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

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Purpose: 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.

Methods: Using the Department of Defense Serum Repository we identified 214 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 mean time in state was also determined to predict time until RA diagnosis.

Results: 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/hazard of developing RA compared to a subject who was not positive for either CCP2 or CCP3.1 ($p < 0.001$). Similarly, a subject positive for RFIgA or RFIgM was at 1.6 times greater risk/hazard of developing RA ($p = 0.002$). These effects mean that a 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. 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.

Conclusion: If a subject has more positive markers it is more likely they will devolve RA, and the time until onset of clinically apparent RA symptoms will likely be shorter as the number of positive markers increases.