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Original Article

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Could Neutrophil-lymphocyte and Platelet-lymphocyte ratio be used to monitor patients with deep vein thrombosis?

Abstract

Aim: The inflammatory process plays an important role in cardiovascular diseases. Therefore, many markers have been used to detect the inflammatory process. It has been reported that neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) can be used to detect the inflammatory process in patients with deep vein thrombosis. In this study, we aim to investigate whether NLR and PLR values change as a result of different deep vein thrombosis treatment protocols.

Material and Methods: A total of 84 patients, 51 male and 33 female were included in the study. The mean age of the participants was 56.32±12.87. The patients were divided into three groups: the control group (group 1), the group treated with warfarin (group 2), and the group treated with rivaroxaban (group 3).

Results: The results of the analysis obtained at the time of the detection of deep vein thrombosis were compared with the results of the blood tests performed in the first month after the treatment.

In patients with deep vein thrombosis, white blood cell, neutrophil, and eosinophil values, as well as NLR and PLR values were found to be higher than the individuals in the control group. After one month of different deep vein thrombosis treatment protocols, there was no significant difference between group 2 and group 3 in terms of NLR and PLR values.

Conclusion: It has been observed that NLR and PLR values increase as a reflection of the inflammatory process after deep vein thrombosis. However, no significant change was observed in NLR and PLR values with rivaroxaban and warfarin treatments, and it was concluded that these two markers may not be suitable for following the inflammatory process.

Keywords: Deep vein thrombosis, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, inflammation

INTRODUCTION

Cardiovascular diseases remain one of the most important health problems in the world. The inflammatory response plays an important role in the pathogenesis and progression of cardiovascular system diseases (1). Studies have shown that platelet activation and inflammation are very important in the development of thrombosis (2). Several markers have been used to detect the inflammatory response. Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) ratios are easily calculated markers that indicate systemic inflammation. Many studies have shown that NLR can be used to predict prognosis in cardiovascular diseases (3). It has been reported that NLR and PLR values are increased in deep venous thrombosis (DVT) and that the NLR level and thrombus burden are parallel to each other (4). However, there is no study examining the effects of different DVT treatment methods on NLR and PLR values.

Our aim in this study is to examine whether the NLR and PLR ratios change with different DVT treatment protocols and to clarify whether these markers can be used in the follow-up of DVT treatment.

MATERIAL AND METHODS

Patient Groups & Participants

The study was carried out among people who applied to the cardiovascular surgery clinic of Amasya University Sabuncuoğlu

Şerefeddin Training and Research Hospital. Before the study, ethics committee approval was obtained from Amasya University Non-Interventional Clinical Research Ethics Committee with the date 08.10.2020 and decision number 110. Throughout the study, the principles of the Declaration of Helsinki were adhered to.

The study was conducted as a retrospective cohort study among healthy participants (group 1 n=30) who were ultrasonographically shown to have no deep vein thrombosis and patients diagnosed with DVT and treated. Previously initiated anticoagulant use, ongoing active infection, a poor general condition requiring intensive care, orthopedic prosthesis surgery in the last six months and the presence of malignancy were determined as exclusion criteria. Patients diagnosed with DVT were also divided into two groups those in whom warfarin (group 2 n=35) and rivaroxaban treatment (group 3 n=19) were initiated.

Analysis of Laboratory Data

Routine blood tests taken before starting treatment from patients diagnosed with DVT by Doppler ultrasonography (Mindray Digital Ultrasound Imaging System Model DC-8; Shenzhen, China) and routine blood tests taken from healthy individuals who were shown to be free of DVT were recorded. NLR was calculated by dividing the neutrophil count by the lymphocyte count, and PLR was calculated by dividing the platelet count by the lymphocyte count. The results of the control blood samples taken in the first month from the patients who were treated for DVT were also included in the study by scanning the patient files. Rivaroxaban treatment was started at 15 mg twice a day (5). The dose was adjusted so that the INR values of the patients who were started on warfarin therapy were between 2-3. Patients whose INR levels could not be maintained between 2-3 were not included in the study.

Statistics Analysis

Statistical analysis was performed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Descriptive statistics were given as number of units (n), percent (%) mean±standard deviation ($\bar{x}$±ss), median (Q1-Q3) values. The normal distribution of the data of numerical variables was evaluated with the Shapiro Wilk test of normality and Q-Q graphs. Comparisons between groups were made with one-way analysis of variance for normally distributed variables, and Kruskal-Wallis analysis or Mann Whitney U Test for non-normally distributed variables. Tukey HSD was used for normally distributed variables and Dunn-Bonferroni test was used for non-normally distributed variables as a multiple comparison test. Statistical significance value was accepted as 5% ($p < 0.05$).

RESULTS

51 of the participants were male and 33 were female, and the mean age was calculated as (56.32±12.87). The results at the time of diagnosis of 'DVT' were compared. White blood cell (WBC), neutrophil and eosinophil values were found to be significantly higher in groups 2 and 3, which were DVT groups, compared to the control group. (Table 1) In addition, PLR and NLR values in groups 2 and 3 were higher than the control group.

In the comparison of blood tests taken in the first month after treatment; A statistically significant decrease in WBC value was detected in group 2 and group 3. There was no significant change in eosinophil, PLR and NLR values in both DVT groups (Tables 2 and 3).

In group 3 treated with rivaroxaban, a significant decrease was observed in neutrophil and monocyte levels after treatment. (Table 3).

Table 1. Laboratory data of patients at diagnosis

	Group 1 (n=30) Median (Q1-Q3)	Group 2 (n=35) Median (Q1-Q3)	Group 3 (n=19) Median (Q1-Q3)	*P*
age	55 (44.50-65.00)	58 (50.00-66.00)	55 (44.00-67.00)	0.798
wbc	7.02 (6.45-8.67)[a,b]	8.78 (6.20-10.99)	8.36 (6.94-10.60)	**0.028**
neu	4.04 (3.54-4.79)[a,b]	5.18 (3.40-6.600)	6.2 (4.38-7.67)	**0.001**
lym	2.28 (1.91-2.82)[a,b]	1.88 (1.80-2.300)	1.77 (1.47-2.16)	**0.001**
mono	0.56 (0.43-0.69)	0.58 (0.60-0.700)	0.6 (0.53-0.82)	0.223
eoz	0.12 (0.09-0.21)	0.19 (0.20-0.300	0.18 (0.05-0.24)	0.353
bas	0.03 (0.02-0.05)	0.04 (0.30-0.050)	0.04 (0.03-0.05)	0.078
plt	236 (211.50-282.50)	257 (241.0-285.0)	234 (192.00-310.00)	0.165
mpv	10.5 (9.70-11.00)[a,b]	9.1 (8.50-9.90)	9.5 (9.20-10.80)	**0.003**
nlr	1.77 (1.47-2.27)[a,b]	2.60 (2.72-3.78)	3.32 (2.14-4.46)	**0.001**
plr	102.85 (89.49-134.50)[a,b]	141.30 (112.8-209.3)	122.29 (105.40-173.07)	**0.003**

a: difference between group 1 and group2 is significant ($p<0.05$), b: difference between group 1 and group3 is significant ($p<0.05$),
Group 1: control group, Group 2: warfarintreatment group, Group 3: rivaroxaban treatment group
wbc: white blood cells, neu: neutrophil, lym: lymphocyte, mono: monocytes, eoz: eosinophil, bas: basophil, plt: platelet, mpv: mean platelet volume, nlr: neutrophil-lymphocyte ratio, plr: platelet-lymphocyte ratio

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Table 2. Coumadin treatment group laboratory data

	T0 Median(Q1-Q3)	T1 Median(Q1-Q3)	*P*
wbc	8.78 (6.20-10.99)	7.61 (6.32-8.30)	**0.008**
neu	5.18 (3.47-6.60)	4.11 (3.51-6.26)	0.074
lym	1.88 (1.52-2.30)	2.14 (1.42-2.60)	0.756
mono	0.58 (0.50-0.70)	0.59 (0.44-0.66)	0.046
eoz	0.19 (0.10-0.30)	0.16 (0.06-0.24)	0.077
bas	0.04 (0.01-0.05)	0.03 (0.02-0.04)	0.968
plt	257 (241.00-285.00)	240 (214.00-271.00)	0.124
mpv	9.1 (8.50-9.90)	9.2 (7.48-10.30)	0.334
nlr	2.60 (2.05-3.78)	2.05 (1.55-2.74)	0.413
plr	141.30 (112.89-209.38)	121.61 (90.08-159.15)	0.326

wbc: white blood cells, neu: neutrophil, lym: lymphocyte, mono: monocytes, eoz: eosinophil, bas: basophil, plt: platelet, mpv: mean platelet volume, nlr: neutrophil-lymphocyte ratio, plr: platelet-lymphocyte ratio

Table 3. Rivaroxaban treatment group laboratory data

	T0 Median(Q1-Q3)	T1 Median(Q1-Q3)	*P*
wbc	8.36 (6.94-10.6)	6.72 (5.61-8.54)	**0.020**
neu	6.2 (4.38-7.67)	4.15 (3.13-5.48)	**0.010**
lym	1.77 (1.47-2.16)	1.92 (1.27-2.64)	0.658
mono	0.6 (0.53-0.82)	0.45 (0.42-0.67)	**0.001**
eoz	0.18 (0.05-0.24)	0.11 (0.05-0.26)	0.717
bas	0.04 (0.03-0.05)	0.03 (0.01-0.04)	0.167
plt	234 (192.00-310.)	215 (161.00-310.)	0.220
mpv	9.5 (9.20-10.8)	9.8 (8.90-11.4)	0.248
nlr	3.3 (2.14-4.46)	2.05 (1.53-2.75)	0.107
plr	122.29 (105.41-173.)	111.90 (88.13-169.)	0.398

wbc: white blood cells, neu: neutrophil, lym: lymphocyte, mono: monocytes, eoz: eosinophil, bas: basophil, plt: platelet, mpv: mean platelet volume, nlr: neutrophil-lymphocyte ratio, plr: platelet-lymphocyte ratio

DISCUSSION

As a result of this study, it was determined that PLR and NLR values were increased in patients who developed DVT. No significant changes were observed in PLR and NLR values after Coumadin and rivaroxaban treatment.

The pathogenesis of DVT is the Virchow triad, which is the basis of thrombosis. Many clinical conditions have been described that lead to the formation of this triad, which is defined as endothelial damage, stasis, and coagulation disorder (6). Immobilization, previous surgery, coagulation disorders, use of oral contraceptives and malignancy can be counted as the most common of these clinical conditions. Inflammation plays an important role in the pathogenesis of these clinical conditions (7). The relationship between DVT and inflammation has been a controversial issue for a long time. It has been suggested that inflammation plays a role in the pathogenesis of DVT by various mechanisms. Depending on inflammation, tissue factor level, platelet reactivity, and fibrinogen level increase, leading to thrombosis predisposition, while thrombomodulin level decreases, inhibiting fibrinolysis (8). In a study, it was shown that microparticles, which play an active role in inflammation, cause the development and progression of thrombosis (9). Microparticles are phospholipid vesicles that separate from platelets, leukocytes, and endothelial cells in a calcium-dependent manner (10). The interaction of microparticles with platelets causes tissue factor activation and initiation of thrombosis (11). In another study, which is an indicator of the inflammatory process; A dose-dependent relationship was found between high nucleosome and elastase-α1-antitrypsin complex levels and DVT (12). Beyond the role of inflammation in the pathogenesis of DVT, inflammatory markers are also elevated during the acute phase of DVT. It has been shown that inflammatory markers IL-6, IL-8 and CRP increase in the acute phase of DVT and gradually decrease in the following days (13). It has even been claimed that IL-6 and CRP are associated with thrombus burden (14).

Many markers have been researched to evaluate this inflammatory process observed in DVT. Following the inflammatory process in DVT is crucial for observing changes in the disease's pathogenesis as well as predicting long-term complications such as postthrombotic syndrome. NLR calculated by neutrophil and lymphocyte counts is used as an indicator of inflammatory response. NLR has been shown to be elevated in pulmonary embolism and DVT (15,16). In addition, NLR has been found to be an independent risk factor for cardiovascular disease (17). PLR, on the other hand, is an important factor that shows the interaction between the two main components of thrombosis and inflammation, since it is calculated with platelet and lymphocyte counts (18). It has been suggested that PLR, like other inflammatory markers, is a prognostic factor, especially in patients with malignancy (19).

In a study, it was predicted that NLR could be used to predict the development of DVT in arthroplasty patients (15). As a result of our study, NLR value was found to be significantly higher in patients with DVT, similar to this study, compared to patients in the control group. This finding may be an indication of the known inflammatory response in DVT patients. Similar to NLR, we found the PLR value to be higher in patients with DVT compared to those in the control group. In a study examining the anatomical localization of thrombus and NLR and PLR values in DVT patients, it was found that NLR and PLR values were increased in parallel with our findings (4). The elevation of NLR and PLR in DVT, like other inflammatory markers, may not mean that these two markers can be used to diagnose DVT and to follow the treatment process. To elucidate this issue, we compared the NLR and PLR values after treatment initiation in DVT patients with the values before treatment. There was no significant change in NLR and PLR values with treatment in patients treated with both warfarin and rivaroxaban. This may be because the inflammatory response takes longer to return to normal.

After one month of treatment, patients treated with rivaroxaban had significantly lower WBC and monocyte values than patients treated with warfarin in the DVT groups. The main cause of this decrease in WBC could be a decrease in monocyte levels. The significant reduction in the number of monocytes observed during rivaroxaban treatment may have resulted in a more significant reduction in the inflammatory response. However, no firm conclusions can be drawn because other inflammatory parameters were not investigated.

There are several limitations of our study. First of all, since this study was retrospective, it was not possible to determine all the variables about the patients. In addition, NLR and PLR values were not compared with other inflammatory markers, so no comparison could be made between them. In addition, since the analyzes of the patients were examined only in the first month of the study, it was not possible to comment on the changes in the long-term. For these reasons, performing a similar prospective study with longer follow-up on a larger study population with more inflammatory parameters in patients with DVT will provide a better understanding of the subject.

CONCLUSION

As a result, it was determined that NLR and PLR values increased as a result of the inflammatory process in DVT patients, but these two markers did not show a significant change with different treatment methods.

Conflict of Interests: The authors declare that there are no conflict of interests.

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REFERENCES

1. Golia E, Limongelli G, Natale F, Fimiani F, Maddaloni V, Pariggiano I, et al. Inflammation and Cardiovascular Disease: From Pathogenesis to Therapeutic Target. Current Atherosclerosis Reports 2014;16:435.
2. Esmon CT, Xu J, Lupu F. Innate immunity and coagulation. Journal of Thrombosis and Haemostasis 2011;9:182-8.
3. Afari ME, Bhat T. Neutrophil to lymphocyte ratio (NLR) and cardiovascular diseases: an update. Expert Rev Cardiovasc Ther 2016;14:573-7.
4. Kuplay H, Erdoğan SB, Bastopcu M, Arslanhan G, Baykan DB, Orhan G. The neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio correlate with thrombus burden in deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2020;8:360-4.
5. EINSTEIN Investigators; Bauersachs R, Berkowitz SD, Brenner B, Buller HR, Decousus H, Gallus AS, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-510.
6. Bagot CN, Arya R. Virchow and his triad: a question of attribution. Br J Haematol 2008;143:180-90.
7. Saghazadeh A, Hafizi S, Rezaei N. Inflammation in venous thromboembolism: Cause or consequence? Cause or consequence?. Int Immunopharmacol 2015;28:655-65.
8. Esmon CT. Inflammation and thrombosis. J Thromb Haemost 2003;1:1343-8.
9. Wakefield TW, Myers DD, Henke PK. Mechanisms of venous thrombosis and resolution. Arterioscler Thromb Vasc Biol 2008;28:387-91.
10. Sabatier F, Roux V, Anfosso F, Camoin L, Sampol J, Dignat-George F. Interaction of endothelial microparticles with monocytic cells in vitro induces tissue factor-dependent procoagulant activity. Blood 2002;99:3962-70.
11. Østerud B. The role of platelets in decrypting monocyte tissue factor. Dis Mon 2003;49:7-13.
12. van Montfoort ML, Stephan F, Lauw MN, Hutten BA, Van Mierlo GJ, Solati S, et al. Circulating nucleosomes and neutrophil activation as risk factors for deep vein thrombosis. Arterioscler Thromb Vasc Biol 2013;33:147-51.
13. Roumen-Klappe EM, den Heijer M, van Uum SH, van der Ven-Jongekrijg J, van der Graaf F, Wollersheim H. Inflammatory response in the acute phase of deep vein thrombosis. J Vasc Surg 2002;35:701-6.
14. Rabinovich A, Cohen JM, Cushman M, Kahn SR, BioSOX Investigators. Association between inflammation biomarkers, anatomic extent of deep venous thrombosis, and venous symptoms after deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2015;3:347-353.e1.
15. Barker T, Rogers VE, Henriksen VT, Brown KB, Trawick RH, Momberger NG, et al. Is there a link between the neutrophil-to-lymphocyte ratio and venous thromboembolic events after knee arthroplasty? A pilot study. J Orthop Traumatol 2016;17:163-8.
16. Kayrak M, Erdoğan HI, Solak Y, Akilli H, Gül EE, Yildirim O, et al. Prognostic value of neutrophil to lymphocyte ratio in patients with acute pulmonary embolism: a restrospective study. Heart Lung Circ 2014;23:56-62.
17. Papa A, Emdin M, Passino C, Michelassi C, Battaglia D, Cocci F. Predictive value of elevated neutrophil-lymphocyte ratio on cardiac mortality in patients with stable coronary artery disease. Clinica Chimica Acta 2008;395:27-31.
18. Kurtul A, Ornek E. Platelet to lymphocyte ratio in cardiovascular diseases: a systematic review. Angiology 2019;70:802-18.
19. Krenn-Pilko S, Langsenlehner U, Thurner EM, Stojakovic T, Pichler M, Gerger A, et al. The elevated preoperative platelet-to-lymphocyte ratio predicts poor prognosis in breast cancer patients. Br J Cancer 2014;110:2524-30.