PROGNOSTIC VALUE OF HEMOGLOBIN TO RED CELL DISTRIBUTION WIDTH RATIO FOR PATIENTS WITH HODGKIN LYMPHOMA

NIKA PUŠELJIĆ[1] , VLATKA PERIŠA [2,3]

[1]*Emergency Hospital Admission Department, University Hospital Center Osijek, Osijek, Croatia;*
[2]*Department for Hematology, Clinic of Internal Medicine, University Hospital Center Osijek, Osijek, Croatia;*
[3]*Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia*

Abstract

Aim: To examine whether the value of hemoglobin to red blood cell distribution width ratio (HRR) at the time of diagnosis of Hodgkin lymphoma (HL) was an independent prognostic factor of overall survival (OS), event-free survival (EFS), and response to therapy, as well as to test the interrelations of HRR with demographic, clinical, and laboratory characteristics.

Materials and methods: This research was designed as a retrospective cohort study of patients with histologically verified HL, diagnosed at the Clinical Hospital Center Osijek in the period from April 2005 to August 2022.

Results: A total of 83 subjects, with a median age of 36 years, ranging from 19 to 82, participated in the research. A significant difference in HRR was found depending on the outcome of treatment, OS, and EFS. A lower HRR was associated with a worse therapeutic response, a higher risk of relapse, and other worse prognostic factors. A positive correlation of HRR with middle corpuscular volume, number of erythrocytes, and albumin level was found, and a negative correlation with erythrocyte sedimentation rate, number of platelets, and C-reactive protein concentration.

Conclusion: Lower HRR was associated with unfavorable clinical and pathological characteristics of HL. There is a good potential for HRR as a prognostic marker and it should be applied with other known biochemical and hematological markers.

Keywords: hemoglobin, Hodgkin lymphoma, red blood cell distribution width, hemoglobin to red blood cell distribution width ratio, survival

Address for correspondence: Assist. prof. Vlatka Periša, MD, PhD
Department for Hematology
Clinic of Internal Medicine
Clinical Hospital Center Osijek
Huttlerova 4, 31 000 Osijek, Croatia
vlatkaperisa@gmail.com

INTRODUCTION

Hodgkin lymphoma (HL) is a rare monoclonal lymphoid neoplasm primarily characterized by malignant transformation of B-lymphocytes, called Reed-Sternberg cells, within an inflammatory microenvironment (1). Cure rates are around 80 % (2). However, despite the high cure rate with initial therapy, approximately 5 to 10 % of HL patients are resistant to initial treatment, and 10 to 30 % of patients will relapse after achieving initial complete remission (3, 4). The International Prognostic Score (IPS) is a widely accepted tool for advanced-stage HL risk stratification. Patients with five or more factors have a 5-year progression-free survival of 42 %, while those without negative prognostic factors have an 84 % chance of being progression-free after 5 years (5, 6). Identifying additional factors for early detection of adverse treatment outcomes is crucial for improved risk stratification and personalized treatment.

Hemoglobin and red cell distribution width (RDW) are laboratory findings widely available and routinely measured in blood tests. Hemoglobin to RDW ratio (HRR) emerges as a potential marker for predicting

outcomes in various cancers, as well as in cardiovascular and cerebrovascular diseases. Within the context of cancer prognosis, it demonstrates the intricate interplay between hematologic parameters and disease trajectory. Low HRR reflects nutritional insufficiency and a higher inflammatory burden resulting in worse disease outcomes (7). Studies of malignancies such as lymphoma and lung carcinoma show that a low HRR correlates with shorter survival, advanced disease, and poorer outcomes (7–12). In cardiovascular contexts, low HRR predicts heart failure mortality and cardiovascular hospitalizations (13–15). Further research is needed to standardize HRR thresholds and assess their inclusion in risk models for diverse conditions.

To our knowledge, there are no studies concerning the association between HRR and HL. Therefore, our aim was to examine whether the value of HRR at the time of HL diagnosis was an independent prognostic factor of overall survival (OS), event-free survival (EFS), and response to therapy, as well as to test the interrelations of HRR with demographic, clinical, and laboratory characteristics.

PARTICIPANTS AND METHODS

The research was conducted on all adult patients with histologically verified HL diagnosed at the Clinical Hospital Center Osijek in the period from April 2005 to August 2022. A total of 83 patients were enrolled. The inclusion criteria required necessary clinical data availability, while exclusion criteria encompassed incomplete clinical data and patients diagnosed with nodular lymphocyte-predominant HL.

Data collection involved reviewing the medical documentation and hospital information system for each participant. The collected information included general participant features, laboratory characteristics, IPS, Ann Arbor disease stage, therapy response (complete or partial remission/progression/relapse/death), Eastern Cooperative Oncology Group Performance status (ECOG), initial HRR (hemoglobin value divided by RDW), EFS (calculated from the day of diagnosis until one of the following: disease progression, initiation of another anti-lymphoma treatment, relapse, death, or last follow-up), and OS (calculated from the day of diagnosis until death or the last follow-up).

Table 1. *Distribution of patients by characteristics (N = 83)*

	Number (%) of patients
Gender	
Male	42 (51)
Female	41 (49)
Clinical Stage Ann Arbor	
Stage I	5 (6)
Stage II	36 (43.4)
Stage III	14 (16.9)
Stage IV	28 (33.7)
PHD*	
Nodular sclerosis	50 (60.2)
Mixed cellularity	18 (21.7)
Lymphocyte predominance	13 (15.7)
Not subtyped	2 (2.4)
B symptoms present	34 (41)
Protocol	
ABVD†	66 (79.5)
eBEACOPP‡	11 (13.3)
Other	6 (7.2)

*pathohistological diagnosis; †doxorubicin, bleomycin, vinblastine, dacarbazine; ‡etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

Statistical analysis

Categorical data were presented using absolute and relative frequencies. The normality of numerical variable distributions was assessed using the Shapiro-Wilk test. Continuous data were described using the median and interquartile range or range from minimal to maximal value. Differences between the two groups were analyzed using the Mann-Whitney U test (with Hodges-Lehmann and a 95% confidence interval of the difference), while the Kruskal-Wallis test was used for three or more independent groups. The association was measured using the Spearman correlation coefficient. The predictive value of the HRR ratio on survival was visualized *via* Kaplan-Meier curves. Receiving operating characteristics (ROC) analysis evaluated the diagnostic utility of the HRR ratio in OS and EFS outcomes. All *P* values were two-tailed, with significance set at alpha = 0.05. Statistical analysis utilized the MedCalc® Statistical Software version 20.218 and IBM SPSS 23.

RESULTS

The study involved 83 patients, with a median age of 36 years (interquartile range 25 – 57), ranging from 19 to 82, at diagnosis. The distribution of patients by characteristics is presented in Table 1.

The HRR was significantly lower in patients with clinical Ann Arbor stages III and IV and in patients who had B symptoms (Table 2).

Spearman's correlation coefficient was used to examine the association of HRR with biochemical indicators. It was observed that as HRR decreased, the values of red blood cells, mean corpuscular volume (MCV), and albumin levels also decreased, while the values of erythrocyte sedimentation rate (ESR), platelet count, and C-reactive protein levels (CRP) values increased and *vice versa* (Table 3).

The largest proportion of patients had an IPS from 0 to 2 (62.7 %), while the smallest number of participants had an IPS from 5 to 7 (10.8 %). In the observed group of subjects, 84.3 % achieved complete remission, 8.4 % relapsed, and 9.6 % died.

The HRR ratio was significantly lower in patients experiencing partial remission compared to those in complete remission, while there was no significant difference in patients with disease progression. Patients experiencing relapse also exhibited significantly lower

Table 2. *Differences in hemoglobin to red cell distribution width ratio based on gender and clinical characteristics (N = 83)*

	Median (IQR‡) HRR‖	§Difference (95% confidence interval)	*P**
Gender			
Male (n = 42)	9.03 (7.91 – 10.35)	-0.47	0.36
Female (n = 41)	8.58 (7.11 – 10.36)	(-1.42 - 0.49)	
Ann Arbor stage			
Stage I and II (n = 41)	9.65 (8.39 – 11.01)	-1.93	**< 0.001**
Stage III and IV (n = 42)	8.14 (6.03 – 9.09)	(-2.76 - -1.09)	
PHD¶			
Nodular sclerosis (n = 50)	8.95 (7.91 – 10.43)		
Mixed cellularity (n = 18)	6.95 (5.59 – 9.65)		0.09†
Lymphocyte predominance (n = 13)	9.42 (8.2 – 10.38)		
Not subtyped (n = 2)	8.25 (7.4 – 9.09)		
B symptoms			
No (n = 49)	9.42 (8.29 – 10.59)	-1.88	**< 0.001**
Yes (n = 34)	7.71 (5.74 – 9.09)	(-2.82 - -0.93)	
Protocol			
ABVD** (n = 66)	9.02 (7.6 – 10.43)		0.15†
eBEACOPP†† (n = 11)	8.85 (7.68 – 9.81)		
Other (n = 6)	7.83 (6.55 – 9.12)		

*Mann-Whitney U test; †Kruskal-Wallis test (*post hoc* Conover); ‡ interquartile range; §Hodges-Lehmann median difference; ‖hemoglobin to red cell distribution width ratio; ¶pathohistological diagnosis; **doxorubicin, bleomycin, vinblastine, dacarbazine; ††etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

HRR ratios. In patients with IPS scores of 3 and 4, as well as greater than 4, the HRR ratio was significantly lower compared to patients with an IPS score of 0 to 2 (Table 4).

To assess the diagnostic value of HRR, the ROC curve calculation method was used (based on specificity and sensitivity), gradually changing the values that distinguished patients concerning positive/negative outcomes

Table 3. *Association of hemoglobin to red cell distribution width ratio with biochemical indicators (Spearman's correlation coefficient), N = 83*

	Spearman's correlation coefficient of HRR*	
	Correlation coefficient ρ (Rho)	*P*†
ESR‡ (mm/3.6ks)	-0.698	< 0.001
Erythrocytes (x10^9/L)	0.637	< 0.001
MCV§ (fL)	0.447	< 0.001
Leukocytes (x10^{12}/L)	-0.124	0.27
Lymphocytes (%)	0.076	0.5
Platelets (x10^9/L)	-0.371	0.001
CRP‖ (mg/L)	-0.54	< 0.001
Albumins (g/L)	0.567	< 0.001
LDH¶ (U/L)	-0.173	0.12

*hemoglobin to red cell distribution width ratio; †Spearman's correlation coefficient; ‡erythrocyte sedimentation rate; §mean corpuscular volume; ‖C-reactive protein; ¶lactate dehydrogenase

Table 4. *Differences in hemoglobin to red cell distribution width ratio according to the treatment outcome, relapse, and International Prognostic Score (N = 83)*

	Median (IQR§) HRR‖	‡Difference (95% confidence interval)	*P**
Treatment outcome			
Complete remission (n = 70)	9.09 (7.91 – 10.45)		**0.008†**
Partial remission (n = 7)	7.23 (5.83 – 8.06)		
Disease progression (n = 6)	7.45 (6.4 – 9.09)		
Relapse			
No (n = 76)	9.02 (7.59 – 10.43)	-2.21 (-3.72 - -0.69)	**0.01**
Yes (n = 7)	6.62 (5.27 – 8.3)		
IPS¶			
0, 1, 2 (n = 52)	9.59 (8.5 – 10.82)		**< 0.001†**
3, 4 (n = 22)	7.36 (5.76 – 8.38)		
5, 6, 7 (n = 9)	6.67 (5.46 – 9.08)		

*Mann-Whitney U test; †Kruskal-Wallis test (*post hoc* Conover); ‡Hodges-Lehmann median difference; §interquartile range; ‖hemoglobin to red cell distribution width ratio; ¶International Prognostic Score

(alive/deceased). The cut-off point for each group was adjusted to create a ROC curve objectively determining the value that best distinguished the compared groups. In the data, considering a negative outcome (death) and the occurrence of events (relapse, progression, death) (EFS outcome), HRR was a significant diagnostic indicator. The cut-off point for HRR value for a negative outcome (death) was ≤ 6.67, and for the occurrence of disease, the cut-off point for HRR was ≤ 8.64 (Table 5, Figure 1).

For analysis of the association of HRR with the observed parameters, the participants were divided into two groups based on the HRR cut-off value for OS (≤ 6.67) obtained from the ROC analysis. Significant differences between the groups of participants with lower HRR and higher HRR values were found in all observed numerical and categorical parameters, except for the number of leukocytes, lymphocytes, lactate dehydrogenase levels, gender, and age. Participants with HRR ≤ 6.67 had signi-

Table 5. *Difference in demographic, clinical, and laboratory parameters according to the category of hemoglobin to red cell distribution width ratio value (N = 83)*

Biochemical indicator		Median (IQR†)		P^*
		HRR‡ ≤ 6.67 (n = 17)	HRR > 6.67 (n = 66)	
Albumin (g/L)		37.7 (31.1 - 40.5)	42.4 (39.7 – 46)	**< 0.0001**
CRP§ (mg/L)		116.3 (91.4 - 160.9)	12.45 (3.2 - 50.5)	**< 0.0001**
Erythrocyte (x10^9/L)		3.9 (3.6 - 4.3)	4.6 (4.3 - 4.9)	**< 0.0001**
Leukocyte (x10^{12}/L)		10.7 (7.2 - 19.8)	8.5 (6.6 - 12.2)	0.13
LDH‖ (U/L)		240 (168 - 327.5)	191 (161.5 – 235.5)	0.07
Lymphocyte (%)		1.45 (0.89 - 2.71)	1.42 (0.97 - 2)	0.45
MCV¶ (fL)		76.3 (72.9 - 83.1)	84.8 (80.6 - 88.03)	**0.001**
ESR** (mm/3.6ks)		98 (71 - 110)	32 (15 - 55)	**< 0.0001**
Platelets (x10^9/L)		424 (256 - 585.5)	292.5 (243.3 – 356)	**0.03**
Age [n (%)]	≤ 60 years	10 (59)	54 (82)	0.06
	> 60 years	7 (41)	12 (18)	
Gender [n (%)]	Female	7 (41)	31 (47)	0.38
	Male	10 (59)	35 (53)	
ECOG†† [n (%)]	0 and 1	12 (71)	62 (94)	**0.02**
	> 2	5 (29)	4 (6)	
B symptoms [n (%)]	Yes	13 (77)	21 (32)	**0.001**
	No	4 (23)	45 (68)	
Ann Arbor stage [n (%)]	I and II	27 (32.5)	40 (61)	**< 0.001**
	III and IV	15 (18.1)	26 (39)	
Relapse [n (%)]	Yes	4 (23)	3 (5)	**0.03**
	No	13 (77)	61 (95)	

*Mann-Whitney test; †interquartile range; ‡hemoglobin to red cell distribution width ratio; §C-reactive protein; ‖lactate dehydrogenase; ¶mean corpuscular volume; **erythrocyte sedimentation rate; ††Eastern Cooperative Oncology Group Performance status

ficantly higher values of ESR, CRP, and platelet values, as well as lower albumin, MCV, and erythrocyte levels. Individuals with HRR less than 6.67 more commonly had B symptoms, advanced stage, higher ECOG value, and relapsed more frequently (Table 5).

The median follow-up of our cohort was 43 months, ranging from a minimum of 4 to a maximum of 199. The 5-year OS and EFS were 90.4 % and 84.3 % for all patients, respectively. Kaplan–Meier analysis showed a significant difference in OS and EFS between the two groups (HRR ≤ 6.67 *vs* HRR > 6.67). The 5-year OS and

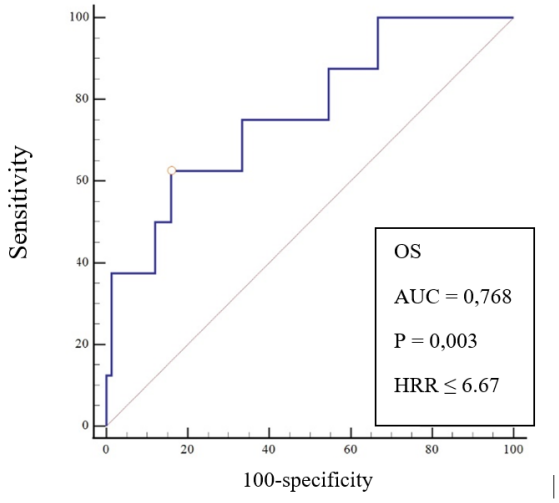

Figure 1a. *Hemoglobin to red cell distribution width ratio (HRR) as a diagnostic indicator of overall survival (OS) (Receiving Operating Characteristics analysis), N = 83. AUC – area under the curve*

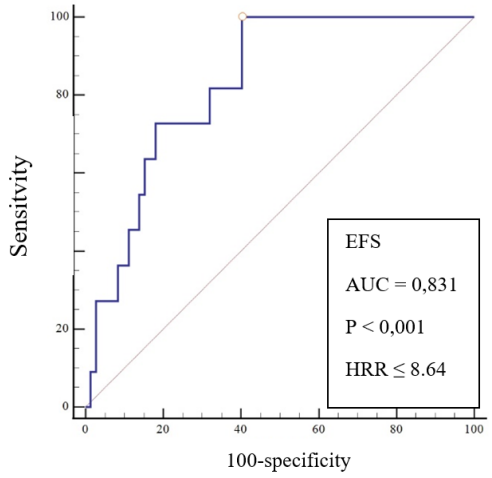

Figure 1b. *Hemoglobin to red cell distribution width ratio (HRR) as a diagnostic indicator of event-free survival (EFS) (Receiving Operating Characteristics analysis), N = 83. AUC – area under the curve*

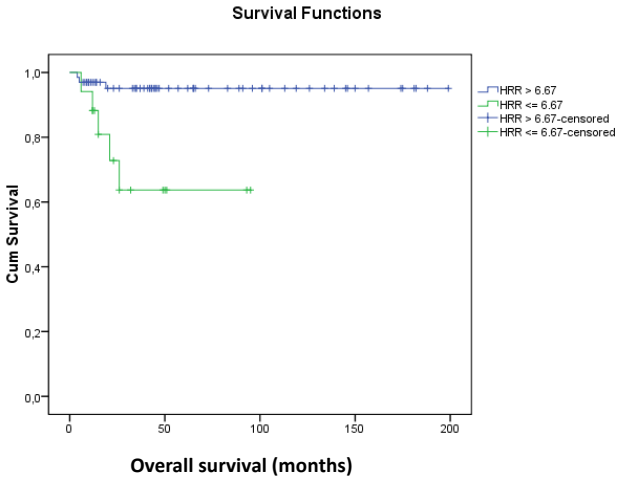

Figure 2a. *Kaplan–Meier curves for overall survival according to baseline hemoglobin to red cell distribution width ratio, HRR (normal > 6.67 (n = 66), low ≤ 6.67 (n = 17)) in patients with Hodgkin lymphoma (N = 83). (64 % vs 95 %, P = 0.001)*

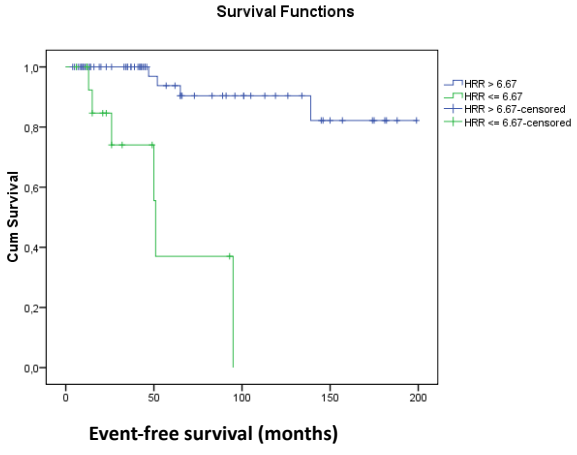

Figure 2b. *Kaplan–Meier curves for event-free survival according to baseline hemoglobin to red cell distribution width ratio, HRR (normal > 6.67 (n = 17), low ≤ 6.67 (n = 66)) in patients with Hodgkin lymphoma (N = 83). (37 % vs 94 %, P < 0.001)*

5-year EFS were significantly lower in those with HRR ≤ 6.67 (64 % *vs* 95% for OS, $P = 0.001$) [Figure 2a] (37 % *vs* 94 % for EFS, $P < 0.001$) [Figure 2b] in comparison with patients with HRR > 6.67. The 5-year OS and EFS for all patients were observed based on the cut-off value for OS.

DISCUSSION

This study showed that a low HRR at diagnosis of HL was associated with a poor prognosis. To our knowledge, this is the first report on the prognostic value of HRR in patients with HL. In our study, HRR strongly correlated with the main prognostic factors in HL, and HRR ≤ 6.67 was shown to be an adverse prognostic factor for EFS and OS.

A lower HRR ratio was associated with adverse outcomes, higher IPS value, advanced clinical stage, elevated CRP, ESR, and platelet levels, as well as reduced albumin, MCV, and erythrocyte levels.

The HRR ratio stands as a significant biomarker initially proposed to predict outcomes in esophageal squamous cell carcinoma and subsequently utilized in various cancer types (7, 8, 2). It is regarded as a novel prognostic marker because it reflects overall health, encompassing nutritional status, inflammation, and immune function (7). Accordingly, our study revealed that lower HRR is associated with more frequent microcytic anemia, elevated inflammatory markers, low albumin levels, and thrombocytosis. Microcytic anemia affects approximately a third of HL patients due to factors such as bone marrow involvement by cancer cells or chronic inflammation (16, 17). Anemia in lymphoma patients independently predicts worse treatment outcomes and higher mortality rates (6, 18, 19). However, the precise association between anemia and poor survival remains incompletely understood. Potential reasons include severe anemia indicating more aggressive tumors, hypoxia from anemia encouraging tumor invasiveness and reducing treatment sensitivity, and the release of cytokines like tumor necrosis factor alpha and interleukin 6 triggered by anemia (20–24). Further research is necessary to elucidate the relationship between anemia and cancer progression, with nutritional status and weakened physical resilience potentially contributing to a poorer prognosis.

The association of lower HRR values with high ESR and CRP levels, as well as low albumin levels, reflects the inflammatory processes and nutritional status. This connection suggests that lower HRR may indicate a higher inflammatory burden and a more pronounced acute phase response, signaling a poorer prognosis. This systemic inflammatory response may elucidate most of the B symptoms present in patients with HL, and our study demonstrated a correlation between lower HRR and the presence of B symptoms and the advanced disease stage. Recent studies investigating the prognostic role of RDW in HL have highlighted a significant association between RDW and hypoalbuminemia, which serves as an indicator of malnutrition and mortality (25-27). Elevated proinflammatory cytokines disrupt erythropoietin production and erythrocyte maturation, resulting in poor nutritional status (hypoalbuminemia) and higher RDW values (28). Inflammation and malnutrition may impair erythropoiesis, thus contributing to increased RDW, which consequently leads to lower HRR values.

In our study, lower HRR values were associated with poorer treatment response, a higher risk of relapse, and higher IPS scores, indicating a worse disease outcome. Alongside all the aforementioned parameters of poor nutritional status and inflammatory burden, platelets also showed a negative correlation with low HRR in our study. In HL, thrombocytopenia is common, while thrombocytosis, though rare, can occur in response to inflammation or infection associated with lymphoma, especially in HL (29). Platelets play a role in tumor cell protection and promote invasion, metastasis, and thrombosis by activating certain pathways (30, 31). Studies indicate that thrombocytosis correlates with a poor cancer prognosis (32, 33). One of the newer prognostic factors that could find its role in future clinical practice is the platelet/lymphocyte ratio (34), and by combining it with HRR it is possible to achieve better specificity and sensitivity (35). Larger studies across different institutions are needed to establish a reliable platelet cut-off for poor prognosis.

However, it is important to consider the limitations of the study. The retrospective study design and data collection from a single center may introduce bias. The sample size was relatively small, which could impact the generalizability of the findings. Further studies with larger sample sizes and prospective designs are warranted to validate the results and evaluate the clinical utility of HRR in treatment decision making and outcome prediction in HL.

CONCLUSION

To our knowledge, this is the first study conducted on the prognostic significance of HRR in HL. In conclusion, the results of this study demonstrate that lower HRR is associated with unfavorable clinical and laboratory characteristics, as well as poorer disease outcomes, therapeutic response, and prognostic factors. While underscoring the potential of HRR as a prognostic marker, further investigations are warranted, emphasizing its integration with established biochemical and hematological markers. Incorporating HRR into risk stratification and treatment decision making processes holds promise for enhancing a personalized and efficacious management of HL patients.

ABBREVIATIONS

ABVD – doxorubicin, bleomycin, vinblastine, dacarbazine

CRP – C-reactive protein

eBEACOPP – etoposide, bleomycin, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone

ECOG – Eastern Cooperative Oncology Group Performance status

EFS – event-free survival

ESR – erythrocyte sedimentation rate

HL – Hodgkin lymphoma

HRR – hemoglobin to red cell distribution width ratio

IPS – International Prognostic Score

IQR – interquartile range

MCV – mean corpuscular volume

OS – overall survival

RDW – red cell distribution width

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SAŽETAK

PROGNOSTIČKA VRIJEDNOST OMJERA VRIJEDNOSTI HEMOGLOBINA I ŠIRINE DISTRIBUCIJE ERITROCITA U BOLESNIKA S HODGKINOVIM LIMFOMOM

N. PUŠELJIĆ[1] , V. PERIŠA [2,3]

[1]Objedinjeni hitni bolnički prijem, Klinički bolnički centar Osijek, Hrvatska;
[2]Zavod za hematologiju, Klinika za unutarnje bolesti, Klinički bolnički centar Osijek, Hrvatska;
[3]Medicinski fakultet Osijek, Sveučilište Josipa Jurja Strossmayera, Osijek, Hrvatska

Ciljevi istraživanja: Istražiti je li vrijednost omjera hemoglobina i širine distribucije eritrocita (HRR, prema eng. hemoglobin to red blood cell distribution width ratio) u vrijeme utvrđivanja dijagnoze Hodgkinovog limfoma (HL) neovisan prognostički čimbenik ukupnog preživljenja, preživljenja bez događaja, odgovora na terapiju te ispitati međusobni odnos HRR-a i demografskih, kliničkih i laboratorijskih obilježja. ***Ispitanici i postupci:*** Istraživanje je ustrojeno kao povijesno kohortno. U istraživanje su uključeni svi bolesnici s histološki verificiranim HL-om u kojih je bolest dijagnosticirana od travnja 2005. do kolovoza 2022. godine u Kliničkom bolničkom centru Osijek. ***Rezultati:*** U istraživanju je sudjelovalo ukupno 83 ispitanika, medijana dobi 36 godina, u rasponu od 19 do 82. Pronađena je značajna razlika prosječne vrijednost HRR-a ovisno o ishodu liječenja, ukupnom preživljenju te preživljenju bez događaja. Manji omjer HRR-a bio je povezan s lošijim terapijskim odgovorom, većim rizikom od relapsa i lošijim drugim prognostičkim čimbenicima. Pronađena je pozitivna korelacija HRR-a s srednjim volumenom eritrocita, brojem eritrocita i razinom albumina, te negativna korelacija sa sedimentacijom eritrocita, brojem trombocita i koncentracijom C-reaktivnog proteina. ***Zaključak:*** Manji HRR bio je povezan s nepovoljnim kliničko-patološkim obilježjima HL-a te postoji dobar potencijal HRR-a kao prognostičkog biljega i potrebno ga je rabiti i s drugim do sada poznatim biokemijskim i hematološkim biljezima.

Ključne riječi: hemoglobin, Hodgkinov limfom, širina distribucije eritrocita, omjer hemoglobina i širine distribucije eritrocita, preživljenje

Autor za korespondenciju: doc. dr. sc. Vlatka Periša, dr. med.
Zavod za hematologiju
Klinika za unutarnje bolesti
Klinički bolnički centar Osijek
Huttlerova 4, 31 000 Osijek, Hrvatska
vlatkaperisa@gmail.com