PREDICTING AUTOIMMUNE CONNECTIVE TISSUE DISEASES: THREE YEAR FOLLOW UP OF AN AT RISK COHORT IDENTIFIES LATE PROGRESSION AND PREDICTS NEED FOR THERAPY

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Background

- Auto-immune connective tissue diseases (AI-CTDs: SLE, pSS, IIM, Scleroderma, MCTD) are preceded by asymptomatic ANA positivity.
- CTD patients are well known to have an interferon signature but we previously showed that a distinct subset of ISGs ("score B") was more predictive of clinical outcomes than ISGs.
- We previously reported results from the first 118 "At-Risk" of AI-CTD individuals (i.e. ANA positivity, non-specific symptoms of ≤1 year and treatment naïve).
  - At 1 year, 16% progressed to meet classification criteria for an AI-CTD.
  - This was predicted by high baseline interferon (IFN) Score B[1] and family history of rheumatic and musculoskeletal diseases (RMD)[2].
- However, some may have progressed at later time points, or had clinically significant disease despite not meeting diagnostic criteria.

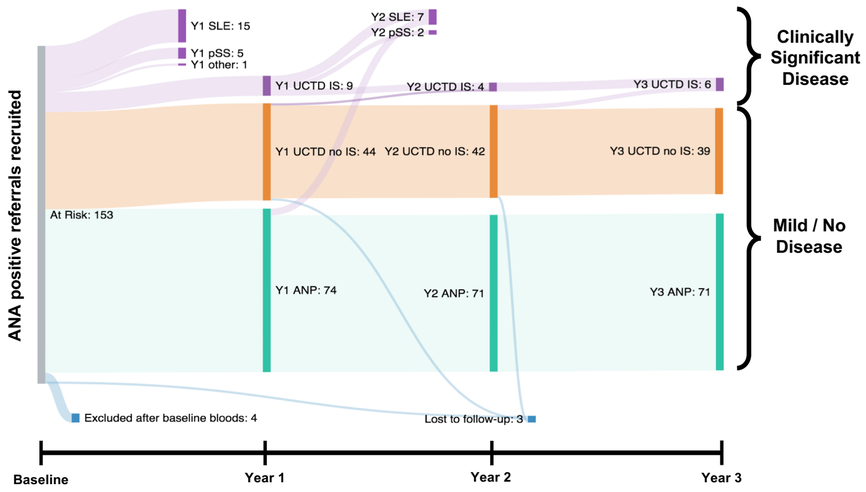
Objectives

- Describe detailed analysis of 3-year follow-up data of the At-Risk cohort.
- Describe detailed clinical data for this cohort.
- Evaluate flow cytometric biomarkers as predictors of these outcomes.

Methods

- 153 patients with ANA positivity referred by GP with suspected disease who did not meet AI-CTD criteria at baseline were recruited prospectively in this observational study.
- Patients were assessed annually for 3 years, and AI-CTD criteria was checked each time.
- Allowed to start therapy if deemed necessary
- Baseline flow cytometry and interferon scores previously described[1] were measured.
- Flow cytometry involved analysis of monocytes and subsets of B and T cells (CD4 T cells, CD8 T cells, naïve B cells, memory B cells, plasmablasts, NK cells)

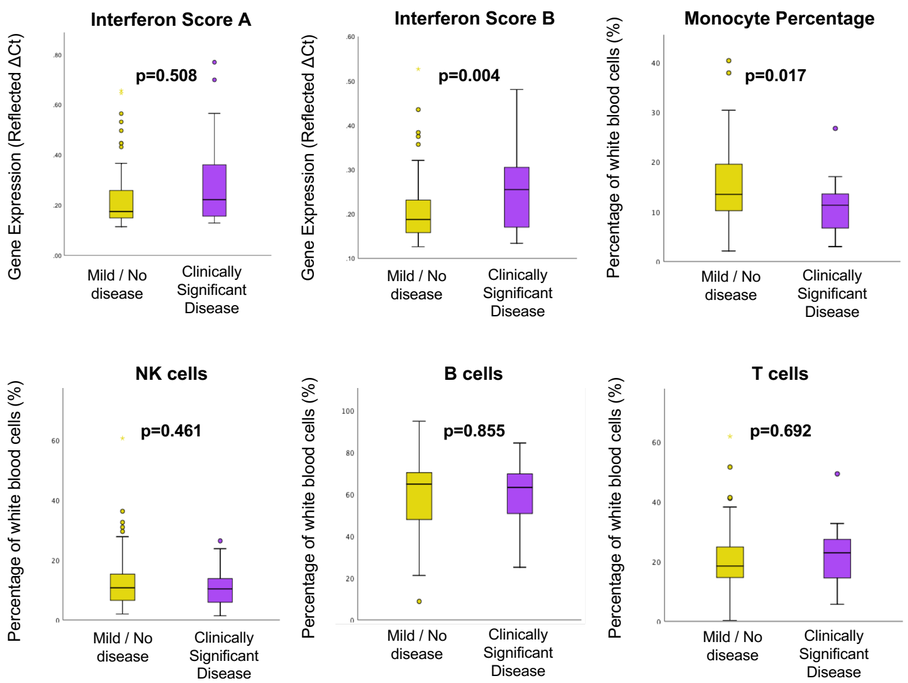
Results – 1. Patient flow



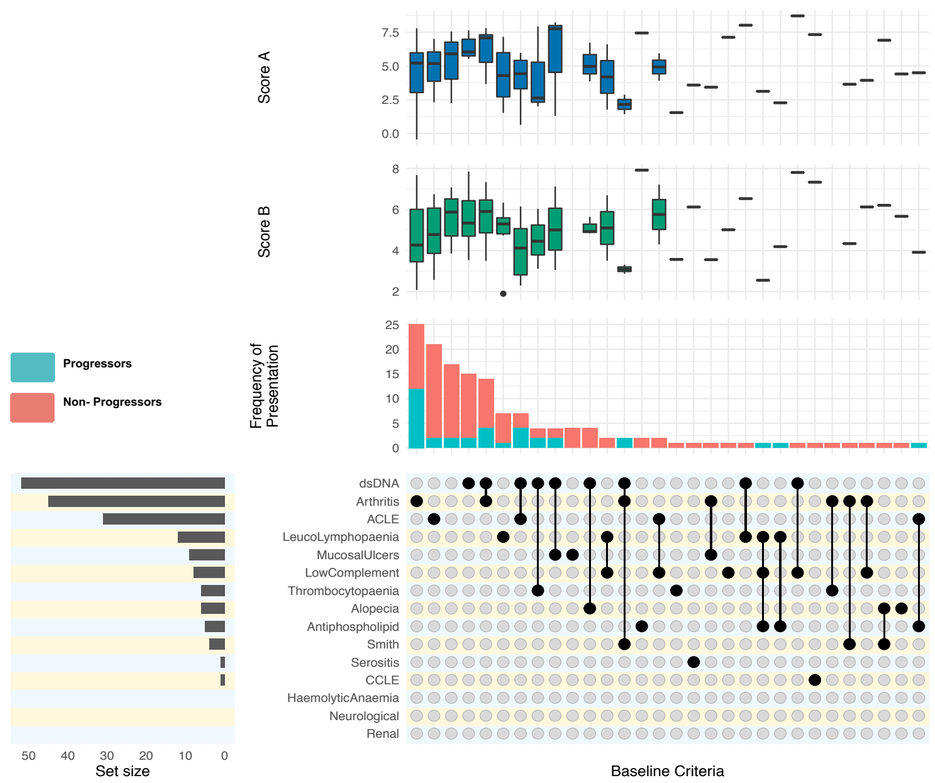
Patients were grouped in the following categories:

- Y1 SLE, Y2 SLE: patients meeting criteria for SLE at end of Y1 or Y2
- Y1 SLE, Y2 pSS: patients meeting criteria for SLE at end of Y1 or Y2
- Y1 other: patients with another autoimmune rheumatic disease at end of Y1
- Y1 UCTD IS: patients with at least one clinical criterion for a CTD and needing immunosuppression but not meeting full criteria
- U-CTD no IS: U-CTD not requiring immunosuppression
- ANP: Absolute Non Progressor

2. Baseline biomarkers predict disease progression and IS need



3. Clinical criteria at baseline does not predict clinical outcome



- Most common SLE criteria at baseline were: dsDNA, arthritis, ACLE
- Commonest combinations: dsDNA & arthritis, arthritis, ACLE, dsDNA alone, or no criteria
- There was variation in IFN scores between these presentations

Conclusions

- A quarter of A-Risk patients developed clinically significant disease.
- No clinical feature or routine laboratory test could predict the need for immunosuppression.
- At-Risk individuals who ultimately developed clinically significant disease are immunologically but not clinically distinctive from those with mild / no disease, as they have:
  - Higher IFN score B,
  - Lower monocyte percentage.
- Future work incorporating biomarkers into clinically applicable risk models will allow earlier exclusion of AI-CTD and trials of preventative treatment.

References

1. El-Sherbiny YM. *Scientific reports*. 2018; 8: 5793.
2. Md Yusof MY. *Annals of the rheumatic diseases*. 2018; 77: 1432-9.

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