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The Clinical Importance of Hematological Parameters in Patients with Pulmonary Thromboembolism Diagnosed in the Emergency Department

Acil Serviste Pulmoner Tromboemboli Tanısı Konulan Hastalarda Hematolojik Parametrelerin Klinik Önemi

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ABSTRACT

Objective: *Acute pulmonary embolism (APE) is a highly fatal acute clinical condition. Herein, we aimed to determine the role of blood parameters in the diagnosis and prognostication of APE.*

Material and Method: *This study was conducted retrospectively on patients who had been admitted to our hospital's emergency department (ED) and diagnosed with APE. Patients with an RV/LV ratio greater than 0,9 on Computed tomography (CT) and hypotension were grouped as massive APE; patients with stable hemodynamics and an RV/LV ratio greater than 0,9 on CT were defined as submissive APE; and patients with stable hemodynamics and an RV/LV ratio smaller than 0,9 on CT were defined as non-massive APE.*

Results: *This study enrolled a total of 200 patients, 82 of which were male (41%) and 118 were female (59%). APE group had a significantly greater D-dimer level than the control group (3.559,5±8.611.3 ng/ml vs 266.6±266.6 ng/ml) (p<0,001). Troponin I levels significantly greater in the patient group than control group (53.3±90 vs 332.9±32,9) (p= 0.013).*

Conclusion: *Analysis of the hematological parameters between the APE subgroups showed that D-Dimer, leukocyte (WBC), neutrophil, lymphocyte, neutrophil to lymphocyte ratio (NLR), and troponin levels were significantly higher in the massive APE group than the sub-massive and non-massive APE groups.*

Keywords:
Acute pulmonary embolism
Hematological parameters
Emergency Department

ÖZET

Amaç: *Akut pulmoner emboli (APE), oldukça ölümcül bir akut klinik durumdur. Burada APE'nin tanı ve prognozunda kan parametrelerinin rolünü belirlemeyi amaçladık.*

Gereç ve Yöntem: *Bu çalışma hastanemizin Acil Servisine (AS) başvuran ve APE tanısı konulan hastalar üzerinde geriye dönük olarak yapıldı. Bilgisayarlı tomografi (BT)'de RV / LV oranı 0.9'dan büyük ve hipotansiyonu olan hastalar masif APE; BT'de RV / LV oranı 0,9'dan büyük olan ve stabil hemodinamik sahip hastalar submasif APE; BT'de RV / LV oranı 0,9'dan küçük ve hemodinamisi stabil olan hastalar masif olmayan APE olarak sınıflandırıldı.*

Bulgular: *Bu çalışmaya 82'si erkek (%41), 118'i kadın (%59) olmak üzere toplam 200 hasta alındı. Hasta ve kontrol grubunun yaş ortalaması sırasıyla 65,2 ± 17,1 ve 60,5 ± 60,5 yıldı. APE grubu, kontrol grubuna göre anlamlı olarak daha yüksek D-dimer düzeyine sahipti (3559,5±8611,3 ng/ml'ye karşı 266,6±266,6 ng/ml) (p<0,001). Troponin I düzeyleri hasta grubunda anlamlı olarak daha yüksekti (53,3±90'a karşı 332,9±32,9) (p= 0,013).*

Sonuç: *Hematolojik parametrelerin APE alt grupları arasındaki analizi, masif APE grubunda D-Dimer, lökosit (WBC), nötrofil, lenfosit, nötrofil / lenfosit oranı (NLR) ve troponin düzeylerinin sub-masif APE ve masif olmayan APE grubuna göre anlamlı olarak daha yüksek olduğunu gösterdi.*

Anahtar Kelimeler:
Akut Pulmoner Emboli
Hematolojik Parametreler
Acil Servis

INTRODUCTION

Despite the fact that acute pulmonary embılism (APE) may have an asymptomatic course depending on the size and extent of pulmonary embolism, is potentially a life-threatening event that may culminate into sudden death. The most common source of a pulmonary embolus is the deep veins of the leg (1). Whereas APE is rarely seen in ambulatory individuals free of any risk factor, coagulation abnormalities, intravascular blood stasis, turbulence, and endothelial dysfunction increase its risk (2).

Since APE is potentially fatal, it is crucial to diagnose and manage it in a timely manner. Its diagnosis and severity sometimes need to be verified by further tests and studies. Utilization of a number of easy-to-use and simple parameters and indices derived from simple and readily available blood studies has recently attracted attention. These may include cardiovascular biomarkers (brain natriuretic peptide, cardiac troponin I or T, high sensitivity troponin T, heart-type fatty acid-binding protein) or hematological markers derived from blood

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counts (3). It has been shown that most of the parameters are actually related to APE diagnosis, its severity, and its clinical presentation. However, it is unknown which hematological parameter has the greatest diagnostic importance in determining the clinical severity of APE.

Hence, this study aimed to determine hematological parameters that are important for diagnosing APE and determining its severity.

MATERIAL AND METHOD

Study population

After it was approved by Health Sciences University Antalya Training and Research Hospital Ethics Committee (05.09.2017-12/14), our study was conducted retrospectively on patients who had been admitted to our hospital's emergency department (ED) and diagnosed with APE. The medical data of the patients were accessed through written medical records of the patients and hospital electronic information management system. A standardized "Study Form" was designed for the study, and after the patients' data were recorded on that form, they were transferred to a digital medium. Demographic information such as age and sex, admission symptoms, comorbidities, vital signs, hemogram and biochemistry tests, treatment regimens, rates of hospital admission/ discharge from ED, and mortality rate were recorded and analyzed in all patients. In addition to APE patients with missing clinical or biochemical data, we also excluded patients with documented heart failure or right and/or left ventricular dysfunction, intracardiac thrombus, pericardial effusion with tamponade, severe pleural effusion, active infection, nephrotic syndrome, acute kidney failure or liver failure, cancer, severe thyroid dysfunction or any other endocrine disorder with hemodynamic disturbances, and any condition deranging hemodynamics, such as severe sepsis or septic shock, major trauma, major surgical procedures, and mechanical ventilation.

Blood samples of all patients were examined using kits of the same brand in the same laboratory. Erythrocyte, Platelets (PLT), WBC, and other parameters obtained from full blood count was quantified by a Sysmex XE 2100 optic laser scatter hematology analyzer (Roche Diagnostic, Corp., Indianapolis, IN, USA) using the impedance method; photometric method was used to measure hemoglobin (Hb) level. Serum C-reactive protein (CRP) level was measured with the turbidimetric method (Roche 24 Cobas C 501). Serum D-dimer level was measured with (Alere Triage Meter) device, and troponin I level with (Roche Diagnostics Elecsys 2010) immunoassay analysis device. The normal reference values of our study parameters were as follows: Hb (11.7–16 g/dL), WBC count (4500-10000/mm³), PLT count (150-400 10³/L), Red Cell Distribution width (RDW) (%11.6-14.8), CRP (0-5 mg/dL), D-dimer (0-500 ng/mL), troponin I (< 0.01 ng/mL).

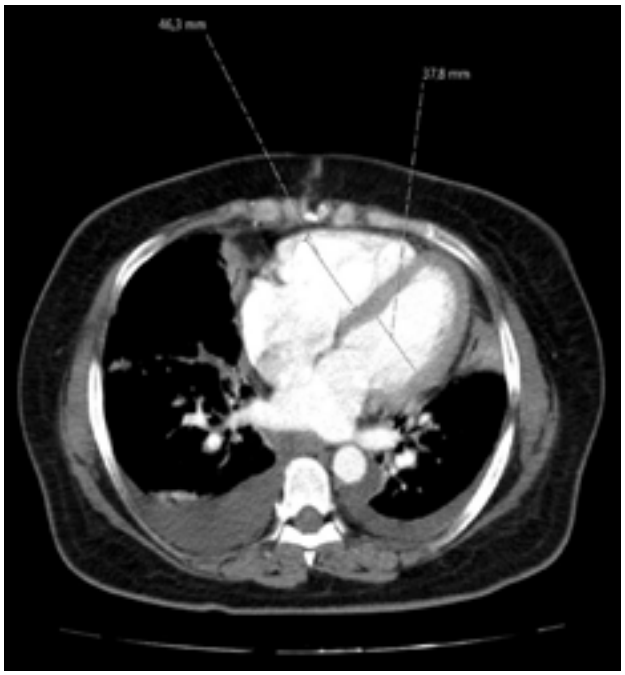

Figure 1: RV/ LV ratio (taken from an actual patient)

CT imaging was performed with a multislice CT device using 64x0.5 mm collimation. Contrast material was injected with an automatic CT injector. All patients were administered 150 ml contrast material at an injection rate of 3.5 ml/sec. Iopromide and iobitridol were used as non-ionic contrast material. The images of all patients were evaluated by an expert radiologist.

The patients were divided into two groups by CT pulmonary angiography (CTA) results. Patients who were diagnosed with APE formed the patient group, and patients without APE formed the control group. Patients diagnosed with APE were subdivided into three groups by hemodynamic data and radiological imaging findings. Right ventricle (RV) / left ventricle (LV) ratio was found by measuring and proportioning the short axis-long axis diameters of both ventricles in the axial plane on CT, measuring the widest distance from the interventricular septum to the endocardial line (Figure 1).

According to this measurement and hemodynamic data, patients with an RV/LV ratio greater than 0.9 on CT and hypotension were grouped as massive APE; patients with stable hemodynamics and an RV/LV ratio greater than 0.9 on CT were defined as submissive APE; and patients with stable hemodynamics and an RV/LV ratio smaller than 0.9 on CT were defined as non-massive APE (1).

Statistical analysis

All statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows 20 (IBM SPSS Inc., Chicago, IL, USA) software. Normality of distribution of the study variables was tested by Kolmogorov-Smirnov test. Normally distributed quantitative data were expressed as mean±SD and non-normally distributed quantitative data as median (min-max). Categorical variables were reported as number and percentage. Risk factors of different APE types were determined by ANOVA (posthoc multiple comparisons performed with Bonferroni test). Categorical data were tested using Chi-square test. $p<0.05$ value was accepted for statistically significant.

RESULTS

This study enrolled a total of 200 patients, 82 of which were male (41%) and 118 were female (59%). The mean age of the patient and control groups were 65.2±17.1 and 60.5±60.5 years, respectively. The patient and control

Table 1: Comparison of the hematological parameters between the patient and control groups

	Patients	Controls	p
Hb	12.5±2.2	12±12	0.047
HTC	39.1±8.3	36.6±36.6	0.019
PLT	236.4±106	306.1±306.1	0.001
WBC	11540	9500	0.001
Neutrophil	9.6±8.6	8.4±8.4	0.245
Lymphocyte	2.7±3.8	1.9±1.9	0.071
NLR	59395	71920	0.687
MPV	8.7±1.5	8.5±8.5	0.391
RDW	16±2.7	15.9±15.9	0.797
CRP	79.3±84.9	64.1±64.1	0.035
D-Dimer	3559.5±8611.3	266.6±266.6	<0.001
Troponin	53.3±90.3	32.9±32.9	0.013
PT	34.2±10.2	31.7±31.7	0.005
PTZ	15.4±4.8	14.8±14.8	0.056
INR	1.3±0.4	1.3±1.3	0.112

groups did not significantly differ with respect to mean age (p=0.035). Sixty percent of the patients were female and 40% were male while 58% of the controls were female and 42% of them were male. The comparison of the sex distribution between the groups with Chi-square test revealed no significant difference (X^2=0.083, sp=1, p=0.774). The comparison between the patient and control groups with respect to the hematological parameters demonstrated significant differences with regard to Hb, hematocrit (HTC), Plt count, CRP, D-Dimer, troponin; However, there was no significant difference regarding WBC, RDW, mean platelet volume (MPV), neutrophil, lymphocyte and NLR (Table 1).

APE group had a significantly greater D-dimer level than the control group (3559.5±8611.3 ng/ml vs 266.6±266.6 ng/ml) (p<0,001). According to the results of the ROC analysis for D-dimer, a cut-off value of >600 had a specificity of 87%, sensitivity of 79%, positive LR of 1.76, negative LR of 0.00, and AUC of 0.884 (p<0.001). The comparison of the troponin I levels between the patient and control groups showed that the patient group had a significantly greater troponin I level (53.3±90 vs 332.9±32.9) (p= 0.013) (Table 1). According to the results of the ROC analysis, a cut-off level of >0.022 for Troponin I had a specificity of 72.41%, sensitivity of 66.67%, positive LR of 2.42, negative LR of 0.46, and AUC of 0.697 (p=0.0005). Although the lowest NLR level in the patient group was 0.02 and the highest level 45.12, the mean NLR level was 5.94. In the control group, on the other hand, the lowest NLR level was 0.21 the highest NLR level was 63.17 and the mean NLR level was 7.19. According to Spearman's rho correlation analysis, there was no significant difference (p>0.05) with respect to NLR at a confidence level of p=0.05. The whole collection of the significantly different hematological parameters between the patient and control groups found in the ROC analysis were presented in figure 2.

The patients were categorized into three subgroups by hemodynamic data and radiological images, which identified 22 patients with massive APE, 49 patients with submassive APE, and 29 patients with non-massive APE. According to the statistical analysis with 95% confidence interval, mean, and standard deviation values, the massive subgroup showed significant differences from the sub-massive and non-massive groups in respect to systolic blood pressure (SBP), diastolic blood pressure (DBP), respiratory rate (RR), oxygen saturation (SO2), pulse rate, fever, Right ventricular diameter, Left ventricular diameter, and Right ventricle/Left ventricle ratio (p<0,05) (Table 2).

Table 3 shows the laboratory parameters pertaining to the APE subgroups. The massive APE subgroup had significantly higher levels of D-dimer, WBC, neutrophil, lymphocyte, NLR, and Troponin compared with the other APE subgroups. The subgroups, however, were similar in

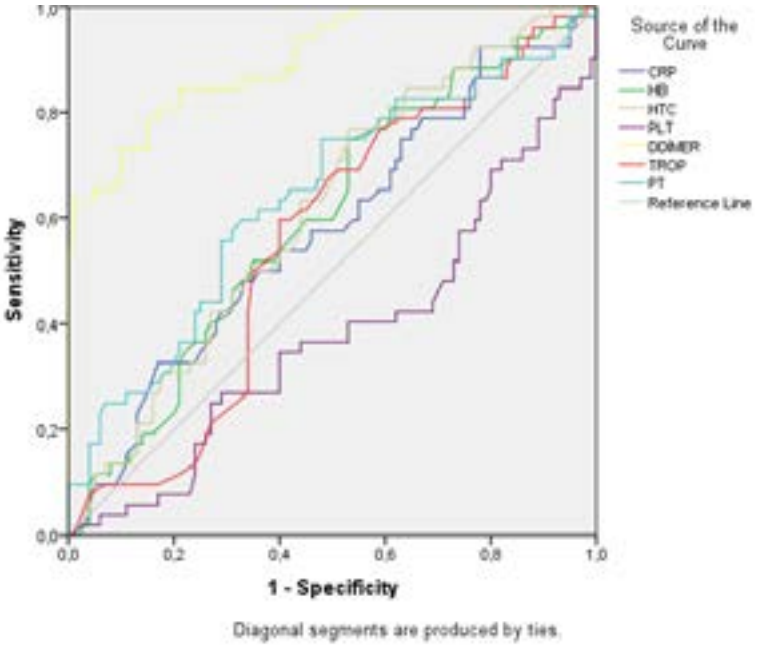

Figure 2: ROC analysis for Hb, Htc, Plt, CRP, D-dimer, and Troponin I

Table 2: Comparison of massive, sub-massive and non-massive APE groups regarding vital parameters and radiological signs.

		n	Mean	Std. Deviation	95% Confidence Interval for Mean		
					Lower Bound	Upper Bound	p
SBP	Massive	22	96.075	17.025	88.50	103.59	.000
	Sub-massive	49	114.78	19.122	109.28	120.27	
	Non-massive	29	121.55	24.589	112.20	130.90	
DBP	Massive	22	56.32	12.830	50.63	62.01	.000
	Sub-massive	49	68.69	11.406	65.42	71.97	
	Non-massive	29	70.17	13.538	65.02	75.32	
Pulse rate	Massive	22	108.14	28.663	95.43	120.84	0.031
	Sub-massive	49	104.27	16.485	99.53	109.00	
	Non-massive	29	95.41	14.234	90.00	100.83	
RR	Massive	22	19.86	2.817	18.61	21.11	.000
	Sub-massive	49	17.47	2.829	16.66	18.28	
	Non-massive	29	16.24	1.766	15.57	16.91	
SO2	Massive	22	86.23	7.752	82.79	89.66	.000
	Sub-massive	49	93.12	4.371	91.87	94.38	
	Non-massive	29	94.72	3.981	93.21	96.24	
RV diameter	Massive	22	45.586	8.1952	41.953	49.220	.000
	Sub-massive	49	40.235	5.6503	38.612	41.858	
	Non-massive	29	34.186	7.3227	31.401	36.972	
LV diameter	Massive	22	34.714	7.6884	31.305	38.122	.000
	Sub-massive	49	37.118	4.6740	35.776	38.461	
	Non-massive	29	42.597	7.2789	39.828	45.365	
RV/LV ratio	Massive	22	1.3672	.37486	1.2010	1.5334	.000
	Sub-massive	49	1.1011	.12821	1.0643	1.1379	
	Non-massive	29	.8013	.08232	.7699	.8326	

terms of Hb, Htc, Plt, RDW, MPV, and CRP.

According to the analysis results, all patients with massive APE diagnosed in the ED were treated as in-patients while 22 patients with sub-massive APE and 19 patients with non-massive APE were treated in the ED and discharged afterwards. Of 41 hospitalized patients, 9 had massive APE, nine had non-massive APE, and 23 had sub-massive APE. Six of eight patients admitted to the intensive care unit had massive APE, one had sub-massive APE, and one had non-massive APE. Five patients with massive APE died. A review of the treatment regimens administered to the patients showed that 18 patients with massive APE received thrombolytic therapy and four patients received anticoagulant therapy. Forty-nine patients with sub-massive APE were administered anticoagulant therapy while 29 patients with non-massive APE received symptomatic treatment.

DISCUSSION

Pulmonary embolism constitutes a frequent cause of ED admissions (4). Since APE is a highly morbid and potentially fatal acute emergency condition and its presence and severity should be rapidly determined, worldwide efforts are ongoing to find simple and readily available parameters or markers to accomplish this goal (5). Herein, we investigated the collective role of blood parameters in APE, which have been previously studied for the same purpose separately. The incidence of APE increases with age, with the risk doubling for each 10-year period after the age of 50. Keller et al. found a mean age of 68.5±15.3 in 182 APE patients (6). In our study, the mean age was 65.2±17.1 years in the patient group and 60.5±60.5 years in the control group. The statistical comparison of the mean age of both groups showed no significant difference (p=0.774).

There is no definitive diagnostic laboratory marker in APE; however, among available laboratory markers, the most valuable one is plasma D-dimer, which can increase up to 8 times in cases of APE. The reported sensitivity of D-dimer levels above 500ng/ml to diagnose APE is 97-100% (7). Huang et al. compared D-dimer levels between patients with APE and the control group, and found significantly higher D-dimer levels in the APE group (3.860 ng/ml vs 583 ng/ml, p<0.01) (8). Our study demonstrated a significantly greater D-dimer level in the APE group (3559.5 ng/ml vs 266.6 ng/ml, p<0.001). In addition, D-dimer in our study had a sensitivity of 79%

Table 3: Laboratory findings of study population according to subtype of APE

Hematological Parameters		n	Mean	Std. Deviation	95% Confidence Interval for Mean		p
					Lower Bound	Upper Bound	
	Massive	22	12564	2.0084	11.673	13.454	
Hb	Sub-massive	49	12690	2.3026	12.028	13.351	0.718
	Non-massive	29	12255	2.2822	11.387	13.123	
	Massive	22	39.1	5.6353	8.618	19.284	
HTC	Sub-massive	49	36.6	7.3595	36.7901	39.013	0.720
	Non-massive	29	37.6	8.3284	36.668	43.185	
	Massive	22	234180	122495	179.87	288.49	
PLT	Sub-massive	49	236240	87660	211.07	261.42	0.878
	Non-massive	29	238390	123581	191.38	285.39	
	Massive	22	73.18	66.967	43.49	102.87	
CRP	Sub-massive	49	69.86	88.603	44.41	95.31	0.109
	Non-massive	29	99.86	89.802	65.70	134.02	
	Massive	22	9871.00	15051.906	3.197.36	16.544.64	
D-dimer	Sub-massive	49	2261.82	5412.672	707.12	3.816.52	.000
	Non-massive	29	964.24	908.167	618.79	1309..69	
	Massive	22	64.73	67.254	34.91	94.55	
Troponin	Sub-massive	49	60.80	111.561	28.75	92.84	0.002
	Non-massive	29	31.93	58.531	9.67	54.19	
	Massive	22	14184.6	5935.9	7.718	18.184	
WBC	Sub-massive	49	9395.7	7159.1	36.901	41.013	<.001
	Non-massive	29	9286	11328.7	35.567	44.185	
	Massive	22	15.282	1.8679	14.454	16.110	
RDW	Sub-massive	49	16.096	2.6454	15.336	16.856	0.620
	Non-massive	29	16.331	3.3918	15.041	17.621	
	Massive	22	8.65	1.541	7.96	9.33	
MPV	Sub-massive	49	8.61	1.191	8.27	8.96	0.926
	Non-massive	29	8.87	1.980	8.11	9.62	
	Massive	22	14541	15367.8	7.727	21.355	
Neutrophil	Sub-massive	49	8353	4954.6	6.930	9.776	0.015
	Non-massive	29	7803	4289.6	6.172	9.435	
	Massive	22	3.13	2.018	2.23	4.02	
Lymphocyte	Sub-massive	49	2.19	1.624	1.72	2.66	0.050
	Non-massive	29	3.34	6.584	.84	5.85	
	Massive	22	7.6	.66019	1.7	30.4	
NLR	Sub-massive	49	3.1	.54834	0.8	10.1	0.046
	Non-massive	29	3.0	.55430	0.9	8.9	

and a specificity of 87% for massive APE, which were generally in accordance with the literature data.

Although troponin level does not confer a diagnostic importance in APE, studies have linked higher troponin levels to increased mortality (9). In a study reported by Çelik et al., troponin I level were significantly higher in patients with APE (10). In accordance with the literature data, our study found a higher troponin level in the patient group (53.3 ng/mL vs 32.9 ng/mL). According to the results of a ROC analysis performed for this parameter, an elevated troponin level had a specificity of 61% and a sensitivity of 60% for APE. Although elevated troponin level alone is not used for diagnosis or exclusion of APE, it appears to be important for determining disease severity and predicting its prognosis.

CRP is an acute-phase reactant that is a marker of inflammation in the body. CRP is mainly synthesized in the liver, but it is also produced by adipose tissue,

endothelial cells, smooth muscle cells, and similar vascular wall cells (11). CRP can be elevated by many conditions such as acute and chronic inflammation, tissue necrosis, infections, tumors, post-surgical period, and obesity (12). Çelik et al. reported a significantly higher CRP level in patients with APE compared to controls (10). However, according to the study by Huang et al., patients with and without APE showed no significant difference in respect to CRP level (8). Our study revealed a higher CRP level in the patient group compared with the controls (79.3 mg/L vs 64.1 mg/L). Although the literature data regarding the relationship between CRP and APE are heterogeneous, it can be argued based on our study results that CRP level alone cannot be used to diagnose APE, but it is one of the supportive laboratory parameters weakly related to APE.

Although a specific relationship between Hb and Htc levels and APE has yet to be explained, they affect a patient's condition at all stages of diagnosis, treatment, and follow-up. A study by Talay and colleagues reported no significant difference between the APE and control groups regarding Hb and Htc levels (13). The Hb level of our patient and control groups were 12.5 and 12 respectively. The statistical analysis found a p-value of 0.047. The mean Htc level was 39.1 in the patients and 36.6 in the controls, with a p-value of 0.19. Accordingly, our study indicated a significant relationship between Hb and Htc levels and APE. However, these parameters were not correlated to disease severity.

While many studies on the platelet count in the diagnosis and prognosis of APE have reported a significantly lower platelet count in patients with APE, some others failed to demonstrate any significant difference. Huang et al. reported that the patients diagnosed with APE and the control group showed no significant difference with respect to thrombocyte count (8). In our study, the patient group had a mean thrombocyte count of 236.4, and the control group of 306.1, with the two groups having differed significantly with regard to this parameter ($p<0.001$). According to the results of a ROC analysis performed for thrombocyte count, the latter had a specificity of 59%, a sensitivity of 69%, and a cut-off value of 252. Our results suggest that although thrombocyte count cannot diagnose PTE, it can be used as an ancillary diagnostic parameter.

RDW is a parameter found in the routine hemogram, which shows erythrocyte heterogeneity. Reflecting the morphology of erythrocytes, RDW is widely used for the differential diagnosis of different types of anemia. However, systemic inflammation, nutritional disorders, ineffective erythropoiesis, and bone marrow dysfunction may also cause RDW increase (14). There are literature studies indicating increased RDW level in cardiovascular diseases, cancer, diabetes, liver and kidney failure, and sepsis (15). Barış et al. reported that RDW level showed a significant increase in patients with APE compared with the control group, with the length of hospital stay and mortality rate having been increased significantly in patients with increased RDW levels (16). Our study found a mean RDW level of 16 in the patient group and 15.9 in the control group, with the two groups being similar in respect to RDW level.

MPV is a parameter measured by automatic hemogram analyzers in routine hemograms, and it is one of the principal indicators of platelet reactivity (17). Based on the assumption that larger thrombocytes are more thrombogenic, it reflects platelet activation by representing their mean volume. So far, MPV has been studied in various different disorders, where it has been gained prominence as an independent risk factor (18,19). Elevated MPV has been strongly associated with acute deep venous thrombosis (DVT) and APE in recent studies (13).Yardan et al. reported that MPV level was significantly greater in patients with APE and right ventricle dysfunction (20). We found no significant difference between the MPV levels of our patient and control groups.

Leukocytes have been implicated in the pathophysiology of venous thrombosis due to their disruptive effects on vascular endothelium. Hence, leukocytosis has been linked to increased rates of venous thromboembolism, major hemorrhage, and death (21). Afzal et al. (22) were the first researchers that pointed to an increased WBC count in APE. As an advance in this field, NLR in peripheral blood has been recently focused on as an inflammatory marker that is superior than the more simple WBC count. It is believed that the ratio of neutrophils to lymphocytes is increased in the presence of systemic inflammation. Kayrak et al. (23) in a study comprising 359 APE patients, found that NLR had a prognostic value for early mortality. In line with literature reports, our study also revealed a significant difference between WBC and NLR levels of the patient and control groups ($p<0,05$).

CONCLUSION

The relationship between the clinical severity of APE and blood parameters were studied in the present study. Our study demonstrated significant differences between the patient and control groups with regard to the blood levels of Hb, HTC, PLT, CRP, D-Dimer, Troponin and PT, but not regarding WBC, RDW, MPV, neutrophil, lymphocyte, and NLR levels. However, an analysis of the hematological parameters between the three APE subgroups, namely massive APE, sub-massive APE, and non-massive APE, showed that D-Dimer, WBC, neutrophil, lymphocyte, NLR, and Troponin levels were significantly higher in the massive APE group than the sub-massive and non-massive APE groups.

Conflict Interest: No conflict of interest was declared by the authors
Ethics: This study was approved by Health Sciences University Antalya Training and Research Hospital Ethics Committee (05.09.2017-12/14),
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