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Evaluation of Complete Blood Count Parameters as Biomarkers for Deep Venous Thrombosis

Derin Ven Trombozunda Tam Kan Sayımı Parametrelerinin Biyobelirteç Olarak Değerlendirilmesi

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Abstract

Purpose: Laboratory markers demonstrating thromboembolic diseases have been investigated widely. However, there have been no serum biomarker established to exclusively confirm or exclude the diagnosis of venous thromboembolism yet. This study investigates possible differences on blood cell count parameters among deep venous thrombosis (DVT) patients and normal subjects.

Materials and Methods: Between December 2012 - December 2013, a total of 399 patients were included in the study. Patients were divided into two groups. Complete blood cell counts and lower extremity venous Doppler ultrasonography results were analyzed for all the patients. Group 1, included 134 patients with ultrasonographically documented DVT and Group 2, consisted of 265 patients with normal lower extremity venous Doppler ultrasonography findings. Complete blood cell count parameters as white blood cell (WBC), red blood cell (RBC), and platelet counts, haemoglobine and haematocrite values, neutrophile, lymphocyte and monocyte levels, neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), mean corpuscular volume (MVC), mean platelet volume (MPV) and MPV/platelet ratio were recorded and statistically compared between two groups.

Results: The mean age and gender ratio were similar between groups. Neutrophil and lymphocyte counts, NLR, RBC count, haemoglobine and haematocrite levels were found to be statistically higher for DVT group. High RBC count and RDW were identified as independent predictors for DVT.

Conclusion: Obtaining hematologic parameters is simple and useful way for determining the DVT risk and may also be helpful for prophylactic treatment of DVT. **(Sakarya Med J 2016, 6(2):94-99)**

Keywords: neutrophil lymphocyte ratio, red cell distribution width, blood cell parameters, deep venous thrombosis, red blood cell, mean platelet volume

Öz

Amaç: *Tromboembolik hastalığı gösteren laboratuvar markerları yaygın bir şekilde araştırılmaktadır. Ancak yalnızca venöz tromboemboli tanısını destekleyecek veya dışlayacak bir serum biyobelirteci henüz yoktur. Bu çalışmada, derin ven trombozu (DVT) olan hastalarda ve normal populasyonda, tam kan sayımı parametreleri açısından mevcut olabilecek farklılıklar araştırılmıştır.*

Yöntem: *Aralık 2012 ile Aralık 2013 tarihleri arasında toplam 399 hasta çalışmaya dahil edildi. Hastalar 2 gruba ayrıldı. Tüm hastalarda tam kan sayımı ve alt extremite venöz Doppler ultrasonografi sonuçları analiz edilmiştir. Grup 1, ultrasonografik olarak tanı konmuş DVT olan 134 hastayı içerirken, Grup 2, alt ekstremite venöz Doppler ultrasonografi normal olan 265 hastayı içermektedir. Tam kan sayımı parametrelerinden beyaz kan hücresi (WBC), kırmızı kan hücresi (RBC), trombosit sayıları, hemoglobin ve hematokrit değerleri, nötrofil, lenfosit ve monosit sayıları, nötrofil/lenfosit oranı (NLR), kırmızı kan hücresi dağılım hacmi (RDW), ortalama eritrosit hacmi (MCV), ortalama trombosit hacmi (MPV) ve MPV/trombosit oranı hesaplandı ve iki grup arasında istatiksel olarak karşılaştırıldı.*

Bulgular: *Ortalama yaş ve cinsiyet oranları gruplar arasında benzerdi. Nötrofil ve lenfosit sayıları, NLR, RBC sayısı, Hb and Htc seviyeleri DVT grubunda istatistiksel anlamlı olarak yüksek saptandı. Yüksek RBC sayısı ve RDW değerinin, DVT için bağımsız risk prediktörleri olduğu belirlendi.*

Sonuç: *Hematolojik parametreleri elde etmek kolay olup, bunlar kişinin DVT riskini belirlemede ve DVT' nun proflaktik tedavisinde yardımcı olabilirler.* ***(Sakarya Tıp Dergisi 2016, 6(2):94-99)***

Anahtar Kelimeler: *nötrofil lenfosit oranı, kırmızı küre dağılım hacmi, tam kan sayımı parametreleri, derin ven trombozu, kırmızı kan hücresi, ortalama trombosit hacmi*

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INTRODUCTION

Deep venous thrombosis is a common disease that may cause serious life-threatening complications such as pulmonary embolism. Among life-threatening cardiovascular diseases, pulmonary embolism is the third most common after myocardial infarction and stroke[1]. Clinical investigations aiming to assign definite biomarkers to predict or diagnose venous thrombosis have been made, but presently there still exists no absolute serum marker to exclusively predict or confirm the diagnosis of venous thromboembolism. The most used serum biomarker is D-Dimer, with others being investigated widely as P-selectin, coagulation factor VIII, coagulation factor XI, thrombin generation, fibrin monomer, microparticles, interleukin-10 and other cytokines[2-4]. Leucocyte count has also became popular in recent years as potential biomarkers for venous disease, but whether leucocytes or other hematological parameters have a role in increased risk of thrombosis is not well known. This study investigates if there is an association between hematologic parameters and venous thrombosis by comparing normal subjects with documented deep venous thrombosis patients.

MATERIAL AND METHODS:

Between December 2012-December 2013, 399 patients who were examined for deep venous thrombosis or chronic venous insufficiency in the out-patient clinic having complete blood cell count and lower extremity venous Doppler ultrasonography examination were included in the study. The Ethics Committee of the local hospital approved the study protocol and informed consent form was obtained from each participant prior to the study entry. Patients without a Doppler ultrasonographic examination and patients with thrombophlebitis, chronic venous insufficiency, venous stasis ulceration or additional peripheral arterial disease were excluded. The patients were then divided into two groups: Group 1, included 134 patients with ultrasonographically documented deep venous thrombosis and Group 2, consisted of 265 patients with documented normal lower extremity venous Doppler ultrasonography findings. Complete blood cell count parameters included: white blood cell, red blood cell, platelet, neutrophil, lymphocyte and monocyte counts, haemoglobine and haematocrite levels, mean corpuscular volume (MCV), neutrophil/lymphocyte ratio (NLR), red cell distribution width (RDW), mean platelet volume (MPV) and MPV/platelet ratio and were then statistically compared between the two groups.

Statistical Analysis :

For continuous variables, the fitness to normal distribution and homogenity were tested by using Kolmogorov-Smirnov test and Levene test, and the data were classified. T test was applied for age variable with normal distribution. The other parameters did not have a normal distribution. Mann-Whitney U test was used for the other numeric variables. Chi-square test was applied for gender variable. The values were presented as mean ± standard deviation (SD). P values < 0.05 were considered statistically significant. Stepwise forward multivariate logistic regression was used to identify risk factors influencing deep venous thrombosis development. The statistical analysis were made using Statistical Package for the Social Sciences Version 16 (SPSS, Statistics for Windows, Version 16.0.,Chicago: SPSS Inc.).

RESULTS:

The mean age and gender ratio were similar between the two groups, being 51.7 ±15.9 years in group 1 and 55.1±17.5 years in group 2 (p = 0.059). For group 1, 66 (49.3%) patients and for group 2, 108 (40.1%) patients were female (p = 0.099). Statistical analysis for the numeric parameters of complete blood cell counts exhibited a positive relationship with some of them promising to be predictor of deep venous thrombosis. All results are summarized on table 1.

White blood cell count

White blood cell count (103/μL) analysis exhibited an insignificant difference with Mann-Whitney U test (p = 0.092). Similarly monocyte counts (K/uL) did not reveal any difference between group 1 and group 2 (0.57 ± 0.22 vs 0.58 ± 0.24; respectively; p = 0.891). Neutrophil counts (103/μL) was significantly lower in group 1 than in group 2 (4.43 ± 1.57 vs 5.26 ± 2.90, respectively, p = 0.032). However, lymphocyte counts (103/μL) was significantly higher in group 1 compared to group 2 (2.15 ± 0.69 vs 1.97 ± 0.78, respectively, p=0.015. NLR was obtained simply with the arithmetic division of neutrophil to lymphocyte count and there was also significant difference in NLR between groups (p=0.004).

Red blood cell indices

Erythrocyte count (M/uL) was significantly higher in group 1 compared to group 2 (4.92 ± 0.58 vs 4.59 ± 0.78, respectively, p = 0.0001). Similarly, there was significant differences in terms of haemoglobin (g/dL) and haematocrit (%) levels between groups (p = 0.0001) (Table 1). Mean corpuscular volume (fL) and red cell distribution width (%) measurements were insignificant between groups (p = 0.057 for both) (Table 1).

Table 1. Statistical analysis of complete blood count parameters in both groups.

	Group 1 (n=134)	Group 2 (n=265)	P value
Age	51,75±15,9	55,18±17,59	0,059
Gender (female)	66 (%49,3)	108 (%40,1)	0,099
WBC(K/uL)	7,31±1,85	7,97±2,07	0,092
Neutrophil(K/uL)	4,43±1,57	5,26±2,9	0,032 *
Lymphocyte(K/uL)	2,15±0,69	1,97±0,78	0,015 *
Monocyte(K/uL)	0,57±0,22	0,58±0,24	0,891
Neu/lym ratio	2,33±1,61	3,56±4,2	0,004 *
RBC(M/uL)	4,92±0,58	4,59±0,78	0,0001*
Haemoglobine(g/dL)	13,72±1,92	12,95±2,67	0,0001*
Haematocrite(%)	40,92±4,81	38,62±6,5	0,0001*
MCV(fL)	81,82±12,19	83,93±8,87	0,057
RDW(%)	15,22±4,89	19,44±11,79	0,057
Platelet(K/uL)	254,3±70,4	261,67±100,89	0,802
MPV/Plt	0,041±0,016	0,052±0,18	0,273
MPV(fL)	10,51±1,11	10,75±6,42	0,126

WBC:white blood cell, RBC:red blood cell, monocyte levels, Neu/lym ratio:neutrophil/lymphocyte ratio, MCV:mean corpuscular volume, RDW:red cell distribution width, MPV:mean platelet volume and MPV/Plt: mean platelet volume/platelet ratio, * p values <0.05

Platelet counts

There were not significant differences in platelet count (K/uL) and MPV/Plt ratio among both groups (p = 0.802 and p = 0.273, respectively). MPV level (fL) was 10.51±1.11 for group 1 and 10.75 ± 6.42 for group 2 (p = 0.126).

As a result, neutrophil, lymphocyte and red blood cell counts, NLR, haemoglobin and haematocrit levels were all found to be significantly higher in the deep venous thrombosis group. However, there was not significant differences in mean platelet volume (MPV) and red cell distribution width (RDW) value and MPV/platelet ratio between the groups.

Multiple logistic regression method was used to identify risk factors for deep venous thrombosis development. Based on the results of this analysis with forward selection method, the RBC and RDW were found to be significantly associated with DVT (p<0.05). RBC was found to be an independent risk factor for DVT (p=0.001, OR:0.532, 95% CI 0.373 to 0.759) as well as RDW (p=0.002, OR:1.066, 95% CI 1.024 to 1.110).

However, the other variables like white blood cell, platelet, haemoglobine, haematocrite, neutrophil, lymphocyte and monocyte levels, neutrophil/lymphocyte ratio, mean platelet volume (MPV) and MPV/platelet ratio were not found as independent predictors (p > 0.05). The results of LR analysis was summarized in Table 2.

Table 2. Independent predictor value of hematological parameters

	B	S.E.	Sig.	OR	95% C.I.for OR	
					Lower	Upper
RBC	-.631	.182	.001	.532	.373	.759
RDW	.064	.020	.002	1.066	1.024	1.110
Constant	2.733	.947	.004	15.377		

RBC:red blood cell, RDW:red cell distribution width, OR:Odds ratio.

DISCUSSION:

Venous thromboembolism (VTE) including deep venous thrombosis and resultant pulmonary embolism still remains an important cause of morbidity and mortality despite a better understanding of the pathophysiologic course of the disease and improvements in the preventive and therapeutic medicine. The etiopathologic mechanism in the formation of venous thrombosis has not been not clearly defined yet. The pathophysiology of venous thromboembolism classically is known to involve endothelial damage, blood stasis and hypercoagulability.[5] Risk factors for venous thromboembolism are related to these pathophysiologic factors and include major surgery, major trauma, advanced age, malignancy, venous insufficiency, a family history of thrombosis, frailty and immobility, thrombophilia, prior venous thromboembolism, preg

nancy and postpartum period.[6-8] Although increasing data exists about a better insight of the disease, 30-50% of the cases remain idiopathic.[9] VTE is a frequent disease with an incidence of 1 to 2 cases per 1000 person per year.[10] The overall age-adjusted incidence is higher for men (114 per 100000) then women (105 per 100000) with a male to female ratio of 1.2:1.[11] Considering the common incidence of VTE among the general population, it would be extremely useful to have clues to predict or diagnose earlier the patients in whom DVT will develop. Serving to this purpose, a variety of serum biomarkers have been identified to date. In the present study, we aimed to evaluate if there is a difference of complete blood cell parameters among deep venous thrombosis patients compared with normal population.

Deep venous thrombosis is a clinical condition that may present with severe symptoms like pain and swelling, or may present with pulmonary embolism symptoms. On the other hand, it may be asymptomatic without any noticeable symptoms in about half of all cases, and this complicates the diagnosis.[3] Although contrast venography is the most reliable way of diagnosing DVT 3, it is not routinely used for screening purposes because of invazive and complex nature of the application. Compression ultrasound (CUS) is currently being used as the reference method for diagnosis of deep venous thrombosis. Nevertheless, sensitivity of CUS is reported to be 60% and specificity 99.4%, with positive and negative predictive values being 75% and 98%, respectively.[12] Therefore, research to identify special molecules with high sensitivity and specificity for screening and early diagnosis of venous thrombosis draw special interest in the recent years.

It is known that venous thrombosis is associated with an inflammatory response. Understanding the pathophysiology of thrombus formation led the investigators to seek after the relationship between inflamatuar indicators and thrombosis. Inflammatory cells, adhesion molecules like selectins, cytokines and procoagulant microparticles seem to be related with the thrombogenic process.[13] Evaluation of these plasma molecules may serve in every stage of venous thrombosis; prediction, early diagnose or treatment. In the past decade, serologic parameters which are named as biomarkers have been investigated aiming to achieve prompt, definite and supportive diagnosis of DVT. Among these plasma molecules, D-Dimer is the best recognized and widely accepted biomarker for the initial diagnosis of venous thrombosis. Despite a negative value of D-Dimer may safely eliminate VTE with a high sensitivity of up to 95% and a negative predictive value of nearly 100%, it has a poor specificity to prove VTE.[14] In other words, D-Dimer is useful for exclusion of the disease because it is highly sensitive but lacks the specificity to confirm the diagnosis.[2] Other studied serum biomarkers are P-selectin, coagulation factor VIII, coagulation factor XI, thrombin generation, fibrin monomer, microparticles, E-selectin, leucocyte count, interleukin-10 and other cytokines.[2-4] Although there is growing evidence about the serum markers for venous thrombosis, currently there is still no single serum marker existing to demonstrate venous thrombosis, but they are being investigated widely.

Among these biomarkers, hematological variables obtained with complete blood cell analysis is especially attractive being a readily and easily attained examination performed almost for all patients. It is reported that leucocytes and erythrocytes play a role in the process of coagulation.[15-17] It has been demonstrated that there is a systemic leukocyte functional alteration in DVT[18] with leukocyte adhesion and transmigration being the early events in the initiation of DVT.[19] A strong association of leukocytosis with development of thrombosis was shown in patients with hematological malignancy.[20] In our study, we did not found a statistically significant relationship between the total white blood cell count and deep venous thrombosis in contrast with the subtypes of leucocytes. Neutrophil and lymphocyte counts were found to correlate with DVT existance, as well as NLR. NLR is accepted as an indicator of systemic inflammation and has been evaluated much in ischemic cardiac events and coronary surgery.[21,22] Recent studies also have demonstrated that NLR can be used as an independent factor in predicting mortality in patients with stable coronary artery disease or following CABG surgery.[23,24] However, there is not much study evaluating these parameters in deep venous thrombosis patients. In the literature search, we could found only one study other than ours, researching a relationship between DVT and NLR.[25] They concluded that NLR may be useful for risk stratification in patients with VTE. Our study confirms that NLR has a statistically significant correlation with DVT patients than normal population. NLR may be

used as a venous thrombosis predictor, but this statement yet needs to be supported with future studies. In our study, we failed to exhibit a relationship between white blood cell count and deep venous thrombosis in contrast with the subtypes of leucocytes. On the other hand, we executed that neutrophil count and lymphocyte count as well as NLR were significantly different in deep venous thrombosis group.

Haematocrit and related hematologic variables as hemoglobin and red blood cell count has also been investigated whether if they play a role in VTE. Haematocrit is associated with increased risk of cardiovascular disease and all cause mortality in general population.[26] Haematocrit is one of the major determinants of blood viscosity and patients with haematocrit levels exceeding normal range are predisposed to VTE.[27] A recent study investigating the impact of hemoconcentration on the risk of VTE prospectively concluded that haematocrit, haemoglobin and red blood cell count are risk factors for venous thromboembolism in general population whereas MCV was found not to be associated with VTE.[28] On the other hand, Rezende et al. reported an association between MCV and venous thrombosis, and exhibited an increased risk with higher blood monocyte count and RDW in a large case control study.[15] In another actual study, Zöller et al. concluded that RDW was found to be associated with VTE.[28] Similiarly, in our study we found that RBC count, haemoglobin and haematocrit levels (p value of all = 0.0001) have a statistically significant difference in DVT group whereas RBC count and RDW were found to be independent predictors. We failed to exhibit a relationship between monocyte counts - MCV and DVT in our study.

Study Limitations:

Although the demographic data of the groups like gender, diabetes mellitus, hypertension or hyperlipidemia were similar, the smoking profile and body mass index values were not included because of the unreliable data due to the retrospective nature of the study. As far as the literature knowledge, smoking and body mass index may influence hemogram parameters.

CONCLUSION:

In conclusion, CBC analysis is a feasible and readily obtained examination which is performed routinely in every speciality of medicine almost for every patient. We assumed that this readily obtained examination results may be telling us more than we already know about it. Although research about the role of the blood cell parameters on venous trombosis is not much to date, studies about finding clues of VTE development is growing. In the present study, we investigated whether if these parameters differ in patients with normal lower extremity Doppler venous function and patients with DVT. We exhibited that neutrophil and lymphocyte counts, NLR, RBC count, hemoglobin and haematocrit levels were all shown statistically significant differences in DVT patients. RBC count and RDW were found to be independent predictors. These parameters may serve as promising predictors in the diagnosis and guidance of treatment for DVT, but further research is required to express more definitive statements.

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