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# Evaluation of the predictive role of standard laboratory tests for disease severity in patients with deep venous thrombosis

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## Abstract

**Introduction:** *Deep venous thrombosis (DVT) can result in fatal outcomes if it is not timely diagnosed and sufficiently treated. Some laboratory markers were identified in previous reports for predicting the disease with low sensitivity or specificity. We aimed to evaluate the predictive value of serum albumin levels and compare them with conventional laboratory parameters.*

**Material** *and methods: Fifty patients with acute lower-extremity DVT who has no previous history of malignancy or hematologic disorder were included in the study. The demographical variables and standard biomarkers of the DVT group were compared with the normal population (n:50). Thereafter patients were divided into two groups extensive DVT (thrombosis involves popliteal, femoral, and iliac veins together) and localized DVT (thrombosis involves popliteal vein and below) and biomarkers were compared in patient groups.*

**Results:** *The demographical variables and white blood cell count (WBC) were found as similar between healthy groups and DVT groups. However, mean platelet volume (MPV), D-Dimer, neutrophil to lymphocyte ratio (NLR), and fibrinogen to albumin ratio (FAR) were found markedly higher in DVT patients. Moreover, statistically incremental FAR and NLR levels were detected ($p < 0.05$) in patients with extensive DVT (involved iliac and femoral veins).*

**Conclusion:** *Serum NLR and FAR levels seem to be significant predictors for the extensive thrombotic event in patients with DVT.*

**Key words:** deep venous thrombosis, extensive disease, neutrophil to lymphocyte ratio, fibrinogen to albumin ratio

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## Introduction

Deep venous thrombosis (DVT) is an important pathology that can progress with highly mortal and morbid outcomes such as pulmonary thromboembolism (PTE) or post-thrombotic syndrome (PTS). Therefore, timely diagnosis and appropriate treatment are necessary for avoiding adverse outcomes [1, 2]. The most simple and definitive diagnoses of this disorder can be confirmed with Doppler ultrasonography. Ultrasonography is a reliable method but not objective [2]. Thus, researchers tried to determine an objective laboratory marker that

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is highly specific and scientific for venous thrombosis. However, any powerful diagnostic laboratory marker to confirmation and follow up the progression of the disease has not been identified [2, 3]. Fibrinogen and D-dimer are commonly studied laboratory parameters in DVT and its complications. Higher levels of these parameters are useful to determine for uncertain patients with precursor symptoms. Despite, higher sensitivity, fibrinogen, and D-dimer are not sufficiently specific for DVT [3, 4]. New parameters were investigated for serving this purpose. Especially, some recent studies were focused on indicators for the tendency of disease and extensive thrombosis burden such as lower albumin levels [5].

In the current study, we aimed to investigate the standard laboratory parameters in DVT and evaluate the predictive role of these biomarkers in progressive disease.

## Material and methods

This prospective study was approved by the local ethical committee of the University (2019-7-17). All protocols of the study were conducted according to Helsinki Declaration and in adherence to local guidelines for good clinical practice. Written informed consent was obtained from each participant. After the designation of the study, 50 healthy control subjects and patients with acute DVT (after major surgery or trauma or etc.) were included in the study. Patients with malignancy, hematologic disorder or previous recurrent DVT were excluded from the study. Totally, 50 DVT patients were enrolled in the study. Patients were divided into two subgroups as extensive DVT [n:26] (thrombosis involves popliteal, femoral, and iliac veins together) and localized DVT [n:24] (thrombosis involves popliteal vein and below) in accordance to Doppler ultrasound findings. Thereafter, Demographic data (age, sex) and some routine blood parameter [Neutrophil to Lymphocyte ratio (%), mean platelet volume [MPV] (fL), white blood cell [WBC] ($10^{-3}$/uL), Platelet ($10^{-3}$/uL), D-dimer (ng/L), Fibrinogen to albumin ratio [FAR] (%), Neutrophil to Lymphocyte ratio [NLR] (%)] values compared between healthy and DVT groups. Finally, the same parameters were compared in localized and extensive DVT subgroups.

### Statistical analyze

Data analysis was applied SPSS software program (ver. 15.0, Chicago, Illinois). Categorical variables were expressed as percentages and continuous values were given as mean ± SD. Normally distributed variables compared with Kolmogorov Smirnov and Shapiro-Wilk tests. Student T-test was used for single analysis and variables were determined differently in single analyzes compared with univariate and multivariate tests. Receiver operator characteristic (ROC) curve analysis was used to detect the optimal cut-off value for serum biomarkers for identifying extensive thrombosis with expressing maximum sensitivity and specificity. The area under the curve (AUC) was used to determine the accuracy of the test. P-value smaller than 0.05 was considered significant.

## Results

Age and sex distributions were similar in the healthy and the DVT groups (Table 1). Similarly, the white blood cell counts (WBC) were insignificant between these groups ($p > 0.05$). Contrarily, platelet count, mean platelet volume (MPV), D-Dimer, neutrophil to lymphocyte ratio (NLR), and fibrinogen to albumin ratio (FAR) were markedly higher in DVT group, when compared with healthy subjects (Table 2). Especially, statistically incremental MPV (9.7 ± 1.3), NLR (3.5 ± 1.6), and FAR (114.8 ± 33.5) values were detected in DVT group ($p = 0.000$). The multiple regression analysis (Table 3) revealed that FAR and MPV values are the most significant parameters in DVT group ($p = 0.000$).

In subgroup analyses, WBC, platelet count, FAR, and NLR values were statistically significant in the extensive DVT group ($p < 0.05$). The comparisons of serum parameters between subgroups were presented in Table 4. The ROC curve analyses of platelet count, WBC, NLR, and FAR values to predict extensive deep venous thrombosis were presented in Figure 1. The optimal cut-off value of NLR levels was found as 3.15% for predicting extensive thrombosis in DVT with 73.1%

**Table 1.** The demographical comparison of healthy subjects and patient group

| | Normal n:50 | DVT* n:50 | p** |
|---|---|---|---|
| Age mean±SD | 58.18 ± 15.81 | 53.42 ± 11.70 | 0.68 |
| Sex Male/n:% | 26 (52%) | 29 (58%) | 0.90 |

*DVT: Deep venous thrombosis; **$p < 0.05$ is considered statistically significant

**Table 2.** The comparison of biochemical markers between healthy subjects and patient group

| | Normal n:50 | DVT n:50 | p |
|---|---|---|---|
| MPV | 9.7 ± 1.3 | 7.9 ± 1.6 | 0.000 |
| WBC | 8.4 ± 2.89 | 7.6 ± 2.4 | 0.137 |
| Platelet | 289.9 ± 96.2 | 241.9 ± 75.4 | 0.007 |
| D-Dimer | 2099.9 ± 5085.2 | 11.01 ± 11.3 | 0.005 |
| Fibrinogen to albumin ratio | 114.8 ± 33.5 | 75.8 ± 31.7 | 0.000 |
| Neutrophil to lymphocyte ratio | 3.5 ± 1.6 | 2.1 ± 1.4 | 0.000 |

DVT: deep venous thrombosis; MPV: mean platelet volume; WBC: white blood cell; $p < 0.05$ is considered statistically significant

**Table 3.** The multiple regression analyze of biochemical markers

| | B | S.E. | Wald | df | Sig. | Exp(B) | 95% C.I.for EXP(B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| MPV | 1.186 | .258 | 21.155 | 1 | .000 | 3.274 | 1.975 | 5.427 |
| Platelet | .011 | .005 | 4.721 | 1 | .030 | 1.011 | 1.001 | 1.021 |
| Fibrinogen to albumin ratio | .050 | .012 | 18.081 | 1 | .000 | 1.052 | 1.028 | 1.077 |

MPV: mean platelet volume; $p < 0.05$ statistically significant

**Table 4.** Analyze of biochemical markers in popliteal DVT and extensive (popliteal+femoral+iliac) DVT patients.

| | Group | N | Mean | Standard Deviation | p |
|---|---|---|---|---|---|
| MPV | Popliteal | 24 | 9.6896 | 1.50607 | 0.735 |
| | Extensive | 26 | 9.8185 | 1.16526 | |
| WBC | Popliteal | 24 | 7.5667 | 2.36388 | 0.044 |
| | Extensive | 26 | 9.2065 | 3.15215 | |
| Platelet | Popliteal | 24 | 259.4583 | 80.66785 | 0.030 |
| | Extensive | 26 | 318.1154 | 102.28209 | |
| Fibrinogen to albumin ratio | popliteal | 24 | 89.4650 | 19.60465 | 0.001 |
| | Extensive | 26 | 138.3073 | 25.62590 | |
| Neutrophil to lymphocyte ratio | popliteal | 24 | 2.8529 | 1.38346 | 0.007 |
| | Extensive | 26 | 4.1058 | 1.74225 | |
| D-Dimer | Popliteal | 24 | 2785 | 7137 | 0.985 |
| | Extensive | 26 | 1374 | 1634 | |

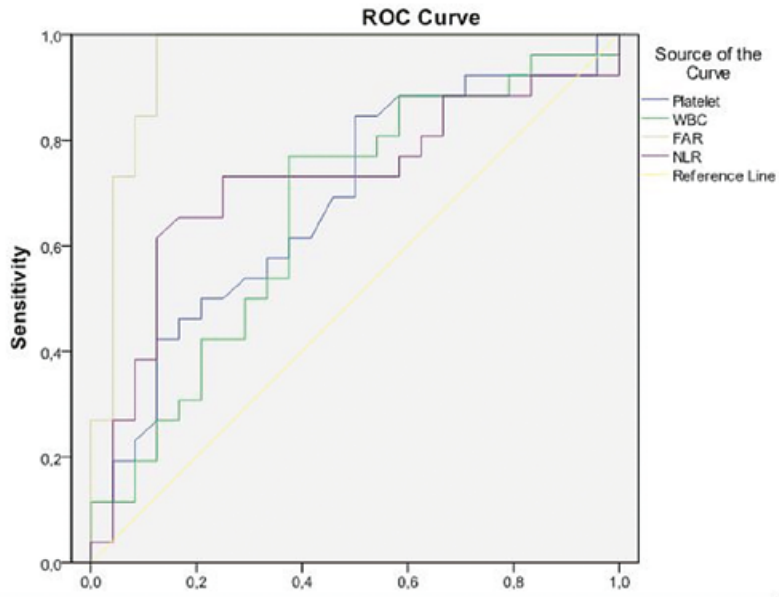
MPV: mean platelet volume; WBC: white blood cell; $p < 0.05$ is considered statistically significant

sensitivity and 75.0% specificity. The optimal cut-off value of FAR levels was found as 110.30 % for predicting extensive thrombosis in DVT with 84.6% sensitivity and 91.7% specificity.

## Conclusions

Despite the pro-thrombotic parameters described in many studies in patients with DVT, the routine serum biomarkers were not completely evaluated for detecting the severity of the disease. According to our knowledge, it is the first study that investigated the relationship between extensive DVT and FAR levels. Our findings demonstrated that serum NLR and FAR levels could be related to the burden of disease in a patient with DVT. In another perspective, DVT can be presented with extensive thrombosis in patients with higher NLR and FAR levels. Additionally, serum FAR levels were found as quite sensitive for thrombosis burden in patients with DVT.

Because of the close interaction between thrombosis and inflammation, complete blood counting parameters were investigated the thrombotic cardiovascular events formerly [6, 7]. The determinants




**Area Under the Curve**

| Test Result Variable(s) | | Area | Std. Error[a] | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| – | Platelet | ,685 | ,076 | ,025 | ,536 | ,834 |
| | WBC | ,665 | ,078 | ,045 | ,512 | ,818 |
| | FAR | ,952 | ,033 | ,000 | ,000 | 1,000 |
| | NLR | ,720 | ,076 | ,008 | ,572 | ,869 |

The test result variable(s): Platelet, NLR has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

**Figure 1.** ROC analysis of the serum WBC, platelet, NLR, and FAR levels for prediction of extensive disease in the deep venous thrombosis

of thrombogenesis and thrombus resolution should be completely understood for the protection and treatment of venous thrombosis. It was previously demonstrated that the extravasation of inflammatory agents can provide more quick resolution of thrombi in experimental models with primates [8]. On the other hand, recent reports indicate that classic serum parameters give brief reflections about the acute thrombotic events, as follows; increased MPV was shown as a potential predictor of high platelet activation and reactivity in thrombotic disorders, white blood cells and their subtypes delineates increased atherosclerotic and thrombotic vascular occlusions in cardiovascular events, neutrophil to lymphocyte ratio (NLR) newly identified expression of the inflammatory process was demonstrated as an independent indicator for cardiovascular mortality, and etc. [7]. Higher MPV values were reported in patients with DVT when compared with healthy controls [9]. Moreover, it was claimed that MPV is an independent predictor of thrombus burden in coronary artery thrombosis [10]. However, we could not detect any difference between distal DVT and extensive DVT. Similarly, neutrophil to lymphocyte ratio (NLR), red cell distribution width (RDW), and other inflammatory markers were investigated in the ST-segment elevation myocardial infarction patients with a high thrombus burden. RDW and NLR were detected as potential predictors of coronary thrombus burden [11, 12]. Furthermore, it was claimed that NLR increased could identify the risk population for venous thrombosis as total knee arthroplasty [13]. Despite WBC levels being similar between the healthy control group and DVT patients, MPV, D-Dimer, platelet, NLR values were statistically higher in DVT patients. Incidentally, WBC, platelet, NLR, FAR levels were found as markedly increased in a subgroup with extensive DVT (both iliac and femoral involvement) patients.

D-dimer and fibrinogen are other important predictors for venous thrombosis. D-dimer fibrin degradation product is a quantitative measurement of fibrinolysis

that is commonly investigated in venous thrombosis. Fibrinogen is suspected as a modulator of the structural properties of fibrin gel formation that are presented in DVT. Also, fibrinogen levels were investigated together with D-dimer levels in DVT. However, the specificity of these markers is quite low for the thrombotic process [13, 14]. Even some recent reports claimed that increased fibrinogen levels were not associated with DVT risk, but it can be related to thrombus fragmentations which can be associated with high pulmonary embolism risk [14]. In this context, higher fibrinogen levels may not reflect the burden of disease but it can be associated with thrombi fracture formations [14]. Albumin is another serum marker that can directly associate with blood viscosity and thrombogenesis. Also, lower plasma albumin concentrations were reported with higher venous thrombosis risk [15]. In another view, acute lower albumin levels were suspected as a reflection of inflammatory status which linked with venous thrombosis and embolism like an acute phase reactant [15, 16]. Namely, lower albumin levels were suggested as a predictor of venous thromboembolism [16]. To obtain a more sensitive marker serum fibrinogen to albumin ratio evaluated in other types of cardiovascular events. It was speculated that fibrinogen and albumin as hemorheological markers will have more significant and specific predictive potentials if they are considered together [17, 18]. Karahan et al. [18] indicated that the fibrinogen to albumin ratio might reflect the severity of disease in patients with venous insufficiency. Similarly, we found higher FAR levels in both comparison healthy vs. DVT groups and popliteal vs. extensive DVT subgroups ($p = 0.000$). Moreover, higher D-dimer levels were detected in patients with extensive disease ($p = 0.005$). Additionally, higher FAR levels were demonstrated as highly sensitive (84.6%) and highly specific (91.7%) for the burden of thrombosis with a cut-off point value of 110.30 g/dL.

To sum up, we found higher MPV, platelet, D-Dimer, NLR, and FAR levels in patients with DVT. Furthermore, incremental WBC, platelet, NLR, and FAR values were found as related to extensive disease. Especially, higher NLR and FAR seem to be highly related to extensive disease in DVT. Serum NLR and FAR levels can be related to progressive disease and these markers should be investigated with more detailed studies as a predictor of extensive disease or thrombosis burden.

## Conflict of interest

None.

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