Immunophenotype of systemic lupus erythematosus and Sjögren´s syndrome patients identified two endotypes with potential therapeutic implications

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BACKGROUND

- Systemic lupus erythematosus (SLE) and primary Sjögren´s syndrome (pSS) are chronic autoimmune rheumatic diseases. Up to 20% of SLE patients present with features of both diseases, known as SLE associated with SS (SLE/SS).
- Previously, we identified similarities between the immune cell profiles of patients with SLE compared with pSS (Figure 1).

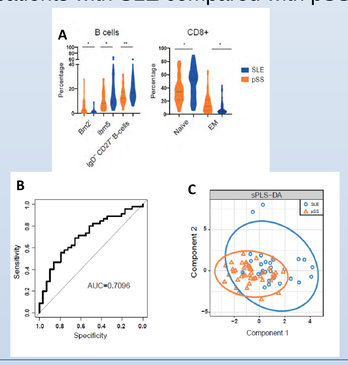

Figure 1. The immunological profile of SLE compared to pSS.
(A) Violin plot: Few immune cell subsets were significantly different between SLE and pSS patients by unpaired t test. Mean+SE, *=p<0.05, **=p<0.01, ***=p<0.001, ****=p<0.0001.**(B)** Receiver operator characteristic (ROC) curve analysis: Area under the curve (AUC) from the balanced random forest (BRF) model are used to represent the model performance (SLE vs pSS). Age and ethnicity were adjusted for in the BRF model.
(C) Sparse Partial Least Squares Discriminant Analysis (sPLS-DA) performed with all 29 immune cell types analysed: Individual distribution points and confidence ellipses for the SLE and pSS group are plotted in blue and orange, respectively.

HYPOTHESIS

Immune-based endotypes could be shared between SLE, SLE/SS and pSS patients which can inform therapeutic strategies.

METHODS

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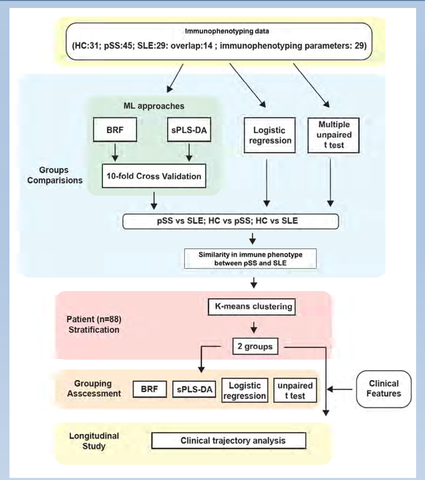


Figure 2: Study design and analysis flow diagram: Abbreviations: HCs (healthy controls), pSS (primary Sjögren's syndrome), SLE (systemic lupus erythematosus), ML (machine learning), BRF (balanced random forest), sPLS-DA (sparse partial least squares discriminant analysis).

RESULTS

1. Two groups of patients shared immune signatures across pSS, SLE and SLE/SS phenotypes irrespective of their diagnosis.

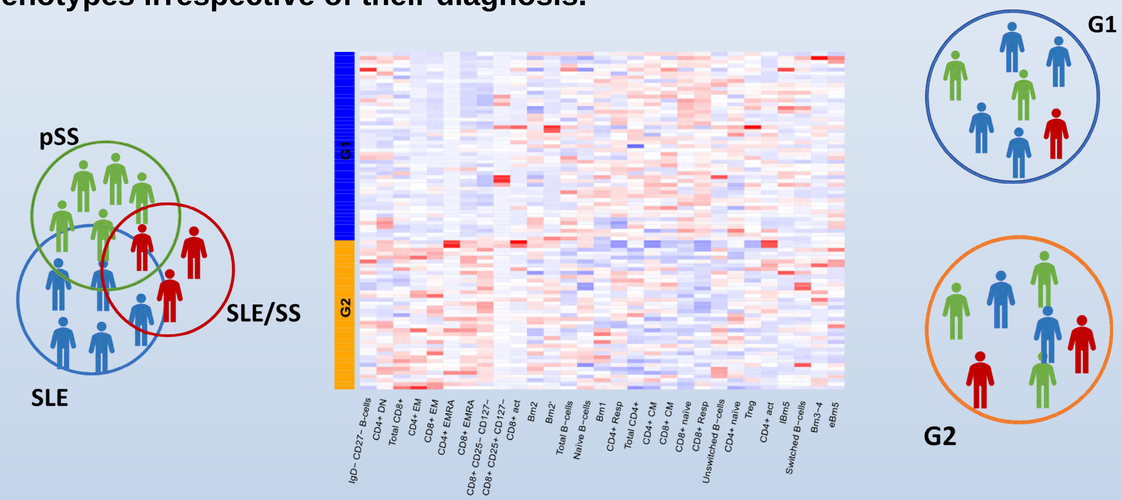
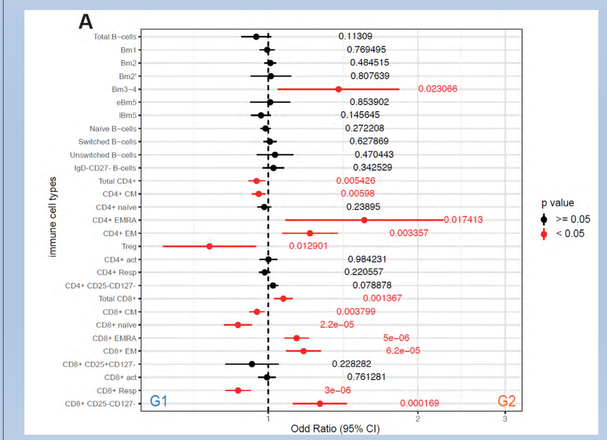


Figure 3. The Combined SLE, pSS and SLE/SS patient cohorts were stratified using k-means clustering. Heat map is used to present the standardised immunophenotype (29 immune cells) by Z score, representing the relationship to the mean of the group (red represents relatively high frequency and blue represents relatively low frequency). Each row represents a patient. Columns were clustered by hierarchical method. Two groups of patients were recognised with distinct immune cell profiles by k-means clustering.

2. The immunological architectures are different between Group-1 (G1) and Group-2 (G2).



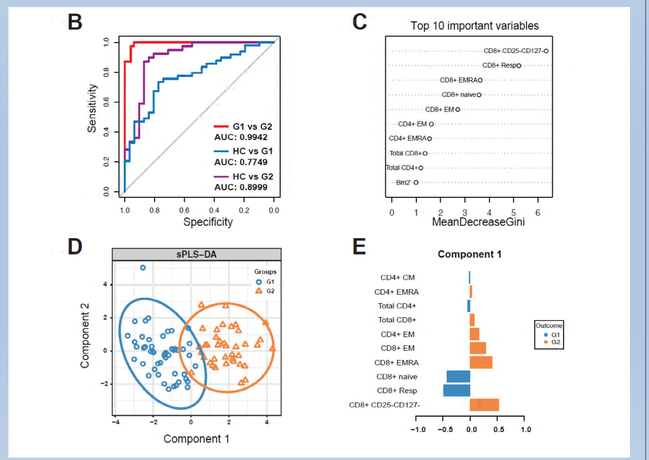


Figure 4.(A) Forest plot: Odds ratios (95% confidence intervals, CIs) of 29 immunological parameters were computed with univariate logistic regression analysis. Demographic variables (age and ethnicity) were adjusted in logistic regression analysis. **(B-C)** Balanced random forest (BRF) performed with demographic variables (age and ethnicity) adjusted. **(B)** Receiver operator characteristic (ROC) curve analysis: Area under the curve (AUC) from the BRF model (G1 vs G2). **(C)** The top 10 variables contributing to the BRF model are shown. The mean decrease in Gini measures the importance of each variable to the model, a higher score indicates a higher importance of the variable.**(D-E)** sparse Partial Least Squares Discriminant Analysis (sPLS-DA) performed with all 29 immune cell types. (D) sPLS-DA plot: to validate the top hits from the predictive model. Individual distribution points and confidence ellipses for the G1 and G2 are plotted in blue and orange, respectively. **(E)** factor loading weights in component 1 for the top 10 ranked immunological parameters. Colours indicate the class with maximal mean value; blue=G1, orange=G2.

3. Clinical differences between the two groups were found and maintained over a period of 5 years.

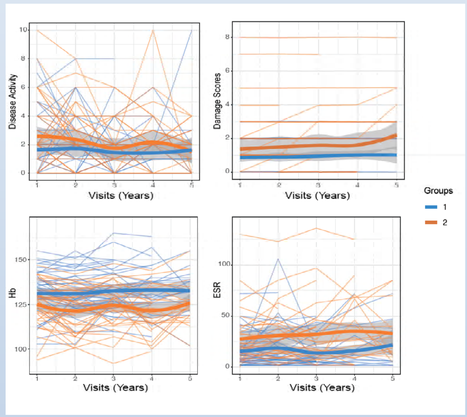


Figure 5: Individual patient trajectories of disease specific activity and damage scores, combined activity (SLEDAI and ESSDAI as the cut-offs for moderately active disease are similar) and damage scores (SLICC and SSDDI) across the three disease phenotypes and laboratory markers over 5 annual clinical encounters displayed as spaghetti plots. Each line represents one patient. Smoothing lines were added to indicate the trend of patient trajectories corresponding to Group-1(blue) and Group-2 (orange).

SUMMARY

- Using machine learning approaches in a mixed cohort of patients with SLE, pSS or SLE/SS we established two new disease endotypes based on peripheral blood immune signatures.
- These endotypes can predict long-term disease activity and damage trajectories.
- Our findings highlight shared immune-pathogenic processes underlying SLE and pSS manifestations which are likely to be more relevant for treatment selection strategies than the patient diagnosis.

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