DISTINCT CLUSTERS OF JIA AT METHOTREXATE INITIATION IDENTIFIED USING TOPOLOGICAL DATA ANALYSIS

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Background: Stratified medicine requires the identification of unique strata of a disease within which to base prognostic and treatment decisions. Juvenile idiopathic arthritis (JIA) offers a unique challenge in its inherent heterogeneity. The current ILAR classification, whilst useful for clinical categorisation, does not correlate with treatment outcomes. Therefore, further refinement, clustering and correlation of patient characteristics with treatment response are urgently required.

Objectives: To identify novel, phenotypically consistent subgroups of children and young people (CYP) with JIA at the point of starting methotrexate, across 19 patient and disease characteristics.

Methods: MTX-naïve CYP with JIA were selected if enrolled prior to April 2021 in one of four national JIA studies contributing to the UK CLUSTER consortium. Data from 19 harmonised study variables were extracted at point of starting MTX. Topological data analysis using a Gower similarity metric was used to identify clusters with distinct characteristics. Intervals and percent overlap between clusters were varied until an optimal model identified stable, potentially clinically plausible clusters. Significant differences in characteristics between identified clusters were tested using Kruskall-Wallis and Chi-Squared statistics.

Results: Of 2915 CYP included, the majority were female (68%), of white ethnicity (90%); with the most common ILAR categories being oligoarthritis (35%) and RF-negative JIA (34%).

The optimal TDA model identified six clusters which significantly differed across 16 of the 19 clinical variables at MTX initiation: Adolescents with low-moderate disease (Cluster 1, 41%), adolescents with predominantly sJIA and moderate-high disease (Cluster 2, 4%), children with predominantly sJIA and high disease (Cluster 3, <1%), children with oligo/RF-polyarthritis and low-moderate disease (Cluster

4, 43%) and two ANA-positive groups of largely females with moderate (Cluster 5, 11%) and high (Cluster 6, 1%) disease (Figure 1). Clustered groups also significantly differed in gender proportions ($p<0.001$), ethnicities ($p<0.001$), history of uveitis ($p<0.001$) and disease duration to both diagnosis ($p<0.001$) and MTX initiation ($p<0.001$), but did not differ in limited joint count ($p=0.117$), height ($p=0.245$) or BMI ($p=0.394$) z-scores.

Conclusions: This study shows substantial heterogeneity in JIA at the point of MTX initiation, with six clusters identified across 19 demographic and clinical variables. ILAR categories across clusters were not always indicators of disease activity or symptom burden. Future analyses will correlate MTX treatment response within each cluster to understand what role these combined factors may have on initial treatment response.
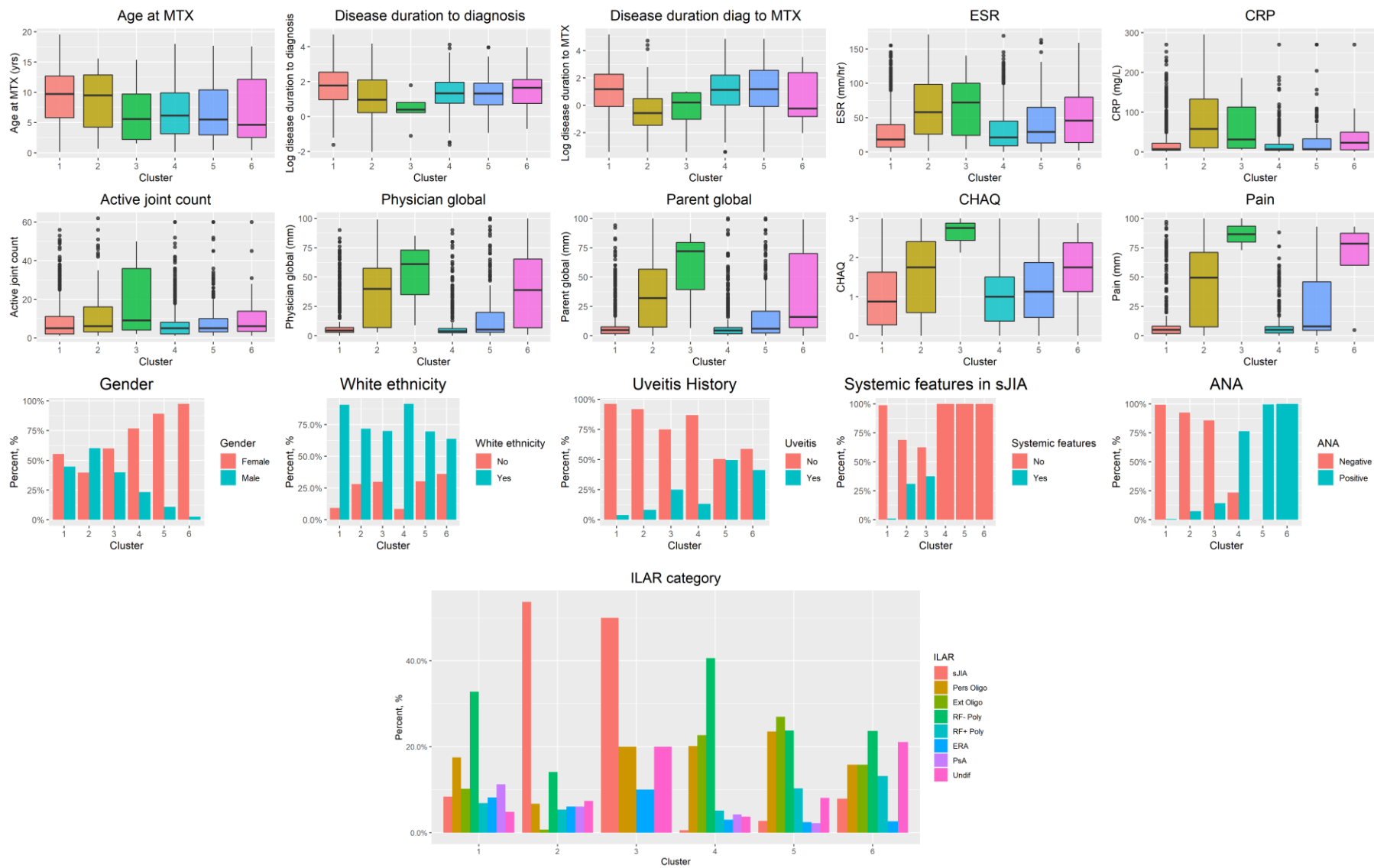
Figure 1. Clusters identified at MTX initiation in children and young people recruited to the UK BSPAR-ETN, BCRD, CAPS and CHARMS studies.