and trainee rheumatologists who enrolled patients in these studies, and all research nurses for their contributions.

Disclosure of Interests: Johanna M. Maassen: None declared, Raquel Dos-Santos: None declared, Sytske Anne Bergstra: None declared, Robbert Goekoop: None declared, Thomas Huizinga: None declared, Cornelia Allaart Grant/research support from: The original BeSt study was realized with a government grant from the Dutch College of Health Insurance Companies, with additional funding from Schering-Plough and Janssen. the IMPROVED study was financially supported by AbbVie in the first year.

DOI: 10.1136/annrheumdis-2021-eular.2442

POS0471

ASSOCIATION OF HLA-DRB1 HAPLOTYPES WITH CARDIOVASCULAR MORTALITY IN INFLAMMATORY POLYARTHRITIS: RESULTS FROM THE NORFOLK ARTHRITIS REGISTER

S. Sharma¹, D. Plant¹, J. Bowes¹, A. MacGregor^{2,3}, S. Verstappen^{1,4}, A. Barton^{1,4}, S. Viatte^{1,5}, ¹Centre for Genetics and Genomics Versus Arthritis, Centre for Musculoskeletal Research, Manchester, United Kingdom; ²Norwich Medical School, University of East Anglia Faculty of Medicine and Health Sciences, Norwich, United Kingdom; ³Rheumatology Department, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, United Kingdom; ⁴NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester NHS Foundation Trust, Manchester, United Kingdom; ⁵Lydia Becker Institute of Immunology and Inflammation, Faculty of Biology, Medicine and Health, The University of Manchester, Manchester, United Kingdom

Background: Haplotypes defined by amino acids at HLA-DRB1 positions 11, 71 and 74 associated with susceptibility to rheumatoid arthritis (RA), are associated with radiological outcome, anti-TNF response and all cause-mortality in RA. (1, 2) RA is associated with cardiovascular (CV) morbidity and mortality, but the increased prevalence of risk factors of CV disease in RA only partially explains this association.

Objectives: The aim was to investigate whether haplotypes associated with RA disease susceptibility and disease severity are also associated with CV mortality.

Methods: The Norfolk Arthritis register (NOAR) is a primary care-based inception cohort of patients with inflammatory polyarthritis (IP). (1, 2) NOAR patients with at least 2 years of follow-up and available mortality and genetic data were included in this study. Mortality data was provided by the Office for National Statistics.

Univariate Cox proportional hazard models were applied using STATA/IC 14.0. Models for CV mortality were adjusted for CV risk factors selected using stepwise regression: namely obesity, gender and hypertension. Hazard models were applied to the entire cohort of patients with inflammatory polyarthritis (IP). When calculating differences between highest and lowest risk genetic factors, bivariate analysis was used.

Results: HLA-DRB1 amino acids, haplotypes or haplotype groups associated with RA susceptibility are also associated with CV mortality as shown in the table 1. HLA-DRB1 polymorphisms encoding amino-acid haplotypes associated with an increased or decreased susceptibility to RA consistently show the same magnitude and direction of association for overall and CV mortality in IP. For example, the SEA-haplotype, associated with the lowest susceptibility to RA, and the best radiographic outcome, was found to be associated with decreased CV mortality (HR 0.67, 95% CI 0.47, 0.91, p=0.023). The relative difference in CV mortality between carriers of the high susceptibility VKA haplotype and carriers of the SEA haplotype was significant (HR 1.67, 95% CI 1.13, 2.48, p=0.01).

Table 1. Hazard ratios for CV mortality by genetic factors among patients with IP. Total number (n) of deaths are also displayed alongside the total number (n) of patients included in each analysis.

Amino acid / Haplotype /Group	Hazard Ratio (95% CI)	N
valine 11	1.10 (0.93, 1.30)	343 (2514)
serine 11	0.82 (0.70, 0.96)*	343 (2514)
Difference	1.23 (1.01, 1.49)*	
VKA haplotype	1.16 (0.94, 1.43)	310 (2328)
SEA haplotype	0.67 (0.47, 0.94)*	310 (2328)
Difference	1.67 (1.13, 2.48)*	
Group 1 †	1.10 (0.93, 1.31)	319 (2328)
Group 4 †	0.73 (0.60, 0.89)*	319 (2328)
Difference	1.37 (1.09, 1.72)*	

* p<0.05†Haplotype groups as defined previously (2)

HLA-DRB1 haplotypes can be ranked according to the magnitude of their association with RA susceptibility and this hierarchy is conserved for various measures of disease outcome and overall mortality.(2, 3) The figure 1 shows that this risk hierarchy is also conserved for CV mortality: HLA-DRB1 haplotypes that

predispose to RA also predispose to increased CV mortality, independent of known CV risk factors.

Figure 1. Haplotypes with frequency >12% in NOAR are shown. X axis: susceptibility to ACPA-positive RA as ORs.(2) Y axis: CV mortality risk in IP as HRs, derived from multi-variate cox-proportional hazard models adjusted for CV risk factors. Values are on a logarithmic scale. A one-tailed p value was calculated using linear regression to determine the association between β coefficients of susceptibility and CV mortality.

Conclusion: The originally reported genetic associations between HLA-DRB1 polymorphisms and overall mortality were likely driven by associations with CV mortality.

REFERENCES:

- [1] S. Viatte *et al.*, *JAMA* **313**, 1645-1656 (2015).
- [2] S. Raychaudhuri *et al.*, *Nat Genet* **44**, 291-296 (2012).
- [3] D. P. Symmons, A. J. Silman, *Clin Exp Rheumatol* **21**, S94-99 (2003).

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2021-eular.2481

POS0472

COMPARATIVE METABOLOMIC ANALYSIS OF SERUM SAMPLES FROM PATIENTS WITH COINCIDENTAL RHEUMATOLOGICAL AND MALIGNANT DISEASES

D. Marx¹, L. Diekmann¹, K. Klika², H. M. Lorenz¹, K. Benesova¹, M. Souto-Carneiro¹, ¹Heidelberg University Hospital, Medicine 5 - Rheumatology, Heidelberg, Germany; ²DKFZ Heidelberg, Molecular Structure Analysis, Heidelberg, Germany

Background: Rheumatic and musculoskeletal diseases (RMDs) and malignancies are both caused by a dysfunctional immune system and the probability of their coincidence in one individual is rising due to advances in cancer treatment and demographic changes. However, the lack of understanding of the complex interrelationship of both conditions often leads to undertreatment and high level of suffering in affected patients. Herein, the Malheur project breaks new ground by systematic analysis of concomitant malignant and rheumatic diseases and closes the knowledge gaps on the clinical and molecular level.

Objectives: To enable early diagnosis of concomitant malignancy and/or identification of patients at risk in the future, changes in serum metabolome were explored in order to create a diagnostic classification model.

Methods: Serum samples from patients with concomitant RMD and cancer or obligate precancerous lesions (n=78, breast cancer (23), melanoma (14), MGUS (12), prostate cancer (8) and others (21)) were collected as a pilot study within the Malheur project, a registry-based study initiated in 2018 at the university hospital Heidelberg, Germany. The following groups were defined by the underlying RMD: rheumatoid arthritis (n=42), psoriasis arthritis (n=23), spondylarthritis (n=9) and systemic lupus erythematosus (n=4). RMD patients without any malignancies were used as controls (n=280: 122 RA, 81 PsA, 46 SpA, 31 SLE).

Samples were analyzed by 1H NMR spectroscopy. For all samples, regular 1H acquisition with presaturation and Carr-Purcell-Meiboom-Gill (CPMG) spectra were acquired using a 600 MHz Bruker NMR spectrometer. Spectra were processed with TopSpin using 0.2 Hz of line broadening and manual phasing. Molar concentrations of 26 metabolites were acquired by integration of NMR spectra. With GraphPad Prism, univariate and ANOVA statistical analysis was performed to find significant differences between each malignant group and their control group as well as between all four malignant groups.