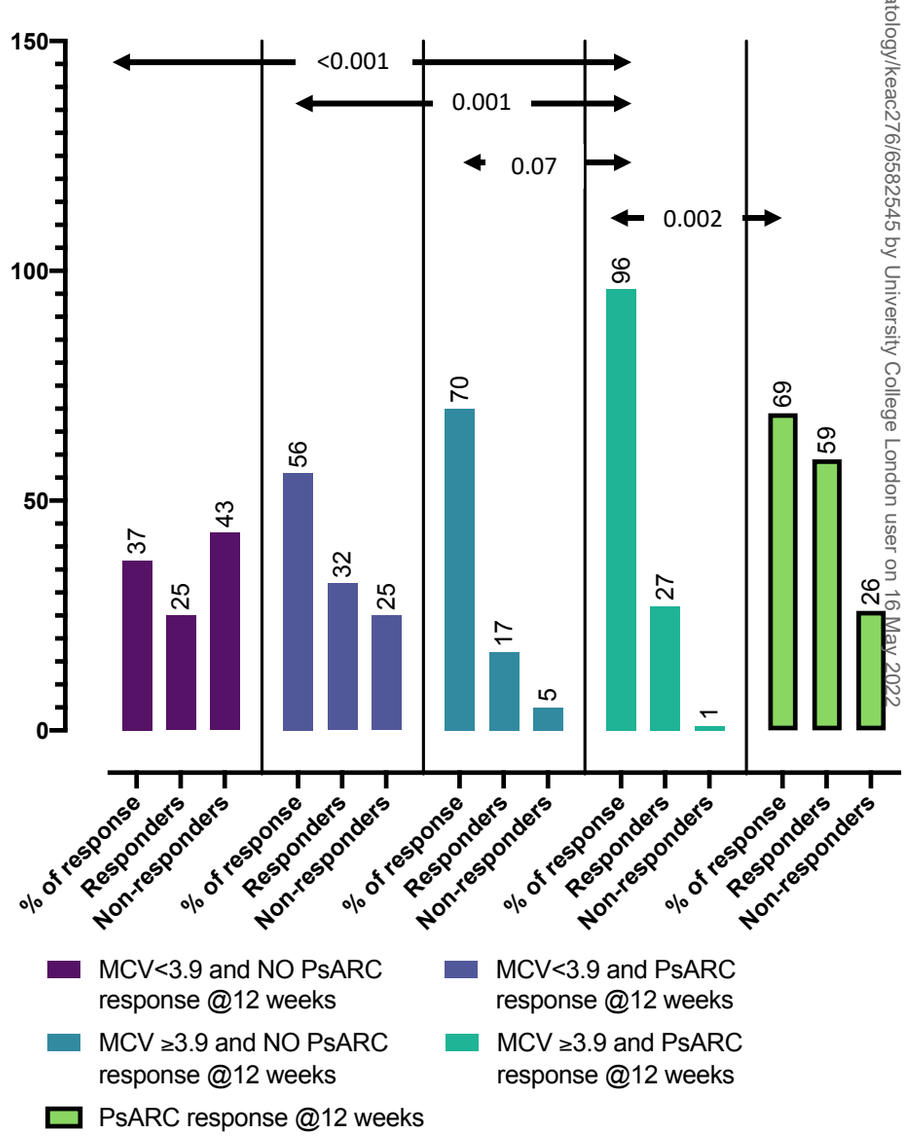
D.

Variables	OR [95% CI]	p–value
MCV change 12 weeks*	1.27 (1.12 to 1.46)	<0.001
• *Responder = 96, Non-responder = 74*		
PsARC response at 12 weeks	2.97 (1.49 to 5.95)	0.002
• *Responder = 59, Non-responder = 26*		
Dactylitis	3.34 (1.34 to 7.17)	0.010
• *Responder = 25, Non-responder = 9*		
Nail change	0.50 (0.24 to 0.94)	0.031
• *Responder = 30, Non-responder =30*		
Axial disease	0.33 (0.11 to 0.97)	0.041
• *Responder = 7, Non-responder = 10*		



AUROC 0.872

E.



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