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– ORIGINAL PAPERS –

Real-Life Data, a Retrospective Report from Romania Hodgkin's Lymphoma Registry - Single Center Experience

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Abstract

Background. *Hodgkin's Lymphoma is a type of cancer originating from the lymphatic system, characterized by Reed-Sternberg cells. It is essential due to its distinct clinical presentation, early age at diagnosis, favorable prognosis with early detection and treatment, and the ongoing need for research to optimize therapeutic strategies and improve patient outcomes.*

Aims: *This study evaluates demographic data and clinical features, staging, and treatment options of newly diagnosed Hodgkin's Lymphoma patients in the biggest Hematology Center in Bucharest, Romania "Fundeni" Clinical Institute*
Study design: Retrospective study

Methods: *Demographic data, histopathological and clinical features, treatment modalities, and treatment responses were systematically extracted from hospital records and integrated into the National Hodgkin's Lymphoma Registry under the auspices of the Romanian Hematology Association. Key dates, including initial diagnosis, remission, relapse, last follow-up, and death, were meticulously documented to facilitate comprehensive survival analysis.*

Results*. We analyzed data from a cohort of Hodgkin Lymphoma patients, comprising both male and female individuals, with a median age of 35. The predominant histological subtype was nodular sclerosis, and the most common stage at diagnosis was stage II. The ABVD chemotherapy regimen (doxorubicin, bleomycin, vinblastine, dacarbazine) was the most frequently administered treatment in the first-line setting. Five-year survival rates were significantly higher in patients diagnosed at an early stage and those with favorable prognostic factors, showing improved overall and relapse-free survival rates. Prognosis factors impacting outcomes included the presence of B-symptoms, serum albumin levels, Eastern Cooperative Oncology Group (ECOG), and LDH levels.*

Conclusion. *The analysis of Hodgkin's Lymphoma data from the Romanian National Registry highlights the critical necessity for the enhancement of diagnostic infrastructure, the promotion of equitable access to advanced treatments, and active engagement in international clinical trials. Addressing these imperative issues through targeted healthcare reforms has the potential to significantly ameliorate patient outcomes and synchronize Romania's management of Hodgkin's Lymphoma with global benchmarks.*

Key Words: *Hodgkin's Lymphoma, diagnosis, treatment, prognosis, Balkan area*

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Introduction

Hodgkin's lymphoma (HL) is a hematological malignancy of the lymph nodes and lymphatic system. There are two main subtypes: classical HL (cHL) and nodular lymphocyte-predominant HL [1]. HL comprises about 10% of all lymphomas. Globally, in 2020, this disease accounted for 0.2% to 0.4% of all newly diagnosed cancer cases [1], [2]. As far as the age distribution is concerned, in this disease, the age profile is bimodal, being the most frequent form of cancer among adolescents and young people (15-19 years) [2]. This type of lymphoma is particularly noteworthy due to its status as one of the most treatable forms of hematological malignancies [3]. Thanks to the latest advancements in modern chemotherapy regimens, survival rates have soared by approximately 80% [1]. It was found in the multivariate analysis that advanced age, reduced serum iron levels, and constitutional symptoms were predictive factors for treatment response [19].

Unfortunately, over the past decade, the existing literature has not provided sufficient information about the outcomes, including survival data, response rates, treatment regimens, and clinical courses, for patients with HL in the Balkans. Upon examination of the literature, a limited number of articles can be found. In the Balkan Medical Journal in 2013, a retrospective study evaluated HL patients treated in the Department of Medical Oncology, Cancer Institute, Hacettepe University: demographic, clinical, and pathological characteristics. [4] In 2021, a single-center retrospective cohort study, which concerned patients over 60 years old, was conducted at the University of Health Sciences, Turkey [5]. In 2014, an article was released by the Clinical Center of Serbia, which analyzed the treatment efficacy in 314 advanced classical Hodgkin lymphoma (HL) patients. The study focused on individuals who were treated with ABVD treatment at the Clinical Center of Serbia from 1997 to 2008[6]. As far as it is known, this is the initial study to evaluate the clinical characteristics and treatment outcomes for Hodgkin's lymphoma in Romania. This study wants to provide a general picture of HL patients in this country. Accordingly, it is essential to exhaustively review our records to evaluate the quality of care and the efficacy of the treatment protocols implemented at our centers.

Therefore, this study aims to comprehensively review treatment adherence among patients diagnosed with Hodgkin's Lymphoma in Romania. Additionally, the study desires to categorize these patients based on their risk factors, response rates, and clinical courses. Furthermore, it seeks to compare this information with data from the Balkan region, thus offering an overview of the situation in the Balkan.

Resistant or refractory Hodgkin lymphoma

Resistant or refractory Hodgkin lymphoma (RRHL) presents significant clinical challenges, often requiring more aggressive and multifaceted treatment strategies. Primary refractory disease is characterized by a lack of response to initial therapy, while relapsed disease refers to recurrence after an initial period of remission.

Treatment Strategies

1. *Salvage Chemotherapy:* Patients with RRHL typically receive salvage chemotherapy regimens such as ICE (ifosfamide, carboplatin, etoposide) or DHAP (dexamethasone, high dose cytarabine, cisplatin). These regimens aim to reduce tumor burden and achieve a sufficient response to allow for further intensive treatments [17].

2. *High-dose chemotherapy and Autologous Stem Cell Transplantation (ASCT):* High-dose chemotherapy followed by ASCT is the standard of care for patients who respond to salvage chemotherapy. This approach has significantly improved progression-free survival (PFS) and overall survival (OS) rates. Studies have demonstrated that ASCT can lead to long-term remission in a substantial subset of patients [18].

3. *Targeted Therapies*: Brentuximab vedotin, an anti-CD30 antibody-drug conjugate, has shown efficacy in RRHL, both as monotherapy and in combination with other agents. Additionally, immune checkpoint inhibitors such as nivolumab and pembrolizumab, which target the PD-1 pathway, have shown promising results in clinical trials, giving an effective treatment option to patients who relapse post-ASCT or are ineligible for transplantation [19][20][21].

4. *Allogeneic Stem Cell Transplantation*: For patients who relapse after ASCT, allogeneic stem cell transplantation may be considered, particularly in younger patients with suitable donors. This approach offers the potential for a graft-versus-lymphoma effect, which can contribute to long-term disease control [18].

Prognosis and Ongoing Research

The prognosis for patients with RRHL varies, depending on factors such as the duration of the first remission, the number of prior therapies, and overall patient health. Current research efforts are focused on improving outcomes through novel therapeutic approaches,

including combination therapies and next-generation targeted agents. Clinical trials continue to explore new treatments to enhance efficacy and reduce toxicity in this challenging patient population (Moskowitz et al., 2015;) [16].

Subjects and Methods

This retrospective study included patients over 18 years old who were diagnosed with Hodgkin's Lymphoma between 2017 and 2023 at Fundeni Clinical Institute. Patients under the age of 18 and those who were not diagnosed and primarily treated at the Fundeni Clinical Institute were excluded from the study. These patients were included in the Hodgkin's Lymphoma National Registry, created by the Romanian Society of Hematology. A total of 182 patients were reviewed from this registry. The records of the study participants were anonymized before access. The research received approval from the Fundeni Clinical Institute's Local Ethics Committee (No 24768), as well as from the Hodgkin's Lymphoma National Registry.

Data about demographics, histopathological and clinical characteristics, examination findings, presenting symptoms, and treatment plans were retrieved from hospital records and introduced in the registry. The registry was also employed to gather data on biochemical test results, liver and renal function, C-reactive protein levels, complete blood counts, lactate dehydrogenase levels (LDH), and imaging techniques. Patients were classified based on the Ann Arbor Staging system and were categorized histologically in accordance with the WHO classification. The staging procedures use an in-depth examination of the patient's medical history, clinical evaluation, contrast-enhanced computed tomography (CT scan) or positron emission tomography (PET-CT), and an assessment of the bone marrow. The treatment plan was determined in accordance with guidelines from the European Society of Medical Oncology (ESMO), the National Comprehensive Cancer Network (NCCN), and the Romanian Hematology Association Guidelines. Treatment was also assessed, covering treatment methods, types of chemotherapy used, results, treatment side effects, and dates of result assessments. Follow-up was conducted every three months for the first two years, every six months for the next three years, and then annually for the rest of the patient's life. For patients who had not been presented to the hospital for over six months, follow-up was conducted by telephoning them or their relatives to gather detailed information about their current health status.

Definitions

Response assessment for lymphoma using the Lugano criteria is generally conducted 4-6 weeks after the completion of treatment [7].

Complete Response (CR)

This is defined as no evidence of disease on PET-CT or CT scans, with a score of 1, 2, or 3 on the 5-point Deauville Scale, regardless of the presence of residual masses [8].

Partial Response (PR)

This involves a score of 4 or 5 on the Deauville Scale, with reduced uptake compared to baseline and residual masses of any size. At interim assessment, this indicates responding disease, while at the end of treatment, it suggests residual disease [8].

Stable Disease (SD) or No Response

This is indicated by a score of 4 or 5 with no meaningful change in FDG uptake from baseline, either at interim assessment or at the end of treatment [8].

Progressive Disease (PD)

This is characterized by a score of 4 or 5, an increase in the intensity of uptake from baseline, and/or the presence of new FDG-avid lesions, either at interim assessment or at the end of treatment [9].

Relapse (RD)

This is identified by new FDG-avid foci consistent with lymphoma rather than other etiologies such as infection or inflammation. In cases of uncertainty regarding the etiology, a biopsy or interval scan may be considered [9].

Overall survival (OS)

Represents the time between the diagnosis and the last visit to the hospital or death.

Relapse-free survival

Represents the time from the date of complete response until the disease reoccurs.

Remission duration

It is defined as the time from the complete response until the last visit to the hospital or date of death.

Statistical Analyses

The study used data from the private national platform limfom.srh.org.ro, which is a specialized database used by physicians across the country to manage lymphoma cases. The platform uses a structured relational database management system, specifically MySQL, to store and organize clinical information. Data extraction and processing were carried out using the PHP programming language without the use of additional frameworks. A specific set of selection criteria was used to create a representative sample of all cases registered in the platform. The analysis involved developing customized SQL queries to extract relevant data, filtering and associating them. Subsequently, PHP scripts were used for manipulation and aggregation. The security measures on the platform have been enhanced to provide additional protection for data extraction and utilization, ensuring comprehensive security. The collected data has undergone full anonymization to safeguard it from unauthorized access. The statistical analysis provides insights into trends and patterns within a specific data subset, offering a focused perspective on cases that meet the established inclusion criteria. The analysis results are briefly summarized in statistical tables and graphs using HTML and MS Excel tools, facilitating clear interpretation and presentation of the study's conclusions. The data processing methodology has been meticulously developed to guarantee the accuracy and relevance of the results, aligning closely with the specific research objectives.

Results

The study analyzed information from 182 patients diagnosed, treated, and followed up for Hodgkin Lymphoma in Fundeni Clinical Institute, Bucharest, Romania, between 2017 and 2023. Of the total patient population, 47.25% were male, while 52.75% were female, as shown in Figure 1. The male-to-female ratio was 0.90:1; 75,27% percent of patients were ≤ 45 years, 19,78 % were ≥ 45 years of age but <65years of age, and 3,85% were >65 years. The most prevalent histological subtype was nodular sclerosis, accounting for 60,99% of cases, followed by mixed cellularity 28,57%, classical not otherwise specified (2,2 %), lymphocyte-rich (3,85%), and lymphocyte-depleted (0,55%). 1,65% of patients were diagnosed with stage I disease, while 43,41% were diagnosed with stage II, 25,27% with stage III, and 29,67% with stage IV disease. Thus, the data shows that 82 patients (45,06%) were diagnosed with limited-stage disease (IA, IB, IIA, IIB), while 100 (54,94%) were diagnosed with advanced-stage (IIIA, IIIB, IVA, IVB). The most frequently observed presentation was palpable lymph node mass, and 62,64 % of the patients had B symptoms at the time of diagnosis.

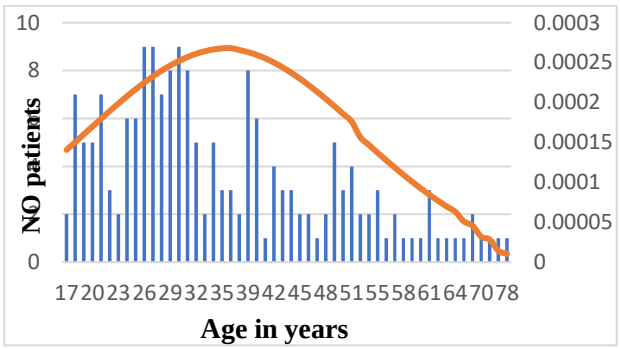
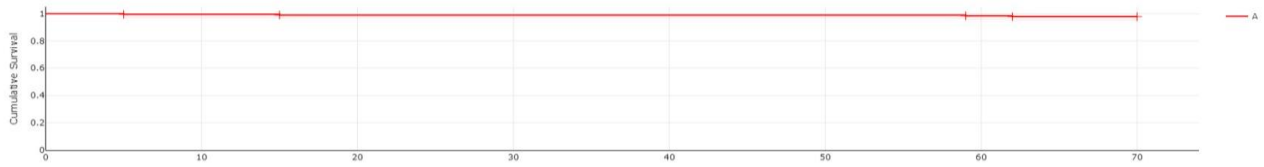


***Figure 1**. Distribution of patients by age*

In 15.38% of patients, bulky disease was observed, with 11.54% showing both bulky disease and B symptoms. At presentation, 11,11% of patients had bone marrow involvement. Mean laboratory values for the time of diagnosis are shown in Table 1. A significant proportion of patients exhibited abnormal laboratory findings at the time of diagnosis. Specifically, 38.46% presented with elevated serum lactate (LDH) levels, while 9.34% had decreased albumin levels. Additionally, 36.26% of patients displayed leukocytosis, 4.95% presented with lymphocytopenia, and 9.34% had anemia. Furthermore, 42.31% of patients showed elevated C-reactive protein levels. It was found in the multivariate analysis that advanced age, reduced serum iron levels, and constitutional symptoms were predictive factors for treatment response[23]. According to the international prognostic score (IPS), 25,27 % of patients were categorized as being in the low-risk group (IPS < 3), while 5,56% were categorized as being in the high-risk group (IPS ≥ 3). LDH level and C reactive protein were higher in patients with advanced-stage disease, bulky disease or B symptoms, and extranodal involvement as shown in Table 1. It is also indicated that the assay values exhibit the most notable variations during the advanced stages.

Overall survival rate



The overall survival rate in this study was not reached, with only 4 deaths (representing a 2.2% rate).

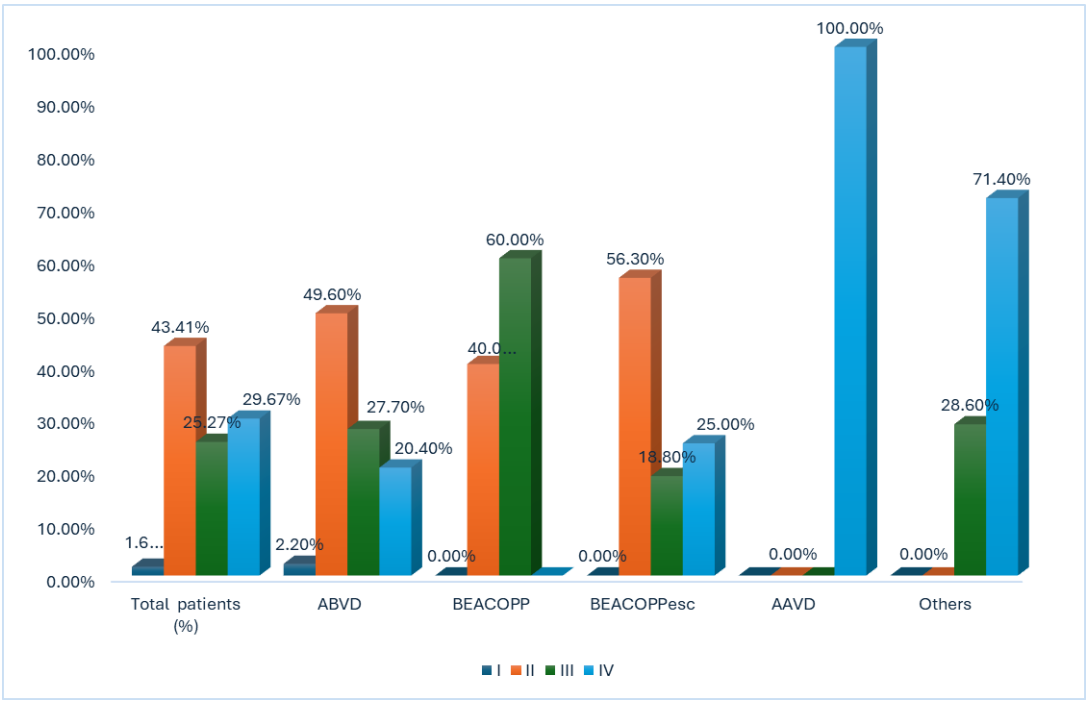


Figure 2. *Distribution of first-line therapies by disease stage*

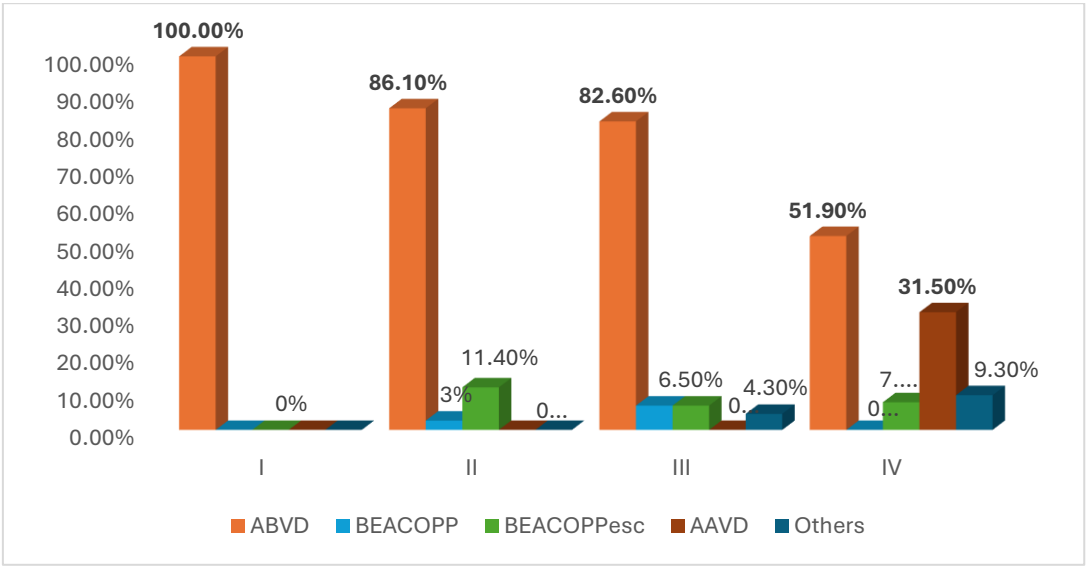


Figure 3*. Distribution of disease stages based on the utilization of various therapies*

	Total n (%)	*IA, IIA (non-Bulky, non-B symptoms) n (%)*	*I B, II B, IA, IB Bulky n (%)*	*III B, IV B Bulky n (%)*
Albumin				
Normal levels	*165 (90,7 %)*	*32 (14,0%)*	*45 (24,7 %)*	*88 (48,4 %)*
Low levels	*17 (9,34%)*	*2 (1,1%)*	*3 (1,6 %)*	*12 (6,6 %)*
Hemoglobin				
Normal levels	*124 (68,1 %)*	*29 (15,9%)*	*36 (19,8 %)*	*59 (32,4 %)*
Low levels	*58 (31,87%)*	*5 (2,7%)*	*12 (6,6 %)*	*41 (22,5 %)*
Leukocytes				
Normal levels	*116 (19,78%)*	*25 (13,7%)*	*27 (14,8 %)*	*64 (35,2 %)*
High levels	*66 (36,26%)*	*9 (4,9%)*	*21 (11,5 %)*	*36 (19,8 %)*
Lymphocyte				
Normal levels	*121 (23.08%)*	*27 (14,8%)*	*30 (16,5 %)*	*64 (35,2 %)*
Low levels	*61 (4,95%)*	*7 (4,7%)*	*18 (9,9 %)*	*36 (19,8 %)*
C-reactive protein				
Normal levels	*105(4,95%)*	*24 (13,2%)*	*33 (18,1 %)*	*48 (26,4 %)*
High levels	*77 (42,31%)*	*10 (5,5%)*	*15 (8,2 %)*	*52 (28,6 %)*
LDH				
Normal levels	*112 (18,13%)*	*26 (14,3%)*	*31 (17,0 %)*	*55 (30,2 %)*
High levels	*70 (38,46%)*	*8 (2,7%)*	*17 (9,3 %)*	*45 (24,7 %)*

Table1. *Mean laboratory values*
Abbreviations: LDH - lactate dehydrogenase

Stages IA, IIA, early favorable stage

This group includes HL that is only on one side of the diaphragm (above or below) and doesn't have any unfavorable factors such as large mediastinal mass (bulky disease), B symptoms, or a high number of lymph nodal groups involved. High ESR (erythrocyte sedimentation rate) could not be evaluated due to low data availability. Treatment for many patients is chemotherapy (usually 2 to 4 cycles of the ABVD regimen), followed by radiation to the initial site of the disease (involved site radiation therapy, or ISRT). Another option is chemotherapy alone (usually for 3 to 6 cycles) in selected patients [14],[15].

All patients were administered chemotherapy. In the favorable stage, ABVD therapy was administered in all cases at first line; it was observed that 26 out of 34 patients (76.5%) showed a complete response at the interim assessment. Among the remaining patients, 4 did not initially achieve a complete response and required treatment escalation to either

BEACOP (1 patient, 2.94%) or BEACOPesc (3 patients, 8.82%), yet resulting in a complete response for all. In summary, 29 patients, representing 85.3% of the total, achieved a complete response. (Table 2). Although radiotherapy is mandatory for limited stages, it was not used for all patients, probably because patients sometimes choose not to receive radiotherapy and prefer two more chemotherapy cycles. Another reason is that radiotherapists avoid using radiation therapy at the primary site and like to administer it to the rest of the tumor.

Stages IA, II A with Bulky, I B, IIB

This category comprises HL that is present only on one side of the diaphragm (above or below) but presents one or more of these risk factors: a large mediastinal mass (bulky disease), B symptoms, and involvement of a high number of lymph nodal groups.

	ABVD	BEACOPP esc	BEACOPP	Radiotherapy*	ABVD and BEACOPP esc	ABVD and BEACOPP
Total n (%)	34 (100%)	0 (0%)	0 (0%)	15 (44.12%)	3 (8.82%)	1 (2.94%)
CR n (%)	26 (76,5%)			14 (93.33%)	0	0
PR n (%)	2 (5,9 %)			1 (6.67%)	0	0
SD n (%)	0			0 (0%)	0	0
PD n (%)	2 (5,9 %)			0 (0%)	0	0
Refractory n (%)	0			0 (0%)	0	0
Final Response	25 (73,5%)			0 (0%)	3 (100%)	1 (100%)
Overall complete response 29 (85,3%)						

Table 2. *Rate of response for patients with stage I and II (non-Bulky, non-B symptoms) who receive primary chemotherapy regimen*

*Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease. * Part of protocol; Includes patients who were escalated due to suboptimal response to intermediate assessment*

The therapy is usually more aggressive than for favorable disease. It generally begins with chemotherapy, often using the ABVD regimen for two cycles, followed by restaging. If the PET scan shows no signs of disease, the treatment continues until four cycles are completed, followed by radiotherapy. In the case of a positive PET scan, the treatment shifts to escalated BEACOPP for two cycles, followed by restaging and radiotherapy [14], [15]. All patients (48) were administered chemotherapy. In these stages, ABVD therapy was administered to 37 (77,1 %) in the first line; it was observed that 25 out of 48 patients (52,1 %) showed a complete response at the interim assessment and maintained it. Three patients did not initially achieve a complete response and required treatment escalation to either BEACOPP (1 patient) or BEACOPPesc (2 patients), resulting in a complete response for all. In summary, 28 patients with ABVD therapy achieved a complete response. (Table 3)

Stages III and IV

This includes Hodgkin Lymphoma patients with enlarged lymph nodes both above and below the diaphragm and/or lymphoma has spread widely through one or more organs outside the lymph system. In this setting, it is typically administered chemotherapy for 6 cycles. The standard regimen is ABVD, but in cases with unfavorable prognostic factors, more aggressive treatment may be necessary, such as up to 6 cycles of escalated BEACOPP regimen. Another treatment option, Brentuximab vedotin plus AVD (doxorubicin, vinblastine, dacarbazine), has been reimbursed in Romania since 2019[14], [15].

	Total n (%)	*CR n (%)*	*PR n (%)*	*SD n (%)*	*PD n (%)*	*Refractory n (%)*	*Final Response*
ABVD	*34 (70.83%)*	*25 (73.53%)*	*3 (8.82%)*	*2 (5.88%)*	*2 (5.88%)*	*0*	*25 (73.53%)*
BEACOPP esc	*4 (8.33%)*	*1 (25%)*	*2 (50%)*	*0 (0%)*	*0*		*1 (25%)*
BEACOPP	*1 (2.08%)*	*0 (0%)*	*0*	*1(100%)*	*0*		*0 (0%)*
Radiotherapy	*19 (39.58%)*	*18 (94.74%)*	*0*	*0*	*1(5.26%)*		*0 (0%)*
ABVD and BEACOPP*	*2 (4.17%)*	*0*	*0*	*0*	*0*		*2 (100%)*
BEACOPPesc ABVD*	*4 (8.33%)*	*0*	*0*	*0*	*0*		*4 (100%)*
BEACOPPesc and other	*1 (2.08%)*	*0*	*0*	*0*	*0*		*1 (100%)*
ABVD and BEACOPP esc*	*1 (2.08%)*	*0*	*0*	*0*	*0*		*1 (100%)*

Table 3. *Rate of response for patients with stage IA, II A with Bulky, I B, IIB who receive primary chemotherapy regimen*

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease; Includes patients who were escalated due to suboptimal response to intermediate assessment

In our study, all patients (100) initially underwent chemotherapy. The majority received the ABVD regimen, resulting in a 52.54% complete response rate at the intermediate evaluation. Seven patients who did not achieve a complete response initially required escalated treatment to either BEACOPPesc (6 patients) or IGEV (1 patient), resulting in a complete response for all. Overall, 62,7 % of patients with advance Hodgkin's Lymphoma treated with ABVD therapy achieved a complete response.

Escalated BEACOPP was used in 6% of cases, with a final complete response rate of 33.33%. Additionally, 17 patients received AVD plus Brentuximab vedotin, which produced a higher response rate of 70.6%,

Radiotherapy was less frequently used for patients with advanced-stage Hodgkin Lymphoma due to a high rate of complete response with no active residual disease, confirmed by PET CT with a Deauville score of <3. (Table 4)

Stage IV Hodgkin's Lymphoma patients treated with Brentuximab vedotin.

The ECHELON-1 trial, which investigated the addition of brentuximab vedotin to the standard ABVD chemotherapy regimen, showed a significant improvement in overall survival for patients with advanced-stage Hodgkin lymphoma.

	Total n (%)	*Intermediary Response*					*Final Response*
		CR n (%)	***PR n (%)***	***SD n (%)***	***PD n (%)***	***Refractory n (%)***	***CR***
ABVD	*59 (59%)*	*31 (52.54%)*	*9 (15.25%)*	*8 (13.56%)*	*8 (13.56%)*	*0*	*30 (50.85%)*
BEACOPP esc	*6 (6%)*	*3 (50%)*	*2 (33.33%)*	*0*	*1 (16.67%)*	*0*	*2 (33.33%)*
BEACOPP	*2 (2%)*	*1 (50%)*	*1 (50%)*	*0*	*0*	*0*	*1 (50%)*
Radiotherapy	*0*	*0*	*0*	*0*	*0*	*0*	*0 (0%)*
Other	*7 (7%)*	*5 (71.43%)*	*1 (14.29%)*	*0*	*1 (14.29%)*	*0*	*5 (71.43%)*
AVD+ Brentuximab= Bv-AVD	*17 (17%)*	*11 (64,7 %)*	*11(11,8 %)*	*2 (11,8 %)*	*0*	*0*	*13 (76,5 %)*
+BEACOPP esc			*1*				
+ICE			*1*				
ABVD BEACOPP esc	*6 (6%)*	*0*	*0*	*0*	*0*	*0*	*6 (100%)*
BEACOPP BEACOPP esc	*1 (1%)*	*0*	*0*	*0*	*0*	*0*	*1 (100%)*
BEACOPPesc ABVD	*1 (1%)*	*0*	*0*	*0*	*0*	*0*	*1 (100%)*
ABVD IGEV	*1 (1%)*	*0*	*0*	*0*	*0*	*0*	*1 (100%)*

Table 4. *Rate of response for patients with stage III, IV who receive primary chemotherapy regimen.*

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease; Includes patients who were escalated due to suboptimal response to intermediate assessment

Specifically, patients receiving the combination of brentuximab vedotin, doxorubicin, vinblastine, and dacarbazine (A+AVD) had a five-year overall survival rate of 93.9%, compared to 89.4% for those treated with the standard ABVD regimen. This highlights the efficacy of incorporating brentuximab vedotin into the treatment regimen [16].

45,9% (17) patients with stage IV Hodgkin's Lymphoma received AVD+ Brentuximab vedotin as first line therapy. At the intermediate evaluation, 64,7 % of patients achieved a complete response. One of the cases required BEACOPPesc treatment as a result of an intermediate PET scan showing a Deauville score of 4. Following this, the patient achieved a sustained complete response. Another patient progressed and required escalation to the

ICE protocol, yet the patient achieved a complete response after completing the ICE protocol. Ultimately, 76,5 % maintained a fully supported response. The NCCN guidelines now advise against intermediate imaging evaluation, instead recommending assessment after completing the six treatment cycles to avoid escalation based only on an intermediate imaging response. It's important to acknowledge that our study did not include a sufficiently large number of subjects to yield statistically significant results in this case.

Partial Response, Recurrent or Relapsed, and primary refractory Hodgkin Lymphoma

Among the cases that were followed up, 38.46% (n=70) required continued treatment due to suboptimal treatment response or disease relapse after first-line therapy. In stages IA and IIA, the most frequently used therapy was ABVD, accounting for 70.7% of cases. For advanced stages, BEACOPesc was the predominant second-line therapy at 45.5%. Additionally, ICE/IGEV/DHAP was utilized as second-line therapy, too, in 41.7%. Among patients requiring second-line therapy, 17.1% underwent auto-transplantation.

Discussion on Hodgkin's Lymphoma Data from the Romanian National Registry

The retrospective study of Hodgkin's lymphoma (HL) data from the Romanian national registry provides crucial insights into the region's epidemiological trends, treatment practices, and outcomes. This analysis highlights several real-world challenges and systemic issues that need to be addressed to improve patient care and outcomes.

The results of our study are similar to those of the US SEER study in terms of predominant histologic type, mean age at diagnosis, male: female ratio, and the predominance of stage 2 at diagnosis (Table 5).

One significant difference between our study and the US SEER study is the low number of patients diagnosed with stage I. This disparity can be largely attributed to the absence of PET-CT scans at the time of diagnosis in our study, with only CT examinations being conducted. This limitation led to a tendency to over-stage due to concerns about potential underestimation, highlighting the crucial role of advanced imaging in accurate staging.

Our study reveals a slight majority of women compared to men. This gender disproportion is potentially linked to the heightened anxiety among women regarding the diagnosis and their preference for seeking treatment at a university medical center.

The advanced stage at diagnosis is comparable to that recorded in the Balkan registers, a situation predominantly attributable to patients' reluctance to undergo additional medical examinations.

Epidemiology and Demographics

The data indicate that Hodgkin's Lymphoma in Romania follows a bimodal age distribution, like global trends, with incidence peaks in young adults and older adults. This demographic pattern underscores the need for targeted public health initiatives aimed at these age groups to improve early detection and intervention strategies [17].

Diagnostic and Prognostic Challenges

One of the most significant issues the registry data reveals is the inconsistent availability of essential diagnostic tests, including complete blood counts, erythrocyte sedimentation rate (ESR), and various biomarkers. This limitation hampers accurate staging and risk stratification, which are critical for determining appropriate treatment plans [21].

The absence of these crucial diagnostic tools results in delays and inaccuracies in staging, leading to suboptimal treatment decisions. Enhancing laboratory infrastructure and ensuring uniform access to essential diagnostic tests across the country are imperative steps to improve the accuracy of HL diagnosis and prognosis [19].

Treatment Patterns and Access

The registry data indicate that ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy remains the standard treatment for HL. (Figure 3) Urban patients usually have better access to medical care, which is why most of our patients come from urban areas. Urban centers generally have better access to comprehensive cancer care, including PET-CT, for accurate staging and advanced treatments such as brentuximab vedotin and immune checkpoint inhibitors like nivolumab and pembrolizumab [22]. Pembrolizumab, a humanized IgG4 monoclonal antibody targeting the programmed death-1 protein, has shown effectiveness in classical Hodgkin lymphoma that has relapsed or is refractory [24].

In contrast, rural and economically disadvantaged areas face substantial barriers to accessing these advanced treatments. This urban-rural divide in healthcare access leads to disparities in treatment outcomes, with patients in

rural areas experiencing delayed diagnoses and suboptimal treatment regimens.

Research and Clinical Trials

The registry data also highlight Romania's limited participation in international clinical trials,
which restricts patients' access to innovative treatments and therapeutic approaches. No clinical trial was conducted in our center during this period.

Real Problems Revealed: The retrospective study identifies several real-world problems:

Inconsistent Diagnostic Capabilities: There is a critical need for uniform access to diagnostic tests essential for staging and prognostic evaluation.

Healthcare Disparities: Significant disparities in treatment access between urban and rural areas impact patient outcomes.

Limited Access to Advanced Therapies: Advanced treatments are not uniformly available, particularly in rural and economically disadvantaged regions.

No Participation in Clinical Trials: Romania's limited involvement in international clinical trials restricts patient access to novel therapies and hampers advancements in treatment.

Parameters	*Present study*	*Indian [10]*	*New Delhi [11]*	*Mumbai [12]*	*US SEER data [13]*
Study period	*2017 - 2023*	*1991-2010*	*1998-2005*	*1993-1996*	*2000-2007*
Number n	*182*	*301*	*262*	*179*	*16,710*
Age range	*18-76years Median 35 years*	*19-75years Median 36 years*	*15-72years Median 30 years*	*<15years,49% >15 years, 51%*	*Mean 42 years (white) Mean 38 (Asian/black)*
Sex Male: female	*0.90:1*	*2.9:1*	*3.1:1*	*4:1*	*1.27:1*
B symptoms (%)	*62.64*	*75.7*	*63*	*55*	*36*
Histology (%)					
MC	*28.57*	*74.4*	*52*	*66-71*	*13.1*
NS	*60.99*	*13.9*	*38*	*12-15*	*59.4*
Stage (%)					
I	*1.65*	*12.2*	*15*	*31*	*19.3*
II	*43.41*	*22.9*	*29*	*22*	*39.4*
III	*25.27*	*38.8*	*31*	*39*	*18.7*
IV	*29.67*	*25.9*	*24*	*8*	*16.6*

Table 5*. Comparative studies*

Conclusion

This examination of Hodgkin's Lymphoma data from the Romanian National Registry underscores the critical importance of improving diagnostic infrastructure, ensuring equitable access to advanced treatments, and actively participating in international clinical trials.
Addressing these imperative issues through targeted healthcare reforms has the potential to significantly improve patient outcomes and align Romania's management of Hodgkin's Lymphoma with global standards. The median age of diagnosed patients was 35 years, with 47.25% males and 52.75% females, resulting in a male-to-female ratio of 0.90:1. Most patients (75.27%) were 45 years or younger, consistent with the global trend of HL predominantly affecting younger individuals.

The most frequently observed histological subtype was nodular sclerosis, representing 60.99% of cases, with mixed cellularity following at 28.57%.
At the time of diagnosis, stage II was the most prevalent (43.41%), succeeded by stage IV (29.67%), signifying a notable proportion of patients were diagnosed at an advanced stage. Limited-stage disease (stages I and II) was diagnosed in 45.06% of patients, while advanced-stage disease (stages III and IV) was present in 54.94% of cases.
In the initial stage, all cases received ABVD therapy as a first-line treatment, and it was found that 26 out of 34 patients (76.5%) exhibited a complete response during the interim evaluation. Among the remaining patients, 4 did not achieve a complete response initially and needed escalated treatment, ultimately leading to a complete response for all. In short, 29 patients, comprising 85.3% of the total, attained an overall complete response.
In IA, II A with Bulky, I B, IIB stages, ABVD therapy was administered to 37 (77,1 %) in the first line; it was observed that 25 out of 48 patients (52,1 %) showed a complete response at the interim assessment and maintained it. Four patients did not initially achieve a complete response and required treatment escalation resulting in a complete response for all (82,4 %). In summary, 28 patients with ABVD therapy achieved a complete response.
In the cohort of patients with stage IV Hodgkin's Lymphoma, 45.9% (17) individuals underwent first-line therapy with a regimen comprising AVD (Adriamycin, Vinblastine, and Dacarbazine) and Brentuximab vedotin. Upon interim assessment, it was noted that 76.5% of the patients attained a complete response showing improving overall response rate.
In stages III and IV, the overall response rate to ABVD was 50.85%, significantly lower than the response rate to AVD-Brentuximab, which was 76.5%.
One significant difference between our study and other studies, like the US SEER study, is the low number of patients diagnosed with stage I. This disparity can be largely attributed to the absence of PET-CT scans at the time of diagnosis in our study, with only CT examinations being conducted. This limitation led to a tendency to over-stage due to concerns about potential underestimation, highlighting the crucial.

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Conflicts of interest

I undersign, certificate that I do not have any financial or personal relationships that might bias the content of this work. The authors declare no conflict of interest.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

References

1. S. Zhang et al., “Hodgkin’s lymphoma: 2023 update on treatment,” Cancer Biol Med, vol. 21, no. 4, pp. 269–273, Apr. 2023, doi: 10.20892/J.ISSN.2095-3941.2023.0427.

2. J. Huang et al., “Incidence, mortality, risk factors, and trends for Hodgkin lymphoma: a global data analysis,” J Hematol Oncol, vol. 15, p. 57, 2020, doi: 10.1186/s13045-022-01281-9.

3. Y. L. Boo, H. S. Y. Ting, D. F. S. Yap, S. G. Toh, and S. M. Lim, “Clinical features and treatment outcomes of Hodgkin lymphoma: A retrospective review in a Malaysian tertiary hospital,” Blood Res, vol. 54, no. 3, pp. 210–217, 2019, doi: 10.5045/br.2019.54.3.210.

4. S. Kiliçkap et al., “Clinical Features and Prognostic Factors of Hodgkin’s Lymphoma: A Single Center Experience,” Balkan Med J, vol. 30, no. 2, pp. 178–185, 2013, doi: 10.5152/BALKANMEDJ.2012.110.

5. P. R. Ferrini, A. Bosi, C. Casini, A. Messori, and G. Bellesi, “Hodgkin’s disease in the elderly: a retrospective clinicopathologic study of 61 patients aged over 60 years,” Acta Haematol, vol. 78 Suppl 1, pp. 163–170, 1987, doi: 10.1159/000205924.

6. B. Andjelic et al., “A single institution experience on 314 newly diagnosed advanced Hodgkin lymphoma patients: the role of ABVD in daily practice,” Eur J Haematol, vol. 93, no. 5, pp. 392–399, Nov. 2014, doi: 10.1111/EJH.12364.

7. B. D. Cheson, “Staging and response assessment in lymphomas: the new Lugano classification,” Chin Clin Oncol, vol. 4, no. 1, 2015, doi: 10.3978/J.ISSN.2304-3865.2014.11.03.

8. F. Ricard et al., “Application of the Lugano Classification for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The PRoLoG Consensus Initiative (Part 1—

Clinical)," Journal of Nuclear Medicine, vol. 64, no. 1, pp. 102–108, Jan. 2023, doi: 10.2967/JNUMED.122.264106.

9. "Response Assessment in Lymphoma: The Lugano Classification and Beyond - Imaging Endpoints." Accessed: Jul. 01, 2024. [Online]. Available: https://imagingendpoints.com/response-assessment-in-lymphoma-the-lugano-classification-and-beyond/

10. R. N. Maddi et al., "Clinical profile and outcome of adult Hodgkin lymphoma: Experience from a tertiary care institution," Indian J Med Paediatr Oncol, vol. 36, no. 4, p. 255, Oct. 2015, doi: 10.4103/0971-5851.171550.

11. P. Ganesan et al., "Hodgkin's lymphoma--long-term outcome: an experience from a tertiary care cancer center in North India," Ann Hematol, vol. 90, no. 10, pp. 1153–1160, Oct. 2011, doi: 10.1007/S00277-011-1262-8.

12. S. Laskar et al., "Consolidation radiation after complete remission in Hodgkin's disease following six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine chemotherapy: is there a need?," J Clin Oncol, vol. 22, no. 1, pp. 62–68, 2004, doi: 10.1200/JCO.2004.01.021.

13. C. R. Flowers, P. Shenoy, A. Maggioncalda, and N. Malik, "Incidence patterns and outcomes for hodgkin lymphoma patients in the United States," Adv Hematol, vol. 2011, 2011, doi: 10.1155/2011/725219.

14. R. N. Maddi et al., "Clinical profile and outcome of adult Hodgkin lymphoma: Experience from a tertiary care institution," Indian J Med Paediatr Oncol, vol. 36, no. 4, p. 255, Oct. 2015, doi: 10.4103/0971-5851.171550.

15. "Hodgkin Lymphoma Treatment Protocol by Stage | American Cancer Society." Accessed: Jul. 01, 2024.[Online].Available:https://www.cancer.org/cancer/types/hodgkin-lymphoma/treating/by-stage.html

16. "Brentuximab Vedotin With Chemotherapy Offers Survival Benefit in Stage III or IV Hodgkin Lymphoma - The ASCO Post." Accessed: Jul. 01, 2024. [Online]. Available: https://ascopost.com/issues/august-10-2022/brentuximab-vedotin-with-chemotherapy-offers-survival-benefit-in-stage-iii-or-iv-hodgkin-lymphoma/

17. B. D. Cheson et al., "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification," J Clin Oncol, vol. 32, no. 27, pp. 3059–3067, Sep. 2014, doi: 10.1200/JCO.2013.54.8800.

18. A. Sureda et al., "Improving outcomes after autologous transplantation in relapsed/refractory Hodgkin lymphoma: a European expert perspective," BMC Cancer, vol. 20, no. 1, pp. 1–14, Dec. 2020, doi: 10.1186/S12885-020-07561-2/FIGURES/1.

19. S. M. Ansell et al., "PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma," New England Journal of Medicine, vol. 372, no. 4, pp. 311–319, Jan. 2015, doi: 10.1056/NEJMOA1411087/SUPPL_FILE/NEJMOA1411087_DISCLOSURES.PDF.

20. R. Chen et al., "Phase II Study of the Efficacy and Safety of Pembrolizumab for Relapsed/Refractory Classic Hodgkin Lymphoma," J Clin Oncol, vol. 35, no. 19, pp. 2125–2132, Jul. 2017, doi: 10.1200/JCO.2016.72.1316.

21. A. Younes et al., "Brentuximab Vedotin (SGN-35) for Relapsed CD30-Positive Lymphomas," New England Journal of Medicine, vol. 363, no. 19, pp. 1812–1821, Nov. 2010, doi: 10.1056/NEJMOA1002965/SUPPL_FILE/NEJMOA1002965_DISCLOSURES.PDF.

22. R. Chen et al., "Results of a Multicenter Phase II Trial of Brentuximab Vedotin as Second-Line Therapy before Autologous Transplantation in Relapsed/Refractory Hodgkin Lymphoma," 2015, doi: 10.1016/j.bbmt.2015.07.018.

23. Oana Stanca, A. Coliță, and Nicoleta Mariana Berbec, "Survival and treatment response in Hodgkin's lymphoma: a multivariate analysis," Documenta Haematologica - Revista Romana de Hematologie, 1(3,), pp. 114–115

24. Catalin Danaila, Angela Dăscălescu, Luana Alexandra Marian, and Irina Florentina Carpen, "Pembrolizumab as long-term treatment option in relapsed or refractory classical Hodgkin lymphoma," Documenta Haematologica - Revista Romana de Hematologie, 1(3), 134– 135