Deep vein thrombosis (DVT) is a blood clot that occurs in the inner veins caused by heart disease, infection, cancer, and prolonged immobilization of the limbs. Neutrophil-Lymphocyte Ratio (NLR) and Platelet Lymphocyte Ratio (PLR) have been known as a marker of the primary hemostasis process related to the inflammatory pathway. This study aims to evaluate the correlation of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio compared to D-dimer as a diagnostic test in Deep Vein Thrombosis (DVT).

Methods: A cross-sectional approach has been conducted in this diagnostic study at the Sanglah General Hospital by using secondary data from medical records during July 2018-2019. The study sample consisted of 49 patients with suspected DVT originating from a population who met the inclusion and exclusion criteria. The variables assessed in this study were NLR, PLR, and D-Dimer. Data collection and data analysis were performed by SPSS version 17 for Windows.

Results: The average age of respondents was 53.10±13.40 years old. Most of the respondents were male (59.20%), having edema in the lower extremity (61.20%), left unilateral laterality (53.10%), and D-Dimer levels ≥0.5 μg/mL (76.1%). There was a statistically significant relationship between the average value of NLR (9.07±4.2) and PLR (183.55±66.52) with the occurrence of DVT (P<0.05). The Area Under Curve (AUC) of ROC Analysis was 94.40% (Cut-off: 8.20; p<0.050) in NLR and 92.10% (Cut-off: 159.66) in PLR to the D-Dimer on the incidence of DVT. There was a significant moderate positive correlation between NLR and PLR combination on DVT incidences (r=0.532; p<0.001).

Conclusion: NLR and PLR can be used as an alternative to DVT diagnostic tools due to high sensitivity and specificity, easy to use, inexpensive, simple, and widely available in Indonesia.

Keywords: NLR, PLR, D-Dimer, DVT, Diagnostic Test

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INTRODUCTION

Deep vein thrombosis (DVT) is a blood clot that occurs in the inner veins. Blocked vein flow is a frequent cause of DVT. The cause is due to heart disease, infection, or prolonged immobilization of the limbs. Venous thromboembolic disease (VTE) is a term that includes deep vein thrombosis (DVT) and pulmonary embolism (PE), or a combination of both. The incidence of DVT in Europe and the United States is approximately 50 per 100,000 population per year. The incidence of DVT increases with age, around 1 per 10,000-20,000 population under the age of 15 years to 1 per 1000 population over the age of 70 years. The incidence of DVT in Asian races is reported to be lower than in Caucasians, African-Latin Americans, and the Asia Pacific. However, there was no significant difference in incidence between men and women. In Bali, the incidence of DVT is increasing every year is influenced by the incidence of chronic degenerative diseases and cancer incidence.

Some diagnostic evaluations that are used to establish or rule out a diagnosis of DVT today include D-dimer examination and ultrasonography. The D-Dimer analysis illustrates the degradation of fibrin in the blood, often used as an initial examination for DVT. Clinical research supports the hypothesis that low D-dimer levels can rule out DVT in patients with low to moderate risk and a Wells scores <2. Ultrasonography is an excellent diagnostic tool, which is widely used today as a standard for establishing DVT. Doppler ultrasound examination has a widely recognized role as the gold standard. Seeing the mechanism of action of neutrophils, platelets, and lymphocytes, we can compare the Neutrophil-Lymphocyte Ratio (NLR) and the Platelet-Lymphocyte Ratio (PLR) as the parameter that reflects the inflammatory response in venous thromboembolic patients, especially patients with DVT.
The NLR, PLR, and the combination of NLR and PLR measurements are markers that are easy to measure, comfortable, and inexpensive for patients, so comparison of the use of NLR and PLR diagnosis as a screening and diagnostic tool compared to D-Dimer can be used as an alternative examination. Based on those mentioned above, this study aims to evaluate the correlation of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio compared to D-dimer as a diagnostic test in Deep Vein Thrombosis (DVT).

METHODS

This study was a cross-sectional study among 49 subjects at the Sanglah General Hospital, Bali, Indonesia, from July 2018-2019. The subjects enrolled in this study were from the Thorax, Cardio Vascular, and Endovascular Polyclinic, who has fulfilled the inclusion criteria. Parameter assessed in this study were age, sex, the occurrence of edema of the lower extremity, laterality, Neutrophil-Lymphocyte Ratio (NLR), Platelet-Lymphocyte Ratio (PLR), and Deep Vein Thrombosis (DVT). NLR and PLR were measured by dividing the absolute number of neutrophil and platelet on complete blood count (CBC) by the absolute number of lymphocyte as a screening tool for patients with DVT.

The data was taken from medical records of patients undergoing complete blood tests, D-Dimer, and Doppler Ultrasound Lower Extremity. They have complete medical records (clinical data, Wells Score records, comprehensive blood examination, Doppler Ultrasound inferior Extremity). The exclusion criteria were patients who have undergone anticoagulant, fibrinolytic, and antithrombotic therapy before or suffering from infections and inflammation, both acute and chronic, such as SLE (systemic Lupus Erythematosus), liver cirrhosis, kidney disorders, allergic reactions, and others.

Data were tabulated and analyzed by univariate (mean, standard deviation, number, and percentage) and bivariate (Chi-Square, ROC, and Pearson Correlation test). Statistical software used in this study was SPSS version 17 for Windows.

RESULTS

Table 1 shows the sample characteristic data based on age obtained with a mean of 53.1±13.4 years with a p-value of 0.157, which means there was no significant relationship between age and the incidence of DVT in this study (Table 2). The characteristics based on gender found that male was the predominant (59.20%). In comparison, the female was 20 respondents (40.80%) with a p-value of 0.953 which indicates there was no significant relationship between age and the incidence of DVT (Table 1).

The characteristics of respondents based on the swelling obtained 30 respondents swelling in the legs that have DVT (61.20%), and about 19 respondents (38.80%) were not swollen (p=0.414) which depict there was no significant relationship between swelling and the incidence of DVT (Table 1). Characteristics based on the section that experienced DVT obtained right unilateral data 19 respondents (38.80%), left unilateral more 26 respondents (53.10%), and bilateral 4 respondents (8.20%) with p-value of 0.063 which means there was no relationship between lateralization and DVT events (Table 1).

Based on NLR value, data obtained with a mean of 9.07±4.2 with a p-value of 0.000 means there was a significant relationship between NLR with the occurrence of DVT. Also, the PLR value was found with an average of 183.55±66.52 (p=0.000) indicating there was a significant relationship between PLR the incidence of DVT (Table 1). Characteristics of D-dimers were categorized into ≥0.5 µg/ml for 39 respondents (76.10%) and <0.5µg/ml for 10 respondents (20.40%) with p-value of 0.001 which means there was a no relationship between lateralization and DVT events (Table 1).

Based on NLR value, data obtained with a mean of 9.07±4.2 with a p-value of 0.000 means there was a significant relationship between NLR with the occurrence of DVT. Also, the PLR value was found with an average of 183.55±66.52 (p=0.000), indicating there was a significant relationship between PLR the incidence of DVT (Table 1). Characteristics of D-dimers were categorized into ≥0.5 µg/ml for 39 respondents (76.10%) and <0.5µg/ml for 10 respondents (20.40%) with a p-value of 0.001 which means there was a no statistically significant relationship between D-Dimer with DVT events (Table 1).

The variables compared in this study were NLR, PLR, and D-Dimer on the incidence of DVT. NLR sensitivity based on the ROC curve was obtained with an AUC of 94.40%. Statistically, the AUC value

| Variables                          | Subjects (n= 49) | p     |
|-----------------------------------|-----------------|-------|
| Age (Years) (mean±SD)             | 53.1± 13.4      | 0.157 |
| Sex, n (%)                        |                 |       |
| Male                              | 29 (59.20)      | 0.953 |
| Female                            | 20 (40.80)      |       |
| Edema lower extremity, n (%)      |                 |       |
| Yes                               | 30 (61.20)      | 0.414 |
| No                                | 19 (38.80)      |       |
| Laterality, n (%)                 |                 |       |
| Right unilateral                  | 19 (38.80)      | 0.062 |
| Left unilateral                   | 26 (53.10)      |       |
| Bilateral                         | 4 (8.20)        |       |
| NLR (mean±SD)                     | 9.07±4.2        | 0.000 |
| PLR (mean±SD)                     | 183.55±66.52    | 0.000 |
| D-Dimer, n (%)                    |                 |       |
| ≥0.5µg/ml                         | 39 (76.10)      | 0.001 |
| <0.5µg/ml                         | 10 (20.40)      |       |
of 94.40% is high. This means that if NLR is used to diagnose the occurrence of DVT in 49 respondents, then the right conclusions are obtained in 46 patients. Clinically, the AUC NLR value is satisfactory because it is higher than the minimum AUC value expected by researchers, which is 70.00%. The best cut-off point was 8.20  

Table 2  Validity Test of NLR, PLR, and D-Dimer against DVT Events

| Variable | Positive (N=39) | Negative (N=10) | Sensitivity (%) | Specificity (%) | NPP (%) | NPN (%) | Accuracy (%) | RR | p  
|----------|----------------|----------------|----------------|----------------|---------|---------|--------------|----|----  
| NLR      | ≥ 8.20         | 29             | 74.30          | 90.00          | 96.60   | 47.30   | 77.50        | 1.80| 0.000  
|          | < 8.20         | 10             | 1              |                |         |         |              |    |  
| PLR      | ≥ 159.66       | 30             | 76.90          | 90.00          | 96.70   | 50.00   | 79.50        | 1.90| 0.050  
|          | < 159.66       | 9              | 1              |                |         |         |              |    |  
| D-Dimer  | ≥ 0.50 µg/ml   | 36             | 92.30          | 50.00          | 87.80   | 62.50   | 83.60        | 2.30| 0.001  
|          | < 0.50 µg/ml   | 3              | 5              |                |         |         |              |    |  

Figure 2 shows the ROC curve of PLR, whereas the AUC value was 92.10%. Statistically, the AUC value of 92.10% is also quite high. This means that if PLR is used to diagnose the occurrence of DVT in 49 respondents, then the right conclusions are obtained in 45 patients. Clinically the AUC of PLR value is satisfactory because it is greater than the minimum AUC value expected by researchers, which is 70.00%. The best cut-off point is 159.66. The validity test of NLR, PLR, and D-Dimer is done based on the cut of point value then crosstabulation so that the data obtained as Table 2.

Table 2 shows the cut-off point NLR variable ≥ 8.20 with positive DVT events of 29 respondents and negative DVT events of 1 respondent. In comparison, the NLR <8.20 obtained fewer positive DVT events, i.e., 10 respondents and 9 DVT negative events. The sensitivity test results based on the 2×2 table found 74.30%, specificity 90.00%, positive predictive value (PPV) 96.60%, negative predictive value (NPV) 47.30%, and accuracy of 77.50%. The RR was found higher than 1, then NLR increases the risk of DVT 1.80 times higher significantly (p=0.000) (Table 2).

The cut-off point PLR variable ≥ 159.66 with positive DVT incidence of 30 respondents and negative DVT incidence of 1 respondent while PLR <159.66 obtained fewer positive DVT events, i.e., 10 respondents and 9 DVT negative events. The sensitivity test results based on the 2×2 table found 76.90%, specificity 90.00%, positive predictive value (PPV) 96.70%, negative predictive value (NPV) 47.30%, and accuracy of 77.50%. Based on the 2×2 table, the relative risk (RR) value is 1.90. The

Table 3  Combination of NLR and PLR and D-Dimer against DVT events

| Variable | Positive (N=39) | Negative (N=10) | Sensitivity (%) | Specificity (%) | NPP (%) | NPN (%) | Accuracy (%) | RR | p  
|----------|----------------|----------------|----------------|----------------|---------|---------|--------------|----|----  
| NLR-PLR Combination | High | 29 | 1 | 74.30 | 90.00 | 96.60 | 47.30 | 77.50 | 1.80 | 0.001  
|          | Low | 10 | 9 |              |         |         |       |       |       |    |  
| D-Dimer  | ≥ 0.50 µg/ml | 36 | 5 | 92.30 | 50.00 | 87.80 | 62.50 | 83.60 | 2.30 | 0.001  
|          | < 0.50 µg/ml | 3  | 5  |              |         |         |       |       |       |    |  

Table 4  Relationship of the Combination of NLR and PLR with D-Dimers

| Variables | r     | p   |
|-----------|-------|-----|
| The combination of NLR and PLR with DVT events | 0.532 | 0.001 |
| D-Dimer with DVT events | 0.461 | 0.001 |
| The combination of NLR and PLR with D-Dimer | 0.215 | 0.138 |
RR was found higher than 1, then PLR increases the risk of DVT 1.90 times higher significantly (p=0.050) (Table 2).

Table 3 shows the variable combination of NLR and PLR with positive DVT events of 29 respondents and negative DVT events of 11 respondents. In comparison, the combination of NLR and PLR with low DVT events obtained fewer positive DVT events, i.e., 10 respondents and 9 DVT negative events. The sensitivity test results based on the 2×2 table found 74.30%, specificity 90.00%, positive predictive value (PPV) 96.60%, negative predictive value (NPV) 47.30% with an accuracy of 77.50%. Based on the 2×2 table, the RR value is 1.80. The RR was higher than 1 indicates that the combination of NLR and PLR with DVT events increases the risk of DVT significantly (p=0.001) (Table 3).

D-Dimer cut off points ≥ 0.5 µg/ml with positive DVT events were 36 respondents and negative DVT events were 5 respondents. In comparison, D-dimers <0.5 µg/ml obtained fewer positive DVT events, i.e., 3 respondents and events DVT negative 5 respondents. The sensitivity test results based on the 2×2 table found 92.30%, specificity 50.00%, positive predictive value (PPV) 87.80%, negative predictive value (NPV) 62.50% with an accuracy of 83.60%. Based on the 2×2 table, the RR value is 2.30. The RR was higher than 1 indicates that D-Dimer increases the risk of DVT significantly (p=0.001) (Table 3).

Table 4 shows the correlation between the combination of NLR and PLR with the occurrence of DVT obtained with the value r=0.532 and p=0.001, which means the combination of NLR and PLR is strongly significant correlated with the incidence of DVT (Table 4). The correlation of D-Dimer with the occurrence of DVT was obtained with the value of r=0.461 and p=0.001 which means that the D-Dimer was moderately related to the occurrence of DVT (Table 4). However, the correlation between the combination of NLR and PLR with D-Dimer was obtained with the value of r=0.215 and p=0.138, which means the combination of NLR and PLR was not significantly correlated to D-Dimer (Table 4).

DISCUSSION
The results showed the average age in the study was obtained with age 53.10±13.40 years with the most respondents were male. The average age in the study of Ming L et al., was almost similar with the recent findings. The incidence of DVT increases with age, around 1 per 10,000-20,000 population under the age of 15 years to 1 per 1000 population over the age
of 70 years. The incidence of DVT in Asian races is reported to be lower than in Caucasians, African-Latin Americans, and the Asia Pacific. There was no significant difference in incidence between men and women.

NLR values was obtained with an average of 9.07±4.20 and PLR was 183.55±66.52. These results are slightly different from the research of Artoni et al., which obtained an average NLR value in the study of 1.80±0.80 and PLR with an average of 124.30±45.90. The difference finding of this study could be related to the difference in the number of samples involved in the study.

The cut-off point of NLR in this study was 8.20. This cut-off point was different from the study of by Ming L et al., which found a cut-off point value of NLR 1.76 with a sensitivity of 83.50% and a specificity of 41.00%. NLR has known as a reflection of the balance of innate immune response (neutrophils) and adaptive immunity (lymphocytes). The previous studies that showed the results of an increase in NLR were associated with an increase in the concentration of various proinflammation-cytokines that cause DNA damage as well as risk of malignancy.

Increased NLR can cause increased mortality and decreased survival in patients with cardiovascular disease. The results of studies with a different cut-off points by Mouabbi J et al. obtained NLR results with values> 3.4 in patients with complaints of swelling at lower extremities by giving positive results when evaluated with Doppler ultrasound. The sensitivity value in the previous study was 90.20%, and the specificity was 80.40%.

PLR in this study, based on the ROC curve, has an AUC value of 92.10%. This means that if PLR is used to diagnose the occurrence of DVT in 49 respondents, then the true diagnosis is obtained in 45 patients (91.83%) with the best cut of points obtained 159.66. Platelets are indispensable for hemostasis, vascular integrity, angiogenesis, inflammation, acquired immunity, wound healing, and cancer biology. The most important thing from platelets is to act as a “first responder” when the wound is exposed to the extracellular matrix and intracellular components occur after an injury; a number of platelet receptors will recognize the protein matrix and will trigger platelet activation, adhesion, aggregation, and stabilization. Once activated, the platelet changes shape and degranulates to release growth factors and bioactive lipids into the bloodstream. This cyclic process will carry and aggregate platelets and cause thrombogenesis. This process will result in wound closure or can even recognize the circulating pathology.

High platelet counts associated with low lymphocytes are associated with poor outcomes.

The importance of lymphocytes has been investigated in several studies. Lymphocytes are associated with their cytotoxic function. PLR is a marker of the primary hemostasis process and the inflammatory pathway, where this calculation has more informative results than a single platelet count. A retrospective study in Canada by Mouabbi J et al. obtained PLR results > 260 in patients with complaints of swelling in lower extremities by giving positive results when evaluated with Doppler ultrasound. The sensitivity value in the study was 62.75%, and specificity was 98.00%.

A standard in the diagnosis of DVT is still based on D-Dimer results. D-Dimer is a global biomarker of active coagulation and fibrinolysis commonly used in clinical algorithms in the diagnostic workup of patients with suspected VTE. VTE itself is a stage of occurrence of DVT that can repeatedly occur 30%-40% in the 10 years since the first event.

This study found that NLR sensitivity based on 2×2 table was 74.3%, specificity was 90%, positive predictive value was 96.6%, negative predictive value was 47.3% with an accuracy of 77.5%. Based on the 2×2 table, the RR value is 1.8. RR> 1, the NLR increases the risk of DVT with a p-value of 0.000 compared to the D-Dimer based on the 2×2 table found 92.3%, specificity 50%, positive predictive value 87.8%, negative predictive value 62.5% with accuracy 83.6%. Based on the 2×2 table, the RR value is 2.3. RR> 1, then D-Dimer increases the risk of DVT with a p-value of 0.001.

Sensitivity illustrates the percentage of effects on samples with positive test results. The calculated results after being entered into the formula show that D-Dimer has higher sensitivity compared to NLR. Specificity is the proportion of samples that are positive with NLR. The results of the 2×2 table show a higher NLR specificity compared to D-Dimer. This means that NLR showed the proportion of samples that were truly positive DVT. Positive predictive value is the proportion of patients who are truly positive among all samples that showed positive confirmation test results. This value explains how likely a positive result is showing a DVT patient. The results showed positive predictive value was shown to be higher with NLR. The negative predictive value is the proportion of patients who is truly negative among all samples that shows negative confirmation test results. Negative predictive results were obtained smaller indicated by NLR. The result of higher accuracy rate and high sensitivity with D-Dimer shows that D-Dimer is still a standard diagnostic test for DVT, but if D-Dimer examination cannot be performed then, NLR can be used for screening for DVT.
The results of the Querol EY and Rosales C stated that neutrophils are the first leukocytes that migrate from the blood to where there is injury or infection to kill pathogens and get rid of cellular debris. Neutrophils migrate to the site of inflammation and infection, which is the place to recognize and phagocytosis of invading microorganisms in order to kill them through cytotoxic mechanisms. This process involves a molecular mechanism that coordinates cell polarization, receptor delivery, and activation of integrins to the farthest places from migrating neutrophils following chemotaxis. When they arrive at the site of infection, neutrophils actively phagocytose microorganisms or form neutrophil extracellular traps (NETs) to trap and kill pathogens. NADPH reduces oxidase complexes in phagosome membranes to create reactive oxygen species (ROS) and delivery of proteolytic enzymes into phagosomes to initiate destruction and get rid of pathogens. Neutrophils are potent regulators of inflammation through the release of pro-inflammatory factors and some cytokines. Neutrophils have two roles in triggering and controlling inflammation. The mechanisms that control the result have not been fully described, but the opposing functions are very balanced.

The NLR can be easily calculated from the results of a complete blood test and is an easily obtained marker that can indicate the status of inflammation in the body. Although in some literature, the mechanism of using the NLR as an inflammatory marker cannot be explained in detail, but the NLR is quite often used as an inflammatory marker. The NLR reflects the balance between the response of innate immunity (neutrophils) and adaptive immunity (lymphocytes). The elucidation shows that in severe systemic inflammation such as severe sepsis and septic shock, the body’s immune system responds with an increase in the ratio of neutrophils to lymphocytes when compared to mild systemic inflammatory conditions. Due to the rise in the number of neutrophils and a decrease in the number of lymphocytes will increase the value of the absolute ratio between neutrophils and lymphocytes, when compared with patients without a systemic inflammatory reaction. As the NLR increases, the risk of morbidity and mortality of patients characterized by damage and organ failure will increase.

The Bakirci et al., in 2015 study involving 111 respondents stated that the AUC NLR value obtained by 84.90% was lower than the results of this study. However, the sensitivity was 74.30% and the specificity was 90.0% while the Bakirci research et al., found a sensitivity value of 88.2% and a specificity of 67.6%. A study by Bakirci et al., concluded that NLR could be used as a useful marker to determine venous thrombosis.

The results of the Artoni A et al., study stated that NLR and PLR were simple and easy parameters to do with all blood counts and have completed information on inflammatory conditions and homeostasis. A study by Artoni A et al., involved 1,159 respondents comparing the relationship between NLR and PLR with the incidence of venous thromboembolism, cerebro-venous thrombus with healthy individuals. The results of this study found that high NLR and PLR were not associated with venous thromboembolic events and thrombus in cerebral veins.

The results of a combination of NLR and PLR on the incidence of DVT were obtained with high sensitivity, specificity, and accuracy. The recent findings also suggest a significant moderate correlation between the combination of NLR and PLR to the incidence of DVT. The relationship between D-Dimer with the occurrence of DVT was also found a moderately correlated to the occurrence of DVT. However, the combination between NLR and PLR with D-Dimer was obtained a weak significant correlation to the DVT events. A previous study by Ming et al., involving 115 respondents with DVT found that high PLR was observed in patients with DVT. A NLR with D-Dimer was found to be an independent factor associated with DVT. NLR is expressed as a potential diagnostic value in DVT. The study of Ming et al., further concluded that the cut-off point value of NLR was 1.76 with lower specificity of NLR and PLR compared to D-Dimer. The results of research Yao C et al., also stated that NLR and PLR are independently related to DVT. Still, the results of the ROC curve show low results so that the accuracy of NLR and PLR to predict DVT still needs to be done research especially in patients with total joint arthroplasty.

**CONCLUSION**

Based on the recent study, there is a moderate significant correlation between the combination of NLR and PLR with the incidence of DVT. The D-Dimer was also found to be moderately correlated to the incidence of DVT, whereas the combination of NLR and PLR was found to be weak insignificant correlation to D-Dimer. D-Dimer in this study is still the main examination followed by Doppler ultrasound of lower extremities because the results of the study show the D-Dimer sensitivity value is higher than NLR and PLR as well as a combination of NLR and PLR, the examination of NLR and PLR combination has several advantages such as low.
cost, easy to do, simple, fast and routine results done in all health facilities in Indonesia.

CONFLICT OF INTEREST
None.

ETHICS CONSIDERATION
This study was declared ethical by the Udayana Medical Faculty Research Unit prior to the study being conducted.

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AUTHOR CONTRIBUTION
All of the authors are equally contributed to the study from the conceptual framework, data gathering, data analysis, until reporting the results through publication.

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