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RESEARCH ARTICLE **ÖZGÜN ARAŞTIRMA**

THE DIAGNOSTIC AND PROGNOSTIC VALUE OF RED CELL DISTRIBUTION WIDTH (RDW) IN CEREBRAL VENOUS THROMBOSIS

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ABSTRACT

INTRODUCTION: This study aimed to assess the diagnostic and prognostic value of red cell distribution width (RDW) which is an easily accesible parameter obtained from complete blood count in patients with cerebral venous thrombosis (CVT) in a single tertiary center.
METHODS: Medical records of 69 patients with cerebral venous thrombosis who were followed in our clinic were reviewed. Demographic characteristics, biochemical parameters, hemogram parameters, localization of the affected venous structures, admission NIHSS scores and mRS scores at discharge were recorded. Demographic characteristics and hemogram values of 60 age-sex matched healthy adults were also recorded.
RESULTS: RDW was demonstrated to be significantly higher in patient group (14.58± 2.33) when compared to controls (12.99± 0.76) ($p<0.001$*). Besides, mean hemoglobin and hematocrit values of patients were found to be lower than controls ($p<0.05$). In ROC curve analysis, an RDW value of >13.11% was found to have a sensitivity of 73.9% and specificity of 61.7% for diagnosis of CVT (AUC: 0.746 95% CI: 0.662-0.829, $p<0.001$). RDW demonstrated a significant positive correlation with mRS scores whilst no correlation was detected regarding NIHSS scores.
DISCUSSION AND CONCLUSION: This study demonstrates an independent association between RDW and presence of CVT. RDW is a simple and easily accessible marker obtained from routine hemogram examinations and our results support its use for diagnostic, as well as prognostic purposes in CVT patients.
Keywords: Cranial cerebral venous sinus thrombosis, erythrocyte indices, red cell distribution width, sinus sagittalis superior, transverse sinus thrombosis, venous infarct.

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SEREBRAL VENÖZ TROMBOZLARDA, ERİTROSİT DAĞILIM GENİŞLİĞİNİN (RDW) TANISAL VE PROGNOSTİK DEĞERİ

ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada, üçüncü basamak bir merkezde serebral venöz tromboz (SVT) olan hastalarda tam kan sayımından elde edilen kolay erişilebilir bir parametre olan eritrosit dağılım genişliğinin (RDW) tanısal ve prognostik değerinin değerlendirilmesi amaçlandı.
YÖNTEM ve GEREÇLER: Kliniğimizde takip edilen serebral ven trombozu olan 69 hastanın tıbbi kayıtları incelendi. Demografik özellikler, biyokimyasal parametreler, hemogram parametreleri, etkilenen venöz yapıların lokalizasyonu, başvuru NIHSS skorları ve taburculuk mRS skorları kaydedildi. Ayrıca 60 yaş-cinsiyet uyumlu sağlıklı yetişkinin demografik özellikleri ve hemogram değerleri kaydedildi.
BULGULAR: RDW'nin hasta grubunda (14,58±2,33) kontrollere (12,99±0,76) göre anlamlı derecede yüksek olduğu gösterildi (p<0,001*). Ayrıca hastaların ortalama hemoglobin ve hematokrit değerleri kontrollere göre daha düşük bulundu (p<0.05). ROC eğrisi analizinde, >%13,11'lik bir RDW değerinin, SVT tanısı için %73.9 duyarlılık ve %61.7 özgüllüğe sahip olduğu bulundu (AUC: 0.746 %95 CI: 0.662-0.829, p<0.001). RDW, mRS puanları ile anlamlı bir pozitif korelasyon gösterirken, NIHSS puanları ile ilgili herhangi bir korelasyon tespit edilmedi.
TARTIŞMA ve SONUÇ: Bu çalışma, RDW ile SVT varlığı arasında bağımsız bir ilişki olduğunu göstermektedir. RDW, rutin hemogram incelemelerinden elde edilen basit ve kolay erişilebilir bir belirteçtir ve sonuçlarımız, SVT hastalarında tanısal ve prognostik amaçlar için kullanımını desteklemektedir.

Anahtar Sözcükler: Kraniyal venöz sinus trombozu, eritrosit indeksleri, eritrosit dağılım, superior sagittal sinus, transvers sinüs trombozu, venöz enfarktüse.

INTRODUCTION

Cerebral venous thrombosis (CVT) is a rare subtype of stroke which comprises 0.5%- 1% of all stroke patients (1) and is estimated to affect about 13-15.7 million persons each year (2,3). Isolated headache or diplopia due to increased intracranial pressure can be the sole presenting symptom which does not alarm the physician to order a further study such as MR venography in case of a normal brain MRI. Early suspicion, of CVT in the differential diagnosis and initiation of a thorough workup procedure is essential since CVT sufferers are mainly young adults and mortality, morbidity can occur up to 30%, 44% of the cases respectively (4).

Red cell distribution width (RDW), which reflects the heterogenity of size in circulating red blood cells, is an easily available parameter obtained from complete blood count. It is calculated by dividing the standard deviation of mean corpuscular volume (MCV) by the MCV and multiplying by 100 (5). It is increasingly recognized as an indicator of diagnosis and prognosis in vascular disorders. The proposed mechanisms include diminution of deformability in microvascular disorder (6); anemia (7); inhibition of bone marrow and Erythropoietin (EPO) induced erythrocyte maturation in response to inflammatory cytokines (8); oxidative stress, free cholesterol and nutritional deficiency (7). The significance of RDW is well defined for acute coronary syndrome, ischemic stroke, deep venous thrombosis (DVT), pulmonary thromboembolism (PTE) and their consequences, whereas the relationship between RDW and CVT is uncertain. The use of RDW as a component of workup procedure in CVT is limited; because of quite few studies and insufficient data to make a comment about its real-life diagnostic value.

RDW is remarkably influenced by hemoglobin (Hb) levels and is known to increase in anemic patients who have decreased levels of Hb. Exclusion of anemic cases is plausible to some extent, for studies that investigate the diagnostic value of RDW. Similar concern is acceptable for CVT cohorts as well (9). On the other side, this exclusion gives rise to a complexity in identification of the diagnostic value of RDW in such cases. Therefore, we did not exclude the patients with anemia which is a frequent disorder among cases examined with the suspicion of CVT, and we aimed to demonstrate the real-life diagnostic and prognostic value of RDW in CVT.

METHODS

Study Population: Medical records of 69 patients who were admitted to our neurocritical care unit and followed in our neurology outpatient clinic with the diagnosis of cerebral venous thrombosis between 2012 and 2018 were retrospectively reviewed. Demographic characteristics, biochemical parameters, localization of the affected sinuses, admission the National Institutes of Health of Stroke Scale (NIHSS) scores and the Modified Rankin Scale (mRS) scores at discharge were recorded. Records of 60 age-sex matched healthy adults without systemic diseases and stroke who served as control group were also evaluated. At admission, all patients with CVT underwent brain MRI and MR Venography (1.5 AND 3 Tesla Magneton Aera and Verio; Siemens, Erlangen, Germany) after a detailed clinical assessment including history and neurological examination. The same experienced neuroradiologists evaluated the MRI scans.

Detailed biochemical and hematological assessment was performed for each patient in order to identify possible etiologies such as malignancy and coagulation disorders. All patients were included in the study to establish a real-life patient population. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and study protocol was approved by Gazi University Non-Interventional Clinical Research Ethics Committee (Date: 12.02.2018, No: 96)

Laboratory Tests: Peripheral venous blood samples were collected from each patient for complete blood cell testing, biochemical tests and thrombophilia screening. For complete blood cell testing, venous blood samples were collected into vacuum tubes containing EDTA as anticoagulant. For biochemical testing, blood samples were collected into standard tubes without anticoagulants. Thrombophilia screening was performed on venous blood samples collected into tubes containing 3.2% sodium citrate. Tests were performed at the same day of blood sample collection.

Complete blood cell tests including hemoglobin level, hematocrit, platelet count, white blood cell (WBC) count and RDW were performed by an automated hematological analyzer (Unicel® DxH800 automated hematology analyzer). Automated analyzer calculated RDW by dividing the standard deviation of the mean corpuscular volume (MCV) by the mean MCV and express the result as a percentage (10). The lower and upper reference range limits for RDW were 11.5% and 14.5% for the analyzer used in our institution's laboratory.

Statistical Analysis: SPSS software (IBM SPSS Statistics for Windows, Version 21.0. SPSS Inc., Chicago, Illinois, USA) was used for statistical analyses. Normality of the distribution of continuous parameters was tested with Shapiro-Wilk test. Normally distributed continuous parameters were presented as mean± standard deviation and compared with Student's t test. Skewed continuous parameters were expressed as median (minimum–maximum) and compared with Mann-Whitney U test. Categorical data were expressed as frequencies and percentages and were compared with chi-square test. Univariate and multivariate logistic regression analyses were performed to determine independent associates of CVT. Diagnostic power was evaluated by receiver operating characteristic (ROC) curve analysis. A two-tailed p value <0.05 was considered statistically significant.

RESULTS

The mean age was 42.2±13.62 years in CVT patients and 39.25±11.89 in the control group. There were 42 (60.9%) females in CVT group and 36 (60%) females in control group. Both age and gender distribution were similar between the two groups ($p>0.05$). The demographic characteristics and hemogram values of patients with CVT and controls are given in the Table 1. The most common involved sinuses were transverse venous sinus in 51 (73.9%), sigmoid sinus in 37 (53.6%) and superior sagittal sinus in 26 (37.6%) patients with multiple cerebral venous sinus involvement in the majority. The most common localization of isolated venous vascular structures were superior sagittal sinus (SSS) (15.9%), transverse sinus (TS) (11.6%) and the cortical veins (8.7%). Multiple venous involvement did comprise the greatest proportion (33.3%) (Table 2). 28 patients (41%) had venous infarction, 59% had normal parenchymal imaging findings.

Etiological workup revealed inherited thrombophilia (DNA analysis for factor V Leiden, MTHFR and G20210A polymorphism in the prothrombin gene) in 31.9% of patients; defects of

Table 1. Demographic characteristics and laboratory findings of the study population.

	CVT patients (n=69) mean± SD	Controls (n=60) mean± SD	p value
Age (years)	42.23±13.62	39.25±11.89	0.233
Gender: Female n (%)	42 (60.9%)	36 (60%)	0.920
Hemoglobin (g/dL)	13.27±2.58	14.19±1.50	
†*Normal range:*			**0.036***
- 12-14.6 (female)			
- 13-16.9 (male)			
Hematocrit (%)	39.84±7.33	43.05± 4.05	
†*Normal range:*			**0.004***
- 36.6-44 (female)			
- 40-49.4 (male)			
WBC (x10³/uL)	7.65±2.27	7.11±1.76	
†*Normal range:*			0.133
- 4.49-12.68 (female)			
- 3.91-10.9 (male)			
PLT (x10³/uL)	265.94±	267.8± 72.84	
†*Normal range:*	114.98		0.585
- 173-390 (female)			
- 166-308 (male)			
MCV (fL)	85.11±7.96	87.02±3.82	
†*Normal range:*			0.692
- 82.9-98 (female)			
- 81.8-95.5 (male)			
RDW (%)	14.58± 2.33	12.99± 0.76	
†*Normal range:*			**<0.001***
- 11.5-14.5 (female)			
- 11.5-14.5 (male)			

WBC; white blood cell, PLT; platelet, MCV; mean corpuscular volume, SD; standard deviation, RDW; red cell distribution width. † Normal range/cut off values of our laboratory.

Table 2. The involved cerebral venous sinuses and corresponding RDW values in patients with CVT.

Localization of CVT	Number of patients (%)	RDW
Isolated TS	8 (11.6 %)	14.57±1.47
Isolated SSS	11 (15.9 %)	14.09±2.17
Isolated SS	1 (1.4 %)	12.1
Isolated IJV	2 (3 %)	13.65±0.74
Cortical veins	6 (8.7 %)	15.09±2.46
TS+SSS/TS+S/S+IJV	16 (23.2 %)	14.78±2.45
TS+SSS+SS/TS+S+IJV	23 (33.3 %)	14.62±2.73
TS+SSS+SS+IJV	2 (2.9 %)	15.99±1.71

RDW; red cell distribution width, TS; transvers sinus, SSS; superior sagittal sinus, SS; Sigmoid sinus, IJV; Internal jugular vein.

the natural anticoagulant pathway (protein C, protein S and antithrombin III deficiencies) in 24.6% of patients and malignancy was found in 14.5% of patients with CVT. Puerperium (13%), oral contraceptive use (11.6%) and infections (10.1%) were the other frequent risk factors (Table 3).

No difference was detected in terms of white blood cell (WBC) and platelet count, as well as

Table 3. Etiology of CVT and related RDW values of the CVT patients.

Risk factors	n (%)	Red cell distribution width (RDW)
Genetic thrombophilia	22 (31.9 %)	14.08±1.76
Protein C-S and Antithrombine-III deficiencies	17 (24.6 %)	14.13±1.69
Malignancy	10 (14.5 %)	15,75±1.76
Puerperium	9 (13 %)	13.86±0.98
Oral contraceptives	8 (11.6 %)	13.04±0.63
Infections	7 (10.1%)	12.82±0.59
Systemic vasculitis	6(8.7 %)	16.91±3.65
Behcet's disease	2 (2.9 %)	16.21±2.41
Secondary to lumbar puncture	1 (1.4 %)	14.77
Pregnancy	1 (1.4 %)	17.34
Trauma	1 (1.4 %)	14.2

MCV between patient and control groups (p>0.05). Considering the other red cell indices, RDW was demonstrated to be significantly increased in the patient group compared to controls (p<0.001*). Besides, mean hemoglobin and hematocrit values of patients were found to be lower than controls. (p<0.05) According to the cut-off values of our laboratory 29% of the patients were anemic, while the corresponding ratio for controls was only 6.7% (p=0.001*) (Table 1). Although hemoglobin and RDW values were both significant in univariate regression analysis; multivariate regression revealed that there was an independent association between RDW and CVT (OR: 2.480 95% CI:1.564-3.933, p<0.001) (Table 4). In ROC curve analysis, a RDW value of >13.11% was found to have a sensitivity of 73.9% and specificity of 61.7% for diagnosis of CVT (AUC: 0.746 95% CI: 0.662-0.829, p<0.001) (Figure). Mean RDW values did not differ between the cases with or without venous infarction. (14.9±2.67 vs 14.3 ±2.04 p=0.277) Both median NIHSS and mRS scores of CVT patients were 0 [median: 0 (0-20), mean: 2.23±4.38 for NIHSS and median:0 (0-5), mean: 0.41±1.11 (0-5) for mRS] on admission. RDW demonstrated a significant positive correlation with mRS scores whilst no correlation was detected regarding NIHSS scores.

DISCUSSION AND CONCLUSION

In this retrospective study, we evaluated the diagnostic role of red cell indices, particularly RDW, in CVT patients. Our results demonstrated that; CVT patients had significantly higher RDW but also lower Hb values when compared to controls.

Table 4. Regression analysis demonstrating independent associates of CVT presence.

Parameters	Univariate analysis			Multivariate analysis	
	B± SE	95% CI	p value	OR (95% CI)	p value
Hemoglobin	0.810±0.091	0.679-0.968	**0.020**	1.026 (0.821-1.283)	0.819
RDW	2.444±0.224	1.577-3.789	**<0.001**	2.485 (1.566-3.944)	**<0.001***

RDW; red cell distribution width, B; Unstandardized Beta, SE; standard error, CI; confidence interval, OR; odds ratio.

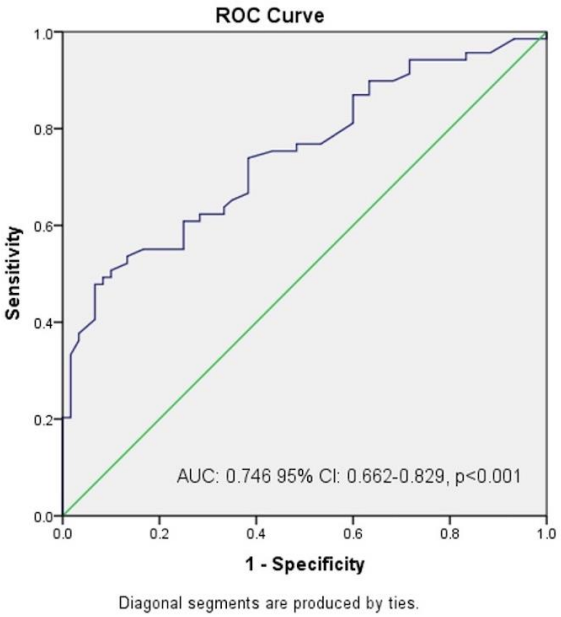

Figure. ROC curve analysis demonstrating the sensitivity and specificity of RDW for diagnosis of CVT.

The predictive role of RDW has been identified in recent years for diagnosis and prognosis of various vascular disorders and their consequences. These include myocardial infarction, coronary atherosclerosis, heart failure, atrial fibrillation, stroke, pulmonary thromboembolism and deep venous thrombosis (7). Nevertheless, data including CVT is quite scarce and insufficient to make a comment about the real-life diagnostic value. In a cohort of 143 patients and 352 controls; Maino et al identified association of increased CVT risk with only extreme RDW values (>90 percentile) (14.6%). However, they observed no graded association between RDW values and CVT risk over quartiles (11). The authors highlighted that the absence of such a stepwise correlation might be plausible since CVT is a very distinctive form of venous thrombosis due to the location and mechanism of pathological process (11). Demir et al examined the significance of RDW in the diagnosis of CVT, among 138 patients who were admitted to emergency unit with headache complaints. They identified RDW as a powerful tool in the differentiation of CVT from primary headache (9). The correlation which we observed between RDW and discharge mRS scores of CVT patients indicate that; RDW is also associated with poor functional status at early stage. In contrast to cerebral venous structures, association between peripheral venous involvement and RDW has been identified many times so far. For instance, Rezende et al defined a strong dose-response relation for RDW and venous thrombosis risk with odds ratio of 3.1 in a cohort of 2473 patients and 2935 controls whose data was derived from MEGA study (12-14). The dose-response effect that they observed for RDW demonstrated increasing odds ratios above 95th percentile and 14.1% was proposed as a cut-off value, although standing within the normal range (12). In a study with 51 hospitalized DVT patients, Oguz demonstrated that DVT patients with mortal course had higher RDW values than discharged ones, and discharged patients with DVT diagnosis –despite their favorable course- had higher RDW values than healthy controls (15). Lippi et al investigated the diagnostic value of RDW in a study population of venous thrombosis patients (superficial and deep venous thrombosis and/or pulmonary thromboembolism patients) and 967 controls who were evaluated in the emergency unit. The authors reported significantly increased RDW in patients when compared to controls and identified a marked incremental trend of values from superficial venous thrombosis, isolated DVT to PTE. Increased RDW was found to be an independent risk factor for isolated DVT and PTE, and ROC curves disclosed its significant diagnostic performance on admission to the emergency unit (16).

Contrary to the majority of abovementioned studies, which did not reveal any difference of red cell indices other than RDW between DVT patients and healthy controls; patient group in our study cohort had lower Hb levels along with higher RDW values. This raised the question whether increased RDW in our patients indeed was situated at a

proximal step throughout this pathological pathway –eg. providing a cause and effect relationship-, or just a simple accompaniment of anemia rather than being a predictor of existing CVT. However multivariate regression revealed that there was an independent association between RDW and presence of CVT.

Increased RDW levels in CVT may be subsequent to various mechanisms and inflammation is one of the most featured ones. There is an indisputable link between CVT and inflammation, since numerous studies in the literature exist which document increased inflammatory markers in serum [Hs-CRP, IL-6, Neutrophil / Lymphocyte ratio (NLR), (Platelet / Lymphocyte ratio (PLR), Monocyte/HDL ratio] and CSF (IgA, IgM, IgG) samples of CVT patients (17-19). Inflammation leads to alterations in erythropoiesis by inhibiting either EPO gene transcription in liver- kidney or erythroid cell maturation in the bone marrow (7) which finally results in impaired production and release of RBCs, together with increased RDW as a result. Additionally, inflammation is known to have negative effects on iron metabolism and nutritional status, which contributes to disordered erythropoiesis and increased RDW through two additional different pathways (20,21). Anemia, especially iron deficiency anemia of which increased RDW is almost sine qua non, is another well defined contributor for CVT. Both increased cerebral blood flow due to reduced oxygen carrying capacity and turbulent flow arising from diminished potential of RBCs' deformability take part in activation of coagulation cascade and subsequent thrombus formation (22,23). Oxidative stress in CVT that have been shown in experimental models, may be another explanation for increased RDW (24,25). Oxidative stress is known to deteriorate the mechanical properties of RBCs whose deformability decreases above RDW levels of 14% and gives rise to insufficient tissue perfusion (6,26).

The study has some limitations due to its retrospective design and limited number of participants. First, long-term mRS scores were not available for all cases and we only took the mRS scores at discharge into account. mRS scores reflect the functional status of patients and it is obvious that scores in the subacute phase go parallel with the scores of follow-up (similar trend in follow up). However, the prognostic value of RDW in CVT patients, as observed in other cardio-cerebrovascular diseases is uncertain because of the limitations of our study. Second, including CVT patients with anemia might be considered as a confounder. However, the frequency of anemia in patients with CVT can not be overlooked and excluding these patients would not be an appropriate approach when the concern is providing a real life diagnostic value for RDW in CVT.

In conclusion, this study demonstrates an independent association between RDW and presence of CVT. RDW is a simple and easily accessible marker obtained from routine hemogram examinations and our results support its use for diagnostic purposes in CVT patients. Further studies with larger cohorts and prospective design would be beneficial for a more precise assessment of its prognostic potential.

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Ethics

Ethics Committee Approval: The study was approved by Gazi University Non-Interventional Clinical Research Ethics Committee (Date: 12.02.2018, No: 96)

Informed Consent: The authors declared that informed consent was not obtained from the patients because of the retrospective study design.

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