+CD3-), T (CD3+CD4+, CD3+CD8+) and NK (CD16/56+CD3-) cells. Monocytes were further classified to classical (CD14++CD16-), intermediate (CD14++CD16+/+) and non-classical (CD14-/++CD16++) subsets. Data were analysed using Mann Whitney test and expressed as median and interquartile range [IQR].

Results: Out of 49 individuals with arthralgia, 36 were ACPA+ and 28 met CSA definition (15 of them were ACPA+), with symptoms duration 21 months [IQR=53], CRP 3.18 mg/L [IQR=3.6], DAS28 score 2.28 [IQR=1.31]. As per definition, there was no evidence of clinical arthritis on examination of 66 joints at baseline. Ten individuals developed RA within a median of 4 months of follow up.

Individuals with arthralgia had higher%CD3+ T cells (78.10 [8.10] vs. 75.04 [9.26], $p=0.001$) and lower%NK (11.20 [7.20] vs. 12.89 [6.62], $p<0.001$) as well as absolute count of NK cells (0.18 [0.13] vs. 0.24 [0.17], $p<0.001$) compared to HC. Similarly, higher%CD3+ T cells (77.95 [8.65] vs. 75.04 [9.26], $p=0.003$) and lower%NK (10.85 [7.81] vs. 12.89 [6.62], $p=0.003$) and absolute count of NK cells (0.20 [0.14] vs. 0.24 [0.17], $p=0.003$) was confirmed in a subgroup of ACPA+ individuals compared to HC. Moreover, individuals who developed RA during follow up, had a lower baseline absolute count of NK cells (0.14 [0.10] vs. 0.19 [0.15], $p=0.039$).

Analysis of monocyte subpopulations revealed higher count of non-classical (5.99 [4.87] vs. 4.03; IQR [3.28], $p=0.022$) and intermediate (5.82 [2.93] vs. 4.31 [2.08], $p=0.034$) monocytes and lower count of classical monocytes (86.06 [7.69] vs. 89.41 [3.52], $p=0.005$) in individuals with arthralgia compared to HC. Specifically, also ACPA+ patients had higher count of non-classical (6.07 [5.84] vs. 4.03 [3.28], $p=0.020$) and intermediate (5.86 [3.05] vs. 4.31 [2.08], $p=0.036$) and lower count of classical (85.43 [8.34] vs. 89.41 [3.59], $p=0.005$) monocytes compared to HC. There was no difference in% or absolute count of lymphocytes and monocytes subpopulations at the time of manifestation of RA and between ACPA+ and ACPA- individuals.

Conclusion: We show lower numbers of NK cells and classical monocytes and expansion of intermediate and non-classical monocytes in individuals in the preclinical phase of RA, especially in ACPA+ individuals. Such disproportion or pro-inflammatory potential of these cells was previously shown in the pathogenesis of established RA. We hypothesize that the dysregulation observed in at-risk individuals may be a prognostic marker and a predisposition leading to further development of RA.

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THU0063

PRE-MRNA SPLICING ALTERATIONS IN FOLYLPOLYGLUTAMATE SYNTHETASE IN BLOOD CELLS OF EARLY RHEUMATOID ARTHRITIS PATIENTS ARE ASSOCIATED WITH UNRESPONSIVENESS TO METHOTREXATE

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Background: Low-dose methotrexate (MTX) serves as the first-line treatment for rheumatoid arthritis (RA). Conversely, for hematological malignancies, high-dose MTX treatment is indicated in combination with folinic acid/leucovorin to prevent untoward toxicity. For both disease modalities, efficient pharmacological response critically depends on the retention and accumulation of intracellular MTX. The latter process is mediated by the enzyme folylpolyglutamate synthetase (FPGS) through MTX conversion into MTX-polyglutamates (MTX-PG). As such, decreased FPGS activity has been recognized as a mode of MTX resistance, but the underlying molecular mechanism has not yet been pinpointed [1,2]. Recently,

aberrant pre-mRNA splicing of FPGS in acute lymphoblastic leukemia cells was associated with reduced FPGS activity, decreased MTX-PG accumulation and lower overall survival. Specifically, a partial retention of FPGS intron 8 (8PR) was identified as a prominent splice variant causing FPGS dysfunction [3].

Objectives: To investigate whether the expression of the FPGS pre-mRNA variant partial retention of intron 8 is associated with MTX unresponsiveness in RA patients over 3-6 months of MTX therapy.

Methods: Patients were enrolled from the COBRA-light trial comprising MTX treatment [4]. After informed consent, blood was obtained from 38 patients in either the COBRA (n=15) or the COBRA-light (n=21) treatment arm [4] and collected in Paxgene tubes for RNA isolation. Two patients were excluded due to insufficient sample quality. Quantitative PCR techniques were used to assess the ratios of FPGS 8PR over wild type FPGS (8WT) expression in whole blood RNA. Remission was defined as a DAS44 < 1.6.

Results: Baseline ratios of 8PR/8WT were associated with a decline in DAS44 at T3 ($p=0.001$) and T6 ($p=0.13$) in the COBRA-light patients. T3 ratios were also associated with DAS44 at T6 ($p=0.001$) and Δ DAS44 at T6 ($p=0.26$). Logistic regression analysis showed that in COBRA-light patients baseline ratios of 8PR/8WT were associated ($p=0.05$) with the probability of T3 remission but not T6 remission. T3 ratios of 8PR/8WT in COBRA-light patients were similarly associated with T6 remission but not with T3 remission. COBRA patients also showed a significant association between baseline 8PR/8WT ratios and DAS44 at T6 ($p=0.04$) while T3 ratios of 8WT/8PR were significantly associated with DAS44 at T3 ($p=0.03$) and T6 ($p=0.05$). However, analysis of COBRA patients showed no significant associations between baseline 8PR/8WT ratios and T3/T6 remission, nor associations between T3 ratios and T3/T6 remission.

Conclusion: These results demonstrate that a higher expression of an intron 8 retention of FPGS mRNA is associated with a higher DAS44 at T3 and T6 in COBRA-light patients, and at T6 for COBRA patients. Moreover, in COBRA-light patients, baseline expression of 8WT/8PR is significantly associated with remission at T3 or T6. This study is the first to show the impact of FPGS pre-mRNA splicing alterations in relation to unresponsiveness to MTX treatment in RA.

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THU0064

COMPARISON OF MORTALITY IN RHEUMATOID ARTHRITIS AND DIABETES – THE HUNT POPULATION-BASED STUDY

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Background: Patients with rheumatoid arthritis (RA) have higher mortality rates than the general population, primarily from cardiovascular disease (CVD). Diabetes is an acknowledged risk factor for early death, mainly due to CVD. The reported risk for CVD is increased for both patients with RA and diabetes, however the effect of diabetes appears to be greater than that of RA (1).

Objectives: To assess whether the increase in all-cause mortality rates in patients with RA and patients with diabetes are similar, compared to the general population.

Methods: Data were obtained from the 2nd and 3rd survey of the population-based Nord Trøndelag Health Study (HUNT) and the Norwegian National Cause of Death Registry. The RA diagnoses have previously been validated (2). The definition of diabetes was self-reported diabetes, self-reported use of antidiabetics, or non-fasting blood glucose level >11.1 mmol/L. The participants were followed from their participation in HUNT to death or to 31.12.2014, whichever came first. Participants with other types of inflammatory arthritis or missing data for any of the variables in

the model were excluded. Furthermore, the patients with both RA and diabetes were not included in the analysis (n=33). Participants with neither RA nor diabetes were defined as controls.

RA patients, diabetes patients and controls were compared using Cox proportional hazard regression modelling, with age as the time scale. The model was adjusted for sex, smoking status, previous CVD, body mass index (BMI), hypertension, total cholesterol and creatinine. To obtain proportional hazards, an interaction term with age ≤ 75 years vs > 75 years was included for diabetes, smoking and previous CVD. The effects of the groups were compared using overlap of confidence intervals.

Results: Table 1. Participant characteristics

	RA N=387	Diabetes N=2,898	Controls N=63,903
Female sex, n (%)	261 (67)	1,369 (47)	33,781 (53)
Age (yrs), median (IQR)	58 (49-68)	63 (51-73)	46 (34-60)
Never smoker, n (%)	132 (34)	1,263 (44)	29,426 (46)
Former smoker, n (%)	129 (33)	682 (23)	19,010 (30)
Current smoker, n (%)	126 (33)	953 (33)	15,467 (24)
Previous CVD, n (%)	41 (11)	594 (20)	4,094 (6)
BMI (kg/m ²), median (IQR)	26.0 (23.7-29.1)	28.7 (25.9-32.0)	25.7 (23.4-28.4)
Hypertension, n (%)	199 (51)	2,098 (72)	25,333 (40)
Total cholesterol (mmol/l), median (IQR)	6.0 (5.3-6.8)	6.0 (5.1-6.9)	5.7 (4.9-6.5)
Creatinine (μ mol/l), median (IQR)	84 (77, 92)	89 (80, 99)	85 (77, 94)
RA duration (yrs), median (IQR)	6 (3-9)		
Seropositive RA, n (%)	277 (72)		
Diabetes duration (yrs), median (IQR)		5 (2-11)	
Observation time (yrs), median (IQR)	18 (13-19)	17 (8-19)	18 (13-19)

There were 123 (32%) deaths in the RA group, 1280 (44%) deaths in the diabetes groups and 11,641 (18%) deaths in the control group. The hazard ratio (HR) for RA was 1.24 (95% confidence interval: CI 1.02-1.46, p-value 0.013). The HR for diabetes was 1.82 (CI 1.60-2.05, p-value < 0.001) for those aged ≤ 75 years and 1.48 (CI 1.39-1.58, p-value 0.004) for those aged > 75 years. RA patients had a significantly lower HR compared to diabetes patients for age ≤ 75 years, but not for age > 75 years.

Conclusion: Patients with RA or diabetes had significantly higher mortality rates than controls, with larger HR for diabetes than for RA. The HR for RA was significantly lower than for diabetes for patients ≤ 75 years, but not for patients > 75 years. This may be due to survival bias in diabetes patients > 75 years.

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THU0065

VALIDATION OF THE ADJUSTED MULTI-BIOMARKER DISEASE ACTIVITY SCORE FOR PREDICTING RISK OF RADIOGRAPHIC PROGRESSION FOR PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: The multi-biomarker disease activity (MBDA) test has been adjusted to account for the effects of age, sex, and leptin (a surrogate for adiposity) in patients with rheumatoid arthritis (RA).¹ Using data from two cohorts (OPERA study and BRASS registry), this adjusted MBDA

score was shown to be the best individual disease activity measure for predicting radiographic progression, and to provide significant additional information to DAS28-CRP in predicting radiographic progression.

Objectives: To validate the association between the adjusted MBDA score and radiographic progression in two additional cohorts, and to evaluate the MBDA score for predicting risk of radiographic progression in four cohorts combined.

Methods: Four cohorts with requisite data were identified: BRASS registry (N=424), OPERA study (N=164), SWEFOT study (N=235), and Leiden registry (N=163). For the SWEFOT and Leiden cohorts, association of disease activity measures and other factors with radiographic progression (change per year in total Sharp score [TSS]), was evaluated using linear regression. These variables included the adjusted MBDA score, seropositivity (RF and/or ACPA positive), DAS28-CRP, SDAI, CDAI, CRP, baseline total TSS, age, and sex, as available for each cohort. Estimates of risk for radiographic progression (change in TSS > 5) as a function of the adjusted MBDA score were calculated using logistic regression in separate and pooled analyses.

Results: Among the tested measures of disease activity, the leptin-adjusted MBDA score was the most statistically significant univariate predictor of radiographic progression in the SWEFOT ($P < 0.0001$) and Leiden ($P < 0.00001$) cohorts, followed by CRP ($p < 0.01$, in each) (Table). No significant predictive ability was observed for DAS28-CRP, SDAI or CDAI in SWEFOT. DAS28-CRP was a weak predictor in the Leiden cohort ($P < 0.05$), (SDAI, CDAI unavailable). Among non-disease activity variables, baseline TSS and seropositivity were statistically significant predictors, to varying degrees. Neither age nor sex was significant (Table). When DAS28-CRP and the adjusted MBDA score were covariates in the same regression model in the Leiden cohort, DAS28-CRP was not a significant predictor, whereas the adjusted MBDA score remained significant ($p = 0.000054$). When the SWEFOT, Leiden, OPERA and BRASS cohorts were combined (N=986), the adjusted MBDA score remained a significant predictor of radiographic progression, enabling the creation of a risk curve for radiographic progression relative to the continuous adjusted MBDA score.

Conclusion: In two population-based observational cohorts, the adjusted MBDA score was validated and shown to be a more significant predictor of radiographic progression than conventional measures of RA disease activity. Four cohorts were combined to predict risk of radiographic progression using the continuous adjusted MBDA score for the first time.

Table: Univariate linear regression of radiographic progression in the SWEFOT and Leiden cohorts.

Variable	N	SWEFOT		N	Leiden	
		Coefficient (95% CI)	p-value		Coefficient (95% CI)	p-value
MBDA score	235	0.11 (0.057, 0.15)	0.000026	163	0.12 (0.069, 0.16)	0.000002
log(CRP + 1)	235	1.1 (0.35, 1.9)	0.0046	156	1.0 (0.28, 1.8)	0.0076
Seropositivity	181/235	2.7 (0.87, 4.5)	0.004	118/162	1.6 (0.064, 3.2)	0.041
Baseline TSS	235	0.11 (0.012, 0.20)	0.028	163	0.042 (0.024, 0.059)	0.000004
DAS28-CRP	235	0.57 (-0.22, 1.4)	0.16	156	0.67 (0.13, 1.2)	0.016
SDAI	233	0.038 (-0.026, 0.10)	0.24	n/a	n/a	n/a
Male sex	66/235	-0.80 (-2.5, 0.94)	0.37	54/163	-0.36 (-1.9, 1.1)	0.64
CDAI	233	0.016 (-0.058, 0.90)	0.67	n/a	n/a	n/a
Age	235	-0.0094 (-0.067, 0.048)	0.74	163	-0.020 (-0.072, 0.033)	0.46

n/a: not applicable because data needed to compute that variable were not available.

Abstract THU0059 – Table 1

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