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Original Article

Comparison of Blood Indices, Including Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV), and Red Cell Distribution Width (RDW), in Patients with Pulmonary Thromboembolism Versus Deep Vein Thrombosis in Hospitalized Patients

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Abstract

Background: Venous Thromboembolism (VTE) is the most common preventable cause of death in hospitalized patients. Inflammatory conditions and blood cells play a direct role in the thrombosis process. This study aimed to investigate the effect of some blood indices on VTE.

Methods: 141 patients with Pulmonary Thromboembolism (PTE) and 138 patients with Deep Vein Thrombosis (DVT) with standard diagnostic methods were assessed. The patients were hospitalized at Imam Khomeini Hospital Complex during 2018-2020. The analysis was performed by IBM SPSS version 22 software.

Results: The mean rank of all the blood indices [Red Cell Distribution Width (RDW), Platelet-to-Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV), and Neutrophil-to-Lymphocyte Ratio (NLR)] in the PTE group was higher than in the DVT group. But only NLR (p=0.00) and MPV (p=0.022) were significantly higher in patients with PTE. In the multivariate analysis, diabetes, NLR, and MPV indices were independently higher in the PTE group.

Conclusion: NLR and MPV were independently and significantly higher in patients with PTE than in those with DVT, and they can indicate an increased likelihood of developing PTE in patients with DVT and lead to an early diagnosis of PTE. To improve the clinical application of these indices, further studies should be conducted to determine their normal range, sensitivity, and specificity with a large number of participants in multiple centers to accurately identify other conditions that affect these blood indices.

Keywords: Blood cell count, Pulmonary embolism, Venous thrombosis

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Introduction

Venous Thromboembolism (VTE) includes Deep Vein Thrombosis (DVT) and Pulmonary Thromboembolism (PTE) and is recognized as the third leading cause of vascular disease-related death after Coronary Artery Disease (CAD) and Cerebrovascular Accident (CVA). PTE is the most common preventable cause of death in hospitalized patients and can result in high mortality rates and serious complications if not detected and treated promptly (1-3).

In recent years, significant efforts have been made to identify effective risk factors for the development of VTE and reliable clinical and laboratory indicators for identifying patients at risk of VTE and its associated complications (4,5). The ultimate goal is to identify patients at high risk of thromboembolic events using a simple and cost-effective approach and to prevent the occurrence of VTE in these patients through effective interventions (6-8). While clinical conditions and various diseases are known to contribute to the development of VTE, the cause of 30-50% of VTE is unknown and considered idiopathic (9). Inflammatory conditions are recognized as one of the underlying factors in the development of thrombosis, and blood cells, particularly platelets and red blood cells, play an important role in the clotting process (10-12).

The Complete Blood Count (CBC) with differential is a simple, readily available, and inexpensive laboratory test used to evaluate the effects of diseases on blood cells in many hospitalized and outpatient patients. Information that can be obtained from this test includes the number of different types of blood cells per unit volume of blood, the mean cell volume, and the ratio of different types of cells.

If a significant relationship can be established between the occurrence of thrombosis and some of these blood indices, which are indicators of inflammatory status or activation of cells involved in thrombosis, it may be possible to use these readily available and cost-effective indices to identify individuals at risk of thrombosis and serious complications and to provide necessary interventions (13,14). One of the important factors in predicting the occurrence of VTE in patients is the extent of thrombosis, including the involvement of the proximal veins of the lower extremities and the risk of embolism entering the pulmonary circulation (15).

This study aimed to investigate whether the site of thrombosis, specifically PTE, compared to DVT, leads to a significant change in these indices.

Materials and Methods

This observational cross-sectional study was conducted on hospitalized patients at Imam Khomeini Hospital Complex, one of the educational and medical centers affiliated with Tehran University of Medical Sciences, Tehran, Iran, from 2018-2020. The patients were given their informed consent for participation in this research study.

The study population included patients whose medical records included a diagnosis of DVT and PTE made by a physician at the time of discharge. The diagnosis of VTE was confirmed with Doppler ultrasonography for DVT and pulmonary CT angiography or nuclear scans (perfusion/ventilation scan) for PTE. If both DVT and PTE were definitively diagnosed concurrently, the patient was considered to have PTE. If a definite evaluation for PTE was not performed for a patient with a definite diagnosis of DVT by the imaging methods mentioned above, the patient was evaluated based on the clinical symptoms, physical examination, and Electrocardiography (ECG) findings.

The main dependent variables of the study, which were obtained from the CBC, included four indices: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Mean Platelet Volume (MPV), and Red blood cell Distribution Width (RDW). Other dependent variables included age, gender, and underlying diseases.

After drafting and approving the research plan in the research council of the internal department of the hospital, obtaining approval from the research deputy of the medical school, and obtaining an ethics code in coordination with the research deputy of the hospital, a formal letter was sent to the Medical Records department requesting the extraction of file numbers and names of the patients who were hospitalized in different sections of the hospital during the years 2018-2020 and were diagnosed with DVT or PTE. Files included the patient's medical history and examination, disease progression, medical orders, nursing reports, consultations, written imaging

reports, and test results. This study was conducted according to the Declaration of Helsinki.

If DVT or PTE was recorded on the patient's file, a comprehensive evaluation of the underlying cause of hospitalization and a review of the CBC with differential at the time of diagnosis were conducted. The ethic code of this study is IR.TUMS.IKHC.REC.1400.043.

At the beginning of the study, patients with diseases that were known to affect the indices in the CBC were excluded from the study, and then the effect of other underlying diseases on these indices was investigated. The exclusion criteria were renal failure, acute infection, hematologic diseases, malignancies, and no CBC with differential being present in records. Additionally, if sudden shortness of breath, chest pain, sinus tachycardia, or ECG changes suggestive of embolism were recorded and no definite evaluation for PTE was performed, the patient was excluded from the study.

To perform appropriate statistical tests for the quantitative variables, it is first necessary to evaluate the normality of their distribution based on statistical tests. If a quantitative variable does not have a normal distribution, the use of mean for comparing two groups and the use of parametric statistical tests are not possible, and non-parametric statistical tests should be used instead. Therefore, the normality of the distribution of the quantitative variables, including the NLR, PLR, MPV, and RDW, was examined using the Kolmogorov-Smirnov test, and all the variables had a non-normal distribution in both the DVT and PTE groups. Individuals with DVT and PTE were completely independent. Thus, a non-parametric Mann-Whitney U test and an index called mean rank instead of mean and standard deviation were used. The data were analyzed using univariate (chi square) and multivariate (linear regression) analyses. Results with $p<0.05$ or $z<-1.64$ were considered significant. The analysis was performed by IBM SPSS version 22 software.

Results

After reviewing 600 patients diagnosed with DVT and 400 patients diagnosed with PTE, 279 individuals were included in the study. Of this number, 141 patients were confirmed to have PTE, and 138 patients were confirmed to have DVT. In terms of gender distribution, there were 147 males (52.7%) and 132 females (47.3%) among all individuals in the study. In the DVT group, there were 72 males (52.2%) and 66 females (47.8%), and in the PTE group, there were 75 males (53.4%) and 66 females (46.6%). The mean age of individuals in the study was 17.7±6.55 years, with a range of 14-91 years. In the DVT group, the mean age of the patients was 18.6±4.55 years with an age range of 15-91 years, and in the PTE group, the mean age of the patients was 16.7±8.55 years with an age range of 14-87 years. Based on the age of 65 years as the age of entering old age, the patients were divided into two groups: elderly and non-elderly, with a total of 186 individuals under the age of 65 years (94 in the PTE group and 92 in the DVT group) classified as non-elderly and 93 individuals over the age of 65 years (47 in the PTE group and 46 in the DVT group) classified as elderly. There was a proportional distribution of age and gender between these two groups.

In table 1, the prevalence of underlying diseases was demonstrated. The most common underlying diseases were hypertension, Diabetes Mellitus (DM), Ischemic Heart Disease, CVA, Chronic Obstructive Pulmonary Disease (COPD), and cirrhosis, respectively. In the comparison between DVT and PTE groups, a significantly higher percentage of patients with PTE had COPD (p-value=0.016), while a higher percentage of patients with DVT had cirrhosis (p-value=0.007).

The mean rank of all blood indices in the PTE group was higher than the DVT group, but this difference was only significant for MPV (p-value=0.022) and NLR indices (p-value=0.00). The statistical coefficient (z) of MPV and NLR was -2.286 and -3.948, which were less than -1.64 (<-1.64 is significant) (Table 2).

After performing a univariate analysis to eliminate confounding factors and determine a more accurate relationship between independent and dependent variables, a multivariate linear regression analysis was used. Variables that had a p-value0.2< in the univariate analysis were included in the multivariate analysis. A multivariate analysis was conducted on variables affecting the occurrence of PTE compared to DVT, and NLR (p-value=0.00), MPV (p-value=0.001), and DM (p-value=0.027) were found to have an independent and significant effect on the increased

Table 1. Prevalence of underlying diseases in patients with DVT and PTE

Underlying diseases		PTE Group	DVT Group	Chi-Square test
Hypertension	Yes	22(15.6%)	28(20.3%)	0.194
	No	119 (84.4%)	110(79.7%)	
DM	Yes	13(9.2%)	22 (15.9%)	0.065
	No	128 (90.8%)	116(84.1%)	
Ischemic heart disease	Yes	15(10.6%)	12(8.7%)	0.365
	No	126(89.4%)	126(91.3%)	
CVA	Yes	10 (7.1%)	14(10.1%)	0.244
	No	131 (92.9%)	124(89.9%)	
COPD	Yes	17 (12.1%)	6(4.3%)	0.016
	No	124 (87.9%)	132(95.7%)	
Cirrhosis	Yes	0	7(5.1%)	0.007
	No	141 (100%)	131(94.9%)	

PTE: Pulmonary Thromboembolism, DVT: Deep Vein Thrombosis, DM: Diabetes Mellitus CVA: Cerebrovascular Accident, COPD: Chronic Obstructive Pulmonary disease, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-lymphocyte Ratio, MPV: Mean Platelet Volume, RDW: Red cell Distribution Width

Table 2. Mean, mean rank, p value, and z coefficient of Mann-Whitney U test of blood indices in PTE and DVT groups

Blood index	Group	Median (Interquartile range)	Mean±SD	p-value
RDW	PTE	14.8(3.1)	3/2±4/15	0.181
	DVT	14.5(3.1)	8/2±3/15	
MPV	PTE	9.9(1.3)	1/1±10	0.022
	DVT	9.7(1.5)	9/0±7/9	
NLR	PTE	4.13(4.11)	8/4±5/5	0
	DVT	2.9(2.4)	9/2±7/3	
PLR	PTE	133.2(104.1)	4/117±9/167	0.128
	DVT	113.7(100.3)	119.6±152.5	

PTE: pulmonary thromboembolism, DVT: deep vein thrombosis, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, MPV: mean platelet volume, RDW: red cell distribution width

PTE: Pulmonary Thromboembolism, DVT: Deep Vein Thrombosis, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-lymphocyte Ratio, MPV: Mean Platelet Volume, RDW: Red cell Distribution Width

occurrence of PTE compared to DVT.

There was no significant difference between the elderly and non-elderly groups in terms of DVT and PTE. Only a significant difference was observed in NLR (p-value=0.010) and PLR (p-value=0.035), and elderly individuals had higher NLR and PLR. There was no significant difference between men and women in terms of DVT and PTE. No significant difference was observed in NLR and MPV, but women had a significantly higher RDW compared to men (p-value=0.038). Also, PLR, in women was significantly higher compared to men (p-value=0.012).

In individuals with ischemic heart disease, the MPV index was significantly higher (p-value=0.008) than in those without ischemic heart disease. In individuals

with COPD, the NLR (p-value=0.003) and RDW (p-value=0.027) were significantly higher than in those without COPD. In patients with cirrhosis, the RDW was significantly higher (p-value=0.001) than in those without cirrhosis.

Discussion

VTE is responsible for a large number of preventable deaths worldwide, making early diagnosis crucial for effective management and intervention (16). Furthermore, the financial burden of VTE-related hospitalizations, diagnostic tests, and long-term complications underscores the necessity of timely identification and appropriate treatment strategies to reduce the overall societal impact of this condition (17,18).

Many studies have been conducted to identify the factors that increase the incidence of thromboembolic events and the individuals at risk of developing them (19-21). On the other hand, due to the clinical similarity of these diseases with other conditions, and the importance of timely treatment in reducing significant complications and mortality, identifying reliable diagnostic clinical signs and paraclinical findings has always been one of the major concerns of physicians. The ideal goal is to prevent invasive, expensive, and less accessible diagnostic tests.

The CBC is a widely available and cost-effective test that can provide information about the immune system's inflammatory response and potential thrombotic events (22-24). Four indices obtained from the CBC, including NLR, PLR, MPV, and RDW, have been identified as potential markers of thrombotic diseases (25,26).

The results showed that NLR and MPV were significantly higher in individuals with PTE than in those with DVT. In the multivariate analysis, NLR and MPV indices were independently higher in the PTE group, and the higher MPV and NLR indices.

Similar studies have been conducted to evaluate the association between blood indices and thromboembolic events. A study conducted in China in 2018 evaluated blood indices in 115 patients with unprovoked DVT and 105 healthy individuals. MPV, NLR, and PLR were significantly higher in the DVT group, and NLR and high D-dimer levels were identified as independent risk factors for DVT (27).

Another study conducted in 2019 compared blood markers between 272 patients with confirmed DVT and 55 without DVT. NLR and MPV were early predictors of venous thrombosis, with an NLR value of 3.5 and an MPV value of 6.8 obtained for comparison with healthy individuals (26).

The diagnostic and predictive value of blood markers in thromboembolic diseases has been extensively studied (28). In a systematic review conducted in China in 2022, the NLR marker was identified as a diagnostic factor for thromboembolic diseases with a sensitivity of 68% and a specificity of 73%. Further studies are needed to determine the precise upper limit of this marker, which has been reported to range from 1.76 to 3.5 in various studies. Additionally, studies have revealed that individuals with higher NLR and Lymphocyte-Monocyte Ratio (LMR) markers have a worse prognosis in PTE (29).

Several studies have also investigated the association between blood indices and the extent of thrombosis. In a study conducted in Turkey in 2015, the NLR and high sensitivity C-Reactive Protein (hs-CRP) indices significantly increased with the extent of thrombosis, with the highest levels found in patients with PTE, followed by proximal and distal DVT. However, no significant difference was observed between the DVT and PTE groups (30).

To improve the clinical application of these indices, further studies should be conducted to determine their normal range, sensitivity, specificity. Moreover, studies should be conducted with a large number of participants in multiple centers to accurately identify other conditions and diseases that affect these blood indices. Physicians should also be aware of other factors that affect these indices and refrain from using them in patients with multiple contributing factors. The present study had some limitations, including its retrospective nature and the lack of direct access to patients. Additionally, the presence of laboratory errors in some cases might be unavoidable.

Conclusion

PTE is a serious medical condition that can lead to death if not identified and treated promptly. Inflammatory conditions and blood cells play a direct role in the thrombosis process. The study found that NLR and MPV were significantly higher in patients with PTE

than in those with DVT. NLR and MPV can indicate an increased likelihood of developing PTE in patients with DVT. These findings had important clinical implications for the early diagnosis and treatment of PTE, which can help prevent serious complications and improve patient outcomes.

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Conflict of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript. There was no funding in conducting this study.

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