



## Can Neutrophil Lymphocyte Ratio Predict the Thrombus Localization in Patient with Acute Pulmonary Embolism?

### Nötrofil Lenfosit Oranı Akut Pulmoner Embolili Hastada Trombüs Lokalizasyonunu Tahmin Edebilir mi?

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#### Abstract

**Objective:** Acute pulmonary embolism (PE) is a life-threatening disease and is commonly seen in the emergency department. The aim of this study was to determine the associations of thrombus localization with white blood cell (WBC) subtypes and the neutrophil-to-lymphocyte ratio (NLR).

**Material-Method:** We retrospectively analyzed the data of acute PE patients who were admitted to the hospital in the period between the dates from 1 January 2017 to 30 June 2018. The coexisting diseases, risk factors, clinical, laboratory, and radiological findings were retrospectively evaluated.

**Results:** The mean age of the patients was 63.40±17.11 years and 119 (53.1%) patients were female. The most frequent complaint was dyspnea (62.5%), the most frequent coexisting disease was the chronic obstructive pulmonary disease (30.4%), and the most frequent risk factor was immobilization (21.4%). Thrombus was mostly present in the pulmonary arteries (PAs) bilaterally (n=103). The thrombus was localized in the lobar PAs in 46.4% of the patients. In the patients having a thrombus in the main PA; the mean WBC and neutrophil counts, platelet distribution width, and NLR values were higher than those in the patients having a thrombus in the distal branches of PA. The parameter with the highest sensitivity and specificity was found to be NLR.

**Conclusions:** A high NLR value is independently associated with a proximal localization of the thrombus in patients with PE.

**Keywords:** Pulmonary Embolism, Neutrophil-Lymphocyte Ratio, Thrombus Localization.

#### Özet

**Amaç:** Acil serviste sıklıkla görülen akut pulmoner emboli (PE) hayatı tehdit edici bir hastalıktır. Bu çalışmanın amacı, nötrofil lenfosit oranı (NLR) dahil olmak üzere trombüs lokalizasyonunun beyaz kan hücresi (WBC) alt tipleri ile ilişkilerini belirlemektir.

**Materyal-Metot:** 1 Ocak 2017-30 Haziran 2018 tarihleri arasında başvuran akut PE tanısı alan hastaların verilerini retrospektif olarak inceledik. Eşlik eden hastalıklar, risk faktörleri, klinik, laboratuvar ve radyolojik bulgular değerlendirildi.

**Bulgular:** Hastaların yaş ortalaması 63,40±17,11 yıl idi ve hastaların 119'u (%53,1) kadındı. En sık görülen şikayet dispne (%62,5), en sık eşlik eden hastalık kronik obstrüktif akciğer hastalığı (%30,4) ve immobilizasyon (%21,4) en sık görülen risk faktörü idi. Trombüs çoğunlukla pulmoner arterlerde (PA) bilateral (n=103) olarak izlendi. Hastaların %46,4'ünde trombüs, lobar PA'da lokalize edildi. Ana PA'da trombüs olan hastalarda ortalama beyaz kan hücresi, nötrofil, trombosit dağılım genişliği ve NLR, daha distal PA dallarında trombüs olanlara göre daha yüksekti. Hassasiyeti ve özgüllüğü en yüksek olan parametre NLR olarak bulundu.

**Sonuç:** Yüksek NLR, PE'li hastalarda proksimal lokalize trombüs ile bağımsız olarak ilişkilidir.

**Anahtar kelimeler:** Pulmoner Emboli, Nötrofil Lenfosit Oranı, Trombüs Yerleşimi.

#### Introduction

Acute pulmonary embolism (PE), which is a serious cardiopulmonary disease with a high mortality rate, has been a common diagnosis in emergency departments in recent years. The disease develops after a complete or partial obstruction in the pulmonary arteries (1, 2). For this reason; clinical examination findings and the results of laboratory and diagnostic imaging tests should be carefully examined in patients, whom a diagnosis of PE was suspected clinically. As the clinical findings of PE are not specific for the disease, various diagnostic tests are studied for their role in making

the diagnosis (3). Clinical findings of PE are variable ranging from asymptomatic clinical pictures to sudden death due to massive embolism (4, 5). Studies have revealed the role of inflammation in the development of PE (6). In recent years, the Neutrophil-to-Lymphocyte Ratio (NLR) as an inflammatory marker, has been shown to be associated with many diseases, including PE (7-9).

In this study, we investigated whether we could predict the localization of the thrombus by evaluating its relationship with the NLR values in patients with PE.

## Material and Methods

All procedures were performed in accordance with the Declaration of Helsinki. The data of 306 patients, admitted to the hospital due to acute PE between the dates from 1 January 2017 to 30 June 2018, were retrieved from the hospital records and retrospectively analyzed. The patients were excluded from the study due to incomplete data or due to the presence of inflammatory, autoimmune, rheumatologic or chronic renal/liver diseases. Of the 306 patients reviewed, 82 were excluded from the study because they met one or more exclusion criteria and a total of 224 patients were included in the study. Computed tomography pulmonary angiography (CTPA) was used for confirming the clinical diagnosis of PE and for defining the localization of the thrombus. The diagnosis of PE was accepted to be confirmed in all patients with complete or partial obstruction of the pulmonary artery (PA). All patients underwent a CTPA scan and the images were evaluated to determine the localization of the thrombus. Demographic characteristics of the patients and the laboratory results at the time of CTPA scanning were recorded including the NLR values. Blood samples were obtained in the emergency service at the time of admission.

The localization of the thrombus was classified as main, lobar, and distal (segmental or subsegmental PA) based on its presence in PA. After assigning the patients to the study groups based on thrombus localization, complete blood count parameters such as white blood cell (WBC), neutrophil, lymphocyte, and platelet counts; the platelet distribution width (PDW); the red cell distribution width (RDW); and the mean platelet volume (MPV) of the study patients were evaluated and the NLR values were calculated using the complete blood count parameters.

The Kolmogorov-Smirnov test was used in the probability distribution. Data were shown as percentage, mean, and standard deviation values (SD). Comparisons between two independent groups were conducted using the Mann-Whitney U test. The chi-square test was used for evaluating the numerical and categorical variables, not conforming to a normal distribution. The optimum cut-off value to determine the association of WBC and neutrophil counts and of the PDW and NLR values with the thrombus in the main PA was derived from the Receiver Operating Characteristic (ROC) analysis. The Area Under the Curve (AUC) was calculated as a measure of the accuracy of the tests. All statistical analyses were performed with the SPSS 18.0. and a p-value of <0.05 was considered statistically significant..

## Results

The study population consisted of 224 patients with PE. There were 105 (46.9%) males and 119 (53.1%) females in the study population. The mean age of the study patients was 63.40±17.11 years. The localization of emboli was categorized as main in 50 (22.3%) patients, lobar in 104 (46.4%), and distal in 70 (31.3%) patients. There was not a statistically significant relationship between the localization of the thrombus with either gender or age. Chronic obstructive pulmonary disease (COPD) was the most common comorbidity. The most

frequent presenting symptom was dyspnea (62.5%), followed by chest pain (44.2%), hemoptysis (6.7%) and syncope (4.5%). Immobilization 48 (21.4%) and recent surgery 43 (19.2%) were detected as the most common risk factors, while no risk factor was detected in 74 (33%) patients. The general clinical features of our patients are depicted in Table 1.

**Table 1.** Demographic and clinical characteristics of patients

	Number of patients (%)
<b>Demographic features</b>	
Female/male (% female)	119/105 (53.1%)
Median age (years)	66 (20-93)
Age over 65 years	117 (52.2%)
<b>Symptoms at presentation</b>	
Dyspnea	140 (62.5%)
Chest pain	99 (44.2%)
Hemoptysis	15 (6.7%)
Syncope	10 (4.5%)
Others	9 (4%)
<b>Risk factors</b>	
Immobilization	48(21.4%)
Recent surgery	43(19.2%)
Cancer	40(17.9%)
Idiopathic	74(33%)
Deep vein thrombosis	27(12.1%)
<b>Co-morbid disease</b>	
Cardiopulmonary disease	62(27.7%)
Chronic obstructive pulmonary disease	68(30.4%)
Cancer	46(20.5%)
Congestive heart failure	48(21.4%)
Ischemic stroke	37(16.5%)
<b>Localization of thrombus</b>	
Main pulmonary arteries	50 (22.3%)
Lobar arteries	104 (46.4%)
Segmental and subsegmental arteries	70 (31.3%)
In-hospital mortality, n (%)	9 (4%)

Based on the anatomic localization of the thrombi in the PAs as shown in the CTPA images, 50 (22.3%) patients were assigned to the main, 104 (46.4%) to the lobar, and 70 (31.3%) patients were assigned to the distal artery categories. The thrombus was bilateral in 66% of the patients with thrombi in the main PA. The thrombi were located in the lobar branches of the PAs in 42.3% of the patients and in the distal arteries in 37.1% of the patients (Table 2).

There were significant differences in the neutrophil and lymphocyte counts and in the NLR levels between the “thrombus in the main PA” and “thrombus in the lobar arteries” groups ( $p<0.05$ ). The neutrophil counts and NLR values were higher and the lymphocyte count was lower in the patients having the thrombus in the main PA compared to the

**Table 2.** Distribution of the characteristics of pulmonary embolism patients according to thrombus localization

Parameter	Group 1 (Main PA)	Group 2 (Lobar PA)	Group 3 (Distal PA)	p1	p2	p3
	n=50	n=104	n=70			
Age (years)	64.4±15.5	65.1±16.6	60.1±18.5	NS	NS	NS
Gender (female / male)	26/24	53/51	40/30	NS	NS	NS
Hospitalization Days	12.46±28.79	11.13±16.33	9.19±8.79	NS	NS	NS
Location of thrombus, n (%)				0.006	0.002	NS
Right PA	12(24%)	46(44.2%)	34(48.6%)			
Left PA	5(10%)	14(13.5%)	10(14.3%)			
Bilateral PA	33(66%)	44(42.3%)	26(37.1%)			
White blood cell (×103/mm3)	12.14±4.64	10.55±3.49	10.15±3.55	NS	0.012	NS
Neutrophils (×103/mm3)	9.64±4.65	7.57±3.16	7.01±3.15	0.011	0.001	NS
Lymphocytes (×103/mm3)	1.54±0.87	1.76±0.75	2.02±0.91	0.049	0.003	NS
NLR	9.68±9.24	5.5±3.88	4.14±2.59	0.008	<0.001	0.024
Platelets(×103/mm3)	234.22±89.13	248.37±85.04	268.67±104.9	NS	NS	NS
MPV (fL)	8.58±1.29	8.59±1.4	8.49±1.07	NS	NS	NS
PDW (fL)	17.24±0.8	16.95±1.03	16.78±0.97	NS	NS	NS
RDW(%)	15.88±2.9	15.79±2.58	15.62±3.1	NS	NS	NS

p1=comparison between main PA group and Lobar PA group (Group1-2).

p2=comparison between main PA group and Distal PA group (Group1-3).

p3=comparison between Lobar PA group and Distal PA group (Group2-3).

(NLR: neutrophil-to-lymphocyte ratio ;MPV: mean platelet volume; PDW: platelet distribution width; RDW: red cell distribution width; NS: non-specific; PA: Pulmonary arteries).

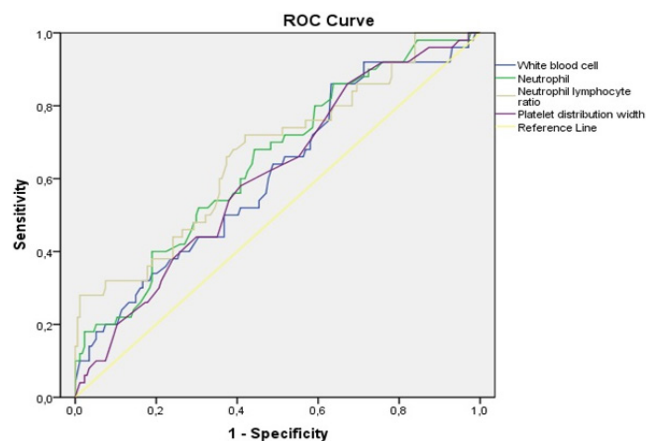
**Table 3.** Diagnostic accuracy of parameters for predicting the presence of main pulmonary arteries thrombus in studied patients

	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	95% CI	p Value
<b>WBC</b>	0.612	10.25	60	63.3	0.523 to 0.700	0.016
<b>Neutrophils</b>	0.648	7.35	62	67.5	0.563 to 0.762	0.001
<b>PDW</b>	0.611	16.95	58	60.2	0.525 to 0.696	0.017
<b>NLR</b>	0.669	4.61	66	72.6	0.582 to 0.756	<0.001

(AUC: area under the curve; WBC: white blood cell ; PDW: platelet distribution width ;NLR :neutrophil-to-lymphocyte ratio; CI: confidence interval).

patients in the “thrombus in the lobar arteries” group (Table 2). There were significant differences in the WBC, neutrophil, and lymphocyte counts, and in the NLR levels between the “thrombus in the main PA” and “thrombus in the distal arteries” groups ( $p<0.05$ ). The WBC and neutrophil counts and the NLR values were higher, and the lymphocyte counts were lower in the “thrombus in the main PA” group compared to the “thrombus in the distal arteries” group (Table 2).

In our study, the mean NLR value in the “thrombus in the main PA” group ( $9.68\pm9.24$ ) was higher compared to the lobar and distal artery groups ( $5.5\pm3.88$ ;  $4.14\pm2.59$ , respectively) ( $p<0.05$ ) (Table 2). The findings from the comparison of the study groups are detailed in Table 2. AUC values were found to be significant in the ROC curve analysis of the variables including the WBC and neutrophil counts, and the PDW and NLR values. The proposed cut-off values and their performance characteristics were shown in Table 3 and in Figure 1.

**Figure 1.** Area under the receiver operating characteristic curve (AUC) for laboratory parameters for predicting the presence of main pulmonary arteries thrombus in studied patients. NLR had the highest AUC (AUC=0.669) followed by neutrophils (AUC=0.648).

## Discussion

Previous studies have reported a strong relationship of common laboratory parameters such as d-dimer and gamma-glutamyl transferase levels with the thrombus localization. These studies reported that these laboratory parameters were significantly higher in the patients with proximal localizations of the thrombus compared to the patients having the thrombus in the more distal parts (4, 10). However, as far as we know, there were no studies in the literature investigating the association of thrombus localization with the WBC subtypes, including the NLR values. In our study, we found that there was a significant association between the WBC subtypes (neutrophils and NLR values) and thrombus localization. The sensitivity and specificity of the remaining WBC subtypes' were lower compared to the NLR values. Compared to the patients having the thrombus in the more distal arterial branches of PAs, higher levels of NLR were detected in the patients with thrombus in the main PAs with a cut-off value of 4.61, with 66% sensitivity, and 72.6% specificity. Our study showed that NLR levels could be used for predicting PE in the proximal parts of PAs in patients presenting with symptoms and signs compatible with PE. Thus, in the clinical settings working under time pressure, such as emergency departments, NLR values may be a predictor of proximal pulmonary embolism.

The process of making the diagnosis begins with a clinical suspicion in medicine, preparing the grounds to start clinical studies. The methods to be involved in making the diagnosis of PE should be able to reliably rule out each and every potential disease listed in the differential diagnosis. This will enable the clinicians to make a precise diagnosis; otherwise, missing a diagnosis of PE and leaving the disease untreated would carry a high risk of mortality (11). Immobility, malignancy, major surgeries, multiple traumas, venous thromboembolism, and advanced age are the acquired risk factors of PE (12). Our study results were similar to those reported in the literature, finding out that immobilization and having undergone a recent surgery were the two most common risk factors at rates of 21.4% and 19.2%, respectively. Using the risk factors mentioned above, some scoring systems such as Wells and Geneva are used in calculating the clinical probability, but these scoring systems cannot predict the thrombus localization precisely (13). Massive PE manifests itself as persistent hypotension and/or bradycardia together with syncope or sudden cardiovascular arrest and these clinical manifestations usually occur in association with proximally located thrombi. If there is a high suspicion of massive pulmonary embolism, thrombolytic treatment is strongly advised for short-term survival (14). In hospitals, where there is no possibility of performing an emergency CTPA in patients, who were highly suspected for having PE, high NLR levels can predict the presence of a proximally located thrombus and starting thrombolytic treatment may be considered.

Recent studies showed that approximately in half of the patients, the thrombus was located bilaterally based on the anatomical localization (15, 16). A study reported that thrombi were located bilaterally in the PAs in 70.7% and

unilaterally in 29.3% of the patients (17). In our study, thrombus was frequently detected unilaterally in the right PA in 92 patients and it was bilateral in 103 patients. Sunnetcioglu et al. (16) detected thrombi in the main PA in 31.1% of the study population consisting of 148 patients. Duru et al. (18) conducted a study on 205 patients and they found thrombi in the main PA at a rate of 14.6%. In another study, 30.8% of 31 patients had thrombi in the main PA (13). In our study, the mean NLR of the patients having the thrombus in the main PA was higher compared to the NLR found in the lobar and distal arteries groups. Most of them were also found out to be bilateral. These results may help predict that thrombi could be localized in the main PA and could be bilateral in the presence of elevated NLR values in patients, who were suspected of suffering from PE.

A study showed that there was a relationship between RDW and thrombus localization (15). In contrast to this study, we found that the mean RDW level was higher in the patients with thrombus in the main PAs ( $15.88 \pm 2.9$ ) compared to the patients having thrombi at more distal locations ( $15.79 \pm 2.58$ ;  $15.62 \pm 3.1$ , respectively) but this difference was not significant ( $p > 0.05$ ). This result could have been caused by the fact that the lobar and distal branches were treated as a single group in our study.

The limitations of our study can be listed as follows: (1) This is a retrospective study. (2) The sample size was small and the results were obtained only from one center. (3) As baseline NLR values in most patients were not available before the diagnosis of PE, it was not possible to compare baseline and follow-up NLR values. (4) NLR was not compared with some of the commonly used inflammatory markers. (5) The patients were not evaluated for their risks or a clinical grading was not performed using current scoring methods.

## Conclusion

In conclusion, in patients, who were highly suspected for developing PE; high NLR levels may help predict that thrombus can be located proximally and scheduling a thrombolytic treatment may be considered. This approach may provide benefits in diagnosing and managing PE in hospitals, where there is no possibility of performing an emergency CTPA.

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