ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

DOI:10.5505/ktd.2022.69926
Kocaeli Med J 2022;11(1):9-14

The Association Between Red Cell Distribution Width and Bone Marrow Fibrosis in Patients with Philadelphia-Negative Myeloproliferative Neoplasms

Philadelphia Kromozomu Negatif Myeloproliferatif Neoplazili Hastalarda Erirosit Dağılım Genişliği İndeksi ile Kemik İliği Fibrozisi Arasındaki İlişkinin Değerlendirilmesi

Ceyda Aslan[1], Abdülkadir Karışmaz[2], Rafet Eren[3], Şermin Altındal[4], Mehmet Hilmi Doğu[5], Elif Suyanı[6]

[1] University of Health Sciences Derince Training and Research Hospital, Department of Hematology, Kocaeli, Turkey
[2] Yozgat City Hospital, Department of Hematology, Yozgat, Turkey
[3] University of Health Sciences Bozyaka Training and Research Hospital, Department of Hematology, İzmir, Turkey
[4] University of Health Sciences İstanbul Training and Research Hospital, Department of Hematology, İstanbul, Turkey
[5] Istinye University Liv Hospital, Department of Hematology, İstanbul, Turkey
[6] Department of Hematology, University of Health Sciences Adana City Training and Research Hospital, Adana, Turkey

ABSTRACT

Objective: Red cell distribution width (RDW) was shown to be increased in primary myelofibrosis (PMF) patients and it is intriguing whether RDW could be used instead of biopsy in predicting presence of bone marrow fibrosis (BMF) to some extend in Philadelphia-negative myeloproliferative neoplasms (MPNs) comprising polycytemia vera (PV), essential thrombocytosis (ET) and PMF. Our aim is to evaluate the relationship between BMF degree and RDW values in patients with MPNs.

Method: We retrospectively reviewed the data of 118 patients, who were followed with the diagnosis of MPNs at our Hematology Clinic between 2010 and 2017.

Results: 52 patients had PV, 60 had ET, 4 had PMF and 2 had unclassifiable MPN. Twentynine (24.6%) patients were with grade 0 and grade 1 reticulin fibrosis were considered to be free of BMF, and the remaining 89 (75.4%) patients with ≥ grade 2 reticulin fibrosis were considered to have BMF. The median RDW value was 14.6% (range 12,4-23,1%). The median RDW value revealed with 14.1% (range, 12.4-17.8) in patients without BMF and 15% (range, 12.4-23.1) in patients with BMF (p=0.054). In subgroup analysis of 8 patients with advanced BMF of grade 3, the median RDW value was 18.45% (range, 16.4-23.1) and it was 14.45% (range, 12.4-23) in the remaining 110 patients (p=0.008).

Conclusion: Although the present study does not provide a precise conclusion about the association between RDW and BMF, it seems that increased RDW can point out the presence of advanced BMF in patients with MPNs.

Keywords: red cell distribution width, chronic myeloproliferative neoplasms, bone marrow fibrosis

ÖZ

Giriş: Eritrosit dağılım genişliğinin (RDW) primer miyelofibroz hastalarında arttığı gösterilmiştir ve Philadelphia-negatif miyeloproliferatif neoplazilerde (MPN) kemik iliği fibrozisi varlığını tahmin etmede biyopsi yerine RDW'nin kullanılıp kullanılamayacağı ilgi çekicidir. Çalışmamızın amacı: Polisitemi vera (PV), esansiyel trombositoz (ET) ve PMF alt tiplerini içeren MPN'li hastalarda myelofibroz derecesi ile RDW değerleri arasındaki ilişkiyi değerlendirmektir.

Yöntem: Hastanemizin Hematoloji Kliniği'nde 2010-2017 tarihleri arasında MPN tanısıyla takip edilen 118 hastanın verilerini retrospektif olarak inceledik

Bulgular: Elli iki hastada PV, 60 hastada ET, 4 hastada PMF ve 2 hastada sınıflandırılamayan MPN saptandı. Derece 0 ve derece 1 retikülin fibrozisi bulunan 29 hasta (% 24,6) myelofibrozisi olmayan olarak, kalan 2 ≥ derece retikülin fibrozisi olan 89 (% 75,4) hasta ise myelofibrozisi bulunan olarak kabul edildi. Medyan RDW değeri %14,6 (%12,4-23,1) idi. Ortanca RDW değeri myelofibrozisi olmayan hastalarda %14.1 (%12.4-17.8) ve myelofibrozisli hastalarda %15 (12.4-23.1) olarak ortaya sonuçlandı (p = 0.054). Derece 3 fibrozisi olup ileri myelofibrozisi olan 8 hastanın alt grup analizinde medyan RDW değeri % 18.45 (16.4-23.1) ve kalan 110 hastada % 14.45 (%12.4-23) saptandı (p = 0.008).

Sonuç: Bu çalışma, RDW ve myelofibroz arasındaki ilişki hakkında kesin bir sonuç sağlamasa da, artmış RDW'nin MPN'li hastalarda ileri kemik iliği fibrozisi varlığına işaret edebileceği görülmektedir.

Anahtar Kelimeler: eritrosit dağılım genişliği, kronik myeloproliferatif neoplaziler, kemik iliği fibrozu

Başvuru Tarihi: 31.03.2021 **Kabul Tarihi:** 04.01.2021

Correspondence: Ceyda Aslan, University of Health Sciences Derince Training and Research Hospital, Department of Hematology, Kocaeli, Turkey
E-mail: ceyda-beray@hotmail.com

Kocaeli Medical Journal published by Cetus Publishing.

INTRODUCTION

Polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) which are among the Philadelphia chromosome negative myeloproliferative neoplasms (MPNs) occur as the result of uncontrolled clonal stem cell-derived myeloid serial proliferation (1). Bone marrow fibrosis (BMF) is characterized by reticulin fibrosis and/or collagen fiber accumulationand can be seen in MPNs in varying grades in onset also can develop later (2). And the presence of ≥ grade 2 reticulin/ collagen fibrosis is the major criteria for the diagnosis of PMF according to the World Health Organization (WHO) 2016 criteria, so performance of bone marrow biopsy is indispensable for the diagnosis of both PMF, post-PV and post-ET myelofibrosis(3). However, instead of biopsy a blood test ensuring information about the presence of BMF would be more comfortable for PV and ET patients especially on follow up.

Anisocytosis is a feature of PMF and can be monitored by red cell distribution width (RDW) which was shown to be increased in PMF patients, previously (4,5). Red cell distribution width is usually reported within the routine complete blood cell count (CBC) panel and makes it easily available. It is intriguing whether RDW could be used in predicting the presence of BMF to some extent. However, there is lack of data about the relationship between RDW and BMF in patients with MPNs.

The aim of this study is to evaluate the relationship between BMF and RDW value in patients with MPNs.

METHODS

We retrospectively reviewed the data of 146 patients, who were followed with the diagnosis of PV, ET and PMF and had bone marrow biopsy at the time of diagnosis, at University of Health Sciences Istanbul Training and Research Hospital Hematology Clinic between August 2010 and January 2018. Total of twenty- eight patients who had concomitant iron/vitamin B12 deficiency or not fully meeting the diagnostic criterions were excluded from the study. The diagnosis of MPNs were made according to the WHO criteria (3). Reticulin and trichromestaining were applied to the specimens and grading was done by an expert pathologist as follows: Grade 0: Scattered linear reticulin with no intersections corresponding to normal bone marrow; grade 1: Loose network of reticulin with many intersections, especially in perivascular areas; grade 2: Diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis; grade 3: Diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis. The data comprising age, gender, RDW values, hemoglobin levels, white blood cell count (WBC), platelet count, lactate dehydrogenase (LDH) levels, JAK2V617 F mutation status, presence of splenomegaly and thromboembolic event history at the time of bone marrow biopsy before any treatment or phlebotomy procedure, were obtained from the hospital documentation system.During the eight-years of data collection period, the RDW values werereported as RDW-CV (%) rather than RDW-SD (fL) parameter in the complete blood count of most of our patients and differences in laboratory reference intervals for RDW-CV were observed. Therefore, we determined the median RDW-CV value of the entire patient group as the RDW cut-off value.

Statistical evaluation was made by SPSS 24 program. Data were described as numbers and percentage or median and range, when appropriate. x^2 Fisher's exact test was used for evaluating categorical values and Mann Whitney U test for continuous values in patient groups. All p-values were 2-sided with statistical significance at 0.05 alpha levels.

RESULTS

A hundred and eighteen patients were included into the study. Among them 52 had PV, 60 had ET, 4 had PMF and 2 had unclassifiable CMPN at the time of diagnosis. The patient characteristics are shown in table 1.

Twenty-nine (24.6%) patients whose bone marrow biopsy revealed with grade 0 and grade 1 reticulin fibrosis were considered to be free of BMF, and the remaining 89 (75.4%) patients with ≥ grade 2 reticulin fibrosis were considered to have BMF. The median RDW value was 14.6% (range 12,4-23,1%). When RDW values were examined according to the presence of BMF, the median RDW value was 14.1% (range, 12.4-17.8) in patients without BMF and 15% (range, 12.4-23.1) in patients with BMF (p=0.054).

In subgroup analysis of 8 advanced BMF patients with grade 3 fibrosis, the median RDW value was 18.45% (range, 16.4-23.1) and the median RDW value in the remaining 110 patients was 14.45% (range, 12.4-23) (p=0.008)

Table 1 : The Patient Characteristics

Characteristis		**N=118**	
		n	**%**
Gender	**Female**	51	43.2
	Male	67	56.8
Age (years)	**median**	53	
	range	18-79	
CMPN	**PV**	52	44.1
	ET	60	50.8
	PMF	4	3.4
	UC	2	1.7
Hemoglobin level, g/dl	**median**	14.45	
	range	8.6-21.3	
WBC, 10^9/L	**median**	10	
	range	2.82-19.94	
Platelet, 10^9/L	**median**	625	
	range	33-1408	
LDH	**High**	38	32.2
	Normal	68	57.6
	Unknown	12	10.2
Splenomegaly	**Present**	23	19.5
	Absent	61	51.7
	Unknown	34	28.8
JAK 2 V617F	**Positive**	68	57.6
	Negative	49	41.5
	Unknown	1	0.9
History of thrombosis	**Positive**	5	4.2
	Negative	112	94.9
	Unknown	1	0.9
RDW-CV %	**median**	14.6	
	range	12.4-23.1	
RDW-CV	**RDW-CV > 14.6**	37	31.4
	RDW-CV ≤ 14.6	81	68.6
BMF	**Present**	89	75.4
	Absent	29	24.6

The cut-off point for RDW was determined as 14.6% according to the median level of RDW. Elevated RDW (>14.6) values were present in 37 (31.4%) of patients and RDW values were normal in 81 (68.6%) patients. The relationship between BMF and RDW was investigated. While BMF was found in 32 (86.5%) patients with high RDW level; 57 (70.4%) patients had BMF in the patient group with normal RDW values (p=0.068) (table 2).

Table 2 : Comparison of Patients according to RDW and Reticulin Fibrosis

		High RDW-CV >14.6		Normal RDW-CV ≤ 14.6		P value
		n	%	n	%	
BMF	Absent (grade 0-1)	5	13.5	24	29.6	0.067
	Present (grade ≥ 2)	32	86.5	57	70.4	

DISCUSSION

Red cell distribution width is an index measuring variability of peripheral blood erythrocyte volumes and represents anisocytosis (4). Besides its function in CBC, RDW has been recognized as a marker of subclinical inflammation by reflecting an increase in level of C-reactive protein, sedimentation rate (6), and cytokines such as hepcidin and interleukin 6 in recent years (7,8). In addition, there has been growing evidence about the negative impact of elevated RDW on inflammatory diseases, cardiovascular diseases, solid organ malignancies and some hematological disorders such as chronic lymphocytic leukemia, multiple myeloma, chronic myeloid leukemia, diffuse large b cell lymphoma and PMF (5,9-15). Unlike previous mentioned functions of RDW, we investigated whether it could give information about the BMF status of the patients with the diagnosis of MPNs. We found that, though not significant statistically, the numberof patients having BMF was higher in the group with increased RDW values and the median RDWvalue increased in patients with BMF. In subgroup analysis, the increase in RDW was more prominentin patients with grade 3 fibrosis.

The presence of BMF, contributing to morbidity and mortality with accompanying risk factors, hasa substantial role in patients with MPNs(16,17).

While BMF is an essential prominent feature of PMF, it occurs in 5-14% PV patients and 15-20% ET patients at diagnosis (3,18,19).Also, rapid progression to overt myelofibrosis can develop during PV and ET course and requires bone marrow biopsy for the diagnosis of post-PV and Post-ET myelofibrosis (20).

Anisocytosis, which can be identified by means of increased RDW,is attributed to the myelofibrosis (4)and has a potential to substitute the bone marrow biopsy in estimating BMF, at least in selected patient groups. Lucijanic et all. demonstrated that increased median RDW, with a median level of 19%in PMF patients was associated with decreased overall survival(5). Similarly, in our study we found that RDW increased significantly in patients with grade 3 myelofibrosis which is consistent with PMF or Post PV, ET myelofibrosis. However,the number of patients with PMF was quite low compared to the patients with other MPNs.

Limitations of the Study

Due to the retrospective nature of our study comparatively low number of patients with primary myelofibrosis might have hindered the influence of RDW on estimating the grade of BMF.

Conclusion

Consequently, although the present study does not provide a precise conclusion about the associationbetween RDW and BMF, it seems that increased RDW can point out the presence of advanced BMF in patients with MPNs.

However, the contribution of RDW value to the estimation of myelofibrosis grade in MPNs should be elucidated with studies including large number of patients with PMF and post-PV/post-ET myelofibrosis.

Competing Interests
The authors declare that there is no conflict of interest regarding the publication of this article.

Authors Contributions
All the authors declare that they have participate in the preparation of this study.

Ethics Committee Approval: This study was approved by local ethic committee (2011-KAEK-50)

Funding: There is no financial support.

Informed Consent: This is a retrosprective study.

REFERENCES

1. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(12):1599-1613.
2. Zahr AA, Salama ME, Carreau N, Tremblay D, Verstovsek S, Mesa R, et al. Bone marrow fibrosis in myelofibrosis: pathogenesis, prognosis and targeted strategies. Haematologica. 2016;101(6):660-71.
3. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391-2405.
4. Simel DL, DeLong ER, Feussner JR, Weinberg JB, Crawford J. Erythrocyte anisocytosis: visual inspection of blood films vs. automated analysis of red blood cell distribution width. Arch IntMed. 1988;148:822–24.
5. Lucijanic M, Pejsa V, Jaksic O, Mitrovic Z, Tomasovic-Loncaric C, Stoos-Veic T, et al. The Degree of Anisocytosis Predicts Survival in Patients with Myelofibrosis. ActaHaematol. 2016;136(2):98-100.
6. Lippi G, Targher G, Montagnana M, Salvagno GL, Zoppini G, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Arch Pathol Lab Med. 2009;133:628-32.
7. de Gonzalo-Calvo D, de Luxan-Delgado B, Rodriguez-Gonzalez S, Garcia-Macia M, Suarez FM, Solano JJ, et al. Interleukin 6, soluble tumor necrosis factor receptor I and red blood cell distribution width as biological markers of functional dependence in an elderly population: a translational approach. Cytokine.2012;58:193-98.
8. Rhodes CJ, Howard LS, Busbridge M, Ashby D, Kondili E, Gibbs JS, et al. Iron deficiency and raised hepcidin in idiopathic pulmonary arterial hypertension: clinical prevalence, outcomes, and mechanistic insights. J Am CollCardiol. 2011;58:300-09.
9. Horta-Baas G, Romero-Figueroa MDS. Clinical utility of red blood cell distribution width in inflammatory and non-inflammatory joint diseases. Int J Rheum Dis. 2019;22(1):47-54.
10. Danese E, Lippi G, Montagnana M. Red blood cell distribution width and cardiovascular diseases. J Thorac Dis. 2015;7(10):E402-11.
11. Montagnana M, Danese E. Red cell distribution width and cancer. Ann Transl Med. 2016;4(20):399.
12. Podhorecka M, Halicka D, Szymczyk A, Macheta A, Chocholska S, Hus M, et al. Assessment of red blood cell distribution width as a prognostic marker in chronic lymphocytic leukemia. Oncotarget. 2016;7(22):32846-53.
13. Lee H, Kong SY, Sohn JY, Shim H, Youn HS, Lee S, et al. Elevated red blood cell distribution width as a simple prognostic factor in patients with symptomatic multiple myeloma. Biomed Res Int. 2014;2014:145619.
14. Iriyama N, Hatta Y, Kobayashi S, Uchino Y, Miura K, Kurita D,et al. Higher Red Blood Cell Distribution Width Is an Adverse Prognostic Factor in Chronic-phase Chronic Myeloid Leukemia Patients Treated with Tyrosine Kinase Inhibitors. Anticancer Res. 2015;35(10):5473-8.

15. Periša V, Zibar L, Sinčić-Petričević J, Knezović A, Periša I, Barbić J. Red blood cell distribution width as a simple negative prognostic factor in patients with diffuse large B-cell lymphoma: a retrospective study. Croat Med J. 2015;56(4):334-43.

16. Tefferi A. Myelofibrosis with myeloid metaplasia. NEngl J Med. 2000;342:1255-1265.

17. Cervantes F, Passamonti F, Barosi G. Life expectancy and prognostic factors in the classic BCR/ABL-negative myeloproliferative disorders. Leukemia. 2008 May;22(5):905-14.

18. Barbui T, Thiele J, Passamonti F, Rumi E, Boveri E, Randi ML, et al. Initial bone marrow reticulin fibrosis in polycythemia vera exerts an impact on clinical outcome. Blood. 2012;119(10):2239-2241.

19. Kreft A, Büche G, Ghalibafian M, Buhr T, Fischer T, Kirkpatrick CJ. The incidence of myelofibrosis in essential thrombocythaemia, polycythaemiavera and chronic idiopathic myelofibrosis: a retrospective evaluation of sequential bone marrow biopsies. ActaHaematol. 2005;113(2):137-43.

20. Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P,et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. Blood Cancer J. 2018;8(2):15.