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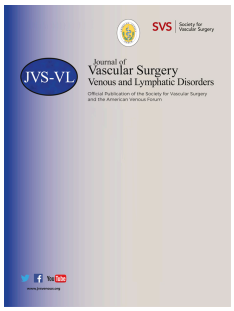

EVALUATION OF SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) IN ACUTE DEEP VENOUS THROMBOSIS: A PROPENSITY-MATCHED ANALYSIS

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EVALUATION OF SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) IN ACUTE DEEP VENOUS THROMBOSIS: A PROPENSITY-MATCHED ANALYSIS.

Short title: Systemic Inflammatory Markers in Venous Thrombosis

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An Original Paper

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Author Note

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Author contributions

Mehmet Tort: Conception and design, administrative support, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

Fehim Can Sevil: Conception and design, provision of study materials or patients, manuscript writing, final approval of manuscript.

Hülya Sevil: Collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

Necip Becit: Conception and design, administrative support, provision of study materials or patients, collection and assembly of data, manuscript writing, final approval of manuscript.

Data Availability Statement

Data cannot be shared for ethical reasons. The data underlying this article cannot be shared publicly due to the retrospective nature of the study and because the consent of the patients was not obtained for sharing. The data are contained in the closed electronic system of a public hospital. If data are requested, data can be provided by hiding patient information. However, the ethics committee is very determined to protect personal data. The data will be shared on reasonable request to the corresponding.

EVALUATION OF SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) IN ACUTE DEEP VENOUS THROMBOSIS: A PROPENSITY-MATCHED ANALYSIS.

Deep vein thrombosis (DVT) progressing to pulmonary embolism is an important cause of mortality and morbidity worldwide. Today, color Doppler ultrasonography (CDUS) is the most effective method in the diagnosis of DVT examination method. The systemic immune-inflammatory index (SII) has been introduced as a new indicator of comprehensive systemic immune-thrombosis and inflammatory status in the body. We think that SII may be more specific and sensitive than NLR and PLR.

In this study, it was aimed to evaluate the predictive potential of systemic immune-inflammatory index (SII), neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) in the diagnosis of DVT.

Methods

The data of patients older than 18 years of age who were diagnosed with acute DVT in our hospital between June 2017 and June 2021 were retrospectively reviewed. Between these dates, the data of 155 patients with acute DVT and 179 healthy control patients without DVT were included in the study. Propensity score analysis (1:1) was performed on it to eliminate the difference between the groups. 63 patients from both groups were included in the study.

Results

When CBC parameters were examined between patients with acute DVT and the control group, Hemoglobin (Hg), Hematocrit (Htc), Lymphocyte (Lym) and Platelet Distribution Width (PDW) were lower in the DVT group. On the other hand, White Blood Cell (WBC), Neutrophil (Neu), Platelets (Plt), NLR, PLR, SII and Mean Platelet Volume (MPV) were found to be higher

in the DVT group. The changes in Hg (p=0.001), Htc (p=0.001), WBC (p=0.001), Neu (p=0.001), Lym (p=0.001), Plt (p=0.001), NLR (p=0.001), PLR (p=0.001), SII (p=0.001) and MPV (p=0.031) were significant in the statistical analysis, but the changes in PDW (p=0.794) were not

The AUCs for NLR, PLR were 0.797 (95% CI: 0.747-0.848, p < 0.001) and 0.788 (95% CI: 0.737-0.840, p=0.01), respectively. A sensitivity of 71.0% and a specificity of 68.7% were found for NLR >3.00. A sensitivity of 70.3% and a specificity of 68.5% were found for PLR >142.66.

The AUC analysis result for SII was 0.861 (95% CI: 0.820-0.902, p < 0.001). A sensitivity of 78.1% and a specificity of 73.1% were found for SII >755.54.

Conclusions

In conclusion, systemic immune-inflammatory index can be used as an auxiliary diagnostic test in patients with venous thrombosis. This parameter is superior to NLR and PLR with its high sensitivity and specificity in venous thrombosis patients.

Keywords: CBC, Deep Venous Thrombosis, NLR, PLR, Systemic Immune-Inflammation Index

EVALUATION OF SYSTEMIC IMMUNE-INFLAMMATION INDEX (SII) IN ACUTE DEEP VENOUS THROMBOSIS: A PROPENSITY-MATCHED ANALYSIS.

Introduction

Deep vein thrombosis (DVT) progressing to pulmonary embolism is an important cause of mortality and morbidity worldwide [1]. DVT that cause pulmonary embolism are in the third place among deaths due to all cardiovascular diseases. [2]. According to previous studies, DVT is associated with an inflammatory response [3-4]. In particular, neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) were found to increase significantly in DVT [5-7]. Systemic immune-inflammation index (SII) was first described in 2014 and its prognostic value has been demonstrated in patients with hepatocellular carcinoma [8]. SII calculated according to neutrophil, lymphocyte and platelet counts (SII=platelets count × neutrophil/lymphocyte ratio), allows patients to assess the inflammatory and immune status simultaneously [9]. SII has the potential to be more definitive than the PLR or NLR alone [10]. There are many studies showing the relationship between SII and malignancies [10-11]. However, SIIE have not been studied as extensively as other inflammatory markers in venous thromboembolic phenomena.

The aim of this study is to evaluate the usability of the SIIE value calculated at the time of diagnosis as an auxiliary parameter in the diagnosis of DVT.

Methods

Study Design

Data from patients older than 18 years diagnosed with acute DVT at our hospital were retrospectively reviewed between June 1, 2017, and June 1, 2021. The data of the patients were analyzed retrospectively and recorded analogously (Supplement Figure 1). Patients diagnosed

with DVT within two weeks from the time of development of clinical symptoms and supported by Color Doppler Ultrasonography (CDUS) findings were considered to have acute DVT [12]. All DVT patients who met the study criteria and were treated as an outpatient or hospitalized between the specified dates were included in the study. Both the patient group and the control group were formed from the same region population. All of the blood and Doppler USG tests used were performed in our hospital. Age, gender, venous CDUS findings, chronic diseases and pre-treatment blood tests of these patients were obtained using the hospital information automation system. In addition to demographic characteristics such as age and gender, the presence of diabetes mellitus, chronic obstructive pulmonary disease, history of stroke, hypertension, renal failure, malignancy, genetic thrombogenic diseases and peripheral arterial disease were examined. The medical treatments used by the patients were recorded.

In accordance with the European Society of Cardiology 2018 guidelines, patients with systolic blood pressure above 140 mm/Hg and diastolic above 90 mm/Hg, and patients who received medical treatment with the diagnosis of hypertension before were considered hypertensive. Diabetes mellitus patients diagnosed or receiving medical treatment; patients with a plasma glucose value of ≥200 mg/dL were accepted as DM in accordance with The American Diabetes Association (ADA) 2022 guideline. Patients receiving routine hemodialysis or peritoneal dialysis treatment; Patients with a glomerular filtration rate of less than 60 mL/min/1.73 m2 for more than 3 months were included in the patient group with renal failure in accordance with the DOQI guideline recommendations. Patients with peripheral arterial disease consisted of patients diagnosed by multislice computed tomography or conventional angiography.

Patients with a history of venous thrombosis or chronic venous thrombosis, deep or superficial venous insufficiency, malignancy, pregnancy, pulmonary embolism, anticoagulant

and antiplatelets therapy, and genetic thrombosis risk (such as protein C resistance, factor V Leiden mutation, and antithrombin III deficiency) were excluded from the study. Patients with active infection, receiving antibiotic, antiviral and anti-inflammatories therapy, trauma, bone frakture and patients who had major surgery in the last one month were not included in the study because CBC parameters may cause statistically erroneous results. In addition, Covid-19 patients with another thrombogenic risk between the study dates were not included in the study because it affected inflammatory parameters. Blood procalcitonin and C-Reactive Protein (CRP) values were measured in patients with symptoms (fever, malaise, etc.) and clinical signs of active infection. Patients with active infection according to the infectious diseases guidelines were excluded from the study [13]. Between study dates, 155 patients with acute DVT were identified who met the above criteria.

Between the specified dates, 179 outpatients who did not have DVT and met the exclusion criteria of our study were determined as the control group. Age, sex, venous CDUS findings, chronic diseases, and CBC parameters at the time of diagnosis of these patients were evaluated using the hospital information automation system Nucleus v9.36.48. Propensity scores analysis (PS) was performed to reduce the bias rate as the baseline characteristics of the two groups were quite different. A multivariate logistic regression model was used to estimate the PS of the study population. PS matching was performed, and the non-parsimonious logistic regression propensity model included the following 8 variables: age; sex; chronic obstructive pulmonary disease (COPD); history of stroke; diabetes mellitus (DM); renal dysfunction (RD); hypertension (HT); peripheral artery disease (PAD). After the estimation of the PS of each participant, A 1:1 matched analysis using the nearest-neighbor matching method was performed, unmatched patients were excluded from this study. The balance was assessed by standardized difference and c statistics.

After PS, 63 patients from both groups were included in the study (Figure 1). NLR, PLR and SII values of these hemogram parameters were calculated with the help of SPSS Statistics data analysis program.

Statistical analysis

The mean ± standard deviation (SD) and median (min-max) were used to express continuous variables, while frequencies and percentages were used to express categorical variables. In order to compare the parameters of both groups, independent sample t-test was used for continuous variables with normal distribution, and Mann Whitney U test was used for continuous variables that did not show normal distribution. The chi-square test was used to test for categorical variables. Statistical analyses were performed using SPSS v. 24.0 (SPSS, Inc., Chicago, IL, USA) for Windows. The significance level was set at $p<0.05$.

Ethics committee

The study protocol adhered to the guidelines stipulated in the Declaration of Helsinki and was approved as an electronic medical record-based retrospective study by the Institutional Review Board of Afyonkarahisar Health Sciences University (with the decision dated 01/04/2022 and numbered 2022/185); as such, which waived the requirement for obtaining informed consent from the patients prior to study participation.

Results

Of the patients in the DVT group, 37 (58.7 %) were male, and 26 (41.3%) were female. The patients' mean age was 55.6±11.2 years (range, 28-83 years). Before PS; the common femoral vein was the most common DVT site in 69 patients (44.5 %). Popliteal vein thrombosis was detected in 40 patients (25.8%), while iliofemoral vein thrombosis was detected in 38

patients (24.5%). Eight patients had axillary and subclavian vein thrombosis in the upper extremities (5.5%). After PS, 25 (39.7%) common femoral, 21 (33.3%) popliteal, 14 (22.2%) iliofemoral, three (4.8%) axillary and subclavian DVT were included in the study.

Of the 63 healthy persons, 38 (60.3%) were men and 25 (39.7%) were women. The mean age of the group, which consisted of healthy subjects, was 58.1±12.1 years (range 26-84 years). The demographic characteristics and comorbidities of the patients are summarized in Table 1.

When CBC parameters were examined between patients with acute DVT and the control group, Hemoglobin (Hg), Hematocrit (Htc), Lymphocyte (Lym) and Platelet Distribution Width (PDW) were lower in the DVT group. On the other hand, White Blood Cell (WBC), Neutrophil (Neu), Platelets (Plt), NLR, PLR, SII and Mean Platelet Volume (MPV) were found to be higher in the DVT group. The changes in Hg (p=0.001), Htc (p=0.001), WBC (p=0.001), Neu (p=0.001), Lym (p=0.001), Plt (p=0.001), NLR (p=0.001), PLR (p=0.001), SII (p=0.001) and MPV (p=0.031) were significant in the statistical analysis, but the changes in PDW (p=0.794) were not (Table 2).

In addition, statistical comparisons of ROC curve analyzes and AUC values of parameters determined to be independent predictors of DVT in multivariate analysis were performed (Figure 1). The AUCs for NLR, PLR were 0.797 (95% CI: 0.747-0.848, $p < 0.001$) and 0.788 (95% CI: 0.737-0.840, p=0.01), respectively. A sensitivity of 71.0% and a specificity of 68.7% were found for NLR >3.00. A sensitivity of 70.3% and a specificity of 68.5% were found for PLR >142.66.

The AUC analysis result for SII was 0.861 (95% CI: 0.820-0.902, $p < 0.001$). A sensitivity of 78.1% and a specificity of 73.1% were found for SII >755.54. (Figure 2).

Discussion

In this retrospective observational study, it was determined that the SII value, which has recently been used as a new bioinflammatory marker, is superior to NLR and PLR with higher specificity and sensitivity rates in DVT patients. In addition, we think that it can be used to support the diagnosis by evaluating together with symptoms and clinical findings in patients who cannot undergo doppler USG.

Studies have shown that there is a close relationship between inflammation and thrombosis. While inflammation inhibits fibrinolytic activity, it increases thrombosis by stimulating thrombotic activity and platelets. [14]. An experimental study in mice is noteworthy in explaining the relationship between inflammation and thrombosis. According to the results of this study, it was found that neutrophils are responsible for the stimulus that initiates thrombus formation in vivo and platelets play a role in the spread of thrombosis [15] Based on this relationship between DVT and inflammation, the effectiveness of E-Selectin and P-Selectin inhibitors in the treatment of DVT has been determined. [16-17]. It is known that thrombocytosis is an important risk factor in the etiology of DVT. [18]. In line with these findings, it is possible to see platelet elevation with inflammatory findings in DVT patients.

Based on this relationship between thrombosis and inflammation, the effectiveness of inflammatory markers NLR and PLR parameters in the diagnosis of DVT has been investigated and it has been stated that NLR and PLR can be used as an auxiliary test in the diagnosis of DVT [3,5-7]. In our study, NLR and PLR levels, which can be calculated from the hemogram parameters of the patients, were found to be significantly higher in the DVT patient group ($p=0.001$). NLR and PLR hemogram parameters are easily calculated data and we determined that they can be used as an auxiliary diagnostic test in DVT patients as in the literature.

Recently, the systemic immune-inflammatory index (SII) has been introduced as a novel indicator of the comprehensive systemic immun-thrombosis and inflammatory status in the body. Compared with the same type of indicators such as NLR, PLR and MLR, which integrate only two cell types (lymphocytes, neutrophils or monocytes), the advantage of SII is that it integrates three types of cells (lymphocytes, neutrophils and platelets). Since then, SII has attracted the attention of researchers, and numerous studies have reported that SII can be a valuable index to predict clinical outcomes for inflammatory diseases, myocardial infarction and malignant tumors [19]. Although SII is a more specific new bioinflammatory marker than NLR and PLR [10], we could not find any studies of DVT in the literature except in patients with pulmonary embolism [20]. SII parameter, which allows the evaluation of neutrophil count, lymphocyte count and platelet count together, was observed significantly higher in the DVT group than in the control group (P=0.001).We think that SII, which allows the evaluation of neutrophil, leukocyte and platelet counts together, will be more specific and sensitive than NLR and PLR values based on separate neutrophil and platelet evaluations for venous thrombosis. According to the AUC results calculated for NLR and PLR in our study, the sensitivity was 71.0% and the specificity was 68.7% for NLR>3.00. For PLR>142.66, the sensitivity was 70.3% and the specificity was 68.5%. On the other hand, the results of the analysis of AUC values of SII support our hypothesis, and it was seen that SII is a more sensitive (78.1%) and specific (73.1%) test than NLR and PLR. Doppler ultrasonography is still the most reliable non-invasive test for venous system diseases of the lower and upper extremities [21]. 78.1% sensitive and 73.1% specificity may be insufficient to make a new diagnosis alone, but we think that the significance will increase when evaluated together with the symptoms and examination findings of the patients. With new studies on SII, its usability in the follow-up of patients receiving treatment can be investigated.

High platelet values continue to be a risk factor for DVT [18]. In our study, when the group with DVT and the group consisting of healthy individuals were compared, the platelet count was high in the DVT group, which was consistent with the literature. This height was statistically significant (p=0.038). Neutrophils are responsible for the inflammatory process in venous thrombus formation, which is considered a double-edged sword during thrombosis [22]. In our study, the number of neutrophils was higher in the DVT group (P=0.001) and the leukocyte count was lower in the DVT group compared to the healthy group (p=0.001). High platelet and neutrophil values in deep vein thrombosis patients are compatible with the general literature and support the close relationship between thrombosis and immunological relationship [4,7].

Low hemoglobin and hematocrit levels were independent risk factors for DVT in our study. Similarly, low hemoglobin values draw attention in some studies on DVT and cardiovascular diseases. [3,23-24]. We believe that this situation may be caused by the common etiology of DVT and anemia and the secondary effect of impaired coagulation. However, since the aim of our study was not to determine the etiology of low hemoglobin and hematocrit, the etiological conditions caused by low hemoglobin and hematocrit were excluded from the study. A larger study with more samples is needed to explain this situation.

MPV provides information about the size of circulating platelets and is directly related to thrombosis. MPV is known to be an important marker of platelet activity, as larger platelets secrete a wide variety of prothrombotic factors and vasoactive substances that promote inflammation [25]. PDW indicates changes in platelet size [26]. MPV and PDW are markers of platelet activation [27]. In our study, MPV values were found to be higher in patients with DVT than healthy group, and this increase was statistically significant (p=0.031). In other venous

thrombosis studies mentioned in the literature, it was observed that the rate of MPV increased after the development of thrombosis [7,28]. In our study, the PDW value was lower in patients with DVT than in control group. However, the low PDW values in DVT patients were not statistically significant (p=0.794). In a study by Velioglu et al., similar to our study, no significant relationship was found between PDW and venous thrombosis [3]. Increased MPV measurements indicate increased release of larger platelets that are more active in circulation. On the other hand, decreasing PDW suggests that platelet size homogeneity begins to occur as a result of the increase in the number of large platelets in the circulation.

Conclusions

In conclusion, we think that SII may be helpful in the diagnosis of patients with venous thrombosis. This parameter is superior to NLR and PLR with its high sensitivity and specificity in venous thrombosis patients.

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1

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Table 1: Comparative analysis of DVT group and control group in terms of demographic characteristics and comorbidities

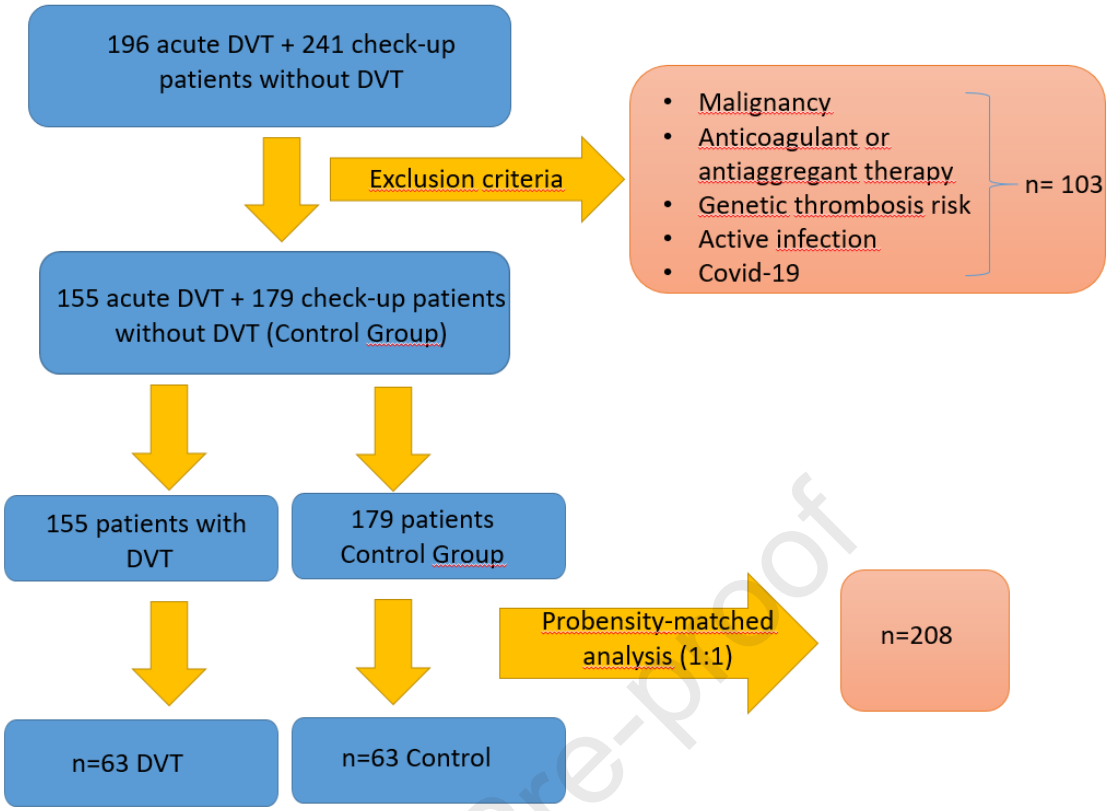
		DVT Group			Control Group			P Value
		Mean±SD	**(N=63)**	**%**	**Mean±SD**	**(N=63)**	**%**	
Age (year)		55.6±11.2			58.1±12.1			**0.829**
Sex								**0.851**
	Male		37	58.7		38	60,3	
	Female		26	41.3		25	39.7	
Diabetes Mellitus			11	17.5		10	15.8	**0.732**
Chronic obstructive pulmonary diseases			9	14.2		9	14.2	**1.000**
Chronik renal failure			4	6.3		3	4.8	**0.843**
Peripheral artery diseases			16	25.4		14	22.2	**0.673**
Hypertension			16	25.4		15	23.8	**0.864**
Cerebrovascular diseases			3	4.7		2	3.2	**0.915**

(DVT: Deep Venous Thrombosis N: Number of patients, SD: Standard deviation)

Table 2: Univariate analysis for deep vein thrombosis and control groups

	DVT Group		Healthy persons		
	Mean	**SD**	**Mean**	**SD**	**P value**
Hemoglobin (g/dL)	12.40	1.88	13.59	1.95	**0.001**
Hematocrit (%)	37.82	5.59	41.20	6.53	**0.001**
White Blood Cell (10 9/L)	9.00	2.32	7.41	1.71	**0.001**
Neutrophil (10 9/L)	6.38	2.01	4.63	1.40	**0.001**
Lymphocyte (10 9/L)	1.66	0.59	2.06	0.68	**0.001**
Platelet (10 9/L)	259.70	93.20	240.58	61.64	**0.038**
Neutrophil-to-lymphocyte ratio (NLR)	4.30	2.05	2.48	1.10	**0.001**
Platelet-to-lymphocyte ratio (PLR)	168.30	62.58	126.35	43.84	**0.001**
Systemic immune-inflammation index (SII)	1074.84	521.41	577.09	241.55	**0.001**
Mean platelet volume (fL)	11.4	1.10	9.7	1.08	**0.031**
Platelet distribution width (%)	13.07	7.56	13.25	2.52	0.794

(DVT: Deep Venous Thrombosis, SD: Standard Deviation)



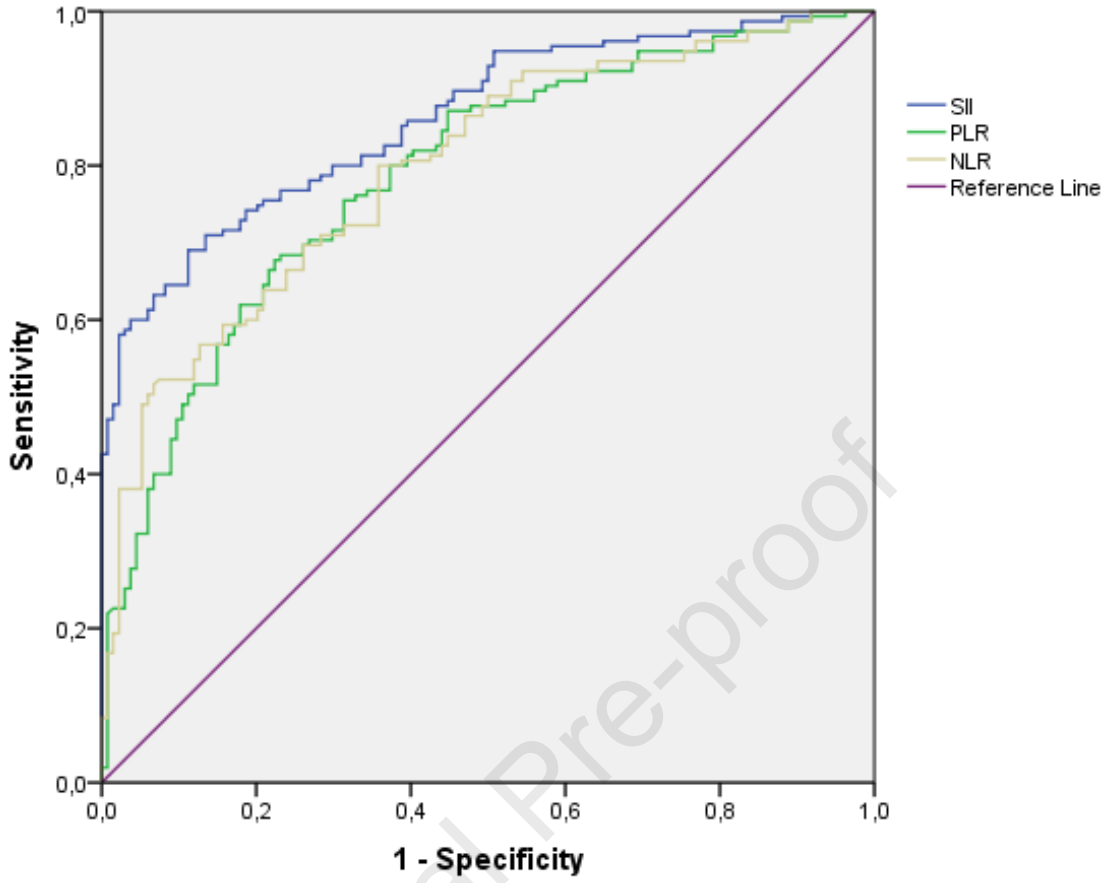


Figure 2: ROC Curve plot for NLR, PLR and SII. The blue line indicates SII, the green line the PLT, the yellow line the NLR, the burgundy line the reference line.

(NLR: Neutrophil-lymphocyte ratio, PLR: Platelet-lymphocyte ratio, SII: Systemic Immune-inflammatory Index)

SII EVALUATION FORM IN PATIENTS WITH VENOUS THROMBOSİS

Name _____ Sex _____ Age _____ ID _____ Date _____

DVT localization: *(If multiple localization, more than one box can be ticked.)*

☐ İliac ☐ Femoral ☐ Popliteal ☐ Crural ☐ Subclavian or Axillary

Other system disorders: *(You can mark more than one)*

☐ DM ☐ COPD ☐ RF ☐ PAD ☐ HT ☐ Malignancy

☐ Cerebrovascular event (Stroke or hemorrhage) ☐ Infection or Covid-19

☐ Coagulopathy ☐ CVD ☐ Use of antiaggregant-anticoagulant drugs

Complete Blood Count: **CBC Date:** _____

Hg:	Htc:	WBC:	Plt:
Neu:	Lym:	PDW:	MPV:
NLR:	PLR:	SII:	

Abbreviations

CVD: Chronic venous disorders

COPD: Chronic obstructive pulmonary disease

DM: Diabetes mellitus

HT: Hypertension

NLR: Neutrophil lymphocyte ratio (Neutrophil count/Lymphocyte count)

PAD: Peripheral artery disease

PLR: Platelet to lymphocyte ratio (Platelet count / lymphocyte count)

RF: Renal failure

SII: Systemic immune-inflammatory index (Platelets count × neutrophil/lymphocyte ratio)

Figure Legends

Table 1: Comparative analysis of DVT group and control group in terms of demographic characteristics and comorbidities

Table 2: Univariate analysis for deep vein thrombosis and control groups

Figure 1: Summary flow diagram of enrolled patients.

Figure 2: ROC Curve plot for NLR, PLR and SII.

Supplement (Figure 1): Retrospective data collection form.