

The Impact of Complex Treatment, Doxorubicin $C_{27}H_{29}NO_{11}$, Bleomycin $C_{55}H_{84}N_{17}O_{21}S_3$, Vinblastine $C_{46}H_{58}N_4O_9$ and Dacarbazine $C_6H_{10}N_6O$ Correlated with Haematological Parameters on Hodgkin's Lymphoma Survival Prognostic

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Abstract: Many prognostic factors for HL have been proposed in the past and some of these were included in several prognostic scores. Tumor stage and spread, age, gender and various biological parameters are considered to have an effect on disease evolution, with the prognostic scores stratifying patients into risk groups and guiding the course of treatment. In the present study we have enrolled 54 patients with Hodgkin's lymphoma admitted in the Hematology Department within the City Emergency Clinical Hospital Timisoara over a 4-year period. We aimed to see if a statistically significant correlation can be made between hemoglobin, white blood cell, lymphocyte, eosinophil, monocyte and platelet levels at the time of diagnosis on the one hand, and response to treatment and patients' survival, on the other hand. Patients' response to treatment was evaluated according to Cheson criteria, with best response to the combination of ABVD(doxorubicin $C_{27}H_{29}NO_{11}$, bleomycin $C_{55}H_{84}N_{17}O_{21}S_3$, vinblastine $C_{46}H_{58}N_4O_9$, dacarbazine $C_6H_{10}N_6O$) and radiation therapy. Response to treatment was also influenced by eosinophil levels at diagnosis and this has effects on survival. Finally, lymphocyte and platelet levels at diagnosis correlated with survival times in our study group. Therefore, eosinophil, lymphocyte and platelet levels at diagnosis could be considered as prognostic factors for HL, although further studies are needed to validate our findings.

Keywords: Hodgkin lymphoma, treatment, prognostic factors

1.Introduction

Hodgkin's lymphoma (HL) is among the most treatable malignancies, over 80% of the patients undergoing a therapy regimen being cured; conversely, left untreated, 90% of patients will die in up to 3 years [1]. Indeed, prognosis of HL has been significantly improved over the past decades by using effective chemotherapy regimens based on the individual risk of patients [2]. Identification of risk factors is therefore critical for providing tailored treatment strategies, while both clinical and biological parameters were utilized as prognostic factors for HL and are widely included in the prognostic scores to discriminate between risk groups [3].

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European Organization for Research and Treatment of Cancer (EORTC) /Lymphoma Study Association and German Hodgkin Study Group (GHSG) have defined three risk groups (limited, intermediate and advanced stages) based on similar prognostic factors [4]. Both groups consider large mediastinal masses and elevated erythrocyte sedimentation rate (ESR) among the risk factors. While both groups define the involvement of nodal areas as a negative prognostic factor, different cut-points are considered by EORTC (≥ 4 nodal areas) and GHSG (≥ 3 nodal areas). Moreover, each of the two groups have described additional risk factors, namely age ≥ 50 years (EORTC) and extranodal disease (GHSG). These prognostic scores are used by both groups to assign patients to a treatment type, which is adjusted according to the risk group.

Hasenclever *et al.* [5] have used data provided by 25 study groups regarding 5,141 HL patients, in order to develop a prognostic scoring system, known as the International Prognostic Score (IPS). IPS includes seven prognostic factors: serum albumin level under 4 g/dL, hemoglobin level < 10.5 g/dL, male sex, age ≥ 45 years, stage IV disease, leukocytosis (white blood cell count $\geq 15,000/\text{mm}^3$), and lymphocytopenia (lymphocyte count $< 600/\text{mm}^3$ or $< 8\%$ of the white blood cell count, or both). According to IPS, patients are stratified into low-risk group (favourable HL), meaning patients having 0 – 3 risk factors, and high-risk group (unfavourable HL), these patients having 4 – 7 risk factors. The latest studies provide data on new factors involved in the prognosis of Hodgkin's lymphoma: value of lymphocyte to monocyte ratio (LMR).

One of these is a very well documented meta-analysis, which brings data about another 8 studies, involving 3319 patients. All studies except one reported the effect of LMR on overall survival (OS); five reported on progression-free survival (PFS), three reported on time to progression and lymphoma-specific survival, and one reported on event-free survival. The pooled estimates showed that a low value of LMR was associated with poor OS. Subgroup analyses of OS stratified by LMR cut-off values and sample sizes both indicated that low baseline LMR was associated with poorer prognosis. Low LMR at diagnosis was associated with poor OS and PFS in HL [15]. Since LMR is easy and cheap to determine and has a high potential role in daily clinical management. More studies are needed to validate this biomarker and explore its interaction with known prognostic factors [15]. Another study obtains similar result in validation of LMR. The optimal cut-off value of LMR was 2.5, progression free survival (PFS) ($P < 0.001$) and overall survival (OS) ($P < 0.001$) were significantly lower in the $\text{LMR} < 2.5$ group than that of $\text{LMR} \geq 2.5$. Multivariate survival analysis showed that $\text{LMR} < 2.5$ was an independent predictor of PFS in Hodgkin's Lymphoma patients [16]. Another recent reports brings data about NLR (the ratio between absolute neutrophils counts, ANC, and absolute lymphocyte count, ALC), as predictor of progression-free survival (PFS) and overall survival (OS) in cancer patients [17].

Although the IPS is not routinely used in clinical practice, its accuracy in predicting survival, deriving from the large set of data used by the authors, makes it a valuable tool for clinicians, which is why we applied it to a certain degree in this study.

2. Materials and methods

Population, sampling and representativeness. This study has included 54 patients with Hodgkin's lymphoma admitted in the Hematology Department within the City Emergency Clinical Hospital Timisoara from January 1st, 2013 until December 31st, 2016. We have enrolled 54 patients, out of which 35 were women and 19 men, with a mean age of 40.4 years (minimum age 18 years, maximum age 69 years). Clinical, biochemical, hematological, immunohistochemical and imagistic parameters for each patient were recorded, as follows: performance status, presence of lymph node/extranodal involvement and of hepatosplenomegaly, ESR, LDH, C-reactive protein, beta2 microglobulin, hemoglobin, white blood cell, lymphocyte, eosinophil, monocyte and platelet levels.

Inclusion criteria were availability of clinical and paraclinical parameters for ascertaining the diagnosis of Hodgkin's lymphoma, and correct and complete diagnosis of the HL type by histologic and immunophenotypic examination of tumour biopsy tissue.

Patients in whom the onset of disease occurred prior to the start of this study were retrospectively followed, by reviewing their medical records, and prospectively, after the study begun. Likewise, prospective analyses were carried out in patients diagnosed for the first time with Hodgkin's lymphoma during the study. All the patients were investigated during the course of disease and up to their death, the end of the study or the time they failed to return for follow-up. We studied both quantitative and qualitative characteristics.

Statistical analysis. Medical records of patients admitted to the Hematology Clinic of City Clinical Hospital were analysed in order to set up the study group. All data were electronically recorded in a table generated in the Excel programme under Microsoft Office 2007. Data were then transferred in the SPSS20.0 programme for statistical processing.

All analyses were performed on weighted data. The results are presented as absolute and relative frequencies. Descriptive statistics were conducted using frequencies and proportions. A logistic regression analysis was used to estimate prognostic factors. A P-value <0.05 was considered statistically significant.

3. Results and discussions

The aim of this study was to identify hematological parameters that could be included as prognostic factors for Hodgkin's lymphoma. We thus intended to see if a statistically significant correlation can be made between hemoglobin, white blood cell, lymphocyte, eosinophil, monocyte and platelet levels at diagnosis on the one hand, and response to treatment and patients' survival, on the other hand.

More than half of the patients included in this study had advanced disease, with lymph node involvement on both sides of the diaphragm (Ann Arbor stage III, 14 patients, 35.2%), or diffuse involvement of an extranodal organ (Ann Arbor stage IV, 19 patients, 25.9%). The remaining patients were diagnosed with stages I (5 patients, 9.3%) or II (16 patients, 29.6%). At the time of diagnosis, 37 (68.5%) patients had B symptoms of fever, night sweats and weight loss. These symptoms are often associated with an unfavourable evolution of disease, patients having either a partial remission, or a short-term complete remission. Histopathology revealed that most patients (30, 55.6%) had nodular sclerosis type, 21 patients (38.9%) had mixed cellularity type, while 3 patients (5.6%) had lymphocyte predominance type. Extranodal involvement was present in 20 patients (37%). Throughout our study, 32 patients (59.3%) survived, while 22 (40.7%) died.

Hematological parameters at baseline

The International Prognostic Score [4] includes four hematological risk factors, out of which three were identified in our study at the time of diagnosis: hemoglobin levels <10.5 g/dL, lymphocyte counts <600/mm³ and white blood cell counts ≥10,000/mm³. Hence, 16 patients (29.6%) had hemoglobin levels <10.5 g/dL, 21 (38.9%) patients had normal values, while 17 patients (31.5%) had elevated hemoglobin levels. Only two patients in stages I and II had low hemoglobin levels, while 14 were diagnosed with stages III and IV (seven patients in each stage). Lymphopenia (lymphocyte count <600/mm³) has been documented in 11 patients (20.4%) and lymphocytosis (lymphocyte count >3,000/mm³) in 5 patients (9.3%), with the remaining patients having values between 600 – 1,000/mm³ (5 patients, 9.3%) or 1,000 – 3,000/mm³ (33 patients, 61.1%). Lymphopenia was found in one patient in stage II, two patients in stage III and 8 patients in stage IV. Clinical importance of lymphopenia rests in that it suggests the lack of an appropriate immune response due to the compromised immune system, thus favouring secondary tumours and worsening the-course of disease, ultimately leading to significantly lower survival time in these patients. A white blood cell count under 4,000/mm³ (leukopenia) was recorded in 3 patients (5.6%), normal counts (4,000 – 10,000/mm³) were seen in most patients (n=38, 70.4%), while 13 patients (24.1%) had levels that exceeded 10,000/mm³ (leukocytosis), out of which three patients had stage II disease, five had stage III and another five were in stage IV.

We have also included in our statistical analysis eosinophil, monocyte and platelet levels. Normal eosinophil counts ($<500/\text{mm}^3$) were found in 33 patients (61.1%), while 21 (38.9%) had eosinophilia, with 19 patients having eosinophil counts between 500 and $1,000/\text{mm}^3$. Of these, two were diagnosed in stage I, six in stage II, six in stage III and five in stage IV. Moreover, one patient in stage III and one in stage IV had eosinophil levels exceeding $1,000/\text{mm}^3$. Monocyte counts under $1,000/\text{mm}^3$ were recorded in 33 patients (61.1%), with the rest of 21 patients having monocytosis, most of them ($n=17$, 31.5%) with counts of 1,000 to $1,500/\text{mm}^3$. Of these 17 patients, one was diagnosed in stage I, six in stage II, four in stage III and six in stage IV. The remaining 4 patients (7.4%) had monocyte levels above $1,500/\text{mm}^3$, out of which one in stage II, two in stage III and one in stage IV. Most patients ($n=45$, 83.3%) had normal platelet counts, *i.e.* $150,000 - 400,000/\text{mm}^3$, with the remaining patients having either thrombocytopenia ($n=3$, 5.6%) or thrombocytosis ($n=6$, 11.1%). Patients with thrombocytopenia were diagnosed in stages II ($n=2$) or IV ($n=1$), while those with thrombocytosis were one each in stages II and III, and four in stage IV.

When evaluating the risk factors of patients with advanced disease included in our study according to IPS, we have found seven patients had favourable HL, while 12 had unfavourable HL. Indeed, six of these patients died by the end of this study.

Treatment and response

Type of treatment and number of cycles have been decided based on the histological stage of disease for each patient (see Table 1), with the following three courses of treatment being applied: 42 patients (77.8%) received standard treatment, with 6 cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine); 8 patients (14.8%) received 3 cycles of ABVD and radiation therapy (Table 2, Figure 1)

Table 1. Patients' distribution by treatment type and stage of disease

Treatment	Disease stage				Total
	I	II	III	IV	
ABVD, 3 cycles + radiation therapy	0	3	3	2	8
ABVD, 6 cycles	5	10	11	16	42
Escalated BEACOPP	0	3	0	1	4
Total	5	16	14	19	54

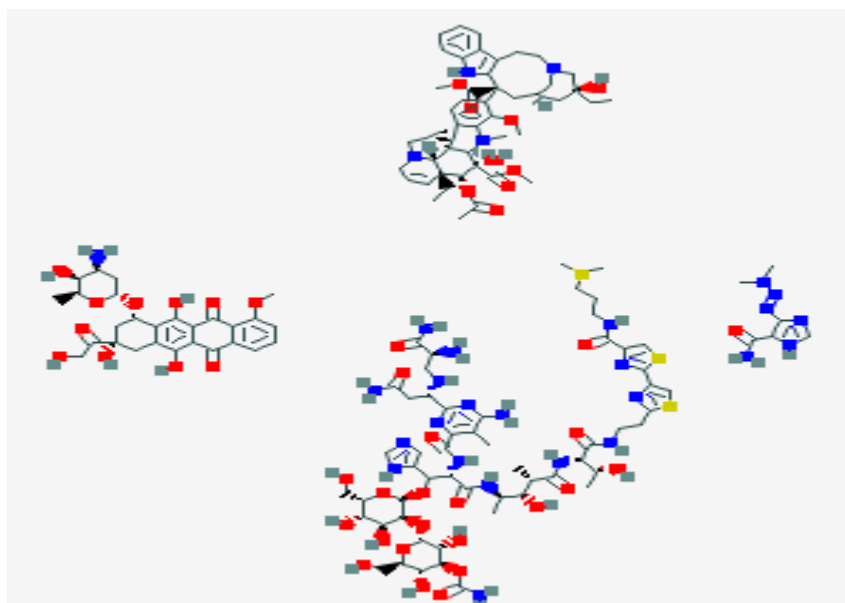


Figure 1. ABVD chemical structure

(Source <https://pubchem.ncbi.nlm.nih.gov/compound/ABVD-protocol>)

Table 2. ABVD regimen

Drug	Dose	Days
Adriamycin	25 mg/m ²	1. 15
Bleomycin	10 mg/m ²	1.15
Vinblastine	6 mg/m ²	1. 15
Dacarbazine	375 mg/m ²	1. 15

4 patients (7.4%) received escalated BEACOPP regimen (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) (Table 3, Figure 2).

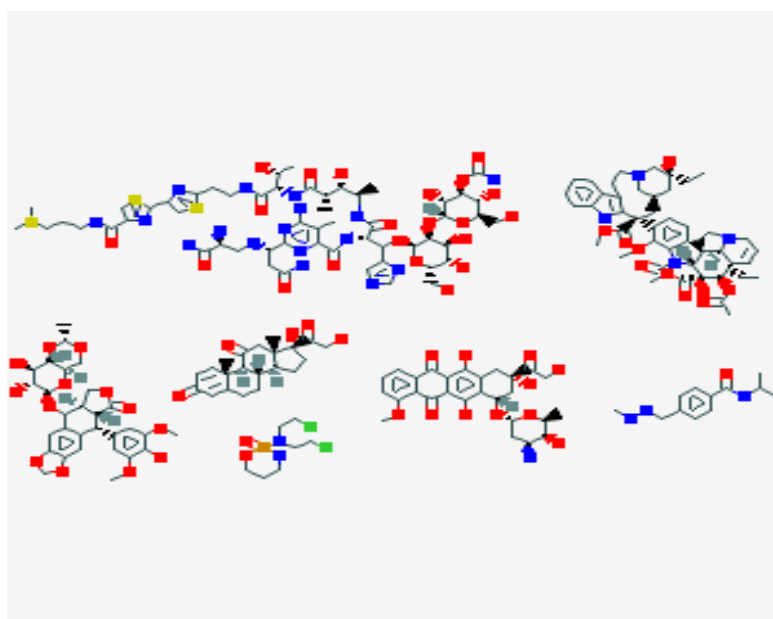


Figure. 2 BEACOPP escaladat chemical structure

(Source: <https://pubchem.ncbi.nlm.nih.gov/substance/135264173>)

Table 3. Escaladate BEACOPP regimen

Drug	Dose	Days
Bleomycin	10 mg/m ²	8
Etoposide	200 mg/m ²	1-3
Doxorubicin	35 mg/m ²	1
Cyclophosphamide	1,250 mg/m ²	1
Vincristine	1.4 mg/m ²	8
Procarbazine	100 mg/m ²	1-7
Prednisone	40 mg/m ²	1-14

Patients' response to treatment was evaluated against the criteria established by an international group of experts, also known as the Cheson criteria [5], which include several types of response: complete remission, partial response, stable disease, relapsed disease (occurring after complete remission) or progressive disease (either after a partial remission or following a period of stable disease).

Table 4. Patients' distribution by treatment type and response

Treatment	Response to treatment				Total
	Complete remission	Partial remission	Progressive disease	Relapsed disease	
ABVD, 3 cycles + radiation therapy	3	3	0	2	8
ABVD, 6 cycles	15	8	12	7	42
Escalated BEACOPP	0	3	0	1	4
Total	18	14	12	10	54

Complete remission, defined as disappearance of all evidence of disease, as confirmed by imaging, physical examination and bone marrow biopsy, has been achieved in 18 patients (33.3%). Partial remission, meaning regression of measurable disease ($\geq 50\%$ decrease of dominant masses without increases in any other lymph nodes) and no new sites involved, as assessed by imaging studies, has been documented in 14 patients (25.9%). Progressive disease, defined as appearance of new lesions or $\geq 50\%$ increase of any existing masses, as shown by imaging, has occurred in 12 patients (22.2%), while relapsed disease, ascertained against the same criteria used for progressive disease, but occurring after a complete remission, was seen in 10 patients (18.5%). Tables 4 and 5 show the distribution of patients according to treatment type they underwent and the response achieved, and according to the response to treatment and stage of disease, respectively.

Table 5. Patients' distribution by response to treatment and stage of disease

Response to treatment	Disease stage				Total
	I	II	III	IV	
Complete remission	2	6	5	5	18
Partial remission	1	5	4	4	14
Progressive disease	2	1	3	6	12
Relapsed disease	0	4	2	4	10
Total	5	16	14	19	54

In order to identify the negative prognostic factors for the response to treatment, we have used the linear regression model to compare patients' response with the levels of hematological parameters (eosinophils, monocytes, white blood cells, lymphocytes, platelets and hemoglobin), as recorded at diagnosis, and found a statistically significant correlation between the levels of eosinophils and the response to treatment ($p = 0.03$). This shows that the level of eosinophils, particularly eosinophilia, might play a role in the way the patient is responding to the treatment, therefore allowing physicians to choose the type and course of treatment.

Survival

Out of the 54 patients included, 32 (59.3%) survived at the end of this study. The mean survival time from the time of diagnosis was 28.33 ± 14.05 months, with a minimum of 2 and a maximum of 45 months.

As expected, statistically significant results were obtained when we analysed the relationship between survival and response to treatment ($p = 0.002$). As shown in Table 6 and Figure 3, the overall mean survival time calculated for the whole group of patients was 28 ± 1.912 months, with significantly higher figures (40 ± 1.722 months) for patients who received 3 cycles of ABVD regimen in combination with radiation therapy, which is also explained by the fact that patients receiving this treatment are diagnosed in stages II and III of disease.

Table 6. Means and medians for survival time by treatment type

Treatment	Mean		Median	
	Months	Std. error	Months	Std. error
ABVD, 3 cycles + radiation therapy	40.000	1.722	40.000	1.697
ABVD, 6 cycles	26.357	2.179	30.000	5.761
Escalated BEACOPP	25.750	8.390	12.000	12.500
Overall	28.333	1.912	34.000	2.296

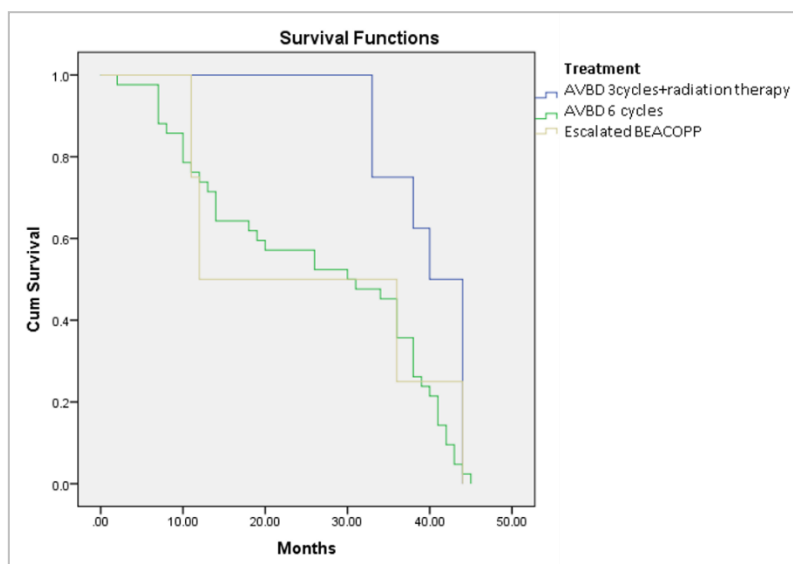


Figure 3. Survival by treatment type

We intended to see whether a correlation can be made between survival and baseline level of hematological parameters (hemoglobin, white blood cells, lymphocytes, eosinophils, monocytes and platelets), and found statistically significant results for lymphocytes ($p = 0.004$) and platelets ($p = 0.049$), meaning that both lymphocytopenia and thrombocytopenia are predictors for a poor outcome. As shown in Table 7, hemoglobin levels between 10.5 and 13 g/dL, white blood cells over 10,000/mm³, lymphocyte counts <600 cells/mm³, eosinophil counts <500 cells/mm³, monocyte counts under 1,000 cells/mm³ and platelet counts under 150,000 cells/mm³ were associated with lowest survival times.

Table 7. Means and medians for survival time by baseline level of hematological parameters

Parameter	Baseline level	Mean		Median		P-value
		Estimate	Std. Error	Estimate	Std. Error	
Hemoglobin	<10,5	29.875	3.376	33.000	1.984	0.560
	10,5-13	23.714	3.174	19.000	4.577	
	>13	32.588	3.153	38.000	1.353	
White blood cells	<4000	28.667	8.876	36.000	20.412	0.718
	4000-10.000	28.789	2.420	36.000	1.533	
	>10.000	26.923	3.325	30.000	7.190	
Lymphocytes	<600	19.000	4.213	12.000	5.505	0.004
	600-1000	24.000	7.596	14.000	3.286	
	1000-3000	30.939	2.326	36.000	1.435	
	>3000	36.000	1.924	36.000	3.286	
Eosinophils	<500	26.515	2.466	33.000	7.656	0.289
	500-1000	31.368	3.302	36.000	3.809	
	>1000	29.500	3.500	26.000	.	
Monocytes	<1000	25.424	2.535	26.000	9.187	0.127
	1000-1500	33.765	2.961	38.000	2.058	
	>1500	29.250	6.498	33.000	13.000	
Platelets	<150000	8.333	1.333	7.000	.	0.049
	150000-400000	29.178	2.070	36.000	1.333	
	>400000	32.000	4.676	31.000	1.837	

Prognostic factors are valuable tools for identifying the HL patients at risk, thus allowing for the stratification of treatment, particularly with the advent of new therapies which might be helpful to patients who are either resistant to conventional treatment or will relapse. Many prognostic factors have been shown to be relevant in HL and entered routine clinical practice, while others have more recently emerged and still need to be validated in large clinical trials. Tumor stage and spread,[Error!

Bookmark not defined.] age[6], gender[7] and presence of B symptoms[8] are among the first risk factors considered at diagnosis.

Levels of hematological parameters were also shown to play a role in the evolution of HL and are therefore used as prognostic factors. The International Prognostic Score **[Error! Bookmark not defined.]** established a cut-off level of 10.5 g/dL for hemoglobin. Indeed, according to the European Cancer Anaemia Survey,[9] low hemoglobin levels were found in 57.4% of the HL patients enrolled. In our study, the mean survival time was lower in patients with hemoglobin counts from 10.5 to 13 g/dL, and not in those having under 10.5 g/dL. Similarly, in this study the white blood cell levels at baseline did not significantly correlated with treatment response and survival, although patients with WBC counts over 10,000/mm³ had a lower mean survival time than those with higher levels. However, in agreement with IPS, lymphocyte counts proved to correlate with survival in this study, with lower survival time for patients having less than 600 cells/mm³.

Ratio of absolute lymphocyte count to absolute monocyte count 1.1 at diagnosis was reported to be a prognostic factor in a study[10] that followed 476 consecutive patients from 1974 to 2010, while monocyte counts higher than 900 cells/mm³ were associated with inferior overall survival. In our study, monocyte counts did not reach statistical significance in relation with survival, although we have seen that patients with monocyte counts under 1000 cells/mm³ survived less than those with higher monocyte levels.

Finally, both tissue, [11] and serum eosinophilia [12,13] have been proposed as prognostic factors. We here reported serum eosinophil counts <500 cells/mm³ at diagnosis as playing a role in the way HL patients respond to treatment, which, in turn, has effects on survival. Furthermore, platelet counts under 150,000 cells/mm³ proved to be the strongest prognostic factor for survival, patients with platelet counts <150,000 cells/mm³ having the lowest mean survival time in the entire group of study, i.e. 8.333±1.333 months.

4. Conclusions

In conclusion, we have shown that eosinophil levels, on the one hand, and lymphocyte and platelet values at the time of diagnosis, on the other hand, correlate with response to treatment and survival, respectively. Likewise, survival is also influenced by the type of treatment, although this is expected since the course of treatment with best response rate was assigned to patients in stages I or II, who have favourable prognosis. The other hematological parameters did not reach statistical significance, which can be explained by the small sample size. Further studies are needed to confirm our findings, possibly leading to inclusion of eosinophil, lymphocyte and platelet levels as prognostic factors for patients with Hodgkin's lymphoma.

Ethics and Field procedure

The study was approved by the Ethical Committee of Victor Babes University of Medicine and Pharmacy Timisoara. Every patient received information about the study in order to give their active consent.

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