Published in final edited form as:
Spine (Phila Pa 1976). 2014 March 15; 39(6): 469–475. doi:10.1097/BRS.0000000000000181.

Correlation of pain with objective quantification of MR images in older adults with chronic low back pain

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Abstract

Study Design—Cross sectional study.

Objective—The goal of this study is to identify relationships between objectively measured and subjectively scored parameters and reported pain.

Summary of Background Data—Studies have demonstrated the unreliability of MRI based parameters to identify pathological pain generators of chronic low back pain patients, but they were based on visual inspection and subjective assessment of lumbar disc features. Advancements in computer image analysis provide objective measurements of lumbar disc features.

Methods—Two radiologists evaluated 39 axial and sagittal T1 and T2 weighted MRI images of chronic axial low back pain patients (age > 65 years) and graded 4 subjective lumbar disc parameters (T2 signal intensity, nucleus shape, Modic changes, and osteophyte formation) whose sum is the cumulative MRI score. Objective parameter, MRIindex, was calculated as the product of the measured lumbar disc area and total disc MRI signal intensity. Discs were sorted from least to most degenerated relative to each parameter. Pearson correlation coefficient and multiple linear regression analysis were performed between the reported pain score and each parameter.

Results—The most and least degenerated discs in each patient, as assessed by MRIindex, had the highest negative and positive correlation coefficient and regression weight contribution

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Level of Evidence: N/A

respectively. All subjective parameters had low correlation coefficients and regression goodness of fit.

Conclusion—Although limited by small sample size, the objective parameter, MRIindex, can be a potential imaging biomarker used to identify possible pain generators. This study presents a potential new application of MR imaging in identifying pain generators of chronic low back pain patients.

Keywords

MRI; lumbar spine; Low back pain; objective parameter; subjective parameter; correlations; image segmentation; pain score; MRI grading; geriatric population

Introduction

Chronic low back pain (CLBP), is among the most important factors influencing the physical health of individuals over 65 years [1] and affects around 25% of the population over 70 years[2]. Correct identification of CLBP generators is essential in guiding the path of intervention. Currently, interventions are planned based on various clinical examinations[3,4], such as qualitative assessment on magnetic resonance imaging (MRI) of the lumbar spine which does not reliably predict pain or response to treatment.

MRI grading methods target different aspects of qualitative changes in intervertebral disc degeneration (IDD). Pathological changes on MR images of patients with IDD include loss of T2-weighted signal [5–7], changes in vertebral-body marrow adjacent to the end plates [5,8], osteophyte formation [5,9,10], and changes in the nucleus pulposus (NP) shape [5,7].

While IDD is one of the most prevalent contributors to CLBP [5,11,12], these imaging changes have proven to be ubiquitous and do not correlate well with patient's symptoms[13–19,21], particularly in older adults. Additionally, there is a high prevalence of abnormal radiographic findings in asymptomatic patients[20,21]. These qualitative measures do not reliably identify pathological pain generators in patients with CLBP.

Advancements in image analysis algorithms such as image segmentation and feature extraction[22–24] provide a more quantitative and objective assessment of changes in imaging identified pathology. Computer algorithms can be used to calculate objective parameters attributed to the lumbar IDD such as disc area and total disc signal intensity. The goal of this study is to identify relationships between these objective parameters and the pain reported by CLBP patients. The objectives of this study are to: 1) compare the correlations of subjective (graded) and objective (calculated) MRI parameters to the patient's reported pain score, 2) establish a regression model relating these objective parameters to the pain score, and 3) assess the sensitivity of these objective parameters to variations in the pain score.

Materials and Methods

Subject Recruitment

Older adults with age greater or equal to 65 years and suffering from CLBP, defined as primary axial low back pain, back pain that is more severe than pain in other parts of the body, every day or almost every day for at least the past 3 months, were screened for this study. Subjects were recruited through Pepper Center, Department of Physical Medicine and Rehabilitation, and University of Pittsburgh Alumni registries as well as advertisements in the clinics. Thirty nine out of 143 participants were consented for the study after screening. Reasons for ineligibility included declined consent (33), patients who cancelled after scheduling (12), lack of back pain every day (or nearly every day) for at least the past 3 months (18), previous back surgery (9), back pain traveling into the legs (10), osteoarthritis of the knee or hip (8), pain elsewhere more severe than low back pain (1), unable to have MRI (13). The average age for those who participated was 78.9 ± 6.7 years with 22 males and 17 females.

Additionally, four healthy asymptomatic control participants without chronic low back pain with age ranging between 25 and 45 years were recruited for this study to build the probability disc atlas for automatic segmentation (see below for details).

Data Collection

MRI scans on the lumbar spine were collected from each participant on a 3T Siemens magnet with a rectangular flat surface coil. The sequences obtained were sagittal and axial T1 and T2 weighted images. The sequence parameters were: for sagittal T2, TR/TE = 3500msec /99msec, number of slices = 23; for axial T2, TR/TE=5800msec / 97msec, number of slices 8 per disc; for sagittal T1, TR/TE=694msec / 10msec, number of slices 23; for axial T1, TR/TE = 676msec / 9.8msec, number of slices 8 per disc. For all sequences the slice thickness was 3mm with 3mm gap spacing.

Two clinical radiologists examined and graded the images of the five lumbar discs following guidelines listed in Benneker et al 2005. Seven disc features each were graded from 0 (healthy) to 3 (pathologic). The features consisted of T2 signal intensity loss, DEBIT score (intact, bulged, protrusion or extrusion/sequestration) [25], nucleus pulposus shape [7], annular tears [26], Modic changes (normal, types I–III) [27], endplate integrity and osteophyte formation. In their 2005 study, Benneker et al found that four main features (T2 signal intensity loss, nucleus pulposus shape, Modic changes and osteophytes) significantly correlated with morphological grades of degeneration as assessed by a five level Pfirmann grading[28]. Hence, Benneker et al calculated a cumulative MRI score (CMS) as the sum of these four main features, which also correlated with the Pfirmann grading [28]. Since in the Benneker study the CMS and the four main features were the only features to display a significant correlation, our study will present results specifically relating to these features. Thus each disc has five different scores (CMS, T2 signal intensity loss, nucleus pulposus shape, Modic changes, and osteophytes) which were considered as subjective parameters determined by the radiologist.

In addition, lumbar discs from L1–L2 to L5-S1 were segmented according to atlas based segmentation using fuzzy c-means algorithm[29,30]. The segmentation was visually inspected to ensure proper identification of the discs. Figure 1 shows the image segmentation in white of five lumbar discs from one participant. After disc segmentation, the disc area and the sum of the pixel intensities (sum(Int)) were calculated for each segmented region (disc). Additionally, an MRIindex parameter was calculated as the product of the disc's area and sum(Int). This value has been used in animal models of disc degeneration[31,32], where lower values indicate a degenerated disc while higher values indicate a healthy disc. Thus for every lumbar disc three objective parameters were calculated: disc area, sum(Int), and MRIindex. These parameters are considered objective since they were calculated using a computer algorithm.

It should be noted that subjective and objective parameters consider both the structural and content changes in the disc. The disc area, osteophyte formation, Modic changes, and shape of nucleus pulposus related to disc structure, while sum(Int) and T2signal related to disc content. Even thou these parameters target both structural and content changes, there is a possibility that they target different aspects of these changes.

Finally, on the same day as the MRI scan, participants reported their low back pain intensity on a pain thermometer which is a vertical verbal descriptor scale from 0 (no pain) to 10 (most pain you have experienced). This pain grading scale is reliable and valid in older adults[33].

Variable Construction

For subject parameters, since the pain generator might not be level specific, the discs of each participant were ordered relative to decreasing CMS. If two discs had the same CMS, then they were ordered in decreasing order of T2 signal intensity loss. Moreover, if two discs had the same CMS and T2 signal intensity loss, then the discs were ordered in decreasing order of nucleus shape, modic changes and osteophyte formation consecutively. An example of this ordering is shown in Table 1 for one participant. The discs were placed in decreasing order of subjective parameters to reflect a decreasing amount of disc degeneration. In other words, the first disc is the most degenerated and the last disc is the least degenerated.

Due to variability in MRI images between participants, and since the images lacked a phantom, each objective parameter was normalized to its total value across the five discs. For example in each subject, %Area parameter for each disc was calculated as the area of that disc divided by the sum of all disc areas in that subject. Similarly, the objective parameters %Sum(Int) and %MRIindex for each disc were calculated as a percentage of the total sum(Int) and total MRIindex across all discs for each subject respectively (Figure 1). Thus this parameter is a disc degeneration parameter relative to the entire spine of each subject. It should be noted that mathematically speaking, it is possible that all discs within a subject will have 20% of a given objective parameter (for example %sum(Int)), but that would imply that 1) all discs have the same amount of degeneration which is highly unlikely and 2) it will be extremely difficult to find the source of pain if related to disc degeneration. The objective parameters for each subject were placed in increasing order reflecting a

decrease in amount of disc degeneration, with the first disc representing the most degenerated disc, and the last disc the least degenerated.

Statistical Analysis

To examine the relationship of each disc, ranked by degree of degeneration via objective or subjective parameters, to the participant's reported pain, Pearson product-moment correlation coefficient were calculated for each disc between the parameter and the pain score. To assess the contribution of all discs simultaneously to pain, a series of 8 multiple linear regression analyses were conducted in each model with pain as the dependent variable, and each of the objective/subjective measures from five discs as predictor variable. The goodness of fit for each model was assessed with the coefficient of determination (R^2) indicating the proportion of variability in pain explained by each objective/subjective measure from the five discs.

Despite the validity of the thermometer pain scale in older adults, it is still a subjective value given by the participants. A sensitivity analysis was conducted between the reported pain score and the %MRIindex to test how variations in participant's reported pain affect the correlation with this objective parameter. This analysis was conducted to ensure that these slight variations in the reporting of the subjective pain score would not dramatically alter the regression relationship. The multiple linear regression model described above was repeated after pain score was randomly shifted by ±1, ±2, ±3, ±4, and randomly selected for each participant.

Matlab Version 7.11 (MathWorks, Natick, Massachusetts) was used for all data processing and statistical analyses.

Results

The average %MRIindex is shown as white bars in Figure 2 for the discs ordered relative to increasing %MRIindex. The corresponding average %Area and average %Sum(Int) for these discs are shown as black and grey bars respectively. The increase in %MRIindex is attributed to an increase in both %Area (disc structure) and %Sum(Int) (disc content) with more contribution from the latter. This increase is not level dependent since discs from all anatomical lumbar levels are distributed across the five categories as sorted by the %MRIindex. The top section of Table 2 illustrates the distribution of 195 discs (39 participants x 5 discs each) as sorted by the %MRIindex. Sorting the discs according to the subjective CMS was not level dependent either as illustrated in the bottom section of Table 2.

Correlations

The reported pain score ranged from 0 to 9 with an average ± standard deviation of 4.0 ± 2.1. To compare the correlation with pain score between objective (computer generated) and subjective (grading scores) parameters, the results of Pearson correlation calculations are presented in Table 3. The %MRIindex had the highest correlations. The least degenerated discs had the highest positive correlation ($\rho = 0.47$), and the second most degenerated disc had the highest negative correlation ($\rho = -0.48$). The most degenerated disc also had a

moderate but statistically significant negative correlation ($\rho = -0.32$). Meanwhile, the second highest positive and negative correlation was attributed to %Sum(Int) (least degenerated, $\rho = 0.42$ and second most degenerated $\rho = -0.42$) both p-value <0.05. All the other objective and subjective parameters had correlations that were lower than %MRIindex or %Sum(Int) and ranged from −0.29 to 0.39.

Regression Analyses

The average R^2 representing the multiple linear regression models' goodness of fit, the proportion of variability explained by the predictors, and the estimated regression coefficients for both objective and subjective parameters are presented in Table 4. The greatest R^2 corresponding to the best regression fit was attributed to %MRIindex ($R^2 = 0.43$) followed by %Sum(Int) ($R^2 = 0.39$). For %MRIIndex, the greatest positive regression coefficient was attributed to the least degenerated disc (0.16±0.09), while the second most degenerated disc had the greatest negative regression coefficient (−0.16±0.18).

Sensitivity Results

With zero shifts in pain score, the R^2 was 0.3070. Shifting the pain score by one point did not cause a significant change ($R^2 = 0.3014$) relative to the zero pain score shift. Meanwhile, subsequent shifts of two, three and four points significantly ($p<0.05$) decreased the goodness of fit to 0.2507, 0.2034 and 0.1721 respectively.

Discussion

This study explored the presence of objective MR imaging features of the lumbar spine and their correlation with the pain reported by older adults with CLBP. Overall, more degenerated discs as assessed by %MRIindex had more negative correlation with pain suggesting lower contributions to overall pain, and less degenerated discs had more positive correlation with pain, suggesting greater contributions to overall pain. For each participant's image, the least degenerated and the second most degenerated discs as assessed by %MRIindex had the highest positive and negative correlations respectively with the reported pain. Moreover, multiple linear regression models demonstrated that the same discs had the largest positive and negative independent contributions respectively to the participant's reported pain. This model was sensitive to shifts in pain score of at least two points. Meanwhile all subjective parameters such as cumulative MRI score, T2 signal intensity loss, nucleus shape, Modic changes, and osteophyte formation as graded by the radiologists had low correlations with pain.

The correlation values for %Sum(Int) were close to %MRIindex, but the %Sum(Int) only captures one aspect of the disc which is related to the biochemical composition of the disc. Since the %MRIindex includes both biologic and geometric information about the disc, it is considered to draw a more comprehensive evaluation of disc degeneration. To put the magnitude of our observed correlation coefficients in Table 3 in perspective, a correlation of approximately 0.5 corresponds to 25% of explained variability and a correlation of 0.3 to 9%.

These results fall in line with the Kirkaldy-Willis three phase spectrum of disc degeneration[34]. Lumbar discs pass through three phases as they degenerate, starting with dysfunction phase, then unstable phase, leading to the stabilization phase. In this last phase, radiographs show degenerated discs with loss of disc height and osteophyte formation among other characteristics and the patient has decreased severity in low back pain. These degenerated discs are reflected in this study with low %MRIindex and are negatively correlated with reported pain. Meanwhile discs in the unstable phase (2nd phase) show early disc changes on radiographs and the patients experience localized low back pain and pain during movement. Discs in this phase are reflected in this study as discs with high %MRIindex and are highly correlated with pain. Therefore, discs with high %MRIindex can be considered as discs going through the unstable phase of disc degeneration and are the potential source of low back pain. It should be noted that the Kirkaldy-Willis results are based on radiographs which emphasizes bone structures, while the results in this study are from MRI imaging which focuses on disc composition in addition to calculated disc area. Nevertheless, the concepts are well aligned.

In addition, %MRIindex is sensitive to the patient's pain score since shifts of two or more scores disrupted the regression model relating this parameter to the patient's reported pain. This result complements the clinical finding by Farrar et al that changes of at least two points in pain score, or 30%, are required to represent a clinically important difference [35]. It should be noted that the sensitivity analysis was not conducted for any of the other parameters since their correlation with the pain score was less than the %MRIindex. Any further changes in the reported pain scores are only going to make the regression fit worse.

Contrary to what we found in older adults, if we extrapolate these results to what would be expected in younger adults with CLBP, then we hypothesize that the relationship will be reversed. Discs with the lowest %MRIindex will be the pain generators since discs with high %MRIindex will be healthier than those with low %MRIindex. Further investigation is required to definitively test this theory by calculating %MRIindex in younger adults with CLBP.

A limitation of this study is that it did not contain a pain free age matched control group since the focus was on finding imaging features that correlate with the patient's CLBP. Since this is a small study, a larger pool of participants is required to solidify the findings and establish the %MRIindex as a means to identify possible low back pain generators. Additionally, it was difficult to recruit numerous participants with high pain scores (greater than 7) that were willing to participate in the study, and therefore the results may not generalize to high pain patients. Finally, this study utilized a 3Tesla MRI magnet where most clinical MRI machines are 1.5Tesla. Since variation in magnet strength affect the MR image quality, the %MRIindex parameter needs to be validated on 1.5Tesla magnet to be considered for clinical use. Moreover a repeatability study, by taking multiple MRI images at various time points, is required to test the accuracy of these results and the effect of changes in MRI imaging.

Although limited by a small sample size, the %MRIindex sheds light on a new feature extracted from MR images of the lumbar spine that has potential to be an imaging biomarker

used in conjunction with radiological assessments to help understand the pain generators in patients with chronic low back pain.

Acknowledgments

The authors would like to acknowledge MaryBeth Kusturiss and Wan Huang for their assistance with recruitment. The authors also gratefully acknowledge the assistance of the University of Pittsburgh Magnetic Resonance Research Center. This study was approved by the University of Pittsburgh Institutional Review Board under the number IRB #PRO08060191. All participants signed an approved consent form.

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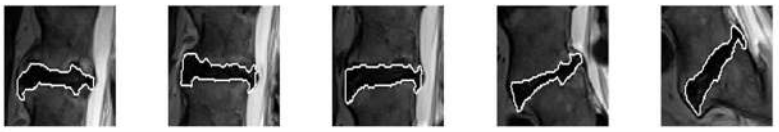

	L1-L2	L2-L3	L3-L4	L4-L5	L5-S1
Area (mm^2)	343.7	342.1	385.2	262.9	370.6
%Area	20.16	20.06	22.60	15.42	21.76
Sum(Int)*10^4 (units)	4.76	5.05	5.68	3.68	5.4
%Sum(Int)	19.28	20.47	23.05	14.93	22.27
MRIindex *10^7 (units*mm^2)	1.63	1.72	2.19	0.96	2.03
%MRIindex	19.11	20.19	25.60	11.32	23.78

Figure 1.

An example of disc segmentation using atlas based segmentation using fuzzy c-means algorithm and calculated objective parameters of 1 participant. White lines in the MR images indicate the segmented region. L1–L2: disc between first & second lumbar vertebra, L2–L3: disc between second & third lumbar vertebra, L3–L4: disc between third & forth lumbar vertebra, L4–L5: disc between fourth & fifth lumbar vertebra, L5-S1: disc between fifth lumbar and first sacral vertebra.

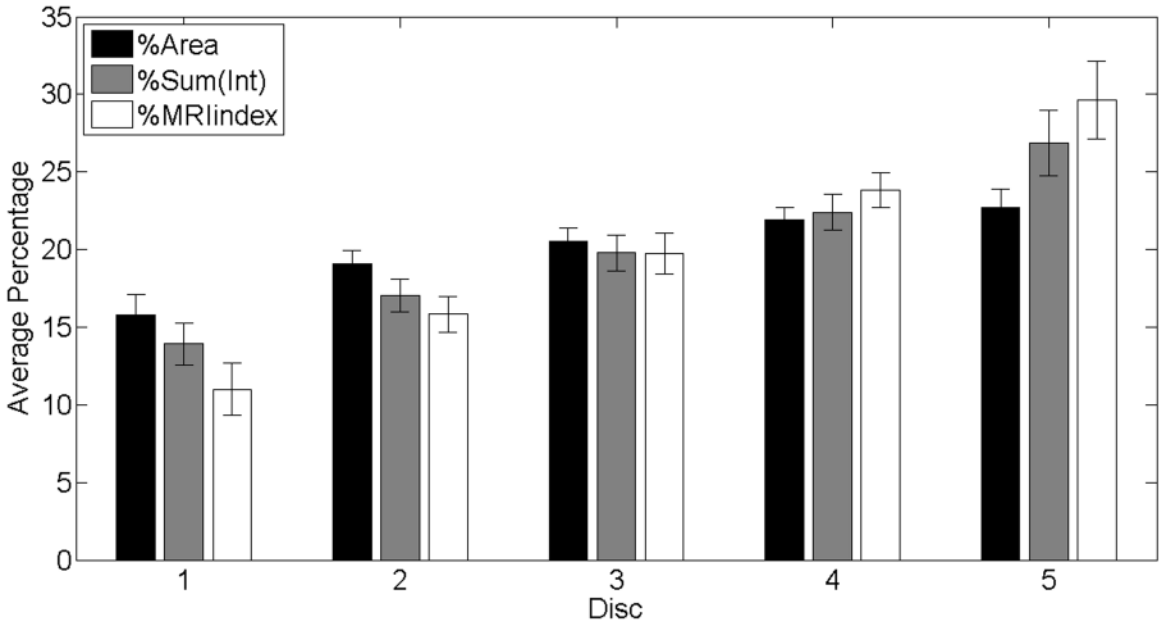

Figure 2.

The increase in the mean %MRIindex (white bars) from 1 to 5 is a result of an increase in both mean %Area (back bars) and mean %Sum(Int) (grey bars) across all participants. Error bars indicate 2 standard deviations from the mean.

Table 1

Example of disc sorting for 1 participant relative to subjective parameters

	CMS	T2 signal	Nucleus	Modic	Osteophytes
$disc_1$	6	2	2	2	0
$disc_2$	6	2	2	0	2
$disc_3$	3	2	0	0	1
$disc_4$	3	0	1	0	2
$disc_5$	1	0	0	0	1

CMS: cumulative MRI score

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Table 2

Distribution of discs across the five categories as sorted by %MRIindex

Disc	Most Degenerated Disc	Second Most Degenerated Disc	Disc with Median Degeneration	Second Least Degenerated Disc	Least Degenerated Disc
L1–L2	3	10	8	11	7
L2–L3	5	5	15	8	6
L3–L4	9	8	3	8	11
L4–L5	15	9	4	4	7
L5–S1	3	10	8	11	7

CMS					
Disc	**Most Degenerated Disc**	**Second Most Degenerated Disc**	**Disc with Median Degeneration**	**Second Least Degenerated Disc**	**Least Degenerated Disc**
L1–L2	4	10	4	9	12
L2–L3	4	9	11	8	7
L3–L4	11	6	11	6	5
L4–L5	11	11	2	10	5
L5–S1	9	4	10	6	10

L1: first lumbar vertebra, L2: second lumbar vertebra, L3: third lumbar vertebra, L4: fourth lumbar vertebra, L5: fifth lumbar vertebra, S1: first sacral vertebra, CMS: cumulative MRI score

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Table 3

Pearson correlations between parameters and reported pain categorized according to amount of degeneration

	Most Degenerated Disc	Second Most Degenerated Disc	Disc with Median Degeneration	Second Least Degenerated Disc	Least Degenerated Disc
Objective Parameter					
% MRIindex	−0.32*	−0.48*	−0.07	0.00	0.47*
% Area	−0.24	−0.08	0.10	0.18	0.19
% Sum(Int)	−0.29*	−0.42*	−0.14	0.01	0.42*
Subjective Parameter					
CMS	0.14	0.02	0.11	0.14	0.04
T2 signal	0.23	0.23	−0.04	0.13	0.15
Nucleus	0.01	−0.02	0.07	0.16	−0.25
Modic	0.13	0.00	0.18	0.09	0.28
Osteophytes	0.02	−0.14	0.13	0.06	0.03

CMS: cumulative MRI score,

*statistical significance ($p<0.05$)

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Table 4

Multiple linear regression coefficients ± standard error & model's goodness of fit

	Most Degenerated Disc	Second Most Degenerated Disc	Disc with Median Degeneration	Second Least Degenerated Disc	Least Degenerated Disc	R^2
Objective Parameter						
% MRIindex	0.034 ± 0.12	0.16 ± 0.18	0.067 ± 0.16	0.07 ± 0.14	0.16 ± 0.09	0.43
% Area	−0.10 ± 0.12	−0.08 ± 0.42	0.21 ± 0.37	−0.10 ± 0.53	0.21 ± 0.41	0.23
% Sum(Int)	0.09 ± 0.18	−0.22 ± 0.26	0.018 ± 0.24	0.12 ± 0.19	0.13 ± 0.09	0.39
Subjective Parameter						
CMS	0.09 ± 0.33	0.0061 ± 0.19	0.46 ± 0.40	0.10 ± 0.29	0.38 ± 0.17	−0.37
T2 signal	0.53 ± 1.05	0.25 ± 1.07	1.27 ± 0.77	0.73 ± 0.40	−0.75 ± 1.2	−0.04
Nucleus	−0.024 ± 0.89	0.96 ± 1.18	1.20 ± 1.03	0.71 ± 0.49	1.58 ± 2.64	−1.02
Modic	0.51 ± 0.45	0.51 ± 1.21	1.26 ± 0.61	1.66 ± 0.60	1.06 ± 0.35	−1.20
Osteophytes	0.68 ± 0.58	1.53 ± 0.89	−0.09 ± 1.04	0.75 ± 0.91	−0.24 ± 1.44	−1.15

CMS: cumulative MRI score