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Analysis of Prognostic Factors As Predictors of Treatment Free Survival in Patients with Chronic Lymphocytic Leukemia-Single Centre Experience

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Abstract
Introduction*: Chronic lymphocytic leukemia (CLL) is a heterogeneous clonal lymphoproliferative disease originating from activated B lymphocytes that have experienced antigen. The clinical course is very heterogeneous. Some patients never look for treatment, as opposed to others who live and die with an aggressive illness. This clinical heterogeneity is likely a reflection of molecular and cellular heterogeneity, on the basis of which patients with CLL can be divided into subgroups with different clinical-biological characteristics.*
Aim of the study*: Evaluation of prognostic factors in terms of treatment free survival, prognosis and adequate therapeutic approach in patients with CLL.*
Material and methods*: The study is set as retrospective, it includes 300 patients with CLL diagnosed and treated at the University Clinic of Hematology in the period of 10 years (January 2009 - January 2019). The study was performed at the University Clinic for Hematology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia. We evaluate several prognostic factors in terms of treatment free survival. All results were processed with the statistical program SPSS18 software program.*
Results*: The multivariate Cox Proportional model of Treatment free survival of CLL patients confirmed ECOG, Rai Stage, and spleen size that influence on treatment free survival..*
Concusion*: In our study, multivariate analysis of treatment free survival and overall survival showed ECOG performance status 0,1 and 2 as a factor influencing both overall survival and treatment free survival.*
Key words*: CLL, prognosis, treatment free survival.*

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I. Introduction

Chronic lymphocytic leukemia (CLL) is a heterogeneous clonal lymphoproliferative disease originating from activated B lymphocytes that have experienced antigen. A biological model for CLL suggests that leukemic cells have different activities in different lymphoid compartments. Leukemic cells in the lymph nodes proliferate and regenerate in the peripheral blood. Leukemic cells proliferate in the bone marrow, lymph nodes, and spleen until they become "depleted" and can no longer respond to proliferative signals. These cells then "leave" in the peripheral blood, where they regenerate and are able to re-enter the lymph nodes and proliferate again. This type of leukemia is characterized by the accumulation of circulating long-lived circulating clonal leukemic B cells as a result of the complex balance between cell proliferation and apoptotic death. Most tumor cells are trapped in the G0 / G1 stage of the cell cycle, while only a small fraction of the clone exhibits proliferative activity, with about 2% of the cells being re-generated daily.

The incidence varies around the world. It is highest in the United States (3.35 - 3.69 per 100,000 inhabitants per year for men, 1.61 - 1.92 per 100,000 inhabitants per year for women), and is rare in the Middle East.CLL is a disease of the adult population, rarely occurring in the young population, and the incidence increases after the fourth decade of life and grows exponentially. The median age is 69.9 years, with more than 80% of patients older than 60 years.

The clinical course is very heterogeneous. Some patients never look for treatment, as opposed to others who live and die with an aggressive illness. This clinical heterogeneity is likely a reflection of molecular and

cellular heterogeneity, on the basis of which patients with CLL can be divided into subgroups with different clinical-biological characteristics.

The clinical division into stages is carried out in two systems, that of Rai and that of Binet. They are based on the patient's physical examination and the results of a routine blood test. The Rai-Sawitsky system divides patients into 5 stages The modified Rai-Sawitsky system divides patients into 3 stages: low , moderate and high risk (1).

The Binet system is based on the number of regions involved, hemoglobin level, platelet count. The median survival of patients with the low-risk Rai system (30%) is> 10 years; these patients do not need to start therapy immediately after diagnosis. Medium-risk patients (61%) have a median survival of 7 to 9 years. High-risk patients (8%) have a median survival of 1 to 1.5 years. The median survival of patients according to the Binet system stage A (63%) is> 10 years, stage B (30%) is 7 years, stage C (7%) is 2-5 years (2). The disadvantage of these two systems is that they do not have prognostic power, they can not identify whether the patient will have an indolent or progressive course of the disease and therefore in the last 2-3 decades intensive research has been done to identify other prognostic markers that will participate in determining overall survival and survival without therapy.

The indication for treatment and the type of therapy to be administered depend on the patient's age and performance status. General treatment recommendations imply that patients with RAI stage 0-II do not seek therapy unless there is evidence of disease progression or B symptomatology, patients with stage III-IV RAI require treatment if the patient has B symptomatology or disease progression. The most common therapeutic modalities for patients with CLL, in addition to careful monitoring for patients with asymptomatic disease, are alkylating drugs (alone or with corticosteroids), such as chlorambucil, which is able to achieve a response in 60 to 70% of patients but achieves a low complete remission, and purine analogues (fludarabine), alone or in combination, for advanced or symptomatic disease. Immunotherapy is performed with new monoclonal antibodies for instance anti CD20-Rituximab and new generation anti CD20 therapy such as Obinutuzumab. Corticosteroids are given in combination with chemotherapy to reduce organomegaly or to clear bone marrow from tumor cells. They have influence over CLL cells with TR53 mutation. The most impressive results showed the use of targeted therapy aimed at the B cell receptor (3). An important question that needs to be answered is how prognostic factors can be implemented in clinical practice about when and which therapy should be to administered. Treatment is indicated according to the recommendations of the International CLL Working Group (1), with a single prognostic marker RAI III / IV and a lymphocyte duplication time of less than 6 months.

Predicting treatment free survival (TFS) and the application of adequate therapy will be more successful by incorporating certain prognostic factors into prognostic models.The motive for this study is evaluation of prognostic factors in terms of treatment free survival, prognosis and adequate therapeutic approach in patients with CLL who have been diagnosed and treated at the University Clinic of Hematology in the past 10 years.

Using the information from the implemented prognostic factors, the newly diagnosed patients will be stratified for individual therapeutic choice.

II. Material And Methods

Patients and specimens

The study is set as retrospective, it includes 300 patients with CLL diagnosed and treated at the University Clinic of Hematology in the period of 10 years (January 2009 - January 2019). The study was performed at the University Clinic for Hematology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia.

The diagnosis of CLL patients was made according to the recommendations of the International CLL Working Group (IWCLL) (2). Patients treated with chemotherapy, it was administered with written consent (Helsinki Declaration) and according to the treatment recommendations of the International Working Group on CLL (IWCLL) (1). All patients had a pre-treatment evaluation that included: history of the disease with physical examination with noted two-dimensional diameter of the enlarged lymph nodes in all regions available for palpation (cervical, axillary, supraclavicular, inguinal, femoral). The dimensions of the spleen and liver are noted by physical examination - palpation. If necessary, imaging tests were used like CT of the chest and abdomen. Performance status according to ECOG (4) was performed. Complete blood count with a number of leukocytes, platelets, haemoglobin value, differential blood count with percentage and absolute number of lymphocytes was performed. Serum biochemical analyses, biochemical markers with prognostic significance in which the following were examined: serum level of LDH, B2 microglobulin. All patients were evaluated for direct and indirect antiglobulin test - Coombs test and serum level of immunoglobulins IgA, IgM, IgG. Data on patients with CLL who have been diagnosed and treated at the the University Clinic for Hematology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia for the past 10 years have been obtained from medical history.

Statistical analysis

All results were processed with the statistical program SPSS18 software program, and the results were presented graphically and in tabular form. Methods of descriptive statistics were used, as well as non-parametric and parametric statistical analyzes. In series with attributive features, the percentage and structure were determined. Significance of differences in the attribute series was determined using the x2 test and the Mann-Whiteney test.In series with numerical features, data distribution with average, standard deviation, minimum and maximum value was tested. The relationship between two phenomena with numerical features was determined by Pearson correlation coefficient (p). Differences between two independent samples with numerical marks were determined by t - test for independent samples. Differences between two independent samples with attributive traits were determined by the Wilcoxon test. Linear regression analysis and the Cox model were used to determine the relationship between different factors (clinical, biological) and the overall survival of patients with CLL. The log-rank test (Kaplan Meier method) was used to determine the significance of the difference in survival between the groups. Levels of probability of achieving the null hypothesis, according to international standards for biomedical sciences, are o.o1 and oo5.

III. Results

The study was set as retrospective, involving 300 patients with CLL diagnosed and treated at the University Clinic for Hematology, Medical Faculty, Ss. Cyril and Methodius University, Skopje, Republic of North Macedonia over the period of 10 years (January 2000 - January 2019).

Regarding the gender distribution, 64.7% of the patients with CLL are male and 35.3% are female, and the percentage difference is statistically significant for p <0.05 (p = 0.00000) (Fig1). The male/ female ratio is 1.8: 1.

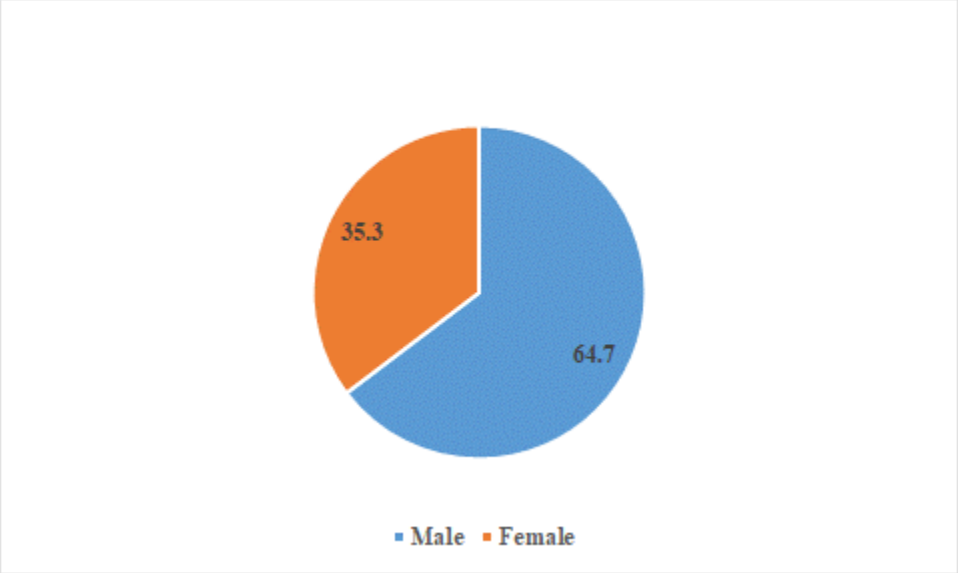

Figure 1. Graphic presentation of the distribution of CLL patients by gender.

The mean age of patients with CLL was 65.1 ± 10.0, the mean age of female patients was 66.1 ± 9.4 with a minimum of 38 years and a maximum of 89 years. The average age of male patients was 64.6 ± 10.4, with a minimum of 35 years and a maximum of 93 years. The difference between the ages of the gender according to the Mann-Whitney U test is statistically insignificant for p> 0.05 (-1.08744, p = 0.276844). Mean age-Me is 66 years. The most common age group with 58.3% is the age of 60 to 69 years, with the percentage difference compared to other age groups is statistically significant for p <0.05 (p = 0.0000) (Fig. 2).

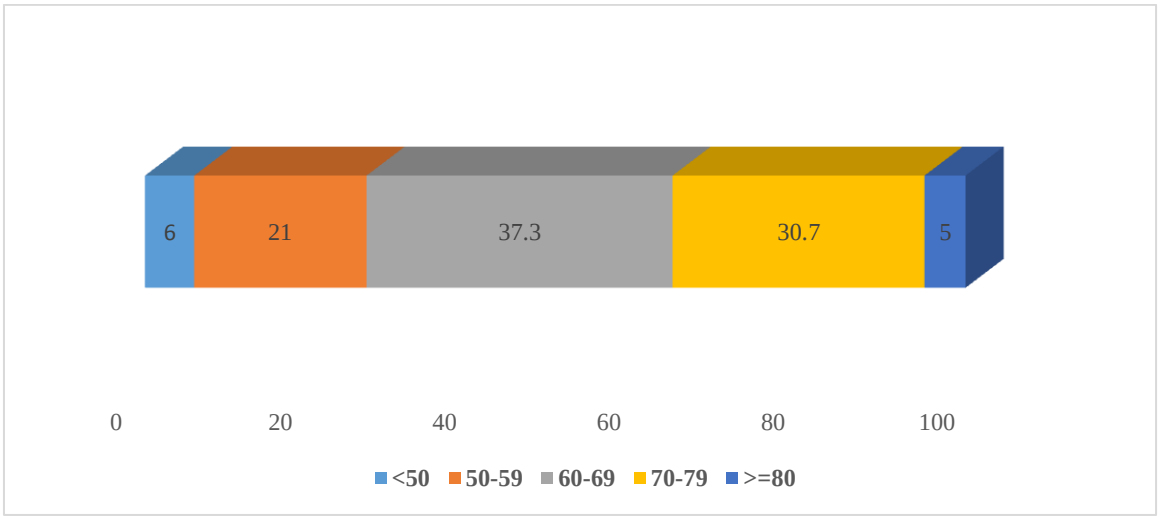

Figure 2. Graphic presentation of the distribution of patients with CLL by age groups.

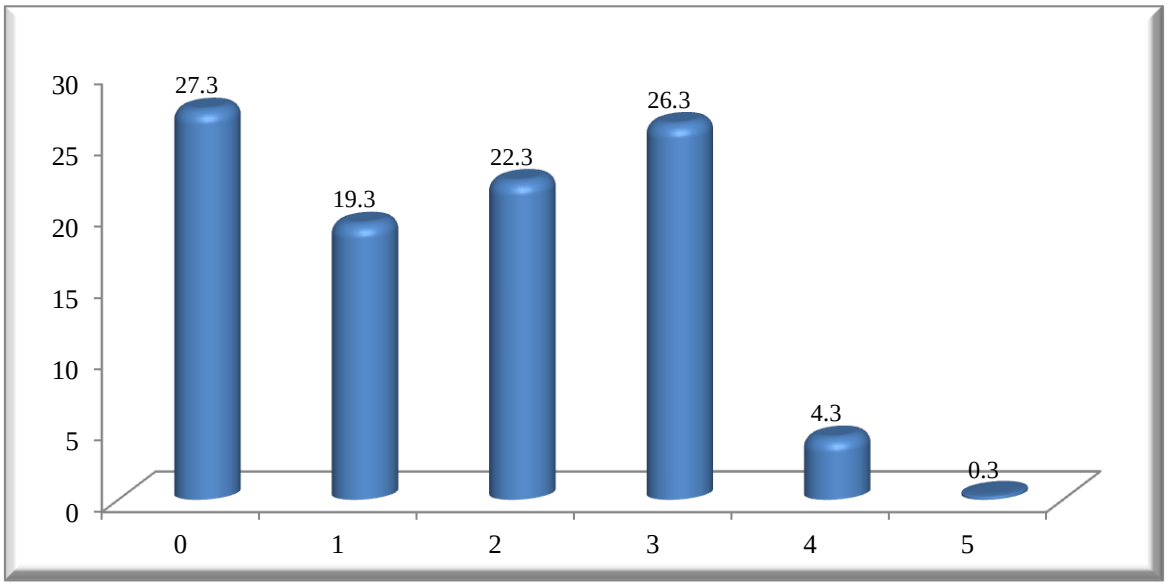

Figure 3. Graphic presentation of the distribution of patients with CLL according to ECOG performance status.

In the examined group of patients with CLL according to ECOG performance status with the highest percentage of 27.3%, there were a fully active patients, capable of all activities without restriction, then with 26.3% were limited ability to take care of themselves, spends more than 50% of the time in bed. With 22.3% were outpatient patients, but able to take care of themselfs, but incapable of work activities, awake more than 50% of the time and with 19.3% were patients with limited physical activity, but capable of light physical activity, such as light homework, office work. Only 4.3% were totally incompetent, who can not take care of themselves, 100% of the time is spent in bed (Fig. 3).The percentage difference registered during the ECOG performance status survey between ECOG 0, ECOG 2, ECOG 3 versus the other modalities of ECOG performance status (ECOG 1 and ECOG 4) is statistically significant for $p < 0.05$.

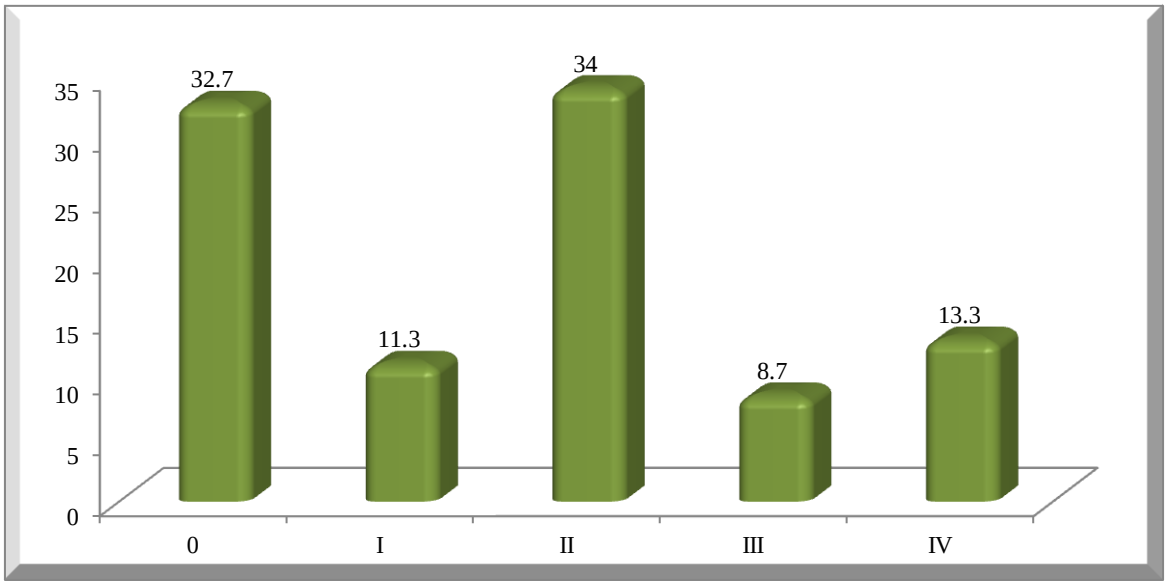

Figure 4. Graphic presentation of the distribution of patients with CLL according to the Rai classification system.

In the largest percentage, patients with CLL according to the Rai classification system, 34.0% belong to Rai II stage, 32.7% belong to Rai II stage, 13.3% belong to Rai IV stage, 11.3% belong to Rai I stage and 8.7% belong to Rai III stage (Fig.4).The percentage difference registered during the research in the Rai classification system between Rai 0 and Rai II stage versus the other modalities of the Rai classification system (I, III, IV stage) is statistically significant for $p < 0.05$ ($p = 0.0000$).

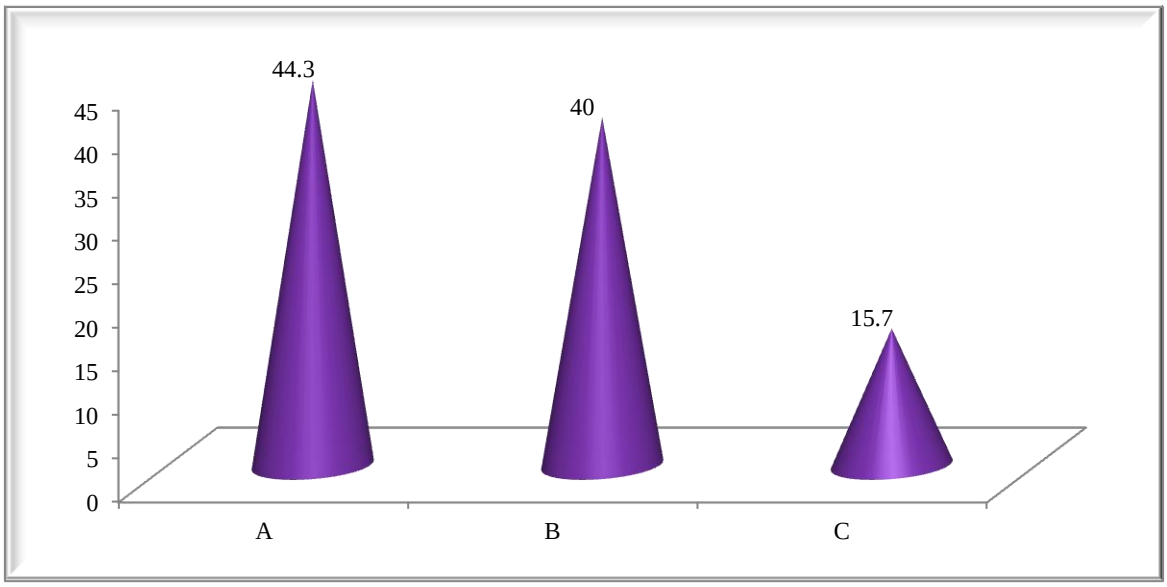

Figure 5. Graphic presentation of the distribution of patients with CLL according to the Binet classification system.

The largest percentage of patients with CLL according to the Binet classification system 44.3% belong to Binet A stage, 40.0% belong to Binet B stage and 15.7% belong to Binet C stage (Fig.5).The percentage difference registered during the research in the Binet classification system between Binet A and Binet B stage versus Binet C stage is statistically significant for $p < 0.05$ ($p = 0.0000$).

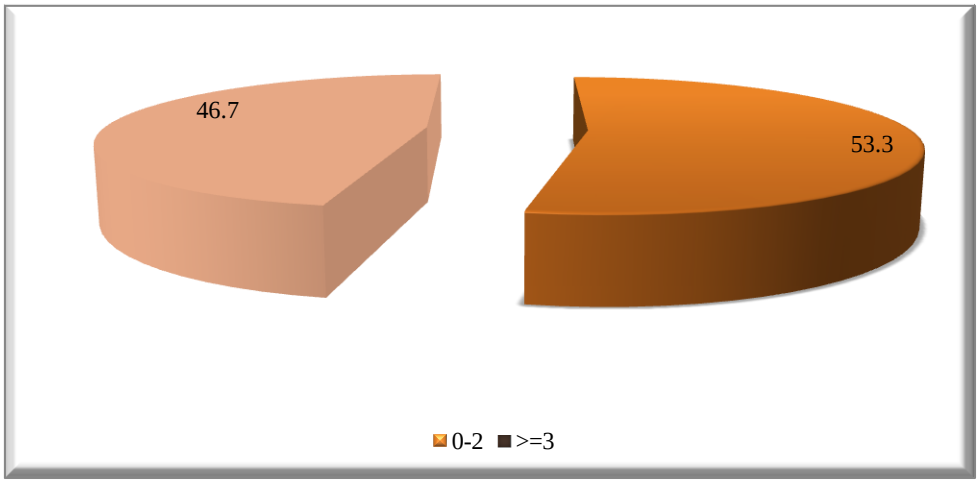

Figure 6. Graphical presentation of the distribution of patients with CLL according to the number of lymph nodes affected by the disease.

The highest percentage of patients with CLL according to the number of affected lymph nodes are registered 53.3% of patients with three or more lymph nodes affected, and 46.7% with those with 0 to 2 lymph nodes affected (Fig.6). Cervical lymphadenopathy was noted in 95% of patients with peripheral lymphadenopathy.

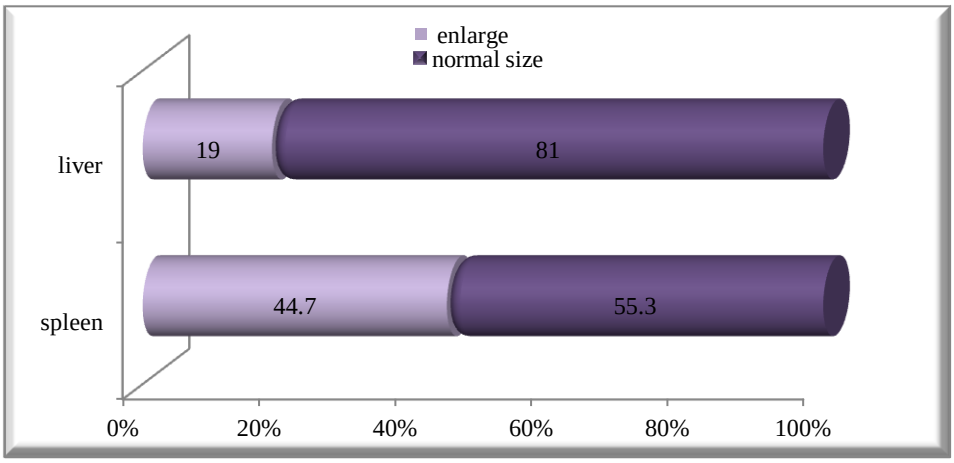

Figure 7. Graphic presentation of the distribution of patients with CLL according to the state of organomegaly. Increased liver is registered in 19.0% of patients with CLL, and increased spleen is registered in 44.7% (Fig.7).

parameters	No.	average	Min.	Max.	Stand.dev.
Hgb	300	117.0	24.0	221.4	26.7
Le	300	65.9	3.4	352.0	63.3
Plt	300	177.5	6.0	516.0	86.2
Lim%	300	85.0	50.0	100.0	10.6
ALB	300	52.8	5.0	220.0	16.6
LDH	300	548.0	102.0	2250.0	375.7
Alb	300	40.6	20.0	65.0	6.6
AP	300	84.1	14.0	536.0	51.8

Table 1. Presentation of the average values of laboratory tests in patients with CLL.

The average hemoglobin value in patients with CLL is 117.0 ± 26.7 g / l within the normal range (110 to 160 g / l), minimum 24.0, maximum 221.4 g / l (Tab.1). The average leukocyte count in patients with CLL is 65.9 ± 63.3 and is above the normal range (4.0 to 10.0), minimum 3.4, maximum 352.0 g / l (Tab.1). The mean platelet count in patients with CLL is 177.5 ± 86.2x109 / l within the normal range (150 to 450), minimum 6, maximum 516 x109 / l (Tab.1). The average albumin value in patients with CLL is 40.6. 6.6 and is in the range of normal ranks (35-50), minimum 20, maximum 65 (Tab.1).

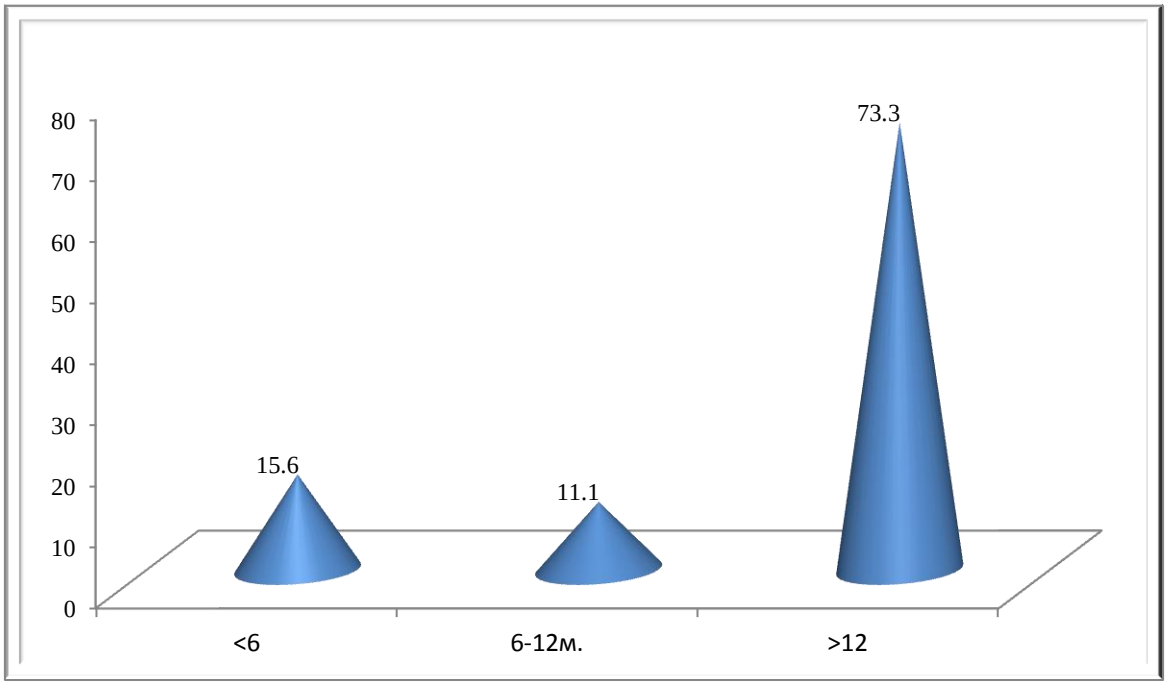

Figure 8. Graphical presentation of the number of patients with CLL with lymphocytes doubling time in a period before the start of therapy.

In 85.0% of patients with CLL there is no duplication of lymphocytes before starting therapy, and in 15.0% there is a doubling of the number of lymphocytes before starting therapy.

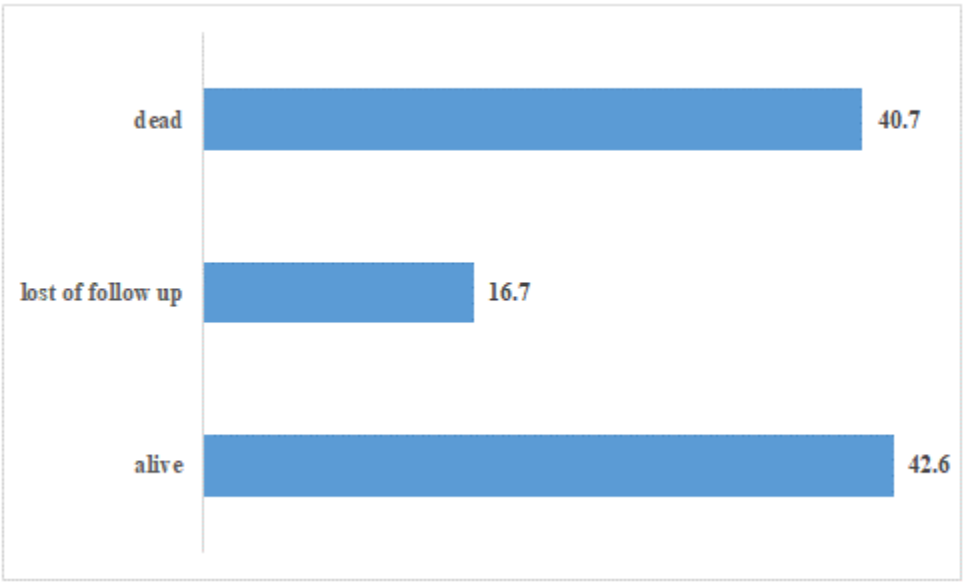

Figure 9. Graphic presentation of the distribution of patients with CLL according to the outcome.

In 40.7% of patients with CLL the outcome was death, 42.6% of patients survived, and 16.7% of patients were lost of follow up in the study period (Fig. 9). On Figure 10 is presented Treatment free survival of CLL patients according to Rai.

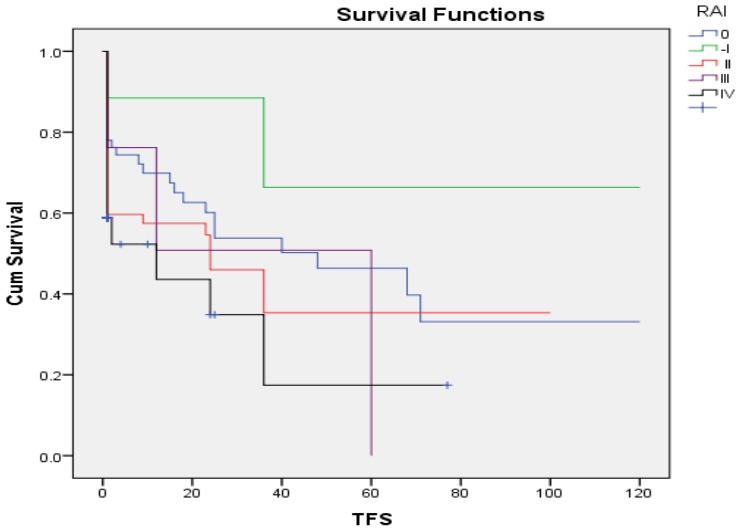

Figure 10. Kaplan Meier curve of Treatment free survival of CLL patients according to Rai

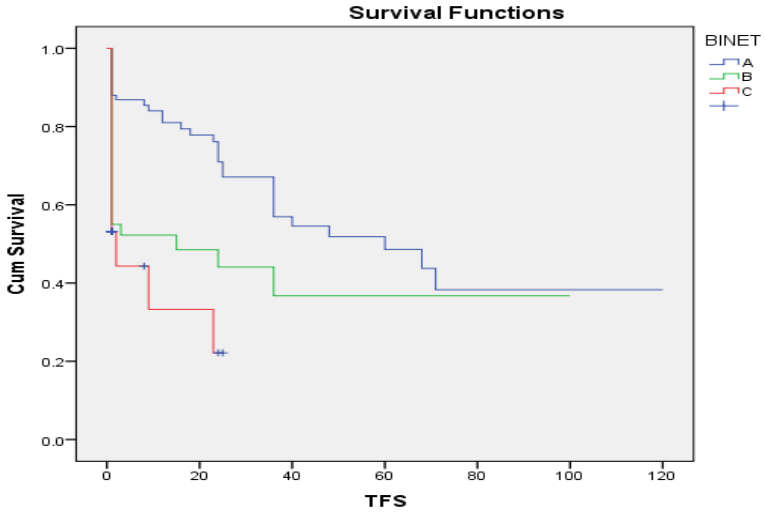

Figure 11. Kaplan Meier curve of Treatment free survival of CLL patients according to Binet

The difference recorded between the Binet stages in patients with CLL in terms of survival time without therapy is statistically significant at $p < 0.05$ (Chi-square = 39.78302, df = 2, p = 0.0000).

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
gender-female vs.male	-.293	.199	2.182	1	.140	.746	.505	1.101
Hgb normal vs. reduced	-.827	.186	19.748	1	.000	.437	.304	.630
WBC-normal vs.elevated	.034	.714	.002	1	.962	1.035	.255	4.198
Plt-normal vs.reduced	-.557	.184	9.135	1	.003	.573	.399	.822
ALC-100 vs.>100	-.893	.217	16.906	1	.000	.410	.268	.627
% of Lym. Normal vs.elevated	-.207	1.005	.042	1	.837	.813	.113	5.835
ecog1			22.485	2	.000			
ecog1(1)	-.952	.206	21.399	1	.000	.386	.258	.578
ecog1(2)	-.640	.251	6.493	1	.011	.527	.322	.863

RAI			9.644	4	.047			
RAI(1)	-.557	.290	3.691	1	.055	.573	.324	1.011
RAI(2)	-1.272	.508	6.278	1	.012	.280	.104	.758
RAI(3)	-.168	.271	.383	1	.536	.846	.497	1.439
RAI(4)	-.426	.446	.915	1	.339	.653	.273	1.564
BINET			23.096	2	.000			
BINET(1)	-.684	.143	22.966	1	.000	.505	.382	.668
BINET(2)	.235	.123	3.656	1	.056	1.265	.994	1.610
Lgl-<2vs.=2	.828	.193	18.416	1	.000	2.289	1.568	3.341
Spleen –enlarged vs. normal	-.459	.185	6.192	1	.013	.632	.440	.907
Liver enlarged vs. normal	-.789	.201	15.390	1	.000	.454	.306	.674
Coombs + vs .-	-.594	.252	5.549	1	.018	.552	.337	.905
IgG-0.4-2.3 vs. <0.4	-.128	.359	.128	1	.721	.880	.435	1.777
IgM-7.0-16.0 vs. <7	-.064	.247	.067	1	.796	.938	.578	1.522
IgA-0.7-4.0 vs. <4.0	-.390	.311	1.574	1	.210	.677	.368	1.245
LDH			.002	2	.999			
normal v.s	-10.003	268.264	.001	1	.970	.000	.000	1.005E+224
elevated	.005	.182	.001	1	.980	1.005	.703	1.436
Alb. normal vs.reduced	-.316	.217	2.128	1	.145	.729	.477	1.115
AP normal vs.elevated	-.293	.317	.850	1	.356	.746	.401	1.390

Hgb-Hemoglobin, WBC-White blood cells, Plt-Platelets, ALC-absolute lymphocyte count, Lym-Lymphocyte,Lgl- lymph gland, Alb-Albumin, AP- Alkaline phosphatase

Table 2. Presentation of univariant Cox Proportional model of Treatment free survival of CLL patients

We evaluated the relationship between 19 factors and the treatment free survival of patients with CLL 10 (are predictors of the event) of 19 associated with the treatment free survival of patients with CLL in the univariate analysis, namely: HGB level, number of Plt, ALC, ECOG, Rai stage, Binet stage, enlarged lymph nodes, organomegaly, Coombs test, but treatment free survival was not associated with sex, albumin level, LDH, AP, IgG, IgM, IgA, percentage of lymphocytes, number of Le (Tab.2).

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
Hgb	-.304	.234	1.685	1	.194	.738	.467	1.168
Plt	-.380	.223	2.896	1	.089	.684	.442	1.059
ALC	-.471	.243	3.736	1	.053	.625	.388	1.007
ECOG			4.514	2	.105			
ECOG(1)	-.520	.257	4.098	1	.043	.595	.359	.984
ECOG(2)	-.382	.267	2.042	1	.153	.683	.405	1.152
RAI			4.206	4	.379			
RAI(1)	-.336	.311	1.165	1	.280	.715	.389	1.315
RAI(2)	-1.047	.521	4.030	1	.045	.351	.126	.976
RAI(3)	-.241	.293	.678	1	.410	.786	.442	1.396
RAI(4)	-.171	.464	.136	1	.712	.843	.339	2.092
BINET			1.906	2	.386			
BINET(1)	-.241	.235	1.051	1	.305	.786	.496	1.246
BINET(2)	.204	.158	1.669	1	.196	1.226	.900	1.670
Lgl	.199	.263	.575	1	.448	1.221	.729	2.043
Spleen	.517	.257	4.033	1	.045	1.677	1.013	2.778
Lever	-.365	.257	2.011	1	.156	.694	.419	1.150
Coombs	-.074	.291	.064	1	.800	.929	.525	1.643

Hgb-Hemoglobin, Plt-Platelets, ALC-absolute lymphocyte count, Lgl- lymph gland

Table 3. Presentation of multivariant Cox Proportional model of Treatment free survival of CLL patients

The multivariate Cox Proportional model of Treatment free survival of CLL patients confirmed ECOG, Rai Stage, and spleen size that influence on survival without treatment. The value of Exp (B) (HR) -0.351 for Rai II (medium risk) reduces the event by 67.9% each month, and ECOG 1 (limited physical activity but compatible with light physical activity, for example light homework, office work) Exp (B) (HR) -0.595 reduces the event by 40.5% each month (Tab.3). The value of Exp (B) -1.677 (HR) for spleen-enhanced indicates an

increased risk of 1.677 times the normal size (Tab.3).Variables that are not statistically significant with the univariate model are eliminated.

IV. Discussion

We have mentioned several times that CLL has a heterogeneous clinical course. In terms of heterogeneity some patients live only a few years after diagnosis, and others live for decades without treatment. To address heterogeneity and predict prognosis, the Rai and Binet clinical scoring systems were introduced in the 1970s. Today, the median survival of CLL patients is estimated to be around 10 years, as opposed to 5-6 years ago when Rai and Binet scoring systems were first introduced into daily practice. The difference may be due to the fact that today the diagnosis is made at an early stage of the disease, but still individual survival is very variable.

Today, in modern hematology, we are experiencing the transition to personalized medicine. Conceptually, this means that patients will be treated with substances that target the tumor based on individual molecular characteristics. However, this personalized targeted therapy also requires the identification of (bio) markers, so that patients will be stratified according to their potential to respond to targeted therapy. CLL is an adequate model of research disease due to clinical heterogeneity, high prevalence in the western population and the presence of clinical and biological parameters. Disease heterogeneity refers to the natural history of the disease and the different outcome of the same therapy in different patients. Patient heterogeneity, including genetic factors, age at diagnosis, and the presence of co-morbidities, are further potential contributing factors to disease heterogeneity. Even in young patients with good performance status with a similar tumor mass size there is a difference in the onset of disease progression and in response to therapy.

Considering the above, there is a need to find new biomarkers that will enable prognostic separation of patients and adequate therapeutic choice. In addition to established clinical systems, such as the Rai and Binet systems and some laboratory parameters, such as lymphocyte duplication time and serum lactate dehydrogenase, many other markers have been identified and evaluated as prognostic factors in CLL. These markers range from general markers, which are determined in serum and blood, through protein markers, which are detected by flow cytometry, to specific genetic markers, which are detected by specific laboratory methods, such as mutation status of the variable genes of the heavy chain immunoglobulin molecule.

In the current management of CLL, prognostic and predictive factors are routinely used that are classified as patient-related or disease-related. Our study uses the term predictive marker as a parameter with different impact on outcome depending on the type of treatment. It helps to compare the outcomes of treatments that are comparable, and differs from a prognostic marker, which assesses the outcome regardless of the type of therapy. Prognostic factors related to the patient are age, performance status, which in our retrospective study with the multivariate Cox Proportional model during treatment free survival and overall survival of patients with CLL confirmed ECOG performance status as a factor influencing survival time without therapy and overall survival. Co-morbidities also directly affect survival or limit the use of effective therapy. In our study, comorbidity was reported in 7.0% of patients with CLL. Most of them are cancers of the skin, prostate, kidney, larynx, breast, etc. One patient was diagnosed with diabetes mellitus, two with dystrophy etc. Disease-related factors affecting overall survival are tumor mass size, disease progression rate, bone marrow cellularity, immunodeficiency, lymphoma progression, and mutation of TP53.

Tumor size measurement, bone marrow cellularity have been encapsulated in the Rai and Binet clinical systems and have in the past been major tools for predicting the outcome of CLL patients and have been key elements of the International CLL Working Group on Treatment Recommendations. However, both systems are insensitive to heterogeneity in cases that present with a small tumor mass and have a poor response to therapy with a poor outcome. There is no doubt about the need to discuss the usefulness of prognostic markers in clinical diagnosis, as well as the need to introduce new predictive and prognostic markers that would be therapeutic guides, so that we can combine these markers as a "CLL prognostic index".

Both clinical scoring systems were independently developed by Rai and Binet to enable stratification of CLL patients into different risk groups and are used in clinical work to determine prognosis. They have been used for about 40 years and are based only on physical examination and standardized blood tests. They predict outcome because patients with stage Binet stage A or Rai stage 0 have a median survival of 10 years, accounting for about 80% of newly diagnosed patients, while patients at moderate risk with stage Binet B stage and Rai I / II show median survival of 5-7 years. High-risk patients with Binet C stage and Rai III / IV survive shorter, about 3 years.

The disadvantages of these two systems are that not all early-stage patients will belong to the same risk group, as shown in several published studies. In 2009, a study by (5) showed that the classical Rai and Binet systems were unable to determine the clinical course at the time of diagnosis, especially at an early stage. In 2010, Letestu and co-workers (6) defined four factors as prognostic in terms of clinical course in patients with Binet stage A - serum thymidine kinase, lymphocytosis, B2 microglobulin level and CD38 expression. Bulian et

al. (7) based on a retrospectivee study, argued that absolute lymphocyte count and Rai stage are not independent predictors of survival, but instead concluded that the Binet system, which includes the number of lymph nodes involved as a variable, independent predictive power.

In our study, patients from the study according to the Rai classification system in the largest percentage, 34.0%, belong to stage II, and patients with Rai 0 stage have the longest median of survival compared to the rest, with the difference registered between Rai stages in overall survival ratio is statistically significant. Multivariate analysis in the our study singled out Rai II stage as a factor influencing survival without therapy, which reduces the event by 67.9% each month.

According to the Binet classification system, the largest percentage, 44.3% of patients with CLL, belong to stage A. The percentage difference registered during the research in the Binet classification system between A and B stage version C stage is statistically significant. Median survival in patients with Binet A is 76 months and is the longest of the remaining 2 categories.

The data from our study correlate with the data from the published studies regarding the length of survival. We could see that the retrospective study was dominated by patients with Rai II stage and the prospective study with Rai 0, suggesting that CLL is diagnosed earlier today than in the past, when it was diagnosed in advanced disease. Better health care today, the introduction of a family doctor, rural doctor, devices for hematological evaluation of patients in each clinic, provided a more regular medical examination, which results in an early diagnosis of Rai 0 disease.

The data we receive from these clinical systems are limiting in terms of the data we need about the course and evolution of the disease that each risk group will have, because it is heterogeneous, and what its response to therapy would be. Although the clinical stage correlates with survival, it is not absolute because patients can progress to a more advanced stage, and thus the course of the disease cannot be predicted in patients in the low-risk groups, which account for about 70-80%. Another limitation is that these systems do not give us information about how patients will respond to therapy, which is information we can obtain from biologically predictive markers.

The selection of a specific treatment for a particular patient is based on the patient's characteristics such as age, comorbidities, organ function, ECOG performance status, medical fitness, and therapy goals (8). Using a risk-adjusted approach to therapy means measuring the potential benefit to the patient of planned therapy versus the potential side effects it may have. When planning treatment aggressiveness, it is important to consider the patient's prognosis, general condition, age, and performance status. Guiding the patient with the risk-adjusted approach along with the patient's medical fitness status and other characteristics led to the following classification. The German CLL Group uses the Cumulative Disease Scale (CIRS) as a tool to determine comorbidities in their clinical trials, to distinguish between physically fit and non-fit patients. The category of fit patient includes patients with ECOG performance status 0-2, and the category of non-fit, or with poor general condition, those with ECOG performance status 3-4. Based on this categorization, the therapy is planned. Patients who are in good general condition with ECOG performance status 0-2 are candidates for aggressive treatment with FCR, and patients with comorbidities are prescribed less toxic modalities, such as: bendamustine + rituximab, fludarabine + rituximab, or plus chlorambucil. In contrast, for patients in poor general condition with ECOG performance status 3-4, the therapy of choice is chlorambucil or fludarabine monotherapy. If they are candidates for anti-CD20 monoclonal antibody therapy, this could prolong overall survival and progression-free survival time.

V. **Concusion**

In our study, multivariate analysis of treatment free survival and overall survival showed ECOG performance status 0.1 and 2 as a factor influencing both treatment free survival and overall survival. Patients with better performance status are treated with more aggressive treatments, which is the goal for better survival.

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