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Determination of Red Blood Cell Distribution Width in Patients with Primary Cutaneous Vasculitis Compared to Systemic Vasculitis

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Abstract

Introduction: *Red blood cell distribution width (RDW) has been considered as an inflammatory marker in various disorders. Evaluation of RDW value can also be used as a novel and additional marker for differentiating systemic vasculitis from primary cutaneous vasculitis. Objective: To compare RDW value between patients with cutaneous vasculitis with systemic vasculitis, thereafter to find out it's role as an effective indicator to distinguish both forms of vasculitis.* ***Materials and Methods:*** *This cross sectional observational study was conduct between from July 2016 to December 2017. Total of 48 patients were divided into primary cutaneous vasculitis and systemic vasculitis. Blood was collected in EDTA tube to measure RDW value. Patient's disease activity also scored and plotted according to Birmingham vasculitis activity score. Statistical analysis was performed by using SPSS.* ***Results:*** *Significantly high mean RDW were found in patients with systemic vasculitis compared to primary cutaneous vasculitis (15.09±0.92 vs. 13.48±1.1, p = 0.000). BVAS was significantly greater (13.93±5.10 vs. 4.87±2.69, p = < 0.001) in systemic vasculitis as well as in patients with high RDW group (11.73±5.71 vs. 5.37±3.96, p = < 0.001). Optimal RDW cut off point for differentiating systemic vasculitis from cutaneous vasculitis was 14.2 with 81.3% sensitivity and 81.2% specificity.* ***Conclusion:*** *Present study revealed importance of RDW monitoring along with disease activity in patients with any form of vasculitis. Systemic vasculitis had higher level of RDW. So RDW can be considered as a marker to discriminate systemic vasculitis from primary cutaneous vasculitis.*

Key words: *Red blood cell distribution width, Vaculitis, BSMMU.*

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Introduction:

Vasculitis refers to a group of disorders in which there is inflammation and damage in blood vessel walls, leading to tissue necrosis[1]. When vasculitis affects small or medium sized blood vessels in the skin, it is known as primary cutaneous vasculitis. The primary systemic vasculitis are heterogeneous, multi-system disorders characterized by inflammation and necrosis of medium or large blood vessels mainly. About half of all patients presenting with cutaneous vasculitis have self limited disease confined to the skin[2,3] Sometimes cutaneous vasculitis occurs as an initial manifestation of primary systemic vasculitis or it can also later progress to systemic vasculitis infrequently. Though the percentage of patients reported to have cutaneous involvement varies according to the type of vasculitis in previous reports, it is regarded to occur around 50% of primary systemic vasculitis [4].

Vasculitis is relatively uncommon disorder, with a reported annual incidence of 40 to 54 cases per 1 million persons[5]. The pathogenesis of vasculitis is poorly understood. Three possible mechanisms of vascular damage are immune complex deposition, ANCAs (humoral response) and T-lymphocyte (cell mediated) response with granuloma formation[6,7].

Red blood cell distribution width (RDW) is a numerical measure of the variability in size of circulating erythrocyte[8] and is routinely reported by analyzer as part of routine CBC. Thus elevated RDW means that there is an increased heterogenecity in size of red cells in the peripheral blood[9]. In fact, various inflammatory cytokines are

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known to induce changes in iron homeostasis, the proliferation of erythroid progenitor cells, the production of erythropoietin and the life span of RBC[10]. Increased inflammatory cytokines in systemic vasculitis may contribute to RDW elevation by releasing immature RBCs into peripheral circulation[11]. As a matter of fact, there is a study which showed increased serum cytokines in systemic vasculitis [12]. Therefore, increased inflammatory cytokines may be attributed to elevation of RDW in systemic vasculitis; it will need further investigation to establish precise relationship between inflammation and RDW elevation in systemic vasculitis.

The vasculitides remain a challenge in terms of diagnosis and treatment. The recognition of disease remains unsatisfactory in the absence of any gold standard tests. The clinical presentation and correct use of appropriate laboratory tests, imaging and pathology are essential to assist in making an early diagnosis. Finding a marker which can indicate systemic vasculitis in patients with cutaneous presentation is very important. Despite many researchers have focused on this issue, there are no single definite standard method to predict systemic vasculitis.

As a possible integrative measure of multiple pathologic factors (nutritional deficiencies, inflammatory stress, and renal dysfunction), RDW has been hypothesised to be associated with several disease processes including occult colon cancer, neoplastic metastases to marrow, liver disease, and heart failure[13,14,15,16]. Recently one report has pointed to a possible role of RDW in inflammatory bowel disease as an additional inflammatory marker[17]. Two other studies have shown that RDW can be potentially used as a marker for differentiating crohn's disease from ulcerative colitis[18,19]. The results were promising because RDW can be routinely obtained from blood count, which is a simple, inexpensive, and readily available tool that provides potential for high rates of patient acceptance and compliance.

Raised RDW is associated with inflammatory cytokines released in systemic vasculitis, it may be analyzed in patients who has cutaneous vasculitis, or cutaneous vasculitis with systemic involvement. We designed the present study to observe whether RDW could be used for the assessment of disease activity severity in our patients with systemic vasculitis and tried to find out whether RDW could serve to differentiate cutaneous vasculitis from systemic vasculitis.

Materials and Methods:

This cross sectional study was conducted in the Department of Dermatology & Venereology and Rheumatology Vasculitis Clinic, Bangabandhu Sheikh Mujib Medical University, Dhaka from July, 2016 to December, 2017.

Total of 48 patients with primary cutaneous vasculitis (32 patients) and systemic vasculitis (16 patients) were enrolled following inclusion and exclusion criteria. Inclusion Criteria were i)Patients with cutaneous vasculitis (clinical, histopathology with DIF) ii) Patients with systemic vasculitis (clinical, histology, urinaiysis, eosinophil count, ANCA and radiology) iii) Patients of any age and both sexes. iv) Patients with medical conditions where RDW is well known to be increased v) Patients with history of taking drugs that may cause vasculitis.

Cutaneous and systemic vasculitis were compared on the basis of following variables, i) Age, ii) Gender, iii) Disease Duration, iv)RDW (Red blood cell distribution width), v) WBC (White blood cell vi) RBC (Red blood cell) vii) Hb (Hemoglobin) viii) MCV (Mean corpuscular volume) ix) Platelet x) ESR (Erythrocyte sedimentation rate), xi) CRP (C-reactive protein) xii) Serum creatinine, xiii) ALT (Alanine aminotransferase), xiv) BVAS (Birmingham vasculitis activity score).

Before enrolment in this study informed written consent were taken from the patients after full explanation of the purpose of the study. The age, sex, disease duration, clinical feature and the investigations along with RDW level were recorded in a standard and pre-tested semi-structured questionnaire. Each patient's disease activity was also scored and plotted according to Birmingham vasculitis activity score (BVAS).

3 ml of venous blood was collected from each patient, drawn into EDTA tube. Within 4 hours of collection sample was run through an automated hematology analyzer (Sysmax-XT 2000 i) at Department of Hematology, BSMMU to assay RDW value as a part of a standard complete blood count and it is used along with other RBC indices, especially mean corpuscular volume (MCV).

The XT-2000i hematology analyzer uses unique fluorescence flow cytometry (FFC) technology. FFC looks at RNA/DNA content, cell size and inner cell complexity rather than cell size alone.

Calculated red cell indices are mean cell hemoglobin (MHC), mean cell hemoglobin concentration (MCHC) and the red cell distribution width (RDW). Red cell distribution width (RDW) is reported on the Sysmax XT as both standard deviation from the mean red cell size (RDW-SD) and as coefficient of variation from the mean (RDW-CV). The RDW-CV is a calculation based on both the width of the distribution curve and the mean cell size. It is calculated by dividing the standard deviation of the mean cell size by the MCV of the red cells and multiplying by 100 to convert to a percentage.

In our laboratory, normal range for the RDW-CV is approximately 11.6% - 14%.

Statistical analyses was performed by using the Statistical Package for the Social Science (SPSS) software version 22.0 for windows (SPSS Inc, Chicago, Illinois, USA). Quantitative variables (age, duration, RDW %, WBC, RBC, Hb%, MCV, Platelet, ESR, CRP, Creatinine, ALT, BVAS) were expressed as mean ± SD & comparison between cutaneous and systemic vasculitis were done by student's t test. Qualitative data (gender) was expressed as frequency & percentage and comparison between the two groups was carried out by Chi-square (X^2) test. Fisher's Exact test was done to compare the severity of disease

activity between both types of vasculitis. A cut off value was drawn between the two groups by ROC curve analysis. According to baseline RDW value, patients were categorized into a high RDW group (>14%) and a normal RDW group as well as systemic and cutaneous vasculitis group were compared. For all statistical tests, p-value less than 0.05 was considered as statistically significant.

Results:

The mean age of systemic vasculitis group and cutaneous vasculitis group were 36.75±13.67 and 25.16±9.47 months respectively which set significant difference by unpaired t test (p<0.001). Males were mostly (68.8%) affected by systemic vasculitis and females (59.4%) were mostly affected by cutaneous vasculitis but not statistically significant. Most of the patients belong to urban area in both vasculitis. A greater portion of patients with systemic vasculitis were service holder but most of the participants from cutaneous vasculitis group were either student or housewife. Majority of patients from both groups were graduate (Table I).

Table-I: Demographic characteristics of study patients (n=48).

Age (years)	Systemic vasculitis (n=16) n (%)	Cutaneous vasculitis (n=32) n (%)	P value
Age (years)	36.75 ± 13.67	25.16 ± 9.47	<0.001[a]
Gender			
Male	11 (68.8)	13 (40.6)	0.066[b]
Female	5 (31.2)	19 (59.4)	
Residence			
Urban	10 (62.5)	25 (78.1)	0.251[b]
Rural	6 (37.5)	7 (21.9)	
Occupation			
Housewife	1 (6.3)	12 (37.5)	0.007[b]
Service	7 (43.8)	6 (18.8)	
Business	5 (31.3)	2 (6.3)	
Student	3 (18.8)	12 (37.5)	
Education			
Illiterate	1 (6.3)	1 (3.1)	0.733[b]
Primary	2 (12.5)	8 (25.0)	
SSC	3 (18.8)	6 (18.8)	
HSC	3 (18.8)	8 (25.0)	
Graduate	7 (43.8)	9 (28.1)	

a = Unpaired t test was done to measure the level of significance
b= Chi-square test was done to measure the level of significance

LCV was the commonest presentation of cutaneous vasculitis (62.5%) and PAN was the commonest presentation of systemic vasculitis (43.8%). (LV=Livedoid vasculopathy, CSS=Churg strauss syndrome, UV=Urticarial vasculitis, WG=Wegener's granulomatosis, HSP=Henoch schönlein purpura, PAN= Polyarteritis nodosa, LCV=Leukocytoclastic vasculitis) (Table II).

Table-II: Distribution of study subjects by type of vasculitis (n=48).

Diagnosis	Systemic vasculitis (n=16) n (%)	Cutaneous vasculitis (n=32) n (%)	Total (n=48) n (%)
LCV	0 (0.0)	20 (62.5)	20 (41.7)
HSP	0 (0.0)	6 (18.8)	6 (12.5)
CSS	3 (18.8)	0 (0.0)	3 (6.3)
PAN	7 (43.8)	0 (0.0)	7 (14.6)
LV	0 (0.0)	4 (12.5)	4 (8.3)
WG	6 (37.5)	0 (0.0)	6 (12.5)
UV	0 (0.0)	2 (6.3)	2 (4.2)

Most of the patient (81.2%) in systemic vasculitis group had high RDW (>14 %) and most of the patients (81.2%) in cutaneous vasculitis had normal RDW (11.6-14)% .

In systemic vasculitis group, 18.8% patients had normal RDW and in cutaneous vasculitis group 18.8% patients had elevated RDW.

Mean RDW value of systemic vasculitis patients was significantly greater than patients with primary cutaneous vasculitis (15.09±0.92 vs. 13.48±1.1, p = 0.000).

Unpaired t test was done to measure the level of significance. The vasculitis activity score (BVAS) along with mean RDW is significantly higher in systemic vasculitis compared to cutaneous vasculitis. Disease duration, WBC, RBC, CRP, Hb% also show significant difference between the two groups.

Most of the patients (87.5%) in systemic vasculitis group had higher disease activity score (more severe) and only small number of patients (6.3%) in cutaneous vascultis group depicted such score(Table : III) .

Table-III:Comparison of disease activity severity between cutaneous and systemic vasculitis (n=48) :

BVAS	Systemic vasculitis (n=16) n (%)	Cutaneous vasculitis (n=32) n (%)	P value
0 - 8	2 (12.5)	30 (93.8)	
>8	14 (87.5)	2 (6.3)	<0.001
Total	16 (100.0)	32 (100.0)	

Fisher's Exact test was done to measure the level of significance

Baseline characteristics of patients according to RDW value. A total of 19 patients (39.58)% had high RDW and 29 patients had normal RDW (11.6-14)%. Patients with RDW above the reference range had significantly higher ESR (28.37±23.93 vs. 50.05±34.07, p = 0.013), higher CRP (4.83±2.86 vs. 15.68±21.56, p = .010) and very significantly high BVAS (5.37±3.96 vs. 11.73±5.71, p = < 0.001) in comparison to patients with normal RDW. There were no significant difference regarding age, sex, disease duration and other laboratory parameters between the two groups (Table IV).

Table-IV: Comparison of clinical and laboratory parameters according to baseline red blood cell distribution width.

Parameter	RDW≤14 (n=29) Mean±SD	RDW>14 (n=19) Mean±SD	p value
Age (years)	27.76±11.52	30.95±13.30	0.382
Sex (M/F)	15/14	9/10	0.768
Duration (months)	12.75±25.04	18.68±23.31	0.414
WBC count (10^9/L)	11.14±3.91	12.82±4.21	0.165
RBC count (10^{12}/L)	4.56±0.63	4.20±0.71	0.072
Hb (%)	12.88±2.04	11.30±2.04	0.052
MCV (fl)	85.74±5.57	82.66±5.77	0.072
Platelet count (10^9/L)	301.31±94.88	315.68±125.98	0.655
ESR (mm)	28.37±23.93	50.05±34.07	0.013
CRP (mg/dl)	4.83±2.86	15.68±21.56	0.010
S. creatinine (mg/dl)	0.83±0.20	0.81±0.28	0.870
ALT (U/L)	26.68±16.47	32.26±21.08	0.310
BVAS	5.37±3.96	11.73±5.71	<0.001

Unpaired t test was done to measure the level of significanc

Discussion:

The present study aimed to compare the mean RDW value between 16 patients of systemic vasculitis and 32 patients of cutaneous vasculitis with a view to observe it's effective

role to predict systemic vasculitis.

The mean age of cutaneous vasculitis group is 25.16±9.47 (mean±SD) months and most (34.4%) of the patients belongs to age group 19-28 with female predominance (59.4%). The findings of this study regarding age and sex is quite resembles with the findings of Hyderabad study[19].

In our study among 32 cutaneous vasculitis patients leukocytoclastic vasculitis (LCV) was commonest (22 patients 62.5%), 6 patients of Henoch–Schönlein purpura (HSP) (18.8%) , 4 patients of livedoid vasculopathy (LV)(12.5% and 2 patients of urticarial vasculitis (UV) (6.3%). This finding is quite similar to the finding of Asaduzzaman et al[20].

Primary systemic vasculitis is more common in males (23.5/ million, 95% CI 17.3-31.3) than females (16.4 million, 95% CI 11.4-22.8). The age and sex specific incidence showed a clear increase with age, with an overall peak in the 65-74 year group[21] .The present study shows that mean age of systemic vasculitis group is more (36.75±13.67 vs 25.16±9.47) than cutaneous vasculitis group along with male predominance (68.8%). All the participants of this study were younger in comparison to other study[21] and this dissimilarity may be due to population based different methodological study.

In our study, PAN was the commonest (43.8%) presentation of systemic vasculitis, then WG (37.5%) followed by CSS (18.8%) respectively. Though MPA was the second most prevalent systemic vasculitis according to Mahr et al study[22], no patient of microscopic polyangitis was found in our study. This could be due to racial difference.

It has been showed that 81.2% patients with systemic vasculitis and only 18.8% patients with cutaneous vasculitis has high RDW value. The mean RDW of patients with cutaneous vasculitis is within normal limit. RDW didn't significantly higher in patients with cutaneous vaculitis than in healthy control[23]. This observation is in agreement with our study.

In the current study, mean RDW value of patients with systemic vasculitis is significantly greater than in patients with primary cutaneous vasculitis (15.09±0.92 vs. 13.48±1.1, p = 0.000). The RDW cut-off point for differentiation of systemic vasculitis from cutaneous vasculitis has observed at 14.2 with 81.3% sensitivity and 81.2% specificity and area under curve was 0.877 (CI 0.779-0.975). This inference is also supported by the other study[24].

RDW elevation strongly correlate with the inflammatory markers including ESR, CRP, Platelet, and MPV[25]. Lippi et al demonstrated graded association of RDW with high sensitive CRP and ESR independent of numerous confounding factors like age, sex, Hb%, MCV, ferritin[26]. This cross sectional study has also delineated that ESR and CRP level change along with rising RDW. Patients with high RDW (>14.2%) has raised ESR and raised CRP compared to patients with RDW within the normal range (11.6-14)%. There is no significant difference in age, sex, disease duration, MCV and other laboratory parameters between the two groups.

In this study, vasculitis activity score also is significantly higher in patients with systemic vasculitis (13.95±5.10 vs. 4.87±2.69, p =0.000) compared to cutaneous vasculitis. Most of the patients (87.5%) in systemic vasculitis group has higher disease activity score (BVAS>8) and only small number of patients (6.3%) in cutaneous vascultis group has depicted such score. BVAS score is also significantly greater in high RDW group (11.37±5.71 vs 5.37±3.96) compared to normal RDW group. In 2014, Kim et al stated RDW as an independent predictor of systemic vasculitis in patients with primary cutaneous vasculitis by performing multivariate logistic regression analysis with different laboratory parameters showing significant difference between cutaneous and systemic vasculitis[24]. Though clinical parameter like disease activity was not included. But the current study has observed significant difference between the two groups on the basis of patient's age, disease duration, WBC, RBC, Hb%, CRP, ESR and BVAS. Here, an attempt has been made to show RDW as a tool to predict vasculitis activity and poor prognosis.

Meanwhile, RDW has been considered to be associated with disease activity or prognosis of various inflammatory diseases. Cytokines act as a diagnostic marker and biomarker of vasculitis disease activity[27]. Therefore, in our study, increased inflammatory cytokines may be the attributed factors for elevation of RDW in systemic vasculitis. Hence, in this study, we have not only compared the mean RDW values but also tried to set up a cut off value between the two groups and observed it as a predictor of systemic vasculitis based on BVAS.

Conclusion:

In this study, increased level of RDW was observed in most of the patients of systemic vasculitis in comparison to primary cutaneous vasculitis. Statistically significant difference of RDW value was found between both forms of vasculitis. As diagnostic dilemma occurs between primary cutaneous vasculitis and initial cutaneous presentation of systemic vasculitis, very high RDW value may be used to differentiate them considering other laboratory and clinical parameter including BVAS.

Conflict of Interest: None.

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