Prognostic role of NLR, PLR, and LMR in patients with pulmonary embolism

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ABSTRACT

Pulmonary embolism (PE) is associated with significant morbidity and mortality. New biological markers are being investigated for estimating the prognosis of PE patients. Since PE is closely associated with inflammatory status, the neutrophil-lymphocyte (NLR), platelet-lymphocyte (PLR), and lymphocyte-monocyte (LMR) ratios were suggested to be useful in predicting patient outcomes. This study aimed to evaluate the prognostic role of NLR, PLR, and LMR in PE. A total of 103 PE cases from a cardiology department were included in the study. We retrospectively evaluated demographic and clinical characteristics, treatments, laboratory and imaging findings, and outcomes of patients. The median follow-up of PE patients was 39 months, and the 5-year overall survival probability was 73.8%. Out of 103 patients, 20 were classified as high risk PE cases (19.4%). Thrombolytic treatment was administered to 23 patients (22.3%). Systolic pulmonary arterial pressure was measured during one year, showing a significant decrease from 51.7 ± 15.7 mmHg at admission to 26.6 ± 4.0 mmHg at first year assessment. Age (OR: 1.06, $p < 0.001$) and NLR (OR: 1.52, $p < 0.0019$) were significantly associated with the disease status. The independent prognostic factors in moderate-low and low risk PE groups were NLR (HR: 1.17, $p = 0.033$) and LMR (HR: 1.58, $p = 0.046$). In moderate-high and high risk PE patients, the independent prognostic factors were age (HR: 1.07, $p = 0.014$) and PLR (HR: 1.01, $p = 0.046$). NLR, PLR, and LMR were associated with the prognosis of PE patients. The clinical severity of PE should be considered when utilizing these markers to assess patient outcomes.

KEYWORDS: Pulmonary embolism; neutrophil-lymphocyte ratio; NLR; platelet-lymphocyte ratio; PLR; lymphocyte-monocyte ratio; LMR; prognosis; patient outcomes

INTRODUCTION

Acute pulmonary embolism (PE) is a life-threatening cardiovascular disease that has an incidence rate of 60–70 cases per 100,000 individuals and is associated with significant morbidity and mortality [1]. PE usually occurs secondary to deep vein thrombosis (DVT), and the mortality rate is particularly high in patients with multiple comorbidities and poor hemodynamics [2,3]. A previous study reported that PE is responsible for about 300,000 deaths per year in Europe [4], and the all-cause short-term mortality rate of PE varies significantly, from 2% to 95%, depending on disease severity [5]. Due to this uncertainty about the prognosis of PE patients, new risk classification methods and biological markers are being investigated for determining the optimal treatment strategy and estimating the prognosis of disease.

The current research suggests that the progression of vein thrombosis is associated with inflammation. Thrombus formation is a result of abnormalities of blood flow, the vascular wall, and blood components. Inflammation both causes endothelial damage and affects blood components by increasing procoagulants and inhibiting anticoagulant pathways and fibrinolytic activity [6]. Therefore, inflammation-related markers in the circulation have emerged as promising prognostic factors in thrombosis associated diseases. Among these biomarkers, the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were suggested to be useful in prognosis of PE patients [7]. However, the results of different studies on the prognostic value of NLR and PLR in PE have been controversial [8]. Based on this background, we aimed to evaluate the prognostic value of NLR, PLR, and lymphocyte-monocyte ratio (LMR) in PE patients in relation to their demographic and clinical characteristics.

MATERIALS AND METHODS

Patients and study design

A total of 103 PE patients hospitalized and treated in a department of cardiology between 2011 and 2015 were included in the study. The risk categories of the patients were determined according to the Wicki and Wells criteria.

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High-risk patients had a systolic blood pressure <90 mmHg or at least 40 mmHg decrease in systolic blood pressure for at least 15 min, developed cardiogenic shock, or had a right atrial thrombus accompanying PE. Moderate-high risk patients were in PE severity index (PESI) class III-V or had a simplified PESI (sPESI) score >1, had right ventricular failure in echocardiography, and increased cardiac troponin T levels. Patients with hematological, oncological, collagen tissue, inflammatory, congenital heart, or severe renal/liver disease were excluded from the study.

Control group consisted of 102 patients selected from outpatient clinics other than cardiology, cardiovascular surgery, and chest diseases.

Treatment protocol

Routine biochemistry, complete blood count (CBC), activated partial thrombin time (aPTT), international normalized ratio (INR), arterial blood gas analysis, troponin T and plasma D-dimer levels were analyzed, and electrocardiography and bedside echocardiography were performed in all cases. Contrast-enhanced chest computed tomography (CT) and/or lower extremity venous Doppler ultrasonography (USG) were performed based on the clinical profile of patients.

The thrombolytic treatment was administered to selected cases in the coronary intensive care unit. An infusion of 100 mg tissue plasminogen activator (tPA, alteplase) was administered for 2 hours. If aPTT levels were lower than two times of the normal value following alteplase administration, intravenous infusion of unfractionated heparin at 18 U/kg/hour after 80 U/kg heparin bolus dose was administered. aPTT assessment was performed every 6 hours during the first 24 hours and every 24 hours afterwards, and heparin dose was adjusted to maintain the aPTT level between 60 to 80 seconds. Warfarin (10 mg) was added to the treatment after the first day. The heparin treatment in combination with warfarin was continued for at least 5 days. When an INR level >2 was maintained for 2 consecutive days, heparin was stopped and warfarin dose was continued for 3 months in patients without any underlying disease and for 6 months in patients with DVT or recurrent PE.

Statistical analysis

Descriptive statistics included a mean ± standard deviation for numerical variables and frequencies and percentages for categorical variables. Comparisons of numerical variables between dependent groups were done using the Friedman test. The survival analyses were conducted using the Kaplan-Meier method. The association of the prognostic indicators with disease presence was analyzed using logistic regression analysis. The logistic regression model fit was evaluated using the Hosmer and Lemeshow test. The prognostic value of factors for predicting mortality in patient group was assessed using Cox proportional-hazards model. A *p* value <0.05 was considered to be statistically significant. IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA) was used for the analyses.

RESULTS

A total of 103 PE patients were included in the study. Fifty-seven patients were female (55.3%) and 46 were male (44.7%). The mean age of patients was 67.6 ± 13.1 years, and the mean body mass index (BMI) was 28.6 ± 3.9 kg/m².

The distribution of previous risk factors and comorbidities among patients is summarized in Table 1. Unprovoked PE, provoked PE, and DVT were present in 56.3%, 39.8%, and 46.6% of patients, respectively. About 15.5% of patients were smokers and 14.6% were immobile. The median number of risk factors was 3 (range: 1–8).

TABLE 1. Distribution of risk factors and comorbidities in patients with pulmonary embolism

	n	%
Unprovoked pulmonary embolism	58	56.3
Hypertension	49	47.6
Deep vein thrombosis	48	46.6
Provoked pulmonary embolism	41	39.8
Diabetes mellitus	22	21.4
History of operation	19	18.4
Smoking	16	15.5
Immobility	15	14.6
Obesity	10	9.7
Chronic heart failure	8	7.8
Prior pulmonary embolism	7	6.8
Lower extremity fracture	7	6.8
Chronic obstructive pulmonary disease	6	5.8
Coronary artery disease	6	5.8
Malignancy	6	5.8
History of deep vein thrombosis	5	4.9
Coronary angiography/Catheterization	3	2.9
Gene mutation	3	2.9
Coronary artery bypass graft	2	1.9
Chronic renal failure	2	1.9
Lower extremity varicosity/Deep venous insufficiency	2	1.9
Oral contraceptive use	2	1.9
Major trauma	1	1.0
Stroke/Transient ischemic attack	1	1.0
Tuberculosis	1	1.0
Alcohol consumption	1	1.0
Total number of risk factors per patient		
1	13	12.6
2	26	25.2
3	17	16.5
4	25	24.3
5	12	11.7
6	7	6.8
7	1	1.0
8	2	1.9

Clinical findings at admission are presented in Table 2. The most common findings at physical examination were dyspnea (95.1%) and tachypnea (80.6%). The mean duration of symptoms prior to admission was 5.04 ± 6.9 days (range 0–30 days). The mean systolic and diastolic blood pressures were 115.4 ± 19.6 mmHg (70–190 mmHg) and 71.9 ± 12.2 mmHg (40–100 mmHg), respectively. The mean heart and respiratory rates were 94.8 ± 22.9 bpm (50–156 bpm) and 29.5 ± 5.3 per min (16–42 per min), respectively.

The findings of routine assessment and imaging studies are presented in Table 3. Lower extremity venous Doppler USG revealed DVT on the right side in 36 cases (35%) and on the left side in 28 cases (27.2%). In electrocardiography, 7 patients (6.8%) had atrial fibrillation, 69 had nonspecific ST changes (67%), 60 had S1Q3T3 (58.3%), and 54 had right precordial T wave inversion (52.4%). The most common echocardiography findings were paradoxical interventricular septal motion and right ventricular dilatation (77.7%) and right ventricular hypokinesia (76.7%). Twenty-four patients (23.3%) had Grade I and 66 had Grade II (64.1%) tricuspid regurgitation. At pulmonary CT-angiography, 1 patient had thrombus in the pulmonary trunk, 40 patients (38.8%) in the right pulmonary artery or its branches, and 33 patients (32%) in the left pulmonary artery or its branches. Bilateral involvement was present in 30 cases (29.1%).

TABLE 2. Clinical findings at admission in patients with pulmonary embolism

	n	%
Dyspnea	98	95.1
Tachypnea	83	80.6
Chest pain	61	59.2
Signs of deep vein thrombosis	44	42.7
Tachycardia	38	36.9
Palpitation	32	31.1
Coughing	26	25.2
Cyanosis	26	25.2
Unilateral leg pain	25	24.3
Homans sign	24	23.3
Pleuritic pain	22	21.4
Syncope	21	20.4
Systolic arterial pressure <90 mmHg	10	9.7
Confusion	5	4.9
Hemoptysis	5	4.9
	Mean	SD
Duration of symptoms (days)	5.04	6.9
pH	7.4	0.1
$PaCO_2$	29.6	3.5
PaO_2	75.0	13.9
Systolic blood pressure at admission	115.4	19.6
Diastolic blood pressure at admission	72.5	9.9
Heart rate at admission	95.6	21.0
Respiration rate at admission	29.5	5.3
O_2 saturation at admission	86.4	3.8

$PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen

The mean PESI and sPESI scores were 3.7 ± 1.2 and 1.6 ± 1.0, respectively, and the mean duration of hospital stay was 6.4 ± 2.1 days. Twenty patients were classified as high-risk PE patients (19.4%). Thrombolytic treatment was administered to 23 patients (22.3%). Only 7 patients (6.8%) had minor hemorrhage, and 3 patients died (2.9%) during hospitalization (Table 4).

TABLE 3. Electrocardiography and imaging findings in patients with pulmonary embolism

	n	%
Lower extremity venous Doppler ultrasonography	56	54.4
Right deep vein thrombosis	36	35.0
Acute	11	10.7
Subacute	21	20.4
Chronic	4	3.9
Left deep vein thrombosis	28	27.2
Acute	10	9.7
Subacute	16	15.5
Chronic	2	1.9
	n	%
Electrocardiographic assessment		
Rhythm		
Atrial fibrillation	7	6.8
Pacemaker	2	1.9
Sinus	94	91.3
Non-specific ST changes	69	67.0
S1Q3T3	60	58.3
Right precordial T wave inversion	54	52.4
Sinus tachycardia	42	40.8
Incomplete right bundle branch block	6	5.8
Complete right bundle branch block	5	4.9
Pseudoinfarct pattern	2	1.9
	Mean	SD
Echocardiographic assessment		
Left ventricular end-diastolic dimension	45.8	3.7
Left ventricular end-systolic dimension	28.4	4.1
Right ventricular dimension	31.5	6.7
Right atrial dimension	44.3	7.0
	n	%
Paradoxical interventricular septal motion	80	77.7
Right ventricular dilatation	80	77.7
Right ventricular hypokinesia	79	76.7
Right atrial thrombus	13	12.6
Tricuspid regurgitation		
None	13	12.6
Grade I	24	23.3
Grade II	66	64.1
	n	%
Pulmonary computed tomography (CT) angiography		
Pulmonary trunk	1	1.0
Right	40	38.8
Right main pulmonary artery	34	33.0
Right upper lobe artery	18	17.5
Right lower lobe artery	21	20.4
Right pulmonary artery segments	2	1.9
Left	33	32
Left main pulmonary artery	25	24.3
Left upper lobe artery	17	16.5
Left lower lobe artery	23	22.3
Left pulmonary artery segments	2	1.9
Bilateral involvement	30	29.1

Patients were followed-up for a median of 39 months. The median survival of 39 months was not reached during the follow-up period, and the mean survival was 115.1 ± 9.4 months in the subsequent follow-ups. The 5-year overall survival probability was 73.8%. The systolic pulmonary arterial pressure was measured during one year and showed a significant decrease from 51.7 ± 15.7 mmHg at admission to 26.6 ± 4.0 mmHg at 1st year assessment ($p < 0.001$) (Table 5).

A logistic regression model was built to evaluate potential risk factors associated with the presence of the disease (dependent variable), including age, sex, NLR, PLR, and LMR (independent variables). The final model revealed that age (OR: 1.06, $p < 0.001$) and NLR (OR: 1.52, $p < 0.0019$) were significantly associated with the presence of PE (Table 6).

The prognostic value of the above risk factors was evaluated in a Cox-regression model. The analyses were conducted separately for each PE risk group. The independent prognostic

factors in moderate-low and low-risk PE patients were NLR (HR: 1.17, $p = 0.033$) and LMR (HR: 1.58, $p = 0.046$). In moderate-high and high risk PE patients, the independent prognostic factors were age (HR: 1.07, $p = 0.014$) and PLR (HR: 1.01, $p = 0.046$) (Table 7).

DISCUSSION

Acute PE is associated with significant morbidity and mortality, and the mortality rate varies from 8% to 30% [2]. Timely assessment and treatment are critical for successful outcomes in PE patients. However, depending on the location and load of thrombus, some patients may be asymptomatic at presentation [9]. Moreover, the current methods for the diagnosis of PE are time consuming and can lead to a delay in the diagnosis and initiation of appropriate therapy. Therefore, new biological markers that can be easily and quickly assessed in PE

TABLE 4. Risk classification and treatment characteristics in patients with pulmonary embolism

	Mean	SD
PESI	3.7	1.2
sPESI	1.6	1.0
Shock index	0.85	0.29
Duration of hospitalization (days)	6.4	2.1
	n	%
Pulmonary embolism risk group		
High	20	19.4
Moderate-High	45	43.7
Moderate-Low	28	27.2
Low	10	9.7
Thrombolytic treatment	23	22.3
≤24 hours	11	47.8
24–72 hours	7	30.4
>72 hours	5	21.7
Complications	n	%
Minor hemorrhage	7	6.8
In-hospital mortality	3	2.9

PESI: Pulmonary embolism severity index; sPESI: simplified PESI

TABLE 5. Survival and follow-up of patients with pulmonary embolism

	Mean	SE
Survival time (months)	115.1	9.4
Survival probabilities	%	SE
1-month	96.1	0.02
6-month	93.1	0.03
1-year	91.1	0.03
2-year	86.1	0.04
3-year	83.4	0.04
4-year	81.7	0.04
5-year	73.8	0.06
Systolic pulmonary arterial pressure	Mean	SD
Admission	51.7	15.7
1st month	31.4	6.4
6th month	28.0	4.1
12th month	26.6	4.0

TABLE 6. Logistic regression models for factors associated with pulmonary embolism

	OR	95% CI for OR		*p*
		Lower	Upper	
Initial model				
Age	1.06	1.03	1.09	<0.001
Sex (ref: female)	0.73	0.37	1.44	0.370
Neutrophil-lymphocyte ratio	1.45	1.10	1.91	0.009
Platelet-lymphocyte ratio	1.00	0.99	1.00	0.453
Lymphocyte-monocyte ratio	0.85	0.69	1.05	0.130
Constant	0.01			<0.001
Final model				
Age	1.06	1.03	1.10	<0.001
Neutrophil-lymphocyte ratio	1.52	1.24	1.87	<0.001
Constant	0.01			<0.001

TABLE 7. Independent prognostic factors in pulmonary embolism

	HR	95% CI for HR		*p*
		Lower	Upper	
Moderate-low and low risk patients				
Initial model				
Age	1.06	0.99	1.14	0.119
Sex (ref: Female)	34.21	0.50	2352.09	0.102
Neutrophil-lymphocyte ratio	1.21	0.98	1.48	0.076
Platelet-lymphocyte ratio	1.00	0.98	1.01	0.545
Lymphocyte-monocyte ratio	1.56	0.94	2.59	0.086
Final model				
Neutrophil-lymphocyte ratio	1.17	1.01	1.35	0.033
Lymphocyte-monocyte ratio	1.58	1.01	2.47	0.046
Moderate-high and high risk patients				
Initial model				
Age	1.07	1.01	1.13	0.016
Sex (ref: Female)	1.09	0.35	3.43	0.88
Neutrophil-lymphocyte ratio	0.99	0.87	1.13	0.859
Platelet-lymphocyte ratio	1.01	1.00	1.01	0.115
Lymphocyte-monocyte ratio	0.95	0.71	1.29	0.751
Final model				
Age	1.07	1.01	1.13	0.014
Platelet-lymphocyte ratio	1.01	1.00	1.01	0.046

patients are being investigated. In this study, we evaluated the prognostic value of NLR, PLR, and LMR in patients with PE, which are easy-to-assess parameters that have been shown to have a prognostic role in PE. Our logistic regression analysis showed that NLR was significantly associated with the presence of PE. Moreover, increased levels of NLR and LMR were associated with an increased mortality risk in patients with moderate-low and low-risk PE, while increased levels of PLR were associated with an increased mortality risk in patients with moderate-high and high-risk PE.

Inflammation has been proposed as the main mechanism underlying the association between PE and changes in hematologic parameters. Inflammation plays a key role in the progression of thrombosis and pathophysiology of PE [10] and the prognostic values of different hematologic parameters have been associated with inflammatory status in PE patients. Since the role of inflammation in PE is well-known, neutrophils, lymphocytes, and platelets were suggested as useful prognostic indicators in those patients [11,12]. Considering that different white blood cell types, including neutrophils, eosinophils, and monocytes, are associated with inflammation, NLR and PLR are particularly convenient as each combines two independent markers of inflammation. In addition, it was reported that patients with a high platelet count and low lymphocyte count have a higher cardiovascular mortality rate [13,14].

Karataş et al. [7] investigated the prognostic value of CBC parameters at admission in 203 patients with PE and showed that NLR and PLR were independent prognostic factors of both short- and long-term mortality, with NLR having a better prognostic value than PLR [7]. Ma et al. [15] and Kayrak et al. [16] showed that NLR can be used as a predictor of 30-day mortality in patients with acute PE. In another, recent study, NLR as well as mean platelet volume (MPV) were suggested to be useful in the early detection of acute venous thromboembolism [17]. Telo et al. [18] further showed that PLR and NLR were increased in high-risk PE patients. They indicated that PLR may have a prognostic value to predict 3-month mortality, whereas NLR may have prognostic value for in-hospital, 3th month, and total 3-month mortality [18]. According to Ertem et al. [19], LMR may also be used to predict short-term mortality in acute PE cases. Several other studies reported similar findings about the prognostic role of NLR and PLR in PE [8,20,21], suggesting that they could be routinely used in the prognostic assessment of PE.

Our results are consistent with the previous findings and, in addition, suggest that the risk stratification of PE patients may be critical for the selection of appropriate prognostic biomarkers. We found that NLR and LMR had a better prognostic value in lower risk PE patients, while PLR was associated with prognosis in higher risk patients. Nevertheless, our findings should be confirmed in larger studies that include more demographic, clinical, and laboratory parameters.

The major limitation of this study is the retrospective design, which significantly affected the number of parameters that could be assessed. Although the completeness of our dataset was satisfactory, a higher number of available parameters may affect the final estimation models. Another limitation of the study is the small number of included patients. A larger sample size should increase the power of statistical analyses, particularly of regression analysis. For example, although the confidence intervals in the regression analyses suggested a statistically significant estimates, a larger study population may affect the HRs even more significantly.

CONCLUSION

We found that NLR, PLR, and LMR were associated with the prognosis of patients with PE. Clinical severity of the disease should be considered when utilizing these parameters to predict patient outcomes.

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