ORIGINAL ARTICLE

The correlations between C-reactive protein and MRI-detected inflammation in patients with axial spondyloarthritis: a systematic review and meta-analysis

Haoran Tian[1] · Ting Li[1] · Yuanqiong Wang[1] · Hongjuan Lu[1] · Li Lin[1] · Xin Wu[1] · Huji Xu[1,2,3]

Abstract

Background C-reactive protein (CRP) and magnetic resonance imaging (MRI) are widely used to monitor inflammation in patients with axial spondyloarthritis (axSpA), but the relationship between CRP and MRI-detected inflammation is incompletely understood. The present study was undertaken to assess correlations between CRP and MRI-detected inflammation in axSpA.

Materials and methods A systematic literature search was performed (Medline, Embase, and Cochrane Library) to identify relevant studies concerning CRP and MRI-detected inflammation in axSpA patients. The MRI-detected inflammation was evaluated by MRI-based disease activity score (DAS). The correlation between CRP and MRI-based DAS was integrated by random-effect models.

Results Eighteen studies reported a total of 1392 axSpA patients which were included in this meta-analysis. CRP was significantly associated with spinal MR DAS (r=0.226, 95%CI [0.149, 0.291], p<0.001, I^2=23%). We also found a moderate correlation between CRP change and spinal MR DAS change (r[ASspiMRI-a]=0.354, 95%CI [0.282, 0.422], p<0.001, I^2=48%; r[SPARCC]=0.544, 95%CI [0.345, 0.701], p<0.001, I^2=19%). CRP at baseline was negatively associated with improvement in spinal MR DAS (r= − 0.327, 95%CI [−0.397, −0.264], p<0.001, I^2=0%). However, no significant association was found between CRP and sacroiliac joint (SIJ) MR DAS.

Conclusions In axSpA patients, CRP is associated with MRI-detected inflammation in the spine but not in SIJ. We speculate that CRP could be a reasonable index to reflect spinal inflammation. Therefore, we suggest it is not essential to repeat spinal MRI in a short term, while SIJ MRI may be necessary to provide additional information on inflammation.

Key Points
• *CRP is associated with MRI-detected inflammation in the spine but not in sacroiliac joints.*
• *CRP at baseline was negatively associated with improvement in spinal MR DAS.*
• *It was not essential to repeat spinal MRI frequently, while SIJ MRI may be necessary to provide additional information on inflammation.*

Haoran Tian and Ting Li contributed equally to this work.

✉ Huji Xu
huji_xu@tsinghua.edu.cn

[1] Department of Rheumatology and Immunology, Shanghai Changzheng Hospital, Naval Medical University, Shanghai 200003, China

[2] Peking-Tsinghua Center for Life Sciences, Tsinghua University, Beijing 100084, China

[3] School of Clinical Medicine, Tsinghua University, Beijing 100084, China

Abbreviations

|	
CRP	C-reactive protein
axSpA	Axial spondyloarthritis
MRDAS	Magnetic resonance imaging-based disease activity score
MRI	Magnetic resonance imaging
SPARCC	Spondyloarthritis Research Consortium of Canada
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity
BME	Bone marrow edema
SIJ	Sacroiliac joints

Introduction

AxSpA is an inflammatory rheumatic disease of unknown etiology characterized by damages primarily in the axial skeleton, mainly in the SIJ and spreading to the whole spine. In previous studies, the prevalence of axSpA in different populations ranged from 0.32 to 1.4% [1]. The most typical manifestations of patients are chronic low back pain, morning stiffness, and fatigue. Pain, reduced mobility, and potential spinal deformity are caused by inflammation and structural damage.

Inflammation is a critical early step in osteoproliferation and structural remodeling [1]. The ultimate goals of axSpA treatment are to control inflammation, reduce disease activity, prevent radiographic progression, and maintain physical function [2]. So how to evaluate inflammation is of critical importance. However, to date, a broadly accepted tool to detect inflammation in axSpA is lacking. The basic so-called objective signs of inflammation, which have generally been recommended by various guidelines, included CRP and MRI. CRP is an acute-phase reactant and plays a prominent role in monitoring patients with axSpA [3]. Owing to its simplicity, repeatability, and reliability, CRP fulfills the "OMERACT filter" as a relevant outcome measurement in axSpA [3], whereas there are still some debates as to whether CRP is a valid indicator of inflammation [1, 4]. Some studies

reported that CRP might not be elevated in active axSpA [5, 6]. In the past decade, the use of MRI has brought our vision into a new phase [7, 8]. MRI studies have contributed to detecting spinal and SIJ inflammation, even minor fluid collections such as bone marrow edema (BME) [9]. MR DAS provided a semi-quantitative measure to evaluate the spinal/ SIJ inflammation in axSpA, including the Spondyloarthritis Research Consortium of Canada (SPARCC) [10, 11], the Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity (ASspiMRI-a) [12], and the Berlin method [13]. Ample evidence suggests that MR DAS provides additional information on top of clinical and biochemical assessments [14]. Despite minor differences between these methods, all showed comparable discriminatory capacity and good sensitivity to change [2]. For the assessment of inflammation in SIJ, the most widely used scoring systems for quantification are the Berlin score and the SPARCC score [15]. As for the evaluation of spinal inflammation, all three scoring systems are commonly used. Although the contribution of MRI to our understanding of axSpA is indisputable [7, 8], MRI is time-consuming and expensive, which limits its clinical application. This has prompted extensive investigation of the correlation between CRP and MRI.

The relationship between MR DAS and CRP is incompletely understood. Some studies indicated weak or inconsistent correlations between CRP and MRI findings [16,

Fig. 1 Flow chart describing the systematic search and study selection
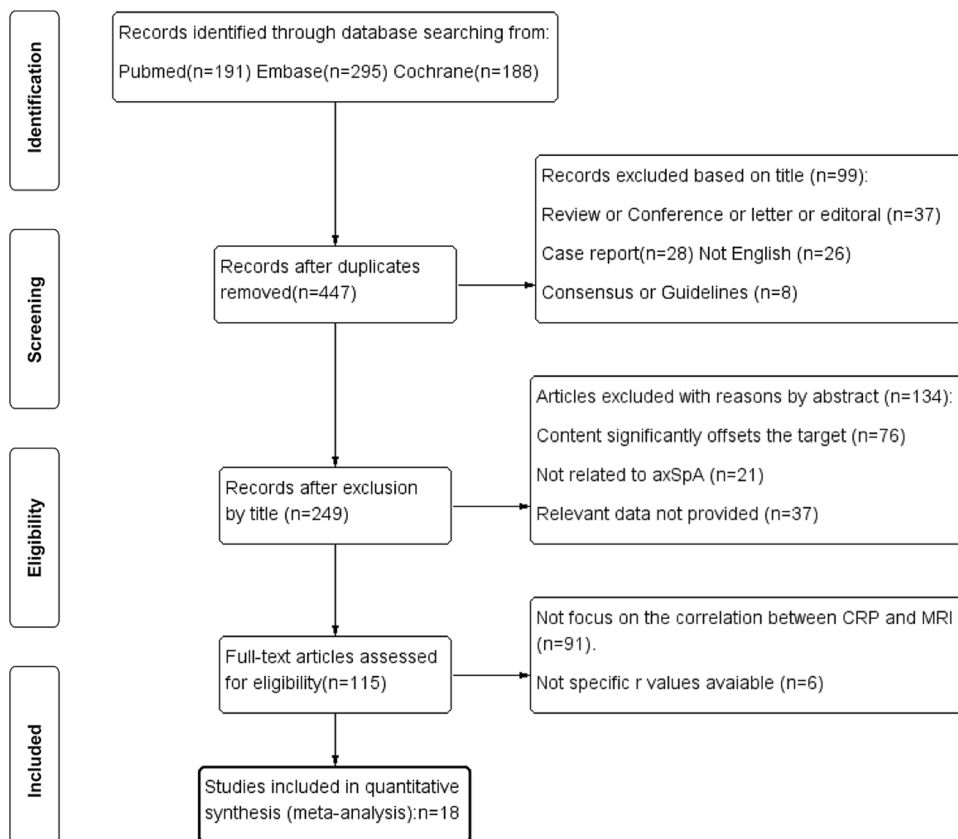
17]; BME could be detected by MRI in a sizable proportion (78.9%) of CRP-negative axSpA patients [18]. Other studies reported that CRP correlated with MR DAS, and a decrease in CRP was related to the improvement in MR DAS [19]. Taken together, the relationship between CRP and MRI-detected inflammation in patients with axSpA remains nebulous.

Considering the conflicting study results, we conducted a systematic review and meta-analysis to determine the correlation between CRP and MRI findings in patients with axSpA. To the best of our knowledge, this is the first meta-analysis to analyze the correlation between CRP and MRI, which may improve clinicians' understanding of inflammation monitoring in axSpA patients.

Methods

Search strategy and study selection

This meta-analysis was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [20] (shown in Supplementary Table S1). PubMed, Cochrane, and Embase were searched for studies assessing CRP and MRI in axSpA patients from inception to 17 December 2020. Medical Subject Headings (MeSH) terms "Spondylitis, Ankylosing," "C-Reactive Protein," "Magnetic Resonance Imaging," and related free text terms were used for the search. Besides, the

Table 1 Correlation between CRP and MR DAS

Study	Scoring method	Location	Number	CRP	ESR	BASDAI	ASDAS	BASMI	BASFI
Rudwaleit 2008 (17)	Berlin	Spine	62	0.136 (NS)	0.195 (NS)	−0.033 (NS)	–	0.235 (NS)	−0.163 (NS)
		SIJ	62	−0.170 (NS)	−0.070 (NS)	0.001 (NS)	–	−0.499 (0.001)	−0.162 (NS)
Pedersen 2010 (16)	Berlin	SIJ	56–60	0.060 (NS)	–	−0.230 (NS)	−0.140 (NS)	–	–
		LS	56–60	0.050 (NS)	–	−0.410 ($p<0.01$)	−0.300 (<0.05)	–	–
Konca 2012 (33)	ASspiMRI-a	Spine	50	0.321 (0.023)	0.244 (0.088)	−0.020 (0.915)	–	0.396 (0.004)	0.222 (0.122)
Machado 2012 (19)	M-ASspiMRI-a	spine	158	0.280 (<0.001)	–	−0.090 (0.174)	0.160 (0.016)	–	–
Kiltz 2012 (32)	Berlin	Spine	100	0.220 (0.030)	–	NS	NS	–	–
Soliman 2012 (34)	BME score	SIJ	30	−0.103 (0.589)	0.256 (0.290)	0.119 (0.537)	–	−0.513 (0.004)	−0.267 (0.161)
Heijde 2014 (36)	SPARCC	SIJ	182	0.094 (NS)	–	−0.187 (0.010)	0.022 (NS)	–	−0.105 (NS)
		Spine	181	0.142 (NS)	–	−0.030 (NS)	0.123 (NS)	–	0.043 (NS)
Praet 2014 (35)	SPARCC	SIJ	62	0.390 (0.002)	–	0.100 (0.440)	0.350 (0.007)	–	–
MacKay 2015 (37)	SPARCC	SIJ	40	NS	NS	0.120 (0.470)	0.120 (0.460)	–	–
		Spine	40	0.370 (0.020)	0.380 (0.020)	0.160 (0.330)	0.280 (0.080)	–	–
Braun2016 (38)	ASspiMRI-a	Spine	89	w0:0.360 (0.009)	–	–	–	–	–
		Spine	85	w14:0.330 (0.036)	–	–	–	–	–
		Spine	67	w104:0.010 (1.000)	–	–	–	–	–
Kang 2017 (39)	SPARCC	SIJ	36 (nr-axSpA)	0.606 (<0.001)	0.576 (0.001)	0.001 (0.995)	0.453 (0.006)	–	–
		SIJ	45 (AS)	0.098 (0.523)	0.066 (0.668)	0.059 (0.698)	0.163 (0.285)	–	–

The Spearman test for rank correlation is used for test of correlation; values are correlation coefficients (rho), if not otherwise indicated. *p*-values indicate the level of statistical significance. *AS*, ankylosing spondylitis; *LS*, lumbar spine; *ASDAS*, Ankylosing Spondylitis Disease Activity Score; *ASspiMRI-a*, ankylosing spondylitis spine MRI score for activity; *M-ASspiMRI-a*, modified ASspiMRI-a; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Score; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *MRI*, magnetic resonance imaging; *NS*, not statistically significant; *SIJ*, sacroiliac joints; *SPARCC*, Spondyloarthritis Research Consortium of Canada Scoring System; –, not done

A

Study or Subgroup	Fisher' Z	SE	Weight	Fisher' Z IV, Random, 95% CI
1.1.1 Spine				
Rudwaleit 2008-Spine	0.13684791	0.13018891	5.6%	0.14 [-0.12, 0.39]
Pedersen 2010-LS	0.05004173	0.13245324	5.5%	0.05 [-0.21, 0.31]
Kiltz 2012	0.33276159	0.14586499	5.0%	0.33 [0.05, 0.62]
Konca 2012	0.28768207	0.08032193	8.1%	0.29 [0.13, 0.45]
Machado 2012	0.22365611	0.10153462	6.9%	0.22 [0.02, 0.42]
Heijde 2014-Spine	0.14296614	0.07495317	8.3%	0.14 [-0.00, 0.29]
MacKay 2015	0.3884231	0.16439899	4.3%	0.39 [0.07, 0.71]
Braun 2016(W0)	0.3768859	0.10783277	6.6%	0.38 [0.17, 0.59]
Braun 2016(W14)	0.34282825	0.11043153	6.5%	0.34 [0.13, 0.56]
Braun 2016(W104)	0.01000033	0.125	5.8%	0.01 [-0.23, 0.25]
Subtotal (95% CI)			62.7%	0.23 [0.15, 0.30]

Heterogeneity: Tau² = 0.00; Chi² = 11.63, df = 9 (P = 0.24); I² = 23%
Test for overall effect: Z = 5.69 (P < 0.00001)

1.1.2 SIJ				
Rudwaleit 2008-SIJ	-0.17166666	0.13018891	5.6%	-0.17 [-0.43, 0.08]
Pedersen 2010-SIJ	0.06007216	0.13245324	5.5%	0.06 [-0.20, 0.32]
Soliman 2012	-0.10336658	0.19245009	3.5%	-0.10 [-0.48, 0.27]
Heijde 2014-SIJ	0.09427834	0.07474351	8.4%	0.09 [-0.05, 0.24]
Praet 2014	0.41180003	0.13018891	5.6%	0.41 [0.16, 0.67]
Kang 2017(AS)	0.70257549	0.17407766	4.0%	0.70 [0.36, 1.04]
Kang 2017(nr-axSpA)	0.09831555	0.15430335	4.7%	0.10 [-0.20, 0.40]
Subtotal (95% CI)			37.3%	0.15 [-0.04, 0.34]

Heterogeneity: Tau² = 0.05; Chi² = 22.89, df = 6 (P = 0.0008); I² = 74%
Test for overall effect: Z = 1.53 (P = 0.13)

| **Total (95% CI)** | | | 100.0% | 0.20 [0.11, 0.28] |

Heterogeneity: Tau² = 0.02; Chi² = 37.24, df = 16 (P = 0.002); I² = 57%
Test for overall effect: Z = 4.46 (P < 0.00001)
Test for subgroup differences: Chi² = 0.51, df = 1 (P = 0.47), I² = 0%

Favours [experimental] Favours [control]

B
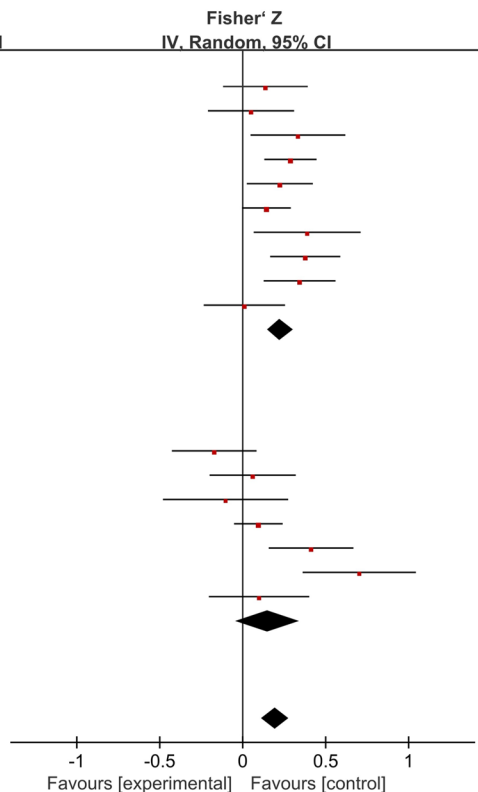
Study or Subgroup	Fisher'Z	SE	Weight	Fisher'Z IV, Random, 95% CI
Braun 2012(14w)	-0.4722308	0.10976426	13.0%	-0.47 [-0.69, -0.26]
Braun 2012(104w)	-0.42364893	0.10976426	13.0%	-0.42 [-0.64, -0.21]
Machado 2012(24w)	-0.25541281	0.08032193	24.3%	-0.26 [-0.41, -0.10]
Machado 2012(102w)	-0.32054541	0.07537784	27.6%	-0.32 [-0.47, -0.17]
Braun 2016(14w)	-0.34282825	0.11396058	12.1%	-0.34 [-0.57, -0.12]
Braun 2016(104w)	-0.34282825	0.12598816	9.9%	-0.34 [-0.59, -0.10]
Total (95% CI)			100.0%	-0.34 [-0.42, -0.27]

Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 8.65 (P < 0.00001)

Favours [experimental] Favours [control]
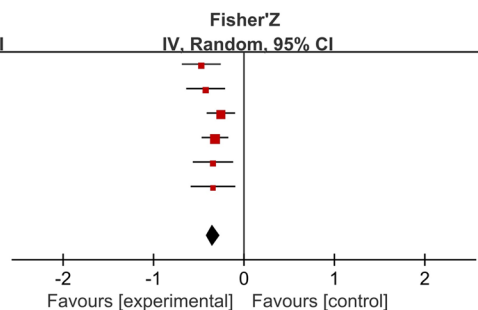
C

Study or Subgroup	Fisher' Z	SE	Weight	Fisher' Z IV, Random, 95% CI
2.1.1 Follow-up period < 52w				
Braun 2012(14w)	-0.4722308	0.10976426	13.0%	-0.47 [-0.69, -0.26]
Machado 2012(24w)	-0.25541281	0.08032193	24.3%	-0.26 [-0.41, -0.10]
Braun 2016(14w)	-0.34282825	0.11396058	12.1%	-0.34 [-0.57, -0.12]
Subtotal (95% CI)			49.5%	-0.34 [-0.47, -0.21]

Heterogeneity: Tau² = 0.00; Chi² = 2.55, df = 2 (P = 0.28); I² = 22%
Test for overall effect: Z = 5.26 (P < 0.00001)

2.1.2 Follow-up period ≥ 52w				
Braun 2012(104w)	-0.42364893	0.10976426	13.0%	-0.42 [-0.64, -0.21]
Machado 2012(102w)	-0.32054541	0.07537784	27.6%	-0.32 [-0.47, -0.17]
Braun 2016(104w)	-0.34282825	0.12598816	9.9%	-0.34 [-0.59, -0.10]
Subtotal (95% CI)			50.5%	-0.35 [-0.46, -0.24]

Heterogeneity: Tau² = 0.00; Chi² = 0.61, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 6.31 (P < 0.00001)

| **Total (95% CI)** | | | 100.0% | -0.34 [-0.42, -0.27] |

Heterogeneity: Tau² = 0.00; Chi² = 3.20, df = 5 (P = 0.67); I² = 0%
Test for overall effect: Z = 8.65 (P < 0.00001)
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%
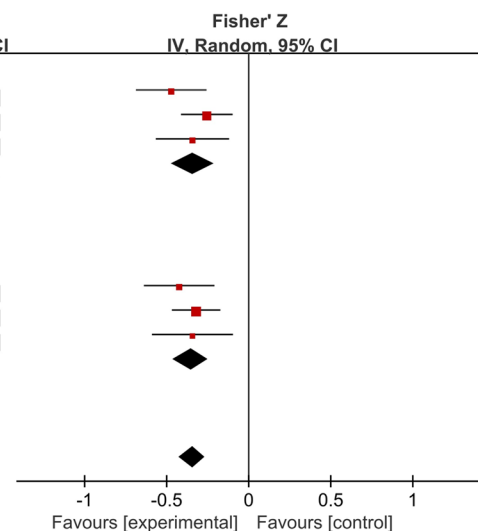
Favours [experimental] Favours [control]

◄**Fig. 2 A** Correlation between CRP and MR DAS. **B** Correlation between baseline CRP and MR DAS change. **C** Subgroup correlation between baseline CRP and MR DAS change

reference lists of the obtained articles were scanned manually to identify additional relevant articles. The detailed search strategy is shown in Supplementary Data S1. After removing duplicate references, two reviewers (HRT and TL) screened titles and abstracts independently. Disagreements between reviewers were resolved by a discussion with a third reviewer (YQW) about eligibility. We registered the study protocol in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021251256) database.

The included studies were subjected to the following inclusion criteria: (1) all participants were adult patients (not less than 18 years old) with axSpA who met either the Modified New York criteria [21] or the Assessment of SpondyloArthritis international Society (ASAS) criteria [22]; (2) the results of correlation analysis between MR DAS and CRP levels were performed. The excluded criteria were manuscripts not (yet) published as original studies; opinion or discussion papers; not English; and no subject-related data could be extracted. Other exclusion criteria and paper screening processes are shown in Fig. 1.

Risk of bias assessment and data extraction

Two authors (HRT and TL) independently assessed the risk of bias in this study. The QUADAS-2 tool for the Quality Assessment of Diagnostic Accuracy Studies includes four sections: patient selection, index test, reference standard, flow and timing [23]. Differences in assessment can be discussed. If consensus cannot be reached, a third reviewer (YQW) will rule. The risk of bias evaluation of this study is detailed in Supplementary Figure S1.

The results of data extraction by two reviewers (HRT and TL) from the first ten studies were identical, so the remaining fifteen articles were finished by one of the reviewers (HRT), and the other one was responsible for proofreading (TL). The contents of the data extraction include study identification (first author, journal, year of publication), number of patients, assessed joints (SIJ or spine), MRI semi-quantitative scoring method, therapy, MRI scanning intervals, correlation coefficient, and p-value of the correlation between MR DAS and clinical features. If there was no specific correlation coefficient (r-value) but only a p-value, we would send an email to ask the author for data.

Statistical analysis

Heterogeneity between studies was assessed using I^2 statistics (I^2 <30% = low heterogeneity; 30–60% = moderate heterogeneity;

>60% = high heterogeneity) [24]. Whenever heterogeneity was high (I^2 >50%), random-effect models were used [25]. Subgroup analyses were performed according to different sites of MRI (SIJ or spine) and different scoring methods (SPARCC, Berlin, ASspiMRI). The correlation coefficient (r-value) extracted from each study was converted using Fisher's Z transformation, and the conversion formulas were shown in Formulas 1, 2, and 3.

$$\text{Fisher's } Z = 0.5 \times \ln \sqrt{\frac{1+r}{1-r}} \tag{1}$$

$$V_z = \frac{1}{n-3} \tag{2}$$

$$\text{SE} = \sqrt{V_z} \tag{3}$$

$$r_{\text{summary}} = \frac{e^{2Z\text{summary Fisher's } Z} - 1}{e^{2Z\text{summary Fisher's } Z} + 1} \tag{4}$$

The converted Fisher's Z value and SE (standard error) value were entered into the ReVman software (version ReVman 5.4); the inverted variance method was used to obtain the summary Fisher's Z value (including 95% confidence interval). $p < 0.05$ was considered statistically significant, and then the summary r value was calculated according to Formula 4.

Results

Study characteristics

Through the screening of 447 studies, there were 24 studies concerning the association between CRP and MR DAS. Six studies [26–31] were excluded from the meta-analysis due to the absence of a specific r-value between CRP change and MR DAS change. Eighteen studies were included in this meta-analysis. There were 11 studies [16, 17, 19, 32–39] involving the correlation between clinical features of CRP and MR DAS, 3 studies [19, 38, 40] analyzing the predictive effects of baseline CRP on MR DAS change, and 10 studies [16, 19, 38, 40–46] focusing on the relationship between CRP change and MR DAS change. We included 6 cross-sectional studies [32–35, 37, 39], 2 clinical trials [30, 43], 3 cohort studies [16, 28, 31], and 12 randomized controlled trials (RCTs) [17, 19, 26, 27, 29, 36, 38, 40, 41, 44–46]. Maksymowych's research [42] included a cross-sectional study and a cohort study. Most of the studies judged by two reviewers were low-risk, except for 2 cross-sectional studies [33, 37] and 1 cohort study [35] (shown in Supplementary Figure S1).

Table 2 Correlation between baseline CRP and MR DAS change

Study	Scoring method	Location	Number	Therapy	Scan interval	CRP	BASDAI	ASDAS	BASFI
Braun 2012 (40)	ASspiMRI-a	Spine	86	GOL	14w	−0.440 (0.001)	−0.060 (NS)	−0.300 (0.015)	0.010 (NS)
		Spine	86	GOL	104w	−0.400 (<0.001)	−0.160 (NS)	−0.330 (0.010)	−0.210 (NS)
Machado 2012 (19)	M-ASspiMRI-a	Spine	158	IFX/PBO	24w	−0.250 (0.002)	0.120 (0.132)	−0.140 (0.076)	–
		Spine	179	IFX/PBO	102w	−0.310 (0.001)	0.140 (0.063)	−0.150 (0.044)	–
Braun 2016 (38)	ASspiMRI-a	Spine	80	GOL	14w	−0.330 (0.046)	–	–	–
		Spine	66	GOL	104w	−0.330 (0.018)	–	–	–

The Spearman test for rank correlation is used for test of correlation; values are correlation coefficients (rho), if not otherwise indicated. *p*-values indicate the level of statistical significance. *AS*, ankylosing spondylitis; *ASDAS*, Ankylosing Spondylitis Disease Activity Score; *ASspiMRI-a*, ankylosing spondylitis spine MRI score for activity; *M-ASspiMRI-a*, modified ASspiMRI-a; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Score; *CRP*, C-reactive protein; *ESR*, erythrocyte sedimentation rate; *MRI*, magnetic resonance imaging; *NS*, not statistically significant; *SPARCC*, Spondyloarthritis Research Consortium of Canada Scoring System; *GOL*, golimumab; *IFX*, infliximab; *PBO*, placebo; –, not done

Meta-analysis

Correlation between CRP and MR DAS

A total of 1325 patients were included in the meta-analysis of CRP/MR DAS correlation. Subgroup analysis was conducted based on different MRI sites (842 patients in the spine subgroup, 483 patients in the SIJ subgroup). The correlation coefficient in the spine subgroup was calculated based on the data extracted from 8 studies [16, 17, 19, 32, 33, 36–38] (shown in Table 1). There was a modest correlation between CRP and spinal MR DAS ($r=0.226$, 95%CI [0.149, 0.291], $p <0.001$, $I^2=23\%$). In the SIJ subgroup, the pooled r of 6 studies [16, 17, 34–36, 39] indicated no statistically significant ($r=0.149$, 95%CI [−0.040, 0.327], $p=0.130$, $I^2=74\%$) (shown in Fig. 2A).

Correlation between baseline CRP and MR DAS change

There were 3 RCTs on the relationship between baseline CRP and spinal MR DAS change [19, 38, 40]. Data on the correlation between baseline CRP and SIJ MR DAS was not available. A total of 655 patients were included in the data synthesis (shown in Table 2). The result of the summary correlation showed that baseline CRP was negatively associated with spinal MR DAS change ($r = −0.327$, 95%CI [−0.397, −0.264], $p <0.001$, $I^2=0\%$) (shown in Fig. 2B). Subgroup analysis was conducted based on the follow-up period (<52 weeks or ≥52 weeks). A significant association was found in both short period subgroup ($r = −0.319$, 95%CI [−0.414, −0.217], $p<0.001$, $I^2=22\%$) and long period subgroup ($r = −0.336$, 95%CI [−0.430, −0.235], $p<0.001$, $I^2=0\%$) (shown in Fig. 2C).

Correlation between CRP change and MR DAS change

As for the relationship between CRP change and spinal MR DAS change, 8 studies [16, 19, 38, 40–44] and 833 patients were included (shown in Table 3). CRP change was significantly associated with spinal MR DAS change ($r=0.380$, 95%CI [0.310, 0.450], $p<0.001$, $I^2=50.6\%$). Subgroup analysis was conducted based on different scoring methods (SPARCC, ASspiMRI-a, Berlin). We found a modest correlation in the ASspiMRI-a subgroup ($r=0.354$, 95%CI [0.282, 0.422], $p<0.001$, $I^2=48\%$) and moderate association in the SPARCC subgroup ($r=0.544$, 95%CI [0.345, 0.701], $p<0.001$, $I^2=19\%$) (shown in Fig. 3A).

As for the relationship between CRP change and SIJ MR DAS change, 3 studies [16, 45, 46] and 340 patients were included (shown in Table 3). Subgroup analysis was conducted based on different scoring methods (SPARCC, Berlin). We found no association in the Berlin subgroup ($p=0.140$) and modest correlation in the SPARCC subgroup ($r=0.336$, 95%CI [0.207, 0.462], $p<0.001$, $I^2=0\%$) (shown in Fig. 3B).

Discussion

AxSpA is a chronic rheumatic disease that affects the function of axial and peripheral joints [47]. Inflammation is a critical early step in new syndesmophyte formation and structural remodeling in axSpA [48]. Sustained inflammation leads to irreversible skeleton damage and poor physical function and therefore should be monitored critically [49]. CRP and MRI are now widely used as objective tools to evaluate inflammation in axSpA. We conducted a systematic review and meta-analysis to analyze the correlation between CRP and MRI findings in patients with axSpA.

Table 3 Correlation between CRP change and MR DAS change

Study	Scoring method	Location	N	Therapy	Scan interval	CRP	ESR	BASDAI	ASDAS	BASMI	BASFI
Baraliakos 2005 (41)	ASspiMRI-a	Spine	40	ETN/PBO	48w	0.005 (NS)	0.016 (NS)	0.110 (NS)	–	–	–
Lambert 2007 (26) #	SPARCC	Spine	38	ADA	12w	$p=0.018$	–	NS	–	NS	–
		SIJ	38	ADA	12w	$p=0.590$	–	NS	–	NS	–
Maksymowych 2007 (42)	SPARCC	Spine	29	IFX/PBO	12/24w	0.650 (<0.001)	–	0.340 (NS)	–	–	–
Visvanathan 2008 (27) #	ASspiMRI-a	Spine	279	IFX/PBO	24w	$p<0.001$	–	—	–	–	–
Treitl 2008 (43)	ASspiMRI-a	Spine	11	IFX	24w	0.675 (<0.023)	–	0.831 (<0.001)	–	–	–
		Spine	11	IFX	48w	0.636 (<0.036)	–	0.369 (<0.001)	–	–	–
Marzo-Ortega 2009 (28) #	Leeds	Spine	76	NSAIDs/SSZ	12m	NS	–	NS	–	–	NS
Pedersen 2010 (16)	Berlin	SIJ	47–53	TNFa	22w	0.270 (NS)	–	0.310 (NS)	0.460 (<0.010)	–	–
		LS	47–53	TNFa	22w	0.250 (NS)	–	–0.050 (NS)	0.220 (NS)	–	–
Maksymowych 2010 (44)	SPARCC	Spine	36	IFX or PBO	12w	0.450 (0.012)	0.570 (0.001)	0.250 (NS)	–	–	0.160 (NS)
Song 2011 (29) #	Modified method	SIJ	76	ETN/SSZ	48w	NS	–	$p=0.040$	–	–	$p=0.007$
		Spine	76	ETN/SSZ	48w	NS	–	NS	–	NS	NS
Braun 2012 (40)	ASspiMRI-a	Spine	86	GOL	14w	0.450 (<0.001)	–	0.260 (<0.050)	0.350 (0.004)	–	0.190 (NS)
	ASspiMRI-a	Spine	86	GOL	104w	0.380 (<0.010)	–	0.110 (<NS)	0.220 (NS)	–	0.050 (NS)
Machado 2012 (19)	Modified ASspiMRI-a	Spine	158	IFX/PBO	24w	0.250 (0.002)	–	0.140 (0.090)	0.220 (0.006)	–	–
		Spine	179	IFX/PBO	102w	0.320 (<0.001)	–	0.140 (0.057)	0.230 (0.002)	–	–
Karpitschka 2013 (30) #	Lesions count	SIJ	10	ETN	52w	NS	–	0.009	–	–	NS
		Spine	10	ETN	52w	NS	–	0.001	–	–	0.003
		Enthesitis	10	ETN	52w	NS	–	NS	–	–	NS
Anja 2014 (45)	Berlin	SIJ (DD <4)	58	ETN/ADA	48w	0.040 (0.900)	–	0.370 (0.010)	–	–	0.400 (0.010)
		SIJ (DD ≥4)	54	ETN/ADA	48w	0.800 (0.010)	–	0.120 (0.500)	–	–	0.100 (0.700)
Maksymowych 2016 (46)	SPARCC	SIJ	94–97	ETN	12w	0.310 (<0.010)	–	0.270 (<0.010)	0.350 (<0.001)	0.070 (NS)	0.170 (NS)
		SIJ	88–90	ETN	48w	0.370 (<0.001)	–	0.420 (<0.001)	0.580 (<0.001)	0.140 (NS)	0.350 (<0.001)
Braun2016 (38)	ASspiMRI-a	Spine	79	GOL	14w	0.540 (<0.001)	–	–	–	–	–
		Spine	65	GOL	104w	0.370 (0.045)	–	–	–	–	–
Tang 2018 (31) #	SPARCC	SIJ	33	NSAIDs	24/48w	NS	NS	–	NS	–	–

The Spearman test for rank correlation is used for test of correlation; values are correlation coefficients (rho), if not otherwise indicated. *p*-values indicate the level of statistical significance. *ASDAS*, Ankylosing Spondylitis Disease Activity Score; *ASspiMRI-α*, ankylosing spondylitis spine MRI score for activity; *BASDAI*, Bath Ankylosing Spondylitis Disease Activity Score; *NS*, not statistically significant; *SPARCC*, Spondyloarthritis Research Consortium of Canada Scoring System; *LS*, lumbar spine; *N*, number; *DD*, disease duration; *IFX*, infliximab; *SSZ*, sulfasalazine; *ADA*, adalimumab; *ETN*, etanercept; *GOL*, golimumab; *IFN*, infliximab; *PBO*, placebo; *NSAIDs*, non-steroidal anti-inflammatory drugs; *y*, year; *m*, month; *w*, week; –, not done

#specific *r* values were not available

A

Study or Subgroup	Fisher'Z	SE	Weight	Fisher'Z IV, Random, 95% CI
1.1.1 ASspiMRI-a method				
Baraliakos 2005	0.00500004	0.16439899	6.8%	0.01 [-0.32, 0.33]
Treitl 2008(24w)	0.81987163	0.35355339	2.0%	0.82 [0.13, 1.51]
Treitl 2008(48w)	0.75142783	0.35355339	2.0%	0.75 [0.06, 1.44]
Braun 2012(14w)	0.48470028	0.10976426	10.8%	0.48 [0.27, 0.70]
Braun 2012(104w)	0.40005965	0.10976426	10.8%	0.40 [0.18, 0.62]
Machado 2012(24w)	0.25541281	0.08032193	13.7%	0.26 [0.10, 0.41]
Machado 2012(102w)	0.33164711	0.07537784	14.3%	0.33 [0.18, 0.48]
Braun2016(14w)	0.6041556	0.11470787	10.3%	0.60 [0.38, 0.83]
Braun2016(104w)	0.3884231	0.12700013	9.3%	0.39 [0.14, 0.64]
Subtotal (95% CI)			80.1%	0.38 [0.27, 0.50]

Heterogeneity: Tau² = 0.01; Chi² = 15.36, df = 8 (P = 0.05); I² = 48%
Test for overall effect: Z = 6.64 (P < 0.00001)

1.1.2 Berlin method				
Pedersen 2010	0.25541281	0.14142136	8.3%	0.26 [-0.02, 0.53]
Subtotal (95% CI)			8.3%	0.26 [-0.02, 0.53]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)

1.1.3 SPARCC method				
Maksymowych 2007	0.77529871	0.19611613	5.3%	0.78 [0.39, 1.16]
Maksymowych 2010	0.48470028	0.17407766	6.3%	0.48 [0.14, 0.83]
Subtotal (95% CI)			11.7%	0.62 [0.33, 0.90]

Heterogeneity: Tau² = 0.01; Chi² = 1.23, df = 1 (P = 0.27); I² = 19%
Test for overall effect: Z = 4.26 (P < 0.0001)

Total (95% CI)			100.0%	0.40 [0.30, 0.51]

Heterogeneity: Tau² = 0.01; Chi² = 20.64, df = 11 (P = 0.04); I² = 47%
Test for overall effect: Z = 7.59 (P < 0.00001)
Test for subgroup differences: Chi² = 3.34, df = 2 (P = 0.19), I² = 40.1%

Favours [experimental]　Favours [control]

B

Study or Subgroup	Fisher'Z	SE	Weight	Fisher'Z IV, Random, 95% CI
1.1.1 SPARCC method				
Maksymowych 2016(12w)	0.32054541	0.10369517	20.8%	0.32 [0.12, 0.52]
Maksymowych 2016(48w)	0.3884231	0.10783277	20.7%	0.39 [0.18, 0.60]
Subtotal (95% CI)			41.5%	0.35 [0.21, 0.50]

Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 1 (P = 0.65); I² = 0%
Test for overall effect: Z = 4.72 (P < 0.00001)

1.1.2 Berlin method				
Pedersen 2010	0.27686382	0.14142136	19.4%	0.28 [-0.00, 0.55]
Anja 2014(DD<4y)	0.04002135	0.13483997	19.6%	0.04 [-0.22, 0.30]
Anja 2014(DD≥4y)	1.09861229	0.14002801	19.4%	1.10 [0.82, 1.37]
Subtotal (95% CI)			58.5%	0.47 [-0.16, 1.10]

Heterogeneity: Tau² = 0.29; Chi² = 32.18, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.47 (P = 0.14)

Total (95% CI)			100.0%	0.42 [0.11, 0.74]

Heterogeneity: Tau² = 0.11; Chi² = 33.37, df = 4 (P < 0.00001); I² = 88%
Test for overall effect: Z = 2.64 (P = 0.008)
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

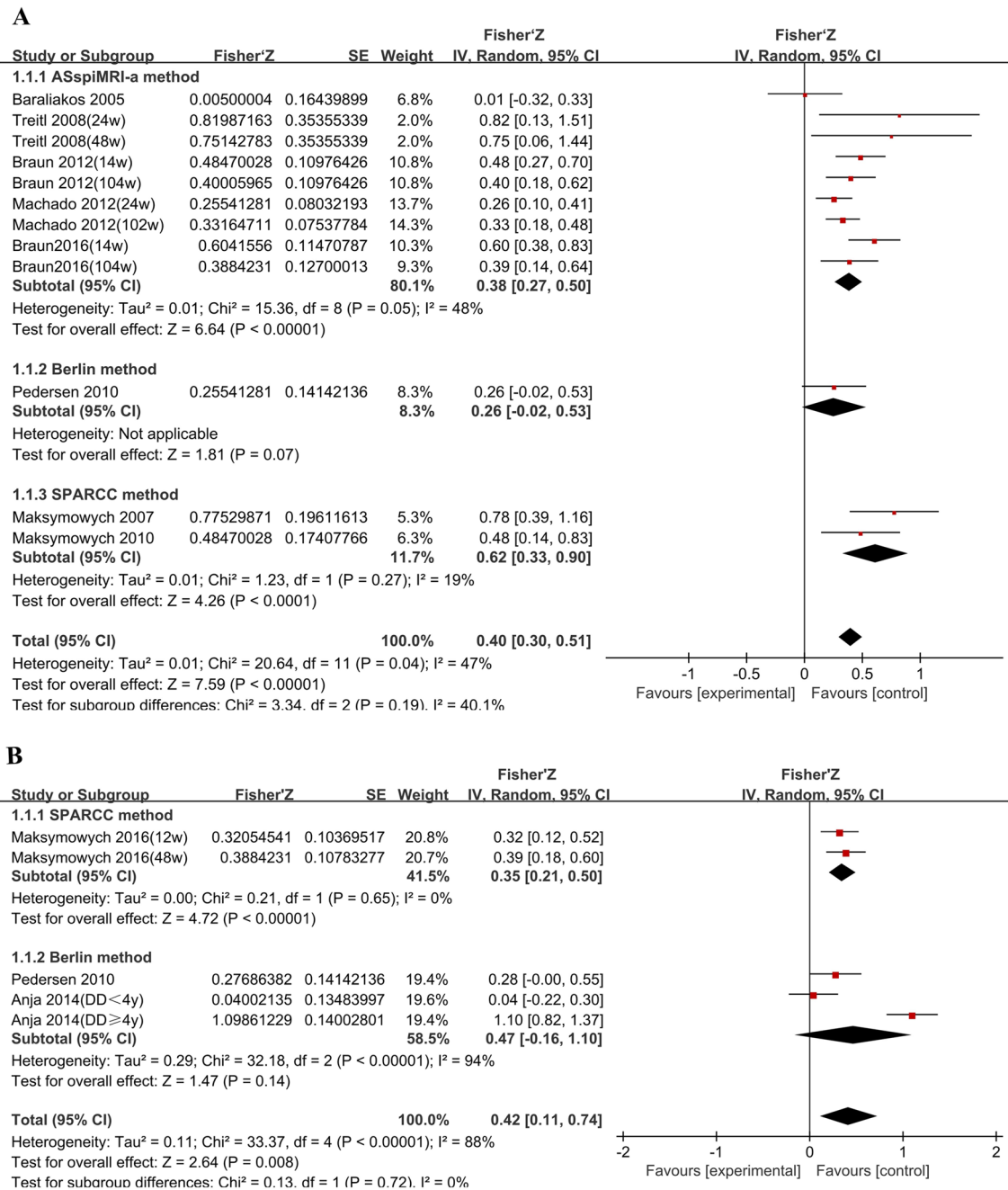Favours [experimental]　Favours [control]

Fig. 3 **A** Correlation between CRP change and MR DAS change (spine). **B** Correlation between CRP change and MR DAS change (SIJ)

Our results illustrated that CRP correlated with spinal MR DAS. We found a modest association between CRP and spinal MR DAS ($r=0.226$, $I^2=23\%$), and a moderate correlation between CRP change and spinal MR DAS change (ASspiMRI, $r=0.354$, $I^2=48\%$; SPARCC, $r=0.544$, $I^2=19\%$). Although CRP is closely related to inflammation, some studies reported that CRP might not be elevated in active axSpA [6, 18]. MRI studies have contributed to detecting spinal inflammation, even minor fluid collections such as BME.

However, it is not feasible in most settings and is too costly to repeat MRIs frequently [9]. Given the lack of evidence that obtaining an MRI in stable patients improves clinical outcomes, the American College of Rheumatology (ACR) and the Spondylitis Association of America (SAA) recommended against obtaining an MRI regularly in axSpA [50]. Our results confirmed the correlation between CRP and spinal MR DAS. We speculated that CRP was a valid index to evaluate spinal inflammation in axSpA patients. Considering

the feasibility of daily clinical practice, CRP is a reliable indicator for evaluating spinal inflammation.

Although our results illustrated the relationship between CRP and spinal MR DAS, we did not find a statistical correlation between CRP and SIJ MR DAS (r=0.149, I^2=74%). It was reported that BME could be detected by SIJ MRI in a sizable proportion of CRP-negative SpA patients [18]. According to our results, MRI may provide additional information on SIJ inflammation in axSpA. We recommend SIJ MRI follow-up, especially in patients with unrelieved clinical manifestations such as low back pain, stiffness, and fatigue. Considering the high heterogeneity of studies included in analyzing the correlation between CRP and SIJ MRI, we look forward to more studies with relatively low heterogeneity to be included in the future.

We also identified a negative correlation between baseline CRP and spinal MRI improvement ($r = -0.327$, I^2=0%). Our results provided valuable information that CRP may predict disease progression in axSpA. We speculated that residual inflammation might exist in axSpA patients with elevated CRP at baseline. In line with our hypothesis, it was reported that CRP could predict subsequent structural remodeling [51–53]. Consequently, we suggested that patients with elevated CRP at baseline needed more robust anti-inflammatory treatment or early initiation of biologicals. Long-term administration of biologics might be necessary for patients with high CRP levels at baseline.

To our knowledge, this is the first systematic review with meta-analysis to investigate the correlation between CRP and MR DAS in axSpA patients. Most studies included in our meta-analysis showed low-to-moderate heterogeneity (shown in Figs. 2 and 3), and some studies (those analyzed for baseline CRP and spinal MR DAS change) had even no heterogeneity (shown in Fig. 2). However, a few studies (those analyzed for CRP and SIJ MR DAS, CRP change, and SIJ MR DAS change) showed high heterogeneity. This may be due to differences in scoring methods and disease duration of patients among the studies. We therefore used subgroup analysis (e.g., SPARCC method versus Berlin method) and random-effect models to reduce heterogeneity. Our study confirmed that CRP is not only a valid indicator for spinal inflammation, but also a predictive parameter for disease course. Our work shed new light on the added value of CRP in diagnosis and disease monitoring.

It should be noted that this meta-analysis also has several limitations. First, different scoring methods are widely used to quantify inflammation in axSpA, and the issue remains about which could be more related to pathological manifestation. It is disputable whether SIJ or spinal inflammation assessment requires all slices/disco-vertebral units (DVUs) or the most heavily involved slices/DVUs. Hence, any scoring method can only be used as a semi-quantitative tool rather than a gold standard. Second, there should be an extensive focus on the disease duration. Anja et al. [45] reported that MR DAS change in SIJ was associated with CRP change in patients with disease duration longer than 4 years. However, there are not enough studies to stratify patients and sufficient evidence may be needed to validate it. Finally, we did not add study types to the inclusion criteria due to the limited number of studies concerning CRP and MRI in axSpA, which led to high heterogeneity in the correlation analysis between CRP and SIJ MR DAS.

In summary, CRP could be a reasonable index to reflect spinal inflammation, while SIJ MRI may be necessary to repeat providing additional information in the short term.

Conclusions

This systematic review and meta-analysis preliminarily explored the relationship between CRP and MR DAS. The available evidence is in favor of CRP as an indicator and predictive parameter for spinal inflammatory lesions in axSpA. Nevertheless, SIJ MRI seems to be indispensable in disease monitoring.

Declarations

Ethics approval and consent to participate Not applicable

Consent for publication All authors gave consent to publish.

Disclosures None.

Competing interests The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Sieper J, Poddubnyy D (2017) Axial spondyloarthritis. Lancet (London, England) 390(10089):73–84

2. van der Heijde D, Ramiro S, Landewé R, Baraliakos X, Van den Bosch F, Sepriano A et al (2017) 2016 update of the ASAS-EULAR management recommendations for axial spondyloarthritis. Ann Rheum Dis 76(6):978–991

3. Benhamou M, Gossec L, Dougados M (2010) Clinical relevance of C-reactive protein in ankylosing spondylitis and evaluation of the NSAIDs/coxibs' treatment effect on C-reactive protein. Rheumatology (Oxford, England) 49(3):536–541

4. Mandl P, Navarro-Compán V, Terslev L, Aegerter P, van der Heijde D, D'Agostino MA et al (2015) EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis 74(7):1327–1339

5. Baraliakos X, Szumski A, Koenig AS, Jones H (2019) The role of C-reactive protein as a predictor of treatment response in patients with ankylosing spondylitis. Semin Arthritis Rheum 48(6):997–1004

6. Landewé R, Nurminen T, Davies O, Baeten D (2018) A single determination of C-reactive protein does not suffice to declare a patient with a diagnosis of axial spondyloarthritis 'CRP-negative'. Arthritis Res Ther 20(1):209

7. Pedersen SJ, Poddubnyy D, Sørensen IJ, Loft AG, Hindrup JS, Thamsborg G et al (2016) Course of magnetic resonance imaging-detected inflammation and structural lesions in the sacroiliac joints of patients in the randomized, double-blind, placebo-controlled Danish multicenter study of adalimumab in spondyloarthritis, as assessed by the Berlin and Spondyloarthritis Research Consortium of Canada Methods. Arthritis Rheumatol (Hoboken, NJ) 68(2):418–429

8. van der Heijde D, Baraliakos X, Hermann KA, Landewé RBM, Machado PM, Maksymowych WP et al (2018) Limited radiographic progression and sustained reductions in MRI inflammation in patients with axial spondyloarthritis: 4-year imaging outcomes from the RAPID-axSpA phase III randomised trial. Ann Rheum Dis 77(5):699–705

9. Maksymowych WP (2019) The role of imaging in the diagnosis and management of axial spondyloarthritis. Nat Rev Rheumatol 15(11):657–672

10. Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Williams M, Stone M et al (2005) Spondyloarthritis research Consortium of Canada magnetic resonance imaging index for assessment of sacroiliac joint inflammation in ankylosing spondylitis. Arthritis Rheum 53(5):703–709

11. Maksymowych WP, Inman RD, Salonen D, Dhillon SS, Krishnananthan R, Stone M et al (2005) Spondyloarthritis Research Consortium of Canada magnetic resonance imaging index for assessment of spinal inflammation in ankylosing spondylitis. Arthritis Rheum 53(4):502–509

12. Braun J, Baraliakos X, Golder W, Brandt J, Rudwaleit M, Listing J et al (2003) Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis, before and after successful therapy with infliximab: evaluation of a new scoring system. Arthritis Rheum 48(4):1126–1136

13. Althoff CE, Sieper J, Song IH, Haibel H, Weiß A, Diekhoff T et al (2013) Active inflammation and structural change in early active axial spondyloarthritis as detected by whole-body MRI. Ann Rheum Dis 72(6):967–973

14. Baraliakos X, Braun J (2016) Imaging scoring methods in axial spondyloarthritis. Rheum Dis Clin North Am 42(4):663–678

15. Landewé RB, Hermann KG, van der Heijde DM, Baraliakos X, Jurik AG, Lambert RG et al (2005) Scoring sacroiliac joints by magnetic resonance imaging. A multiple-reader reliability experiment. J Rheumatol 32(10):2050–2055

16. Pedersen SJ, Sørensen IJ, Hermann KG, Madsen OR, Tvede N, Hansen MS et al (2010) Responsiveness of the Ankylosing Spondylitis Disease Activity Score (ASDAS) and clinical and MRI measures of disease activity in a 1-year follow-up study of patients with axial spondyloarthritis treated with tumour necrosis factor alpha inhibitors. Ann Rheum Dis 69(6):1065–1071

17. Rudwaleit M, Schwarzlose S, Hilgert ES, Listing J, Braun J, Sieper J (2008) MRI in predicting a major clinical response to anti-tumour necrosis factor treatment in ankylosing spondylitis. Ann Rheum Dis 67(9):1276–1281

18. Brown MA, Bird PA, Robinson PC, Mease PJ, Bosch FVD, Surian C et al (2018) Evaluation of the effect of baseline MRI sacroiliitis and C reactive protein status on etanercept treatment response in non-radiographic axial spondyloarthritis: a post hoc analysis of the EMBARK study. Ann Rheumatic Dis 77(7):1091–1093

19. Machado P, Landewé RB, Braun J, Baraliakos X, Hermann KG, Hsu B et al (2012) MRI inflammation and its relation with measures of clinical disease activity and different treatment responses in patients with ankylosing spondylitis treated with a tumour necrosis factor inhibitor. Ann Rheum Dis 71(12):2002–2005

20. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ (Clinical research ed). 339:b2535

21. van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 27(4):361–368

22. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J et al (2009) The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 68(6):777–783

23. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al (2011) QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Int Med 155(8):529–536

24. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Stats Med 21(11):1539–1558

25. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ (Clinical research ed). 327(7414):557–560

26. Lambert RG, Salonen D, Rahman P, Inman RD, Wong RL, Einstein SG et al (2007) Adalimumab significantly reduces both spinal and sacroiliac joint inflammation in patients with ankylosing spondylitis: a multicenter, randomized, double-blind, placebo-controlled study. Arthritis Rheum 56(12):4005–4014

27. Visvanathan S, Wagner C, Marini JC, Baker D, Gathany T, Han J et al (2008) Inflammatory biomarkers, disease activity and spinal disease measures in patients with ankylosing spondylitis after treatment with infliximab. AnnRheum Dis 67(4):511–517

28. Marzo-Ortega H, McGonagle D, O'Connor P, Hensor EM, Bennett AN, Green MJ et al (2009) Baseline and 1-year magnetic resonance imaging of the sacroiliac joint and lumbar spine in very early inflammatory back pain. Relationship between symptoms, HLA-B27 and disease extent and persistence. Ann Rheum Dis 68(11):1721–1727

29. Song IH, Hermann K, Haibel H, Althoff CE, Listing J, Burmester G et al (2011) Effects of etanercept versus sulfasalazine in early axial spondyloarthritis on active inflammatory lesions as detected by whole-body MRI (ESTHER): a 48-week randomised controlled trial. Ann Rheum Dis 70(4):590–596

30. Karpitschka M, Godau-Kellner P, Kellner H, Horng A, Theisen D, Glaser C et al (2013) Assessment of therapeutic response in ankylosing spondylitis patients undergoing anti-tumour necrosis factor therapy by whole-body magnetic resonance imaging. Eur Radiol 23(7):1773–1784

31. Tang M, Xue L, Shen Y, Bo L, Yang R, Wen J et al (2018) Efficacy of long-term nonsteroidal antiinflammatory drug treatment on magnetic resonance imaging-determined bone marrow oedema in early, active axial spondyloarthritis patients. Clin Rheumatol 37(1):245–250

32. Kiltz U, Baraliakos X, Karakostas P, Igelmann M, Kalthoff L, Klink C et al (2012) The degree of spinal inflammation is similar in patients with axial spondyloarthritis who report high or low levels of disease activity: a cohort study. Ann Rheum Dis 71(7):1207–1211

33. Konca S, Keskin D, Cılız D, Bodur H, Sakman B (2012) Spinal inflammation by magnetic resonance imaging in patients with ankylosing spondylitis: association with disease activity and outcome parameters. Rheumatol Int 32(12):3765–3770

34. Soliman E, Labib W, El-Tantawi G, Hamimy A, Alhadidy A, Aldawoudy A (2012) Role of matrix metalloproteinase-3 (MMP-3) and magnetic resonance imaging of sacroiliitis in assessing disease activity in ankylosing spondylitis. Rheumatol Int 32(6):1711–1720

35. Van Praet L, Jans L, Carron P, Jacques P, Glorieus E, Colman R et al (2014) Degree of bone marrow oedema in sacroiliac joints of patients with axial spondyloarthritis is linked to gut inflammation and male sex: results from the GIANT cohort. Ann Rheum Dis 73(6):1186–1189

36. van der Heijde D, Sieper J, Maksymowych WP, Brown MA, Lambert RG, Rathmann SS et al (2014) Spinal inflammation in the absence of sacroiliac joint inflammation on magnetic resonance imaging in patients with active nonradiographic axial spondyloarthritis. Arthritis Rheumatol (Hoboken, NJ) 66(3):667–673

37. MacKay JW, Aboelmagd S, Gaffney JK (2015) Correlation between clinical and MRI disease activity scores in axial spondyloarthritis. Clin Rheumatol 34(9):1633–1638

38. Braun J, Baraliakos X, Hermann KG, Xu S, Hsu B (2016) Serum C-reactive protein levels demonstrate predictive value for radiographic and magnetic resonance imaging outcomes in patients with active ankylosing spondylitis treated with golimumab. J Rheumatol 43(9):1704–1712

39. Kang KY, Jung JY, Hong YS, Ju JH, Park SH (2017) Positive correlation between inflammation on sacroiliac joint MRI and serum C-terminal telopeptide of type-I collagen in ankylosing spondylitis but not in non-radiographic axial spondyloarthritis. Clin Exp Rheumatol 35(3):415–422

40. Braun J, Baraliakos X, Hermann KG, van der Heijde D, Inman RD, Deodhar AA et al (2012) Golimumab reduces spinal inflammation in ankylosing spondylitis: MRI results of the randomised, placebo-controlled GO-RAISE study. Ann Rheum Dis 71(6):878–884

41. Baraliakos X, Davis J, Tsuji W, Braun J (2005) Magnetic resonance imaging examinations of the spine in patients with ankylosing spondylitis before and after therapy with the tumor necrosis factor alpha receptor fusion protein etanercept. Arthritis Rheum 52(4):1216–1223

42. Maksymowych WP, Dhillon SS, Park R, Salonen D, Inman RD, Lambert RG (2007) Validation of the spondyloarthritis research consortium of Canada magnetic resonance imaging spinal inflammation index: is it necessary to score the entire spine? Arthritis Rheum 57(3):501–507

43. Treitl M, Korner M, Becker-Gaab C, Tryzna M, Rieger J, Pfeifer KJ et al (2008) Magnetic resonance imaging assessment of spinal inflammation in patients treated for ankylosing spondylitis. J Rheumatol 35(1):126–136

44. Maksymowych WP, Salonen D, Inman RD, Rahman P, Lambert RG (2010) Low-dose infliximab (3 mg/kg) significantly reduces spinal inflammation on magnetic resonance imaging in patients with ankylosing spondylitis: a randomized placebo-controlled study. J Rheumatol 37(8):1728–1734

45. Weiß A, Song IH, Haibel H, Listing J, Sieper J (2014) Good correlation between changes in objective and subjective signs of inflammation in patients with short-but not long duration of axial spondyloarthritis treated with tumor necrosis factor-blockers. Arthritis Res Ther 16(1):R35

46. Maksymowych WP, Dougados M, van der Heijde D, Sieper J, Braun J, Citera G et al (2016) Clinical and MRI responses to etanercept in early non-radiographic axial spondyloarthritis: 48-week results from the EMBARK study. Ann Rheum Dis 75(7):1328–1335

47. Braun J, Kiltz U, Baraliakos X (2022) Significance of structural changes in the sacroiliac joints of patients with axial spondyloarthritis detected by MRI related to patients symptoms and functioning. Ann Rheum Dis 81(1):11–14

48. Baraliakos X, Heldmann F, Callhoff J, Listing J, Appelboom T, Brandt J et al (2014) Which spinal lesions are associated with new bone formation in patients with ankylosing spondylitis treated with anti-TNF agents? A long-term observational study using MRI and conventional radiography. Ann Rheum Dis 73(10):1819–1825

49. Braun J, Baraliakos X, Kiltz U (2021) Treat-to-target in axial spondyloarthritis - what about physical function and activity? Nat Rev Rheumatol 17(9):565–576

50. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA et al (2019) 2019 update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis. Arthritis Rheumatol (Hoboken, NJ). 71(10):1599–1613

51. Blachier M, Canouï-Poitrine F, Dougados M, Lethuaut A, Fautrel B, Ferkal S et al (2013) Factors associated with radiographic lesions in early axial spondyloarthritis. Results from the DESIR cohort. Rheumatology (Oxford, England) 52(9):1686–1693

52. Poddubnyy D, Rudwaleit M, Haibel H, Listing J, Märker-Hermann E, Zeidler H et al (2011) Rates and predictors of radiographic sacroiliitis progression over 2 years in patients with axial spondyloarthritis. Ann Rheum Dis 70(8):1369–1374

53. Deminger A, Klingberg E, Geijer M, Göthlin J, Hedberg M, Rehnberg E et al (2018) A five-year prospective study of spinal radiographic progression and its predictors in men and women with ankylosing spondylitis. Arthritis Res Ther 20(1):162