

Comment on: Clinical impact of anti-SSA antigenic specificity on disease activity and patient-reported outcomes in primary Sjögren's disease: a real-life cohort study

Dear Editor,

We read with great interest the recent article by Fonzetti *et al.* regarding the impact of anti-SSA antigenic specificity on clinical phenotypes in primary Sjögren's disease (SjD) (1). The authors observed that patients with isolated anti-Ro60 positivity reported the highest symptom burden despite low systemic inflammation, whereas triple-positive patients (anti-Ro52/Ro60/La) showed the reverse. While this stratification provides a valuable framework, the clinical interpretation of these dissociated profiles requires careful scrutiny of comorbidities and biological mechanisms.

Firstly, the significantly high symptom burden associated with the isolated anti-Ro60 phenotype may be driven by factors other than SjD-specific autoimmunity. The authors reported that 53.3% of these patients had comorbid fibromyalgia, a known confounder that significantly inflates EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) scores (pain and fatigue) independent of glandular inflammation. Other large-scale cohorts indicate that isolated anti-Ro60 reactivity lacks specificity for SjD, being frequently associated with systemic lupus erythematosus or undifferentiated connective tissue disease and often exhibiting the least objective glandular damage (2, 3). Consequently, the profound pain and fatigue in this subgroup likely reflect a complex interplay of comorbid fibromyalgia and overlapping connective tissue features, rather than a distinct "symptom-dominant" SjD

phenotype. Attributing these predominantly comorbidity-driven symptoms solely to SjD risks obscuring their true pathological origin and compromising the accurate assessment of the primary disease burden.

Conversely, the triple-positive phenotype exhibits a paradoxical dissociation between biological severity and patient-reported symptoms. Despite having the highest systemic activity (ESSDAI), these patients report lower ESSPRI scores compared to the isolated anti-Ro60 group. This finding contrasts with established immunopathology. Bettacchioli *et al.* demonstrated that this serological profile is associated with intense interferon pathway activation (4), which typically induces significant fatigue. Moreover, Deroo *et al.* confirmed that these patients show the most extensive objective glandular destruction (5). That patients with such severe autoimmune inflammation and tissue damage report lower distress than the isolated anti-Ro60 group suggests a critical conclusion: the scores in the comparator group are likely inflated by non-inflammatory pain mechanisms.

We commend the authors for highlighting the clinical utility of detailed serological profiling. Their work reinforces the vital concept that antibody profiles are not merely diagnostic tags but markers of distinct biological trajectories. Integrating this serological stratification with deeper mechanistic phenotyping will be crucial for refining therapeutic strategies and realising the promise of precision medicine in SjD.

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