Q07 THE INCREASE IN ERYTHROCYTE MEAN CORPUSCULAR VOLUME BY METHOTREXATE IS POTENTIATED BY HYDROXYCHLOROQUINE AND IS AN EARLY INDICATOR OF CLINICAL RESPONSE IN RHEUMATOID ARTHRITIS

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Background/Aims
Rheumatologists are facing a significant challenge in the management of early rheumatoid arthritis (RA) due to limitations placed on outpatient visits during the COVID-19 pandemic. Frequent clinical assessments of disease activity are recommended during implementation of the treat to target strategy to achieve remission. A biomarker indicating response to methotrexate during the early phase of therapy could complement clinical examination. Methotrexate increases erythrocyte mean corpuscular volume (MCV), which is measured routinely, prompting us to investigate whether changes in MCV could act as an early indicator of response.

Methods
Patients with early RA who were started on methotrexate therapy were included from two independent cohorts. The larger cohort (discovery cohort, n = 655) was used to build the model and the second cohort (validation cohort, n = 225) was applied to test the prediction of the model. Conventional statistical, and machine learning approaches were adopted to identify key determinants that influence the potential relationship between MCV and clinical response, defined as attainment of remission or low disease activity, at six months after starting methotrexate.
Results
A LASSO penalised logistic regression model was built with the discovery cohort (area under the receiver operating characteristics (AUROC) curve = 0.76), where change of MCV from three months [Odds ratio (OR) 1.53 (95% CI 1.38-1.70)], concomitant use of hydroxychloroquine [OR 2.16 (95% CI 1.52 - 3.07, p < 0.001)], and seropositivity [OR 1.83 (95% CI 1.12 - 3.03, p = 0.02)] were associated with favourable methotrexate response (accuracy 81% (95% CI 76%-86%) of the model testing against discovery model). Different machine learning classification methods were applied. Random forest exhibited the maximum accuracy and AUROC (89%, and 86%, respectively), confirming the above three predictors as the most significant. Two latent classes (class 1: smaller MCV increase and class 2: greater MCV increase) were identified based on the MCV changes over six months. Class 1 had fewer responders and a lower number of patients on hydroxychloroquine compared to class 2. The earliest time point of significant difference of MCV between responders and non-responders was three months [mean difference 1.43 (95% CI 0.57-2.3)]. Combination hydroxychloroquine and methotrexate caused the greatest increase in MCV with a difference between responders and non-responders at 2 months. Change of MCV at three months showed AUROC of 0.75 to predict treatment response to the combination of methotrexate and hydroxychloroquine at six months with an optimal cut-point of MCV 3.5 fl (95% CI 3.5-3.6) with 71% sensitivity and 75%, specificity.

Conclusion
Our data provides mechanistic insight into the synergistic clinical benefit of concomitant hydroxychloroquine with methotrexate, boosting the rise in erythrocyte MCV which could serve as an early biomarker of treatment response.

Disclosure
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