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Systematic review and meta analysis

Clinical science

Multibiomarker disease activity score: an objective tool for monitoring rheumatoid arthritis? A systematic review and meta-analysis

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Abstract

Objectives: The multibiomarker disease activity (MBDA) score is an objective tool for monitoring disease activity in RA. Here we report a systematic review and meta-analysis of the clinical value of the MBDA score in RA.

Methods: We performed a systematic literature search in five medical databases—MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Scopus and Web of Science—from inception to 13 October 2021. Original articles reporting on the performance of the MBDA score's correlation with conventional disease activity measures or the predictive and discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse were included.

Results: Our systematic search provided a total of 1190 records. After selection and citation searches, we identified 32 eligible studies. We recorded moderate correlations between MBDA score and conventional disease activity measures at baseline [correlation (COR) 0.45 (CI 0.28, 0.59), $I^2 = 71.0\%$ for the 28-joint DAS with CRP (DAS28-CRP) and COR 0.55 (CI 0.19, 0.78), $I^2 = 0.0\%$ for DAS28 with ESR] and at follow-up [COR 0.44 (CI 0.28, 0.57, $I^2 = 70.0\%$ for DAS28-CRP) and found that the odds of radiographic progression were significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) [OR 1.03 (CI 1.02–1.05), $I^2 = 10.0\%$].

Conclusion: The MBDA score might be used as an objective disease activity marker. In addition, it is also a reliable prognostic marker of radiographic progression.

Keywords: RA, MBDA score, disease activity monitoring, radiographic progression

Rheumatology key messages

- The multibiomarker disease activity (MBDA) score is an objective tool for the monitoring of rheumatoid arthritis.
- The MBDA score showed moderate correlations with conventional disease activity measures.
- The MBDA score may be an independent predictor of radiological progression.

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Introduction

RA is a systemic autoimmune disease affecting ≈0.5–1% of the population [1]. According to the EULAR recommendations, the aim of the therapy in RA is to achieve remission, or at least low disease activity [2]. Early treatment with DMARDs and a treat-to-target treatment strategy are recommended by current guidelines and are considered to be the optimal way to prevent long-term functional decline by minimizing cartilage and bone damage [3–5].

Given that the treat-to-target therapeutic approach requires close monitoring of disease activity, the need for reliable, objective disease activity measures (DAMs) is undeniable. The currently available, widely used options for monitoring disease activity and progression are either subjective or non-specific: the 28-joint DAS (DAS28), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) all include subjective assessments of disease activity by the patient and/or the provider [6–8]. Although non-specific inflammatory markers such as CRP and ESR are used to calculate the DAS28 and SDAI, the incorporation of a scoring system based on the combination of inflammatory markers and additional biomarkers could further objectify the measurement of disease activity. Structural damage, a major factor defining the course of the disease, can be assessed by radiography and quantified with the Sharp–van der Heijde (SvdH) scoring system [9]. There are several known risk factors for radiographic progression, including high disease activity monitored by non-specific inflammatory markers such as CRP, RF and ACPA seropositivity [10]. However, RF and ACPA are not suitable for monitoring disease activity [11].

The multibiomarker disease activity (MBDA) score system is an algorithm based on the serum level of 12 biomarkers [IL-6, TNF receptor type 1 (TNFR1), vascular cell adhesion molecule 1 (VCAM-1), epidermal growth factor (EGF), vascular EGF A (VEGF-A), YKL-40, matrix metalloproteinase-1 (MMP-1), MMP-3, CRP, serum amyloid A (SAA), leptin and resistin], resulting in a scale from 0 to 100 [12]. The MBDA score presents an objective disease monitoring system and thus may contribute to personalized therapeutic plans conforming to modern medical views. In addition to monitoring disease activity, the MBDA score may also predict radiographic progression [13–16].

Several studies have evaluated the utility of the MBDA score and a meta-analysis has been conducted on the correlation of the MBDA score with conventional DAMs; however, the predictive and discriminative values of the MBDA score has yet to be analysed in a comprehensive manner [17]. Here we report a systematic review and meta-analysis of the clinical value and utility of the MBDA score for monitoring RA by determining the correlation of the MBDA score with conventional DAMs and the predictive and the discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse.

Materials and methods

Our systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Statement [18]. The recommendations of the Cochrane Prognosis Methods Group [19] were followed and the review protocol was registered on PROSPERO.

We performed a systematic literature search of five medical databases—MEDLINE (via PubMed), Cochrane Library (CENTRAL), Embase, Scopus and Web of Science—from inception to 13 October 2021. Original articles reporting on the performance of the unadjusted MBDA score's correlation with conventional DAMs or the predictive and discriminative values of the MBDA score for radiographic progression, therapy response, remission and relapse were included in the systematic review and meta-analysis. Single case reports were excluded.

RA was defined by the ACR 1987 [20] and ACR/EULAR 2010 [21] classification criteria. Radiographic progression was measured by the change in the SvdH score per time unit, therapy response was defined by the EULAR criteria for therapy response and remission and relapse were defined by the different cut-off values of conventional DAMs.

Study selection and data extraction were carried out by two independent reviewers and disagreements were resolved by a third reviewer. The quality assessment of the outcomes was carried out separately by two reviewers using the Quality In Prognosis Studies (QUIPS) tool for assessing the risk of bias [22].

Further details regarding the search and selection strategy, data extraction, data synthesis and analysis are detailed in the supplementary methods available at *Rheumatology* online.

Results

Search and selection and characteristics of the included studies

Our systematic search provided 1190 records; after duplicate removal we screened 708 duplicate-free records. Thirty eligible studies [13–16, 23–48] were identified after title, abstract and full-text selection and two additional studies [49, 50] during citation search. Of these studies, we included 24 in the quantitative analysis [13–15, 23–25, 27–29, 31, 32, 34–38, 40, 41, 43, 44, 46, 47, 49, 50] and 8 in the qualitative analysis [16, 26, 30, 33, 39, 42, 45, 48]. The summary of the selection process is shown in Fig. 1. We conducted a meta-analysis assessing the correlation of MBDA scores with conventional DAMs and the predictive value of the MBDA score for radiographic progression. Studies that could not be included in the meta-analysis and reports of other outcomes are detailed in the systematic review.

The characteristics of the identified studies for the systematic review and meta-analysis and the patient characteristics of included studies are detailed in Table 1 and Supplementary Table S1, available at *Rheumatology* online.

MBDA score for the assessment of disease activity

Studies assessing the utility of the MBDA score for disease activity monitoring calculated the correlation of MBDA scores with conventional DAMs. Studies using Pearson's correlations could not be included in the meta-analysis due to a lack of statistical power, but are displayed in forest plots for visualization (see Supplementary Figs S1–S3, available at *Rheumatology* online). The results of studies using Spearman's correlation are detailed below.

Six study groups in five publications [27, 29, 36, 46, 47] with a total of 667 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP [correlation (COR) 0.45 (CI 0.28, 0.59), $I^2 = 71.0\%$] (see

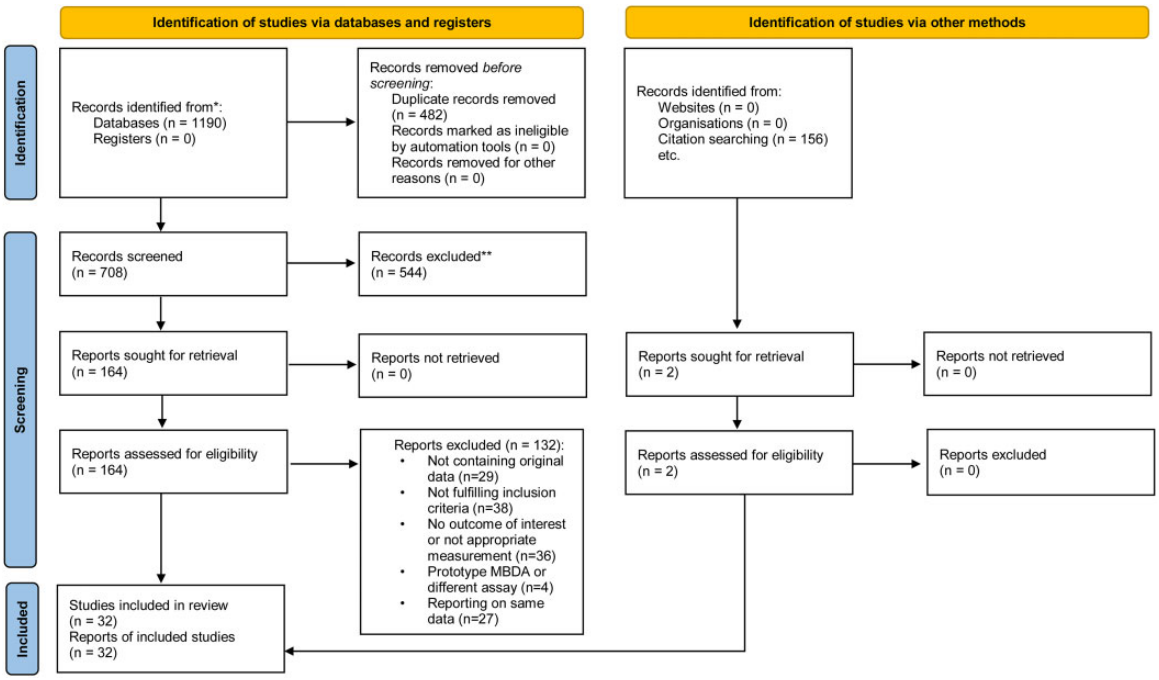

Figure 1. PRISMA flow diagram of the screening and selection process according to PRISMA 2020 guidelines [18]

Fig. 2A). Excluding conference abstracts from the analysis, similar results were observed; four publications [27, 36, 46, 47] with a total of 324 subjects demonstrated a moderate correlation between baseline MBDA score and baseline DAS28-CRP [COR 0.46 (CI 0.10, 0.72), $I^2 = 81.0\%$].

Assessing the correlations of baseline MBDA scores with baseline DAS28-ESR, a moderate correlation was found based on the results of two publications with a total of 127 subjects [COR 0.55 (CI 0.19, 0.78), $I^2 = 0.0\%$] (see Fig. 2A).

Further metrics associated with disease activity [CRP, ESR, 28-joint swollen joint count,28-joint tender joint count, patient global assessment (PtGA), CDAI, power Doppler ultrasound (PDUS)] showed low and moderate correlations and are detailed in Supplementary Fig. S4, available at *Rheumatology* online.

Six study groups from four publications [29, 36, 46, 47] with a total of 287 subjects revealed a moderate correlation between follow-up MBDA score and follow-up DAS28-CRP [COR 0.44 (CI 0.28, 0.57), $I^2 = 70.0\%$] (see Fig. 2B). After the exclusion of conference abstracts from the analysis, three articles [36, 46, 47] with a total of 137 subjects showed a moderate correlation between baseline MBDA score and baseline DAS28-CRP [COR 0.38 (CI −0.02, 0.68), $I^2 = 18.0\%$].

The only study investigating the correlations of follow-up MBDA scores with follow-up DAS28-ESR found a moderate correlation [COR 0.49 (CI 0.22, 0.69)] between MBDA score and DAS28-ESR (Fig. 2B) [47].

Other parameters associated with disease activity (ESR, SJC28, TJC28, PtGA, PDUS) showed low–moderate correlations and are detailed in Supplementary Fig. S5, available at *Rheumatology* online.

Ten study groups from six articles [14, 28, 29, 36, 47, 50] with a total of 698 subjects demonstrated a moderate correlation between the change in MBDA score and the change in DAS28-CRP [COR 0.40 (CI 0.32, 0.48), $I^2 = 19.0\%$]. Seven study groups from six articles [25, 35, 38, 47, 49, 50] with a total of 543 subjects exhibited a moderate correlation between the change in MBDA score and the change in DAS28-ESR [COR 0.56 (CI 0.51, 0.60), $I^2 = 71.0\%$] (see Fig. 2C). Excluding conference abstracts from the analysis, similar results were recorded. The change in MBDA score moderately correlates with the change in DAS28-CRP [COR 0.43 (CI 0.25, 0.59), $I^2 = 47.0\%$] based on the results of six study groups of four publications [14, 36, 47, 50] with a total of 418 subjects, and with DAS28-ESR [COR 0.52 (CI 0.43, 0.60), $I^2 = 0.0\%$] based on the results of four publications [35, 47, 49, 50] with a total of 298 subjects.

Further parameters linked to disease activity (CRP, CDAI, SDAI, HAQ) showed low–moderate correlations and are shown in Supplementary Fig. S6, available at *Rheumatology* online.

The results of the subgroup analysis based on the length of the follow-up showed similar results and are displayed in Supplementary Figs S7 and S8, available at *Rheumatology* online.

MBDA score for the assessment of radiographic progression

Three study groups of three articles with a total of 22 subjects showed a low correlation between baseline MBDA score and baseline SvdH score [COR 0.13 (CI −0.25–0.47), $I^2 = 79.0\%$] and five study groups of four articles with a total of 307 subjects demonstrated a low correlation between the change in MBDA score and the change in SvdH score [COR 0.08 (CI −0.06–0.21), $I^2 = 79.0\%$] as well (see Fig. 3).

When evaluating the predictive value of the MBDA score for radiographic progression, three studies [13–15] with a total of 481 subjects showed that the odds of radiographic progression are significantly higher for patients with a high baseline MBDA score (>44) than for patients with a low baseline MBDA score (<30) [OR 1.03 (CI 1.02, 1.05), $I^2 = 10.0\%$] (see Fig. 4). In contrast, the odds of progression

Table 1. Characteristics of included studies

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Studies included in the meta-analysis									
Baker, 2021 [23]	Journal article	POS	Pennsylvania and Philadelphia VA Medical Centre	–	N/A	Baseline[a]	USA (Pennsylvania)	MTX, bDMARD, GC	Spearman's correlation with conventional DAMs
Bakker, 2012 [13]	Journal article	RCT	CAMERA	N/A	2 years	Baseline[a], month 1,3,6[a], year 2[b]	Netherlands	MTX, CsA, intra-articular GC, NSAID	Pearson's correlation with conventional DAMs[c] predicting radiographic progression and remission[c]
Bechman, 2018 [24]	Journal article	POS	REMIRA	–	1 year	Months 3, 6, 9 and 12[a]	UK	csDMARD, bDMARD, GC	Spearman's correlation with conventional DAMs, relapse[c]
Bijlsma, 2013 [25]	Conference abstract	RCT	CAMERA-II	https://isrctn.com (ISRCTN 70365169)	1 year	Baseline[a], months 1–12[a]	Netherlands	Group A: MTX + PBO; group B: MTX + GC	Spearman's correlation with conventional DAMs
Bouman, 2017 [27]	Journal article	RCT	DRESS	https://trialregister.nl (NTR3216)	18 months	Baseline[a], months 3, 6, 9, 12, 15 and 18	Netherlands	MTX, csDMARD, ADA, ETN, NSAID, GC	Spearman's correlation with conventional DAMs, predicting radiographic progression[c] and relapse[c]
Brahe, 2016 [28]	Conference abstract	RCT	OPERA	https://clinicaltrials.gov (NCT00660647)	1 year	Baseline[a], months 3[a], 6 and 12[a]	Denmark	Group A: MTX + PBO; group B: MTX + ADA	Spearman's correlation with conventional DAMs
Brahe, 2019 [14]	Journal article	RCT	OPERA	https://clinicaltrials.gov (NCT00660647)	1 year	Baseline[a], months 1, 2, 3[a], 6[a], 9 and 12	Denmark	Group A: MTX + PBO; group B: MTX + ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression and remission[c]
Genovese, 2017 [29]	Conference abstract	RCT	DARWIN 1, DARWIN 2	https://clinicaltrials.gov (NCT01888874; NCT01894516)	24 weeks	Baseline[a], week 12[a]	USA	Group A: MTX + PBO; group B: MTX + 100 mg filogitinib; group C: MTX + 200 mg filogitinib	Spearman's correlation with conventional DAMs
Hambardzumyan, 2013 [31]	Conference abstract	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	1 year	Baseline[a], year 1[a]	Sweden	MTX, other DMARD, IFX	Spearman's correlation with conventional DAMs
Hambardzumyan, 2015 [15]	Conference abstract	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	1 year	Month 3, year 1[b]	Sweden	MTX, HCQ, SSZ, IFX	Predicting radiographic progression
Hirata, 2013 [49]	Journal article	RCT	BEST	N/A	1 year	Baseline[a], year 1[a]	Netherlands, Japan	DMARD, IFX	Spearman's correlation with conventional DAMs, remission[c]
Hirata, 2015 [50]	Journal article	ROS	UOEH	–	1 year	Baseline[a], weeks 24 and 52[a]	Japan	ADA, ETN, IFX, MTX	Spearman's correlation with conventional DAMs, therapy response[c]
Hirata, 2016 [34]	Journal article	ROS	UOEH	–	7 years	Baseline[a], week 52[a]	Japan	MTX, ADA, ETN, IFX	Spearman's correlation with conventional DAMs, predicting radiographic progression[c]

(continued)

Table 1. (continued)

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Jurgens, 2020 [35]	Journal article	RCT	CAMERA-II	https://www.isrctn.com (ISRCTN 70365169)	1 year	Baseline[a], months 1, 2, 3[a], 4–12	Netherlands	MTX, GC, CsA, ADA, PBO	Spearman's correlation with conventional DAMs
Krabbe, 2017 [36]	Journal article	POS	HURRAH	–	52 weeks	Baseline[a], weeks 26 and 52[a]	Denmark	MTX, ADA	Spearman's correlation with conventional DAMs, predicting radiographic progression[c]
Lee, 2016 [37]	Journal article	POS	BRASS	–	2 years	Baseline[a]	USA	(Massachusetts)	csDMARD, bDMARD
Spearman's correlation with conventional DAMs									
Li, 2013 [38]	Conference abstract	POS	EIRA	–	3 months	Baseline[a], month 3[a]	Sweden	MTX	Spearman's correlation with conventional DAMs, therapy response[c]
Ma, 2014 [41]	Conference abstract	POS	REMIRA	–	1 year	Baseline[a], year 1[a]	UK	N/A	Spearman's correlation with conventional DAMs
Maijer, 2013 [43]	Conference abstract	POS	Academic Medical Centre Amsterdam	–	2 years	Baseline[a]	Netherlands	N/A	Spearman's correlation with conventional DAMs
Reiss, 2016 [46]	Journal article	RCT	ACT-RAY	N/A	24 weeks	Baseline[a], weeks 4, 12 and 24[a]	USA (California)	TCZ, MTX, GC	Spearman's correlation with conventional DAMs
Roodenrijs, 2018 [47]	Journal article	POS	LUMC, UMC, HORUS	–	1 year	Baseline[a], month 6[a]	Netherlands, UK	RTX, GC	Spearman's correlation with conventional DAMs, therapy response[c]
Studies included only in the systematic review									
Boeters, 2019 [26]	Journal article	POS	LUMC	–	N/A	Annually	Netherlands	csDMARDS, bDMARDS	Relapse
Hambardzumyan, 2019 [30]	Journal article	RCT	SWEFOT	https://clinicaltrials.gov (NCT00764725)	3 months	months 0, 3	Sweden	MTX, HCQ, SSZ, IFX	Therapy response
He, 2020 [32]	Conference abstract	Database analysis	N/A	–	N/A	Baseline[a]	USA	DMARD	Pearson's correlation with conventional DAMs
Hirata, 2012 [33]	Conference abstract	RCT	BEST	N/A	1 year	Baseline, year 1	Netherlands	N/A	remission

(continued)

Table 1. (continued)

First author, year of publication	Type of publication	Original study type	Original study name	Clinical trial registration number of RCT	Study duration	Time points of study	Country	Treatment	Outcome
Li, 2016 (48)	Journal article	POS	LUMC	–	N/A	Annually	Netherlands	csDMARD, TNFi	predicting radiographic progression
Luedders, 2020 [40]	Journal article	POS	N/A	–	16 weeks	Baseline[a], weeks 8 and 16[a]	USA (Nebraska)	MTX, FA, GC, NSAID	Pearson's correlation with conventional DAMs, remission
Ma, 2020 [42]	Journal article	POS	REMIRA	–	1 year	Baseline, months 3 and 6	UK, Singapore	csDMARDs, TNFi, GC	Remission
Markusse, 2014 [16]	Journal article	RCT	BEST	N/A	1 year	Baseline, year 1	Netherlands	csDMARD, IFX, GC	predicting and discriminating radiographic progression
Ghiti Moghadam, 2018 [48]	Journal article	RCT	POET	https://trialregister.nl (NTR3112)	1 year	Baseline, months 3, 6, 9 and 12	Netherlands	csDMARD	Relapse
Razmjou, 2020 [44]	Journal article	POS	N/A	–	12 weeks	Baseline[a], weeks 2, 6 and 12[a]	USA (California)	csDMARD, tofacitinib	Pearson's correlation with conventional DAMs
Rech, 2016 [45]	Journal article	RCT	RETRO	https://www.clinicaltrialsregister.eu (2009-015740-42)	1 year	Baseline, months 3, 6, 9 and 12	Germany	csDMARDS, bDMARDS	Relapse

[a] Time point used for calculating correlation.
[b] Time point used for calculating radiological progression.
[c] Not included in the meta-analysis.
ADA: adalimumab; CsA: ciclosporin A; bDMARD: biological DMARD; csDMARD: conventional synthetic DMARD; ETN: etanercept; FA: folic acid; GC: glucocorticoid; IFX: infliximab; N/A: no data available; PBO: placebo; POS: prospective observational study; RCT: randomized clinical trial; ROS: retrospective observational study; RTX: rituximab; TCZ: tocilizumab; TNFi: TNF-α inhibitor.

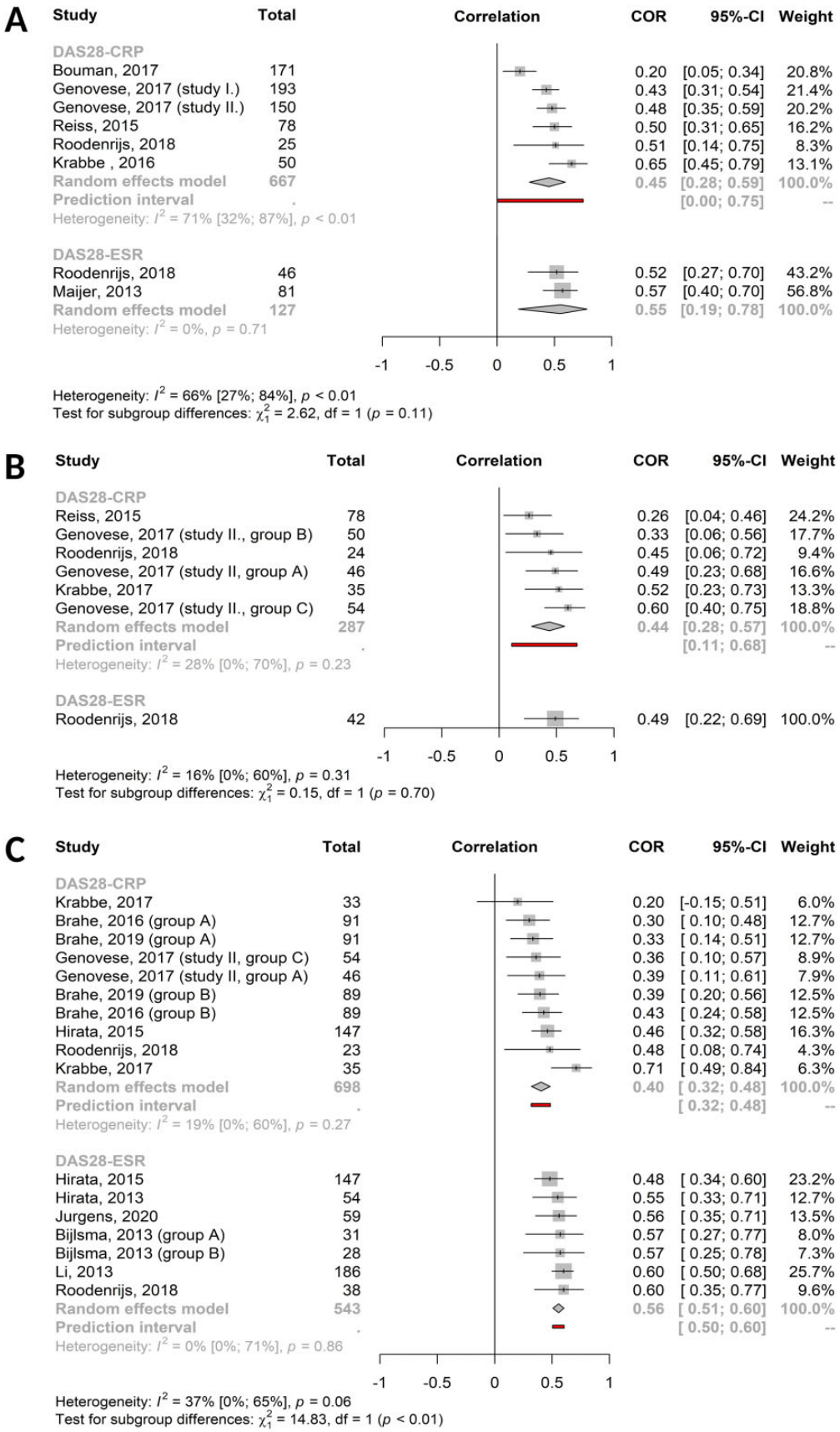

Figure 2. Forest plot for the correlation of MBDA score with DAS28-CRP/ESR. (**A**) Forest plot for the correlation of baseline MBDA score with baseline DAS28-CRP/ESR. (**B**) Forest plot for the correlation of follow-up MBDA score with follow-up DAS28-CRP/ESR. (**C**) Forest plot for the change in baseline MBDA score with the change in DAS28-CRP/ESR

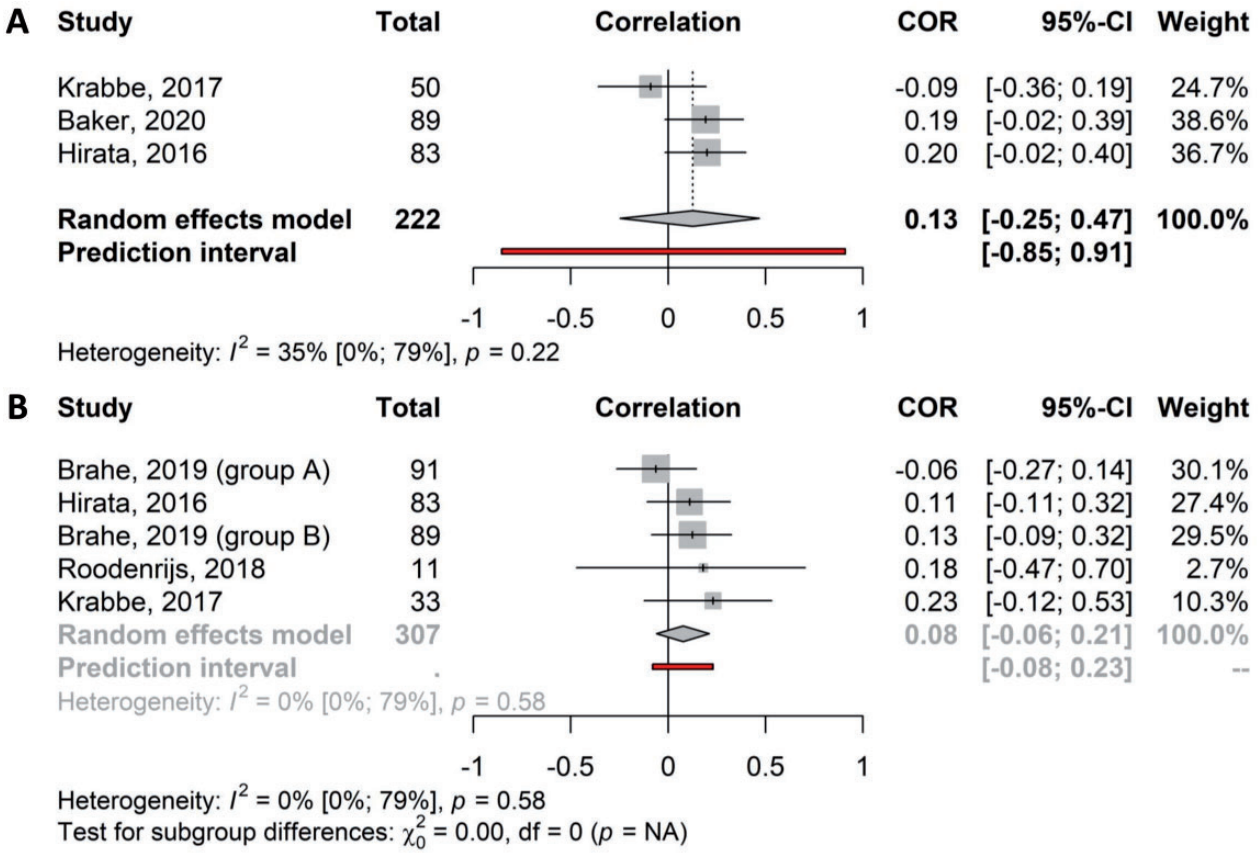

Figure 3. Forest plots for the correlations of MBDA score with SvdH score. (**A**) Forest plot for the correlation of baseline MBDA score with baseline SvdH score. (**B**) Forest plot for the correlation of the change in MBDA score with the change in SvdH score

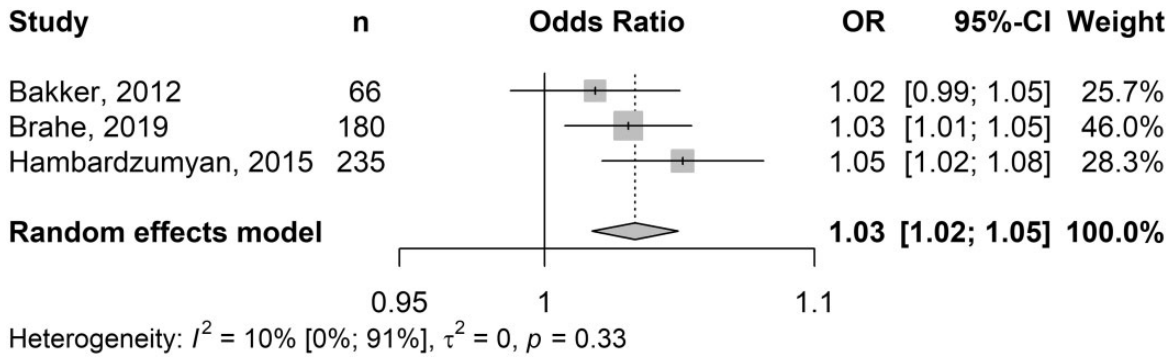

Figure 4. Forest plot of the predictive value of MBDA score for radiographic progression

for patients with a high baseline DAS28-CRP were not significantly higher than for patients with a low baseline DAS28-CRP [OR 1.12 (CI 0.91–1.37), $I^2 = 0.0\%$] (see Supplementary Fig. S9, available at *Rheumatology* online). The characteristics of the studies evaluating the predictive value of the MBDA score and DAS28-CRP for radiographic progression are detailed in Table 2.

Five additional studies evaluating the utility of the MBDA score for the assessment of radiographic progression could not be included in our quantitative synthesis [16, 27, 34, 36, 39]. Markusse *et al.* [16] found that higher MBDA scores at baseline were associated with an increased risk of radiographic progression in the subsequent year, therefore the MBDA score can be considered an independent predictor for radiographic progression. The discriminative value of the MBDA score was also assessed and the results showed that the MBDA score discriminated more between radiographic progression and no radiographic progression than the DAS at baseline and 1 year. Hirata *et al.* [34] reported that patients with moderate or high MBDA scores had a greater risk of radiographic progression than patients with low or moderate MBDA scores. Li *et al.* [39] also found that radiographic progression was not frequent when MBDA scores were low; univariate and multivariate analyses showed that high MBDA scores were strongly associated with radiographic progression. In a study by Krabbe *et al.* [36], none of the patients

Table 2. Characteristics of studies evaluating the predictive value of MBDA score and DAS28-CRP for radiographic progression

First author, year of publication	Time of evaluating RP	Definition of RP	Low MBDA score	High MBDA score	Low DAS28-CRP	High DAS28-CRP
Studies included in the meta-analysis						
Bakker, 2012 [13]	2 years	>0 units increase of SvdH score	<30	>44	≤2.7	>2.7
Brahe, 2019 [14]	1 year	>2 units increase of SvdH score	<30	>44	≤5.1	>5.1
Hambardzumyan, 2015 [15]	1 year	>5 units increase of SvdH score	<30	>44	≤2.7	>4.1
Studies included in the systematic review						
Bouman, 2017 [27]	1.5 years	>0.5 unit increase in SvdH score	<30	>44	<2.7	>4.1
Hirata, 2016 [34]	1 year	>3 unit increase in SvdH score	<30	>44	≤3.2	>5.1
Krabbe, 2017 [36]	0.5, 1 year	N/A	<30	>44	≤3.2	>5.1
Li, 2016 [39]	1 year	>3 unit increase in SvdH score	<30	>44	≤2.67	>4.09
Markusse, 2014 [16]	1 year	>0.5 unit increase in SvdH score	<30	>44	≤2.4	>3.7

N/A: no data available; RP: radiographic progression.

with radiographic progression had low MBDA scores. In contrast, Bouman *et al.* [27] found no association between baseline MBDA score and radiographic progression.

MBDA score for the assessment of therapy response, remission and relapse

We identified four studies [30, 34, 38, 47] investigating the utility of the MBDA score for the assessment of therapy response, six studies [13, 14, 33, 40, 42, 49] for remission and five studies [24, 26, 27, 45, 48] for relapse. However, these studies were not eligible for quantitative synthesis due to the widely varying outcome measures.

The change of MBDA score from baseline to 6 months was significantly associated with good or moderate EULAR response *vs* non-response at 6 months by Roodenrijs *et al.* [47]; however, the baseline MBDA score was not associated with EULAR response *vs* non-response. Similar results were recorded by Li *et al.* [38]. Although the baseline MBDA score was not associated with EULAR response at 3 months, changes in MBDA scores differentiated responders from non-responders. Hambardzumyan *et al.* [30] also reported that the MBDA score was significantly associated with treatment outcomes at 3 months. In the study of Hirata *et al.* [49], EULAR good responders were found to have significantly greater reductions in the MBDA score from baseline than EULAR moderate responders and EULAR moderate responders had significantly greater reductions than EULAR non-responders.

The MBDA score was found to be an appropriate discriminator of remission/low disease activity and moderate/high disease activity, according to two studies [13, 42]. Ma *et al.* [42] reported that the baseline MBDA score and the time-integrated MBDA score discriminated between remission and non-remission at 1 year as well. Two studies found no significant association between baseline MBDA score and remission, although, according to Brahe *et al.* [14, 40], the change in MBDA score was associated with clinical remission. Hirata *et al.* [33, 49] recorded the association of MBDA remission with clinical remission.

High baseline MBDA scores were associated with significantly greater proportions of patients experiencing relapse based on the results of Ghiti Moghadam *et al.* [48] and significantly higher MBDA scores were recorded in relapsed patients by Rech *et al.* [45]. Boeters *et al.* [26] found that high MBDA scores during DMARD treatment and before treatment reduction were associated with an increased risk of relapses in patients who reduced or stopped DMARD treatments. Bouman *et al.* [27] reported the borderline positive predictive value of baseline MBDA score for flare of patients with low disease activity at baseline. According to Bechman *et al.* [24], baseline MBDA scores were not predictive of flare. However, a sensitivity analysis limited to flares with an increase in high disease activity determined by MBDA score (> 44) did show an association between baseline MBDA value and flare risk.

Funnel plots and leave-one-out analysis

No evidence of publication bias was observed in the funnel plots for the correlations of MBDA scores with conventional DAMs (see Supplementary Figs S10–S12, available at *Rheumatology* online). The results of the leave-one-out analysis are detailed in Supplementary Tables S2–S4, available at *Rheumatology* online, showing no outlier article.

Risk of bias assessment

The majority of the outcomes of the studies included in the meta-analysis ($n = 79$) and the systematic review ($n = 37$) were rated as having a low or moderate risk of bias. The risk of bias was low in 35 outcomes of the studies included in the meta-analysis and 29 outcomes of the studies included in the systematic review, moderate in 32 outcomes of the studies included in the meta-analysis and 5 outcomes of the studies included in the systematic review and high in 12 outcomes of the studies included in the meta-analysis and 3 outcomes of the studies included in the systematic review. Common methodological limitations across studies were attrition rates, study confounding and statistical analysis and reporting. The quality assessment scores for all outcomes are shown in Supplementary Tables S5 and S6, available at *Rheumatology* online.

Discussion

Since the recommendation for the treatment of RA—the treat-to-target therapeutic approach—requires close monitoring of disease activity, the importance of objective scoring systems is indisputable. By conducting a systematic review and meta-analysis on the utility of the MBDA score to assess disease activity, radiographic progression, remission and relapse, we aim to promote decision making on the applicability of the MBDA score in clinical practice.

When analysing the correlations of MBDA score with conventional DAMs by a random-effects model, moderate correlations were recorded, similar to the meta-analysis conducted by Johnson *et al.* [17]. DAS28-CRP and DAS28-ESR, which

are considered the gold standard DAMs in RA, both showed moderate correlations with MBDA at baseline and follow-up, as well as in the change in DAS28-CRP and DAS28-ESR with the change in MBDA. Other DAMs detailed in the supplement showed weaker correlations with MBDA score, except for CRP. The correlation of the MBDA score with CRP individually was stronger than with DAS28-CRP. As the MBDA score does not contain the results of clinical assessment, its deviation from the conventional DAMs is not surprising. However, the MBDA score was designed to complement, not replace conventional DAMs, therefore its deviation from conventional DAMs can even be advantageous [51].

Since the MBDA score contains markers of cartilage and bone damage, such as MMP-3, in addition to the inflammatory markers implemented in currently used DAMs, such as CRP, it is a realistic possibility that it can outperform conventional DAMs in predicting radiological progression [52]. The results of our meta-analysis suggest that the MBDA score can be an independent predictor of radiological progression, as the odds of radiographic progression were significantly higher for patients with a high baseline MBDA score than for patients with a low baseline MBDA score, while there was no significant difference between low- and high-baseline DAS28-CRP. However, while the cut-off values for high and low MBDA scores were the same in the included studies, different cut-off values were used to define DAS28-CRP subgroups, which may influence these results and highlight the need for further investigations (see Table 2). Furthermore, the SvdH score showed a low correlation with the MBDA score at baseline and at follow-up, which suggests that these data should be interpreted with caution. These results are in line with the results of the studies included in our systematic review and also with the results of the previous meta-analysis by Curtis *et al.* [53] and the systematic review by Abdelhafiz *et al.* [54]. The limitation of both our study and the study by Curtis *et al.* [53] is the lack of included studies investigating the efficacy of DAS28-CRP for predicting radiographic progression independent of the MBDA score, potentially leading to biased results.

Based on the studies included in the systematic review, the change in MBDA score is associated with therapeutic response and seems to discriminate between therapy responders and non-responders [30, 38, 47, 49]. However, baseline MBDA scores were not predictive of therapy response [38, 47]. Similarly, while the change in MBDA score was found to be associated with remission and MBDA score discriminated remission/low disease activity and moderate/high disease activity [13, 14, 33, 42, 49], no significant associations were found between baseline MBDA scores and remission [14, 40]. In contrast, in the case of relapse, the baseline MBDA score was reported to be a predictor, although no clear conclusions can be drawn due to the heterogeneity of study designs and the potential for false positivity due to multiple testing [24, 27, 48].

There are several strengths of our study. We implemented a rigorous methodology to achieve the highest quality of evidence and provide a structured analysis of the outcomes discussed in the literature. We provide a comprehensive summary on the utility of the MBDA score for monitoring RA disease activity and also the predictive and discriminative value of the MBDA score for radiographic progression, therapy response, remission and relapse, presenting the results of quantitative analysis for both the correlation of the MBDA score with conventional DAMs and the predictive value of the MBDA score for radiographic progression.

Our main limitation is the heterogeneity of the populations. A wide range of anti-rheumatic drugs was used in the included studies, with potentially varying effects on the MBDA score: the IL-6 receptor-blocker tocilizumab may increase the serum level of IL-6 by preventing receptor binding, therefore influencing the change in MBDA score via one of the 12 included biomarkers [46]. TNF inhibitors may also influence MBDA score indirectly by decreasing the serum level of TNF-α. Hirata *et al.* [34] compared anti-TNF-α and anti-TNF-α-receptor drugs and found no significant difference between the two groups; however, further studies are needed to assess the effect of targeted therapies on the serum level of the biomarkers included in the MBDA score and therefore their effect on the change of MBDA score [34]. Furthermore, the different follow-up times used for the assessment of disease activity may also increase the heterogeneity.

By including a higher number of patients and uniformizing the follow-up time for evaluation and the cut-off values of DAS28-CRP for remission, future studies would enable further comprehensive analysis to urge implementation of the MBDA score in daily clinical practice.

Conclusion

The MBDA score can be highly valuable in RA patient care, both for monitoring disease activity and for predicting radiological progression. However, further studies are needed to better assess the utility of the MBDA score and also the potential role of individual biomarkers in disease activity monitoring.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The datasets used in this study can be found in the full-text articles included in the systematic review and meta-analysis. The data underlying this article will be shared upon reasonable request to the corresponding author.

Authors' contributions

L.V.K. and F.A.M. were responsible for conceptualization, project administration, data curation, visualization and writing the original draft. E.G. was responsible for conceptualization, project administration, data curation and visualization. E.B. was responsible for conceptualization and data curation. F.D. was responsible for conceptualization, data curation and methodology. B.S. was responsible for methodology, formal analysis, validation and visualization. A.A. and E.L. were responsible for data curation and visualization. D.C. and P.H. were responsible for conceptualization, methodology and supervision. A.B. and G.N. were responsible for conceptualization, methodology, supervision and writing the original draft. All authors provided critical conceptual input and approved the final version of the article.

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References

1. Alamanos Y, Voulgari PV, Drosos AA. Incidence and prevalence of rheumatoid arthritis, based on the 1987 American College of Rheumatology criteria: a systematic review. Semin Arthritis Rheum 2006;36:182–8.
2. Smolen JS, Landewé RBM, Bijlsma JWJ *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
3. Singh JA, Saag KG, Bridges SL Jr *et al.* 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2016;68:1–25.
4. Smolen JS, Breedveld FC, Burmester GR *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. Ann Rheum Dis 2016;75:3–15.
5. Nagy G, Roodenrijs NMT, Welsing PMJ *et al.* EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Ann Rheum Dis 2022;81:20–33.
6. van Gestel AM, Prevoo ML, van 't Hof MA *et al.* Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. Arthritis Rheum 1996;39:34–40.
7. Aletaha D, Martinez-Avila J, Kvien TK, Smolen JS. Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. Ann Rheum Dis 2012;71:1190–6.
8. Aletaha D, Nell VP, Stamm T *et al.* Acute phase reactants add little to composite disease activity indices for rheumatoid arthritis: validation of a clinical activity score. Arthritis Res Ther 2005;7:R796–806.
9. van der Heijde D. How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 2000;27:261–3.
10. Scott DL. Radiological progression in established rheumatoid arthritis. J Rheumatol Suppl 2004;69:55–65.
11. Barra L, Bykerk V, Pope JE *et al.* Anticitrullinated protein antibodies and rheumatoid factor fluctuate in early inflammatory arthritis and do not predict clinical outcomes. J Rheumatol 2013;40:1259–67.
12. Curtis JR, van der Helm-van Mil AH, Knevel R *et al.* Validation of a novel multibiomarker test to assess rheumatoid arthritis disease activity. Arthritis Care Res (Hoboken) 2012;64:1794–803.
13. Bakker MF, Cavet G, Jacobs JW *et al.* Performance of a multibiomarker score measuring rheumatoid arthritis disease activity in the CAMERA tight control study. Ann Rheum Dis 2012;71:1692–7.
14. Brahe CH, Østergaard M, Johansen JS *et al.* Predictive value of a multi-biomarker disease activity score for clinical remission and radiographic progression in patients with early rheumatoid arthritis: a post-hoc study of the OPERA trial. Scand J Rheumatol 2019;48:9–16.
15. Hambardzumyan K, Bolce R, Saevarsdottir S *et al.* Pretreatment multi-biomarker disease activity score and radiographic progression in early RA: results from the SWEFOT trial. Ann Rheum Dis 2015;74:1102–-9.
16. Markusse IM, Dirven L, van den Broek M *et al.* A multibiomarker disease activity score for rheumatoid arthritis predicts radiographic joint damage in the BeSt study. J Rheumatol 2014;41:2114–-9.
17. Johnson TM, Register KA, Schmidt CM *et al.* Correlation of the multi-biomarker disease activity score with rheumatoid arthritis disease activity measures: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2019;71:1459–72.
18. Page MJ, McKenzie JE, Bossuyt PM *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
19. Debray TP, Damen JA, Snell KI *et al.* A guide to systematic review and meta-analysis of prediction model performance. BMJ 2017;356:i6460.
20. Arnett FC, Edworthy SM, Bloch DA *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
21. Kay J, Upchurch KS. ACR/EULAR 2010 rheumatoid arthritis classification criteria. Rheumatology (Oxford) 2012;51(Suppl 6):vi5–9.
22. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. Ann Intern Med 2013;158:280–6.
23. Baker JF, Curtis JR, Chernoff D *et al.* Evaluation of the impact of age and adiposity on a multi-biomarker disease activity score before and after adjustment. Clin Rheumatol 2021;40:2419–26.
24. Bechman K, Tweehuysen L, Garrood T *et al.* Flares in rheumatoid arthritis patients with low disease activity: predictability and association with worse clinical outcomes. J Rheumatol 2018;45:1515–21.
25. Bijlsma JWJ, Jurgens MS, Jacobs JWG *et al.* Response to MTX plus prednisone in camera II using a multi-biomarker disease activity (Vectra^{TM} DA) test and DAS28-ESR. Ann Rheum Dis 2013;72:A80.1–A80.
26. Boeters DM, Burgers LE, Sasso EH, Huizinga TWJ, van der Helm-van Mil AHM. ACPA-negative RA consists of subgroups: patients with high likelihood of achieving sustained DMARD-free remission can be identified by serological markers at disease presentation. Arthritis Res Ther 2019;21:121.
27. Bouman CAM, van der Maas A, van Herwaarden N *et al.* A multibiomarker score measuring disease activity in rheumatoid arthritis patients tapering adalimumab or etanercept: predictive value for clinical and radiographic outcomes. Rheumatology (Oxford) 2017;56:973–80.
28. Brahe CH, Ostergaard M, Johansen J *et al.* Changes in multibiomarker disease activity (MBDA) score correlate with changes in established disease activity measurements in patients with early RA from the OPERA study. Ann Rheum Dis 2016;75:450.1.
29. Genovese MC, Galien R, Pan Y *et al.* Correlation of multibiomarker disease activity score with clinical disease activity measures for the JAK1-selective inhibitor filgotinib as monotherapy and in combination with methotrexate in rheumatoid arthritis patients. Arthritis Rheumatol 2017;69(Suppl 10):abstract 1458.
30. Hambardzumyan K, Bolce RJ, Wallman JK, van Vollenhoven RF, Saevarsdottir S. Serum biomarkers for prediction of response to methotrexate monotherapy in early rheumatoid arthritis: results from the SWEFOT trial. J Rheumatol 2019;46:555–63.

31. Hambardzumyan K, Saevarsdottir S, Bolce R *et al.* Multi-biomarker disease activity (MBDA) score and the 12 individual biomarkers in early rheumatoid arthritis patients relate differentially to clinical response and radiographic progression: results from the SWEFOT trial. Ann Rheum Dis 2013;72(Suppl 3):A388–9.
32. He E, Yalamanchi P, Arnold W, Arnold E. Assessment of the components of RAPID3 patient reported outcomes in a community rheumatology practice. Arthritis Rheumatol 2020;72:3484–5.
33. Hirata S, Dirven L, Cavet G *et al.* A multi-biomarker disease activity score (the VECTRA^{TM} DA algorithm score) reflects clinical remission for rheumatoid arthritis (RA) in the best study. Ann Rheum Dis 2012;71:355.
34. Hirata S, Li W, Kubo S *et al.* Association of the multi-biomarker disease activity score with joint destruction in patients with rheumatoid arthritis receiving tumor necrosis factor-alpha inhibitor treatment in clinical practice. Mod Rheumatol 2016;26:850–6.
35. Jurgens MS, Safy-Khan M, de Hair MJH *et al.* The multibiomarker disease activity test for assessing response to treatment strategies using methotrexate with or without prednisone in the CAMERA-II trial. Arthritis Res Ther 2020;22:205.
36. Krabbe S, Bolce R, Brahe CH *et al.* Investigation of a multibiomarker disease activity score in rheumatoid arthritis by comparison with magnetic resonance imaging, computed tomography, ultrasonography, and radiography parameters of inflammation and damage. Scand J Rheumatol 2017;46:353–8.
37. Lee YC, Hackett J, Frits M *et al.* Multibiomarker disease activity score and C-reactive protein in a cross-sectional observational study of patients with rheumatoid arthritis with and without concomitant fibromyalgia. Rheumatology (Oxford) 2016;55:640–8.
38. Li W, Hensvold AH, Saevarsdottir S *et al.* Characterization of the multi-biomarker disease activity (Vectra Da^{TM} algorithm) score in a subgroup of patients from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) cohort receiving methotrexate. Ann Rheum Dis 2013;72:A591.1.
39. Li W, Sasso EH, van der Helm-van Mil AH, Huizinga TW. Relationship of multi-biomarker disease activity score and other risk factors with radiographic progression in an observational study of patients with rheumatoid arthritis. Rheumatology (Oxford) 2016;55:357–66.
40. Luedders BA, Johnson TM, Sayles H *et al.* Predictive ability, validity, and responsiveness of the multi-biomarker disease activity score in patients with rheumatoid arthritis initiating methotrexate. Semin Arthritis Rheum 2020;50:1058–63.
41. Ma MH, Garrood T, Li W *et al.* Multi-biomarker disease activity (Vectra® DA algorithm) score is associated with power Doppler ultrasound in patients with rheumatoid arthritis in low disease activity state: the Remira cohort. Ann Rheum Dis 2014;73:606.
42. Ma MHY, Defranoux N, Li W *et al.* A multi-biomarker disease activity score can predict sustained remission in rheumatoid arthritis. Arthritis Res Ther 2020;22:158.
43. Maijer KI, De Hair MJH, Li W *et al.* Evaluation of a multibiomarker disease activity (vectra ^{TM} da algorithm) in early rheumatoid arthritis and unclassified arthritis patients. Ann Rheum Dis 2013;72:A389.
44. Razmjou AA, Brook J, Elashoff D *et al.* Ultrasound and multibiomarker disease activity score for assessing and predicting clinical response to tofacitinib treatment in patients with rheumatoid arthritis. BMC Rheumatol 2020;4:55.
45. Rech J, Hueber AJ, Finzel S *et al.* Prediction of disease relapses by multibiomarker disease activity and autoantibody status in patients with rheumatoid arthritis on tapering DMARD treatment. Ann Rheum Dis 2016;75:1637–44.
46. Reiss WG, Devenport JN, Low JM, Wu G, Sasso EH. Interpreting the multi-biomarker disease activity score in the context of tocilizumab treatment for patients with rheumatoid arthritis. Rheumatol Int 2016;36:295–300.
47. Roodenrijs NMT, De Hair MJH, Wheater G *et al.* The multibiomarker disease activity score tracks response to rituximab treatment in rheumatoid arthritis patients: a post hoc analysis of three cohort studies. Arthritis Res Ther 2018;20:256.
48. Ghiti Moghadam M, Lamers-Karnebeek FBG, Vonkeman HE *et al.* Multi-biomarker disease activity score as a predictor of disease relapse in patients with rheumatoid arthritis stopping TNF inhibitor treatment. PLoS One 2018;13:e0192425.
49. Hirata S, Dirven L, Shen Y *et al.* A multi-biomarker score measures rheumatoid arthritis disease activity in the BeSt study. Rheumatology (Oxford) 2013;52:1202–7.
50. Hirata S, Li W, Defranoux N *et al.* A multi-biomarker disease activity score tracks clinical response consistently in patients with rheumatoid arthritis treated with different anti-tumor necrosis factor therapies: a retrospective observational study. Mod Rheumatol 2015;25:344–9.
51. Curtis JR, Wright GC, Strand V *et al.* Reanalysis of the multibiomarker disease activity score for assessing disease activity in the abatacept versus adalimumab comparison in biologic-naive rheumatoid arthritis subjects with background methotrexate study: comment on the article by Fleischmann. Arthritis Rheumatol 2017; 69:863–65.
52. Lerner A, Neidhöfer S, Reuter S, Matthias T. MMP3 is a reliable marker for disease activity, radiological monitoring, disease outcome predictability, and therapeutic response in rheumatoid arthritis. Best Pract Res Clin Rheumatol 2018;32:550–62.
53. Curtis JR, Brahe CH, Østergaard M *et al.* Predicting risk for radiographic damage in rheumatoid arthritis: comparative analysis of the multi-biomarker disease activity score and conventional measures of disease activity in multiple studies. Curr Med Res Opin 2019;35:1483–93.
54. Abdelhafiz D, Baker T, Glascow DA, Abdelhafiz Ah. Biomarkers for the diagnosis and treatment of rheumatoid arthritis – a systematic review. Postgrad Med 2022:1–10.