PREDIKTIVNI ZNAČAJ EOZINOFILIJE U PERIFERNOJ KRVI KOD PACIJENATA OBOLELIH OD HOČKINOVOG LIMFOMA

ORIGINALNI RAD

ORIGINAL ARTICLE

THE PREDICTIVE SIGNIFICANCE OF EOSINOPHILIA IN PERIPHERAL BLOOD IN PATIENTS WITH HODGKIN LYMPHOMA

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SAŽETAK

Uvod/Cilj: Hočkinov limfom (HL) je retka neoplazma limfnog sistema, koja predstavlja jedan od najčešćih karcinoma u odrasloj mladoj populaciji. Klasičan Hočkinov limfom (engl. *classic Hodgkin lymphoma – cHL*) je najzastupljeniji histopatološki podtip i čini 95% svih dijagnostikovanih Hočkinovih limfoma. Eozinofilija, kako periferno, tako i u tkivima, relativno je česta pojava kod bolesnika sa Hočkinovim limfomom, posebno u podtipu nodularne skleroze i mešovite celularnosti. Njeno prisustvo ukazuje na složenu interakciju između tumorskih ćelija i imunološkog sistema. Pored eozinofilije prisutne u tkivnom uzorku, detektuje se i eozinofilija u perifernoj krvi. Ciljevi studije su bili da se analiziraju pacijenti oboleli od Hočkinovog limfoma, prema polu, starosti, kliničkom stadijumu, Internacionalnom prognostičkom skoru (IPS) i B simptomima, kao i da se utvrdi povezanost veličine tumorske mase sa kompletnom krvnom slikom, sedimentacijom eritrocita (SE), C reaktivnim proteinom (SRP), kliničkim stadijumom i Internacionalnim prognostičkim skorom, uz poseban osvrt na značaj eozinofilije u perifernoj krvi kao prediktora veličine tumorske mase i terapijskog odgovora.

Materijal i metode: Učinjena je retrospektivna analiza 58 novoobolelih od Hočkinovog limfoma u periodu od 31. 12. 2018. godine do 31. 12. 2023. godine, dijagnostikovanih i lečenih u Univerzitetskom kliničkom centru Kragujevac, na Klinici za hematologiju. Podaci su dobijeni iz pisane medicinske dokumentacije. Analizirani su inicijalni laboratorijski parametri krvi pri dijagnozi, a terapijski odgovor je procenjen nakon lečenja prvom terapijskom linijom. Za statističku obradu podataka korišćen je softver *IBM SPSS Statistics, Version 23.* Statistička značajnost definisana je na nivou $p < 0,05$.

Rezultati: Na prezentaciji, u posmatranoj populaciji je dominirala uznapredovala bolest – *CS* III (27,6%) i *CS* IV (39,7%), potom B simptomi kod 76% pacijenata, te visok IPS (48,3%). „*Bulky*" masa lokalizovana medijastinalno je utvrđena u 48,3% slučajeva, a sa nemedijastinalnom lokalizacijom kod 34,3% obolelih. Nije pronađena korelacija između broja leukocita, broja eozinofila, vrednosti hemoglobina, sedimentacije eritrocita, vrednosti C reaktivnog proteina, kliničkog stadijuma, Internacionalnog prognostičkog skora i maksimalnog prečnika merenih limfnih žlezda ($p > 0,05$). Međutim, analiza je pokazala statistički značajnu povezanost između eozinofilije i terapijskog odgovora ($p = 0,024$), što ukazuje na njen mogući prognostički značaj.

Zaključak: Eozinofilija u perifernoj krvi se pokazala kao mogući prediktor terapijskog odgovora, ali ne kao prediktor veličine tumorske mase. Standard za procenu tumorskog opterećenja ostaje kliničko radiološka dijagnostika.

Ključne reči: Hočkinov limfom, *bulky* bolest, eozinofilija periferne krvi

ABSTRACT

Introduction/Objective: Hodgkin lymphoma (HL) is a rare neoplasm of the lymphatic system and is one of the most common cancers in the young adult population. Histopathologically, 95% of Hodgkin lymphoma is classic Hodgkin lymphoma (cHL). Eosinophilia, both peripherally and in tissues, is relatively common in patients with HL, especially in the nodular sclerosis and mixed cellularity subtypes. Its presence indicates a complex interaction between tumor cells and the immune system. In addition to eosinophilia present in the tissue sample, eosinophilia is also detected in the peripheral blood. The study aimed to analyze HL patients by sex, age, clinical stage, the International Prognostic Score (IPS), and B symptoms, as well as to determine the association between tumor mass size and the complete blood count, erythrocyte sedimentation rate (ESR), the C reactive protein (CRP) level, the clinical stage, and the IPS, with special reference to the significance of eosinophilia in peripheral blood as a predictor of tumor mass size and therapeutic response.

Materials and methods: A retrospective analysis of 58 new cases of HL, diagnosed and treated at the Clinic for Hematology of the University Clinical Center Kragujevac, was performed between December 31, 2018, and December 31, 2023. Data was obtained from written medical records. The initial blood laboratory parameters at diagnosis were analyzed, and the therapeutic response was assessed after the first-line therapy was administered. IBM SPSS Statistics, Version 23, software was used for statistical data processing. Statistical significance was defined at $p < 0.05$.

Results: At presentation, the observed population had advanced disease – CS III (27.6%) and CS IV (39.7%); B symptoms were present in 76% of the patients, and a high IPS was registered in 48.3% of the subjects. Bulky mediastinal mass was present in 48.3% of patients, while 34.3% of patients presented with nonmediastinal localization. No correlation was found between the leukocyte count, the eosinophil count, the hemoglobin level, the erythrocyte sedimentation rate, CRP values, the clinical stage, IPS, and the maximum diameter of the measured lymph nodes ($p > 0.05$). However, the analysis showed a statistically significant association between eosinophilia and therapeutic response ($p = 0.024$), indicating its potential prognostic significance.

Conclusion: Peripheral blood eosinophilia was shown to be a potential predictor of therapeutic response, but not a predictor of tumor mass size. Clinical and radiological diagnostics remain the standard for assessing tumor burden.

Keywords: Hodgkin lymphoma, bulky disease, peripheral blood eosinophilia

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UVOD

Hočkinov limfom (HL) je retka neoplazma limfnog sistema, jedan je od najčešćih karcinoma u odrasloj mladoj populaciji [1]. Učestalost Hočkinovog limfoma je 2–3 obolela na 100.000 ljudi, pokazuje bimodalnu raspodelu, pri čemu prvi pik čine odrasli mladi pacijenti (20–30 godina), dok su drugi pik pacijenti stariji od 55 godina [2]. Histopatološki gledano, 95% Hočkinovog limfoma čini klasičan Hočkinov limfom (engl. *classic Hodgkin lymphoma – cHL*) [3].

Hočkinov limfom je maligna limfoproliferativna bolest koju karakteriše prisustvo Rid-Šternbergovih ćelija u visoko upalnom okruženju. Eozinofilija, kako periferno tako i u tkivima, relativno je česta pojava kod bolesnika sa Hočkinovim limfomom, posebno u podtipu nodularne skleroze i mešovite celularnosti. Njeno prisustvo ukazuje na složenu interakciju između tumorskih ćelija i imunološkog sistema [4].

Rani klinički radovi u časopisu *British National Lymphoma Investigation* (*BNLI*), šezdesetih godina dvadesetog veka ukazivali su na to da blaga periferna eozinofilija može imati povoljan prognostički značaj, verovatno kao pokazatelj intaktne imunološke aktivnosti. Međutim, kasnija istraživanja su pokazala suprotno. Von Vasielevski i saradnici su analizirali više od 1.500 pacijenata sa Hočkinovim limfomom i pokazali da izražena eozinofilija, posebno u tkivu, ali i perifernoj krvi, značajno korelira sa lošijom prognozom i kraćim preživljavanjem bez progresije bolesti [5]. Novije studije, međutim, potvrđuju da se eozinofilija češće javlja u uznapredovalim stadijumima ove bolesti (*CS* III i IV) i kod prisutne B simptomatologije [6].

Međutim, kako pokazuju multivarijantne analize, u eri savremenog lečenja (ABVD, BEACOPP) eozinofilija nije nezavistan prognostički faktor, već se više posmatra kao marker aktivnog mikrookruženja i veće tumorske mase [6,7]. Istraživanja eozinofilije povezane s malignitetima usmerena su na proučavanje hemokina i citokina, uključujući IL5, *TARC* (engl. *thymus and activation-regulated chemokine*) i eotaksin, koji učestvuju u regulaciji migracije i aktivacije eozinofila. Proučavana je i interakcija između eozinofila i Rid-Šternbergovih ćelija i utvrđeno je da eozinofili obezbeđuju ćelijske ligande za superfamiliju receptora faktora nekroze tumora (superfamilija TNF receptora) (*CD40, CD30, CD95/Fas*) i da su sposobni da transdukuju proliferativne i antiapoptotične signale na površini Hočkinovih Rid-Šternbergovih ćelija.

Što je veća tumorska masa (engl. *bulky disease*) to je veća proizvodnja ovih citokina, što dovodi do povećane produkcije eozinofila u koštanoj srži i njihovog „prelivanja" u perifernu krv [8,9]. Ovo dovodi do povećanja broja eozinofila u perifernoj krvi i u samom tumoru

INTRODUCTION

Hodgkin lymphoma (HL) is a rare neoplasm of the lymphatic system and is one of the most common cancers in the young adult population [1]. The incidence of Hodgkin lymphoma is 2–3 cases per 100,000 people. It shows a bimodal distribution, with the first peak comprising young adult patients (20–30 years old) and the second peak comprising patients older than 55 years [2]. Histopathologically, 95% of Hodgkin lymphoma cases are classic Hodgkin lymphoma (cHL) [3].

Hodgkin lymphoma is a malignant lymphoproliferative disease characterized by the presence of Reed-Sternberg cells in an inflammatory-rich environment. Eosinophilia, both peripheral and in tissues, is a relatively common occurrence in patients with Hodgkin lymphoma, especially in the nodular sclerosis and mixed cellularity subtypes. Its presence indicates a complex interaction between tumor cells and the immune system [4].

Early clinical articles published during the 1960s in the *British National Lymphoma Investigation* (BNLI) indicate that mild peripheral eosinophilia might have a favorable prognostic significance, possibly as an indicator of intact immune activity. However, subsequent research has shown the opposite. Von Wasielewski et al. analyzed more than 1,500 patients with Hodgkin lymphoma, demonstrating that pronounced eosinophilia, especially in tissue but also in peripheral blood, significantly correlates with a poorer prognosis and shorter progression-free survival [5]. More recent studies, however, confirm that eosinophilia occurs more frequently in advanced stages of the disease (CS III and IV) and when B symptoms are present [6].

However, as multivariate analyses show, in the era of modern treatment (ABVD, BEACOPP), eosinophilia is not an independent prognostic factor; rather, it is regarded more as a marker of an active microenvironment and a larger tumor mass [6,7]. Research on malignancy-associated eosinophilia has focused on the study of chemokines and cytokines, including IL-5, thymus and activation-regulated chemokine (TARC), and eotaxin, which are involved in the regulation of eosinophil migration and activation. The interaction between eosinophils and Reed-Sternberg cells has also been studied, and it has been established that eosinophils provide cellular ligands for the tumor necrosis factor receptor superfamily (TNF receptor superfamily) (CD40, CD30, CD95/Fas) and that they are capable of transducing proliferative and anti-apoptotic signals on the surface of Hodgkin Reed-Sternberg cells.

The greater the tumor burden (bulky disease), the greater the production of the said cytokines, resulting in an increased production of eosinophils in the bone marrow and their "overflow" into the peripheral blood

(tkivna eozinofilija). Eozinofilija je generalno povezana sa minornom prednošću, ali prednost preživljavanja za obolele od Hočkinovog limfoma sa selektivnom eozinofilijom se pokazala kao veoma značajna. Eozinofiliji je dodeljen prognostički značaj, što je u suprotnosti sa Kaplanovim nalazima, koji je u velikom pregledu Hočkinove bolesti zaključio da nema dokaza da je eozinofilija u krvi u korelaciji sa prognozom [4].

Prepoznavanje eozinofilije pri uspostavljanju dijagnoze u ovim stanjima i razumevanje mehanizma delovanja eozinofila pruža uvid u potencijalne prognostičke implikacije i moguće strategijske tretmane.

Približno oko 80% obolelih od Hočkinovog limfoma može biti izlečeno prvom linijom lečenja, hemioterapijom ili/i radioterapijom, a u zavisnosti od kliničkog stadijuma bolesti – rani stadijum (*CS* I i *CS* II) ili uznapredovali (*CS* III i *CS* IV) [10,11].

CILJEVI RADA

Ciljevi rada su sledeći:

1. Analiza obolelih od Hočkinovog limfoma prema polu, starosnom dobu, kliničkom stadijumu bolesti, Internacionalnom prognostičkom skoru (IPS) i prisutnim B simptomima.
2. Prikaz povezanosti veličine tumorske mase (mereni promer žlezda) sa vrednostima – kompletna krvna slika, sedimentacija eritrocita (SE), C reaktivni protein (CRP), klinički stadijum bolesti i IPS.
3. Utvrđivanje potencijalnog značaja eozinofilije u perifernoj krvi, kao pokazatelja aktivnosti bolesti kod obolelih od Hočkinovog limfoma, njene korelacije sa veličinom tumorske mase, te eventualnog prognostičkog značaja za terapijski odgovor.

MATERIJAL I METODE

Sprovedena je retrospektivna analiza 58 pacijenata obolelih i lečenih od Hočkinovog limfoma, na Klinici za hematologiju Univerzitetskog kliničkog centra Kragujevac, tokom pet godina, u periodu od 31. 12. 2018. godine do 31. 12. 2023. godine. Kriterijum za uključivanje u studiju bila je novodijagnostikovana bolest, dok je relaps bolesti predstavljao eliminacioni kriterijum. Podaci su dobijeni iz pisane medicinske dokumentacije (istorije bolesti). Dijagnoza je postavljena patohistološkom analizom bioptirane limfne žlezde. Klinički stadijum (engl. *clinical stage* – *CS*) je određivan po En Arbor klasifikaciji a utvrđen je i Internacionalni prognostički skor. IPS je definisan zbrajanjem negativnih poena i to: starost ≥ 45 godina, muški pol, klinički stadijum IV, broj leukocita veći od 15 x 10^9, broj limfocita ≤ od 600/µl ili limfociti < 8% , albumin < 40 g/l i hemoglobin < 105 g/l. Analiza kompletne krvne slike izvršena je na Bekman Kolter brojaču. *Bulky* bolest je definisana kao tu-

[8,9]. This leads to an increase in the eosinophil count in the peripheral blood and within the tumor itself (tissue eosinophilia). Eosinophilia is generally associated with a minor advantage, but the survival advantage for patients with Hodgkin lymphoma with selective eosinophilia has proven to be very significant. Eosinophilia has been assigned prognostic significance, which is in contrast with Kaplan's findings. In a large review of Hodgkin disease, Kaplan found no evidence of blood eosinophilia correlating with prognosis [4].

Recognizing eosinophilia at diagnosis in these conditions and understanding the mechanism of action of eosinophils provides insight into potential prognostic implications and possible strategic treatments.

Approximately 80% of patients with Hodgkin lymphoma can be cured with first-line therapy, chemotherapy and/or radiotherapy, depending on the clinical stage of the disease – early stage (CS I and CS II) or advanced stage (CS III and CS IV) [10,11].

STUDY AIMS

The study aims are as follows:

1. Analyzing patients with Hodgkin lymphoma in relation to sex, age, clinical stage of disease, the International Prognostic Score (IPS), and presence of B symptoms.
2. Presenting the association between tumor mass size (measured lymph node diameter) and the following values: complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), clinical stage of the disease, and IPS.
3. Determining the potential significance of eosinophilia in peripheral blood as an indicator of disease activity in patients with Hodgkin lymphoma, its correlation with tumor mass size, and its potential prognostic significance for therapeutic response.

MATERIALS AND METHODS

A retrospective analysis of 58 patients diagnosed with and treated for Hodgkin lymphoma at the Clinic for Hematology of the University Clinical Center Kragujevac was conducted over five years, between December 31, 2018, and December 31, 2023. Newly diagnosed Hodgkin lymphoma was the inclusion criterion, while disease relapse was an exclusion criterion. Data were obtained from written medical records (patient charts). The diagnosis was established through histopathological analysis of a biopsied lymph node. The clinical stage (CS) was determined according to the Ann Arbor classification, and the International Prognostic Score (IPS) was also established. The IPS was defined by summing negative points: age ≥ 45 years, male sex, clinical stage IV, a white blood cell count < 15 x 10^9, a lymphocyte count ≤ 600/µl

morska masa veća od 7 cm. U perifernom uzorku krvi, eozinofili su činili od 0,3%–5% ukupnog broja leukocita, što je ekvivalentno 0,05–0,5 × 10^9/l. Broj veći od 0,5 × 10^9/l smatran je eozinofilijom, dok broj jednak ili veći od 1.5 × 10^9/l definisan kao hipereozinofilija. Lečenje je sprovedeno hemioterapijom po protokolu ABVD (adriblastin + bleomicin + velbe + dakarbazin). Odgovor na terapiju je definisan kao kompletna remisija – odsustvo bolesti (engl. *complete remission – CR*), parcijalna remisija – delimičan odgovor (engl. *partial remission – PR*) i kao progresija bolesti (engl. *progressive disease – PD*). Za statističku obradu podataka korišćen je softver *IBM SPSS Statistics Version 23*.

Statistička obrada podataka izvršena je primenom deskriptivnih i inferencijalnih statističkih metoda, u skladu sa tipom i distribucijom analiziranih varijabli. Kontinuirane varijable prikazane su pomoću medijana, s obzirom na to da podaci nisu pratili normalnu raspodelu, kao i kroz minimalne i maksimalne vrednosti. Kategorijske varijable prikazane su putem apsolutnih i relativnih frekvencija. Normalnost raspodele kontinuiranih varijabli proverena je primenom Šapiro-Vilk testa normalnosti, te su na osnovu dobijenih rezultata u daljoj analizi primenjeni neparametrijski statistički testovi. Za ispitivanje povezanosti između veličine tumorske mase (izražene kao maksimalni promer zahvaćenih limfnih žlezda) i kontinuiranih varijabli, korišćen je Spirmanov koeficijent korelacije (ρ). Rezultati su prikazani kroz vrednosti koeficijenta korelacije, broj stepeni slobode i pripadajuće p vrednosti. Za analizu razlika u veličini tumorske mase u odnosu na kategorijske varijable primenjeni su: Man-Vitnijev U test za poređenje dve nezavisne grupe i Kruskal-Volisov test za poređenje tri ili više nezavisnih grupa. U analizi povezanosti eozinofilije (kategorizovane varijable) sa kontinuiranim parametrima, korišćen je Kruskal-Volisov test, dok je za ispitivanje povezanosti sa kategorijskim varijablama primenjen χ^2 test nezavisnosti. Statistička značajnost definisana je na nivou $p < 0,05$.

Studija je u celini sprovedena poštujući sve odredbe Helsinške deklaracije i odobrena je od strane Etičkog odbora UKC Kragujevac (broj Odluke 1/25-835).

REZULTATI

Istraživanjem je obuhvaćeno 58 novodijagnostikovanih pacijenata obolelih od Hočkinovog limfoma (HL), u posmatranom periodu od pet godina, i to 20 (34,48%) žena i 38 (65,52%) muškaraca. Oboleli su bili starosti od 18 do 75 godina, pri čemu je prosečna starost iznosila 40,02±16,01 godina. Analizom starosnog doba pacijenata prilikom uspostavljanja dijagnoze Hočkinovog limfoma, utvrđeno je da je bilo 34,5% mlađih od 30 godina, dok je pacijenata starijih od 55 godina bilo 20,6%.

or lymphocytes < 8%, albumin < 40 g/l, and hemoglobin < 105 g/l. Complete blood count analysis was performed using a Beckman Coulter counter. Bulky disease was defined as a tumor mass greater than 7 cm. In the peripheral blood sample, eosinophils accounted for 0.3%–5% of the total white blood cell count, which is equivalent to 0.05–0.5 × 10^9/l. An eosinophil count above 0.5 × 10^9/l was considered as eosinophilia, while an eosinophil count equal to or greater than 1.5 × 10^9/l was defined as hypereosinophilia. Treatment was carried out using chemotherapy according to the ABVD protocol (adriblastin + bleomycin + velbe + dacarbazine). Response to therapy was defined as complete remission – absence of disease (CR), partial remission – partial response (PR), and progressive disease (PD). IBM SPSS Statistics Version 23 software was used for statistical data processing.

Statistical data processing was performed using descriptive and inferential statistical methods, in accordance with the type and distribution of the analyzed variables. Continuous variables were presented as median values, given that the data did not follow a normal distribution, and as minimum and maximum values. Categorical variables were presented as absolute and relative frequencies. The normality of the distributions of continuous variables was assessed using the Shapiro-Wilk test, and, based on the obtained results, nonparametric statistical tests were applied in subsequent analyses. To examine the association between the size of the tumor mass (expressed as the maximum diameter of the affected lymph nodes) and continuous variables, the Spearman correlation coefficient (ρ) was applied. The results were presented as correlation coefficient values, the number of degrees of freedom, and the corresponding p-values. To analyze differences in tumor mass size in relation to categorical variables, the following were applied: the Mann-Whitney U test for comparing two independent groups and the Kruskal-Wallis test for comparing three or more independent groups. The Kruskal-Wallis test was applied in analyzing the association between eosinophilia (categorized variable) and continuous parameters, while the χ^2 test of independence was used to examine the association with categorical variables. Statistical significance was defined at $p < 0.05$.

The study was conducted in its entirety in compliance with all the provisions of the Declaration of Helsinki and was approved by the Ethics Committee of the University Clinical Center Kragujevac (Decision number 1/25-835).

RESULTS

The study included 58 newly diagnosed patients with Hodgkin lymphoma (HL) – 20 (34.48%) women and 38 (65.52%) men, who were followed up over a five-year

Deskriptivna statistika kliničkih karakteristika ispitivane populacije novoobolelih od Hočkinovog limfoma prikazana je u Tabeli 1.

Deskriptivna statistička analiza kontinuiranih kliničkih i laboratorijskih parametara kod bolesnika sa Hočkinovim limfomom prikazana je u Tabeli 2.

U skladu sa postavljenim ciljem, izvršena je deskriptivna statistička analiza kliničkih i laboratorijskih karakteristika bolesnika sa Hočkinovim limfomom. Analiza kontinuiranih varijabli (Tabela 2) pokazuje značajnu varijabilnost ispitivanih parametara. Srednja vrednost sedimentacije eritrocita bila je povišena (56,24±34,34), što ukazuje na prisustvo izražene inflamatorne aktivnosti u posmatranoj grupi. Takođe, vrednosti C-reaktivnog proteina (75,11±73,78) i laktat dehidrogenaze (560,26±346,16) pokazuju širok raspon i visoke srednje vrednosti, što može reflektovati heterogenost bolesti i različit stepen biološke aktivnosti. Parametri kompletne krvne slike ukazuju na značajnu disperziju vrednosti, posebno leukocita (0–32,4), trombocita (17–801) i neutrofila (0–90), što može biti posledica različitog stadijuma bolesti, kao i individualnog odgovora organizma. Srednja vrednost hemoglobina (112,93±23,62) ukazuje na prisustvo anemije kod dela bolesnika. Takođe, uočena je značajna varijabilnost vrednosti D-dimera (55–9.500) i laktat dehidrogenaze (LDH), što može da ukazuje na različit stepen aktivacije koagulacionog i tumorskog procesa.

Veličina tumorske mase je uzeta kao kontinuirana promenljiva. U odnosu na kontinuirane promenljive, primenjena je korelaciona analiza, odnosno tumačena je vrednost Spirmanovog koeficijenta korelacije. Za analizu u odnosu na kategorijske promenljive, primenjen je Man-Vitnijev U test i Kruskal-Volisov test. Učiobservation period. The patients were aged 18 to 75, with an average age of 40.02±16.01 years. An analysis of patient age at the time of Hodgkin lymphoma diagnosis determined that 34.5% were under 30 years old, while 20.6% were over 55. Descriptive statistics of the clinical characteristics of the newly diagnosed Hodgkin lymphoma patient study population are presented in Table 1.

Descriptive statistical analysis of continuous clinical and laboratory parameters in patients with Hodgkin lymphoma is presented in Table 2.

In keeping with the defined study aim, a descriptive statistical analysis of the clinical and laboratory characteristics of patients with Hodgkin lymphoma was performed. The analysis of continuous variables (Table 2) shows significant variability in the examined parameters. The mean erythrocyte sedimentation rate (ESR) was elevated (56.24±34.34), indicating the presence of pronounced inflammatory activity in the observed group. Also, the levels of C-reactive protein (75.11±73.78) and lactate dehydrogenase (560.26±346.16) show a wide range, as well as high mean values, which may reflect the heterogeneity of the disease and different degrees of biological activity. Complete blood count parameters indicate significant dispersion of values, especially for leukocytes (0–32.4), platelets (17–801), and neutrophils (0–90), which may be a consequence of the different stages of the disease, as well as of different individual responses. The mean hemoglobin value (112.93±23.62) indicates the presence of anemia in a portion of the patients. Also, significant variability in D-dimer (55–9,500) and lactate dehydrogenase (LDH) values was observed, which may indicate different degrees of activation of the coagulation and tumor processes.

Tabela 1. Osnovne farmakokinetske i farmakodinamske karakteristike ranolazina

Table 1. Key pharmacokinetic and pharmacodynamic properties of ranolazine

Parametar / *Parameter*		**Broj (n) / *Number (n)***	**Procenat (%) / *Percentage (%)***
Klinički stadijum / *Clinical stage*	1	1	1.7%
	2	18	31.0%
	3	16	27.6%
	4	23	39.7%
Bulky masa u medijastinumu / *Bulky mediastinal mass*	Ne / No	30	51.7%
	Da / Yes	28	48.3%
Ekstranodalna bolest / *Extranodal disease*	Ne / No	37	63.8%
	Da / Yes	21	36.2%
Nemedijastinalna *bulky* masa / *Nonmediastinal bulky mass*	Ne / No	38	65.5%
	Da / Yes	20	34.5%
IPS / *IPS score*	Nizak / Low	30	51.7%
	Visok / High	28	48.3%
A simptomi / *A symptoms*	Ima / Present	14	24%
B simptomi / *B symptoms*	Ima / Present	44	76%

Tabela 2. Osnovne farmakokinetske i farmakodinamske karakteristike ranolazina

Table 2. Key pharmacokinetic and pharmacodynamic properties of ranolazine

Analiza / *Type of test/analysis*	Min	Max	Median
Maksimalni promer limfne žlezde / *Max diameter of the lymph node*	20	150	47.5
Sedimentacija eritrocita / *Erythrocyte sedimentation rate*	2	120	56
Hemoglobin / *Hemoglobin*	56	159	118
Leukociti / *Leukocytes*	0	32.4	9.95
Neutrofili / *Neutrophils*	0	90	68
Limfociti / *Lymphocytes*	0.78	43.20	8.85
Monociti / *Monocytes*	0.40	25.00	5.5
Eozinofili / *Eosinophils*	0	15	4
Trombociti / *Platelets*	17	801	297
Albumin / *Albumin*	19	48	38
C-reaktivni protein (CRP) / *C-reactive protein (CRP)*	0.6	268.0	50.35
Laktat dehidrogenaza (LDH) / *Lactate dehydrogenase (LDH)*	226	2,043	491.5
Koncentracija D-dimera / *D-dimer concentration*	55	9,500	492

njena analiza novoobolelih od Hočkinovog limfoma je utvrdila tumorsku masu veću od 7 cm u merenom promeru kod ukupno 82% obolelih. Analizom najvećih promera limfnih žlezda merenih pomoću multislajsne kompjuterizovane tomografije (engl. *multislice computed tomography – MSCT*) pri pregledu na prezentaciji, nije utvrđena statistički značajna razlika u maksimalnom promeru limfnih žlezda, između kliničkog stadijuma (I + II) odnosno kliničkih stadijuma (III + IV), (p = 0,074). Tabela 3 prikazuje statističku analizu povezanosti veličine tumorske mase (mereni promer žlezda) sa starošću i laboratorijskim parametrima pri uspostavljanju dijagnoze (kompletna krvna slika, albumin, sedimentacija eritrocita (SE), C-reaktivni protein (CRP), laktat dehidrogenaza (LDH) i D-dimer).

Nije utvrđena statistički značajna korelacija između veličine tumorske mase i parametara kompletne krvne slike (hemoglobin, leukociti, neutrofili, limfociti, monociti, eozinofili, trombociti), odnosno sedimentacije eritrocita. Nema korelacije C-reaktivnog proteina i IPS skora sa veličinom tumorske mase. Dobijeni rezultati ukazuju da je od ispitivanih kontinuiranih varijabli jedino starost pokazala statistički značajnu korelaciju sa veličinom tumorske mase (r = -0,415; p = 0,001), pri čemu je uočena negativna povezanost, što ukazuje na manju tumorsku masu kod starijih bolesnika, dok su mlađi bolesnici u našoj ispitivanoj populaciji bili opterećeni većom tumorskom masom pri uspostavljanju dijagnoze Hočkinovog limfoma.

U ovoj studiji, ispitivan je potencijalni značaj eozinofilije u perifernoj krvi kao pokazatelja aktivnosti bolesti kod bolesnika sa Hočkinovim limfomom, kao i njena povezanost sa veličinom tumorske mase i terapijskim odgovorom. Dobijeni rezultati ukazuju na

Tumor mass size was considered a continuous variable. Correlation analysis was applied to continuous variables, specifically interpreting the value of the Spearman correlation coefficient. The Mann-Whitney U test and the Kruskal-Wallis test were applied for analysis related to categorical variables. Analysis of newly diagnosed Hodgkin lymphoma patients found a tumor mass greater than 7 cm in diameter in a total of 82% of patients. Analysis of the largest diameters of lymph nodes measured using multislice computed tomography (MSCT) at patient presentation did not find a statistically significant difference in the maximum lymph node diameter in relation to clinical stage (I + II), i.e., clinical stages (III + IV) (p = 0.074). Table 3 shows the statistical analysis of the association between tumor mass size (measured gland diameter) and age and laboratory parameters at the time of diagnosis (complete blood count, albumin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), lactate dehydrogenase (LDH), and D-dimer).

No statistically significant correlation was found between tumor mass size and complete blood count parameters (hemoglobin, leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, platelets) or erythrocyte sedimentation rate. There is no correlation between C-reactive protein and the IPS score, on the one hand, and tumor mass size, on the other. The obtained results indicate that, of the examined continuous variables, only age shows a statistically significant correlation with tumor mass size (r = -0.415; p = 0.001), where a negative association was observed, indicating a smaller tumor mass in older patients, while younger patients in our study population were burdened with a larger tumor mass at the time of Hodgkin lymphoma diagnosis.

Tabela 3. Osnovne farmakokinetske i farmakodinamske karakteristike ranolazina

Table 3. Key pharmacokinetic and pharmacodynamic properties of ranolazine

Rezultati laboratorijskih analiza / *Laboratory test results*	Rho (ρ)	Broj (N) / *Number (N)*	*p*
Starost / *Age*	-0.415	58	0.001
Sedimentacija eritrocita (SE) / *Erythrocyte sedimentation rate (ESR)*	-0.124	58	0.355
Hemoglobin / *Hemoglobin*	-0.002	58	0.990
Leukociti / *Leukocytes*	0.125	58	0.349
Neutrofili / *Neutrophils*	-0.217	58	0.104
Limfociti / *Lymphocytes*	-0.160	58	0.232
Monociti / *Monocytes*	-0.024	58	0.858
Eozinofili / *Eosinophils*	0.160	58	0.229
Trombociti / *Platelets*	0.205	58	0.122
Albumin / *Albumin*	0.119	58	0.372
C-reaktivni protein (CRP) / *C-reactive protein (CRP)*	0.008	58	0.954
Laktat dehidrogenaza (LDH) / *Lactate dehydrogenase (LDH)*	0.077	58	0.567
Koncentracija D-dimera / *D-dimer concentration*	-0.078	58	0.561

postojanje statistički značajne povezanosti između eozinofilije i pojedinih parametara inflamatornog odgovora, pre svega neutrofila (p = 0,033) i monocita (p = 0,002). Ovakav nalaz sugeriše da eozinofilija može da reflektuje intenzitet sistemske inflamacije i time indirektno ukaže na aktivnost bolesti. Sa druge strane, nije utvrđena statistički značajna korelacija između eozinofilije i veličine tumorske mase, kako u prisustvu *bulky* bolesti tako ni kod maksimalnih merenih dijametara limfnih čvorova, što ukazuje da eozinofilija nema pouzdanu vrednost kao marker opterećenja tumorskom masom. Međutim, analiza je pokazala statistički značajnu povezanost između eozinofilije i terapijskog odgovora (p = 0,024), što ukazuje na njen moguć prognostički značaj.

Distribucija ispitanika prema odgovoru na prvu terapijsku liniju ABVD (adriblastin + bleomicin + velbe + dakarbazin) pokazuje da je kompletna remisija postignuta kod 64,9% obolelih od Hočkinovog limfoma, da je 14% pacijenata imalo parcijalni odgovor, a da je kod 21,1% obolelih utvrđena progresija bolesti. Na kraju posmatranog perioda od pet godina, od ukupno 58 novoobolelih od Hočkinovog limfoma, 45 (77,6%) pacijenata je bilo živo, dok je preminulo 13 (22,4%) obolelih.

DISKUSIJA

Učestalost Hočkinovog limfoma je 2–3 obolela na 100.000 ljudi. Hočkinov limfom pokazuje bimodalnu raspodelu kod odraslih mladih ljudi (20–30 godina) i pacijenata starijih od 55 godina [2]. Analiza naših ispitanika ne pokazuje ovakav raspored, odnosno, u našoj ispitivanoj populaciji je bilo 34,5% pacijenata mlađih od 30 godina, dok je starijih od 55 godina bilo 20,6%,

Our study examined the potential significance of peripheral blood eosinophilia as an indicator of disease activity in patients with Hodgkin lymphoma, as well as its association with tumor mass size and therapeutic response. The results indicate a statistically significant association between eosinophilia and certain inflammatory response parameters, primarily the neutrophil count (p = 0.033) and monocyte count (p = 0.002). This finding suggests that eosinophilia may reflect the intensity of systemic inflammation and thus indirectly indicate disease activity. On the other hand, no statistically significant correlation was found between eosinophilia and tumor mass size, either in the presence of bulky disease or with maximum measured lymph node diameters, which indicates that eosinophilia does not have a reliable value as a marker of tumor mass burden. However, the analysis showed a statistically significant association between eosinophilia and therapeutic response (p = 0.024), indicating its potential prognostic significance.

The distribution of subjects according to their response to first-line ABVD (adriblastin + bleomycin + velbe + dacarbazine) therapy shows that complete remission (CR) was achieved in 64.9% of Hodgkin lymphoma patients; 14% of patients had a partial response (partial remission – PR) to treatment, while disease progression (progressive disease – PD) was determined in 21.1% of patients. At the end of the five-year observation period, out of a total of 58 newly diagnosed Hodgkin lymphoma patients, 45 (77.6%) patients were alive, while 13 (22.4%) patients had passed away.

DISCUSSION

The frequency of Hodgkin lymphoma is 2–3 per 100,000 people. Hodgkin lymphoma shows a bimodal distribu-

što nije u skladu sa literaturnim podacima o bimodalnosti obolevanja. Mnoge studije su ispitivale prognostičke faktore kod Hočkinovog limfoma. Pol, godine, histološki tip, postojanje simptoma, postojanje medijastinalne mase, visina sedimentacije, nivo serumskih albumina i hemoglobina, pominju se kao važni u prognozi [12,13].

Naši ispitanici nisu pokazali razliku po pitanju pola a ni histološkog podtipa, odnosno 57 ispitanika je imalo patohistološki utvrđen tip klasičnog Hočkinovog limfoma, a samo jedan bolesnik je imao podtip sa limfocitnom predominacijom.

Povišena sedimentacija eritrocita je nespecifičan marker inflamacije i često je prisutna kod Hočkinovog limfoma zbog povećane koncentracije fibrinogena i drugih proteina akutne faze. Sedimentacija eritrocita se koristi u inicijalnoj proceni bolesti, jer visoke vrednosti (SE > 50 mm/h kod simptomatskih bolesnika) ukazuju na aktivnu bolest i veće tumorsko opterećenje. Shodno tome, praćenje ove jednostavne analize moglo bi biti pokazatelj odgovora na lečenje kod obolelih od Hočkinovog limfoma. Međutim, 1998. godine, nekoliko faktora je definisalo IPS, ali među njima nije bila sedimentacija [13,14].

Prema podacima iz literature, vrlo važne negativne prognostičke faktore u diseminovanoj bolesti predstavljaju velika tumorska masa u sredogrudju, ekstranodalna lokalizacija bolesti, te zahvaćenost slezine. *Bulky* forma u sredogrudju kao komplikaciju ima nastanak sindroma gornje šuplje vene [15,16].

Incidencija eozinofiije na prezentaciji u velikim serijama pacijenata obolelih od Hočkinovog limfoma opisana je u oko 15% slučajeva. Kada postoji leukocitoza na prezentaciji, eozinofilija je kod novoobolelih zastupljena i do 51%. U našem istraživanju, eozinofilija je bila prisutna kod 60,3% obolelih. Povišeni eozinofili u perifernoj krvi češće se javljaju kod uznapredovale bolesti (klinički stadijum III ili IV) i kod bolesnika sa B simptomatologijom (noćno preznojavanje, gubitak u težini i povišena temperatura).

U našem istraživanju, novodijagnostikovani pacijenti oboleli od Hočkinovog limfoma dominantno su imali ove karakteristike. Prema literaturnim podacima, iako nije univerzalno priznat nezavisni prognostički faktor, nestanak eozinofilije tokom terapije ukazuje na dobar terapijski odgovor, a njeno perzistiranje indirektno ukazuje na suboptimalni odgovor [8,17,18]. I u našem istraživanju je ustanovljena statistički značajna povezanost između eozinofilije i terapijskog odgovora ($p = 0,024$), što ukazuje na njen moguć prognostički značaj. Ovaj nalaz sugeriše da eozinofilija može imati ulogu u predikciji ishoda lečenja kod bolesnika sa Hočkinovim limfomom.

tion in young adults (20–30 years) and patients older than 55 years [2]. The analysis of our subjects does not show this distribution. In fact, there were 34.5% of patients younger than 30 years and 20.6% patients older than 55 years in our study population, which is not in accordance with literature data on the bimodality of incidence. Many studies have examined prognostic factors in Hodgkin lymphoma. Sex, age, histological type, presence of symptoms, presence of mediastinal mass, sedimentation rate, and serum albumin and hemoglobin levels have been mentioned as important for prognosis [12,13].

Our subjects did not demonstrate a difference in relation to sex or histological subtype – 57 subjects had a histopathologically confirmed form of classic Hodgkin lymphoma, and only one patient had a lymphocyte-predominant subtype.

An elevated erythrocyte sedimentation rate is a nonspecific marker of inflammation and is often present in Hodgkin lymphoma due to increased concentrations of fibrinogen and other acute-phase proteins. The erythrocyte sedimentation rate is used in the initial assessment of the disease because high values (ESR > 50 mm/h in symptomatic patients) indicate active disease and a greater tumor burden. Accordingly, following up on this simple analysis could serve as an indicator of treatment response in patients with Hodgkin lymphoma. However, in 1998, several factors were established as those defining the IPS score, but the erythrocyte sedimentation rate was not among them [13,14].

According to the literature, a large mediastinal tumor mass, extranodal disease localization, and splenic involvement are very important negative prognostic factors in disseminated disease. Superior vena cava syndrome is a complication of the presence of a bulky mediastinal mass [15,16].

The incidence of eosinophilia at presentation in large series of patients with Hodgkin lymphoma has been reported to be about 15%. When leukocytosis is present at presentation, eosinophilia is observed in up to 51% of newly diagnosed patients. In our study, eosinophilia was present in 60.3% of patients. An elevated eosinophil count in peripheral blood occurs more frequently in advanced disease (clinical stages III or IV) and in patients with B symptoms (night sweats, weight loss, and fever).

In our study, newly diagnosed patients with Hodgkin lymphoma predominantly had the abovementioned characteristics. According to literature, although not a universally recognized independent prognostic factor, the disappearance of eosinophilia during therapy indicates a good therapeutic response, while its persistence indirectly indicates a suboptimal response [8,17,18]. Our study also established a statistically significant association between eosinophilia and thera-

Naše istraživanje nije pokazalo da je eozinofilija u perifernoj krvi u korelaciji sa detektovanom *bulky* formom bolesti, odnosno tumorskom masom većom od 7 cm u merenom promeru. Ovi rezultati ukazuju da procena tumorske mase ostaje primarno kliničko-radiološki parametar, a ne parametar zasnovan na laboratorijskim ispitivanjima. Imajući prethodno navedeno u vidu, može se objasniti loš odgovor kod naših ispitanika, s obzirom da je bio dominantan uznapredovali klinički stadijum, prisutnost velike tumorske mase u medijastinumu kod 48% obolelih, te ustanovljena ekstranodalna lokalizacija bolesti u 36,2% slučajeva, sa dominacijom ekstranodala u plućima kod 24,1%. Sve ovo odgovara literaturnim podacima koji navedeno opisuju kao loše prognostičke prediktore [19–21].

Uprkos napretku u lečenju, Hočkinov limfom i dalje predstavlja izazov u pogledu procene aktivnosti bolesti i praćenja terapijskog odgovora. Pored imidžing dijagnostike – *PET/CT*, važnu ulogu imaju ipak i laboratorijski parametri inflamacije i imunološkog odgovora, kao što su povišena vrednost sedimentacije i eozinofilija, kako u perifernoj krvi tako i u samom patološkom supstratu obolele limfne žlezde [22]. Jednostavnim praćenjem visine sedimentacije i broja eozinofila mogu se dobiti rane informacije o efektu terapije i pre *PET/CT* snimanja. Obe analize su jeftine, brze i dostupne u svakodnevnoj kliničkoj praksi.

Analizom terapijskog odgovora utvrđeno je da je on bio lošiji kod naših ispitanika u odnosu na one opisane u literaturi, jer je 64,9% obolelih od Hočkinovog u našem istraživanju postiglo kompletnu remisiju (*CR*) pri primeni prve terapijske linije.

ZAKLJUČAK

Istraživanjem je utvrđeno da je kod naših ispitanika na prezentaciji dominirao odmakli stadijum bolesti, prisustvo B simptoma i *bulky* forma, kako medijastinalne tako i vanmedijastinalne lokalizacije.

U našem istraživanju, eozinofilija u perifernoj krvi se nije pokazala kao prediktor *bulky* forme bolesti, ali se pokazala kao mogući prediktor terapijskog odgovora. Zbog dostupnosti i kliničke koristi, preporučujemo rutinsko praćenje eozinofila, kao dopunu imidžing metodama u praćenju terapijskog odgovora, uz ograničenje koje nosi naše mala grupa ispitanika.

Naši rezultati sugerišu da rutinski laboratorijski parametri nemaju pouzdanu vrednost kao pokazatelji opterećenja tumorskom masom, odnosno kliničko radiološka dijagnostika ostaje standard procene tumorske mase kod obolelih od Hočkinovog limfoma.

peutic response ($p = 0.024$), which indicates its potential prognostic significance. This finding suggests that eosinophilia may have a role in predicting treatment outcomes in patients with Hodgkin lymphoma.

Our research did not find that peripheral blood eosinophilia correlated with the detected bulky form of the disease, i.e., a tumor mass greater than 7 cm in diameter. These results indicate that the assessment of tumor mass remains a primarily clinical and radiological parameter, rather than a laboratory-based parameter. Bearing this in mind, the poor response in our subjects can be explained, given that the advanced clinical stage was dominant, that the presence of a large tumor mass in the mediastinum was found in 48% of patients, and that extranodal localization of the disease was established in 36.2% of cases, with a predominance of extranodal disease in the lungs in 24.1%. All of this corresponds to literature data which describe the aforementioned as poor prognostic predictors [19–21].

Despite advances in treatment, Hodgkin lymphoma remains a challenge in terms of disease activity assessment and therapeutic response monitoring. Besides imaging diagnostics – PET/CT, laboratory parameters of inflammation and immune response, such as elevated sedimentation and eosinophilia, continue to have an important role, both in peripheral blood and in the pathological substrate of the affected lymph node itself [22]. By simply monitoring the sedimentation rate and eosinophil count, early information about the effect of therapy can be obtained even before PET/CT imaging. Both analyses are inexpensive, fast, and available in everyday clinical practice.

Analysis of therapeutic response found it to be poorer in our subjects, as compared to those described in the literature, as 64.9% of Hodgkin lymphoma patients in our study achieved complete remission (CR) upon application of the first-line therapy.

CONCLUSION

The study determined that, at presentation, advanced disease stage, the presence of B symptoms, and bulky disease, both of mediastinal and extramediastinal localization, were dominant in our subjects.

In our study, peripheral blood eosinophilia did not prove to be a predictor of bulky disease, but was found to be a possible predictor of therapeutic response. As it is available and clinically useful, we recommend routine monitoring of the eosinophil count as a supplementary tool to imaging methods in monitoring therapeutic response, bearing in mind, however, the limitation of our small group of subjects.

Our results suggest that routine laboratory parameters do not have reliable value as indicators of tumor

SPISAK SKRAĆENICA

HL – Hočkinov limfom

cHL – klasičan Hočkinov limfom (engl. *classic Hodgkin lymphoma*)

IPS – Internacionalni prognostički skor

CRP – C-reaktivni protein

LDH – Laktat dehidrogenaza

BNLI – British National Lymphoma Investigation

ABVD – adriblastin, bleomicin, velbe, dakarbazin

BEACOPP – bleomicin, etopozid, doksorubicin, ciklofosfamid, onkovin, prokarbazin, prednizon

CS – klinički stadijum (engl. *clinical stage*)

MSCT – multislajsna kompjuterizovana tomografija (engl. *multislice computed tomography*)

PET/CT – pozitronska emisiona tomografija/kopmjuterizovana tomografija (engl. *positron emission tomography/computed tomography*)

Hb – hemoglobin

SE – sedimentacija eritrocita

CR – kompletna remisija (engl. *complete remission*)

PR – parcijalna remisija (engl. *partial remission*)

SD – stabilna bolest NEMA NIGDE U TEKSTU

PD – progresija bolesti (engl. *progressive disease*)

Sukob interesa: Nije prijavljen.

mass burden; i.e., clinical and radiological diagnostics remain the standard for tumor mass assessment in patients with Hodgkin lymphoma.

LIST OF ABBREVIATIONS AND ACRONYMS

HL – Hodgkin lymphoma

cHL – classic Hodgkin lymphoma

IPS – International Prognostic Score

CRP – C-reactive protein

LDH – Lactate dehydrogenase

BNLI – British National Lymphoma Investigation

ABVD – adriblastin + bleomycin + velbe + dacarbazine

BEACOPP – bleomycin, etoposide, doxorubicin, cyclophosphamide, oncovin, procarbazine, prednisone

CS – clinical stage

MSCT – multislice computed tomography

PET/CT – positron emission tomography/computed tomography

Hb – hemoglobin

ESR – erythrocyte sedimentation rate

CR – complete remission

PR – partial remission

SD – stable disease NEMA NIGDE U TEKSTU

PD – progressive disease

Conflict of interest: None declared

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