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The Role of Hemogram Parameters in Predicting the Severity of Pulmonary Embolism

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ABSTRACT

Introduction: Acute pulmonary embolism (PE) is a disease with serious mortality and morbidity. Therefore, early diagnosis and treatment are important. A PE is a process accompanied by inflammation. Therefore, our study was designed to examine the relationship between hemogram parameters, which are easily accessible and indicative of inflammation, and late mortality from PE.

Methods: Two hundred and two patients who were hospitalized in our hospital between January 1, 2017 and July 1, 2020 and who were diagnosed with pulmonary angio computed tomography were included. Demographic and clinical data, laboratory, radiology and echocardiography results of the patients were analyzed retrospectively from the hospital information system.

Results: Seventy-eight of 202 patients included in the study were male (38.6%), 124 females (61.4%), mean age was 58.27±16.26 years. According to the results of univariate Cox regression analysis, age [hazard ratio (HR): 1,058, p=0.001], D-dimer (HR: 1,057, p=0.015), presence of malignancy (HR: 6,274, p=0.001), trauma history (HR: 2,931, p=0.039), long travel history (HR: 0.163, p=0.003), C-reactive protein (HR: 1,004, p=0.021), PE severity index (HR: 1,033, p=0.001), EF (HR: 0.944 , p=0.001), red-cell distribution width (HR: 1,125, p=0.001), lymphocyte (HR: 0.999, p=0.001), platelet-lymphocyte ratio (PLR) (HR: 1.013, p=0.001) and neutrophil-lymphocyte ratio (NLR) (HR: 1,017, p=0.001) significantly and it was associated with mortality.

Conclusion: Because of our study, we determined that NLR and PLR can be used as 12-month prognostic factors in patients with acute PE.

Keywords: Pulmonary embolism, mortality, PLR, NLR

Introduction

Acute pulmonary embolism (PE) is a cardiopulmonary disease with an incidence of 70 per 100,000 people, with significant mortality and morbidity. Therefore, early diagnosis and treatment are vital. It is usually observed after deep vein thrombosis (1-3). Biochemical markers such as troponin, brain natriuretic peptide (BNP), N-terminal proBrain natriuretic peptide (proBNP), heart type fatty acid binding protein, myoglobin and white blood cells (WBC) count as prognostic indicators in acute PE is used (4).

It has been shown that the progression of thrombosis in pulmonary arteries is associated with inflammation. Therefore, circulating inflammation-related markers are used as promising prognostic factors in thrombosis-related diseases. Among these biomarkers, it has been suggested that the neutrophil-lymphocyte ratio (NLR) and the platelet-lymphocyte ratio (PLR) are useful in determining the prognosis of patients with PE (5,6). Recent studies have found that NLR and PLR are better indicators of inflammation than WBC counts (5-12). In another study, it was suggested that NLR and PLR values are useful in determining the prognosis in patients with PE (13).

These studies included the groups in which the studies were conducted and inconsistencies due to the severity of the diseases and accompanying comorbidities. For this reason, we planned to evaluate the relationship between NLR and PLR, which are both cheap, easily accessible and can be evaluated from a routine hemogram, and prognosis in the service patients we follow-up. Unlike other studies, pulmonary embolism severity index (PESI), PE risk determination score (WELLS), computed tomography (CT) findings and cardiac findings were also evaluated.

Methods

Patients and Study Design

The study, which was planned as a retrospective cohort, was followed up with the diagnosis code ICD-10 "I26" in our service between January 1, 2017 and July 1, 2020, the data could be accessed from the electronic patient information system, the diagnosis of PE was confirmed by

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pulmonary CT angiography, 202 patients in whom no massive PE was detected; in whom there was no need for thrombolytic; not requiring intensive care follow-up were included.

Our study was conducted with University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee cognitive consent (approval number: 2020-08, date: 06.08.2020). Informed consent was not obtained from the patients as it was a retrospective cross-sectional study.

Age, gender, comorbidities of the patients (diabetes mellitus, hypertension, Cerebrovascular disease, congestive heart failure, chronic renal failure, ischemic heart disease, chronic obstructive pulmonary disease, asthma, hyperlipidemia, malignancy, etc.), vital signs (blood pressure arterial, pulse and fingertip saturation), thoracic CT findings, echocardiography (ECHO) findings [ejection fraction (EF), right ventricular overload finding, pulmonary artery pressure (PAP), tricuspid regurgitation, mitral insufficiency, left ventricular hypertrophy, left ventricular diastolic dysfunction, left atrium dilatation, biatrial dilatation, pericardial effusion, mitral stenosis, left ventricular systolic dysfunction], hemogram and biochemical parameters (NLR, PLR), thrombocyte, neutrophil, lymphocyte, D-dimer, C-reactive protein (CRP), procalcitonin, proBNP, troponin level risk factors (immobilization or surgery history in the last 4 weeks, malignancy history, oral contraceptive use, trauma, thrombophilia), bilateral venous lower extremity doppler findings were obtained from the electronic patient information system and the 12th month mortality was questioned from the "Death Notification System".

Hemogram, D-dimer, troponin 1, proBNP, CRP values were obtained at the time of admission and before treatment. In our hospital, peripheral blood samples are taken into calcium-EDTA tubes and blood counts and differentials are analyzed using an autoanalyzer. PLR was calculated as the ratio of platelets (PLTs) to lymphocytes, and NLR was calculated as the ratio of neutrophils to lymphocytes in peripheral blood. ProBNP and troponin 1 levels and their quantitative analysis were studied in the ADVIA Centaur Analyzer (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). All D-dimer levels in plasma samples taken from patients [1 part sodium citrate (3.2%) 9 parts venous blood] were evaluated using the BCS XP coagulation analyzer. The PESI of the patients was evaluated using the data obtained from the electronic patient information system. ECHO findings and bilateral lower extremity Doppler ultrasonography results performed within the first 48 h were obtained from the hospital's electronic system. Philips Affiniti 30 ECHO devices were used for the ECHO evaluations.

Statistical Analysis

All statistical analysis were conducted using the SPSS 21.0 (IBM Statistical Product and Service Solutions version 21 Inc., Chicago, USA) program. Descriptive statistics were reported in the study, including mean (standard deviation), median (interquartile range), and percentage. Whether continuous variables showed a normal distribution was examined by Kolmogorov-Smirnov test. The difference in continuous variables between the living and death groups was evaluated by the two-sample t-test and the Mann-Whitney U test. Pearson's chi-square and Fisher's exact tests were used to the difference between categorical variables. Univariate Cox regression analysis was used to investigate the univariate predictors of total mortality throughout the study period. Receiver operating characteristic (ROC) analysis was used to determine the cut-off value of the NLR.

Results

Two hundred and two cases hospitalized in our clinic with the diagnosis of PE between January 1, 2017 and July 1, 2020 were included in the study. Seventy-eight of the patients were male (38.6%), 124 of them were female (61.4%), their mean age was 58.27±16.26 years. While 128 of the patients (63.4%) had a history of smoking, 74 patients (36.6%) did not smoking. Table 1 shows the comparison of demographic data of the patients according to the groups who died and survived. When the living and deceased populations were compared, a statistically significant difference was found in terms of age and body mass index (BMI) ($p<0.05$). While the age was higher in the deceased group (56.41±16.31 vs 69.86 ±10.05; $p=0.001$), it was found to be higher in the group with BMI (28.77±6.26 vs 23.81±10.01; $p=0.006$).

PESI, saturation, EF, PAP of the patients were statistically significant ($p<0.05$). PESI and PAP was higher in the deceased group (78.12±27.45 vs 108.04±18.95, 27.27±16.22 vs 32.75±20.41; $p=0.001$, $p=0.04$, respectively), saturation and EF was higher in the living group (95.09±3.94 vs 92.56±4.57, 58.31±5.96 vs 53.0±11.36; $p=0.004$ and $p=0.006$, respectively). In the statistical evaluation of 145 patients in terms of thoracic CT findings, WELLS score, and ECHO findings, there was no statistically significant difference between the two groups.

When laboratory parameters were compared, a statistically significant difference was found between the CRP, RDW, NLR, PLR and lymphocyte values between the surviving and deceased groups ($p<0.05$). CRP, RDW, PLR and NLR were higher in the deceased group (60.85±72.3 vs 95.41±62.51, 43.23±4.69 vs 46.71±6.49, 163.63±102.75 vs 255.21±256.74, 4.62±4.18 vs 8.16±9.25; $p=0.001$, $p=0.009$, $p=0.016$ and $p=0.003$ respectively), and lymphocyte was higher in the living group 2037.99±979.31 vs 1410±637.94, $p=0.001$. No statistically significant difference was observed between D-dimer, troponin, ProBNP, procalcitonin, mean platelet volume, PLT and neutrophil. A comparison of laboratory parameters is given in Table 2.

Long-term mortality predictors were examined using Cox regression analysis. According to the results of univariate Cox regression analysis, age [hazard ratio (HR): 1,058, $p=0.001$)], D-dimer (HR: 1,057, $p=0.015$), presence of malignancy (HR: 6,274, $p=0.001$), trauma history (HR: 2,931, $p=0.039$), long travel history (HR: 0.163, $p=0.003$), CRP (HR: 1,004, $p=0.021$), PESI (HR: 1,033, $p=0.001$), EF (HR: 0.944 , $p=0.001$), RDW (HR: 1,125, $p=0.001$), lymphocyte (HR: 0.999, $p=0.001$), PLR (HR: 1,013, $p=0.001$) and NLR (HR: 1,017, $p=0.001$) significantly affect mortality. Age, D-dimer, malignancy, CRP, PESI, RDW, NLR and PLR have affect on mortality since the HR is greater than 1. According to the results of multivariate Cox regression analysis, malignancy (HR: 0.087, $p=0.013$), trauma history (HR: 7,985, $p=0.049$), long travel history (HR: 0.144, $p=0.032$), Procalsitonine (HR: 1,586, $p=0.017$) and EF (HR: 0.924, $p=0.017$) significantly affect mortality. Table 3 provides Univariate ve Multivariate Cox regresyon analysis of the possible predictors of total mortality in the study population.

Table 1. Comparison of demographic and clinical parameters and outcomes of the study population

Demographic and clinical characteristics	Total population (n=202)	Alive (n=174)	Dead (n=28)	p-value
Age (years-mean ± st. dev.)	58.27±16.26	56.41±16.31	69.86±10.05	0.001
BMI (kg/m² - mean ± st. dev.)	28.08±7.08	28.77±6.26	23.81±10.01	0.006
Female, n (%)	124 (61.4)	105 (60.3)	19 (67.9)	0.449
Smoking history, n (%)	128 (63.4)	111 (63.8)	17 (60.7)	0.754
Risk factor, n (%)	168 (83.2)	143 (82.2)	25 (89.3)	0.351
Immobilization, n (%)	158 (78.2)	134 (77)	24 (85.7)	0.301
Malignancy, n (%)	34 (16.8)	20 (11.5)	14 (50)	0.001
Surgical operation history, n (%)	30 (14.9)	28 (16.1)	2 (7.1)	0.216
Oral contraceptive, n (%)	3 (1.5)	3 (1.7)	0 (0)	0.484
Trauma, n (%)	9 (4.5)	6 (3.4)	3 (10.7)	0.113
Travel, n (%)	81 (40.1)	78 (44.8)	3 (10.7)	0.001
Deep vein thrombosis, n (%)	15 (7.4)	15 (8.6)	0 (0)	0.232
History of thrombophilia, n (%)	2 (1)	2 (1.1)	0 (0)	0.569
Segmental involvement in tomography, n (%)	135 (66.8)	117 (67.2)	18 (64.3)	0.758
ECHO findings, n (%)	94 (46.5)	83 (47.7)	11 (39.3)	0.121
Wells score	5.32±2.42	5.23±2.43	5.86±2.36	0.201
PESI	81.9±28.3	78.12±27.45	108.04±18.95	0.001
Oxygen saturation, %	94.77±4.1	95.09±3.94	92.56±4.57	0.004
Pulse, min	87.57±158.61	86.87±15.54	92.44±15.54	0.095
Ejection fraction	57.63±7.07	58.31±5.96	53.0±11.36	0.006
Follow-up period, day	576.5 (315.5)	644.0 (291.7)	90.5 (105.5)	0.001

BMI: Body mass index, PESL: Pulmonary embolism severity index, st. dev.: Standard deviation, ECHO: Echocardiography, PESI: Pulmonary embolism severity index

Table 2. Comparison of laboratory parameters in the study population

Laboratory parameters	Total population (n=202) (mean ± st.dev)	Alive (n=174) (mean ± st. dev.)	Dead (n=28) (mean ± st. dev.)	p-value
D-dimer (mg/L)	4.26±5.79	3.89±5.09	6.560±8.81	0.279
Troponin 1 (ng/mL)	54.56±491.72	58.6±529.42	29.44±57.59	0.084
CRP (mg/L)	65.64±71.89	60.85±72.3	95.41±62.51	0.001
ProBNP (pg/mL)	116.54±519.47	98.27±505.45	230.11±596.96	0.192
Procalsitonine (ng/mL)	0.36±0.95	0.33±0.84	0.6±1.45	0.372
PAP, mm/Hg	28.03±16.92	27.27±16.22	32.75±20.41	0.040
MPV (fL)	9.28±1.59	9.28±1.52	9.26±2.01	0.409
RDW (%)	43.71±5.11	43.23±4.69	46.71±6.49	0.009
LYM ($10e^3$/uL)	1,950.94±963.04	2037.99±979.31	1,410±637.94	0.001
PLT ($10e^3$/uL)	270153.47±104,390.68	271,632.18±105,742.86	260,964.29±96,844.08	0.836
NEU ($10e^3$/uL)	7,089.21±3,207.47	6,984.71±3,148.69	7,738.57±3,543.34	0.216
NEU/LYM ratio (NLR)	5.11±5.46	4.62±4.18	8.16±9.25	0.003
PLT/LYM ratio (PLR)	176.32±137.65	163.63±102.75	255.21±256.74	0.016
PLT/NEU ratio (PNR)	45.16±25.42	45.92±25.43	40.41±25.27	0.156

CRP: C-reactive protein, PAP: Pulmonary arterial pressure, PROBNP: ProBrain natriuretic peptide, MPV: Mean platelet volume, RDW: Red-cell distribution width, LYM: Lymphocyte, PLT: Platelet, NEU: Neutrophil, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, PNR: Platelet-to-neutrophil ratio

In the ROC analysis, cut off values, area under the curve, sensitivity and specificity for NLR and PLR were found to be 4.365 and 174.72; 0.675 (0.576-0.774) and 0.642 (0.535-0.748); 64.3% and 53.6%; 67.2% and 70.1% respectively (Figure 1).

Discussion

PE, as a disease with a high mortality incidence, challenges clinicians in patient management in emergency units and inpatient services. There are many studies on mortality predictive parameters, and researches are still ongoing. Early detection of this disease is important for predicting

Table 3. Univariate ve multivariate cox regression analysis

Variables	Univariate model		Multivariate model	
	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Age	1,058 (1,027-1,089)	0.001	-	-
Gender	0.758 (0.340-1,659)	0.479	-	-
BMI	1,469 (0.614-3,518)	0.388	-	-
Smoking history	0.876 (0.410-1,872)	0.733	-	-
D-dimer	1,057 (1,011-1,106)	0.015	-	-
Troponin 1	1,000 (0.998-1,001)	0.785	-	-
Risk factor	1,790 (0.540-5,930)	0.304	-	-
Immobilization	1,779 (0.517-5,127)	0.286	-	-
Malignancy	6,274 (2,982-13,204)	0.001	0.087 (0.013-0.603)	0.013
Surgical operation	0.432 (0.103-1,821)	0.253	-	-
Oral contraceptive	0.152 (0.021-4,754)	0.653	-	-
Trauma	2,931 (0.883-9,727)	0.039	7,985 (1,012-62,986)	0.049
Travel history	0.163 (0.049-0.540)	0.003	0.144 (0.025-0.844)	0.032
Deep vein thrombosis	0.152 (0.089-2,785)	0.310	-	-
History of thrombophilia	1,325 (0.627-3,589)	0.720	-	-
Segmental involvement in tomography	0.897 (0.414-1,942)	0.782	-	-
CRP	1,004 (1,001-1,008)	0.021	-	-
Procalsitonine	1,167 (0.913-1,493)	0.218	1,586 (1,086-2,317)	0.017
Wells score	1,122 (0.950-1,325)	0.176	-	-
PESI	1,033 (1,019-1,047)	0.001	-	-
Pulse, min	1,019 (0.997-1,0429	0.096	-	-
Ejection fraction	0.944 (0.913-0.976)	0.001	0.924 (0.866-0.986)	0.017
RDW	1,125 (1,054-1,200)	0.001	-	-
Lymphocyte	0.999 (0.999-1,000)	0.001	-	-
NEU/LYM ratio (NLR)	1,071 (1,030-1,114)	0.001	-	-
PLT/LYM ratio (PLR)	1,013 (1,004-1,035)	0.001	-	-

BMI: Body mass index, CRP: C-reactive protein, RDW: Red-cell distribution width, NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, CI: Confidence interval

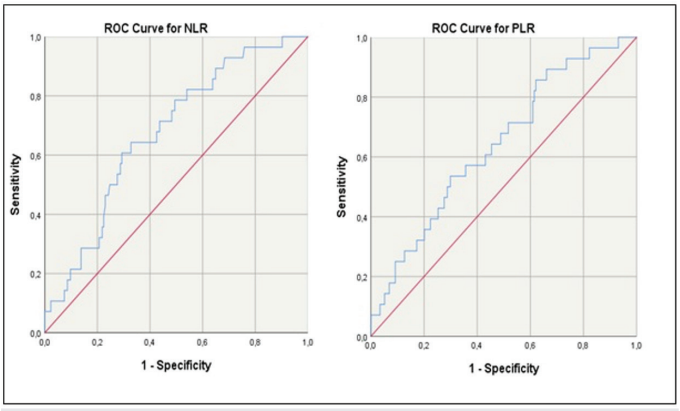

Figure 1. Receiver operating characteristic curve for NLR and PLR
ROC: Receiver operating characteristic NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio

mortality (1-3). Biochemical markers such as troponin, BNP, myoglobin and WBC count are used as prognostic indicators in acute PE (4). In our study, we predicted the mortality of the disease with the Complete Blood Count analysis found in each unit.

The incidence of PE increases with advanced age. Studies have shown that the average age is 50 years and above, and the risk of venous thromboembolism (VTE) increases with increasing age (12-16). In our study, 86 (42.57%) of the patients were under the age of 65 and 116 (57.43%) of them were over the age of 65, and the average age was 58 years, which was consistent with the literature. As in our study, a relationship between age and mortality was found in the study conducted by Karataş et al. (12).

It has been shown in the literature that the risk of VTE increased 6-22 times in the last 45-90 days after major surgical intervention (16). In our study, in accordance with the literature, 30 patients (14.9%) had a history of major surgical intervention, but it was not found to be associated with mortality. While PE was less mortal in patients with underlying long-travel history (41%) as a risk factor, mortality was higher in the group with a history of malignancy.

It has been shown in previous studies that NLR and PLR show increased inflammatory response in cardiovascular diseases and PE and have a prognostic value. Additionally, studies have shown that the increase in NLR and PLR is associated with 30-day mortality (17-19). In a study

performed in a group with massive PE and high PESI, the rate of NLR and PLR was found to be high (20). In the study conducted in 195 patients by Ozcan Cetin et al. (21), they found that NLR is a prognostic indicator of in-hospital adverse events and long-term mortality due to all causes. In another study, it was determined that NLR can be used as a 30-day mortality indicator depending on the increased inflammatory response (22). Additionally, in the study by Telo et al. (23), it was found that NLR and PLR increased in high-risk patients with PE, PLR could be a prognostic factor to predict 3-month mortality and showed that NLR can be used as a prognostic factor in-hospital, 3 months, and in total. Although most of the studies included patients with massive PE and in need of intensive care and thrombolytics, and short-term (1st and 3rd month) mortality was examined, we excluded this patient group in our study because we planned long-term mortality (12-month) study. Therefore, our mortality was found to be lower in our study. In our 12-month mortality study, consistent with the literature, NLR was associated with mortality according to both Cox regression analysis and hazard ratio. In another study, conducted with patients who were followed up after PE, NRL and PLR values at the time of diagnosis were found to be higher in the group who died during long-term follow-up, similar to our study (12). In the same study in which 203 patients were included in Turkey, NLR and PLR were associated with short- and long term mortality, and it was shown that NLR has a better prognostic value than PLR (12). In our study, it was found that NLR was more sensitive than PLR as a prognostic factor, while PLR was observed to be more specific.

In studies on RDW, RDW was found to be higher in patients with PE compared to the control group, and no statistically significant difference was found between those who lived or those who died (24). In contrast to other studies, we found RDW to be higher in the deceased group and was associated with mortality in univariate Cox regression analysis (25).

In studies examining the mean values of PESI in patients with PE, it was found that the mean values of PESI in patients who died were higher and the PESI score was associated with mortality (12,23,26). In our study, similar to the literature, the mean PESI value was found to be higher in the deceased group and it was observed that it was associated with mortality.

Additionally, we found that D-dimer, malignancy, and CRP are independent predictors of mortality in the 12-month period, in accordance with the literature (27-29).

Study Limitations

Our study was a single center retrospective study including a small sample group. The power of regression analysis can be increased with a larger sample group. We did not know the hemogram parameters of our patient before the acute PE. Therefore, it was impossible to compare the hemogram parameters before and after acute PE. Patients who were hospitalized in the ward were included in the study, and those who were followed up in an outpatient clinic or those who needed intensive care or thrombolytics were not included. Therefore, our mortality was found to be lower than that of other studies.

Conclusion

Our goal in this study was to determine the role of hemogram parameters in predicting the severity of PE. We found that NLR, PLR and RDW parameters were associated with long-term mortality. We think that hemogram parameters, which are easily accessible, can take their place in predicting the severity of PE and can be used as an indicator of mortality.

Ethics Committee Approval: Our study was conducted with University of Health Sciences Turkey, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital Ethics Committee cognitive consent (approval number: 2020-08, date: 06.08.2020).

Informed Consent: Informed consent was not obtained from the patients as it was a retrospective cross-sectional study.

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Authorship Contributions: Concept - K.K., S.N.S., S.T.Ö.; Design - K.K., S.N.S., C.Ö.; Data Collection or Processing - S.N.S., S.T.Ö., C.Ö., F.T.A., Ö.K.; Analysis or Interpretation - K.K., S.N.S., S.T.Ö., C.Ö.; Literature Search - K.K., F.T.A., Ö.K.; Writing - K.K., S.N.S., S.T.Ö.

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