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Clinical value of neutrophil to lymphocyte ratio in the region of lower extremity deep venous thrombosis

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ABSTRACT

Objectives. Many studies have demonstrated a significant association between cardiovascular disease and neutrophil to lymphocyte ratio (NLR). To our knowledge, no study has been reported in patients with deep venous thrombosis (DVT) which affecting proximal or distal leg. In this study we analyzed proximal and distal DVT according to the NLR. ***Methods.*** This retrospective study was obtained from patients' records of a tertiary university hospital between May 2011 to January 2014. A total of 57 patients with the diagnosis of acute primary DVT and 30 patients as control group included in the study. All of them were confirmed with lower extremity venous duplex examinations. Of these, 37 examinations with the diagnosis of proximal DVT were compared to 20 examinations with distal DVT. The groups compared regarding to complete blood counter values. ***Results.*** Mean eosinophil level was higher in the distal DVT group (0.28±0.24 vs. 0.12±0.01, p=0.001), whereas median NLR were higher in the proximal DVT group than the distal DVT group (3.5 [0.5-4.3] vs. 2.3 [1.2-9.7], respectively; p=0.002). In addition, median NLR, leukocyte and neutrophil counts were statistically lower in the control group than the others (p=0.014, p=0.027 and p=0.004, respectively). ***Conclusion.*** NLR, an inexpensive and easily measurable laboratory variable, was independently and significantly associated with the presence and severity of DVT, especially acute proximal DVT.

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Keywords: Deep venous thrombosis; neutrophil to lymphocyte ratio (NLR)

Introduction

Deep venous thrombosis (DVT), a part of clinical diagnosis called venous thromboembolism, is an important cause of morbidity and mortality. Various predisposing clinical conditions for higher risk of DVT are prolonged immobility and postoperative bed rest, malignancy, advanced age, cardiorespiratory and other organ failures, neurological disorders, and a wide variety of inherited and acquired hematological disease [1].

DVT commonly affects the leg veins, such as the femoral vein or the popliteal vein, or the deep veins of the pelvis [2]. Proximal DVT is related pulmonary embolism and the mortality. In case of proximal DVT

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identified, anticoagulant treatment should initiate immediately [2, 3]. Doppler ultrasonography is the gold standard technique for diagnosis it is noninvasive and safe [4].

Blood neutrophil to lymphocyte ratio (NLR) could be an important measure of systemic inflammation as it is cost effective, readily available and could be calculated easily. Recently, the NLR has become an emerging marker of inflammation, and a useful marker of cardiovascular disease as well as an independent predictor of cardiac or non-cardiac mortality [5].

High NLR levels show that inflammatory response occurs in patients with DVT. According to our knowledge no studies have been performed in patients with complete blood counter analysis to detect the DVT whether proximal or distal. We aimed to demonstrate any association between NLR and DVT with respect to presence and location.

Methods

Study Population

From May 2011 to January 2014, 57 consecutive patients with first time acute DVT which confirmed by venous duplex examinations in Evliya Celebi Training and Research Hospital were included to the study retrospectively. Thirty-seven patients with proximal acute DVT and 20 patients with distal acute DVT included in the study group. Thirty consecutive patients who came to the hospital with varicous veins complaints without venous thrombosis were added as control group to the study. The local ethical committee approved the study protocol.

Clinical evidence of cancer, acute coronary syndrome, congestive heart failure, chronic obstructive lung disease, chronic inflammatory disease, or any systemic infection that occurred during the first 48 hours after admission was excluded. Patients whose hospital records were incomplete, who were under the age of 18 were also excluded.

Laboratory and Radiologic Analyses

Venous Doppler ultrasonography was performed in our hospital radiology department. In this study, only patient which proximal and distal DVT corrected with lower extremity venous duplex examinations were considered in DVT group.

Complete blood count, leukocyte count, neutrophil, lymphocyte, eosinophil, mean platelet volume and NLR were recorded by using Beckman Coulter LH780. Patient clinical findings were also recorded.

Statistical Analysis

Continuous variables were shown as mean ± standard deviation. While, the mean differences between groups were compared by Student's t test, Mann-Whitney U test was applied for comparisons of the median values. Whether the distributions of continuous variables were normally or not was determined by Kolmogorov Smirnov test. Categorical data were analyzed by Pearson's Chi-Square test. The optimal cut-off points of NLR to determine both proximal and distal DVT was evaluated by receiver operating characteristic (ROC) analysis as giving the maximum some of sensitivity and specificity for the significant test. Predictive effect of NLR on the DVT was evaluated by binary logistic regression analyses after adjustment for all possible confounding factors. Odds ratios and 95% confidence intervals for each independent variable were also calculated. p value less than 0.05 was considered statistically significant. Data analysis was performed using SPSS for Windows, version 21 (SPSS Inc., Chicago, IL, United States).

Results

Clinical and laboratory characteristics of the patients with DVT were summarized in Table 1. There was no significant difference between proximal and distal DVT groups regarding age, sex, clinical risk factors including hypertension, diabetes and smoking. Laboratory parameters including leukocyte, red cell distribution width, neutrophil, mean platelet volume and platelet count were also similar in both DVT groups (see Table 1).

The mean age of the patients with proximal DVT and distal DVT groups were 49.4±6.3 and 55.9±13.3, respectively; p=0.148. Patients with distal DVT were predominantly older and also were predominantly males compared to the proximal DVT group patients but statistical significant difference was not found (p=0.237) (see Table 1).

Mean eosinophil level was higher in the distal DVT group (0.28±0.24 vs. 0.12±0.01, p=0.001); in contrast the median value and the interquartile range (25^{th} and 75^{th}) of NLR were higher in the proximal DVT group than the distal DVT group (3.5 [0.5-4.3] vs. 2.3 [1.2-9.7], respectively; p=0.002) (Table 1, Figure 1).

Table 1. Demographic features of the patients with deep venous thrombosis

Variables	Proximal DVT group (n=37)	Distal DVT group (n=20)	*p*
Age (years)	49.6±16.3	55.9±13.3	0.148
Female	19 (51.3%)	7 (35%)	0.237
Leukocyte ($X10^9$/L)	8.05 (3.1-17.5)	8.1 (3.6-13)	0.904
MPV (fL)	8.2±0.9	8.5±0.7	0.078
Hemoglobin (g/dL)	13±1.9	14.1±1.3	**0.003**
Smoking	23 (62.1%)	8 (40%)	0,178
Hypertension	19 (51.3%)	8 (45%)	0,623
Diabetes mellitus	4 (64%)	4 (64%)	0,432
RDW (%)	13.5 (12-18)	14.6 (12-19)	0.146
Lymphocyte ($X10^9$/L)	1.7 (1-4)	2.3 (1-5)	**0.001**
Neutrophil ($X10^9$/L)	5.4 (2-14)	5 (1-8)	0.260
NLR	3.5 (0.5-4.3)	2.3 (1.2-9.7)	**0.002**
Eosinophil ($X10^9$/L)	0.12±0.01	0.28±0.24	**0.001**
Platelets ($X10^9$/L)	265 (85-464)	247 (85-410)	0.477

Data are shown as mean±standard deviation or median (interquartile range) or number (%). DVT=deep venous thrombosis, MPV=mean platelet volume, NLR=neutrophil to lymphocyte ratio, RDW=red cell distribution width

Median NLR, leukocyte and lymphocyte counts were statistically lower in the control group than the others (p=0.014, p=0.027 and p=0.004, respectively) (Table 2). The other variables including gender, age, lymphocytes, and eosinophil were similar in patients with or without DVT. According to the ROC curve analysis, the optimal cut-off value of NLR to predict proximal DVT was ≥1,9637 with 75% sensitivity and 65% specificity (area under curve=0.778, CI=95%) (Figure 2).

According to the binary logistic regression analysis, lymphocyte count, hemoglobin level, NLR were able to define patients with proximal DVT compared to the other two groups independently (Table 3).

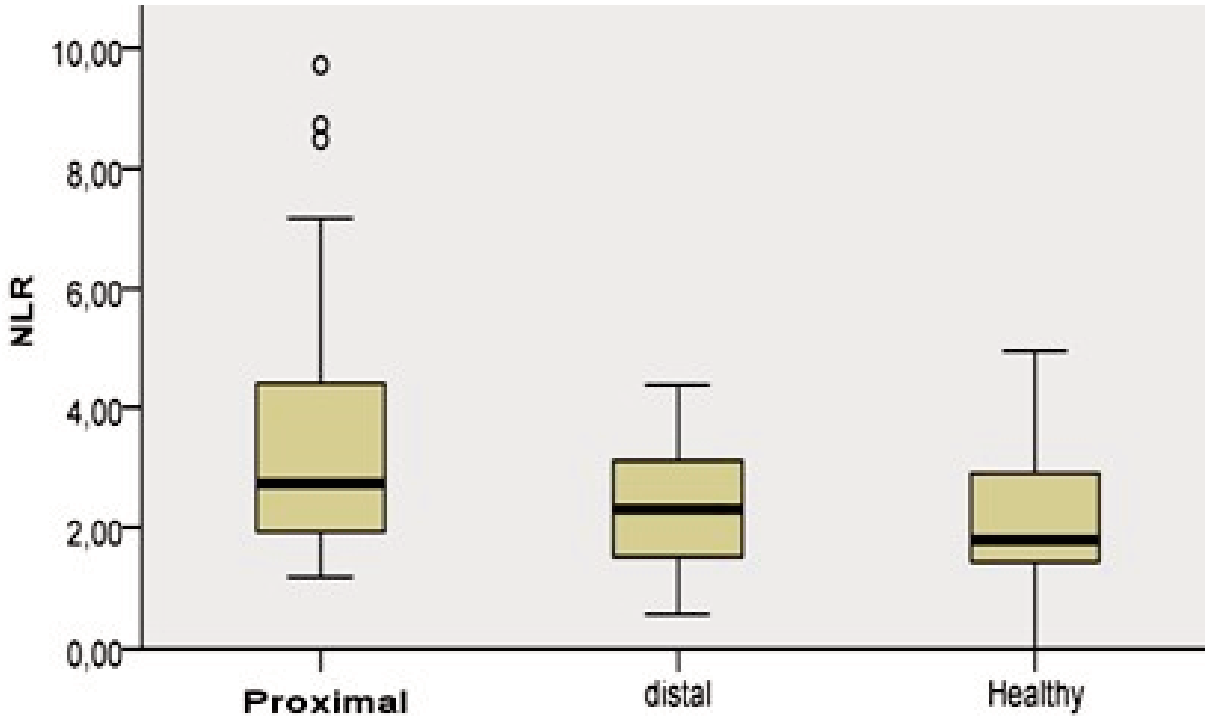

Figure 1. Kruskal-Wallis test for NLR in the healthy and DVT groups. The median value and the interquartile range (25th and 75th) of NLR (%) level were higher in proximal DVT group. DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio

Table 2. Demographic features of the patients with or without DVT

Variables	Control group (n=30)	DVT group (n=57)	*p*
Age (years)	49.3±15	51.7±15	0.499
Female	15 (50%)	26 (45.6%)	0.697
Leukocyte ($X10^9$/L)	6.7 (3.8-11)	8.3 (3.1-17.5)	**0.027**
MPV	8.4±0.9	8.3±0.9	0.446
Hemoglobin	13.2±1.6	13.4±1.7	0.331
RDW	13.6 (12-19)	14.8 (12-19)	0.104
Lymphocyte ($X10^9$/L)	1.8 (1-4)	1.8 (1-5)	0.881
Neutrophil ($X10^9$/L)	3.7 (1-8)	5.6 (1-14)	**0.004**
NLR	1.88 (0.1-4.9)	2.6 (0.5-9.7)	**0.014**
Eosinophil ($X10^9$/L)	0.13 (0-3.3)	0.12 (0-1.1)	0.316
Platelets ($X10^9$/L)	221 (109-528)	230 (85-723)	0.382

Data are shown as mean±standard deviation or median (interquartile range) or number (%). DVT=deep venous thrombosis, MPV=mean platelet volume, NLR=neutrophil to lymphocyte ratio, RDW=red cell distribution width

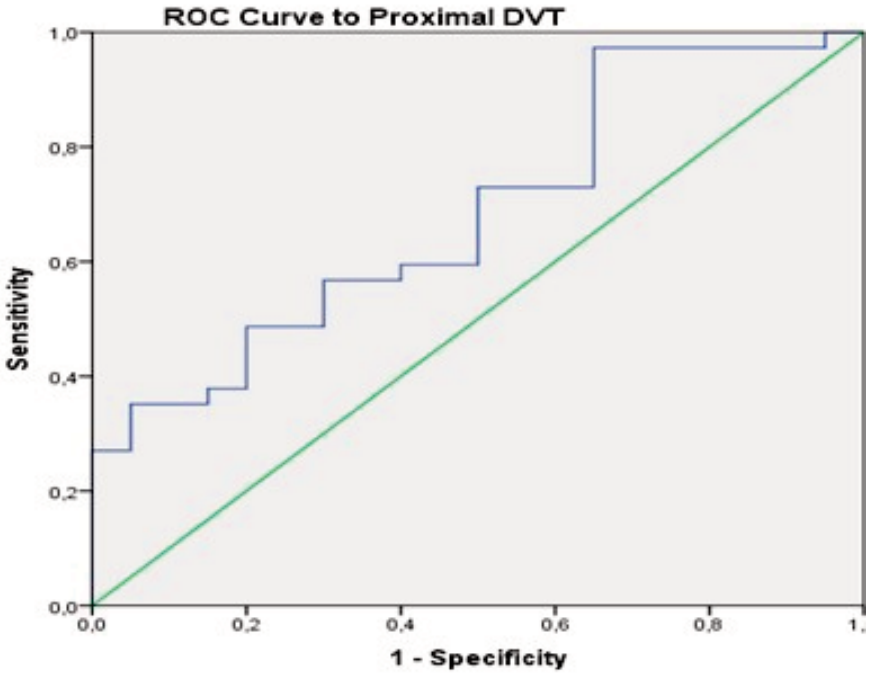

Figure 2. According to the ROC curve analysis, the optimal cut-off value of NLR to predict proximal DVT was ≥1,9637 with 75% sensitivity and 65% specificity (area under curve=0.778, CI=95%). CI=confidence interval, DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio, ROC=receiver operating characteristic

Discussion

In this study we evaluated the relationship between NLR and the presence proximal DVT in 57 patients with acute DVT. The findings of the present study indicated for the first time that NLR, lymphocyte, hemoglobin, and eosinophil are independent predictor of proximal DVT in patients.

The number of leukocytes and the ratio of their subtypes are regarded as markers of inflammation in all cardiovascular disease [5, 6]. NLR is an indicator of subclinical inflammation. Elevated NLR means higher neutrophil count compared to lymphocyte count in response to stress such as infection and inflammation. This ratio, which can be calculated easily, may be used as an independent prognostic factor in DVT whether it affect proximal or distal.

Previous studies had shown its prognostic

Table 3. Binary logistic regression analysis to define patients with proximal DVT

Variables	Score	*p* value
Gender	1.393	0.273
Hemoglobin	4.239	**0.040**
Lymphocytes	5.00.	**0.025**
NLR	5.980	**0.014**
Eosinophil	8.496	**0.004**

DVT=deep venous thrombosis, NLR=neutrophil to lymphocyte ratio

significance in cardiovascular disease including heart failure, stable and acute coronary artery disease [7-9]. It also shows that mortality increased with the increase in NLR in patients with acute coronary syndrome and those who underwent cardiovascular intervention [7, 10]. In some studies, elevated neutrophil count was found to be associated with decompensated heart failure related to acute myocardial infarction [8].

In this study, there are high NLR values in proximal DVT. Previous studies showed that pulmonary embolism and mortality is associated with high NLR values. In previous studies thrombus development is associated with vein wall inflammation marked by an early extravasation of leukocytes and elevation in pro-inflammatory mediators. In particular, neutrophils are the first leukocytes to be found in the damaged intravascular area. Pro-coagulants are secreted locally by leukocytes that contribute to oxidative and proteolytic injury especially in case of pulmonary embolism [11, 12].

After the acute phase the monocyte and macrophages cells are accumulated in the inflammation area including leg vein wall, pulmonary artery wall or lung parenchyma. These cells likely play an important role in embolism resolution.

The majority of pulmonary embolism cases were reported to be between the ages of 60-70 years and in clinical studies and between the ages of 70-80 years in autopsy series [13-15]. Mortality rate in males was found to be higher. Mortality difference between males and females is more prominent after the age of 40 years [13]. In the present study, the number of males was higher than the number of females in the patients with distal DVT. In addition distal DVT group was more prominent advanced age.

The Limitations of the Study

Our study was a single institution, retrospective study, which had a relatively small sample size, so subject to various unaccounted confounders inherent in such an analysis. We could not compare NLR with other inflammatory markers, such as C-reactive protein because of they were not routinely obtained in our study population.

Conclusions

In conclusion, increased NLR as a simple non-specific marker of inflammation is associated with proximal DVT. With its universal availability, it may serve as an inexpensive new tool for deep venous thrombosis clinical property. Further large-scale and randomized prospective studies are required to clearly understand the exact role of NLR in the pathophysiology of DVT.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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