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Research Article

Inflammatory biomarkers in venous thromboembolism: distinguishing proximal from distal DVT and predicting pulmonary embolism

Venöz tromboembolizmde inflamatuar biyobelirteçler: proksimal ve distal DVT ayrımı ve pulmoner emboli öngörüsü

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Abstract

Aim: Deep vein thrombosis (DVT) is a major cause of morbidity and mortality worldwide. Proximal DVT carries a higher risk of pulmonary embolism (PE); however, the distinct inflammatory profiles of proximal and distal DVT remain unclear. This study aimed to compare the distribution of next-generation systemic inflammatory indices (SII, SIRI, AISI, NLR, PLR, MLR) and conventional biomarkers (CRP, D-dimer) and to evaluate the diagnostic and prognostic value of these parameters in predicting PE. Additionally, the effects of demographic and etiological differences between groups on the systemic inflammatory response were analyzed, and the findings were validated using logistic regression models and ROC curve metrics to identify independent predictive markers.

Material and Methods: In this retrospective case-control study, 750 patients (2019–2025) with suspected lower extremity DVT were classified into proximal DVT (n=250), distal DVT (n=250), and Doppler-negative control (n=250) groups. Inflammatory indices (SII, SIRI, AISI, NLR, PLR, and MLR), conventional biomarkers (CRP and D-dimer), and biochemical parameters were evaluated. Group differences were tested using ANOVA/Kruskal–Wallis, while logistic regression and ROC analyses were used to identify predictors of proximal DVT and PE.

Results: Patients with proximal DVT had significantly higher inflammatory markers, CRP, and D-dimer levels than those with distal DVT and the controls (all $p < 0.001$). Distal DVT showed no significant difference from controls except for high SIRI ($p<0.001$). Proximal DVT was also associated with higher creatinine and LDH (lactate dehydrogenase) and lower sodium levels (all $p<0.001$). In multivariate regression, NLR (OR 1.24, $p=0.042$) and D-dimer (OR 1.43, $p<0.001$) independently predicted proximal DVT. For PE, D-dimer showed the highest accuracy (AUC 0.827, sensitivity 95.6%, specificity 61.8%), whereas NLR showed moderate discriminatory power (AUC 0.669).

Keywords: deep vein thrombosis, pulmonary embolism, inflammatory indices, D-dimer, NLR

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Öz

Amaç: Derin ven trombozu (DVT), dünya çapında önemli bir morbidite ve mortalite nedenidir. Proksimal DVT, pulmoner emboli (PE) açısından daha yüksek risk taşısa da, proksimal ve distal DVT'nin inflamatuar profilleri arasındaki farklar henüz netleşmemiştir. Bu çalışmada, yeni nesil sistemik inflamatuar indekslerin (SII, SIRI, AISI, NLR, PLR, MLR) ve geleneksel biyobelirteçlerin proksimal/distal DVT ayrımı ile PE öngörüsündeki tanısal değerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu retrospektif vaka-kontrol çalışmasında, 2019–2025 yılları arasında alt ekstremite DVT şüphesi olan 750 hasta; proksimal DVT (n=250), distal DVT (n=250) ve Doppler-negatif kontrol (n=250) grubu olarak sınıflandırıldı. Sistemik inflamatuar indeksler, CRP, D-dimer ve biyokimyasal parametreler gruplar arasında karşılaştırıldı. Bağımsız öngördürücü belirteçleri saptamak için lojistik regresyon ve ROC eğrisi analizleri kullanıldı.

Bulgular: Proksimal DVT'li hastaların inflamatuar belirteçleri, CRP ve D-dimer düzeyleri, distal DVT ve kontrol grubuna göre anlamlı derecede yüksek bulundu (tümü için $p < 0,001$). Distal DVT ile kontrol grubu arasında yüksek SIRI ($p < 0,001$) dışında anlamlı fark saptanmadı. Çok değişkenli regresyon analizinde, NLR (OR: 1,24; $p = 0,042$) ve D-dimer (OR: 1,43; $p < 0,001$) proksimal DVT için bağımsız öngördürücü olarak belirlendi. PE öngörüsünde D-dimer en yüksek doğruluğu gösterirken (AUC: 0,827; duyarlılık %95,6; özgüllük %61,8), NLR orta düzeyde ayırt edici güce (AUC: 0,669) sahipti.

Sonuç: Yeni nesil inflamatuar indeksler, özellikle NLR, D-dimer ile birlikte proksimal DVT tanısında ve PE riskinin değerlendirilmesinde değerli ve düşük maliyetli araçlardır. Proksimal DVT, distal yerleşime göre çok daha şiddetli bir sistemik inflamatuar yanıtla ilişkilidir.

Anahtar Kelimeler: derin ven trombozu, pulmoner emboli, inflamatuar indeksler, D-dimer, NLR

Introduction

Deep vein thrombosis (DVT) is a significant vascular pathology characterized by thrombotic events in the veins of the lower extremities, which can cause significant morbidity and mortality. DVT develops as a result of the complex interaction between venous stasis, endothelial damage, and hypercoagulability factors, known as Virchow's triad [1]. Its clinical significance stems from the risk of acute pulmonary embolism (PE) and the potential to cause chronic complications, such as post-thrombotic syndrome (PTS), in the long term [2].

DVT is classified into two subtypes based on its anatomical location: distal DVT, which involves veins below the knee, and proximal DVT, which involves the popliteal, femoral, or iliac veins [3]. This distinction is critical in terms of treatment strategies and prognosis, as proximal DVT is known to have more serious consequences in terms of the risk of PE and clinical course [4]. Uncertainties regarding the diagnosis, treatment, and follow-up of isolated distal DVT persist [5, 6]. Recent studies have revealed a strong relationship between thrombosis and inflammation, leading to the development of new-generation inflammatory indices derived from complete blood count parameters, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), Systemic Immune-Inflammation Index (SII), Systemic Inflammatory Response Index (SIRI), and Aggregate Immune System Index (AISI) [1, 7]. While these indices have prognostic value in various cardiovascular diseases and malignancies, studies directly comparing proximal and distal DVT, supported by extensive clinical-demographic datasets, are limited in the literature. There is a significant knowledge gap regarding how the inflammatory profiles of distal DVT differ from those of proximal DVT and healthy controls [8].

The main hypothesis of this study was that new-generation inflammatory indices, such as SII and SIRI, would demonstrate superior diagnostic performance compared to classical markers, such as CRP and D-dimer, in distinguishing proximal DVT from distal DVT and the control group. Secondarily, it is predicted that the prognostic value of these indices will increase when evaluated in conjunction with demographic characteristics, comorbidities, and risk factors.

This study aimed to reveal the role of inflammatory markers in the anatomical subtypes of DVT, evaluate the potential contribution of easily calculable and cost-effective indices in predicting proximal DVT, and compare the demographic, clinical, and etiological characteristics of proximal and distal DVT.

Material and Methods

This single-center, retrospective case-control study was designed and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ankara Bilkent City Hospital Clinical Research Ethics Committee (Date: 05/21/2025, Decision No: TABED 1-25-1301). Owing to the retrospective nature of the study, individual informed consent was not obtained from the patients. Patient data confidentiality and anonymity were maintained throughout the study.

All patients who underwent venous Doppler ultrasound (VDUS) at Ankara Bilkent City Hospital between January 2019 and January 2025 due to suspected lower extremity DVT were retrospectively screened for inclusion. Patient selection was performed using a sequential sampling approach; random case selection or subjective file reviews were not applied. Patients who met the predefined inclusion and exclusion criteria were included in the study, forming a cohort of 750 patients. To minimize selection bias, data were extracted systematically from the hospital's electronic medical record system and picture archiving and communication system (PACS), independent of clinical outcomes. The patient selection and grouping processes are summarized in Figure 1.

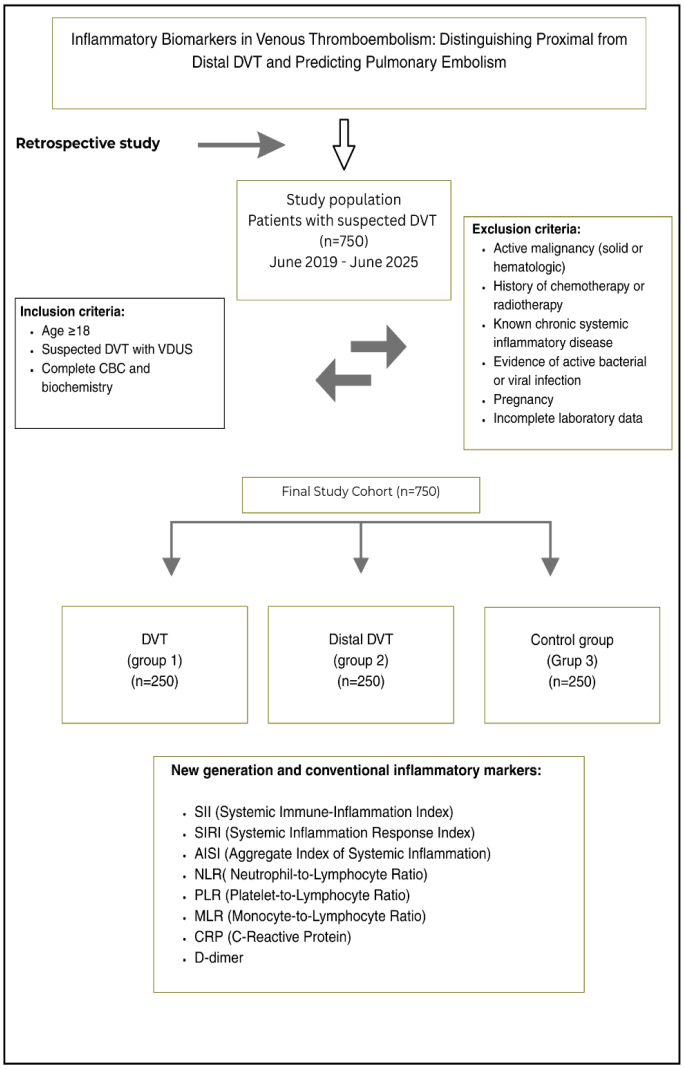

Figure 1. Flow chart of patient selection and study design.

Patients were divided into three groups based on their VDUS findings:

1. Proximal DVT group (n=250): Patients with acute thrombi detected in the popliteal vein or more proximal segments (femoral and iliac veins).

2. Distal DVT group (n=250): Patients with thrombi limited to the infrapopliteal veins (anterior tibial, posterior tibial, and peroneal veins).

3. Control group (n=250): Patients who presented with DVT-like symptoms during the same period but had no DVT detected on VDUS and no known history of DVT.

No direct matching was performed in this study; however, the control group was selected based on symptom similarity to increase the internal validity and minimize potential confounding effects. This method provided a more comparable analysis platform by equalizing the rationale for applying diagnostic tests in the case and control groups.

The inclusion criteria for all groups were age ≥ 18 years, having undergone VDUS due to suspected DVT, and having complete blood count and biochemistry tests at the time of application. Patients with active malignancies, a history of chemotherapy/radiotherapy, chronic systemic inflammatory diseases, signs of active infection, pregnancy, or incomplete laboratory data were excluded from the study.

Complete blood count (CBC), basic biochemical parameters, and D-dimer levels obtained during the initial examination were retrospectively retrieved from the hospital information system. To minimize variability, all analyses were performed using the first venous blood samples taken at the time of diagnosis before any anticoagulant therapy was initiated. The systemic inflammatory indices calculated from these data are shown in Figure 2.

- **Neutrophil-Lymphocyte Ratio (NLR)** = Absolute neutrophil count / Absolute lymphocyte count
- **Platelet-Lymphocyte Ratio (PLR)** = Absolute platelet count / Absolute lymphocyte count
- **Systemic Immune-Inflammation Index (SII)** = (Platelet count × Neutrophil count) / Lymphocyte count
- **Systemic Inflammation Response Index (SIRI)** = (Neutrophil count × Monocyte count) / Lymphocyte count
- **Aggregate index of systemic inflammation (AISI)** = (Neutrophil count × Monocyte count
- × Platelet count) / Lymphocyte count

Figure 2. Calculation formulas of hematological inflammatory indices.

DVT and PE diagnoses were retrospectively confirmed based on clinical and radiological findings in the patient records. DVT was defined based on lower extremity VDUS performed for suspected symptoms using the criteria of non-compressible vein, intraluminal thrombus, and loss of flow. Acute PE was diagnosed by the detection of an intraluminal filling defect in at least one pulmonary artery branch on computed tomography pulmonary angiography (CTPA). Cases based solely on clinical suspicion were excluded.

DVT is classified as provoked or unprovoked, based on the presence of recognized transient or permanent risk factors. Provoked DVT is defined as thrombosis occurring in the context of recent surgery or trauma, prolonged immobility (including immobility associated with medical conditions such as long-distance travel or stroke-related hemiplegia), active malignancy, pregnancy or postpartum period, or hormone therapy.

Patients' anticoagulant treatment protocols were retrospectively obtained from their electronic health records and patient files. Treatment protocols at our center were found to be generally consistent with guidelines [9, 10], and it was determined that the majority of patients received DMAH→VKA or DMAH→NOAC. Treatment approaches were divided into four groups based on the predominant treatment regimen used within the first 30 days after diagnosis:

1. DMAH →VKA (warfarin, with overlap): Patients who received DMAH for at least 5 days and were simultaneously started on VKA (warfarin); maintenance therapy was continued with VKA after reaching an INR ≥2.0.

2. DMAH→NOAC: Patients who received DMAH therapy for 7–15 days after diagnosis and then switched to NOACs, such as apixaban, rivaroxaban, dabigatran, or edoxaban.

3. Direct oral NOAC regimen: Patients treated directly with NOACs without parenteral initial therapy according to protocols defined in randomized controlled trials (e.g., rivaroxaban: 15 mg twice daily for 21 days, then 20 mg once daily; apixaban: 10 mg twice daily for 7 days, then 5 mg twice daily).

4. DMAH monotherapy: Patients treated exclusively with DMAH during the follow-up period who did not switch to oral anticoagulants.

Statistical Analysis

Data are summarized as means, standard deviations, medians, frequencies, and percentages. Categorical variables are expressed as counts and percentages, and continuous variables are reported as mean ± SD or median. The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Intergroup comparisons were performed using ANOVA–Tukey for normally distributed variables, Kruskal–Wallis–Dunn–Bonferroni for non-normally distributed variables, and the chi-square test for categorical variables. The diagnostic power of the inflammatory indices (SII, SIRI, AISI, NLR, PLR, and MLR) and biomarkers (CRP and D-dimer) in predicting proximal DVT and PE was evaluated using receiver operating characteristic (ROC) analysis. The AUC, optimal cutoff values, sensitivity, and specificity were reported. Predictors of proximal DVT were identified by including variables with p<0.05 after univariate analysis in a multivariate logistic regression model (Backward LR). Results are presented as odds ratios (OR) and 95% CI; p<0.05 was considered significant. All statistical analyses were performed using SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA). Microsoft® Excel® MSO for Microsoft 365 (Version 2503) and Microsoft® Visio® 2019 MSO (Version 2505) were used for graphical representation of data distribution. A flowchart was created using Canva Pro.

Results

The baseline demographic and clinical characteristics of the study population are presented in Table 1. The mean age was 46.2 ± 11.5 years in the control group, 55.4 ± 15.7 years in the proximal DVT group, and 54.0 ± 16.4 years in the distal DVT group; both DVT groups were older than the control group. The mean body weight and body mass index (BMI) values were similar among the three groups. There were no differences between the groups in terms of comorbidity prevalence (all p>0.05).

Comparisons of systemic inflammatory indices, classic biomarkers, and hematological and biochemical parameters between the study groups are presented in Table 2. Significant differences were found between the three groups in terms of all inflammatory indices (SII, SIRI, AISI, NLR, PLR, and MLR) as well as CRP and D-dimer levels (p < 0.05). In the proximal DVT group, all indices and conventional biomarkers were significantly higher than those in the distal DVT and control groups (all p<0.001). In the distal DVT group, only SIRI showed a significant increase compared to that in the control group (p<0.001). In biochemical analysis, creatinine and lactate dehydrogenase (LDH) levels were significantly elevated in the proximal DVT group (all p<0.005), whereas sodium levels were low (p<0.05). Additionally, ALT and urea levels were significantly higher than those in distal DVT (p<0.05).

Table 3 compares the clinical variables of the two groups. Unprovoked DVT was more common in the proximal DVT group than in the distal group (61.2% vs. 46.8%; p=0.001). From an etiological perspective, immobilization (13.2% vs. 6.8%; p=0.017), malignancy (7.6% vs. 2.4%; p=0.008), and genetic predisposition (6.4% vs. 2.4%; p=0.024) were significantly higher in the proximal group. In terms of localization distribution, the left side was predominant in both groups (proximal 60.4%; distal 55.6%), and there was no difference in terms of right-sided and bilateral involvement (p>0.05). The frequency of PE was significantly higher in the proximal group (16.8% vs. 1.2%; p<0.01). There were no differences between the groups in terms of anticoagulant use history and treatment models (p>0.05).

In the univariate logistic regression analysis, high SII, SIRI, NLR, PLR, MLR, and D-dimer levels significantly increased the risk of proximal DVT compared with distal DVT (all p < 0.05), whereas age, sex, BMI, and CRP did not show predictive value (p > 0.05). In the multivariate model, only NLR (OR=1.243; p=0.042) and D-dimer (OR=1.426; p<0.001) remained independent predictors (Table 4). In the ROC analysis for PE, D-dimer was the strongest marker (AUC=0.827; p<0.001) and showed high sensitivity (95.6%) and acceptable specificity (61.8%). NLR provided moderate accuracy (AUC=0.669; p<0.01), whereas SII and SIRI had limited discriminatory power (Table 5). As shown in Figures 3, NLR, and especially D-dimer elevation, showed a positive correlation with the likelihood of PE.

Table 1. Comparison of baseline characteristics between control, proximal DVT, and distal DVT groups

		Control group				Proximal DVT				Distal DVT				
		Mean ± Sd			Median	Mean ± Sd			Median	Mean ± Sd			Median	p*
Age		46,18	±	11,54	45,00	55,37	±	15,68	58,00	53,98	±	16,41	57,00	0,010
Gender														
Male	n / %	118		47%				145	58%	119		48%		0,024
Female	n / %	132		53%				105	42%	131		52%		
Weight	n / %	79,48	±	10,91	79,00	79,06	±	11,78	78,00	78,61	±	11,40	77,00	0,613
BMI	n / %	27,80	±	4,98	27,42	28,29	±	5,06	27,32	27,70	±	4,88	26,47	0,310
HT	n / %	57		23%		93		37%		78		31%		0,184
DM	n / %	40		16%		66		26%		51		20%		0,156
HL	n / %	64		26%		86		34%		64		26%		0,190
PAD	n / %	45		18%		62		25%		49		20%		0,147
CRI	n / %	25		10%		9		4%		18		7%		0,650
COPD	n / %	26		10%		29		12%		20		8%		0,393
Smoker	n / %	54		22%		78		31%		64		26%		0,049

SD, standard deviation; BMI, body mass index; HT,hypertansion; DM, diabetes mellitus; HL,hyperlipidemia; PAD, Peripheral arterial disease; CRI, Chronic Renal Injury; COPD, chronic obstructive pulmonary disease
*Statistically significant values at the 95% confidence level (P = 0.05).

Table 2. Baseline Systemic Inflammatory and Conventional Biomarkers across Control, Proximal DVT, and Distal DVT Groups

	Control group[1]				Proximal DVT[2]			Distal DVT[3]				
	Mean±Sd			Median	Mean±Sd		Median	Mean±Sd			Median	p
Coımposite Inflamatuar Indices												
SII	754,89	±	311,21	729,66[2]	1090,64	439,57	1052,73[3]	787,92	±	308,80	751,92	0,000
SIRI	2,48	±	1,14	2,36[23]	3,83	1,69	3,71	2,70	±	1,21	2,59	0,000
AISI	581,04	±	285,36	544,46[2]	922,52	439,24	833,83[3]	630,02	±	298,65	576,70	0,000
NLR	3,20	±	1,14	3,145[2]	4,50	1,57	4,44[3]	3,37	±	1,17	3,18	0,000
PLR	149,19	±	45,54	138,05[2]	178,88	51,68	171,64[3]	150,36	±	42,46	141,42	0,000
MLR	0,48	±	0,11	0,47[2]	0,62	0,15	0,61[3]	0,50	±	0,13	0,50	0,000
Conventional biomarkers												
CRP (mg/L)	3,22	±	4,62	2,5[2]	25,46	25,83	15,78[3]	2,88	±	2,64	2,35	0,000
D-dimer (ng/mL)	1,66	±	3,54	1,15[2]	5,85	3,14	6,24[3]	2,00	±	1,94	1,24	0,000
Basic hematologic parameters												
WBC (x109/L)	7,44	±	1,98	7,14[2]	8,24	2,18	7,905[3]	7,70	±	1,97	7,37	0,000
Hemoglobin (g/dL)	13,36	±	2,39	13,72[23]	11,96	2,43	12,52[3]	12,56	±	2,39	12,92	0,000
Hematocrit (%)	40,49	±	7,73	42,14[23]	37,11	7,66	38,06	38,69	±	7,73	40,35	0,000
Platelet (x109/L)	239,16	±	68,91	219,50	245,52	69,39	227,00	238,82	±	69,01	218,00	0,356
Biochemical parameters												
Urea (mg/dl)	36,97		14,31	35,5[2]	42,12	16,04	41[3]	36,31		13,04	35,75	0,002
Creatinine (mg/dl)	1,09		0,41	1,02[23]	1,17	0,36	1,13	1,10		0,24	1,10	0,000
Sodium (mmol/L)	137,87		5,20	138[23]	139,44	3,42	140,00	139,65		2,97	140,00	0,000
Potassium (mmol/L)	4,45		0,71	4,41	4,48	0,73	4,40	4,54		0,80	4,50	0,366
LDH (U/L)	187,02		50,61	167,5[23]	278,36	91,38	251[3]	219,06		87,25	180,50	0,000
AST (U/L)	35,76		42,83	29,00	33,01	59,38	28,10	28,81		12,44	27,50	0,307
ALT (U/L)	41,11		32,37	36,00	44,91	78,79	39[3]	36,30		19,62	34,00	0,004

Data are presented as mean ± standard deviation (Sd).
SII , Systemic immune–inflammation index; SIRI , Systemic inflammation response index; AISI , Aggregate index of systemic inflammation; NLR , Neutrophil-to-lymphocyte ratio; PLR., Platelet-to-lymphocyte ratio; MLR , Monocyte-to-lymphocyte ratio; CRP , C-reactive protein; DVT , Deep vein thrombosis ; LDH, Lactate Dehydrogenase; AST, aspartate aminotransferase; ALT, alanine aminotransferase
[2] Difference with the proximal DVT group p<0.05 ; [3] Difference with the distal DVT group p<0.05

Table 3. Baseline Clinical and Etiological Differences between Proximal and Distal DVT Patients

	Proximal DVT		Distal DVT		p
	n	%	n	%	
Provoked/Unprovoked by DVT Type					
Unprovoke group	153	61,2%	117	46,8%	0,001
Provoke group	97	38,8%	133	53,2%	0,001
Etiology					
Surgical/trauma history	37	14,8%	46	18,4%	0,279
Immobilization	17	6,8%	33	13,2%	0,017
Malignancy	19	7,6%	6	2,4%	0,008
Genetic factors	16	6,4%	6	2,4%	0,024
Other factors	16	6,4%	12	4,8%	0,437
DVT localization					
Right side	94	37,6%	111	44,4%	0,122
Left side	151	60,4%	139	55,6%	0,277
Bilateral	5	2,0%	0	0,0%	0,061
Pulmonary embolism	42	16,8%	3	1,2%	<0,01
History of anticoagulant use	15	6,0%	7	2,8%	0,081
Anticoagulant type					
DMAH + Warfarin	40	16,0%	36	14,4%	0,618
DMAH + NOAC	139	55,6%	158	63,2%	0,084
Only NOAC	48	19,2%	42	16,8%	0,485
DMAH monotherapy	18	7,2%	12	4,8%	0,259

Abbrev.: DVT, Deep vein thrombosis; LMWH, Low-molecular-weight heparin; NOAC, novel oral anticoagulants.
*Statistically significant values at the 95% confidence level (P = 0.05).

Table 4. Univariate and Multivariate Logistic Regression Analyses of Demographic and Inflammatory Markers Predicting Proximal versus Distal DVT

	Univariate Model				Multivariate Model *			
	OR	95% C.I		p	OR	95% C.I		p
Age	1,013	0,993	1,033	0,215				
Sex	0,803	0,438	1,474	0,479				
BMI	0,984	0,924	1,047	0,604				
Systemic inflammatory markers								
SII	1,001	1,001	1,002	<0,001				
SIRI	1,402	1,186	1,658	<0,001				
NLR	1,573	1,301	1,903	<0,001	1,243	1,008	1,533	0,042
PLR	1,006	1,000	1,012	0,041				
MLR	16,770	2,453	114,675	0,004				
CRP	1,006	0,994	1,019	0,320				
D-dimer	1,475	1,320	1,649	<0,001	1,426	1,270	1,602	<0,001

Abbrev.: DVT, deep vein thrombosis; BMI, body mass index; SII, systemic immune–inflammation index; SIRI, systemic inflammation response index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval.
In the multivariate analysis, variables were reduced using the Backward: Likelihood Ratio (LR) method.
*Statistically significant values at the 95% confidence level (P = 0.05).

Table 5. ROC Curve Analysis of Systemic Inflammatory Markers for Predicting Pulmonary Embolism in Proximal and Distal DVT Groups

Variables	AUC	p	95% CI		Cut-off	Sensitivity	Specifity	PPV	NPV
SIRI	0,635	0,003	0,550	0,719	2,42	84,44%	34,51%	11,31%	95,73%
SII	0,642	<0,01	0,553	0,732	1052,73	55,56%	68,13%	14,71%	93,94%
NLR	0,669	<0,01	0,579	0,759	4,26	66,67%	64,84%	15,79%	95,16%
PLR	0,596	0,033	0,516	0,677	123,19	97,78%	21,32%	10,95%	98,98%
D-dimer	0,827	<0,001	0,777	0,877	4,205	95,56%	61,76%	19,82%	99,29%

Data are expressed as area under the curve (AUC) with 95% confidence interval (CI), optimal cut-off values, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).
Abbrev.:DVT = Deep vein thrombosis; SII = Systemic immune–inflammation index; SIRI = Systemic inflammation response index; NLR = Neutrophil-to-lymphocyte ratio; PLR = Platelet-to-lymphocyte Ratio ; NLR: Neutrophil-to-Lymphocyte Ratio; CRP: C-Reactive Protein;

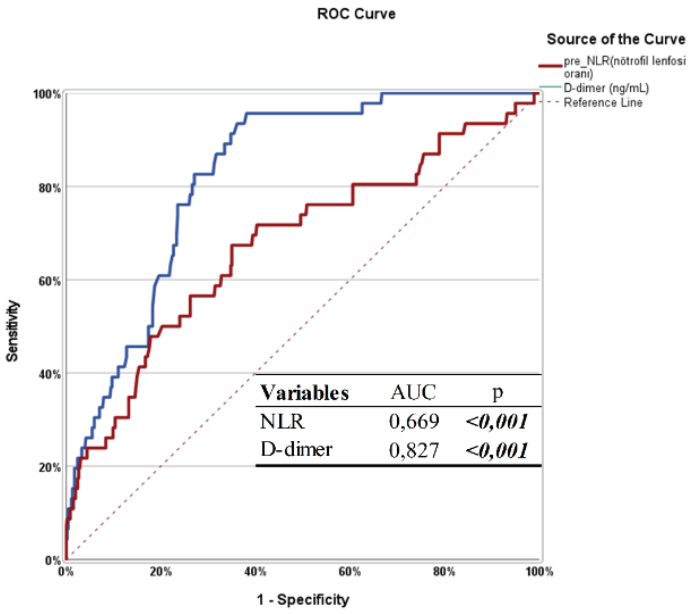

Figure 3. ROC curves of NLR and D-dimer for pulmonary embolism prediction, showing D-dimer as the strongest discriminator (AUC 0.827) compared with NLR (AUC 0.669).

Discussion

This study examined the systemic inflammatory response according to the anatomical subtypes of DVT using next-generation and classic markers. The groups were also compared in terms of inflammatory markers, demographic characteristics, etiological factors, probabilities of PE, and anticoagulant strategies. In the literature, DVT has mostly been evaluated as a single entity, and studies examining the inflammatory profile according to proximal–distal distinction are limited [9, 11]. Our findings provide a unique contribution to the literature by demonstrating that these two subtypes are differentiated by distinct inflammatory mechanisms and clinical outcomes.

The most fundamental finding of our study is that proximal DVT is associated with a much stronger and more widespread systemic inflammatory response than distal DVT and the control group. The significantly higher systemic inflammatory indices in the proximal DVT group indicate that DVT is not merely a local venous occlusion but a complex thromboinflammatory process with systemic repercussions proportional to the thrombus burden and location [12]. Large-volume thrombi forming in the proximal veins cause greater endothelial damage, activating the coagulation cascade and triggering an intense inflammatory response [13]. During this process, platelet and leukocyte activation increases the release of proinflammatory cytokines, such as IL-6, IL-8, and TNF-α, into the circulation; neutrophil and monocyte production increases, while lymphocyte apoptosis accelerates [12,14]. The relationship between DVT and inflammation has been strongly emphasized in both experimental models and clinical studies. Our findings are generally consistent with those of previous studies supporting the association between inflammatory markers and DVT [14,15]. Previous studies have shown that the increase in NLR and PLR detected in DVT [8,16] is specific to proximal DVT. However, the absence of a significant inflammatory response in distal DVT contradicts some previous reports [8,12]. This may stem from the heterogeneous analyses of DVT subtypes. Furthermore, ROC analyses revealed that D-dimer was the strongest predictor of PE, NLR retained its independent predictive value, and SII, SIRI, and PLR had limited predictive power.

In our study, most inflammatory markers in the distal DVT group were at levels similar to those in the control group, with only SIRI showing a significant elevation. This may be related to SIRI's ability to reflect both proinflammatory cell increases (neutrophils and monocytes) and immunoregulatory balance (lymphocytes) on the same scale [17]. In the literature, distal DVT is defined as a subtype that generally does not trigger systemic inflammation due to limited thrombus load and has a lower risk profile in terms of mortality, PTS, and PE compared with proximal DVT [4,18]. However, the significant increase observed only in SIRI in our study indicates that distal DVT is not entirely silent from an inflammatory perspective and that this index may be more sensitive in detecting low-level inflammation than other indices. This finding suggests that considering distal DVT as "benign" carries the risk of overlooking clinical outcomes and that composite indices capable of revealing subclinical inflammatory responses may provide additional prognostic value in this patient group.

Differences in creatinine, sodium, and LDH levels in the proximal DVT group suggest that the thrombotic process may have effects not only at the vascular level but also at the systemic and organ levels of the body. Increased creatinine levels may be associated with impaired renal perfusion, while sodium changes may be related to hemodynamic stress and inappropriate ADH syndrome due to inflammation [4]. Elevated LDH levels may reflect cellular breakdown in large thrombi [4,19]. However, the fact that these parameters did not show significant deviation from the normal reference ranges indicates that, although statistically significant, the differences point to milder organ involvement at the clinical level.

This study shows that proximal DVT is more commonly associated with unprovoked cases and is linked to permanent risk factors such as malignancy, immobilization, and genetic predisposition [20], whereas distal DVT is mostly triggered by temporary causes such as surgery and trauma [18,21]. This difference suggests that proximal thrombi reflect a more aggressive and systemic prothrombotic background, whereas distal thrombi reflect transient risk factors. The high prevalence of unprovoked proximal DVT is clinically significant in terms of recurrence risk and the need for long-term anticoagulation [22], whereas the bilateral involvement observed only in the proximal group is consistent with an increased thrombotic burden. These findings support the notion that proximal and distal DVT represent distinct phenotypes with different risk profiles and clinical outcomes. Furthermore, the findings suggest that inflammatory indices may provide additional information on DVT pathophysiology, thereby strengthening the clinical prediction models. The strong performance of D-dimer and the independent predictive value of NLR are particularly important for PE risk assessment. High index values may suggest the possibility of proximal DVT, while normal values, together with D-dimer levels, may contribute to reducing unnecessary imaging. However, it should be noted that these markers are not diagnostic on their own and must always be used in conjunction with clinical evaluation.

Limitations of the study

This study has some limitations. The single-center nature of this study reduces its generalizability. Given the retrospective design of the study, treatment-related factors such as the timing and type of anticoagulation could not be fully standardized, which may have affected the inflammatory marker levels and their association with PE risk. This limitation should be considered when interpreting these results. Furthermore, although the control group was selected from symptomatic but DVT-negative individuals to ensure clinical similarity, the use of this group instead of a healthy community sample may have introduced a potential bias. This approach was deliberately chosen to minimize indication bias by ensuring that all groups underwent VDUS for comparable clinical indications. While this method strengthens internal validity, it limits external generalizability and prevents direct comparison with a truly healthy population. Furthermore, full balancing for age, sex, BMI, and comorbidities was not achieved, and Propensity Score Matching (PSM) was not applied. Although the groups were systematically compared, the absence of PSM may have led to residual imbalances in key characteristics, such as age and comorbidities. This does not invalidate the observed relationships but may partially affect the comparability between groups. Furthermore, although the overall study population was of sufficient size, the number of patients with pulmonary embolism was relatively limited, which may have reduced the statistical power of the ROC and multivariate regression analyses. Therefore, the predictive performances of the evaluated biomarkers should be interpreted with caution. Since inflammatory indices were calculated from a single blood sample at the time of diagnosis, they may not reflect temporal changes. Therefore, multicenter prospective studies supported by advanced statistical methods are required to validate these findings.

In conclusion, this study demonstrated that proximal and distal DVT are two distinct phenotypes with different risk profiles and pathophysiological characteristics. While proximal DVT is characterized by a marked systemic inflammatory response, distal DVT can only be distinguished using a sensitive index, such as the SIRI. Simple and cost-effective markers, such as SII and SIRI, can provide additional information about the anatomical location of DVT by supporting risk classification. However, it should be noted that these parameters are not diagnostic on their own and should be used in conjunction with clinical assessment and traditional biomarkers.

Declaration of conflicting interests

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Ethics approval

This study was approved by the Ethics Committee of Ankara Bilkent City Hospital (Approval No: TABED 1-25-1301

Authors' contribution

MY: Concept, Design, Materials, Data Collection and/or Processing, Analysis and/or Interpretation, Writing of the Article. OK: Design, Materials, Data Collection and/or Processing, Literature Review. MFS: Data Collection and/or Processing, Analysis and/or Interpretation, Methodology. KEE: Materials, Data Collection and/or Processing, Literature Review. SG: Supervision, Analysis and/or Interpretation, Critical Review, Final Approval.

References

1. Navarrete S, Solar C, Tapia R, Pereira J, Fuentes E, Palomo I. Pathophysiology of deep vein thrombosis. Clin Exp Med 2022; 23: 645-54.
2. MacDougall DA, Feliu AL, Boccuzzi SJ, Lin J. Economic burden of deep-vein thrombosis, pulmonary embolism, and post-thrombotic syndrome. Am J Health Syst Pharm 2006; 63: 20.
3. Stubbs MJ, Mouyis M, Thomas M. Deep vein thrombosis. BMJ 2018; 360: k351.
4. Bikdeli B, Caraballo C, Trujillo-Santos J, Galanaud JP, di Micco P, Rosa V et al. Clinical Presentation and Short- and Long-term Outcomes in Patients With Isolated Distal Deep Vein Thrombosis vs Proximal Deep Vein Thrombosis in the RIETE Registry. JAMA Cardiol 2022; 7: 1-10.
5. Chang J. Pathogenesis of Two Faces of DVT: New Identity of Venous Thromboembolism as Combined Micro-Macrothrombosis. Life 2022; 12: 1256.
6. Kirkilesis G, Kakkos SK, Bicknell C, Salim S, Kakavia K. Treatment of distal deep vein thrombosis. Cochrane Database Syst Rev 2019; 4: CD013322.
7. Yao M, Ma J, Wu D, Fang C, Wang Z, Guo T, Mo J. Neutrophil extracellular traps mediate deep vein thrombosis: from mechanism to therapy. Front Immunol 2023; 14: 1144244.
8. Kuplay H, Erdoğan SB, Bastopcu M, Arslanhan G, Baykan DB, Orhan G. The neutrophil-lymphocyte ratio and the platelet-lymphocyte ratio correlate with thrombus burden in deep venous thrombosis. J Vasc Surg Venous Lymphat Disord 2020; 8: 100-7.
9. Bozkurt AK, Akay HT, Çalkavur İT, Şırlak M, Balkanay OO, Uğuz E et al. National guidelines on the management of venous thromboembolism: Joint guideline of the Turkish Society of Cardiovascular Surgery. Turk Gogus Kalp Damar Cerrahisi Derg 2021; 29: 562-76.
10. Stevens SM, Woller SC, Kreuziger LB, Bounameaux H, Doerschug K, Geersing GJ et al. Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report. Chest 2021; 160: e545-e608.
11. Kearon C. Natural History of Venous Thromboembolism. Circulation 2003; 107: I22-I30.
12. Liu H, Chen X, Wang Z, Liu Y, Liu M. High systemic inflammation response index level is associated with an increased risk of lower extremity deep venous thrombosis. Ann Med 2023; 55: 2195444.
13. Theofilis P, Sagris M, Oikonomou E, Antonopoulos AS, Siasos G, Tsioufis C et al. Inflammatory Mechanisms Contributing to Endothelial Dysfunction. Biomedicines 2021; 9: 781.
14. Branchford B, Carpenter S. The Role of Inflammation in Venous Thromboembolism. Front Pediatr 2018; 6: 142.
15. Mukhopadhyay S, Johnson TA, Duru N, Buzza MS, Pawar NR, Sarkar R, Antalis TM. Fibrinolysis and Inflammation in Venous Thrombus Resolution. Front Immunol 2019; 10: 712.
16. Bakirci EM, Topcu S, Kalkan K, Tanboga IH, Borekci A, Sevimli S, Acikel M. The Role of Nonspecific Inflammatory Markers in Determining the Anatomic Extent of Venous Thromboembolism. Clin Appl Thromb Hemost 2013; 21: 181-5.
17. Xia Y, Xia C, Wu L, Li Z, Li H, Zhang J. Systemic Immune Inflammation Index (SII), System Inflammation Response Index (SIRI) and Risk of All-Cause Mortality and Cardiovascular Mortality. J Clinical Med 2023; 12: 4425.
18. Schellong SM, Goldhaber SZ, Weitz JI, Ageno W, Bounameaux H, Turpie AGG et al. Isolated Distal Deep Vein Thrombosis: Perspectives from the GARFIELD-VTE Registry. Thromb Haemost 2019; 119: 1675-85.
19. Chan F, Moriwaki K, De Rosa M. Detection of necrosis by release of lactate dehydrogenase activity. Methods Mol Biol 2013; 979: 65-70.
20. Barco S, Klok FA, Mahé I, Marchena PJ, Ballaz A, Rubio CM et al. Impact of sex, age, and risk factors for venous thromboembolism on the initial presentation of first isolated symptomatic acute deep vein thrombosis. Thromb Res 2019; 173: 166-71.
21. Galanaud JP, Sevestre-Pietri MA, Bosson JL, Laroche JP, Righini M, Brisot D et al. Comparative study on risk factors and early outcome of symptomatic distal versus proximal deep vein thrombosis: results from the OPTIMEV study. Thromb Haemost 2009; 102: 493-500.
22. Kyrle PA, Eischer L, Šinkovec H, Gressenberger P, Gary T, Brodmann M et al. The Vienna Prediction Model for identifying patients at low risk of recurrent venous thromboembolism. Eur Heart J 2023; 45: 45-53.