Neutrophil-to-lymphocyte ratio for the assessment of hospital mortality in patients with acute pulmonary embolism

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Abstract

Introduction: Neutrophil-to-lymphocyte ratio (NLR), which is an essential marker of inflammation, has been shown to be associated with adverse outcomes in various cardiovascular diseases in the literature. In this study we sought to evaluate the association between NLR and prognosis of acute pulmonary embolism (APE).

Material and methods: We retrospectively evaluated blood counts and clinical data of 142 patients with the diagnosis of pulmonary embolism (PE) from Ondokuz Mayis University Hospital between January 2006 and December 2012. The patients were divided into two groups according to NLR: NLR < 4.4 (low NLR group, $n = 71$) and NLR ≥ 4.4 (high NLR group, $n = 71$).

Results: Massive embolism (66.2% vs. 36.6%, $p < 0.001$) and in-hospital mortality (21.1%, 1.4%, $p < 0.001$) were higher in the high NLR group. In multivariate regression analysis NLR ≥ 5.7, systolic blood pressure (BP) < 90 mm Hg, serum glucose > 126 mg/dl, heart rate > 110 beats/min, and PCO_2 < 35 or > 50 mm Hg were predictors of in-hospital mortality. The optimal NLR cutoff value was 5.7 for mortality in receiver operating characteristic (ROC) analysis. Having an NLR value above 5.7 was found to be associated with a 10.8 times higher mortality rate than an NLR value below 5.7.

Conclusions: In patients presenting with APE, NLR value is an independent predictor of in-hospital mortality and may be used for clinical risk classification.

Key words: neutrophil lymphocyte ratio, pulmonary embolism, mortality.

Introduction

Acute pulmonary embolism (APE) is the most common cause of cardiovascular death after ischemic heart disease and stroke in Western countries [1]. The clinical presentation ranges from asymptomatic cases to cardiogenic shock and sudden death with a wide spectrum. For this reason risk classification is very important in the selection of treatment. Various clinical and biochemical markers have been tested for prediction of APE prognosis [2–4]. However, the results could not terminate the search for alternative markers.

AMS

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Leukocytosis is the most classical inflammatory marker. It is used almost in every kind of disease because the analysis is widely available, it can be repeated easily and the cost is low. In many diseases elevated leukocyte count is found to be associated with the severity and prognosis of the disease [5–7]. Recent studies showed that increased neutrophil-to-lymphocyte ratio (NLR) was a better marker for vascular inflammation compared to leukocytosis alone. There have been reports which demonstrated that NLR is a useful marker in acute coronary syndromes [8, 9], malignancies [10], contrast nephropathy [11], heart failure [12] and pulmonary hypertension [13]. Nevertheless, the importance of NLR in PE is not clear.

The aim of this study was to evaluate the use of NLR in determining the severity and prognosis of APE.

Material and methods

Study population

This study was designed as a retrospective, case-control study. The diagnosis code of the patients who were admitted to the emergency department of Ondokuz Mayıs University between January 2006 and December 2012 were screened from the electronic database of the hospital. The inclusion criterion for the study was the determination of PE diagnosis code (ICD-9). The files of the patients with the ICD-9 code were taken from the archive and analyzed by the researchers. Suspected diagnosis, hematological disease, infectious and inflammatory disease, recent myocardial infarction (< 30 day), severe renal disease (GFR < 30), severe liver disease and immune suppressant treatment were accepted as exclusion criteria.
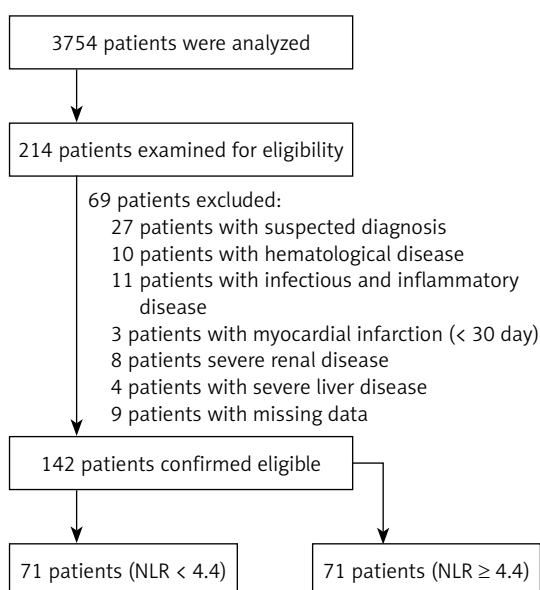

Figure 1. Study flow diagram

According to the NLR values the patients were divided into two groups: NLR < 4.4 for the low NLR group and NLR ≥ 4.4 for the high NLR group.

Definitions of clinical data

Massive pulmonary embolism

Acute PE with sustained hypotension (systolic blood pressure < 90 mm Hg for at least 15 min or requiring inotropic support, not due to a cause other than PE, such as arrhythmia, hypovolemia, sepsis, or left ventricular dysfunction), pulselessness or persistent profound bradycardia (heart rate < 40 bpm with signs or symptoms of shock) [14].

Submassive pulmonary embolism

Acute PE without systemic hypotension (systolic blood pressure > 90 mm Hg) but with either right ventricular (RV) dysfunction or myocardial necrosis [14].

Laboratory parameters

The laboratory results were evaluated according to the first venous blood samples taken on admission to the emergency department. Total blood cell counts and its subtypes were analyzed using an automated blood cell counter. The NLR was calculated as the ratio of neutrophil count to lymphocyte count, both obtained from the same blood samples.

Statistical analysis

All data were entered into the SPSS 15 program. Subsequently, the normal distribution of the data was tested using the Kolmogorov-Smirnov test. Transformation was applied to non-parametrically distributed data. Comparison of data between the two groups was performed by Student's t test for continuous variables and the χ^2 test for proportional data. Any correlation between data was tested with the Spearman and Pearson correlation analysis. Logistic regression analysis was used to test the indicative significance of data on mortality. The forward selection technique was preferred in the elimination of variables. While the continuous data were expressed with 'mean ± SD (standard deviation)', the categorical data were expressed with percentage values, and a p value of < 0.05 was accepted as statistically significant.

Results

The ICD codes of 3754 patients were screened from the electronic database and the ICD-9 code was determined in 214 patients. After their files were analyzed, 27 patients with a suspected diagnosis, 10 patients with hematological disease,

11 patients with infectious and inflammatory disease, 3 patients with recent myocardial infarction (< 30 day), 8 patients with severe renal disease, 4 patients with severe liver disease and 9 patients with missing data were excluded from the study (Figure 1). As a result 142 patients were included in the study. The diagnosis of PE was made by pulmonary computed tomography in 138 (97%) patients and by ventilation perfusion scintigraphy in 4 (3%) patients. Forty-one (28.9%) patients had thrombolytic therapy (25 streptokinase and 16 tissue plasminogen activator).

Demographic characteristics

Demographic and clinical characteristics of the patients are depicted in Table I. In the high NLR group the age ($p = 0.013$) and the heart rate ($p = 0.033$) were higher but systolic blood pressure ($p = 0.005$) was lower than the low NLR group. In terms of co-morbidities, cancer ($p = 0.016$) and heart failure ($p = 0.034$) were higher in the high NLR group than the low NLR group.

Laboratory parameters

In the high NLR group troponin I ($p < 0.001$), serum glucose ($p = 0.001$), leukocytes ($p = 0.040$), values of RV/ left ventricular (LV) ratio ($p = 0.018$) and hs-C-reactive protein reaction (CRP) ($p < 0.001$) were significantly higher compared to the low NLR group (Table I). Additionally, a significant positive correlation was found between the CRP and NLR levels ($r = 0.388$, $p < 0.001$).

Table I. Baseline characteristics

Parameter	Total (*n* =142)	NLR < 4.4 (*n* = 71)	NLR ≥ 4.4 (*n* = 71)	*P*-value
Demographic and clinical characteristics:				
Age [years]	58.9 ±14.5	56.0 ±14.7	61.9 ±13.7	**0.013**
Men (%)	85 (59.8)	42 (59.2)	43 (60.6)	0.864
BMI [kg/m²]	32.5 ±6.4	33.3 ±6.6	31.7 ±6.1	0.122
Systolic BP < 90 mm Hg	22 (15.5)	7 (9.9)	15 (21.1)	**0.005**
Heart rate > 110 beats/min	21 (14.8)	6 (8.5)	15 (21.1)	**0.033**
Co-morbidities:				
Hypertension (%)	46 (32.4)	20 (28.2)	26 (36.6)	0.282
Diabetes mellitus (%)	31 (21.8)	13 (18.3)	18 (25.3)	0.264
Smoke (%)	51 (35.9)	24 (33.8)	27 (38)	0.600
Cancer	20 (14.1)	5 (7)	15 (21.1)	**0.016**
Heart failure	16 (11.3)	4 (5.6)	12 (16.9)	**0.034**
Chronic lung disease	19 (13.4)	6 (8.5)	13 (18.3)	0.084
Prior surgery	22 (15.5)	8 (11.3)	14 (19.7)	0.164
Renal failure	6 (4.2)	1 (1.4)	5 (7)	0.095
History of stroke/TIA	7 (4.9)	1 (1.4)	6 (8.5)	0.053
Laboratory parameters:				
SO$_2$ (%)	91.8 ±8.7	92.9 ±7.3	90.7 ±9.9	0.953
PCO$_2$ (%)	32.8 ±7.2	32.9 ±5.9	32.7 ±8.1	0.857
PO$_2$ (%)	76.0 ±32.7	76.1 ±29.0	75.9 ±36.3	0.632
Troponin I [ng/ml]	1.7 ±1.8	1.1 ±1.2	2.2 ±2.0	**< 0.001**
Total cholesterol [mg/dl]	190.2 ±49.1	187.6 ±42.6	194 ±58	0.595
Serum creatinine [mg/dl]	0.94 ±0.57	0.91 ±0.53	0.96 ±0.61	0.602
Serum glucose [mg/dl]	134.4 ±50.6	120.9 ±41.6	147.9 ±55.4	**0.001**
Hemoglobin [g/l]	12.7 ±1.9	12.9 ±1.9	12.3 ±1.9	0.070
Platelets [/mm³]	249.5 ±96.4	257.6 ±97.6	241.2 ±95.1	**0.315**
Leukocytes (10³/μl)	11.3 ±5.1	9.5 ±4.3	13.1 ±5.2	**0.040**
RV/LV ratio (*n* = 46)	1.44 ±0.67	1.27 ±0.70	1.61 ±0.66	**0.018**

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Clinical events

The massive embolism rate was significantly higher in the high NLR group (66.2% vs. 36.6%, $p < 0.001$). Thrombolytic therapy was higher in the high NLR group than the low NLR group (38% vs. 19.7%, $p = 0.016$). Also the in-hospital mortality rate was higher in the high NLR group (21.1% vs. 1.4%, $p < 0.001$) (Table II). The survival curve (Figure 2) illustrates the mortality rate during 50 days.

The optimal NLR cutoff value for in-hospital mortality was determined as 5.7 with ROC analysis. The NLR cutoff value of 5.7 had sensitivity of 81%, specificity of 71% and negative predictive value of 96% (Figure 3). The same cutoff value for massive embolism had sensitivity and specificity of 51% and 78%, respectively (Figure 4).

When NLR and mortality were examined in multivariate regression analysis, NLR ≥ 5.7, systolic blood pressure < 90 mm Hg, heart rate > 110 beats/min, and PCO_2 < 35 or > 50 mm Hg were found to be independent predictors of mortality. According to this, having NLR above 5.7 is found to be associated with 10.8 times higher mortality (CI: 1.47–79.31, $p = 0.019$) (Table III).

Discussion

This study evaluated the prognostic value of NLR at hospital admission in patients with acute PE. It also investigated the possibility that NLR could be effective in the distinction between massive and submassive embolism. The primary finding of this study is that high NLR value is an independent predictor of in-hospital mortality in patients with acute PE. An NLR value above 5.7 is found to be associated with a 10.8 times higher mortality rate.

Previous studies have shown that elevated NLR is associated with increased rate of intracoronary thrombus presence in cardiovascular events. Neutrophil-to-lymphocyte ratio was found to be high in patients with left atrial thrombus and atrial fibrillation. Neutrophil-to-lymphocyte ratio was also elevated in patients with acute ST segment elevation myocardial infarction with a high angiographic thrombus burden [15, 16]. It is known that leukocytes contribute to the increased local thrombogenic activity [17]. Moreover, it has been demonstrated that leukocyte count could be related to fibrinogen, factor VII and factor VIII levels [18]. Thus NLR could provide indirect knowledge about increased thrombus burden in vascular events. In our study massive embolism and mortality were found to be high in the High NLR group. Neutrophil-to-lymphocyte ratio could be related to thrombotic burden and the severity of perfusion defect as the pathogenesis of PE was thought to be directly related to thrombotic burden.

Table II. Clinical events in the high and low NLR groups

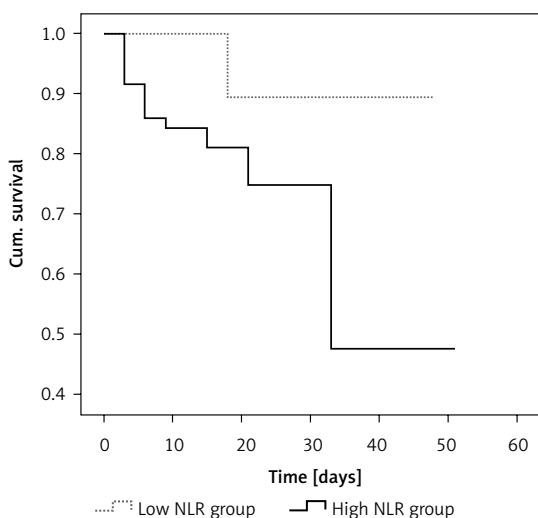| Parameter	NLR < 4.4 (n = 71)	NLR ≥ 4.4 (n = 71)	P-value
NLR	2.6 ±0.8	9.3 ±5.9	< 0.001
CRP [mg/l], n = 93	36.4 ±25.5	70.8 ±52.7	< 0.001
Massive embolism (%)	26 (36.6)	47 (66.2)	< 0.001
Thrombolytic therapy (%)	14 (19.7)	27 (38.0)	0.016
In-hospital mortality (%)	1 (1.4)	15 (21.1)	< 0.001

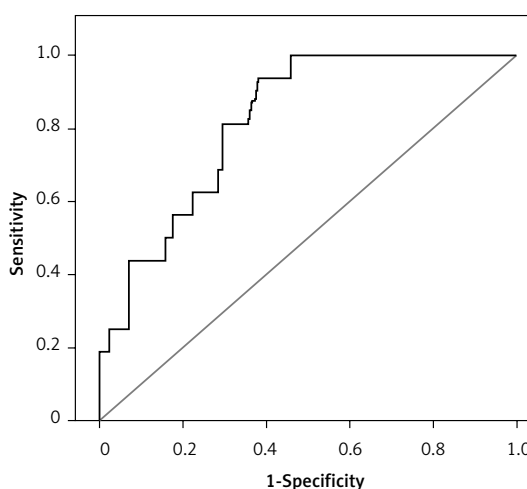**Figure 2.** Survival curve illustrating the mortality rate during 50 days

Figure 3. ROC analysis of NLR data for in-hospital mortality. Optimal NLR cutoff value for in-hospital mortality was determined as 5.7 (AUC = 0.821)

Table III. Independent predictors of death (*n* = 142)

Predictor	Univariate logistic regression			Multivariate logistic regression analysis		
	Odds ratio	95% CI	*P*-value	Odds ratio	95% CI	*P*-value
NLR ≥ 5.7	10.4	2.81–38.73	< 0.001	10.8	1.47–79.31	0.019
Systolic BP < 90 mm Hg	11.2	3.57–35.03	< 0.001	6.2	1.35–28.85	0.019
Serum glucose > 126 mg/dl	6.8	1.85–25.12	0.004	2.9	0.56–15.29	0.206
Heart rate > 110 beat/min	6.4	2.12–19.4	0.001	5.7	1.11–29.61	0.037
SO_2 < 90 mm Hg	1.7	0.47–5.96	0.424			
PCO_2 < 35 or > 50 mm Hg	4.1	1.16–14.19	0.028	6.4	1.03–39.50	0.046
Sex (male)	1.1	0.39–3.31	0.819			
Age [years]	1.1	0.99–1.07	0.204			
Creatinine > 1.5 mg/dl	2.9	0.71–12.28	0.137			
Hemoglobin [g/dl]	1.1	0.80–1.37	0.733			
Platelets	0.9	0.99–1.00	0.076			
RDW	0.9	0.92–1.07	0.874			
MPV	1.1	0.64–1.72	0.840			

RDW – red cell distribution width, MPV – mean platelet volume.

Right ventricular dilatation and dysfunction due to PE are important prognostic markers. Choi *et al.* [19, 20] found that elevated RV/LV ratio is an independent prognostic factor for PE. In another study Vitarelli *et al.* [21] demonstrated that the assessment of RV function with 3D echocardiography and speckle-tracking echocardiography is a determining factor for prognosis. In our study in the high NLR group the RV/LV ratio was significantly high. Also there was a significant correlation between NLR and RV/LV ratio. Increased levels of NLR may support the role of inflammation. As a matter of fact, in a rat model of acute PE Watts *et al.* [22] have shown the importance of significant neutrophil infiltration in the right ventricle causing RV damage. The secondary striking finding of this study is that when the optimal NLR cutoff value is determined as 5.7, it has a negative predictive value of 96%. This result shows that a low NLR value is a powerful indicator for a good prognosis.

Previous studies have shown that troponin I and T are related to prognosis in patients with PE [23, 24]. In our study troponin I was elevated in the High NLR group. Also there was positive correlation between troponin I and NLR.

The present study is the second study which have shown the association between increased NLR and prognosis in patients with PE. Recently, Kayrak *et al.* [25] demonstrated that NLR at hospital admission could be a predictor of 30-day mortality in PE. The optimal NLR cutoff for 30-day mortality was determined as 9.2. In our study the
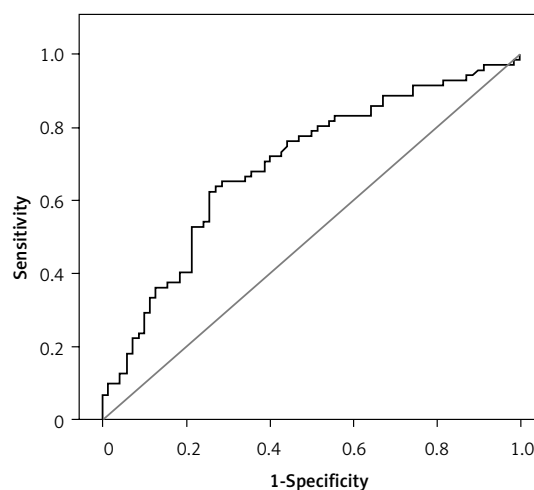

Figure 4. ROC analysis of NLR data for massive embolism (AUC = 0.697)

optimal NLR cutoff for in-hospital mortality was found to be 5.7. This difference might be due to different demographic characteristics of the patient population between the two studies. In the study by Kayrak *et al.* the patients were older (63.5 vs. 58.9), and malignancy (16.4% vs. 14.1%) and chronic lung disease (25% vs. 13.4%) rates were higher compared to the patients in our study.

The major limitation of our study is that it is a single center study with retrospective design. Also small sample size is another limitation. As all data were not available in echocardiography reports, multivariate analysis could not be performed for RV function and dimensions.

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In conclusion, NLR was found to be associated with the severity of the disease and prognosis in patients with acute pulmonary embolism. As this marker is measured in almost every patient in emergency departments, it could be useful in clinical risk classification.

Conflict of interest

The authors declare no conflict of interest.

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