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Inflammatory Events in Patients with Sagittal Imbalance through Platelet-Associated Inflammation

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ABSTRACT

AIM: To determine whether platelet-associated inflammation parameters (PAIP) could be useful for evaluating inflammation in sagittal imbalance (SI) by investigating its relationship with pelvic tilt (PT), sacral slope (SS), pelvic incidence (PI), lumbar lordosis (LL) and thoracic kyphosis (TK).

MATERIAL and METHODS: The study included 57 patients (19 males, 38 females) who were diagnosed with SI and 44 healthy control subjects. Spinal sagittal balance was evaluated using digitalized-standing lumbar lateral radiographs of the patients. All parameters including SS, PI, LL and PT were evaluated through from the lateral radiographs.

RESULTS: In the analysis, Mean Platelet Volume (MPV) (10.6 ± 0.9; p<0.0001), Platelet Distribution Width (PDW) (12.7 ± 2.2; p<0.001) and Platelet Distribution Width (RDW) (41.9 ± 4.4; p<0.0001) were observed to be much higher in the SI than in the control. The neutrophil-lymphocyte ratio (NLR) was higher in the SI group (p=0.033), and no difference was determined in respect of the platelet-lymphocyte ratio (PLR) (p>0.05). The PT had a positive correlation with hospital length of stay in SI patients (r=0.655; p=0.008). MPV showed a strong positive correlation with comorbidity (r=0.715; p=0.001). A positive correlation was determined between NLR and PLR (r=0.692; p=0.002), and between MPV and RDW (r=0.788; p=0.001). No correlation was determined between the PAIP and radiological measurements (PI, PT, SS) that were used for SI.

CONCLUSION: The results suggest that the neurosurgical approach should cover not only the sagittal parameters and their angles but also PAIP showing inflammatory events originating from platelets.

KEYWORDS: Spine, Sagittal imbalance, Platelet, Inflammation

INTRODUCTION

Sagittal imbalance (SI) in the spine includes kyphosis and lordosis in the form of an inconsistent state (1). In a standing person, the center of mass of the body is located in front of the thoracic spine and near the lumbar region (32). In this way, the person can stand upright with support from the ground. If we look at a person in normal sagittal equilibrium, in which these two lines are in harmony, it can be seen that the projection of the head is inside the pelvis (7). In pathological conditions in which sagittal balance is impaired, the organism tries to maintain the sagittal balance by numbing the line of tension and the weight line with each other (16). That results in the development of restricted mobility with a low quality of life, which is accepted as the most critical reason for spinal surgery (29). With the deterioration of a systemic or functional unit, compensation mechanisms develop to provide the sagittal balance against changes in the spine (1,33). When the spine begins to change shape, changes also occur in the pelvis in an effort to keep sagittal balance strong. As neurosurgeons, we evaluate these changes in the spine using spinopelvic measurements such as lumber lordosis (LL), pelvic incidence (PI), sacral slope (SS), pelvic tilt (PT), and thoracic kyphosis (TK) (9).

Considering the occurrence of the SI, degenerative disc disease, lumbar disc hernia, degenerative and isthmic spondylolisthesis and similar pathologies, changes in the spine and

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pelvis as a result of the complementary mechanisms cause inflammation around the resistant pain and deterioration in quality of life (9,15). All these events caused by inflammatory conditions have been the major reasons of back pain affecting people (19). Recent studies have pointed out that increased inflammatory conditions strongly affect the efficacy of surgical intervention in the affected spinal areas and the recovery period after surgery (21). Evaluation of the inflammatory condition may allow important predictions of the effectiveness of the surgical procedure and postoperative recovery (28). Recent studies have shown a significant relationship between platelets and inflammatory events in several diseases (2,17,23,30). Therefore, it can be considered that novel platelet-associated inflammation parameters (PAIP) such as Platelet Distribution Width (PDW), Mean Platelet Volume (MPV), Platelet-to-Lymphocyte Ratio (PLR) and Neutrophil-to-Lymphocyte Ratio (NLR) could provide information about inflammatory events.

The aim of the current study was to determine whether PAIP could be useful in the evaluation of inflammation in SI by investigating its relationship with SS, PI, PT, LL and TK.

MATERIAL and METHODS

Study Design

Adult SI patients were examined by a single surgeon in Mugla Sitki Kocman University, Faculty of Medicine Hospital, between June 2015 and February 2019 in this single-center retrospective cohort study. A total of 57 patients (male/female: 19/38) who were diagnosed with SI and needed a posterior-approach spinal surgery of L4 and L5 including posterior instrumentation, decompression, and lateral fusion with/without lumbar-interbody fusion were enrolled in this study. The healthy individuals were selected from laboratory and examination records obtained from the hospital patient information system. All the patients and controls were aged higher than18 years and all provided written-informed consent for participation in the study. Any procedures in the current study were in accordance with the Decleration of Helsinki. The Human Experiment and Ethical Committee of Mugla Sitki Kocman University Medical Center approved all the procedures (Decision date and number: 02.May.2019 and 08/IX).

Radiological Evaluation

Lateral radiographs were analysed in all patients with SI. Patient records were obtained from the hospital electronic database. The presentation of lower back pain with intermittent claudication or sciatica and radiographic image showing SI findings was accepted as the reference for the diagnosis. Spinal sagittal balance was evaluated using digitalized-standing lumbar lateral radiographic images of the patients (Figure 1, 2). The standing position was used to obtain the preoperative films, radioscopy to see the placement of the pedicle screws was used for intraoperative films. All patients used a standard pad in the position of prone decubitus to provide 40°-hip flexion and 30°-knee flexion, both measured with an angle ruler.

All parameters for SI were measured and evaluated through from the radiographs. The PI is morphological/anatomical measurement independent of the pelvis spatial orientation. PI measurement that we used was as followings: we provided a line on the S1 superior end plate; found the middle point for this and draw a vertical line downwards; pointed a line of the head of the central sacrum line from the head of the femoral headline. Calculating the angle in this line provided us PI. Angulation of the inferior angle of T12 with the superior end plate of S1 provided us the SI. The PT was obtained by the angle between the two lines that involves one line found by drawing a line from the midpoint of the sacral end plate running perpendicular down to the bottom of the X-ray; and by the second line by drawing a line from the centre of the femoral heads to the center of the sacrum. We found "PI" adding "PT" to "SS" as another way. The SS was found by a line draw along the superior sacral-end-plate in addition to another line draw from the anterior superior-edge parallel to the bottom of the X-ray.

Laboratory Analysis for PAIP

Venous blood samples were taken within 24 hours preoperatively for complete blood count (CBC) analysis. Immediate analysis was applied to determine leukocyte count, neutrophil count, platelet count, MPV, PDW and RDW. The ratio of PAIP was calculated from the neutrophil, platelet and lymphocyte count values. Haematological parameters were measured using an automated haematology analyser (Coulter LH 780 Haematology Analyser, Beckman Coulter Inc, CA, USA). The upper limits of the reference intervals were as follows: Leukocyte count (WBC) 4500-10300×10^3/μL, Platelet: 130-400×10^3/μL, Neutrophil: 2-6.9×10^3/μL (37%-80%), Lymphocyte: 0.6-3.4×10^3/μL (10%-50%), MPV: 7.2-11 fL, RDW: 11%-16%, and PDW: 10%-18%. The haematological parameters were assayed in the ethylene diamine tetraacetic acid treated (EDTA) blood samples within 1 hour of vein puncture.

Statistical Analyze

Data of the present study were analysed statistically using SPSS Windows version 20 software (SPSS Inc., Chicago, IL, USA). All data were expressed as mean and standard deviation (mean ± SD) values. Distribution of data was assessed using the Shapiro-Wilk test. The Chi-square test was applied to comparisons of groups of categorical variables. For independent samples, the t-test was applied to continuous variables. The Pearson or Spearman test was performed for the correlation analysis according to the Shapiro-Wilk test results. A value of $p<0.05$ was considered statistically significant. All outcomes were evaluated within a 95% Confidence-Interval (CI).

RESULTS

The mean age of SI patients was 54.2 ± 24 years (range: 22-78 years), and of the control group, 49.8 ± 23 years (range: 29-71 years) ($p>0.05$). No significant difference was determined between the groups in terms of demographics including age and BMI ($p>0.05$). The LL evaluation was defined as 29 normal, 22 hypolordosis, 15 hyperlordosis, and 1 kyphosis.

Measurement of SS and PT were different within the groups, as seen in Table I.

In the routine biochemistry comparisons between the groups, all parameters were similar except Erythrocyte Sedimentation Rate (ESR) (24 ± 19; p<0.0001) and C-reaktive protein (CRP) (7 ± 7.2; p<0.001), which were naturally found to be higher in SI patients. No significant differences were observed between the groups in respect of the hormone analyses including 25-OH vitamin D, thyroid stimulating hormone (TSH) and Parathyroid Hormone (PTH) (Table II). In haematological findings, leukocyte, neutrophil, lymphocyte, platelet, red blood cell (RBC) and haemoglobin were within normal ranges. In the PAIP analyses, MPV (10.6 ± 0.9; p<0.0001), PDW (12.7 ± 2.2; p<0.001) and RDW (41.9 ± 4.4; p<0.0001) were determined to be much higher in the SI group than in the control group. NLR was significantly higher in the SI group (p=0.033), and no difference was determined in respect of PLR (p>0.05).

A positive correlation was determined between PT and length of hospital stay in SI patients (r=0.655; p=0.008). MPV showed a strong positive correlation with comorbidity (r=0.715;

Table I: Demographic Data of the Groups

Variables		Control	Patient	p
Age (years)		49.8 ± 23	53.2 ± 24	0.511
Gender (m/f)	Male	25	19	**0.023**
	Female	19	38	
BMI (kg/m^2)		25 ± 3	26 ± 3	0.162
Comorbidity		-	1 ± 1	
Length of Hospital Stay (days)		-	8 ± 3	
Follow-up Period (months)		-	2 ± 2	
Lumbar Lordosis	Normal	44	29	
	Hypo	0	12	
	Hyper	0	15	
	Kyphosis	0	1	
Pelvic incidence (PI)		54.7 ± 15.1	53.8 ± 13.2	0.746
Sacral slope (SS)		40.1 ± 12.7	30.5 ± 11.8	**0.0001**
Pelvic tilt (PT)		18.1 ± 13.9	23.7 ± 12.7	**0.036**

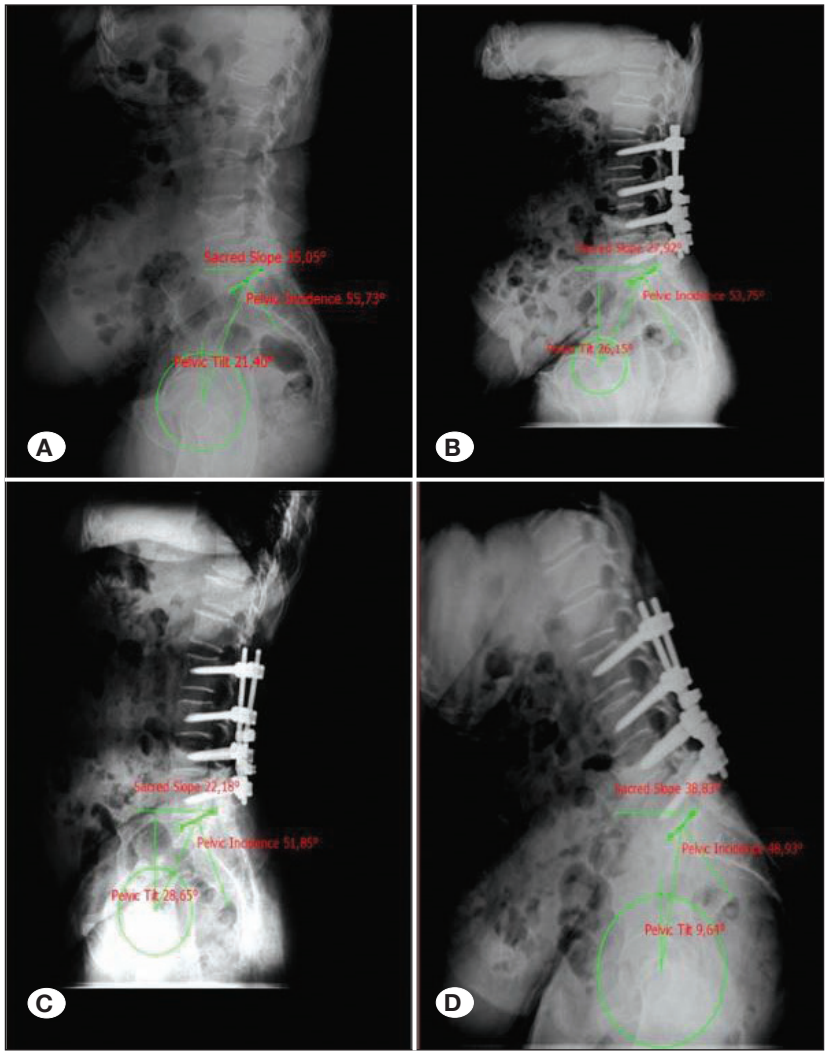

Figure 1: A) Lateral radiograph of a preoperative patient with lumbar spinal pathology. **B-D)** Postoperative radiological sagittal balance assessments after posterior segmental stabilization between L2 and S1 levels.

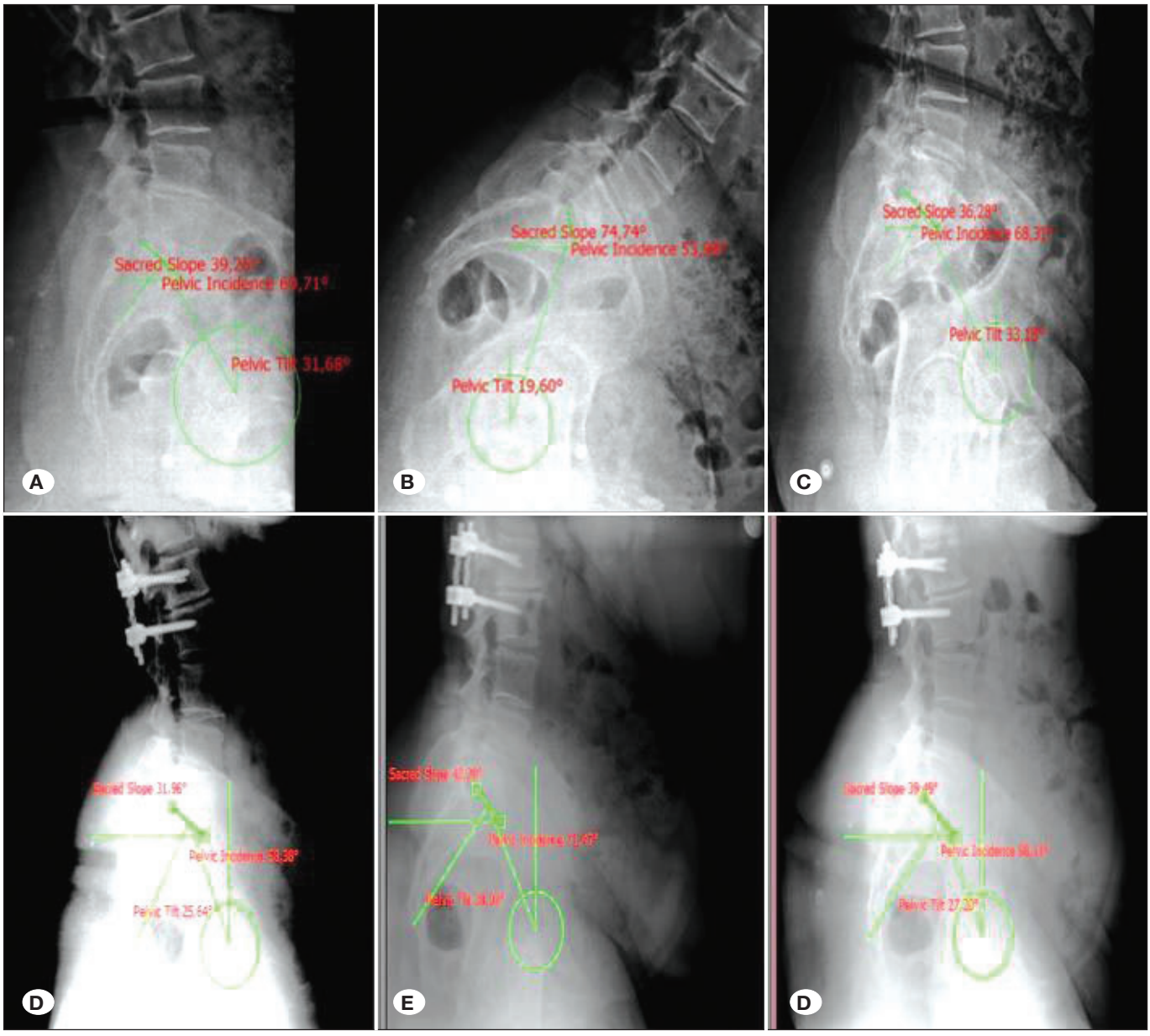

Figure 2: Lateral lumbar spinal radiograps of a patient in neutral **(A)**, flexion **(B)**, and extension **(C)** positions before surgery. Neutral **(D)**, flexion **(E)** and extension **(F)** radiographs (including measurements) of a patient who underwent surgery for lumbar (L) 1-2 extruded disc herniation. Discectomy and dynamic posterior stabilization was performed.

p=0.001). A positive correlation was determined between NLR and PLR (r=0.692; p=0.002), and between MPV and RDW (r=0.788; p=0.001). No correlation was determined between PAIP and the radiological measurements (PI, PT, SS) used for SI.

DISCUSSION

Surgical restoration of global alignment and minimization of complications through several options can successfully improve the pain and function of sagittal deformity. This restoration cannot be considered without evaluating the inflammatory conditions. The objective of this retrospective cohort study was to determine which PAIP could contribute to understanding inflammatory events in the SI, which has important implications for neurosurgeons. The results of the study suggested that the surgical approach should cover not only the sagittal parameters and angles but also the PAIP showing inflammatory events originating from platelets.

Neurosurgeons must keep in mind that spinal surgeons should carefully consider the spinopelvic parameters in spinal pathologies prior to surgical intervention and perform surgical procedures to provide postoperative balance of spine (4).

Table II: Laboratory Results of the Groups

Variables	Control	Patients	p
Glucose (mg/dL)	95 ± 8	97 ± 10	0.221
Uric Acid (mg/dL)	4.7 ± 1.2	4.5 ± 1.3	0.465
Albumin (g/dL)	4.5 ± 0.2	4.5 ± 0.4	0.344
BUN (mg/dL)	34.7 ± 15.2	32.9 ± 13.8	0.525
Creatinine (mg / L)	0.7 ± 0.2	0.8 ± 0.2	0.209
AST (U/L)	20 ± 9	20 ± 9	0.992
ALT (U/L)	21 ± 14	22 ± 13	0.798
ESR (mm/h)	3 ± 1	24 ± 19	**0.0001**
CRP (mg/dL)	2.5 ± 1.3	7 ± 7.2	**0.001**
Fibrinogen (mg/dL)	269 ± 51	277 ± 71	0.401
Calcium (mg/dL)	9.1 ± 0.5	9.3 ± 0.5	0.069
Magnesium (mg/dL)	1.9 ± 0.1	1.9 ± 0.1	0.345
ELISA Findings			
25-OH-D (pg/mL)	19.7 ± 5.6	22 ± 7.4	0.094
TSH (ng/ml)	2.2 ± 0.95	2.1 ± 0.88	0.235
Free T_3 (pg/ml)	1.5 ± 0.38	1.4 ± 0.55	0.408
Free T_4 (pg/ml)	3.1 ± 0.78	3 ± 0.51	0.178
PTH (ng/ml)	29.2 ± 6.25	31 ± 4.41	0.589
Haematological Findings			
Leukocyte (x10^9/L)	6.2 ± 1.6	6.3 ± 1.6	0.645
Neutrophyl (x10^9/L)	3.9 ± 1.2	6.5 ± 8	0.095
Lymphocyte (x10^9/L)	1.7 ± 0.7	2 ± 0.8	**0.045**
Platelet (x10^9/L)	244 ± 64	293 ± 104	0.086
Heamoglobin (g/dl)	13.3 ± 1.1	13.2 ± 1.1	0.574
Hematocrite (%)	38.2 ± 2.8	37.9 ± 2.7	0.672
RBC (x10^9/L)	4.4 ± 0.4	4.4 ± 0.4	0.893
MCV (fL)	86 ± 6	86 ± 7	0.878
MCH (pg)	98.3 ± 453	82.6 ± 398	0.876
MCHC (g/dL)	34.9 ± 0.7	34.8 ± 0.6	0.853
N/L Ratio (NLR)	2.5 ± 1.1	4.2 ± 5.7	**0.033**
P/L Ratio (PLR)	158 ± 74.4	162.3 ± 74	0.774
MPV (fL)	8.5 ± 0.8	10.6 ± 0.9	**0.0001**
PDW (%)	15.2 ± 2.2	12.7 ± 2.2	**0.001**
RDW (%)	14.5 ± 1.5	41.9 ± 4.4	**0.0001**

If the LL and spinopelvic adaptation required to restore the balance cannot be achieved after the surgical interventions, the expected positive response from the surgical treatment will not be attained due to the continued SI (15). Kocyigit et al reported that measurements taken from radiographs such as PI, SS, PT, and LL, have a critical role in providing sufficient information about SI (14). For example, ankylosing spondylitis is a chronic inflammatory rheumatic disease characterized by inflammation of the vertebrae, which progresses to bone fusion of the spinal column (33). Sagittal spinal balance can be influenced from the onset of the disease and can result in the development of a rigid, non-flexible spinal column and thoracolumbar kyphosis (24). Therefore, the aim of this study was to investigate if these measurements can provide information not only for conditions of SI but also for events with an inflammatory process.

The synovial tissue and cartilage of the facets contain inflammation related cytokines, which may be in touch with a nerve root, and as reported by Cohen and Raja, with the occurrence of pathological changes in nerve tissue, behavioural deficits may be seen (3). All the reports show that radicular symptoms can be induced by biochemical factors generated by facet degeneration affecting to nerve roots. Increased expression of interleukins in the facets supports the outcome that biochemical inflammatory agents may be the major reason (20). It is clear that there are inflammatory events in diseases that progress to conditions of SI. Tsang and Chung stated that CRP was the most useful tool in screening for axial-joint inflammation (27), and this test is still accepted as useful despite its low sensitivity and specificity. This also led to a search for novel useful markers similar to CRP. Recent studies have shown platelets to be the most important potential inflammatory candidates and changing values could be useful to demonstrate events of SI (2,30). Therefore, platelet-related parameters were analysed in this study in addition to CPR and ESR. As previously reported, the ESR and CRP values in the current study patients were found to be reased as expected in SI (3,27). However, it is clear that additional parameters are necessary for further evaluations of inflammation in SI.

The benefit of using PAIP has been shown in the evaluation of systemic inflammation in various health problems such as diabetes mellitus, ulcerative colitis, cirrhosis and cancer [18–24]. In recently, increased level of PLR was strongly associated with activity and severity of psoriasis and RA, as well as psoriatic arthritis (8,12,31). Apart from rheumatology disorders, higher PLR, as a ratio of inflammation, behaves to be associated with lessened survival in gastric and pancreatic malignities (25). Similarly, levels of MPV were investigated widely in the recent decade. Increased MPV was on the other hand mainly found in states of low grade inflammation such as: cellulitis, idiopathic subjective tinnitus, symptom/attack-free periods of familial Mediterranean fever patients and irritable bowel syndrome, obstructive sleep apnea syndrome (5,6,11,22).

In a few recent studies, the NLR value has been determined to be higher in RA patients compared to control subjects, and to be associated with disease activity (25–27). Kantola

et al. reported that there was a positive correlation between increased NLR in neoplastic disorders and certain cytokines (10), some of which are present in the pathogenesis of RA and AS (18,26). According to Kisacik et al., MPV values in RA could provide additional information about inflammatory events (13). While a positive correlation between MPV and ESR was reported in a study by Sag et al., no correlation with CRP was found (23). In the current study, MPV and PDW showed a significant increase in the SI patients although NLR showed only slight significance in the SI patients compared to the control group. In contrast, PLR, which is accepted as a significant inflammatory indicator, had no significance when the SI group was compared with the control group. Unlike other relevant studies, Sag et al. found no relationship between CRP and PAIP such as NLR, PLR, MPV, PDW (23). Similar to that study, no significant correlations were determined between CRP and PAIP in the current study patient group. Although the SS and PT values varied significantly in the SI patients, the value of PI was not different from that of the control group. When the correlations were considered, the PT value had a positive correlation with length of hospital stay in the SI patients. MPV demonstrated a strong positive correlation with comorbidity. In contrast, there was no correlation between PAIP and the radiological measurements (PI, PT, SS) used for SI.

This study had limitations in terms of design and capacity. As the study was retrospective and cross-sectional, it was not possible to analyse inflammatory cytokines such as IL-1, TNF-a, IL-10 and rheumatology-related biomarkers such as ANA, ASA, RF in these patients. A second limitation was the small number of patients for a retrospective analysis and the relationship of PAIP with pain scores could not be evaluated, as it was not a prospective analysis. In addition, any difference between the deformity patients regarding inflammatory parameters may change the outcome scores. We were unable to indicate if any relation between the surgical results and inflammatory parameters in the SI patients. The diagnostic history could not be fully determined from the patient database for all the SI patients and thus the comprehensive diagnosis was accepted as SI.

CONCLUSION

The results of this study suggest that the neurosurgical approach should cover not only the sagittal parameters and their angles but also PAIP showing inflammatory events originating from platelets. There is still much to be learned about the interactions and the influence of the many components that regulate the inflammatory process in SI. It can be considered that improvements in the knowledge and understanding of platelet-related inflammation and its effects on spinal surgery could improve future diagnostic and therapeutic approaches.

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