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Relationship Between D-Dimer Levels and Neutrophil Lymphocyte Ratio and Platelet Lymphocyte Ratio in Deep Vein Thrombosis Patients

Maisyarah Farhati Lubis [1*], Heny Syahrini Lubis [2], Dairion Gatot [2]

[1] *Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Indonesia*
[2] *Division of Medical Hematology and Oncology, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, Indonesia*

***Corresponding Author**: Maisyarah Farhati Lubis, E-mail: maisyarahfarhati@gmail.com

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ABSTRACT

Introduction: Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with activation of coagulation and inflammation. In DVT, the coagulation process is often accelerated by inflammatory mediators, causing fibrinolytic disruption and increasing D-dimer levels. D-dimer testing, with its high negative predictive value, is commonly used as a screening tool for thromboembolic events. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are inflammatory markers that can be easily calculated from routine blood tests and may assist in the early detection of DVT. This study aims to evaluate the relationship between D-dimer levels and both NLR and PLR in DVT patients at Adam Malik Hospital.

Method: This analytical observational study used a cross-sectional design. Secondary data were collected from medical records of DVT patients treated at Adam Malik Hospital between June 2022 and June 2024. NLR and PLR were the independent variables, while D-dimer level was the dependent variable. Data were analyzed using Spearman's rho correlation test.

Results: Among 100 patients, 38% were aged over 59 years, with equal gender distribution. The most common comorbidity was infection (71%), and 62% had hospital stays longer than 7 days. A significant positive correlation was found between D-dimer levels and NLR ($p = 0.001$, $r = +0.350$). However, there was no significant correlation between D-dimer levels and PLR ($p = 0.610$, $r = –0.052$).

Conclusion: There is a significant association between D-dimer levels and NLR, but no significant relationship between D-dimer levels and PLR in DVT patients.

Keywords

Deep Vein Thrombosis, D-Dimer, NLR, PLR

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INTRODUCTION

Venous thromboembolism (VTE) is a vascular condition that leads to deep vein thrombosis (DVT) and pulmonary embolism (PE), with an incidence of 1–2 per 1,000 people in Europe and the United States, although the occurrence is lower in Asia.[1,2]

DVT is characterized by obstruction of venous return, most commonly occurring in the lower extremities. Clot formation usually begins in the distal areas (such as the calf) and can extend to more proximal veins, with reported distributions of 40% in the distal veins, 16% in the popliteal vein, 20% in the femoral vein, 20% in the common femoral vein, and 4% in the iliac vein. In addition, DVT can occur in the mesenteric and cerebral veins, and it is one of the three major causes of cardiovascular death following myocardial infarction or stroke.[3] Epidemiological data show that there are 80 cases of DVT per 100,000 population annually worldwide, with

15–20% of these cases occurring in Asia.[3,4] In Indonesia, particularly in 2020, 37.1–40.3% of inpatients were recorded as having DVT, although specific data from Medan are incomplete, and DVT has a mortality rate of approximately 6%.[5]

Triggers for DVT include acquired conditions such as post-operative status, pregnancy, immobilization, and infection, as well as hereditary factors like antithrombin deficiency, factor V Leiden mutation, and polymorphisms in the protein C gene promoter (C2405T and A2418G).[6] The pathogenesis of DVT is associated with Virchow's triad: stasis of blood flow, endothelial injury, and hypercoagulability. Currently, the involvement of platelets is also recognized; endothelial injury due to inflammation increases the expression of P-selectin, which facilitates the adhesion of leukocytes and platelets, as well as creates a hypoxic environment that further enhances the expression of adhesion molecules and activation of the coagulation cascade.[6]

The link between inflammation and thrombosis forms the basis of thromboinflammation, wherein the activation of non-adaptive immune cells and platelets contributes to the activation of the complement system and the coagulation cascade, potentially leading to both microvascular and macrovascular occlusion.[7] Furthermore, two phenotypes of DVT exist: microthrombus and macrothrombus formation, which depend on the depth and extent of vascular wall injury; limited endothelial injury, as seen in sepsis, leads to disseminated microthrombi, whereas trauma that extends into the subendothelial layer produces macrothrombi.[8]

In addition to D-dimer, a complete blood count provides information on the inflammatory status through parameters such as the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR). With a normal range of 1–2, NLR reflects the balance between the non-specific and specific immune responses; an NLR above 3.0 indicates pathology, and values above 11–17 suggest severe inflammation and stress.[9-13] Rinaldi et al. demonstrated that the diagnostic value of NLR is comparable to that of D-dimer, especially in patients with a low clinical probability of DVT.[14]

The activation of coagulation factors accelerated by inflammatory mediators and disturbances in the fibrinolysis process are key factors in the development of DVT. Fibrinolysis, which degrades fibrin, produces D-dimer—a sensitive marker for intravascular thrombus—that also increases in conditions such as acute aortic dissection, pregnancy, aging, and malignancy.[11,12] The D-dimer assay has a high negative predictive value, although high values require further investigation to confirm VTE.

Platelets also play a role in inflammation, and PLR is an additional parameter calculated from a complete blood count. PLR is not only useful in assessing thromboembolic risk but also serves as a prognostic factor in cardiovascular diseases, where higher PLR is associated with long-term mortality and a threefold increased risk of thromboembolic symptoms.[15–18] The combination of NLR, PLR, and D-dimer has been shown to significantly improve the diagnostic performance for DVT compared to using D-dimer alone.[19,20] Based on this background, the present study was conducted to evaluate the relationship between D-dimer levels and both NLR and PLR in patients with DVT at Adam Malik Hospital.

METHOD

This study utilized an analytical observational design with a cross-sectional approach to evaluate the relationship between D-dimer levels and NLR and PLR in patients with DVT at Adam Malik Hospital. The independent variables were NLR and PLR, and the dependent variable was the D-dimer level. The study was conducted at Adam Malik Hospital in Medan from July 2024 to September 2024, with the population comprising patients with DVT and the sample collected consecutively from patients diagnosed between June 2022 and June 2024. The minimum sample size was calculated using a correlational formula,35 resulting in 34 patients. Sampling was performed using purposive sampling based on the inclusion criteria (age ≥18 years, newly diagnosed DVT, and complete medical records) and exclusion criteria (patients with hematologic malignancies, previous DVT, and incomplete medical records).

Data collected included demographic characteristics (age, sex, and comorbidities) and laboratory values (neutrophils, lymphocytes, platelets, and D-dimer) extracted from medical records. Data processing involved editing, coding, entry, cleaning, and analysis, with the results presented in tables or graphs. Statistical analysis

was performed using SPSS 26, employing Pearson's test for normally distributed data or Spearman's test for non-normally distributed data to determine the relationship between NLR, PLR, and D-dimer levels.

RESULTS

Based on 100 samples, all subjects were diagnosed with DVT using Doppler ultrasound. As shown in Table 1, the sex distribution was perfectly balanced (50% male, 50% female). The majority of patients were over 59 years old (38%), followed by those aged 45–59 years (35%) and 19–44 years (27%).

Table 1. Demographic Characteristics of the Study Participants.

Characteristics	n = 100
Gender, n (%)	
Male	50 (50,0)
Female	50 (50,0)
Age, n (%)	
19–44 years	27 (27,0)
45-59 years	35 (35,0)
> 59 years	38 (38,0)
Comorbidities	
Infection, n (%)	
Yes	71 (71,0)
No	29 (29,0)
Type 2 Diabetes Mellitus, n (%)	
Yes	40 (40,0)
No	60 (60,0)
Cardiovascular Disease, n (%)	
Yes	49 (49,0)
No	51 (51,0)
Cancer, n (%)	
Yes	14 (14,0)
No	86 (86,0)
Chronic Kidney Disease, n (%)	
Yes	12 (12,0)
No	88 (88,0)
Autoimmune Disease, n (%)	
Yes	9 (9,0)
No	91 (91,0)
Length of Hospital Stay, n (%)	
< 7 days	38 (38,0)
≥ 7 days	62 (62,0)
Laboratory Parameters	
Hemoglobin, mean ± SD	9,58 ± 2,55
Leukocytes, median (min. – maks.)	12.935 (2.460 – 52.930)
Platelets, mean ± SD	261.680 ± 145.948
Basophils, median (min. – maks.)	0,20 (0,00 – 1,20)
Eosinophils, median (min. – maks.)	0,90 (0,00 – 45,20)
Neutrophils, median (min. – maks.)	82,45 (30,40 – 97,50)
Limphocytes, median (min. – maks.)	6,45 (0,70 – 37,00)
Monocytes, mean ± SD	6,88 ± 3,59
NLR, median (min. – maks.)	13,37 (2,07 – 139,29)
PLR, median (min. – maks.)	186,82 (15,29 – 1.944,44)
D-dimer, median (min. – maks.)	2.685 (140 – 35.000)

The most common comorbidity was infection (71%), followed by cardiovascular disease (49%), type 2 diabetes mellitus (40%), cancer (14%), chronic kidney disease (12%), and autoimmune diseases (9%). All subjects were inpatients, with 62% staying for more than 7 days and 38% for less than 7 days. Most laboratory parameters had a non-normal distribution and were presented as median (minimum–maximum): leukocytes 12,935 (2,460–52,930), basophils 0.2 (0.00–1.20), eosinophils 0.90 (0.00–45.20), neutrophils 82.45 (30.40–97.50), lymphocytes 6.45 (0.70–37.00), NLR 13.37 (2.07–139.29), PLR 186.82 (15.29–1,944.44), and D-dimer

2,685 (140–35,000). Parameters with normal distribution (hemoglobin, platelets, and monocytes) were expressed as mean ± SD: hemoglobin 9.58 ± 2.55, platelets 261,680 ± 145,948, and monocytes 6.88 ± 3.59.

Table 2 shows the statistical results of the relationship between D-dimer levels and the neutrophil-to-lymphocyte ratio in patients with DVT. Spearman's correlation test revealed a significant relationship (p = 0.001) between D-dimer and NLR among the 100 subjects, with a weak positive correlation (r = +0.315). This indicates that although an increase in NLR is associated with higher D-dimer levels, the strength of this correlation is relatively low.

Table 2. Relationship Between D-Dimer and Neutrophil-to-Lymphocyte Ratio

Variable	p-value	r*
D-Dimer With NLR	0.001	0.315

Noted: *Spearman's rho

Table 3 presents the statistical analysis of the relationship between D-dimer levels and the P/L ratio in patients with DVT. Spearman's correlation test revealed no significant relationship (p = 0.610) between D-dimer and PLR among the 100 subjects, with a very weak negative correlation (r = –0.052).

Table 3. Relationship Between D-Dimer and Platelet-to-Lymphocyte Ratio

Variable	p-value	r*
D-Dimer With PLR	0.61	-0.052

Noted: *Spearman's rho

DISCUSSION

This study demonstrated that the sex distribution among patients with DVT was nearly equal, despite a slight difference noted in a systematic review by Lee et al.[21,23], which reported that women were more frequently diagnosed with DVT than men. Other studies, such as that by Rinaldi et al.,[14] reported a 53.2% prevalence of DVT among female patients with suspected DVT. These discrepancies are likely due to variations in the sample size and comorbid conditions among the study populations. The majority of patients in the current study were older than 59 years (38%), which supports the notion that the risk of DVT increases with age, as confirmed by the systematic review by Fowkes et al21 and the study by Rinaldi et al.,[14] where the incidence was higher in patients aged ⩾45 years. Age-related physiological changes such as endothelial dysfunction, decreased fibrinolytic activity, and increased coagulation factors contribute to the heightened risk of thrombosis in the elderly.[22]

The comorbidity data showed that most patients had infections (71%), followed by cardiovascular disease (49%), type 2 diabetes mellitus (40%), cancer (14%), chronic kidney disease (12%), and autoimmune disorders (9%). Tambunan et al5 found that cancer and acute infection were the most common comorbidities in patients with DVT, whereas Rinaldi et al.[14] reported that cancer (44%), type 2 diabetes mellitus (20.37%), and chronic kidney disease (14.81%) were predominant. Additionally, a systematic review by Lee et al.[23] indicated that many DVT cases are related to predispositions such as cancer, severe neurological diseases, major trauma, and major surgery within the last three months. The heterogeneity of the study population may explain these differences.

All subjects in the study were inpatients, with most having a hospital stay of more than seven days. This finding is consistent with the study by Amawi et al.,[24] who reported that patients with venous thromboembolism tend to have longer hospital stays. Both age and the presence of comorbidities significantly influenced the length of hospitalization, reflecting the complexity of patient conditions and the need for more intensive management of these patients.

The distribution of NLR and PLR values showed non-normal patterns, with a median NLR of 9.8 and PLR of 193.2, indicating a high systemic inflammatory response in patients with DVT. Both NLR and PLR are widely used as inflammatory markers in various medical conditions, including DVT. In the pathogenesis of DVT, neutrophils and platelets play critical roles in hemostasis and inflammation.[10] The findings are

consistent with the meta-analysis by Hu et al.,[25] which involved 11 studies with a total of 4,289 participants and showed increased NLR and PLR values in patients with DVT.

Regarding coagulation biomarkers, the study found a median D-dimer value of 2,685, with 95% of the subjects showing high D-dimer levels. Elevated D-dimer levels reflect increased fibrinolytic activity in response to thrombus formation. Peng et al,[26] demonstrated that patients with DVT had significantly higher D-dimer levels compared to non-DVT patients. The combination of increased NLR, PLR, and D-dimer levels provides a comprehensive picture of the role of inflammation and hypercoagulability in the pathophysiology of DVT. These results are in line with the findings of Gao et al.,[20] which indicate that the combined use of these three parameters significantly improves the diagnostic accuracy for DVT.

Spearman's correlation analysis showed a significant relationship between D-dimer and NLR ($p = 0.001$, $r = +0.315$), indicating parallel increases in systemic inflammation and fibrinolytic activity. This supports inflammation's central role in DVT pathogenesis. Neutrophils, through NETs release, activate coagulation factors and recruit platelets, enhancing thrombus formation.[12-27] Higher NLR reflects systemic inflammation that may predict DVT severity and increased coagulation activation.

No significant correlation was found between D-dimer and PLR ($p = 0.610$, $r = –0.052$). While PLR indicates platelet involvement in thrombus formation, D-dimer directly measures fibrinolytic activity, unlike PLR which reflects systemic inflammation indirectly. PLR can be affected by chronic inflammation, while D-dimer levels change rapidly post-thrombotic events. Studies by Gao et al. and Sujana et al.[20-28] suggest combining NLR, PLR, and D-dimer improves diagnostic performance.

The findings highlight the value of combining inflammatory biomarkers (NLR and PLR) with D-dimer in DVT diagnosis and treatment. Elevated NLR and PLR with high D-dimer levels indicate thrombotic risk in DVT patients. These combined parameters help predict inflammation and thrombosis severity while guiding anticoagulant therapy. The collective use of NLR, PLR, and D-dimer has prognostic value in predicting complications like pulmonary embolism or recurrent DVT. Using these parameters enhances DVT diagnosis accuracy and treatment planning, crucial for reducing mortality in complex cases with multiple comorbidities.

This study is the first to evaluate NLR, PLR, and D-dimer relationships in DVT patients at Adam Malik Hospital. NLR from complete blood count serves as an accessible early detection tool. However, the cross-sectional design, small sample size without controls, and single-center nature limit result generalizability, indicating the need for larger multicenter studies.

CONCLUSION

A significant correlation was observed between D-dimer levels and the neutrophil-to-lymphocyte ratio (NLR) in patients with deep vein thrombosis (DVT), whereas no such relationship was found between D-dimer levels and the platelet-to-lymphocyte ratio (PLR). Future research should explore the diagnostic and prognostic utility of NLR and PLR in comparison to D-dimer for differentiating DVT from similar conditions.

DECLARATIONS

Ethics approval and consent to participate. Permission for this study was obtained from the Ethics Committee of the Universitas Sumatera Utara and Haji Adam Malik General Hospital.

CONSENT FOR PUBLICATION

The Authors agree to publication in the Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare no conflicts of interest in this report.

AUTHORS' CONTRIBUTIONS

All authors significantly contributed to the work reported in the execution, acquisition of data, analysis, and interpretation, or in all these areas. Contributed to drafting, revising, or critically reviewing the article. Approved the final version to be published, agreed on the journal to be submitted, and agreed to be accountable for all aspects of the work.

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