RESEARCH ARTICLE

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Prognostic Role of Red Cell Distribution Width (RDW) in Patients with Diffuse Large B-cell Lymphoma

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Abstract

Introduction: Several A number of prognostic blood markers related tofor Diffuse Large B-Cell Lymphoma (DLBCL) have been identified, most of which are costly and not easily availableaccessible. Although the relationship between the prognostic role of RDW and some cancers has been well established, the role it of RDW plays in DLBCL patients is unclear still questionable and requires more investigations. **Methods:** All patients diagnosed with DLBCL who had referred to Imam Reza Hospital, during were included in this retrospective cohort study. Based onRegarding their RDW, the subjects were divided into two groups of normal (RDW ≤14.6%) and elevated RDW (RDW > 14.6%) RDW, and the outcomes were investigated. **Results:** One hundred fifty patients with DLBCL were included in this study. The results showed a significant relationship between the RDW values of the DLBCL patients and stage frequency distribution, relapse, mortality, and complete remission (P value<0.05). It was also found out that elevated RDW > 14.6% was associated with the risk of relapse (OR=2.50, P value<0.05), mortality (OR=3.59, P value<0.01), and lack of complete remission (OR=0.115, P value< 0.01). The results of the survival analysis indicated that the subjects with higher RDWs had a lower median survival rate than those with low RDWs. In addition, the mortality risk for the individuals with RDW > 14.6% was 2.44 times that of those with RDW≤14.6% (HR=2.44, P value<0.05). **Conclusion:** The results of this study well indicated that as an independent prognostic factor, RDW was associated with the stage of DLBCL patients, failure to achieve complete remission, disease relapse, and patient mortality. However, further studies are would be needed to realize determine the role of RDW in DLBCL patients.

Keywords: Lymphoma- DLBCL- Red Cell Distribution Width factor- prognosis- survival

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Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of Non-Hodgkin lymphoma (NHL), accounting for 30-40% of all lymphoma cases in Europe and the United States, and even 50-60% in Latin American countries (Anderson et al., 1998; Beltran et al., 2007). Many therapeutic advances have been achieved in the field of blood cancers, using chemotherapy regimens to treat the disease (Beltran et al., 2019). DLBCL is a heterogeneous disease, the prognosis of which is affected by several factors (Li et al., 2019a). In recent years, numerous blood and molecular markers of DLBCL with prognostic roles have been identified, most of which are costly and not easily accessible (Patel et al., 2009; Patel et al., 2010). Furthermore, it is very difficult to interpret their results. However, some of these markers are cost-effective and accessible by most doctors (Li et al., 2019a).

Recent studies have clearly shown that inflammatory responses associated with tumors can determine tumor progression and biology as well as patient survival (Hanahan and Weinberg, 2011). Some tumor-related parameters are PLT, NLR (neutrophil/lymphocyte ratio), LMR (lymphocyte/monocyte ratio), and RDW, whose relationships with tumor progression and patient survival have been demonstrated in various studies (Stotz et al., 2014; Chen et al., 2015; Salvagno et al., 2015; Schleicher et al., 2015). Red Cell Distribution Width (RDW) is one of the routinely-used, readily available, and relatively inexpensive factors used in CBC tests and is commonly and widely indicated for identifying various types of anemia (Patel et al., 2010; Koma et al., 2013). RDW is also a systemic marker associated with morbidity and mortality from cardiovascular diseases, hepatitis B, cerebrovascular diseases, septicemia, chronic obstructive pulmonary diseases (COPD), and malnutrition (Förhécz et al., 2009; Lou et al., 2012). In addition, such a relationship between RDW and increased mortality has been observed in the general population (Patel et al., 2009; Patel et al., 2010). Recently, RDW has been recognized

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as an independent prognostic factor in a number of malignancies such as gastrointestinal cancer (Ay et al., 2015), lung cancer (Koma et al., 2013), breast cancer (Seretis et al., 2013), prostate cancer (Albayrak et al., 2014), and hematological cancer (Ai et al., 2018), while its possible mechanism in increasing the death rate of cancer patients is unknown (Koma et al., 2013). On the other hand, RDW values increase under the influence of MCV in chronic inflammatory diseases and improper nutritional conditions, affecting the morbidity and mortality of these patients (Douglas and Adamson, 1975; Ferrucci et al., 2005; Patel et al., 2009).

There is little evidence of the prognostic role of RDW in DLBCL patients. Having aimed at investigating the prognostic role of RDW in the patients with DLBCL, this study was conducted to recognize such a role of RDW in these patients so that it could be used as an important and effective factor in survival of the patients.

Materials and Methods

This is a retrospective cohort study conducted on all patients diagnosed with DLBCL, who had referred to Imam Reza hospital, Qaem hospital, or Zakaria (Isar) Clinic during 2010-2018. Prior to the study, the required permission was obtained from the Organizational Ethics Committee of Mashhad University of Medical Sciences (Ethics Committee License No. IR.MUMS.MEDICAL.REC.1398.777). The medical records of the patients who hadwith histopathological evidence of DLBCL and who had undergone chemotherapy as well as the onesthose containing with complete information of clinical evidence and who had been fully followed up were included in the study. On the other hand, the patients with cardiovascular diseases, cerebrovascular complications, active hepatitis B and C as well as HIV infections, and the MCV levels outside the normal range were excluded from the study process.

The dDemographic information and clinical characteristics of the DLBCL patients, including disease stage, LDH levels, ki67 levels, MCV, RDW, International Prognostic Index (IPI), type of regimen received, date of infection as well as recurrence and death, and response to treatment were collected using a checklist. In addition, the final status of the disease outcomes in the patients, which that had not been determined in the study period, was collected and determined through phone calls. Furthermore, the patients were examined in terms of undergoing bone marrow transplant. Regarding the types of treatment regimens received, most of the participants had received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) and CHOP regimens. As far as RDW was concerned, the subjects were divided into two groups of normal and elevated red cell distribution width (RDW ≤14.6% and RDW > 14.6%, respectively), and the outcomes such as the 3-year survival rates, and complete response to treatment, and as well as other independent variables were investigated examined in both groups.

Statistical Methods

The dDescriptive statistics such as mean, standard deviation, and frequency distribution were used to describe the data. The area under the Kaplan-Meier plot and the Log Rank test were also used to examine and compare the survival functions in the two groups. Moreover, the Cox Proportional Hazard Model was applied to investigate the prognostic role of RDW, and the univariate and multivariate logistic regressions were used to investigate the risk factors effective in increasing RDW in the patients. To this end, the variables with a significance level of < 0.2 in the univariate model were also included in the final multivariate model, and the area under the ROC curve was used to check the fit of the model. The statistical analysis was performed using the Stata 12 software (Corp, College Station, Texas), and the significance level in this study was considered < 0.05.

Results

A total of 150 DLBCL patients with DLBCL whosethe mean age was of 52.71 ± 15.52 with (the rangeing from of 22 to- 84 years old) were included in this study. In terms of the disease stage, the results showed that 56% (n = 84), 28.67% (n = 43), and 15.33% (n = 23) of the subjects were in Stage II, Stage III, and Stage IV, respectively, and t. The mean RDW in the studied patients was 15.13 ± 2.33 with (rangingthe range of from 11.8% to - 21.6%). In addition, 52% of the subjects (n = 78) and 48% (n = 72) of the patients had elevated RDW ≤14.6% and 48% (n = 72) had and normal RDW> 14.6, respectively% as well.

The mean age and as well as the LDH and ki67 levels in the individuals with elevated RDW > 14.6 were significantly higher than in those with normal RDW ≤14.6 (P value<0.05). According to the results, there was a statistically significant difference between the frequency distributions of the DLBCL patients' stage and the Nnormal and elevated RDWs rates of ≤14.6% and >14.6% (P value<0.01).

Regarding the relationship between the incidence of relapse and the patients' RDWs, the results showed that the subjects with elevated RDW > 14.6% had a higher incidence rate of relapse, and there was a statistically significant relationship between relapse and elevated RDW (P value<0.05). The results of response to treatment and the IPI of the patients also indicated well that the people those with elevated RDW > 14.6 showed significantly less response to treatment and had an IPI of > 2 (P value<0.05) (Table 1).

The Regarding the stage of the disease, the results of the univariate logistic regression related to the stage of the disease showed that the odds ratio of the elevated RDW > 14.6% in the patients with DLBCL in Stage III was 3.03 times that of Stage II (OR=3.03, 95% CI: 1.41-6.51, P value<0.01). The odds ratio in Stage IV was 3.37 times that of Stage II as well (OR=3.37, 95% CI: 1.28-8.87, P value<0.01). It was also found out that complete response to treatment (CR) in the patients with elevated RDW > 14.6% decreased significantly, so that the patients without complete response to treatment were about 8.69 times more likely to have elevated RDW > 14.6% than

Table 1. Basic Information of Individuals Participating in the Study

Variable	Overall	RDW (%)		P value
		Normal RDW (≤14.6)	Elevated RDW (>14.6)	
Age (year), mean ± SD	52.71±15.52	49.21±1.85	56.5±1.61	0.003
Gender, n (%)				
Male	91 (60.67%)	44 (56.41%)	47 (65.27%)	0.267
Female	59 (39.33%)	34 (43.59%)	25 (34.73%)	
LDH (U/l), mean ± SD	494.26±265.09	427.48±16.84	559.27±35.91	0.001
ki67 (%),mean ± SD	66.72±19.14	62.96±2.18	70.69±2.17	0.013
Stage, n (%)				
II	84 (56%)	54 (69.23%)	30 (41.66%)	0.003
III	43 (28.67%)	16 (20.51%)	27 (37.5%)	
IV	23 (15.33%)	8 (10.26%)	15 (20.84%)	
IPI, n (%)				
≤ 2	91 (60.67%)	62 (79.48%)	29 (40.27%)	0.001
> 2	59 (39.33%)	16 (20.52%)	43 (59.73%)	
MCV (FL), mean ± SD	86.31±10.35	85.40±12.48	88.34±13.52	0.168
Relapse				
Yes	32 (21.34%)	11 (14.10%)	21 (29.16%)	0.029
No	118 (78.66%)	67 (85.9%)	51 (70.84%)	
Response to Treatment				
Response	123 (82%)	74 (94.87%)	49 (68.05%)	0.001
No response	27 (18%)	4 (5.13%)	23 (31.95%)	

those with complete treatment response (OR=0.115, 95% CI:0.037-0.335, P value<0.01).

On the other hand, the patients with relapse were 2.50 times more likely to have elevated RDW > 14.6% than those without relapse (OR=2.50, 95% CI: 1.40-5.66, P value<0.05). The results of the multivariate logistic regression with the controlcontrolled of confounding factors (such as age, gender and clinical factors that adjusted in Llogistic regression) indicated that the disease stage and the incidence of relapse had a significant relationships with the RDW levels of the DLBCL patients. In other words, the individuals experiencing Stage III were 2.90 times more likely to have elevated RDW >14.6% than those in Stage II (OR=2.90, 95% CI: 1.155-7.31, P value<0.05) (Table 2).

The results of the survival analysis regarding the occurrence of relapse due to the RDW levels showed that there was no statistically significant difference between the survival functions of the two groups with elevated RDW > 14.6% and normal RDWs ≤ 14.6% (P value Log Rank = 0.089) (Figure 1). The As shown in Figure 2, the survival rates of the studied subjects with regard to their RDWs also showedindicated in graph 2 that the ones patients with elevated RDW > 14.6% had a lower

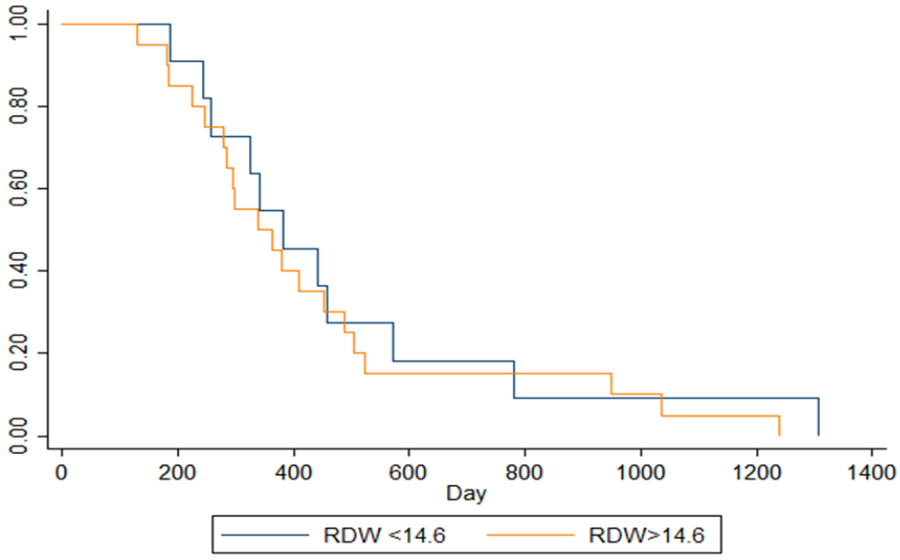

Figure 1. Kaplan-Meier Plot of Relapse based on RDW of Patients

Table 2. The Results of Univariate and Multivariate Logistic Regression between the RDW of Patients and the Studied Variables

	Univariate			Multivariate		
	Odds Ratio	95% Confidence Interval	P value	Odds Ratio	95% Confidence Interval	P value
Age	1.032	0.894-1.055	0.345	-	-	-
Gender (Female)	0.688	0.355-1.33	0.267	-	-	-
LDH	1.2	0.745-1. 43	0.2	-	-	-
ki67	1.44	0.530-2.23	0.16	-	-	-
Stage						
III	3.03	1.41-6.51	0.004	2.9	1.155-7.31	0.023
IV	3.37	1.28-8.87	0.014	2.13	0.656-6.92	0.208
IPI (>2)	5.74	2.78-11.84	0.001	1.48	0.671-4.652	0.305
Relapse (yes)	2.5	1.10-5.66	0.027	3.78	1.50-9.51	0.005
Treatment (response)	0.115	0.037-0.353	0.001	0.322	0.069-1.49	0.147

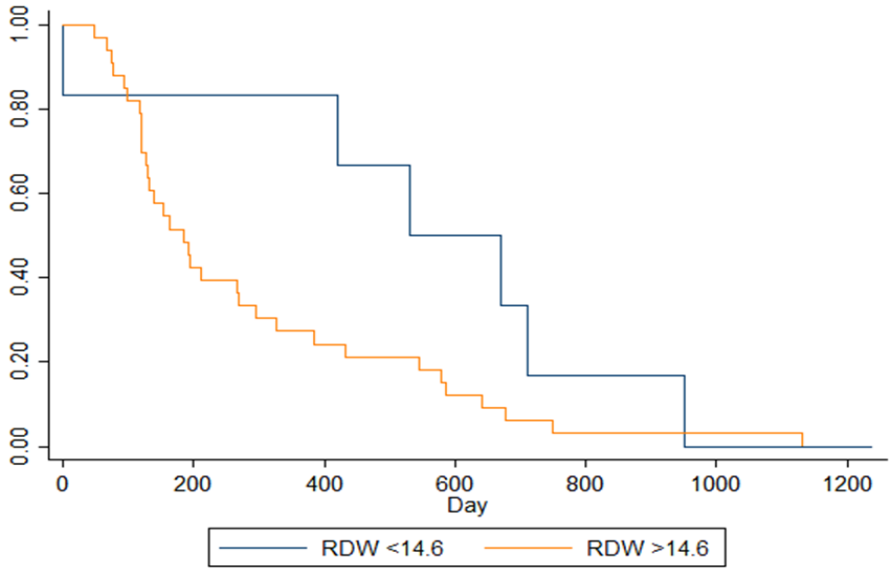

Figure 2. Kaplan-Meier Plot of Mortality based on RDW of Patients

survival rate compared to the subjectsthose with normal RDW ≤ 14.6%, which was statistically significant (P value Log Rank = 0.008).

Discussion

The results of the present study showed the independent and prognostic role of RDW in the survival of DLBCL patients. It was indicated that the rates of response to treatment and incidence of relapse changed significantly with RDW and increased in the patients with higher RDWs. In addition, the patients with IPI > 2 and those in higher stages of the disease had higher RDWs as well.

Evidence has also shown that high RDW is a prognostic factor in various types of malignancies such as CLL (chronic lymphocytic leukemia), ovary, lung, and prostate cancers, and some studies showed a close relationship between high RDW and stages of various malignancies (Spell et al., 2004; Koma et al., 2013). This is consistent with the results of the present study in which the patients with higher DLBCL stages had higher RDWs as well. Although the exact mechanism of RDW elevation in patients with DLBCL is unknown, some studies have identified hypertension, dysfunction of erythropoietin, dyslipidemia, poor nutritional conditions, oxidative stress, and inflammation as the main reasons for elevated RDW in DLBCL patients (Patel et al., 2010; Hunziker et al., 2012).

The relationships between RDW and IL-6, ESR, CRP, leukocyte, fibrinogen, and low neutrophil and hemoglobin have also been reported by some studies (Miyamoto et al., 2015; Vayá et al., 2015). Furthermore, a significant relationship between RDW and erythropoietin and albumin has been observed recently. In the present study, a significant relationship was observed between RDW levels and LDH, ki67, IPI, and tumor stage (Rhodes et al., 2011; Periša et al., 2015; Goyal et al., 2016).

Li et al., (2019b) well indicated that RDW at Cut off Point > 14.35% was associated with worse prognosis in the survival rate of the DLBCL patients. Thus, the risk of death in the patients with RDW > 14.35% was about 2.652, which is in line with the results of the present study in which the mortality risk of the DLBCL patients with

RDW > 14.6% was 2.44. The researchers concluded in this study that elevated RDW values as an independent prognostic factor in the DLBCL patients were associated with their worse prognosis. Cancer-related inflammation is considered a main component of progression and prognosis in all types of cancers (Hanahan and Weinberg, 2011). Although inflammatory components such as cytokines and inflammatory mediators are considered important factors in tumor progression, the role of poor nutritional conditions is also undeniable and its possible mechanism works through erythropoiesis damage as a result of poor nutritional conditions and malnutrition, which is associated with an increase in RDW (Tetè et al., 2012). Given the fact that malnutrition conditions such as iron deficiency affect the MCV and RDW of individuals (Periša et al., 2015), this study was conducted on the people with a normal MCV range to eliminate the effect of malnutrition on their RDWs.

Beltran et al., (2019) suggested that the frequency of the patients with Stage III and IV was significantly higher in high RDW values. In addition, elevated RDW was associated with a significant decrease in the response to treatment. On the other hand, it was determined through the survival analysis that the mortality risk of the DLBCL patients with higher RDW was 2.04 times that of those with low RDW, which is in line with the results of this study. In the present research, it was found out that there was a significant difference between the frequency distribution of the disease stage and elevated RDW, so that stages III and IV of the disease were associated with a significant increase in RDW. Furthermore, a significant relationship was observed between response to treatment and RDW levels, so that elevated RDW was associated with reduced remission rates. On the other hand, the mortality risk in the patients with RDW > 14.6% was 2.44 times that of the ones with lower RDW, confirming the results of Beltran et al.'s study. Periša et al., (2015) suggested that the RDW at the Cutoff Point > 15% had a significant relationship with the stage of DLBCL, so that 85.7% of the patients with elevated RDW were in Stages III & IV of the disease. The results of the survival analysis by Periša et al also showed well that the survival rate of the people with elevated RDW was significantly lower than that of the patients with low RDW. The mortality risk ratio of the people with high RDW was also about 7.14 times that of the individuals with low RDW, which is consistent with our findings.

In conclusion, the results of this study clearly showed that as an independent prognostic factor, RDW was associated with the stage of DLBCL, the rate of complete remission, disease relapse, and patient mortality. It was also found out that the subjects with elevated RDW were at risk of relapse, failure to achieve complete remission, and mortality, and had lower survival rates and higher mortality risk compared to those with low RDW. Thus, RDW could be used as an independent predictive factor to identify and predict the final outcome of DLBCL patients, even though further studies are needed to identify the role of RDW in DLBCL patients.

Author Contribution Statement

MK, NK and AA contributed to the design and implementation of the study, analysis, and interpretation of data, and were involved in drafting the manuscript. AS and NK contributed to the interpretation of data and were involved in drafting and revising the manuscript. All authors read and approved the final manuscript.

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Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Conflict of Interest

The researchers reported no conflict of interest in this research.

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