Original Article

Importance of the Neutrophil-to-Lymphocyte Ratio and the Platelet-to-Lymphocyte Ratio in Patients With Venous Thromboembolism

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ABSTRACT

Background: Acute pulmonary thromboembolism (PTE) is the most common manifestation of venous thromboembolism (VTE). Due to the physiological response of circulating leukocytes to stress, circulation neutrophils increase and lymphocytes decrease. Therefore, the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR) can be important measures to assess the severity of systemic inflammation. We sought to study NLR and PLR and their relationships with the severity of VTE and mortality.

Methods: The study enrolled 331 patients with VTE from 2014 through 2018. Based on the complete blood count obtained from the peripheral blood samples of the patients on admission, NLR and PLR were calculated. The incidence of VTE with or without PTE, as well as its severity, was determined based on computed tomography angiography findings and the patients' clinical status.

Results: A positive relationship was observed between PTE and NLR (P=0.01). There was a significant relationship between the NLR and PLR values and PTE based on computed tomography angiography findings (NLR: P=0.001, PLR: P=0.012), but no relationship was detected between the ratios and the patients' PTE severity based on clinical status. A significant relationship was also observed between NLR and the main pulmonary artery and segmental involvement (P=0.009), while no such association was seen with PLR. Additionally, the results revealed a significant relationship between NLR and mortality (P=0.030).

Conclusions: Our results demonstrated a significant relationship between the NLR and PLR values and PTE severity based on computed tomography angiography results and also mortality in patients with PTE. ***(Iranian Heart Journal 2022; 23(1): 65-73)***

KEYWORDS: Neutrophil, Lymphocyte, Platelet, Venous thromboembolism

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Acute pulmonary thromboembolism (PTE) is a cardiovascular condition of great significance, with a mortality rate of up to 15%. [1] The incidence of PTE is about 60 to 70 per 10 000 people each year, and it is the most common cause of sudden deaths in admitted patients. PTE as a result of deep vein thrombosis (DVT) is the most common manifestation of venous thromboembolism (VTE). Although surgery, trauma, hospitalization, malignancies, immobility, pregnancy, estrogen use, and hereditary thrombophilia are related to the incidence of VTE, about 30% to 50% of VTE cases occur with no known risk factors. [2]

Inflammation plays a major role in the incidence and progression of cardiovascular disease and atherosclerosis, and the main cause of myocardial infarction and stroke is an inflammatory disease. The atherosclerotic process starts when low-density lipoproteins accumulate in the intima and activate the endothelium, releasing the inflammatory cascade. [3] During PTE, white blood cell (WBC) invasion of the thromboembolism location occurs 24 hours after the incidence of VTE. Then, rapid thrombus development, along with pulmonary artery wall inflammation and deep vein wall inflammation, occurs and continues to expand with the extravasation of leukocytes, and the increase of pro-inflammatory mediators and cytokines, all reflecting the strong immune response seen during a PTE event. [1, 2]

The prevalence of leukocytosis during acute PE, despite numerous studies of PTE over many years, is unclear. [4] However, the levels of WBCs and their subgroups have been studied as inflammatory markers that predict unwanted cardiovascular outcomes. Further, the increase in WBCs can have prognostic value during any cardiovascular event. [5] In the rat model of PTE, severe right ventricular dysfunction plays a role in premature mortality; and significant neutrophil infiltration into the right ventricle seen microscopically was suggested as a cause of severe right ventricular dysfunction. [1] In recent years, the value of the peripheral blood neutrophil-to-lymphocyte ratio (NLR) has been suggested as a better predictor of inflammation than WBCs, and the balance between neutrophils and lymphocytes has been taken into account as a marker of systemic inflammation. NLR is easily calculated from the WBC count, which is routinely taken on hospital admission and is universally available. [1, 3] Neutrophilia and relative lymphopenia have also been considered independent predictors of mortality in patients with acute heart failure. In addition, recent studies have demonstrated the role of NLR as an independent predictor of premature mortality in various other cardiovascular and non-cardiovascular conditions. For instance, NLR has been suggested as a predictor of long-term mortality in patients undergoing primary coronary intervention. Moreover, numerous studies have shown the relationship between NLR and disease severity and prognosis, and there is a relationship between a rise in NLR and hospital mortality and coronary plaque rupture during acute coronary states. [6, 7] Despite all the published data on the value of NLR in different clinical situations, the prognostic significance of NLR in acute PTE is still unclear.

In addition to various coagulation factors, platelets and prokaryotes disc-like cells play a role in the onset of thrombosis and have a significant part in the onset of inflammation. The adhesion of platelets to the endothelial surface can stimulate the migration and adhesion of leukocytes, especially in the presence of shear stress. Therefore, platelet activation also plays a key role in the development of atherosclerosis. [8] The increase of platelet activity in PTE, unlike leukocytosis, has been demonstrated in previous studies, reflecting the underlying inflammation. Nonetheless, the mechanism of this activation has not been clearly revealed. [2]

Inflammatory processes play a vital role in the process of VTE. NLR and the platelet-to-lymphocyte ratio (PLR) on the strength of their cost-effectiveness, availability, and easy measurability can be easy, albeit significant, scales for assessing the degree of systemic inflammation. Still, their use in clinical situations has yet to be elucidated. For all the studies on these markers and coronary heart disease, only a few studies have been performed on NLR and PLR and their relationships with the severity of VTE and mortality during hospitalization. The present study, regarding the lack of studies in this area, aimed to evaluate NLR and the newer marker, PLR, and their relationships with VTE severity and mortality during hospitalization among patients admitted to Rajaie Cardiovascular Medical and Research Center.

METHODS

This investigation is a retrospective, descriptive-analytic study. Patients admitted to Rajaie Cardiovascular Medical and Research Center with a diagnosis of DVT or PTE as confirmed by imaging (color Doppler ultrasonography and computed tomography [CT] pulmonary angiography) between 2014 and 2018 were enrolled. Data were extracted from the patients' medical records. NLR and PLR were calculated based on complete blood cell and WBC counts from the patients' initial laboratory records. The severity of PTE was determined based on a collection of echocardiographic data (degree of right ventricular dysfunction), cardiac troponin (CTnI) levels, and CT pulmonary angiography findings (saddle, segmental and subsegmental embolism). Additionally, the patients' clinical status, including decreased blood pressure and syncope, was recorded. All the aforementioned information was obtained from the patients' medical records.

Thereafter, the relationships between NLR and PLR and VTE severity were assessed statistically. Moreover, the relationships between these markers and the levels of high-sensitivity C-reactive protein (hs-CRP), the erythrocyte sedimentation rate (ESR), and CTnI were studied. Finally, in-hospital mortality data were extracted from the patients' records and compared vis-à-vis the mentioned markers.

This study was approved by the Ethics Committee of Iran University of Medical Sciences.

Statistical Analysis

The data were analyzed with SPSS software, version 19. The mean of all nominal data was obtained, and categorical variables were shown as numbers and percentages. The normality of quantitative variables was controlled. The distinction in continuous variables between groups was determined using a *t* test for Gaussian and the Mann–Whitney test for non-Gaussian data. In addition, the χ^2 test was utilized to compare binomial variables in percentage terms. The correlations between Gaussian and non-Gaussian variables were also assessed by using the Pearson test and the 2-tailed Spearman test.

RESULTS

This retrospective, descriptive-analytic study enrolled 331 patients with PTE or DVT or both, whose diagnosis was confirmed by imaging findings. The mean age of the patients was 54.33±17.98 years, and the average length of hospitalization was 10.09±7.02 days. The study population was composed of 55% male and 45% female patients.

The most common symptom was dyspnea, which was seen in 77% of the patients.

Lower extremity edema (56.5%) and chest pain (29.3%) were other common symptoms.

The most common associated risk factors in the patients were immobility (32%), high blood pressure (23.9%), history of previous VTE (22.4%), and smoking (22.4%) (Fig. 1).

The ultrasound findings of the patients' limbs included DVT in 267 patients (80.7%): 266 cases (99.7%) in the lower limbs and 1 case (0.3%) in the upper limb. Additionally, 251 patients (94%) had proximal DVT, and distal DVT was seen in 16 patients (6%). Based on CT angiography results, 50 subjects (15.2%) had main pulmonary artery involvement, 169 (51.2%) had segmental pulmonary artery involvement, and 32 (9.7%) had subsegmental pulmonary artery involvement.

On transthoracic echocardiography, 36 patients (10.9%) had severe right ventricular enlargement and 20 (6%) severe right ventricular dysfunction. Highly positive CTnI was reported in 41 patients (12.4%), and clinically massive PTE was detected in 3 patients (0.9%). Thirty-four patients (10.3%) were treated with intravenous fibrinolytics, 49 (14.8%) were treated with catheter-directed fibrinolysis, and 8 (2.4%) were treated surgically. The rest were treated with anticoagulation alone.

NLR and PLR were then calculated in both DVT and PTE patients. NLR and PLR were 4.29±3.67 and 137.84±79.44 in the patients with DVT, respectively, and 4.50±3.67 and 585.58±81.08 in the patients with PTE, respectively. There was no relationship between DVT and NLR (*P*=0.87) according to the Mann–Whitney test, but that was not the case for PTE (*P*=0.01). There was also no relationship between PLR and DVT (*P*=0.54) or PTE (*P*=0.27).

The relationships between NLR and PLR and PTE severity based on the location of the involvement of the main pulmonary artery and its segmental and subsegmental arteries were evaluated by ANOVA, which showed statistical significance (NLR: *P*=0.001, PLR: *P*=0.012) (Table 1).

Furthermore, according to the Mann–Whitney test, the relationships between NLR and PLR and PTE severity were assessed. There were no normal distributions for NLR and PLR at different levels of severity based on the Kolmogorov–Smirnov test. For the comparison of the means of NLR and PLR at different levels of severity, the Kruskal Wallis test was used (NLR: χ^2=2.28, *P*=0.32, PLR: χ^2=2.85, *P*=0.241). Therefore, there were no relationships between NLR and PLR and the severity of PTE based on the patients' clinical situation.

The mean levels of hs-CRP and ESR were 37.42±45.37 and 27.76±23.32, respectively. According to the results, there was a significant positive correlation between NLR and hs-CRP (*P*=0.009), but not with ESR. While there was also a significant positive correlation between PLR and ESR (*P*=0.0001), no such correlation was observed with hs-CRP. While 63 patients (19%) had a positive CTnI level, only 41 (12.4%) had highly positive CTnI levels. There were also correlations between CTnI and NLR (*P*=0.043) and between CTnI and PLR (*P*=0.005) (Table 2).

The mean levels of proBNP and D-dimer were 3342.11±6643.10 and 4543.44±3047.41, respectively. According to the Spearman correlation test, the correlation between NLR and D-dimer in DVT was insignificant (*P*=0.052), while the relationship was greatly significant in the patients with PTE (*P*=0.013). Regarding PLR, the tests showed a significant relationship with DVT (*P*=0.035) and PTE (*P*=0.003). Concerning proBNP, its relationship with NLR and PLR in the patients with DVT was nonsignificant (*P*=0.102 and *P*=0.114, respectively), while its relationship with NLR was significant in the patients with PTE (*P*=0.028), but not in those with PLR (*P*=0.227).

The relationships between NLR and PLR and the final outcome of death were evaluated. A significant relationship was observed between NLR and mortality. The patients who died had higher NLR values (17.64 vs 4.18; *P*=0.030); however, this relationship was not seen between no mortality (mean =137.14) and mortality (mean=220.25) and PLR (*P*=0.224).

The most common complication was hemorrhage within the first 72 hours of diagnosis, which was seen in 3 patients (0.9% of the study population), with the next most common complication being stroke, which occurred in 2 patients (0.6%).

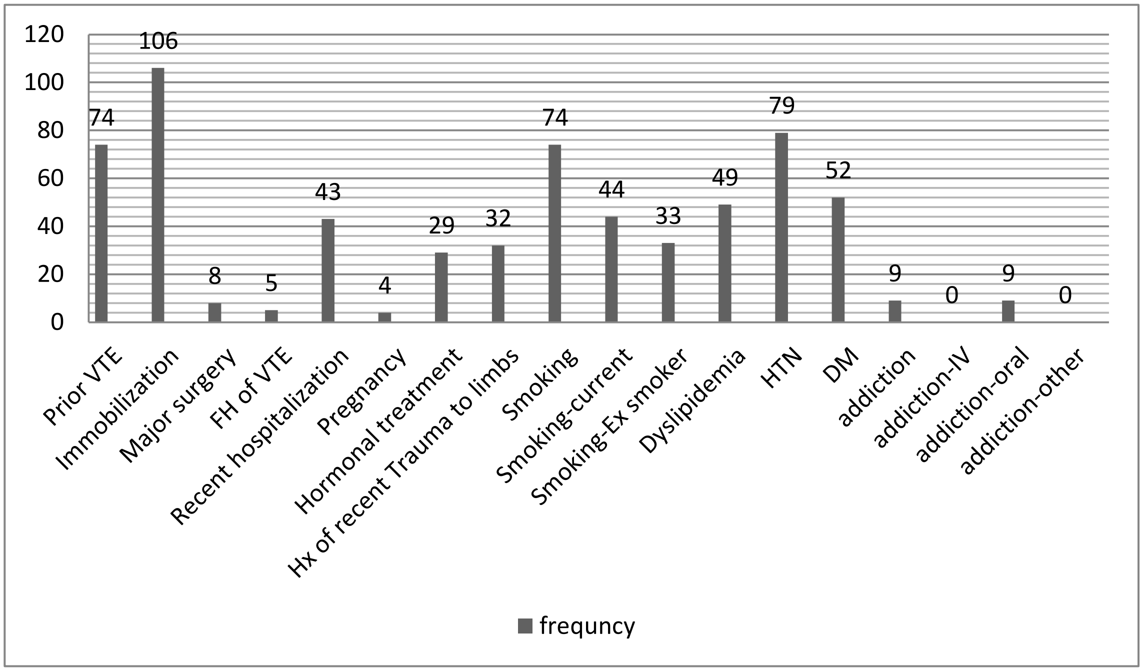

Figure 1. The image depicts the frequencies of risk factors in the patients with pulmonary thromboembolism (PTE).
VTE, Venous thromboembolism; FH, Family history; HTN, Hypertension; DM, Diabetes mellitus; IV, Intravenous

Table 1. Evaluation of NLR and PLR in the location of PA involvement and its segmental and subsegmental arteries (ANOVA)

		PA Clot Location		
		Main PA	Segmental	Subsegmental
NLR	Mean	4.26	4.92	3.07
	SD	3.29	4.05	1.61
	P value	**0.001**		
PLR	Mean	115.92	151.13	123.79
	SD	61.06	88.7	61.78
	P value	**0.012**		

PA, Pulmonary artery; NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio

Table 2. Correlations between NLR and PLR and laboratory variables

Lab Data		hs-CRP	ESR	CTnI
NLR	Correlation coefficient	0.305	0.098	0.141
	P value	0.009	0.078	0.043
PLR	Correlation coefficient	0.006	0.205	0.195
	P value	0.963	0.000	0.005

NLR, Neutrophil-to-lymphocyte ratio; PLR, Platelet-to-lymphocyte ratio; hs-CRP, High-sensitivity C-reactive protein; ESR, Erythrocyte sedimentation rate; CTnI, Cardiac troponin

DISCUSSION

VTE, which includes both DVT and PE, is one of the main causes of cardiovascular disease-related deaths and also one of the most important health-related challenges in the world, with a prevalence rate of 0.1% in industrialized countries. [9, 10]

The plasma levels of P-selectin, fibrin, CTnI, tissue factor, and blood cell counts, including WBCs, platelets, NLR, and PLR, are of great significance since they have high predictive values for more severe events, in particular VTE-related deaths. [4, 11-13] The role of blood parameters as the first evaluated parameter when admitting a patient suspected of VTE is vital.

Correct processing of patient condition when symptoms indicating a potential acute VTE are available can help the physician consider appropriate clinical interventions, thereby helping to prevent subsequent unpleasant events. We designed and conducted the present study at Rajaie Cardiovascular Medical and Research Center to investigate the relationships between NLR and PLR and the severity of VTE and in-hospital mortality.

In the current study, the mean age of the patients was 54.33 years, and the mean length of hospitalization was 10.09 days. The most common risk factors were inactivity (32%), blood pressure (23.9%), previous VTE (22.4%), and smoking (22.4%). Additionally, the most common symptom was dyspnea, which was seen in 77% of patients. Other prevalent symptoms were lower extremity edema in 56.5% of the study population, and chest pain, which was reported in only 29.3% of the patients. The most frequently reported history of a previous disease was a history of heart failure or coronary artery disease, each of which was seen in 6.9% of the patients. The most common treatment for the patients was anticoagulants, and the most common complication was hemorrhage with a known source within the first 72 hours of diagnosis, which was seen in 3 patients (0.9%). Stroke was the next most frequent complication, occurring in 2 patients (0.6%).

We found a significant positive correlation between NLR and hs-CRP (*P*=0.009) and also CTnI; however, the correlation was statistically weak (*P*=0.043). There was also a significant positive correlation between PLR and ESR (*P*=0.0001) and also CTnI; nonetheless, again, the correlation was statistically weak (*P*=0.005). These findings are compatible with those reported by Yang et al, [15] who also stated that increased NLR was significantly associated with an increased CRP. In this study, increased NLR was accompanied by increased hematocrit and decreased albumin levels.

In a study by Gu et al, [14] similar to our investigation, clinical features, laboratory parameters, and NLR in 114 patients with lung cancer and new VTE were evaluated retrospectively. The results showed that NLR at the time of the diagnosis of VTE could be a biomarker to predict response and prognosis after receiving anticoagulants in patients with lung cancer and VTE. Bozcus et al [2] found that the average MPV platelet volume was significantly higher in nonliving patients than in living patients with VTE. These studies, chiming in with ours, emphasize the significance of this index, although the design of both studies and their statistical populations were quite different.

We assessed the relationships between NLR and PLR with or without PE and DVT based on CT angiography and lower limb sonography findings and found a significant statistical relationship between PTE and NLR (*P*=0.01), while we observed no significant statistical relationship between CT angiography findings and PLR (*P*=0.27). There was no relationship between DVT and NLR (*P*=0.87) and PLR (*P*=0.54) according to our Mann–Whitney test. The results of a study performed by Yang et al, [15] in 2014 in China, which aimed to evaluate PLR as a significant predictor index in patients with cancer and VTE, demonstrated that PLR at the time of cancer diagnosis could be an independent and important clinical predictor to diagnose VTE risk in these patients. The results of that study are inconsistent with our study because, in our studied patients, there was no relationship between PTE and PLR, and there was only a significant relationship with NLR. This difference may be due to differences in the statistical populations of the 2 studies. While the study by Yang and colleagues only included patients with cancer, in our research, patients with cancer comprised only a small percentage of all the studies cases.

In a study by Kurtipek et al, [17] similar to our study, there was a direct relationship between PTE with NLR and PLR. Nevertheless, in an investigation by Artoni et al, [16] there was a weak relationship between VTE and PTE and the values of NLR and PLR, but increasing PLR played a role in provoking cerebral vein thrombosis. In a study by Kose et al, [18] NLR was identified as a prognostic marker in patients with low-risk and low-moderate-risk PTE, and PLR was a prognostic factor in high-risk and moderate-high-risk PTE patients. In our study, however, there were no relationships between NLR and PLR and the severity of PTE based on the patients' clinical situation.

In an investigation by Langhroudi et al, [19] NLR also helped to determine the severity of PTE and, thus, aided in the clinical management of these patients. Nonetheless, the authors found no relationship between PLR and the severity of PTE in CT. Also in their study, the proximal involvement of the pulmonary arteries was associated with higher NLR levels. Similarly, in our study, the involvement of the proximal arteries (the main pulmonary artery and its segmental arteries) was associated with higher NLR values, but this relationship was also seen between PLR and these arteries. Moreover, we detected a significant statistical relationship between NLR and the involvement of the main pulmonary artery and its segmental arteries insofar as the mean NLR was higher in the involvement of the main pulmonary artery and its segmental arteries in PTE (*P*=0.001). There was also a significant statistical relationship between PLR and the involvement of the main pulmonary artery and its segmental arteries (*P*=0.012) (Table 2).

Furthermore, we evaluated the relationship between NLR and PLR and the final outcome of death and detected a significant relationship between NLR and the incidence of death (mean=17.64) and between NLR and the absence of death in the patients' outcomes (mean=4.18, *P*=0.030). This relationship was not seen between no mortality (mean =137.14) and mortality (mean=220.25) and PLR (*P*=0.224). The mortality rate was 0.3%. In this regard, Kayrak et al [1] assessed the prognostic value of NLR in 359 patients with acute PTE and reported that 51 patients (14.2%) had passed away at 30 days. In that study, NLR was able to predict 30-day mortality in acute PTE at the time of hospital admission, which

is similar to our study, although patient mortality in the mentioned study was much higher than that in our investigation.
Pan et al [20] concluded that there was a relationship between increased preprocedural NLR in patients undergoing percutaneous coronary intervention and the increased risk of long-term mortality. Tamhane et al [3] also emphasized that NLR at the time of hospital admission was an independent predictor of mortality during hospitalization and until 6 months in patients with acute coronary syndromes.
Finally, Ghaffari et al [21] reported that PLR was correlated with the simplified pulmonary embolism severity index (PESI). However, PLR was not different between patients with and without adverse events, and it only had a fair predictive performance in predicting in-hospital mortality. In contrast, in our investigation, PLR was not associated with mortality in patients with PTE.

CONCLUSIONS

The results of the present study showed significant relationships between NLR and mortality and PTE in the main pulmonary artery and its segmental arteries. Thus, NLR can be used as a predictor for mortality or a prognostic marker in PTE, and PLR can be utilized as a predictor and prognostic marker only in PTE in the main pulmonary artery and its segmental arteries. Since obtaining a complete blood count is one of the most common tests performed at any hospital and treatment center during admission, the role of NLR as a predictor of subsequent adverse events in patients with spontaneous VTE is of high value.
We suggest that in the future, more studies be conducted with larger patient populations and as a cohort. Laboratory kit homogenization is also recommended for a more detailed examination.

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