Kufa Medical Journal | Vol. 21, No. 1, 2025

Original article | DOI: https://doi.org/10.36330/kmj.v21i1.18970

p-ISSN: 1993-517X
e-ISSN: 2709-4464

A Predictive Value of Red Blood Cell Distribution Width in Hodgkin Lymphoma in Iraqi Patients

Alaa Kadhum Mossa[1] and Adel S. Aqabi[2]

[1]*Senior Hematologist, Al-Diwaniyah General Hospital, Iraq*
[2]*C.A.B.M. (internal medicine). F.I.B.M.S. (Hematology) Consultant Hematologist and internist, Center of Hematology Medical City Complex, Baghdad, Iraq*

E-mail: dralaaalkafaji@gmail.com, adilaqabi@gmail.com

ABSTRACT

Aim: *to assess role of Red Blood cell Distribution Width as predictive factor in Hodgkin lymphoma.* ***Patient, material, methods:*** *the study to assess Iraqi patient including male and female with Hodgkin lymphoma age between (16-55 years) by compare RDW level at time of diagnosis then after 2 cycle and lastly at the end of chemotherapy. We enrolled in this study for period from Dec.2021 to Dec.2022 in Baghdad medical city. All patient included was send for full laboratory evaluation before beginning and during follow up.* ***Result:*** *The mean age of the patients was 30.49±11.24 years (range 16-55 years). Males were more common than females (56% vs. 44%). The most common disease stage was IIB stage accounting for 42%, followed by IVB stage (36%) and IIIB stage (24%). B-symptoms present in 82% of the patients, while bulky disease (>10cm) was reported in 18% of them .The mean RDW-SD in patients with complete response at diagnosis and after two cycles therapy was 48.02±9.66 fl and 51.17±9.8 fl, respectively which was much higher than that of patients with progressive disease/partial response (28.83±10.23 fl and 43.03±11.37 fl, respectively) with significant differences. Furthermore, patients with complete response demonstrated higher mean value of RDW-CV and RDW-SD at the end of treatment (17.66±3.5% and 52.0±6.6 fl, respectively) than those with progressive disease/partial response (14.67±2.45% and 36.87±12.71 fl), with highly significant differences* ***Conclusion:*** *High RDW CV and SD showed no significant association with high disease activity. Higher RDW showed significant association with anemia and low albumin. patients with complete response demonstrated higher mean value of RDW-CV and RDW-SD at the end of treatment than those with progressive disease/partial response with highly significant differences. RDW showed no significant correlation of these parameters neither with age nor with the disease stage*

Keywords: Hematology, RDW, Hodgkin lymphoma.

Article Information
Received: March 5, 2025; Revised: June 11, 2025; Online June, 2025

INTRODUCTION

Among all blood cancers, classic Hodgkin lymphoma (CHL) is considered one of the most manageable [1]. It comprises a category of B-cell neoplasms that arise from germinal center B-cells and are characterized by a limited number of tumor cells embedded in an immune cell dense reactive environment. A defective B-cell program is characteristic of the prominent diagnostic Hodgkin and Reed-Sternberg (HRS) cells [2]. In comparison, NLPHL is noted for having lymphocyte-predominant cells, often called popcorn cells, while being devoid of Reed-Sternberg cells [3]. In recent decades, there has been notable advancement in treating patients with HL; it is now curable in at least 80% of cases. The emergence of better treatment alternatives has enhanced 5-year survival rates, which remain unparalleled in any other cancer type over the last 40 years. Every patient with a recent HL diagnosis has a significant chance of being cured with the right treatment.

In reality, the healing rates for HL have improved so significantly that primary treatment concerns frequently pertain to long-term toxicity, particularly for those with early or intermediate-stage conditions. Clinical trials continue to focus on enhancing cure rates for individuals with advanced illnesses. However, the possible long-term effects of treatment are still a crucial factor to consider [3] Thomas Hodgkin served as the curator of the Anatomy Museum at Guy's Hospital in London and detailed the disease (4) Documented the clinical histories and significant postmortem observations of seven cases experiencing extensive enlargement of lymph nodes and spleen, identifying it as a novel disease entity as early as 1832, which would later be named after him [5]. In 1898, Carl von Sternberg in Vienna recognized the atypical cell that characterizes this lymphoma sub type, and in 1902, Dorothy Reed, a pathology intern at Johns Hopkins, became the first to differentiate the cell from granulomas present in nodal tuberculosis. The distinct RS cells, along with the related atypical mono-nuclear cells, are neoplastic, while the invading inflammatory cells are reactive [4]. a later series of 15 cases published in 1865 [5]

CLASSIFICATION

WHO-HAEM5 still categorizes nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) within the Hodgkin lymphoma family; the current terminology for NLPHL.

After finding Hodgkin's initial report, the term "Hodgkin's Disease" was applied in is preserved to avoid disrupting ongoing clinical trials. Nonetheless, NLPHL could more precisely be referred to as "nodular lymphocyte predominant B-cell lymphoma" because the neoplastic cells exhibit a functional B-cell program, making this terminology acceptable for the eventual formal adoption of the new naming convention. A significant concern in

NLPHL is identifying the various growth patterns. intersecting with T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL) at the far edge[6].

Table 1: classification of Hodgkin lymphoma.

Histologic Subtype	Immunophenotype
Nodular lymphocyte-predominant	CD20+ CD30– CD15– Ig+
Classical	CD20–* CD30+ CD15+ Ig–
Nodular sclerosis	
Mixed cellularity	
Lymphocyte-rich	
Lymphocyte-depleted	

Ig, immunoglobulin.
*Infrequently positive.

EPIDEMIOLOGY

Hodgkin's lymphoma is a rare condition in 2021, around 8830 individuals are anticipated to receive a diagnosis of HL in the United States, and 960 individuals are projected to succumb to this cancer. The illness exhibits a bimodal age distribution, showing one peak in the early 20s and another in the mid-70s. There is a minor male predominance (male to female incidence ratio of 1:3) [7]. The nodular sclerosis subtype is more prevalent in young adults, while the mixed cellularity subtype is found more frequently in children and older individuals. At all age groups, there is a higher prevalence of males (~1.4:1). Initial research linked a higher risk of Hodgkin lymphoma in young adults to elevated socioeconomic status. Residing in a rented house, sharing a room, and going to daycare or preschool, along with early childbirth in women, have been linked to a lower risk. The presence of the Epstein-Barr virus (EBV) in Hodgkin and Reed-Sternberg cells occurs more frequently in underdeveloped nations and in cases involving children and older adults [5]. Research indicates that Asians exhibit a markedly lower incidence of HL compared to other races; however, within the Asian population in the US, there are notable differences in incidence rates between US-born Asians and those born in their native countries [8].

PATHOGENESIS

The cancerous lymphocyte in cHL is referred to as the Hodgkin and Reed–Sternberg

(HRS) cell. Although the precise cell of origin for the HRS cell was debated and studied for many years, the evidence of clonal rearrangements in the immunoglobulin heavy- and light-chain loci has affirmed their B-cell origin. EBV can be identified in HRS cells in varying proportions of HL cases, influenced by age, Sex, race and histological subtype. HRS cells with damaging, or 'crippling' rearrangements of immunoglobulin loci are nearly always positive for EBV. In 1966, MacMahon suggested that the initial age peak in young adults was due to infections, while the subsequent peak stemmed from factors such as other lymphoma [5]. A significant population study indicated that individuals who contracted the disease exhibited unusually elevated levels of EBV viral capsid antigen and early antigen in their pre-diagnostic sera. The median incubation period was about 4.1years; genomes have been found in 30 to 50 percent of cHL tissues in developed nations, and EBV-related cases are more prevalent in instances with mixed cellularity histology, Hispanic ethnicity, and in patients over 60 years old [5].

CLINICAL FEATURES

Clinically, cHL typically manifests as a consequence of one (or multiple) of three primary mechanisms:

1. Enlarged lymph nodes – lymphadenopathy in cHL is usually without pain. The patient's reported rate of enlargement varies, but it is generally not swift; instead, a gradual growth over several months is more typical. The cervical and supraclavicular nodal areas are the most common locations for lymphadenopathy, with isolated infradiaphragmatic cases [1].

2.The systemic 'B' symptoms that are crucial to identify in history because of their significance for staging. B symptoms, characterized by fevers exceeding 100.4°F (38.0°C), excessive night sweats, and unintentional weight loss greater than 10% of body weight over the last 6 months, are found in some patients with advanced-stage disease but are seen in 10% to 20% of those with early-stage disease.

3.Pruritus, often severe and usually not linked

to a rash (though patients might experience secondary excoriations), occurs in 10% to 15%

of individuals. Even though it happens infrequently (< 5% of instances), some patients might endure severe pain in affected areas after consuming alcohol [7].

4. Mediastinal involvement is observed in as many as 10% of patients upon presentation. This is a characteristic of the nodular sclerosing variant, especially in young females. Pleural effusions or obstruction of the superior vena cava may be present [4]

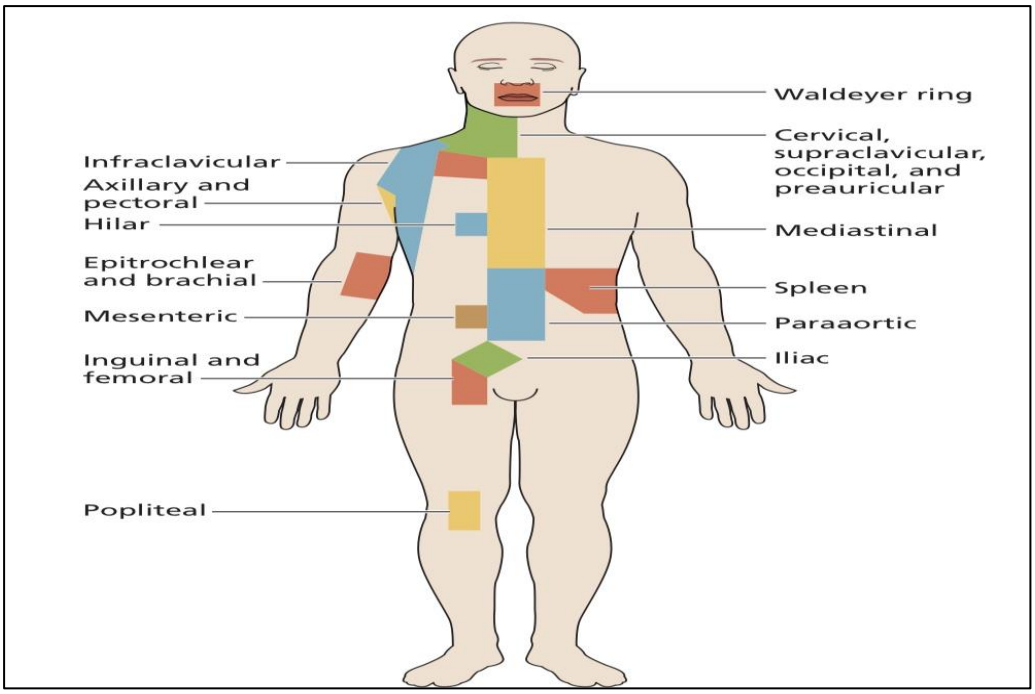

Figure 1: Nodal map. The Waldeyer ring includes the pharyngeal tonsil (adenoids), palatine tonsil, and lingual tonsil (base of tongue) [7].

DIAGNOSIS

HL is identified through the morphological identification of the HRS cell amidst the correct cellular context. The ideal tissue for identifying cHL is a fully intact lymph node obtained through an excisional lymph node biopsy [1]. Excisional lymph node biopsy is typically conducted, although a core needle biopsy might suffice if it is diagnostic. A diagnostic evaluation that relies exclusively on fine-needle aspiration biopsy is Inadequate, except in rare cases where, when paired with immunohistochemistry, an expert hematopathologist or cytopathologist determines it to be diagnostic of HL [9] Immunostaining for CD3, CD15, CD20, CD30, CD45, CD79a, and PAX5 is recommended for CHL. The Reed-Sternberg cells of CHL express CD30 in all patients and CD15 in most patients; they are usually negative for CD3 and CD45. CD20 may be detectable in fewer than 40% of patients [3]. Additional tests conducted in the diagnostic evaluation of patients with cHL (and suspected cHL) include Complete blood count, Bone marrow examination, HIV serology, Kidney and liver function tests, Respiratory function tests, a pregnancy test, and PET/CT imaging.

In this study, we seek to assess the prognostic significance of RDW levels in patients with HL at the time of diagnosis. RDW is an uncomplicated blood test measure that indicates the size variation of red blood cells (anisocytosis) in peripheral circulation and has traditionally been employed to investigate anemias [10].

Over the past ten years, increased levels of this parameter have been identified as a negative prognostic indicator in cardiovascular diseases, inflammation, and cancer [11][12] Physiological factors that may elevate RDW levels include aging, erythropoietin, pregnancy, African descent, and physical activity. In earlier years, a rise in RDW levels was identified as an unfavorable prognostic indicator that heightens mortality rates in the general population, linked to various acute and chronic illnesses, where inflammation acts as a crucial element, encompassing metabolic, cardiovascular, and thrombotic diseases [13]. In cancer patients, elevated RDW levels may correlate with an increased level of inflammation. Elevated cytokine levels can alter iron metabolism by raising hepcidin and oxidative stress. At the same time, the production of erythropoietin decreases, leading to increased anisocytosis and elevated RDW values [14] RDW in cancer indicates ongoing inflammation and inadequate nutritional health [15] (such as lack of nutrients like vitamin B12 and folate), which has been associated with diminished treatment responses and worse outcomes in cancer patients [16]Some research indicates that cytokines significantly influence RDW, correlating with later stages and increased mortality rates. It has been associated with various inflammatory markers including interleukin-6, ESR, CRP, soluble tumor necrosis factor receptors I and II, and soluble transferrin receptor [17]. Increased concentrations of proinflammatory cytokines resulted in insufficient erythropoietin production, hindered erythrocyte development, an unfavorable nutritional state (hypoalbuminemia), alongside elevated hepcidin levels and oxidative stress.

These are various biological processes that could result in increased RDW levels [18]Importantly, RDW has been noted to play a prognostic role in various lymphoproliferative disorders, including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), and multiple myeloma [19][20].In aggressive lymphomas like DLBCL, increased RDW levels at diagnosis correlated with poorer ECOG PS, B-symptoms, and a higher IPI. They forecasted a worse outlook [21].

Nonetheless, there is limited information on HL, where a proinflammatory environment plays a crucial role in its pathogenesis and physiopathology [22]. RDW is an uncomplicated, inexpensive, and readily accessible prognostic indicator in HL, which points out a population with poorer EFS, OS, and an increased

likelihood of developing secondary cancers. RDW appears to be associated with many negative prognostic factors in HL, suggesting that it could be a viable option for inclusion in existing or novel prognostic scores for HL [23].

METHODOLOGY

1. STUDY DESIGN

A prospective and retro prospective cohort study conducted at Hematology Center in Medical City from December 2021 till December 2022.

2. STUDY POPULATION, INCLUSION, AND EXCLUSION CRITERIA

A total of 50 patients aged from 16 to 70 years old of either gender was included in this study during their attendance to the Hematology Consultant Clinic for follow-up visits.

2.1 INCLUSION CRITERIA

1. Confirmed diagnosis of HL by histological and immunohistochemistry study.
2. Age from 14 to 55 years old.
3. Patients on treatment with chemotherapy with or without radiotherapy.

2.2 EXCLUSION CRITERIA

1. Age < 14 years or > 70 at diagnosis.
2. Prior blood transfusion.
3. Iron deficiency anemic patients, thalasse-mia, liver disease.
4. Patients who had a NYHA grade of III/IV.
5. 5.Patients who lost follow up.

3. DATA COLLECTION

The data collection included three parts.

First part: Patient's data that included:

a) Age,
b) Gender,
c) CBC (Automatic Hematology Analyzer Ruby Abbott Laboratories)

which include:

a) WBC
b) Hb
c) RDW
d) MCV
e) Platelet count
f) Iron profile, B12 level, Folate level

4. RISK ASSESSMENT

According to EORTC criteria (table 4-1) and IPS table (5-1)

5. ASSESSMENT OF RESPONSE

By FDG-PET imaging or CT scan for each patient on following period:

1. At baseline
2. After two cycles of treatment
3. After end of chemotherapy cycle
4. At 6 months after treatment
5. At 12 months after treatment
6. At 18 months after treatment

For restaging using PET/CT, the Deauville 5-point scale (5PS) allows for more accurate measurement. Values are recorded by comparing disease uptake to a reference organ with generally consistent metabolic activity, reducing inter-reader and inter-device inconsistencies.

6. RDW CATEGORIZATION

The RDW CV normal range was calculated based on normal range for red cell distribution width which is 12.2 to 16.1 percent in adult females and 11.8 to 14.5 percent in adult males. Patients have been divided for two groups:

• ***Group A***: included patients with high RDW at baseline

• ***Group B***: included patients with normal RDW at baseline

7. PATIENT CONSENT AND ETHICAL APPROVAL

Administrative approvals were granted from the following:

1. The Council of Iraqi Board of Medical Specializations.

2. Informed approval consent was taken from all participants for participate in the study, all personal information was kept anonymous. Data were exclusively used for the sake of this study.

8. CLINICAL EVALUATION AND MEASUREMENTS

We reported the following information:

a) Sociodemographic data such as age, gender, educational level, occupation, marital status, and smoking status.

b) Medical history that includes comorbidities (hypertension, DM, dyslipidemia and renal disease), current medications, and family history in first-degree relatives for malignancies

c) Physical examination including (general, eye, cardiovascular, respiratory, and abdominal examination, searching for extranodal manifestations).

d) RDW were collected from Hematology registry data of Hematology Consultant Clinic in our hospital and follow up investigations.

Responses were categorized into two groups, these are: complete and partial. Complete Response (CR) is considered if FDG uptake on PET/CT is less than or equal to uptake in the liver with no FDG uptake in the bone marrow. While Partial Response (PR) is considered if FDG uptake on PET/CT is greater than that of liver but reduced compared to pretreatment PET/CT.

RESULTS

1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

The mean age of the patients was 30.49±11.24 years (range 16-55 years). Males were more common than females (56% vs. 44%). The most common disease stage was IIB stage accounting for 42%, followed by IVB stage (36%) and IIIB stage (24%). Less common stages are early stages (IIA, 12 % and IVA, 6%). B-symptoms present in 82% of the patients, while bulky disease (>10cm) was reported in 18% of them. The mean Hb concentration, WBC, lymphocyte and platelets count was 11.18±2.0 g/dl, 8.11±4.2 × 103/mL, 2.0±1.46× 109/mL and 318.48±117.14× 103/mL, respectively. Finally, the mean serum level of albumin and LDH was 3.73±0.79 g/dl and 295.7±154.9 U/L, respectively (Table 2).

Other types of NHL included 2 cases of nodular lymphocyte predominant, and 2 cases of classical/ lymphocyte depleted.

2. RESPONSE RATE AFTER TWO CYCLES THERAPY

Partial and complete response were accounting for the vast majority of patients (42.86% and 42.82%, respectively). On the other hand, progressive disease was reported in 2 patients (4.08%), while excellent response was reported in 6 patients (12%) as shown in Figure 2.

Variables	Values
Age, years	
Mean±SD (range)	30.49±11.24 (16-55)
Gender	
Male	28(56%)
Female	22(44%)
Type of HL	
Classical/ Nodular sclerosis	24(48%)
Classical/ Mix cellularity	16(32%)
Classical/ Lymphocyte rich	6(12%)
Others	4(8%)
Stage	
IIA	6(12%)
IIB	21(42%)
IIIB	12(24%)
IVA	3(6%)
IVB	18(36%)
B symptoms	
Absent	9(18%)
Present	41(82%)
Bulky disease (>10cm)	
No	41(82%)
Yes	9(18%)
Hb, g/dl	
Mean±SD (range)	11.18±2.08 (6-16)
WBC× 10^3/mL	
Mean±SD (range)	8.11±4.2 (2.5-22)
Lymphocyte×10^3/mL	
Mean±SD (range)	2.0±1.46 (0.4-6)
PLT×10^3/mL	
Mean±SD (range)	318.48±117.14 (77-572)
Albumin, g/dL	
Mean±SD (range)	3.73±0.79 (2.1-6)
LDH, U/L	
Mean±SD (range)	295.7±154.9 (112-943)

Table2: Baseline Demographic and clinical characteristics of the patients (n=50).

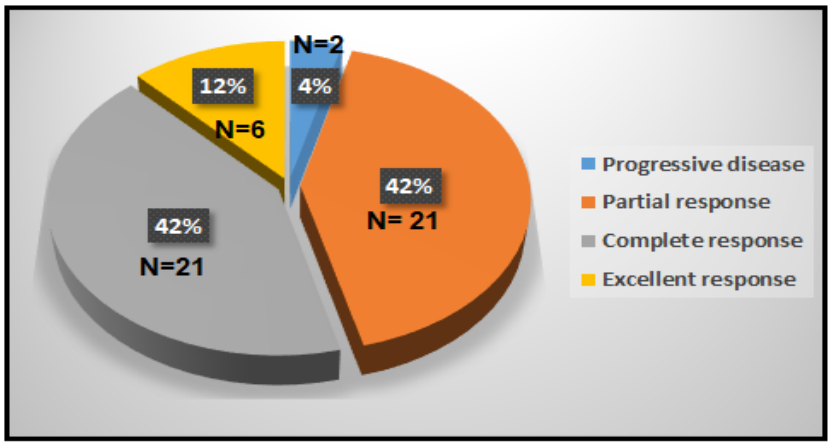

Figure2: Response rate after two cycles therapy.

3. ASSOCIATION OF RWD-CV AND RDW-SD AT DIAGNOSIS AND AFTER TWO CYCLES THERAPY WITH RESPONSE RATE

Due to relatively small number of patients with disease progression and excellent response, they were merged with partial response and complete response group, respectively. Thus, the patients were categorized into progressive disease/ partial response (n=23) and complete/excellent response(n=27).

Generally, there were no significant differences between the two groups in mean RDW-CV or RDW-SD neither at diagnosis nor after two cycles therapy. Although, the mean RDW-SD after two cycles therapy was higher in patients with complete/excellent response (50.85±8.98 fl) than those with progressive disease/ partial response (45.15±12.47 fl), the difference did not reach the acceptable level of significant (Table 3).

Table 3: Association of RWD-CV and RDW-SD at diagnosis and after two cycles therapy with response rate.

Variables	Progressive disease/ partial response (N=23)	Complete/Excellent response (N=27)	p-value
At diagnosis			
RDW-CV, %			
Mean Range	15.78±3.12	15.76±2.66	0.980
Low	11-25	10-22	
Normal	0(0%)	1(3.7%)	
Elevated	17(73.91%)	17(62.96%)	0.525
	6(26.09%)	9(33.33%)	
RDW-SD, fl			
Mean Range	42.64±12.71	46.41±8.51	0.225
Normal	22-70	23-59	
Elevated	21(91.3%)	24(88.89%)	0.778
	2(8.7%)	3(11.11%)	
After 2 cycles therapy			
RDW-CV, %			
Mean Range	16.5±3.88	17.07±3.03	0.571
Normal	11-28	10-25	
Elevated	13(56.52%)	13(48.15%)	
	10(43.48%)	14(51.85%)	0.555
RDW-SD, fl			
Mean Range	45.15±12.47	50.85±8.98	0.071
Normal	27-69	32-66	
Elevated	19(82.61%)	19(70.37%)	0.313
	4(17.39%)	13(48.15%)	

4. RESPONSE RATE AT THE END OF TREATMENT

Thirty-two patients (64%) achieved complete response, while 8 patients (16 %) had partial response. However, progressive disease was encountered in 10 patients (20%) as shown in figure 3.

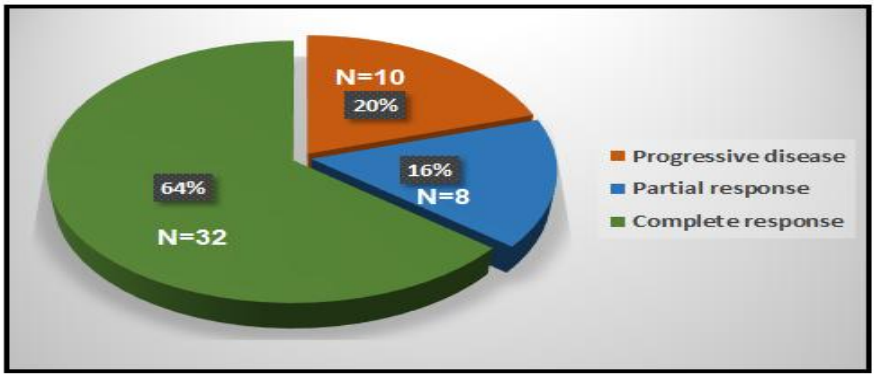

Figure 3: Response rate at the end of treatment.

5. ASSOCIATION OF RWD-CV AND RDW-SD AT DIAGNOSIS, AFTER TWO CYCLES THERAPY AND AT THE END OF TREATMENT WITH RESPONSE RATE

Patients with progressive disease were also merged with those of partial responses. For RDW-CV, there were no significant differences between the two group neither at diagnosis nor after two cycles therapy. In contrast, the mean RDW-SD in patients with complete response at diagnosis and after two cycles therapy was 48.02±9.66 fl and 51.17±9.8 ft, respectively which was much higher than that of patients with progressive disease/partial response (28.83±10.23 fl and 43.03±11.37 fl, respectively) with significant differences. Furthermore, patients with complete response demonstrated higher mean value of RDW-CV and RDW-SD at the end of treatment (17.66±3.5% and 52.0±6.6 fl, respectively) than those with progressive disease/partial response (14.67±2.45% and 36.87±12.71 fl), with highly significant differences (table 3-4).

Table4: Association of RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment with response rate, SD: standard deviation, fl: femtoliter .

Variables	Progressive disease/ partial response (N=18)	Complete response (N=32)	p-value
At diagnosis			
RDW-CV, %			
Mean Range	15.22±2.49	16.09±3.08	0.308
Low	11-21	10-25	
Normal	0(0%)	1(3.23%)	
Elevated	14(77.78%)	20(62.5%)	0.466
	4(22.22%)	11(34.38%)	
RDW-SD, fl			
Mean Range	28.83±10.23	48.02±9.66	**0.003**
Normal	22-55	23-70	
Elevated	18(100%)	26(81.25%)	**0.048**
	0(0%)	6(18.75%)	
After 2 cycles therapy			
RDW-CV, %			
Mean Range	15.86±2.41	17.35±3.84	0.146
Normal	12-20	10-28	
Elevated	11(61.11%)	15(46.88%)	0.333
	7(38.89%)	17(53.12%)	
RDW-SD, fl			
Mean Range	43.03±11.37	51.17±9.8	**0.011**
Normal	27-68	32-69	
Elevated	16(88.89%)	22(68.75%)	0.109
	2(11.11%)	10(31.25%)	
At the end of treatment			
RDW-CV, %			
Mean Range	14.67±2.45	17.66±3.5	**0.002**
Normal	11-20	13-25	
Elevated	14(77.78%)	15(46.88%)	**0.034**
	4(22.22%)	17(53.12%)	
RDW-SD, fl			
Mean Range	36.87±12.71	52.0±6.6	**<0.001**
Normal	23-63	39-67	
Elevated	16(88.89%)	25(78.13%)	

6. PREDICTIVE VALUE OF RDW-CV AND RDW-SD

Receiver operating characteristic (ROC) curve was used to evaluate the predictive value of RDW-CV and RDW-SD in predicting response to treatment. Factors that had significant variation in the previous analysis were entered the model. In the context of predicting complete response at the end of treatment, the area under the curve (AUC) for RDW-SD at diagnosis was 0.745, 95%CI=0.693-0.887, p=0.005. The sensitivity and specificity of the test at cut off value of RDW-SD= 40.5 fl were 81% and 56% respectively. For, RDW-CV after two cycles therapy, the AUC was 0.710, 95%CI=0.557-0.862, p=0.015. The sensitivity and specificity of the test at cut off value of RDW-SD= 43.5 fl were 81% and 50% respectively (Figure 4).

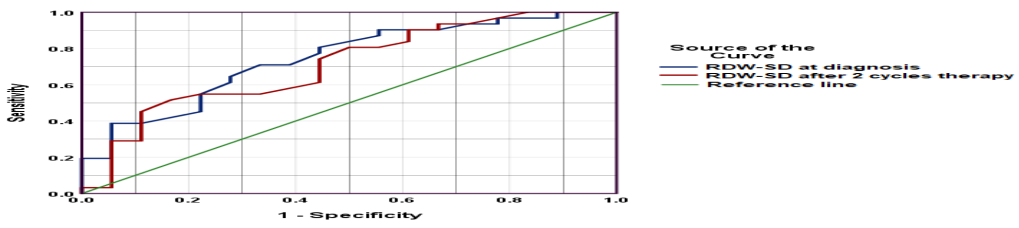

Figure4: Receiver operating characteristic curve for RDW-SD at diagnosis and after 2 cycles therapy in predicating response to treatment

For RDW-CV at the end of treatment, the AUC was 0.757, 95%CI=0.617-0.897, p=0.003. The sensitivity and specificity of the test at cut off value of RDW-CV= 15.5% were 65% and 78% respectively. For RDW-SD at the end of treatment, the AUC was 0.843, 95%CI=0.700-0.987, p<0.001. The sensitivity and specificity of the test at cut off value of RDW-SD= 45.05fl were 87% and 83% respectively as depicted in Figure 5.

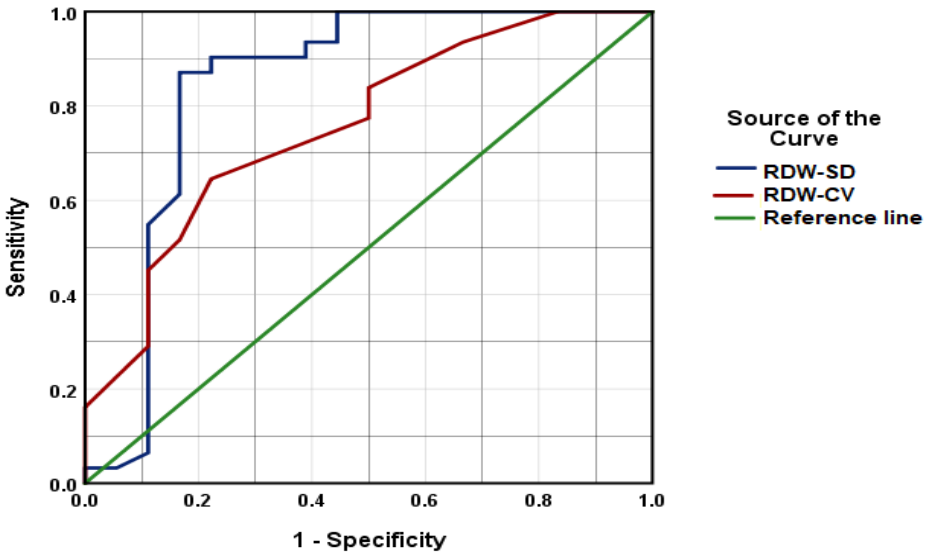

Figure 5: Receiver operating characteristic curve for RDW-SD and RDW-CV at the end of treatment in predicating response to treatment

7. CORRELATION OF RWD-CV AND RDW-SD AT DIAGNOSIS, AFTER TWO CYCLES THERAPY AND AT THE END OF TREATMENT WITH AGE AND DISEASE STAGE

Pearson's correlation test was used to explore the possible correlation of RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment with age and disease stage. Generally, there were no significant correlation of these parameters neither with age nor with the disease stage (Table 5)

Table 5: Pearson's correlation of rwd-cv and rdw-sd at diagnosis, after two cycles therapy and at the end of treatment with age and disease stage

Variable	Age		Stage	
	Coefficient	p-value	Coefficient	p-value
RDW-CV at diagnosis	0.019	0.896	0.230	0.111
RDW-SD at diagnosis	0.087	0.554	0.106	0.470
RDW-CV after 2 cycles therapy	-0.108	0.459	-0.171	0.908
RDW-SD after 2 cycles therapy	-0.013	0.931	0.013	0.930
RDW-CV at the end of therapy	-0.048	0.742	0.061	0.678
RDW-SD at the end of therapy	0.006	0.968	0.039	0.789

8. ASSOCIATION OF RWD-CV AND RDW-SD AT DIAGNOSIS, AFTER TWO CYCLES THERAPY AND AT THE END OF TREATMENT WITH GENDER

Mostly, the included parameters did not have a significant correlation with gender. However, the mean RDW-SD after tow cycles therapy and RDW-CV at the end of treatment were remarkably higher in females (51.45±10.73fl and 17.57±3.88%) than males (45.51±10.72 fl and 15.74±2.87%, respectively) although the differences were not significant. Similarly, there were no significant difference in RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment between bulky and non-bulky disease (Table 6).

Table 6: Association of RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment with gender.

Variables	Gender		p-value	Bulky disease		p-value
	Male (N=28)	Female (N=22)		No (N=41)	Yes (N=9)	
At diagnosis						
RDW-CV, %						
Mean±SD	15.59±2.3	15.98±3.46	0.640	16.1±3.22	14.98±0.73	0.311
Range	12-22	10-25		14-25	14-16	
RDW-SD, fl						
Mean±SD	44.1±10.59	45.31±11.14	0.701	45.0±10.8	43.0±9.27	0.610
Range	22-65	22-70		22-70	22-54.4	
After 2 cycles therapy						
RDW-CV, %						
Mean±SD	16.34±2.86	17.25±4.05	0.413	17.08±3.48	15.9±3.18	0.315
Range	10-25	12-28		11-28	10-21	
RDW-SD, fl						
Mean±SD	45.51±10.72	51.45±10.73	0.060	47.39±11.46	50.08±9.7	0.517
Range	27-62	32-69		27-69	34-66	
At the end of treatment						
RDW-CV, %						
Mean±SD	15.74±2.87	17.57±3.88	0.064	16.57±3.31	16.78±4.18	0.873
Range	11-22	13-25		11-25	12-25	
RDW-SD, fl						
Mean±SD	46.30±11.64	46.62±12.21	0.924	45.94±11.81	47.89±11.76	0.656
Range	23-67	23-63		23-67	28-62	

9. ASSOCIATION OF RWD-CV AND RDW-SD AT DIAGNOSIS, AFTER TWO CYCLES THERAPY AND AT THE END OF TREATMENT WITH THE SUBTYPE OF HL

In general, the RWD-CV and RDW-SD values at diagnosis, after two cycles therapy and at the end of treatment are comparable between different types of NHL with no significant differences (Table 7).

10. CORRELATION OF RWD-CV AND RDW-SD AT DIAGNOSIS, AFTER TWO CYCLES THERAPY AND AT THE END OF TREATMENT WITH HEMATOLOGICAL INDICES, ALBUMIN AND LDH

Pearson correlation test was used to explore the possible correlation of RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment with Hb, WBC, lymphocyte, PLT and albumin. RDW-SD at the end of treatment showed a positive significant correlation with each of Hb (r= 0.327, p = 0,021) and albumin (r= 0.395, p= 0.007) as shown in table 7, figures 6 and 7.

Table 7: Association of RWD-CV and RDW-SD at diagnosis, after Two Cycles Therapy and at the End of Treatment with the subtype of HL

Variables	Nodular sclerosis	Mix Cellularity	Lymphocyte rich	Others	p-value
At diagnosis					
RDW-CV, %					
Mean Range	16.53±2.8 12-22	15.43±3.5 10-25	15.33±2.8 12-19	14.8±0.5 10-25	0.523
RDW-SD, fl					
Mean Range	45.75±7.28 30-59	43.74±12.96 22-70	44.82±11.89 25-57	42.5±18.6 22-65	0.932
After 2 cycles therapy					
RDW-CV, %					
MeanRange	17.19±2.9 12-25	17.11±4.04 12-28	16.67±3.61 11-21	14.3±3.68 10-19	0.462
RDW-SD, fl					
Mean Range	48.97±9.93 28-65	47.52±13.11 28-65	45.5±14.15 27-66	46.25±6.7 41-56	0.901
At the end of treatment					
RDW-CV, %					
Mean Range	16.44±3.21 11-24	16.63±3.46 12-25	18.0±4.7 13-25	15.5±3.32 1-20	0.703
RDW-SD, fl					
Mean Range	46.11±9.57 25-62	45.07±12.87 23-63	51.0±15.91 23-67	42.3±15.2 25-60	0.768

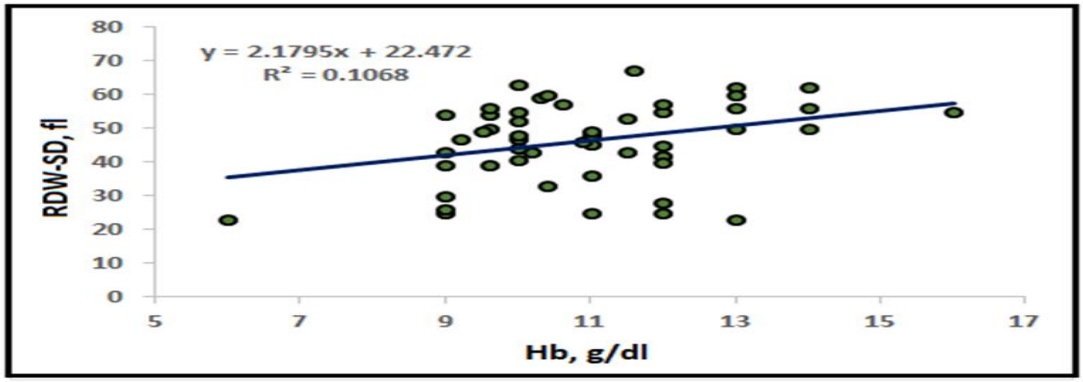

Figure 6: Scatter plot and regression line between Hb and RDW-SD at the end of treatment.

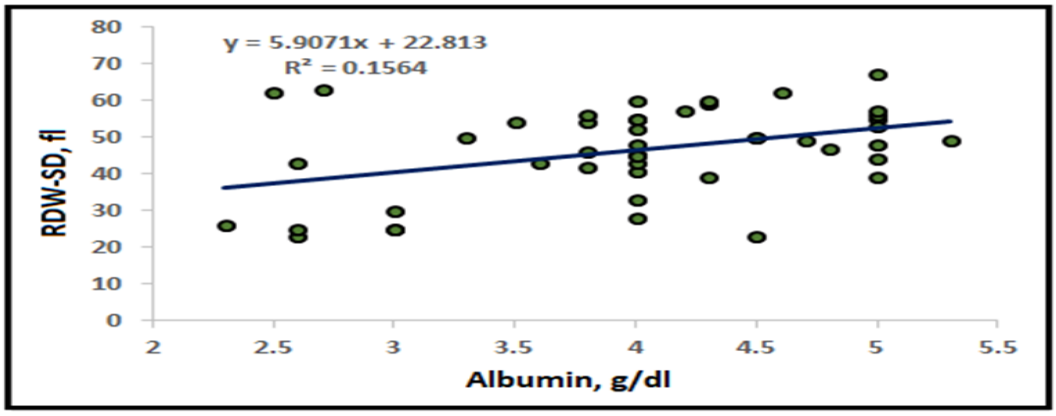

Figure 7: Scatter plot and regression line between albumin and RDW-SD at the end of treatment

DISCUSSION

In this study, we assessed RDW level among fifty Iraqi patients with Hodgkin Lymphoma treated with ABVD +/- RT, the median age was 30.49-/+11.24 years old, of them 56% was male and 44% female most of them in advance stage; of them 64% achieved complete response while 20% has progressive disease and the rest has partial response. RDW is an automatically measured index of the heterogeneity of the erythrocytes [(23)]. Traditionally, this parameter was used for the differential diagnosis of anemias [(24)]. In cancer, anemia could be present due to inflammation, and after treatment [(25)]. In previous years, an increase in RDW levels was described as an adverse prognostic factor that increases mortality in the general population, associated with many acute and chronic conditions, in which inflammation represents a critical factor, including metabolic, cardiovascular, and thrombotic disorders [(26)]. The baseline RDW SD among all HL patients included was 30.4 fl with range from (16 – 55 FL). By comparison RDW at the diagnosis then after two cycles of chemotherapy and lastly at end of cycles, our finding reveled there were no significant correlation of these parameter neither with age nor with the disease stage. Mostly, the included parameters did not have a significant correlation with gender. However, the mean RDW-SD after two cycles therapy and RDW-CV at the end of treatment were remarkably higher in females than males although the differences were not significant.

Also, the RDW-CV and RDW-SD values at diagnosis, after two cycles therapy and at the end of treatment are comparable between different types of HL with no significant differences. While the correlation of RWD-CV and RDW-SD at diagnosis, after two cycles therapy and at the end of treatment with Hb, WBC, lymphocyte, PLT and albumin and LDH; RDW-SD at the end of treatment showed a positive significant correlation with each of Hb ($p = 0,021$) and albumin ($p= 0.007$).

Similar study was done in at Son Espases ($n = 165$) and Son Llatzer ($n = 99$) University Hospitals in the Balearic Islands, between 1990

and 2018 by Ines Herraez et al (2020) ,total number of 264 patients, the median RDWin the cohort was 13.9 , The median age was 37 years (14–83 years), 52% of patients had an advanced stage, 16% had bulky disease, with frontline therapy, 88% of the patients reached complete response (CR), 4% had a partial response (PR), and 8% a stable/progressive disease (SD/PD). With a median follow-up of 81 months. They found that patients with sRDW >0.95 were significantly older patients, with more advanced disease, with a higher incidence of B-symptoms, and several worse adverse prognostic factors such as higher erythrocyte sedimentation rate (ESR), lower albumin levels, lower counts of lymphocytes and low hemoglobin (Hb) levels at diagnosis. Multivariate analysis showed that sRDW >0.95 was independently associated to patients with anemia (Hb < 10.5) (p = 0.001), B-symptoms (p = 0.007) and low albumin level (p = 0.019).

In this study, RDW strongly correlated with main prognostic factors in HL, and sRDW > 0.95 is shown to be an independent adverse prognostic factor for EFS and OS.RDW seems to be related to most adverse prognostic factors in HL, making RDW an excellent candidate to be included in prognostic scores for HL. Another study done in Spain in the Son Espases University Hospital by Bernardo et al. Were retrospectively evaluated 119 patients with HL homogenously treated in frontline with ABVD from 2001 to 2015, median age was 37 (15-75) years, 61% were males, 13% had ECOG PS>1, 47% advanced III-IV Ann Arbor (AA) stage, 42% B-symptoms and 29% IPS>2 Median RDW was14.1.

Patients with RDW CV>16.6 were associated with worse responses compared to those with RDW≤16.6: 29% versus 6% of stable/progressive disease and lower complete or partial responses: 67% and 5% versus 93% and 1%, respectively (p=0.004). The result that higher RDW at diagnosis was related with more aggressive and advanced disease in HL and lower response rates, probably reflecting a higher inflammatory activity of the lymphoma and its microenvironment. RDW>16.6 was independently associated with a worse PFS. Our study agrees with at Son Espases study that RDW-SD has positive significant correlation with each of Hb and albumin. And disagree with both previous mention study that RDW has no significant role as prognostic factor in HL; may be due to limited number of cases included in our study in addition to limited duration of study.

CONCLUSION

Based on study results, we concluded the that high RDW showed no significant association with high disease activity. Also, we have noticed that higher RDW showed significant association with anemia and low albumin. Furthermore, our findings reveal that patients with complete response demonstrated higher mean value of RDW-CV and RDW-SD at the end of treatment than those with progressive disease/partial response with highly significant differences. Finally, our study shows that RDW has no significant correlation of these

parameters neither with age nor with the disease stage.

This study recommends that RDW should be incorporated in work up of HL patients as simple available parameter. Also, correct anemia in patient with low HB. As a future work, our plan is to conduct further investigation to recommend RDW as predictive for response.

Ethical approval

The present study Which is conducted by authors **Dr. Alaa** and **Dr. Adel** was approved by the local Department of the **Iraqi Board for Medical Specializations** committee.

Statement of Permission and Conflict of Interests

The authors declare that there is no conflict-of-interest associates with this submission.

ACKNOWLEDGMENT

We acknowledge that all the references are listed in the reference list and written in **APA 7th (American Psychological Association) format** using Mendeley reference manager software.

REFERENCES

1. Hoffbrand, A. V., Higgs, D. R., Keeling, D. M., & Mehta, A. B. (Eds.). (2016). *Postgraduate haematology*. John Wiley & Sons.
2. Ebied, A., Thanh Huan, V., Makram, O. M., Sang, T. K., Ghorab, M., Ngo, H. T., ... & Huy, N. T. (2018). The role of primary lymph node sites in survival and mortality prediction in Hodgkin lymphoma: a SEER population-based retrospective study. *Cancer Medicine*, *7*(4), 953-965.
3. Hoppe, R. T., Advani, R. H., Ai, W. Z., Ambinder, R. F., Armand, P., Bello, C. M., ... & Ogba, N. (2020). Hodgkin lymphoma, version 2.2020, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *18*(6), 755-781.
4. Hoffbrand, V., Collins, G., & Loke, J. (2024). *Hoffbrand's essential haematology*. John Wiley & Sons.
5. Prchal, J. T., Prchal, J. T., & Polycythemia, V. (2021). *Williams hematology* (pp. 1291-1301). New York: McGraw-Hill.
6. Fan, Z., Natkunam, Y., Bair, E., Tibshirani, R., & Warnke, R. A. (2003). Characterization of variant patterns of nodular lymphocyte predominant Hodgkin lymphoma with immunohistologic and clinical correlation. *The American journal of surgical pathology*, *27*(10), 1346-1356.
7. Celeste Bello and Pamela B.All.Hodgkin lymphoma. American Sociaty Of hematology . eight ed.2022. P 603 ; P 604 .
8. Ahmed, R., Tariq, F., Ashfaq, J., Thakur, W., Zafar, S., Danish, A., & Borhany, M. (2022). The Outcome of Hodgkin Lymphoma with Reference to Prognostic Markers. *Cureus*, *14*(8).
9. Hoppe, R. T., Advani, R. H., Ai, W. Z., Ambinder, R. F., Armand, P., Bello, C. M., Benitez, C. M., Bierman, P. J., Boughan, K. M., Dabaja, B., Gordon, L. I., Hernandez-Ilizaliturri, F. J., Herrera, A. F., Hochberg, E. P., Huang, J., Johnston, P. B., Kaminski, M. S., Kenkre, V. P., Khan, N., Lynch, R. C., … Ogba, N. (2020). Hodgkin Lymphoma, Version 2.2020, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network: JNCCN*, *18*(6), 755–781. https://doi.org/10.6004/jnccn.2020.0026
10. Montagnana, M., & Danese, E. (2016). Red cell distribution width and cancer. *Annals of translational medicine*, *4*(20).
11. Ai, L., Mu, S., & Hu, Y. (2018). Prognostic role of RDW in hematological malignancies: a systematic review and meta-analysis. *Cancer cell international*, *18*, 1-8.
12. Weitzman, D., Raz, R., Steinvil, A., Zeltser, D., Berliner, S., Chodick, G., ... & Arbel, Y. (2014). Red blood cell distribution width and the risk of cardiovascular morbidity and all-cause mortality. *Thrombosis and Haemostasis*, *112*(02), 300-307.
13. Lippi, G., Targher, G., Montagnana, M., Salvagno, G. L., Zoppini, G., & Guidi, G. C.

(2009). Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. *Archives of pathology & laboratory medicine*, *133*(4), 628-632.

14. Salvagno, G. L., Sanchis-Gomar, F., Picanza, A., & Lippi, G. (2015). Red blood cell distribution width: a simple parameter with multiple clinical applications. *Critical reviews in clinical laboratory sciences*, *52*(2), 86-105.
15. Wang, P. F., Song, S. Y., Guo, H., Wang, T. J., Liu, N., & Yan, C. X. (2019). Prognostic role of pretreatment red blood cell distribution width in patients with cancer: A meta-analysis of 49 studies. *Journal of Cancer*, *10*(18), 4305.
16. Periša, V., Zibar, L., Sinčić-Petričević, J., Knezović, A., Periša, I., & Barbić, J. (2015). Red blood cell distribution width as a simple negative prognostic factor in patients with diffuse large B-cell lymphoma: a retrospective study. *Croatian medical journal*, *56*(4), 334-343.
17. Ai, L., Mu, S., & Hu, Y. (2018). Prognostic role of RDW in hematological malignancies: a systematic review and meta-analysis. *Cancer cell international*, *18*, 1-8.
18. Lee, H., Kong, S. Y., Sohn, J. Y., Shim, H., Youn, H. S., Lee, S., ... & Eom, H. S. (2014). Elevated red blood cell distribution width as a simple prognostic factor in patients with symptomatic multiple myeloma. *BioMed research international*, *2014*(1), 145619.
19. Zhou, S., Fang, F., Chen, H., Zhang, W., Chen, Y., Shi, Y., ... & Jiang, S. (2017). Prognostic significance of the red blood cell distribution width in diffuse large B-cell lymphoma patients. *Oncotarget*, *8*(25), 40724.
20. Lopez Andrade, B., Robredo, B., Sartori, F., Herráez, I., Duran Pastor, M. A., Garcia Recio, M., ... & Gutierrez, A. (2016). Red cell distribution width (RDW) at diagnosis is associated to advanced stage, worse response and poor prognosis in Hodgkin lymphoma.
21. Herraez, I., Bento, L., Del Campo, R., Sas, A., Ramos, R., Ibarra, J., ... & Gutierrez, A. (2020). Prognostic role of the red blood cell distribution width (RDW) in Hodgkin lymphoma. *Cancers*, *12*(11), 3262.
22. Adeli, K., Raizman, J. E., Chen, Y., Higgins, V., Nieuwesteeg, M., Abdelhaleem, M., ... & Blais, D. (2015). Complex biological profile of hematologic markers across pediatric, adult, and geriatric ages: establishment of robust pediatric and adult reference intervals on the basis of the Canadian Health Measures Survey. *Clinical chemistry*, *61*(8), 1075-1086.
23. Montagnana, M., & Danese, E. (2016). Red cell distribution width and cancer. *Annals of translational medicine*, *4*(20).
24. Herraez, I., Bento, L., Del Campo, R., Sas, A., Ramos, R., Ibarra, J., ... & Gutierrez, A. (2020). Prognostic role of the red blood cell distribution width (RDW) in Hodgkin lymphoma. *Cancers*, *12*(11), 3262.
25. Macciò, A., Madeddu, C., Gramignano, G., Mulas, C., Tanca, L., Cherchi, M. C., ... & Ganz, T. (2015). The role of inflammation, iron, and nutritional status in cancer-related anemia: results of a large, prospective, observational study. *haematologica*, *100*(1), 124.
26. Salvagno, G. L., Sanchis-Gomar, F., Picanza, A., & Lippi, G. (2015). Red blood cell distribution width: a simple parameter with multiple clinical applications. *Critical reviews in clinical laboratory sciences*, *52*(2), 86-105.