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Original Article / Orjinal Araştırma

The clinical ımportance of neutrophil to lymphocyte ratio and plateled to lymphocyte ratio in patients with pulmonary embolism

Pulmoner emboli hastalarında nötrofil/lenfosit oranı ve trombosit/lenfosit oranının klinik önemi

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Abstract

Introduction: The aim of our study was to investigate clinical and prognostic importance of neutrophil to lymphocyte ratio (NLR) and plateled to lymphocyte ratio (PLR) in patients with acute pulmonary embolism (PE).

Methods: 50 patients with a diagnosis of acute PEincluded into the studybetween January2016 and December 2017. NLR level was measured by dividing neutrophil count to lymphocyte count. PLR level was measured by dividing plateled count to lymphocyte count. Pre-treatment and post-treatment groups of NLR and PLR values were compared.

Results: All patients with diagnosis of acute PE had received anticoagulation therapy. The basal patient characteristics for WBC, neutrophil, platelet and d-dimer were significantly higher in pre- than post-treatment groups ($p<0.05$). There was no statistically significant difference between the two groups with respect to age, gender, RDW, lymphocyte and haemoglobin ($p>0.05$).It has been NLR and PLR ratio have a significantly higher value in admission and patients with pre-treatment groups were found statistically significant variable to predict the treatment effects($p<0.0001$). Also, correlation analysis showed a significant correlation between NLR and PLR ($p=0.0001$).

Discussion and Conclusion: NLR and PLR values may be a useful biomarker for risk stratification and also prognosis for PE.

Keywords: Neutrophil to lymphocyte ratio, platelet to lymphocyte ratio; pulmonary embolism; ventilation-perfusion scintigraphy.

Özet

Amaç: Çalışmanın amacı akut pulmonerembolisi (PE)olan hastalarda nötrofil/lenfositoranının (NLR) veplateled/lenfositoranının (PLR) klinik ve prognostik önemini araştırmaktır.

Gereç ve Yöntem: Ocak 2016 ileAralık 2017 tarihleri arasında akut PEtanısıkonan 50 hasta çalışmaya dahil edildi. NLR düzeyi, nötrofil sayısının lenfosit sayısına bölünmesiyle hesaplandı. PLR düzeyi, plateled sayısının lenfosit sayımına sayısına bölünmesiyle hesaplandı. NLR ve PLR değerleri tedavi öncesi vetedavi sonrası grupları ile karşılaştırıldı.

Bulgular: Akut PE tanısı alan hastaların hepsinde antik oagülasyon tedavisi uygulandı. Hasta özellikleri değerlendirildiğinde WBC, nötrofil, trombositve d-dimer düzeyleri tedavi öncesi grup ile tedavi sonrası grup arasında anlamlı olarak daha yüksekti ($p<0.05$). Yaş, cinsiyet, RDW, lenfosit ve hemoglobin açısından iki grup arasında istatistiksel olarak anlamlı bir fark yoktu ($p>0.05$). Başvuruda NLR ve PLR oranı anlamlı olarak yüksekti ve tedavi öncesi grupların tedavi etkilerini tahmin etmek için istatistiksel olarak anlamlı bir değişken olarak bulundu ($p<0.0001$).Ayrıca, NLR ve PLR arasında anlamlı bir korelasyon saptandı ($p=0.0001$).

Sonuç: NLR ve PLR düzeyleri tedavi sonrası komorbidite için risk sınıflandırmasında yararlı ve invazif olmayan bir biyobelirteç olabilir.

Anahtar Sözcükler: Nötrofil/lenfositoranı; pulmoner emboli; trombosit/lenfositoranı; ventilasyon-perfüzyonsintigrafisi.

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Acutepulmonary embolism (PE) is an important cardiovascular emergency with a 15-20% mortality rate.[1] The incidancerates of PE is about 23 to 69 cases per 100.000 persons annually in the United States. Besides, 300.000 deaths from PE were reported for a year in Europe. The percentage of short-term mortality is about 2 to 95% in PE.[2, 3] In literature, there are some studies that present the relationship between leukocytosis and venous thromboemboli (VTE) and also, it is related with high mortality.[4] Next to high mortality; recurrence, major haemorrhage was found associated with white blood cells (WBC) count in patients with malignancy.[5] It is suggested that WBC count can be useful for determine the prognosis of VTE instead of diagnosis. The important prognostic values were reported as >11.000/mm^3 or <4000 mm^3 WBC.[6,7]

The equilibrium of neutrophils and lymphocytes was shown for an indicator of systemic inflammation. There are some studies that suggested the ratio of peripheral neutrophils to lymphocyte ratio (NLR) and plateled to lymphocyte ratio (PLR) for a better marker than leukocytosis in inflammation.[8]

Considering the role of inflammation on pathogenesis of PE, it is aimed to evaluate the diagnostic value of NLR in acute PE. According to our knowledge, there is not enough study on this issue in literature. The aim of this retrospective study was to investigate the clinical and prognostic value of NLR and PLR in patients with acute PE during 30 days follow-up.

Materials and Method

Study Population

This retrospective study included adult patients admitted to emergency department (ED) of a university hospital with diagnosis of acute PE between January 2016 and December 2017. A total of 98 patients were screened. Patients with hepatic or renal insufficiency, previous coronary artery bypass grafting, heart failure (left ventricular ejection fraction<40%), malignancy (pulmonary sarcoma), known chronic systemic inflammatory disease (Behçet's disease, systemic lupuserythematosus, poliomyelitis, ulcerative colitis, Takayasuvasculitis), were excluded from the present study. 50 patients [23 female (46%) and 27 male (54%), average age: 63.84±13.14, range 28-88 years] were determined as having a diagnostic method of PE by pulmonary computed tomographic angiography (PCTA) (n=32) or ventilation/perfusion scintigraphy (V/Q-scan) (n=18). All patients or respective relatives were queried with regards to 30-day follow-up.

Blood Sample Analyses

Complete blood counts and serum biomarker levels (i.e. WBC, neutrophil, lymphocyte, platelet, red cell distribution width (RDW), haemoglobin, d-dimer) were studied for the peripheral venous blood samples taken on admission to ED. NLR was calculated as the ratio of neutrophils to lymphocytes in peripheral blood. PLR was calculated as the ratio of platelets to lymphocytes in peripheral blood. Other routine laboratory parameters were recorded by using electronic database of the hospital. Baseline NLR and PLR were compared the post-treatment groups.

Scintigraphic Analyses

In the V/Q-scan protocol, ventilation was performed after inhalation of 99mTc-Diethylenetriamine pentacetic acid (DTPA), reaching 30MBq in the lungs; perfusion was performed after intravenous administration of 60-120MBq of 99mTc-Macroaggregated albumin (MAA). The European Association of Nuclear Medicineguidelinesfor ventilation/perfusion scintigraphy reference was used as the evaluation criteria of V/Q SPECT imaging.[9]

Statistical Analyses

Data were analysed by using SPSS software version 15.0 and presented as mean±standard deviation.The comparisons and correlation analysis were carried out with Spearman correlation test, one-way ANOVA, Kruskal-Wallis tests, chi-square test or Fisher's exact test for non-parametrically distributed variables. The difference between the two groups was tested via Independent Student's t-tests for normally distributed variables and Mann-Whitney U test was used for non-parametrically distributed variables. A $p<0.05$ (two-sided) was considered statistically significant.

Results

The demographic, clinical, and laboratory characteristics of pre-treatment group and post-treatment group were investigated. All patients with diagnosis of acute PE had received anticoagulation therapy. Three (6%) patients who were diagnosed with high-risk PE received thrombolytic therapy. The remaining 47 (94%) patients received low molecular weight heparin therapy(Enoksaparin sodium 80 mg). One (2%) of the 50 patients had died within 30 days after the diagnosis was made (Table 1).

The basal patient characteristics for WBC, neutrophil, platelet and d-dimer were significantly higher in pre- than post-treatment groups ($p<0.05$). There was no statistically significant difference between the two groups with respect to age, gender, RDW, lymphocyte and haemoglobin ($p>0.05$). Laboratory characteristics of the pre- and post-treatment group patients are depicted in Figure 1.

Nötrofilwritten as neutrophile and lenfosit written aslymphocyte in graphic. Pre-treatment NLR was significantly higher among PE patients who compared to post-treatment (4.88±3.37 vs 3.38±2.43, $p<0.0001$). There was a significant positive correlation on NLR between pre- and post-treatment in the positive direction ($r=0.654$, $p=0.0001$) (Fig. 2).

Pre-treatment PLR was significantly higher among PE patients who compared to post-treatment (93.75±55.35 vs 61.46±38.33, $p<0.0001$). There was a significant positive corre-

Table 1. The demographic, clinical, and laboratory characteristics of study patients (NLR1: Pre-treatment neutrophil to lymphocyte ratio, NLR2: Post-treatment neutrophil to lymphocyte ratio, PLR1:Pre-treatment plateled to lymphocyte ratio, PLR2: Post-treatmentplateled to lymphocyte ratio)

Number	Gender	Age	Pe Localization	Treatment	Nlr1	Nlr2	Plr1	Plr2
1	M	78	both lung main bronchus	heparin therapy	4.1	2.7	138.5	98.7
2	F	72	right lung	heparin therapy	2.1	1.3	160.5	80.6
3	M	40	left lung distal bronchus	heparin therapy	2.3	2.4	118.9	104.1
4	F	52	right lung distal bronchus	heparintherapy	2.6	1.3	118.7	95.5
5	F	84	right lung	heparintherapy	2.3	2.8	136.1	187.7
6	F	77	both lung main bronchus	heparintherapy	4.6	3.2	75.1	78.9
7	M	52	right lung distal bronchus	heparintherapy	5.3	1.5	178.1	54.3
8	M	59	left lung distal bronchus	heparintherapy	4.9	2.8	212.7	162.3
9	F	45	left lung	heparintherapy	4.6	5.1	46.6	44
10	M	68	both lung main bronchus	thrombolytic therapy	15.7	7.4	101.3	27.2
11	M	52	left lung distal bronchus	heparin therapy	2.4	4.4	146.3	100
12	F	59	right lung main bronchus	heparintherapy	3.9	2	129.2	31.9
13	F	59	left lung main bronchus	heparintherapy	3.6	1.6	233.3	89.7
14	M	28	right lung main bronchus	heparintherapy	1.1	1.1	76.1	64.8
15	M	69	both lungs distal bronchus	heparintherapy	7.3	3.3	143.5	121.8
16	M	46	right lung main bronchus	heparintherapy	2.8	2.7	70.8	69.1
17	M	88	both lungs distal bronchus	heparintherapy	3.5	3.6	89.4	52.3
18	M	66	both lungs distal bronchus	heparintherapy	12.3	10.1	183.3	116.6
19	M	68	both lungs distal bronchus	heparintherapy	3.8	0.8	75.3	22.8
20	F	59	right lung main bronchus	heparintherapy	3.8	1.2	103.8	32.6
21	M	55	right lung	heparintherapy	5	5.2	58	56.6
22	F	65	both lungs	heparintherapy	4.3	1.3	60	37.6
23	F	46	right lung	thrombolytic therapy	2.8	7.9	24.5	95
24	F	82	both lungs distal bronchus	heparin therapy	9.1	10.8	111.8	80
25	M	51	both lungs	heparintherapy	0.9	1.9	21.1	14.5
26	M	60	both lung main bronchus	heparintherapy	1.6	1.2	49.6	24.3
27	M	57	both lungs distal bronchus	heparintherapy	8.6	4.5	116.6	49.2
28	F	60	both lung main bronchus	heparintherapy	4.5	2.2	30.6	24.6
29	F	66	both lungs	heparintherapy	3.4	2.6	42.6	44.2
30	F	83	left lung distal bronchus	heparintherapy	6	6.6	64.4	36.6
31	F	71	both lungs	thrombolytic therapy	10.6	4.6	63.1	45
32	M	73	right lung distal bronchus	heparin therapy	4.5	2.3	39.5	39.2
33	M	70	both lungs	heparintherapy	9.1	2.8	56.6	18.7
34	M	80	left lung	heparintherapy	1.4	2.8	29.6	42.5
35	F	46	both lungs	heparintherapy	5	7.2	70.6	57.2
36	M	58	left lung distal bronchus	heparintherapy	8.3	5.1	183.3	128.5
37	M	69	right lung distal bronchus	heparintherapy	3.5	2.9	72.8	62.5
38	M	52	both lungs distal bronchus	heparintherapy	1.1	1.9	56.2	42.6
39	F	59	both lungs distal bronchus	heparintherapy	10.1	2.6	81.6	37.7
40	F	66	both lungs distal bronchus	heparintherapy	1.4	0.4	14	9.7
41	F	72	right lung distal bronchus	heparintherapy	5.2	2.1	120	87.7
42	M	52	right lung main bronchus	heparintherapy	3	1.5	225	82.5
43	F	87	both lungs	heparintherapy	4	2.4	104	41.1
44	M	73	right lung	heparintherapy	13.4	6.5	124.2	64
45	F	86	right lung main bronchus	heparintherapy	5.3	3.8	84.6	31.1
46	F	72	right lung	heparintherapy	1.2	0.6	44.1	28.6
47	M	59	left lung	heparintherapy	4.3	1.6	85.7	37.6
48	M	65	left lung	heparintherapy	1.9	1.9	67.1	75
49	M	77	left lung	heparintherapy	7,9	7,5	35.5	34.2
50	F	59	both lungs distal bronchus	heparintherapy	2,2	1,4	11.5	8.1

Table 2. The correlation of study patients (NLR1: Pre-treatment neutrophil to lymphocyte ratio, NLR2: Post-treatment neutrophil to lymphocyte ratio, PLR1:Pre-treatment plateled to lymphocyte ratio, PLR2: Post-treatmentplateled to lymphocyte ratio)

Correlations			NLR1	NLR2
Spearman'srho	NLR1	CorrelationCoefficient	1.000	0.654(**)
		Sig. (2-tailed)	.	0.000
		N	50	50
	NLR2	CorrelationCoefficient	0.654(**)	1.000
		Sig. (2-tailed)	0.000	.
		N	50	50
	PLR1	PLR2		
Spearman'srho	PLR1	CorrelationCoefficient	1.000	0.670(**)
		Sig. (2-tailed)	.	0.000
		N	50	50
	PLR2	CorrelationCoefficient	0.670(**)	1.000
		Sig. (2-tailed)	0.000	.
		N	50	50

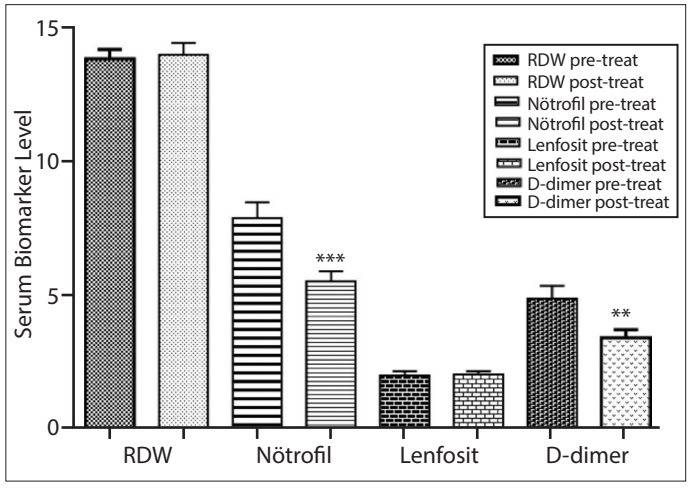

Figure 1. Serum biomarker levels of study patients.

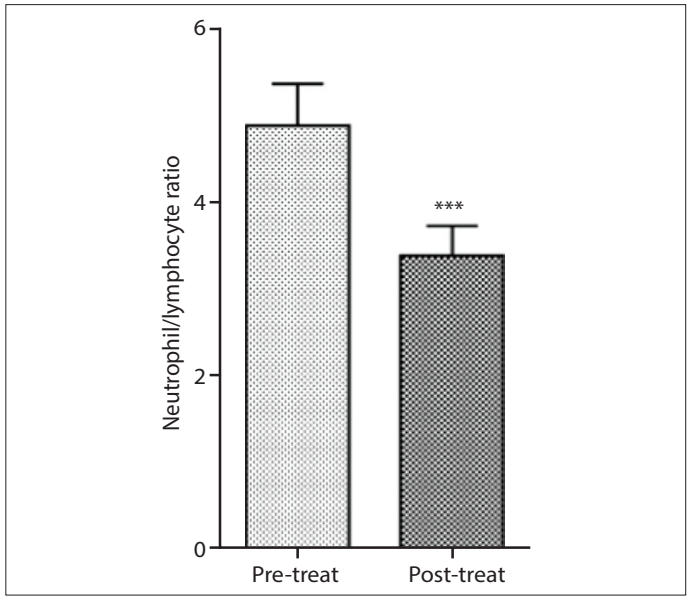

Figure 2. NLR of patients with pre- and post-treatment.

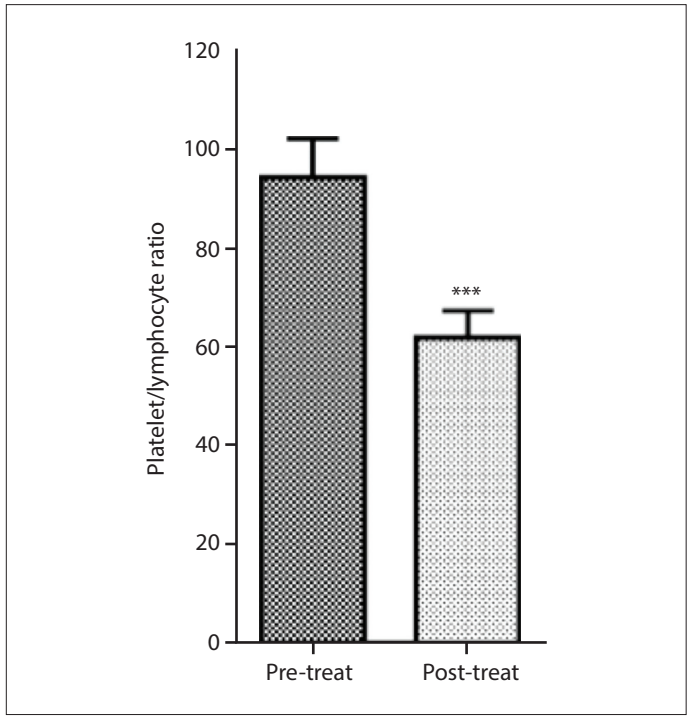

Figure 3. PLR of patients with pre- and post-treatment.

lation on PLR between pre- and post-treatment in the positive direction (r=0.670, p=0.0001) (Fig. 3) (Table 2).

The incidence and frequency of PE involvement in patients diagnosed by PCTA (n=32); right lung main bronchus (19%), right lung distal bronchus (15%), left lung main bronchus (3%), left lung distal bronchus (15%), both lung main bronchus (15%) and both lungs distal bronchus (33%). Additionally, the incidence and frequency of PE involvement in patients diagnosed by V/Q-scan (n=18); right lung (34%), left lung (27%) and both lungs (39%). V/Q-scan of a study patient was shown in Figure 4.

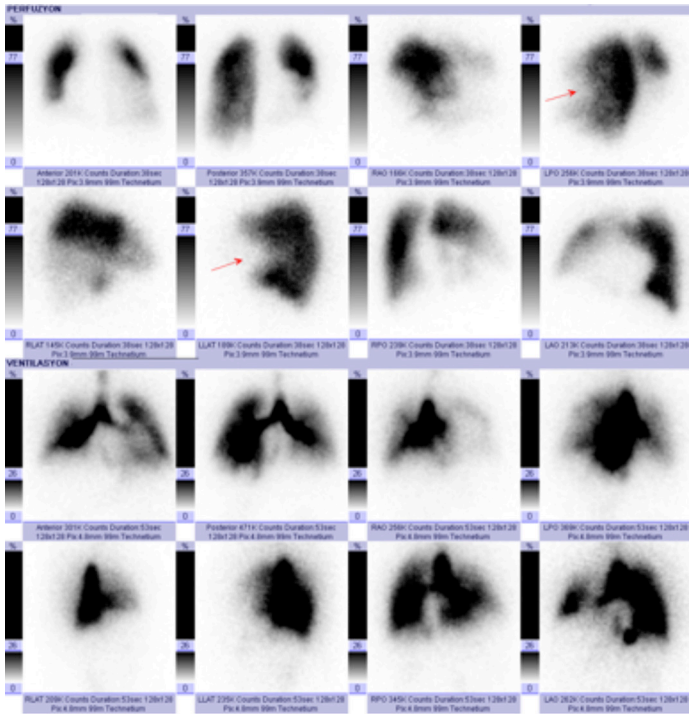

Figure 4. V/Q-scan of the study patient. A subsegmental perfusion defect was observed in the upper lobe superior lingual, inferior lingual and lower lobe superior segments of the left lung (red arrow). Ventilation scintigraphy showed ventilation in these areas (mis-match defect).

Discussion

PE is a serious cardiovascular emergency and it is one of the avoidable reasons of death for patients in hospital.[2,10] The identification of the severity of the disease is very important due to predicting the high risk of mortality and morbidity and choosing the treatment option in PE.[11] The anticoagulation therapy is one of the proven choices in VTE for years.[12] There are many researc hes and also arguments for more aggressive treatment option slast 40 years.[13, 14] The acute treatment of PE with unfractionated heparin has been well documented for almost 100 years; however, the use of thrombolytic agents for PE treatment has been a relatively new practice.[15] The study groups were used thrombolytic therapy and low molecular weight heparin therapy.

The elevation of WBC is first documented by Afzal et al. in PE 19 years ago. It was related with haemorrhage/infarction syndrome and comorbid condition saccording to their suggestions.[16] NLR is a new diagnostic parameter that indicates systemic inflammation in most diseases. Nextto NLR, there lation between platelet to lymphocyte ratio (PLR) and inflammation was also found according to literature.[17] In literature, there are many researches that present relation ship between NLR and poor prognosis with cardiovascular diseases. They suggest that high NLR is a result of increased neutrophil countand decreased lymphocyte count.[18-21] According to our knowledge, there is not enough data presenting predicative abilities of NLR and PLR in patients with PE in terms of short term mortality.[22, 23]

Both NLR and PLR are easily figured out by total blood count. Their prognostic values can be very helpful in the management of PE patients.[11] Cavus et al. was suggested that median NLR values were higher in patients with PE than control group.[24] In literature showed that high NLR has a weighted mean sensitivity of 77% and a weighted mean specificity of 74% and high NLR positive and negative predictive values are 24.4% and 96.7%, respectively.[25] Next to these parameters, cut-off value of NLR was suggested as 9.2 with high specificity and admissible sensitivity.[4] In our study; we found that NLR and PLR values were significantly higher pre-treatment group than post-treatment group.

The components of diagnosis of PE begin with clinical opinion with some scoring systems as Well`s Criteria. D-dimer test is a useful laboratory test for management. The main diagnostic tool is imaging technics such as PCTA and V/Q scan. Modern PCTA, V/Q-scanare rather equal in terms of sensitivity, specificity and inconclusive results for the diagnosis of PE, outperforming planar lung scintigraphy.[26,27] Although diagnostic imaging is more effective and accessible in hospitals recently, clinical assessment and D-dimer can be useful for election of patients for imaging technics considering side effects of these imaging technics.[28,29] Lung perfusion scintigraphy with 99mTc-MAA is well established in the diagnostic of PE. The sensitivity, specificity and accuracy of diagnostic technics were presented in the research of Meng et al. According to that, sensitivities of V/Q-scan, planar imaging and PCTA were 85.9%, 93.5%, 88.1%, specificities were 75.7%, 92.9%, 81.4% and accuracies were 85.5%, 90.0%, 86.8% respectively.[30] Considering with side effects of imaging techniques, Lung perfusion scintigraphy with 99mTc-MAA is safer than other techniques.[31] The side effects of radiation exposure are especially important for pregnant patients suspected PE. V/P-SPECT is used for these patients. The absorbing radiation doses of embryo/fetus are same with both techniques but the exposure of lungs are higher at PCTAthan V/Q-scan.[32] In this study, PE was diagnosed by V/Q-scan for 36% of patients.

In conclusion, it is found that NLR and PLR values are high in acute PE patients. Besides, these values tend to be decreased after treatment. Therefore, we suggest that both NLR and PLR values may be a useful biomarker for risk stratification and also prognosis for PE.

Conflict of interest: There are no relevant conflicts of interest to disclose.

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