Background: Primary Sjögren’s syndrome (pSS) and systemic lupus erythematosus (SLE) are chronic autoimmune rheumatic diseases (ARDs) that share a strong female gender bias, as well as genetic, clinical and serological characteristics. Although significant progress has been made in improving treatment and patient-related outcomes in pSS and SLE, there is a need for improved early diagnosis, adequate therapy monitoring, treatment of refractory manifestations and strategies to address co-morbidities. However, the results of many clinical trials are disappointing, and no biologic treatments are licensed in pSS, while few are available for SLE patients with refractory disease.

Objectives: Identifying shared immunological features between patients with pSS and SLE that could lead to better treatment selection using a stratification approach.

Methods: Immune-phenotyping of 29 immune-cell subsets in peripheral blood from patients with pSS (n=45), SLE (n=29) and secondary SS associated with SLE (SLE/SS) (n=14) with low disease activity or in clinical remission, and sex-matched healthy controls (n=31), was performed using flow cytometry. Data were analysed using logistic regression, BRF (AUC=0.9942, assessed by 10-fold cross-validation) and sPLS-DA analysis. Patients were stratified by k-means clustering. Clinical trajectories were analysed over 5 year follow-up.

Results: Comparing the immune profile of pSS and SLE patients using a variety of statistical and machine learning (ML) approaches, identified very few statistically significant differences between the two cohorts despite patients having a different clinical presentation and diagnosis. Thus, we hypothesised that immune-based subtypes could be shared between pSS, SLE and SLE/SS patients. Unsupervised k-means clustering was applied to the immunological features of the combined patient cohorts and two distinct patient endotypes, were identified: Group-1 (n=49; pSS=24, SLE=19, SLE/SS=6) and Group-2 (n=39; pSS=21, SLE=10, SLE/SS=8). Significant differences in immune-cell phenotypes across B-cell and T-cell subsets were identified by logistic regression, BRF (AUC=0.9942, assessed by 10-fold cross-validation) and sPLS-DA analysis. Comparison of the multiple analysis approaches identified eight common immune-cell subsets, including total and memory CD4+ and CD8+ T-cell subsets but no B-cell subsets. Using this common immune-signature the stratification between the groups was maintained and slightly improved (AUC=0.9979 and accuracy 96.16%). Interestingly, patients in Group-2 had elevated disease activity measures at baseline and over a 5-year trajectory compared to Group-1. Finally, correlation analysis identified correlations between disease activity markers and the top ranked immune features from the ML models.

Conclusion: The identified immune-cell signatures could reflect the underlying disease pathogenesis that spans diagnostic criteria and could be used to select patients for targeted therapeutic approaches.

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