Online supplementary

The value of magnetic resonance imaging and ultrasound for prediction of therapeutic response and erosive progression in early rheumatoid arthritis patients managed by an aggressive treat-to-target strategy

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Sundin U, *et al. RMD Open* 2021; 7:e001525. doi: 10.1136/rmdopen-2020-001525

1. Supplementary methods

1.1 Baseline prediction models adjusted for calprotectin

Supplementary analyses were performed including plasma calprotectin (µg/L) as a covariate in the multivariate baseline prediction models, as calprotectin has previously been shown predictive of disease activity and radiographic progression.[1] Calprotectin was not included in the one-year prediction models due to lack of data.

Sundin U, *et al. RMD Open* 2021; 7:e001525. doi: 10.1136/rmdopen-2020-001525

2. Supplementary results

2.1 Intra- and inter-reader comparisons of RAMRIS scorings.

Supplementary table S1: Intra- and inter-reader comparisons of RAMRIS scorings.

Inter-reader	Baseline score	2-year score	2-year score change
Synovitis	0.98	0.95	0.87
Tenosynovitis	0.97	0.92	0.90
BME	0.96	0.94	0.94
Erosion	0.92	0.95	0.94
JSN	0.60	0.34	0.49
Intra-reader	**Baseline score**	**2-year score**	**2-year score change**
Synovitis	0.95	0.95	0.85
Tenosynovitis	0.94	0.87	0.76
BME	0.89	0.88	0.89
Erosion	0.98	0.95	0.89
JSN	0.93	0.95	0.95

BME: Bone marrow oedema. JSN: Joint space narrowing. Inter-reader comparisons: Intraclass correlation coefficients for RAMRIS scores of 12 patients scored separately by D.Glinatsi and U.Sundin, 2-way mixed effects model, individual measure, consistency of agreement. Intra-reader comparisons: Intraclass correlation coefficients for RAMRIS scores of 12 patients scored on separate occasions by U.Sundin, 2-way mixed effects model, individual measure, absolute agreement.

2.2 Baseline prediction models adjusted for calprotectin

Supplementary table S2: Predictive association of baseline MRI and ultrasound scores to early methotrexate failure, radiographic erosive progression and MRI erosive progression, odds-ratios (95% CI), model additionally adjusted for baseline calprotectin

	Univariate		**Multivariate**	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Early methotrexate failure				
MRI synovitis	1.03 (0.95 to 1.11)	0.49	1.00 (0.89 to 1.12)	0.94
MRI tenosynovitis	1.02 (0.97 to 1.08)	0.37	1.00 (0.92 to 1.08)	0.90
MRI bone marrow oedema	0.98 (0.93 to 1.04)	0.59	0.98 (0.92 to 1.05)	0.63
MRI combined inflammation	1.00 (1.00 to 1.01)	0.53	1.00 (0.99 to 1.01)	0.81
Ultrasound grey scale	1.01 (0.98 to 1.03)	0.63	0.97 (0.94 to 1.01)	0.15
Ultrasound power Doppler	1.01 (0.98 to 1.04)	0.62	0.97 (0.93 to 1.02)	0.27
Radiographic erosive progression				
MRI synovitis	1.05 (0.98 to 1.13)	0.19	0.96 (0.86 to 1.08)	0.49
MRI tenosynovitis	1.01 (0.96 to 1.07)	0.58	0.96 (0.88 to 1.04)	0.31
MRI bone marrow oedema	1.03 (0.98 to 1.08)	0.30	0.96 (0.90 to 1.03)	0.24
MRI combined inflammation	1.00 (1.00 to 1.01)	0.23	1.00 (0.99 to 1.00)	0.22
Ultrasound grey scale	1.04 (1.02 to 1.07)	**<0.001**	1.05 (1.01 to 1.08)	**0.008**
Ultrasound power Doppler	1.05 (1.02 to 1.08)	**0.001**	1.05 (1.00 to 1.10)	**0.04**
MRI erosive progression				
MRI synovitis	1.23 (1.12 to 1.36)	**<0.001**	1.24 (1.05 to 1.46)	**0.01**
MRI tenosynovitis	1.11 (1.05 to 1.18)	**0.001**	1.09 (0.99 to 1.19)	0.07
MRI bone marrow oedema	1.13 (1.06 to 1.19)	**<0.001**	1.10 (1.02 to 1.19)	**0.01**
MRI combined inflammation	1.01 (1.01 to 1.02)	**<0.001**	1.01 (1.00 to 1.02)	**0.003**
Ultrasound grey scale	1.05 (1.02 to 1.07)	**<0.001**	1.07 (1.01 to 1.13)	**0.03**
Ultrasound power Doppler	1.05 (1.02 to 1.08)	**0.003**	1.04 (0.96 to 1.13)	0.37

Early methotrexate failure: Escalation from initial treatment methotrexate monotherapy to triple therapy or bDMARD within the first 6 months of treatment. Radiographic erosive progression: increase ≥2 vdHSS erosion score during follow-up. MRI erosive progression: increase ≥2 RAMRIS erosion score during follow-up. Multivariate model adjusted for age, gender, SJC, RAI, PGA, CRP, calprotectin, ACPA-status and radiographic erosions. P-values < 0.05 marked in bold typeface.

2.3 Baseline prediction models: Clinical prediction model estimates

Supplementary table S3: Predictive association of baseline clinical, laboratory and biochemical variables, and imaging adjustment variables, to early methotrexate failure, radiographic erosive progression and MRI erosive progression, odds-ratios (95% CI)

	Univariate		**Multivariate**	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Early methotrexate failure				
Female gender	1.9 (0.96 to 3.78)	0.07	1.66 (0.79 to 3.5)	0.18
ACPA positive	0.75 (0.34 to 1.63)	0.47	0.79 (0.3 to 2.1)	0.64
Age (years)	1 (0.98 to 1.03)	0.86	1.01 (0.98 to 1.04)	0.55
Ritchie articular index	1.08 (1.03 to 1.12)	**0.001**	1.04 (0.99 to 1.09)	0.14
Swollen joint count 44	1.05 (1.01 to 1.1)	**0.02**	1.01 (0.95 to 1.06)	0.86
Patient global assessment (VAS)	1.03 (1.02 to 1.05)	**<0.001**	1.03 (1.01 to 1.04)	**0.002**
C-reactive protein (mg/L)	1.01 (1 to 1.03)	**0.04**	1.01 (0.99 to 1.02)	0.56
vdHSS erosion score	0.98 (0.9 to 1.07)	0.66	0.95 (0.85 to 1.07)	0.40
DAS*	1.73 (1.29 to 2.31)	**<0.001**		
Radiographic erosive progression				
Female gender	0.71 (0.39 to 1.3)	0.27	0.77 (0.4 to 1.47)	0.43
ACPA positive	1 (0.46 to 2.16)	0.99	1.75 (0.66 to 4.68)	0.26
Age	1.04 (1.01 to 1.06)	**0.003**	1.03 (1 to 1.06)	**0.04**
Ritchie articular index	1.02 (0.98 to 1.07)	0.26	1 (0.95 to 1.05)	0.96
Swollen joint count 44	1.03 (0.99 to 1.07)	0.15	1 (0.95 to 1.06)	0.95
Patient global assessment (VAS)	1.01 (1 to 1.02)	0.08	1.01 (0.99 to 1.02)	0.25
C-reactive protein (mg/L)	1.02 (1.01 to 1.04)	**0.001**	1.02 (1 to 1.04)	**0.02**
vdHSS erosion score	1.08 (1 to 1.17)	**0.05**	1.03 (0.94 to 1.13)	0.52
DAS*	1.33 (1.03 to 1.73)	**0.03**		
MRI erosive progression				
Female gender	0.77 (0.36 to 1.64)	0.50	0.96 (0.34 to 2.72)	0.94
ACPA positive	0.29 (0.13 to 0.65)	**0.003**	0.45 (0.11 to 1.84)	0.27
Age	1.05 (1.01 to 1.08)	**0.007**	1 (0.96 to 1.04)	0.96
Ritchie articular index	0.96 (0.9 to 1.02)	0.17	0.92 (0.84 to 1.01)	0.08
Swollen joint count 44	1.04 (0.99 to 1.09)	0.17	0.95 (0.87 to 1.04)	0.29
Patient global assessment (VAS)	0.99 (0.98 to 1.01)	0.33	0.99 (0.96 to 1.02)	0.41
C-reactive protein (mg/L)	1.03 (1.02 to 1.05)	**<0.001**	1.05 (1.02 to 1.07)	**<0.001**
vdHSS erosion score	1.14 (1.04 to 1.25)	**0.005**	1.15 (1 to 1.34)	0.06
MRI erosions	1.03 (0.92 to 1.17)	0.60	0.88 (0.73 to 1.07)	0.20
DAS*	1 (0.72 to 1.39)	0.99		

Early methotrexate failure: Escalation from initial treatment MTX monotherapy to triple therapy or bDMARD within the first 6 months of treatment. Radiographic erosive progression: increase ≥2 vdHSS erosion score during follow-up. MRI erosive progression: increase ≥2 RAMRIS erosion score during follow-up. Multivariate model adjusted for age, gender, SJC, RAI, PGA, CRP, ACPA-status and radiographic erosions. P-values < 0.05 marked in bold typeface.
**DAS not included as a covariate in multivariable models, as the multivariable model consists of components of DAS, univariate estimates for DAS are presented for reference.*
Abbreviations: ACPA: Anti-citrullinated peptide antibody. DAS: Disease activity score. MRI: Magnetic resonance imaging. VAS: Visual analogue scale 0-100. vdHSS: Van der Heijde Sharp score.

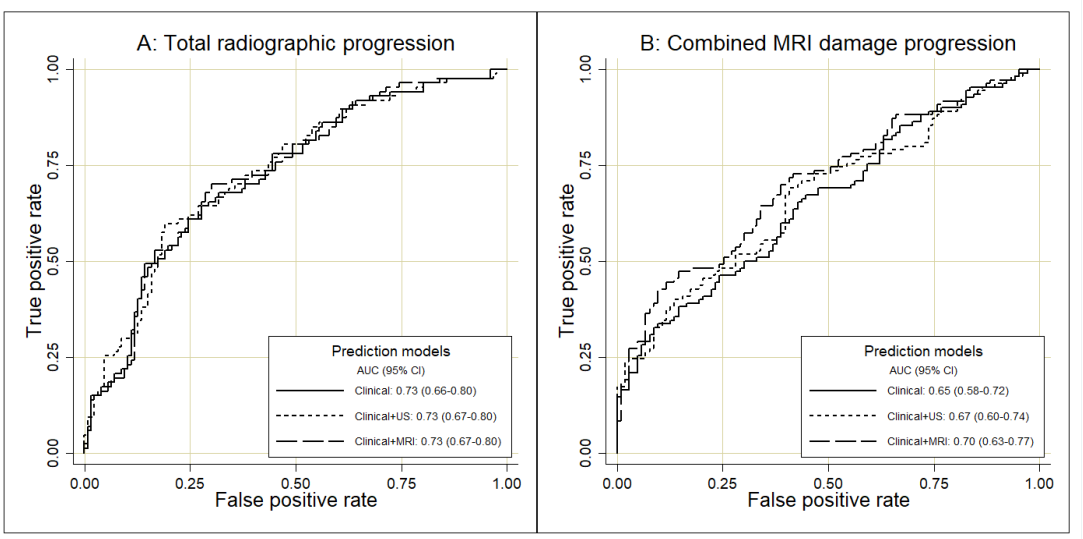
2.4 Baseline prediction models: Total radiographic progression and combined MRI damage progression outcomes

Supplementary table S4: Predictive association of baseline MRI and ultrasound scores to total radiographic progression and combined MRI damage progression, odds-ratios (95% CI)

	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Total radiographic progression				
MRI synovitis	1.08 (1.01 to 1.15)	**0.02**	1.00 (0.90 to 1.11)	0.98
MRI tenosynovitis	1.01 (0.97 to 1.06)	0.54	0.97 (0.90 to 1.04)	0.39
MRI bone marrow edema	1.05 (1.00 to 1.10)	**0.03**	0.98 (0.92 to 1.05)	0.59
MRI combined inflammation	1.00 (1.00 to 1.01)	**0.05**	1.00 (0.99 to 1.00)	0.58
Ultrasound grey scale	1.03 (1.01 to 1.05)	**<0.001**	1.03 (1.00 to 1.07)	0.08
Ultrasound power Doppler	1.04 (1.01 to 1.07)	**0.01**	1.01 (0.96 to 1.06)	0.63
Combined MRI damage progression				
MRI synovitis	1.10 (1.03 to 1.17)	**0.007**	1.10 (1.00 to 1.21)	**0.06**
MRI tenosynovitis	1.05 (1.00 to 1.10)	**0.04**	1.05 (0.98 to 1.12)	0.16
MRI bone marrow edema	1.11 (1.05 to 1.19)	**0.001**	1.10 (1.02 to 1.18)	**0.01**
MRI combined inflammation	1.01 (1.00 to 1.01)	**0.002**	1.01 (1.00 to 1.01)	**0.02**
Ultrasound grey scale	1.02 (1.00 to 1.04)	0.09	1.02 (0.99 to 1.06)	0.23
Ultrasound power Doppler	1.02 (0.99 to 1.04)	0.27	1.02 (0.97 to 1.08)	0.41

Radiographic erosive progression: increase ≥2 vdHSS total score during follow-up. Combined MRI damage progression: increase ≥2 of the sum of the RAMRIS erosion and joint space narrowing scores during follow-up. Radiographic progression occurred in 91 (42%) of patients, MRI damage progression occurred in 112 (51%) of patients. Multivariate model adjusted for age, gender, SJC, RAI, PGA, CRP, ACPA-status and radiographic erosions. P-values < 0.05 marked in bold typeface.

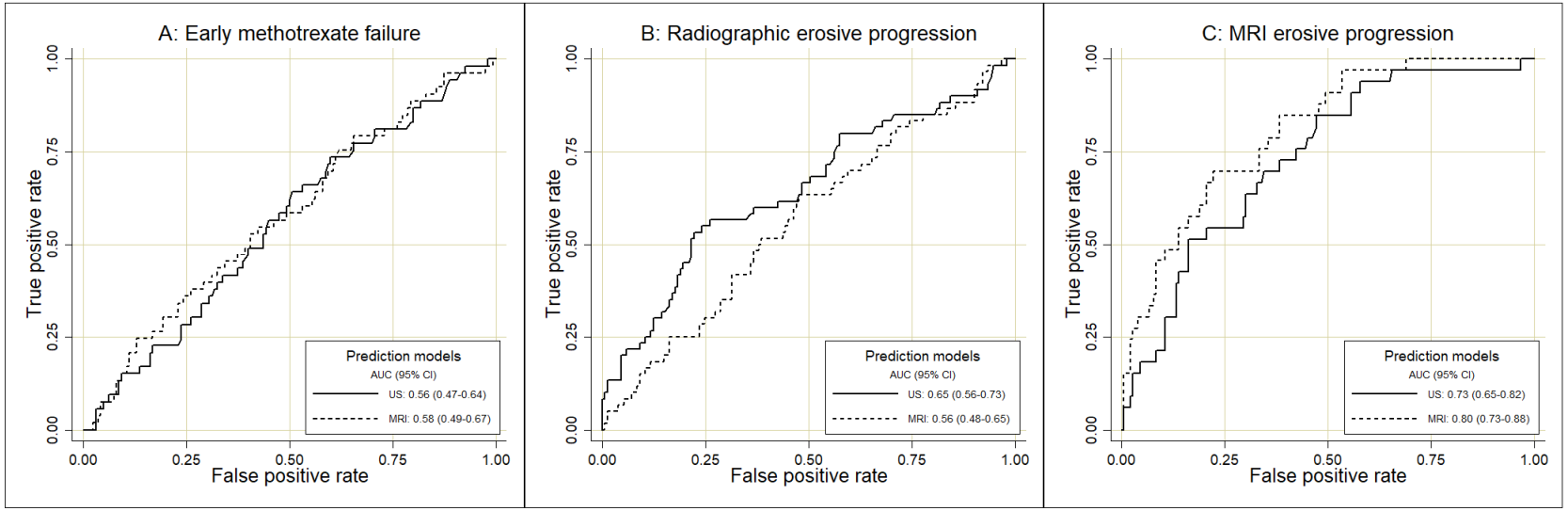
Supplementary figure S1 A-B: ROC curves of the clinical, clinical + ultrasound and the clinical + MRI prediction models for (A) Total radiographic progression, and (B) Combined MRI damage progression



Radiographic erosive progression: increase ≥2 vdHSS total score during follow-up. Combined MRI damage progression: increase ≥2 of the sum of the RAMRIS erosion and joint space narrowing scores during follow-up. MRI erosive progression: increase ≥2 RAMRIS erosion score during follow-up. ROC: Receiver operating characteristics. AUC: Area under the curve.

2.5 Baseline prediction models: Receiver operating characteristics analyses of MRI and ultrasound prediction models without clinical variables

Supplementary figure S2 A-C: ROC curves of MRI and Ultrasound models for (A) early methotrexate failure, (B) radiographic erosive progression, and (C) MRI erosive progression



Early methotrexate failure: Escalation from initial treatment MTX monotherapy to triple therapy or bDMARD within the first 6 months of treatment. Radiographic erosive progression: increase ≥2 vdHSS erosion score during follow-up. MRI erosive progression: increase ≥2 RAMRIS erosion score during follow-up. AUC: Area under the curve. ROC: Receiver operating characteristics.

2.6 Patients in remission at one year: Clinical prediction model estimates

Supplementary table S5: Predictive association of clinical, laboratory and biochemical variables, and imaging adjustment variables, of patients in clinical remission after 1 year to treatment escalation, radiographic erosive progression and MRI erosive progression during the second year of follow-up, odds-ratios (95% CI)

	Univariate		**Multivariate**	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Treatment escalation				
Female gender	0.89 (0.42 to 1.89)	0.77	0.74 (0.33 to 1.65)	0.47
ACPA positive	0.99 (0.96 to 1.01)	0.32	1 (0.97 to 1.03)	0.99
Age (years)	1.55 (0.55 to 4.41)	0.41	1.52 (0.51 to 4.54)	0.46
Ritchie articular index	1.28 (0.78 to 2.11)	0.34	1.3 (0.77 to 2.19)	0.33
Swollen joint count 44	1.07 (0.58 to 1.99)	0.82	1.11 (0.59 to 2.1)	0.75
Patient global assessment (VAS)	1.01 (0.98 to 1.03)	0.57	1 (0.98 to 1.03)	0.73
C-reactive protein (mg/L)	0.99 (0.88 to 1.11)	0.82	0.98 (0.87 to 1.1)	0.70
vdHSS erosion score	0.92 (0.83 to 1.03)	0.16	0.92 (0.81 to 1.04)	0.18
DAS*	1.64 (0.58 to 4.63)	0.35		
Radiographic erosive progression				
Female gender	0.87 (0.44 to 1.73)	0.69	1.08 (0.5 to 2.31)	0.84
ACPA positive	1.05 (1.02 to 1.08)	**0.001**	1.04 (1 to 1.07)	0.06
Age	0.93 (0.39 to 2.18)	0.86	1.27 (0.48 to 3.32)	0.63
Ritchie articular index	1.03 (0.64 to 1.64)	0.91	1.18 (0.68 to 2.03)	0.56
Swollen joint count 44	1.17 (0.65 to 2.09)	0.60	0.93 (0.46 to 1.91)	0.85
Patient global assessment (VAS)	1.01 (0.98 to 1.04)	0.49	1.01 (0.98 to 1.04)	0.45
C-reactive protein (mg/L)	1.02 (0.93 to 1.13)	0.65	1.01 (0.91 to 1.13)	0.80
vdHSS erosion score	1.19 (1.08 to 1.31)	**<0.001**	1.14 (1.03 to 1.27)	**0.01**
DAS*	1.7 (0.66 to 4.38)	0.27		
MRI erosive progression				
Female gender	0.82 (0.3 to 2.22)	0.70	1.23 (0.36 to 4.14)	0.74
ACPA positive	1.06 (1.01 to 1.11)	**0.01**	1.03 (0.98 to 1.09)	0.28
Age	0.61 (0.2 to 1.88)	0.39	1.21 (0.28 to 5.16)	0.80
Ritchie articular index	0.42 (0.12 to 1.41)	0.16	0.47 (0.13 to 1.72)	0.26
Swollen joint count 44	1.34 (0.7 to 2.57)	0.38	1.21 (0.55 to 2.64)	0.63
Patient global assessment (VAS)	1.01 (0.98 to 1.05)	0.55	1.01 (0.97 to 1.05)	0.54
C-reactive protein (mg/L)	1.06 (0.94 to 1.19)	0.37	1.06 (0.9 to 1.24)	0.50
vdHSS erosion score	1.11 (1 to 1.22)	**0.04**	1.04 (0.9 to 1.2)	0.60
MRI erosions	1.13 (1.01 to 1.26)	**0.04**	1.09 (0.93 to 1.29)	0.29
DAS*	1.74 (0.44 to 6.88)	0.43		

Treatment escalation: change to a higher level of therapy during the second year. Radiographic erosive progression: increase ≥1 vdHSS erosion score during second year. MRI erosive progression: increase ≥1 RAMRIS erosion score during second year. Multivariate model adjusted for age, gender, SJC, RAI, PGA, CRP, ACPA-status and radiographic erosions. P-values < 0.05 marked in bold typeface.

**DAS not included as a covariate in multivariable models, as the multivariable model consists of components of DAS, univariate estimates for DAS are presented for reference.*

Abbreviations: ACPA: Anti-citrullinated peptide antibody. DAS: Disease activity score). MRI: Magnetic resonance imaging. VAS: Visual analogue scale 0-100. vdHSS: Van der Heijde Sharp score.

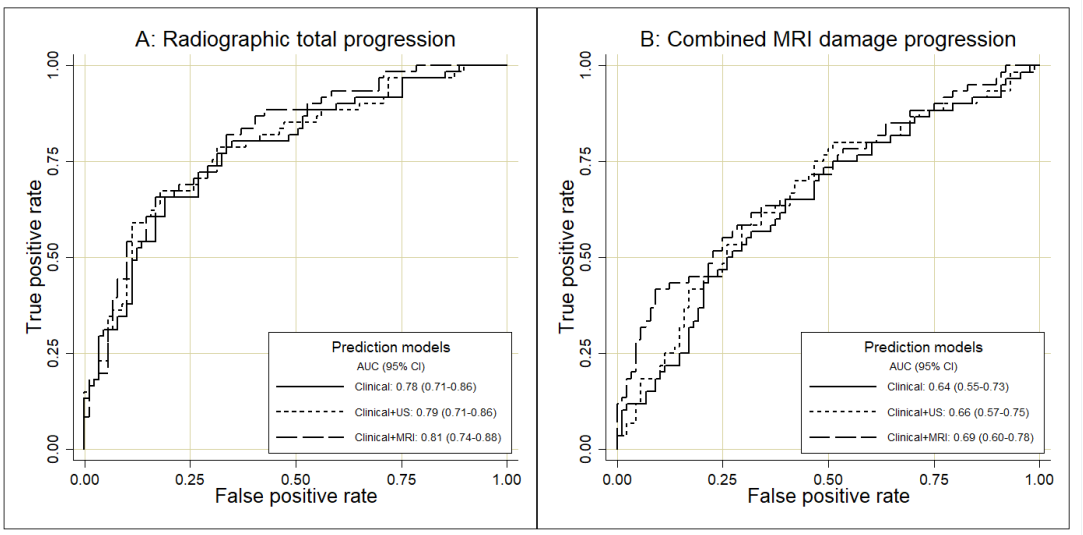
2.7 Patients in remission at one year: Total radiographic progression and combined MRI damage progression outcomes

Supplementary table S6: Predictive association of baseline MRI and ultrasound scores to total radiographic progression and combined MRI damage progression, odds-ratios (95% CI)

	Univariate		Multivariate	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Total radiographic progression				
MRI synovitis	1.26 (1.1 to 1.44)	**0.001**	1.11 (0.95 to 1.31)	0.20
MRI tenosynovitis	1.35 (1.13 to 1.61)	**0.001**	1.24 (1.02 to 1.51)	0.03
MRI bone marrow edema	1.23 (1.09 to 1.39)	**0.001**	1.09 (0.96 to 1.25)	0.18
MRI combined inflammation	1.02 (1.01 to 1.03)	**<0.001**	1.01 (1 to 1.03)	**0.03**
Ultrasound grey scale	1.08 (1.02 to 1.14)	**0.01**	1.06 (0.99 to 1.14)	0.11
Ultrasound power Doppler	1.13 (0.97 to 1.32)	0.12	1.08 (0.93 to 1.26)	0.32
Combined MRI damage progression				
MRI synovitis	1.11 (0.98 to 1.24)	0.09	1.09 (0.94 to 1.26)	0.24
MRI tenosynovitis	1.13 (0.99 to 1.28)	0.06	1.14 (1 to 1.31)	0.06
MRI bone marrow edema	1.18 (1.05 to 1.31)	**0.004**	1.21 (1.06 to 1.38)	**0.004**
MRI combined inflammation	1.01 (1 to 1.02)	**0.01**	1.01 (1 to 1.02)	**0.02**
Ultrasound grey scale	1.03 (0.99 to 1.07)	0.20	1.04 (0.99 to 1.1)	0.14
Ultrasound power Doppler	1.02 (0.96 to 1.08)	0.51	1.01 (0.95 to 1.08)	0.65

Radiographic erosive progression: increase ≥1 vdHSS total score during second year. Combined MRI damage progression: increase ≥1 of the sum of the RAMRIS erosion and joint space narrowing scores during second year. Radiographic progression occurred in 62 (41%) of patients, MRI damage progression occurred in 60 (40%) of patients. Multivariate model adjusted for age, gender, SJC, RAI, PGA, CRP, ACPA-status and radiographic erosions. P-values < 0.05 marked in bold typeface.

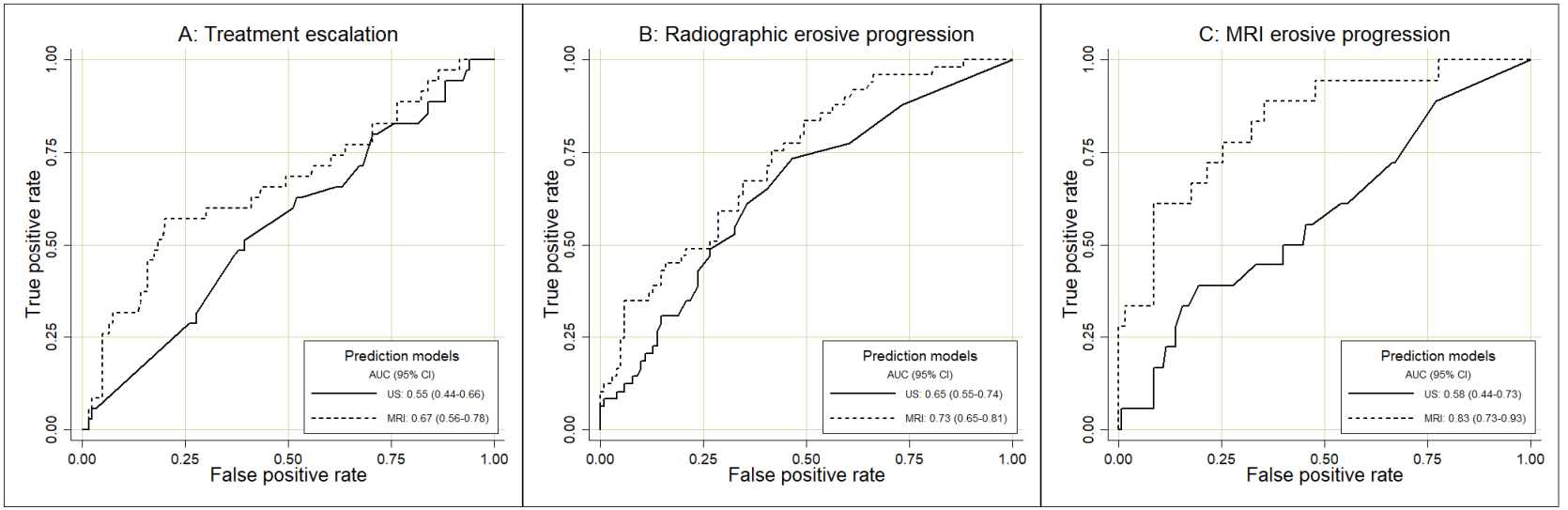
Supplementary figure S3 A-B: ROC curves of the clinical, clinical + ultrasound and the clinical + MRI prediction models for (A) Total radiographic progression, and (B) Combined MRI damage progression during the second year in patients in clinical remission after 1 year



Radiographic erosive progression: increase ≥2 vdHSS total score during follow-up. Combined MRI damage progression: increase ≥2 of the sum of the RAMRIS erosion and joint space narrowing scores during follow-up. MRI erosive progression: increase ≥2 RAMRIS erosion score during follow-up. ROC: Receiver operating characteristics. AUC: Area under the curve.

2.8 Patients in remission at one year: Receiver operating characteristics analyses of MRI and ultrasound prediction models without clinical variables

Supplementary Figure S4 A-C: ROC curves of MRI and Ultrasound models for (A) treatment escalation, (B) radiographic erosive progression, and (C) MRI erosive progression during the second year in patients in clinical remission after 1 year



Treatment escalation: change to a higher level of therapy during the second year. Radiographic erosive progression: increase ≥1 vdHSS erosion score during the second year. MRI erosive progression: increase ≥1 RAMRIS erosion score during the second year. AUC: Area under the curve. ROC: Receiver operating characteristics.

3. References

1. Jonsson MK, Sundlisaeter NP, Nordal HH, et al. Calprotectin as a marker of inflammation in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2017;76(12):2031-7.