Effect of ozone therapy on neutrophil/lymphocyte, platelet/lymphocyte ratios, and disease activity in ankylosing spondylitis: a self-controlled randomized study

Habibe İnci[1,*], Fatih İnci[2]
1 Department of Family Medicine, Faculty of Medicine, Karabuk University, Karabuk, Turkey
2 Department of İnternal Medicine and Medical Oncology, Faculty of Medicine, Karabuk University, Karabuk, Turkey

*Correspondence to: Habibe İnci, MD, drhbesler@hotmail.com.
orcid: 0000-0003-2883-259X (Habibe İnci); 0000-0002-7590-7630 (Fatih İnci)

Abstract

This retrospective self-controlled randomized study was carried out with the participation of 53 patients diagnosed with ankylosing spondylitis according to the modified New York criteria. The patients who did not receive medical treatment or did not change their medical treatment within the last 6 months were included in the study. There was a statistically significant decrease in the patients' neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, monocyte/lymphocyte ratio, C-reactive protein, Visual Analog Scale, Bath Ankylosing Spondylitis Functional Index, and Bath Ankylosing Spondylitis Disease Activity Index scores measured after ozone therapy. There was a positive correlation between neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, mean platelet volume/lymphocyte ratio, monocyte/lymphocyte ratio and C-reactive protein, Visual Analog Scale, Bath Ankylosing Spondylitis Functional Index, Bath Ankylosing Spondylitis Disease Activity Index before and after ozone therapy. Our study revealed that the changes in the decreasing tendency of the markers measured in complete blood count after ozone therapy were correlated with the disease activity, which can contribute to understand the effect of ozone therapy on biomarkers.

Key words: ankylosing spondylitis, Bath Ankylosing Spondylitis Disease Activity Index, Bath Ankylosing Spondylitis Functional Index, C-reactive protein, monocyte/lymphocyte ratio, neutrophil/lymphocyte ratio, ozone therapy, platelet/lymphocyte ratio, Visual Analog Scale

doi: 10.4103/2045-9912.344981
How to cite this article: İnci H, İnci F. Effect of ozone therapy on neutrophil/lymphocyte, platelet/lymphocyte ratios, and disease activity in ankylosing spondylitis: a self-controlled randomized study. Med Gas Res. 2023;13(2):53-58.

Introduction

Ozone therapy (OT) is a treatment method used in traditional and complementary medicine. OT can be used to increase body resistance, help treat diseases or reduce symptoms.[1,2] Studies have shown that systemic application of OT is very effective in reducing the organ damage mediated by inflammation and oxidative stress.[3] OT is known to have some cytoprotective effects against the tissue damage in many inflammatory diseases.[3]

Ankylosing spondylitis (AS) is a chronic, systemic, and inflammatory disease that often affects the sacroiliac joint and spine. It represents the archetype of spondyloarthropathies. The etiology of AS is unknown, but in 90–95% of the cases, it is associated with the presence of human leukocyte antigen B27.[4] AS mostly affects male patients, and its prevalence is between 0.5% and 1% worldwide.[5-7] It can be diagnosed clinically and radiographically using modified New York diagnostic criteria.[7,8] There is no diagnostic test specific to AS.[7]

Parameters of hemogram have a significant place in the assessment of various diseases. Neutrophils, lymphocytes, and platelets play a role in the control of inflammation, as well as the changes secondary to inflammation. They are responsible for the production of many lytic enzymes, free oxygen radicals, and cytokines. Cytokines have a very significant role in the pathogenesis of a great number of inflammatory diseases.[9] Complete blood count (CBC) is routinely performed in clinics for the diagnosis of rheumatic diseases. Neutrophil and platelet counts increase and lymphocyte counts decrease with the increase of inflammation in autoimmune diseases.[10] Neutrophil/lymphocyte ratio (NLR) and platelet/lymphocyte ratio (PLR) are used as indicators for inflammation and disease activity in systemic lupus erythematosus, rheumatoid arthritis, and AS.[7,9] Lymphocytes, neutrophils, platelets, mean platelet volume (MPV), and monocytes play a central role in the inflammatory response. NLR, PLR, MPV/lymphocyte ratio (MPVLR), and monocyte/lymphocyte ratio (MLR), which can be obtained by total blood count, are shown as new markers in the evaluation of systemic inflammatory response and they are used to monitor the prognosis, morbidity, and mortality of many diseases.[11-13] NLR, PLR, MPVLR, and MLR are easily determined by CBC and have been reported to increase in the presence of inflammation. There are studies showing that NLR, PLR, MLR, and MPVLR are higher in individuals with inflammation than in healthy individuals, and their levels are directly proportional to disease activity. There are similar findings for other inflammatory diseases.[12,14] NLR, PLR, MPVLR, and MLR can be used as systemic inflammatory response markers in rheumatoid arthritis, AS, ulcerative colitis, malignancies, diabetes mellitus, chronic obstructive pulmonary disease, and other rheumatic diseases.[15-18] High NLR and PLR point to a predominance of inflammatory factors in the etiopathogenesis of different conditions. PLR is also a new

biomarker that refers to the presence inflammation. PLR has been studied in many inflammatory conditions like rheumatoid arthritis and systemic lupus erythematosus in addition to malignancies in different organs such as hepatocellular carcinoma and gastrointestinal stromal tumors.[19] Systemic inflammation is known to elevate the C-reactive protein (CRP) and change the relative proportion of white blood cells, raising the neutrophil count and lowering the lymphocyte count.[20] These parameters can be evaluated quickly, cheaply, and easily by clinicians in laboratory.

In patients with AS, Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) are used to evaluate the functional limitation and disease activity, respectively; on the other hand, Visual Analog Scale (VAS) is used to evaluate the degree of pain.[21]

We thought that OT would have positive effects on inflammatory parameters and disease activity in patients with AS. In this study, we aimed to investigate the effect of OT in patients with AS by comparing the outcomes before and after the OT sessions.

Subjects and Methods

Subjects

An informed consent form was obtained from each patient for the procedure. The patients' written informed consent and the sample procedure documents were submitted to the ethics committee. In addition, the ethics committee was informed that the study was retrospective. Ethical approval was obtained for this study from the Karabuk University Ethics Committee (approval No. 2020/238, approval date: May 28, 2020).

Study design

This retrospective self-controlled randomized study was carried out with the participation of the patients who were previously diagnosed with AS according to the modified New York criteria.[8] 53 patients with AS who underwent OT in the Traditional and Complementary Medicine Clinic in the Karabuk University Training and Research Hospital between February 2019 and April 2020 participated in the study. The patients who did not receive medical treatment or who did not change their medical treatment within the last 6 months were included in the study. The patients' parameters of CRP and CBC and their BASFI, BASDAI, and VAS scores were obtained from their files before and after the OT. In our clinic, BASFI, BASDAI, and VAS forms are routinely filled in at the first visit. After all the treatment sessions are completed, these forms are filled in again and put in the patient file. In our clinic, in order to evaluate the effectiveness of the treatment, CRP values are routinely measured before and after OT. CBC and CRP values were measured in the morning after 12 hours of fasting and then the NLR, PLR, MPVLR, and MLR were calculated. It was evaluated whether there were statistically differences in terms of these parameters before and after OT, and a correlation analysis was carried out.

The patients meeting the following inclusion criteria were recruited in the study: patients at the age of 18–65 years, who were previously diagnosed with AS according to the Modified New York criteria were included in the study. Patients who did not receive medical treatment or who did not change their medical treatment within the last 6 months were included in the study. Patients with normal results from CBC test, coagulation tests, and thyroid, and renal and liver function tests were included in the study. Patients with an active infection, pregnant patients, those who could not complete the OT sessions for any reason (financial problems, transportation problems, etc.), and those with missing file data were excluded from the study (**Figure 1**).

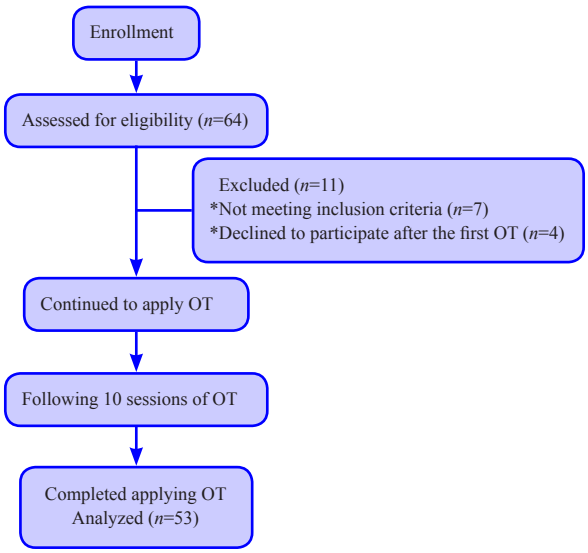

Figure 1: Flow diagram of the study.
Note: Sixty-four AS patients were studied. Eleven persons from AS patients were excluded from the study. Of these, seven patients were excluded from the study because they did not meet the inclusion criteria, and also four patients were excluded from the study because they discontinued therapy after the first OT. As a result, data of 53 AS patients who underwent 10 sessions of OT were analyzed. AS: Ankylosing spondylitis; OT: ozone therapy.

Statistical differences and relationships between the CBC, NLR, PLR, MPVLR, MLR, and CRP values and the BASFI, BASDAI, and VAS scores were evaluated before and after the OT sessions.

CBC and CRP values were measured in the morning after 12 hours of fasting and then, NLR, PLR, MPVLR, and MLR were calculated.

BASFI is a fast, reliable, easy-to-apply, and sensitive-to-changes index used to determine and monitor the functional status in patients with AS. It consists of questions that evaluate patients' ability to bend, reach, stand, change positions, climb stairs, and cope with daily life activities. The higher the score, the more deteriorated the functional state.[22] The Turkish validation study of BASFI was carried out by Ozer et al.[23] and we used the Turkish version of the index reported in that study.

BASDAI evaluates disease-specific symptoms such as fatigue, spinal and peripheral joint pain, swelling and morning stiffness in patients with AS. The higher the score, the higher the disease activity. It is a reliable, variable, and sensitive index developed to evaluate disease activity and progression.[24] The Turkish validation study of BASDAI was carried out by Akkoc et al.[25] and we used the Turkish version of the index reported in that study.

VAS evaluates the pain level of patients, and its scoring is within the range of 0–10, where 0 refers to "no pain," and 10 refers to "unbearable pain."[26] BASFI, BASDAI, and VAS were measured and recorded by a medical doctor.

OT is carried out in our clinic by a medical doctor who has OT training and is certified in this regard. In our clinical practice, the treatment consists of 10 sessions applied twice a week in chronic painful diseases (AS, fibromyalgia, rheumatoid arthritis, etc.).

In our clinic, the OT protocol is routinely applied to patients with AS in accordance with the Madrid Declaration by the International Scientific Committee of Ozone Therapy.[2] OT procedures for patients with AS consist of Major Auto-Hemotherapy. Major Auto-Hemotherapy involves the injection of medical grade ozone gas in Turkey into the blood drawn from a patient. The ozone (20 µg/mL) is allowed to mix with the blood (100 mL) for a few minutes. The ozonated blood is then intravenously infused back into the same patient. A total of 10 sessions of OT were applied twice a week, depending on the age and general condition of the patients. VAS, BASFI, and BASDAI scores and blood tests were measured for each patient with AS just before the first OT session in the first week and after the last OT session in the fifth week. No treatment-related complications were observed in the patients. There was no cessation of treatment due to side effects in our patients.

Statistical analysis

IBM SPSS software package (v.22.0; SPSS Inc., Armonk, NY, USA) was used in the statistical data analysis. In the comparison before and after the intervention, paired samples *t*-test was used for normally distributed values and Wilcoxon signed rank test for non-parametric data. Categorical data were compared with chi-square test. Pearson test were used for the correlation analysis between the NLR, PLR, MPVLR, MLR, and CRP values, and the BASFI, BASDAI, and VAS scores. The statistical significance was set at $P < 0.05$.

Results

53 patients with AS were included in the study. 50.9% (n = 27) of the patients were male and 49.1% (n = 26) were female. Their average age was 44.50 ± 8.85 years.

Parameters and scores of patients before and after OT

There was a statistically significant decrease in their neutrophil, platelet, and CRP values and NLR, PLR, and MLR measured after the OT sessions. After the OT, the patients' mean VAS, BASFI, BASDAI scores decreased (**Table 1**).

Correlation analysis between parameters and scores in patients

Correlation analysis was carried out before the OT sessions to evaluate the relationships between the patients' BASFI, BASDAI, and VAS scores, and their CRP values and NLR, PLR, MPVLR, and MLR. NLR was found to have a positive correlation with CRP levels ($r = 0.697$; $P < 0.001$), VAS scores ($r = 0.482$; $P < 0.001$), BASFI scores ($r = 0.465$; $P < 0.001$), and BASDAI scores ($r = 0.655$; $P < 0.001$). PLR was found to have a positive correlation with CRP levels ($r = 0.583$; $P < 0.001$), VAS scores ($r = 0.335$; $P = 0.014$), and BASDAI scores ($r = 0.382$; $P = 0.005$). MPVLR was found to have a positive correlation with CRP levels ($r = 0.286$; $P = 0.038$) and VAS scores ($r = 0.351$; $P = 0.010$). MLR was found to have a positive correlation with CRP levels ($r = 0.361$; $P = 0.008$).

The second correlation analysis was carried out after the OT sessions, again, to evaluate the relationships between the patients' BASFI, BASDAI and VAS scores, and their CRP

Table 1: Complete blood count parameters, C-reactive protein, Visual Analog Scale, Bath Ankylosing Spondylitis Functional Index and Bath Ankylosing Spondylitis Disease Activity Index scores of ankylosing spondylitis patients before and after OT

Variables	Before OT	After OT	Mean difference	95% confidence interval	*P*-value
Age (yr)	44.50±8.85	–	–	–	N/A
Neutrophil (×10^3/mm^3)	3.81±1.67	3.03±1.01	0.776	0.339–1.214	0.001
Lymphocyte (×10^3/mm^3)	2.46±0.12	2.44±0.80	0.024	–0.122–0.171	0.74
Platelet (×10^3/mm^3)	299.51±75.01	271.83±55.72	27.679	18.135–37.224	< 0.001
Mean platelet volume (fL)	9.47±0.69	9.06±1.88	0.4	–0.075–0.876	0.098
Monocyte (×10^3/mm^3)	0.52±0.16	0.49±0.21	0.032	–0.004–0.069	0.082
Eosinophil (×10^3/mm^3)	0.22±0.16	0.20±0.13	0.015	–0.024–0.055	0.433
Neutrophil/lymphocyte ratio	1.74±0.99	1.36±0.08	0.374	0.137–0.612	0.003
Platelet/lymphocyte ratio	137.10±58.78	124.67±54.03	12.431	2.168–22.694	0.019
Mean platelet volume/lymphocyte ratio	4.42±1.70	4.03±1.60	0.391	–0.045–0.828	0.078
Monocyte/lymphocyte ratio	0.23±0.10	0.21±0.10	0.022	0.002–0.043	0.03
C-reactive protein (mg/L)	5.84±8.56	2.02±2.92	3.822	2.157–5.487	< 0.001
Visual Analog Scale	7.40±1.81	3.64±1.78	3.755	3.469–4.040	< 0.001
Bath Ankylosing Spondylitis Functional Index	5.98±1.72	3.42±1.56	2.558	2.147–2.969	< 0.001
Bath Ankylosing Spondylitis Disease Activity Index	6.39±1.89	3.68±1.46	2.709	2.273–3.145	< 0.001

Note: Data are expressed as mean ± SD (n = 53) and were analyzed by paired samples *t*-test. N/A: Not applicable; OT: ozone therapy.

values and NLR, PLR, MPVLR, and MLR. NLR was found to have a positive correlation with CRP levels ($r = 0.307$; $P = 0.025$), VAS scores ($r = 0.294$; $P = 0.033$). PLR was found to have a positive correlation with CRP levels ($r = 0.644$; $P < 0.001$), VAS scores ($r = 0.399$; $P = 0.003$). MLR was found to have a positive correlation with CRP levels ($r = 0.565$; $P < 0.001$) (**Table 2** and **Figure 2**).

No adverse events were reported during the study.

Discussion

Although AS is more common in male patients, OT use is higher in women.[27] For this reason, the numbers of female and male patients with AS treated with OT were close to each other in our study.

NLR, PLR, and MLR can be used as systemic inflammatory response markers in rheumatoid arthritis, ulcerative colitis, malignancies, diabetes mellitus, chronic obstructive pulmonary disease, and other rheumatic diseases.[15-18] The patients' CRP, CBC parameters, and VAS, BASFI, and BASDAI scores before and after the OT sessions were compared. We examined the changes in easily detectable markers such as NLR, PLR, MPVLR, and MLR with OT application in AS. We observed that there was a significant decrease in CRP, NLR, PLR, and MLR levels, and VAS, BASFI, and BASDAI scores after the OT in the patients with AS.

In the literature, it has been reported that patients with AS have higher rates of NLR and PLR compared to the control group. Counts of neutrophil, NLR, CRP levels, and PLR were

Table 2: Pearson partial correlation analysis between NLR, PLR, MPVLR, MLR, CRP, VAS, BASFI and BASDAI scores in ankylosing spondylitis patients

	Before ozone therapy				After ozone therapy			
	CRP	VAS	BASFI	BASDAI	CRP	VAS	BASFI	BASDAI
Neutrophil/lymphocyte ratio								
r	0.697	0.482	0.465	0.655	0.307	0.294	0.025	0.216
95% confidence interval	0.461–0.839	0.295–0.613	0.289–0.621	0.496–0.758	0.025–0.575	0.051–0.503	–0.218–0.303	–0.100–0.470
P	< 0.001	< 0.001	< 0.001	< 0.001	0.025	0.033	0.858	0.121
Platelet/lymphocyte ratio								
r	0.583	0.335	0.226	0.382	0.644	0.399	–0.063	0.104
95% confidence interval	0.285–0.759	0.140–0.508	–0.066–0.460	0.135–0.573	0.392–0.806	0.176–0.610	–0.284–0.220	–0.155–0.389
P	< 0.001	0.014	0.103	0.005	< 0.001	0.003	0.651	0.459
Mean platelet volume/ lymphocyte ratio								
r	0.286	0.351	0.075	0.04	0.02	0.166	0.042	0.099
95% confidence interval	0.058–0.500	0.127–0.558	–0.180–0.332	–0.212–0.290	–0.369–0.423	–0.117–0.472	–0.216–0.304	–0.121–0.315
P	0.038	0.01	0.592	0.778	0.888	0.236	0.766	0.479
Monocyte/lymphocyte ratio								
r	0.361	0.206	0.118	0.056	0.565	0.251	–0.238	–0.101
95% confidence interval	–0.028–0.634	–0.014–0.421	–0.099–0.360	–0.230–0.325	0.177–0.830	0.046–0.450	–0.409 to –0.024	–0.222–0.000
P	0.008	0.139	0.402	0.691	< 0.001	0.07	0.086	0.474

Note: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; VAS: Visual Analog Scale.

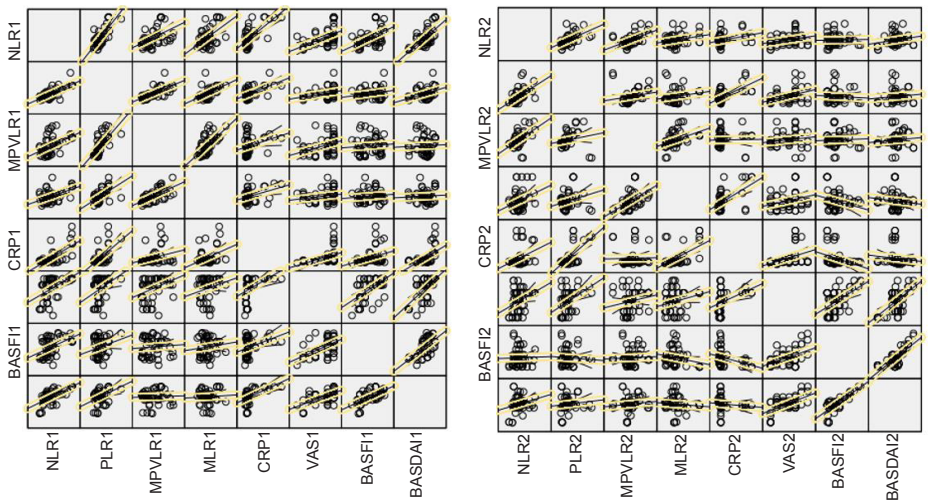

Figure 2: The scatter diagram (scatterplot, matrix) for the correlation analysis between NLR, PLR, MPVLR, MLR, CRP, VAS, BASFI and BASDAI scores in ankylosing spondylitis patients.
Note: BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein; MCR: monocyte/lymphocyte ratio; MPVL: mean platelet volume/lymphocyte ratio; NLR: neutrophil/lymphocyte ratio; PLR: platelet/lymphocyte ratio; VAS: Visual Analog Scale.

reported to be significantly higher in the patients having a BASDAI score ≥ 4 with a moderate-severe disease activity compared to the healthy controls and the patients having a BASDAI score < 4 with mild disease activity.[7] In the patients with AS in our study, the BASDAI score was > 4 (6.39 ± 1.89) at baseline, indicating the activation period. After the OT, BASDAI score decreased to < 4 (3.68 ± 1.46). The BASDAI scores correlated weakly with the neutrophil counts, NLR, and PLR, and moderately with CRP and erythrocyte sedimentation rate. It has been reported that NLR and PLR may indicate disease activity in AS.[28]

The previous observational studies have thoroughly investigated the role of CRP and total leukocyte count in different chronic conditions.[29-32] NLR could be an important measure of systemic inflammation as it is cost effective, readily available and could be calculated easily.[32] In our study, in the patients with AS, the disease function and activity, NLR, PLR, MLR, CRP, and pain levels were found to decrease after the OT application. The NLR levels in the patients with AS correlated positively with the CRP levels, pain levels, and disease function and activity. The PLR levels positively correlated with the CRP levels, pain levels, and disease activity. The MPVLR levels positively correlated with the CRP levels and pain levels. The MLR levels positively correlated with CRP levels.

In addition, it was observed that the pain level and disease impact were high before the OT application. There was a significant decrease in the patients' mean BASDAI, BASFI, and VAS scores after the OT sessions were completed.

In our study, a decrease was observed in the laboratory values and scores after the OT. Since this is a retrospective study, other factors that might have affected the results (lifestyle changes, food consumption habits, etc.) have not been clearly defined. There is a need for prospective randomized controlled trials in future to directly correlate these positive results with OT, since the laboratory parameters are highly affected by some uncontrolled factors.

One limitation of our study is that this is a retrospective study, but not a randomized controlled study. Another limitation is that it is a single-center study. The significance of our study lies in that, in the literature, there is no other study investigating the change in disease activity and blood parameters (NLR, PLR, MPVLR, MLR) in patients with AS undergoing OT treatment.

This study compared the blood parameters before and after OT in patients with AS, which contributes to understanding the effect of OT on biomarkers. OT could decrese disease function and activity, NLR, PLR, MLR, CRP, and pain levels in such patients. Their NLR levels were positively correlated with the CRP and pain levels, disease function, and disease activity. Their PLR levels were positively correlated with the CRP and pain levels and disease activity. Their MPVLR levels were positively correlated with the CRP levels and pain levels. Their MLR levels were positively correlated with the CRP levels. Therefore, there is a need for prospective randomized controlled studies in future to understand the effects of OT treatment on blood parameters in patients with AS.

Author contributions
Hİ and Fİ participated in study design, literature search, sample and data collection, data analysis, manuscript writing and review. All authors approved the final version of the manuscript.
Conflicts of interest
No conflict of interest was declared by the authors.
Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Additional file
Additional file 1: CONSORT Checklist.

References

1. Cespedes-Suarez J, Martin-Serrano Y, Carballosa-Peña MR, Dager-Carballosa DR. Clinical study of patients with heart failure under treatment with ozone therapy. *J Ozone Ther*. 2018;2.
2. International Scientific Committee. Madrid declaration on ozone therapy. Madrid: 2010.
3. Martínez-Sánchez G, Schwartz A, Donna VD. Potential cytoprotective activity of ozone therapy in SARS-CoV-2/COVID-19. *Antioxidants (Basel)*. 2020;9:389.
4. Sheehan NJ. The ramifications of HLA-B27. *J R Soc Med*. 2004;97:10-14.
5. Farooqi A, Gibson T. Prevalence of the major rheumatic disorders in the adult population of north Pakistan. *Br J Rheumatol*. 1998;37:491-495.
6. Hameed K, Gibson T. A comparison of the prevalence of rheumatoid arthritis and other rheumatic diseases amongst Pakistanis living in England and Pakistan. *Br J Rheumatol*. 1997;36:781-785.
7. Zeb A, Khurshid S, Bano S, et al. The role of the neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as markers of disease activity in ankylosing spondylitis. *Cureus*. 2019;11:e6025.
8. Khurshid MA. Current rheumatology diagnosis & treatment. In: Imboden J, Hellmann D, Stone. J, eds. *Rheumatology*. Vol 4. New York: McGraw-Hill (Lange Medical Publications); 2008:578.
9. Qin B, Ma N, Tang Q, et al. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) were useful markers in assessment of inflammatory response and disease activity in SLE patients. *Mod Rheumatol*. 2016;26:372-376.
10. Li L, Xia Y, Chen C, Cheng P, Peng C. Neutrophil-lymphocyte ratio in systemic lupus erythematosus disease: a retrospective study. *Int J Clin Exp Med*. 2015;8:11026-11031.
11. Yucel C, Keskin MZ, Cakmak O, et al. Predictive value of preoperative inflammation-based prognostic scores (neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and monocyte-to-eosinophil ratio) in testicular sperm extraction: a pilot study. *Andrology*. 2017;5:1100-1104.
12. Kose N, Akin F, Yildirim T, Ergun G, Altun I. The association between the lymphocyte-to-monocyte ratio and coronary artery disease severity in patients with stable coronary artery disease. *Eur Rev Med Pharmacol Sci*. 2019;23:2570-2575.
13. Hudzik B, Szkodziński J, Lekston A, Gierlotka M, Poloński L, Gąsior M. Mean platelet volume-to-lymphocyte ratio: a novel marker of poor short- and long-term prognosis in patients with diabetes mellitus and acute myocardial infarction. *J Diabetes Complications*. 2016;30:1097-1102.

14. Uslu AU, Küçük A, Şahin A, et al. Two new inflammatory markers associated with Disease Activity Score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. *Int J Rheum Dis*. 2015;18:731-735.
15. Zengin O, Onder ME, Kalem A, et al. New inflammatory markers in early rheumatoid arthritis. *Z Rheumatol.* 2018;77:144-150.
16. Jeong Y, Jeon SR, Kim HG, et al. The role of platelet to lymphocyte ratio and neutrophil to lymphocyte ratio in ulcerative colitis. *Intest Res*. 2021;19:62-70.
17. Jan HC, Yang WH, Ou CH. Combination of the preoperative systemic immune-inflammation index and monocyte-lymphocyte ratio as a novel prognostic factor in patients with upper-tract urothelial carcinoma. *Ann Surg Oncol.* 2019;26:669-684.
18. Gumus F, Solak I, Eryilmaz MA. The effects of smoking on neutrophil/lymphocyte, platelet/ /lymphocyte ratios. *Bratisl Lek Listy.* 2018;119:116-119.
19. Hammad M, Shehata OZ, Abdel-Latif SM, El-Din AMM. Neutrophil/lymphocyte ratio and platelet/lymphocyte ratio in Behçet's disease: which and when to use? *Clin Rheumatol*. 2018;37:2811-2817.
20. Song A, Eo W, Lee S. Comparison of selected inflammation-based prognostic markers in relapsed or refractory metastatic colorectal cancer patients. *World J Gastroenterol.* 2015;21:12410-12420.
21. Madsen OR. Stability of fatigue, pain, patient global assessment and the Bath Ankylosing Spondylitis Functional Index (BASFI) in spondyloarthropathy patients with stable disease according to the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). *Rheumatol Int.* 2018;38:425-432.
22. Calin A, Garrett S, Whitelock H, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. *J Rheumatol.* 1994;21:2281-2285.
23. Ozer HT, Sarpel T, Gulek B, Alparslan ZN, Erken E. The Turkish version of the Bath Ankylosing Spondylitis Functional Index: reliability and validity. *Clin Rheumatol*. 2005;24:123-128.
24. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. *J Rheumatol.* 1994;21:2286-2291.
25. Akkoc Y, Karatepe AG, Akar S, Kirazli Y, Akkoc N. A Turkish version of the Bath Ankylosing Spondylitis Disease Activity Index: reliability and validity. *Rheumatol Int*. 2005;25:280-284.
26. Wewers ME, Lowe NK. A critical review of visual analogue scales in the measurement of clinical phenomena. *Res Nurs Health.* 1990;13:227-236.
27. Kayhan M, Dilekci E. Evaluation of the applications of traditional and complementary medicine in the perspective of family medicine in a tertiary referral center. *Med Sci.* 2020;9:216-220.
28. İnal EE, Sunar İ, Sarataş Ş, Eroğlu P, İnal S, Yener M. May neutrophil-lymphocyte and platelet-lymphocyte ratios indicate disease activity in ankylosing spondylitis? *Arch Rheumatol*. 2015;30:130-137.
29. Lee S, Choe JW, Kim HK, Sung J. High-sensitivity C-reactive protein and cancer. *J Epidemiol*. 2011;21:161-168.
30. Saito K, Kihara K. C-reactive protein as a biomarker for urological cancers. *Nature reviews Urology.* 2011;8:659-666.
31. Yasue H, Hirai N, Mizuno Y, et al. Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers. *Circ J.* 2006;70:8-13.
32. Imtiaz F, Shafique K, Mirza SS, Ayoob Z, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. *Int Arch Med*. 2012;5:2.

Date of submission: December 9, 2020
Date of decision: January 25, 2021
Date of acceptance: March 27, 2021
Date of web publication: May 12, 2022