Combinations of Autoantibodies Improve the Prediction of Timing of Onset of Future Rheumatoid Arthritis

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Introduction

Published data suggest that combinations of Anti-citrullinated protein antibodies (ACPA) and Rheumatoid Factor (RF) are highly predictive of future rheumatoid arthritis (RA) as well as predictive of onset of RA within a relatively short time period. We have evaluated the role of combinations of ACPA and RF testing, and change over time, in predicting the time of onset of future clinically apparent RA.

Methodology

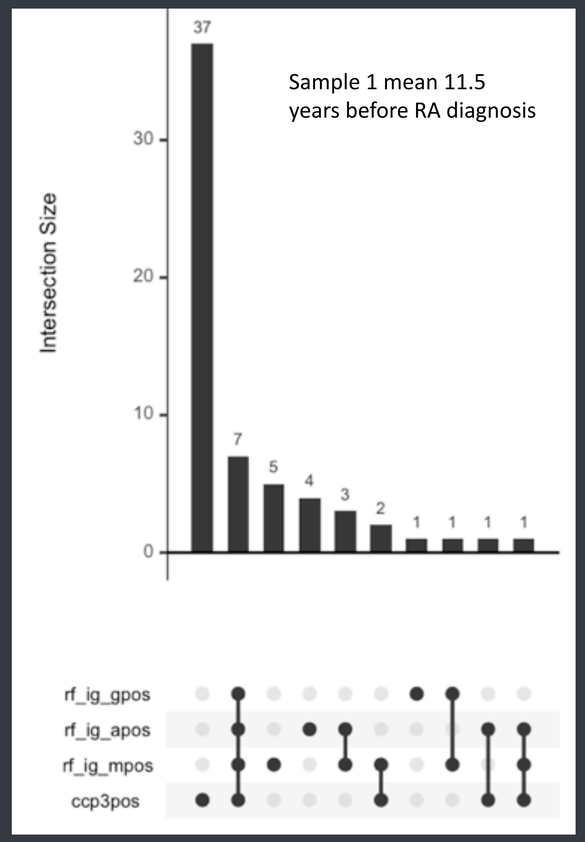
Using the Department of Defense Serum Repository we identified 215 RA cases. A mean of 3 pre-RA and 1 post-RA diagnosis serum samples were tested for RF immunoglobins (Ig) A, IgG, and IgM and anti CCP 2 ,3, and 3.1. The timing and trajectories of elevations of autoantibodies were evaluated. A gap-time cox regression model was used to develop hazard ratios for the risk of developing RA. Restricted meantime in state was also determined to predict time until RA diagnosis.

Results

Table 1: Percent male and age at time of samples

(N=215)	
age_earliest	
Mean (SD)	25.200 (6.305)
Range	17.000 - 45.000
age_latest	
Mean (SD)	38.014 (7.851)
Range	20.000 - 58.000
male	113 (52.6%)

Controlling for age, gender, RFIgA and RFIgM status, if a subject had a positivity for either CCP2 or CCP3.1, they were at 3.3 times greater risk of developing RA compared to a subject who was not positive for either CCP2 or CCP3.1 ($p < 0.001$). A subject positive for RFIgA or RFIgM was at 1.6 times greater risk of developing RA ($p = 0.002$). These effects mean than subject testing positive for either CCP test and either RF test would be at 5.4 times greater risk than one who tested positive for neither.



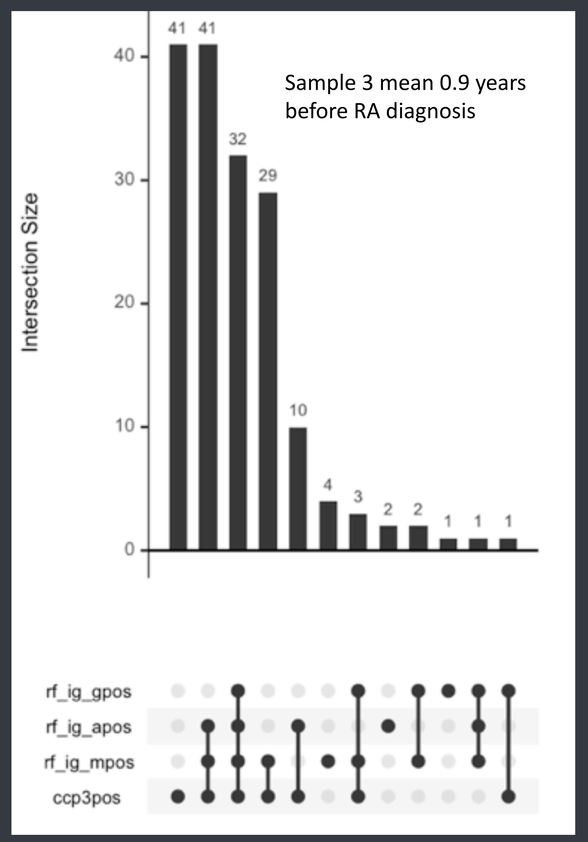


Figure 1: Sero Positivity over time

Testing positive for CCP3 and any RF resulted in a restricted mean time of 2.16 years compared to 3.59 for only CCP3 positive and 4.27 when negative for CCP3 and all RF isotypes. CCP3, CCP3.1, and CCP2 were highly corelated, however CCP3 was most sensitive therefore it was selected for RF combinations in the Restricted mean time in state analysis.

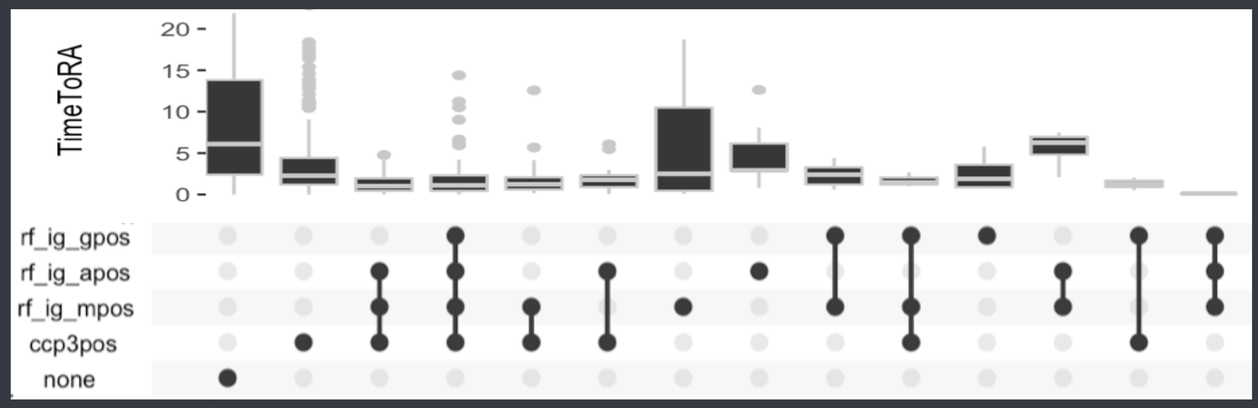


Figure 2: Restricted mean state by seropositivity

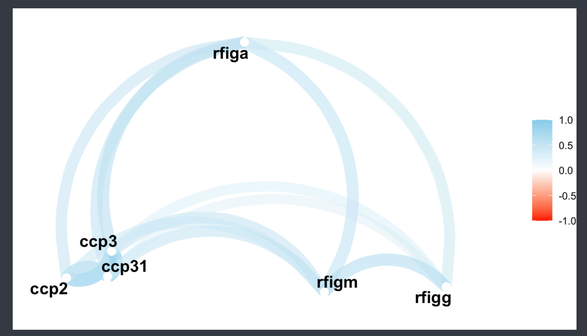


Figure 3: (Spearman) correlations among biomarkers

Table 2:Restricted mean time of CCP3 and any RF

Group	records	events	*rmean
CCP3 and any RF			
ccp3pos=0, any_rf=0	273	47	4.27
ccp3pos=0, any_rf=1	37	11	3.65
ccp3pos=1, any_rf=0	129	41	3.59
ccp3pos=1, any_rf=1	203	116	2.16
CCP3 and 2 of 3 RFs			
ccp3pos=0, any_2_rfs=0	299	55	4.22
ccp3pos=0, any_2_rfs=1	11	3	3.78
ccp3pos=1, any_2_rfs=0	197	81	3.12
ccp3pos=1, any_2_rfs=1	135	76	2.18

Implications

There is relatively little understanding of how longitudinal changes of autoantibody positivity in Pre-RA may further inform the timing of the appearance of clinically-apparent arthritis. Utilizing longitudinal serum samples from patients could potentially help identify which individuals will benefit from preventive treatment for RA . Our evaluation is the first step in determining the role of combinations of ACPA and RF testing, and change over time, in predicting the time of onset of future clinically apparent RA.

References

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If a person has more positive sero markers it is more likely they will devolve RA, and the time until onset of clinically apparent RA symptoms will likely be shorter.