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Prognostic value of neutrophil/lymphocyte ratio in patients with pulmonary embolism

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Aim: Preliminary evidence suggests that inflammation plays a role in the development and prognosis of pulmonary embolism (PE). We used the neutrophil/lymphocyte ratio (NLR) as a measure of systemic inflammation and investigated its association with PE.

Materials and methods: A total of 266 patients who were diagnosed with PE and a control group of 124 age- and sex-matched healthy subjects were included in this study. We further classified the PE patients into 2 groups: those who survived and those who died in the first 30 days. Baseline NLR was measured by dividing neutrophil count to lymphocyte count and was compared between the groups.

Results: Median NLR was significantly higher among patients with PE compared to the healthy control group (3.9 (interquartile range (IQR): 5.0) vs. 1.9 (IQR: 0.6), $P < 0.001$). Of the 266 patients with PE, 16 (6%) died within 1 month. Median NLR was significantly higher among PE patients who died compared to those who survived, as well (3.7 (IQR: 4.3) vs. 9.0 (IQR: 7.9), $P < 0.001$). The optimal cut-off values, sensitivities, and specificities of NLR for predicting PE and in-hospital mortality of PE were >2.565 and >5.465, 70.3% and 75.0%, and 92.7% and 67.6%, respectively. Multiple logistic regression analysis showed that NLR values of >5.465 could define those patients with a mortal clinical course independently (odds ratio: 13.446, 95% confidence interval: 3.141–57.566, $P < 0.001$).

Conclusion: A higher NLR, as an emerging marker of inflammation, may be beneficial in determining prognosis in PE patients.

Key words: Neutrophil/lymphocyte ratio, pulmonary embolism, inflammation

1. Introduction

Pulmonary embolism (PE) is well known as an important disease with high rates of morbidity and mortality. An approximate annual incidence of 60–70 cases per 100,000 people has been reported, and it is the most common cause of sudden deaths in hospitals (1).

Systemic inflammation can be measured using a variety of biochemical and hematological markers. Since the physiological response to stress of the leukocytes in circulation leads to an increase in the number of neutrophils and a decrease in the number of lymphocytes, the ratio of these subgroups to each other is used as a marker of inflammation. During inflammatory response, changes occur in the ratios of leukocyte subgroups in the circulation. Neutrophilia is accompanied by relative lymphopenia (2). Therefore, the blood neutrophil/lymphocyte ratio (NLR) could be an important measure of systemic inflammation as it is cost-effective, is readily available, and can be calculated easily. Recently, the NLR, an emerging marker of inflammation, has been a "hot topic" as a useful marker of cardiovascular disease as well as an independent predictor of cardiac or cancer-related mortality (3).

PE is known to be associated with a leukocyte influx that occurs early after a thromboembolic event (1 day). Thrombus development is associated with pulmonary arterial and deep venous wall inflammation, marked by an early extravasation of leukocytes and an elevation in proinflammatory mediators and selectins, indicating a robust immune response following PE (4–7). As far as we know, there is no study in the literature on the role of NLR – which is part of routine blood analysis, can be obtained easily with the whole blood count, and is quite easy to calculate – in the determination of the prognosis of PE. We investigated the prognostic value of NLR in patients with PE.

2. Materials and methods

2.1. Design

From January 2011 to June 2012, 368 consecutive patients with PE, as confirmed by spiral computerized tomography (CT), who were admitted to Dışkapı Yıldırım Beyazıt

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Training and Research Hospital (a tertiary care hospital) were included in this retrospective study. The local ethics committee approved the study protocol.

2.2. Study population

A total of 266 patients with a definitive diagnosis of PE were included in the study and their clinical and laboratory data were compared with those of a total of 124 healthy adults who were attending their annual check-up as a control group. There were 102 patients who were prediagnosed with PE but whose diagnosis was not proven by spiral CT; they were excluded. In addition, patients with clinical evidence of cancer, acute coronary syndrome, congestive heart failure, chronic obstructive lung disease, chronic inflammatory disease, or any systemic infection that occurred during the first 48 h after admission were excluded. Patients whose hospital records were incomplete, who were under the age of 18, or who were diagnosed with PE using methods other than spiral CT were also excluded. We classified the PE patients into 2 groups: those who survived 30 days after PE and those who died in the first 30 days.

2.3. Laboratory and radiologic analyses

Multislice spiral CT examinations were carried out in the radiology clinic, using PE protocol (field of view: 35 cm, section thickness: 3 mm, pitch: 2, and intravenous 120 mL contrast material), and pulmonary arteries, their branches, and lung parenchyma were evaluated in detail. Ventilation-perfusion scintigraphy was not used for diagnosis because it is impractical in an emergency department.

In this study, only the first parameters obtained within 30 min of admission were considered. Whole blood count, white blood cell (WBC) count, neutrophil, lymphocyte, NLR, D-dimer, troponin-I, and arterial blood gas (pO_2, pCO_2, pH) values were recorded. D-dimer values of >500 μg/L and troponin-I values of >0.06 ng/mL were considered positive.

2.4. Statistical analyses

Whether the distributions of continuous variables were normal or not was determined by a Kolmogorov–Smirnov test. Continuous variables were shown as mean ± standard deviation or median interquartile ranges (IQR) as applicable. The mean differences between groups were compared by Student's t test; otherwise, the Mann–Whitney U test was applied for comparisons of the median values. Nominal data were analyzed by Pearson's chi-square test. The optimal cut-off points of the NLR to determine both PE and prognosis were evaluated by a receiver operating characteristic (ROC) analysis as giving the maximum sum of sensitivity and specificity for the significant test. Whether the predictivity of NLR on both PE and prognosis was statistically significant or not was evaluated by multiple logistic regression analyses after adjustment for all possible confounding factors. Odds ratios (ORs) and 95% confidence intervals (CIs) for each independent variable were also calculated. A P-value of less than 0.05 was considered statistically significant. Data analysis was performed using SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

The mean age and the female/male ratio of the patients with PE and the control group were 64.8 ± 14.3 years (min: 18, max: 86) and 1.23 and 66.1 ± 9.6 years (min: 37, max: 82) and 1.07, respectively. Patients with PE and the control group were similar in respect to age and sex (Table 1). Compared to the control group, NLR values of patients with PE were statistically higher (R = 3.080; 95% CI: 2.227–4.260; P < 0.001) (Table 1).

Of the 266 patients with PE, 16 (6%) died within 1 month of diagnosis. According to the ROC curve analysis, the optimal cut-off value of NLR to predict PE was >2.565 with 70.3% sensitivity and 92.7% specificity (area under the curve (AUC) = 0.817, 95% CI: 0.776–0.859; Table 2).

Table 1. Demographical and clinical characteristics regarding case and control groups. OR: odds ratio, CI: confidence interval.

Variables	Controls	Cases	P-value	OR (95% CI)
Age, years	66.1 ± 9.6	64.8 ± 14.3	0.299	0.992 (0.976–1.009)
Sex				
Male, n (%)	60 (48.4%)	119 (44.7%)	-	1.000
Female, n (%)	64 (51.6%)	147 (55.3%)	0.501	1.158 (0.755–1.775)
Neutrophils (%)	59.9	61.5	0.253	0.536 (0.480–0.591)
Lymphocytes (%)	31.3	15.6	<0.001	0.132 (0.097–0.162)
NLR	1.9	3.9	<0.001	3.080 (2.227–4.260)

Table 2. The results of ROC analysis for NLR determination of disease and mortality. AUC: area under the curve, CI: confidence interval, TP: true positive, FN: false negative, TN: true negative, FP: false positive, PPV: positive predictive value, NPV: negative predictive value, OR: odds ratio.

Statistics	Definitions	Disease	Mortality
AUC		0.817	0.752
95% CI		0.776–0.859	0.652–0.852
Best cut-off point		>2.565	>5.465
No. of cases	N	390	266
Sensitivity	TP / (TP + FN)	187/266 (70.3%)	12/16 (75.0%)
Specificity	TN / (TN + FP)	115/124 (92.7%)	169/250 (67.6%)
PPV	TP / (TP + FP)	187/196 (95.4%)	12/93 (12.9%)
NPV	TN / (TN + FN)	115/194 (59.3%)	169/173 (97.7%)
OR (95% CI)		30.246 (14.611–62.613)	6.259 (1.958–20.010)
P-value		<0.001	<0.001

The ROC curve analysis was performed to detect the best cut-off value of NLR in the prediction of early all-cause mortality. Serum NLR of >5.465 demonstrated a sensitivity of 75.0% and a specificity of 67.6% for the prediction of early all-cause mortality (AUC = 0.752; 95% CI: 0.652–0.852; Table 2). Additionally, the positive predictive value (PPV) and the negative predictive value (NPV) of this ratio to predict early all-cause mortality were 12.9% and 97.7%, respectively (OR = 6.259, 95% CI: 1.958–20.010, P < 0.001; Table 2).

According to the multiple logistic regression analysis, NLR of >2.565 was able to define patients with PE compared to the control group independently (OR = 35.077; 95% CI: 16.595–74.143; P < 0.001). Further multiple logistic regression analysis showed that NLR of >5.465 could define cases of death among patients with PE independently (OR = 13.446, 95% CI: 3.141–57.566, P < 0.001; Table 3).

Demographic and laboratory characteristics of patients with PE were compared between those who survived and those who died due to PE. Although D-dimer and troponin levels were higher in the patients that died, the differences were not statistically significant (Table 4). Mean WBC levels were significantly higher in the group of patients who survived (P = 0.002). On the other hand, NLR values were higher in the deceased group compared to the surviving patients (OR = 1.104, 95% CI: 1.024–1.191, P < 0.001; Table 4).

Table 3. The effect of NLR on both disease and mortality after adjustment for all confounding factors.

Variables	Odds ratio	95% Confidence interval	P-value
Case vs. controls			
Age	0.977	0.955–1.000	0.051
Female factor	1.594	0.922–2.756	0.095
NLR > 2.565	35.077	16.595–74.143	<0.001
Surviving vs. mortal			
Female factor	3.677	0.968–13.975	0.056
WBC	0.690	0.549–0.868	0.002
NLR > 5.465	13.446	3.141–57.566	<0.001

Table 4. Demographical and clinical characteristics regarding surviving and deceased groups.

Variables	Alive	Deceased	P-value	OR (95% CI)
Age, years	64.7 ± 14.5	66.9 ± 9.0	0.548	1.012 (0.974–1.051)
Sex				
Male, n (%)	115 (46.0)	4 (25.0)	-	1.000
Female, n (%)	135 (54.0)	12 (75.0)	0.101	2.556 (0.802–8.141)
pH	7.43 (0.07)	7.42 (0.07)	0.289	0.002 (0.000–19.331)
pO_2 (IQR)	56.5 (27.3)	50.9 (35.1)	0.981	1.008 (0.981–1.037)
pCO_2 (IQR)	39.2 (13.8)	39.8 (16.0)	0.756	0.991 (0.955–1.028)
D-dimer, mg/L (IQR)	1.6 (1.7)	2.9 (2.3)	0.170	1.212 (0.882–1.666)
Troponin, ng/mL (IQR)	0.02 (0.08)	0.07 (0.21)	0.167	1.361 (0.805–2.301)
WBC, %	11.8 ± 2.8	9.4 ± 2.5	0.002	0.755 (0.625–0.912)
Neutrophil, %	61.1	74.6	0.001	0.755 (0.619–0.892)
Lymphocyte, %	16.5	9.2	0.003	0.275 (0.175–0.375)
NLR	3.7	9.0	<0.001	1.104 (1.024–1.191)

4. Discussion

We evaluated the relationship between NLR and the presence and prognosis of PE detected in 266 subjects undergoing multislice CT pulmonary angiography for suspected PE. The findings of the present study indicated for the first time that NLR is an independent predictor of acute mortality in patients with PE. Our results encourage the use of NLR as a powerful and inexpensive parameter for the risk stratification of patients with PE.

The number of leukocytes and the ratio of their subtypes are regarded as markers of inflammation in cardiovascular diseases (8). NLR is an indicator of subclinical inflammation. The meaning of elevated NLR remains unclear; however, it causes a higher neutrophil count compared to lymphocyte count in response to stress such as infection and inflammation. This ratio, which can be calculated easily, may be used as an independent prognostic factor in PE. Previous studies have shown its prognostic significance in heart failure and stable or acute coronary artery disease (9–11). It has been demonstrated that mortality increased with the increase in NLR in patients with acute coronary syndrome and those who underwent cardiovascular intervention (9,12). In some studies, neutrophilia was found to be associated with decompensated heart failure related to acute myocardial infarction while relative lymphopenia was reported to be an independent marker of mortality in heart failure. Given these data, NLR is being used as a sign of prognosis following coronary bypass grafting and during the course of chronic heart failure (10,13).

NLR can be useful not only as a prognostic tool but also as a diagnostic tool. The presence of T lymphocytes in a tumor is an indicator of increased immune response to a lesion. Recent data demonstrate that a low number of lymphocytes in a colorectal tumor is associated with poor prognosis. The prognostic value of NLR was investigated in patients diagnosed with colorectal, ovary, and lung cancer and those who underwent liver transplantation, and a strong correlation was found with overall survival (14–19).

In the present study, a correlation was found between NLR and mortality due to PE. We know that PE is associated with a leukocyte influx that occurs early after PE. Thrombus development is associated with deep venous and pulmonary arterial wall inflammation marked by an early extravasation of leukocytes and an elevation in proinflammatory mediators and selectins, indicating that a robust immune response occurred with right ventricle damage following PE. In particular, neutrophils are the first leukocytes to be found in the damaged pulmonary area. Procoagulants are secreted locally by leukocytes that contribute to oxidative and proteolytic injury (4–6). There is also an accumulation of the monocyte/macrophages that occurs within both the pulmonary artery wall and the parenchyma after PE, and these cells likely play an important role in embolism resolution. In contrast to neutrophils, monocytes migrate from capillaries to the extravascular space and are transformed into macrophages and outnumber neutrophils 2–3 days after the acute episode. Macrophage-secreted cytokines stimulate fibroblast proliferation and collagen production

and also promote monocytosis (20). It is well known that right ventricular damage contributes to poor clinical outcome after PE, and one study reported that neutrophils contribute to right ventricular dysfunction in PE (21).

It is well known that advanced age and D-dimer levels, although nonspecific, have prognostic value and have high sensitivity in PE. The majority of PE patients were reported to be between the ages of 60 and 70 years in clinical studies and between the ages of 70 and 80 years in autopsy series (22,23). The ratio of males to females was reported to be approximately 1.24. The mortality rate in males was found to be higher. Mortality difference between males and females is more prominent after the age of 40 years (22). In the present study, the number of females was higher than the number of males. However, in terms of age distribution and mortality rates, our results were comparable with the literature. In a study by Galle et al., the plasma D-dimer level was reported to be directly proportional to the severity of PE (24). In most PE patients, D-dimer levels are high, but D-dimer levels may also rise in the presence of advanced age, inflammatory conditions, trauma, pregnancy, infection, and malignity and in the postoperative period. One or more of these conditions, causing an increase in D-dimer levels, may coexist in patients diagnosed with PE. Therefore, it is proposed that D-dimer should be used to exclude the diagnosis of PE, not as a marker of prognosis (25). In the present study, a significant relationship was found between D-dimer and the diagnosis of PE, but no significant relation was revealed between D-dimer levels and mortality. However, a higher NLR was associated with increased mortality in patients with PE.

Our present study has some major limitations. First, this is an observational, single-institution, retrospective study, which had a relatively small sample size and was thus subject to various unaccounted confounders inherent in such an analysis. Additionally, we could not compare NLR with other inflammatory markers, such as C-reactive protein, fibrinogen, or myeloperoxidase, because they were not routinely obtained in our study population. Long-term outcomes of the patients discharged from hospital are unknown. No autopsy was performed for defining purely PE-related deaths.

In conclusion, increased NLR as a simple nonspecific marker of inflammation is associated with increased mortality in patients with PE. With its universal availability, it may serve as an inexpensive new tool for risk stratification in PE. Regardless of whether the association between NLR and mortality reflects a fundamental pathophysiological process or is a marker of the severity of the embolic episode, the results of this study have important clinical implications. Further large-scale randomized prospective studies are required to clearly understand the exact role of NLR in the pathophysiology of PE.

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