Methods: 55 persons were included, divided into 20 RA patients, 25 FDR of RA patients (without evidence of arthritis) and 10 healthy matched controls. Clinical evaluation, with emphasis on joint symptoms and signs was done for all, in addition to measurement of ESR, CRP, RF, anti-CCP, serum OPN and serum OPG.

Results: Mean ESR was significantly higher in RA (64.15 ± 34.29) than in FDR (15.6 ± 11.04 , $p \leq 0.001$) and controls (6.0 ± 2.05 , $p \leq 0.001$) and significantly higher in FDR than controls ($p = 0.001$). Mean CRP was significantly higher in RA (26.38 ± 29.14) than FDR (5.99 ± 5.08 , $p \leq 0.001$) and controls (2.02 ± 0.53 , $p \leq 0.001$) and significantly higher in FDRs than in controls ($p = 0.011$). Mean RF and anti-CCP were statistically higher in RA than in FDR and controls. Mean anti-CCP was higher in FDR than in controls but without reaching statistical significance while there was no difference regarding mean RF between FDR and controls. OPN was higher in RA (3.66 ± 4.20) than in FDR (1.97 ± 1.04) and controls (2.81 ± 1.31) without statistical significance ($p = 0.102$). While OPG was significantly higher in RA (143.89 ± 365.47) than in both FDR (22.23 ± 65.73 , $p = 0.009$) and controls (6.20 ± 12.43 , $p = 0.003$). Mean serum OPN in RA was higher in RF and CCP positive (3.77 ± 4.43 and 4.13 ± 3.48 respectively) than RF and CCP negative (2.65 ± 0.35 and 3.58 ± 2.58 respectively) but without reaching statistical difference. Mean serum OPG in RA was higher in RF and CCP positive (153.15 ± 384.64 and 161.78 ± 394.67 respectively) than RF and CCP negative (60.50 ± 85.56 and 42.47 ± 68.09 respectively) but without reaching statistical difference. 8/25 (32%) FDR had arthralgia while 17/25 (68%) FDR were asymptomatic. FDRs with arthralgia had significantly higher ESR (27.88 ± 11.22) and CRP (10.36 ± 5.21) than asymptomatic FDR (9.82 ± 4.13 , $p = 0.003$) and (3.93 ± 3.58 , $p = 0.003$) respectively. OPG was higher in FDR than in controls and higher in those with arthralgia (51.55 ± 114.68) than those without (8.44 ± 9.67) but without reaching statistical difference ($p = 0.314$). Similarly, serum OPN was higher in FDR with arthralgia (2.09 ± 1.19) than asymptomatic (1.70 ± 0.55) but also without significant difference ($p = 0.620$). Furthermore, mean RF and anti-CCP were higher in FDR with arthralgia but didn't reach significant difference.

Conclusions: OPN and OPG are markers of altered bone metabolism in RA. Their elevation in FDR than controls denotes a state of altered bone metabolism. Moreover, FDR with arthralgia experience higher levels of OPN, OPG, ESR, CRP, RF, and anti-CCP than asymptomatic FDR. These findings reflect an ongoing disturbed bone metabolism and inflammation in FDR which could precede the clinical disease phase. Thus, OPN and OPG could serve as markers of altered preclinical bone metabolism in rheumatoid FDR. Results need to be confirmed on larger numbers of FDR.

Disclosure of Interest: None declared

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SAT0083

THE GENETIC AND CLINICAL PREDICTION MODELS FOR EFFICACY AND HEPATOTOXICITY OF METHOTREXATE IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: The efficacy and toxicity of methotrexate (MTX) depend on individual patients with rheumatoid arthritis (RA) and are difficult to predict before treatment although MTX is the anchor drug and achieving the treatment target earlier is desirable to prevent progression of structural and functional damage. Our previous studies revealed high predictive accuracy of single nucleotide polymorphisms (SNPs) to predict the efficacy and toxicity of MTX, suggesting the influence of genetic variations in enzymes associated with MTX metabolism and folate metabolic pathway^{1,2}. However, higher accuracy and replicability is demanded for clinical application.

Objectives: To develop combined genetic and clinical models to predict the efficacy and hepatotoxicity of MTX.

Methods: Patients with RA under the treatment of MTX according to Japanese guideline for the management of RA with MTX were enrolled. To predict the efficacy and hepatotoxicity, 1971 polymorphisms of 246 enzymes/transporters potentially relevant to pharmacokinetics and pharmacodynamics of MTX were measured by the DMET microarray (Affymetrix Inc.) and direct-sequencing method and clinical variables at baseline were collected. As for efficacy, the EULAR-CRP response criteria was chosen to classify patients with RA as responders (good response) and non-responders (moderate or no response). Hepatotoxicity was defined as either serum AST or ALT levels higher than 1.5 times the upper limit of the normal range. Among SNPs and clinical variables with significant association with outcomes using univariate analyses, stepwise model selection

was conducted by Akaike information criterion in logistic regression model and receiver operating characteristic (ROC) analyses were performed. Bootstrapping ($n=100,000$) was used to assess the robustness of the results.

Results: A total of 166 patients with RA was included. The median age was 61.5 years with 81.3% of women. For efficacy, genetic prediction model using 7 SNPs showed area under the curve of ROC (AUC) was 0.822 with sensitivity of 74.3% and specificity of 76.8%, while combined clinical and genetic model indicated AUC was 0.844 with sensitivity of 81.5% and specificity of 76.9%. By incorporating clinical variables into the genetic model, overall category-free net reclassification improvement (NRI) was 0.700 ($p < 0.0001$) and overall integrated discrimination improvement (IDI) was 0.089 ($p = 0.0005$). For hepatotoxicity, genetic prediction model using 7 SNPs showed AUC was 0.783 with sensitivity of 70.0% and specificity of 80.0%, while combined clinical and genetic model indicated AUC was 0.906 with sensitivity of 85.1% and specificity of 87.8%. Overall category-free NRI was 1.122 ($p < 0.0001$) and overall IDI was 0.279 ($p < 0.0001$).

Conclusions: Genetic and clinical models showed higher predictive accuracy for both efficacy and hepatotoxicity of MTX. These models should be validated with a larger scale of prospective study.

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SAT0084

ANTI-CARBAMYLATED PROTEIN ANTIBODIES AS POTENTIAL BIOMARKERS OF DISEASE ACTIVITY IN EARLY ARTHRITIS PATIENTS

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Background: It has become increasingly clear that appropriate initial management of rheumatoid arthritis (RA) increases the chances of success and improves long-term prognosis. Therefore, rheumatologists need prognostic biomarkers to select patients requiring aggressive management. It is possible that anti-carbamylated protein antibodies (anti-CarPA) may serve as such biomarkers because they are associated with erosions and their progression, and with mortality in some studies. Recently, the possibility that they are also associated with disease activity in early arthritis (EA) has been examined by several studies with discordant results.

Objectives: We aimed to explore the relationship between variation in disease activity and anti-CarPA in EA patients.

Methods: EA patients from two prospective clinics, Hospital Universitario La Paz ($n=492$) and Hospital Universitario La Princesa ($n=501$), were included. DAS28 was available at baseline and at months 6 (M6), 12 (M12) and 24 (M24) of follow-up. Anti-CarPA were determined in baseline serum samples by ELISA using *in vitro* carbamylated fetal calf serum. Student t test and main effects general linear regression were used for analysis.

Results: The 27.4% of EA patients that were positive for anti-CarPA showed higher DAS28 at baseline than the negative patients (4.93 vs 4.31 , $p=1.6 \times 10^{-5}$). The difference persisted at all visits during follow-up (3.60 vs 3.19 at M6; 3.47 vs 3.09 at M12; and 3.31 vs 2.79 at M24; all with $p \leq 0.001$). These differences were independent of patient sex and age, smoking, time since symptoms onset, the specific EA clinic and the year of onset. In addition, they persisted after accounting for the presence of RF or ACPA at baseline ($p=1.3 \times 10^{-5}$, and $p=5.7 \times 10^{-5}$, respectively) and at later visits ($p < 0.05$ for all analyses). Analysis of the relation

between anti-CarPA and ΔDAS28 showed association only with ΔDAS28 from baseline to M6 (p=0.005). In this period, the positive patients showed less decrease of DAS28 than the negative patients. This was independent of all the variables mentioned above and of the initial DAS28. As a result of this association, 20.5% of the anti-CarPA positive patients reached remission at M6, in comparison with 34.6% of the negative patients. In contrast, ΔDAS28 from M6 to M12 and from M12 to M24 were small and not associated with anti-CarPA.

Conclusions: Anti-CarPA were associated with high disease activity at presentation and with less improvement in the first 6 months of follow-up in EA patients. These results reinforce the possibility that anti-CarPA could be useful in the clinic as prognostic biomarkers.

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SAT0085 RELATIONSHIP BETWEEN SERUM CALPROTECTIN, DISEASE ACTIVITY PARAMETERS AND THE 7-JOINT ULTRASOUND SCORE IN RHEUMATOID ARTHRITIS

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Background: Calprotectin may be a sensitive biomarker of rheumatoid arthritis (RA) disease activity.

Objectives: In this study we aimed to investigate whether calprotectin is a better biomarker than known inflammation markers for predicting clinical activity and ultrasound parameters in patients with RA.

Methods: A total of 80 RA patients were underwent to clinical (swollen joint count, tender jointcount, disease activity score-DAS28, simplified disease activity index-SDAI and clinical disease activity index-CDAI) and ultrasound (German US7) examination. Correlation of clinical, laboratory and ultrasound measures were analyzed using Spearman's correlation coefficient. The RA patients were divided into two subgroups according to their DAS28-ESR (erythrocyte sedimentation rate) score; group 1 (DAS-28 ≤3.2 remission and low activity), group 2 (DAS28 >3.2 moderate and high activity), respectively. Thirty healthy controls were simultaneously studied.

Results: The serum calprotectin levels of the RA patients were significantly higher than those of healthy controls (96.3±45.9, 54.7±50.0, respectively; p<0.001). Distribution of age (years; 57.2±9.6, 53.9±10.5, respectively; p=0.115) and sex (female; 78.8%, 70%, respectively, p=0.336) between these groups were similar. The clinical, laboratory and ultrasound characteristics of the patients are shown in table 1. The calprotectin levels were 74.8±45.5 in group 1 (n=37) and 114.7±37.9 in group 2 (n=43) (p<0.001). The association between calprotectin and scores of DAS28-ESR are shown in figure 1A. Serum calprotectin was significantly associated with DAS28-ESR, DAS28-CRP (C-reactive protein), SDAI, CDAI, ESR, CRP and US7 parameters. We also found a moderate to strong correlation of US7 score with DAS28-ESR, DAS28-CRP, SDAI, CDAI, CRP and ESR (table 2). The correlation between calprotectin and US7 is shown in figure 1B.

Abstract SAT0085 – Table 1. Baseline characteristics of patients with RA

	Group 1 (n=37)	Group 2 (n=43)	p
Female Sex, n (%)	30 (81.1)	33 (76.7)	0.64
Age, years	55.4±9.4	58.8±9.6	0.12
Disease duration, years	13.2±9.1	12.2±7.6	0.61
Seropositivity, n (%)	24 (64.9)	28 (65.1)	0.98
ESR, mm/hour	14.2±7.2	42±18.5	<0.001
CRP, mg/dl	8.2±11.8	23±25.7	0.002
CDAI	4.3±2.1	11.4±6.9	<0.001
SDAI	12.4±11.9	34.4±29.4	<0.001
US7 total score	4.9±4.8	8.1±6.9	0.021
Calprotectin, ng/ml	74.8±45.5	114.7±37.9	<0.001

Table.2 Spearman's rank correlation coefficients between calprotectin, US7 scores and other variables:

	ESR	CRP	DAS28-ESR	DAS28-CRP	CDAI	SDAI	US7
Calprotectin	0.361***	0.306**	0.488***	0.495***	0.482***	0.429***	0.444***
ESR		0.494***	0.816***	0.561***	0.467***	0.554***	0.247*
CRP			0.512***	0.780***	0.408***	0.923***	0.309**
DAS28-ESR				0.828***	0.846***	0.695***	0.441***
DAS28-CRP					0.856***	0.924***	0.501***

CDAI 0.670*** 0.509***
SDAI 0.418***
***p<0.001, **p<0.01, *p<0.05

Abstract SAT0085 – Figure 1. A Box plots between calprotectin and DAS28-ESR. B. Correlation graph between calprotectin and US7 score

Conclusions: The results of our study support an additional role of calprotectin in assessing inflammatory activity in patients with RA. Therefore, the combination of serum calprotectin levels and the US7 score could be a simple and practical assessment approach for detection of RA disease activity.

Disclosure of Interest: None declared

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SAT0086 EVALUATION OF DIAGNOSTIC PERFORMANCE OF MAGNETIC RESONANCE IMAGING (MRI) AND ULTRASOUND (US) TOWARD EARLY RHEUMATOID ARTHRITIS FROM NAGASAKI EARLY ARTHRITIS COHORT

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Background: We previously reported that the presence of autoantibodies, magnetic resonance imaging (MRI) bone oedema, ultrasound (US) power Doppler (PD) ≥ grade 2 articular synovitis are indispensable markers to predict the development of RA from undifferentiated arthritis whereas combination analysis used by the above variables, focusing on very early phase of arthritis, remains to be done in our cohort.

Objectives: To investigate and re-confirm the diagnostic performance of autoantibodies, MRI findings and US findings toward early RA from NAGASAKI EARLY ARTHRITIS COHORT.

Methods: One hundred and three patients, suffering arthralgia less than 6 months and examined by both MRI and US of wrist and finger joints, were selected from NAGASAKI EARLY ARTHRITIS COHORT dating from September 2009 to August 2017. US were evaluated by synovitis score of semi-quantitative manner by gray-scale (GS) and power Doppler (PD) proposed from EULAR. In MRI, synovitis, bone oedema and bone erosion were assessed by the Rheumatoid Arthritis Magnetic Resonance Imaging Scoring system (RAMRIS). After univariate analysis, multivariate analysis was employed to clarify the diagnostic predictors of early RA.

	odds ratio	95% confidence interval	p-value
ACPA titer	1.05	1.01-1.08	0.0069
PD ≥ grade 2	17.43	5.15-59.06	0.00025

Results: Median of age was 60 years and that of symptomatic duration was 2 months. Female was 68.9%, positive rate of RF was 64.7% and that of ACPA was 47.1%. Total GS score was 4.0, total PD score 2.0, MRI synovitis score 3.0, MRI bone oedema score 0, MRI bone erosion score 0. Seventy patients were diagnosed as early RA during follow-up periods. A univariate analysis showed ACPA, CRP, MMP-3, fulfilment of 2010 ACR/EULAR criteria, MRI synovitis score, MRI bone oedema score, total GS score, total PD score and PD ≥ grade 2 articular synovitis were associated with early RA. Multivariate analysis revealed ACPA and PD ≥ grade 2 articular synovitis at any joints were independent predictors toward diagnosis of early RA.