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Original article

Prognostic Value of Red Cell Distribution Width in Patients with Lymphoma

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Abstract:

Background: A diverse category of malignant lymphocyte neoplasms, lymphomas may affect extra nodal locations, bone marrow, or lymphatic tissue. This study aimed to determine the lymphoma patients' red cell distribution width (RDW) and how it relates to their prognosis. **Methods:** One hundred lymphoma patients who visited Benha University hospitals for follow-up were included in this prospective cohort research. There were two groups of patients: Group A: 77 patients who responded fully to therapy. Group B: 23 patients who responded partially or refractorily to therapy. **Results:** The international prognostic index (IPI) and RDW were shown to be independent predictors of partial/refractory therapy response by multivariate analysis. High stage lymphoma, extra nodal lymphoma, B symptoms, lactate dehydrogenase level, and bone marrow involvement were all significant predictors of partial/refractory treatment response, according to the univariate analysis. A 75.6% higher chance of a partial or refractory treatment response was linked to a one unit rise in RDW in the multivariate. **Conclusion:** For instances of lymphoma, RDW and IPI are independent, significant predictors of partial or refractory response. Analysis of the receiver operating characteristics curve was done for RDW in order to forecast the response to partial or refractory therapy. With a 95% CI between 0.620 and 0.899 and a large area under the curve of 0.760, the results indicate a decent capacity to predict partial or refractory treatment response. Sensitivity, specificity, positive predictive value, and negative predictive value were 69.57%, 92.21%, 72.7%, and 91%, respectively, at the optimal cutoff of >15.8%.

Keywords: Lymphoma; Prognostic Value; Red Cell Distribution Width.

Introduction

A diverse category of malignant lymphocyte neoplasms, lymphomas may affect extra nodal locations, bone marrow, or lymphatic tissue. There are almost 90 distinct subtypes identified by the World Health Organization's categorization scheme [(1)]. The B-cell, T-cell, or natural killer cell origin provides the basis for the first stratification. Morphology, immunophenotype, genetic, molecular, and clinical characteristics finally distinguish each of them [(2)].

In 2019, the Egyptian government paid for the treatment of 324,949 individuals with malignant neoplasms. Non-Hodgkin lymphoma (NHL) was one of the most prevalent malignant neoplasms in Egypt, with an estimated 19,096 cases, according to the Global Cancer Observatory in December 2020 [(3)].

Tissue biopsy is utilized to confirm a diagnosis of lymphoma; excisional biopsy, core biopsy, incision/wedge biopsy, and fine-needle aspiration are often used techniques. Since excisional biopsy makes it possible to evaluate the architecture of the whole lymph node, it is regarded as the "gold standard" [(4)].

The presence of pathogenic Hodgkin Reed-Sternberg cells, which are B-cell derived, against a backdrop of lymphocyte-predominant, impoverished stroma, or nodular sclerosis is what defines Hodgkin lymphoma (HL). The four kinds of classical HL are lymphocyte rich, lymphocyte deficient, mixed cellularity, and nodular sclerosing, in decreasing order of frequency. There is just one kind of non-classical HL, and it is nodular lymphocyte-predominant [(5)].

With 25% to 30% of cases, diffuse large B cell lymphoma (DLBCL) is the most prevalent NHL. This lymphoma is clinically aggressive. Although it may occur anywhere in the body, DLBCL most often occurs in the lymph nodes. The most prevalent system outside of the lymphatic system is the gastrointestinal tract. The central nervous system, eyes, and testes are other often affected areas. Among the NHL forms are peripheral T cell lymphomas, mantle cell lymphoma (MCL), Burkitt lymphoma, extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue, and follicular lymphoma [(6)].

As part of a complete blood count (CBC), the red blood cell distribution width is often assessed in clinical practice. It is a coefficient of the volume variation of circulating erythrocytes. Cardiovascular illness and generally elevated progressive inflammation are among the numerous pathophysiological disorders that have been linked to the red cell distribution width (RDW), an easy-to-measure indicator of the systemic inflammatory response. It is becoming more well acknowledged that the RDW plays a significant part in the prognosis and development of tumors [(7)].

Higher RDW levels may indicate a greater level of inflammation in cancer patients. By raising hepcidin and oxidative stress levels, elevated cytokine levels may alter iron metabolism. Higher RDW readings and increased anisocytosis are the results of concurrently decreased erythropoietin production [(8)].

RDW has been shown to have a prognostic role in several lymphoproliferative disorders, including multiple myeloma, DLBCL, MCL, and chronic lymphocytic leukemia [(9)].

This research sets out to evaluate RDW in lymphoma patients (with any type of lymphoma) and its relationship to prognosis.

Patients and methods

One hundred lymphoma patients who visited the Haemato-Oncology Department and Clinic at Benha University Hospitals during February 2024 to February 2025 for follow-up were included in this prospective cohort research.

The patients gave their signed, informed permission. Each subject was given a secret code number and an explanation of the study's objectives. After receiving

approval from Benha University's Faculty of Medicine's Research Ethics Committee, the research was carried out.

Males and females with a diagnosis of any kind of lymphoma who were older than 20 years were eligible to apply.

Patients with cardiovascular illnesses, cerebrovascular problems, chronic inflammatory disease, git bleeding, other malignancies, active HIV infections, hepatitis B and C, anemia, and mean corpuscular volume (MCV) values that were beyond the normal range were excluded.

Patients were split up into two groups. Group A (n=77): patients who responded fully to therapy. Patients in Group B (n=23) had a partial or refractory response to therapy.

The criteria of diagnosis of lymphoma is made using an open lymph node biopsy, based on morphology, immunohistochemistry, and flow cytometry and Hodgkin lymphoma is verified via the presence of Reed-Sternberg cells [(1)]. The standard response criteria currently in use for lymphoma are the Lugano Criteria which are based on [18F]2-fluoro-2-deoxy-D-glucose positron emission tomography or bidimensional tumor measurements on computerized tomography scans [(10)].

Every patient under study underwent the following tests: Taking a complete medical history includes the following: [sociodemographic information: age, gender; lifestyle: smoking status, degree of physical activity; history of current illness and treatment regimen: details of current symptoms, duration, and progression; current treatment regimen (chemotherapy, immunotherapy); medical history: history of any medical conditions (cardiovascular disease, diabetes, chronic kidney disease, prior hospitalizations); family history: hematologic malignancies or anemia/iron deficiency; medication history: current and past medications (chemotherapy, immunosuppressants, iron supplements); dietary history: nutritional intake, particularly iron, vitamin B12, and folate; review of gastrointestinal, neurological, and other systemic symptoms; constitutional symptoms (fatigue, fever, and weight loss); and lymphatic/hematologic symptoms (lymphadenopathy, pallor, and bleeding). Vital signs (heart rate, respiratory rate, blood pressure, temperature), anthropometric measurements (weight, height, waist circumference, hip circumference, and body mass index (BMI)), lymph node examination, systemic examination (cardiovascular: abnormal breath sounds, respiratory: abnormal breath sounds), abdominal: organomegaly, masses, ascites, neurologic: signs of vitamin B12 deficiency, and skin are all included in the physical examination. CBC, lactate dehydrogenase (LDH), electrolytes (sodium, potassium, chloride, and bicarbonate), kidney function (creatinine, BUN), liver function (alanine transaminase, aspartate aminotransferase, alkaline phosphatase, and bilirubin), and bone marrow examination are examples of routine laboratory tests. radiological tests such as positron emission tomography CT, pan CT with contrast neck, chest, abdomen, and pelvis, and chest X-ray and pelviabdominal ultrasound.

Criteria of disease including staging, the International Prognostic Index (IPI) [(11)], the kind of regimen administered, the response to therapy as defined by Cheson and the World Health Organization [(12, 13)], recurrence, and mortality.

A Sysmex XE-2100 hematological analyzer (Sysmex Corporation, Kobe, Japan) was used to calculate CBC counts and MCV. A Cobas E411 analyzer was used to quantify procalcitonin levels, and the neutrophil-lymphocyte count ratio was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count.

Initial values of RDW and of other laboratory parameters were defined as values obtained within 2 weeks before a front line-treatment. CBC, including RDW

calculation was determined from whole blood with K2 EDTA or K3 ethylenediaminetetraacetic acid (EDTA) as an anticoagulant on Adiva 2100 analyzer (Siemens Healthcare Diagnostics, Tarrytown, NY, USA).

RDW readings were grouped according to the current laboratory's reference range, which is between 9% and 15%; that is, patients were split into two groups using a 15% cut-off value. Additionally, receiver operating characteristics (ROC) study yielded a 15% cutoff value.

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Statistical analysis

SPSS version 27 was used for data administration and statistical analysis (IBM, Armonk, New York, United States). The Shapiro-Wilk test and direct data visualization techniques were used to evaluate the normality of quantitative data. Means and standard deviations or medians and ranges were used to describe quantitative data based on normalcy. Numbers and percentages were used to summarize categorical data. The Independent T Test and the Mann-Whitney U Test were used to compare quantitative data across the groups for parametric and non-parametric variables, respectively. Fisher's exact test or the Chi-square test were used to compare categorical data. To forecast partial or refractory treatment response, ROC analysis was performed for RDW. Diagnostic indices, the optimal cutoff point, and the area under the curve with its 95% CIs were computed. Pearson's and Spearman's correlations were used to examine the relationship between RDW and other factors. RDW was compared using the Independent T Test based on several characteristics. To forecast partial or refractory treatment response, univariate and multivariate logistic regression analyses were performed. 95% confidence intervals for the odds ratios were computed. There were two sides to every statistical test. P-values were deemed significant if they were less than 0.05.

Results

Seventy-seven % of patients had a full response to therapy, 2% had a partial response, and 21% were refractory. The groups under study did not vary substantially in terms of age, sex, BMI, or lymphoma type. Lymphoma stages were substantially more advanced in patients with partial or refractory response (91.3% in stages III–IV vs 59.8% in the full response group; P = 0.001). The partial/refractory group's Eastern Cooperative Oncology group performance status (ECOG PS) was considerably poorer, with 73.9% of them scoring ≥2, compared to 42.9% in the full response group (P = 0.019). Patients who had a partial or refractory response were more likely to have extra nodal involvement (P < 0.001). The partial/refractory group had a substantially greater prevalence of B symptoms (P = 0.037). Patients with partial or refractory response had a considerably higher likelihood of bone marrow involvement (P < 0.001). The partial/refractory group had a higher prevalence of high-risk IPI scores (≥3) (P < 0.001). LDH levels were substantially greater in patients with partial or refractory response than in those with full response (P = 0.001). In addition, the partial/refractory group's platelet-to-lymphocyte ratio (PLR) was noticeably greater than that of the full responder group. The partial/refractory group had a considerably higher RDW (P < 0.001). Serum albumin, serum creatinine, neutrophil-to-lymphocyte ratio, hemoglobin, and platelet count did not vary substantially across the groups. **Table 1**

RDW's partial/refractory treatment response was predicted using ROC curve analysis. With a 95% CI ranging from 0.620 to 0.899 and a substantial AUC of 0.760, it indicated a decent capacity to predict partial or refractory treatment response. Sensitivity, specificity, PPV, and NPV were 69.57%, 92.21%, 72.7%, and 91%, respectively, at the optimal threshold of >15.8% (P < 0.001). **Table 2**

Table 1: General characteristics, clinical characteristics and laboratory findings in the studied patients and according to treatment response

				Treatment response		
			Total (n=100)	**Complete (n = 77)**	**Partial/ Refractory (n = 23)**	**P-value**
General characteristics	**Age (years)**		45 (18 - 75)	40 (18 - 75)	55 (21 - 73)	0.099
	Sex	**Males**	49 (49)	36 (46.8)	13 (56.5)	0.411
		Females	51 (51)	41 (53.2)	10 (43.5)	
	BMI (kg/m^2)		27 ±5	27 ±5	26 ±6	0.3
Clinical characteristics	**Type of lymphoma**	**Hodgkin**	22 (22)	19 (24.7)	3 (13)	0.237
		Non-Hodgkin	78 (78)	58 (75.3)	20 (87)	
	Lymphoma stages	**I**	2 (2)	2 (2.6)	1 (4.3)	**0.001***
		II	31 (31)	29 (37.7)	1 (4.3)	
		III	45 (45)	34 (44.2)	11 (47.8)	
		IV	22 (22)	12 (15.6)	10 (43.5)	
	ECOG PS	**Scale 0**	2 (2)	2 (2.6)	1 (4.3)	**0.019***
		Scale 1	48 (48)	42 (54.5)	5 (21.7)	
		Scale 2	37 (37)	23 (29.9)	14 (60.9)	
		Scale 3	13 (13)	10 (13)	3 (13)	
	Lymphoma site	**Nodal**	67 (67)	59 (76.6)	8 (34.8)	**<0.001***
		Extra nodal	33 (33)	18 (23.4)	15 (65.2)	
		B symptoms	59 (59.6)	41 (53.9)	18 (78.3)	**0.037***
		BM involvement	21 (21)	10 (13)	11 (47.8)	**<0.001***
	IPI	**Low risk (< 3 points)**	66 (66%)	59 (76.6)	7 (30.4)	**<0.001***
		High risk (>= 3 points)	34 (34%)	18 (23.4)	16 (69.6)	
	LDH (U/L)		365 ±105	347 ±99	427 ±103	**0.001***
Laboratory Findings	**Hb (g/dL)**		12.4 ±1.3	12.5 ±1.3	12 ±1.3	0.112
	Platelets (10^3/µL)		195 ±62	196 ±56	191 ±81	0.725
	NLR		3.9 ±1.1	3.8 ±1.1	4.1 ±0.8	0.182
	PLR		97 (70 - 648)	95 (70 - 648)	105 (78 - 379)	**0.035***
	Serum albumin (g/dL)		3.9 ±0.3	3.9 ±0.3	3.9 ±0.3	0.368
	Serum creatinine (mg/dL)		1.05 ±0.21	1.06 ±0.21	1.01 ±0.22	0.346
	RDW (%)		14.1 ±1.6	13.8 ±1.4	15.3 ±1.8	**<0.001***

Data presented as Median (range), Mean ±SD or frequency (%), n: number, SD: standard deviation, BMI: body mass index. ECOG PS: Eastern Cooperative Oncology Group Performance Status, BM: Bone Marrow, IPI: International Prognostic Index, LDH: Lactate Dehydrogenase, Hb: Hemoglobin, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, RDW: Red Cell Distribution Width, *: Significant P-value.

Table 2: ROC analysis of RDW to predict partial/refractory treatment response

ROC characteristics	
AUC	0.760
95% CI	0.620 - 0.899
Best cut-off point	>15.8
Sensitivity	69.57%
Specificity	92.21%
PPV	72.7 %
NPV	91%
P-value	**<0.001***

Data presented as frequency (%), AUC: Area Under Curve, 95% CI: 95% Confidence interval, PPV: Positive predictive value, NPV: Negative predictive value, *: Significant P-value.

Significant positive relationships were seen between RDW and both LDH levels (r = 0.497, P < 0.001) and lymphoma stages (r = 0.43, P < 0.001). Conversely, there was a noteworthy inverse relationship between it and platelet count (r = -0.203, P = 0.043). Age, BMI, ECOG PS, hemoglobin levels, NLR, PLR, serum albumin, and serum creatinine did not significantly correlate with RDW. Patients with extra nodal lymphoma had a significantly higher RDW than those with nodal lymphoma (P < 0.001), B symptoms patients had a significantly higher RDW than those without (P = 0.011), bone marrow involvement patients had a significantly higher RDW than those without (P < 0.001), and patients with high-risk IPI (≥3 points) had a significantly higher RDW than those with low-risk IPI (<3 points) (P = 0.005). There was no discernible difference in RDW between men and females. **Table 3**

Table 3: Correlation between RDW and different parameters and RDW (%) according to other parameters in partial/refractory patients.

RDW (%)		
	r	**P-value**
Age (years)	0.07	0.488
BMI (kg/m^2)	-0.068	0.503
Lymphoma stages	0.43	**<0.001***
ECOG performance status	0.074	0.467
LDH (U/L)	0.497	**<0.001***
Hb (g/dL)	-0.103	0.309
Platelets (10^3/µL)	-0.203	**0.043***
NLR	0.054	0.594
PLR	0.156	0.124
Serum albumin (g/dL)	-0.121	0.231
Serum creatinine (mg/dL)	-0.077	0.444
In partial/refractory patients		
	Mean ±SD	**P-value**
Sex		
Males	14 ±1.5	0.440
Females	14.3 ±1.7	
Lymphoma site		
Nodal	13.7 ±1.5	**<0.001***
Extra nodal	15 ±1.5	
B symptoms		
Present	14.5 ±1.7	**0.011***
Absent	13.7 ±1.3	
BM involvement		
Yes	15.5 ±1.2	**<0.001***
No	13.8 ±1.5	
IPI		
Low risk (< 3 points)	13.8 ±1.5	**0.005***
High risk (≥ 3 points)	14.8 ±1.7	

Data presented as Mean ±SD or numbers, LDH: Lactate Dehydrogenase, Hb: Hemoglobin, NLR: Neutrophil-to-Lymphocyte Ratio, PLR: Platelet-to-Lymphocyte Ratio, RDW: Red Cell Distribution Width, r: correlation coefficient, *: Significant P-value.

A forward stepwise multivariate logistic regression analysis was conducted after a univariate logistic regression study using all significant variables. RDW and IPI were shown to be independent predictors of partial/refractory treatment response by the multivariate analysis. The univariate analysis revealed that bone marrow

involvement (OR = 6.142, 95% CI = 2.141 - 17.62, P = 0.001), high stage lymphoma, extra nodal lymphoma (OR = 6.146, 95% CI = 2.244 - 16.83, P < 0.001), presence of B symptoms (OR = 3.073, 95% CI = 1.035 - 9.128, P = 0.043), and LDH level (OR = 1.007, 95% CI = 1.003 - 1.012, P = 0.002) were all significant predictors of partial/refractory treatment response. PLR (P = 0.518) and ECOG PS 3 (P = 0.713) did not, however, significantly predict partial or refractory treatment response. A 75.6% higher chance of a partial or refractory treatment response was linked to a one unit rise in RDW in the multivariate (OR = 1.756, 95% CI = 1.204 - 2.56, P = 0.003). The likelihood of a partial or refractory treatment response was 5.46 times higher for patients with a high-risk IPI (≥3) (OR = 5.463, 95% CI = 1.808 - 16.511, P = 0.003). **Table 4**

Table 4: Univariate and multivariate logistic regression analysis to predict partial/refractory treatment response

	Univariate		Multivariate	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
High stage lymphoma	7.076 (1.547 - 32.361)	**0.012***	-	-
ECOG PS 3	0.6 (0.039 - 9.156)	0.713	-	-
Extra nodal Lymphoma	6.146 (2.244 - 16.83)	**<0.001***	-	-
B symptoms	3.073 (1.035 - 9.128)	**0.043***	-	-
LDH (U/L)	1.007 (1.003 - 1.012)	**0.002***	-	-
PLR	1.002 (0.996 - 1.008)	0.518		
RDW (%)	1.963 (1.373 - 2.807)	**<0.001***	1.756 (1.204 - 2.56)	**0.003***
BM involvement	6.142 (2.141 - 17.62)	**0.001***	-	-
IPI (≥3)	7.492 (2.666 - 21.052)	**<0.001***	5.463 (1.808 - 16.511)	**0.003***

Data presented as numbers. ECOG PS: Eastern Cooperative Oncology Group Performance Status, LDH: Lactate Dehydrogenase, PLR: Platelet-to-Lymphocyte Ratio, RDW: Red Cell Distribution Width, IPI: International Prognostic Index, OR: Odds Ratio, CI: Confidence Interval, *: Significant P-value.

Discussion

A diverse collection of malignant lymphocyte neoplasms, lymphomas may affect extra nodal locations, bone marrow, or lymphatic tissue. More than 90 distinct subtypes are identified by the World Health Organization's categorization system [(14)]. RDW is a straightforward blood test metric that has historically been used to investigate anemias. It measures the size variety of red blood cells (anisocytosis) in peripheral blood. Higher values of this parameter have been identified as a poor prognostic factor for cancer, inflammation, and cardiovascular disorders throughout the last ten years [(15)]. Compared to HL (22%), NHL was more common in the current study sample (78%). With just 2% of patients in stage I, stage III was the most prevalent illness stage (45%), followed by stage II (31%), and stage IV (22%). In 48% of cases, ECOG PS was scale 1, 37% in 37%, 13% in 13%, and 2% in 2%. Thirty-three % of patients had extra nodal illness, while 67% of cases had nodal involvement. Of the patients, 59.6% had B symptoms. In 21%, bone marrow involvement was found. Two out of 40%, three out of 27%, one out of 22%, four out of 6%, zero out of 4%, and five out of 1% were the IPI scores. These findings are consistent with those of Zhou et al. [(16)], who found that among patients with DLBC, 27 (16.8%) had B symptoms, and 129 (80.1%) had ECOG PS <2. Furthermore, while both cancers are rather uncommon, Thandra et al. [(17)] observed that NHL is more prevalent than HL. Additionally, according to Kaseb et al. [(18)], B symptoms are often more prevalent in stages 3 to 4 of the illness and may be seen in as many as 30% of lymphoma patients.

The mean RDW in the current study sample was 14.1 ± 1.6%.

Furthermore, Oura et al. [19] showed that the median RDW coefficient of variation in 115 DLBCL patients was 14.8 (range 12.2-21.5).

According to the findings, 77% of patients had a complete response to therapy, 2% experienced a partial response, and 21% experienced refractory behavior. Two groups of patients were created depending on how well they responded to treatment: the Partial/Refractory group (n = 23) and the Complete response group (n = 77). Lymphoma stages were substantially more advanced in patients with partial or refractory response (91.3% in stages III–IV vs 59.8% in the full response group; P = 0.001). In the partial/refractory group, 73.9% of respondents had a score of ≥2, which was considerably worse than the 42.9% in the full response group (P = 0.019). Patients who had partial or refractory response were more likely to have extra nodal involvement (65.2% vs. 23.4%, P < 0.001). The partial/refractory group had a considerably greater prevalence of B symptoms (78.3% vs. 53.9%, P = 0.037). Patients with partial or refractory response had a considerably higher prevalence of bone marrow involvement (47.8% vs. 13%, P < 0.001). The partial/refractory group had a higher prevalence of high-risk IPI scores (≥3) (69.6% vs. 23.4%, P < 0.001).

The same findings were also described by Bock et al. [20], who noted that extra nodal involvement and advanced staging were features of refractory lymphoma.

LDH levels were substantially greater in patients with partial or refractory response than in those with full response in the current research (427 ± 103 vs. 347 ± 99 U/L, P = 0.001). The partial/refractory group's PLR was considerably higher (median: 105 [78–379]) than that of the full responder group (median: 95 [70–648], P = 0.035). The partial/refractory group had a substantially higher RDW (15.3 ± 1.8% vs. 13.8 ± 1.4%, P < 0.001). In addition, patients with extra nodal lymphoma had a significantly higher RDW than those with nodal lymphoma (15 ±1.5 vs. 13.7 ±1.5, P < 0.001), those with B symptoms had a significantly higher RDW than those without (14.5 ±1.7 vs. 13.7 ±1.3, P = 0.011), those with bone marrow involvement had a significantly higher RDW than those without (15.5 ±1.2 vs. 13.8 ±1.5, P < 0.001), and patients with high-risk IPI (≥3 points) had a significantly higher RDW than those with low-risk IPI (<3 points) (14.8 ±1.7 vs. 13.8 ±1.5, P = 0.005) and those with B symptoms than those without.

The current study was confirmed by Kim et al. [21], who noted that refractory lymphoma was linked to higher levels of LDH than full response lymphoma. Furthermore, the current findings were corroborated by Chen et al. [22] who discovered that refractory lymphoma had a higher PLR than full remission.

Additionally, Herraez et al. [9] supported the current position by showing that RDW was a predictive factor that was higher in patients with refractory lymphoma than in those with full remission.

RDW in cancer reflects low nutritional condition and persistent inflammation, which explains why it is higher in refractory lymphoma than in full remission. According to some research, cytokines are linked to advanced stages and increased mortality, supporting the idea that they play a major role in RDW. Numerous inflammatory indicators, including interleukin-6, ESR, CRP, soluble transferrin receptor, and soluble tumor necrosis factor receptors I and II, have been linked to it. Increased hepcidin and oxidative stress, poor erythrocyte maturation, low nutritional status (hypoalbuminemia), and insufficient erythropoietin synthesis were all caused by elevated proinflammatory cytokine levels. Higher RDW levels might result from these many biological processes [23, 24].

RDW's partial/refractory treatment response was predicted using ROC curve

analysis. With a 95% CI ranging from 0.620 to 0.899 and a substantial AUC of 0.760, it indicated a decent capacity to predict partial or refractory treatment response. Sensitivity, specificity, PPV, and NPV were 69.57%, 92.21%, 72.7%, and 91%, respectively, at the optimal threshold of >15.8% (P < 0.001). Furthermore, RDW at Cut off Point > 14.35% was linked to a poorer prognosis in terms of the survival rate of DLBCL patients, according to Fan et al. [25].

Furthermore, the RDW values of the DLBCL patients were shown to be significantly correlated with stage frequency distribution, recurrence, death, and full remission (P value<0.05) by Kamandi et al. [8]. The probability of recurrence (OR=2.50, P value<0.05), death (OR=3.59, P value<0.01), and incomplete remission (OR=0.115, P value<0.01) were likewise linked to increased RDW > 14.6%.

The current findings showed that RDW significantly correlated positively with both LDH levels (r = 0.497, P < 0.001) and lymphoma stages (r = 0.43, P < 0.001). Conversely, there was a noteworthy inverse relationship between it and platelet count (r = -0.203, P = 0.043). Zhou et al. [15] concurred with the current findings, stating that RDW had a positive correlation with both LDH level and lymphoma stage.

Low platelets and elevated RDW in advanced lymphoma may indicate thrombocytopenia, which may be caused by a few different reasons. According to Liebman H [26], a number of reasons, including medication, immune-mediated destruction, consumptive infection, splenic sequestration, pre-existing viral hepatitis, myelodysplasia, and malignant infiltration of bone marrow, might result in a decrease in platelet count.

RDW and IPI were shown to be independent predictors of partial/refractory treatment response by the multivariate analysis. We were supported by Beltrán et al. [27] who found that RDW was a significant predictor of a partial or refractory response in individuals with lymphoma. The current study was corroborated by Marcheselli et al. [28] who showed that IPI is still a useful model for risk assessment in patients with aggressive lymphomas.

High stage lymphoma (OR = 7.076, 95% CI = 1.547 - 32.361, P = 0.012), extra nodal lymphoma (OR = 6.146, 95% CI = 2.244 - 16.83, P < 0.001), B symptoms (OR = 3.073, 95% CI = 1.035 - 9.128, P = 0.043), LDH level (OR = 1.007, 95% CI = 1.003 - 1.012, P = 0.002), and bone marrow involvement (OR = 6.142, 95% CI = 2.141 - 17.62, P = 0.001) were all significant predictors of partial/refractory treatment response, according to the univariate analysis. PLR (P = 0.518) and ECOG PS 3 (P = 0.713) did not, however, significantly predict partial or refractory treatment response.

Rodday et al. [29] found that advanced lymphoma was a strong predictor of partial/refractory response, which is in line with the current findings.

Furthermore, Yang et al. [30] found that bone marrow involvement, extra nodal lymphoma, and the presence of B symptoms were indicators of how well lymphoma therapy would work. However, the current findings were contradicted by Seo et al. [31], who discovered that PLR was a predictor of response and PFS in patients with lymphoma (P=0.014).

A 75.6% higher chance of a partial or refractory treatment response was linked to a one-unit rise in RDW in the multivariate (OR = 1.756, 95% CI = 1.204 - 2.56, P = 0.003). The likelihood of a partial or refractory treatment response was 5.46 times higher for patients with a high-risk IPI (≥3) (OR = 5.463, 95% CI = 1.808 - 16.511, P = 0.003). Similarly, Maurer et al. [32] demonstrated a correlation between a higher IPI score and a poor response to lymphoma therapy. Furthermore, Nakamura et al. [33]

demonstrated that a higher RDW was linked to a higher risk of lymphoma that was resistant to therapy.

The limitations of the study were a single-center design that limited the study's statistical power and a very small sample size that made the findings less generalizable.

Conclusion

For instances of lymphoma, RDW and IPI are independent, significant predictors of partial or refractory response. RDW's partial/refractory treatment response was predicted using ROC curve analysis. With a 95% CI ranging from 0.620 to 0.899 and a substantial AUC of 0.760, it indicated a decent capacity to predict partial or refractory treatment response. Sensitivity, specificity, PPV, and NPV were 69.57%, 92.21%, 72.7%, and 91%, respectively, at the optimal cutoff of >15.8%.

Therefore, multi-center studies, bigger, stratified sample sizes, and the use of RDW as a readily ascertainable, low-cost biomarker for risk assessment in lymphoma patients are advised for more reliable findings.

References

1. Lewis WD, Lilly S, Jones KL. Lymphoma: Diagnosis and Treatment. Am Fam Physician. 2020;101:34-41.
2. Sánchez-Beato M, Méndez M, Guirado M, Pedrosa L, Sequero S, Yanguas-Casás N, et al. A genetic profiling guideline to support diagnosis and clinical management of lymphomas. Clin Transl Oncol. 2024;26:1043-62.
3. Ibrahim AH, Shash E. General Oncology Care in Egypt. In: Al-Shamsi HO, Abu-Gheida IH, Iqbal F, Al-Awadhi A, editors. Cancer in the Arab World. Singapore: Springer Singapore; 2022. p. 41-61.
4. Jelloul FZ, Navarro M, Navale P, Hagan T, Cocker RS, Das K, et al. Diagnosis of Lymphoma Using Fine-Needle Aspiration Biopsy and Core-Needle Biopsy: A Single-Institution Experience. Acta Cytol. 2019;63:198-205.
5. Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, et al. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016;127:75-90.
6. Sethi A, Tandon A, Mishra H, Singh I. Diffuse large B-cell lymphoma: An immunohistochemical approach to diagnosis. J Oral Maxillofac Pathol. 2019;23:284-8.
7. Ai L, Mu S, Hu Y. Prognostic role of RDW in hematological malignancies: a systematic review and meta-analysis. Cancer Cell Int. 2018;18:1-8.
8. Kamandi N, Soleimanian A, Allahyari A, Kamandi M. Prognostic role of red cell distribution width (RDW) in patients with diffuse large B-cell lymphoma. Asian Pac J Cancer Prev: APJCP. 2023;24:26-67.
9. Herraez I, Bento L, Del Campo R, Sas A, Ramos R, Ibarra J, et al. Prognostic Role of the Red Blood Cell Distribution Width (RDW) in Hodgkin Lymphoma. Cancers (Basel). 2020;12:20-40.
10. Younes A, Hilden P, Coiffier B, Hagenbeek A, Salles G, Wilson W, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). Ann Oncol. 2017;28:1436-47.
11. Hermans J, Krol AD, van Groningen K, Kluin PM, Kluin-Nelemans JC, Kramer MH, et al. International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. Blood. 1995;86:60-3.
12. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25:79-86.
13. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. 1981;47:7-14.
14. Paquin AR, Oyogoa E, McMurry HS, Kartika T, West M, Shatzel JJ. The diagnosis and management of suspected lymphoma in general practice. Eur J Haematol. 2023;110:3-13.
15. Stachel G, Jentzsch M, Oehring M, Antoniadis M, Schwind S, Noack T, et al. Red blood cell distribution width (RDW) is associated with unfavorable functional outcome after transfemoral transcatheter aortic valve implantation. IJC Heart & Vasculature. 2024;51:10-83.
16. Zhou S, Fang F, Chen H, Zhang W, Chen Y, Shi Y, et al. Prognostic significance of the red blood cell distribution width in diffuse large B-cell lymphoma patients. Oncotarget. 2017;8:40-72.
17. Thandra KC, Barsouk A, Saginala K, Padala SA, Barsouk A, Rawla P. Epidemiology of Non-Hodgkin's Lymphoma. Med Sci (Basel). 2021;9:20-30.

18. Kaseb H, Babiker HM, Doerr C. Hodgkin Lymphoma (Nursing). StatPearls [Internet]: StatPearls Publishing; 2023. p. 20-40.
19. Oura K, Morishita A, Hamaya S, Fujita K, Masaki T. The roles of epigenetic regulation and the tumor microenvironment in the mechanism of resistance to systemic therapy in hepatocellular carcinoma. Int J Mol Sci. 2023;24:28-50.
20. Bock AM, Mwangi R, Wang Y, Khurana A, Maurer MJ, Ayers A, et al. Defining primary refractory large B-cell lymphoma. Blood Adv. 2024;8:3402-15.
21. Kim SJ, Hong JS, Chang MH, Kim JA, Kwak JY, Kim JS, et al. Highly elevated serum lactate dehydrogenase is associated with central nervous system relapse in patients with diffuse large B-cell lymphoma: Results of a multicenter prospective cohort study. Oncotarget. 2016;7:72033-43.
22. Chen B-J, Fend F, Campo E, Quintanilla-Martinez L. Aggressive B-cell lymphomas—from morphology to molecular pathogenesis. Ann Lymphoma. 2019;3:20-40.
23. 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 Path Lab. 2009;133:628-32.
24. Wang P-F, Song S-Y, Guo H, Wang T-J, Liu N, Yan C-X. Prognostic role of pretreatment red blood cell distribution width in patients with cancer: A meta-analysis of 49 studies. J Cancer. 2019;10:4305.
25. Fan KC, Tran KD, Harbour JW, Dubovy SA, Patel NA, Albini TA. Vitreoretinal lymphoma followed by systemic diffuse large B cell lymphoma. J Ophthalmic Inflamm Infect. 2019;9:1-5.
26. Liebman H. Other immune thrombocytopenias. Semin Hematol. 2007;44:24-34.
27. Beltran BE, Quiñones P, Morales D, Malaga JM, Chavez JC, Sotomayor EM, et al. Response and survival benefit with chemoimmunotherapy in Epstein-Barr virus-positive diffuse large B-cell lymphoma. Hematol Oncol. 2018;36:93-7.
28. Marcheselli R, Bari A, Tadmor T, Marcheselli L, Cox MC, Papotti R, et al. Improving the international prognostic index score using peripheral blood counts: results of a large multicenter study involving 520 patients with diffuse large B cell lymphoma. Hematol Oncol. 2020;38:439-45.
29. Rodday AM, Parsons SK, Upshaw JN, Friedberg JW, Gallamini A, Hawkes E, et al. The advanced-stage Hodgkin lymphoma international prognostic index: development and validation of a clinical prediction model from the HoLISTIC consortium. J Clin Oncol. 2023;41:2076-86.
30. Yang H, Xun Y, Ke C, Tateishi K, You H. Extranodal lymphoma: pathogenesis, diagnosis and treatment. Mol Biol. 2023;4:29-40.
31. Seo J, Kim WS, Kim JS, Kim SJ, Lee JH, Hong JS, et al. Platelet to lymphocyte ratio (PLR) retains independent prognostic significance in advanced stage marginal zone lymphoma patients treated with rituximab, cyclophosphamide, vincristine, and prednisone combination chemotherapy (R-CVP): Consortium for Improving Survival of Lymphoma trial. Blood Res. 2017;52:200-50.
32. Maurer MJ, Jakobsen LH, Mwangi R, Schmitz N, Farooq U, Flowers CR, et al. Relapsed/Refractory International Prognostic Index (R/R-IPI): an international prognostic calculator for relapsed/refractory diffuse large B-cell lymphoma. Am J Hematol. 2021;96:595-9.
33. Nakamura N, Jo T, Arai Y, Kitawaki T, Nishikori M, Mizumoto C, et al. Utilizing red blood cell distribution width (RDW) as a reliable biomarker to predict treatment effects after chimeric antigen receptor T cell therapy. Clinical and Experimental Medicine. 2024;24:105-20.

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