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Original Article

Platelet Indices Are Associated with Disease Activity Scores and the Severity of Sacroiliitis on Magnetic Resonance Imaging in Axial Spondyloarthritis Patients

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Objective. To investigate the associations among platelet indices, disease activity scores, and inflammatory markers in axial spondyloarthritis, and to determine the relation between platelet indices and inflammation measured on magnetic resonance imaging (MRI). **Methods.** The study included 161 patients who fulfilled Assessment of Spondyloarthritis International Society criteria. Platelet indices such as mean platelet volume (MPV), plateletcrit (PCT), platelet large cell ratio (PLCR), and platelet distribution width (PDW) were measured. Ninety patients underwent sacroiliac (SI) MRI at baseline. Bone marrow edema (BME) and erosion on MRI were scored using the SPondyloArthritis Research Consortium of Canada (SPARCC) method. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Ankylosing Spondylitis Disease Activity Score (ASDAS) and spinal radiologic progression were also assessed. The associations among platelet indices and disease activity scores and inflammatory markers were evaluated. **Results.** Of the 161 patients, 130 (81%) were male. MPV, PLCR, and PDW were negatively associated with ASDAS and inflammatory marker expression, whereas PCT was positively associated with these parameters. MPV, PLCR, and PDW were negatively associated with BME and erosion scores on SI MRI. However, platelet indices were not associated with the BASDAI and BASFI. The mean erythrocyte sedimentation rate, C-reactive protein, and BME and erosion scores were significantly higher in patients with low MPV. Changes in MPV, PCT, and PDW at baseline and after one year were associated with changes in ASDAS and inflammatory marker expression. **Conclusion.** Platelet indices are associated with ASDAS, inflammatory marker levels, and severity of BME and erosion measured on MRI. **(J Rheum Dis 2016;23:288-296)**

Key Words. Platelet index, Bone marrow edema, Erosion, Axial spondyloarthritis, Magnetic resonance imaging

INTRODUCTION

Axial spondyloarthritis (axSpA) is a group of inflammatory diseases predominantly affecting the axial skeleton and is associated with chronic back pain due to sacroiliac (SI) joint and spinal inflammation [1]. The Assessment of SpondyloArthritis International Society (ASAS) recently developed a new set of classification criteria for axSpA, which covers the whole spectrum of axial involvement ranging from patients with non-radiographic axSpA (nr-axSpA) to ankylosing spondylitis (AS) with definite radiographic sacroiliitis [2].

AxSpA is caused by chronic inflammation in the axial and peripheral joints; thus tools that objectively measure inflammation are needed. In routine practice, disease activity in axSpA is assessed and monitored using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [3] or the Ankylosing Spondylitis Disease Activity Score (ASDAS) [4]. The BASDAI includes only patient-reported measures and is therefore not an objective meas-

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ure of inflammation. The ASDAS combines patient-reported assessments with measurements of acute phase reactant (C-reactive protein [CRP] or erythrocyte sedimentation rate [ESR]) levels; however, it is based largely on subjective measures. Thus, despite biomarkers that reproducibly assess disease activity in axSpA are needed, there is no reliable and specific biomarker for axSpA [5].

Platelet indices, potential markers of platelet activation, are useful biomarkers for various diseases. They are easily measurable in clinical practice due to the widespread availability of reliable automated complete blood cell (CBC) counters. These counters provide a platelet count in addition to derived indices related to platelet size; these include plateletcrit (PCT), mean platelet volume (MPV), platelet distribution width (PDW), and platelet large cell ratio (PLCR) [6,7]. Since accurate measurement of platelet indices is cost effective and the obtained values can be affected by inflammation associated with disease, it has known as an useful and cheap non-invasive biomarkers for accessing the disease status, such as diabetes, hyperlipidemia, atherosclerosis, stroke, infective endocarditis and cardiovascular disease [8,9].

Several studies have suggested a link between platelets and inflammation [7,10,11]. Platelet indices are not only associated with white blood cell counts in the general population, but are also significantly related to CRP levels [7]. Platelet counts are also associated with the levels of other acute phase reactants [11]. Among the various platelet indices, only MPV has been reported its association with the activity of several chronic inflammatory diseases. MPV is significantly reduced in those with active inflammatory bowel disease (IBD) and correlates well with the activity of disease [12]. Also, MPV is associated with disease activity in patients with rheumatoid arthritis (RA) [13,14]. In addition, another study revealed that the MPV values of patients with osteoarthritis and synovitis serve as markers of inflammation [15].

A few studies have examined the association between MPV and disease activity in AS. MPV levels in patients with active AS are lower than those healthy controls; indeed, there is a negative correlation between MPV values and BASDAI scores after treatment [13]. By contrast, in the other study, MPV values are positively correlated with disease activity [16]. Therefore, it is unclear whether platelet indices are associated with disease activity in patients with AS.

To date, the relationship between platelet indices and ASDAS has not been examined in patients with axSpA, including those without radiographic evidence of sacroiliitis. Also, the association between platelet indices and sacroiliitis, as measured by magnetic resonance imaging (MRI), has not been studied. Furthermore, no study has examined the association between other platelet indices, such as PCT, PDW, and PLCR, and disease activity in axSpA. Therefore, the present study aimed to investigate the correlation between platelet indices and disease activity parameters in axSpA patients, and to determine the association between platelet indices and objective inflammation on SI MRI.

MATERIALS AND METHODS

Patients

Patients (n=161) with axSpA (aged >20 years) and followed up at Incheon St. Mary's Hospital between August 2013 and June 2015 were retrospectively recruited. All fulfilled the imaging arm of the ASAS axSpA criteria [2], and 108 patients (67.1%) fulfilled the modified New York criteria for the classification of AS [17]. Patients were excluded if they had diabetes mellitus or dyslipidemia. No patients had hematologic disease. The study was approved by the ethics committee at Incheon St. Mary's Hospital (XC13RIMI0129O). The requirement for informed consent was waived because the usual clinical management of the patients was not altered and it was a retrospective study.

Clinical data

Demographic data (age, gender, age at the time of axSpA diagnosis, disease duration, a family history of axSpA, and smoking habits) were collected. Medications, including nonsteroidal anti-inflammatory drugs, sulfasalazine, methotrexate, and tumor necrosis factor (TNF) inhibitors, were recorded. Disease activity measures at the time of blood sampling were obtained using a patient global assessment score (disease activity rated by the patient at the time of the assessment), the BASDAI and the ASDAS [3,4]. The ASDAS, which includes ESR and CRP levels, was calculated using different formulae [4]. The Bath Ankylosing Spondylitis Functional Index (BASFI) [18] was also recorded.

Laboratory assessment

A CBC, including platelet indices, ESR (mm/h), and CRP (mg/L), was obtained. Blood samples were collected between 8 a.m. and 10 a.m. after an overnight fast.

Venipuncture of the cubital vein was performed, and blood samples were collected in EDTA-containing tubes and used to measure platelet indices. CBCs were performed within 1 hour of blood sampling. Four platelet indices (MPV, PCT, PLCR, and PDW) were measured. The MPV describes the mean platelet size reported in femtoliters (fL), PCT describes the total volume of platelets in a given volume of blood (expressed as a percentage), and PLCR describes the percentage of platelets with a volume larger than 12 fL [6]. PDW is a measure of the heterogeneity in platelet size and is calculated as the standard deviation (SD) of platelet volume divided by MPV×100 [19]. MPV, PCT, PLCR, and PDW were analyzed using the Sysmex XE 2100 automated blood cell counter (Sysmex, Kobe, Japan). The expected values for MPV, PCT, and PDW in our laboratory ranged from 9.1～11.9 fL, 0.19% ～0.38%, and 9.3～15.1 fL. Platelet indices, ESR, and CRP were also measured in 36 patients at 1 year after the initial measurement.

Radiological assessment

Radiographs of the cervical spine, lumbar spine, and pelvis were obtained at the time platelet indices were measured. Lateral views of the cervical and lumbar spine were scored according to the modified Stoke AS Spinal Score (mSASSS). To obtain the mSASSS, the anterior vertebral corners of the cervical (C2 lower–T1 upper) and lumbar (T12 lower–S1 upper) spine were scored from 0～3 points, where 0=normal; 1=erosion, sclerosis, and/or squaring; 2=syndesmophyte formation; and 3=a bridging syndesmophyte [20]. The mSASSS was then calculated as the sum of the scores at all individual sites (range, 0～72). Sacroiliitis was scored from right-sided and left-sided pelvic radiographs using the modified New York criteria [17]. The average score for both sides was used for analysis. Sacroiliitis and the mSASSS were scored by a single trained expert who was blinded to the patient characteristics.

MRI assessment

Ninety patients underwent MRI of the sacroiliac joints (SIJs) at baseline. Images were obtained using a 3.0 T MRI unit (Verio/Skyra; Siemens Medical, Erlangen, Germany) and a body flexed array coil (Siemens Medical). Assessment of SIJ erosion was based on T1-weighted turbo spin echo (TSE) MRI sequences. Assessment of inflammatory lesions and bone marrow edema was based on T2-weighted fat-suppressed (FS) TSE sequences. The sequence protocols were as follows: semi-coronal (along the long axis of the sacral bone) TSE (slice thickness [ST], 3 mm; repetition time/echo time [TR/TE], 636/11 ms) and semi-coronal T2-weighted FS TSE (ST, 3 mm; TR/TE, 5,210/55 ms). Erosion and bone marrow edema on SIJ MRI were scored using the SPondyloArthritis Research Consortium of Canada (SPARCC) method [21,22]. All scores were measured by an experienced musculoskeletal radiologist (JY Jung) who was blinded to the patient characteristics. Bone marrow edema was scored on six consecutive coronal slices depicting the synovial portion of the joint [21]. The score for bone marrow edema ranged from 0～48. Erosion on SIJ MRI was scored according to standardized definitions using the SPARCC SI structural lesion score (SSS) [22]. The SSS was scored using slices selected according to well-defined anatomical principles. Scoring was dichotomous (lesion present/absent) and based on five consecutive slices through the cartilaginous portion of the joint. The scores for erosion ranged from 0～40.

Statistical analysis

Continuous data were expressed as the mean±SD, and categorical data as percentages. Normally distributed demographic and radiologic variables were compared using the independent t-test, and non-normally distributed variables were compared using the Mann-Whitney U test. Spearman's correlation coefficient was used to analyze the correlation between variables. All tests were two-tailed and a p-value$<$0.05 was considered statistically significant. Statistical analyses were performed using PASW Statistics 18 (IBM Co., Armonk, NY, USA).

RESULTS

Table 1 shows the characteristics of the 161 axSpA patients. Of these, 130 patients (80.7%) were male, the mean age was 36±13 years, and the mean symptom duration and time after axSpA diagnosis were 7.6±9.2 and 3.3±6.0 years, respectively. The mean BASDAI, ASDAS-ESR, and ASDAS-CRP scores were 4.4±2.2, 2.8±1.1, and 2.5±1.2, respectively. The mean grade of sacroiliitis on x-ray and the mean mSASSS were 2.3±1.2 and 8.9±16.6, respectively. The mean MPV, PCT, PLCR, and PDW were 9.7±0.8 fL, 0.25%±0.05%, 21.7%±6.3%, and 10.5±1.7 fL, respectively.

Table 2 lists the r coefficients for the correlation between hemoglobin. platelet counts, platelet indices and disease

Table 1. Baseline characteristics of patients with axial spondyloarthritis

Characteristic (n=161)	
Male	130 (80.7)
Age (yr)	35.9±12.5
Time from symptoms onset (yr)	7.6±9.2
Time from diagnosis (yr)	3.3±6.0
Smoking, current	56 (34.8)
Family history	23 (14.3)
HLA B27-positive	135 (83.9)
Patient global assessment	5.1±2.3
BASDAI, score (range, 0~10)	4.4±2.2
BASFI, score	2.0±2.3
ASDAS-ESR	2.8±1.1
ASDAS-CRP	2.5±1.2
ESR, mm/hr	23.4±22.3
CRP, mg/L	10.2±17.8
Grade of sacroiliitis on X-ray	2.3±1.2
mSASSS	8.9±16.6
Number of syndesmophytes	3.0±6.2
Patients taking NSAIDs	150 (93.2)
Patients taking sulfasalazine	47 (29.2)
Patients taking MTX	5 (3.1)
Patients taking TNF inhibitors	14 (8.7)
Hemoglobin (g/dL)	14.4±1.7
Platelet (10^3/mm^3)	276.5±57.6
Platelet count ($\times 10^3/\mu$L)	271.8±59.2
MPV (fL)	9.7±0.8
PCT (%)	0.26±0.05
PLCR (%)	21.7±6.3
PDW (fL)	10.5±1.7

Values are presented as mean±standard deviation and number (%). HLA: human leukocyte antigen, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, mSASSS: modified Stoke Ankylosing Spondylitis Spinal Score, NSAIDs: nonsteroidal anti-inflammatory drugs, MTX: methotrexate, TNF: tumor necrosis factor, MPV: mean platelet volume, PCT: plateletcrit, PLCR: platelet large cell ratio, PDW: platelet distribution width.

activity scores and the severity of sacroiliitis measured by MRI. Hemoglobin, platelet counts and all platelet indices showed a significant correlation with ASDAS and inflammatory marker levels. Hemoglobin and MPV, PLCR, and PDW were negatively correlated with disease activity scores, whereas platelet counts and PCT showed a positive correlation. All platelet indices and platelet counts, not hemoglobin, correlated with the scores for bone marrow edema on SI MRI. Additionally, MPV, PLCR, and

Table 2. Correlation between platelet indices and disease activity variables in patients with axial spondyloarthritis

Variable	MPV (fL)	PCT (%)	PLCR (%)	PDW (fL)	Platelet (10^3/mm^3)	Hb (g/dL)
Disease activity variables						
BASDAI	−0.106 (0.183)	0.138 (0.081)	−0.110 (0.164)	−0.121 (0.126)	0.089 (0.408)	−0.109 (0.312)
BASFI	−0.083 (0.299)	0.127 (0.111)	−0.086 (0.282)	−0.105 (0.186)	0.187 (0.082)	−0.206 (0.054)
PGA score	−0.059 (0.462)	0.082 (0.302)	−0.063 (0.429)	−0.063 (0.430)	0.090 (0.407)	−0.089 (0.407)
ASDAS-ESR	−0.200 (0.011)*	0.216 (0.006)**	−0.204 (0.010)*	−0.200 (0.011)*	0.257 (0.014)*	−0.259 (0.013)*
ASDAS-CRP	−0.166 (0.036)*	0.229 (0.004)**	−0.164 (0.038)*	−0.168 (0.034)*	0.171 (0.033)*	−0.225 (0.035)*
ESR	−0.253 (0.001)**	0.391 (<0.001)**	−0.256 (0.001)**	−0.269 (0.001)**	0.548 (<0.001)**	−0.586 (<0.001)**
CRP	−0.228 (0.004)**	0.163 (0.039)*	−0.224 (0.004)*	−0.219 (0.005)**	0.216 (0.006)**	−0.204 (0.010)*
Sacroiliac MRI findings						
Erosion	−0.319 (0.002)**	0.060 (0.577)	−0.309 (0.003)*	−0.262 (0.013)*	0.218 (0.053)	−0.176 (0.099)
Bone marrow edema	−0.257 (0.014)*	0.209 (0.048)*	−0.263 (0.012)*	−0.251 (0.017)*	0.272 (0.013)*	−0.120 (0.264)

Data are expressed as r coefficients (p-value). MPV: mean platelet volume, PCT: plateletcrit, PLCR: platelet large cell ratio, PDW: platelet distribution width, Hb: hemoglobin, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, PGA: patient global assessment, ASDAS: Ankylosing Spondylitis Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MRI: magnetic resonance imaging. *$p<0.05$, **$p<0.01$.

PDW were negatively correlated with the erosion scores on SI MRI (p=0.002, 0.003, and 0.013, respectively). However, platelet counts and hemoglobin did not correlate with the erosion scores on SI MRI. Also, there were no correlations between platelet counts platelet indices and hemoglobin and the BASDAI, BASFI, or patient global assessment score.

Among the 161 patients, 30 patients (18.6%) had a low MPV (<9.1 fL) and 32 (19.9%) had a low PDW (<9.3 fL). Table 3 compares the disease activity scores and erosion and bone marrow edema scores for patients with and without a low MPV and PDW. There were no differences between patients with a normal MPV and those with a low MPV with respect to the BASDAI and ASDAS. ESR and CRP levels were higher in patients with a low MPV (p=0.018 and 0.008). The erosion and bone marrow edema scores on SI MRI were also higher in the low MPV group (p=0.032 and 0.017). The mean ESR and CRP levels and bone marrow edema scores were significantly higher in patients with a low PDW (p=0.047, 0.010, and 0.033); however, there was no significant difference in the erosion score. There were no differences between patients with a normal PDW and those with a low PDW with respect to BASDAI and ASDAS.

Table 3. Disease activity scores and MRI findings at the sacroiliac joints according to MPV and PDW values

Variable	MPV (fL)			PDW (fL)		
	<9.1 (n=30)	≥9.1 (n=131)	p-value	<9.3 (n=32)	≥9.3 (n=129)	p-value
Disease activity variables						
BASDAI	4.5±2.2	4.4±2.2	0.843	4.4±2.4	4.4±2.1	0.962
ASDAS-ESR	3.0±1.3	2.8±1.1	0.226	3.0±1.3	2.8±1.1	0.278
ASDAS-CRP	2.7±1.4	2.5±1.2	0.472	2.6±1.4	2.5±1.2	0.518
ESR, mm/h	32.0±26.3	21.3±21.0	0.018*	31.4±25.8	21.4±21.1	0.047*
CRP, mg/l	17.9±25.7	8.5±15.0	0.008**	17.5±25.1	8.4±15.1	0.010*
Sacroiliac MRI findings						
Erosion	6.6±3.1	4.4±4.4	0.032*	5.4±3.6	4.5±4.5	0.219
Bone marrow edema	14.0±12.9	6.3±3.4	0.017*	11.9±11.8	6.3±6.5	0.033*

Values are presented as mean±standard deviation. MRI: magnetic resonance imaging, MPV: mean platelet volume, PDW: platelet distribution width, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. *p<0.05, **p<0.01.

Table 4. Correlation between platelet indices, disease activity scores, inflammatory marker levels, and the severity of sacroiliitis on MRI (stratified according to symptom duration)

Variable (r coefficient)	ASDAS-ESR	ASDAS-CRP	ESR	CRP	Erosion	Bone marrow edema
Symptom duration ≤3 years (n=67)						
MPV	−0.338**	−0.301*	−0.417**	−0.339**	−0.303*	−0.375**
PCT	0.164	0.233	0.378**	0.251*	0.185	0.194
PLCR	−0.323**	−0.273*	−0.400**	−0.318**	−0.293*	−0.370**
PDW	−0.332**	−0.261*	−0.402**	−0.311*	−0.279	−0.370**
Symptom duration >3 years (n=94)						
MPV	−0.108	−0.073	−0.147	−0.136	−0.329*	0.097
PCT	0.261*	0.236*	0.406**	0.104	−0.031	0.163
PLCR	−0.123	−0.087	−0.164	−0.142	−0.334*	0.062
PDW	−0.121	−0.109	−0.194	−0.151	−0.267	0.093

Ninety patients underwent sacroiliac MRI to assess erosion and bone marrow edema. MRI: magnetic resonance imaging, MPV: mean platelet volume, PCT: plateletcrit, PLCR: platelet large cell ratio, PDW: platelet distribution width, ASDAS: Ankylosing Spondylitis Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. *p<0.05, **p<0.01.

Table 5. Correlation between differences in platelet indices, disease activity scores, and inflammatory markers at baseline and at 1 year in patients with axial spondyloarthritis

Difference (Baseline value–FU value)	ASDAS-ESR	ASDAS-CRP	ESR	CRP
MPV	−0.474 (0.026)*	−0.452 (0.035)*	−0.297 (−0.180)	−0.459 (0.031)*
PCT	0.521 (0.013)*	0.461 (0.031)*	0.648 (0.001)**	0.398 (0.066)
PLCR	−0.327 (0.138)	−0.333 (0.130)	−0.249 (0.264)	−0.349 (0.112)
PDW	−0.571 (0.005)**	−0.493 (0.020)*	−0.552 (0.008)**	−0.409 (0.059)

Data are expressed as r coefficients (p-value). ASDAS: Ankylosing Spondylitis Disease Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, MPV: mean platelet volume, PCT: plateletcrit, PLCR: platelet large cell ratio, PDW: platelet distribution width. *$p<0.05$, **$p<0.01$.

Subgroup analysis of patients with symptom duration ≥ 3 years and those with symptom duration > 3 years revealed a correlation between platelet indices and disease activity scores, inflammatory markers, and the scores for erosion and bone marrow edema on SI MRI (Table 4). MPV, PLCR, and PDW in patients with short symptom duration were negatively correlated with ASDAS, inflammatory marker expression, and severity of sacroiliitis; however, in patients with long symptom duration, none of these indices correlated with ASDAS, ESR, CRP level, or the bone marrow edema score. In patients with long symptom duration, only MPV and PLCR correlated with the bone erosion score ($r=-0.329$, $p=0.034$ and $r=-0.034$, $p=0.030$, respectively).

We also examined the relationship between changes in platelet indices and changes in ASDAS and inflammatory marker levels at baseline and after 1 year (n=36 patients) (Table 5). Changes in MPV levels negatively correlated with differences in ASDAS-ESR, ASDAS-CRP, and CRP levels. Changes in PCT were positively correlated with ASDAS and ESR, and PDW levels were negatively correlated with ASDAS and ESR, but not with CRP levels. Changes in the PLCR were not associated with the ASDAS or inflammatory marker levels.

DISCUSSION

Here, we examined the relationship between disease activity and platelet indices in patients with axSpA. MPV, PLCR, and PDW were negatively correlated with ASDAS and inflammatory marker levels, as well as with severity of sacroiliitis measured on MRI. PCT was positively correlated with these parameters.

Platelet indices are a group of parameters that are reproducible and inexpensive to measure. They are derived from routine CBCs. Of these indices, MPV and PDW are the most validated and suited to use in a clinical setting because of their widespread availability. Platelet size, as measured by these parameters, correlates with platelet activity [8].

The functional capacity of platelets is determined by megakaryocytosis and circulation. Megakaryocytosis is thought to have a more pronounced impact on the size and function of platelets [23]. Systems that regulate platelet function aim to maintain total platelet mass (platelet count multiplied by MPV) and hemostatic potential [24]. Thrombopoietin, granulocyte-macrophage colony-stimulating factor, interleukin (IL)-1, TNF-α, and IL-6 influence the maturation of thrombopoietic cells and the release of platelets into the circulation [25]. The frequently described inverse relationship between platelet count and MPV under physiological (and some pathological) conditions reflects the tendency to maintain homeostasis by maintaining a constant platelet mass [26].

The intensity of systemic inflammation is a distinctive factor for classifying conditions associated with large and small circulating platelets. During a high-grade inflammatory state, increased thrombocytosis increases the quantity of circulating platelets and can lead to an inverse relationship between platelet count and platelet size [26]. Therefore, high-grade inflammatory disorders such as IBD or RA are predominantly associated with the circulation of small platelets; however, during remission or after treatment, these disorders are associated with large circulating platelets [27].

We found that platelet counts not only negatively correlated with MPV, PLCR, and PDW, but positively correlated with disease activity scores and bone marrow edema scores on SI MRI. Also, platelet counts correlated with both ESR and CRP levels. This suggests that regulation of

megakaryocytosis, which is increased by chronic inflammation in axSpA, may result in production of small platelets to maintain a constant platelet mass. In the present study, platelet counts did not show the association with erosion scores on SI MRI, whereas platelet indices are associated with both the severity of SIJ erosion measured on MRI and disease activity scores.

Among the different platelet indices, MPV is a possible biomarker for monitoring the activity of several chronic inflammatory disorders. Several studies have examined the association between MPV and disease activity in patients with rheumatic disease. The MPV is lower in active SLE patients with low albumin levels [28]. In RA, high-grade inflammation is accompanied by a reduced MPV; suppression of inflammation by disease-modifying and anti-TNF-α agents reverses this [13,29]. Another study also showed that MPV is negatively correlated with inflammatory marker levels and DAS-28 in patients with RA [30].

There are only two previous studies of MPV values in AS patients and how they change upon treatment [13,16]. The results presented herein showed an inverse relationship between platelet indices and disease activity in axSpA. It seems likely that axSpA patients with high disease activity tend to have smaller platelets than those with low activity. This is consistent with one of the previous studies [13]. However, the other study showed opposite data; MPV values in patients were significantly higher than those in the healthy controls, and decreased after treatment [16]. Neither of these studies showed a correlation between MPV and inflammatory marker levels at baseline. The discrepancies between these studies and our own might be explained, at least in part, by different patient characteristics such as age, sample size, inclusion of patients with comorbidities, and different diagnostic criteria. In contrast with earlier studies, the patients enrolled herein fulfilled ASAS criteria, including nr-axSpA as well as AS.

In conditions associated with high levels of inflammatory markers, such as active axSpA, overproduction of pro-inflammatory cytokines and acute-phage reactants suppresses platelet size by interfering with megakaryopoiesis, resulting in release of small platelets from the bone marrow [31]. Another possible explanation for the low platelet indices in active axSpA relates to the intensive consumption of large platelets at sites of inflammation (the vascular wall and synovial membrane). Large platelets secrete more pro-inflammatory cytokines and thrombotic agents than small platelets, and demand for large platelet increases during high-grade inflammation [27].

The results presented herein show that an inverse relationship between platelet indices and sacroiliitis measured by MRI and inflammatory markers seem to be expressed more strongly in patients with short disease duration. A previous study by Weiβ et al. [32] showed that CRP levels in axSpA patients with short symptom duration correlated only with the SI MRI inflammatory score; this correlation was not observed in patients with long symptom duration. This suggests that correlations between MRI-measured inflammation and/or disease activity scores and biomarker levels may be different as the disease advances.

To date, assessment and monitoring of disease activity in axSpA patients is mostly limited to patient-reported outcomes that do not necessarily correlate with objective inflammation measured on MRI [33]. Currently, inflammation assessed on MRI is the best measure of disease activity and correlates well with histopathological features [34]; however, MRI is costly, not widely available, and requires experienced staff to interpret the findings. Therefore, it would be beneficial to identify biomarkers of inflammation that accurately reflect the findings of MRI in axSpA patients. CRP levels show a moderate correlation with MRI inflammation scores [33], but the results are inconsistent [35,36]. Recent studies identified new biomarkers of inflammation, including markers of angiogenesis and tissue turnover. Biomarkers, such as calprotectin, vascular endothelial growth factor (VEGF), C-telopeptides of type II collagen (CTX-II), and dickkopf-1 (DKK-1), may predict progression of spinal deterioration, but they do not reflect disease activity [37]. Studies show that matrix metalloproteinase-3 (MMP-3) levels correlate with disease activity and functional status as assessed by the BASDAI and BASFI [38,39]; however, another showed that MMP-3 levels do not correlate with inflammatory marker expression or disease activity scores [40].

CBCs are routinely performed during diagnosis and follow-up of patients with inflammatory arthritis. Currently, automated cell counters provide an extended panel of platelet indices, which are a component of the CBC test, at no additional cost. The results presented herein suggest that MPV and PDW may be useful biomarkers for axSpA as they negatively correlate with disease activity scores and inflammatory marker levels and are associated with

the severity of sacroiliitis as measured on MRI. Thus, MPV and PDW values may be a more objective reflection of inflammation in axSpA than activity scores based on subjective measures. Therefore, MPV and PDW may be cheap non-invasive biomarkers of disease activity that reflect inflammation measured by MRI.

This study has some limitations. First, it was of cross-sectional design. Although a relationship between changes in platelet indices and disease activity was observed, we did not investigate which platelet indices reflect changes in inflammation detected by MRI. Longitudinal MRI studies are needed to determine whether platelet indices are a useful biomarker for objective monitoring of sacroiliitis in axSpA. Also, because this was an observational study, we were not able to establish a causal relationship between platelet indices and disease activity. Thus, the results should be interpreted with some caution. We also included smokers in the study. There is a significant association between platelet indices and cardiovascular risk factors such as smoking, diabetes, hyperlipidemia, and metabolic syndrome [27]. Although we excluded those with hyperlipidemia and diabetes mellitus, smokers were included.

CONCLUSION

The present study showed that, while platelet indices such as MPV, PLCR, and PDW are negatively correlated with disease activity scores in axSpA patients, they are associated with the severity of SIJ inflammation measured on MRI. Additionally, changes in MPV and PDW negatively correlated with changes in ASDAS and inflammatory marker levels. These findings suggest that platelet indices may be a useful marker for monitoring disease activity in axSpA.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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